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Original Research Article

Quetiapine Adsorption on the Surface of Boron Nitride Nanocage ($B_{12}N_{12}$): A Computational Study

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ABSTRACT

In this research, IR and frontier molecular orbital (FMO) computations were employed for investigating the performance of $B_{12}N_{12}$ as a novel recognition element for fabrication of quetiapine thermal and electrochemical sensors. All of the computations were done by density functional theory method in the B3LYP/6-31G(d) level of theory and in the aqueous phase. The obtained enthalpy changes (ΔH_{ad}), Gibbs free energy variations (ΔG_{ad}) and thermodynamic equilibrium constants (K_{th}) indicated that quetiapine interaction with boron nitride nanocage is exothermic, spontaneous, irreversible and experimentally feasible. The bond lengths between the adsorbent and the adsorbate and adsorption energy values showed quetiapine interaction with $B_{12}N_{12}$ is a chemisorption. The temperature was also optimized and the findings revealed 298.15 K is the best temperature for quetiapine adsorption on the $B_{12}N_{12}$ surface. The DOS spectrums showed $B_{12}N_{12}$ is an appropriate electroactive recognition for fabrication of new quetiapine electrochemical sensors. The specific heat capacity values (C_V) proved the thermal conductivity of quetiapine has improved after its interaction with the nanostructure. Some structural parameters including energy gap, chemical hardness, chemical potential, electrophilicity, maximum transferred charge, zero-point energy and dipole moment were also calculated and discussed in details.

Keywords: Quetiapine, Density functional Theory, Boron nitride nanocage ($B_{12}N_{12}$), Adsorption, Sensor.

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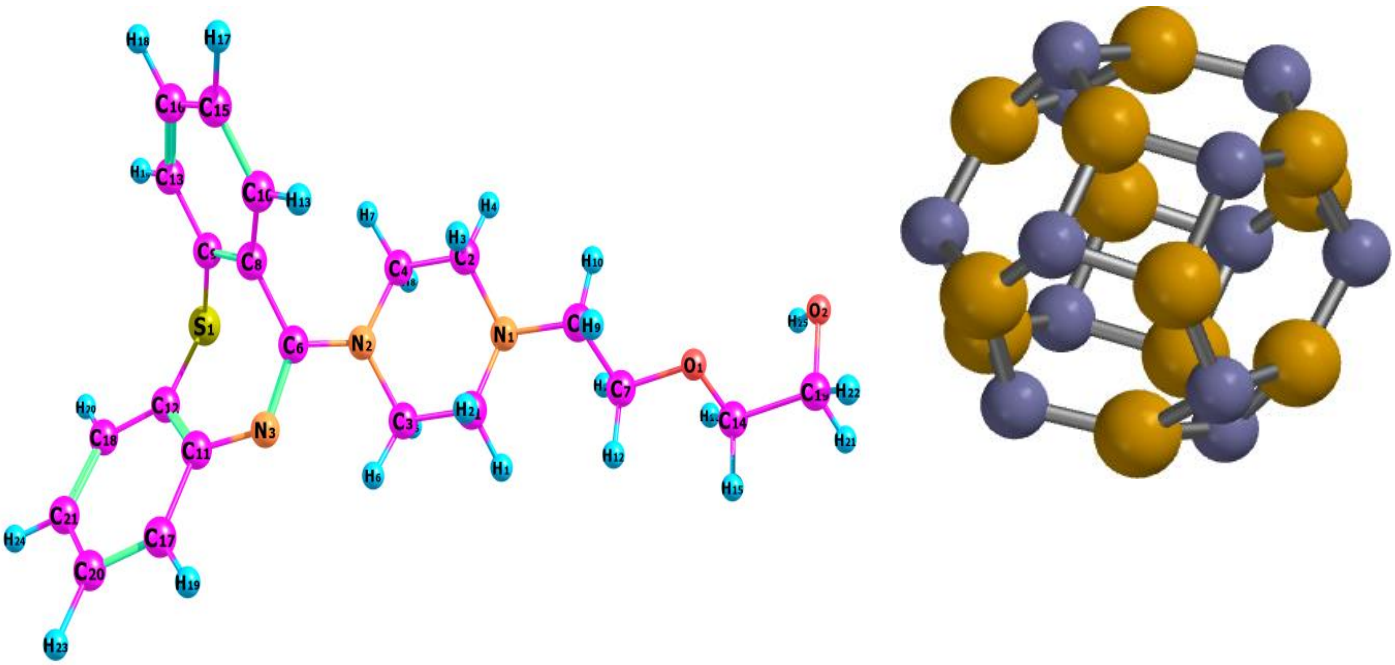
Introduction

