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Structural and Electronic Properties of Theophylline- InP Diamantane Drug Carrier

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Abstract

Modeling and simulation of nanostructure parameters of Theophylline bound with indium phosphide in diamantane structure have been performed with Gaussian 09 program. Density functional theory with hybrid B3LYP/3-21 basis sets was used to investigate the electronic and structural properties for Theophylline bound with InP diamantane nanocrystal as drug carrier. The optimized structures, total energies, energy gaps, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) energy, ionization potentials, electron affinities, chemical potential, global hardness, softness, and electrophilicity index have been investigated. Molecule has the smallest energy gap and the largest value of electrophilicity index in which this indicates that this molecule is more reactive than the others and has large chance to interact with the surrounding species in comparison with the other original Theophylline drug structure. A measure of molecular electrophilicity depends on both the chemical potential and the chemical hardness. The study suggests that the electrophilicity equalization principle is most likely to be a valid theoretical proposition, similar in nature to the electronegativity and hardness equalization principle. Indium Phosphide diamantane nanocrystal and its uses in drug-delivery are also discussed.

Keywords: Density functional theory; Indium phosphide diamondoid; Drug-delivery; Theophylline; Energy gap.

1. Introduction

Theophylline is a methylxanthine drug used in therapy for respiratory diseases such as asthma.

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The main actions of theophylline involve: relaxing bronchial smooth muscle, increasing heart muscle contractility and efficiency, increasing heart rate, increasing blood pressure, chronic obstructive pulmonary disease (COPD), and asthma. It is not known how theophylline causes bronchodilatation in asthmatics. Theophylline inhibits phosphodiesterase enzyme and increases cellular cAMP levels. The concentration of theophylline that inhibits most phosphodiesterases is higher than the therapeutic range, but there is some evidence that a subtype of the enzyme (perhaps type 4 isoform) in airway smooth muscle is more sensitive to the drug [1].

Nanocrystals of the group III-V in periodic table exhibited better optical properties for applications in areas such as biology and medicine. The presence of covalent bonds, little toxicity to the environment, specific features of excitation, radiative emission

taking place in the visible and near IR range, resistance to degradation, high extinction coefficients, as well as the great possibility of bio-conjugation, make the III-V nanocrystals ideal candidates for the development of new luminescent biomarkers. At present, indium phosphide (InP) is one of the most promising compounds in this context [2].

Diamondoids show unique physicochemical properties due to their exceptional atomic arrangements. It is demonstrated that due to their six or more linking groups diamondoids have found major applications as templates and as molecular building blocks in nanotechnology, drug-delivery and medicine. Adamantane consists of cyclohexane rings in ‘chair’ conformation. The name adamantane is derived from the Greek language word for diamond since its chemical structure is like the three-dimensional diamond subunit as shown in Figure (1) [4]. In fact, adamantane derivatives can act as a central core for such drug systems.

If the drug doesn’t accumulate in its exact sight of action, it would not be able to produce the intended therapeutic effects even by using it at a high concentration. The nanometer size of diamondoid molecules makes them possible to enter living cells while carrying the drug into the cells. Commonly particles with less than 100 nm size can enter the cells, whereas diamondoids are even smaller than 10 nm [3].

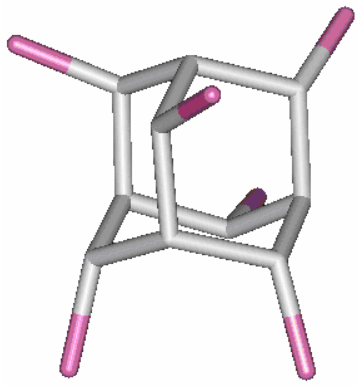


Figure 1: Demonstration of the six linking groups of adamantane [4].

