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Smart drug delivery: a DFT study of C₂₄ fullerene and doped analogs for pyrazinamide†

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The potential applicability of the C_{24} nanocage and its boron nitride-doped analogs ($C_{18}B_3N_3$ and $C_{12}B_6N_6$) as pyrazinamide (PA) carriers was investigated using density functional theory. Geometry optimization and energy calculations were performed using the B3LYP functional and 6-31G(d) basis set. Besides, dispersion-corrected interaction energies were calculated at CAM (Coulomb attenuated method)-B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p) levels of theory. The adsorption energy (E_{ads}), enthalpy (ΔH), and Gibbs free energy (ΔG) values for C_{24} -PA, $C_{18}B_3N_3$ -PA, and $C_{12}B_6N_6$ -PA structures were calculated. The molecular descriptors such as electrophilicity (ω), chemical potential (μ), chemical hardness (η) and chemical softness (S) of compounds were investigated. Natural bond orbital (NBO) analysis confirms the charge transfer from the drug molecule to nanocarriers upon adsorption. Based on the quantum theory of atoms in molecules (QTAIM), the nature of interactions in the complexes was determined. These findings suggest that C_{24} and its doped analogs are promising candidates for smart drug delivery systems and PA sensing applications, offering significant potential for advancements in targeted tuberculosis treatment.

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Introduction

Tuberculosis (TB) is a prevalent and often fatal infectious disease caused by various species of mycobacteria, particularly Mycobacterium tuberculosis.1 TB remains one of the most significant infectious diseases of our time, capable of affecting all organs of the body, especially the lungs. Despite widespread optimism in the 1980s that TB would be controlled by the turn of the century, the World Health Organization (WHO) declared it a global emergency in 1993.2,3 According to WHO reports, approximately 10 million people were diagnosed with TB in 2017, with the number increasing to about 6.4 million in 2019. Annually, around 1.3 million patients succumb to TB.4 The treatment of TB has become increasingly challenging due to the emergence of drug-resistant strains of Mycobacterium tuberculosis. In 2012, there were about 45 000 cases of multidrugresistant TB (MDR-TB), resulting in an estimated 170 000 deaths. The situation is exacerbated when these strains develop resistance to multiple drugs, undermining the significant advances made in TB control over the past century.5 Currently, more than 8 million people worldwide contract TB each year, and approximately one-third of the global population harbors

One of the four first-line anti-tuberculosis drugs is pyrazinamide (PA), which, in addition to shortening the treatment period from nine to six months, eradicates the organism by destroying the active and inactive forms of bacillus tuberculosis in the acidic environment inside the macrophages. Like other drugs, PA has important side effects, such as fever, anorexia, liver enlargement, jaundice, and liver failure. Targeted drug delivery is a new way to reduce problems caused by direct drug use and drug resistance.7-9 Considering the common challenges of using drugs such as PA, the controlled release of the drug has attracted the attention of researchers. Targeted drug delivery and controlled release has advantages such as the possibility of drug delivery in nanometer dimensions, the ability to maintain the drug concentration in a relatively constant amount for a certain time, the ability to adjust the drug release rate depending on the place of drug delivery, and the ability to transfer several drug substances to a specific tissue or organ. 10,11 Nowadays, drug delivery based on nanocarriers is at the center of attention of many companies acting in the pharmaceutical industry since nanomaterials have special properties and potential applications that make them superior to the traditional drug delivery vectors. The use of nanocarriers in medical science helps to increase the availability of the drug at the site of disease, and reduces the dose frequency and adverse side effects.12-15 As new drugs are developed, significant efforts have been directed toward exploring innovative delivery routes.

the bacterium asymptomatically. Despite significant efforts to control TB, the emergence of drug resistance remains a critical concern, underscoring the need for rapid and accurate diagnosis to facilitate timely and effective treatment.

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Targeted delivery systems represent a promising solution to overcome the limitations of conventional methods. To realize this potential, a wide range of nanoparticles have been proposed and extensively studied. 16-20 These nanoparticles must interact well with biological environments and pass through the cell membrane to deliver therapeutic molecules. Fullerenes (C₆₀) are one of the pioneering classes of carbon-based nanoparticles, which have been widely studied for targeted drug delivery applications.21 Fullerenes have a unique structure and have suitable properties for interaction with drugs. Although fullerene toxicity is somewhat of a concern, several watersoluble fullerene derivatives have shown acceptable cytotoxicity for drug delivery applications.22 Recently, new fullerenelike compounds and hexagonal boron nitrides have been developed, and their potential applications as advanced delivery systems have been investigated.23-27 Studies provide a detailed drug interaction mechanism with boron nitride fullerenes (BNF) and reveal that the BNF can be a smart drug delivery vehicle for the drugs. 23,28-30 In this study, the interaction of the pyrazinamide drug with C24, C18B3N3, and C12B6N6 nanocages was investigated using density functional theory (DFT) calculations. To achieve this, we employed a range of analytical tools, including adsorption energy (E_{ads}), thermochemical parameters $(\Delta H \text{ and } \Delta G)$, frontier molecular orbitals, ionization energy, electrophilicity, chemical hardness, softness, electronegativity, natural bond orbitals (NBO), and atoms in molecules (AIM), as well as NMR, IR, and UV-Vis spectroscopy. These comprehen-

sive analyses provide a detailed understanding of the interaction mechanisms and potential applications of these nanocages

Computational details

in drug delivery and sensing systems.

All of the calculations were performed using the Gaussian 09 package.31 In the first stage, geometry optimization and energy calculations were carried out using the B3LYP32,33 functional and 6-31G(d)34 basis set. Besides, dispersion-corrected adsorption energies employing CAM-B3LYP35 and M06-2X36 functionals with the 6-31G(d,p)34 basis set were calculated. The counterpoise procedure (CP)37 was used to correct for basis set superposition error (BSSE) in the calculation of the adsorption energies. To obtain the thermal and Gibbs free energies and ensure that the optimized structures are true local minima on the potential energy surface (not saddle points or transition states), the vibrational frequency calculations were performed at all computational levels. All reported structures were identified as true minima on the PES. The adsorption energy (E_{ads}) of the obtained structures of the interaction between pristine and doped C_{24} with PA at T = 298 K and P = 1 atm is given by the following equation:

$$E_{\text{ads}} = E_{\text{complex}} - (E_{\text{nanocage}} + E_{\text{PA}}) \tag{1}$$

Natural bond orbital analysis provides a chemical viewpoint of van der Waals interactions using a donor–acceptor type interpretation of molecular orbitals.³⁸ Therefore, we used NBO analyses to calculate the charge distribution over the atoms of

interacting species and to estimate the stabilization energies $(E^{(2)})$ of bond–antibond interactions. The energy difference between the highest occupied (HOMO) and the lowest unoccupied molecular orbital (LUMO), known as $E_{\rm g}$, for a system is given as:

$$E_{\rm g} = E_{\rm LUMO} - E_{\rm HOMO} \tag{2}$$

The electronic sensitivity of the pristine and doped C_{24} nanocage toward PA is calculated as follows:

$$\Delta E_{\rm g} = \frac{\left(E_{\rm g} \text{ complex} - E_{\rm g} \text{nanocage}\right)}{E_{\rm g} \text{nanocage}} \times 100 \tag{3}$$