Quetiapine which its optimized structure is presented in Figure 1, is an atypical antipsychotic. This medication is prescribed for treatment of schizophrenia, manic phase of bipolar disorder, hallucinations of Parkinson, panic disorder and insomnia. Quetiapine is known as a tetracyclic dibenzothiazepine antipsychotic which induce its medical effects by blocking dopamine, serotonin, adrenergic and cholinergic receptors [1-3]. Quetiapine is one of the top 15 best-selling medications in the world and it can cause serious side effects such as diabetes, gaining weight, sudden cardiac attack, bone marrow suppression and suicidal thinking/behavior. Therefore, quetiapine detection is very important [4-6]. Several analytical techniques are reported for determination of quetiapine including UV-Visible Spectrophotometry, High performance liquid chromatography (HPLC), Fluorescence spectroscopy, LC-MS-MS, Chemiluminescence and Capillary zone electrophoresis. However, the mentioned techniques need expensive instruments, sophisticated operators and large amounts of toxic organic solvents. In addition, these techniques are based on pretreatment steps which prolong the analysis time. Hence, developing a rapid, economical and simple thermal or electrochemical sensor for detection of quetiapine is very significant [7-10].

On the other hand, boron nitride nanocage ($B_{12}N_{12}$), which its optimized structure is given in Figure 1, is the most energetically stable boron nitride nanostructure that was firstly synthesized by Oku et al [11-14]. $B_{12}N_{12}$ has 8 hexagonal and 6 tetragonal rings in its structure and has special properties that make it a prominent candidate as a recognition element for construction of thermal and electrochemical sensors including good thermal stability, high thermal conductivity, excellent oxidation resistance and high specific surface area [15-18]. In this regard, detection of various analytes like proline amino acid, tetryl, TNT and PATO by $B_{12}N_{12}$ have been evaluated so far [19, 20].

Therefore, in this research, quetiapine interaction with $B_{12}N_{12}$ was evaluated by density functional theory in the B3LYP/6-31G(d) level of theory, for the first time. Thermodynamic parameters, frontier molecular orbital (FMO) parameters, DOS spectrums, structural changes and adsorption energy values were computed and discussed in details.



Quetiapine **Boron Nitride Nanocage ($B_{12}N_{12}$)**

Figure 1. Optimized Structures of quetiapine and boron nitride nanocage ($B_{12}N_{12}$)

Computational Details

At first, the structures of $B_{12}N_{12}$, quetiapine and their complexes were designed by Gauss view 6 software. Then, geometrical optimizations, IR and FMO computations were performed by Gaussian 16 using density functional theory method in the B3LYP/6-31G (d) level of theory. This method and level of theory was selected because its results about nanostructures are in an admissible agreement with the experimental findings. The DOS spectrums were also obtained by GuassSum software [17-20]. All of the calculations were done in the aqueous phase and in the temperature range of 298.15-398.15 at 10˚ intervals.

