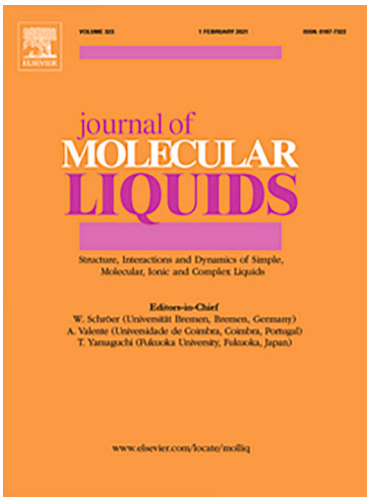

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Abstract

A comprehensive computational investigation was performed in this study on the adsorption of a penicillamine (PCA) molecule as drug onto Al- and Ga-doped $B_{12}N_{12}$ nanoclusters in aqueous and chloroform environments, using density functional theory calculations. The main aim was to evaluate the capability of the nanocluster in drug delivery applications. The PCA molecule

interacts effectively with Al- and Ga-doped clusters via its four nucleophilic sites: amine, carbonyl, hydroxyl, and thiol. Using the computational results, the most stable adsorption complexes were obtained when the PCA molecule adsorbs through its amine group with -4.75 and -4.67 eV adsorption energies for Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ nanocages, respectively. The adsorption of the PCA molecule decreases the HOMO–LUMO gaps and the global hardness of the doped clusters, which corroborated increases in reactivity of the considered clusters for drug delivery purpose. Our computational studies exhibit that Al and Ga atoms doping improves the drug delivery capacity of $B_{12}N_{12}$ nanoclusters.

Keywords: Computational chemistry; Drug delivery; Nanotechnology; Boron nitride

1. Introduction

Penicillamine ($C_5H_{11}NO_2S$) is a degradation product of penicillin antibiotic and beta-dimethyl analog of the cysteine amino acid. Three functional groups mainly control its pharmacological effect (thiol(-SH), carboxylic(-COOH), and alpha-amine(-NH2). It has D and L configurations, in which L enantiomer is toxic [1] and, D configuration is an optically active, non-proteinogenic alpha-amino acid that plays a crucial role in the treatment of various diseases such as cystinuria, Wilson's disease, treatment of rheumatoid arthritis, and scleroderma, it is also used to treat heavy metal poisoning and as a metal chelating factor such as copper, lead, and mercury [2-10]. In addition to the beneficial effects of this drug, it has side effects that can be very serious; it may cause allergic reactions such as urticarial and erythema accompanied by hyperpyrexia, fever, etc. [11-14]. Therefore, investigating its functional mechanism is an essential area of research.

In recent years boron nitride nanomaterials ($B_{12}N_{12}$ and $B_{16}N_{16}$), including nanoclusters, nanotubes, and nanosheets, have attracted extreme attention because of their suitable physical and chemical properties such as thermal conductivity, wide band gap (~4.00-6.00 eV) and nontoxicity in biomedical [15, 16]. On the other hand, due to their non-cytotoxicity, biocompatibility, and diagnostic and therapeutic applications, a lot of research has been done on their role in drug-delivery systems [17-21]. Gianni Ciofani, for the first time, proposed boron nitride nanotubes, that have more stability and compatibility in a biological context than carbon nanomaterials [22]. Based on the computational study by Fowler et al. [23] $(BN)_x$ clusters consist of four and six-membered rings, and the fullerene-like structures $B_{12}N_{12}$, $B_{16}N_{16}$, and $B_{28}N_{28}$ introduced as "magic" clusters. On the other hand, $(BN)_{12}$ has more stability than the other $(BN)_x$ clusters [24, 25]. Therefore, various theoretical assessments have been carried out on the pristine $B_{12}N_{12}$ and doped- $B_{12}N_{12}$ nanoclusters and their applications in various fields [26-31]. Shakerzadeh et al. reported effective phosgene adsorption upon the surface of Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ nanocages [32].

These nanoclusters (e.g., BN) can be employed for pharmaceutical applications to enhance the targeted therapeutic effects of medicines and reduce their side effects. However, their surface chemistry and interactions with the drug molecules need to be well understood in order to design the nano-based drug delivery systems using BN materials [25].

In this regard, we are motivated to investigate the adsorption of D-penicillamine as an essential drug on doped Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ clusters as potential drug delivery agents. Hence, a

comprehensive study on the adsorption energies, dipole moment, HOMO-LUMO gaps of energies, frontier molecular orbitals, NBO and, DOS properties was carried out by means of DFT-B3LYP method.

2. Computational method

The geometry optimization of the PCA molecule as the drug component, Al-$B_{11}N_{12}$, Ga-$B_{11}N_{12}$ and, their considered interactions in aqueous and chloroform environment were carried out using density functional theory (DFT) at B3LYP functional [33, 34] in conjunction with 6-311*G(d) basis set. Vibrational frequencies were calculated to check the stationary points at the same computational level of theory. Molecular electrostatic potential (MEP), natural bond orbital (NBO)[35, 36] and, frontier molecular orbital (FMO) analysis were performed using the Gaussian09 program [37, 38]. The basis set superposition errors (BSSE) were calculated for all configurations with different orientations of the PCA molecule. The density of state (DOS) plots were reported by using the GaussSum program [39]. The GaussView code [40] was employed to visualize the optimized structures and charge density distributions in the computations.

