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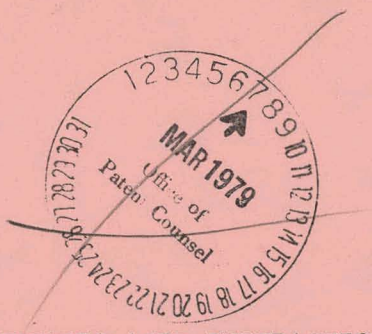

MASTER

VISUALIZATION OF DRUG-NUCLEIC ACID INTERACTIONS AT ATOMIC RESOLUTION

V. STRUCTURE OF TWO AMINOACRIDINE/ DINUCLEOSIDE MONOPHOSPHATE CRYSTALLINE COMPLEXES, PROFLAVINE: 5-IODOCYTIDYLYL(3'-5')GUANOSINE AND ACRIDINE ORANGE: 5-IODOCYTIDYLYL(3'-5')GUANOSINE

by

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ABSTRACT:

Acridine orange and proflavine form complexes with the dinucleoside monophosphate, 5-iodocytidylyl(3'-5')guanosine (iodoCpG). The acridine orange-iodoCpG crystals are monoclinic, space group $P2_1$, with unit cell dimensions $\underline{a}$ = 14.36 Å, $\underline{b}$ = 19.64 Å, $\underline{c}$ = 20.67 Å, β = 102.5°. The proflavine-iodoCpG crystals are monoclinic, space group C2, with unit cell dimensions $\underline{a}$ = 32.14 Å, $\underline{b}$ = 22.23 Å, $\underline{c}$ = 18.42 Å, β = 123.3°. Both structures have been solved to atomic resolution by Patterson and Fourier methods, and refined by full matrix least squares.

Acridine orange forms an intercalative structure with iodoCpG in much the same manner as ethidium, ellipticine and 3,5,6,8-tetramethyl-N-methyl phenanthrolinium (Jain et al., 1977; Jain et al., 1979), except that the acridine nucleus lies asymmetrically in the intercalation site. This asymmetric intercalation is accompanied by a sliding of base-pairs upon the acridine nucleus and is similar to that observed with the 9-aminoacridine-iodoCpG asymmetric intercalative binding mode described in the previous paper (Sakore et al., 1977; Sakore et al., 1979). Base-pairs above and below the drug are separated by about 6.8 Å and are twisted about 10°; this reflects the mixed sugar puckering pattern observed in the sugar phosphate chains: C3' $\underline{endo}$ (3'-5') C2' $\underline{endo}$ (i.e., each cytidine residue has a C3' $\underline{endo}$ sugar conformation, while each guanosine residue has a C2' $\underline{endo}$ sugar conformation), alterations in glycosidic torsional angles and other small but significant conformational changes in the sugar-phosphate backbone.

Proflavine, on the other hand, demonstrates symmetric intercalation with iodoCpG. Hydrogen bonds connect amino- groups on proflavine with phosphate oxygen atoms on the dinucleotide. In contrast to the acridine orange structure,

ABSTRACT: (continued)

base-pairs above and below the intercalative proflavine molecule are twisted about 36°. The altered magnitude of this angular twist reflects the sugar puckering pattern that is observed: C3' endo (3'-5') C3' endo. Since proflavine is known to unwind DNA in much the same manner as ethidium and acridine orange (Waring, 1970), one cannot use the information from this model system to understand how proflavine binds to DNA (it is possible, for example, that hydrogen bonding observed between proflavine and iodoCpG alters the intercalative geometry in this model system).

We propose a model for proflavine-DNA binding in which proflavine lies asymmetrically in the intercalation site (characterized by the C3' endo (3'-5') C2' endo mixed sugar puckering pattern) and forms only one hydrogen bond to a neighboring phosphate oxygen atom. Our model for proflavine-DNA binding, therefore, is very similar to our acridine orange- DNA binding model. We will describe these models in detail in this paper.

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DRUG-NUCLEIC ACID INTERACTIONS V

1. Introduction.

Along with 9-aminoacridine (see previous paper), proflavine and acridine orange (shown in Fig. 1 and 2) are aminoacridine dyes that bind to DNA and possess mutagenic activity. Both molecules bind to DNA by intercalation, as evidenced by spectroscopic and hydrodynamic studies with linear DNA (Lerman, 1961, 1963; Cohen and Eisenberg, 1969). Proflavine, in particular, has been demonstrated to unwind covalently circular superhelical DNA about the same order of magnitude as ethidium bromide (i.e., about 20°, on the ethidium scale)(Waring, 1970; Wang, 1974), a feature diagnostic of intercalation into DNA.

Here, we describe the structures of two aminoacridine complexes with the self-complementary dinucleoside monophosphate, 5-iodocytidylyl(3'-5')guanosine (iodoCpG): proflavine-iodoCpG and acridine orange-iodoCpG. Although both structures demonstrate intercalation of acridine dye molecules between guanine-cytosine base-pairs, they differ in their detailed sugar-phosphate backbone conformations and intercalative geometries.

A preliminary account of this work has already been presented at the American Crystallographic Association Meeting at the University of Oklahoma, Norman, Oklahoma (Reddy, Seshadri, Sakore & Sobell, 1978; Seshadri, Sakore, Reddy & Sobell, 1978).

2. Materials and Methods.

Proflavine and acridine orange were obtained from K & K Laboratories, Inc., Plainview, New York and used without further purification. Cytidylyl(3'-5')guanosine was purchased from the Sigma Chemical Company and used directly as the ammonium salt. This material was iodinated using the synthesis described in a previous communication (Tsai et al., 1977). Plate-like crystals of both complexes were obtained by slow evaporation over several days of equimolar mixtures of proflavine

(or acridine orange) and 5-iodocytidylyl(3'-5')guanosine (Fig. 3) dissolved in an 80% water/methanol (vol/vol) solvent system with a few drops of 2-methyl-2,4-pentanediol. A comparison of the ultraviolet absorption spectra of solutions obtained from washed single crystals with solutions containing known stoichiometric mixtures of these compounds indicated 1:1 complexes. Preliminary characterizations of these crystals were done from precession photographs using Ni-filtered CuKα radiation. The unit cell dimensions were then refined by least squares using 12 independent reflections for each structure measured on a Picker FACS-1 automatic diffractometer.

Proflavine-iodoCpG crystals are monoclinic, C2, with $\underline{a}$ = 32.14 ± 0.04 Å, $\underline{b}$ = 22.23 ± 0.03 Å, $\underline{c}$ = 18.42 ± 0.03 Å, β = 123.3 ± 0.5°. Acridine orange-iodoCpG crystals are monoclinic, $P2_1$, with $\underline{a}$ = 14.36 ± 0.02 Å, $\underline{b}$ = 19.64 ± 0.03 Å, $\underline{c}$ = 20.67 ± 0.03 Å, β = 102.5 ± 0.4°. Single crystals of the proflavine-iodoCpG complex measuring 0.2 mm x 0.2 mm x 0.3 mm were mounted with some mother liquor in 0.5 mm quartz capillaries; larger crystals of the acridine orange-iodoCpG complex could be obtained (0.7 mm x 0.4 mm x 0.4 mm), and these were mounted with mother liquor in 0.7 mm quartz capillaries. Data for both structures were collected at room temperature with Ni-filtered CuKα radiation on a FACS-1 automatic diffractometer using the theta- two theta scan method out to a maximum two-theta angle of 72° for the proflavine structure and 90° for the acridine orange structure. Of the 2850 and 3950 reflections measured, 1045 and 2200 reflections were considered to be significantly above background (i.e., 1.5σ) in the proflavine and acridine orange structure, respectively, and used for the analyses. The measured intensities were corrected for the Lorentz and polarization factors. No absorption corrections were applied. Absolute structure factors and overall temperature factors were obtained by the usual Wilson (1942) method.

The proflavine-iodoCpG structure was solved by the heavy atom method. Atomic positions for iodine atoms were located from a sharpened Patterson function, and these were then used to calculate phases for the first Fourier synthesis. The positions of both phosphate groups were determined from the simultaneous interpretation of this Fourier map and the Patterson map. Since the 8 0 0 reflection had very high intensity and the 4 0 0 reflection had low intensity, this suggested base-pairs and proflavine molecules to lie close to the 8 0 0 plane. With this in mind, subsequent Fourier syntheses sectioned perpendicular the the a axis gave interpretable positions of base-pairs and proflavine molecules. Because of the limited data, the structure had to be developed slowly and carefully, many times leaving out portions of the structure that were either unclear or in doubt and then allowing them to reappear in later Fourier maps. This minimized the bias in the structure analysis and assisted the Fourier refinement. The final structure contains 131 atoms; this includes two iodoCpG molecules, two proflavine molecules, 15 water molecules and 1 methanol molecule. Several cycles of block diagonal least squares were carried out in which individual atomic isotropic temperature factors were allowed to vary. This left a residual of 20.2%.

The acridine orange-iodoCpG structure was solved using a combination of Patterson superposition and Fourier methods. First, iodine positions were obtained from a sharpened Patterson function and used to compute a Patterson superposition and Fourier map. From these, a partial structure structure containing both base-pairs and phosphate groups could be identified. The complete structure was then developed and refined through a series of Fourier, sum-Fourier and difference Fourier steps. This contains two iodoCpG molecules, two acridine orange molecules and 24 water molecules, a total of 146 atoms. Two cycles of full matrix least squares were then carried out using 2200 observed reflections. The positional

parameter shifts were damped to 60%, while the isotropic temperature factor shifts were damped to 30%. Several abnormal bond lengths and angles were obtained after refinement. These were idealized with the help of Fourier and difference Fourier maps. The final residual is 17.5% for 2200 reflections.

The observed and calculated structure factors for both structures have been microfilmed and stored at ASIS/NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, New York 10017 under document number 00000.

3. Results.

Tables 1 and 2 summarize final coordinates and temperature factors obtained from these crystal structure analyses. Estimated standard deviations of $\underline{x}$, $\underline{y}$ and $\underline{z}$ coordinates of light atoms lie between 0.04 Å and 0.06 Å in the proflavine-iodoCpG structure and between 0.02 Å and 0.04 Å in the acridine orange-iodoCpG structure. This results in standard deviations for bond lengths between light atoms of about $\pm$ 0.10 Å, and for bond angles of about $\pm$ 6.0° in the proflavine complex, and about $\pm$ 0.06 Å and $\pm$ 4.0° for the acridine orange structure. The enhanced accuracy of the acridine orange analysis probably reflects the quality and quantity of the diffraction data available.

(a) Proflavine and acridine orange intercalative binding.

Figures 4-11 show the proflavine-iodoCpG and acridine orange-iodoCpG complexes viewed approximately parallel and perpendicular to the planes of guanine-cytosine base-pairs and drug molecules. Although both structures demonstrate intercalation of the acridine dye molecules between guanine-cytosine base-pairs, they differ in their detailed intercalative geometries and sugar-phosphate backbone conformations.

Proflavine demonstrates symmetric intercalation with iodoCpG. Hydrogen

bonds connect amino- groups on proflavine molecules with phosphate oxygen atoms on the dinucleotide (2.98 Å, 3.05 Å) -- a feature different from all other drug-nucleic acid complexes we have studied. Acridine orange, on the other hand, demonstrates asymmetric intercalation with iodoCpG -- no hydrogen bonds exist between acridine orange and iodoCpG. Rather, an asymmetric binding mode accompanied by a "sliding" of base-pairs above and below the drug molecule is observed. Although smaller in magnitude, this 'sliding' effect is similar to that observed in the 9-aminoacridine-iodoCpG asymmetric binding mode described in the preceding paper (Sakore et al., 1979).

As with the other drug-dinucleoside monophosphate crystalline complexes we have analyzed, the proflavine- and acridine orange- iodoCpG structures contain 2:2 drug dinucleoside monophosphate stoichiometric ratios. This reflects intercalation by one drug molecule and stacking by the other drug molecule with Watson-Crick base-pairs formed by the iodoCpG miniature double helices. The proflavine complex, however, differs from the acridine orange complex in that only <u>one</u> guanine-cytosine base-pair forms a stacked complex with proflavine while <u>two</u> guanine-cytosine base-pairs stack with each acridine orange molecule (compare Fig. 4,5 with 8,9). These differences in molecular associations are correlated with different lattice symmetries and will be discussed more completely below.

(b) <u>Sugar-phosphate backbone stereochemistries accompanying drug intercalation</u>.

Table 3 summarizes the torsional angles that define the sugar-phosphate conformations in these structures. Two distinctly different stereochemical conformations have been detected.

The first -- observed with proflavine-iodoCpG binding -- involves the sugar puckering pattern: C3' <u>endo</u> (3'-5') C3' <u>endo</u>. Both C4'-C5' bonds are

gauche-gauche and glycosidic torsional angles (denoted χ) are in the low anti range for iodocytidine residues and in the high anti range for guanosine residues. The twist angle relating base-pairs above and below the intercalative proflavine molecule (calculated by projecting the interglycosidic carbon vectors on a common plane and then measuring the angle between them (see Tsai et al., 1977)) is about 36° -- this stereochemistry, therefore, would not lead to significant unwinding in double helical DNA (or RNA) at the immediate drug intercalation site.

