DFT analysis of valproic acid adsorption onto Al₁₂/B₁₂-N₁₂/P₁₂ nanocages with solvent effects

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Abstract

Using density functional theory, the adsorption of valproic acid onto the surface of fullerene-like nanocages was investigated. Valproic acid interact the nanocages through the carboxylic group with energies of -144.14, -109.71, -105.22 and -84.96 kcal/mol. The FMOs energy levels were considerably altered upon adsorption, resulting in a reduction in energy gap and increase in electrical conductivity. This suggests that nanocages could be used as sensors as well as options for drug administration in biological systems. Solvation effects in water are also reported.

Introduction

The impact of nanotechnology on industry and medicine is enormous [1, 2]. Many advancement in numerous sectors of research, including microscopic particles and nano-structured materials, have been made in recent years [3-8]. Currently a variety of types have been constructed as possible volunteers for the development of sensors and drug carriers [9-12]. The properties of the drug-nanostructure complex are undergo changes as a result of the electron exchange between the adsorbed molecules and the nanomaterials, which can be monitored as a possible sensor [6, 7, 13, 14]. Due to the unique features, particularly the narrow energy gap, fullerenes are one of the most appealing families of nanostructures [13-15]. According to a review of literature, the $Al_{12}/B_{12}-N_{12}/P_{12}$ structures are the most stable of all the fullerene like structures [13, 14, 16, 17]. The medical applications of valproic acid (VLA) and its derivatives are numerous. VLA is a fatty acid that has been used to treat epilepsy, mood disorders, migraines and neuropathic pain [18-21]. Despite its medical benefits, VLA exposure during the pregnancy has been linked to the development of autism [22]. To avoid adverse effects, it is crucial to detect the presence of the VLA in living creatures and give it properly. Due to advantageous physico-chemical features, fullerenes have been studied extensively. Since drug detection has serious ramifications, researchers have looked into targeted drug delivery and sensor applications of fullerenes [23, 24]. Fullerenes have been reported to be employed in the hunt for anticancer medication delivery [25, 26]. The major goal of the work is to use DFT to investigate possibilities of chemical functionalization of $Al_{12}/B_{12}-N_{12}/P_{12}$ with VLA. The findings will serve as a foundation for future experimental investigations of drug delivery system development.

DFT calculations

The Gaussian 16 program suite was used to do all theoretical computations [27, 28]. Quantum chemistry computations were used to investigate the interaction of VLA with nanocages (NC) with B3LYP/6-311G* basis which is suitable for modeling [29]. To confirm the lowest energy point of all structures, frequency studies were performed in addition to chemical descriptors. The adsorption energy: $E_{ads} = E_{VLA-NC} - E_{NC} - E_{VLA}$ [30-32] and CPCM model was used to examine solvation effects [33].

Results And Discussion

Properties of NCs and VLA

The relaxed ground state structure of VLA and all four NCs, as well as their FMOs distribution and MEP are shown in Figs.1 and 2. The equilibrium bond length are Al-N =1.7927, 1.8554, Al-P =2.3406, 2.2927, B-N = 1.4385, 1.4862 and B-P = 1.9279, 1.9047Å for all pristine cages. The HOMO and LUMO were roughly on the vicinity of N, P and Al, B atoms, as shown in Fig.2. HOMO and LUMO energies of AlN (AlP) and BN (BP) NCs are -7.1781, -2.5227 (-6.8169, -3.4272) and -7.8594, -1.1050 (-6.9600, -3.2278) eV respectively (table 1). In addition band gaps for AlN (AlP) and BN (BP) NCs are 4.6554 (3.3897) and 6.7544 (3.7322) eV respectively. Based on E_g values, BN and AlP are the least and the most electrically conductive ones. Using values of E_g , the kinetic stability of the NCs may be examined. The values of relaxed NCs revealed that AlP with low kinetic consistency have more reactivity than the others. The HOMO and LUMO energies for VLA were -7.7222 and -0.4177 eV [34, 35].

