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Quantum Mechanical Study of Drug-Nucleic Acid Interactions: Prothracarcin

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Abstract **– Prothracarcin belongs to the family of pyrrolo [1, 4] - benzodiazepines (PBDs). It possesses pharmacological properties, which are attributed to its ability to bind to DNA and interfere with the functions of DNA. In the present paper, intermolecular interactions between prothracarcin (drug) and DNA base pairs have been evaluated using quantum mechanical methods. Second order perturbation theory valid for medium range interactions has been used to obtain binding sites of the prothracarcin drug. Binding patterns, relative stability of various drug-base pair complexes and preferred molecular associations have been discussed. The molecular dynamics results support the dynamically stable model of drug-DNA complex over the entire length of trajectory and also may provide valuable information for drug-DNA interaction.**

Keywords **– Intermolecular Interactions, Computer Simulation, CNDO/2, Multicentred-Multipole Technique, Nucleic Acids, Perturbation Theory, Antitumour Antibiotic, Pyrrolobenzodiazepines, Polymer, Biological Macromolecules.**

I. INTRODUCTION

Despite the relatively large number of DNA-binding drugs currently used in the clinic, selective toxicity towards disease-affected tissue (particularly tumours) remains an elusive goal. Furthermore, the exact mode of action for many of these compounds is poorly defined. As a result there is a major research effort, which seeks to gain a deeper insight into the molecular basis of interactions between small molecules and DNA with special emphasis on the site, mode, sequence and structural specificity of their binding reactions. In order to understand better the molecular basis of these important and complex interactions, it is often advantageous to use simplified model systems. The study of DNA-small molecule interactions provides well-defined models that allow general principles for biomolecular complex formation to be established. Many of the anticancer drugs employed clinically exert their antitumour effect by inhibiting nucleic acids or protein synthesis. 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 [1-4]. Pyrrolobenzodiazepines (PBDs) are sequence selective DNA alkylating agents with remarkable antineoplastic activity. They are either naturally produced by actinomycetes or synthetically produced. The remarkable broad spectrum of activities of the naturally produced PBDs encouraged the synthesis of several PBDs, including dimeric and hybrid PBDs yielding to an improvement in the DNA-binding sequence specificity and in the potency of this class of compounds. The biosynthetic gene clusters for PBDs have been identified opening the doors to the production of glycosylated PBDs by mutasynthesis and biosynthetic engineering. This review describes the recent studies on the biosynthesis of naturally produced pyrrolobenzodiazepines.

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In addition, it provides an overview on the isolation and characterization of naturally produced PBDs, chemical synthesis of PBDs, mechanism of DNA alkylation, and DNA-binding affinity and cytotoxic properties of both naturally produced and synthetic pyrrolobenzodiazepines.

A novel antibiotic, prothracarcin was isolated from the culture broth of Streptomyces. Structural studies established that prothracarcin is a new member of the pyrrolo [1, 4] benzodiazepine group antibiotics having only one substituent on the benzene ring. The antibiotic exhibited antimicrobial activity against Gram-positive bacteria and experimental murine tumor sarcoma and leukemia [5]. Prothracarcin (PROTH) is a member of the pyrrolo [1, 4] - benzodiazepine family. It is an antibiotic drug with potent antitumour, antimicrobial, amebicidal and chemosterilant activities. By virtue of its ability to form complexes with DNA, prothracarcin inhibits the activity of DNA-dependent RNA polymerase and certain DNA nucleases [6]. To understand the molecular basis of drug-DNA interactions, considerable efforts have been made in our laboratory [7-14]. The present paper reports the binding behaviour of prothracarcin with nucleic acid base pairs with an aim to elucidate the site, mode and structural specificity of the binding patterns G-C and A-T base pairs using quantum mechanical methods.

II. Method of Calculation

Modified Rayleigh-Schrodinger second order perturbation theory along with multicentred-multipole expansion technique as developed by Claverie and co-workers has been used to calculate interaction energy between drug molecule and DNA base pairs.

Accordingly, the total interaction energy (E_{TOT}) between two molecules is expressed as: $E_{TOT} = E_{EL} + E_{POL} + E_{DISP} + E_{REP}$

Where E_{EL}, E_{POL}, E_{DISP} and E_{REP} represent electrostatic, polarization, dispersion and repulsion energy components respectively [15]. The long range terms (electrostatic, polarization, dispersion) of the interaction energy between molecules at intermediate distances (i.e. distances of the order of magnitude of the molecular dimensions) is considered.

The electrostatic energy term is expressed as: $E_{EL} = E_{QQ} + E_{QMI} + E_{MIMI} + \ldots\ldots\ldots$

where E_{QQ}, E_{QMI} and E_{MIMI} etc. represent monopole-monopole, monopole-dipole, dipole-dipole and interaction energy terms consisting of multipoles of higher orders respectively. However, consideration upto the first three terms has been found to be sufficient for most of the molecular interaction problems [16].

