DFT investigation on the application of pure and doped $X_{12}N_{12}$ ($X = B$ and Al) fullerene-like nano-cages toward the adsorption of temozolomide

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The sensitivity of pure and doped $X_{12}N_{12}$ ($X = B$ and Al) fullerene-like nano-cages (FLNs) toward the anti-cancer drug temozolomide (TMZ) is probed herein at DFT/M06-2X-D3/6-311G(d,p) theoretical level in both gas phase and water. A noticeable affinity of the FLNs toward TMZ was observed along with the negative gas-phase adsorption energies $-1.37$ and $-2.09$ eV for the most stable configurations of pure B$_{12}$N$_{12}$ and Al$_{12}$N$_{12}$ pristines, respectively. Considerable charge transfer from TMZ to the FLNs was also revealed via NBO analysis and the Hirshfeld atomic charges, making the dipole moment vector of the molecular complexes to be oriented from the nano-cages to the TMZ moiety. Furthermore, a percentage decrease in the HOMO-LUMO energy gap ($\Delta E_g$) of 38.09 and 17.72% was obtained for the B$_{12}$N$_{12}$ and Al$_{12}$N$_{12}$ pristines, respectively. The percentage change in $\Delta E_g$ was found to be reduced upon doping and solvation of the FLNs. Finally, a recovery time in vacuum ultraviolet light of 1.06 s is found for the complex with pure B$_{12}$N$_{12}$, which in addition to the above-mentioned parameters make this boron nitride cage the best sensor for TMZ, among the FLNs considered in the present work.
1. Introduction

Temozolomide (TMZ) (marketed under the trademarks temodar or temodal) is an oral chemotherapeutic agent approved for the treatment of anaplastic astrocytoma and gliomas (the most common and most malignant primary tumours of the central nervous system). Malignant gliomas diffuse infiltration into adjacent brain parenchyma and resistance to cell death [1]. TMZ is spontaneously converted into the active alkylation metabolite (methyl-triazene-1-yl)-imidazole-4-carboxamide (MTIC) under physiological conditions. The commonest side effects of TMZ include nausea, diarrhea, vomiting, headaches, constipation, taste changes and rashes. The less common side effects are hair loss (including eyebrows and eyelashes), dizziness, shortness of breath, infertility (depending on the combination of medicines and the dose that is given) [2]. TMZ has also been reported to affect CD4 + T cells, leading to clinically significant opportunistic infections like Pneumocystis carinii, Aspergillus pneumoniae, herpes simplex, herpes zoster, hepatitis B virus etc. [1–5]. It is worthy of note that patients suffering from glioma may easily die from infectious complications. Owing to the wide therapeutic scale and effects of TMZ, Mariano and co-workers have reported several analytical methods for its detection [6]. In this regard, nanotechnologies have been of paramount importance in recent decades.

Experimental and theoretical chemistry methods are widely used in probing the sensing ability of nanoparticles (NPs) toward various classes of chemicals. Organic NPs (like lipids and micelles), inorganic NPs (like metal oxide, quantum dots and fullerenes) or a hybrid of these components are the common classes of NPs used for sensing and drug delivery. Several studies have been published on carbonic and non-carbonic nanostructures such as nano-sheets [7–9], fullerene-like nano-cages (FLN) [10,11] and nano-tubes [12,13], due to their excellent physical, chemical and surface characteristic properties. Among these NPs, FLNs are recently receiving considerable attention. They have been found to be excellent gas sensors [14–16]. One of the most prominent fields of application of the FLNs is their use as drug sensors, as well as carriers for drug delivery. In that regard, the adsorption of anti-cancer drugs, including thioguanine isomers [11], melphalan [17], Zolinza drug [10], 5-fluorouracil [18], exemestane [19] and Celecoxib [20] at the external surface of FLNs has been reported. The aforementioned works have highlighted the potential of FLNs as a medium for anti-cancer drug delivery.

The main objective of this work was to probe the adsorption of the anti-cancer drug TMZ onto the external surface of pure and doped X12N12 (X = B and Al) using the density functional theory (DFT) computational chemistry method. Interestingly, DFT calculations have been used to study the adsorption of TMZ onto the surface of iron-oxide (Fe3O4) nanoparticles via an interaction involving the oxygen and nitrogen atoms of the former, and the Fe2+ and/or Fe3+ ion of the latter [21]. Furthermore, Zhu and co-workers have recently shown, via the DFT/B3LYP/6-31G (d) method, that pristine BC3NT is a promising drug deliverer for TMZ [8]. Nevertheless, B12N12 and Al12N12 have been proven to be the most stable FLN structures, which have been synthesized by Oku et al. [22] and Liu et al. [23], respectively. These compounds possess unique physico-chemical properties such as high thermal conductivity, chemical stability, wide band gap and oxidation resistance [24]. Owing to the exceptional results obtained for the delivery of many anti-cancer drugs by B12N12 and Al12N12, the adsorption of TMZ at the surface of these nano-cages is investigated herein in order to propose a new drug delivery system for TMZ. The adsorbent–adsorbate interactions have been extensively described using the quantum theory of atoms in molecules (QTAIM) and natural bond orbital (NBO) analysis. The effects of adsorption on the electronic properties (such as molecular orbitals energy and distribution and electronic spectra) of the nano-cages have also been evaluated. The calculations have been performed using DFT methods in gas phase and water. The findings of this research endeavour can be useful for designing an appropriate and novel carrier for the detection, as well as the delivery, of TMZ.

2. Computational details

All molecular structures considered here have been relaxed at DFT/M06-2X/6-311G(d,p) [25–27] level of theory using the Gaussian 09 package [28]. The reliability of the M06-2X hybrid functional for such calculations has long been proven since it accurately estimates structural, energetic and electronic properties [29–31]. The Gordon dispersion GD3 correction was applied in order to better describe the non-covalent interactions (NCI) in the molecules studied [32]. Harmonic vibrational frequencies have been calculated at the same computational level after geometry relaxation, and their analysis showed that all structures corresponded to minima on their potential energy surfaces. The adsorption ability of the nano-cages toward TMZ was evaluated through adsorption energies ($\Delta E_{ads}$), enthalpies ($\Delta H$)
and free energy changes ($\Delta G$), calculated as shown in equations (2.1)–(2.3). $E_{\text{FLN-TMZ}}$ is the total energy of the complex formed between the nano-cage and TMZ, whereas $E_{\text{FLN}}$ and $E_{\text{TMZ}}$ are the total energies of the FLNs and TMZ, respectively.

$$E_{\text{ads}} = E_{\text{FLN-TMZ}} - E_{\text{FLN}} - E_{\text{TMZ}}, \quad \Delta H = H_{\text{FLN-TMZ}} - H_{\text{FLN}} - H_{\text{TMZ}}, \quad \Delta G = G_{\text{FLN-TMZ}} - G_{\text{FLN}} - G_{\text{TMZ}}.$$  

(2.1)  

(2.2)  

(2.3)

The energy and distribution of the frontier molecular orbitals of the investigated molecular systems were also studied in a bid to gain more insight into their stability. The NBO analysis at the above-mentioned level of theory has been performed to deepen our understanding of the FLN–TMZ interactions. This was further buttressed via QTAIM and NCI index analyses performed using the multiwfn 3.8 software [33]. The electronic transition spectra were calculated using the TD-DFT method at the M06-2X-D3/6-311G(d, p) theoretical level. Calculations in water medium were performed using the SMD solvation method [34].

