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Theoretical Study on Interactions Between Berberine as an Anticancer Drug and DNA

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In this study, we present the work on the physicochemical interaction between the anticancer alkaloid berberine (BRB) and DNA with the purpose of designing drugs that interact more with DNA. Molecular modeling on the complex formed between berberine and DNA presented that this complex was undeniably fully able of participating in the formation of a stable intercalation site. Besides, the molecular geometries of berberine and the DNA bases (adenine, guanine, cytosine and thymine) were optimized with the aid of the B3LYP/6-31G method. This intercalator has a large polarizability and is a good electron acceptor, while base pairs are good electron donors. B3LYP/6-31G stabilization energies of intercalator… DNA base pair complexes are large (-7.65 kcal/mol for AT···BRB and -3.58 kcal/mol for GC···BRB). It was eventually concluded that the dispersion energy and the electrostatic interaction influenced the stability of the intercalator···DNA base pair complexes. The results exhibited that the berberine changes affected the DNA structure with reference to the bond length, the bond angle, the torsion angle and the charges.

Key Words: DNA, Intercalator, Berberine, Density functional theory.

INTRODUCTION

Berberine (BRB), a benzodioxolo-benzoquinolizine alkaloid is a natural isoquinoline plant alkaloid endowed with diverse pharmacological and biological activities[1,2]. Berberine was initially isolated from the herbs Rhizoma coptidis (Huang-Lian), belonging to the camptothecin family of drugs[3]. Berberine has inhibitory effect against telomerase activity[4], induces apoptosisand necrosis[5-7] and prevents the invasion of human cancer cells[8]. Berberine is known as an important compound in cancer therapy, possessing anticancer activity *in vitro* and *in vivo*[9].

The interaction of small molecules with DNA plays an important role in life phenomena, such as mutations of genetic information leading to diseases, by causing changes in replication and transcription of DNA. On the other hand, the analytical results carry information for molecular recognition in DNA hybridization and for sensing of bioactive species, such as anticancer drugs, usefulness also in clinical diagnostics and general biomedicine. Several studies have characterized the interaction of berberine to DNA[10-12]. The wide ranging biological activities of berberine in general and the anticancer activities in particularly have generated considerable interest to correlate its mechanism of action to the biophysical parameters of DNA binding[13-15]. Binding of small molecules and drugs to the altered DNA structures has been an active area of investigation[16-20]. Variety of experimental methods exist for measuring the changes in the DNA structure upon drug insertion or for determining the structure of the resulting complexes[21-23]. Despite the presence of numerous published papers, the complete characterization and interaction of drugs with nucleic acids remains not fully understood. However, computational studies provide great potential for the comprehension of such properties.

This paper presents the recently introduced approximate density functional theory (DFT) method, density functional tight-binding (DFTB) technique, empirical London dispersion energy term, which is accurate and reliable for computational studies[24] and calculations performed using the DFTB technique for H-bonded and stacked DNA base pairs[25,26]. The aim of this work was to study the geometries, the electronic BRB structures and its molecular complexes with the nucleo bases by the DFTB methods. This study will shed more light on the nature of the intercalations between the drug and DNA, dominantly from the viewpoint of charge transfer, dispersion and electrostatic forces. Hence, the study can help designing new intercalators (drugs) to interact more with DNA.

COMPUTATIONAL METHOD

Calculations on the isolated molecules and molecular complexes were performed within GAUSSIAN 98 package[27]. The structure and geometry of BRB were optimized at the

B3LYP level using a 6-31G, basis set. The structure of Watson-Crick base pairs was determined at the B3LYP/6-31G level with the assumption of their planarity. Structures of BRB···AT and BRB···GC complexes used idealized geometries prepared in the following way. The intercalator (BRB) and base pairs (AT and GC) were located in coplanar planes in such a way that the main system axes were parallel. Intersystem separation (vertical), twist angle and in plane displacements were optimized. In all cases, QM-optimized geometries of the base pairs and intercalator were used for QM calculation. Thus, when utilizing the idealized geometries, the interacting molecules were overlaid by their B3LYP/6-31G optimized geometries based on the least-squares fitting method. In the case of empirical potential calculations, either the subsystem geometries were relaxed by the empirical potential or QM-optimized geometries were retained. This difference has a negligible effect on the calculated energies.

