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Calixarene Drug deleivery invistegation of Calixarene compounds with conection by histidine L and D stereochemistry

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Abstract- In this research, Quantum-mechanical calculations were performed at the HF method with the 6-31+G*basis set and at the B3LYP method with the 6-31+G* basis set in the gas phase and five solvents such as water, DMSO, methanol, ethanol and dichloromethane at six temperatures. According to these theoretical results of IR, we extracted thermo chemical parameters such as enthalpy (ΔH Kcal/mol), Gibbs free energy (ΔG Kcal/mol) and entropy (ΔS cal/molK). Important relationship have been found between solvent effect and structure of Calixarens with histidine L and D stereochemistry. Also, nuclear shielding parameters of Calixarene, such as chemical shift isotropic value (σ_{iso}) and the anisotropy shielding (σ_{aniso}, $\Delta\sigma$), have been taken into account using GIAO method at the HF method with the 6-31+G* basis set and at the B3LYP method with the 6-31+G* basis set in the gas phase and in different solvents such as water, DMSO, methanol, ethanol and dichloromethane. The results were revealed that the NMR chemical shielding

parameters are strongly affected by inducing different solvent media. According to these theoretical results,it can be drastically concluded that the dielectric permittivity of the solvent is a key factor that determines the chemical behavior of Calixarene with histidine L and D stereochemistry in solution. Also the natural bond orbital (NBO) analysis has been performed at the six levels in the gas phase and different solvent media which show some important atomic and structural features.

Keywords: Calixarene; IR; thermo chemical parameters; NMR chemical shielding parameters; NBO; gas phase; solvent effect.

Introduction:

Calixarenes are macrocyclic vases which are easily available through the cyclocondensation of parasubstituted phenols with formaldehyde [1, 2]. Calixarenes are widely used as molecular platforms for the construction of specific receptors capable of highly selective recognition between fairly similar substrates. Apparently, the outstanding receptor properties of functional calixarenes make them highly promising materials for sensor technology [3], radioactive waste management [4], pharmaceutical science [5], and analytical application [6–8].

Calixarenes are phenolic metacyclophanes with rigid cone-like structures, which posses an upper rim defined by the para-positions of the aromatic rings and a lower rim defined by oxygen atoms. This conformation of calixarenes allows the formation of complexes with cation, anion, and neutral molecules [9-11] Modified calixarenes, having additional binding sites, both at the lower rim and upper rim, enhance the binding ability of the parent calixarene[12] Various methods for functionalizing calixarenes have been developed and numerous calixarene derivatives have been synthesized during the past 2 decades.[13-18] The binding properties of these molecules appear to be highly dependent upon the nature and number of donor atoms of the calixarene moiety [19-23].

In biological systems, the cooperative action of peptide hydrogen bonds plays an important role in organization, assembly, and molecular recognition processes. On the other hand, specially engineered synthetic peptides are able to assemble into nanotubes or other supramolecular structures or act as hosts for a variety of guest molecules. The attachment of R-amino acids or peptides to the calixarene framework can be achieved through the terminal amino or carboxylic groups.

The macrocyclic ring in calixarenes acts as a molecular backbone to which ligating functional groups are attached. There are many examples however where the ring itself engages in binding such as with its p- basic phenolic cavities to class B cations, to class A cations with the phenolic oxygen atoms or to organic molecules by CH-p or p-p-stacking interactions. The molecular design allows the rational control of binding properties such as complex stability and selectivity. The main design features are:

a) The size of the cavity is large enough to accommodate the metal cation. During complexation, the hydration shell is removed from the cation and substituted by the donor atoms of the ligand.

b) There is a sufficient number of donor atoms in the ligand in order to match the coordination number.

c) The donor atoms are held by the calixarene backbone with limited flexibility in positions suitable to match the shape of the coordination sphere.

d) The 'classical' mechanisms of complexation apply to calixarenes as well, ion exchange or ion pairing, with the difference that now several iononizable, chelation or solvating donor groups are combined within one molecule.

e) Often, synergy is observed if these are different functional groups, e.g. neutral and ionizable.

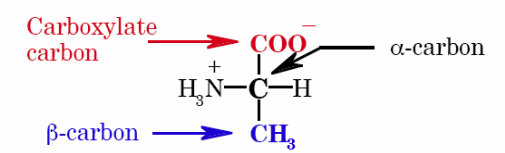
f) Using the macrocyclic backbone, an excess of certain ligating groups can be avoided, thus improving the selectivity. E.g. for a divalent cation two ionizable groups are introduced into calixarene which could hold a maximum of four of them. The remaining two neutral binding groups fill up the coordination sphere.