3. Results and discussion

3.1. Geometric and energetic parameters

The optimized structures of TMZ, $B_{12}N_{12}$ and $Al_{12}N_{12}$ are depicted in figure 1, alongside the distribution of the FMOs of TMZ. The geometric parameters obtained herein from the optimized structures of pure $B_{12}N_{12}$ (B-N bond lengths and angles) and $Al_{12}N_{12}$ (Al-N bond lengths and angles) are in perfect agreement with those reported in the literature [35–37]. The structure obtained from the relaxation of TMZ is displayed in figure 1, along with the interatomic distances in gas phase. In order to locate the sites of TMZ exhibiting the greatest Lewis basic character, the Hirshfeld atomic charges of its atoms have been calculated. According to the results, O$_{12}$ ($-0.36\, e$), O$_{16}$ ($-0.32\, e$), N$_{10}$ ($-0.19\, e$) and N$_{13}$ ($-0.16\, e$) carry the most negative charges. The molecular electrostatic potential (MEP) maps of TMZ depicted in electronic supplementary material, figure 1S corroborates this finding. Indeed, the region near the vicinity of O$_{12}$ and O$_{16}$, coloured in red in electronic supplementary material, figure 1S indicates the high nucleophile character of these atoms. The yellow coloured of the MEP map around N$_{10}$ of TMZ also shows an electron-rich site. These atoms are, therefore, predicted to be the most prominent to form Lewis-type acid-base interactions with the boron and aluminium atoms of the FLNs. This observation is in good agreement with the findings of Harris [21] who predicted, via frontier molecular orbitals analysis, that these atoms are the most reactive sites of TMZ. Therefore, the ability of the pure FLNs considered in the present work to adsorb TMZ at their external surface has been evaluated by simulating the adsorbent–adsorbate interactions including the foregoing atoms. The relaxed structures of the complexes simulated at the M06-2X-D3/6-311G(d,p) level in the case of $B_{12}N_{12}$ are depicted in figure 2, whereas those of $Al_{12}N_{12}$ are presented in electronic supplementary material, figure S1. The energetic parameters ($E_{\text{ads}}$, $\Delta H$ and $\Delta G$) describing the adsorption process are summarized in table 1. In order to facilitate the discussion of the results, the complexes are denoted A, B, C and D corresponding to O$_{12}$, O$_{16}$, N$_{10}$ and N$_{13}$ respectively. The complexes involving the $B_{12}N_{12}$ and $Al_{12}N_{12}$ FLNs are distinguished by the use of the roman numerals I and II, respectively, after the above-mentioned letters (figure 2 and electronic supplementary material, figure 2S).

From the values in table 1, all complexes comprising $B_{12}N_{12}$ are interestingly found to be stable, since they are characterized by negative values of $E_{\text{ads}}$. The adsorption energies follow the trend: $Al < Cl < DI < BI$. Accordingly, Al is the most stable of all the complexes studied. Zhu and co-workers studied the adsorption of TMZ on pristine $BC_{3}NT$ by linking the former to the adsorbent via its two oxygen atoms [8]. The adsorption energies found at the B3LYP/6-31G(d) level are, respectively, $-18.84\, \text{kcal mol}^{-1} (-0.8717\, \text{eV})$ when $BC_{3}NT$ is linked to O$_{12}$ and $-16.73\, \text{kcal mol}^{-1} (-0.7256\, \text{eV})$ when it is linked to O$_{16}$. Therefore, the $B_{12}N_{12}$ FLN is a better adsorbent of TMZ than $BC_{3}NT$, since the most stable complex herein has a lower adsorption energy ($-1.3697\, \text{eV}$) than that of Zhu et al. [8]. However, in the case of O$_{16}$, our $E_{\text{ads}}$ value ($-0.6564\, \text{eV}$) is similar to that of Zhu et al. The gas-phase enthalpy and Gibbs free energy change are also negative, suggesting exergonic and exothermic processes. The values of these thermodynamic parameters are found to follow the same trend as the adsorption energy. Increment in the bond lengths around the adsorption sites of both TMZ and the $B_{12}N_{12}$ FLN are observed upon adsorption. In the case of Al, the interatomic distance between C$_{11}$ and O$_{12}$ increases from 1.209 to 1.259 Å, and the B-N bond lengths.
of the nano-cage are found to increase from 1.483 to 1.562 and 1.597 Å (in the four-membered ring (4-MR) of the nano-cage), as well as from 1.437 to 1.503 Å in the 6-MR. The increment in the C=O bond length in BI is also 0.050 Å (from 1.199 to 1.249 Å). Additionally in BI, the B-N bond lengths of the nano-cage increased from 1.483 to 1.536 or 1.567 Å in the 4-MRs, and from 1.437 to 1.503 Å in the 6-MR. Similar observations were made in the cases of CI and DI. Moreover, the lengths of the B-O/B-N bonds linking the nano-cage (B_{12}N_{12}) to TMZ are found to be 1.547, 1.626, 1.627 and 1.683 Å respectively in AI, BI, CI and DI. Consequently, the most stable complex (AI) is characterized by the smallest adsorbent–adsorbate interatomic interaction. Zhu and co-workers obtained B-O_{12} and B-O_{16} interatomic distances of 1.82 and 1.91 Å, respectively, in their previous work [8]. These values are obviously greater than those obtained from the B_{12}N_{12} nano-cages in the present work (AI and BI).

Table 1 also shows that all of the four complexes of Al_{12}N_{12} (denoted XII, where X = A, B, C and D) have negative adsorption energy, ΔH and ΔG values in gas-phase. Moreover, these energetic parameters

Figure 1. Gas-phase relaxed structures of TMZ, B_{12}N_{12} and Al_{12}N_{12}.

Figure 2. Gas-phase optimized structures of complexes formed between B_{12}N_{12} and TMZ.
are more negative for each of these molecular systems than those of their respective counterparts comprising B_{12}N_{12} as the adsorbent. However, these parameters are found to increase in the same order as those for the boron-nitride nano-cage. In studying the adsorption of pyrrole on some fullerene-like nano-cages, Rad and Ayub also found that the adsorption energy of the complex involving Al_{12}N_{12} was more negative than that of B_{12}N_{12} [38]. A similar observation has been made by other researchers [24,39,40].

The values of the bond lengths around the adsorption sites of AII, BII, CII and DII are provided in electronic supplementary material, figure S1. The Al-O/Al-N interatomic distances within these complexes have the values 1.870, 1.918, 2.009 and 2.066 Å, which are greater than those obtained from the complexes of B_{12}N_{12}. In this case, the complexes involving O_{12} (AII) which is the most stable, also features the lowest adsorbent–adsorbate interatomic interaction. The C_{11}=O_{12}, N_{10}-C_{3} and N_{10}-C_{4} bond lengths of TMZ upon adsorption to the external surface of Al_{12}N_{12} FLN (AII and CII), are similar to those of Al and Cl. However, the C_{2}=O_{16} interatomic distance in BII (1.241 Å) is shorter than that in BI (1.249 Å). A similar observation is made with regard to the C_{11}-N_{13} bond length in BL, which is shorter in DII (1.441 Å) than in DI (1.462 Å).