Table 1 Chemical descriptors of VLA and NCs

Property	VLA	Al ₁₂ N ₁₂	Al ₁₂ P ₁₂	B ₁₂ N ₁₂	B ₁₂ P ₁₂
EHOMO (eV)	-7.7222	-7.1781	-6.8169	-7.8594	-6.9600
ELUMO (eV)	-0.4177	-2.5227	-3.4272	-1.1050	-3.2278
E_g (eV)	7.3045	4.6554	3.3897	6.7544	3.7322
Fermi level (eV)	-4.0700	-4.8504	-5.1221	-4.4822	-5.0939
Chemical potential (eV)	-4.0700	-4.8504	-5.1221	-4.4822	-5.0939
Hardness (eV)	3.6523	2.3277	1.6949	3.3772	1.8661
Softness (1/eV)	0.1369	0.2148	0.2950	0.1481	0.2679
Electrophilicity index (eV)	2.2677	5.0536	7.7395	2.9744	6.9524
DM (Debye)	1.4902	0	0	0	0
Polarizability (a.u.)	94.7800	292.6810	613.5573	151.9643	410.6030

Interaction of VLA and NCs

The VLA is coupled to surfaces of Al₁₂/B₁₂-N₁₂/P₁₂ via COOH group (Fig.3). The reactive regions of VLA and NCs attached to each other for adsorption process. The values of charges of atoms in VLA interacting with AlN, AlP, BN and BP are -0.531092, -0.424069, -0.436418, -0.497144 (O1), -0.330518, -0.442946, -0.280203, -0.343344 (O2), 0.433564, 0.469323, 0.424040, 0.437267 (H26) while that of VLA are -0.560731, -0.384422, 0.378393e (table 2) [13].

Table 2 Mulliken Charges

Atom	VLA	VLA-Al ₁₂ N ₁₂	VLA-Al ₁₂ P ₁₂	VLA-B ₁₂ N ₁₂	VLA-B ₁₂ P ₁₂
O1	-0.560731	-0.531097	-0.424069	-0.436418	-0.497144
O2	-0.384422	-0.330518	-0.442946	-0.280203	-0.343344
C3	-0.275644	-0.282228	-0.284642	-0.286427	-0.265944
C4	-0.322307	-0.399891	-0.415465	-0.409100	-0.405663
C5	-0.322280	-0.423527	-0.415437	-0.409368	-0.405191
C6	-0.341586	-0.414817	-0.408842	-0.403168	-0.396584
C7	-0.341591	-0.399876	-0.408853	-0.403102	-0.397055
C8	0.519910	0.462745	0.512177	0.515327	0.439798
C9	-0.518929	-0.621978	-0.618323	-0.616498	-0.614369
C10	-0.518933	-0.620194	-0.618319	-0.616491	-0.614306
H11	0.200684	0.229944	0.244201	0.242565	0.226290
H12	0.175035	0.202266	0.217839	0.215336	0.204066
H13	0.189464	0.219044	0.238217	0.230850	0.217143
H14	0.189481	0.214726	0.238214	0.230841	0.216991
H15	0.175025	0.212242	0.217833	0.215419	0.204001
H16	0.180652	0.230321	0.223462	0.212781	0.207948
H17	0.173591	0.196923	0.206066	0.205727	0.200714
H18	0.180667	0.227612	0.223454	0.212719	0.208131
H19	0.173577	0.200085	0.206063	0.205807	0.200654
H20	0.176851	0.209436	0.217475	0.213320	0.206819
H21	0.176191	0.208677	0.215915	0.215970	0.209171
H22	0.171934	0.203035	0.206508	0.206126	0.202755
H23	0.171928	0.203361	0.206511	0.206147	0.202758
H24	0.176187	0.210058	0.215915	0.215986	0.209184
H25	0.176855	0.205341	0.217467	0.213297	0.206808
H26	0.378393	0.433564	0.469323	0.424040	0.437267