Indium has the atomic number of forty-nine and atomic number of phosphorus is fifteen. Density functional theory (DFT) is better choice to compute stability and electronic properties of nanocrystals which depend on electron density functional and it is suitable to study InP nanocrystals building using diamantane structure. The geometry optimization was performed at the B3LYP density functional theory with the same basis set [8]. Harmonic vibration frequencies were computed at the same level of theory. The hybrid functional B3LYP has shown to be highly successful for calculation the electronic properties such as ionization potential, electron affinity, electronic states and energy gap. The DFT partitions the electronic energy as [9]:

$$E = E_T + E_V + E_J + E_{XC} \qquad (1)$$

where E_T, E_V, and E_J are the electronic kinetic energy, the electron nuclear attraction and the electron-electron repulsion terms respectively. The electron correlation is taken into account in DFT via the exchange correlation term E_{XC}, which includes the exchange energy arising from the anti-symmetry of the quantum mechanical wave function and the dynamic correlation in the motion of individual electrons; it makes DFT dominant over the conventional Hartree-Fock procedure [10].

The geometry optimized structures in Figure (2) are obtained without any symmetry restriction, and vibration analysis for each structure does not yield any imaginary frequencies, which indicates that the structure of each molecule corresponds to a local minimum on the potential energy surface [10].

In this investigation, ionization potential IP and the electron affinity EA are calculated depending on the difference between the total energies for the ground state of a molecule and for the ground state of the appropriate ion. Variance of energies from correlated quantum mechanical techniques gave very accurate results [11].

The ionization potential is calculated in present work as the energy difference between the energy of the molecule derived from electron-transfer (radical cation) and the respective neutral molecule [11]:

$$IP = E_{cation} - E_n \qquad (2)$$

The EA was computed as the energy difference between the neutral molecule and the anion molecule:

$$EA = E_n - E_{anion} \qquad (3)$$

Within the framework of the density functional theory (DFT), one of the global quantities is the chemical potential (ℵ), which measures the escaping tendency of an electronic cloud, and equals [12]:

$$\kappa \approx -\chi = -\frac{(IP + EA)}{2} \qquad (4)$$

The theoretical definition of chemical hardness has been provided by the density functional theory as the

second derivative of electronic energy with respect to the number of electrons N, for a constant external potential *v(r)* and the finite difference approximation to chemical hardness gives [12]:

$$\eta = (IP - EA)/2 \qquad (5)$$

And the softness is given as:

$$S = \frac{1}{2\eta} = \left(\frac{\partial^2 N}{\partial E^2}\right)_{v(r)} = \left(\frac{\partial N}{\partial \mu}\right)_{v(r)} \qquad (6)$$

Electrophilicity index measures the stabilization in energy when the system acquires an additional electronic charge from the environment. Electrophilic index (ω) is defined as [13]:

$$\omega = \frac{\kappa^2}{2\eta} \qquad (7)$$

Electronegativity squared divided by hardness measures the electrophilic power of a ligand, its propensity to "soak up" electrons, so to speak. The charge transfer process is energetically favorable. It was proposed that ω as the measure of electrophilicity of the ligand. In view of the analogy between equation (7) and the equation, power $\equiv W = V^2/R$ in classical electricity, one may think of ω as a sort of "electrophilic power" [13].

A molecule can be theoretically dissected into a Lewis acid and a Lewis base, and the formation of the molecule can be conceived as a reaction between an acid and a base or between an electrophile and a nucleophile. Electrophilicity is the intrinsic structural property of being an electrophile. In general, the electrophiles are electron lovers or electron deficient and hence prefer to accept electrons and form bonds with nucleophiles. Thus electrophilicity is a useful structural depicter of reactivity and is frequently used in the analysis of the chemical reactivity of molecules. Electrophilicity physically means that it simultaneously encompasses both the properties of the electrophile to acquire an additional electronic charge driven by μ^2 and the resistance of the system to exchange electronic charge with the environment described by η [14].

It is anticipated that ω should be related to EA, because both ω and EA measure the capability of an agent to accept electrons. However, EA reflects the capability of accepting only one electron from the environment, whereas the electrophilicity index ω measures the energy lowering of a ligand due to maximal electron flow between donor and acceptor. The electrophilicity index depends not only on EA, but also on IP, and ω differs only by a factor of 2 within the two models, having similar forms within different models. EA and ω are related; yet they are not equal [13].