The second stereochemical conformation -- observed with acridine orange-iodoCpG binding and with all other drug-dinucleoside monophosphate crystalline complexes we have analyzed -- involves the mixed sugar puckering pattern: C3' endo (3'-5') C2' endo. Again, the conformation around the C4'-C5' bond is gauche-gauche and glycosidic torsional angles fall in the low anti range for iodocytidine residues and in the high anti range for guanosine residues. However, unlike the proflavine-iodoCpG intercalative stereochemistry, the twist angle relating base-pairs above and below the intercalated acridine orange molecule is about 10°. This stereochemistry would, therefore, give rise to significant double helix unwinding at the immediate site of drug intercalation.

Stereo- pairs of the proflavine- and acridine orange- intercalative geometries are shown in Fig. 12 and 13.

(c) Crystal lattice structures.

Figure 14 shows the proflavine-iodoCpG structure viewed down the a^* axis. Intercalated proflavine molecules (shown with dark solid bonds) are oriented in a criss-cross manner -- an arrangement not observed in any other drug-dinucleoside monophosphate crystalline complex we have analyzed. Due to C2 symmetry, proflavine-iodoCpG demonstrates the following stacking pattern arrangement:

proflavine(2) - proflavine(2) - guanine-cytosine base-pair - proflavine(1) - guanine-cytosine base-pair - guanine-cytosine base-pair - proflavine(1) - guanine-cytosine base-pair - proflavine(2) - proflavine(2) - etc. This is shown clearly in Fig. 15, which views the structure down the b axis. This stacking arrangement of 2:2 complexes gives rise to columns of base-pairs and proflavine molecules separated by channels of water molecules. This water structure is extensively hydrogen bonded to the hydrophillic groups of dinucleoside monophosphate and proflavine molecules.

The acridine orange-iodoCpG structure (shown in Fig. 16 and 17) consists of drug molecules interleaved with guanine-cytosine base-pairs in much the same way as observed with the ellipticine- and 3,5,6,8-tetramethyl-N-methyl phenanthrolinium-iodoCpG structures (Jain et al., 1979). The stacking arrangement is: acridine orange(2) - guanine-cytosine base-pair - acridine orange(1) - guanine-cytosine base-pair - acridine orange(2) - etc. Similar stacking arrangements have been observed in the ethidium-iodoUpA and -iodoCpG structures (Tsai et al., 1977; Jain et al., 1977), and in the 9-aminoacridine-iodoCpG structure described in the preceding paper (Sakore et al., 1977; Sakore et al., 1979). Twenty-four water molecules have been found in the asymmetric unit, many of these forming hydrogen bonds to the phosphate oxygens. This provides a heavily hydrated environment for the complex and suggests that crystal lattice forces play a secondary role in determining the intercalative stereochemistry that is observed.

Relevant hydrogen bonding contacts observed in both structures are summarized in Table 4.

4. Discussion.

Figure 18 compares the intercalative geometries that have been observed with proflavine and with acridine orange in this model study. Although each

structure demonstrates intercalative binding, there are several important differences between them. These can be summarized as follows:

1) Proflavine intercalates symmetrically, forming hydrogen bonds between its amino- groups and phosphate oxygens on the dinucleotide, whereas acridine orange intercalates asymmetrically and -- being a methylated proflavine derivative -- is unable to hydrogen bond to these phosphate oxygens.

2) Base-pairs above and below the intercalated proflavine molecule are twisted about 36°, whereas, with acridine orange this value is 10°. The geometric difference between these structures mainly reflects the sugar puckering patterns that are observed -- these are C3' endo (3'-5') C3' endo in the proflavine-iodoCpG complex and C3' endo (3'-5') C2' endo in the acridine orange-iodoCpG structure.

3) Associated with these two different sugar-phosphate intercalative geometries are different distances that connect phosphate oxygen atoms on opposing chains. In the proflavine complex, this distance is 15.3 Å -- a distance that allows proflavine to simultaneously hydrogen bond (or span) both phosphate oxygens. In the acridine orange complex, however, this distance is 17.3 Å -- a distance too large for this to happen. Hydrogen bonding, therefore, may play a key role in determining the proflavine-iodoCpG intercalative geometry observed in this model study.

Neidle et al. (1977) have described a 3:2 proflavine-CpG crystalline complex that has very similar structural information to that presented here. Their study provides additional evidence that proflavine has its own characteristic intercalative geometry in these dinucleoside monophosphate model systems. There are, however, several reasons to suspect that these studies may not be completely relevant to understanding the detailed nature of proflavine-DNA (or -RNA) binding.

In the first place, proflavine has been demonstrated to unwind DNA in much the same manner as ethidium, unwinding DNA approximately -20° on the ethidium scale

(Waring, 1970; Wang, 1974). Secondly, proflavine (as well as all other intercalative drugs and dyes) demonstrates an upper binding limit of one drug molecule bound for every four nucleotides, an observation most easily understood in terms of a neighbor-exclusion model in which proflavine molecules intercalate between every other base-pair in the double-helix (Crothers, 1968). Structural evidence for neighbor exclusion has been provided by Bond et al. (1975) in a fiber X-ray diffraction study of a terpyridine platinum compound complexed to DNA.

Although alternative models are possible, the simplest model to understand these data postulates the mixed sugar puckering geometry C3' endo (3'-5') C2' endo to occur in drug-DNA (and -RNA) interactions (Sobell et al., 1976; Sobell et al., 1977a, b). This model -- or, more accurately, this class of models -- explains the magnitude of angular unwinding and the phenomenon of neighbor-exclusion, features characteristic of drug intercalation into DNA, and, more generally, provides a unified understanding of a large number of related drug-DNA (and -RNA) associations. Finally, it leads to concepts of dynamic DNA and RNA structure to explain kinetic features of drug intercalation and relates these to understanding the nature of protein-DNA interactions -- we have described these concepts in detail elsewhere (Sobell et al., 1978; Lozansky et al., 1979).

Although ethidium and acridine orange differ somewhat in their intercalative geometries with iodoCpG (ethidium intercalates symmetrically from the minor groove, while acridine orange intercalates asymmetrically from the major groove), the detailed stereochemistry of the sugar-phosphate chains in both structures is remarkably similar. Our models to understand acridine orange- and proflavine- DNA binding use this information: we postulate proflavine and acridine orange to bind asymmetrically to the intercalation site -- characterized by a C3' endo (3'-5') C2' endo mixed sugar puckering pattern -- proflavine, however, forming only one hydrogen

bond to the neighboring phosphate oxygen atom.

We have already discussed the possible implications this asymmetry could have in promoting frameshift mutagenesis in the preceding paper (Sakore et al., 1979).

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FIGURE CAPTIONS:

Figure 1. Chemical structure of proflavine.

Figure 2. Chemical structure of acridine orange.

Figure 3. Chemical structure of 5-iodocytidylyl(3'-5')guanosine.

Figure 4. A portion of the proflavine-iodoCpG crystal structure viewed approximately parallel to the planes of the guanine-cytosine base-pairs and proflavine molecules showing bond distances of sugar-phosphate chains. IodoCpG molecules are drawn with dark solid bonds; intercalative proflavine molecules (proflavine(1)) and stacked proflavine molecules (proflavine (2)) have been drawn with light open bonds.

Figure 5. Same as Fig. 4, but showing bond angles of sugar-phosphate chains.

Figure 6. Illustration of the proflavine-iodoCpG structure viewed perpendicular to the planes of the guanine-cytosine base-pairs and proflavine molecules, showing bond distances of base-pairs and proflavine molecules. See text for discussion.

Figure 7. Same as Fig. 6, but showing bond angles of base-pairs and proflavine molecules.

Figure 8. A portion of the acridine orange-iodoCpG crystal structure viewed approximately parallel to the planes of the guanine-cytosine base-pairs and acridine orange molecules showing bond distances of sugar-phosphate chains. IodoCpG molecules are drawn with dark solid bonds; intercalative acridine orange molecules (acridine orange(1)) and stacked acridine orange molecules (acridine orange(2)) have been drawn with light open bonds.

Figure 9. Same as Fig. 8, but showing bond angles of sugar-phosphate chains.

Figure 10. Illustration of the acridine orange-iodoCpG structure viewed perpendicular to the planes of the guanine-cytosine base-pairs and acridine orange molecules, showing bond distances of base-pairs and acridine orange molecules. See text for discussion.

Figure 11. Same as Fig. 10, but showing bond angles of base-pairs and acridine orange molecules.

Figure 12. Stereo- pairs of the proflavine-iodoCpG intercalative geometry.

Figure 13. Stereo- pairs of the acridine orange-iodoCpG intercalative geometry.

Figure 14. A lattice picture of the proflavine-iodoCpG crystalline complex drawn down the $\underline{a}^*$ direction to show relations between the proflavine-iodoCpG complexes and the surrounding water structure. Due to C2 symmetry, criss-cross stacking patterns within columns of proflavine-iodoCpG molecules are observed. See text for additional discussion.

FIGURE CAPTIONS: (continued)

Figure 15. View of the proflavine-iodoCpG crystalline complex drawn down the b axis. For simplicity, water structure and screw related molecules have been omitted from this figure. See text for discussion.

Figure 16. A lattice picture of the acridine orange-iodoCpG crystalline complex drawn down the a crystallographic direction to show relationships between columns of acridine orange-iodoCpG complexes and the surrounding water structure. This figure should be compared carefully with Fig. 15 and 16 in the next paper that show the ellipticine- and 3,5,6,8-tetramethyl-N-methyl phenanthrolinium- iodoCpG crystalline complexes.

Figure 17. View of the acridine orange-iodoCpG crystalline complex drawn down the b axis. For simplicity, water structure has been omitted in this figure.

Figure 18. Figure that compares the intercalative geometries observed in (a) proflavine-iodoCpG, and in (b) acridine orange-iodoCpG. Intercalative drug molecules are drawn with solid bonds. See text for discussion.

Table 1. Final coordinates and temperature factors for proflavine-iodoCpG crystal structure.

