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The formation, structure, and electronic properties of anticancer doxorubicin drug and cucurbit[n]urils complexes, n= 7, 8 (Theoretical Study)

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Abstract : The present theoretical study deals with host-guest complex formation between cucurbit [n] urils,n= 7,8 as a host and doxorubicin as a guest using semi-empirical calculation (PM3 level). In these complexes, the formation of Hydrogen bonding it could be occurred through portal oxygen atoms of cucurbit [n] urils and hydroxyl groups of the drug. The energies of HOMO orbital and LUMO orbital have been calculated for the host- guest complexes and their components. The result of stabilization energy is explained the complex formation.
Key words : PM3, Cucurbit [n]urils, molecular capsules.

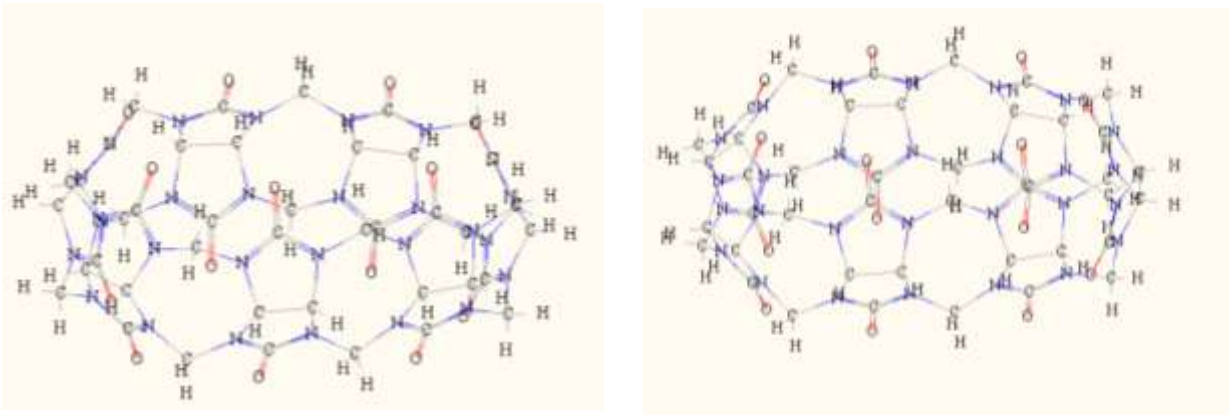
Introduction

In past several decades, the coordination chemistry of cat ions has become well developed, while the chemistry of anion encapsulation is still in its infancy [(1)]. Recently, a new host–guest chemistry of anions is becoming a field of great interest [(2, 3)].Because anions are ubiquitous throughout biological systems [(4)], and they also play important roles in the areas of temptation (or directed self-assembly) catalysis, environmental pollution and so on [(5, 6)].gradually established as versatile host molecules for the inclusion of smaller guest molecules. In several cucurbit uril homologues investigation of fundamental studies for understanding the properties of cucurbit[n] urils is still an essential subject at present[(7)].Cucurbit[n]uril CB[n] (n=5-8) or more are cyclic methylene bridged glycouril oligomers that represent fascinating class of molecules which are composed of a hydrophobic cavity surrounded by hydrophilic portals lined up with the polar uredo carbonyl groups[(8)].Cucurbit[n] uril host molecules have the potential to encapsulate biologically relevant guests and act as drug carriers, drug solubilizes, drug stabilizer, and drug bioavailability enhancers[(4)] . Self-assembled host-guest chemistry has become atopic of strong current interest in super molecules chemistry [(5,6)]. In 1981, The crystal structure of a novel host, cucurbituril(CB[6]) was determined by Freeman and co-workers[(7)], and then, Day and Kim discovered and reported the cucurbituril homologues, cucurbit[*n* = 5,7,8 and10]urils at almost the same time between 1999_2000 [(8)] (here after CB[5], CB[7], CB[8] and CB[10]). Cucurbit[n]urils have two identical dipole carbonyl-fringed portals that can interact with different cations (so called the portal interaction), and have a hydrophobic cavity with various sizes. That permits entrance and exit of organic guests with various sizes. These offer a chance to study new forms of molecular recognition, separation and purification systems, controlled release of drugs, molecule container or catalysis[(9)], adsorbents for wastewater treatment[(10)] and nano materials and super molecular entities. In recent studies of host-guest inclusions with cucurbit[n]urils hosts, the relevant reports to encapsulation involve with those of CB [6] with metal ions there are few detailed studies on the interactions of cucurbit [*n* = 5-8]urils with organic molecules Cucurbit[n] uril have highly symmetrical structures with a hydrophobic cavity, accessible on both sides through two identical carbonyl –rimmed portals

