CHAPTER 7

INTERCALATION MODEL OF DRUG BETWEEN SEQUENCES OF DNA

SUMMARY

The intercalation models of aminoazaacridinecarboxamide with sequences of DNA have been studied for analyzing the stacking of this drug with two base pair. The chromophore is more stabilized within two AT and two GC sequence than the stacking of chromophore with single AT and GC. All these drugs are highly GC specific and 9-oxoazaacridone-4-carboxamide intercalates more favourably within GC sequences compared to 9-aminoazaacridine-4-carboxamide and 9-chloroazaacridine-4-carboxamide.

7.1 INTRODUCTION

There are abundant investigations on the sequence specific binding of drugs through intercalation into DNA ***[1-10]***. In this context the sequence preference of intercalator has been monitored by the crystallographic, NMR and florescence methods. In some cases the knowledge of intercalating ability is obtained from the florescence methods, where the results do not always well agreed with the findings of other methods ***[7-13]***. The intercalation of drug with poly(dG-dC).poly(dC-dC) and poly(dA-dT).poly(dA-dT) has been examined by constructing different intercalation model of this drug with GC and AT sequence, and similar study can be taken up for mixed sequences like d(CGTACG)2 ***[10-12]***. It is seen that aminoacridinecarboxamides stacks preferably with GC sequences ***[14-15]***. Tthough aminoacridine-4-carboxamide acquires strong preference for GC sequences, it is felt to be more appropriate to consider the complete intercalation model, where the drug molecule is placed in between two sequences. The mode of interaction can be demonstrated with respect to the specific location of drug in sequences. It is obvious that the basic concept of drug intercalation, in addition to single base pair stacking, can be determined by constructing the intercalation model consisting of two sequences ***[5-10]***. Though the idea of sequence specificity has been developed from the stacking ability of acridine-4-carboxamide with single base pair, it may be appropriate to look further for the intercalation model of drug with two base pairs. Experimental studies in the DNA binding of this drugs

do not indicate much preference for dA-dT or dC-dG oligonucleotides, and also the stacking energies of chromophore with AT and GC sequences show less significance in spite of having more specificity for GC sequences *[5-13]*. At the same time some acridine chromophore acquires AT specificity. The electronic properties of intercalators may cause shifting of specificity from GC to AT sequence. In that case the sequences at the intercalation site have been expected to influence the intercalator. In the present study the various intercalation models of chromophore and two sequences will be taken up for estimating intercalation abilities of chromophores.

7.2 METHODOLOGY

We have selected the most stable stacked structures of 9-oxoazaacridone-4-carboxamide (AZO), 9-aminoazaacridine-4-carboxamide (AZN) and 9-chloroazaacridine-4-carboxamide (AZCl) with AT and GC for modeling intercalative binding between drug and two sequences of DNA (**Figure 7.1a-l**). In this case another base pair was placed on top of the first base pair exactly at the same position and orientation as the drug-sequence stacking. The stacking distances D of both the base pairs are optimized. In this way intercalation model of AT-drug-AT and GC-drug-GC were analysed (**Figure 7.1a-l**). We have completely optimized all the drugs and base pairs with HF/6-31G route before constructing the intercalation models *[16]*.

7.3 RESULTS AND DISCUSSION

The variation of stacking energies of the intercalated aza analogues of acridine-4-carboxamide is shown in **Table 7.1**. The energy values are computed by adding another base pair on the top of the drug at a similar orientation and at equal stacking distances of the other base pair (**Figure 7.1a-l**). As expected, the stacking of drug with two base pairs results more stabilization of intercalated model (**Table 7.1**).

It is seen that the interaction energies change with respect to stacking distances and in some cases optimum stacking distance lies at the longer distances than drug-base pair stacking (**Table 7.2a-b**). We have found the optimum stacking distance for AZN and AZO with AT and GC at 3.9 Å (**Table 7.2a-b** and **Figure 7.2a-d**). However in case of AZCl the optimum stacking distance with AT is 4.0 Å and with GC is 4.1 Å (**Table 7.2a-b** and **Figure 7.2e-f**). The AZO intercalates preferably within GC sequence and the corresponding stacking distance is found to be at 3.9Å. Similarly, the stacked AZN with GC