Equations 1-5 were used for calculation the values of adsorption energy (E_{ad}), and important thermodynamic parameters of the adsorption process such as adsorption enthalpy changes (ΔH_{ad}), Gibbs free energy variations (ΔG_{ad}), thermodynamic equilibrium constants (K_{th}) and adsorption entropy changes (ΔS_{ad}) respectively [9-12].

$$E_{ad} = \left(E_{(\text{Quetiapine}-\text{B12N12})} - \left(E_{(\text{Quetiapine})} + E_{(B12N12)}\right)\right) \quad (1)$$

$$\Delta H_{ad} = \left(H_{(\text{Quetiapine–B12N12})} - \left(H_{(\text{Quetiapine})} + H_{(B12N12)}\right)\right) \quad (2)$$

$$\Delta G_{ad} = \left(G_{(\text{Quetiapine–B12N12})} - \left(G_{(\text{Quetiapine})} + G_{(B12N12)}\right)\right) \quad (3)$$

$$K_{th} = \exp\left(-\frac{\Delta Gad}{RT}\right) \quad (4)$$

$$\Delta S_{ad} = \left(S_{(\text{Quetiapine–B12N12})} - \left(S_{(\text{Quetiapine})} + S_{(B12N12)}\right)\right) \quad (5)$$

Where E denotes the total electronic energy of each structure, H is the sum of the thermal correction of enthalpy and total energy of the evaluated materials, G is the sum of the thermal correction of Gibbs free energy and total energy for each of the studied structures, R represents the ideal gas constants, T stands for the temperature (K) and S is the thermal correction of entropy for each structure. Frontier molecular orbital parameters like energy gap (HLG), chemical hardness (η), chemical potential (μ), electrophilicity (ω) and the maximum transferred charge (ΔN_{max}) were calculated by the Equations 6-10 [13-16].

$$\text{HLG} = E_{LUMO} - E_{HOMO} \quad (6)$$

$$\eta = {}^{(E_{LUMO} - E_{HOMO})}/_{2} \quad (7)$$

$$\mu = {}^{(E_{LUMO} + E_{HOMO})}/_{2} \quad (8)$$

$$\omega = {}^{\mu^2}/_{2\eta} \quad (9)$$

$$\Delta N_{max} = -{}^{\mu}/_{\eta} \quad (10)$$

E_{LUMO} and E_{HOMO} in Equations 6 to 8 are the energy of the lowest unoccupied molecular orbital and the energy of the highest occupied molecular orbital respectively.

