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# Theoretical Study of Drug-DNA Interactions: Neothramycin A

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**ABSTRACT:** Neothramycin A is a potential antibiotic drug. It is reported to bind to DNA and thereby inhibits the functions of DNA. In view of this fact, stacking interactions between Neothramycin A and DNA base pairs have been evaluated using quantum mechanical methods. Binding patterns, relative stability of various drug-base pair complexes and preferred binding sites of the drug have been presented. An attempt has been made to elucidate the pharmacological properties of the drug.

**KEYWORDS:** Intermolecular interactions, CNDO, Nucleic acids, Perturbation theory, Antibiotic drug. Computer simulation

## I. INTRODUCTION

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. 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. Many of the anticancer drugs employed clinically also exert their antitumour effect by inhibiting nucleic acid (DNA or RNA) 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.[3, 5, 7 & 10]

Neothramycin A (NA) 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, it inhibits the activity of DNA-dependent RNA polymerase and certain DNA nucleases [4, 6]. With an aim to gain a deeper insight into the molecular basis of drug-DNA interactions, considerable efforts have been made in our laboratory [11, 12, 13, 14 & 15]. In continuation, the present paper deals with the binding mechanism of Neothramycin A with nucleic acid base pairs with an emphasis on the site, mode and structural specificity of the binding patterns.

## II. METHOD OF CALCULATION

Modified Rayleigh-Schrodinger second order perturbation theory along with multicentred-multipole expansion technique as developed by Claverie and coworkers has been used to calculate interaction energy between drug molecule and DNA base pairs. According to this, 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 [2].

The electrostatic energy term is expressed as:

$$E_{EL} = E_{QQ} + E_{QM} + E_{MM} + \dots$$

where  $E_{QQ}$ ,  $E_{QM}$  and  $E_{MM}$  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 [9].

The molecular geometry of Neothramycin A has been constructed using the crystallographic data from literature and standard values of bond lengths and bond angles [1]. Net atomic charge and corresponding dipole moment components at each of the atomic centres of the molecule have been computed by CNDO/2 method [8]. During energy minimization, base pairs are kept fixed throughout the process while both lateral and angular variations are introduced in the Neothramycin A molecule in all respects relative to the fixed one and vice versa. Accuracies up to 0.1 Å in sliding (translation) and 1° in rotation have been achieved. The details of the mathematical formalism and optimization process may be found in literature [2, 16 & 13].

### III. RESULTS AND DISCUSSION

The molecular geometry of Neothramycin A as used for CNDO/2 studies is shown in Fig. 1. The molecular charge distribution is listed in Table 1.

As expected, Table 1 shows that atoms such as nitrogen and oxygen always bear electronegative charges while carbon atoms adjust their charges according to their position.

Table.1.Molecular charge distribution of the Neothramycin A

Atom No.	Atom symbol	Charge (e.u.)	Atomic dipole components (debye)		
			X	Y	Z
1	C	0.143	-0.010	-0.078	-0.024
2	C	0.130	0.092	-0.065	0.052
3	C	-0.011	-0.172	-0.003	0.005
4	C	-0.070	0.006	-0.144	-0.078
5	C	0.125	-0.098	0.018	-0.044
6	C	-0.051	0.140	-0.078	0.067
7	N	-0.151	1.523	0.383	0.375
8	C	0.039	-0.111	-0.264	0.409
9	C	0.113	0.166	0.005	-0.107
10	N	-0.227	-0.010	0.068	0.098
11	C	0.358	-0.034	0.213	0.070
12	C	0.419	0.001	-0.153	-0.054
13	C	-0.037	-0.067	-0.142	0.003
14	C	0.001	0.128	-0.087	-0.117
15	O	-0.350	-1.293	0.174	0.486
16	O	-0.255	-0.641	1.099	-0.076
17	O	-0.214	0.555	1.211	-0.083
18	C	0.134	-0.331	0.007	0.004
19	O	-0.303	-0.869	-0.892	-0.053
20	O	-0.301	-0.566	-1.023	0.426
21	H	0.151	0.000	0.000	0.000
22	H	0.139	0.000	0.000	0.000
23	H	0.024	0.000	0.000	0.000
24	H	0.024	0.000	0.000	0.000
25	H	0.002	0.000	0.000	0.000

26	H	0.003	0.000	0.000	0.000
27	H	-0.010	0.000	0.000	0.000
28	H	0.022	0.000	0.000	0.000
29	H	0.018	0.000	0.000	0.000
30	H	0.133	0.000	0.000	0.000
31	H	-0.009	0.000	0.000	0.000
32	H	-0.012	0.000	0.000	0.000
33	H	0.001	0.000	0.000	0.000
34	H	0.024	0.000	0.000	0.000

(Total energy = -218.71 a.u., Binding energy = -17.06 a.u., Total dipole moment = 3.82 debyes)

