Chapter 32. Stereochemistry of Drug-Nucleic Acid Interactions and its Biological Implications

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Introduction - The nucleic acids DNA and RNA are undoubtedly among the best defined of all target molecules for the action of drugs, antibiotics, antineoplastic agents, antiparasitic agents, and antibacterial agents.[1,2] This has encouraged many workers over the years to define the molecular geometries of such drug-nucleic acid interactions and to understand the mechanisms of drug action for a wide spectrum of drugs and antibiotics known to bind to double-stranded nucleic acids, often with the hope of more effective and rational drug design.

A variety of techniques have been used to study the binding of drugs to nucleic acids and to provide information concerning the precise nature of drug-nucleic acid interactions,[3-24] Two main modes of binding drugs to nucleic acids have been suggested.[3-6] The primary and generally stronger mode of binding has been interpreted as intercalation where a planar part of the bound drug molecule slides between adjacent base-pairs in the DNA helix.[3,4] The second and generally weaker mode of binding is thought to be an electrostatic interaction between the phosphate groups in the double-stranded nucleic acids and the drug molecules.[5,6] This review focuses primarily on the stereochemical studies of the interaction of drugs with double-stranded nucleic acids.

It has been suggested that three classes of intercalative drugs or agents may be distinguished by their directional entrance into the DNA helix.[39] The first class intercalates exclusive from the minor groove. Drugs in this class may include actinomycin D and ethidium. The second class may intercalate exclusively from the major groove. Examples of drugs in this class may be daunomycin, proflavine, and acridine orange. Finally, there may be a third class of intercalative drugs that can intercalate from either the major or minor grooves. Drugs in this class may include 9-aminoacridine and ellipticine. It is possible that the biological activities of these drugs and the kinetics of their binding reactions to DNA reflect their directional entrance into DNA helix, as defined by these three classes.[39]

The stereochemistry of actinomycin D binding to DNA demonstrates a general principle that drugs and proteins may utilize in recognizing symmetrically arranged nucleotide sequences on the DNA helix, and suggests a rationale for the synthesis of new variants of the actinomycin molecule that may be used clinically in the chemotherapy for neoplastic disease and viral infection.[12,75]

Le Pecq et al.[74] have used the intercalating properties of ellipticine in a systematic attempt to obtain highly active anticancer drugs by consideration of various ellipticine molecular modifications, and have

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demonstrated that 9-hydroxyellipticine had the highest DNA affinity and the strongest pharmacological activity. It seems plausible that the introduction of the hydroxy group has enhanced binding, by means of a hydrogen bond to a DNA phosphate.

Recently there have been encouraging signs that interpretation of the molecular model for the interaction of daunomycin with DNA proposed by Pigram et al.[56] may well lead to more active derivatives of daunomycin.[60] A detailed examination of the daunomycin-DNA model reveals that intercalation of the chromophore is only partial compared with simple intercalative agents such as proflavine; on the basis of the model it was proposed that removal of the bulky methoxy group on the chromophore ring would result in a molecule that could intercalate more effectively. Di Marco and his coworkers[61] have now synthesised, and exhaustively examined new daunomycin derivatives that lack just this methoxy group. The modified molecule does indeed bind to DNA somewhat better than its parent molecule. Significantly, in vivo testing of these 4-demethoxy derivatives in mouse cancer systems, both of the leukaemic and solid tumor type, show that it is as effective as daunomycin itself, but at dose levels four to eight times lower.