NO.	ATOM	X/A	Y/B	Z/C	B	NO.	ATOM	X/A	Y/B	Z/C	B
				5-IODOCYTIDYLYL(3'-5')GUANOSINE							
		IODO-CPG(1)						IODO-CPG(2)			
1	I5 C1	0.2042	0.2500	0.1611	10.5	42	I5 C2	0.4044	0.4487	0.7038	10.4
2	N1 C1	0.1944	0.3883	-0.0017	11.8	43	N1 C2	0.4389	0.6162	0.6378	11.3
3	C2 C1	0.1889	0.4392	0.0322	8.9	44	C2 C2	0.4389	0.6075	0.5667	20.1
4	O2 C1	0.1833	0.4875	-0.0028	2.8	45	O2 C2	0.4389	0.6517	0.5278	13.3
5	N3 C1	0.1889	0.4367	0.1061	1.1	46	N3 C2	0.4333	0.5517	0.5328	5.3
6	C4 C1	0.1916	0.3833	0.1433	7.7	47	C4 C2	0.4250	0.5042	0.5711	8.7
7	N4 C1	0.1889	0.3800	0.2111	9.5	48	N4 C2	0.4222	0.4496	0.5394	17.7
8	C5 C1	0.1944	0.3317	0.1050	8.1	49	C5 C2	0.4250	0.5133	0.6483	5.6
9	C6 C1	0.1944	0.3367	0.0328	1.7	50	C6 C2	0.4306	0.5704	0.6772	10.1
10	C1'C1	0.1889	0.3867	-0.0872	6.5	51	C1'C2	0.4514	0.6717	0.6833	5.5
11	C2'C1	0.2347	0.4142	-0.0722	9.1	52	C2'C2	0.4083	0.7125	0.6389	22.1
12	C3'C1	0.2619	0.3583	-0.0733	15.5	53	C3'C2	0.3944	0.7167	0.7056	9.1
13	C4'C1	0.2229	0.3183	-0.1333	16.1	54	C4'C2	0.4388	0.7125	0.7889	8.4
14	O1'C1	0.1806	0.3300	-0.1294	11.5	55	O1'C2	0.4694	0.6700	0.7778	11.4
15	C5'C1	0.2417	0.2558	-0.0972	16.2	56	C5'C2	0.4222	0.6892	0.8472	16.3
16	O5'C1	0.2167	0.2292	-0.0578	23.5	57	O5'C2	0.4167	0.6258	0.8389	8.0
17	O2'C1	0.2194	0.4500	-0.1528	8.2	58	O2'C2	0.4222	0.7650	0.6200	17.9
18	O3'C1	0.2861	0.3733	-0.1194	10.0	59	O3'C2	0.3611	0.7667	0.6833	5.6
19	P1	0.3403	0.3708	-0.0611	11.2	60	P2	0.3028	0.7558	0.6278	10.7
20	O1 P1	0.3406	0.3167	-0.0083	16.2	61	O1 P2	0.2806	0.8117	0.6444	18.6
21	O2 P1	0.3658	0.3654	-0.1111	8.7	62	O2 P2	0.2847	0.6917	0.6300	17.1
22	O5'G1	0.3500	0.4242	0.0022	22.2	63	O5'G2	0.2861	0.7592	0.5250	12.1
23	C1'G1	0.4422	0.5583	0.1111	6.8	64	C1'G2	0.2139	0.7542	0.2999	5.6
24	C2'G1	0.4562	0.5157	0.0600	17.6	65	C2'G2	0.1861	0.8017	0.3189	13.5
25	C3'G1	0.4069	0.4896	-0.0139	10.9	66	C3'G2	0.2278	0.8371	0.3944	15.6
26	C4'G1	0.3694	0.5354	-0.0250	7.4	67	C4'G2	0.2750	0.8187	0.4000	13.1
27	O1'G1	0.3916	0.5707	0.0588	20.0	68	O1'G2	0.2667	0.7654	0.3500	13.4
28	C5'G1	0.3347	0.4904	-0.0167	16.0	69	C5'G2	0.3111	0.8050	0.4956	9.9
29	O2'G1	0.4847	0.5521	0.0333	23.5	70	O2'G2	0.1583	0.8417	0.2488	23.5
30	O3'G1	0.4097	0.4917	-0.0917	20.6	71	O3'G2	0.2181	0.8987	0.3633	23.0
31	N1 G1	0.4389	0.5354	0.3789	10.2	72	N1 G2	0.1806	0.5483	0.1778	4.3
32	C2 G1	0.4361	0.5846	0.3372	12.0	73	C2 G2	0.1903	0.5983	0.1472	10.9
33	N2 G1	0.4306	0.6371	0.3656	11.4	74	N2 G2	0.1917	0.5975	0.0722	5.4
34	N3 G1	0.4361	0.5867	0.2633	4.9	75	N3 G2	0.1944	0.6525	0.1822	22.2
35	C4 G1	0.4389	0.5321	0.2378	0.8	76	C4 G2	0.1917	0.6483	0.2539	6.1
36	C5 G1	0.4417	0.4796	0.2761	1.5	77	C5 G2	0.1806	0.6000	0.2833	8.7
37	C6 G1	0.4417	0.4792	0.3539	6.9	78	C6 G2	0.1792	0.5458	0.2500	5.9
38	O6 G1	0.4444	0.4317	0.3922	19.4	79	O6 G2	0.1750	0.5000	0.2833	8.5
39	N7 G1	0.4431	0.4333	0.2333	15.3	80	N7 G2	0.1833	0.6158	0.3578	8.5
40	C8 G1	0.4424	0.4583	0.1656	14.4	81	C8 G2	0.1883	0.6742	0.3644	6.2
41	N9 G1	0.4396	0.5179	0.1667	19.2	82	N9 G2	0.1972	0.6958	0.3083	7.4
		PROFLAVINE(1)						PROFLAVINE(2)			
83	C1 P1	0.3056	0.6292	0.3700	23.5	99	C1 P2	0.0694	0.3417	0.0009	4.3
84	C2 P1	0.3056	0.6292	0.4423	1.3	100	C2 P2	0.0680	0.3146	-0.0694	20.2
85	C3 P1	0.3053	0.5750	0.4844	19.2	101	C3 P2	0.0694	0.3521	-0.1306	9.8
86	N3 P1	0.3013	0.5812	0.5567	14.1	102	N3 P2	0.0722	0.3270	-0.1971	8.5
87	C4 P1	0.3046	0.4217	0.4522	23.5	103	C4 P2	0.0694	0.4167	-0.1222	17.6
88	C5 P1	0.3150	0.4016	0.2411	15.9	104	C5 P2	0.0639	0.5917	0.0444	1.3
89	C6 P1	0.3167	0.3972	0.1678	13.6	105	C6 P2	0.0639	0.6104	0.1167	9.9
90	N6 P1	0.3177	0.3383	0.1300	10.8	106	N6 P2	0.0640	0.6700	0.1361	9.6
91	C7 P1	0.3167	0.4500	0.1244	9.6	107	C7 P2	0.0639	0.5658	0.1739	12.7
92	C8 P1	0.3150	0.5083	0.1578	11.4	108	C8 P2	0.0639	0.5050	0.1578	11.3
93	C9 P1	0.3111	0.5683	0.2611	12.9	109	C9 P2	0.0667	0.4271	0.0778	9.4
94	N10P1	0.3111	0.4625	0.3467	11.3	110	N10P2	0.0666	0.5062	-0.0389	10.9
95	C11P1	0.3083	0.5208	0.3767	14.7	111	C11P2	0.0681	0.4433	-0.0522	15.2
96	C12P1	0.3125	0.5117	1.2295	0.9	112	C12P2	0.0639	0.4871	0.0889	1.2
97	C13P1	0.3117	0.5742	0.3389	11.1	113	C13P2	0.0666	0.4042	0.0083	3.4
98	C14P1	0.3111	0.4584	0.2722	2.4	114	C14P2	0.0639	0.5279	0.0311	3.3
				SOLVENT MOLECULE ATOMS							
115	OW1	0.3056	0.3667	0.4334	16.0	124	OW10	0.0917	0.2042	0.8022	17.5
116	OW2	0.0750	0.2542	0.6722	23.5	125	OW11	0.1722	0.1166	0.2666	14.1
117	OW3	0.3222	0.1808	0.4583	19.0	126	OW12	0.4555	0.3208	0.4445	10.2
118	OW4	0.3111	0.0750	0.5000	23.5	127	OW13	0.4111	0.2750	0.5944	20.6
119	OW5	0.1833	0.4250	0.4000	18.2	128	OW14	0.4389	0.0667	0.4055	23.1
120	OW6	0.0333	0.4333	0.5945	23.5	129	OW15	0.1555	0.4625	0.5111	23.5
121	OW7	0.3222	0.0583	0.1777	23.5	130	OME	0.3611	0.2458	0.2445	21.1
122	OW8	0.1389	0.3125	0.6333	17.2	131	CME	0.3694	0.1917	0.2111	14.6
123	OW9	0.2055	0.0166	0.2722	17.6						

Table 2. Final coordinates and temperature factors for acridine orange-iodoCpG crystal structure.

NO.	ATOM	X/A	Y/B	Z/C	B	NO.	ATOM	X/A	Y/B	Z/C	B
				5-IODOCYTIDYLYL(3'-5')GUANOSINE							
		IODO-CPG(1)						IODO-CPG(2)			
1	I5 C1	1.0174	0.3265	0.4364	9.8	42	I5 C2	0.2206	0.2500	-0.0193	9.9
2	N1 C1	1.0220	0.5376	0.3956	2.2	43	N1 C2	0.2157	0.4733	-0.0370	4.5
3	C2 C1	0.9812	0.5417	0.3297	2.5	44	C2 C2	0.2603	0.4912	0.0255	2.6
4	N3 C1	0.9498	0.4877	0.2912	2.7	45	N3 C2	0.2897	0.4440	0.0719	3.0
5	C4 C1	0.9628	0.4266	0.3227	1.7	46	C4 C2	0.2770	0.3776	0.0622	1.4
6	C5 C1	1.0053	0.4210	0.3906	4.5	47	C5 C2	0.2338	0.3553	-0.0015	1.6
7	C6 C1	1.0330	0.4754	0.4250	1.5	48	C6 C2	0.2033	0.4044	-0.0486	1.6
8	O2 C1	0.9705	0.5978	0.3016	7.8	49	O2 C2	0.2675	0.5528	0.0321	4.1
9	N4 C1	0.9307	0.3746	0.2816	5.1	50	N4 C2	0.3133	0.3379	0.1129	4.4
10	C1'C1	1.0562	0.5990	0.4339	0.8	51	C1'C2	0.1713	0.5163	-0.0874	3.6
11	C2'C1	0.9790	0.6373	0.4576	9.2	52	C2'C2	0.2478	0.5429	-0.1133	13.6
12	C3'C1	0.9882	0.6074	0.5242	13.9	53	C3'C2	0.2333	0.5091	-0.1818	23.0
13	C4'C1	1.0980	0.6048	0.5502	5.5	54	C4'C2	0.1287	0.4812	-0.1956	13.5
14	O1'C1	1.1217	0.5800	0.4895	8.2	55	O1'C2	0.1037	0.4785	-0.1316	9.9
15	C5'C1	1.1322	0.5531	0.6060	5.7	56	C5'C2	0.1093	0.4124	-0.2355	4.6
16	O5'C1	1.0920	0.4872	0.5869	10.9	57	O5'C2	0.1558	0.3486	-0.1986	15.3
17	O2'C1	0.9888	0.7088	0.4705	9.4	58	O2'C2	0.2245	0.6138	-0.1195	9.7
18	O3'C1	0.9345	0.6491	0.5614	4.6	59	O3'C2	0.2820	0.5481	-0.2261	9.1
19	P1	0.8273	0.6312	0.5756	9.0	60	P2	0.3887	0.5255	-0.2311	8.4
20	O1 P1	0.8390	0.5599	0.5991	12.8	61	O1 P2	0.4052	0.4533	-0.2456	9.3
21	O2 P1	0.8087	0.6814	0.6225	20.5	62	O2 P2	0.4035	0.5713	-0.2849	16.0
22	O5'G1	0.7652	0.6348	0.5014	8.9	63	O5'G2	0.4470	0.5550	-0.1635	4.9
23	C1'G1	0.5273	0.6276	0.4099	6.5	64	C1'G2	0.6820	0.5784	-0.0765	6.0
24	C2'G1	0.5293	0.6471	0.4825	10.8	65	C2'G2	0.6683	0.5736	-0.1486	6.4
25	C3'G1	0.5877	0.7130	0.4974	16.4	66	C3'G2	0.6205	0.6423	-0.1725	9.6
26	C4'G1	0.6447	0.7128	0.4442	6.9	67	C4'G2	0.5467	0.6512	-0.1265	6.6
27	O1'G1	0.6130	0.6555	0.4011	6.4	68	O1'G2	0.5942	0.6106	-0.0709	5.8
28	C5'G1	0.7513	0.6991	0.4684	11.9	69	C5'G2	0.4447	0.6264	-0.1514	6.1
29	O2'G1	0.4410	0.6418	0.5034	11.1	70	O2'G2	0.7547	0.5765	-0.1720	15.5
30	O3'G1	0.5072	0.7573	0.4960	12.7	71	O3'G2	0.6832	0.6984	-0.1746	10.0
31	N1 G1	0.3818	0.5003	0.2036	1.8	72	N1 G2	0.8563	0.5071	0.1549	4.4
32	C2 G1	0.3912	0.5702	0.2131	1.7	73	C2 G2	0.8412	0.5724	0.1304	5.2
33	N3 G1	0.4348	0.5955	0.2740	4.7	74	N3 G2	0.7953	0.5805	0.0662	3.8
34	C4 G1	0.4673	0.5450	0.3206	2.5	75	C4 G2	0.7667	0.5200	0.0341	3.5
35	C5 G1	0.4620	0.4760	0.3130	6.1	76	C5 G2	0.7743	0.4550	0.0575	1.5
36	C6 G1	0.4170	0.4493	0.2530	2.4	77	C6 G2	0.8220	0.4447	0.1232	2.0
37	O6 G1	0.4040	0.3883	0.2377	5.2	78	O6 G2	0.8437	0.3912	0.1517	4.3
38	N2 G1	0.3520	0.6053	0.1590	3.1	79	N2 G2	0.8737	0.6252	0.1690	6.7
39	N7 G1	0.5040	0.4460	0.3721	5.6	80	N7 G2	0.7337	0.4118	0.0070	5.2
40	C8 G1	0.5368	0.4944	0.4140	4.3	81	C8 G2	0.6975	0.4501	-0.0443	3.2
41	N9 G1	0.5172	0.5546	0.3850	4.1	82	N9 G2	0.7160	0.5162	-0.0326	6.4
		ACRIDINE ORANGE(1)						ACRIDINE ORANGE(2)			
83	C1 A1	0.4750	0.4760	-0.0163	7.9	103	C1 A2	-0.0098	0.5241	0.0173	12.1
84	C2 A1	0.4425	0.4240	-0.0620	11.0	104	C2 A2	-0.0443	0.4793	-0.0333	13.1
85	C3 A1	0.4560	0.3559	-0.0404	4.3	105	C3 A2	-0.0340	0.4074	-0.0186	9.7
86	C4 A1	0.5045	0.3426	0.0275	7.4	106	C4 A2	0.0106	0.3854	0.0454	9.0
87	C5 A1	0.6687	0.4202	0.2507	4.0	107	C5 A2	0.1792	0.4289	0.2753	7.1
88	C6 A1	0.7025	0.4754	0.2956	3.9	108	C6 A2	0.2196	0.4778	0.3276	10.6
89	C7 A1	0.6910	0.5422	0.2754	9.5	109	C7 A2	0.2098	0.5466	0.3125	10.1
90	C8 A1	0.6448	0.5531	0.2125	7.6	110	C8 A2	0.1644	0.5703	0.2505	9.6
91	C9 A1	0.5602	0.5156	0.0970	5.1	111	C9 A2	0.0779	0.5477	0.1358	7.8
92	N10A1	0.5867	0.3835	0.1352	6.8	112	N10A2	0.0976	0.4120	0.1616	12.2
93	C11A1	0.5367	0.3977	0.0696	4.2	113	C11A2	0.0517	0.4333	0.0975	7.5
94	C12A1	0.6088	0.5022	0.1647	5.2	114	C12A2	0.1258	0.5237	0.1988	7.0
95	C13A1	0.5225	0.4646	0.0485	6.2	115	C13A2	0.0436	0.5021	0.0857	14.0
96	C14A1	0.6208	0.4330	0.1851	4.5	116	C14A2	0.1354	0.4557	0.2134	4.5
97	N15A1	0.4238	0.3050	-0.0836	17.9	117	N15A2	-0.0783	0.3643	-0.0727	19.0
98	C15A1	0.4460	0.2376	-0.0586	12.9	118	C15A2	-0.1270	0.3863	-0.1389	24.3
99	C15'1	0.3788	0.3204	-0.1518	19.1	119	C15'2	-0.0664	0.2920	-0.0600	24.8
100	N16A1	0.7513	0.4624	0.3594	7.0	120	N16A2	0.2612	0.4571	0.3874	11.5
101	C16A1	0.7863	0.5133	0.4104	6.5	121	C16A2	0.2716	0.3826	0.4019	9.2
102	C16'1	0.7688	0.3925	0.3830	7.6	122	C16'2	0.3015	0.5088	0.4372	17.5
				SOLVENT MOLECULE ATOMS							
123	OW1	0.7251	0.2780	0.9753	16.2	135	OW13	0.6579	0.2627	0.8445	17.3
124	OW2	0.5090	0.3151	0.3980	16.9	136	OW14	0.5360	0.5815	0.6335	14.7
125	OW3	0.1629	0.7036	0.7471	18.6	137	OW15	0.8935	0.7722	0.8212	24.7
126	OW4	0.6046	0.3826	0.8002	15.1	138	OW16	0.1830	0.7493	0.2455	32.7
127	OW5	0.0380	0.2057	0.2706	19.4	139	OW17	0.2409	0.3828	0.6066	25.9
128	OW6	0.7549	0.2687	0.1523	20.5	140	OW18	0.9023	0.4436	0.5830	29.3
129	OW7	0.5490	0.2606	0.2412	20.2	141	OW19	0.7223	0.4502	0.7232	34.9
130	OW8	0.3466	0.2030	0.3139	15.4	142	OW20	0.4682	0.7366	0.2623	32.0
131	OW9	0.9523	0.6701	0.8754	38.4	143	OW21	0.8020	0.2955	0.5456	37.8
132	OW10	0.6910	0.1831	0.3365	17.6	144	OW22	0.0914	0.2686	0.6554	25.0
133	OW11	0.2764	0.7452	0.5505	26.9	145	OW23	0.6707	0.7284	0.2705	34.2
134	OW12	0.6616	0.4841	0.5695	36.1	146	OW24	0.5234	0.3671	0.6183	34.0

Table 1. (continued).