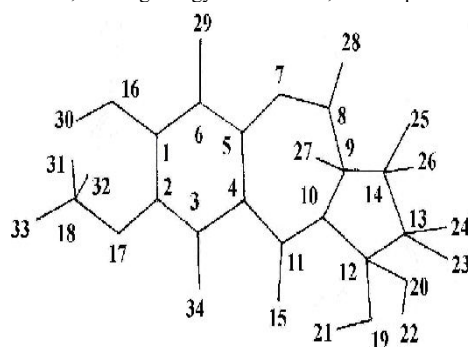


Fig.1. Molecular geometry of Neothramycin A with various atomic index numbers

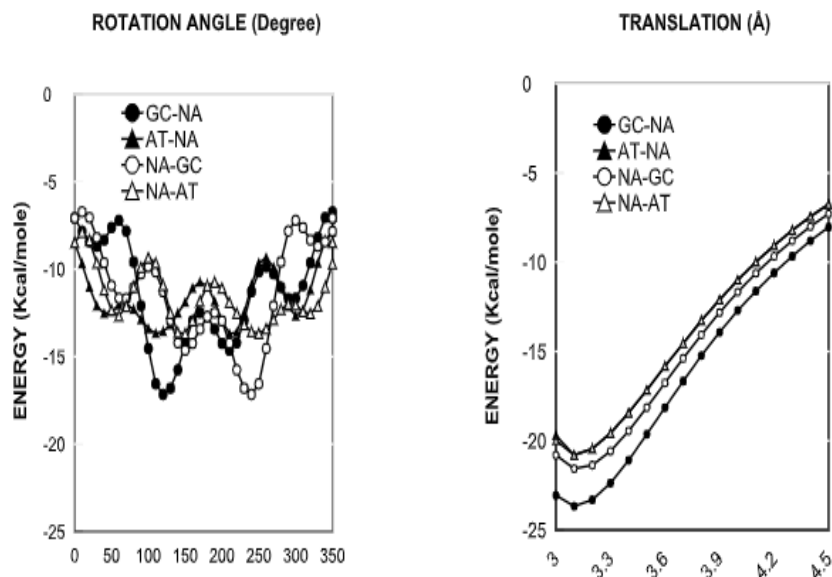


Fig. 2. Variation of total stacking energy of Neothramycin A molecule with various base pairs as a function of (a) angular rotation and (b) interplanar separation.

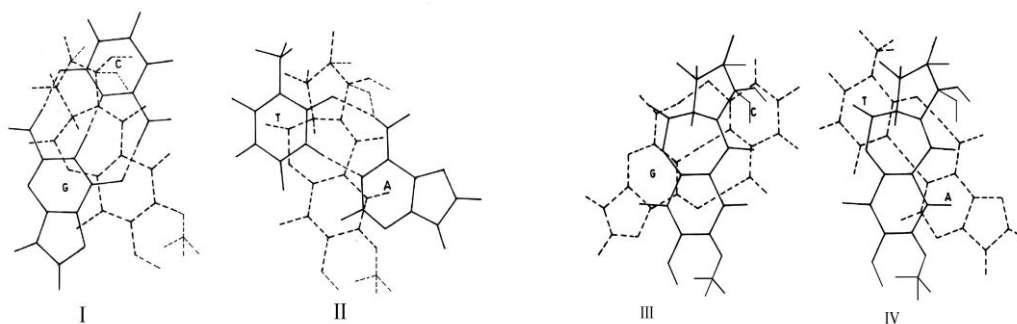


Fig. 3. Stacked minimum energy configurations of Neothramycin A molecule with DNA base pairs. The geometry shown by dotted lines represents the upper molecule in each case.

Table 2. Stacking energy of various complexes formed between Neothramycin A (NA) and base-pairs.

Energy terms (Kcal/mole)	Stacked Complexes			
	GC-NA (I)	AT-NA (II)	NA-GC (III)	NA-AT (IV)
EQQ	-2.30	-0.42	-2.14	-0.42
EQMI	-3.95	-3.86	-3.44	-3.83
EMIMI	-1.15	-2.33	-1.12	-2.23
<b>EEL</b>	<b>-7.40</b>	<b>-6.61</b>	<b>-6.70</b>	<b>-6.48</b>
EPOL	-4.00	-2.21	-4.05	-2.23
EDISP	-27.94	-23.33	-28.67	-23.62
EREP	13.95	11.13	14.67	11.36
ETOT	<b>-25.38</b>	<b>-21.01</b>	<b>-24.75</b>	<b>-20.98</b>
Separation (Å)	3.1	3.1	3.1	3.1

