Theoretical investigation of antioxidant activity of hydroxy-quinoline derivatives and their delivery via boron nitride nanocage in gas phase and solvent

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The antioxidant activity of hydroxy-quinoline derivatives was studied in gas phase and solvent. Results indicate that substituents in hydroxy-quinoline decrease the bond dissociation enthalpy and ionization potential values and thus increase the antioxidant activity of hydroxy-quinoline. Results also show that NHMe hydroxy-quinoline has the highest antioxidant activity. The ability and potential of boron nitride ($B_{36}N_{36}$) nanocage in the delivery of hydroxy-quinoline derivatives via DFT method was studied. Results show that adsorption of hydroxy-quinoline derivatives on the surface of $B_{36}N_{36}$ nanocage was exothermic. There were linear dependencies between antioxidant parameters and adsorption energy (E_{ad}) values of hydroxy-quinoline derivatives. We thus propose to synthesize novel hydroxy-quinoline derivatives with higher antioxidant activity.

Keywords: BN nanocage, DFT and solvent, drug delivery, hydroxy-quinoline.

IT is well known that hydroxy-quinoline (ArOH) derivatives have high antioxidant activity and protect us against diseases[1–4]. Hydroxy-quinoline derivatives deactivate free radicals ($ROO^{\bullet}$) by hydrogen atom transfer (HAT) and single-electron transfer followed by proton transfer (SET–PT) mechanisms (eqs (1)–(3))[5–9]

$$ArOH \rightarrow ArO^{\bullet} + H^{\bullet}. \quad (1)$$

$$ArOH \rightarrow ArOH^{+\bullet} + e^{-}. \quad (2)$$

$$ArOH^{+\bullet} \rightarrow ArO^{\bullet} + H^{+}. \quad (3)$$

Bond dissociation enthalpy (BDE) and ionization potential (IP) represent enthalpies of the HAT and SET–PT mechanisms respectively[5–9]. The enthalpy of X and the BDE and IP parameters were calculated as follows

$$H(X) = E_0 + ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT. \quad (4)$$

$$BDE = H(ArO^{\bullet}) + H(H^{\bullet}) - H(ArOH). \quad (5)$$

$$IP = H(ArOH^{+\bullet}) + H(e^{-}) - H(ArOH). \quad (6)$$

Here H is enthalpy and ZPE is zero point energy. In the present study, the antioxidant activity of hydroxy-quinoline derivatives was investigated using the HAT and SPLET mechanisms. The effects of solvent and substituents on the antioxidant activity of hydroxy-quinoline derivatives were studied (Figure 1). The results obtained will help identify novel hydroxy-quinoline derivatives with higher antioxidant activity.

In recent years nanocages have been used for the delivery of important drugs. Fullerenes have several conjugated double bonds; they can attach to radical species, and thus exhibit high biological activity[10–13]. Boron nitride (BN) nanocages have bio-compatibility properties and biomedical applications; thus they have been used in the delivery of antioxidants. The interactions of BN nanocages with various drugs showed that the nanocages have suitable structures to transfer the useful antioxidant drugs[10–13].

The ability and potential of BN nanocages ($B_{36}N_{36}$) to transfer hydroxy-quinoline derivatives were studied (Figure 2). The adsorption energy is calculated as follows

$$E_{ad} = E\,(B_{36}N_{36}\text{ nanocage/hydroxy-quinoline}) - E\,(B_{36}N_{36}\text{ nanocage}) - E\,(\text{hydroxy-quinoline}) + E_{BSSE}, \quad (7)$$

where E ($B_{36}N_{36}$ nanocage) is the energy of the $B_{36}N_{36}$ nanocage, E (hydroxy-quinoline) the energy of hydroxy-quinoline, and E_{BSSE} is the energy of basis set superposition error calculated by counterpoise correction method.

The structures of hydroxy-quinoline derivatives and their radical and cation radical conformers were geometry-optimized by DFT/B3LYP method. The structures of the $B_{36}N_{36}$ nanocage and their complexes with hydroxy-quinolines were geometry-optimized by DFT/B3LYP method using GAMESS software[14–16]. All solvent calculations were done by polarized continuum model (PCM) and 6-31++G (d, p) basis set[17–21]. Our aim is to (1) study the antioxidant activity of hydroxy-quinoline derivatives; (2) find hydroxy-quinoline derivatives with higher antioxidant activity and (3) study the adsorption of hydroxy-quinoline derivatives on the surface of $B_{36}N_{36}$ nanocage.

Table 1 shows the computed BDE and IP values of NHMe, OEthyl and Me-substituted hydroxy-quinoline

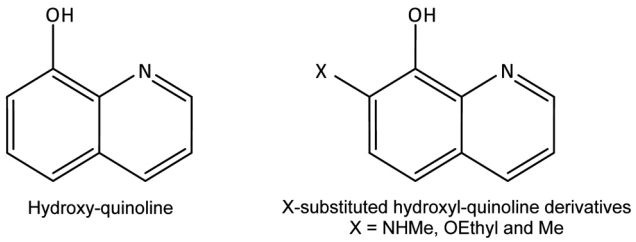

Figure 1. Structure of hydroxy-quinoline derivatives.