Temperature factors shown for iodine atoms are equivalent isotropic factors calculated from the anisotropic temperature parameters obtained from full matrix least squares. These are:

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I5C1	0.1536	0.1058	0.1600	0.0103	0.1956	0.0201
I5C2	0.1518	0.1223	0.1335	-0.0275	0.1742	-0.0246

Table 2. (continued).

Temperature factors shown for iodine atoms are equivalent isotropic factors calculated from the anisotropic temperature parameters obtained from full matrix least squares. These are:

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I5C1	0.1403	0.1197	0.1114	0.0190	0.0489	0.0203
I5C2	0.1397	0.1501	0.0861	0.0000	0.0485	0.0000

Table 3. Torsional angles describing conformations of sugar-phosphate chains in proflavine- and acridine orange- iodoCpG crystalline complexes.

		proflavine-iodoCpG		acridine orange-iodoCpG	
Torsional Angle*	Greek symbol	I-CpG(1)	I-CpG(2)	I-CpG(1)	I-CpG(2)
O1'C-C1'C-N1C-C6C	χ	4	19	19	15
O1'G-C1'G-N9G-C8G	χ	103	85	95	90
O5'C-C5'C-C4'C-C3'C	ψ	106	82	52	69
C5'C-C4'C-C3'C-O3'C	ψ'	102	79	84	81
C4'C-C3'C-O3'C-P	ϕ'	224	273	217	226
C3'C-O3'C-P-O5'G	ω'	294	273	294	284
O3'C-P-O5'G-C5'G	ω	305	323	291	299
P-O5'G-C5'G-C4'G	ϕ	273	206	235	228
O5'G-C5'G-C4'G-C3'G	ψ	3	53	58	60
C5'G-C4'G-C3'G-O3'G	ψ'	122	119	145	139
C4'C-O1'C-C1'C-C2'C	τ_0	6	-4	-3	-4
O1'C-C1'C-C2'C-C3'C	τ_1	-23	-17	-26	-8
C1'C-C2'C-C3'C-C4'C	τ_2	32	33	43	16
C2'C-C3'C-C4'C-O1'C	τ_3	-31	-36	-43	-19
C3'C-C4'C-O1'C-C1'C	τ_4	16	24	28	14
C4'G-O1'G-C1'G'C2'G	τ_0	3	-1	-26	-25
O1'G-C1'G-C2'G-C3'G	τ_1	-17	-8	28	40
C1'C-C2'G-C3'G-C4'G	τ_2	23	13	-20	-42
C2'G-C3'G-C4'G-O1'G	τ_3	-22	-15	5	26
C3'G-C4'G-O1'G-C1'G	τ_4	13	10	14	-1

* The torsional angle is defined in terms of 4 consecutive atoms, ABCD; the positive sense of rotation is clockwise from A to D while looking down the BC bond.

Table 4. Hydrogen bonding distances observed in proflavine- and acridine orange- iodoCpG crystal structures.

proflavine-iodoCpG

Atoms	Distance (Å)	Atoms	Distance (Å)
OW1 - N10P1 (1)	2.73	OW6 - OW14 (3)	3.10
OW1 - O1P2 (2)	2.62		
		OW7 - O2'C1 (4)	2.67
OW2 - OW8 (1)	2.83		
OW2 - OW10 (1)	2.42	OW9 - OW11 (1)	2.45
OW2 - N3P2 (1)	2.94	OW9 - O3'G2 (5)	3.01
OW2 - N2G1 (1)	2.68		
		OW10 - N3P2 (6)	2.80
OW3 - OW4 (1)	2.56	OW10 - N2G1 (2)	3.14
		OW10 - N3G1 (2)	2.81
OW4 - OW15 (2)	2.77		
OW4 - N7G2 (2)	2.69	OW11 - O5'C2(2)	2.42
		OW11 - O2P2 (2)	2.33
OW5 - OW15 (1)	2.77	OW11 - N3P1 (2)	2.98
OW5 - O6G2 (1)	2.62		
OW5 - O1P2 (2)	3.07	OW12 - O6G1 (1)	2.98
		OMe - N6P1 (1)	2.73

(1)	x	y	z
(2)	½-x	-½+y	1-z
(3)	½-x	½+y	1-z
(4)	½-x	-½+y	-z
(5)	x	-1+y	z
(6)	x	y	1+z

acridine orange-iodoCpG

Atoms	Distance (Å)	Atoms	Distance (Å)
OW1 - OW13 (1)	2.68	OW8 - O3'G2 (6)	2.82
OW1 - N7G2 (2)	2.70	OW8 - P3P1 (5)	2.86
		OW8 - OW14 (5)	2.99
OW2 - O3'G1 (3)	2.52		
OW2 - N7G1 (1)	2.62	OW9 - OW15 (1)	2.40
OW3 - OW6 (7)	2.51	OW10 - OW11 (5)	2.59
OW3 - OW5 (7)	2.83	OW10 - O3P2 (4)	2.68
OW3 - OW10 (7)	3.02		
		OW11 - OW21 (7)	2.40
OW4 - OW13 (1)	2.58		
OW4 - OW19 (1)	2.88	OW12 - O1P1 (1)	2.90
OW5 - OW15 (5)	2.66	OW13 - OW20 (3)	2.58
OW5 - O3P1 (5)	2.80	OW13 - N2G1 (3)	3.09
OW6 - O6G2 (1)	2.72	OW14 - O3P2 (2)	2.81
		OW14 - O2'G1 (1)	2.98
OW7 - OW10 (1)	2.93		

Table 4. (continued).

Atoms		Distance (Å)	Atoms		Distance (Å)
OW17 - O5'C1	(1)	2.92	OW20 - N3G1	(1)	2.83
OW18 - O1P1	(1)	2.51	OW22 - O2'C1	(5)	2.86
OW18 - O5C1	(1)	2.84			

(1)	x	y	z
(2)	x	y	1+z
(3)	1-x	-½+y	1-z
(4)	1-x	-½+y	-z
(5)	2-x	-½+y	1-z
(6)	2-x	-½+y	-z
(7)	2-x	½+y	1-z

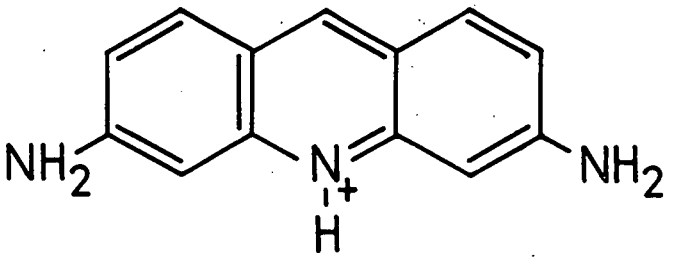


Figure 1.

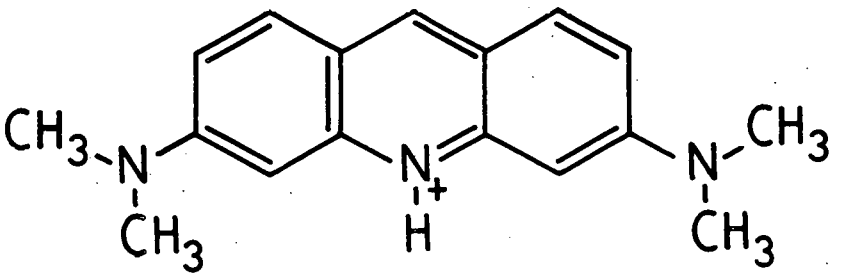


Figure 2.