fig 1. They function as molecular containers forming strong non covalent 1:1 as well as 2:1 host-guest inclusion complexes with neutral and positively charged organic molecules [(11)].

The present work is to predict the formation, structure and stability of doxorubcin inside the CB[n] with n = 7, 8 and we avoid n= 5,6 because CB[8] (or sometimes CB[7]) can form ate molecule complex accommodating two aromatic molecules simultaneously[(12)].

To understand the nature of interaction that stabilizes the guest doxorubicin inside the cucurbituril molecule by using the semi empirical method (PM3 level) [(13)] in detail.



CB[8] **Scheme 1** CB[7]

Computational Method:

Geometry optimization of CB[n], n= 7,8 and doxorubicin drug and complexes using semi empirical method (PM3 level) [(13)].All the computations were performed with GAUSSIAN GO9 [(14)] a quantum mechanical program for theoretical computations. Energy minimization and calculation molecular orbital by using semi empirical method (PM3 level) [(13)]. The optimum host molecule position to guest molecule position, it should be obtain to get optimized structure and minimum energy of host- guest complexes formation with using PM3 level. All calculations in this investigation were performed in gas phase .All calculate has down on computer Intel® Core ™ Duo Cup 2.20GHz, 3.46GB of RAM.

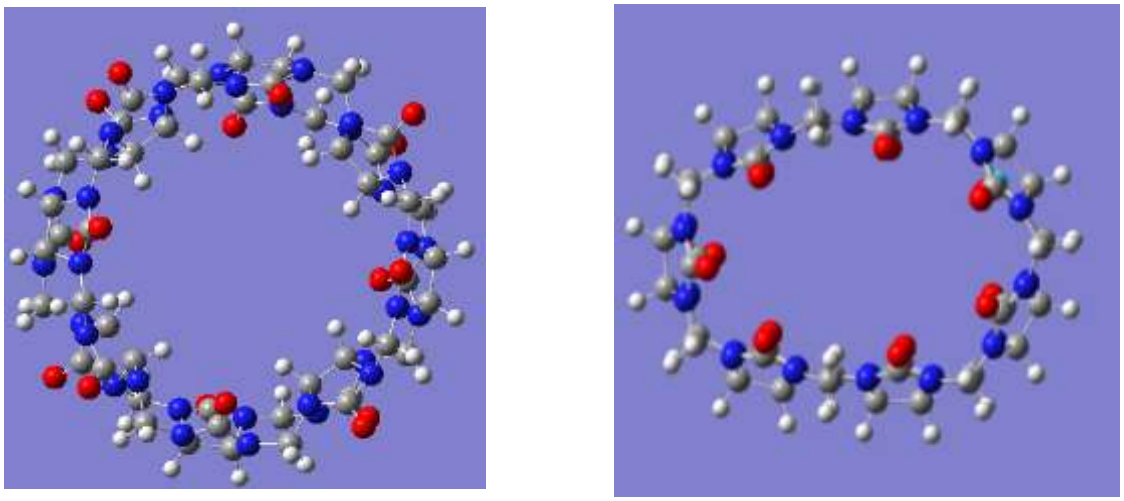
Results and Discussion:

From note the optimization geometry of cucurbit [n], n= 7,8, CB[n] content two main parts:

1. Portals surrounded by oxygen this gives it hydrophilic property.
2. Hydrophobic cavity its container of guests.

Complex between CB[n] and guests formed when hydrogen bonding formed between CB[n] and guests [(15)].

