THEORETICAL STUDY OF DRUG-NUCLEIC ACID INTERACTIONS:

5-F-9-AMINO-[N-(2-DIMETHYLAMINO) ETHYL] ACRIDINE-4-CARBOXAMIDE

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Abstract*— *5-F-9-amino-[N-(2-dimethylamino)ethyl]acridine-4-carboxamide elicits its antitumour activity through intercalative binding with the genetic material, DNA molecule. The binding of this acridine molecule with DNA fragments has been examined using quantum mechanical methods. Second order perturbation theory valid for medium range interactions has been used to obtain binding sites of the acridine drug. Relative stability of various acridine-base pair complexes and preferred molecular associations have been discussed.

***Keywords*— DNA, Acridine, CNDO/2 Method, Molecular** Interactions and Computer Simulation.

Introduction

DNA is a well-characterized intracellular target but its large size and sequential nature makes it an elusive target for selective drug action. Binding of low molecular weight ligands to DNA causes a wide variety of potential biological responses. The biological activity of certain low molecular weight antitumour compounds appears to be related to their mode and specificity of interaction with particular DNA sequences. Such small molecules are of considerable interest in chemistry, biology and medicine [1,2]. 5-F-9-amino-[N-(2-dimethylamino) ethyl] acridine- 4-carboxamide (5F9AC) is an antibiotic drug with potent antitumour, antimicrobial, amebicidal and chemosterilant activities. It is DNA intercalating agent that form ternary complexes with mammalian topoisomerases and poison their cleavage and rejoining activities [3,4]. It preferentially binds to GC-rich nucleotide sequences [5, 6]. Correlations between ligand structure, cytotoxicity and DNA-binding kinetics for the 9-aminoacridine-4- carboxamide class of compounds has been experimentally studied [7,8]. The structure of the intercalated complex enables a rationalization of the known structure-activity relationships for inhibition of topoisomerase II activity, cytotoxicity, and DNA-binding kinetics for 9-aminoacridine-4-carboxamides [9]. The present paper describes the binding mechanism of 5-F-9-amino-[N-(2-dimethylamino)ethyl] acridine-4- carboxamide with nucleic acid base pairs namely, G-C and A-T using quantum mechanical methods.

II. METHOD OF CALCULATION

The molecular geometry of 5-F-9-amino-[N-(2-dimethylamino) ethyl]acridine-4-carboxamide (5F9AC) has been constructed using the crystallographic data from literature and standard values of bond lengths and bond angles [10]. Net atomic charge and corresponding dipole moment components at each of the atomic centres of the molecule have been computed by CNDO/2 method [11]. Modified Rayleigh-Schrodinger second order perturbation theory along with multicentred-multipole expansion technique has been used to calculate interaction energy between drug molecule and DNA base pairs. According to the energy decomposition obtained by perturbation treatment, the total interaction energy (ETOT) between two molecules is expressed as [12]:

ETOT = EEL+ EPOL+ EDISP+ EREP

where EEL, EPOL, EDISP and EREP represent electrostatic, polarization, dispersion and repulsion energy components respectively. The calculation of electrostatic energy has been restricted only up to first three terms namely monopole-monopole, monopole-dipole and dipole-dipole interaction energy [13]. During energy minimization, base pairs are kept fixed throughout the process while both lateral and angular variations are introduced in the acridine molecule in all respects relative to the fixed one and vice versa. Accuracies up to 0.1Å in sliding (translation) and 10 in rotation have been achieved. The details of the mathematical formalism and optimization process may be found in literature [9,12,14].

II. RESULTS AND DISCUSSION

The molecular geometry of 5-F-9-amino- [N-(2- dimethylamino) ethyl] acridine-4-carboxamide has been shown in figure 1.