2. Materials and methods

All the computational studies were carried out using the density functional theory (DFT) implemented in the Gaussian 09W suite of programs. Gaussian 09 is generally referred to as an *Ab*-initio electronic structure

program, while 09 referred to year 2009. Gaussian, a commercial quantum chemical software package from Gaussian incorporation is considered by many to be the industry standard in the area of molecular modeling and computational chemistry.

Gaussian is capable of running all of the major methods in molecular modeling, including molecular mechanics; *Ab*-initio; semi empirical, and density functional theory (DFT) [5]. The molecular properties of the compounds have been computed by DFT using the standard 3-21G basis set. In the DFT calculations the Lee, Yang and Parr correlation functional [6] is used together with Becke's three parameters exchange functional B3LYP[7]. Conformational analysis of the molecules has been performed to have an idea about the lowest energy structures of the species.

3. Results and discussion

The optimized structure parameters of InP diamantane nanocrystal calculated by DFT-B3LYP levels with the 3-21G basis set are in accordance with the atom numbering scheme given in Figure 2. From the simulation values, it can be found that most of the optimized values are slightly larger than the experimental values, due to the simulation calculations belong to isolated molecules in gaseous phase and the experimental results belong to molecules in solid state.

Figure (2) shows the geometric structures and atomic numbering of the neutral InP diamantane nanocrystal (atoms in the molecule are numbered according to their order in the molecule specification section of the input). Figure (3) shows the optimized structure of theophylline-InP diamantane with B3LYP/3-21G method and this is a good agreement with reference [15]. It can be noticed from Figure (4) that the most dense bond length lays at about 1.44 Å for (P-H) bond and the other densities are at 1.8 Å for (In-H) bond, 2.6 and 2.7 Å for (In-P) bond. It can be noticed from Figure (5) that the most dense bond length lies at about 1.44 Å for (P-H) bond and the other densities are at 1.8 Aº for (In-H) bond, 2.6 and 2.7 Aº for (In-P) bond as that from Figure (4) with an additional bond desity equal to 1.1 for (C-H) bond. The most dense angle 110º which is approximately equal to 109.5º of tetrahedral angle in zinc blende structure as it is shown in Figure (6). The distribution shows a narrow range around this angle 109.5º with the highest peak shifted 0.5º from this value. This is due to the effect of surface reconstruction that has an effect on all the atoms in InP diamantane where the atoms are bonded to H – atoms. In Figure (7) it can be seen that the most dense tetrahedral angle at approximately 110º and this was rational with 109.5º of tetrahedral angle structure.

Table (1) shows the values of the total energy and electronic states for the analyzed structures and the energy gap (of the studied nanocrystals). The final total energy of the product is the collection of total energy of all small atoms which build the product nanocrystal. Results of Table (1) can be explained based on the principle of Heisenberg ($\Delta E \cdot \Delta t \geq \hbar$) as the outer electrons of each atom in the system spend long time in region between atoms bonded according to coulomb's law, which is lead to more minimum in total energy value and that is an indication of high stability of the structure and this is a good agreement with reference [16].

The values of HOMO and LUMO energy levels are negative, that shows neither adding nor removing electrons

from InP diamantane are energetically favorable. This reflects high stability and inertness of the InP diamantane structure which is useful for drug carriers.

The three dimensions plots of the frontier orbitals HOMO, LUMO for InP diamantane are shown in Figures (8) and (9), respectively. It can be seen from Figure (8), that the majority of the molecular orbital density in the HOMO at one side and LUMO orbitals in the other side of the structure. The energy of HOMO is often associated with the electron-donating ability of a molecule; high values of E_{HOMO} are likely to indicate a tendency of the molecule to donate electrons to appropriate acceptor molecules with low energy and empty molecular orbital. Therefore, the energy of LUMO indicates the ability of the molecule to accept electrons [15]. After conjugation of Theophylline with InP diamantane, the HOMO-LUMO energy of molecules is lower than that of the original theophylline molecule, with decreasing energy gap. Thus electrons can be easily excited from the ground state.