Atomic charges of the intercalator and base pairs were derived using the restrained electrostatic potential (RESP) fitting procedure[28] at the B3LYP/6-31G level. This charge parameterization is identical to that used in the Cornell *et al*., force field[29].

Other one-electron properties (dipole moment, polarizability, energies of frontier molecular orbitals) were determined at the B3LYP/6-31G level. For charged species, the dipole moment was derived with respect to their center of mass, because for non-neutral molecules the calculated dipole moment depends on the origin of the coordinate system.

Stabilization energies of the selected complexes were determined using a density functional technique, DFTB, whose calculations were made using a recently introduced method based on a combination of the approximate tight-binding DFTB with empirical dispersion energy. Density functional tight-binding methods are known to be inherently very deficient for stacking interactions, as they basically ignore the dispersion attraction[30]. Thus, augmenting them by an empirical dispersion term currently appears to be a very reasonable way to improve the major deficiency of a DFTB method for evaluation of molecular complexes. The DFTB method is described previously[31], where its ability to describe H-bonding and stacking of nucleic acid base pairs was also demonstrated. The key advantage of the method used is its unprecedented computational efficiency. Interaction energies were obtained as the difference between the energy of the complex and the combined energies of the molecules in isolation, using the super molecule method[32,33].

RESULTS AND DISCUSSION

Berberine characteristics: The optimized structure, the atom numbering and the atom charges of BRB are shown in Fig. 1. The equilibrium geometries of the BRB subsystem were determined and confirmed by subsequent calculations of the vibrational frequencies. The geometrical optimizations were performed using the DFTB method and the significant computed geometrical parameters are available in Tables 1-3. These tables contain some significant geometrical values

