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Note

Ab initio molecular orbital and force field calculations on the interaction of daunomycin with GC base-pair and intercalation within DNA

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The intercalative binding of daunomycin within dG-dC oligonucleotides has been reported but the contribution of stacking interaction is not clearly known. So the stacking interaction between aglycon ring and GC base pair has been studied. The intercalated structure of daunomycin within dG-dC oligonucleotides is also studied by force field calculation. The stacking energy is found to be not so significant for the stabilization of aglycon ring within GC sequences. Both the stacked structure and the intercalated structure are stabilized at the non steric orientations and the approach of drug towards minor groove is found to be favourable for both the stacking interaction and the intercalation.

Keywords: *Ab initio*, force field, DNA, interacalation, Daunomycin

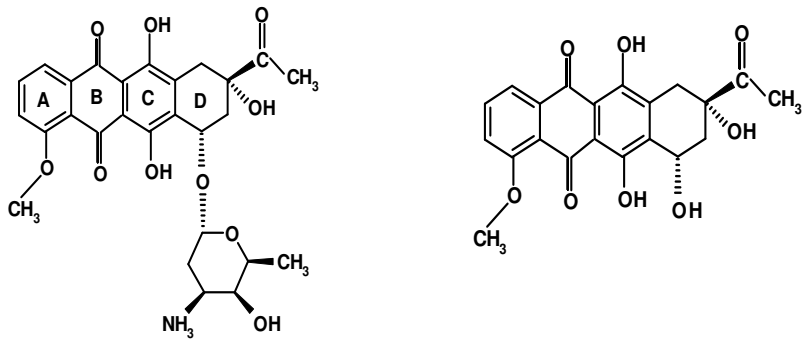
In cancer research many studies on mode of interaction between drug and DNA have been reported, and a few theoretical calculations are also available for supporting the experimental results[1-12]. Among the different types of binding modes that are generally found in drug-DNA complex, the intercalation of drug molecule (chromophore) within the sequences of DNA has been considered as one of the important basis for being an anticancer drug[4-15]. Hence, many intercalators having tricyclic as well as tetra-cyclic rings have been known, nevertheless the minimum requirement of chromophores for intercalation must have three member aromatic ring, and intercalators are designed by modifying these three or four member rings[11-15].

The intercalative mode of binding arises from the weak intermolecular stacking of aromatic rings and nonbonding electrons at large distances. In some systems, with the presence of strong steric effect of large groups present in drug molecules, it is not possible to precisely understand the contribution of stacking stabilization at long-range interaction. In certain cases this hindrance may be too large for binding with DNA through intercalation mode, because of which they may prefer to interact with other biomolecules present in the cellular system. For some drugs, the intercalative ability shown within DNA sequences is considered to be an important factor for enhancement of anticancer property. In the area of rational drug design, the efficiency of intercalation for molecules having tricyclic and tetra-cyclic chromophore as in the acridine-4-carboxamide and anthracyclic drugs should have some logical background[11-22]. Some researchers are interested to design intercalators having tricyclic chromophore whereas others are interested in tetra-cyclic ones. Hence the present study focuses on the intercalation of daunomycin (a tetra-cyclic chromophore) in order to justify the advantages of four-member ring in intercalation. Moreover it is necessary to understand the distinguishable stacking stabilization by tetra-cyclic chromophore at the intercalation site.

Here it is proposed to perform *ab initio* calculations for estimating the stacking of daunomycin chromophore and the force field studies for the intercalative mode of binding within dG-dC oligonucleotides, as the drug has been observed to show high specificity for GC sequences and poorly binds with dA-dT oligonucleotides. There are studies on the site-selective binding of this drug within various oligonucleotides, but it is not clearly known intercalation of this drug within dG-dC oligonucleotides is the factor for GC-sequence preference. It is, therefore, necessary to understand the ability of stacking as well as of intercalative binding mode within GC region of dG-dC oligonucleotides. Herein is described both the stacking stabilization as well as the site-specific binding affinity of daunomycin within dG-dC oligonucleotide[10].