To investigate the relative stability of adsorbed complexes, the adsorption energies (E_{ads}) were calculated by the following expression:

$$E_{ads} = E_{PCA/cage} - (E_{cage} + E_{PCA}) + E_{BSSE} \quad (1)$$

where E_{PCA} is the total energy of the PCA molecule, and E_{cage} is the total energy of Al and Ga doped clusters. $E_{PCA/cage}$ is the total energy of doped clusters loaded with the PCA drug.

The thermodynamics of penicillamine adsorption onto Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ nanoclusters were also studied based on the Gibbs free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) values of adsorption per molecule. The thermodynamic parameters were examined at 298 K and 1 atm using B3LYP functional with 6-311*G (d) basis set [25].

Based on the Koopman theory [41], the physicochemical properties of all considered configurations were calculated by defining the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) according to the following equations:

$$\mu = -\frac{I + A}{2} \quad (2)$$

$$\mu = -x \quad (3)$$

$$\eta = \frac{1}{2}(I - A) \quad (4)$$

$$S = \frac{1}{2\eta} \quad (5)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (6)$$

where I ($-E_{HOMO}$) and A ($-E_{LUMO}$) are the ionization potential and the electron affinity of the system, respectively. μ is chemical potential, x the electronegativity, η the global hardness, S the global softness and based on Parr et al [42] definition, ω is electrophilicity.

3. Result and discussion

The optimized penicillamine molecule and its MEP and FMO plots are depicted in Fig. 1. As presented in Fig. 1, four nucleophilic sites in the PCA drug: amine, carbonyl, hydroxyl and thiol, can be formed in four functionalized systems with adsorption of the drug on the surface of M-$B_{11}N_{12}$(M= Al, Ga) nanoclusters. The geometry optimizations of AL-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$, in which one Al or Ga atom is substituted by a boron atom in the BN (Boron Nitride) structure to generate doped clusters, were performed by B3LYP functional conjugated with 6-311*G(d) standard basis set. As shown in Fig. 2, the ground state structures of nanocages include tetragonal and hexagonal rings. Two kinds of bonds are recognized in the doped cluster, the first is an M-N (M=Ga, Al) bond shared by two hexagonal frameworks, and the next sit between a tetragonal and a hexagonal ring. The average bond lengths of Al-N and Ga-N are about 1.81 Å and 1.88 Å respectively, which is in good agreement with previous reports [32]. To investigate the adsorption complexes of PCA-M-$B_{11}N_{12}$, various possible initial adsorption configurations are examined. In this regard, the PCA molecule closes to different sites of the doped clusters, including heads upon the outer surface and the bridge site of both kinds of identified M-N bonds of the Al atom in Al-$B_{11}N_{12}$ and the Ga atom in Ga-$B_{11}N_{12}$ structure through its nitrogen, sulfur, oxygen of hydroxyl and oxygen of carbonyl. After full geometry optimizations, four stable configurations are identified for each nanocage, displayed in Figs. 3 and, S1 (Supporting File) as panels A-D and A´-D´.

NBO analysis illustrates that there are strong interactions with nucleophilic sites of penicillamine (mentioned above), due to the empty 3p and 4p valence shells of the Aluminum and Gallium elements respectively. The calculated adsorption energies, using Equation (1), are summarized in Table 1. Based on our results, the adsorption energies for A-D configurations are -4.75, -4.61, -4.09, and -3.75 for PCA/Al-$B_{11}N_{12}$ and the corresponding values for PCA/Ga-$B_{11}N_{12}$, states A´-D´ are -4.67, -4.57, -3.96, and -3.59 eV in the aqueous environment. The decreasing trend of adsorption energies concerning nucleophilic sites is the same as the pure boron nitride cluster was reported by Cao et al. [25].

The results illustrate that the amine site adsorption in A configuration has the largest E_{ads} between other interactions in each group, consistent with the obtained charge transfers. NBO analysis shows that PCA molecule donates lone pairs electrons to the nanocages because of the lack of electrons on the Al and Ga sites. Hence, charge transfer occurs from PCA to doped clusters. The higher adsorption energy is for the PCA/cluster complexes with more charge transfer. The obtained dipole moments are tabulated in Table 1, illustrating an increase in polarization for all adsorption systems, compared to pure doped clusters. On the other hand, by switching from water to chloroform solvent, a reduction in dipole moments is observed because chloroform is less polarizing than water (Table S1, Supporting file). Therefore, the NH_2-doped cluster adsorption functional has a lower dipole moment for both Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$, confirming its greater stability than other functionals. In addition, calculated values of the ΔH_{ads}, ΔG_{ads} and ΔS_{ads} are reported in Table 2.