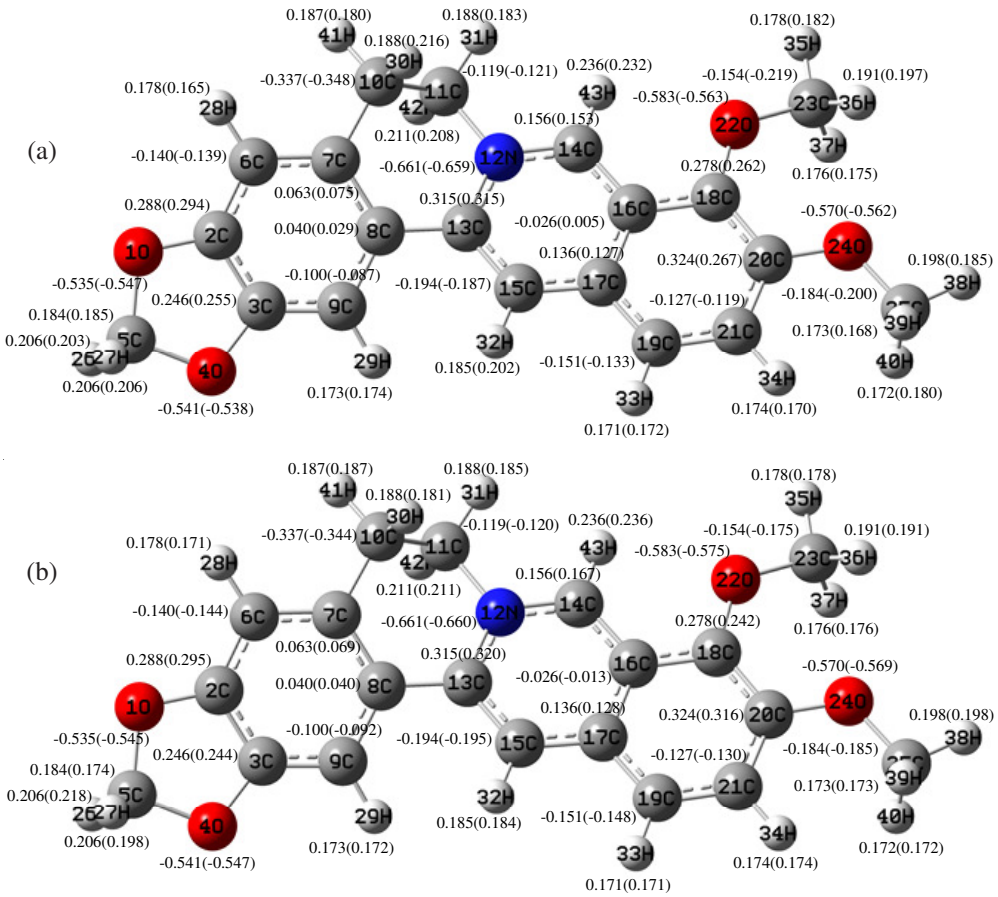


Fig. 1. (a,b) The optimized structure and the atom charges of BRB and GC…BRB (a), BRB and AT…BRB (b), before and after the complex formation (parentheses include the changes after the complex formation)

TABLE-1
SIGNIFICANT COMPUTED BOND LENGTHS FOR BERBERINE (BRB) AND DNA BASE PAIRS BEFORE AND AFTER THE COMPLEX FORMATION

BRB	Single	Comp-GC	Comp-AT	AT	Single	Complex
1,5	1.482	1.485	1.453	10,14	1.008	1.008
4,5	1.477	1.473	1.451	12,24	2.701	2.762
8,13	1.470	1.467	1.476	13,23	1.873	1.909
11,12	1.499	1.498	1.492	16,18	1.383	1.379
11,42	1.096	1.096	1.094	16,24	1.248	1.256
12,14	1.346	1.345	1.321	18,19	1.391	1.394
14,16	1.398	1.397	1.393	18,26	1.060	1.061
16,17	1.440	1.438	1.413	19,23	1.263	1.261
16,18	1.430	1.431	1.422	–	–	–
17,19	1.412	1.420	1.404	GC	Single	Complex
18,20	1.401	1.390	1.374	1,2	1.412	1.415
18,22	1.369	1.383	1.353	1,10	1.266	1.265
19,21	1.384	1.380	1.369	2,3	1.384	1.382
20,21	1.418	1.421	1.410	2,12	1.039	1.041
20,24	1.380	1.393	1.367	3,11	1.352	1.356
22,23	1.477	1.489	1.456	10,29	1.714	1.738
23,36	1.088	1.094	1.075	11,15	1.024	1.025
23,37	1.091	1.090	1.076	11,16	1.006	1.008
24,25	1.462	1.093	1.439	12,22	1.851	1.859
–	–	–	–	15,24	1.854	1.863
AT	Single	Complex	–	17,22	1.354	1.356
1,2	1.368	1.369	–	17,23	1.339	1.340
1,10	1.344	1.345	–	21,22	1.367	1.366
2,3	1.360	1.361	–	21,24	1.260	1.266
2,26	1.719	1.724	–	23,28	1.008	1.008
3,12	1.083	1.084	–	23,29	1.041	1.037
10,13	1.024	1.023	–	–	–	–