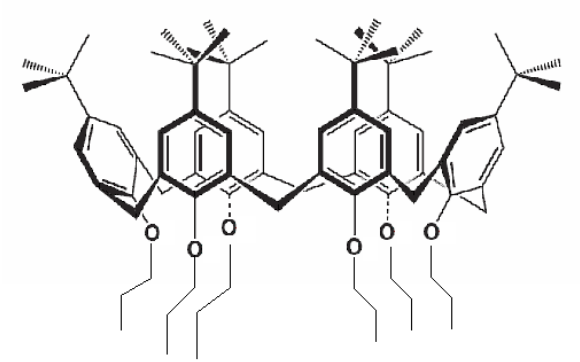
g) There is a possibility to attach chelating moieties onto calixarenes, thus combining the chelate and the macrocyclic effect. However, the chelating groups increase the flexibility of the ligand and may reduce the overall selectivity. Our own approach is therefore the use of short functional groups.

h) Branched alkyl groups are attached to the phenyl rings for high hydrophobicity and to avoid crystallized membrane phases.

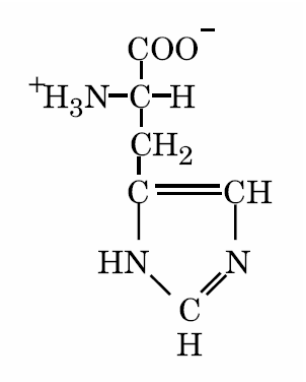
Amino acid structure

Structurally, the standard amino acids (with the exception of glycine) can be considered to be derivatives of alanine. (Note: these amino acids are not synthesized from alanine; instead, looking at the amino acids as alanine derivatives is merely an aid to understanding the structures). The "first" carbon of the amino acid is the carboxylate carbon. The next carbon is called the α-carbon, because it is in the position α to the first carbon. The side chain is then bonded to the α-carbon. The side-chain carbons are given Greek letters in the order β, γ, δ, ε counting away from the α-carbon. Because most amino acids are structurally based on alanine, the modifications to the alanine structure are varying compounds attached to the β -carbon.

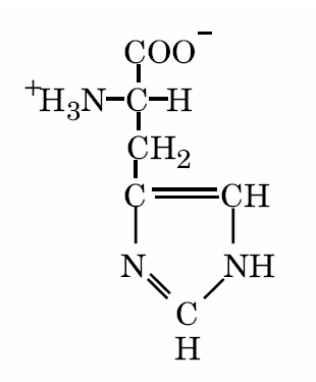




Histidine can also be protonated, but the side-chain pKa is 6.0 and therefore only a very small percentage of the side-chain is protonated at pH 7.4. The pKa of the sidechain is heavily environment dependent, and varies considerably in proteins. (Note: histidine exists in two neutral forms, α and β, shown below. These are generally equivalent structures, with the only difference being the nitrogen that bears a proton, but they exhibit different geometric constraints on hydrogen bonding properties).



α-Histidine (His)



β-Histidine (His)

Under most conditions, a total of six amino acid side-chains can be ionized: aspartate, glutamate, cysteine, histidine, lysine, and arginine. Aspartate, glutamate, and cysteine are ionized and negatively charged when they are deprotonated. Histidine, lysine, and arginine are ionized and positively charged when they are protonated. Of these, aspartate, glutamate, lysine, and arginine are predominantly ionized under physiological conditions, while histidine and cysteine are ionized only in some cases.

Computational Details

IR approach

At first, we have modeled the Calixarenes[6] with ChemDraw package. The Ab initio molecular calculations were carried out using the Gaussian 98 program. Then using Chem3D performs an energy minimization. Geometry optimization in the gas phase and solution for Calixarenes with amino acids compound were performed at the HF level with the 6-31+G* basis set. The enthalpies (ΔH), free energies (ΔG), entropies (ΔS) of Calixarenes with L and D Histidine (His) compound were carried out in solution and gas phase at the six temperatures [24].