Quantum molecular descriptors (also known as the conceptual density functional theory (CDFT) parameters), including the electronegativity (χ), global hardness (η), electrophilicity index (ω), ionization potential (I), electron affinity (A), and electronic chemical potential (μ), were calculated with the help of HOMO and LUMO values. The electrophilicity index (ω) measures the stability of a compound in the presence of an additional electronic charge from the environment. In a charge transfer process, higher values of ω indicate the higher electrophilic power of the structure.^{39,40}

$$\mu = -\chi = -(E_{\text{HOMO}} + E_{\text{LUMO}})/2 \tag{4}$$

$$\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2 \tag{5}$$

$$\omega = \mu^2 / 2\eta \tag{6}$$

The ionization energy (*I*) and electron affinity (*A*) can be expressed as $-E_{\text{HOMO}}$ and $-E_{\text{LUMO}}$, respectively. Chemical shielding (CS) calculations were performed using the gauge-including atomic orbital (GIAO) method.⁴¹ The chemical shift isotropy (σ_{iso}) and anisotropy ($\Delta\sigma$) parameters were calculated applying principal components ($\sigma_{11} \leq \sigma_{22} \leq \sigma_{33}$) of the chemical shift tensor, as follows:

$$\sigma_{\text{iso}} \text{ (ppm)} = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3$$
 (7)

$$\Delta \sigma \text{ (ppm)} = \sigma_{33} - (\sigma_{11} + \sigma_{22})/2$$
 (8)

The NBO and AIM analysis was carried out at the M06-2X/6-31G(d) level of theory. 38,42

Results and discussion

Optimized geometry of the adsorbents

The fully optimized geometry, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), and molecular electrostatic potential (MEP) maps of the adsorbent nanocages (C_{24} , $C_{18}B_3N_3$, and $C_{12}B_6N_6$) are shown in Fig. 1. The optimized structures of these nanocages are characterized by two hexagons joined by twelve pentagons with D6, C3, and C3 point groups for C_{24} , $C_{18}B_3N_3$, and $C_{12}B_6N_6$, respectively. The C–C bond length within the hexagons of C_{24} is about 1.42 Å; however, the value of the C–C bond length is in the

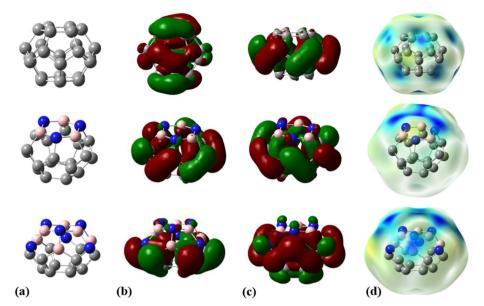


Fig. 1 (a) Optimized geometries, (b) HOMOs, (c) LUMOs, and (d) MEP plots for C_{24} , $C_{18}B_3N_3$, and $C_{12}B_6N_6$ nanocages at the M06-2X/6-31G(d,p) level of theory.

range of 1.36 Å to 1.53 Å in pentagons. The average value of the C-C bond length is calculated to be about 1.44 Å, which is in agreement with the reported values in the literature. 43,44 The C₁₈B₃N₃ is derived by substituting the carbon atoms of a hexagon of C24 with boron and nitrogen atoms as one in between. Thus, C₁₈B₃N₃ includes a B₃N₃ ring, six pentagons with C₃BN formula, six pentagons with C₅ formula, and a C₆ ring. The average length of C-C, B-C, N-C, and B-N bonds is about 1.47, 1.57, 1.46, and 1.48 Å, respectively. In the structure of C₁₂B₆N₆, five distinct types of rings are present: a B₃N₃ ring, six pentagons with B₂N₂C formula, three C₄N pentagons, three C₄B pentagons, and a C₆ ring. Here, the C-C, B-C, N-C, and B-N average bond lengths are about 1.47 Å, 1.54 Å, 1.41 Å, and 1.50 Å, respectively.

The molecular electrostatic potential (MEP) plot is a valuable tool for determining the electron density distribution over the atoms of a molecule and predicting its most reactive sites. It is widely known that the chemical and physical properties of a molecule are associated with its electrostatic potential. Therefore, the MEP plot can be utilized to characterize electrophilic and nucleophilic sites within an electrostatic interaction.45 In a MEP contour, the surfaces are defined based on electron density and represented by an RGB color model, in which red regions are more negative than -0.010 a.u., yellow shows the regions with electron density between 0 and -0.010a.u., green regions are between 0.010 and 0.0 a.u., and blue color represents regions more positive than 0.010 a.u. Fig. 2 reveals that O13, N8, and N10 atoms are the most negatively charged centers of the PA molecule. Additionally, the oxygen atom is more prone to contribute to the nucleophilic attack. The most positive atoms are C12 (0.68 |e|), H9 (0.45 |e|), H16 (0.43 |e|), H11 (0.41 |e|), and H15 (0.42 |e|), respectively, as shown by NBO analysis, which is in agreement with the MEP plot of the PA molecule.

The frequency calculations were performed at the M06-2X/6-31G(d,p) level of theory. The vibrational frequency modes of C_{24} , C₁₈B₃N₃, and C₁₂B₆N₆ appear in a positive range of 343-1630 cm⁻¹, 345-1603 cm⁻¹, and 282-1473 cm⁻¹, respectively, indicating that the optimized geometries are true local minima on the potential energy surface. Frontier molecular orbitals (HOMO and LUMO) of a molecule play a vital role in determining its reactivity. HOMO and LUMO energy levels are usually considered as the electron-donating and electronaccepting abilities of an organic molecule. A higher E_{HOMO} value indicates that the molecule can donate electrons, while a lower E_{LUMO} implies the molecule's willingness to accept electrons. Considering eqn (2), it can be concluded that molecules with a low HOMO-LUMO energy gap are more polarizable and have high chemical reactivity and low kinetic stability.46 The HOMO levels of C24 are distributed over the C-C bonds throughout the nanocage except some C-C bonds in pentagons, whereas the LUMO levels are located on the C-C bonds of 5membered rings. In the case of C₁₈B₃N₃ and C₁₂B₆N₆, the HOMO levels are mainly located on the N atoms and C-C bonds of pentagons, while the LUMO levels are situated on the B atoms and C-C bonds. The HOMO-LUMO energy gaps of C24, C18B3N3, and $C_{12}B_6N_6$ are about 3.92, 4.24, and 4.86 eV, respectively, indicating that these nanocages are semiconductors. In the following sections, we will discuss the role of frontier molecular orbitals in the electronic properties of molecules.