sequence is found to be stable at 3.9 Å (**Figure 7.2d**). The drugs AZO and AZN intercalates preferably between the GC sequences. In **Table 7.2a-b** and **Figure 7.2a-f** there observed significant increase of stacking distances of drugs within AT sequences. This may be due to the change in the electronic behavior at the site of intercalation of these two sequence combinations, 2GC and 2AT. Hence we further focus on the more favorable orientation of drug in between the base pairs. Hence we further carry out calculation to locate for the optimum orientation of drug chromophore (AZO8) in between these base pair (**Figure 7.3** and **Table 7.3**). There observed slight variation in the orientation of drug from the optimum stacked structure. Thus the additional sequence results better stacking than the single base pair and also elongats the stacking distances between chromophore and base pairs (**Table 1** and **2a-b**). Nevertheless these intercalated chromophores may be stabilized by intermolecular interaction between the chromophore of drug with both the sequences. In this case the electronic polarization from both the sequences might operate in the stabilization of the intercalated chromophore. This may be the reason why the double stacking is more favorable than the single stacking. It may be noted that the use of more electron correlation is always recommended, but it is almost impossible for the present system. Here the computed values show a fair comparison of various intercalation models. Moreover compatibility of 6-31G calculation with those of 6-31G** and MP2 calculations in predicting optimum stacked structure have been shown in chapter 4. Hence the results obtained from this method may be taken for qualitative interpretation on the intercalation model of chromophore with base pairs.

7.4 CONCLUSION

The interaction energies of intercalated model are much improved than the stacking energies of this drug with single base pair. There may be shifting of sequence specificity of this drug depending on the sequence combination of drug binding region of DNA.

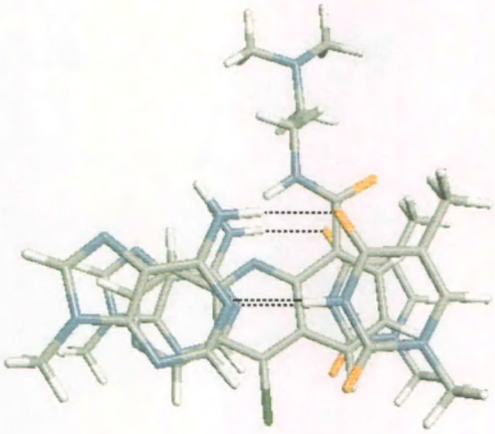

Figure 7.1a-Intercalation model of AT-AZCl7-AT (Top view)

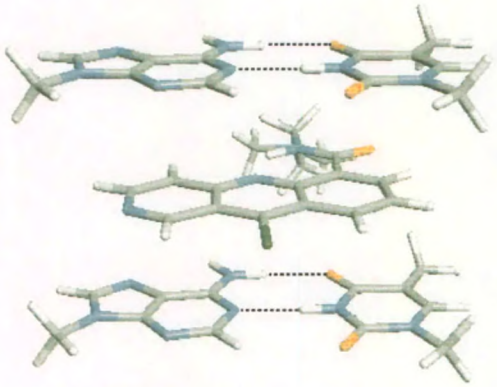

Figure 7.1b- Intercalation model of AT-AZCl7-AT (Side view)

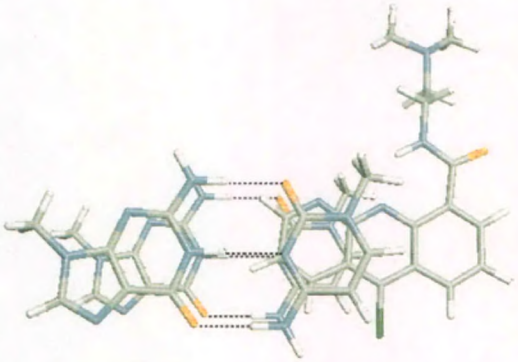

Figure 7.1c-Intercalation model of GC-AZCl5-GC (Top view)

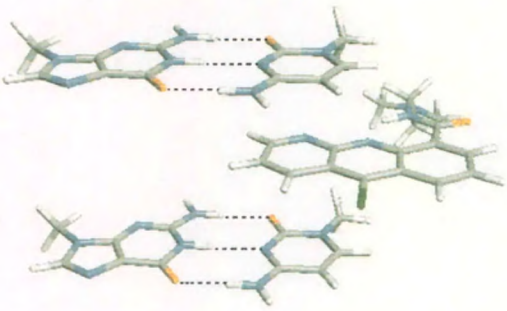

Figure 7.1d- Intercalation model of GC-AZCl5-GC (Side view)