The molecular geometry of prothracarcin has been constructed using the crystallographic data from literature and standard values of bond lengths and bond angles [17]. Net atomic charge and corresponding dipole moment components at each of the atomic centres of the molecule have been computed by CNDO/2 method [18]. During energy minimization, base pairs are kept fixed throughout the process while both lateral and angular variations are introduced in the prothracarcin molecule in all respects relative to the fixed one and vice versa. Accuracies up to 0.1Å in sliding (translation) and 1^0 in rotation have been achieved. The details of the mathematical formalism and optimization process may be found in literature [10-14, 15].

III. Results and Discussion

The molecular geometry of prothracarcin as used for CNDO / 2 studies is shown in Fig. 1. The molecular char-

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-ge distribution is listed in Table 1.

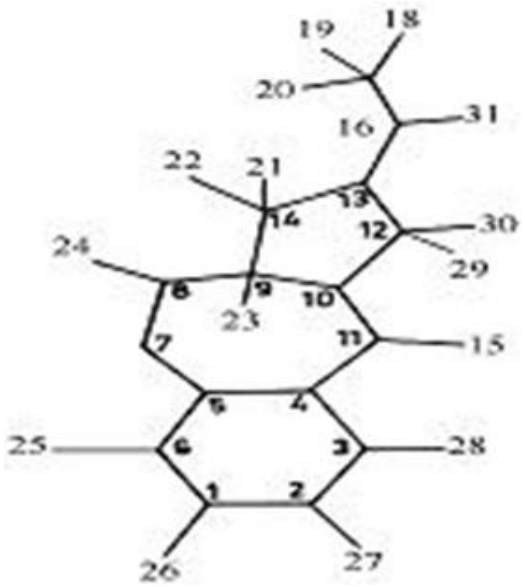

Fig. 1. Molecular geometry of prothracarcin with various atomic index numbers.

As expected, Table 1shows that atoms such as nitrogen and oxygen always bear electronegative charges while carbon atoms adjust their charges (e.u. = electron unit) according to their position.

The total energy, defined as the sum of atomic as well as electronic energies of all the constituents of the molecule in the equilibrium geometry, exhibits the following order (Table 2): Porothramycin > Mazethramycin > Chicamycin > Neothramycin B > Abbeymycin > **Prothracarcin** > Neothramycin A.

The binding energy of a molecule is the difference between the total energy of the equilibrium molecular geometry and the sum of the atomic energies of the constituent atoms. A comparison of binding energies of the various drugs shows the following order (Table 2): Porothramycin > Mazethramycin > Chicamycin > Neothramycin A > Abbeymycin > Neothramycin B > **Prothracarcin.**

The dipole moment shows the following order (Table 2): Porothramycin > Mazethramycin > Chicamycin > Abbeymycin > Neothramycin A > Neothramycin B > **Prothracarcin.**

The present investigation reveals that electronegative atoms like nitrogen and oxygen, in most of the cases, bear high negative charges. A comparative study with in the present set of molecules, shows that the differences in molecular structures introduced by the attachment or removal of specific groups lead to local changes in the molecular charge distribution.

The variation of stacking energy with respect to change of orientation of drug molecule keeping base pairs fixed and vice versa, is shown in Fig. 2(a). As evident from this figure, two minima are located for GC-PROTH complex having energy values –10.81 kcal/mole at 40^0 and –13.73 kcal/mole at 210^0. Similarly for AT-PROTH stacking, two minima-one at 120^0 with energy –11.40 kcal/mole and the other at 220^0 with energy –12.36 kcal/mole are obtained. Further, two minima are located for PROTH-GC complex having energy values –13.73 kcal/mole at 150^0 and –10.81 kcal/mole at 320^0. Similarly, in case of PROTH-AT complex, two minima are located- one at 140^0 with energy -12.36 kcal/mole and the other at 240^0 with energy -11.40 kcal/mole. Although two minima are located by each curve, these minima are separated by nearly 3.0 kcal/mole in case of GC base

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pairs while in case of AT base pair the energy difference between the minimum positions is reduced to approximately 1.0 kcal/mole. Obviously, the two minima located by either GC-PROTH or PROTH-GC curves show an energy difference of nearly 3.0 kcal/mole, which demonstrates strong orientational specificity of prothracarcin–GC base pair stacking patterns. However, in case of AT base pairs, orientational specificity is quite poor because both the minima correspond approximately to the same energy value. However, minima having lower energy values are subjected to further refined calculations.