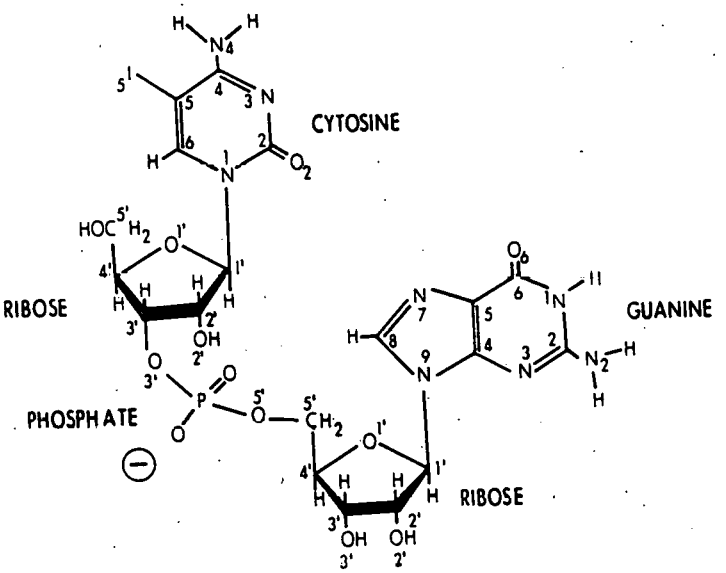
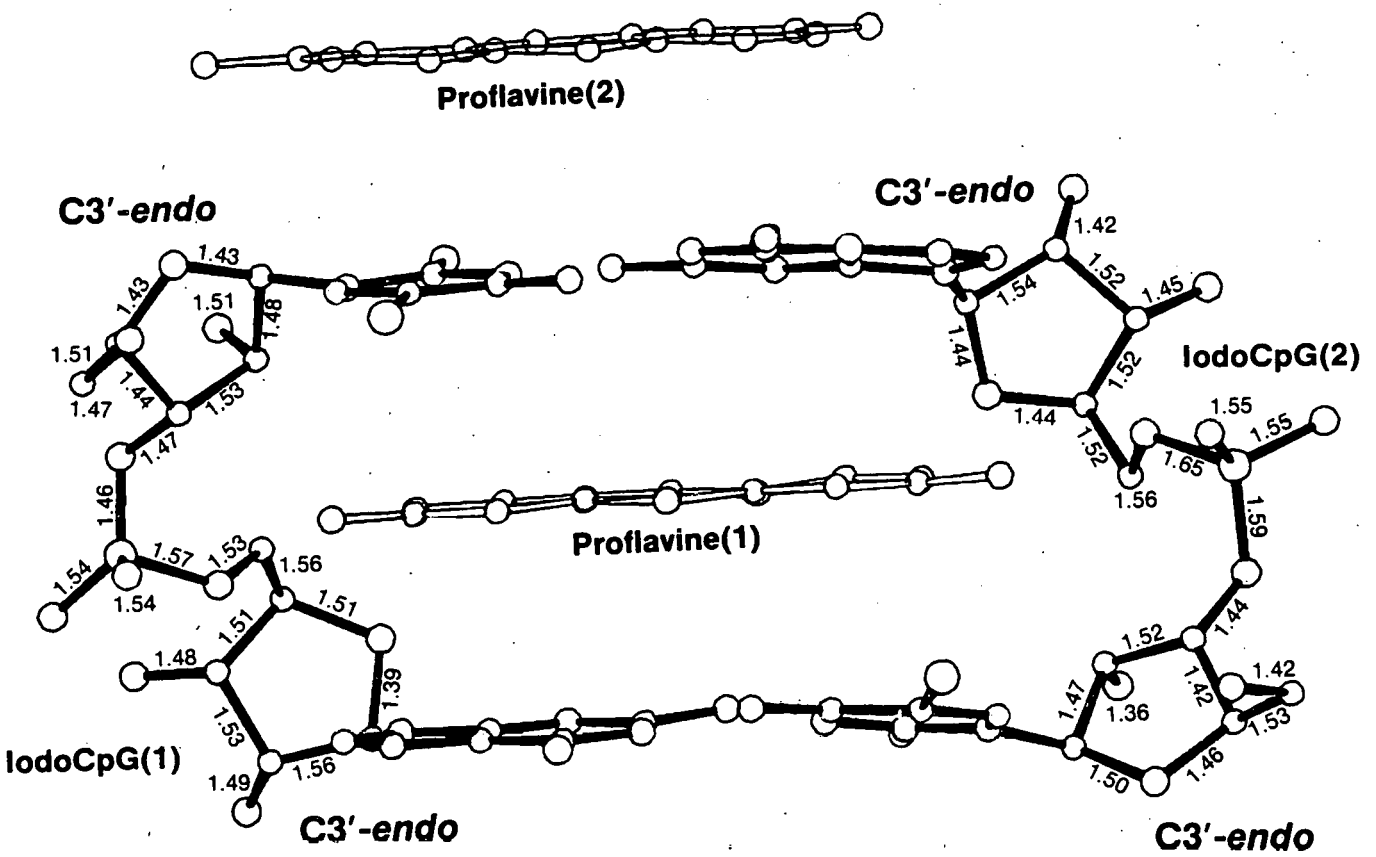
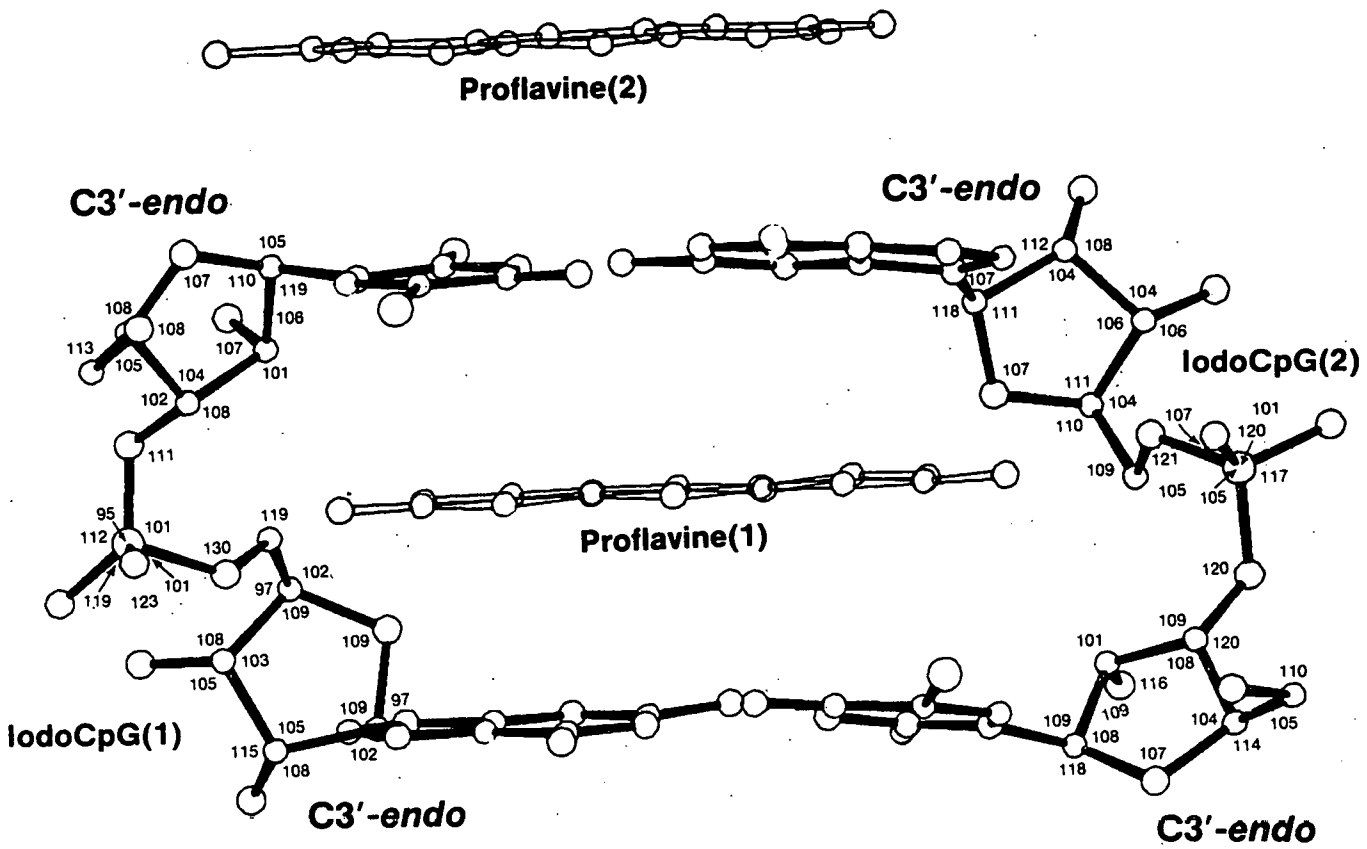
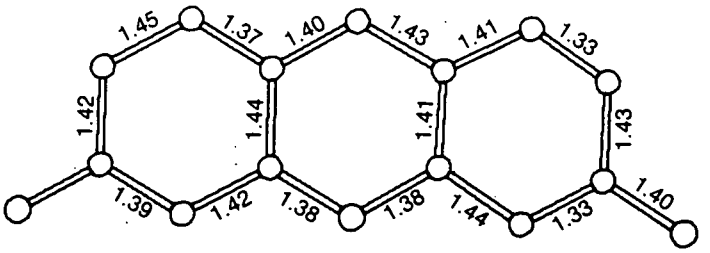


Figure 3.


Proflavine(2)
C3′-endo
C3′-endo
IodoCpG(2)
Proflavine(1)
IodoCpG(1)
C3′-endo
C3′-endo


Proflavine(2)
C3′-endo
C3′-endo
IodoCpG(2)
Proflavine(1)
IodoCpG(1)
C3′-endo
C3′-endo



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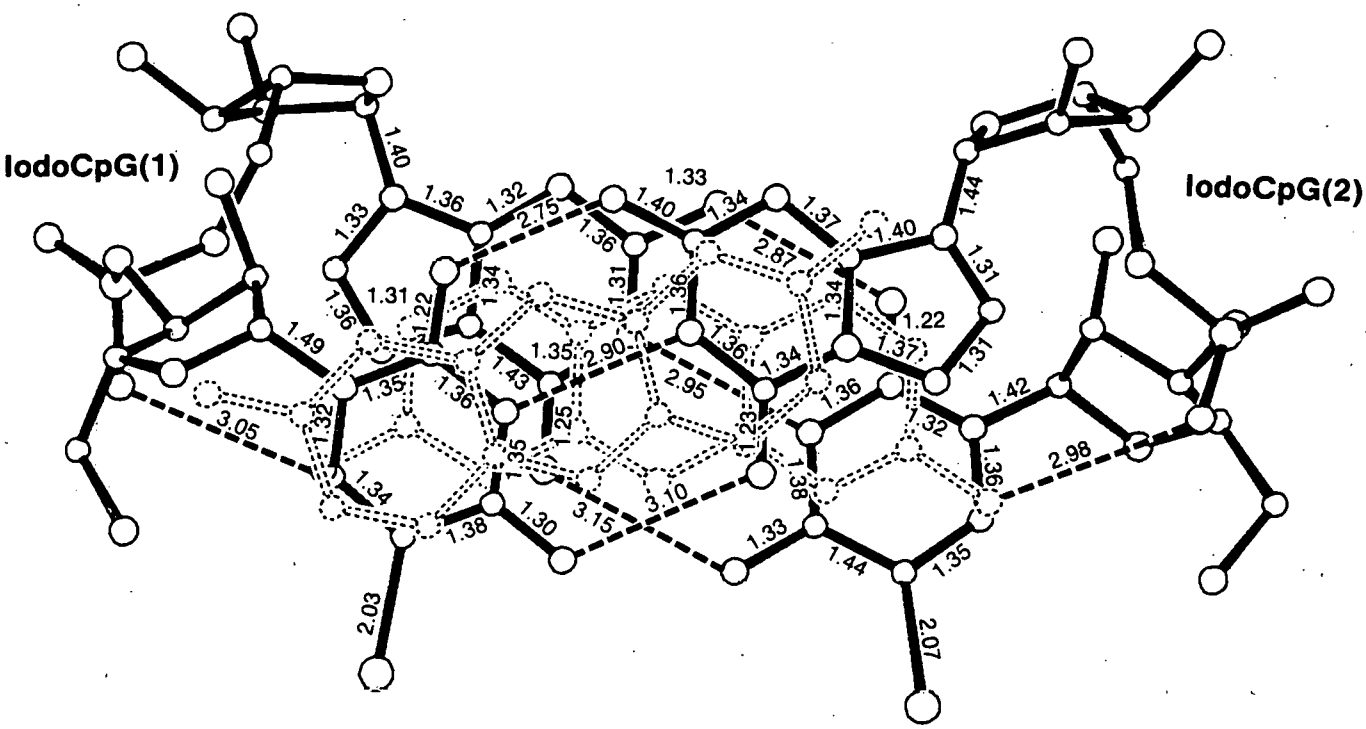
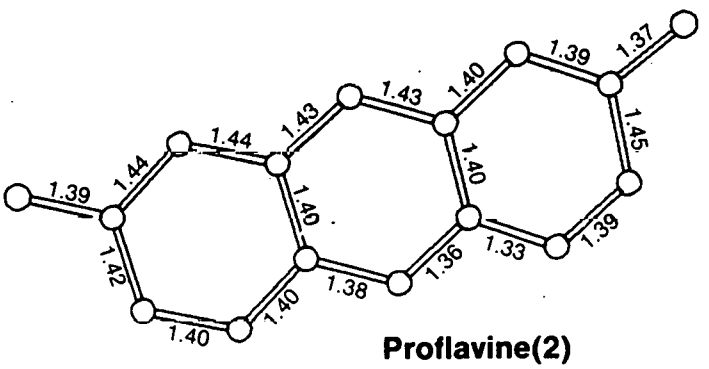
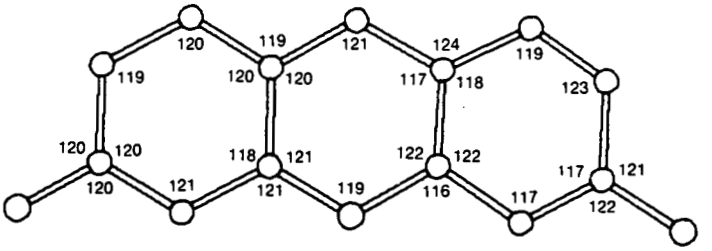




Proflavine(2)



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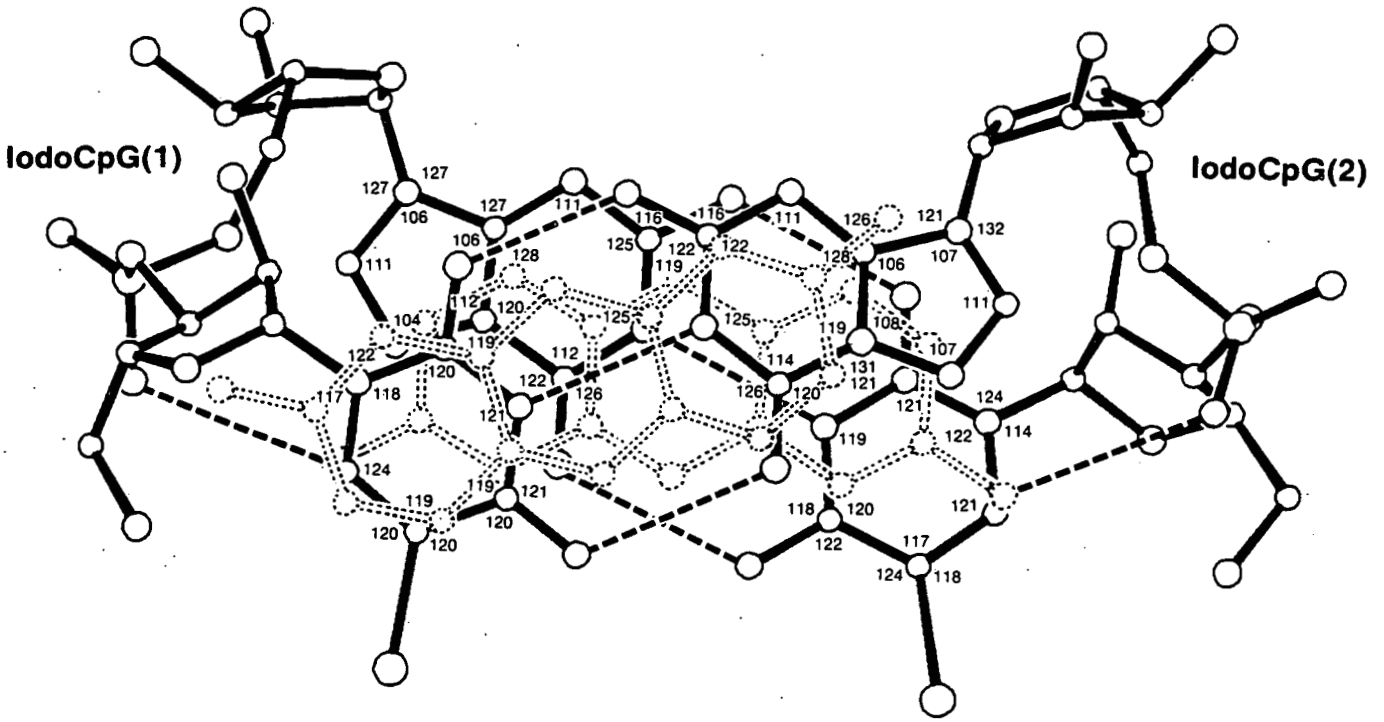