Nuclear magnetic resonance approach

The calculations also provide valuable information for exploring the experimental NMR chemical shifts with the molecular geometry and environment. Also NMR chemical shifts are quite sensitive to intermolecular interactions. NMR is based on the quantum mechanical property of nuclei. The chemical shielding refers to the phenomenon which associated with the secondary magnetic field created by the induced motions of the electrons that surrounding the nuclei when in the presence of an applied magnetic field for chemical shielding (CS) tensors, which describes how the size of shielding varies with molecular orientation, we often use the following convention for the three principle component:

$\sigma_{11} \leq \sigma_{22} \leq \sigma_{33}$

The three values of the shielding tensor are frequently expressed as the isotropic value (σ_{iso}), the anisotropy shielding ($\sigma_{aniso,}$ $\Delta\sigma$). In our current study, extensive quantum mechanical calculation of Calixarenes with amino acids compound on ^{1}N, ^{2}C, ^{4}O, ^{5}C, ^{12}C, ^{13}C, ^{14}C, ^{66}O, ^{93}C, ^{94}C and ^{95}C -NMR parameters have been performed in gas phase using Gaussian 98 program [25].

The calculation procedures are as follows. First, the geometries of Benzoic acid, Gallic acid, Vanillic acid and Flavone were fully optimized by DFT and B3LYP functional with 6-31+G*, Gaussian basis set . Also, we calculated NMR chemical shielding tensors data that shown in Table 2.

If $|\sigma_{11} - \sigma_{iso}| \geq |\sigma_{33} - \sigma_{iso}|$, $\Delta\sigma$, Chemical Shift Anisotropy, η, Asymmetry Parameter, Ω, Shielding Tensor Anisotropy for molecule and *k*, slop are shown as below:

$$\Delta\sigma = \sigma_{22} - \frac{\sigma_{22} + \sigma_{33}}{3}$$

$$\eta = \frac{\sigma_{22} + \sigma_{33}}{\delta}$$

$$\delta = \sigma_{11} + \sigma_{iso}$$

but if $\Delta\sigma = \sigma_{33} - \frac{\sigma_{22} + \sigma_{11}}{3}$

$\eta = \frac{\sigma_{22} + \sigma_{11}}{\delta}$

$\delta = \sigma_{33} - \sigma_{iso}$

$\Omega = \sigma_{33} - \sigma_{11}$

$k = \frac{3(\sigma_{iso} - \sigma_{22})}{\Omega}$

Chemical shifts of the considered compounds were calculated at the same level using the Gauge- Included Atomic Orbital (GIAO) approach.

NBO approach

A full NBO analysis is obtained in Gaussian 98. NBO analysis did using one method in gas phase and the output is obtaind for the molecule. The main listing of NBOs, displaying the form and occupancy of the complete set of NBOs that span the input AO space and for each orbital gives the type of orbital and the occupancy. We were extaracted just BD for 2-center bond from NBO-output.

Results and Discussion:

Calixarene connection to the desired amino acid (L and D Histidine (His)) in five different solvents (Water, DMSO, Methanol, Ethanol, Dichloroethane) were investigated. All thermodynamic parameters were calculated. The Gibbs free energy diagram, enthalpy and entropy were drawn in terms of solvent dielectric. Interestingly, the solvent DMSO in all amino acids and in all temperature we see the most value of the Gibbs free energy.

And because ΔG=ΔH-TΔS, This has an impact on energy. However, this also varies in different types of amino acid. Also the Gibbs free energy generated in a low state. In fact, we can Using the methods measurements of solvent and Measuring the dielectric thermodynamic quantities and types of L and D Histidine (His) used in the identification Protein.

As shown in Alanine Table the three values of the shielding tensor are frequently expressed as the isotropic value (σiso), the anisotropy shielding (σaniso, Δσ). In our current study, extensive quantum mechanical calculation of Calixarenes with L and D Histidine (His) compound on 1N, 2C, 4O, 5C, 12C, 13C, 14C, 66O, 93C, 94C and 95C -NMR parameters have been performed in gas phase.

The reason is that the dipole moment and changes isotropic value (σiso), the anisotropy shielding (σaniso, Δσ) in terms atomic charges in connection there. In this section we report and analyze on share of orbitals contribute in the bonds (BD) for the Calixarenes[6] with L and D Histidine (His) compound. Calculations obtain at the HF and B3LYP methods with the 6-31+G* basis set. The answer to this relationship in order to determine the P values of NBO in the hybrid nature of the bonds. This indicates that electrostatic association between the amounts has been said.

aromaticity changes in L and D Histidine (His) bonds and calixaren intended to be taken to examine. The first case of specific actions for each amino acid and its connection with calixaren and The second factor is the recipient of electron and donor electron factors, How can aromaticity be involved in the calixaren rings, and The third factor to consider using calixaren with L and D Histidine (His) in the binding of drug carriers and send them to the target position is.