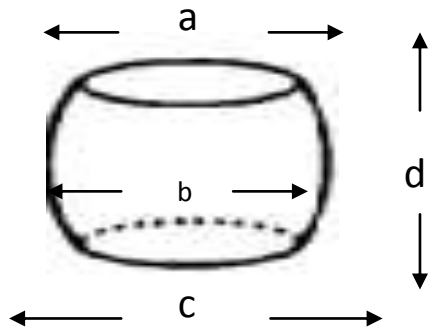
The optimized geometry of cucurbit [n], n= 7, 8 is shown in Figure1 were determined using semi empirical method (PM3 level).



CB[8] **CB [7]**

Figure 1 optimization geometry of cucurbit [n], n= 7 ,8 Color

CB[n], n=7, 8 with cavities different sizes and notably, the diameter of CB[8] is large than CB[7], the C=O and C-N bond distances remain unchanged in the C[7] and CB[8], Diameter of oxygen portal in CB[7] is 7.9663 A^0 and in CB[8] is 11.9406 A^0 while Cavity diameter about 10.6222 A^0 in CB[7] and 11.7714 A^0 in CB[8], The structural parameter for CB[7] and CB[8] shown in Table 1.

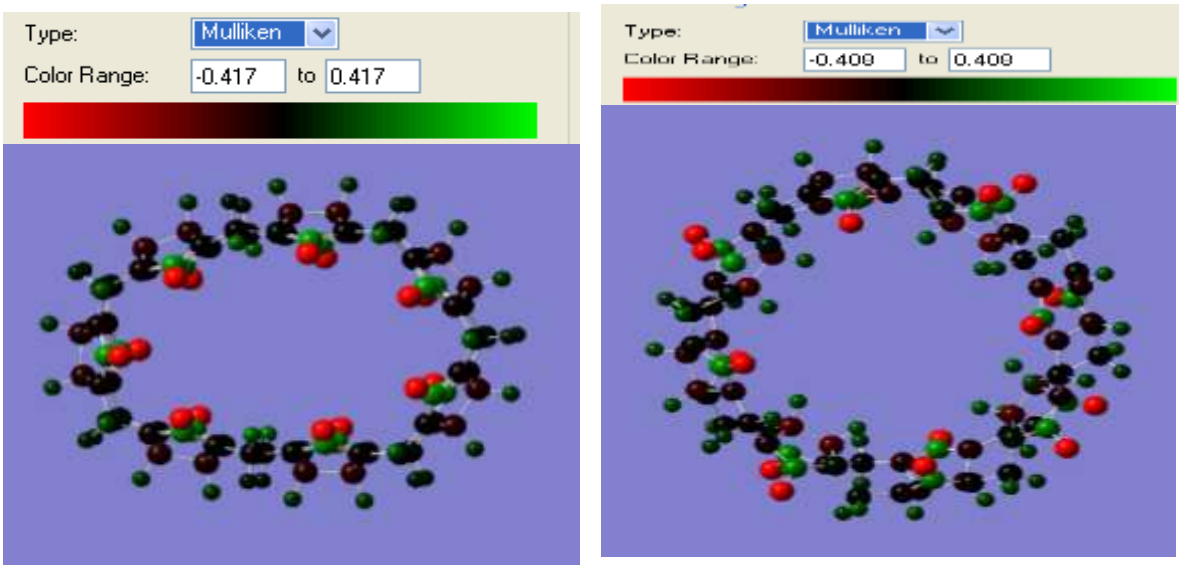


Scheme 2

Table 1. Geometrical parameters of optimized geometrics calculated using semi empirical method (PM3 level).

geometrical parameters	**CB[7]**	**CB[8]**
Diameter of oxygen portal A^0(a)	7.9663	11.9406
Cavity diameter A^0(b)	10.6222	11.7714
height A^0(d)	5.9637	5.7752
Outer diameter A(c)	8.6348	12.1594

The charge distribution on CB[7] and CB[8] was Relative location of negative potential around the carbonyl groups oxygen's; and a gradual loss of negative potential over the molecular, The charge distribution on CB[7] and CB[8] shown in figure 2.