It can be seen from Figure (9), that the majority of the molecular orbital density in HOMO orbitals is delocalized along the C-C and C-N backbone, i.e. the electronic clouds of these orbitals are localized on the purine structure of theophylline drug and not on the InP diamantane carrier while the LUMO orbitals are delocalized on the far side of InP diamantane as it was shown from Figure (9).

Electronegativity, Hardness, Softness and Electrophilicity Index for InP Diamantane nanocrystal, Theophylline, and with InP nanocrystal using B3LYP/3-21G Energy-Vertical Method, are shown in Figures (10), (11) and (12).

The properties that are displayed in Figures (10), (11) and (12) for each property are computed by employing the difference between the total energies of the neutral InP diamantane and the ions (charge equal -1 or +1) of InP diamantane.

The ionization potential for the Theophylline -InP diamantane is higher than that for theophylline drug molecule; this indicates that the INP theophylline molecules need more energy to become cation comparing with theophylline molecule alone. As it was shown from Figures (10), (11) and (12), the resulting Theophylline-InP diamantane structure is highly reactive because of its tendency to capture electrons from environment and this is due to increasing E.A value, this large number indicates that it forms a stable negative ion; i.e. it is an electrophilic structure.

An important application of electronegativity is the prediction of polar nature of the resulting structure after conjugation with InP diamantane and this is convinced with a lower hardness, a higher softness and much higher electrophilicity index. I.P is small value; this small ionization may make the diamantane useful for high energy particle detectors (cancer cells) or as catalysis for infections. E.A value indicates that binding the drug with the diamantane reduces the ability of the detector affinity for diamantane. Electronegativity value reflects the enable of diamantane to be more reactive toward electron to accept and exchange reactions. The decreasing of hardness is the main feature as a sign for the band gap that goes to be rather soft and lowering the resistance of species to lose an electron.

The behavior of softness shows that binding of the drug give the diamantane more softness. Electrophilicity value indicates that diamantane can be work as electron commentator with infected cells. The changing of different electronic parameters with type of molecule is shown in Figures (11) and (12) below.

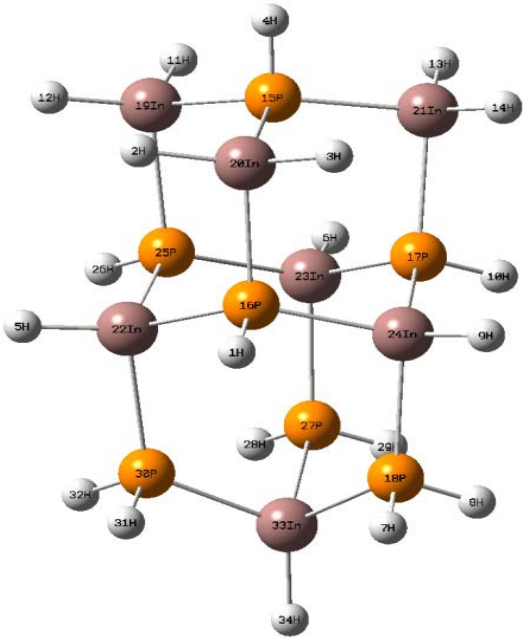


Figure 2: The optimized structure of InP diamantane nanocrystal with B3LYP/3-21G method.

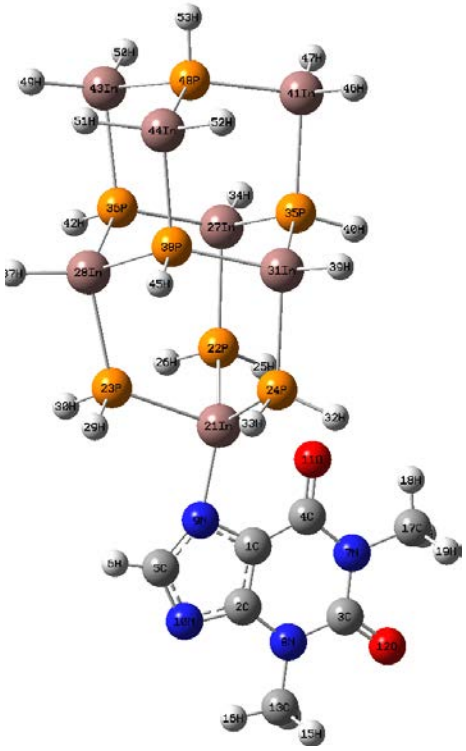


Figure 3: The Optimized Structures of Theophylline with InP Diamantane Nnocrystal using B3LYP/3-21G method.