IR data (Solvent effects on thermochemical parameters)

In this paper the calculations of the IR frequencies of Calixarenes with L and D Histidine (His) compound were performed at the HF method with the 6-31G* basis set. Thermochemical parameters such as standard enthalpies (Δ*H*), entropies (Δ*S*), free energies (Δ*G*) and (ΔE) was obtained in gas phase and four solvent at the six temperatures 298, 300, 302, 304, 306 and 308K. The influence of the solvent on the relative stability of Calixarenes with L and D Histidine (His) compound were studied and effect of solvents on the stabilization of Calixarenes with amino acids compound show interesting results. Calixarenes with amino acids compound was studied in the gas phase (ε = 1) and in various

solvent media with dielectric constants of water (ε = 78.39), DMSO (ε = 46.8), methanol (ε = 32.63), ethanol (ε = 24.55), CH_2Cl_2 (ε = 8.93). At present, in this section, we considered these thermochemical parameters.

in gas for largest value ΔS (entropy) is observed with B3LYP/6-31G level, also the largest value ΔE (energy), ΔH(enthalpy) and ΔG (Gibbs free energy) is observed with HF/6-31+G* level. The Δ*E,* Δ*S* and Δ*H* values increased with increasing of temperatures and as in can be seen the Δ*G* decreased with increasing of temperatures (see fig3). As can be seen, the Δ*E,* Δ*H* and Δ*S* values increased with increasing of temperatures and Δ*G* decreased with increasing of temperatures. As pointed in the Δ*E,* Δ*H*, Δ*G* and Δ*S* values in water, methanol and ethanol are smaller than in the gas phase, DMSO and dichloromethane. This difference is due to the formation of intermolecular hydrogen bonding. When solvent is added to Calixarenes with L and D Histidine (His) compound the intermolecular hydrogen bonds are formed between Calixarenes with amino acids compound and molecule of solvent. Water, methanol and ethanol are protic solvents and from two sites with Calixarenes with amino acids compound have interaction furthermore are formed strong hydrogen bonds. DMSO and dichloromethane have interaction with Calixarenes with amino acids compound but intermolecular hydrogen bonds are not formed. We found that the stability of the hydrogen-bonded Calixarenes with amino acids compound increase as the number of intermolecular hydrogen-bonded units increases. According to the Δ*E,* Δ*H*, Δ*G* and Δ*S* values in gas phase are smaller than in the DMSO and dichloromethane but are larger than in the water, methanol and ethanol (see fig3). This show Calixarenes with L and D Histidine (His) compound in gas phase is more stable than in DMSO and dichloromethane.

NMR data

In this section we report and analyze our NMR shielding tensors of ^{1}N, ^{2}C, ^{4}O, ^{5}C, ^{12}C, ^{13}C, ^{14}C, ^{66}O, ^{93}C, ^{94}C and ^{95}C-NMR shielding of Calixarenes[6] with L and D Histidine (His) compound obtain at the HF and B3LYP methods with the 6-31+G*basis set. In our current research, we have presented the results of our extensive studies on the of ^{1}N, ^{2}C, ^{4}O, ^{5}C, ^{12}C, ^{13}C, ^{14}C, ^{66}O, ^{93}C, ^{94}C and ^{95}C-NMR shielding of Calixarenes with amino acids compound in a wide range of amino acids encompassing a broad spectrum of polarity and hydrogen-bonding properties. According to our theoretical data, it is apparent that the different amino acids seem quite significant in physicochemical behavior.

The ^{1}N, ^{2}C, ^{4}O, ^{5}C, ^{12}C, ^{13}C, ^{14}C, ^{66}O, ^{93}C, ^{94}C and ^{95}C-NMR shielding of Calixarenes with L and D Histidine (His) compound are given in Table 1and 3.

