CHAPTER - II

Scope and Object of the Present Work

The interaction of a defined macromolecular species, nucleic acids with antibacterial mutagenic dyes and antibiotics as well as carcinogenic hydrocarbons provides a rational approach for studying site specific drug binding processes. The structural orientation within the nucleic acid molecule caused by the binding of the interacting species affords a unique scope to study the nature of the forces existing between the interacting molecules. Such interactions produce profound pharmacological effects by interfering with biological processes in which nucleic acids participate.

It is, therefore, of great interest to know the principles which govern the reactivity of bases in DNA towards certain carcinogens or mutagens. The reactivity of DNA or RNA or polynucleotides towards chemical reagents has been found to depend on nucleotide sequence of secondary or tertiary structure. The difference between DNA and RNA in their susceptibilities to base hydrolysis is known to be due to the secondary structure in the former.

Certain polycyclic hydrocarbons and nitrogen containing polycyclic carcinogens form complexes and are intercalated by native DNA and polynucleotides in much the same manner as acridines and phenanthrenes. Polycyclic hydrocarbons, which

are neutral, bind to DNA to a lesser extent than nitrogen containing polycyclics. Apparently, electrostatic factors play an important, if not major, role in the intercalation of heterocyclic carcinogens with DNA, even though hydrophobic force involved in intercalation probably determines the precise structure of the complex.

Lerman, on the basis of his investigation on the interactions of cationic dyes with DNA has shown that structural requirement is an important factor of intercalation. Hence, if some requirements of size and planarity are satisfied, heterocyclic dyes, antibiotics and hydrocarbons may intercalate into the DNA active structure and bind in a somewhat less specified way to single chain polynucleotides. This is known as strong binding or intercalation, and is a slower process than the weaker but faster binding to an outside region of the nucleic acid structure. Further more, the relative distribution of binding on the various sites available is also dependent on ionic strength.

Keeping all these in view, the object of the present investigations have been chosen. Different aspects of the present work are as follows:

(i) Four phenothiazine dyes of different size have been synthesized. The aggregation of the dyes in aqueous solution have been studied spectrophotometrically. The dependence

of the aggregation tendency on the shape and size of the dyes has been investigated.

(ii) The interactions of the four dyes with some polynucleotides, namely, poly A, poly U, poly I, poly C and poly G having single chain structure have been studied spectrophotometrically in the visible region.

(iii) Three different mixtures, namely, poly A plus poly U, poly A plus poly I, and poly I plus poly C have been prepared, which have been considered to possess doubly stranded helical structure. The interactions of these mixtures of polynucleotides with the four dyes have been similarly studied.

(iv) The interaction of the four dyes with native and denatured DNA have also been studied spectrophotometrically.

(v) The data obtained in the present investigation have been examined in the light of various models proposed by different workers to explain binding of dye by polynucleotides as well as DNA.

The object in the study of the interaction of the phenothiazine dyes with the synthetic polynucleotides is (a) to discuss the interaction of the dyes with various polynucleotides, with particular regard to the stoichiometry of the process, the site of binding, the degree of specificity and the behaviour of the dyes on the polymer surface; (b) to ascertain whether a difference in the nature of their interactions in solution reflects a general difference in the response of single stranded and multistranded polynucleotides.