Adsorption of PA on the C24 nanocage

Aimed at identifying the most stable C24-PA configuration, we considered all probable orientations of the PA molecule on the surface of C24 using the MEP plots of adsorbent and adsorbate molecules. All initial configurations were optimized employing the B3LYP/6-31G(d), CAM-B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p) levels of theory. The adsorption energies (E_{ads}) for

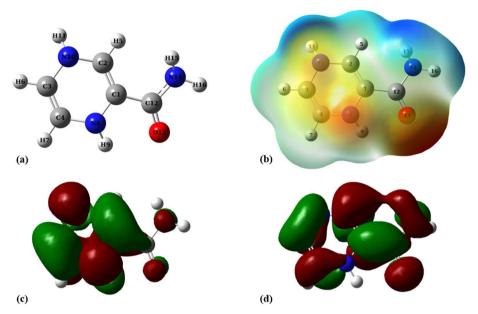


Fig. 2 (a) Optimized geometry, (b) MEP, (c) HOMO, and (d) LUMO profiles of PA at the M06-2X/6-31G(d,p) level of theory.

different configurations have been summarized in Table 1. More precisely it should be said that in the initial structures of C₂₄-PA, the drug molecule approached the 5- and 6-membered rings of C_{24} through (a) N8-H9, (b) N10-H11, (c) C12-O13, and (d) NH₂ group. The last configuration was the structure where PA is adsorbed in parallel on top of C24. After careful optimization and performing vibrational frequency calculations, it was found that the drug molecule adopts a parallel orientation towards C24. From Table 1, adsorption energies depend on both the method and basis set. Also, the energy difference between the configurations is significant in different methods. The amount of adsorption energy at the B3LYP/6-31G(d), CAM-B3LYP/6-31G(d,p), and M06-2X/6-31G(d,p)levels $-13.88 \text{ kJ mol}^{-1}$, $-25.72 \text{ kJ mol}^{-1}$, and $-125.58 \text{ kJ mol}^{-1}$, respectively. The minimum interaction distance between PA and C_{24} in the mentioned theoretical levels is 2.85 Å, 2.81 Å, and 2.82 Å, respectively (Fig. 3).

The values of enthalpy (ΔH) and Gibbs free energy changes (ΔG) of the C₂₄-PA complex are negative (with the exception of the B3LYP/6-31G(d) level), indicating that an exothermic and spontaneous reaction has occurred.

The changes in bond length and bond angles of the drug molecule, upon interaction with C_{24} at the M06-2X/6-31G(d,p) level of theory are illustrated in Tables 2 and S1,† respectively. The length of the C1–C2, C4–N8, C1–N8, N8–H9, and C12–O13 bonds increases while the length of other bonds decreases upon complexation. The results show that the interaction between the drug molecule and $C_{12}B_6N_6$ has no significant effect on the bond lengths of the PA molecule. The most obvious change in the bond angles of the PA molecule is related to the C12–N14–H16 angle, which ranges from 114.5° to 119.1°. Table 3 summarizes the quantum chemistry reactivity parameters of the nonionic surfactants, including $E_{\rm HOMO}$, $E_{\rm LUMO}$, and their associated energy gap $(E_{\rm g})$, ionization potential (I), electron affinity (A),

Table 1 Adsorption energies (E_{ads}), enthalpy changes (ΔH), and Gibbs free energy changes (ΔG) calculated for C_{24} -PA, $C_{18}B_3N_3$ -PA, and $C_{12}B_6N_6$ -PA complexes at different levels of theory

Method	$E_{\rm ads}$ (kJ mol ⁻¹)	$E_{\rm ads}^{\rm bsse}$ (kJ mol ⁻¹)	ΔH (kJ mol ⁻¹)	ΔG (kJ mol ⁻¹)	
B3LYP/6-31G(d)					
C ₂₄ -PA	-13.88	-1.34	-9.86	27.48	
$C_{18}B_3N_3$ -PA	-25.72	-5.75	-22.16	21.98	
$C_{12}B_6N_6$ -PA	-125.58	-98.05	-120.99	-70.88	
CAM-B3LYP/6-31G(d,	p)				
C ₂₄ -PA	-14.81	-8.34	-9.57	-35.40	
$C_{18}B_3N_3$ -PA	-124.73	-97.78	-119.43	-68.50	
$\mathrm{C}_{12}\mathrm{B}_6\mathrm{N}_6$ -PA	-138.55 -124.21		-309.76	-83.07	
M06-2X/6-31G(d,p)					
C ₂₄ -PA	-45.95	-29.98	-40.08	-3.62	
$C_{18}B_3N_3$ -PA	-163.63	-56.62 -1		-95.25	
$C_{12}B_6N_6$ -PA	-156.48	-137.69	-150.71	-99.17	

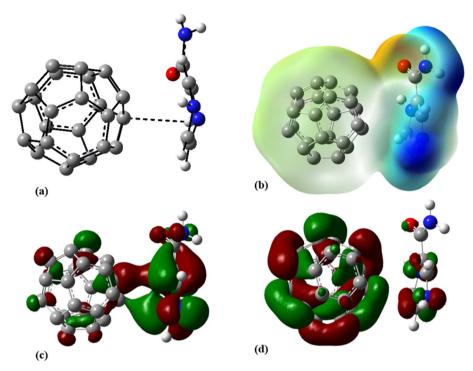


Fig. 3 (a) Optimized geometry, (b) MEP, (c) HOMO, and (d) LUMO profiles of C_{24} -PA at the M06-2X/6-31G(d,p) level of theory.

Table 2 Changes in the length of bonds of the PA molecule in interaction with C24 at the M06-2X/6-31G(d,p) level of theory

	Bond length (Å)			
Bond	After interaction	Before interaction	Δr	
C1-C2	1.343	1.341	0.002	
C3-C4	1.331	1.333	-0.002	
C2-H5	1.083	1.085	-0.002	
C3-H6	1.081	1.082	-0.001	
C4-H7	1.082	1.083	-0.001	
C4-N8	1.418	1.403	0.015	
N8-H9	1.017	1.011	0.006	
C1-N8	1.425	1.407	0.018	
C2-N10	1.400	1.413	-0.013	
C3-N10	1.423	1.434	-0.011	
N10-H11	1.011	1.016	-0.005	
C1-C12	1.481	1.486	-0.005	
C12-O13	1.223	1.221	0.002	
C12-N14	1.367	1.369	-0.002	
N14-H15	1.009	1.009	0.000	
N14-H16	1.007	1.007	0.000	

electronegativity (χ), electronic chemical potential (μ), chemical hardness (η) , electrophilicity index (ω) , and dipole moments (in Debye). Frontier molecular orbital (FMO) analysis implies that the $E_{\rm HOMO}$ and $E_{\rm LUMO}$ of C_{24} become more stable by about 1.15 and 0.29 eV, respectively, upon complex formation (Fig. 4). Therefore, the E_g value decreases by 21.9%; thus, the electronic properties of C24 change considerably in the presence of PA molecules. The reduction of parameters ω , χ , A, and I is in agreement with the reduction of $E_{\rm g}$. It is also observed that with the decrease of the E_g value, the softness and chemical hardness

have increased and decreased, respectively, which indicates the tendency of the nanocarrier to interact with PA. The decrease in electrophilicity by 0.42 eV after interaction with the PA molecule confirms the charge transfer from the drug to the nanocarrier. The dipole moment of the C24-PA complex is significantly higher than that of its components. Therefore, the solubility of the C_{24} -PA complex is expected to be higher than the solubility of C24 and PA.