NBO data

In this section we report and analyze on share of orbitals contribute in the bonds for the Calixarenes[6] with L and D Histidine (His) compound. Calculations obtain at the HF and B3LYP methods with the 6-31+G* basis set (See Table 2,4)

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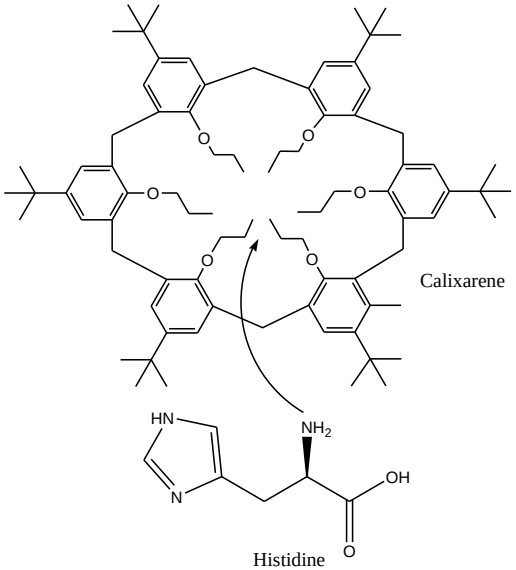


Fig.1.Calixarene and histidine

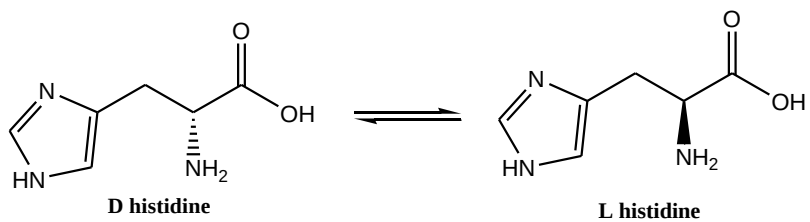
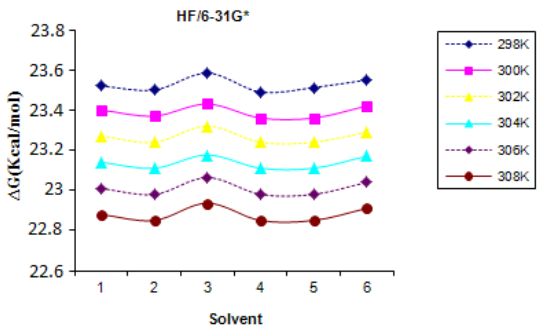
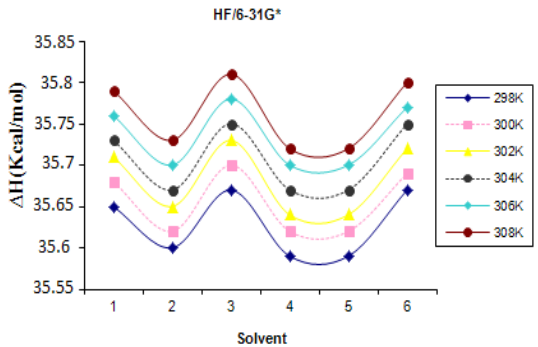


Fig.2:D histidine and L histidine


HF/6-31G*
ΔG(Kcal/mol)
23.8
23.6
23.4
23.2
23
22.8
22.6
1
2
3
4
5
6
Solvent
298K
300K
302K
304K
306K
308K


HF/6-31G*
ΔH(Kcal/mol)
35.85
35.8
35.75
35.7
35.65
35.6
35.55
1
2
3
4
5
6
Solvent
298K
300K
302K
304K
306K
308K

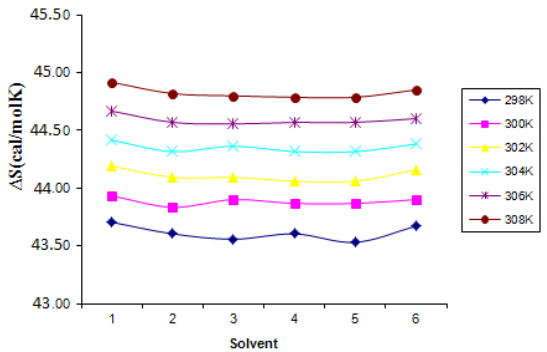


Fig3- enthalpies, Gibbs free energies and entropies for Histidine (His)

Table1. Calixarene+ L Histidine (His)