In a recent report,[23] Krugh and Young have shown that daunomycin and adriamycin facilitate strong binding of actinomycin D to poly(dA-dT).poly (dA-dT). This new observation suggests that combinations of intercalative drugs, such as daunomycin (or adriamycin) with actinomycin D, should be explored clinically.[23]

The concept of drug-DNA intercalation has stimulated the synthesis and study of a new compound, bis(methidium)spermine,[76] that binds DNA very tightly by polyintercalation as echinomycin[77,78] and bisacridine.[79] The compound is a dimer of a well-characterized DNA-binding compound, ethidium. The two ethidium molecules in the dimer are joined by spermine; the linker is long enough to permit the planar ethidium portions to fit between nonadjacent DNA base-pairs. The binding of bis(methidium)spermine not only is tight, but it has significant sequence specificity for p(dC-dG), a synthetic DNA polymer, over calf thymus DNA.[76]

Unifying Structural Concepts in Understanding Drug-Nucleic Acid Interactions and their Broader Implications in Understanding Protein-DNA Interactions - The structural information and stereochemical features afforded by the X-ray crystallographic studies of ethidium-dinucleoside monophosphate crystalline complexes have led Sobell, Tsai et al.[39,42] to generate a detailed molecular model for ethidium-DNA binding. The model predicts that at maximal drug-nucleic acid binding ratios, ethidium intercalates between every other base pair in DNA (i.e. a neighbor exclusion model for intercalative drug binding); this follows from the mixed sugar puckering pattern, C3'endo (3'-5') C2'endo, that is observed in the crystalline complexes. Base-pairs in the immediate region of intercalation are twisted by 10^{o}; this gives rise to an angular unwinding of -26^{o} at the immediate site of the drug intercalation. Base-pairs in the immediate region of intercalation are separated by about 6.7 Å; this distance

reflects the presence of an ethidium molecule intercalated between base-pairs. The phenyl and ethyl groups of the ethidium molecule lie in the minor groove of DNA; this suggests that the direction of entrance by this drug is from the minor groove of the double helix. A weak pyrimidine-purine sequence binding preference is predicted from stacking considerations of ethidium on adjacent base pairs. The model explains a large mass of physical and biochemical data concerning the interaction of ethidium with DNA and contains the more general stereochemical postulate that drug intercalation gives rise to a helical screw axis dislocation in DNA, a variable whose magnitude determines the relative ring overlap between an intercalative drug molecule and adjacent base-pairs. The conformational changes in the sugar-phosphate backbone that accompany drug intercalation