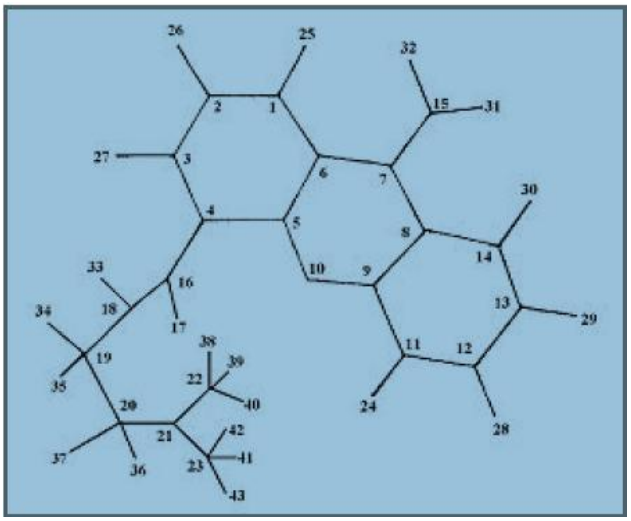
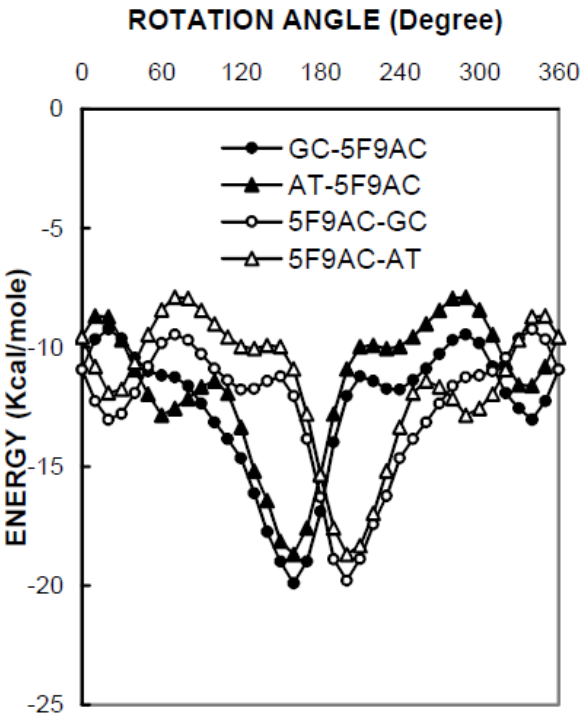


Fig 1 Molecular geometry of 5-F-9-amino[N-(2-dimethylamino) ethyl] acridine-4-carboxamide with various atomic index numbers.

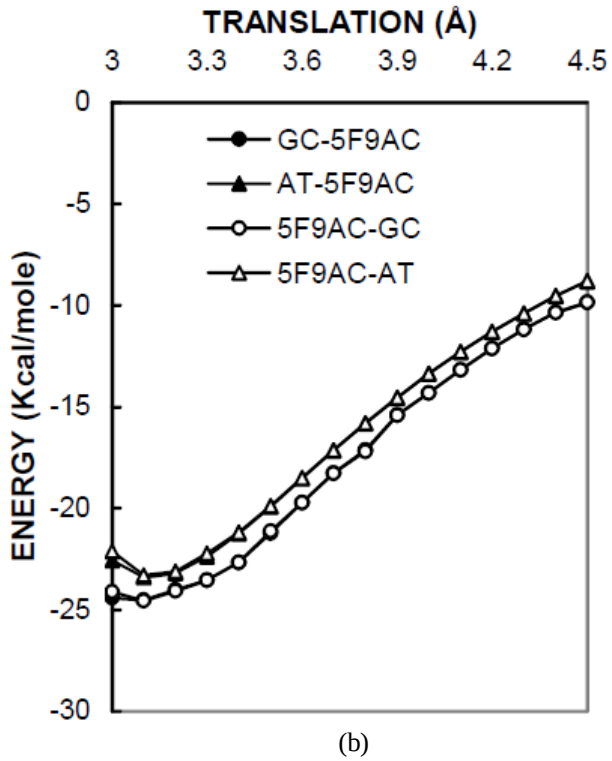
TABLE I
MOLECULAR CHARGE DISTRIBUTION OF THE 5-F-9-AMINO-[N-(2-DIMETHYLAMINO)ETHYL]ACRIDINE-4-CARBOXAMIDE MOLECULE.