CB[7] **CB[8]**

Figure 2: Charge Distribution for Cucurbit[7] and Cucurbit[8]

The optimized geometry of doxorubicin calculated by semi empirical method (PM3), From noted Conformational features of the tricycles' naphtoquinone (cycle A, B, C) planer conformation because of aromatics properties. While a different relative orientation of the aminosugar moieties was encountered among low energy-conformers, they all were indeed characterized by hydrogen bonds established between the phenols of the C-ring with the carbonyls of the B-ring as previously reported by Bhattacharjee al.and Monteagudo et al. [(16)]. Protonated doxorubicin Conformation gives it positive charge it's lead to attribute to the carbonyl groups that line each end of the cavity of cucurbit[n]uril. The optimized geometry of doxorubicin shown in figure 3.

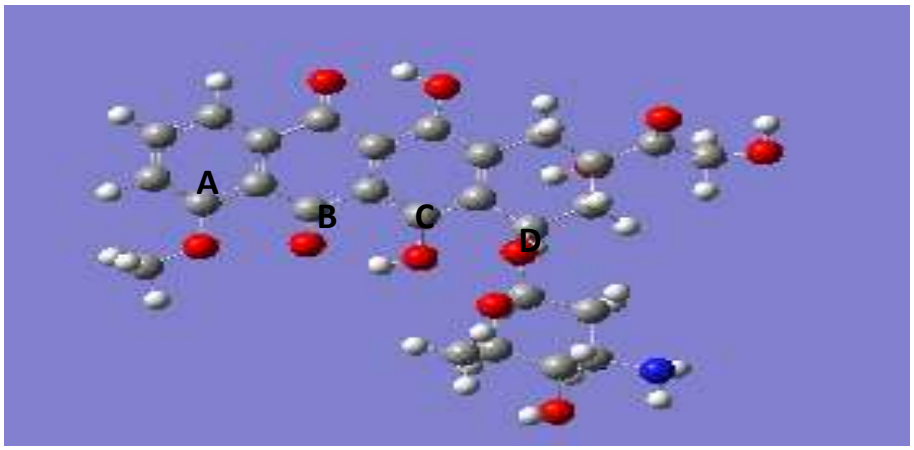


Figure 3 **optimization geometry of doxorbicin Color codes: carbon, gray; nitrogen, blue; oxygen, red.**

Relative location of negative potential around hydroxyl and quinonoid oxygens; and a gradual loss of negative potential over the molecular plane due to the presence and typiorientation of the hydroxyl groups in the phenolic part of the molecules its shown in figure 3 was calculated by PM3 method.