The variation of stacking energy with respect to change of interplanar separation between base pairs and the drug molecule has been shown in Fig. 2(b) which shows that all the complexes exhibit their minima at 3.1Å. The energy for GC-PROTH and PROTH–GC complexes is found to be the same (–19.34 kcal/mole). Similarly, the AT-PROTH and PROTH-AT complexes are also stabilized with nearly the same energy, –17.66 kcal/mole. The minimum energy stacked complexes, thus obtained, are depicted in Fig.3 which shows that prothracarcin molecules stack through the hydrogen bonded region of base pairs in all the cases. Further, it is observed that the long molecular axis of the drug molecule lies nearly perpendicular to the base pair tilt axis and stacking occurs primarily through the hydrogen-bonded region of the base pairs. The details of the stacking energy of various complexes (Fig.3) are listed in Table 3.

It is clear from this table that complexes formed between the drug and GC base pairs are more stable as compared to those formed with A-T base pairs. Further, it indicates the following order of the stability of the stacked complexes (Table 3): $I \geq III > II \geq IV$

Evidently, dispersion component plays a dominant role in stabilizing all the complexes. Electrostatic energy has larger contribution (-6.11 kcal/mole) in case of complexes formed with GC base pair (Table 3).

These results suggest that complexes formed between GC base pair and the drug molecules are more favoured. The largest contribution to the stability of complexes is derived from dispersion forces irrespective of the base pair involved. Thus, prothracarcin drug like anthramycin, mazethramycin and porothramycin also prefers to stack in a dinucleotide unit having guanine (G) and cytosine (C) bases. Recently, the structure of the anthramycin-DNA adduct was studied by NMR, fluorescence spectroscopy, and molecular modelling techniques. Similar results have been observed in case of anthramycin and tomaymycin well known drug of PBD family. These results suggest that complexes formed between GC base pair and the prothracarcin (drug) molecules are more favoured.

Table 1. Molecular charge distribution of the Prothracarcin molecule.

Atom No.	Atom Symbol	Charge (e. u.)	Atomic Dipole Components (Debye)		
			X	Y	Z
1	C	0.023	0.058	0.125	-0.013
2	C	-0.009	-0.086	0.127	0.006
3	C	0.034	-0.139	0.010	0.014
4	C	-0.071	0.001	-0.139	-0.077
5	C	0.127	-0.088	0.047	-0.041
6	C	-0.021	0.118	-0.036	0.060

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Atom No.	Atom Symbol	Charge (e. u.)	Atomic Dipole Components (Debye)		
			X	Y	Z
7	N	-0.155	1.521	0.390	0.376
8	C	0.042	-0.119	-0.256	0.400
9	C	0.112	0.146	-0.002	-0.104
10	N	-0.183	0.020	0.114	0.090
11	C	0.352	-0.034	0.203	0.065
12	C	0.131	-0.207	-0.137	0.088
13	C	0.017	-0.022	-0.062	-0.008
14	C	-0.012	0.083	-0.097	-0.085
15	O	-0.356	-1.293	0.172	0.485
16	C	-0.011	-0.063	-0.082	0.038
17	C	-0.013	0.048	-0.143	-0.104
18	H	0.009	0.000	0.000	0.000
19	H	0.003	0.000	0.000	0.000
20	H	0.009	0.000	0.000	0.000
21	H	0.005	0.000	0.000	0.000
22	H	0.006	0.000	0.000	0.000
23	H	-0.013	0.000	0.000	0.000
24	H	0.019	0.000	0.000	0.000
25	H	-0.002	0.000	0.000	0.000
26	H	-0.005	0.000	0.000	0.000
27	H	-0.002	0.000	0.000	0.000
28	H	0.003	0.000	0.000	0.000
29	H	-0.012	0.000	0.000	0.000
30	H	-0.019	0.000	0.000	0.000
31	H	-0.011	0.000	0.000	0.000

Table 2. Total energy, binding energy and total dipole moment of various Drug Molecules studies.

S.N.	Drug Molecules	Total Energy (A.U.)	Binding Energy (A.U.)	Total Dipole Moment (Debyes)
1	Mazethramycin	-244.14	-21.64	5.64
2	Porothramycin	-252.80	-22.86	5.67
3	**Prothracarcin**	**-151.95**	**-16.46**	**2.26**
4	Chicamycin	-229.09	-18.72	4.91

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5	Abbeymycin	-183.52	-16.76	4.49
6	Neothramycin A	-118.71	-17.06	3.82
7	Neothramycin B	-200.26	-16.69	3.52