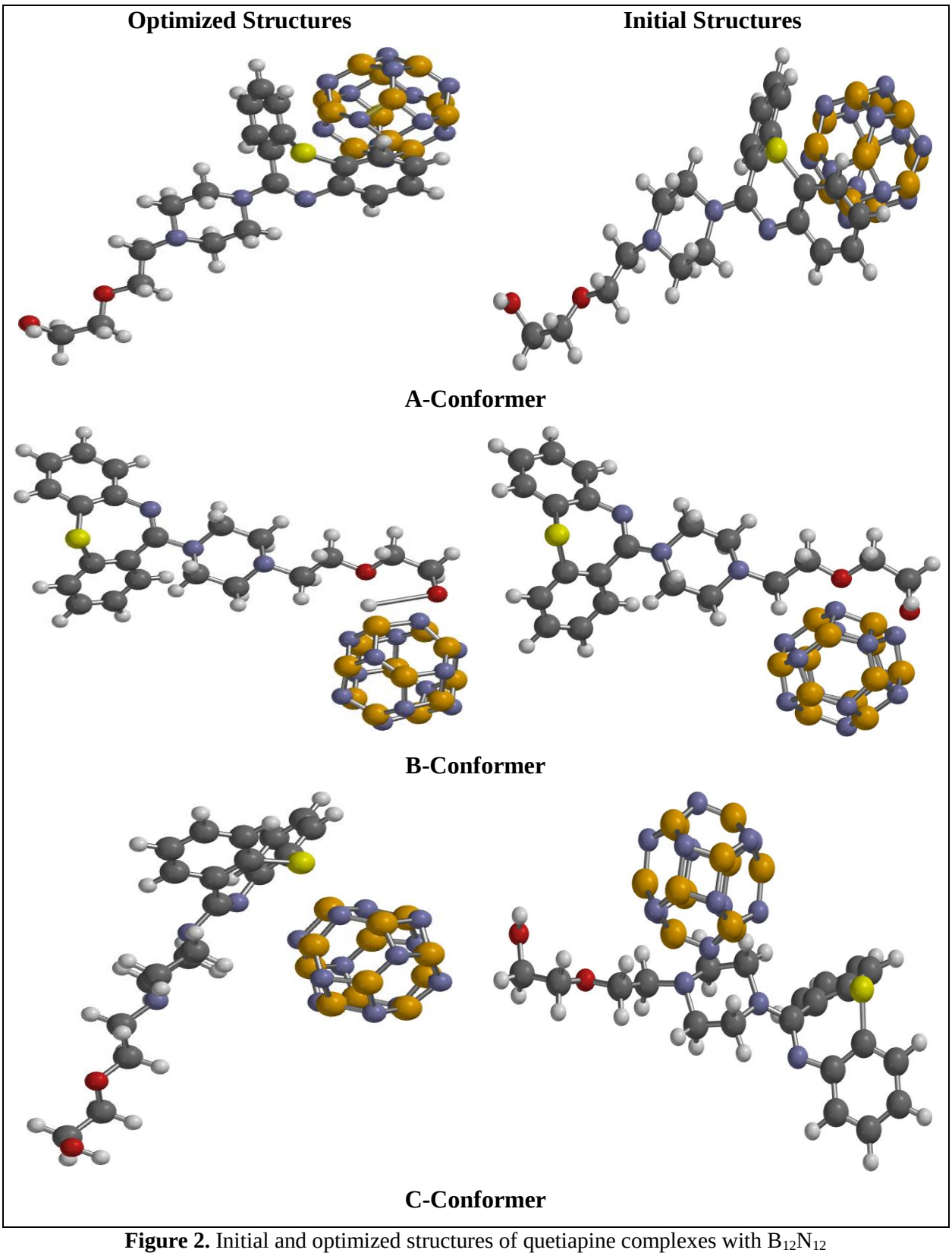


Figure 2. Initial and optimized structures of quetiapine complexes with $B_{12}N_{12}$

Results and Discussion

Adsorption Energy Values and Structural Traits

As it is obvious from Figure 2, in order to find the most stable configuration, quetiapine interaction with $B_{12}N_{12}$ was evaluated at three different situations. At A-conformer, boron nitride cage was inserted near the central thiazepine ring of quetiapine initially and after optimization the nanostructure keep its initial location with partial angle and length differences. At B-conformer $B_{12}N_{12}$ was inserted near the hydroxyl group of quetiapine, it seems a chemical bond is formed in this configuration because after geometrical optimizations sharp variations had occurred in the bond lengths and angles of hydroxyl group. In C-conformer, boron nitride cage was located near the piperazine ring of the drug molecule but after optimization the adsorbent location changed significantly and it approached to the sulfur atom of thiazepine ring.

The calculated adsorption energy values are reported in Table 2. As the provided data in the table revealed obviously, the adsorption energy is highly negative at all of conformers which indicates adsorption process is experimentally feasible in all situations. In addition, the short bond lengths between quetiapine and nanostructure and also structural alterations in Figure 2 showed quetiapine interaction with $B_{12}N_{12}$ is a chemisorption [9-13].

The total electronic energy of the three evaluated conformers are compared in Table 1. As can be seen, C-conformer is the most stable configuration because it has the lowest total electronic energy. The dipole moment values of the investigated structures are also presented in Table 1. As it is clear, the solubility of quetiapine has increased after its adsorption on the surface of boron nitride cage because the dipole moment of quetiapine-$B_{12}N_{12}$ complexes are higher than the pure drug without Nano adsorbent. The zero-point energy of quetiapine has also increased tangibly after its adsorption on the surface of boron nitride cage. As can be seen from Table 1, none of the studied structures have negative IR frequency values [14-16].