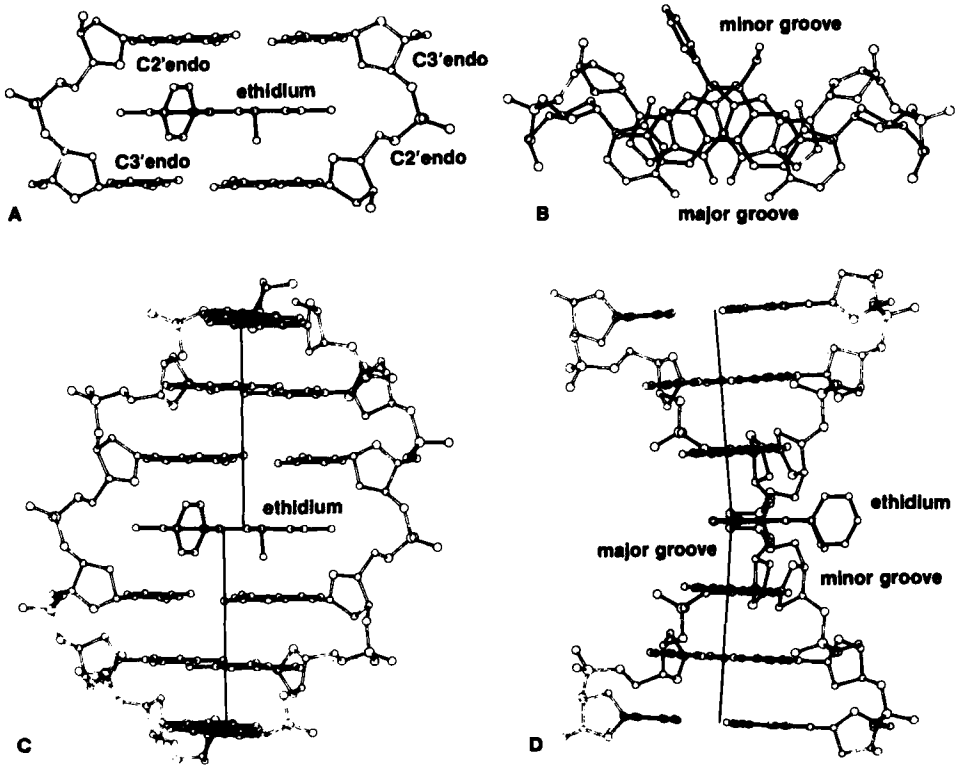
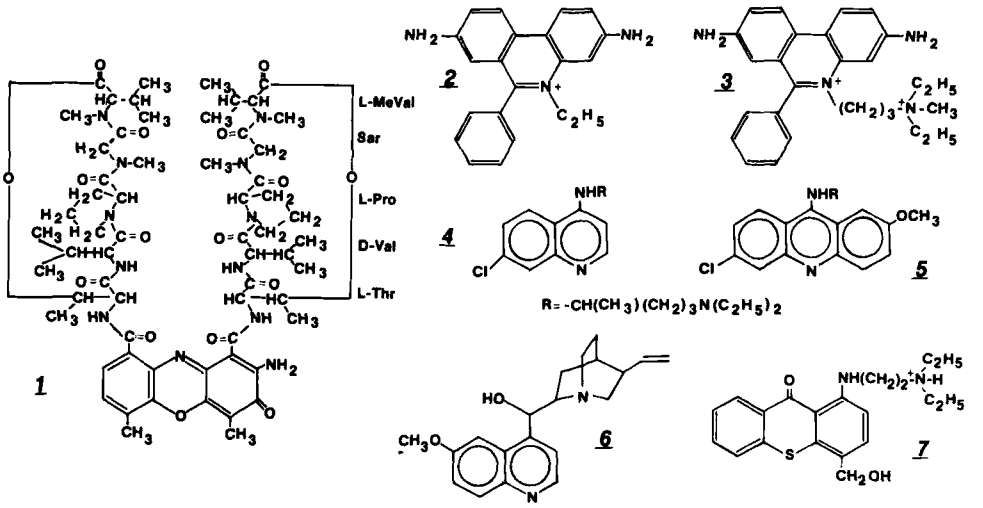


Fig. 1. Computer-graphic illustrations of the detailed stereochemistry for ethidium-DNA binding. (From Ref. 39 with permission of publisher.)
(A) Structure of ethidium-CpG intercalated complex, viewed down the dyad axis and parallel to the planes of ethidium and base-pair molecules.
(B) Structure of ethidium-CpG intercalated complex, viewed perpendicular to the planes of ethidium and base-pair molecules.
(C) Ethidium-DNA intercalation, shown down the dyad axis.
(D) Ethidium-DNA intercalation, side view. Long solid lines indicate helix axes for B-form DNA sections above and below ethidium intercalation structures. Notice that these helix axes are not colinear.

and a small residual "kink" of 8° at the intercalation site have led Sobell, Tsai et al. [39,42] to propose that DNA first bends or "kinks" to accept an intercalative drug or dye. This is made possible by altering the normal C2'endo deoxyribose sugar ring puckering in B-DNA to a mixed puckering pattern of the type: C3'endo (3'-5') C2'endo and partially unstacking base-pairs.

Utilizing the structural features of drug-DNA intercalation, Sobell, Tsai et al.[39,42] have proposed a detailed molecular model for the kinking of B-DNA. A variety of superhelical DNA structures can be formed by kinking B-DNA periodically varying numbers of base-pairs apart. Perhaps the most interesting of these is the one in which a kink occurs every ten base pairs. This gives rise to a left-handed superhelical structure that contains 1½ turns per 140 base pairs and has an axial length of 80 Å. These and other structural features make it an attractive model for the organization of DNA within the nucleosome in chromatin.[39,42]