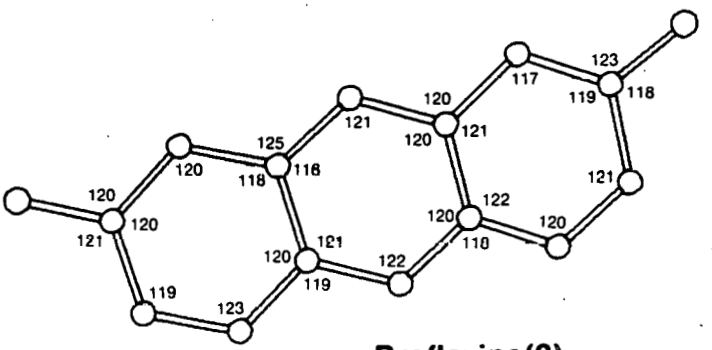

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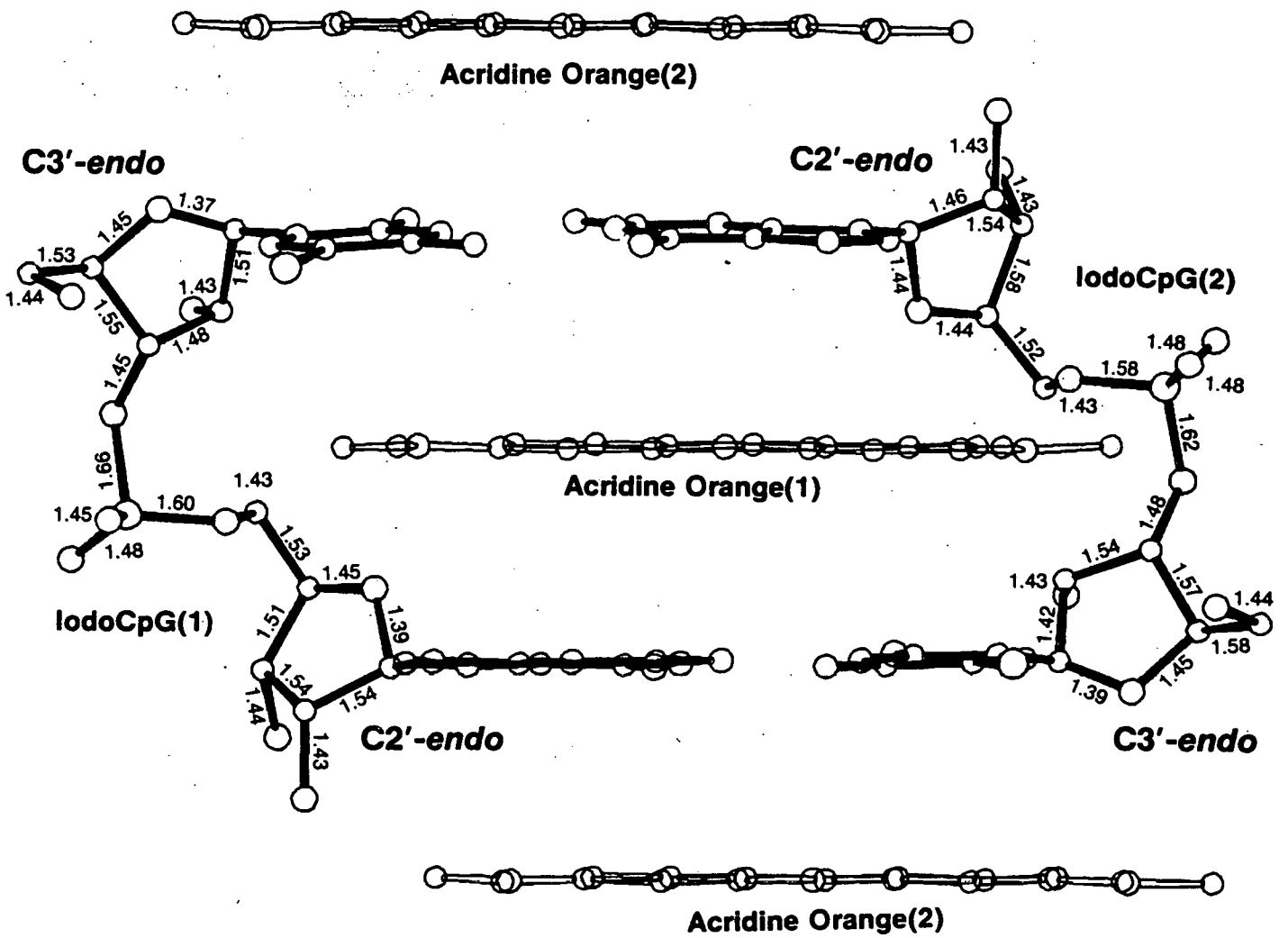
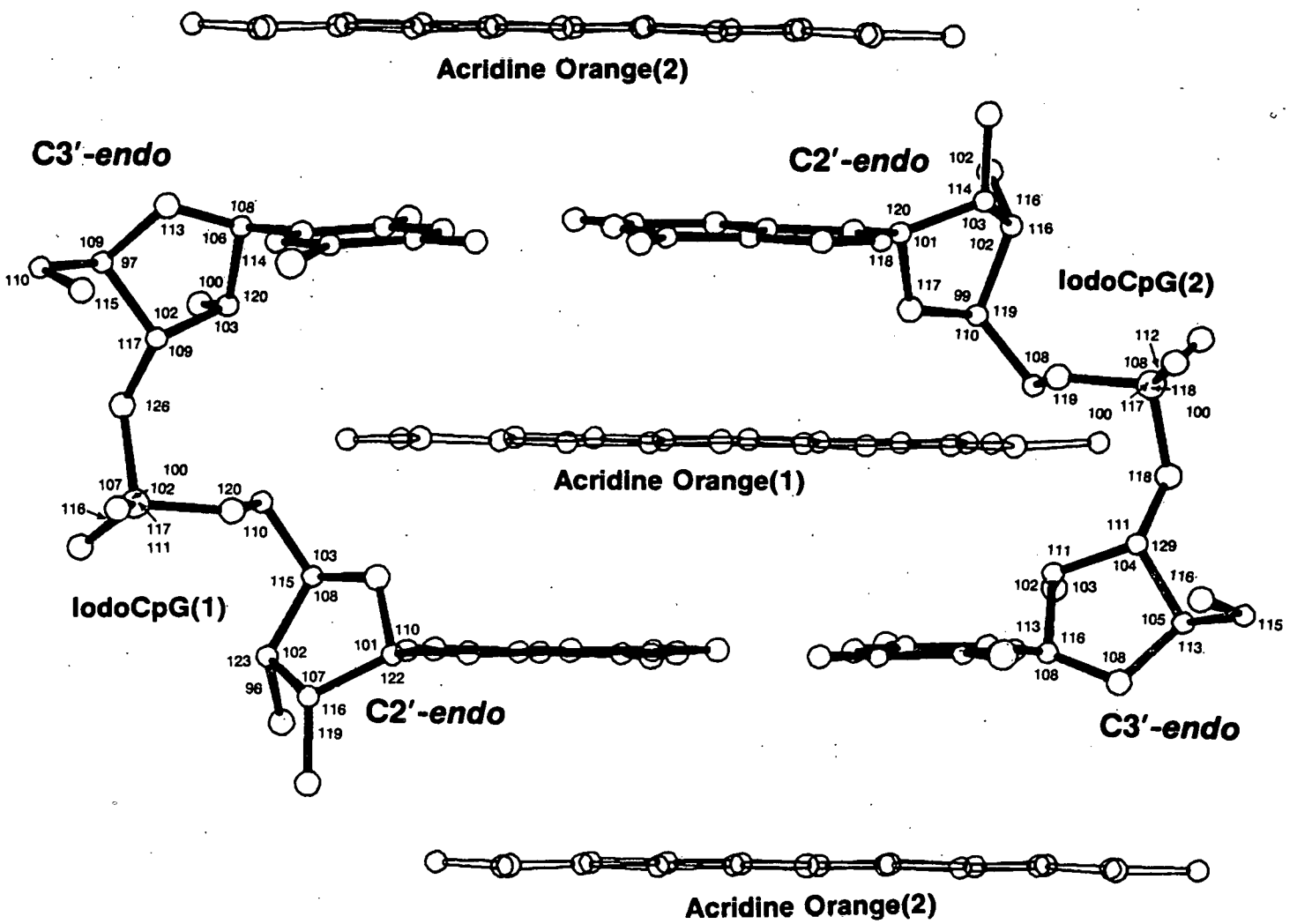
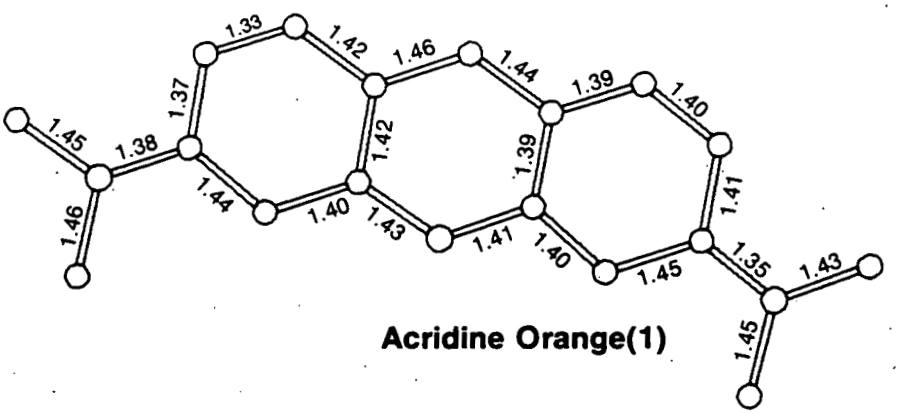

Acridine Orange(2)
C3'-endo
C2'-endo
IodoCpG(2)
Acridine Orange(1)
IodoCpG(1)
C2'-endo
C3'-endo
Acridine Orange(2)

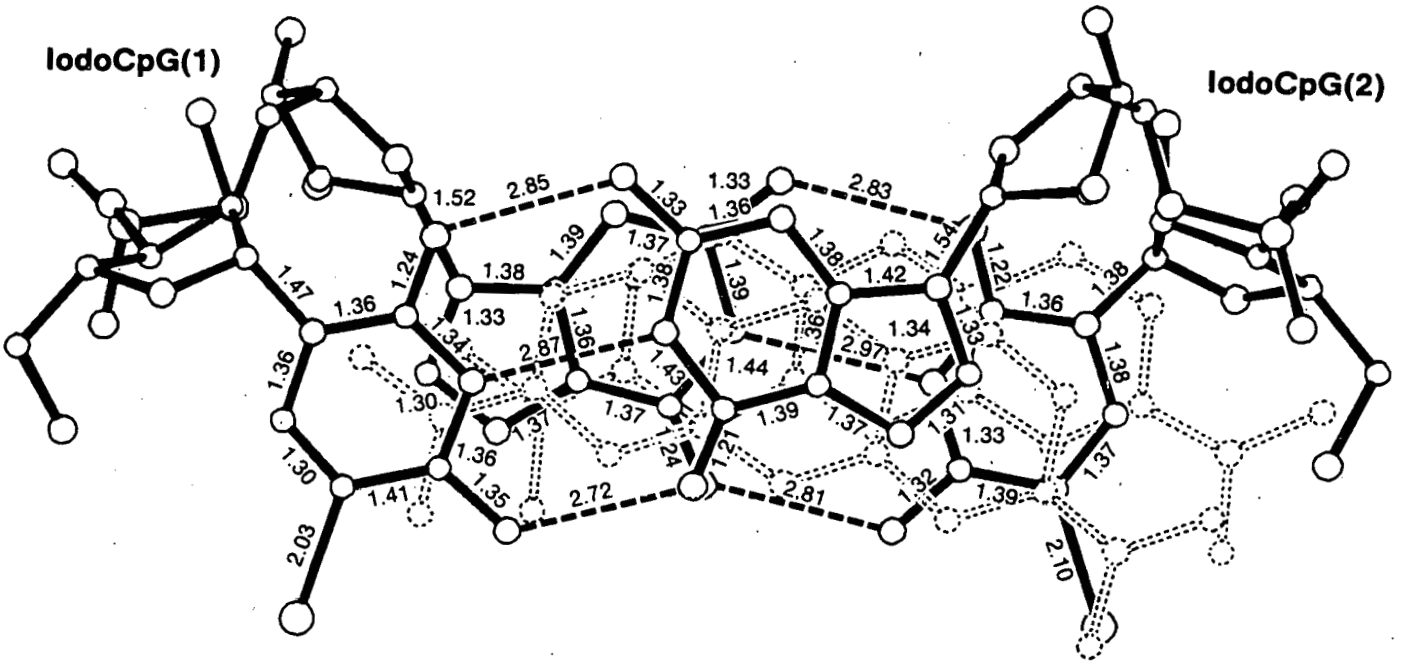

Acridine Orange(2)
C3′-endo
C2′-endo
IodoCpG(2)
Acridine Orange(1)
IodoCpG(1)
C2′-endo
C3′-endo
Acridine Orange(2)