Table 1. The values of total electronic energy, adsorption energy, the lowest frequency, bond lengths between adsorbate and adsorbent, dipole moment and zero-point energy

	Quetiapine	$B_{12}N_{12}$	A-Conformer	B-Conformer	C-Conformer
Total energy (a.u)	-1502.078	-938.547	-2440.723	-2440.714	-2440.746
Adsorption energy (kJ/mol)	---	---	-259.922	-235.266	-319.731
Lowest frequency (cm^{-1})	13.431	369.919	5.610	5.636	10.069
S_1-B (Å)	---	---	2.210	---	---
S_1-B (Å)	---	---	---	---	1.413
O_2-N (Å)	---	---	---	1.183	---
Dipole moment (Deby)	5.03	0.00	6.05	5.87	7.81
Zero-point energy (kJ/mol)	1308.181	391.632	1723.734	1729.367	1726.642

Thermodynamic Parameters of Adsorption Process

The calculated adsorption enthalpy changes and Gibbs free energy variations are presented in Table 2. As it is obvious, quetiapine interaction with $B_{12}N_{12}$ is exothermic and spontaneous at all of the configurations. The influence of temperature on these thermodynamic parameters was also studied. As can be seen, by increasing of temperature the adsorption process becomes less spontaneous because ΔG_{ad} values become more positive. The obtained ΔH_{ad} values proved $B_{12}N_{12}$ is an ideal sensing material for construction of new thermal sensors. In thermal sensors, an exothermic or endothermic reaction between the analyte and the recognition element is followed and the changes in temperature is measured by an ultrasensitive thermistor [9-13].

Table 2. The values of adsorption enthalpy changes and Gibbs free energy variations in the temperature range of 2981.15-398.15 K at 10˚ intervals

Temperature (K)	ΔH_{ad} (KJ/mol)			ΔG_{ad} (KJ/mol)		
	A-Conformer	B-Conformer	C-Conformer	A-Conformer	B-Conformer	C-Conformer
298.15	-240.046	-211.733	-297.433	-163.712	-131.773	-219.910
308.15	-240.260	-211.960	-297.626	-160.889	-128.898	-217.017
318.15	-240.448	-212.148	-297.784	-158.098	-126.046	-214.148
328.15	-240.639	-212.360	-297.977	-155.228	-123.163	-211.300
338.15	-240.854	-212.586	-298.175	-152.355	-120.250	-208.411
348.15	-241.081	-212.829	-298.395	-149.506	-117.371	-205.512
358.15	-241.280	-213.051	-298.597	-146.663	-114.510	-202.630
368.15	-241.500	-213.302	-298.799	-143.759	-111.642	-199.736
378.15	-241.733	-213.575	-299.002	-140.913	-108.850	-196.909
388.15	-241.940	-213.841	-299.179	-138.038	-106.033	-194.012
398.15	-242.151	-214.090	-299.348	-135.156	-103.169	-191.054

The calculated adsorption entropy changes (ΔS_{ad}), thermodynamic equilibrium constants (K_{th}) are presented in Table 3. As it is clear, quetiapine interaction with boron nitride nanocage is irreversible and non-equilibrium. One of the advantages of K_{th} is that it depicts the effect of temperature sharper than other thermodynamic parameters. As the provided data in Table 2, show obviously K_{th} decrease remarkably by temperature increasing. Therefore, the optimized temperature for quetiapine interaction with $B_{12}N_{12}$ is 298.15 K [14-16].

The entropy changes values (ΔS_{ad}) are negative for all of the evaluated configurations which indicate after quetiapine adsorption on the boron nitride cage surface aggregation occurred sharply.

Table 3. The values of adsorption entropy changes and thermodynamic equilibrium constants in the temperature range of 2981.15-398.15 K at 10˚ intervals