Based on these results (ΔH_{ads} *and* ΔG_{ads}) at 298 K, drug adsorption on the nanoclusters is an exergonic process and the reduction of ΔG_{ads} compared to ΔH_{ads} is due to the entropy effect. Thermodynamic analysis indicates that the A-state for Al-$B_{11}N_{12}$ and A´-state for Ga-$B_{11}N_{12}$ (adsorption via amine group) have the highest values of ΔH_{ads} (-4.11 and -4.05 eV, respectively) and ΔG_{ads} (-3.98 and 3.85 eV, respectively) than others adsorption complexes.

The calculated adsorption energies, HOMO(E_{HOMO}) and LUMO (E_{LUMO}) energy values, and HOMO-LUMO gap (E_{gap}=E_{LUMO}-E_{HOMO}) of the optimized geometries are tabulated in Table 1 for water solvent. The HOMO-LUMO orbitals for the considered systems are depicted in Figs. 4 and S2. HOMO-LUMO gaps for Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ are 4.26 and 3.76 respectively. This implies that the investigated clusters have semiconducting properties. Compared to pristine $B_{12}N_{12}$ (E_{gap}=6.84 eV) [43], M-$B_{11}N_{12}$(M=Al and Ga) nanoclusters have lower energy gaps. Systems with lower energy gaps tend to be more reactive and less stable from the kinetic point of view. Therefore, by replacing Al or Ga atom with B in the BN structure, the functionalized systems' adsorption energies increase which is following decreasing of HOMO-LUMO gaps.

Further, we calculated quantum molecular descriptors (described in section 2) for PCA interaction with Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ nanocages, which are demonstrated in Table 1 and S1. It was found that by exchanging the B atom in the BN cluster with Al and Ga atoms, the energy gaps in new clusters are reduced and the global hardness values by the adsorption process also show the reduction trend, confirming the increase in reactivity.

The total density of states (TDOS) for all complexes is obtained and displayed in Figs. 5, and Figs. S3, S4. The DOS spectrums of Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ imply that the semiconducting characteristics, and the HOMO-LUMO energy gaps, reported in the above section, are in good accordance with earlier works [32]. The DOS plots show the decrease of E_{gap} upon the adsorption process like the other calculations in this work.

To investigate the nature of the interaction between drug and nanocages the electron localization function (ELF) of the most stable functionalized configurations were calculated. The ELF values span from 0 to 1, which reveals the electron localization. ELF=1 implies the strong covalent bonds or lone pair electrons (red area) and the small values of ELF consistent with low electron density localization (green area) [25, 44]. Based on Fig. 6 and Fig. S5 (Supporting file) the electron localization around electrophilic sites (N, O, S) of PCA molecule are observed significantly. The ELF of the adsorption configurations demonstrates localization of electrons upon adsorption between PCA and Al or Ga atom of considered clusters which adjusts with the result of the NBO analysis. Therefore, it can be realized that covalent bonds are formed between drug and nanoclusters.

4. Conclusion

In summary, the chemisorption of penicillamine onto Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ doped clusters were investigated in aqueous and chloroform environments. It has been observed that the interaction of the PCA molecule by considered clusters occurs through its four nucleophilic sites: amine, carbonyl, hydroxyl, and thiol. Our calculations reveal that adsorption via the amine and the

carbonyl groups formed the most stable complexes for Al and Ga nanocages compared to the other functional systems. Our results also illustrate that in a solvent with higher polarity and higher hydrogen bond strength (water), the adsorption energy of the PCA upon the surface of the nanocage is higher. NBO studies show that charge transfer occurs from the PCA nucleophilic site to empty aluminum and gallium atomic orbitals. Calculations of HOMO-LUMO gaps and DOS exhibit that considered complexes have semiconductor properties. The values of quantum molecular descriptors are reported, and a decreasing trend was observed in the global hardness compared to increasing in adsorption energies which confirms the more reactivity of the complexes.

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Property	E_{ads} (eV)	μ_D *Deby*	*D* Å	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{gap} (eV)	*I* *(eV)*	*A* *(eV)*	χ *(eV)*	μ *(eV)*	η *(eV)*	*S* *(eV^{-1})*	ω *(eV)*
PCA	-	4.30		-7.06	-0.96	6.09	7.06	0.96	4.01	-4.01	3.04	0.16	2.63
Al-$B_{11}N_{12}$	-	3.58		-7.53	-3.26	4.26	7.53	3.26	5.40	-5.40	2.13	0.23	6.84
A	-4.75	9.47		-7.29	-3.27	4.02	7.29	3.27	5.28	-5.28	2.01	0.24	6.94
B	-4.61	18.75		-6.95	-2.26	4.68	6.95	2.26	4.60	-4.60	2.34	0.21	4.52
C	-4.09	26.15		-6.82	-1.16	5.65	6.82	1.16	3.99	-3.99	2.82	0.17	2.81
D	-3.54	17.82		-6.68	-2.74	3.93	6.68	2.74	4.71	-4.71	1.96	0.25	5.63
Ga-$B_{11}N_{12}$	-	3.11		-7.55	-3.78	3.76	7.55	3.78	5.66	-5.66	1.88	0.26	8.53
A´	-4.67	13.03		-6.90	-1.16	5.74	6.90	1.16	4.03	-4.03	2.87	0.17	2.83
B´	-4.57	27.46		-6.77	-1.06	5.70	6.77	1.06	3.91	-3.91	2.85	0.17	2.68

Table 1. Calculated adsorption energy (E_{ads}), chemisorption bond distance (D), dipole moment (μ_D), HOMO energy (E_{HOMO}), LUMO energy (E_{LUMO}), energy gap (E_{gap}), and quantum molecular descriptors for PCA, Al- $B_{11}N_{12}$, Ga-$B_{11}N_{12}$, PCA/ Al-$B_{11}N_{12}$ and PCA/ Ga-$B_{11}N_{12}$ in aqueous environment.