Table 3 Chemical descriptors in gaseous (water) phase

Property	VLA-Al ₁₂ N ₁₂	VLA-Al ₁₂ P ₁₂	VLA-B ₁₂ N ₁₂	VLA-B ₁₂ P ₁₂
EHOMO (eV)	-6.1973 (-6.2999)	-6.3165 (-6.1546)	-7.0262 (-7.0003)	-6.9146 (-6.5119)
ELUMO(eV)	-2.5935 (-2.2569)	-3.0694 (-2.6433)	-1.5698 (-1.0033)	-3.2161 (-2.7023)
Eg(eV)	3.6038 (4.0430)	3.2471 (3.5113)	5.4564 (5.9970)	3.6985 (3.8096)
Fermi level (eV)	-4.3954 (-4.2784)	-4.6930 (-4.3990)	-4.2980 (-4.0018)	-5.0654 (-4.6071)
Hardness (eV)	1.8019 (2.0215)	1.6236 (1.7557)	2.7282 (2.9985)	1.8493 (1.9048)
Softness (1/eV)	0.2775 (0.2473)	0.3080 (0.2848)	0.1833 (0.1668)	0.2704 (0.2625)
Chemical potential (eV)	-4.3954 (-4.2784)	-4.6930 (-4.3990)	-4.2980 (-4.0018)	-5.0654 (-4.6071)
Electrophilicity index (eV)	5.3609 (4.5275)	7.7824 (5.5108)	3.3855 (2.6704)	6.9372 (5.5715)
DM (Debye)	2.7098 (3.8107)	7.2774 (9.2743)	6.3482 (7.7125)	1.0255 (1.9339)
Polarizability (a.u.)	390.9723 (580.1210)	726.7756 (1409.0643)	257.6080 (377.4406)	515.5046 (961.5546)

Adsorption of VLA on NCs alters the electronic characteristics of both the nanocages and VLA (tables 1 and 3). The electronic and chemical features of nanocages and complexes were investigated using the value of dipole moment (DM). Significant changes in values are detected after the adsorption process. The DM of isolated nanocages was zero due to symmetry, but it increased after adsorption. The DM values in VLA-NCs are varying from 1.0255 (BP-VLA) to 7.2774 (AIP-VLA) Debye. The global reactivity values were crucial for reactivity and stability of VLA, nanocages and nanocages-VLA complexes. Hardness decreased in VLA-NCS, indicating higher reactivity than that of NCs, allowing for more VLA to be adsorbed (tables 1 and 3). As a result, the decrease in hardness was followed by an increase in

softness and chemical potential. Chemical potential for AlN, AlP, BN and BP NCs changed from -4.8504 to -4.3954, -5.1221 to -4.6930, -4.4822 to -4.2980 and -5.0939 to -5.0654 eV, after adsorption. The highest and the least values of chemical potential shift caused by complexation belong to AlN (0.4550 eV) and BP (0.0285 eV). The electrophilicity index measures the fragments' capacity to receive electrons [36]. Except for BP, the electrophilicity index increased with VLA adsorption resulting with a higher tendency to accept electrons. The complexes HOMO plots revealed a higher density of electrons around nanocages except AlP while LUMO is over the cages except BN (Fig.4).

Adsorption of VLA onto NCs caused small modifications in FMOs energies. Energies of HOMO, LUMO and E_g for AlN-VLA (AlP-VLA) and BN-VLA (BP-VLA) systems were calculated -6.1973, -2.5935, 3.6038 (and -6.3165, -3.0694, 3.2471) and -7.0262, -1.5698, 5.4564 (-6.9146, -3.2161, 3.6985) respectively. E_g values of all nanocage-VLA systems were lowered after adsorption, increases conductivity which is suitable for an electrochemical biosensor for VLA [37, 38]. The most reactive sites of VLA (Fig.1) and VLA-NCs (Fig.5) are identified as favourable charge transfer and interactions in the adsorption process which is supported by the chemical descriptors and Mulliken charge values. The adsorption energies of VLA onto AlN, AlP, BN and BP NCs were calculated -144.14, -109.71, -105.22 and -84.96 kcal/mol at the optimum distances. The large negative E_{ads} for VLA adsorption suggested a chemisorption.