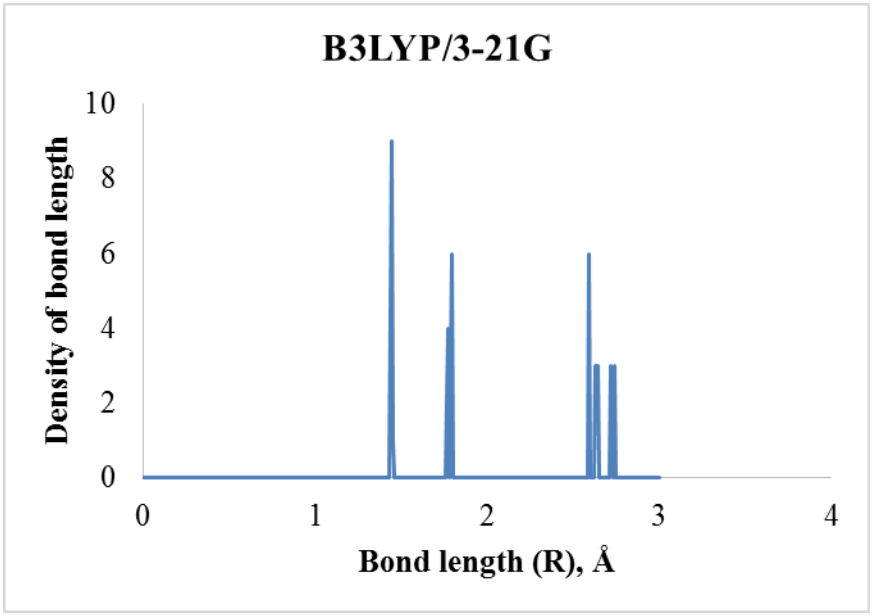


Figure 4: Distribution of Bond lengths (R) in InP Diamantane Structure using B3LYP/3-21G.

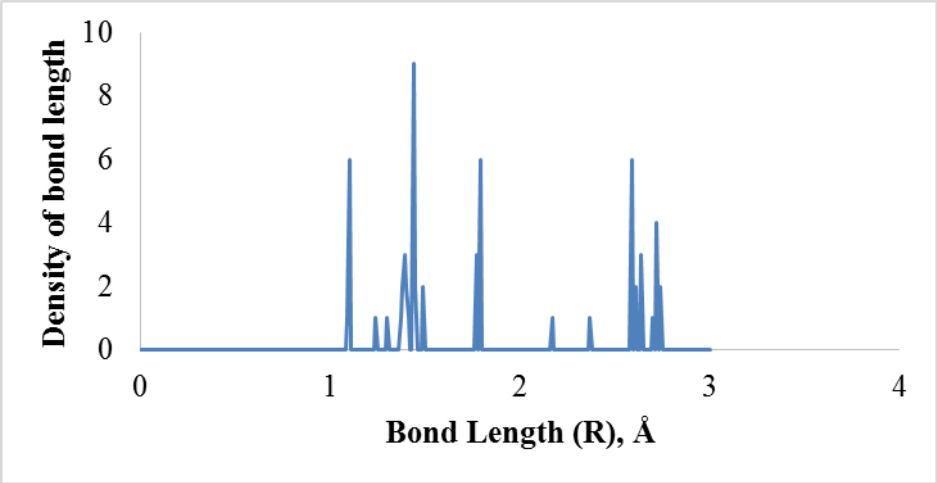


Figure 5: Influence of bond length on density of bond length of Theophylline-InP diamantane.