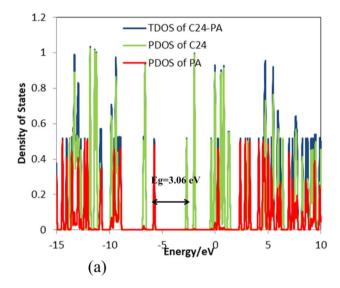
The mechanism of action of a chemical sensor is directly related to the change in its resistance due to charge exchange with the chemical agent. It is known that the E_g is a dependable indicator to determine the sensitivity of a sensor towards a molecule. The electrical conductivity of a molecule decreases with increasing $E_{\rm g}$.^{47,48} The population of conduction electrons of a nanostructure increases significantly upon the decrease of $E_{\rm g}$ and vice versa. Changing the population of conducting electrons after the adsorption process causes the generation of an electrical signal.⁴⁹ The work function (Φ) is another electronic parameter that is affected by the adsorption process and is defined as the minimum amount of energy (i.e., thermodynamic work) required to remove an electron from a solid to a point in the vacuum immediately outside the solid surface (i.e., the Fermi level) and is defined as follows:

$$\Phi = V_{\text{el}(+\infty)} - E_{\text{F}} \tag{9}$$

where $E_{\rm F}$ is the energy of the Fermi level and $V_{{\rm el}(+\infty)}$ is the electron electrostatic potential energy far from the solid surface. The value of $V_{el(+\infty)}$ is estimated to be zero, and therefore, we can write eqn (9) as $\Phi = -E_F$. The energy of the Fermi level is given as:

Table 3 Frontier molecular orbital energies (E_{HOMO} and E_{LUMO}) and their associated energy gaps (E_g) as well as CDFT parameters for the investigated structures at the M06-2X/6-31G(d,p) level of theory

Structure	E_{HOMO} (eV)	E_{LUMO} (eV)	$E_{\rm g}$ (eV)	$E_{\rm F}$ (eV)	I (eV)	A (eV)	χ (eV)	η (eV)	μ (eV)	S (1/eV)	ω (eV)	μ (Debye)
PA	-5.68	0.31	5.99	0.15	5.68	-0.31	2.69	3.00	-2.69	0.17	1.20	2.73
C_{24}	-6.92	-3.00	3.92	-1.50	6.92	3.00	4.96	1.96	-4.96	0.25	6.27	0.00
C ₂₄ -PA	-5.77	-2.70	3.06	-1.35	5.77	2.70	4.24	1.53	-4.24	0.33	5.86	3.79
$C_{18}B_3N_3$	-7.04	-2.80	4.24	-1.40	7.04	2.80	4.92	2.12	-4.92	0.24	5.70	1.10
$C_{18}B_3N_3$ -PA	-5.84	-1.65	4.19	-0.83	5.84	1.65	3.75	2.10	-3.75	0.24	3.35	11.46
$C_{12}B_6N_6$	-7.14	-2.27	4.87	-1.14	7.14	2.27	4.70	2.43	-4.70	0.21	4.55	2.10
$C_{12}B_6N_6$ -PA	-6.00	-1.38	4.62	-0.69	6.00	1.38	3.69	2.31	-3.69	0.22	2.95	14.48



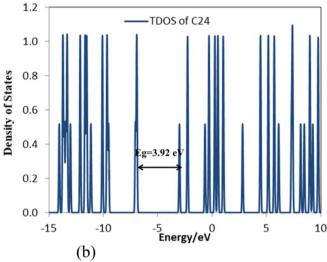


Fig. 4 DOS plots of (a) C_{24} -PA and (b) C_{24} .

$$E_{\rm F} = E_{\rm HOMO} + (E_{\rm LUMO} - E_{\rm HOMO})/2 \tag{10}$$

The Φ -type sensors apply a Kelvin oscillator instrument to calculate the values of Φ before and after adsorption. In these sensors, the adsorption of a molecule changes the gate voltage and produces an electrical signal that leads to chemical agent detection. The value of Φ is changed by about -0.147 eV going from C_{24} to C_{24} -PA; therefore, C_{24} can be used as a Φ -type sensor for PA detection.

To understand the donor–acceptor (bond–antibond) interactions between the drug molecule and the nanocages, NBO analysis has been performed at the M06-2X/6-31G(d,p) level of theory. In this analysis, all possible interactions between filled (donors) Lewis-type NBOs and empty (acceptors) non-Lewis NBOs are examined. Then, their energetic relevance is evaluated by second order perturbation theory. These interactions are called delocalization corrections to the zeroth-order natural Lewis structure because they result in a donation of electrons from the localized NBOs of the idealized Lewis structure into the empty non-Lewis orbitals. The stabilization energy ($E^{(2)}$) associated with delocalization $i \rightarrow j$ is defined as:

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i-j)^2}{\varepsilon_j - \varepsilon_i}$$
 (11)

where q_i is the donor orbital occupancy, ε_i and ε_i are diagonal elements (orbital energies), and F(i,j) is the off-diagonal NBO Fock matrix element. This equation states a direct relationship between the off-diagonal NBO Fock matrix element and the orbital overlap. The greater values of $E^{(2)}$ indicate stronger interactions. The NBO analysis results showed that the highest values of stabilization energies $E^{(2)}$ of the C_{24} nanocarrier are: BD*(2) C12-C13 \rightarrow BD*(2) C18-C19; $E^{(2)} = 30.29 \text{ kcal mol}^{-1}$. BD*(2) C10-C11 \rightarrow BD*(2) C2-C16; $E^{(2)} = 30.36$ kcal mol⁻¹ BD*(2) C21-C22 \rightarrow BD*(2) C18-C19; $E^{(2)} = 22.63$ kcal mol⁻¹ BD*(2) C9-C24 \rightarrow BD*(2) C6-C7; $E^{(2)} = 30.47 \text{ kcal mol}^{-1}$, and BD*(2) C21-C22 \rightarrow BD*(2) C15-C17; $E^{(2)} = 30.36 \text{ kcal mol}^{-1}$. Additionally, the most important stabilization energies related to the interaction of C_{24} and PA are BD (1) C3-C4 \rightarrow RY*(3) C26; $E^{(2)} = 0.48 \text{ kcal mol}^{-1} \text{ and BD(2) C3-C4} \rightarrow \text{BD*(2)C26-C27}; E^{(2)}$ = 3.19 kcal mol⁻¹. The changes in the atomic charges of the PA molecule due to the interaction with C24 are shown in Table S2† and confirm a charge transfer of 0.07 |e| from the drug to the nanocarrier. A closer look into the atomic charges shows that the partial charge of C1, C2, C3, and N10 atoms has decreased by about 0.016, 0.018, 0.012, and 0.033 |e| after the adsorption process. However, no noticeable change is observed in the charge of other atoms. The calculated partial atomic charges using the NBO technique are in good agreement with the MEP plots. Comparing the MEP plots of C24 and PA molecules with that of the C₂₄-PA complex shows that the interaction between the drug molecule and the nanocarrier causes the transfer of electron density from PA to the nanocage. The contours in Fig. S1[†] show the atoms involved in electron resonance in C₂₄-PA, C₁₈B₃N₃-PA, and C₁₂B₆N₆-PA complexes. As seen, most of the atoms in the structure of the complexes contribute to the resonance interactions.