Drugs Intercalate from the Minor Groove of DNA - Actinomycin D (1) is a cyclic polypeptide-containing antibiotic which is a potent antitumor agent. The activity of the antibiotic stems from its ability to bind double-stranded DNA and inhibit RNA synthesis.[12] The interaction of actinomycin D with DNA has been studied by a variety of techniques.[13-28] When actinomycin D binds to DNA, there is a general, but not absolute, requirement for the presence of a guanine base at the interaction site. Sobell and coworkers have cocrystallized actinomycin D with its DNA substrate, deoxyguanosine, and have solved the three-dimensional structure of the complex by X-ray crystallography.[28-30] The structure of the co-crystalline complex provided an excellent basis for proposing a model for the actinomycin D-DNA binding.[30] The model involves intercalation of the phenoxazone ring system between base pairs in the DNA double helix and the utilization of specific hydrogen bonds, van der Waals forces, and hydrophobic interaction between pentapeptide chains on actinomycin D and chemical groups in the minor groove of the DNA helix. Important elements in the recognition of actinomycin D for DNA are the guanine specificity and the

use of symmetry in the interaction. A mixed sugar puckering has been postulated to occur at the intercalation site of the type: C3'endo (3'-5') C2'endo.

Ethidium (2) and propidium (3) are phenanthridinium compounds which are useful as tools for binding studies of nucleic acids. Of the two, ethidium is a well-established drug in widespread use for the chemotherapy of trypanosomiasis. Propidium is not employed in chemotherapeutic practice; it has only recently become of interest for its value in closed circular DNA isolation studies.[32] The medicinal action of ethidium stems from its ability to bind to DNA and RNA and to inhibit nucleic acid function.[32] The precise nature of ethidium binding to nucleic acids has been elucidated.[31-41] It is generally believed that ethidium binds to DNA (and perhaps to RNA) through intercalation. Although a variety of physical techniques have been used to provide evidence concerning intercalative binding, direct information has been provided by the single-crystal X-ray analysis of ethidium-nucleic acid crystalline complexes. Tsai, Jain and Sobell [35-38] have cocrystallized ethidium with several dinucleoside monophosphates, and have solved the three-dimensional structure of two of these (ethidium:5-iodouridylyl(3'-5')adenosine and ethidium:5-iodocytidylyl(3'-5')guanosine). Both structures demonstrate

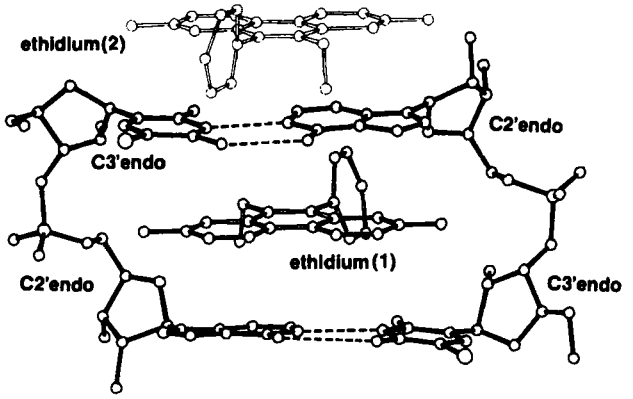


Fig. 2. A computer-graphic illustration of a portion of the ethidium:iodoUpA crystal structure viewed approximately parallel to the planes of the base-pairs and ethidium molecules. (Redrawn from Ref. 36 with permission of publisher.)

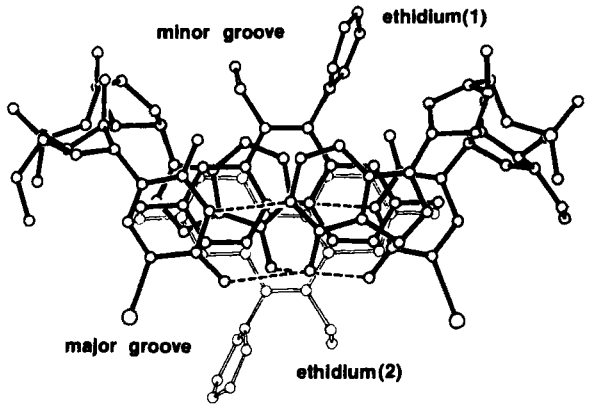


Fig. 3. A computer-graphic illustration of the ethidium:iodoUpA complex viewed perpendicular to the planes of the base-pairs and ethidium molecules. This figure illustrates the non-crystallographic 2-fold symmetry that is found in this model drug-nucleic acid interaction. (Redrawn from Ref. 36 with permission of publisher.)