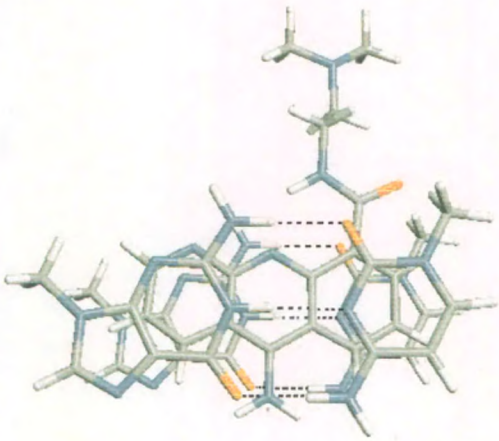

Figure 7.1e- Intercalation model of GC-AZN5-GC (Top view)

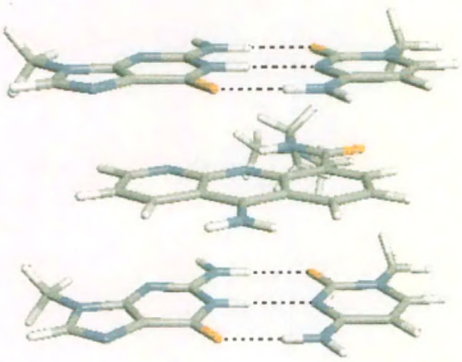

Figure 7.1f- Intercalation model of GC-AZN5-GC (Side view)

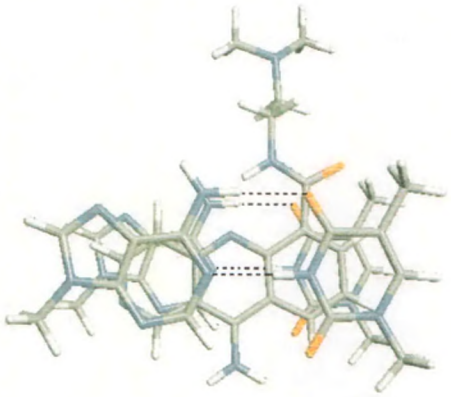

Figure 7.1g- Intercalation model of AT-AZN7-AT (Top view)

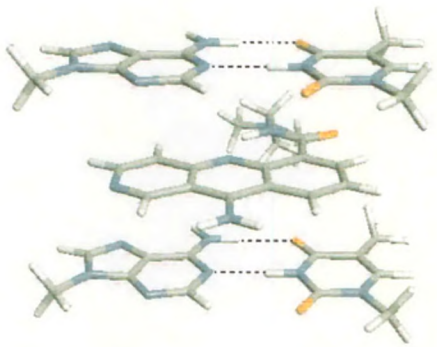

Figure 7.1h- Intercalation model of AT-AZN7-AT (Side view)

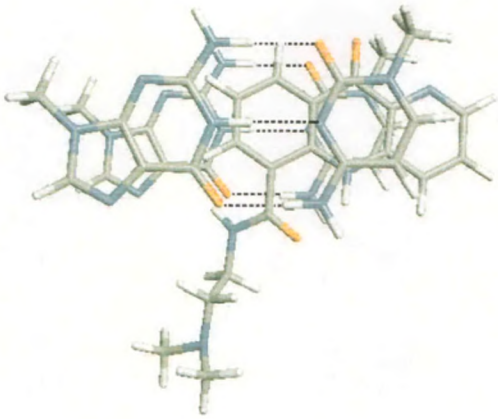

Figure 7.1i- Intercalation model of GC-AZO8-GC (Top view)

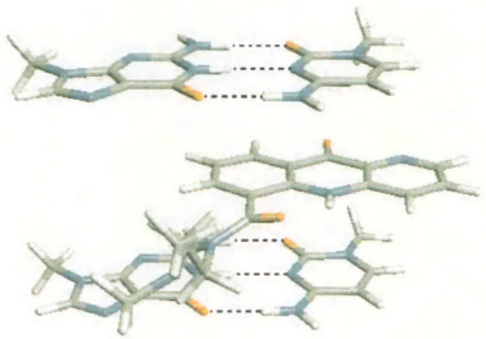

Figure 7.1j- Intercalation model of GC-AZO8-GC (Side view)

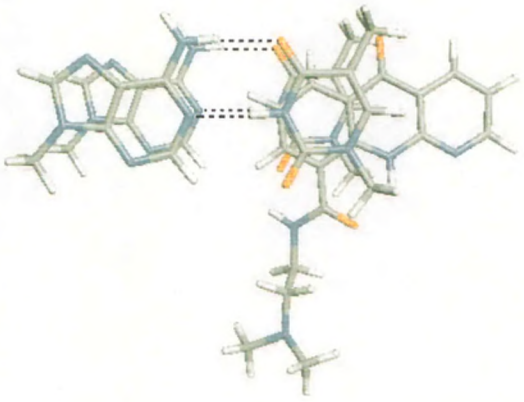

Figure 7.1k-Intercalation model of AT-AZO5-AT (Top view)