TABLE-2
SIGNIFICANT COMPUTED BOND ANGLES FOR BERBERINE (BRB) AND DNA BASE PAIRS BEFORE AND AFTER THE COMPLEX FORMATION

BRB	Single	Comp-GC	Comp-AT	AT	Single	Complex
1,5,26	109.1	109.0	109.4	13,10,14	120.3	119.9
26,5,27	113.2	113.3	113.9	18,16,24	124.1	123.5
13,12,14	122.3	118.1	122.2	16,18,19	126.5	126.2
11,12,13	118.5	122.3	119.1	16,18,26	116.1	116.6
10,11,42	110.6	110.8	111.8	19,18,26	117.4	117.1
12,11,42	107.5	107.4	107.1	18,19,20	116.5	116.3
11,12,14	119.2	119.6	118.6	–	–	–
16,18,22	114.0	116.8	115.4	GC	Single	Complex
20,18,22	127.5	124.2	125.4	2,1,10	119.6	119.3
19,21,34	118.8	121.1	119.0	1,2,3	125.3	125.1
20,21,34	118.8	117.0	119.0	1,2,12	115.4	115.4
18,20,24	117.3	122.1	117.4	3,2,12	119.3	119.4
21,20,24	123.1	117.7	123.0	2,3,11	117.4	117.3
18,22,23	124.7	118.0	124.1	1,10,29	127.0	126.6
20,24,25	120.1	116.3	122.6	2,12,22	177.3	177.6
35,23,36	111.1	111.2	110.6	3,11,15	123.1	122.4
35,23,37	110.8	110.8	111.2	3,11,16	116.8	116.6
–	–	–	–	10,29,23	179.1	175.7
AT	Single	Complex	–	11,15,24	177.2	177.4
2,1,10	119.5	119.3	–	15,11,16	120.1	119.3
1,2,3	120.4	120.3	–	22,17,23	117.8	117.9
1,2,26	123.2	123.7	–	22,21,24	124.2	123.5
3,2,26	116.4	116.0	–	12,22,17	123.2	123.3
2,3,12	115.3	115.4	–	12,22,21	115.3	115.4
1,10,13	120.6	120.4	–	17,22,21	121.5	121.2
1,10,14	119.1	119.4	–	17,23,29	120.6	120.7
2,26,18	179.7	179.3	–	28,23,29	118.8	118.7
10,13,23	173.6	172.7	–	15,24,21	120.9	121.2
3,12,24	133.8	130.4	–	–	–	–

TABLE-3
SIGNIFICANT COMPUTED DIHEDRAL ANGLES FOR BERBERINE (BRB) AND DNA BASE PAIRS BEFORE AND AFTER THE COMPLEX FORMATION

BRB	Single	Comp-GC	Comp-AT	AT	Single	Complex
2,1,5,26	-118.7	-123.1	-110.7	1,2,18,19	0.0	10.3
2,1,5,27	117.1	112.7	123.8	3,2,18,19	180.0	-171.4
3,4,5,26	118.6	123.7	110.6	10,1,2,26	0.0	-2.9
3,4,5,27	-116.8	-111.5	-123.4	24,16,18,19	-180.0	-170.0
2,6,7,8	-0.2	-1.3	13.8	24,16,18,26	0.0	6.4
10,11,12,14	-140.2	-134.6	-146.8	16,18,19,23	180.0	173.3
31,11,12,14	-17.9	-12.3	-24.5	19,18,26,2	7.6	142.0
42,11,12,14	99.3	104.9	91.5	26,18,19,23	0.0	-3.1
8,13,15,17	-179.6	-173.9	174.0	–	–	–
15,17,19,21	-179.1	-0.4	179.2	GC	Single	Complex
15,17,19,33	0.7	173.8	-0.3	10,1,2,3	-180.0	177.0
16,18,22,23	-166.7	123.1	142.6	10,1,2,12	0.0	-6.5
20,18,22,23	14.9	-56.9	-41.8	2,1,10,29	0.0	13.9
18,20,24,25	179.8	-69.4	176.3	1,2,3,11	180.0	-178.1
21,20,24,25	0.4	112.2	-5.4	1,2,22,17	0.0	1.4
18,22,23,35	172.6	-171.0	-166.7	1,2,22,21	-180.0	180.0
18,22,23,36	-68.3	-51.9	-48.4	3,2,22,17	-180.0	176.8
18,22,23,37	54.0	69.9	73.6	2,3,11,15	0.0	-6.5
–	–	–	–	2,3,11,16	180.0	-171.8
AT	Single	Complex	–	1,10.23,17	0.0	-11.3
10,1,2,3	-180.0	178.6	–	3,11,24,21	0.0	0.0
10,1,2,26	0.0	-2.9	–	16,11,24,21	-180.0	165.6
2,1,10,13	0.0	-4.4	–	23,17,22,12	0.0	-1.9
2,1,10,14	180.0	-178.9	–	24,21,22,12	0.0	-0.4
2,3,12,24	0.0	-20.3	–	22,21,24,15	0.0	3.2
1,2,3,12	180.0	-179.4	–	23,17,22,21	-180.0	-179.5
26,2,3,12	0.0	2.0	–	24,21,22,17	-180.0	177.4
1,2,18,16	180.0	-166.2	–	–	–	–

including: bond lengths, bond angles and dihedral angles for BRB, before and after the complex formation (BRB···AT and BRB···GC).