drug intercalation into Watson-Crick-type double helices. In each structure, one ethidium molecule is intercalated between base pairs, while the second ethidium molecule is stacked above (and below) this intercalated base-paired dinucleoside monophosphate structure. The phenyl and ethyl substitutents of the intercalated ethidium molecule lie in the minor groove of the double helix. Non-crystallographic 2-fold symmetry is utilized in this model drug-nucleic acid interaction; this reflects the pseudo-2-fold symmetry of the phenanthridinium ring system in ethidium coinciding with the approximate 2-fold symmetry that relates the base-paired dinucleoside monophosphates. Adjacent base-pairs within the paired dinucleoside monophosphate structure are separated by about 6.7 Å; this separation results from the intercalative binding by one ethidium molecule between base pairs. A mixed sugar puckering of the type: C3'endo (3'-5') C2'endo is observed in both structures. This sugar-phosphate conformational change partly results in the 8° twist angle that is observed between base pairs. Base-pairs are not parallel to each other, but instead are tilted about 8° to form a V-type notch that opens into the minor groove of the miniature double helix (this is best seen in the stereo picture of the intercalated complex, shown in Fig. 4). On the basis of these two structures a detailed molecular model for ethidium-DNA binding, a nearest neighbor exclusion model for intercalative drug binding to DNA, and a detailed sequence of conformational changes leading to drug-DNA intercalation have been proposed and applied to a wide range of drug-DNA interactions.[39]

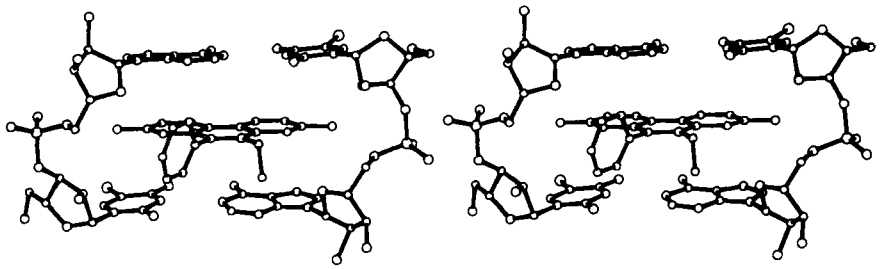
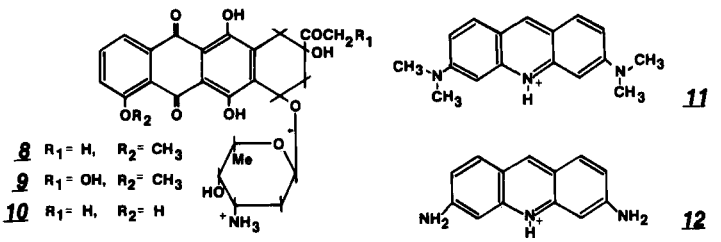


Fig. 4. Stereo pair of ethidium:iodoUpA intercalated complex, as visualized in the ethidium:iodoUpA crystal structure. (Redrawn from Ref. 37 with permission of publisher.)