### 3.2. Effects of doping and solvation

Doping is a routinely used method for improving the sensing and adsorption ability of FLNs. In this perspective, Bahrami and co-workers reported the good adsorption ability of Al-doped B_{11}N_{12} FLN toward amphetamine [41]. Similar results were published for the adsorption of aspirin by Vessally et al. [35]. Moreover, the B_{11}GaN_{12} nano-cluster was also reported to be a better sensor for CO than pure B_{12}N_{12} [14]. In the present research endeavour, the ability of Al-doped B_{12}N_{12} and B-doped Al_{12}N_{12} to adsorb TMZ is probed. In this analysis, only the two most stable structures obtained with the pure nano-clusters (AI, CI, AII and CII) are considered. The optimized structures of the doped FLNs and their complexes are displayed in electronic supplementary material, figure 3S alongside some of their interatomic distances around the adsorption sites. The complexes involving the Al-doped B_{12}N_{12} are dubbed AI-Al and CI-Al, whereas those of the BAl_{11}N_{12} are represented by AII-B and CII-B. The length of the Al-N bond in the relaxed structure of AlB_{11}N_{12} is found to be 1.785 and 1.824 Å, values which perfectly agree with those obtained by Vessally et al. [35] The B-N bond lengths in the BAl_{11}N_{12} nano-cluster are 1.515 Å (in the 4-MR) and 1.447 Å (in the 6-MR).

The gas-phase values of $E_{\text{Ads}}$, $\Delta H$ and $\Delta G$ describing the adsorption of TMZ at the surface of the doped nano-clusters are summarized in table 1. It turns out from the table that all the values of the adsorption energy for both doped FLN are negative, but those involving the O_{12}-atom of TMZ are the lowest. Accordingly, Al-Al and AlI-B are more stable than CI-Al and CII-B, respectively. Furthermore, the values of $E_{\text{Ads}}$ obtained with AlB_{11}N_{12} are more negative than those of pure B_{12}N_{12},

| gas     | $E_{\text{Ads}}$ | $\Delta H$  | $\Delta G$  | water | $E_{\text{Ads}}$ | $\Delta H$  | $\Delta G$  |
|---------|------------------|-------------|-------------|-------|------------------|-------------|-------------|
| Al      | -1.37            | -30.03      | -16.43      | Al    | -1.16            | -27.23      | -13.20      |
| BI      | -0.65            | -14.01      | -0.82       | BI    | —                | —           | —           |
| CI      | -1.29            | -28.83      | -14.01      | CI    | -1.04            | -24.55      | -10.14      |
| DI      | -0.92            | -19.53      | -6.42       | DI    | —                | —           | —           |
| Al-Al   | -2.80            | -63.01      | -49.78      | Al-Al | -2.48            | -57.87      | -44.59      |
| Cl-Al   | -2.35            | -52.53      | -39.27      | Cl-Al | -2.07            | -48.47      | -35.08      |
| All     | -2.09            | -47.27      | -33.88      | All   | -1.83            | -42.88      | -28.89      |
| BII     | -1.39            | -30.76      | -17.91      | BII   | —                | —           | —           |
| CI     | -1.78            | -39.74      | -26.44      | CI    | -1.48            | -34.68      | -21.58      |
| DII     | -1.33            | -29.06      | -16.40      | DII   | —                | —           | —           |
| AlI-B   | -0.36            | -7.81       | 5.03        | AlI-B | -0.11            | -1.74       | 12.06       |
| CII-B   | -0.36            | -7.22       | 5.99        | CII-B | -0.02            | 0.40        | 14.51       |
which interestingly reveals an improvement in the adsorption ability of the doped nano-cages. In addition, the adsorption reactions involving AlB_{12}N_{12} are more exothermic and more exergonic than those of pure B_{12}N_{12}. However, unlike the non-doped BN nano-cage, the doping of Al_{12}N_{12} leads to an increment in the $E_{\text{Ads}}$, $\Delta H$, and $\Delta G$ values (yielding more positive values). Although exothermic, the gas-phase adsorption of TMZ at the external surface of the B-doped Al_{12}N_{12} FLN is non-spontaneous under standard conditions.

Adsorption at the external surface of the Al-doped B_{12}N_{12} leads to a greater change in the C_{11}=O_{12} bond length of TMZ than is the case with adsorption at the surface of pure B_{12}N_{12}. Indeed, the length of these bonds increase by 0.058 Å (i.e. from 1.209 to 1.267 Å) in Al_AL, which is slightly greater than 0.050 Å in the case of AI. An opposite trend is observed between AII and AII_B, implying that the length of the C_{11}=O_{12} bond in the first complex (1.260 Å) is greater than that in the second (1.248 Å). Furthermore, the discrepancies in the values of the C_{3}=N_{10} and C_{4}=N_{10} bond lengths between the complexes comprising the pure and doped FLN are negligible.

3.3. Topological analysis

In theoretical chemistry, the nature and strength of non-covalent interactions are frequently characterized via a set of methods known as topological analysis techniques, of which the quantum theory of atoms in molecules (QTAIM) is the most popular. QTAIM topological analysis is based on the partitioning of a molecular space into a set of interconnected critical points (CPs) [42]. A CP is a space point where the first derivative of the electron density function $\rho(r)$ is null. Therefore, the philosophy of the Bader’s QTAIM approach is to define bonds using the electron density. According to that theory, an interaction between two atoms is identified by the presence of a bond path between them. The presence of a bond path or a bond critical point (BCP) between two atoms confirms the existence of a covalent or non-covalent interaction between the atoms. Within the QTAIM framework, covalent and non-covalent interactions can be distinguished as follows [43]:

- Shared interactions for which the Laplacian of the electron density $\nabla^2 \rho(r)$ is negative at the BCP $(3, -1)$ are classified as covalent bonds.
- Closed shell interactions for which $\nabla^2 \rho(r)$ greater than 0 are ionic or Van der Waals (VdW) interactions.

In the present work, the Bader’s QTAIM has been used as implemented in the multiwfns 3.8 package, to characterize FLN-TMZ interactions in all the complexes under investigation. For that purpose, in addition to $\rho(r)$ and $\nabla^2 \rho(r)$, the identified hydrogen bonds (HBs) were also characterized by their energy, approximated as half of the potential energy density $v(r)$ at the BCPs. The sum (denoted $h(r)$) of the kinetic energy density at the BCP, $g(r)$, and the potential energy density, $v(r)$, is also useful in determining the nature of HBs. Negative values of $h(r)$ are associated with strong HBs, while positive values are associated with both intermediate and weak HBs.

The Bader’s topological analysis in this work has been complemented by the visual analysis of non-covalent interactions using the reduced gradient density (RDG) to identify non-covalent interactions (NCIs) [44]. This method uses coloured iso-surfaces to distinguish between different types of NCIs. Strong interactions like conventional HBs are characterized by blue-coloured iso-surfaces, whereas the green-coloured surfaces indicate attractive VDW interactions. Red-coloured iso-surfaces describe repulsive interactions.