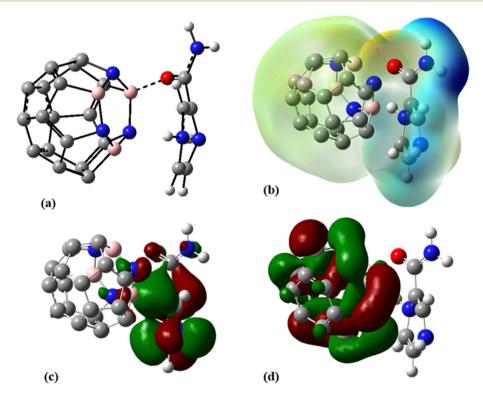
Adsorption of PA on the C₁₈B₃N₃ nanocage

To improve the interaction between the C24 and PA drug molecule, we adopted the doping technique so that six carbon atoms were replaced by three boron and three nitrogen atoms to form the C₁₈B₃N₃ nanocage. The most stable complex between C₁₈B₃N₃ and the PA drug molecule was obtained by adopting a method similar to that used for C24-PA. The drug molecule approached the 5- and 6-membered rings of C₁₈B₃N₃, B, and N heteroatoms through (a) N8-H9, (b) N10-H11, (c) C12-O13, and (d) NH2 group. Adsorption of PA on the surface of the C₁₈B₃N₃ nanocage is an exothermic process. The adsorption energies of PA on the C18B3N3 at the mentioned levels of theory are reported in Table 1. The nearest interaction distance between PA and C₁₈B₃N₃ is 1.5 Å, in which the drug molecule has adopted a parallel orientation towards C18B3N3 (Fig. 5). It seems that the weak π - π interactions are also effective in stabilizing the $C_{18}B_3N_3$ complex. The values of ΔH and ΔG of the C₁₈B₃N₃-PA complex at T=298 K and P=1 atm are shown in Table 1, which are more negative than the corresponding values of C24-PA.

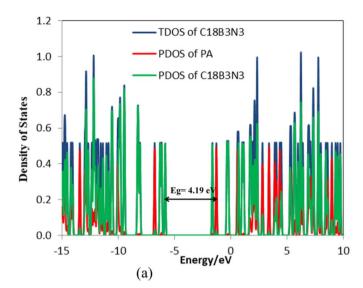
Table 4 Change in the length of bonds of the PA molecule upon interaction with C₁₈B₃N₃ PA at the M06-2X/6-31G(d,p) level of theory

	Bond length (Å)			
Bond	After interaction	Before interaction	Δr	
C1-C2	1.352	1.341	0.012	
C3-C4	1.331	1.333	-0.002	
C2-H5	1.084	1.085	-0.001	
C3-H6	1.080	1.082	-0.002	
C4-H7	1.082	1.083	-0.001	
C4-N8	1.423	1.403	0.02	
N8-H9	1.019	1.011	0.008	
C1-N8	1.427	1.407	0.020	
C2-N10	1.375	1.413	-0.038	
C3-N10	1.427	1.434	-0.0.007	
N10-H11	1.011	1.016	-0.005	
C1-C12	1.450	1.486	-0.036	
C12-O13	1.284	1.221	0.063	
C12-N14	1.324	1.369	-0.045	
N14-H15	1.008	1.007	0.001	
N14-H16	1.011	1.009	0.002	

Tables 4 and S3† show the structural parameters (bond lengths and bond angles) of the drug molecule before and after interaction with the C₁₈B₃N₃ nanostructure. The interaction between the drug molecule and C18B3N3 does not have a significant effect on the length of bond of the PA molecule and is similar to the structure of C24PA. In any case, these changes are very small and can be ignored. The greatest decrease in the bond angle due to PA adsorption on the C18B3N3 surface is related to the C4-N8-H9 angle, which decreased by 8.8°, while



(a) Optimized geometry, (b) MEP, (c) HOMO, and (d) LUMO profiles of $C_{18}B_xN_3$ -PA at the M06-2X/6-31G(d,p) level of theory.



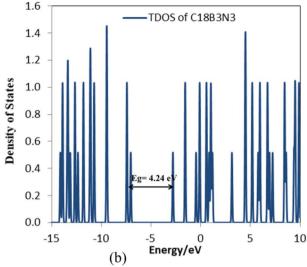


Fig. 6 DOS plots of (a) $C_{18}B_3N_3$ -PA and (b) $C_{18}B_3N_3$

C12–N14–H15 and C1–C12–N14 bond angles show increases of 3.8° and 2.6°, respectively. Frontier molecular orbital (FMO) analysis reveals that $E_{\rm HOMO}$ of $C_{18}B_3N_3$ changes from -7.04 eV to -5.84 eV after adsorption of PA; also, $E_{\rm LUMO}$ stabilizes by approximately 1.14 eV (Fig. 5). Therefore, the $E_{\rm g}$ value decreases by 1.2%; thus, the electronic properties of $C_{18}B_3N_3$ are sensitive to the presence of PA molecules. Here again the reductions in parameters ω , χ , A, and I are in agreement with the reduction in $E_{\rm g}$ (Fig. 6).

The decrease in electrophilicity upon adsorption of PA is calculated to be approximately 0.159 eV, showing that charge transfers from the drug molecule to $C_{18}B_3N_3$. Table S4† represents the partial atomic charges of the PA molecule before and after interaction with $C_{18}B_3N_3$. The charge of C1, C4, N8, and O13 atoms increased by approximately 0.048, 0.012, 0.001, and 0.022 |e|, respectively. The comparison of the total atomic charges of PA and $C_{18}B_3N_3$ shows that due to the formation of a complex between PA and $C_{18}B_3N_3$, 0.398 |e| of charge is transferred from the drug to the nanocarrier.

The NBO analysis results showed that the highest values of stabilization energies $E^{(2)}$ of the $C_{18}B_3N_3$ nanocarrier are BD*(2) C33-C34 \rightarrow BD*(2) C23-C24; $E^{(2)} = 49.82 \text{ kcal mol}^{-1}$, BD*(2) C29-C30 \rightarrow BD*(2) C31-C32; $E^{(2)} = 50.27 \text{ kcal mol}^{-1}$, BD*(2) C27-C28 \rightarrow BD*(2) C25-C26; $E^{(2)} = 49.69 \text{ kcal mol}^{-1}$, BD(2) C33-C34 \rightarrow LP*(1) B21; $E^{(2)} = 45.12 \text{ kcal mol}^{-1}$, and BD(2) C25-C26 \to LP*(1) B21; $E^{(2)} = 44.91$ kcal mol⁻¹. The antibonding orbitals of boron atoms are the most important non-Lewis acceptors. The greatest values of stabilization energy in the C₁₈B₃N₃-PA complex are related to transitions within the $C_{18}B_3N_3$ molecule: BD*(2) C33-C34 \rightarrow BD*(2) C23-C24; $E^{(2)}$ = 34.89 kcal mol⁻¹, BD*(2) C29-C30 \rightarrow BD*(2) C31-C32; $E^{(2)} =$ 42.29 kcal mol⁻¹, BD*(2) C27-C28 \rightarrow BD*(2) C25-C26; $E^{(2)}$ = 37.10 kcal mol⁻¹, and BD*(2) C37-C36 \rightarrow BD*(2) C23-C24; $E^{(2)}$ $= 57.13 \text{ kcal mol}^{-1}$. The most important stabilization energies related to the interaction between C₁₈B₃N₃ and PA are BD(2) $C25-C26 \rightarrow LP*(1) B21; E^{(2)} = 46.33 \text{ kcal mol}^{-1} \text{ and } BD(1) C25-$ C26 \rightarrow LP*(1) B21; $E^{(2)} = 3.43$ kcal mol⁻¹, which indicates charge transfer from the drug molecule to C₁₈B₃N₃.