Methodology

The structure of daunomycin molecule shown in **Figure 1a** was completely optimised with 6-31G basis set[23a]. The sugar attached to the chromophore-(aglycon ring) is removed for constructing the stacked



(a) (b)

Figure 1 – (a) Daunomycin, (b) Aglycon ring of Daunomycin.

models (**Figure 1b**). In turn, the geometry of GC base-pair was also optimised with 6-31G basis set. These two subcomponents (chromophore and base-pair) were taken for constructing the stacked models of drug and base-pair. Using a package called *JoinMolecules* developed[22d] by this research group, the stacked supermolecule models have been designed here in a manner such that the steric repulsion and stacking stabilization could be distinguished clearly.

Initially, the stacked structure of chromophore and base pair at 90° orientation (perpendicular fashion) was taken for the calculation to avoid the repulsive interactions from steric groups attached in chromophore (**Figure 2a**). Again the stacking of the daunomycin chromophore with GC along the horizontal plane (parallel fashion) was constructed, and the stacking energies at 6-31G** basis set was computed (**Figure 2b**). Within the parallel and perpendicular stacking of chromophore with GC base pair, the chromophore was rotated within –45° and 45° to get the optimum stacked structure. The present approach attempts to estimate the stacking stabilization in presence of repulsive forces from the visible steric groups present in the optimum stacked structure. Here models are constructed to avoid repulsion from highly steric groups in the stacked structures. The stacking energies are computed only for the stacked chromophore-GC supermolecule with orientations for which no visible steric effect occurs.

In addition to this, force-field calculation for the intercalated drug within dG-dC oligonucleotides having 12 base-pairs was carried out using CHARMm to understand the stabilization of chromophore within certain sequences[23b]. Initially, the intercalation of chromophore along the parallel fashion and perpendicular fashion within sequences were constructed for computing binding affinities. Consequently the minimized structure was located by rotating the chromophore to various orientations (**Figure 3**).

Results and Discussion

The results obtained from the study may be looked at in two ways: (a) the stacking energy shown in **Table I** for analysing the stabilization due to overlapping of base pair and daunomycin chromophore (stacked structure), and (b) the force field calculation on the intercalated model of drug and dG-dC oligonucleotides for the stabilization of drug particularly within non steric region **(Table II)**. The stacking energy for the overlapping of chromophore with GC sequence in parallel fashion is found to be highly unstable compared to that of stacking models in perpendicular fashion **(Table II)**. The distinctly visible steric parts in the stacked model (parallel fashion) are the substituents attached to rings A and D (**Figure 1**). Due to these steric groups, the stacking stabilization in parallel fashion between GC and chromophore may not be possible (**Figure 2b**). In order to locate the optimum stacked structure, the chromophore is rotated to various orientations over GC . The variation of stacking energies with respect to orientations both for the entry of drug towards minor and major grooves are shown in **Figures 4** and **5**. These stacked structures are stabilized within the non-steric regions and the computed stacking energies do not indicate much stabilization of chromophore within GC sequence (**Table I**).

The importance of stacking interactions between base-pairs has been known in the stabilization of DNA structure, and also on various topics on the stability of macromolecules. But it is essential to analyse how such interactions operate within the regions where the steric repulsion are significant (**Figure 2b**). The predominance of steric repulsion over the stacking stabilization or *vice versa* should be