The molecular diagrams of AI, BI, CI and DI are displayed in figure 3, along with their respective NCI iso-surfaces. Some topological parameters describing the interactions between the B_{12}N_{12} FLNs and TMZ are summarized in table 2. A close inspection of figure 3 reveals that apart from DI, all complexes involving the boron nitride FLN have, in addition to the B-O/B-N bonds, HB interactions. These HBs apparently contribute significantly to the stability of the complexes. A closer examination of table 2 reveals that the absolute value of the B-O/B-N energies increases as in the order: BI < DI < CI < AI. Interestingly, this trend shows that the stability of the complexes is directly proportional to their B-O/B-N interaction, since the most stable complex AI (with the lowest $E_{\text{Ads}}$ value and the most spontaneous formation reaction) exhibits the strongest B-O interaction ($\sim$81.33 kcal mol$^{-1}$). Similarly, the least stable complex has the lowest B-O interaction energy. Moreover, table 2 shows that among these complexes, only AI possesses a hydrogen bond that satisfies the intermediate HB conditions, which according to Rozas et al. [45] are positive values of $\nabla^2 \rho(r)$ (0.1040 a.u.) and negative values of $h(r)$ ($-0.0002$ a.u.). This observation is confirmed by the blue-coloured iso-surface in NCI plot of AI. The strength of this HB with energy $-8.30$ kcal mol$^{-1}$ certainly increases the stability of AI. The NH
...N and CH...N interactions in BI and CI rather have the characteristics of weak HBs, which are positive values of $\nabla^2 \rho(r)$ and $h(r)$. The green-coloured iso-surface in their NCI diagrams confirm the attractive character of these interactions, which seemingly impact the stability of the molecular systems.

The molecular diagrams of XII (X = A, B, C and D) complexes as well as their visual NCIs are depicted in electronic supplementary material, figure 4S. The topological parameters describing the Al_{12}N_{12}-TMZ interactions are listed in table 2. As can be easily seen, electronic supplementary material, figure 4S reveals that in addition to the B-O/B-N bonds, the HBs in the XI (X = A, B, C and D) complexes are localized between the Al_{12}N_{12} and TMZ moieties. However, CII and DII present a C$_3$H...N and a C$_4$...N attractive interaction, respectively, that are not found in CI and DI. Analysis of table 2 shows that the B-O/B-N interactions have lower interaction energy values in the Al_{12}N_{12}-TMZ complexes than in the B$_{12}$N$_{12}$ ones. Nevertheless, the HBs and attractive VdW interactions in these complexes are stronger (with higher absolute values of interaction energies, as well as higher value of $\rho(r)$) than those of the B$_{12}$N$_{12}$ FLN under investigation. Furthermore, unlike the N$_{13}$H...N HB of CI, that of CII is an intermediate type HB. This is corroborated by the blue-coloured iso-surface of the NCI diagram of CII that is contrary to the green colour in the case of CI.

It can be observed from table 2 that the values of electron density as well as those of the interaction energy of Al-O$_{12}$ and Al-N$_{10}$ bonds in Al-doped complexes (Al$_{Al}$ and Cl$_{Al}$) are lower than those
obtained with pure $B_{12}N_{12}$ ($B-O_{12}$ and $B-N_{10}$). The reverse is observed when the $\rho(r)$ and $E$ values of $Al_{12}N_{12}$ and $BAI_{11}N_{12}$ are compared. However, the values of adsorption energy in the molecular systems involving direct interactions of TMZ with the boron atom were found in the previous section to be lower than those involving direct Al-TMZ interactions ($Al_{12}N_{12}$ and $AlB_{11}N_{12}$). This is indicative of the fact that the said interactions might not be playing a prominent role in stabilizing the molecular systems obtained via adsorption.

### 3.4. Natural bond orbital analysis

Natural bond orbital (NBO) allows the quantification of interaction of electron based on the Lewis theory. It uses the stabilization energy $E^{(2)}$, which is estimated based on the second order perturbation theory, to predict the strength of Lewis-type donor-acceptor interactions that contribute to the electron delocalization from bonding (BD) or lone pair orbitals (LP) to anti-bonding orbitals (BD$^*$) [46,47]. Large values of $E^{(2)}$ indicate strong interactions. Several interactions in both the nano-cage and TMZ moieties have been observed from calculations of NBO parameters. In the present work, only the values of the stabilization energy $E^{(2)}$ (greater than 10 kcal mol$^{-1}$) describing the interactions between the FLNs and TMZ are reported (table 3) in order to deepen the description of the said interactions obtained from QTAIM and NCI analyses. It can be observed from table 3 that AI and BI are mainly

|             | $\rho(r)$ | $\nabla^2 \rho(r)$ | $h(r)$ | $E$ (kcal mol$^{-1}$) |
|-------------|-----------|-------------------|--------|-----------------------|
| $Al$ $B-O_{12}$ | 0.1156    | 0.5181            | -0.0649 | -81.33               |
| $N_{13}H \ldots N$ | 0.0329    | 0.1040            | -0.0002 | -8.30                |

| $B_{12}$ $B-O_{16}$ | 0.0922    | 0.3632            | -0.0501 | -59.95               |
| $C_{17}H \ldots N$ | 0.0068    | 0.0229            | 0.0008  | -1.26                |
| $C_{9}H \ldots N$ | 0.0105    | 0.0323            | 0.0012  | -1.79                |

| $Cl$ $B-N_{10}$ | 0.1156    | 0.3249            | -0.0789 | -75.00               |
| $N_{13}H \ldots N$ | 0.0203    | 0.0746            | 0.0025  | -4.28                |

| $Di$ $B-N_{13}$ | 0.1042    | 0.2390            | -0.0712 | -63.42               |

| $Al_{12}N_{12}$ $B-O_{12}$ | 0.0710    | 0.5428            | -0.0067 | -38.34               |
| $N_{13}H \ldots N$ | 0.0328    | 0.0965            | -0.0008 | -8.08                |

| $Cl_{11}N_{12}$ $B-N_{10}$ | 0.0632    | 0.3723            | -0.0016 | -30.21               |
| $N_{13}H \ldots N$ | 0.0231    | 0.0797            | 0.0019  | -5.06                |

| $Al_{11}N_{12}$ $Al-O_{12}$ | 0.0630    | 0.4652            | 0.0068  | -32.22               |
| $N_{13}H \ldots N$ | 0.0507    | 0.1028            | -0.0104 | -14.60               |

| $B_{11}N_{12}$ $Al-O_{16}$ | 0.0529    | 0.3759            | 0.0064  | -25.43               |
| $C_{17}H \ldots N$ | 0.0104    | 0.0280            | 0.0007  | -1.75                |
| $C_{9}H \ldots N$ | 0.0144    | 0.0443            | 0.0014  | -2.60                |

| $Cl_{11}N_{12}$ $Al-N_{10}$ | 0.0541    | 0.3088            | -0.0003 | -24.38               |
| $N_{13}H \ldots N$ | 0.0315    | 0.0938            | -0.0005 | -7.69                |
| $C_{9}H \ldots N$ | 0.0156    | 0.0530            | 0.0017  | -3.09                |