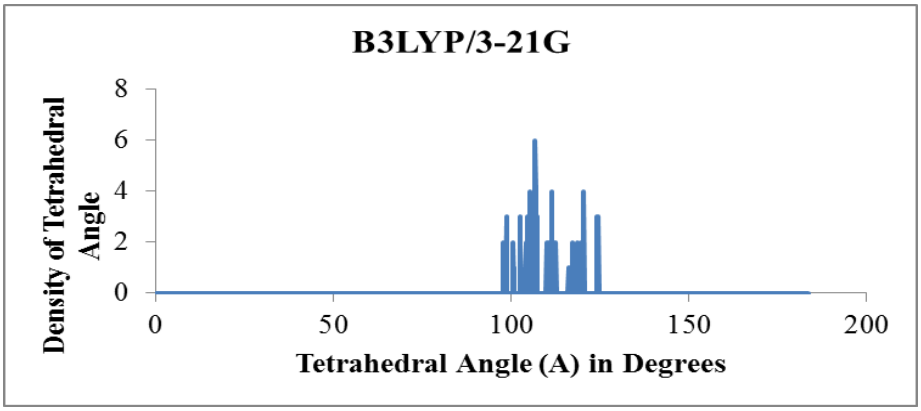


Figure 6: Distribution of Tetrahedral Angles(A) in degree of InP diamantane structure.

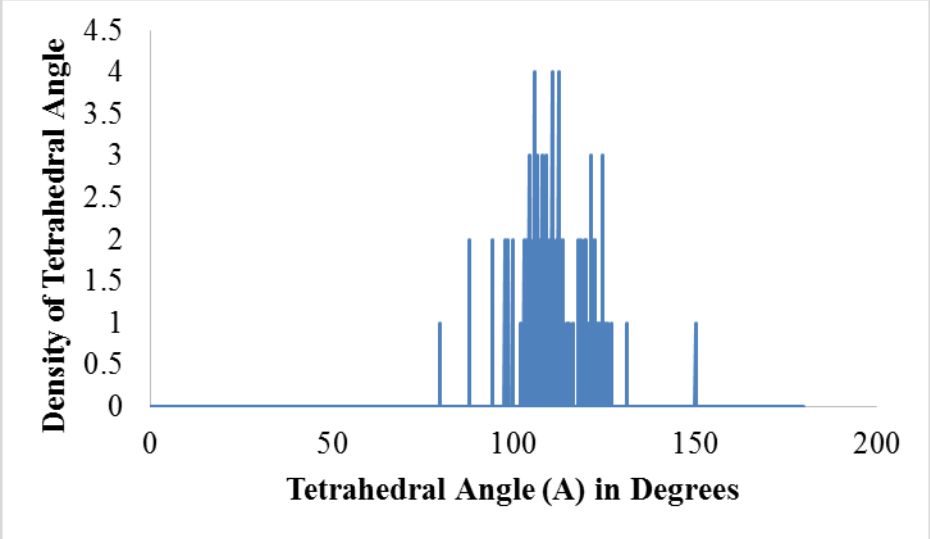
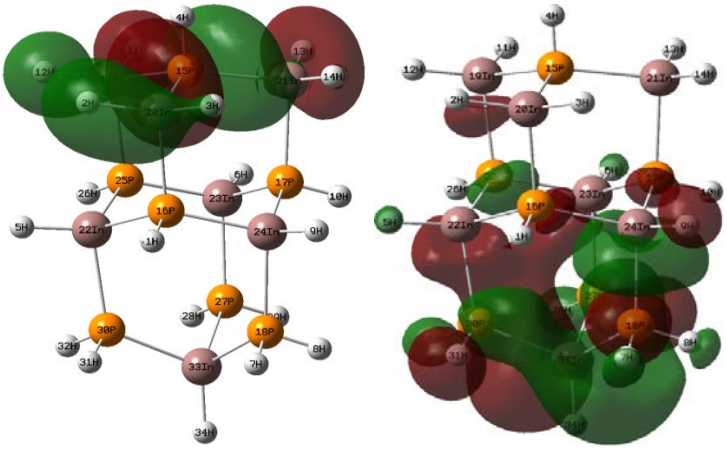


Figure 7: Influence of tetrahedral angle on density of tetrahedral angle of Theophylline-InP diamantane.