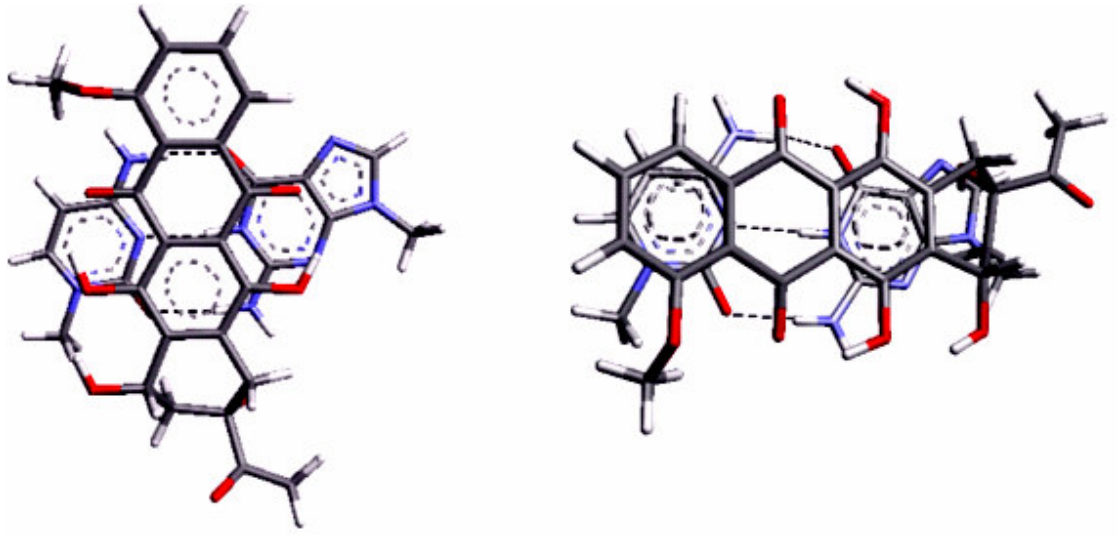


Figure 2 – (a) Stacking of aglycon ring of Daunomycin with GC in perpendicular fashion, (b) Stacking of aglycon ring of Daunomycin with GC in parallel fashion.