D´	-3.59	14.31	-6.99	-1.37	5.61	6.99	1.37	4.18	-4.18	2.80	0.17	3.11

Property	$\triangle H$ *(eV)*	$\triangle G$ *(eV)*	$\triangle S$ *(eV/K)*	ν_{min} cm^{-1}	ν_{max} cm^{-1}
PCA	-	-	-		
Al-$B_{11}N_{12}$	-	-	-	235.27	1440.93
A	-4.11	-3.98	-0.0004	23.91	3491.64
B	-3.38	-2.94	-0.0014	7.98	3602.97
C	-3.09	-2.36	-0.0024	27.53	3508.49
D	-2.98	-2.26	-0.0024	13.39	3624.62
Ga-$B_{11}N_{12}$	-	-	-	193.12	1442.04
A´	-4.05	-3.85	-0.0006	32.46	3517.04
B´	-3.85	-3.65	-0.0006	18.15	3493.43
C´	-3.33	-3.11	-0.0007	22.26	3655.15

Table 2. Calculated enthalpy change (ΔH_{ads}), Gibbs free energy change (ΔG_{ads}), entropy change (ΔS_{ads}) at 298 K and 1 atm, minimum vibrational frequencies (ν_{min}) and maximum vibrational frequencies (ν_{max}).

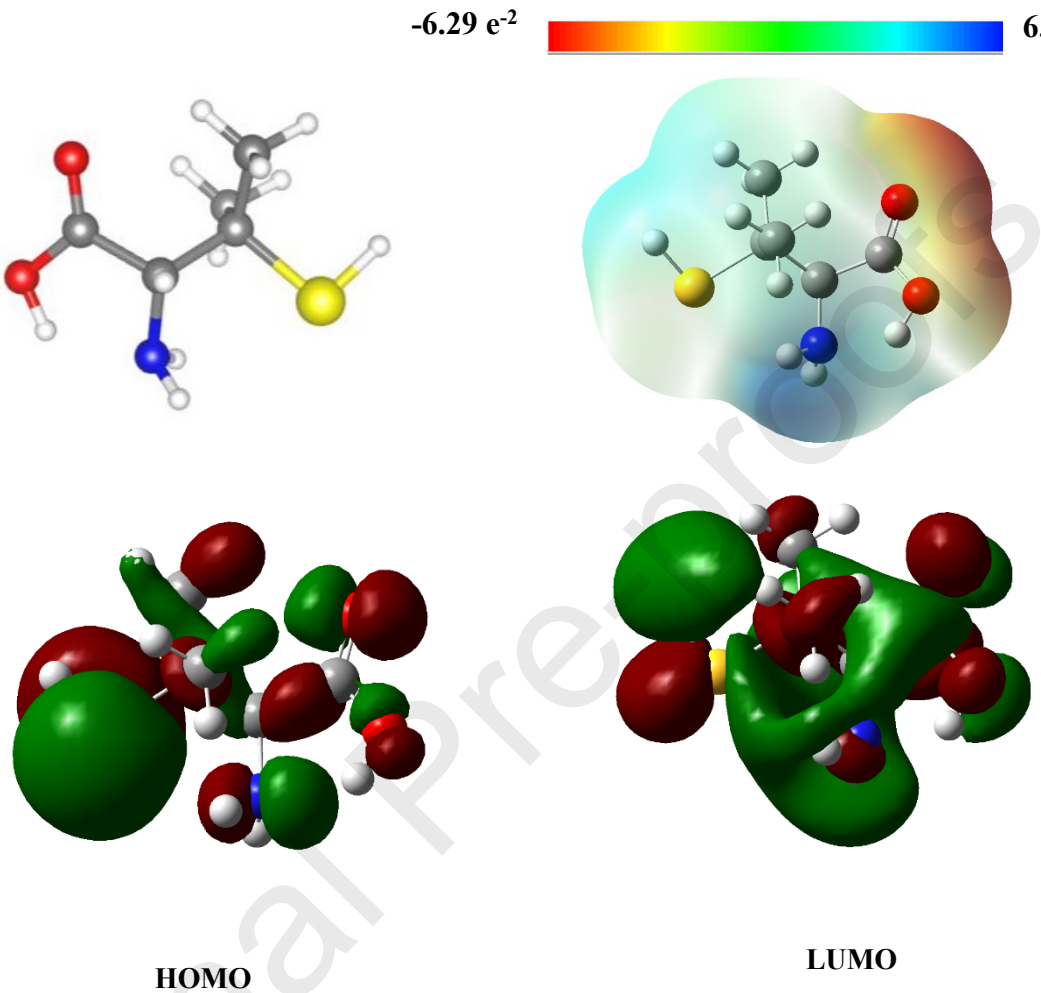


Fig. 1 Optimized structure, MEP and FMO plots of penicillamine.