Atom No.	Atom Symbol	Charge (e.u.)	Atomic dipole components (debye)		
			X	Y	Z
1	C	0.023	0.033	0.081	-0.013
2	C	-0.031	-0.106	0.133	0.012
3	C	0.029	-0.069	-0.056	0.003
4	C	-0.081	0.042	-0.190	0.036
5	C	0.177	-0.009	-0.098	-0.176
6	C	-0.099	-0.162	-0.136	0.127
7	C	0.150	-0.137	-0.226	-0.065
8	C	-0.089	-0.007	-0.158	0.027
9	C	0.134	-0.078	-0.033	0.007
10	N	-0.129	-0.973	-1.564	0.143
11	C	0.214	0.139	0.323	-0.003
12	C	-0.053	0.054	-0.136	0.021
13	C	-0.004	0.144	-0.007	-0.054
14	C	-0.023	0.072	0.080	0.043
15	N	-0.239	0.066	0.115	0.031
16	C	0.312	0.185	0.030	-0.054
17	O	-0.278	0.628	-1.217	-0.170
18	N	-0.222	-0.463	0.810	-1.079
19	C	0.093	-0.175	-0.120	-0.067
20	C	0.079	0.173	0.069	0.062
21	N	-0.160	-1.108	0.879	0.106
22	C	0.081	0.006	-0.105	0.208
23	C	0.080	-0.063	-0.149	-0.182
24	F	-0.188	-0.477	-0.756	-0.055
25	H	-0.018	0.000	0.000	0.000
26	H	-0.004	0.000	0.000	0.000
27	H	-0.016	0.000	0.000	0.000
28	H	0.013	0.000	0.000	0.000
29	H	-0.005	0.000	0.000	0.000
30	H	-0.014	0.000	0.000	0.000
31	H	0.128	0.000	0.000	0.000
32	H	0.130	0.000	0.000	0.000
33	H	0.097	0.000	0.000	0.000
34	H	-0.013	0.000	0.000	0.000
35	H	0.004	0.000	0.000	0.000
36	H	0.001	0.000	0.000	0.000
37	H	-0.009	0.000	0.000	0.000
38	H	-0.015	0.000	0.000	0.000
39	H	-0.009	0.000	0.000	0.000
40	H	-0.015	0.000	0.000	0.000
41	H	-0.007	0.000	0.000	0.000
42	H	-0.012	0.000	0.000	0.000
43	H	-0.014	0.000	0.000	0.000

(Total energy = -235.4 a.u., Binding energy = -22.3 a.u., Total dipole moment = 5.03 debye).



(a)

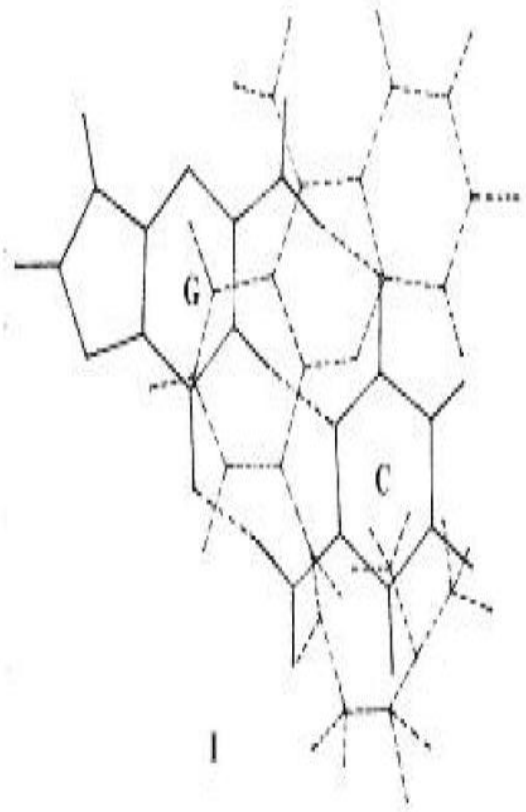


(b)

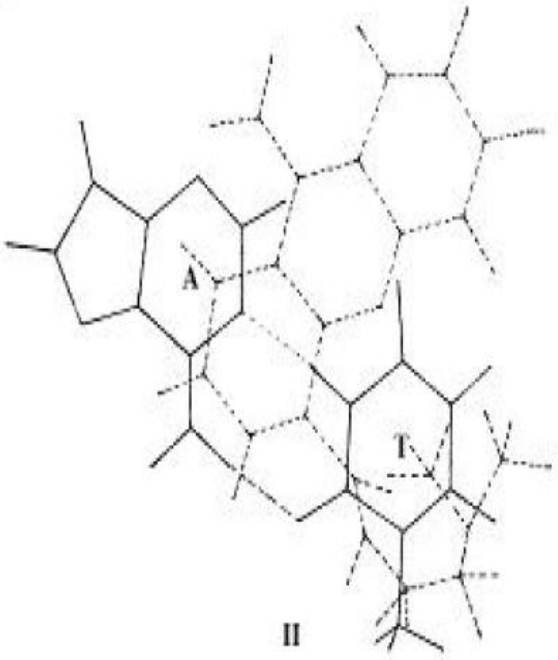
Fig 2 Variation of total stacking energy of 5-F-9-amino-[N-(2-dimethylamino)ethyl]acridine-4-carboxamide with various base pairs as a function of (a) angular rotation and (b) interplanar separation.