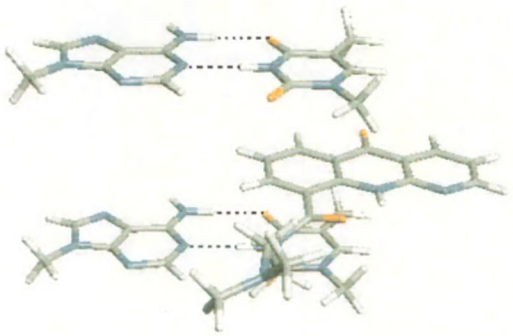

Figure 7.1l- Intercalation model of AT-AZO5-AT(Side view)

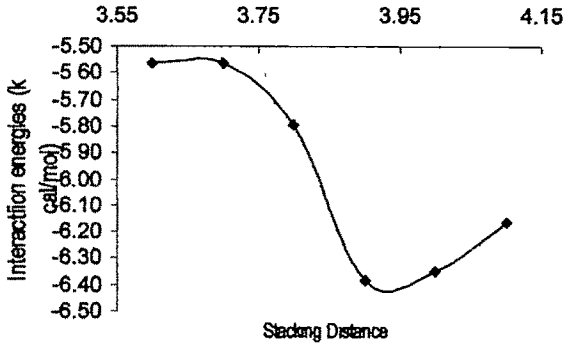

Figure 7.2a - Plot of stacking distance versus Interaction energies of AZO5 and AT-AT stacking.

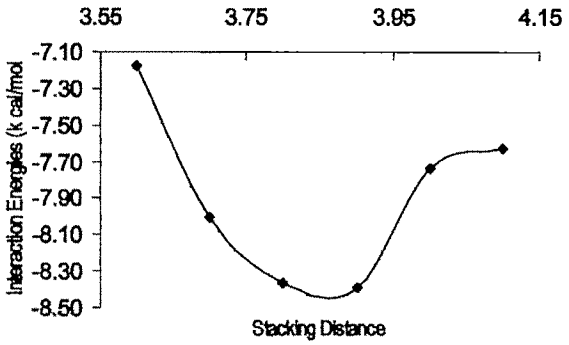

Figure 7.2b - Plot of stacking distance versus Interaction energies of AZO8 and GC-GC stacking.

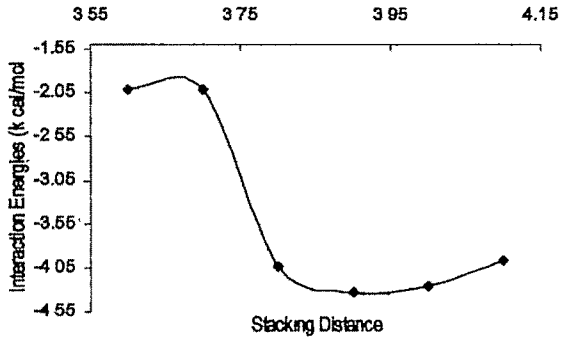

Figure 7.2c - Plot of stacking distance versus Interaction energies of AZN7 and AT-AT stacking.

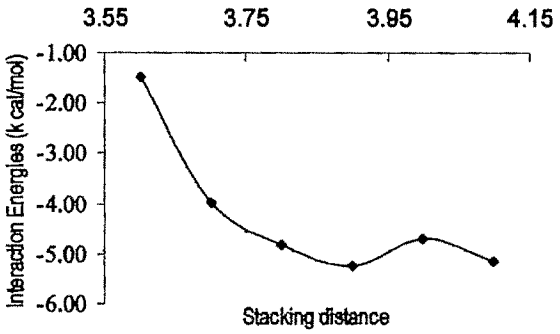

Figure 7.2d - Plot of stacking distance versus Interaction energies of AZN5 and GC-GC stacking.

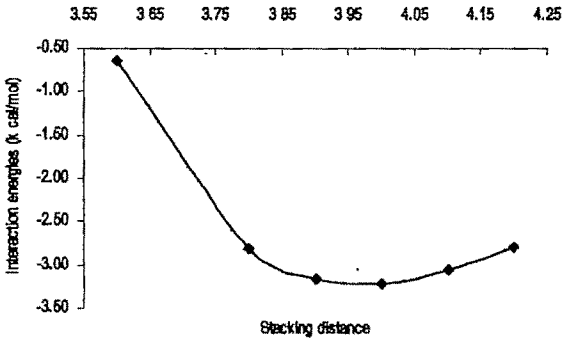

Figure 7.2e - Plot of stacking distance versus Interaction energies of AZCl7 and AT-AT stacking.