Among the atoms of BRB, five carbon atoms 3, 13, 18 and 20, have the maximum positive charge which is the cause of theirs connection to oxygen and nitrogen atoms with high electro negativity and maximum negative charge. Their calculated atomic charges (Fig. 1) nevertheless show significant delocalization of the excessive charge. From Fig. 1, it is clear that the atoms which are connected to oxygen of BRB in BRB···AT and BRB···GC have the highest charge difference. It can be seen that the oxygen charges (O1 and O4), have shifted toward higher values. These changes show that the oxygen atoms provide part of their charges from the atoms of hydrogen in AT or GC. The significant bond length, bond angles and dihedral angles changes are shown in Tables 1-3. Changes are seen more in C-H bonding in compare with others which is the cause of dispersion energy.

Table-4 showed the one-electron properties (dipole moment and polarizability) and the energies of the frontier molecular orbital (HOMO and LUMO) of BRB, using the DFTB computational method. The dipole moment 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 nucleo bases.

Base pairs characteristics: The optimized structures of the adenine...thymine (AT) and guanine...cytosine (GC) based pairs in the Watson-Crick structures are visualized in Figs. 2 and 3, respectively. Tables 1-3 show the significant computed geometrical parameters, using the DFTB method before and after the complex formation. In addition, Table-4 presents the one-electron properties (dipole moment and polarizability) and the energies of the frontier molecular orbital (HOMO and LUMO) of the bases and the base pairs. From Table-4, it is

TABLE-4
DIPOLE MOMENT, POLARIZIBILITY, HOMO AND LUMO ENERGIES (IN eV) OF THE DRUG, THE BASES AND THE BASE PAIRS BY THE DFT AND HF METHODS

Molecule	HOMO		LUMO		Dipole moment		Polarizability	
	DFT	HF	DFT	HF	DFT	HF	DFT	HF
AT	-8.2	-8.5	3.2	2.8	1.77	2.44	217.10	183.31
GC	-7.5	-8.3	2.9	2.9	6.73	7.12	221.36	189.49
BRB	-8.4	-10.7	-5.5	-2.2	4.48	5.06	471.87	366.80
A	-8.4	-8.6	3.7	3.2	2.48	2.58	108.83	96.02
T	-9.5	-8.3	3.2	3.7	4.57	7.49	95.54	100.75
G	-8.1	-9.7	4.1	2.7	3.63	5.21	126.70	84.19
C	-9.2	-9.2	3.3	2.8	7.78	7.99	100.77	79.85

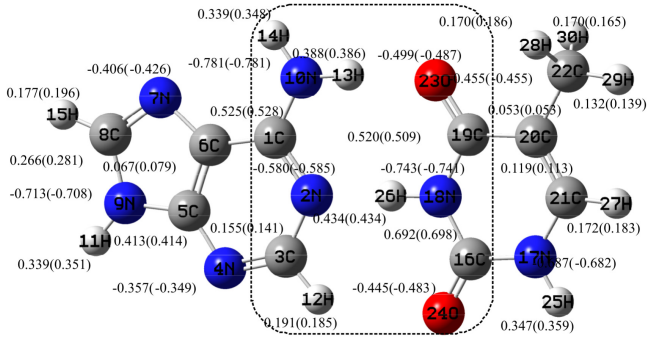


Fig. 2. Optimized structure and charge of adenine/thymine (AT) base pair and AT...BRB before and after the complex formation (parentheses include the changes after the complex formation)