NMR=GIAO

Method		**HF/NMR**							**B3LYP/NMR**						
Basis set		6-31+G*							6-31+G*						
Name	**Atoms**	**Atomic charge**	**Δσ**	**η**	**δ**	**HOMO-LUMO**	**HF Energy**	**Dipole moment**	**Atomic charge**	**Δσ**	**η**	**δ**	**HOMO-LUMO**	**HF Energy**	**Dipole moment**
Aln	N(1)	-0.342387	20.5477	41.11686681	13.6985	-0.42923	-3897.7548244	-0.5612432	-0.316890	13.2032	58.77174765	8.8021	-0.14721	-3922.850781	-0.6613851
	O(4)	-0.225261	-533.7953	-1.78212621	813.7124				-0.189697	-541.376633	-1.743985273	733.9859			
	C(2)	0.028036	70.00923333	24.91223105	15.4394				-0.008438	64.42903333	23.0307066	15.3778			
	C(5)	-0.014880	2.77235	241.4662374	1.8482				-0.217506	4.6697	135.2332402	3.1131			
	C(12)	0.001380	104.2761	2.349221921	69.5174				-0.013530	90.82065	2.809718385	60.5471			
	C(13)	-0.068070	97.39405	2.277176441	64.9294				0.091809	72.59075	3.406438428	48.3938			
	C(14)	-0.000056	110.93055	2.172236142	73.9537				-0.015866	95.2168	2.672534335	63.4778			
	O(66)	-0.266758	72.70235	14.52995779	48.4682				-0.212099	92.0261	9.523180665	61.3507			
	C(93)	-0.078689	55.14066667	36.95564033	10.0925				-0.024334	48.7624	-1.743985273	10.0856			
	C(94)	-0.158396	72.87893333	89.92471969	4.7715				-0.141679	68.11333333	23.0307066	3.2648			
	C(95)	0.025668	72.92766667	33.17940035	11.9604				-0.059886	68.95783333	-1.743985273	12.3448			

Table2. Calixarene+ L Histidine (His)

Method	**HF/NBO**		**B3LYP/NBO**	
Basis set	6-31+G*		6-31+G*	
Bonding	N1–C2	$0.7444*(Sp^{3.04})_{N1}+0.6677*(Sp^{3.11})_{C2}$	N1–C2	$0.7453*(Sp^{3.17})_{N1}+0.6667*(Sp^{3.13})_{C2}$
	C2-C3	$0.7000*(Sp^{2.95})_{C2}+0.7141*(Sp^{1.96})_{C3}$	C2-C3	$0.7017*(Sp^{2.96})_{C2}+0.7125*(Sp^{1.95})_{C3}$
	C3-O4	$0.6404*(Sp^{1.99})_{C3}+0.7681*(Sp^{2.99})_{O4}$	C3-O4	$0.6392*(Sp^{2.02})_{C3}+0.7691*(Sp^{3.21})_{O4}$
	C2-C5	$0.7101*(Sp^{2.64})_{C2}+0.7041*(Sp^{2.81})_{C5}$	C2-C5	$0.7098*(Sp^{2.64})_{C2}+0.7044*(Sp^{2.80})_{C5}$
	N1-C95	$0.7462*(Sp^{3.01})_{N1}+0.6657*(Sp^{3.07})_{C95}$	N1-C95	$0.7459*(Sp^{3.10})_{N1}+0.6661*(Sp^{3.09})_{C95}$
	C94-C95	$0.7110*(Sp^{2.87})_{C94}+0.7032*(Sp^{2.82})_{C95}$	C94-C95	$0.7101*(Sp^{2.88})_{C94}+0.7101*(Sp^{2.83})_{C95}$
	C93-C94	$0.7132*(Sp^{2.78})_{C93}+0.7010*(Sp^{3.05})_{C94}$	C93-C94	$0.7141*(Sp^{2.76})_{C93}-0.7001*(Sp^{3.07})_{C94}$
	O66-C93	$0.7756*(Sp^{4.63})_{O66}+0.6312*(Sp^{3.38})_{C93}$	O66-C93	$0.7757*(Sp^{5.25})_{O66}+0.6311*(Sp^{3.44})_{C93}$
	LP(1)N1	$(Sp^{2.79})$	LP(1)N1	$(Sp^{2.53})$
	LP(1)O4	$(Sp^{0.34})$	LP(1)O4	$(Sp^{0.31})$
	LP(2)O4	$(Sp^{99.99})$	LP(2)O4	$(Sp^{99.99})$
Anti bonding	N1–C2	$0.6677*(Sp^{3.04})_{N1}-0.7444*(Sp^{3.11})_{C2}$	N1–C2	$0.6667*(Sp^{3.17})_{N1}-0.7453*(Sp^{3.13})_{C2}$
	C2-C3	$0.7141*(Sp^{2.95})_{C2}-0.7000*(Sp^{1.96})_{C3}$	C2-C3	$0.7125*(Sp^{2.96})_{C2}-0.7017*(Sp^{1.95})_{C3}$
	C3-O4	$0.7681*(Sp^{1.99})_{C3}-0.6404*(Sp^{2.99})_{O4}$	C3-O4	$0.7691*(Sp^{2.02})_{C3}-0.6392*(Sp^{3.21})_{O4}$