The DOS plots (Fig.S1) showed how adsorption modifies the electronic characteristics of the nanocages, which may be utilized to estimate their sensitivity to the VLA. The VLA-NCs interaction results in new energy levels near to Fermi level and resulted in low E_g values (Fig.S1). The ΔE_g s are 1.0516, 0.1426, 1.2980 and 0.0337 for complexation of Al/B-N/P. It can be inferred that for the complexation of BN and BP, the maximum and lowest changes in E_g was observed [39, 40]. Because E_g is a key element in determining a materials electrical conductivity, the BN system is expected to produce more changes in conductivity after complexation. A decrease in E_g produces larger electrical conductivity: $\sigma \propto \exp(-E_g/2KT)$ [41]. These findings clearly show that while AlN and AlP are strong adsorbents for VLA, but they are not the greatest options for making a VLA sensor. However, while BN is not the best adsorbent for VLA, it is quite sensitive to it. The findings also suggest that BP is a viable candidate for use as a VLA sensor.

Conjugated structures' thermodynamic properties were also investigated to ensure their thermal stability. Reaction is endothermic/exothermic if $\Delta H > / < 0$ and ΔG tells us whether the VLA and MCs have a spontaneous interaction ($\Delta G < 0$) or not ($\Delta G > 0$). The ΔG and ΔH are given as [42, 43]: $\Delta U = U_{MC-VLA} - U_{MC} - U_{VLA}$, where U is the Gibbs free energy (G) and enthalpy (H). In the adsorption behavior of the VLA-MC conjugated structures, VLA interacts with MCs, maintaining distances of 1.7992, 2.8629 (O to Al and O to N) for VLA-AlN, 1.9220, 2.2209 (O to Al and OH to P) for VLA-AlP, 1.5602, 2.5486 (O to B and OH to N) for VLA-BN and 3.6114, 3.8407, 2.6434 Å (O to P, OH to B, and OH to P) for VLA-BP systems. The adsorption energies are highest for all systems except BP-VLA. Furthermore, significant differences in thermodynamic properties were identified for nanocages and the complexes MCs (table 4). The negative values of the above suggest exothermic, spontaneous and thermodynamically ordered interactions. The

frequencies of all systems are positive, indicating that the examined VLA-MC clusters studied occur naturally [44-48].

Table 4.1. Thermochemical (Thermodynamic) quantities

Compounds	$\Delta E/\text{Hartree}$	$\Delta H/\text{Hartree}$	$\Delta G/\text{Hartree}$	$S/\text{cal/molK}$
VLA	-464.713963	-464.700517	-464.754008	112.581
$\text{Al}_{12}\text{N}_{12}$	-3567.559815	-3567.538483	-3567.604394	138.720
$\text{Al}_{12}\text{P}_{12}$	-7006.756850	-7006.722940	-7006.816434	196.774
$\text{B}_{12}\text{N}_{12}$	-956.212430	-956.201377	-956.247316	96.688
$\text{B}_{12}\text{P}_{12}$	-4394.912764	-4394.889848	-4394.956779	140.869
Gaseous phase				
VLA- $\text{Al}_{12}\text{N}_{12}$	-4032.502568	-4032.467233	-4032.567416	210.853
VLA- $\text{Al}_{12}\text{P}_{12}$	-7471.643894	-7471.596248	-7471.722815	266.384
VLA- $\text{B}_{12}\text{N}_{12}$	-1421.093560	-1421.069040	-1421.147595	165.333
VLAB $_{12}\text{P}_{12}$	-4859.761784	-4859.723918	-4859.835292	234.407
Water (solvent)				
VLA- $\text{Al}_{12}\text{N}_{12}$	-4032.561110	-4032.527040	-4032.621532	198.875
VLA- $\text{Al}_{12}\text{P}_{12}$	-7471.682466	-7471.637230	-7471.757034	252.149
VLA- $\text{B}_{12}\text{N}_{12}$	-1421.123953	-1421.100070	-1421.175654	159.080
VLAB $_{12}\text{P}_{12}$	-4859.783702	-4859.747681	-4859.849936	215.214