Temperature (K)	ΔS_{ad} (J/mol. K)			K_{th}		
	A-Conformer	B-Conformer	C-Conformer	A-Conformer	B-Conformer	C-Conformer
298.15	-256.153	-268.320	-260.143	$4.817\times10^{+28}$	$1.222\times10^{+23}$	$3.379\times10^{+38}$
308.15	-257.698	-269.682	-261.717	$1.877\times10^{+27}$	$7.084\times10^{+21}$	$6.137\times10^{+36}$
318.15	-258.963	-270.760	-263.007	$9.074\times10^{+25}$	$4.958\times10^{+20}$	$1.448\times10^{+35}$
328.15	-260.401	-271.943	-264.260	$5.128\times10^{+24}$	$4.033\times10^{+19}$	$4.322\times10^{+33}$
338.15	-261.831	-273.182	-265.575	$3.430\times10^{+23}$	$3.766\times10^{+18}$	$1.566\times10^{+32}$
348.15	-263.146	-274.304	-266.905	$2.704\times10^{+22}$	$4.078\times10^{+17}$	$6.841\times10^{+30}$
358.15	-264.292	-275.255	-268.064	$2.460\times10^{+21}$	$5.028\times10^{+16}$	$3.579\times10^{+29}$
368.15	-265.601	-276.250	-269.194	$2.499\times10^{+20}$	$6.930\times10^{+15}$	$2.190\times10^{+28}$
378.15	-266.720	-277.052	-270.089	$2.919\times10^{+19}$	$1.087\times10^{+15}$	$1.586\times10^{+27}$
388.15	-267.789	-277.856	-271.048	$3.775\times10^{+18}$	$1.861\times10^{+14}$	$1.288\times10^{+26}$
398.15	-268.832	-278.698	-272.096	$5.397\times10^{+17}$	$3.432\times10^{+13}$	$1.164\times10^{+25}$

The specific heat capacity values (C_V) were also computed and the results are presented in Table 4. Specific heat capacity has a direct relationship with thermal conductivity. Indeed, the molecules with higher C_V values have better higher conductivity. As can be seen from Table 4, C_V values of quetiapine and boron nitride cage increased significantly after their interaction [16].

Therefore, quetiapine complexes with $B_{12}N_{12}$ have higher thermal conductivity than the pure drug and nanostructure. Hence, $B_{12}N_{12}$ is an excellent sensing material for developing new thermal sensors for sensitive detection of quetiapine.

Table 4. The values of specific heat capacity (C_V) for $B_{12}N_{12}$, quetiapine and their complexes in the temperature range of 2981.15-398.15 K at 10˚ intervals

Temperature (K)	C_V (J/mol. K)				
	$B_{12}N_{12}$	Quetiapine	A-Conformer	B-Conformer	C-Conformer
298.15	177.536	363.597	552.314	540.283	550.325
308.15	185.935	374.607	571.427	559.705	569.583
318.15	194.259	385.659	590.529	579.112	588.821
328.15	202.497	396.737	609.593	598.478	608.012
338.15	210.635	407.829	628.593	617.775	627.130
348.15	218.665	418.920	647.504	636.979	646.151
358.15	226.577	429.995	666.302	656.066	665.052
368.15	234.364	441.040	684.966	675.012	683.811
378.15	242.019	452.042	703.474	693.798	702.408
388.15	249.536	462.986	721.806	712.403	720.824
398.15	256.912	473.862	739.946	730.809	739.042

Frontier Molecular Orbital Analysis

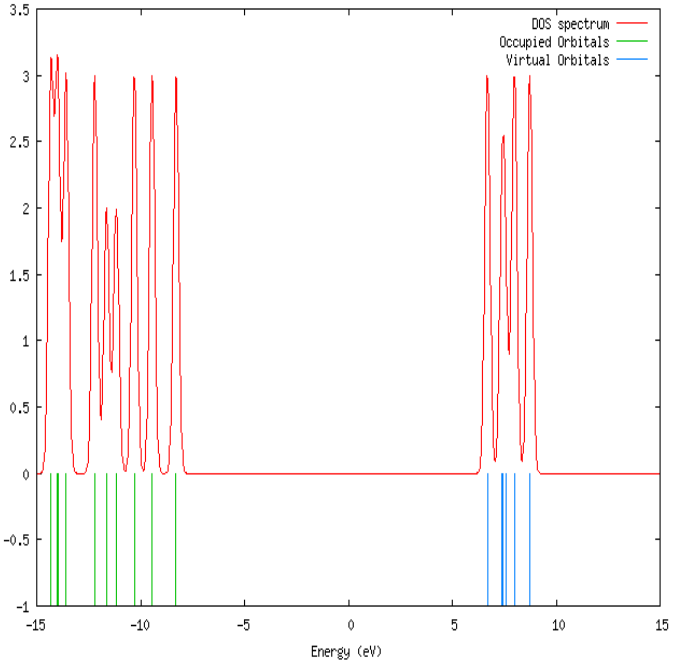
The values of band gap, chemical potential, chemical hardness, electrophilicity and maximum transferred charge for boron nitride cage and its complexes with quetiapine were calculated and the results are given in Table 5. As can be seen from Table 5 and DOS spectrums in Figure 3, band gap of $B_{12}N_{12}$ has declined remarkably after adsorption of quetiapine on the surface of the nanostructure. Band gap has a direct relationship with electrocatalytic activity and electrochemical conductivity. In fact, molecules with lower band gap have higher conductivity in comparison to molecules with higher band gap. Therefore, DOS spectrums show $B_{12}N_{12}$ can be used as a new sensing material for construction of new quetiapine electrochemical sensors [9-12].