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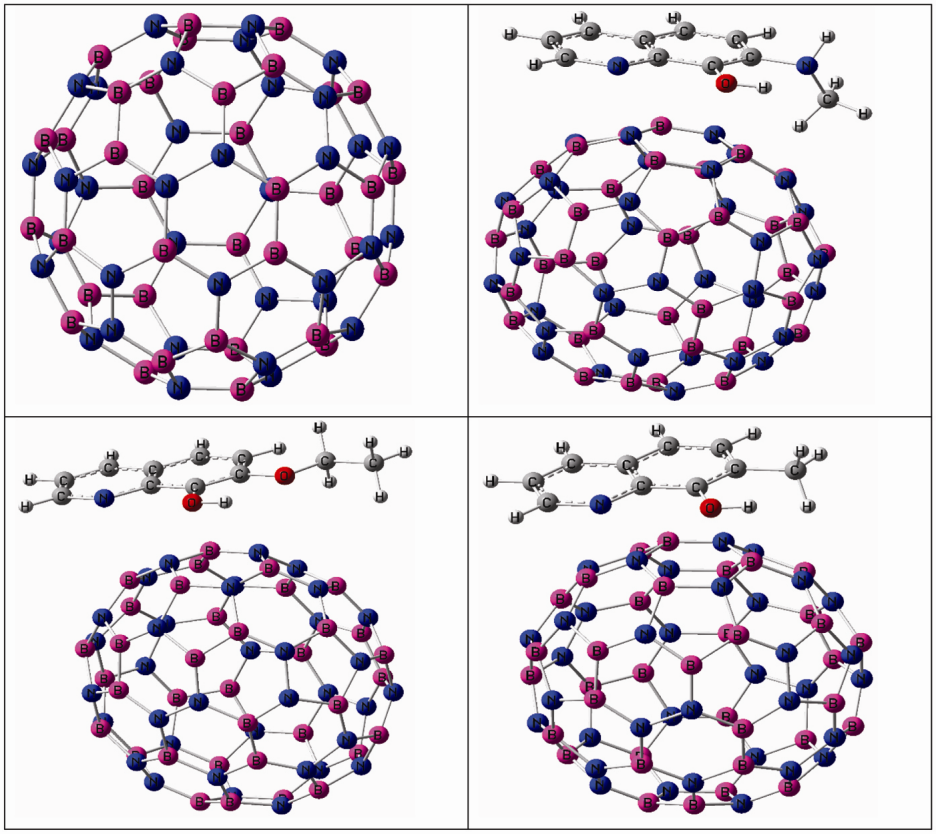

Figure 2. Complexes of hydroxy-quinoline derivatives with $B_{36}N_{36}$ nanocage.

Table 1. Computed bond dissociation enthalpy (BDE) and ionization potential (IP) (kJ/mol) of hydroxy-quinoline derivatives in gas and solvent

	Gas		Ethanol		Water	
Structure	BDE	IP	BDE	IP	BDE	IP
Hydroxy-quinoline	362	741	355	343	349	341
NHMe-hydroxy-quinoline	324	680	320	294	315	283
OEthyl-hydroxy-quinoline	340	707	337	314	330	305
Me-hydroxy-quinoline	351	724	344	331	337	320

derivatives. The calculated BDE values of hydroxy-quinoline were 362, 355 and 349 kJ/mol in gas phase, ethanol and water respectively. The BDE values of NHMe-hydroxy-quinoline were lower than BDE values of hydroxy-quinoline – 38, 33 and 34 kJ/mol in gas phase, ethanol and water respectively. Results show that BDE values of NHMe hydroxy-quinoline were lower than those of OEthyl and Me-hydroxy-quinoline – 16 and 27 kJ/mol respectively.

Calculated IP values of hydroxy-quinoline were 741, 343 and 341 kJ/mol in gas phase, ethanol and water respectively. The IP values of NHMe-hydroxy-quinoline were – 61, 49 and 58 kJ/mol in gas phase, ethanol and water respectively. Results showed that IP values of NHMe hydroxy-quinoline were lower than those of OEthyl and Me hydroxy-quinoline – 27 and 44 kJ/mol in gas phase respectively. Results showed that BDE and IP values of hydroxy-quinoline derivatives in ethanol and water were lower than the corresponding values in gas phase – 10 and 400 kJ/mol respectively.