| $D_{11}N_{12}$ $Al-N_{13}$ | 0.0484    | 0.2561            | -0.0007 | -20.54               |
| $C_{4} \ldots N$ | 0.0130    | 0.0402            | 0.0009  | -2.58                |

| $Al_{11}B_{11}N_{12}$ $B-O_{12}$ | 0.0912    | 0.3296            | -0.0507 | -57.66               |
| $N_{13}H \ldots N$ | 0.0460    | 0.1103            | -0.0069 | -13.01               |

| $Cl_{11}B_{11}N_{12}$ $B-N_{10}$ | 0.0895    | 0.2057            | -0.0575 | -51.19               |
| $N_{13}H \ldots N$ | 0.0223    | 0.0704            | 0.0016  | -4.53                |
| $N_{13} \ldots N$ | 0.0082    | 0.0254            | 0.0008  | -1.52                |
stabilized by interactions between lone pairs from O_{12} or O_{16} to the anti-bonding orbitals involving the boron-atom through which the FLN links to TMZ as well as the N-atoms adjacent to it. In Al for instance, a strong electron delocalization from a LP of O_{16} to a \( \sigma^* (B_8-N_{14}) \) with \( E^{(2)} \) value of 149.30 kcal mol\(^{-1}\) is observed. A similar observation is made in BI, with stabilizing energy of 144.14 kcal mol\(^{-1}\) corresponding to the LP(O_{16}) \( \rightarrow \sigma^* (N_{15}-B_{13}) \) interaction. In addition to these interactions, Al and BI are also stabilized by \( \sigma(C_2=O_{16}) \rightarrow \sigma^* (N_{4}-B_{9}) \) (\( E^{(2)} = 14.82 \) kcal mol\(^{-1}\)) and \( \sigma(C_{11}=O_{12}) \rightarrow \sigma^* (N_{15}-B_{13}) \) (\( E^{(2)} = 14.32 \) kcal mol\(^{-1}\)) interactions, respectively. Moreover, the N28-H...N hydrogen bond previously observed in the molecular structure of Al is also confirmed to greatly contribute to the stabilization of the said complexes. Indeed, an interaction energy of 12.05 kcal mol\(^{-1}\) describing that HB bond is found from the NBO analysis. Interactions within the frameworks of FLN and TMZ are found to be of paramount importance to the stability of the CI and DI complexes, and only one major interaction involving both structures is obtained in CI. Specifically, this interaction involves the delocalization of electron density from the LP of one N-atoms of the FLN (adjacent to the B-atom of the cage linked to TMZ) to the anti-bonding orbital of the B-N_{10} bond enabling the interaction between the adsorbent and the adsorbate. Similarly, electron density delocalization from the LP of all three N-atoms neighbouring the B-atom of B_{12}N_{12} bearing the TMZ structure to \( \sigma^* (B-N_{13}) \) (leading to the B_{12}N_{12}-TMZ complex) are observed in DI.

Concerning the complexes of pure Al_{12}N_{12}, the interactions found in AI are similar to those in Al. The interaction from LP(O_{16}) to \( \sigma^* (Al_{33}N_{8}) \) (with \( E^{(2)} = 44.37 \) kcal mol\(^{-1}\)) is the main interaction involving both the cage and TMZ. The delocalization from \( \sigma(Al_{33}N_{8}) \) to \( \sigma^* (N_{28}-H_{10}) \) describing the HB with \( E^{(2)} \) value of 25.01 kcal mol\(^{-1}\) is observed. In the case of BII, the O-atom of TMZ (O_{12}) that is linked to the FLN was found to delocalize electrons from its LP to the \( \sigma^* (Al-N) \) of the cage, which stabilizes the complex. A similar observation is made in the case of CII. Finally, no major interaction involving both the nano-cage and TMZ is found in DI.

In the Al-doped complexes, electron transfer from the LP of O_{16} and N_{10} to the empty orbital of the doping Al-atom is considerably important in stabilizing the systems. The transitions with \( E^{(2)} \) values 56.57 and 59.13 kcal mol\(^{-1}\) are obtained in Al-Al and CI-Al, respectively. In the B-doped complexes, interactions involving the N_{12}Al_{11}B-TMZ bond (B-O_{16} and B-N_{10} of AlII_B and CII_B, respectively) and the B-N anti-bonding orbital of the cage represent the principal electron delocalization interactions stabilizing the structures, as shown in table 3. An interesting interaction from \( \sigma(N-B) \) to \( \sigma^* (O_{16}-B) \) is revealed, with \( E^{(2)} \) value 509.78 kcal mol\(^{-1}\).

The absolute value of the Hirshfeld charges (HCs) of the B and N atoms in pure B_{12}N_{12} is 0.33 e. The gas-phase HCs on the B and Al atoms linked to TMZ in all molecular complexes considered herein are summarized in electronic supplementary material, table 1S, along with those of the N-atoms adjacent to the B and Al atoms.

Concerning the complexes of pure Al_{12}N_{12}, the interactions found in AI are similar to those in Al. The interaction from LP(O_{16}) to \( \sigma^* (Al_{33}N_{8}) \) (with \( E^{(2)} = 44.37 \) kcal mol\(^{-1}\)) is the main interaction involving both the cage and TMZ. The delocalization from \( \sigma(Al_{33}N_{8}) \) to \( \sigma^* (N_{28}-H_{10}) \) describing the HB with \( E^{(2)} \) value of 25.01 kcal mol\(^{-1}\) is observed. In the case of BII, the O-atom of TMZ (O_{12}) that is linked to the FLN was found to delocalize electrons from its LP to the \( \sigma^* (Al-N) \) of the cage, which stabilizes the complex. A similar observation is made in the case of CII. Finally, no major interaction involving both the nano-cage and TMZ is found in DI.

Electronic properties

Electronic properties are key parameters in the description of the sensing ability of nano-cage materials. The HOMO and LUMO levels are of paramount importance in evaluating these parameters. The calculated gas and aqueous phases values of HOMO-LUMO gap (\( E_g \)) and Fermi level (\( E_F \)) of the molecular systems under investigation are summarized in table 4. The distributions of the FMOs of TMZ are also presented in figure 1, while those of Al, AlAI, AlII and AlIIAI are presented in figure 4. It can be seen from figure 4 that the HOMO iso-surface distribution of all molecular complexes are nearly the same, and are exclusively centred on the N-atoms of the nano-cages. The LUMO iso-surfaces are similarly distributed but are mainly localized around the TMZ atoms. These findings corroborate the density of states (DOS) of these systems, which are also similar (reasons why only that of Al is presented in figure 5). Therefore, the adsorption of TMZ at the external surface of the pure and doped FLNs considered herein greatly modifies their FMOs, thereby altering their properties. Inspection of table 4 indicates an increment in the HOMO levels, as well as a change in the LUMO levels of all the FLNs upon adsorption of TMZ. This is a very important observation when
Table 3. Values of the second-order perturbation energy $E^{(2)}$ calculated in gas phase.