Table 4.2. Changes of the thermochemical quantities

Compounds	$\Delta E/\text{kcal/mol}$	$\Delta H/\text{kcal/mol}$	$\Delta G/\text{kcal/mol}$	$S/\text{cal/molK}$
Gaseous phase				
VLA-Al ₁₂ N ₁₂	-143.57	-143.22	-131.16	-40.448
VLA-Al ₁₂ P ₁₂	-108.61	-108.43	-95.62	-42.971
VLA-B ₁₂ N ₁₂	-104.90	-104.89	-91.79	-43.936
VLAB ₁₂ P ₁₂	-84.75	-83.81	-78.13	-19.043
Water (solvent)				
VLA-Al ₁₂ N ₁₂	-180.30	-180.75	-165.12	-52.426
VLA-Al ₁₂ P ₁₂	-132.81	-134.14	-117.09	-57.206
VLA-B ₁₂ N ₁₂	-123.97	-124.36	-109.39	-50.189
VLAB ₁₂ P ₁₂	-98.50	-98.72	-87.32	-38.236

Solvation energies

In solution phase, the total energy values of nanocage-VLA are higher than that in the gaseous phase. This shows that the examined complex's stability is higher in the solution phase than in the gas phase. The solvation energy $SFE = E_{\text{solvent}} - E_{\text{gas}}$. The solvation energies are -179.23, -131.66, -122.48 and -98.00 kcal/mol for Al/B-N/P with VLA systems. For all systems in solvent water, the thermodynamic parameter changes are negative showing the processes as spontaneous and exothermic (table 4). In solution phase, the DM values (table 3) of the complex increase, which is due to long range interactions of the solvent with the solute molecule. In solution phase, the complex's polarizability values are higher and the stability of HOMO and LUMO rises and the high energy gap indicates that energy is transferred efficiently between them. The E_g value in solution phase increases as compared to the gaseous phase which reveals that the nanocages are set to share electrons (table 3). The ΔE_g of VLA-MCs conjugated structures in solvents was also calculated as 0.6124/0.1216/0.7574/0.0774 for VLA-AlN/AIP/BN/BP and discussed in order to nominate an electrical sensor for the VLA. In VLA-MCs clusters energy gap increases in all solvents. It means the nanocages are good sensors as supported by its solvation or adsorption energies. This is also evident from the Raman spectra (Fig.S2) in which in the finger print regions maximum enhancements are for VLA-MCs clusters due to SERS effects [44, 49]. Most of the modes are enhanced in complexes due to the interaction between VLA and nanocages.

Conclusion

DFT computations were used to study adsorption of valproic acid on Al/B-N/P nanocages. The chemical descriptors and electronic features are modified due to the adsorption process. The drug was attached to

the nanocages via the COOH groups' oxygen and hydrogen atoms with reasonable adsorption energies. The exothermic nature of process was demonstrated by negative adsorption energies and thermodynamic parameters. The adsorption energies are -144.14, -109.71, -105.22, -84.96 and the solvation energies in water are -179.23, -131.66, -122.48 and -98.00 kcal/mol for VLA in Al/B-N/P nanocages. Most reactive sites are identified which are suitable for adsorption and charge transfer.

Declarations

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Author contribution

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Y.Shyma Mary: Manuscript preparation, conceiving the problem and data analysis and correction

Data availability: The supplementary information files include additional materials

Code availability: No new codes have been created. Existing codes were utilized and quoted correctly

Conflict of interest The authors declare no competing interests

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Figures

Figure 1

(a) Optimized geometry of VLA (b) FMO plots (c) MEP plot

Figure 2

Optimized geometries, FMO plots and MEP plots of (a) Al₁₂N₁₂ (b) Al₁₂P₁₂ (c) B₁₂N₁₂ (d) B₁₂P₁₂

Figure 3

Optimized geometries of (a) VLA-Al₁₂N₁₂ (b) VLA-Al₁₂P₁₂ (c) VLA-B₁₂N₁₂ (d) VLA-B₁₂P₁₂

Figure 4

HOMO-LUMO plots of (a) VLA-Al₁₂N₁₂ (b) VLA-Al₁₂P₁₂ (c) VLA-B₁₂N₁₂ (d) VLA-B₁₂P₁₂

Figure 5

MEP plots of (a) VLA-Al₁₂N₁₂ (b) VLA-Al₁₂P₁₂ (c) VLA-B₁₂N₁₂ (d) VLA-B₁₂P₁₂

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