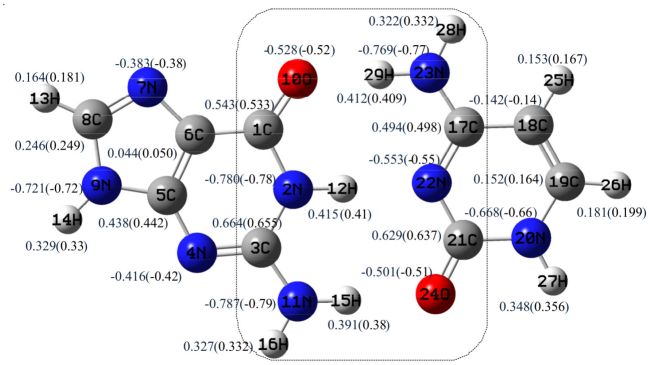
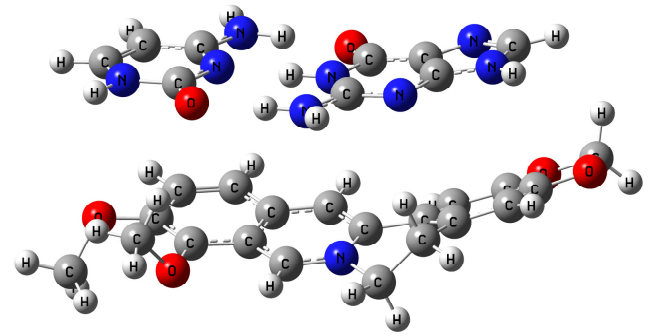


Fig. 3. Optimized structure and charge of guanine/cytosine (GC) base pair and GC...BRB, before and after the complex formation (parentheses include the changes after the complex formation)

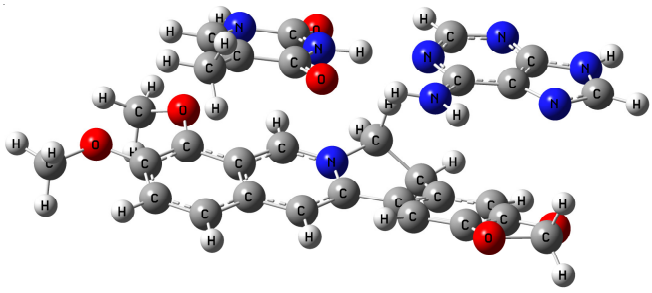
clear that all the bases and base pairs are very poor electron acceptors (all LUMO energies are positive in contrast to the LUMO energy of BRB which is negative). The bases and the base pairs are apparently good electron donors and among the isolated bases, the best one is guanine. This is in accordance with the experimental and theoretical studies, illustrating that the ultimate carcinogens primarily react with DNA at the N7 atom of guanine[34,35]. Base pairing further magnifies the electron donor ability of all bases. For example, the HOMO energy of guanine (-8.1 eV) increases by 0.6 eV upon pairing by cytosine. Furthermore, the high polarizability and dipole moment values of AT and GC revealed that the electrostatic and dispersion contribution influenced considerably the interaction with the intercalator.

From the previously published papers, it was concluded that the DFT method was more accurate. Moreover, the results attained after the comparison of the DFTB and HF method indicated that both methods presented similar results. However, it should be stated that the DFT method was considered as more accurate and reliable, since it involved a higher amount of information (Table-4).

Complex characteristics: The BRB···GC and BRB···AT optimized geometries are summarized in Fig. 4a-b, respectively. The atom charge differences of BRB, AT and GC are presented in Figs. 1a and 1b, 2 and 3, respectively. From Fig. 1a, it becomes obvious that the charge difference after the complex formation is greater. For instance, in GC···BRB, the atom charge O1, C8, C10, C17, C18, C23 and C25 change significantly. In contrast, the oxygen charge moves to more



(a)



(b)

Fig. 4. (a,b) Optimized structures of BRB, GC, BRB and AT, respectively

negative values (*i.e.*, for O1, the atom charge shifted from -0.535 to -0.547). These changes indicated that the oxygen receives a part of its charge from the hydrogen atoms in GC. Therefore, the weak hydrogen bonding was formed between BRB and GC.