| donor | acceptor | $E^{(2)}$ (kcal mol$^{-1}$) | donor | acceptor | $E^{(2)}$ (kcal mol$^{-1}$) |
|-------|----------|----------------------------|-------|----------|----------------------------|
| AI    | LP(O16)  | $\sigma'$ (B8-N15) 18.94 | AI    | LP(O16)  | $\sigma'$ (Al33-N8) 44.37 |
|       | LP(O16)  | $\sigma'$ (B8-N4) 95.21 |       | LP(O16)  | $\sigma'$ (Al33-N7) 21.03 |
|       | LP(O16)  | $\sigma'$ (B8-N4) 12.68 |       | LP(O16)  | $\sigma'$ (Al33-N7) 10.86 |
|       | $\sigma$(C2-O16) 14.82 |       |       | $\sigma$(C2 =O16) 14.76 |
|       | LP(O16)  | $\sigma'$ (B8-N4) 12.68 |       | LP(O16)  | $\sigma'$ (Al33-N7) 21.03 |
|       | LP(O16)  | $\sigma'$ (B8-N14) 44.37 |       | LP(O16)  | $\sigma'$ (Al33-N10) 14.78 |
|       | LP(O16)  | $\sigma'$ (B8-N14) 10.44 |       | LP(O16)  | $\sigma'$ (Al33-N10) 24.02 |
|       | $\sigma$(C11-O12) 14.32 |       |       | $\sigma$(C11-O12) 16.79 |
|       | LP(N12)  from FLN $\sigma'$ (N13-B18) 11.52 | CII  | LP(N10)  | $\sigma'$ (Al33-N10) 16.44 |
|       | LP(N12)  from FLN $\sigma'$ (B-N13) 12.97 |       | LP(N10)  | $\sigma'$ (Al33-N10) 38.74 |
|       | LP(N12)  from FLN $\sigma'$ (B-N13) 13.66 |       | LP(N10)  | $\sigma'$ (Al33-N10) 11.21 |
|       | LP(N12)  from FLN $\sigma'$ (B-N13) 12.82 | All-B | $\sigma$(N7-B) 509.78 |
|       | $\sigma$(N12-B) 10.00 |       |       | $\sigma$(N12-B) 23.01 |
|       | $\sigma$(C-012) 10.00 |       |       | $\sigma$(C-012) 19.36 |
|       | $\sigma$(Al) 40.90 |       |       | $\sigma$(Al) 15.80 |
|       | LP(O16)  | $\sigma'$ (Al) 15.80 |       | LP(O16)  | $\sigma'$ (Al) 15.78 |
|       | LP(O16)  | $\sigma'$ (Al) 15.78 |       | LP(O16)  | $\sigma'$ (Al) 56.57 |
|       | LP(O16)  | $\sigma'$ (Al) 56.57 |       | LP(O16)  | $\sigma'$ (Al) 16.85 |
|       | $\sigma$(Al) 16.85 |       |       | $\sigma$(Al) 44.91 |
|       | LP(O16)  | $\sigma'$ (Al) 16.85 |       | LP(O16)  | $\sigma'$ (Al) 10.46 |
Table 4. Energy of HOMO, LUMO, HOMO-LUMO gap ($E_g$) in eV, percentage of the change of $E_g$ after adsorption ($\Delta E_g$%), Fermi level ($E_F$), dipole moment (Debye) and amount of charge transfer (Q(e)) between TMZ and the FLNs.

| gas       | $E_{\text{HOMO}}$ | $E_{\text{LUMO}}$ | $E_{\text{gap}}$ | $\Delta E_g$ (%) | $E_F$ | $\mu$ | Q(e) | water       | $E_{\text{HOMO}}$ | $E_{\text{LUMO}}$ | $E_{\text{gap}}$ | $\Delta E_g$ (%) | $E_F$ | $\mu$ |
|-----------|------------------|------------------|------------------|------------------|--------|--------|------|-------------|------------------|------------------|------------------|------------------|--------|------|
| TMZ       | −8.38            | −1.43            | 6.95             | —                | −4.91  | 3.46   | —    | −8.19       | −1.39            | 6.80             | —                | −4.79  | 5.22 |
| B_{12}N_{12} | −9.45           | −0.01            | 9.44             | —                | −4.73  | 0.00   | —    | −9.13       | −0.47            | 8.66             | —                | −4.80  | 0.00 |
| Al        | −8.25            | −2.39            | 5.85             | 38.09            | −5.33  | 12.34  | −0.13| −8.41       | −1.76            | 6.65             | 23.21            | −5.08  | 15.03 |
| Bi        | −8.79            | −2.44            | 6.34             | 32.91            | −5.62  | 4.48   | −0.40| —           | —                | —                | —                | —                | —                |
| Cl        | −8.69            | −2.21            | 6.48             | 32.43            | −5.45  | 7.85   | −0.38| −8.55       | −1.65            | 6.90             | 20.32            | −5.10  | 10.67 |
| Di        | −8.52            | −2.30            | 6.22             | 34.18            | −5.41  | 8.66   | −0.42| —           | —                | —                | —                | —                | —                |
| AlB_{11}N_{12} | −9.02          | −2.40            | 6.62             | —                | −5.71  | —      | —    | −8.81       | −1.53            | 7.28             | —                | −5.17  | 5.54 |
| Al_{2}Bi | −8.14            | −2.67            | 5.46             | 17.52            | −5.41  | 15.16  | −0.38| −8.35       | −1.86            | 6.49             | 10.85            | −5.10  | 19.36 |
| Cl_{2}Bi | −8.38            | −2.58            | 5.79             | 12.54            | −5.49  | 10.61  | −0.36| −8.37       | −1.80            | 6.56             | 10.03            | −5.09  | 15.31 |
| Al_{11}Bi | −8.02            | −1.70            | 6.32             | —                | −4.86  | —      | —    | −8.09       | −1.54            | 6.55             | —                | −4.81  | —    |
| Al_{2}Bi | −7.32            | −2.12            | 5.20             | 17.72            | −4.97  | 9.53   | −0.26| −7.78       | −1.69            | 6.08             | 7.18             | −4.19  | 12.24 |
| Bi_{11}Cl | −7.76            | −2.17            | 5.59             | 11.55            | −5.36  | 2.79   | −0.33| —           | —                | —                | —                | —                | —                |
| Cl_{2}Bi | −7.74            | −1.96            | 5.78             | 8.54             | −4.85  | 5.14   | −0.28| −7.84       | −1.63            | 6.21             | 5.19             | −4.73  | 7.59 |
| Di_{11}Cl | −7.60            | −2.05            | 5.55             | 12.18            | −4.83  | 5.82   | −0.36| —           | —                | —                | —                | —                | —                |
| Al_{11}Bi | −7.85            | −1.69            | 6.16             | —                | −4.77  | 1.63   | —    | −7.97       | −1.51            | 6.46             | —                | −4.74  | 2.92 |
| Al_{11}Bi | −7.08            | −1.87            | 5.21             | 15.42            | −4.48  | 7.40   | −0.33| −7.50       | −1.59            | 5.91             | 9.31             | −4.54  | 9.39 |
| Cl_{11}Bi | −7.63            | −1.72            | 5.91             | 4.06             | −4.68  | 4.32   | −0.30| −7.61       | −1.47            | 6.14             | 4.95             | −4.54  | 6.97 |
probing the sensing ability of nanostructures via the theoretical chemistry methods. The $E_g$ value of TMZ is 6.95 eV as evidenced in table 4. This parameter is, however, known to be very sensitive to the theoretical level. Zhu and co-workers published for TMZ, an $E_g$ value of 3.97 eV at the B3LYP/6-31G(d) level of theory [8]. The gas-phase magnitudes of $E_g$ obtained herein for B$_{12}$N$_{12}$ (9.44 eV) and Al$_{12}$N$_{12}$ (6.32 eV) perfectly agree with those obtained by Padash and co-workers at M062X/6-311G(d,p) level of theory [24]. Analysis of the values in table 4 also reveals that adsorption of TMZ at the external surface of pure B$_{12}$N$_{12}$ FLN leads to a huge reduction in its $E_g$ value. The values of $\Delta E_g(\%)$ (calculated taking the FLNs as references) for the molecular complexes of that nano-cage increase as follows: CI < BI < DI < AI. The reference point for changes in HOMO and LUMO is the adsorbent (nano-cage here) [8,24]. It turns out that AI, which was found to be the most stable of these complexes has the greatest $\Delta E_g(\%)$ value of 38.09%. The magnitude of this value clearly shows that the FLN is very sensitive to TMZ, and can accordingly be efficiently applied as sensor for its detection. This result is consistent with the change in the Fermi levels, for which AI is still the molecular complex exhibiting the greatest change. In the case of pure Al$_{12}$N$_{12}$, the percentages of energy gap change upon adsorption of TMZ at the external surface of pure Al$_{12}$N$_{12}$ are significantly lower than those of B$_{12}$N$_{12}$. In that case, the greatest value of $\Delta E_g(\%)$ is 17.72, which is still obtained with AII. Furthermore, the change in the $E_F$ values of the Al$_{12}$N$_{12}$ FLN is smaller than that of the B$_{12}$N$_{12}$ FLN. These observations clearly confirm the fact that pure B$_{12}$N$_{12}$ FLN is a better TMZ sensor than Al$_{12}$N$_{12}$.