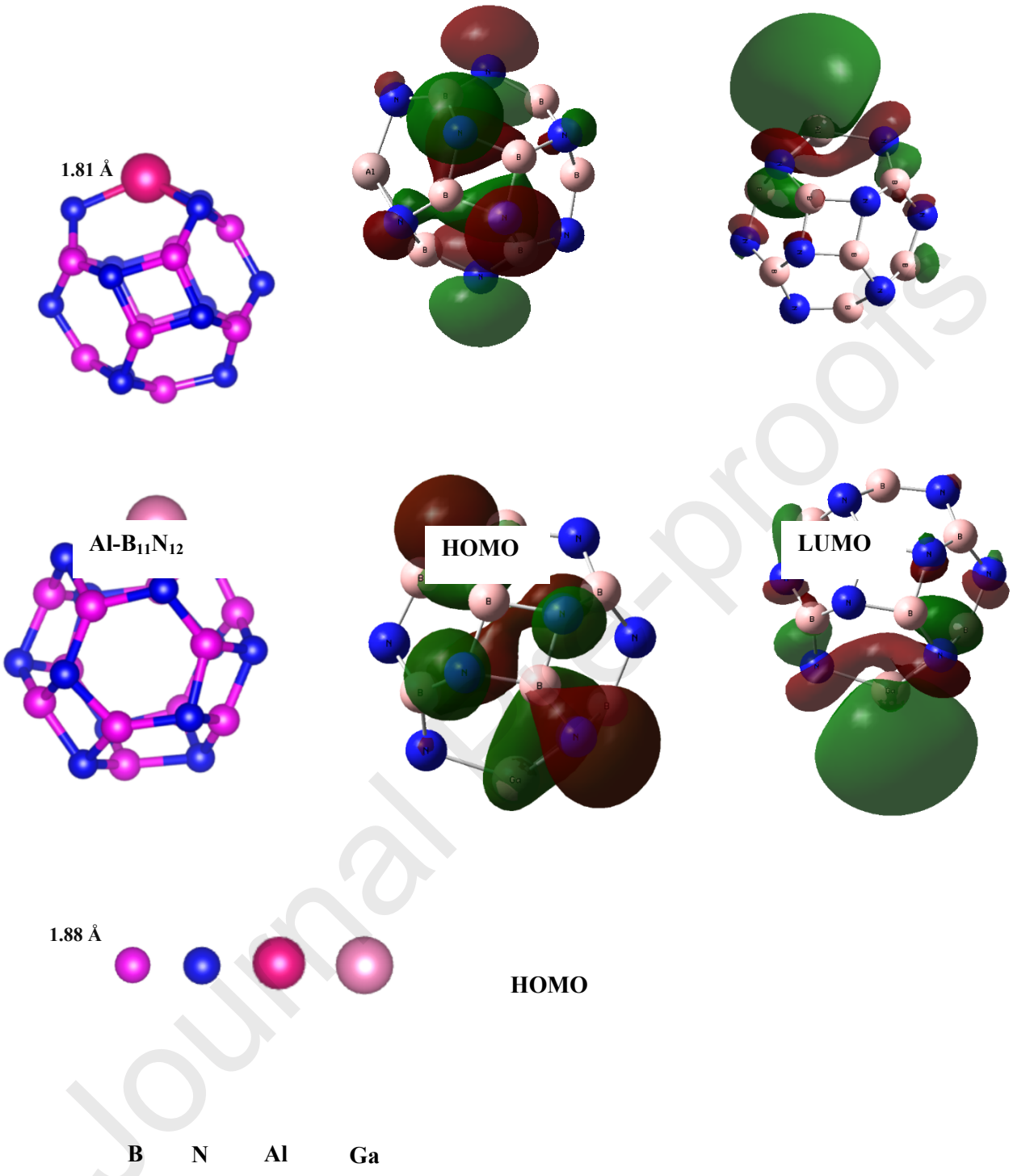


Fig. 2 Optimized structures and FMO plots of AL-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ nanocages.