Table 1: Total energy, HOMO – LUMO and energy gap for InP diamantane nanocrystal and drug – InP nanocrystal.

Properties	**InP**	**Theophylline**	**Theophylline with InP**
Total energy, SCF	-1.1541155 MeV	-0.017347 MeV.	-1.171432 MeV.
E_{HOMO}	- 6.390 eV	-5.985 eV	-6.2866 eV
E_{LUMO}	-1.537 eV	-0.851 eV	-1.9475 eV
E_{Gap}	4.854 eV	5.134 eV	4.339 eV



(a) (b)

Figure 8: HOMO and LUMO level of InP diamantane nanocrystal. (a) HOMO (B3LYP/3-21G). (b) LUMO (B3LYP/3-21G)

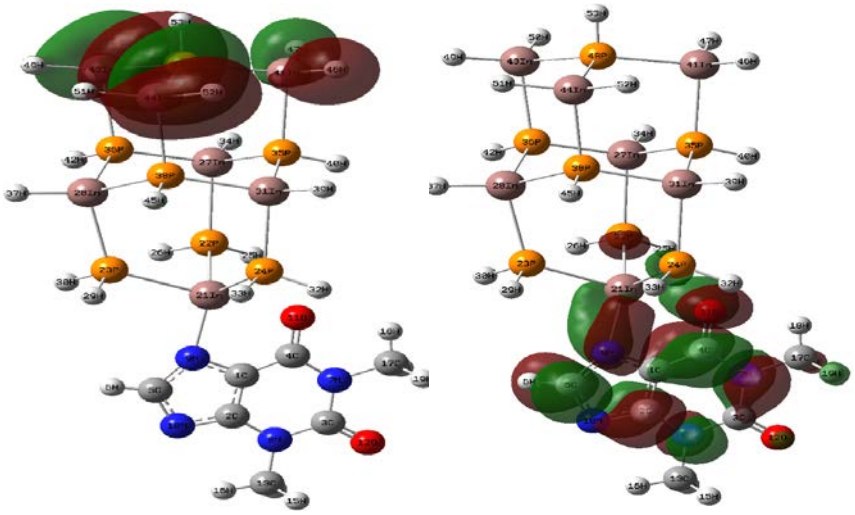


Figure 9: HOMO (left) and LUMO (right) levels of Theophylline bound with InP diamantane.

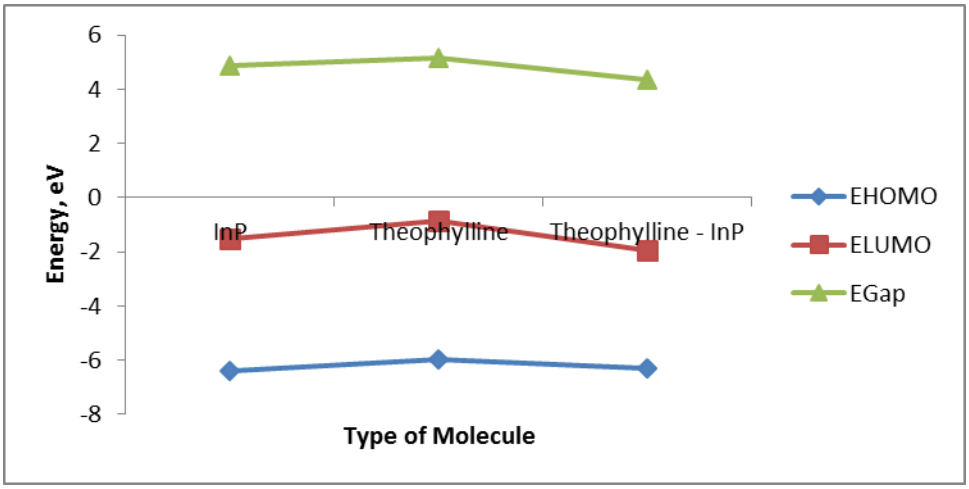


Figure 10: Relation of energy with type of molecule.