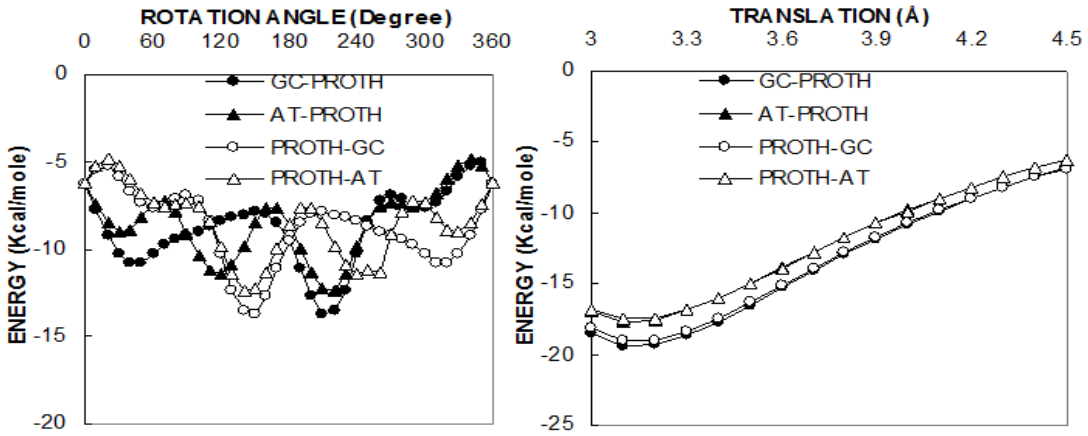

Fig. 2. Variation of total stacking energy of prothracarcin with various base pairs as a function of (a) angular rotation and (b) interplanar separation.

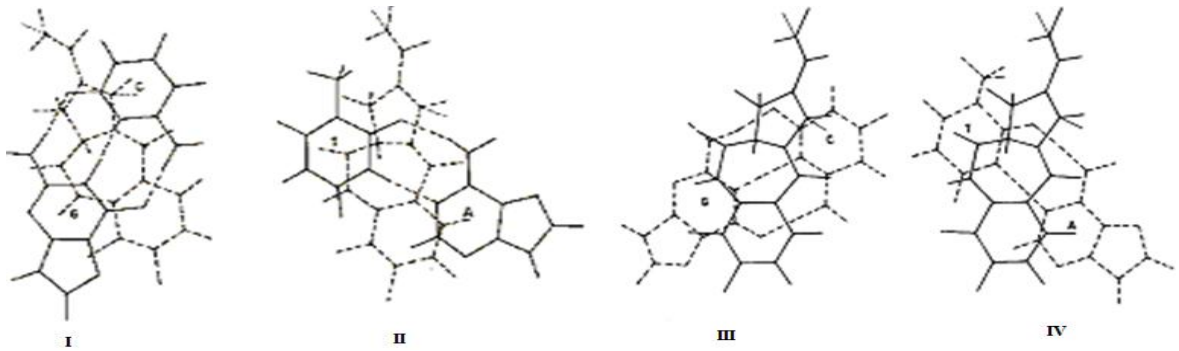

Fig. 3. Stacked minimum energy configurations of prothracarcin with DNA base pairs. The geometry shown by dotted lines represents the upper molecule in each case.

Table 3. Stacking energy of various complexes formed between prothracarcin and DNA base-pairs.

Energy Terms (Kcal/mole)	**Stacked Complexes**			
	GC-PROTH(I)	**AT-PROTH(II)**	**PROTH-GC(III)**	**PROTH-AT(IV)**
E_{QQ}	**-1.72**	**-1.63**	**-1.66**	**-1.63**
E_{QMI}	-2.80	-2.69	-2.64	-2.67
E_{MIMI}	-1.59	-1.09	-1.43	-1.02
E_{EL}	-6.11	-5.40	-5.73	-5.32
E_{POL}	-3.15	-2.35	-3.11	-2.36
E_{DISP}	-24.93	-22.65	-25.25	-22.60
E_{REP}	13.91	11.72	14.28	11.76
E_{TOT}	**-20.27**	**-18.68**	**-19.80**	**-18.52**
Inter-planar separation (A)	3.1	3.1	3.1	3.1

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IV. CONCLUSION

The present paper reveals that the binding of prothracarcin drug in a dinucleotide unit having guanine (G) and cytosine (C) bases will be more stabilized as compared to other sequences of DNA and GC rich region of DNA helices is more preferred and the mode of binding is similar to that of prothracarcin drug like mazethramycin, porothramycin, anthramycin also prefers to stack in a dinucleotide unit having guanine (G) and cytosine (C) bases. The largest stability contribution is derived from dispersion forces irrespective of the base pairs involved. Also as observed from the stacking patterns, there exists a possibility of the bond formation/interaction between the functional groups associated with the chromophore of the drug molecule and the backbone of the nucleic acid helices. These results are similar to those obtained in case of other intercalating drugs [7-14].

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