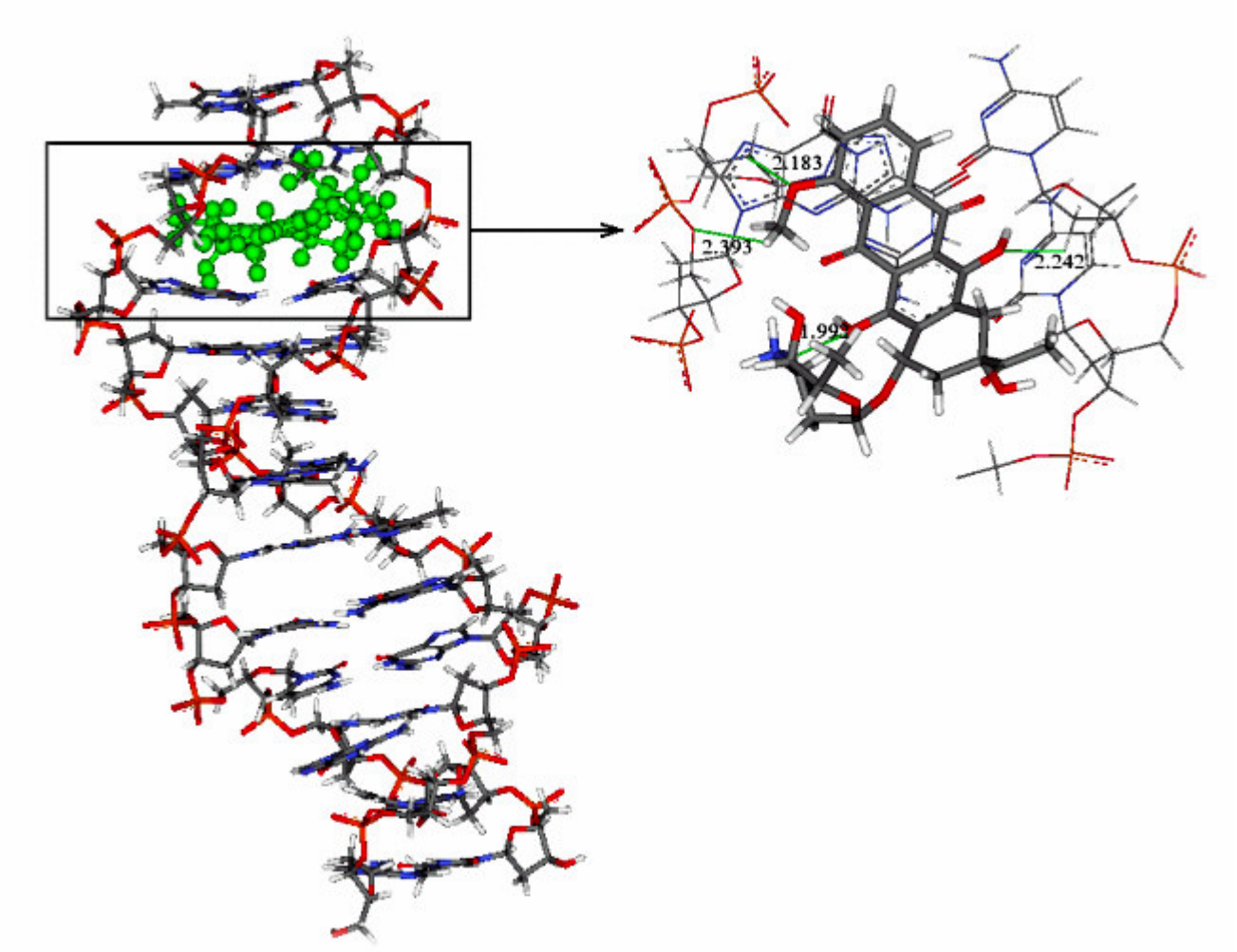


Figure 3 – Minimised structure of intercalated daunomycin within dG-dC.

Table I — The computed interaction energies (*ab initio/6-31G***) between the aglycon ring of Daunomycin and GC base-pair

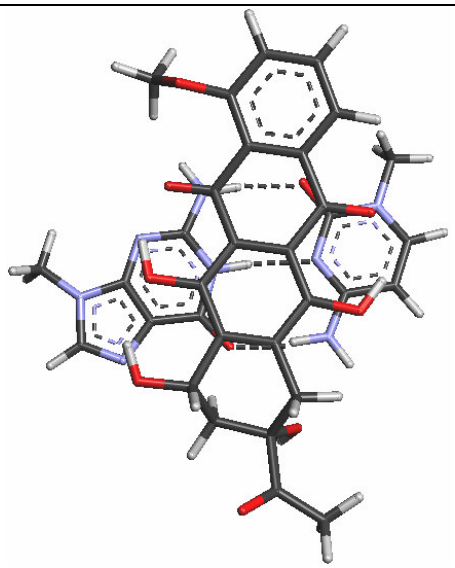
Orientation of Chromophore towards	Angles of rotation	Interaction energies (kcal/mol)	Interaction energies for the optimum stacked structures(kcal/mol)
Minor groove	0°	354.813	-2.840
	-45°	46.466	
	45°	24.665	
	90°	2.569	
Major groove	0°	543.801	0.691
	-45°	154.607	
	45°	8.620	
	90°	2.823	

sorted out to understand the intercalation mode of binding for daunomycin at non-steric region **(Table I)**. The stacking energies at 0°, 45° and 90° are computed to understand the steric orientation of daunomycin in its stacked structures with GC base-pair. It appears that the stacking stabilization between daunomycin chromophore and GC is not so significant.

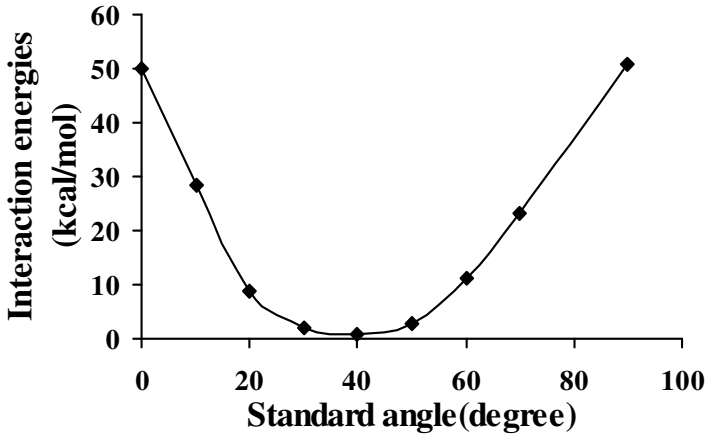
It may be important to understand the stabilization of intercalated structure of daunomycin-DNA complex. Alternatively, the binding affinity of intercalated drug has been analysed within GC sequences of DNA by using force-field calculation. Here, it is opted to investigate the binding affinity of daunomycin with dG-dC segment having 12 sequences, where the binding affinities for both the