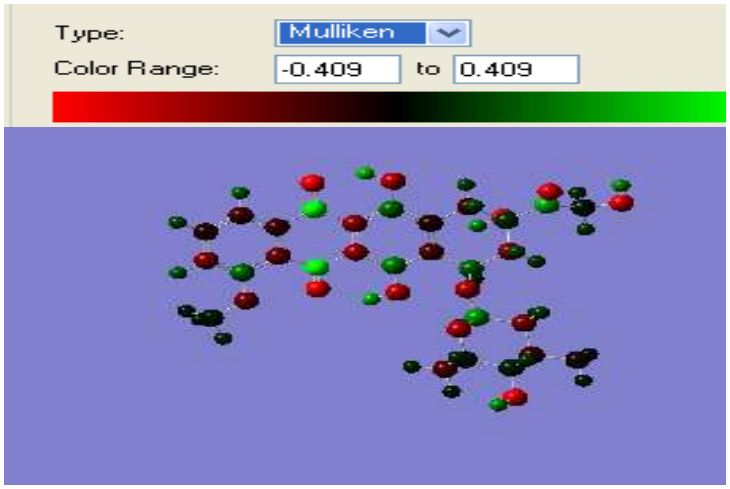


Figure 4 Charge Distributions for Doxorubicin

The geometry parameter was found by calculated the distance between atom placed on the side of the structure, the Width was found by average of summation distance between H-atom on A-ring and H-atom on methyl group on same ring and distance between O-atom in B-ring and O-atom in same ring and distance between H-atom in hydroxyl group on D-ring and H-atom in hydroxyl group in amino sugar on same ring, the length was found by calculated the distance between the H-atom on A-ring and O- atom hydroxyl group on D-ring, shown the parameter in Table 2.

Table 2: PM3 method calculation Selected geometrical parameters for optimized geometrics (in A °) for doxorubicin

Length (A^0)	**Width(A^0)**
14.5489	7.1699

Cucurbit[n]uril play as containers that are capable of binding other molecules within their cavities[17]. Complexes between doxorubicin and cucurbiturils happen when hydrogen bonding happens between doxorubicin and cucurbit[n] urils. thus means the Cavity diameter

Must larger than Width of doxorubicin, when the width of doxorubicin is 7.1699 A^0 that's means CB[7] and CB[8] is suitable to contain drug and conformation complexes. To determine the geometries of the possible CB[7] and CB[8]–doxorubicin complexes, doxorubicin was placed inside the cavity of cucurbit urils, optimization geometry for complexes determined by PM3 method shown in figure 5.

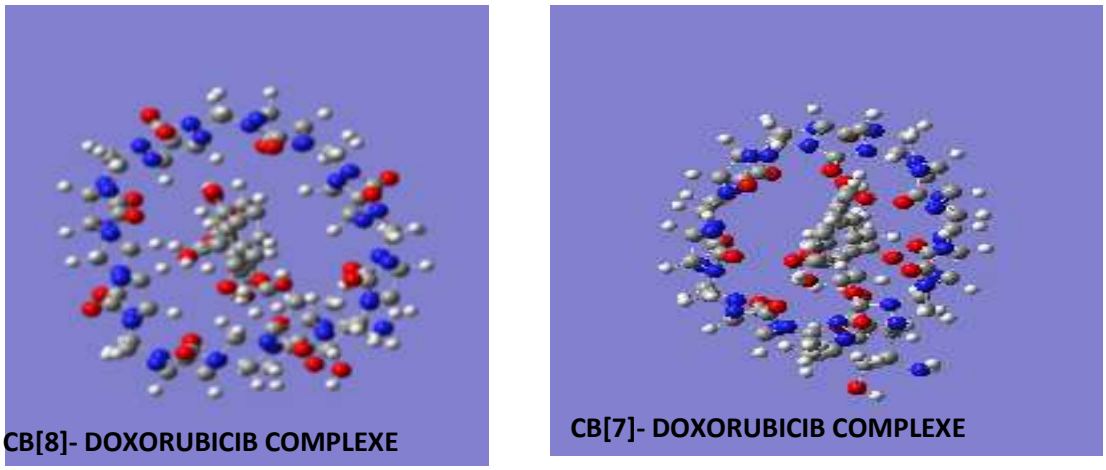


Figure 5 optimization geometry of doxorubicin and cucurbit[n], n= 7,8

To understand the formation and stability of the inclusion complex we have calculation the formation energy for CB [7] and CB [8] with doxorubicin as the host at the PM3 level of theory and the results are provided in table 3. We have defined the formation energy (ΔE) as the energy gained during the formation of inclusion complex from CB[n] and doxorubicin. The negative values of ΔE indicate that there is an energy gain during the formation of the inclusion complex. The smallest value of ΔE for CB [8] shows the stability of the complex. ΔE data in the gas phase predict that the complex formation is favored in CB [7], CB [8].