The dipole moment of a molecular system strongly depends on the magnitude and separation of charges within the system, and is thus important in predicting their chemical reactivity. It is evident in table 4 that adsorption leads to huge increments in the dipole moment of the FLNs. In all cases, complex A is found to have the greatest value of the DM, indicating the strength of the covalent

![Figure 4. Distribution of FMO of the most stable configuration of molecular complexes obtained from the FLNs under investigation.](image-url)
interaction between FLN and TMZ. This is corroborated by values of AIM and NBO parameters as well as the short adsorbent-TMZ interactions obtained in the molecular complexes investigated. The orientation of the DM vector in all the complexes shown (some of them depicted in electronic supplementary material, figure 5S) are from FLN to TMZ. The average values of the FLN HCs in all molecular complexes, as summarized in table 4, are all negative, implying those of TMZ are positive. This result affirms both the direction of the DM vector and the charge transfer from TMZ to the FLNs as highlighted previously.

Short recovery period (fast desorption) is a requirement for a suitable sensor. Therefore, too strong chemical interactions are not ideal for sensors, since such adsorption often leads to long recovery times which are not ideal for sensor applications [8]. The recovery time ($\tau$) for complexes indexed as A (the most stable with respect to the different FLNs) was calculated as:

$$\tau = \frac{1}{\nu_0} \exp \left( -\frac{\Delta G_{\text{Ads}}}{kT} \right)$$  \hspace{1cm} (3.1)

$\nu_0$ is the frequency of the ultraviolet light in the vacuum ($= 10^{12}$ s$^{-1}$), used to extract the adsorbed molecule (TMZ), k is the Boltzmann’s constant (1.99 kcal mol$^{-1}$ K$^{-1}$) and T is the room temperature (298.15 K). The recovery time thus depends on the exponential part ($\Delta G_{\text{Ads}}$). Values of $\tau$ summarized in table 5 clearly reveal that only A1 with a recovery time of 1.06 s can be applied as sensor for the detection of TMZ. This result corroborates those observed on the analysis of electronic properties.

**3.6. Electronic spectra analysis**

The TD-DFT/M06-2X-D3/6-311G(d,p) level of theory has been used to predict the absorption spectra of TMZ alongside its most stable complexes (A1, AII, A1_Al and AII_B) in both gas phase and aqueous environments. The results obtained are summarized in table 6, while the corresponding spectra diagrams are displayed in figure 6. Figure 6a shows three absorption maxima of the electronic spectrum.
Table 6. Absorption maxima ($\lambda_{\text{max}}$), absorption energy ($E$), oscillator strength ($F$) and composition of electronic transfer obtained from the electronic spectra of the studied compounds.