Table II — The computed interaction energies (force field) for the intercalated Daunomycin placed within dG-dC

Orientation of drug towards	Angles of rotation	Interaction energies (electrostatic) (kcal/mol)	Interaction energies (VDW) (kcal/mol)	Potential difference (kcal/mol)
Minor groove	0°	-2428.237	-330.943	-2948.185
	-45°	-2532.908	-312.345	-3044.510
	45°	-1962.530	-352.775	-2678.460
	90°	-2274.124	-296.664	-2754.833
Major groove	0°	-1831.587	-342.338	-2534.416
	-45°	-1846.384	-409.176	-895.356
	45°	-2011.195	-348.625	-2695.266
	90°	-2006.626	-375.024	-2734.385



(a)



(b)

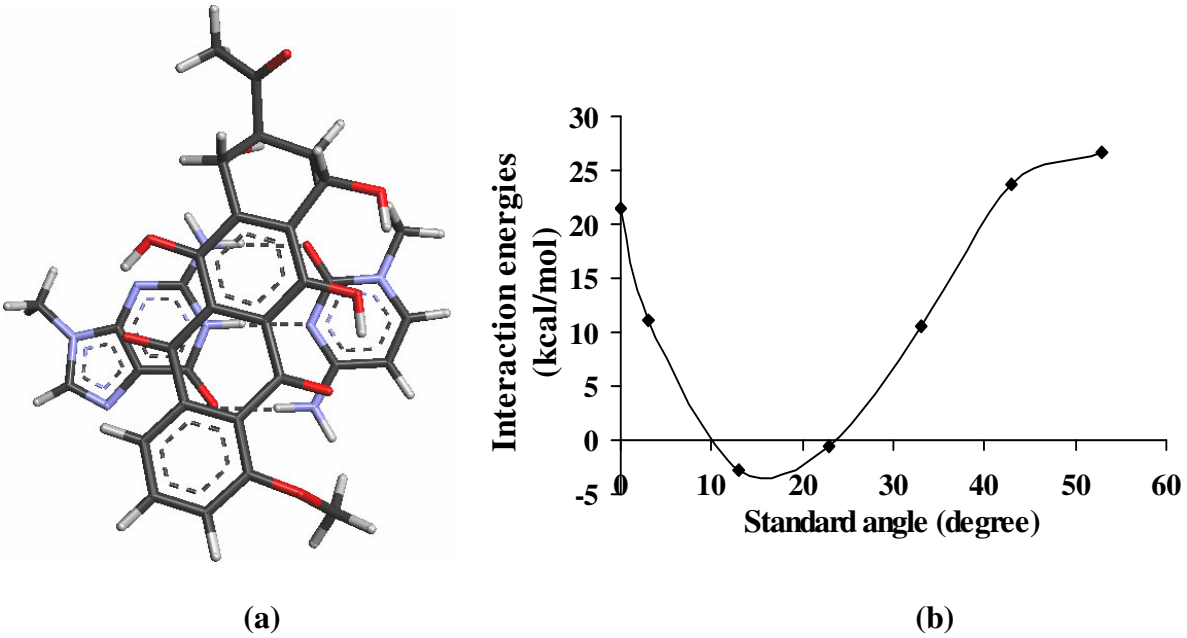


Figure 5 – (a) Optimum stacked structure of aglycon ring of Daunomycin and GC (major groove), (b) plot of orientation of aglycon ring of Daunomycin over GC versus interaction energies (major groove).

intercalated chromophore in parallel and perpendicular fashions are computed (**Table II**). The optimum intercalated structure within the minor groove of DNA where the binding affinities are due to electrostatic energy and van der Waals contacts are shown in **Figure 5**.

In addition, **Table II** shows the interaction energies of the intercalated daunomycin within GC sequences of dG-dC at various orientations. The van der Waals contacts in the minimised structure of drug-DNA obtained from force field calculation are shown in **Figure 5**. The van der Waals contacts present in the minimized structure might be important in the stabilization of intercalated drug. Hence, the steric factor and some stacking interaction should be considered in determining the structure and stability of intercalated daunomycin within DNA.

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