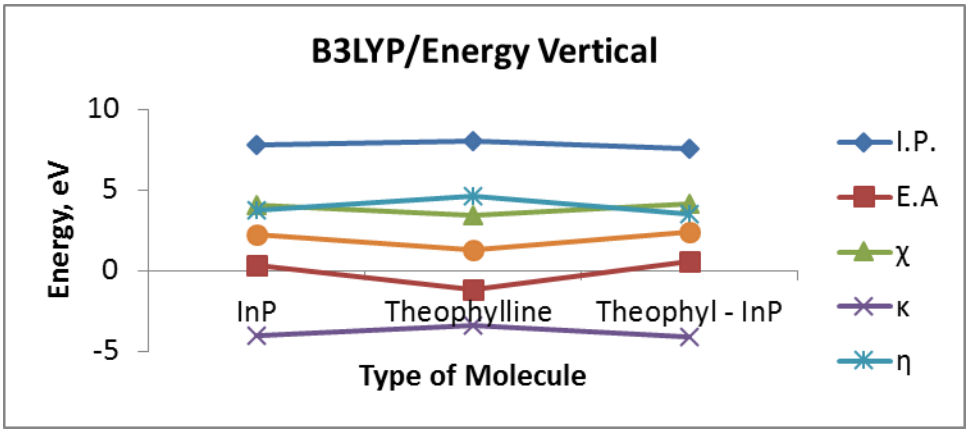


Figure 11: Effect of InP binding on the original Theophylline molecule with different electronic parameters.

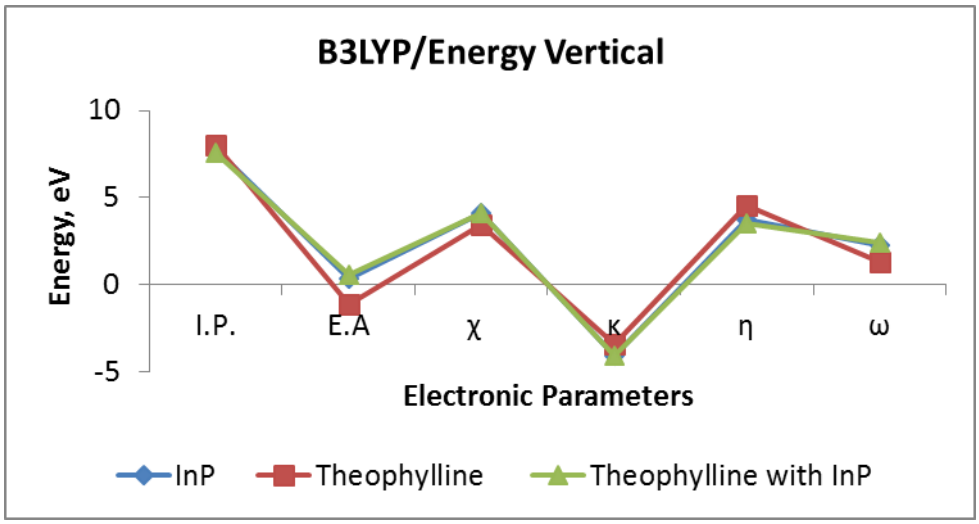


Figure 12: Effect of InP binding on the original Theophylline molecule with different electronic parameters.

4. Conclusions

From this study it can be concluded:

1- InP diamantane- Theophylline nanocrystal carrier can be used to know the mechanism of action for theophylline drug especially when we know that the mechanism of action of theophylline on how its produce bronchdilatation in asthmatic patients and for what enzyme subtype is sensitive to the drug due to the luminescent nature of InP nanocrystals.

2- The total energies for InP diamantane-Theophylline compound causes decreasing in energy and more stable structure .

3- A small energy gap means small excitation energies of manifold of the excited states.

4- Ligand-binding phenomena are of general interest in drug design, and protein and DNA functioning. In many cases partial charge transfer through covalent bonding takes place.

5- The capability of a ligand to accept precisely one electron from a donor is measured by its electron affinity (EA). The strength of an accepter molecule is measured by its electron affinity (EA) which the energy released when adding one electron to LUMO. An accepter must have a high EA.

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