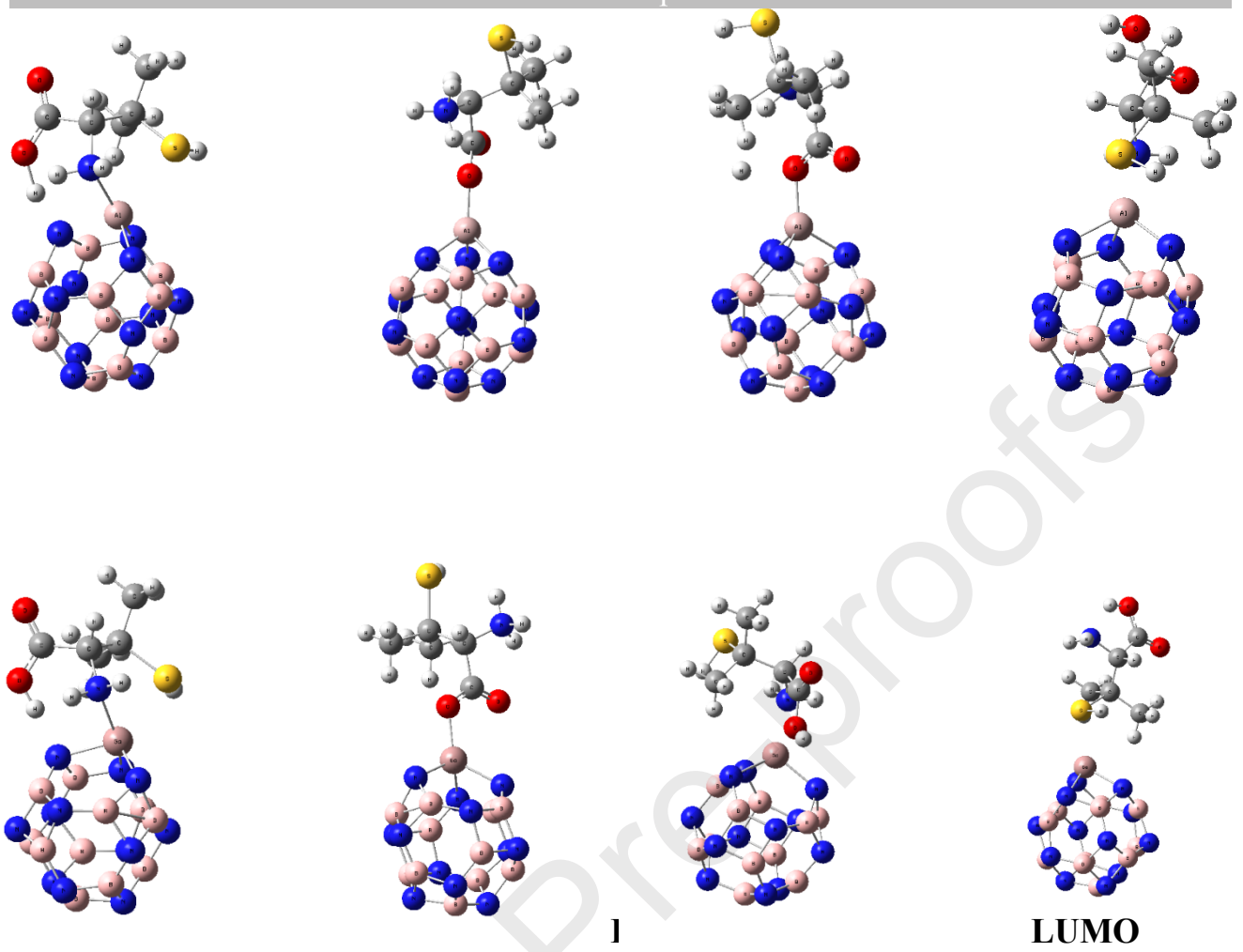
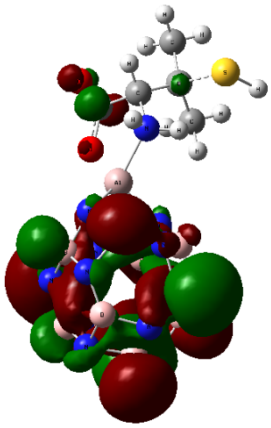
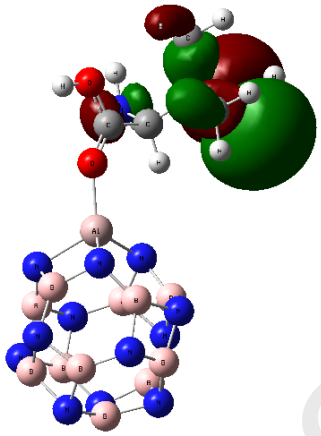
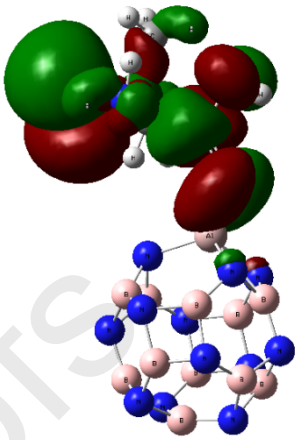


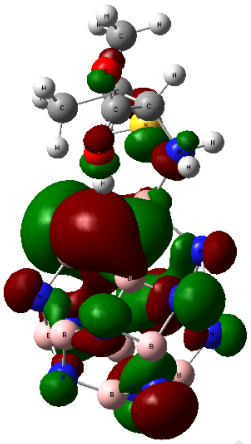
Fig. 2 Optimized structures and FMO plots of Al-$B_{11}N_{12}$ and Ga-$B_{11}N_{12}$ nanocages.