The results showed that NHMe hydroxy-quinoline has an intermolecular hydrogen bond between lone pair of N (NHMe) and the anti-bonding orbital of O–H (hydroxy-quinoline). The radical conformer of NHMe-hydroxy-quinoline has an intermolecular hydrogen bond between lone pair of O (radical form of hydroxy-quinoline) and the anti-bonding orbital of N–H (NHMe). The OEthyl hydroxy-quinoline has an intermolecular hydrogen bond between the lone pair of O (OEthyl) and the anti-bonding orbital of O–H (hydroxy-quinoline). The intramolecular

Table 2. Experimental and theoretical (DFT/B3LYP method) ΔBDEs and ΔIPs of various substituted phenols (kJ mol^{-1}) in gas and water

	ΔBDE			ΔIP		
		Theoretical			Theoretical	
Substituent	Exp[a]	Gas[b]	Water[c]	Exp[d]	Gas[e]	Water[f]
NHMe	–35.3	–38.1	–22.9	–73.5	–78.6	–73.8
OMe	–13.2	–15.6	–16.7	–22.4	–23.0	–28.6
Me	–2.3	–3.6	–3.6	–8.2	–10.0	–7.9

[a]From ref. 34; [b]From ref. 35; [c]From ref. 36; [d]From ref. 37; [e]From ref. 38; [f]From ref. 39.

Table 3. Calculated E_{ad} (kJ/mol) of hydroxy-quinoline derivatives on $B_{36}N_{36}$ nanocage surface in gas and solvent

Structure	Gas	Ethanol	Water
Hydroxy-quinoline	–334	–311	–301
NHMe-hydroxy-quinoline	–382	–361	–350
OEthyl-hydroxy-quinoline	–365	–343	–331
Me-hydroxy-quinoline	–350	–332	–319

Table 4. Computed BDE and IP (kJ/mol) of complexes of hydroxy-quinoline derivatives with $B_{36}N_{36}$ nanocage surface in gas phase

Complex	BDE	IP
Hydroxy-quinoline with $B_{36}N_{36}$ nanocage	260	502
NHMe-hydroxy-quinoline with $B_{36}N_{36}$ nanocage	218	437
OEthyl-hydroxy-quinoline with $B_{36}N_{36}$ nanocage	245	460
Me-hydroxy-quinoline with $B_{36}N_{36}$ nanocage	253	481

hydrogen bonding interactions decrease the BDE and IP values of hydroxy-quinoline derivatives. Results showed that NHMe hydroxy-quinoline has lower BDE and IP values and so NHMe hydroxy-quinoline has the highest antioxidant activity[22,33].

Table 2 shows the obtained experimental and theoretical ΔBDE and ΔIP values of phenols by experimental and theoretical methods[34–39]. The results showed that the obtained ΔBDE and ΔIP values of hydroxy-quinoline in this study and the corresponding values of phenols from other studies have the same trends[34–39].

Table 3 shows the calculated E_{ad} values of hydroxy-quinoline derivatives on the surface of $B_{36}N_{36}$ nanocage. Results showed that the E_{ad} values were negative and so the obtained adsorptions were exothermic and possible from a theoretical viewpoint. The E_{ad} values of hydroxy-quinoline on $B_{36}N_{36}$ nanocage in gas phase, ethanol and water were –334, 311, –301 kJ/mol respectively.

The NHMe and OEthyl substituents increased the absolute E_{ad} values of hydroxy-quinoline – 48 and 31 kJ/mol in gas phase respectively. Absolute E_{ad} values in solvent were lower than the corresponding values in gas phase – 20 and 30 kJ/mol respectively. The NHMe-hydroxy-quinoline showed the highest ability of adsorption on the surface of $B_{36}N_{36}$ nanocage in gas phase.

The linear dependencies between BDE and IP values and E_{ad} values were studied and linear eqs (8)–(13) were obtained as follows

$$E_{ad} = 1.26 \times (BDE) - 792. \quad \text{(gas phase)} \quad (8)$$

$$E_{ad} = 1.40 \times (BDE) - 813. \quad \text{(ethanol)} \quad (9)$$

$$E_{ad} = 1.45 \times (BDE) - 807. \quad \text{(water)} \quad (10)$$

$$E_{ad} = 0.78 \times (IP) - 917. \quad \text{(gas phase)} \quad (11)$$

$$E_{ad} = 0.96 \times (IP) - 645. \quad \text{(ethanol)} \quad (12)$$

$$E_{ad} = 0.84 \times (IP) - 588. \quad \text{(water)} \quad (13)$$

The results obtained can be useful to propose novel hydroxy-quinoline derivatives with lower BDE and IP values and higher antioxidant activity.

The calculated BDE and IP values of complex of hydroxy-quinoline with $B_{36}N_{36}$ nanocage were 260 and 502 kJ/mol respectively (Table 4). The BDE and IP values of complexes of NHMe hydroxy-quinoline with $B_{36}N_{36}$ nanocage were 218 and 437 kJ/mol respectively.

In conclusion, the antioxidant activity of hydroxy-quinoline derivatives was studied using DFT/B3LYP. The ability and potential of $B_{36}N_{36}$ nanocage in the delivery of hydroxy-quinoline derivatives were studied. The NHMe and OEthyl groups were found to decrease the BDE and IP values of hydroxy-quinoline and so NHMe and OEthyl increase the antioxidant activity of hydroxy-quinoline. The interactions between $B_{36}N_{36}$ nanocage and hydroxy-quinoline derivatives were exothermic and possible from a theoretical viewpoint. The calculated E_{ad} values and BDE and IP values of the studied derivatives have linear dependencies. The results obtained can be used to propose novel hydroxy-quinoline derivatives with higher antioxidant activity.

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