Adsorption of PA on the C₁₂B₆N₆ nanocage

In the next step, 12 carbon atoms of C_{24} were replaced by six boron atoms and six nitrogen atoms to obtain the $C_{12}B_6N_6$ structure. In the most stable $C_{12}B_6N_6$ -PA complex, the oxygen atom of the drug molecule has established a bond with one of the boron atoms of the nanostructure with a length of 1.523 Å, which leads to an adsorption energy of -125.58 kJ mol $^{-1}$, -138.55 kJ mol $^{-1}$, and -156.48 kJ mol $^{-1}$ at the B3LYP/6-31G(d), CAM-B3LYP/6-31G(d,p), and M06-2X/6-31G(d,p) levels of theory, respectively (Fig. 7 and Table 1).

Table 5 shows that despite the relatively strong interaction between the drug molecule and $C_{12}B_6N_6$, the geometrical parameters of PA did not change significantly. However, the bond length changes are more evident in the areas involved in the interaction with the nanostructure. For example, after forming the $C_{12}B_6N_6$ -PA complex, the C–O bond length of PA has increased by approximately 0.057 Å. The process of bond length changes in $C_{12}B_6N_6$ -PA is similar to that in the $C_{18}B_3N_3$ -PA and C_{24} -PA complexes. Additionally, the lengths of C1–C12 and C1–N8 bonds increased, which can be attributed to resonance effects. The highest bond angle increase due to PA adsorption on the $C_{12}B_6N_6$ surface is related to C1–C12–N14, C2–N10–H11, and C12–N14–H16 angles, which increased by 4.7° , 2.5° and 2.4° , respectively. The C1–C12–O13 bond angle decreased from 120.1° to 115.4° (Table S5†).

According to Table 3, the $E_{\rm g}$ of ${\rm C}_{12}{\rm B}_6{\rm N}_6$ has decreased by 0.24 eV after interaction with the drug molecule, which indicates the high reactivity of the nanocarrier (Fig. 8). The significant decrease of $E_{\rm g}$ shows that the electronic properties of ${\rm C}_{12}{\rm B}_6{\rm N}_6$ are very sensitive to the presence of drug molecules in the environment, and therefore, ${\rm C}_{12}{\rm B}_6{\rm N}_6$ can be used as a PA sensor. The reduction in parameters ω , χ , A, and I is in agreement with the reduction in $E_{\rm g}$. It is also observed that with the

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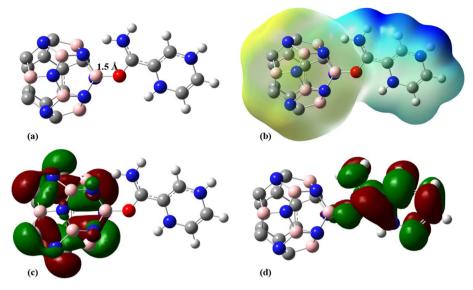


Fig. 7 (a) Optimized geometry, (b) MEP, (c) HOMO, and (d) LUMO profiles of $C_{12}B_6N_6$ -PA at the M06-2X/6-31G(d,p) level pf theory.

Table 5 Change in the length of bonds of the PA molecule upon interaction with $C_{12}B_6N_6$ at the M06-2X/6-31G(d,p) level of theory

	Bond length (Å)			
Bond	After interaction	Before interaction	Δr	
C1-C2	1.350	1.341	0.009	
C3-C4	1.329	1.333	-0.004	
C2-H5	1.084	1.085	-0.001	
C3-H6	1.080	1.082	-0.002	
C4-H7	1.081	1.083	-0.002	
C4-N8	1.416	1.403	0.013	
N8-H9	1.014	1.011	0.003	
C1-N8	1.425	1.407	0.018	
C2-N10	1.375	1.413	-0.038	
C3-N10	1.433	1.434	-0.001	
N10-H11	1.009	1.016	-0.007	
C1-C12	1.450	1.486	-0.036	
C12-O13	1.278	1.221	0.057	
C12-N14	1.326	1.369	-0.043	
N14-H15	1.006	1.007	-0.001	
N14-H16	1.024	1.009	0.015	

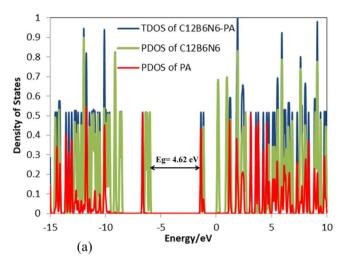
decrease in the E_g value, the softness and chemical hardness have increased and decreased, respectively, which indicates the tendency of the nanocarrier to interact with the PA molecule. A considerable decrease in the electrophilicity parameter by 1.60 eV confirms the charge transfer from the drug to the nanocarrier.

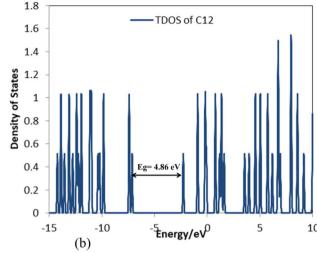
Table S6† shows that the partial charge of PA atoms is affected by the presence of the C₁₂B₆N₆ nanocarrier in the environment. Therefore, the charges of the C1, C3, N8, and O13 atoms increased by 0.029, 0.001, 0.009, and 0.020 |e|. On the other hand, the charges of the C2, N14 and N10 atoms have become more positive by 0.078, 0.067, and 0.053 |e| respectively. Additionally, NBO calculations show that due to the formation of a complex between PA and C₁₂B₆N₆, a charge amount of 0.324 |e| is transferred from the drug to the nanocarrier. The dipole

moment is an important parameter for understanding the symmetry of the complex; the higher the dipole moment, the higher the interaction between the adsorbate and adsorbent molecules.52 The significant increase in the dipole moment of C₁₂B₆N₆ indicates that the solubility of C₁₂B₆N₆-PA increases upon the adsorption process.