The antimalarial drugs chloroquine (4), quinacrine (5), and quinine (6) have been shown to interact with DNA and to inhibit the ability of DNA to act as a template for DNA replication and for RNA synthesis.[43-45] These effects are thought to result from intercalation of the drugs with DNA and may account for part of their antimalarial activity. Hahn and coworkers[46] have shown that the probable mode of action for chloroquine involves formation of a complex with DNA through intercalation of the chloroquine aromatic ring system and interaction of the positively charged side chain with the negatively charged DNA phosphate groups. The evidence for this model, its simplicity, and the lack of a definite bioreceptor for alternative models have helped it gain widespread acceptance; chemists have used the model to design new antimalarial drugs.[44]

Hycanthone (7) has been used in the treatment of schistosomiasis.[47] The accumulated evidence suggests that hycanthone binds to DNA through intercalation in the same manner as actinomycin D and ethidium. The three-ring heterocyclic system in a planar configuration provides strong hydrophobic interaction with the DNA base pairs; the proximal nitrogen atom of the molecule has an intramolecular hydrogen bond; and the terminal nitrogen atom contributes to hycanthone activity by interacting with a phosphate group at the periphery of the DNA helix, thereby stabilizing the drug-DNA complex.[48,49]

Drugs Intercalate from the Major Groove of DNA - Daunomycin (8), adriamycin (9), and carminomycin (10) are anthracycline antibiotics that have been used in the treatment of a wide spectrum of cancer. Their biological activities have been related to their ability to interact with double-stranded DNA by intercalation.[50-55] Pigram, Fuller and Hamilton[56] have suggested a molecular model for the interaction of daunomycin with DNA, based on X-ray fiber diffraction data and molecular model-building study. They proposed that the aromatic chromophore of the drug intercalates into the DNA helix, and the sugar is hydrogen-bonded to the nucleic acid backbone through its amino group. Di Marco and his coworkers have done the majority of mechanistic studies on the anthracycline antibiotics;[57-61] and Di Marco and Arcamone[57] have recently reviewed this subject, and have suggested that DNA-adriamycin interaction involves three types of binding: hydrophobic interaction due to the intercalated aglycone, electrostatic attraction between the protonated 3'-amino group of the daunosamine and phosphate groups of the helix, and hydrogen bonds of unspecified character.



Acridine orange (11) and proflavine (12) are aminoacridine dyes that bind to DNA and possess mutagenic activity.[3,4] The precise nature of aminoacridine-DNA binding was proposed by Lerman[3,4] over a decade ago, who introduced the stereochemical concept of drug intercalation to explain his spectroscopic and hydrodynamic DNA-dye binding data. Recently several aminoacridine-dinucleoside monophosphate complexes have been cocrystallized and their structures have been determined by X-ray crystallographic analysis.[62-66]

The X-ray crystallographic study of acridine orange:5-iodocytidylyl-(3'-5')guanosine crystalline complex by Reddy et al.[66] demonstrates the intercalative binding by this drug to miniature Watson-Crick double-helical structure. The amino groups of the intercalated acridine lie in the major groove. A mixed sugar puckering conformation of the type: C3'endo (3'-5') C2'endo is observed in the structure.

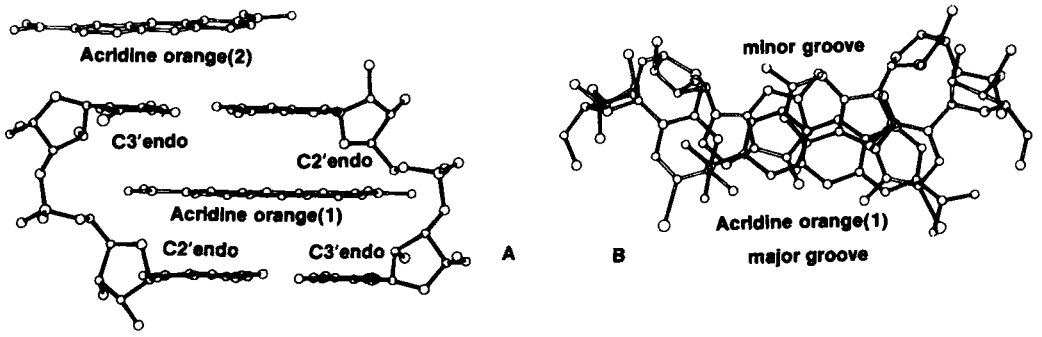
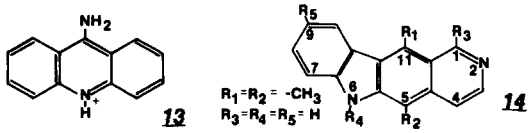


Fig. 5. Structure of acridine orange:iodoCpG complex.
(A) Viewed down the dyad axis and parallel to the planes of acridine and base-pair molecules.
(B) Viewed perpendicular to the planes of acridine and base-pair molecules.