The study of the atom charges in GC and BRB···GC exhibits that the part (shown with dash marks), which is going to be discussed afterwards, displays the highest changes, because of the BRB and GC interactions. Similar changes have also been obtained in AT Since the BRB heteroatoms interact with the GC hydrogen in the zone, the charge changes are not important for the other heteroatom of the GC or AT bases pairs. On the other hand, a decrease in the GC hydrogen charges in the area proves the fact that the hydrogen bonding has become weak, *i.e.*, H15 has shifted from 0.391 to 0.380 and its bond length (15, 24)) has increased from 1.854-1.863 Å. After interacting with the BRB molecule, the bond angles of the base pairs have changed in the mentioned area, *i.e.*, in GC, A (10, 29, 23) shifted from 179.1-175.7. The changes in the dihedral angles denote that the base pairs structure have shifted from the planar, *i.e.*, D (1, 10, 23, 17) in GC displays a high difference. As it is evident from Tables 1-3, bond lengths, bond angles and the dihedral angles alter significantly in a way that the hydrogen bonding becomes weak, causing changes in the DNA molecule structure. To avoid repetition, the results attained for AT are only listed in Tables 1-3 and Fig. 2, 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, related to an electric field. Table-4 delineates the high BRB, GC and AT polarizability values, supporting the fact that the dispersion energy is always important. Another way is the

dipole moment of the base pairs and the studied intercalator, which is presented in Table-4. The significant polarizability and the dipole moment values proved the existence of the dispersion and electrostatic interactions between DNA and BRB. The polarizability and the dipole moment of the intercalator have the same effects on the interaction with DNA. Hence, a drug should be designed with high polarizability and dipole moment to increase the interactions between DNA and the drugs. To evaluate the dependence of the Intercalator-Base Pair Stacking interaction energy on their vertical separation, the vertical distance between the interacting systems was investigated. The interaction energies were corrected for the basis set superposition error using the counterpoise method[36,37]. Fig. 5a-b illustrate the investigated structures for AT and GC with BRB, respectively. As it is apparent from Fig. 5a-b, the minimum values of the corresponding potential energy curve for both GC···BRB and AT···BRB were found at 4.2 Å. The stabilization energies (energy necessary to separate BRB and the AT pair to infinity) of AT···BRB and GC···BRB were equal to -7.65 and -3.58 kcal/mol, respectively. Consequently, as the interaction energy increases, the distance between the DNA molecule and the drug reduces. In addition, the computational chemistry methods, as an extension of the experimental approach, have received an increasing interest regarding the chemotherapy studies of the DNA-drug binding. These theoretical studies are used to predict convenient structures of the DNA-drugs in order to control the DNA changes.

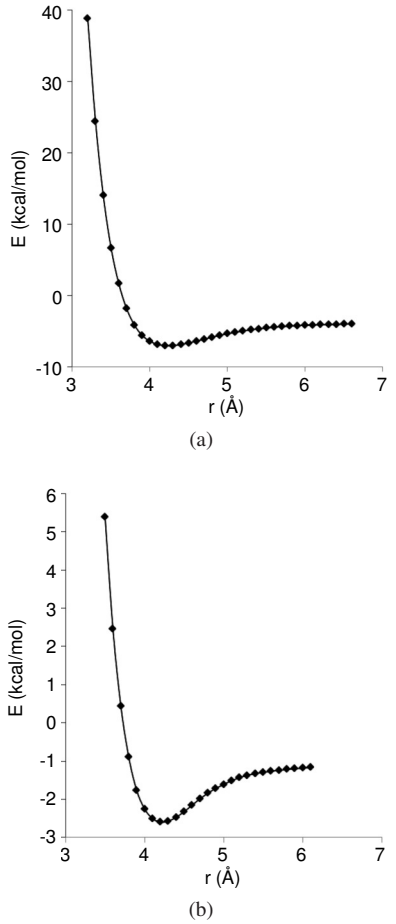


Fig. 5. (a,b) Stabilization energies (ΔE) of AT…BRB and GC…BRB, respectively

Conclusion

In this research, it was demonstrated that BRB was a good electron acceptor with high polarizability and dipole moment. In contrast, the AT and GC base pairs were good electron donors. These outcomes are very favorable for the aromatic stacking interactions between these two systems. In the drug design, the changes in the structure and the addition of the specific groups should facilitate the value increase of the main parameters, such as polarizability, dipole moment and interaction energy. Consequently, it can be concluded that when these factors illustrate high values, the drug design is suitable. It should also be mentioned that this method could be used as a preliminary study for predicting drugs effects on the target molecules (*i.e.*, DNA molecule) before their production.

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