TABLE II
STACKING ENERGY OF VARIOUS COMPLEXES FORMED BETWEEN 5-F-9-AMINO-[N-(2-IMETHYLAMINO) ETHYL] ACRIDINE-4-CARBOXAMIDE AND DNA BASE-PAIRS.

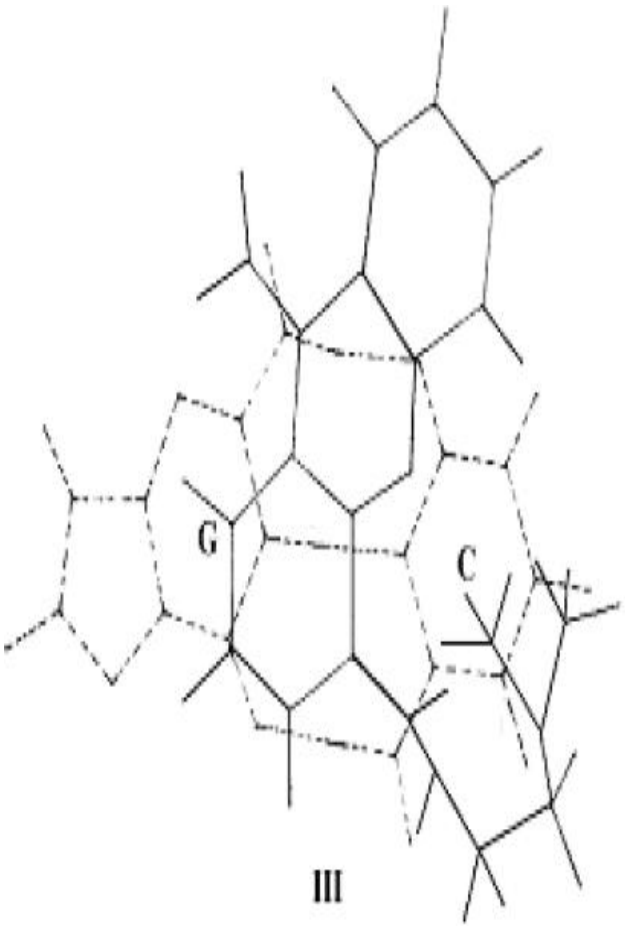
Energy Terms (Kcal/mole)	Stacked Complexes			
	GC-5F9AC (I)	AT-5F9AC (II)	5F9AC-GC (III)	5F9AC-AT (IV)
E_{QQ}	-2.32	-1.83	-2.31	-1.82
E_{QMI}	-4.90	-3.39	-4.78	-3.37
E_{MIMI}	-1.59	-1.96	-1.50	-1.94
E_{EL}	-8.81	-7.18	-8.59	-7.13
E_{POL}	-3.23	-2.96	-3.24	-2.99
E_{DISP}	-27.15	-26.68	-27.25	-26.97
E_{REP}	14.06	13.26	14.05	13.47
E_{TOT}	**-25.13**	**-23.56**	**-25.03**	**-23.65**
Inter-planar separation (Å)	3.1	3.1	3.1	3.1



I



II



III

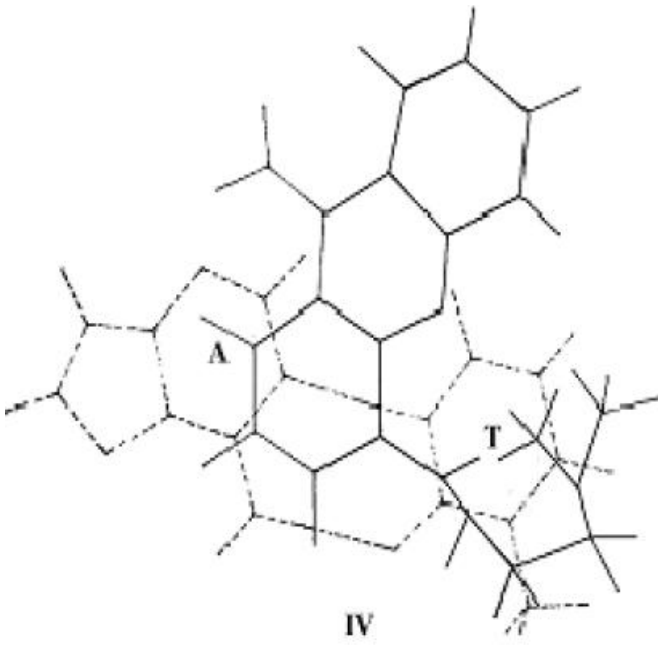


Fig 3 Stacked minimum energy configurations of 5-F-9-amino-[N-(2-dimethylamino)ethyl]acridine-4-carboxamide with DNA base pairs. The geometry shown by dotted lines represents the upper molecule in each case.