Chemical hardness is the next evaluated parameter. As can be seen this index decreased after quetiapine adsorption on the surface of nano-adsorbent. Chemical hardness is a good probe for estimating the reactivity of a molecule. Because the substances with lower chemical hardness have more reactivity because electron transmissions that are essential for chemical reactions can be done in them more conveniently [13-15].

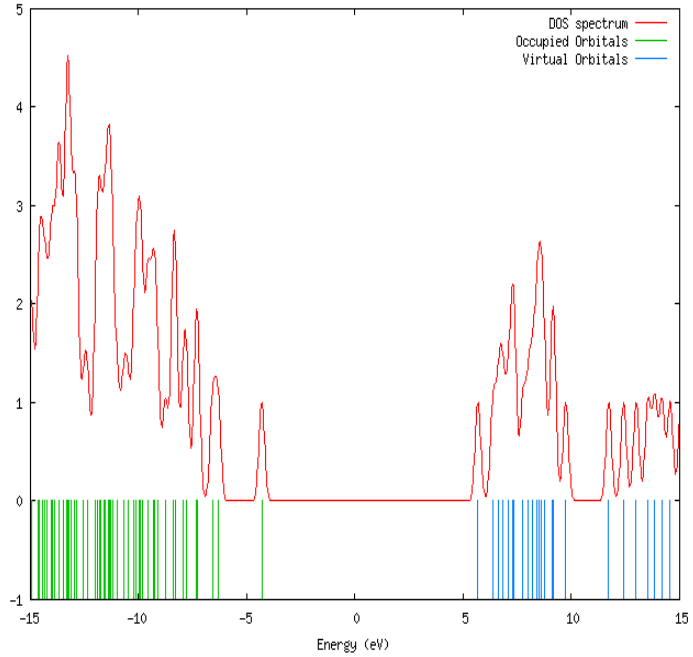
Electrophilicity and maximum transferred charge capacity indices were also investigated. These parameters show the tendency of a molecule for absorbing electron. As it is clear from the table both of the mentioned indices have decreased after quetiapine adsorption on the surface of $B_{12}N_{12}$ which indicates boron nitride cage complexes with quetiapine have lower tendency toward electron than the pure $B_{12}N_{12}$ [16].

Table 5. The values of E_H, E_L, band gap, electrophilicity, chemical hardness, chemical potential, electrophilicity and maximum transferred charge for $B_{12}N_{12}$ and its complexes with quetiapine