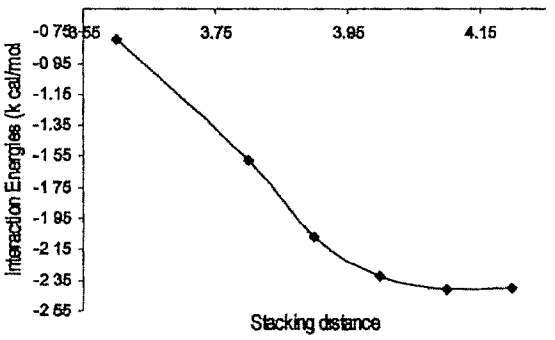

Figure 7.2f - Plot of stacking distance versus Interaction energies of AZCl5 and GC-GC stacking.

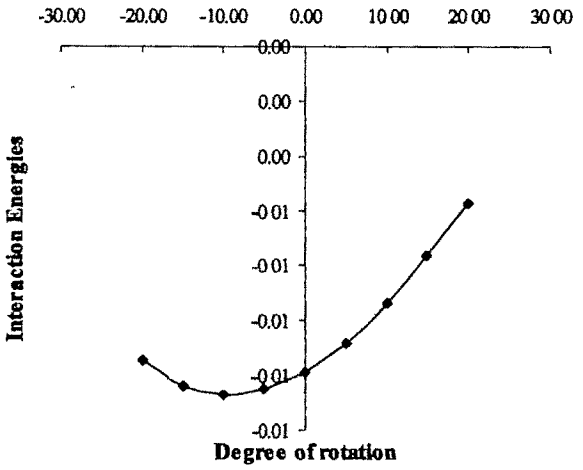

Figure 7.3 - Plot of orientation versus Interaction energies of AZO8 and two GC stacking.

Table 7.1 – Comparison of the Interaction Energies (HF/6-31G) of Chromophore (AZO, AZN, AZCl) with one and two base pairs at stacking distance of 3.6 Å.

Stacked model (XX-DRGx)	Interaction energies of chromophore Interacted with	
	Single base pair (k cal/mol)	Double base pair (k cal/mol)
AT-AZO5	-0.501	-5.566
AT-AZN7	-1.531	-2.008
AT-AZCl7	-0.882	-0.647
GC-AZO8	-2.788	-7.174
GC-AZN5	-2.132	-1.471
GC-AZCl5	-1.282	-0.796

XX= AT or GC; DRG = name of the drug; x = position of Nx; (Drugs are 9-oxoazaacridone-4-carboxamode (AZO), 9-aminoazaacridine-4-carboxamode (AZN) and 9-chloroazaacridine-4-carboxamode (AZCl))

Table 7.2a- The optimum stacking distance of drugs with two AT base pair

Stacked model (AT-DRGx)	Optimum interaction distance (Å)	Interaction Energies (k cal/mol)
2AT-AZO5	3.9	**-6.385**
2AT-AZN7	3.9	**-4.327**
2AT-AZCl7	4.0	**-3.209**

DRG = name of the drug; x = position of Nx; (Drugs are 9-oxoazaacridone-4-carboxamode (AZO), 9-aminoazaacridine-4-carboxamode (AZN) and 9-chloroazaacridine-4-carboxamode (AZCl))

Table 7.2b- The optimum stacking distance of drugs with two GC base pair

Stacked model (GC-DRGx)	Optimum interaction distance (Å)	Interaction Energies (k cal/mol)
2GC-AZO8	3.9	**-8.391**
2GC- AZN5	3.9	**-5.254**
2GC- AZCl5	4.1	**-2.417**

DRG = name of the drug; x = position of Nx; (Drugs are 9-oxoazaacridone-4-carboxamode (AZO), 9-aminoazaacridine-4-carboxamode (AZN) and 9-chloroazaacridine-4-carboxamode (AZCl))

Table 7.3- Variation of Interaction Energies with Rotation of Drug molecule (AZO8) between Base pair (GC-GC)

Degree of rotation	Interaction Energies (k cal/mol)
-20.00	-7.175982
-15.00	-7.773003
-10.00	**-7.981079**
-5.00	-7.843162
0.00	-7.459839
5.00	-6.788154
10.00	-5.881683
15.00	-4.790987
20.00	-3.594261

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