	C2-C5	$0.7041*(Sp^{2.64})_{C2}-0.7101*(Sp^{2.81})_{C5}$	C2-C5	$0.7044*(Sp^{2.62})_{C2}-0.7098*(Sp^{2.80})_{C5}$
	N1-C95	$0.6657*(Sp^{3.01})_{N1}-0.7462*(Sp^{3.07})_{C95}$	N1-C95	$0.6661*(Sp^{3.17})_{N1}-0.7453*(Sp^{3.13})_{C95}$
	C94-C95	$0.7032*(Sp^{2.87})_{C94}-0.7110*(Sp^{2.82})_{C95}$	C94-C95	$0.7041*(Sp^{2.88})_{C94}-0.7101*(Sp^{2.83})_{C95}$
	C93-C94	$0.7010*(Sp^{2.78})_{C93}-0.7132*(Sp^{3.05})_{C94}$	C93-C94	$0.7001*(Sp^{2.76})_{C93}-0.7141*(Sp^{3.07})_{C94}$
	O66-C93	$0.6312*(Sp^{4.63})_{O66}-0.7756*(Sp^{3.38})_{C93}$	O66-C93	$0.6311*(Sp^{5.25})_{O66}-0.7757*(Sp^{3.44})_{C93}$
	LP(1)N1	---	LP(1)N1	---
	LP(1)O4	---	LP(1)O4	---
	LP(2)O4	---	LP(2)O4	---

Table3. Caliarene+ D Histidine (His)

NMR=GIAO

Method		**HF/NMR**							**B3LYP/NMR**						
Basis set		6-31+G*							6-31+G*						
Name	**Atoms**	**Atomic charge**	**Δσ**	**η**	**δ**	**HOMO-LUMO**	**HF Energy**	**Dipole moment**	**Atomic charge**	**Δσ**	**η**	**δ**	**HOMO-LUMO**	**HF Energy**	**Dipole moment**

Val	N(1)	-0.342387	102.4126	54.23387623	10.7326	-0.43084	-3974.9478873	3.2802	-0.324423	-11.241	-73.41638644	-7.494	-0.16107	-4000.575686	-0.4484869
	O(4)	-0.225261	-92.1546	-2.006113887	621.405				-0.192466	-39.51533333	-1.9521363	555.0156			
	C(2)	0.028036	56.04556667	69.19435548	5.4956				-0.002595	7.4453	70.49654478	4.9635			
	C(5)	-0.014880	9.66675	65.22844286	6.4445				-0.041846	11.14885	52.47255335	7.4326			
	C(12)	0.001380	-29.1284	-13.12832344	-19.4189				-0.007521	-30.5178	-12.50201522	-20.3452			
	C(13)	-0.068070	91.0452	-30.55547077	-8.125				-0.084908	-57.35115	-7.275973542	-38.2341			
	C(14)	-0.000056	77.01465	3.564457542	51.3431				-0.010330	70.91665	3.961193203	47.2778			
	O(66)	-0.266758	29.02325	37.84263107	19.3488				-0.214596	18.68925	51.66428027	12.4595			
	C(93)	-0.078689	113.3256667	45.00138709	5.4791				-0.092397	-84.63305	-5.397286519	-56.422			
	C(94)	-0.158396	75.95436667	71.35199299	5.9308				-0.206282	-13.80445	-44.93534647	-9.2029			
	C(95)	0.025668	50.04666667	25.11029482	14.6054				-0.026946	8.60055	60.01135393	5.7337			

Table4. Caliarene+ D Histidine (His)