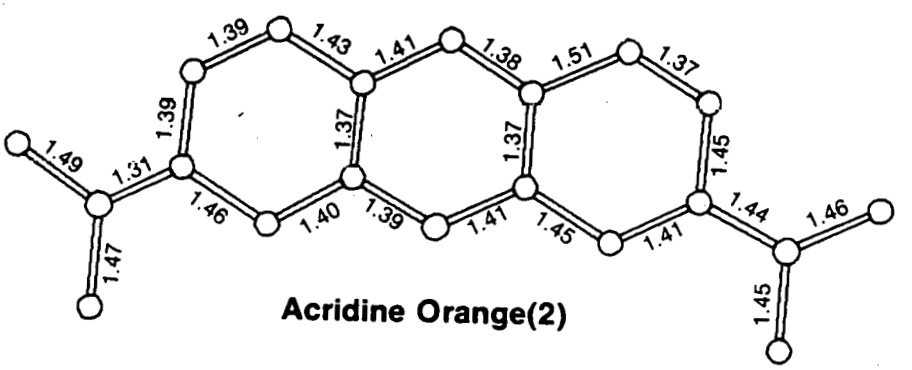


Acridine Orange(1)

IodoCpG(1)

IodoCpG(2)





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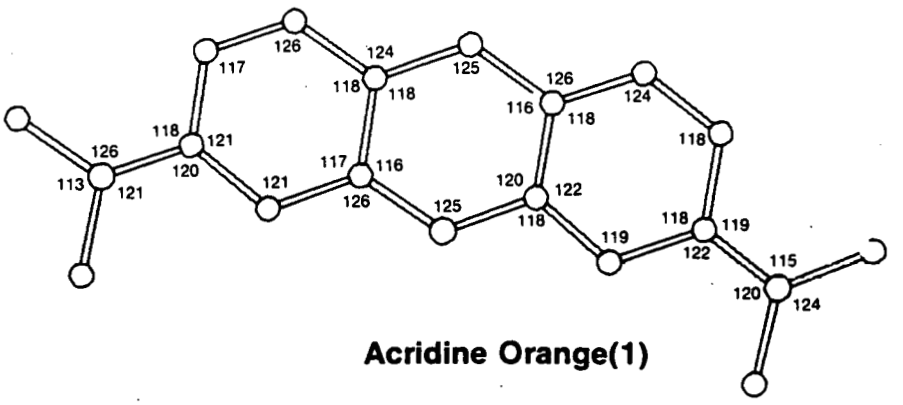
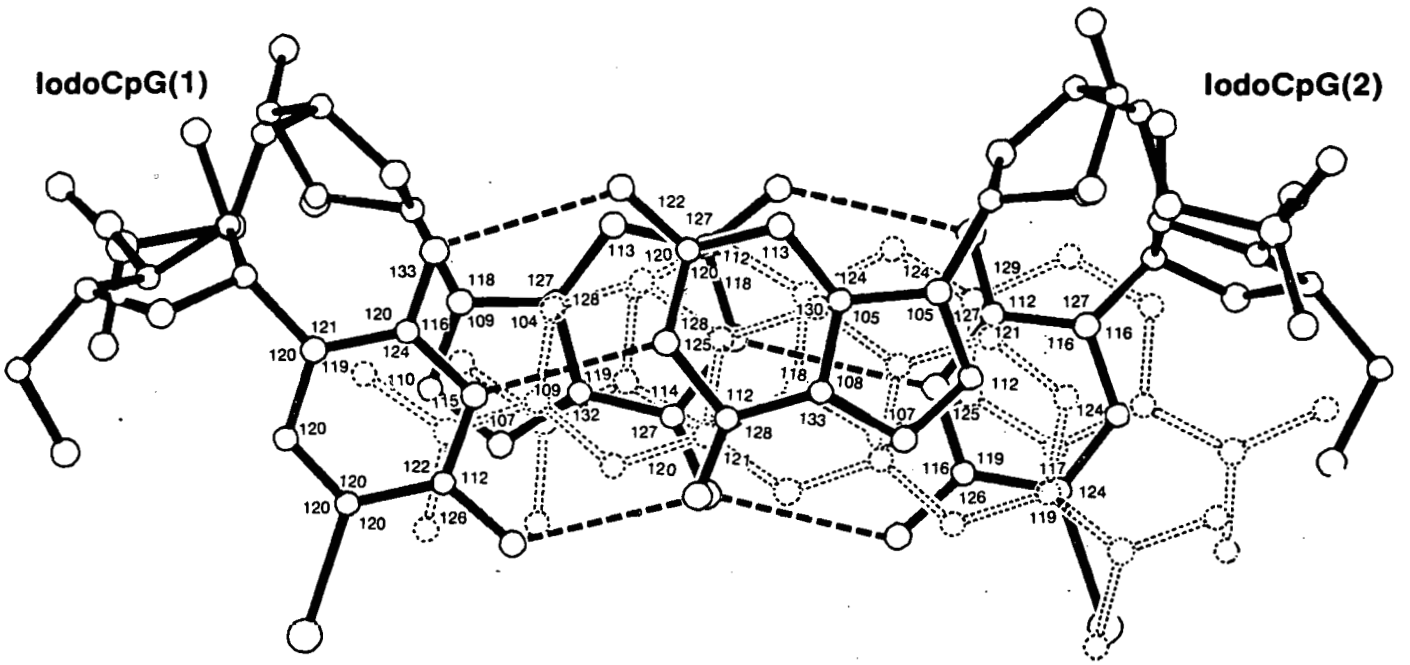
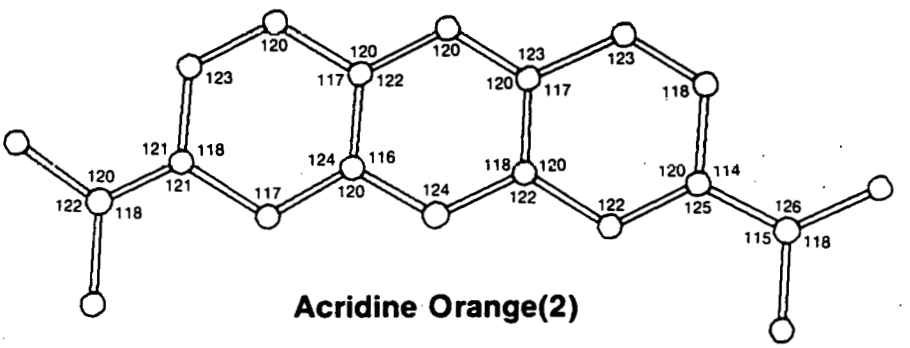


Acridine Orange(1)

IodoCpG(1)

IodoCpG(2)





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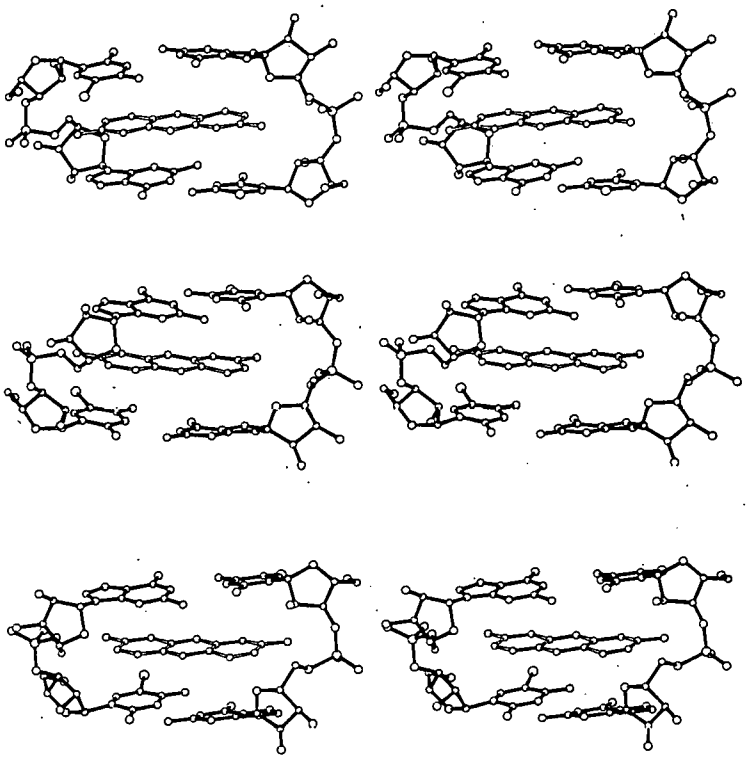

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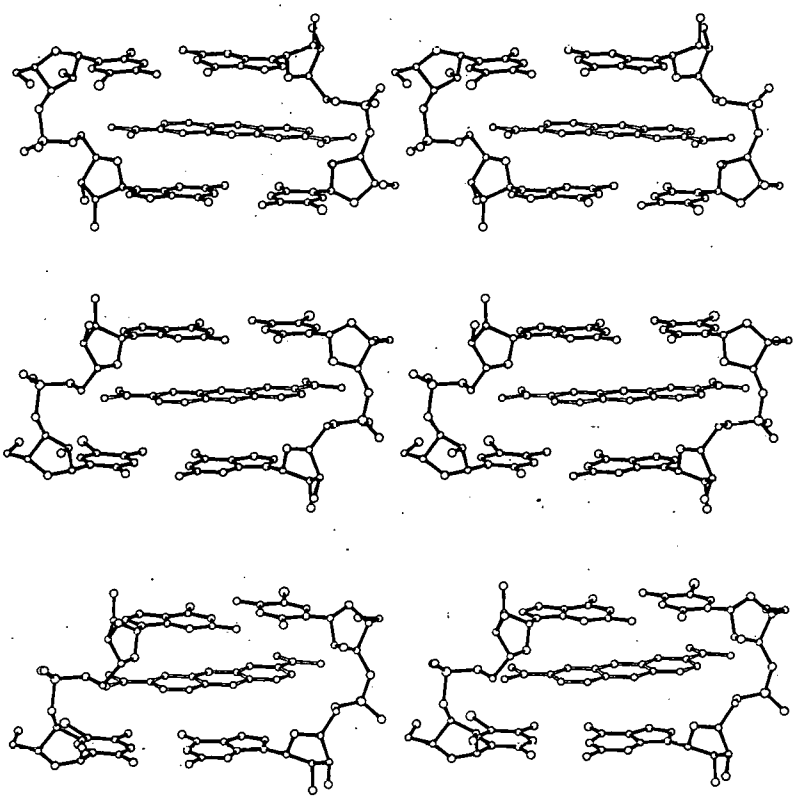
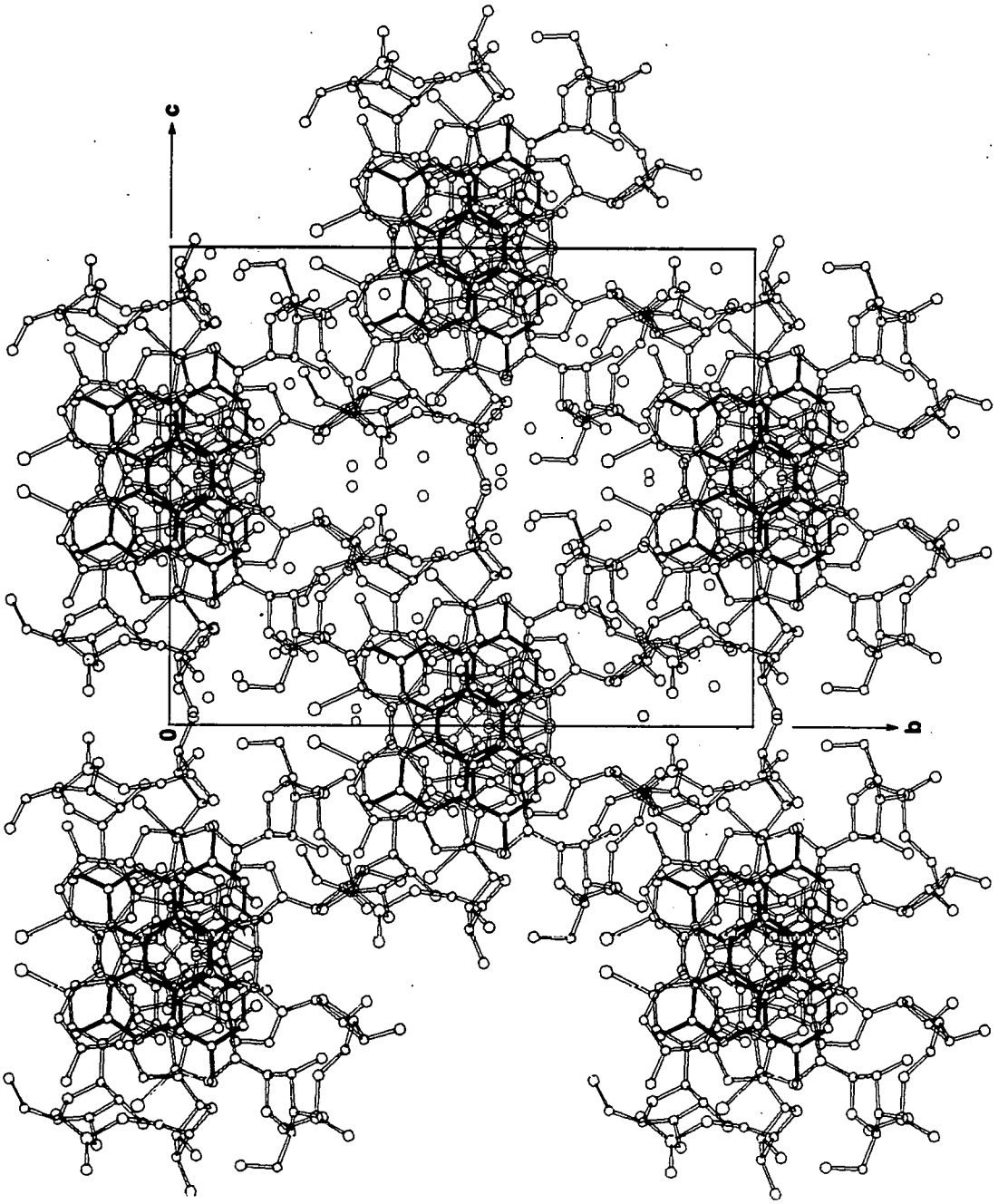