Examining the stabilization energies $E^{(2)}$ shows that the most important electron transfers of the drug molecule are: LP(1) N14 → BD*(2) C12-O13; $E^{(2)} = 56.14 \text{ kcal mol}^{-1}$, LP(1) N10 → BD*(2) C1-C2; $E^{(2)} = 34.28 \text{ kcal mol}^{-1}$, LP(1) N8 \rightarrow BD*(2) C1-C2; $E^{(2)} = 33.13 \text{ kcal mol}^{-1}$, LP(2) O13 \rightarrow BD*(1) C12-N14; $E^{(2)} =$ 29.41 kcal mol⁻¹, and BD(2) C1-C2 \rightarrow BD*(2) C12-O13; $E^{(2)} =$ 19.41 kcal mol⁻¹. The most important donors are free electron pairs of nitrogen and oxygen that fill the C1-C2 and C12-O13 antibonding orbitals. Additionally, the greatest stabilization energy $E^{(2)}$ values of the nanocarrier are: LP(1) N25 \rightarrow LP*(1) B17; $E^{(2)} = 24.73 \text{ kcal mol}^{-1}$, LP(1) N29 \rightarrow LP*(1) B19; $E^{(2)} =$ 24.75 kcal mol⁻¹, BD(2) N17-B19 \rightarrow LP*(1) B19; $E^{(2)}$ = 62.33 kcal mol⁻¹, BD(2) N17-B19 \rightarrow LP*(1) B121; $E^{(2)}$ = 63.09 kcal mol⁻¹, and BD(2) N33-B21 \rightarrow LP*(1) B19; $E^{(2)} =$ 62.86 kcal mol⁻¹. As seen, non-Lewis acceptors are antibonding orbitals of boron atoms. Regarding the donor-acceptor transitions in the C₁₂B₆N₆-PA complex, it should be said that the largest amounts of stabilization energy are related to transitions within the $C_{12}B_6N_6$ molecule which are: BD*(2) C24-N25 \rightarrow $LP*(1) B23; E^{(2)} = 99.29 \text{ kcal mol}^{-1}, LP(1) C2 \rightarrow LP*(1) C4; E^{(2)} =$ 90.21 kcal mol⁻¹, LP(1) C26 \rightarrow BD*(2) C24-N25; $E^{(2)} =$ 74.59 kcal mol⁻¹, BD(2) N27-B18 \rightarrow LP*(1) B17; $E^{(2)} =$ 70.14 kcal mol⁻¹, and BD*(2) C12-N14 \rightarrow BD*(2) C1-C2; $E^{(2)}$ = 69.22 kcal mol⁻¹. The most important stabilization energies related to the interaction between C₁₂B₆N₆ and PA are: BD(2) B17-N18 \rightarrow BD*(1) B17-O13; $E^{(2)} = 13.34 \text{ kcal mol}^{-1}$, LP(2) O13 \rightarrow BD*(1) B17-N25; $E^{(2)} = 6.22 \text{ kcal mol}^{-1}$, and BD(2) C12-N14 \to BD*(1) B17-O; $E^{(2)} = 1.35$ kcal mol⁻¹, which is in agreement with the increase of the C12-O13 bond and also bond formation between the PA oxygen and the boron atom of

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DOS plots of (a) $C_{12}B_6N_6$ -PA and (b) $C_{12}B_6N_6$

C₁₂B₆N₆. As can be seen, the replacement of carbon atoms with boron and nitrogen atoms increased the stabilization energies.

Atoms in molecule analysis

Bader's quantum theory of atoms in molecules (OTAIM)53 was utilized to explore electron density and bonding characteristics of the investigated systems. This theory states that upon chemical bond formation between two atoms a bond critical point (BCP) appears between them. The characteristics of BCPs are of great relevance in determining the electron density (ρ_C) and its corresponding Laplacian $(\nabla^2 \rho_C)$, and therefore, designating the nature of interactions at a molecular level. $\nabla^2 \rho_{\rm C}$ is the second derivative of a scalar function and provides information about the tendency of electron density to concentrate or deplete. The total electronic energy density at the BCP (H_C) elucidates the energetic properties of BCPs and it is the sum of the local kinetic energy density (G_C) and local potential energy density (V_C) at the BCP.

$$H_{\rm C} = G_{\rm C} + V_{\rm C} \tag{12}$$

On the other hand, the virial theorem states a relation between the Laplacian of the electron density at BCP and its other characteristics.

$$(1/4)\nabla^2 \rho_{\rm C} = 2G_{\rm C} + V_{\rm C} \tag{13}$$

A negative value of the Laplacian indicates the concentration of the electron density among the nuclei of interacting atoms, and one may assume a shared interaction such as covalent bonds and lone pairs. A positive Laplacian electron density value at corresponding BCP shows the depletion of electron density as in ionic, van der Waals, and hydrogen bond interactions. Fig. 9 illustrates the molecular graph of C24-PA, C₁₈B₃N₃-PA, and C₁₂B₆N₆-PA complexes obtained from AIM calculations. The graphs were obtained at the M06-2X/6-31G(d,p) level of theory. Large circles correspond to attractors and small red and yellow circles are bond and ring critical points, respectively. However, sometimes $\nabla^2 \rho_C > 0$ but the total electronic energy density, $H_{\rm C}$, is negative and such a situation is attributed to the partially covalent interaction. Fig. 9 shows that the adsorption of the PA molecule on the surface of the C24 nanocage led to the appearance of two critical points between the drug and the nanostructure. The electron density properties calculated for the C24-PA complex reveal that for the O13PA... C19 interaction $\nabla^2 \rho_{\rm C} > 0$ and $H_{\rm C} > 0$; hence, this interaction belongs to the category of electrostatic interactions. The C4_{PA}··· C20 interaction has more electron density (0.006 a.u.), and the

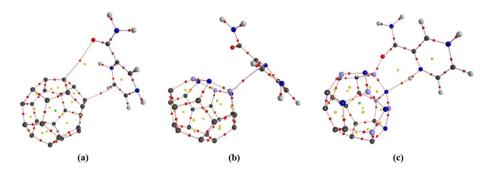


Fig. 9 Molecular graphs for C_{24} -PA, $C_{18}B_3N_3$ -PA, and $C_{12}B_6N_6$ -PA complexes at the M06-2X/6-31G(d,p) level of theory (large circles correspond) to attractors, while small red and yellow circles are bond and ring critical points, respectively).

Table 6 Topological parameters (all in atomic units) for the optimized structures analyzed here at the M06-2X/6-31G(d,p) level of theory

Complex	Interaction site	$ ho_{ m C}$	$ abla^2 ho_{ m C}$	$G_{ m C}$	$V_{ m C}$	$H_{ m C}$	Type of interaction
C ₂₄ -PA	O13(PA)···C19	0.010	0.031	0.007	-0.006	0.001	Electrostatic
	C4(PA)···C20	0.006	0.019	0.004	-0.003	0.001	
$C_{18}B_3N_3$ -PA	O(PA)···B17	0.117	0.512	0.194	-0.259	-0.065	Partly covalent
$C_{12}B_6N_6$ -PA	O13(PA)···B17	0.126	-0.138	0.209	-0.280	-0.071	Covalent
	H(PA)···N18	0.033	0.089	0.023	-0.024	-0.001	Partly covalent

values of $\nabla^2 \rho_{\rm C}$ (0.019 a.u.) and $H_{\rm C}$ (0.001 a.u.) are positive. Therefore, this bond is also the result of an electrostatic interaction (Table 6).