|     | $\lambda_{\text{max}}$ (nm) | $E$ (eV) | $F$  | assignment and composition |
|-----|-----------------------------|--------|-----|---------------------------|
| Gas | TMZ                         | 193.59 | 6.40| 0.0322 H-4 $\rightarrow$ L (47%) |
|     | 221.95                      | 5.58  | 0.1161 H $\rightarrow$ L+1 (44%) |
|     | 268.47                      | 4.62  | 0.2942 H $\rightarrow$ L (47%) |
| Al  | 218.75                      | 5.67  | 0.0601 H-5 $\rightarrow$ L+1 (24%); H-4 $\rightarrow$ L (11%) |
|     | 271.49                      | 4.57  | 0.3203 H-5 $\rightarrow$ L (31%); H $\rightarrow$ L (10%) |
|     | 277.11                      | 4.47  | 0.1362 H $\rightarrow$ L (36%); H-5 $\rightarrow$ L (11%) |
| Cl  | 221.08                      | 5.61  | 0.0554 H-3 $\rightarrow$ L+1 (23%) |
|     | 228.07                      | 5.44  | 0.0796 H $\rightarrow$ L+1 (30%) |
|     | 253.94                      | 4.88  | 0.1834 H-8 $\rightarrow$ L (15%); H-3 $\rightarrow$ L (13%) |
|     | 269.91                      | 4.59  | 0.1558 H-3 $\rightarrow$ L (30%) |
| Al_Al| 218.29                      | 5.68  | 0.0669 H-7 $\rightarrow$ L+1 (43%) |
|     | 274.36                      | 4.52  | 0.3113 H-7 $\rightarrow$ L (31%) |
|     | 275.79                      | 4.50  | 0.1723 H-1 $\rightarrow$ L (31%) |
| Cl_Al| 224.88                      | 5.51  | 0.0691 H-7 $\rightarrow$ L+1 (23%); H-2 $\rightarrow$ L+1 (19%) |
|     | 258.53                      | 4.80  | 0.3111 H-7 $\rightarrow$ L (32%) |
|     | 275.22                      | 4.51  | 0.0419 H-7 $\rightarrow$ L (13%) |
| All | 311.45                      | 3.98  | 0.0043 H-13 $\rightarrow$ L (41%) |
|     | 313.60                      | 3.95  | 0.0060 H $\rightarrow$ L+1 (29%); H $\rightarrow$ L (13%) |
|     | 314.81                      | 3.94  | 0.0092 H $\rightarrow$ L (33%); H $\rightarrow$ L+1 (12%) |
| CII | 261.71                      | 4.74  | 0.2336 H-13 $\rightarrow$ L (28%) |
|     | 277.76                      | 4.46  | 0.0485 H-13 $\rightarrow$ L (8%) |
| All_B| 271.44                      | 4.57  | 0.3644 H-12 $\rightarrow$ L (23%); H-13 $\rightarrow$ L (14%) |
|     | 328.59                      | 3.77  | 0.0305 H $\rightarrow$ L (45%) |
| CII_B| 266.42                      | 4.65  | 0.0393 H-1 $\rightarrow$ L+3 (15%) |
|     | 275.36                      | 4.50  | 0.0780 H-1 $\rightarrow$ L (33%) |
|     | 280.84                      | 4.42  | 0.0715 H-1 $\rightarrow$ L (30%) |
|     | 224.05                      | 5.53  | 0.1443 H-11 $\rightarrow$ L+1 (45%) |
|     | 225.05                      | 4.50  | 0.0562 H-4 $\rightarrow$ L (47%) |
|     | 225.22                      | 5.55  | 0.0958 H-4 $\rightarrow$ L+1 (44%) |
|     | 281.29                      | 4.39  | 0.3844 H $\rightarrow$ L (48%) |
| water| TMZ                         | 197.01 | 6.29| 0.0562 H-4 $\rightarrow$ L (47%) |
|     | 223.22                      | 5.55  | 0.0958 H-4 $\rightarrow$ L+1 (44%) |
|     | 288.13                      | 4.30  | 0.5405 H $\rightarrow$ L (47%) |
| Al  | 205.57                      | 6.03  | 0.0571 H-11 $\rightarrow$ L (26%) |
|     | 223.22                      | 5.55  | 0.0958 H-11 $\rightarrow$ L+1 (44%) |
|     | 288.13                      | 4.30  | 0.5405 H $\rightarrow$ L (47%) |
| Cl  | 273.03                      | 4.54  | 0.4169 H $\rightarrow$ L (18%); H-2 $\rightarrow$ L (16%); H-1 $\rightarrow$ L (16%) |
|     | 207.64                      | 5.97  | 0.0532 H-11 $\rightarrow$ L (29%); H-1 $\rightarrow$ L+2 (16%) |
| Al_Al| 223.23                      | 5.55  | 0.0882 H-1 $\rightarrow$ L+1 (45%) |
|     | 290.16                      | 4.27  | 0.5660 H-1 $\rightarrow$ L (49%) |
| Cl_Al| 207.80                      | 5.97  | 0.0533 H-8 $\rightarrow$ L (26%) |
|     | 224.71                      | 5.52  | 0.1419 H-8 $\rightarrow$ L (26%) |
|     | 273.30                      | 4.54  | 0.4366 H-3 $\rightarrow$ L (47%) |
| All | 287.83                      | 4.31  | 0.4756 H-4 $\rightarrow$ L (40%) |
|     | 302.99                      | 4.09  | 0.0053 H $\rightarrow$ L+1 (40%) |
| CII_B| 275.31                      | 4.50  | 0.0713 H $\rightarrow$ L (35%) |
|     | 265.00                      | 4.68  | 0.0805 H $\rightarrow$ L (39%) |
of TMZ, the most intense of which appears at 268 nm in gas phase and at 282 nm in water. A red shift of the absorption maxima is evident upon solvation of TMZ. These maxima arise from electronic transitions originating from the HOMO to the LUMO of TMZ, which according to these frontier molecular orbital distributions, are attributable to $\pi \to \pi'$ type transitions. It is clear from figure 6b that in the gas phase, the electronic spectra of Al and Al_AI are similar, the only difference being the slight bathochromic effect caused by the doping of the B_{12}N_{12} FLN. Indeed, the main absorption bands of these complexes are centred around 271 nm (due to H-5 $\to$ L(31%)) and 274 nm (H-7 $\to$ L(31%)), respectively, for Al and Al_AI. A strong bathochromic effect can also be observed from figure 6b induced by the solvation of these compounds, but their spectra remain similar in aqueous solution. The increments in the values of $\lambda_{\text{max}}$ are 11 and 15 nm for Al and Al_AI respectively, upon solvation.

As concerns the molecular complexes based on Al_{12}N_{12} nano-cage, doping also leads to a red shift in both study media. An increment of about 15 nm in the value of $\lambda_{\text{max}}$ is observed when passing from Al to Al_I-B. However, unlike the BN-based complexes studied, a blue shift is observed for the absorption maxima of the Al_{12}N_{12}-based complexes upon solvation. It should, however, be noticed that the values of excited-state energies as well as the HOMO-LUMO gap of the compounds studied might be improved using range-separated functionals. Indeed, it has been shown that these functionals best describe the mentioned parameters due to their $-1.00/R$ dependence on the exchange potential instead of the $-0.50/R$ dependence of the M06-2X Minnesota functional [48–51].

4. Concluding remarks

The adsorption of the anti-cancer drug dubbed TMZ herein at the external surface of pure and doped X_{12}N_{12} (X = B and Al) using the DFT/M06-2X-D3/6-311G(d,p) theoretical chemistry method was the main concern of the present work. Quantum chemical calculations were carried out in both gas and aqueous phases. The results have revealed that apart from the doped BAl_{11}N_{12} FLN, all the other investigated nano-cages can spontaneously adsorb TMZ in both study media. Moreover, TMZ was...
found to bind onto the FLNs preferentially through O₁₂, via a partially covalent interaction. The complexes involving that O-atom are also found to exhibit the greatest dipole moment values. Charge transfer from TMZ to the respective FLNs was clearly elucidated via NBO and Hirshfeld atomic complexes involving that O-atom.

The analysis of calculated electronic parameters has shown that Al (the most stable molecular complex) witnessed the greatest change in FMOs distribution, $E_{\text{gap}}$, and $E_{\text{g}}$. In addition, the release time in vacuum ultraviolet light of Al was found to be only 1.06 s at room temperature. Finally, the best sensor must strongly link the adsorbed molecule (giving rise to negative values of adsorption energy as well as Gibbs free energy), must greatly alter (reduce) the HOMO-LUMO energy gap of the sensor (FLNs herein). The desorption time too must be the smallest possible so that the FLN can be easily regenerated and re-used. So all these parameters are combined to elect the best sensor, the most important being the change in the HOMO-LUMO energy gap as well the desorption time.

From the foregoing observations, B₁₂N₁₂ among the FLNs investigated is the most sensitive to TMZ and can be proposed for industrial applications.

Data accessibility. All output files as well as supplementary materials are available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.6m905qq12 [52].

Authors’ contributions. B.L.N.W.: data curation, formal analysis, investigation, writing—original draft; A.D.T.F.: conceptualization, data curation, investigation, methodology, software, writing—original draft, writing—review and editing; N.K.N.: methodology, software, writing—review and editing; R.A.N.: conceptualization, methodology, supervision, validation, writing—review and editing; A.W.: conceptualization, project administration, supervision, writing—review and editing.

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