$E_{\text{Formation of complex}} = E_{\text{complex}} - E_{\text{Components}}$

Table3 Energy (E) and formation energy (ΔE) of doxorubicin- CB[n] and its components

	E kcal/ mol	**ΔE**
Doxorubicin	-390.05562	__
CB[7]	-107.1160	__
CB[8]	-39.0556	__
CB[7]-doxorubicin	-737.6380	-240.1480
CB[8]-doxorubicin	-782.9442	-353.0140

Hydrogen bonding sometimes plays crucial role during recognition, al-though a hydrogen bonding interaction is weaker than an electrostatic interaction. Hydrogen bonding only occur when the functional groups that are interacting are properly oriented. Hydrogen bonding one type of Dipole-Dipole interaction [18]. The next table show dipole moment (is measured of the total polarity of molecule), and total charge on molecules.

Table 4 dipole moment in Debye and total charge in molecules

	Dipole moment(Debye)	**Mullikan charge**
Doxorubicin	7.1513	0
CB[7]	0.6180	0
CB[8]	2.5059	0
CB[7]-doxorubicin	5.2298	0
CB[8]-doxorubicin	11.0360	0

The highest occupied molecular orbital (HOMO) of CB[8]- doxorubicin complex and the lowest unoccupied molecular orbital (LUMO) are shown in figure 5. The HOMO orbital is localized on phenol ring on doxorubicin and the LUMO orbital is localized on the cucurbituril unit in the CB [8]- doxorubicin. For the doxorubicin, the HOMO orbital is observed on the phenol ring and the LUMO orbital observed on naphtoquinone (cycle A, B, C) this show in figure 6.

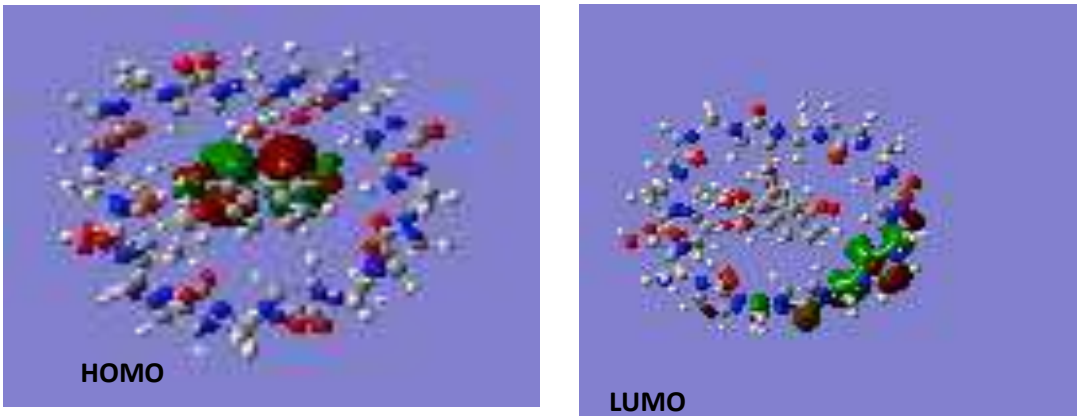


Figure 5. HOMO orbital and LUMO orbital for CB[8]-doxorubicin complex.