AIM calculations showed that only one critical point has appeared between O13 of the PA molecule and B17 of the $C_{18}B_3N_3$ nanostructure, for which the values of ρ_C , $\nabla^2\rho_C$ and H_C are 0.117, 0.512, and -0.065 a.u. respectively. Therefore, the OPA···B17 interaction is partially covalent. The electron density properties calculated for the C₁₂B₆N₆-PA complex show that the O13_{PA}···B17 bond possesses a significant charge density (0.126 a.u.). Moreover, the values of $\nabla^2 \rho_{\rm C}$ (-0.138 a.u.) and $H_{\rm C}$ (-0.071 a.u.) are negative. Therefore, as we mentioned before, the O13_{PA}····B17 bond is a covalent interaction. AIM calculations show that the H_{PA} ...N18 interaction has lower values of ρ_C and $\nabla^2 \rho_{\rm C} > 0$; however, this interaction is categorized as a partly covalent interaction because $\nabla^2 \rho_{\rm C} > 0$ and $H_{\rm C} < 0$.

NMR and IR spectra

The changes in charge density around the nuclei involved in the adsorption process can be very efficient in verifying the nature of host-guest interactions because the magnitude of these variations reveals the contribution of each nucleus to the interaction.54 Therefore, we performed NMR chemical shift calculations using the GIAO method to investigate the nature of interactions involved in the adsorption of PA on the surface of C₂₄, C₁₈B₃N₃, and C₁₂B₆N₆. The chemical shift (CS) principal components (σ_{ii}), CS isotropy (σ_{iso}), and CS anisotropy values of ¹³C, ¹⁵N, ¹⁷O, and ¹H for the surfactant molecules calculated at the M06-2X/6-31G(d,p) level of theory are shown in Tables S7 to S13.† The isotropy (σ_{iso}) parameter shows the average value of the CS tensor, while the anisotropy $(\Delta \sigma)$ parameter specifies the orientations of the CS tensor at the atomic site. The calculated chemical shift tensors for 13C, 15N, 17O, and 1H nuclei are sensitive to complex formation at the active site. The values of $\sigma_{\rm iso}$ and $\Delta\sigma$ parameters of the C12, O13, and N14 atoms of the drug molecule increase significantly due to the adsorption on $C_{12}B_6N_6$. After complex formation, the values of $\sigma_{\rm iso}$ and $\Delta\sigma$ of the N8 and N10 atoms in the PA molecule decrease and increase, respectively. The value of $\sigma_{\rm iso}$ for C1 to C4 atoms in the drug molecule increases, while the $\Delta \sigma$ value for these atoms decreases. The changes in the $\sigma_{\rm iso}$ and $\Delta \sigma$ values of the PA atoms in $C_{18}B_3N_3$ -PA and C_{24} -PA complexes also follow the same trend. The values of $\sigma_{\rm iso}$ and $\Delta \sigma$ parameters of the C10, C11, C12, B13, B14, and B15 atoms of the C₁₂B₆N₆ nanocage increase due to complex formation, while the values of σ_{iso} and $\Delta \sigma$ of the C1, C5, C8, N18, B19, B20, N22, N23, and N24 atoms have decreased. In general, the results obtained from NMR spectra

are in agreement with the previous results. Fig. S2 to S7† show the IR spectra of the compounds investigated in this study. Fig. S6† shows that a new peak appears in the region of 3300 cm⁻¹ after C₁₂B₆N₆-PA complex formation, which indicates the interaction between the functional groups of the host and guest molecules. Although the interaction of the drug molecule with C18B3N3 and C24 nanocarriers also leads to changes in the IR spectrum of the nanocages, due to the orientation of the interacting molecules, the intensity and the location of the peaks are different.

UV-Vis spectra

The interaction between light and matter has always been of interest and is used to investigate the electronic properties of molecules precisely. The UV-Vis spectrum of the PA molecule (Fig. S9†) shows that the highest peak corresponds to the wavelength of 228 nm with f = 0.099. The higher the value of f, the higher the transition peak. The highest peak for the C₁₂B₆N₆ molecule appears at 327 nm with f = 0.002 and for $C_{12}B_6N_6$ -PA at 496 nm with f = 0.069. In general, as shown in Tables S15–S20 and Fig. S9-S14,† adsorption of PA on the surface of nanocarriers, the wavelengths of the C24, C18B3N3, and C12B6N6, and thus, the highest peaks are shifted to higher values. Therefore, a redshift occurs after the adsorption process.

Conclusions

In this study, we investigated the potential of the pristine C_{24} nanocage and its doped boron nitride analogs (C18B3N3 and $C_{12}B_6N_6$) as carriers for the pyrazinamide (PA) drug using density functional theory (DFT). All calculations including geometry optimization, vibrational frequencies, QTAIM, NBO, NMR, and IR were carried out using the B3LYP/6-31G(d), CAM-B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p) levels of theory. To calculation of the dispersion energy, the modified CAM-B3LYP and M06-2X methods were used. The results show that the adsorption energies calculated by B3LYP, CAM-B3LYP, and M06-2X methods are different. The M06-2X values are greater than those calculated by B3LYP and CAM-B3LYP methods. The adsorption energy (E_{ads}), enthalpy (ΔH), and Gibbs free energy (ΔG) of C_{24} -PA, $C_{18}B_3N_3$ -PA, and $C_{12}B_6N_6$ -PA complexes were calculated using the B3LYP/6-31G(d), CAM-B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p) levels of theory. The results show that the interaction of the drug with the nanocages is exothermic and a spontaneous reaction has occurred at all theoretical levels (with the exception of the B3LYP/6-31G(d) level for C24-PA and $C_{18}B_3N_3$). The results show that doping has increased the

molecules.

conductivity of nanocages. On the other hand, the interaction of PA with nanocages leads to a reduction in the energy gap of complexes. The E_g values of C_{24} , $C_{18}B_3N_3$, and $C_{12}B_6N_6$ at the M06-2X/6-31G(d,p) level decrease by approximately 21%, 1.2%, and 5%, respectively, upon complexation. Furthermore, the decrease of E_g in complexes suggests that nanocages can be utilized for sensing PA molecules. Despite the relatively strong interactions between the drug molecule and nanocages, the geometrical parameters of PA did not change significantly. The changes in the atomic charges of the PA molecule due to the interaction with C24, C18B3N3, and C12B6N6 confirm a charge transfer of 0.07, 0.327, and 0.398 |e| from the drug to the nanocage, respectively. Based on the NBO results, the replacement of carbon atoms with boron and nitrogen atoms increased the stabilization energies $(E^{(2)})$. AIM calculations revealed that the observed interactions between the nanocage and PA drug in C₁₂B₆N₆-PA and C₁₈B₃N₃-PA nanocages are stronger than those with the C_{24} -PA nanocage. The results show that all three types of nanocages can be used as drug delivery systems for PA

Ethics approval and consent to participate

This study did not involve human subjects, animal experimentation, or other activities necessitating ethical review.

Consent for publication

The authors of this manuscript confirm that all authors have reviewed and approved the final version of the manuscript for submission to the journal of *Nanoscale Advances*.

Data availability

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The datasets generated during the current study are available upon request from the corresponding author. Additionally, some of the data and materials supporting this article have been included in the main text and ESI.†

Author contributions

F. Naderi: conceived and designed the study, reviewing, editing of the manuscript, conceptualization, supervision; A. Moumivand: writing, software; O. Moradi: validation, visualization, methodology; B. Makiabadi: editing of the manuscript.

Conflicts of interest

All authors declare that they have no competing interests.

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