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-NA complex having energy values  $-17.17$  kcal/mole at  $120^\circ$  and  $-14.63$  kcal/mole at  $210^\circ$ . In case of AT-NA stacking, two minima one at  $40^\circ$  with energy  $-12.54$  kcal/mole and the other at  $110^\circ$  with energy  $-13.67$  kcal/mole are obtained. Similarly, two minima are located for NA-GC complex having energy values  $-14.63$  kcal/mole at  $150^\circ$  and  $-17.16$  kcal/mole at  $240^\circ$ . In case of NA-AT complex, again two minima are located -one at  $60^\circ$  with energy  $-12.67$  kcal/mole and the other at  $150^\circ$  with energy  $-13.69$  kcal/mole. Although two minima are located by each curve, these minima are separated nearly by a difference of  $3.0$  kcal/mole in case of GC base pairs while in case of AT base pairs the energy difference between the minimum positions is reduced to approximately  $1.0$  kcal/mole. The minima having lower energy values have been chosen for 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  $3.1 \text{ \AA}$ . The energy for GC-NA and NA-GC complexes is found to be different,  $-23.67$  kcal/mole and  $-21.57$  kcal/mole respectively. Similarly, the AT-NA and NA-AT complexes are also stabilized with nearly the same energy,  $-20.81$  kcal/mole.

The minimum energy stacked complexes, thus obtained, are depicted in Fig. 3, which shows that Neothramycin A molecules stack through the hydrogen bonded region of base pairs in all the cases. The long molecular axis of the drug molecule lies nearly perpendicular to the base pair tilt axis. The details of stacking energy are listed in Table 2. It is clear from the table that complexes formed between the drug and GC base pairs are more stable as compared to those formed with AT base pairs. Further, Table 2 indicates the following order of the stability of the stacked complexes:

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

It seems worthwhile to mention that the dispersion component plays a dominant role in stabilizing all the complexes and electrostatic energy is largest (-7.40 kcal/mole) in case of GC-NA 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. The largest stability contribution is derived from dispersion forces irrespective of the base pairs involved. Further, it is observed that long molecular axis of the drug lies nearly perpendicular to the base pair tilt axis and stacking occurs primarily through the hydrogen-bonded region of the base pairs. Thus binding of Neothramycin A drug in a dinucleotide unit having guanine and cytosine bases will be more stabilized as compared to other sequences. Also as observed from the stacking patterns, there exists a possibility of the bond formation due to interaction between the functional groups associated with the chromophore of the drug molecule and the backbone of the nucleic acid helices.

#### IV. CONCLUSION

Molecular complexes formed between the drug and base pairs are stabilized mainly by dispersion type of interactions. Binding of Neothramycin A to GC rich region of nucleic acid helices is more preferred. Further, the mode of binding seems to be intercalative which may be held responsible for the pharmacological properties of the drug.

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#### REFERENCES

- [1] S. K. Arora, Acta Cryst. **B 35**, 2945, 1979.
- [2] P. Claverie, "In: Intermolecular Interactions: From Diatomics to Biopolymers, editor, B. Pullman, John Wiley", New York, pp. 69, 1978.
- [3] I. Haq, and J. Ladbury, J. Mol. Recognit., **13**, 188, 2000.
- [4] S. B. Horwitz, "In: Progress in Molecular and Subcellular Biology, editors, F.E. Hahn et al", Springer-Verlag, New York, vol **2**, pp. 39, 1971.
- [5] R. Kumar, and J.W. Lown, Org. Biomol. Chem., **1** 3327, 2003.
- [6] A. Kamal, M.V. Rao, N. Laxman, G. Ramesh, and G.S.K. Reddy, Curr. Med. Chem. Anti-Cancer Agents, **2**, 215, 2002.
- [7] M. Maiti, "In: Perspectives in Structural Biology, editors, M. Vijayan, N. Yathindra and A.S. Kolaskar", Universities Press, India, 583, 1999.
- [8] J.A. Pople, and D.L. Beveridge, Approximate Molecular Orbital Theory, Mc-Graw Hill Pub Co, New York, 1970.
- [9] R. Rein, "In: Intermolecular Interactions: From Diatomics to Biopolymers, editor, B. Pullman", John Wiley, New York, pp. 307, 1978.
- [10] W. Saenger, Principles of Nucleic Acid Structure, Springer-Verlag, New York, 1984.
- [11] N.K. Sanyal, M. Roychoudhury, S.N. Tiwari, and K.R. Ruhela, Indian J. Biochem. Biophys., **27**, 213; **27**, 222, 1990.
- [12] N.K. Sanyal, and S.N. Tiwari, J. Biosci, **24 (S-1)** 91, 1999.
- [13] R. Shukla, M. Mishra, and S. N. Tiwari, Progress in Crystal Growth and Characterization of Materials, USA, 52,107, 2006.
- [14] S.N. Tiwari, K.R. Ruhela, M. Roychoudhury, and N.K. Sanyal, Indian J. Phys., **65B**, 495, 1991.
- [15] S.N. Tiwari, and N.K. Sanyal, J. Biosci, **24 (S-1)** 92, 1999.
- [16] S.N. Tiwari, M. Mishra, and N.K. Sanyal, Indian J. Phys., **76B**, 17, 2002.

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