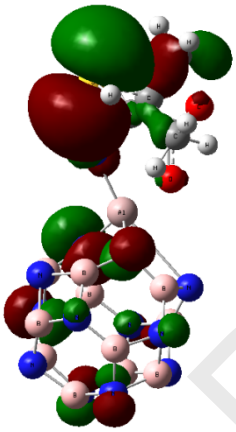
Fig. 3 Adsorption of neutral PCA on Al-$B_{11}N_{12}$ via amine (A), carbonyl (B), hydroxyl (C), thiol (D) groups and on Ga-$B_{11}N_{12}$ via amine (A´), carbonyl (B´), hydroxyl (C´), thiol (D´) groups.





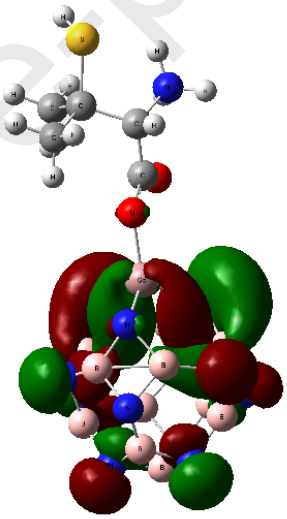


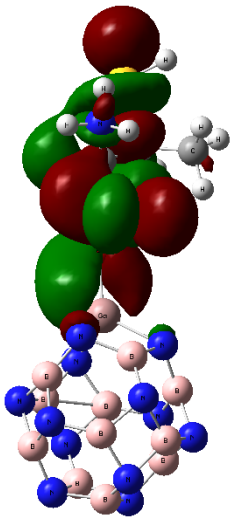




LUMO

(State A)





HOMO (State A′) LUMO (State A′) HOMO (State B′) LUMO (State B′)

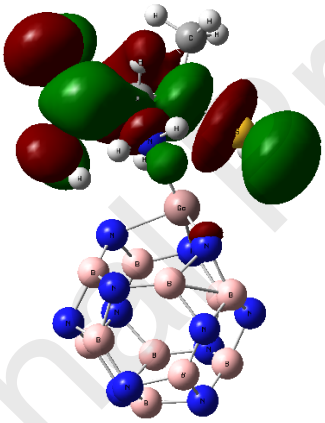
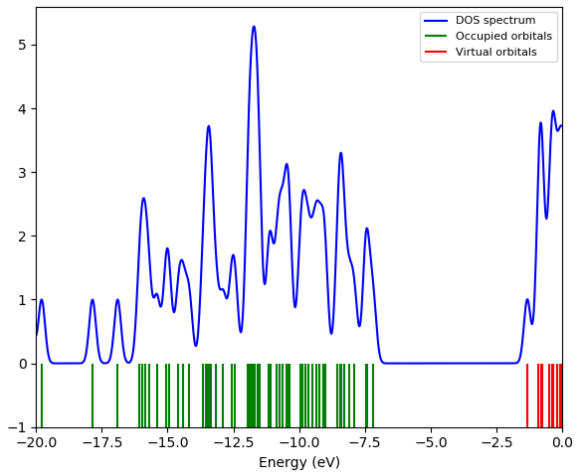
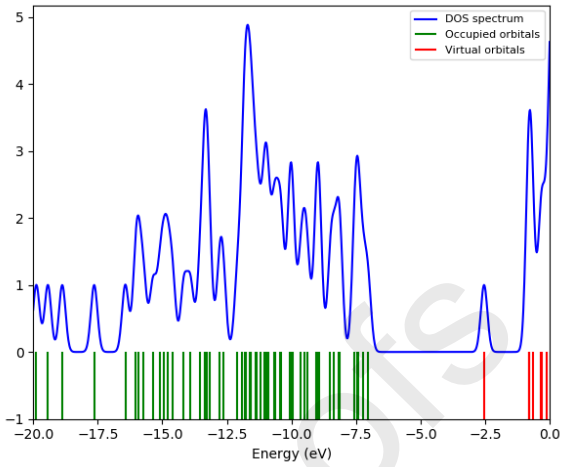


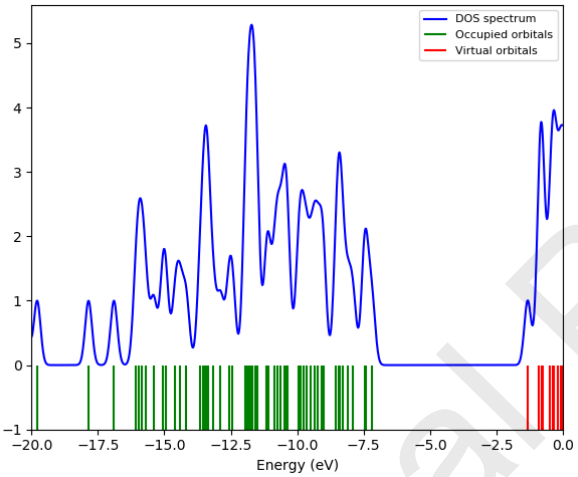
Fig. 4 FMO p l PCA/Ga- $B_{11}N_{12}$ (A′ and B′) complexes.