The crystal structure of proflavine:5-iodocytidylyl(3'-5')guanosine complex (reported by Seshadri et al.[65]) and the crystal structure of proflavine:cytidylyl(3'-5')guanosine (reported by Neidle et al.[64]) both demonstrate the intercalative binding by this drug to miniature Watson-Crick double-helical structure. Some unexpected features are observed in these two structures: all the sugars are in C3'endo conformation; base-pairs in the immediate region of intercalation are twisted by about 33°.

Drugs Intercalate from either the Major or Minor Grooves of DNA - 9-Aminoacridine (13) has long been known to be a potent mutagen.[67] It is one in a general class of aminoacridine dyes that bind to DNA. The precise nature of 9-aminoacridine binding to nucleic acids has been elucidated.[3,4] The structure analysis of 9-aminoacridine:5-iodocytidylyl(3'-5')guanosine crystalline complex by Sakore et al.[62] demonstrates two distinct intercalative binding modes by this drug to miniature Watson-Crick double-helical structures. There are two 2:2 complexes in one crystal; each complex has an intercalated and a stacked acridine. In one complex, the intercalated 9-aminoacridine is oriented such that its amino group points toward the minor groove. For the other complex, the amino group of the intercalated acridine is oriented such that it points toward the major groove. The same C3'endo (3'-5') C2'endo mixed sugar puckering conformation is observed in both complexes.



Ellipticine (14) is a plant alkaloid which has a planar ring structure capable of being inserted between base pairs in the DNA helix. Ellipticine has received widespread attention on account of its high anti-leukaemia activity, which is believed to be related to its ability to bind nucleic acids.[69-72] Kohn, Waring and their coworkers[73] have established

that ellipticine does bind to DNA by intercalation, based on effects on the sedimentation and viscosity of sheared DNA fragments, removal and reversal of the supercoiling of closed circular DNA, and electric dichroism measurements. Recently Jain et al.[68] have cocrystallized ellipticine with 5-iodocytidylyl(3'-5')guanosine, and have solved the three-dimensional structure of the complex by X-ray crystallography. The structure of this cocrystalline complex has allowed the visualization of the intercalative binding by this drug to Watson-Crick-type double helix.[68]

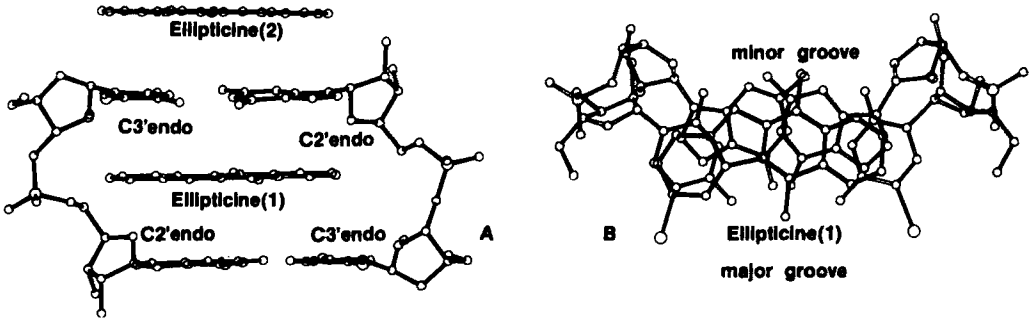


Fig. 6. Structure of ellipticine:iodoCpG complex. (A) Viewed down the dyad axis and parallel to the planes of ellipticine and base-pairs. (B) Viewed perpendicular to the planes of ellipticine and base-pairs.

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