Net atomic charge and dipole moment components corresponding to each atomic enter of the molecule are given in Table 1. The variation of stacking energy with respect to change of relative orientation between drug molecule and base pairs, has been shown in fig 2(a). Here, the interplanar separation corresponds to 3.1Å in each case.

As evident from fig 2(a), two minima are exhibited by each energy curve. The energy curve for GC-5F9AC complex shows one minima at 1600 with energy –19.90 kcal/mole and the other at 3400 with energy –13.04 kcal/mole. The energy curve for AT-5F9AC complex also shows two minima, one at 600 with energy values -12.84 kcal/mole and the other at 1600 with energy –13.02 kcal/mole. Similarly, the energy curve for 5F9AC-GC complex exhibits two minima, one at 200 with energy –13.04 kcal/mole and the other at 2000 having energy –19.79 kcal/mole. The energy curve for 5F9AC-AT complex also shows one minima at 2000 with energy –18.68 kcal/mole and the other at 2900 with energy –12.85 kcal/mole. Obviously, GC-5F9AC and 5F9AC-GC curves show an energy difference of nearly 7.0 kcal/mole between their two minima positions while in case of AT base pairs this energy difference is reduced to approximately 6.0 kcal/mole. Similar to that noticed for 9-amino-[N-(2-dimethylamino)ethyl]acridine-4-carboxamide (9AC), the present acridine drug (5F9AC) also shows strong orientational specificity of stacking interactions in case of both AT and GC base pairs [9,16]. The minima for GC- 5F9AC and AT-5F9AC correspond to the same orientation and similar is the situation with 5F9AC-GC and 5F9ACAT complexes. The minima located by GC-5F9AC and 5F9AC-GC curves are having more energy as compared to those noticed in case of AT-5F9AC and 5F9AC-AT energy curves though the energy difference is less than 1.0 kcal/mole.

The variation of stacking energy with interplanar distance between the drug (5F9AC) and base pairs is shown in fig. 2(b), which indicates that complexes with GC and AT base pairs are stabilized at 3.1 Å and 3.2 Å respectively. These minima are subjected to further refined calculations. The minimum energy configurations, thus obtained, are depicted in figure 3 which clearly shows that acridine chromophore of the drug (5F9AC) is stacked nearly perpendicularly through the hydrogen bonded regions of base pairs and partially over the purine (guanine and adenine) base of the base pairs. It is interesting to note that 9-aminoacridine also stacks in a similar way at least over the guanine base of the GC base pair [15]. Since the acridine chromophore of the drug molecule possesses functional groups such as amino and carboxamide, the stacking patterns further indicate the possibility of formation of hydrogen/covalent bonds between the intercalated drug molecule and the backbone and /or the nucleotide bases of nucleic acid helices. The stacking energy values corresponding to various stacked complexes are shown in Table II, which implies that the drug (5F9AC) like 9-aminoacridine prefers to bind and intercalate into a dinucleotide unit containing guanine and cytosine bases [9,15]. Further, Table II indicates the following order of the stability of the stacked complexes:

$$I \geq III > IV \geq II$$

It seems worthwhile to mention that the dispersion component plays a dominant role in stabilizing all the complexes and electrostatic energy is largest (-8.81 kcal/mole) in case of GC-5F9AC complex. These results suggest that complexes formed with GC base pair are energetically more favoured and exhibit strong orientational specificity as compared to those formed with AT base pair.

IV. CONCLUSION

The present study reveals that binding of 5-F-9-amino-[N-(2-dimethylamino)ethyl]acridine-4- carboxamide (5F9AC) to GC rich region of nucleic acid helices is more preferred and the mode of binding is almost similar to 9-amino-[N-(2-dimethylamino) ethyl]acridine-4-carboxamide [9,16] and 9-amino acridine [15].

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