Method	**HF/NBO**		**B3LYP/NBO**	
Basis set	6-31+G*		6-31+G*	
Bonding	N1–C2	$0.7406*(Sp^{3.06})_{N1}+0.6719*(Sp^{3.00})_{C2}$	N1–C2	$0.7413*(Sp^{3.19})_{N1}+0.6712*(Sp^{3.03})_{C2}$
	C2-C3	$0.7017*(Sp^{3.06})_{C2}+0.7018*(Sp^{2.91})_{C3}$	C2-C3	$0.7034*(Sp^{3.05})_{C2}+0.7108*(Sp^{1.97})_{C3}$
	C3-O4	$0.6402*(Sp^{1.99})_{C3}+0.7682*(Sp^{3.04})_{O4}$	C3-O4	$0.6389*(Sp^{2.02})_{C3}+0.7693*(Sp^{3.26})_{O4}$
	C2-C5	$0.7124*(Sp^{2.63})_{C2}+0.7018*(Sp^{2.91})_{C5}$	C2-C5	$0.7116*(Sp^{2.59})_{C2}+0.7025*(Sp^{2.90})_{C5}$

	N1-C97	$0.7496*(Sp^{2.97})_{N1}+0.6619*(Sp^{3.03})_{C97}$	N1-C97	$0.7484*(Sp^{3.06})_{N1}+0.6632*(Sp^{3.05})_{C97}$
	C95-C96	$0.7139*(Sp^{2.70})_{C95}+0.7002*(Sp^{2.90})_{C96}$	C95-C96	$0.7144*(Sp^{2.67})_{C95}+0.6997*(Sp^{2.90})_{C96}$
	C96-C97	$0.7086*(Sp^{2.84})_{C96}+0.7056*(Sp^{2.73})_{C97}$	C96-C97	$0.7081*(Sp^{2.84})_{C96}+0.7061*(Sp^{2.72})_{C97}$
	O68-C95	$0.7761*(Sp^{4.59})_{O68}+0.6306*(Sp^{3.31})_{C95}$	O68-C95	$0.7762*(Sp^{5.19})_{O68}+0.6305*(Sp^{3.37})_{C95}$
	LP(1)N1	$(Sp^{2.80})$	LP(1)N1	$(Sp^{2.55})$
	LP(1)O4	$(Sp^{0.33})$	LP(1)O4	$(Sp^{0.31})$
	LP(2)O4	$(Sp^{1.00})$	LP(2)O4	$(Sp^{1.00})$
Anti bonding	N1–C2	$0.6719*(Sp^{3.06})_{N1}-0.7406*(Sp^{3.00})_{C2}$	N1–C2	$0.6712*(Sp^{3.19})_{N1}-0.7413*(Sp^{3.03})_{C2}$
	C2-C3	$0.7125*(Sp^{3.06})_{C2}-0.7017*(Sp^{1.98})_{C3}$	C2-C3	$0.7108*(Sp^{3.05})_{C2}-0.7034*(Sp^{1.97})_{C3}$
	C3-O4	$0.7682*(Sp^{1.99})_{C3}-0.6402*(Sp^{3.04})_{O4}$	C3-O4	$0.7693*(Sp^{2.02})_{C3}-0.6389*(Sp^{3.26})_{O4}$
	C2-C5	$0.7018*(Sp^{2.63})_{C2}-0.7124*(Sp^{2.91})_{C5}$	C2-C5	$0.7025*(Sp^{2.59})_{C2}-0.7116*(Sp^{2.90})_{C5}$
	N1-C97	$0.6619*(Sp^{2.97})_{N1}-0.7496*(Sp^{3.03})_{C97}$	N1-C97	$0.6632*(Sp^{3.06})_{N1}-0.7484*(Sp^{3.05})_{C97}$
	C95-C96	$0.7002*(Sp^{2.70})_{C95}-0.7139*(Sp^{2.90})_{C96}$	C95-C96	$0.6997*(Sp^{2.67})_{C95}-0.7144*(Sp^{2.90})_{C96}$
	C96-C97	$0.7056*(Sp^{2.84})_{C96}-0.7086*(Sp^{2.73})_{C97}$	C96-C97	$0.7061*(Sp^{2.84})_{C96}-0.7081*(Sp^{2.72})_{C97}$
	O68-C95	$0.6306*(Sp^{4.59})_{O68}--0.7761*(Sp^{3.31})_{C95}$	O68-C95	$0.6305*(Sp^{5.19})_{O68}--0.7762*(Sp^{3.37})_{C95}$
	LP(1)N1	---	LP(1)N1	---
	LP(1)O4	---	LP(1)O4	---
	LP(2)O4	---	LP(2)O4	---