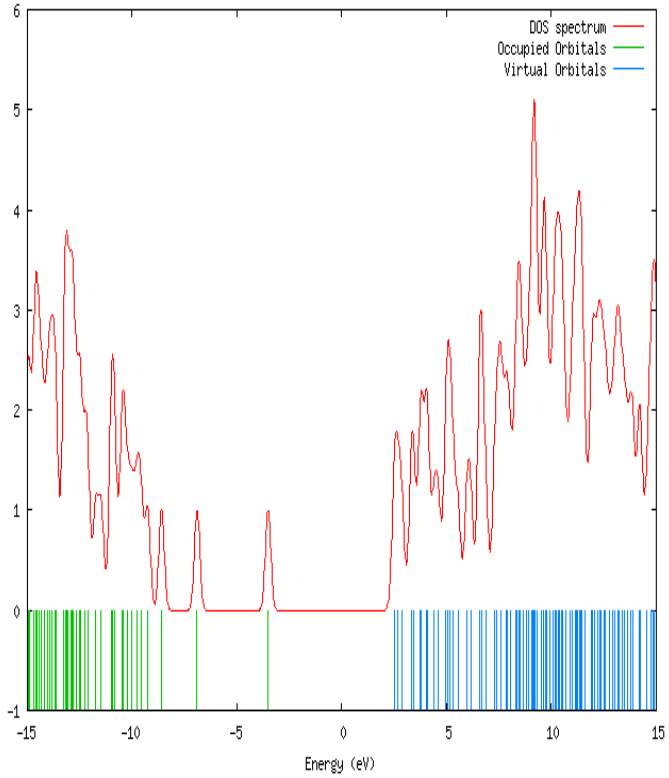
	$B_{12}N_{12}$	**A-Conformer**	**B-Conformer**	**C-Conformer**
E_H (eV)	-8.29	-6.43	-6.34	-6.95
E_L (eV)	6.69	5.73	5.81	5.00
HLG (eV)	14.98	12.21	12.15	11.95
η (eV)	7.49	6.11	6.08	5.98
μ (eV)	-0.8	-0.33	-0.27	-0.98
ω (eV)	0.04	0.01	0.01	0.08
ΔN_{max}(eV)	0.11	0.05	0.04	0.16



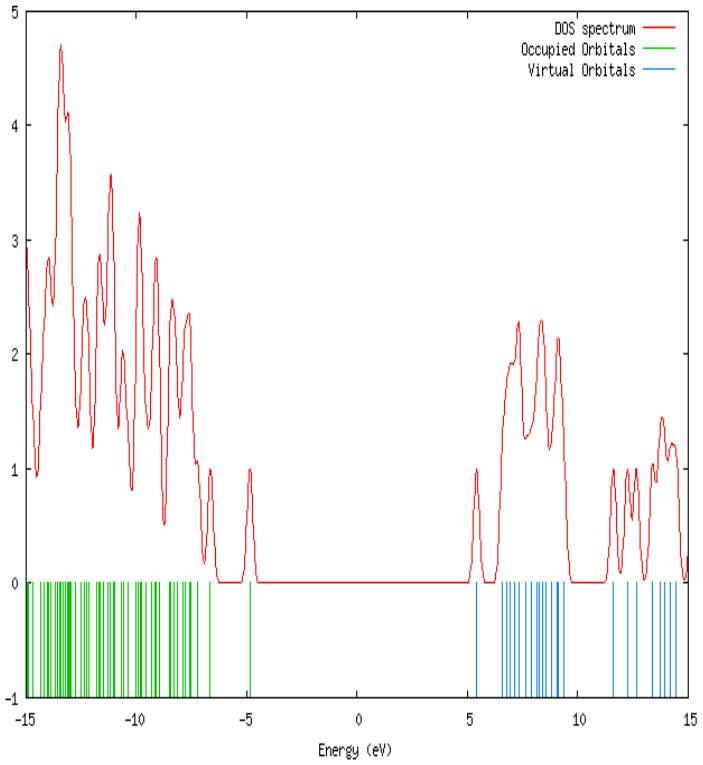
$B_{12}N_{12}$



A-Conformer



B-Conformer



C-Conformer

Figure 3. DOS spectrums of $B_{12}N_{12}$ and its complexes with quetiapine

Conclusions

Quetiapine is a drug which is prescribed for schizophrenia and its detection is very important. Therefore, the performance of boron nitride nanocage ($B_{12}N_{12}$) as a sensing material for thermal and electrochemical detection of quetiapine was investigated by density functional theory. The calculated adsorption energy values, enthalpy changes, Gibbs free energy changes and thermodynamic constants proved quetiapine interaction with $B_{12}N_{12}$ is exothermic, spontaneous and irreversible and the optimized temperature for this interaction is 298.15 K. The values of specific heat capacity and band gap indicated boron nitride nanocage is an excellent sensing materials for construction of new thermal and electrochemical sensors for quetiapine determination.

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