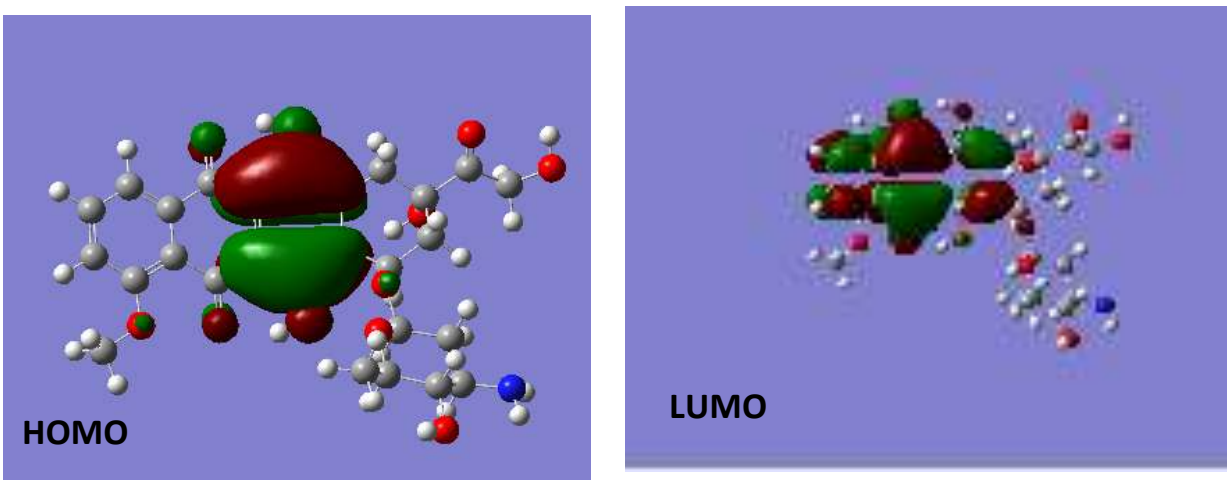


Figure 6 HOMO orbital and LUMO orbital for doxorubicin drug.

ΔE_{Gap}= HOMO energy- LUMO energy for each complex

Table 5: Frontier Orbital Energies (HOMO, LUMO) in e.V calculate by PM3 level.

component	E_{HOMO}, eV	E_{LUMO}, eV
Doxorubicin	-0.39188	-0.04575
CB[7]	-0.3509	-0.0088
CB[8]	-0.3919	-0.0458
Doxorubicin-CB[7]	-0.2930	-0.0190
Doxorubicin-CB[8]	-0.3490	-0.0720

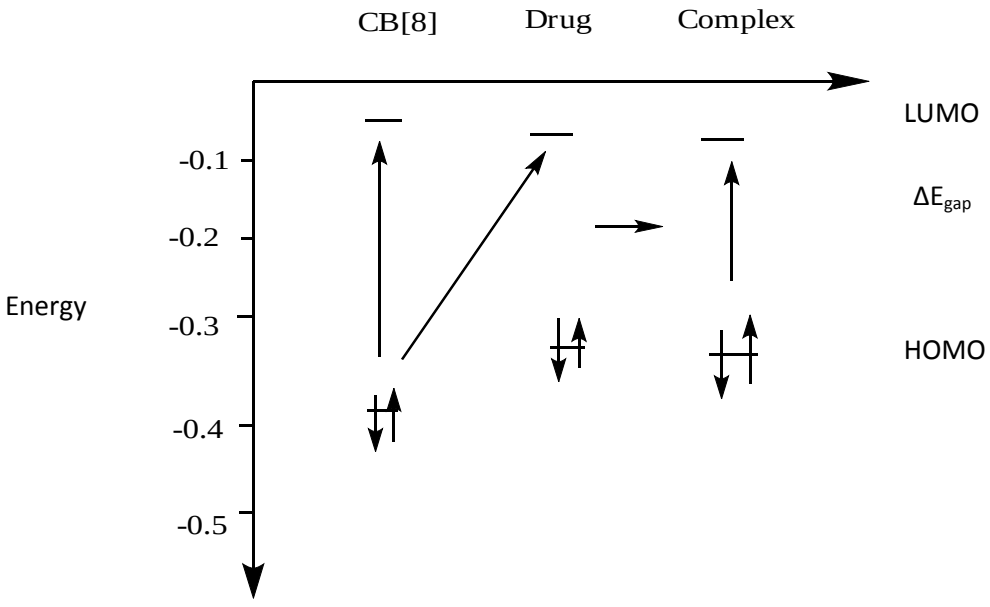


Figure 7 show the correlation diagram for the formation of doxorubicin-CB[8] complex from their components

To understand the conformation of complex we show the LUMO energy of drug is less than LUMO energy of CB[8] that's mean transfer the electron from HOMO orbital of cucurbituril to LUMO orbital of drug.

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