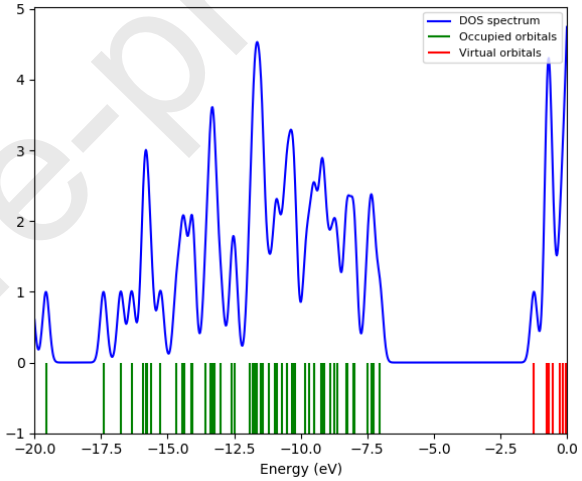
(State A)



(State B)

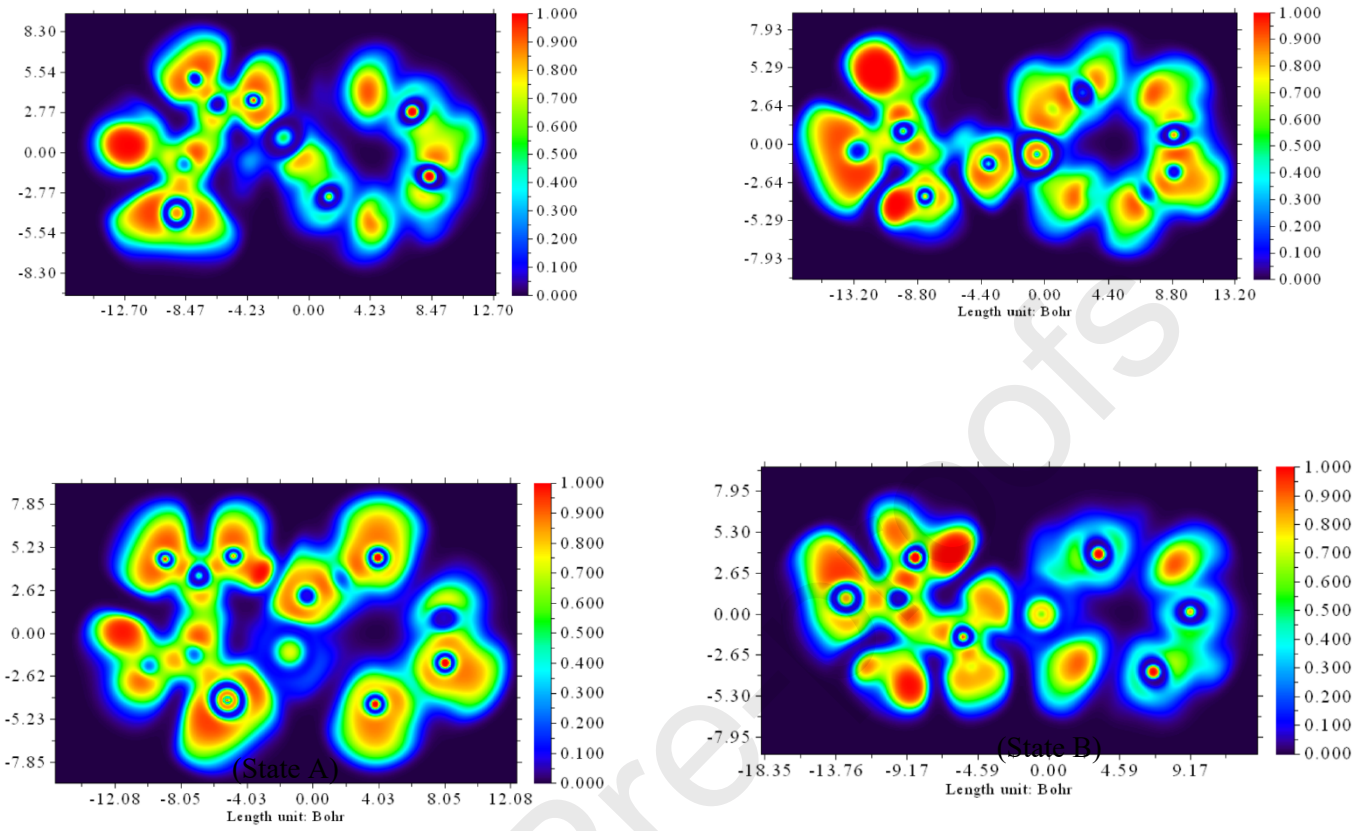


(State A´)



(State B´)

Fig. 5 DOS plots for Al-$B_{11}N_{12}$, States A, B, and Ga-$B_{11}N_{11}$ State A´ and B´ in aqueous environment.



(State A´)

(State B´)

Fig. 6 Electron Localization Function plots Al-$B_{11}N_{12}$, States A, B, and Ga-$B_{11}N_{11}$ State A´ and B´.

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Research highlights:

- Adsorption of PCA molecule as drug onto Al- and Ga-doped B12N12 nanoclusters
- Computational calculation of adsorption process using DFT analysis
- PCA interacts effectively with Al- and Ga-doped clusters via nucleophilic sites

Declaration of interests

■ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: