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Computational Modeling of Interaction between Camptothecin and DNA Base pairs

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Understanding the physicochemical interaction between the novel drug Camptothecin (CTTC) and its biological receptor DNA is very important. Molecular modeling on the complex formed between CTTC and DNA presented this complex to be fully capable of participating in the formation of a stable intercalation site. The molecular geometries of CTTC and DNA bases were optimized with the aid of B3LYP/6-31G* method. Properties of the isolated intercalator and its stacking interactions with adenine···thymine (AT) and guanine···cytosine (GC) nucleic acid base pairs were studied with the DFTB method. Interaction energies of drug···base pair complexes were found to be -6.65 and -9.71 kcal/mol for AT···CTTC and GC···CTTC, respectively.

Keywords: Stacking interaction, Base pairs, CTTC, DFTB, Electron parameters

1. INTRODUCTION

Camptothecin (CTTC) and its derivatives are endowed with high antitumor activity and are used in therapy of human solid cancers [1]. It is a cytotoxic drug and a strong inhibitor of nucleic acid synthesis in mammalian cells, and a potent inducer of strand breaks in chromosomal DNA. Neither equilibrium dialysis nor unwinding measurements indicate any interaction between camptothecin and purified DNA [2].

In addition, camptothecin is an alkaloid derived from the Chinese tree Camptotheca acuminata Decne. Camptothecin and its derivatives are unique in their ability to inhibit DNA By stabilizing a

covalent reaction intermediate termed the cleavable complex, Topoisomerase I ultimately causes tumor cell death. Clinically it is widely believed that camptothecin analogs exhibited remarkable anti-tumour and anti-leukaemia activity. Topoisomerase is a basilic enzyme in the process of DNA replication; it is responsible for winding / unwinding of the supercoiled DNA composing the chromosomes. If the chromosomes cannot be unwound, transcription of DNA message cannot occur and the protein cannot be synthesized, it ultimately causes cell death. Application of camptothecin in clinic is limited due to its serious side effects and poor water-solubility. At present some camptothecin analogs, either semi-synthetic or synthetic drugs based on camptothecin, have been applied in cancerous therapy such as topotecan and irinotecan, while others have been obtained satisfying curative effects in clinic [3].

In recent years the DFT method was applied in different branches of chemistry [4-38]. The quantum mechanical description of interactions between CTTC and DNA base pairs (*Watson-Crick base pairing*) employing the DFTB method are reported in this paper. To achieve this goal CTTC and DNA base pairs were simulated and; atomic charges, geometrical values (bond lengths, bond angles and dihedral angles), dipole moment, polarizability, and energies of the frontier molecular orbitals (HOMO and LUMO) were obtained. According to a literature survey this is the first paper that studies CTTC and DNA base pair intercalations using the DFT method.

2. COMPUTATIONAL DETAILS

Calculations on the isolated molecules and molecular complexes were performed within GAUSSIAN 98 package [39].

Each species was initially optimized with PM3 method and, then the optimized structures were again optimized with density functional theory using the 6-31G* basis set.

Full geometry optimizations and frequency calculations were performed and each species was found to be at a minima, by having no negative values in the frequency calculation. The calculations gave internal energies at 0 K. In order to obtain gas phase free energies at 298.15 K, it is necessary to calculate the zero-point energies and thermal corrections together with entropies to convert the internal energies to Gibbs energies at 298.15 K [40-41].

The CTTC structure and geometry were optimized at the B3LYP level using the 6-31G* basis set. The structures of the CTTC···AT and CTTC···GC complexes using ideal geometries were prepared in the following way:

The intercalator (CTTC) and the base pairs (AT and GC) were situated in co-planar planes in such a way that the major system axes were parallel. There is special definition for the molecular geometries of DNA base pairs. Thus, when the idealized geometries were utilized, the interacting molecules were overlaid by their B3LYP/6-31G* optimized geometries, based on the least-squares fitting method. In the case of the empirical potential calculations, either the subsystem geometries were relaxed by the empirical potential or the QM-optimized geometries were saved. This difference had an insignificant effect on the calculated energies.

Other one-electron properties (dipole moment, polarizability, energies of the frontier molecular orbital) were also determined at the B3LYP/6-31G* level. For charged species the dipole moment was

derived with respect to their mass center, because for the non-neutral molecules the calculated dipole moment depended on the origin of the coordinate system. The stabilization energies of the selected complexes were determined with the help of the DFT calculations.

The DFT methods are known to be inherently very deficient for stacking interactions as they basically ignore the dispersion attraction [42-44]. As a consequence their enlargement by an empirical dispersion term currently appears to be a very reasonable way to improve the major deficiency of the DFT method for the evaluation of the molecular complexes. It should also be mentioned that the interaction energies were obtained as the difference between the complex energy and the combined energies of the molecules in isolation [45].

Processes in DNA environment depend on a delicate balance between stacking interactions, hydrogen bonding and hydration effects [46]. Hydration free energies could be calculated by implicit models like solvent reaction field [47] and Langevin dipole [48] methods, or by explicit models in conjunction with free-energy calculations and molecular dynamic simulations [49]. Due to complexity of these calculations, hydration effects shall be evaluated in future studies.

3. RESULTS AND DISCUSSION

3.1. Isolated subsystem

The optimized structure, atom numbering and atom charges of CTTC before and after complex formation are shown in Fig.1a and Fig.1b, respectively. The equilibrium geometries of the CTTC subsystem were determined and confirmed by subsequent calculations of the vibrational frequencies.

Significant computed geometrical parameters are available in Table 1. This table contains significant geometrical values including: bond length, bond angles and dihedral angles for CTTC, before and after the complex formation.

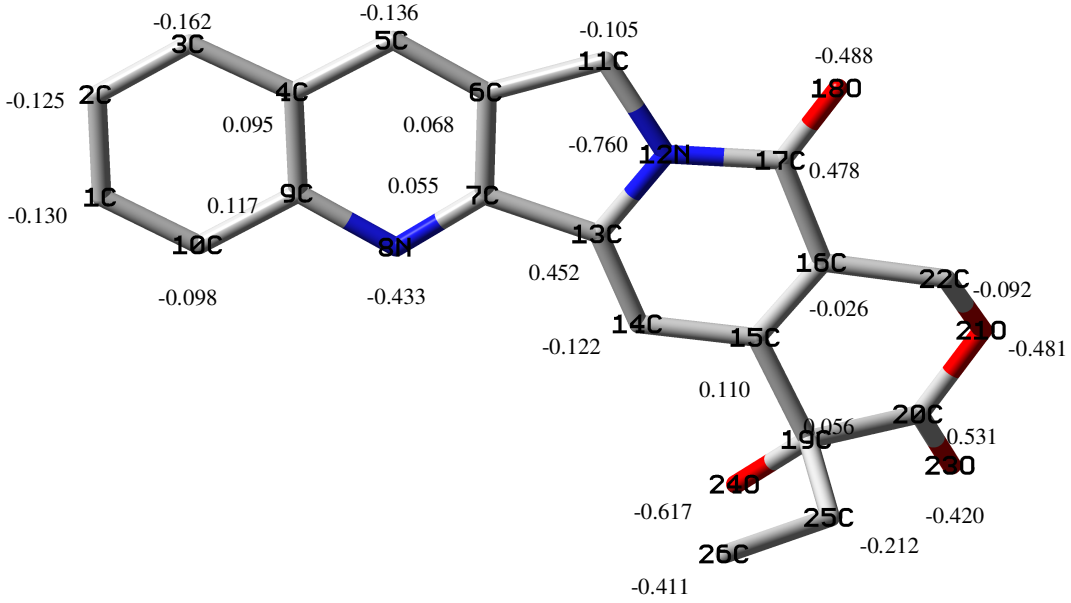


Figure 1(a). The optimized structure and the atom charges of CTTC

CTTC does not have a planar structure. In fact, it illustrates 1 equal branch which is entirely out of plane (it demonstrates 112° out of planarity of the whole geometry). Also, the atom charge distribution in CTTC is delocalized. C20 exhibited the highest positive charges which caused the bonding to oxygen atoms with high electronegativity. The most negative charge is N12 because it has contact with three electropositive carbons. The presence of electronegative elements in CTTC facilitated its interaction with the DNA molecule through hydrogen bonding with GC and AT hydrogen. In addition there are three kinds of interactions between CTTC and DNA; Hydrogen bonding, electrostatic interactions and dispersion interactions, which are discussed in the following paragraphs. Table 2 depicts the one-electron properties (dipole moment and polarizability) and the energies of the frontier molecular orbital (HOMO and LUMO) of CTTC using the DFTB computational method. The dipole moment, which is the first derivative of the energy with respect to an applied electric field as a measure of asymmetry in the molecular charge distribution.

The high values of the dipole moment and the polarizability present that the electrostatic and the dispersion contribution will play a key role in the interaction with the nucleobases.

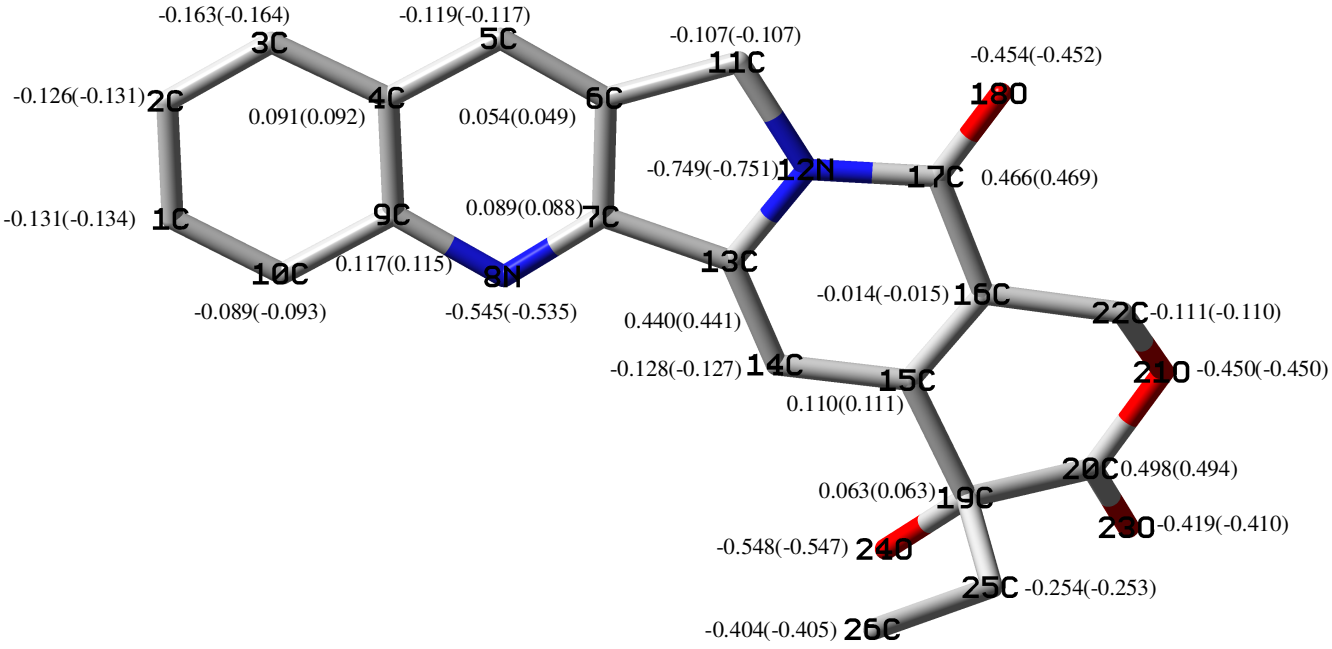


Figure 1(b). The optimized structure and the atom charges of CTTC after the complex formation with GC and AT (Parentheses include the changes after the complex formation with AT)

Table 1. Significant computed geometrical parameters for CTTC before and after complex formation

Bond lengths	CTTC	CTTC-GC	CTTC-AT	Bond Angles	CTTC	CTTC - GC	CTTC - AT	Bond Dihedrals	CTTC	CTTC - GC	CTTC - AT
R(4,9)	1.441	1.415	1.415	A(11,12,17)	122.1	126.4	126.4	D(15,19,20,21)	42.3	29.9	28.3
R(8,9)	1.378	1.398	1.398	A(13,12,17)	124.6	121.6	121.6	D(24,19,20,21)	161.6	147.5	145.7
R(12,13)	1.388	1.415	1.415	A(12,17,18)	120.8	117.6	117.6	D(24,19,20,23)	-20.5	-31.0	-32.8
R(12,17)	1.398	1.421	1.420	A(24,19,25)	109.1	112.6	112.6	D(15,19,24,37)	137.1	-176.1	-177.6
R(14,34)	1.079	1.097	1.097	A(19,20,21)	118.2	123.0	123.0	D(20,19,24,37)	18.0	66.0	64.2
R(16,17)	1.449	1.467	1.467	A(19,20,23)	120.8	126.8	126.7	D(25,19,24,37)	-99.3	-53.4	-55.0
R(17,18)	1.261	1.226	1.226	A(21,20,23)	120.9	110.3	110.2				
R(19,24)	1.443	1.415	1.415	A(20,21,22)	120.6	117.8	117.9				
R(20,23)	1.235	1.215	1.214	A(16,22,36)	113.2	110.5	110.4				
R(21,22)	1.488	1.422	1.421	A(21,22,35)	105.1	102.3	102.3				
R(24,37)	0.985	0.949	0.949	A(19,25,38)	106.4	109.3	109.2				
R(25,26)	1.533	1.511	1.511								

Table 2. Dipole moment [D], polarizibility [B^3], HOMO and LUMO energies (in eV) of the drug, the bases and the base pairs

Compound	HOMO	LUMO	Dipole moment	Polarizability
AT	-8.64	3.01	1.28	213.2
GC	-7.35	2.74	2.51	223.4
CTTC	-6.06	-2.39	7.25	174.3
A	-8.83	3.12	2.49	101.2
T	-9.53	2.94	3.88	89.1
G	-8.45	3.52	2.76	109.2
C	-9.93	3.01	6.12	80.4

The optimized structures of the adenine...thymine (AT) and guanine...cytosine (GC) base pairs in the Watson-Crick structures are visualized in Figs. 2 and 3, respectively. Tables 3 and 4, show the significant computed geometrical parameters using the DFTB method before and after complex formation.

In addition, Table 2 presents the one-electron properties (dipole moment and polarizability) and the energies of the frontier molecular orbital (HOMO and LUMO) of the bases and base pairs. From Table 2, it is clear that all bases and base pairs are very poor electron acceptors (all LUMO energies are positive in contrast to the LUMO energy of CTTC which is negative).

The bases and base pairs are apparently good electron donors and amongst the isolated bases, the best one is guanine. The electron donor ability of all bases is further magnified by base pairing.

Table 3. Significant computed geometrical parameters for AT and CTTC before and after the complex formation.

Bond lengths	AT	AT-CTTC	Bond Angles	AT	AT-CTTC	Bond Dihedrals	AT	AT-CTTC
R(1,2)	1.368	1.376	A(2,1,10)	119.5	117.8	D(10,1,2,3)	-180.0	173.4
R(1,10)	1.344	1.376	A(1,2,3)	120.4	120.4	D(10,1,2,26)	0.0	-13.2
R(2,3)	1.360	1.376	A(1,2,26)	123.2	122.3	D(2,1,10,13)	0.0	18.3
R(2,26)	1.719	1.687	A(3,2,26)	116.4	117.0	D(2,1,10,14)	180.0	163.9
R(3,12)	1.083	1.100	A(2,3,12)	115.3	116.3	D(1,2,3,12)	180.0	-179.2
R(10,13)	1.024	1.008	A(1,10,13)	120.6	118.4	D(26,2,3,12)	0.0	7.0
R(10,14)	1.008	0.990	A(1,10,14)	119.1	115.8	D(24,16,18,19)	-180.0	-173.7
R(12,24)	2.701	2.599	A(13,10,14)	120.3	116.5	D(24,16,18,26)	0.0	1.9
R(13,23)	1.873	1.815	A(18,16,24)	124.1	121.5	D(16,18,19,23)	180.0	177.2
R(16,18)	1.383	1.417	A(16,18,19)	126.5	120.7	D(26,18,19,23)	0.0	1.6
R(16,24)	1.248	1.227	A(16,18,26)	116.1	118.7	D(2,3,12,24)	0.0	-9.2
R(18,19)	1.391	1.421	A(19,18,26)	117.4	120.5	D(1,10,13,23)	0.2	7.3
R(18,26)	1.060	1.034	A(18,19,23)	120.6	116.1	D(19,18,26,2)	174.8	-8.1
R(19,23)	1.263	1.230	A(2,26,18)	179.7	176.6			
			A(10,13,23)	173.6	177.2			
			A(3,12,24)	133.8	128.7			

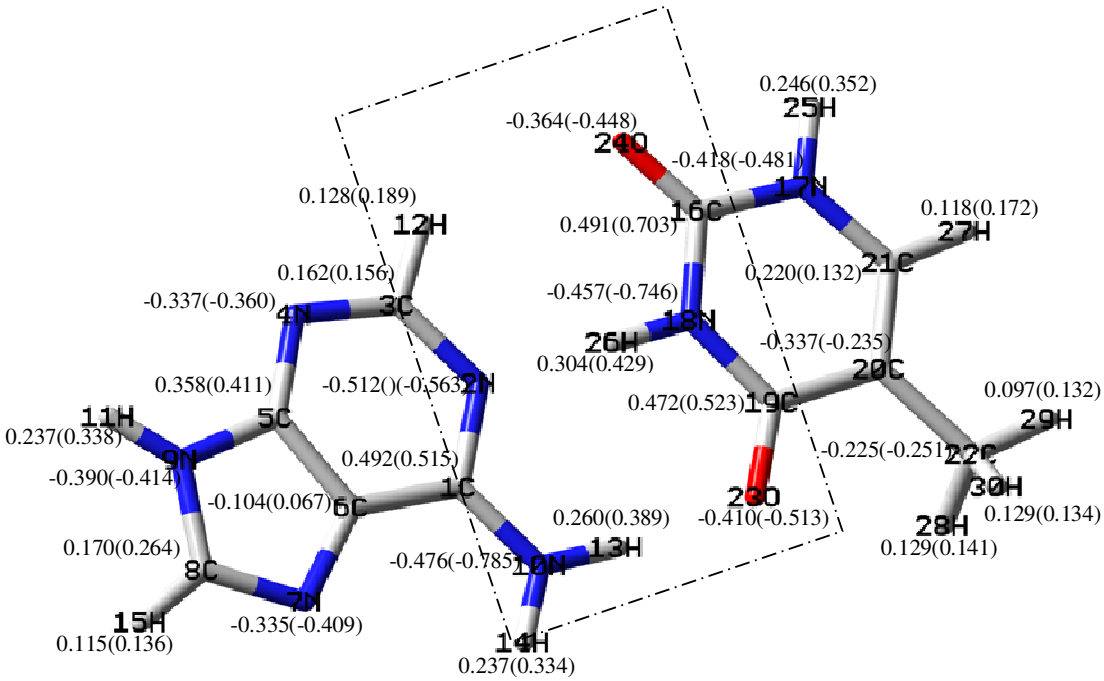


Figure 2. Optimized structure and charge of AT base pair & CTTC···AT before and after the complex formation (Parentheses include the changes after the complex formation)

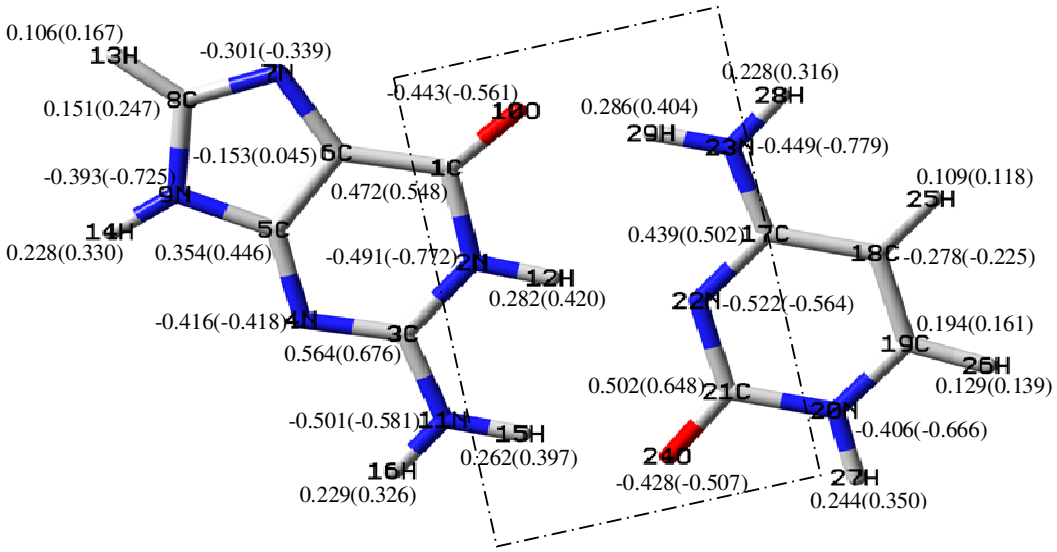


Figure 3. Optimized structure and charge of GC base pair & CTTC···GC, before and after the complex formation (Parentheses include the changes after the complex formation)

For example, the HOMO energy of guanine (-8.45 eV) increases by 1.1 eV upon pairing by cytosine. Furthermore, the high polarizability and dipole moment values of AT and GC (but more than those of CTTC) reveal that electrostatic and dispersion contributions considerably influence the interaction with the intercalator.

From previous papers we can acknowledge that the DFT method is more accurate. Moreover, the results concluded from the comparison of the DFTB method and the HF method indicates that these methods show close results and support each other.

Table 4. Significant computed geometrical parameters for GC and CTTC before and after the complex formation

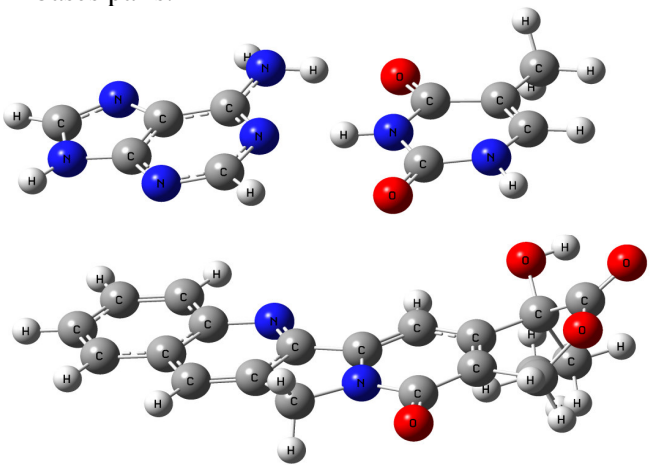
Bond lengths	GC	GC-CTTC	Bond Angles	GC	GC-CTTC	Bond Dihedrals	GC	GC-CTTC
R(1,2)	1.412	1.438	A(2,1,10)	119.6	116.0	D(10,1,2,3)	-180.0	178.5
R(1,10)	1.266	1.230	A(1,2,3)	125.3	122.2	D(10,1,2,3)	0.0	8.2
R(2,3)	1.384	1.413	A(1,2,12)	115.4	118.5	D(10,1,2,12)	0.0	-16.5
R(2,12)	1.039	1.030	A(3,2,12)	119.3	118.6	D(2,1,10,29)	180.0	174.0
R(3,11)	1.352	1.404	A(2,3,11)	117.4	118.2	D(1,2,3,11)	0.0	27.5
R(10,29)	1.714	1.607	A(1,10,29)	127.0	124.7	D(2,3,11,15)	-180.0	163.4
R(11,15)	1.024	1.012	A(3,11,15)	123.1	116.3	D(2,3,11,16)	0.0	19.0
R(11,16)	1.006	0.994	A(3,11,16)	116.8	114.4	D(1,10,23,17)	180.0	165.7
R(12,22)	1.851	1.779	A(15,11,16)	120.1	113.7	D(1,10,23,28)	0.0	19.6
R(15,24)	1.854	1.828	A(22,17,23)	117.8	115.7	D(23,17,22,12)	-180.0	-174.7
R(17,22)	1.354	1.356	A(22,21,24)	124.2	122.1	D(23,17,22,21)	-180.0	-164.2
R(17,23)	1.339	1.374	A(12,22,17)	123.2	123.1	D(22,17,23,28)	0.0	-13.5
R(21,22)	1.367	1.406	A(12,22,21)	115.3	116.5	D(24,21,22,12)	-180.0	179.8
R(21,24)	1.260	1.231	A(17,22,21)	121.5	119.0	D(24,21,22,17)	0.0	13.1
R(23,29)	1.041	1.012	A(17,23,29)	120.6	119.6	D(22,21,24,15)	61.2	1.2
			A(15,24,21)	120.9	122.1	D(1,10,29,23)	73.1	-0.3
			A(11,15,24)	177.2	174.5	D(1,2,12,22)	-96.2	-0.1
			A(2,12,22)	177.3	173.5	D(3,11,15,24)	-180.0	178.5

3.2. Complex subsystems

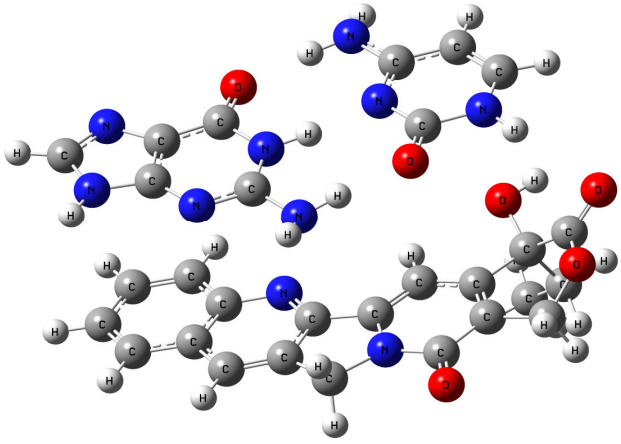
CTTC···AT and CTTC···GC optimized geometries are summarized in Figs. 4a and 4b, respectively.

The atom charge differences of CTTC, GC and AT before and after complex formation are presented in Figs. 1 (1a and 1b), 2 and 3 respectively. For instance, the O_{24} charge differences are -0.617 to -0.548, bond length (19,24) shifted from 1.443Å to 1.415Å and the O_{18} charge moves to-0.488 to -0.454, bond length (17, 18) shifted from 1.261Å to 1.226Å. These changes indicated that oxygen receives a part of its charge from hydrogen atoms in GC. Therefore, weak hydrogen bonding was formed between CTTC and GC.

The study of atom charges in GC and CTTC···GC exhibit that the part illustrated with dash marks (the only part which is going to be discussed afterwards), displays the highest changes because of the CTTC and GC interactions. Similar changes have also been obtained in AT. Since CTTC heteroatoms interact with GC hydrogen in the zone, the charge changes are not important for the other heteroatom of GC or AT bases pairs.



(a)

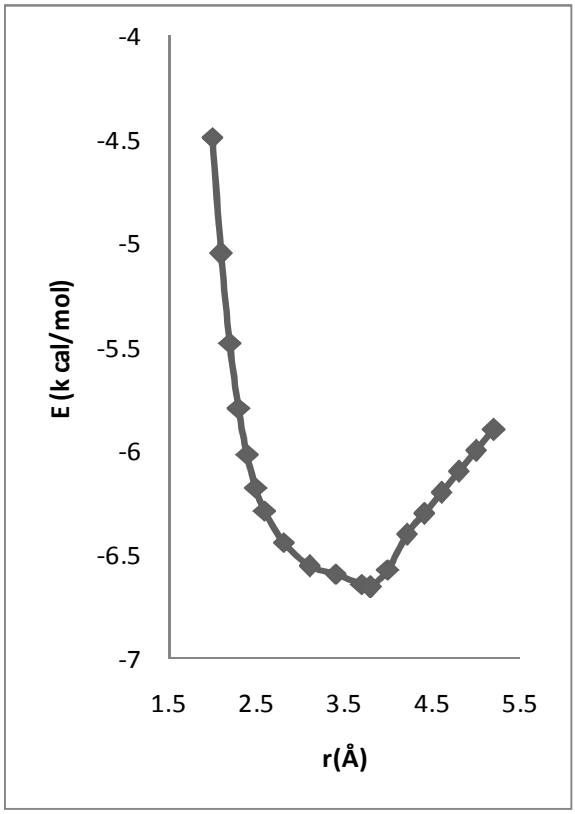


(b)

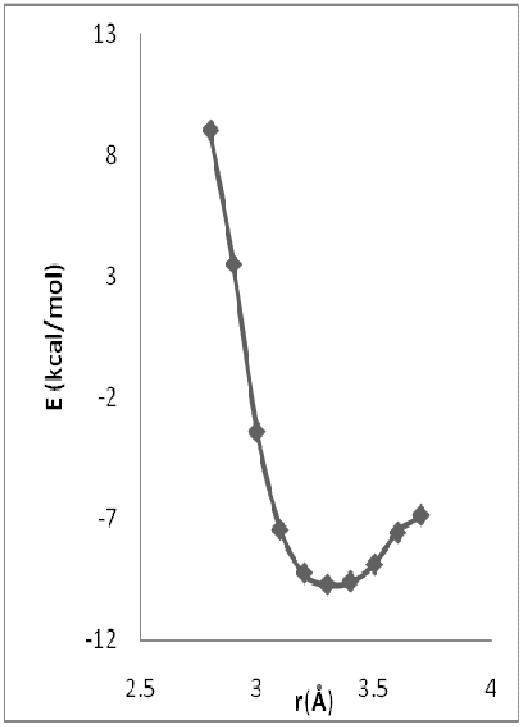
Figure 4(a,b). Optimized structures of CTTC ···AT and CTTC ···GC, respectively

After interacting with the CTTC molecule, the bond angle of the base pairs have changed in the mentioned area, i.e. in GC, A (1,10,29) shifted from 127.0 to 124.7 and bond dihedral moves to -180.0 to 163.4. As it is evident from Tables 1 and 2, bond lengths, bond angles and dihedral angles alter significantly in a way that the hydrogen bonding becomes weak, causing changes in the DNA molecule structure. Therefore, we should try to design drugs which bring about the most changes in the above mentioned area. To avoid repetition, results attained for AT are only listed in Table 1 and Fig. 4, which are in agreement with those of GC.

In general, a way for information collection regarding the electrons distribution is by computing the polarizability. This property depends on the second derivative of the energy relating to an electric field. Table 2 delineates the high CTTC, GC and AT polarizability values, supporting the fact that dispersion energy is always important. Another way is dipole moment of the base pairs and the studied intercalator which is presented in Table 2. The significant polarizability and dipole moment values proved the existence of the dispersion and electrostatic interactions between DNA and CTTC.



(a)



(b)

Figure 5(a,b). Stabilization energies (Δ*E*) of CTTC ···AT and CTTC ···GC, respectively

To evaluate the dependence of the Intercalator-Base Pair Stacking interaction energy on their vertical separation, investigations were carried out with the vertical distance between the interacting systems. The interaction energies were corrected for the basis set superposition error using the counterpoise method [50-51].

Figs. 5a and 5b illustrate the investigated structures for AT and GC with CTTC, respectively. As it is apparent from Figs. 5a and 5b, the minimum values of the respective potential energy curve for AT···CTTC and GC···CTTC were found at 3.8 Å and 3.3 Å, respectively.

The stabilization energies (energy necessary to separate CTTC and the AT pair to infinity) of AT···CTTC and GC···CTTC were equal to -6.65, -5.31 and -9.71, -8.93 kcal/mol, by DFTB and HF methods, respectively.

Furthermore the intercalation reaction between CTTC and different double base pairs of DNA (A–T/A–T, A–T/T–A, A–T/G–C, A–T/C–G, C– G/G–C, C–G/C–G) were also studied by the PM3 method. Fig 6 is a sample related to this study. The double base pairs of DNA were built by the nucleic acid database of Hyperchem and their 3D geometry was optimized with PM3 method.

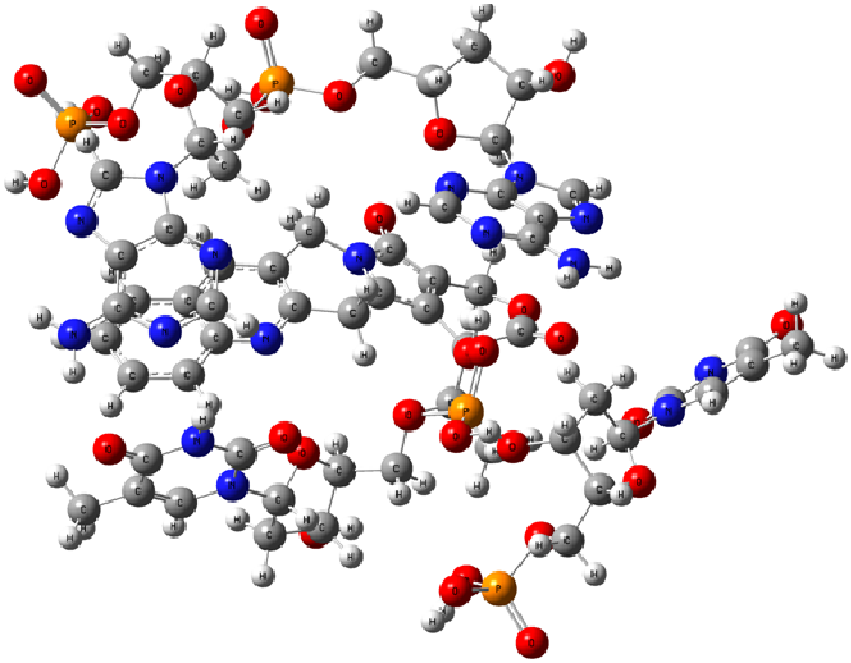


Figure 6. Optimized structures of CTTC with different DNA double base pairs.

4. CONCLUSIONS

In designing a drug, changes in structure and addition of specific groups should be in order to increase values of the main parameters such as: polarizability, dipole moment and interaction energy. With high values of these factors it can be concluded that the drug design is suitable. Since the LUMO energy of CTTC is negative, it is a good electron acceptor but AT and GC base pairs have positive LUMO energies and are good electron donors.

The binding interactions between CTTC and DNA base pairs were studied by means of DFTB quantum mechanical calculations. Geometrical and electronic properties of the isolated systems and their complexes have been investigated. CTTC molecule and DNA bases show a homogeneous charge distribution with no centers of high charge accumulation. This accounts for the low contribution of the electrostatic forces in the binding involving these molecules. Both intercalators and bases have high polarizability allowing a leading role for the dispersion forces.

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