Figure 13.


c
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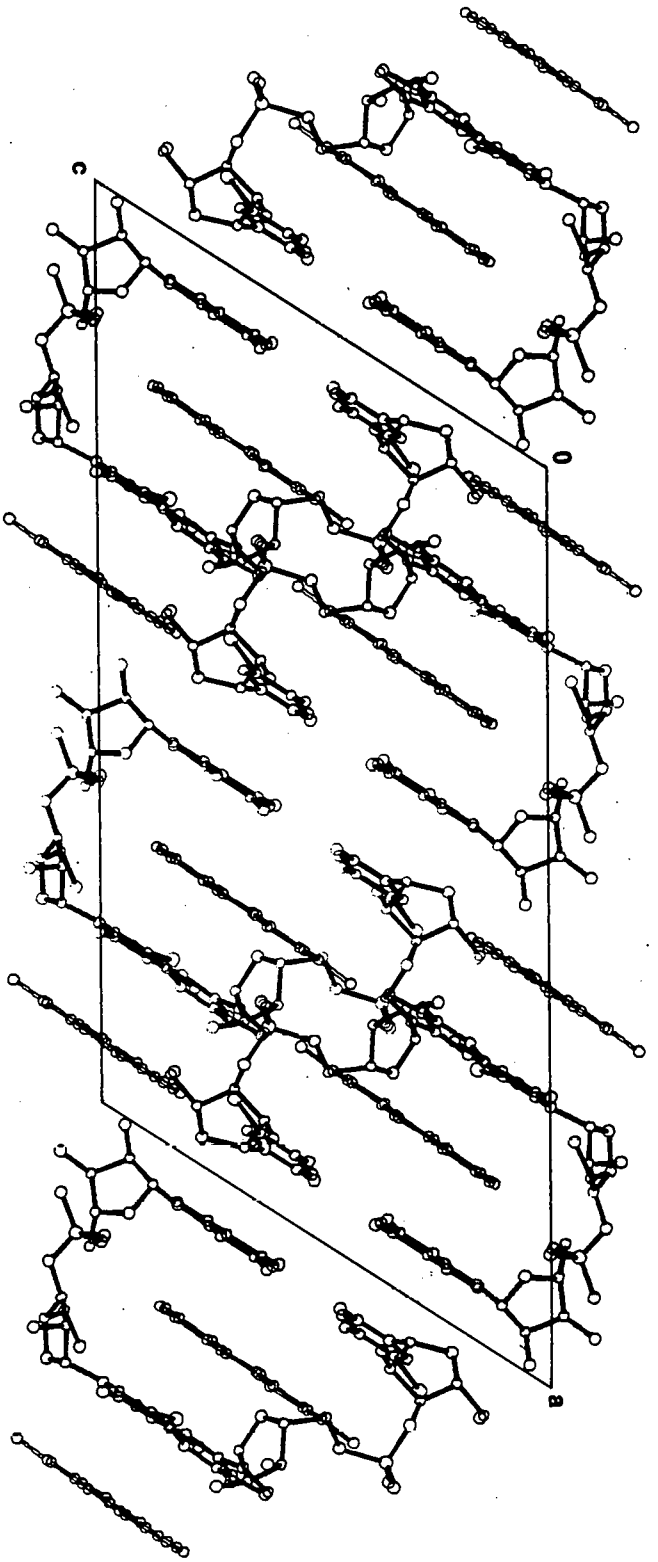
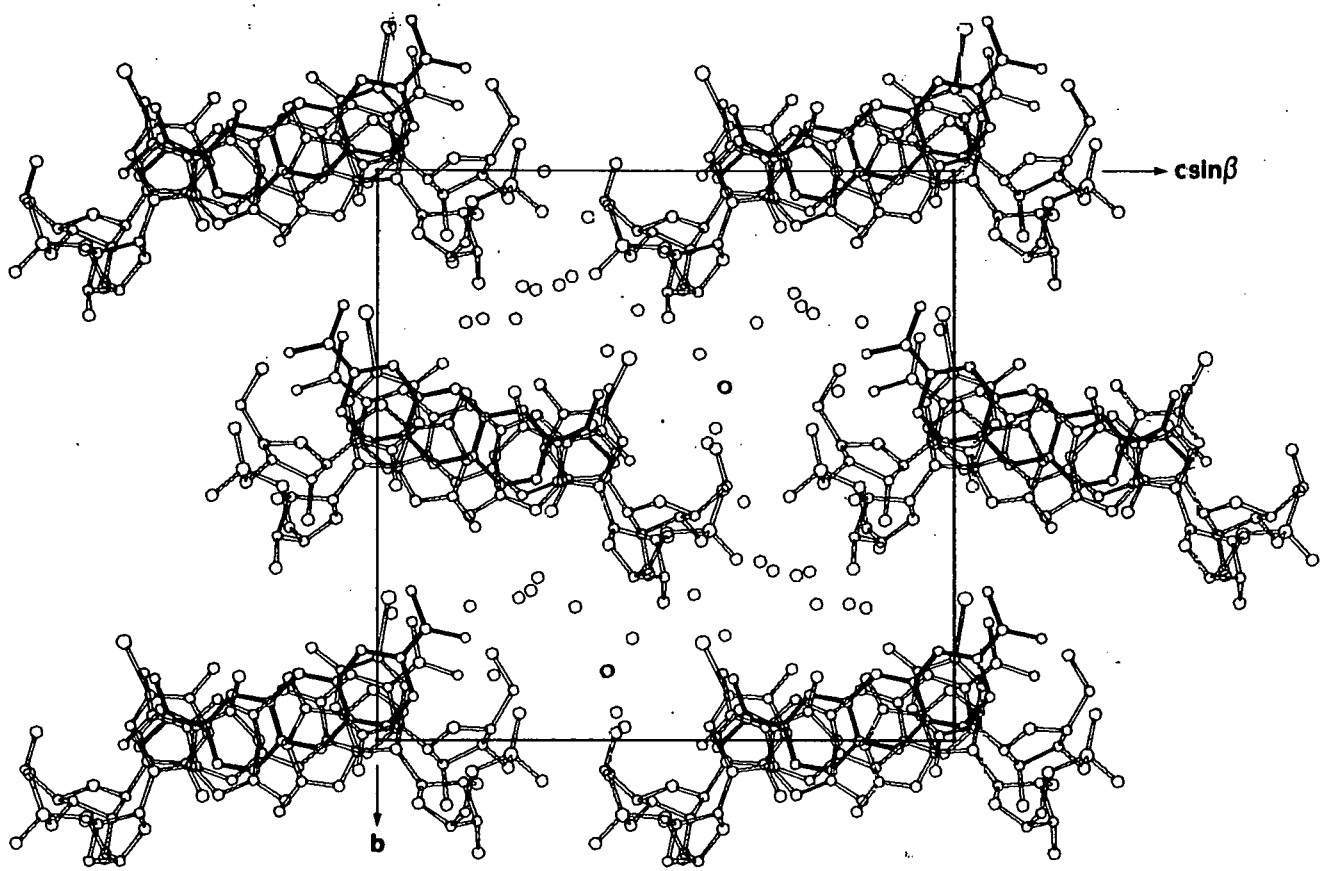
b


C
O
B


csinβ
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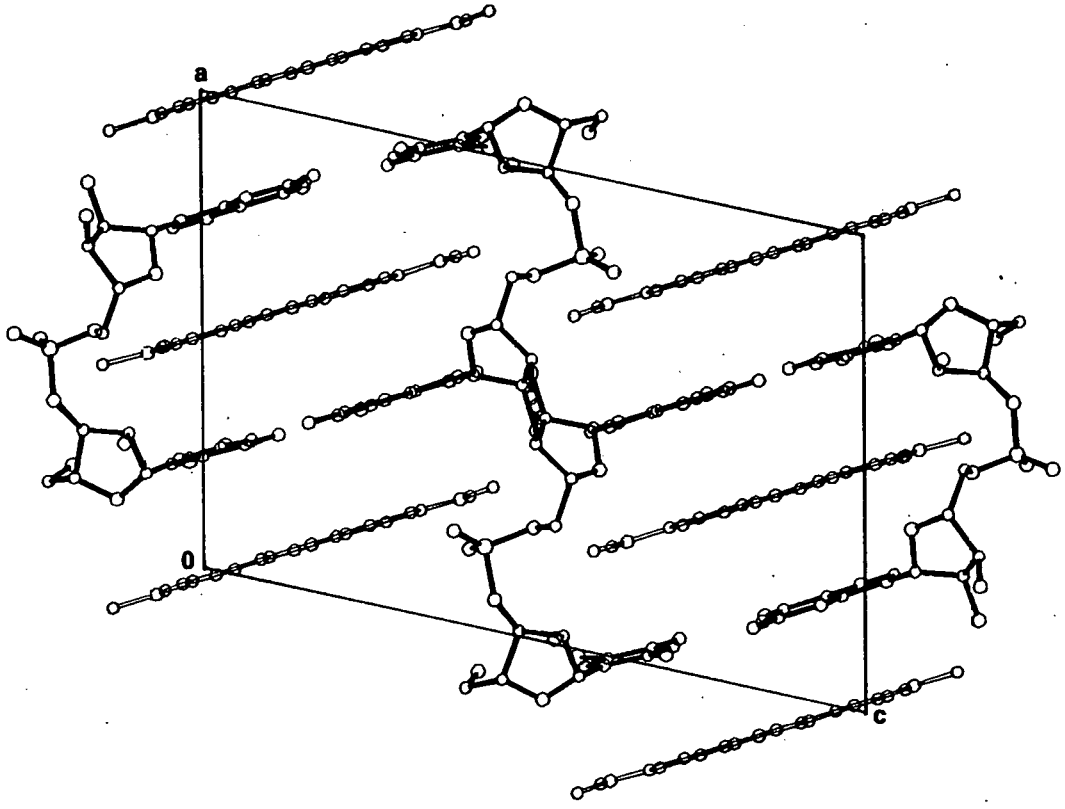
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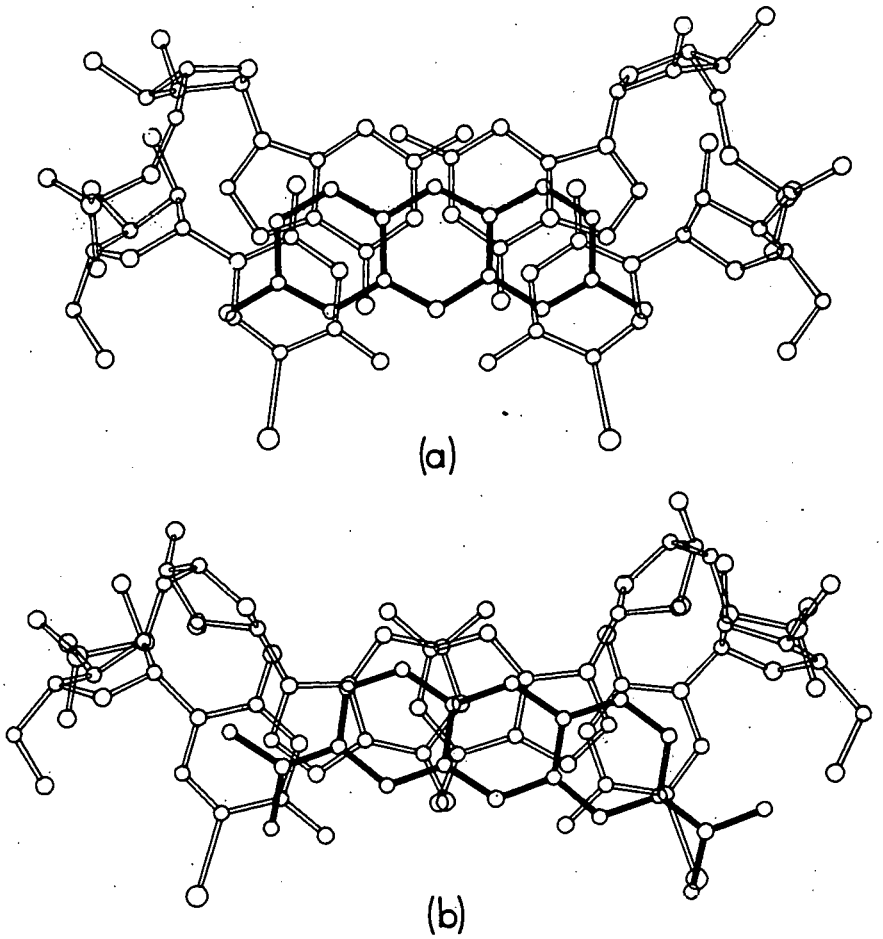

Figure 18.