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VISUALIZATION OF DRUG-NUCLEIC ACID INTERACTIONS AT ATOMIC RESOLUTION

VI. STRUCTURE OF TWO DRUG/ DINUCLEOSIDE MONOPHOSPHATE CRYSTALLINE COMPLEXES, ELLIPTICINE: 5-IODOCYTIDYLYL(3'-5')GUANOSINE AND 3,5,6,8-TETRAMETHYL-N-METHYL PHENANTHROLINIUM: 5-IODOCYTIDYLYL(3'-5')GUANOSINE

by

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ABSTRACT:

Ellipticine and 3,5,6,8-tetramethyl-N-methyl phenanthrolinium (TMP) form complexes with the dinucleoside monophosphate, 5-iodocytidylyl(3'-5')guanosine (iodoCpG). These crystals are isomorphous: ellipticine-iodoCpG crystals are monoclinic, space group $P2_1$, with a = 13.88 Å, b = 19.11 Å, c = 21.42 Å, β = 105.4°; TMP-iodoCpG crystals are monoclinic, space group $P2_1$, with a = 13.99 Å, b = 19.12 Å, c = 21.31 Å, β = 104.9°. Both structures have been solved to atomic resolution by Patterson and Fourier methods, and refined by full matrix least squares.

The asymmetric unit in the ellipticine-iodoCpG structure contains two ellipticine molecules, two iodoCpG molecules, 16 water molecules and 2 methanol molecules, a total of 140 atoms, whereas, in the tetramethyl-N-methyl phenanthrolinium-iodoCpG complex, the asymmetric unit contains two TMP molecules, two iodoCpG molecules, 17 water molecules and 2 methanol molecules, a total of 141 atoms. In both structures, the two iodoCpG molecules are hydrogen bonded together by guanine-cytosine Watson-Crick base-pairing. Adjacent base-pairs within this paired iodoCpG structure are separated by about 6.7 Å; this separation results from intercalative binding by one ellipticine (or TMP) molecule and stacking by the other ellipticine (or TMP) molecule above or below the base-pairs. Base-pairs within the paired nucleotide units are related by a twist of 10-12°. The magnitude of this angular twist is related to conformational changes in the sugar-phosphate chains that accompany drug intercalation. These changes partly reflect the mixed sugar puckering pattern observed: C3' endo (3'-5') C2' endo (i.e., both iodocytidine residues have C3' endo conformations, whereas both guanosine residues have C2' endo conformations), and additional small but systematic changes in torsional angles that involve the phosphodiester linkages and the C4'-C5' bond.

ABSTRACT: (continued)

The stereochemistry observed in these model drug-nucleic acid intercalative complexes is almost identical to that observed in the ethidium-iodoUpA and -iodo CpG complexes determined previously (Tsai et al., 1975a, b; 1977; Jain et al., 1977). This stereochemistry is also very similar to that observed in the 9-amino-acridine-iodoCpG and acridine orange-iodoCpG complexes described in the accompanying papers (Sakore et al., 1979; Reddy et al., 1979). We have already proposed this stereochemistry to provide a unified understanding of a large number of intercalative drug-DNA (and RNA) interactions (Sobell et al., 1977a, b), and discuss this aspect of our work further in this paper.

RUNNING TITLE:

DRUG-NUCLEIC ACID INTERACTIONS VI

1. Introduction.

Ellipticine (Fig. 1) is a plant alkaloid that possesses pharmacological activity in the treatment of an experimental mouse leukemia, L 1210 (Hartwell and Abbott, 1969; Svoba et al., 1969). This compound (as well as other related chemical derivatives) has been studied by Le Pecq et al. (1974) and Kohn et al. (1975) and established to bind to DNA by intercalation. It is possible that the biological activity of ellipticine and its chemical derivatives reflect their DNA binding properties.

3,5,6,8-tetramethyl-N-methyl phenanthrolinium (Fig. 2) is one in a series of phenanthrolinium compounds that has been synthesized by Gabbay et al. (1973) to probe the dynamic structure of DNA in solution. Although these compounds have no known biological activity, Gabbay has shown many of these compounds to bind to DNA by intercalation. His studies have helped to establish stereochemical features of the intercalation process and point to a possible relationship between drug intercalation and DNA breathing phenomena (Gabbay, 1976).

This paper describes the structures of two drug-nucleic acid crystalline complexes: ellipticine-5-iodocytidylyl(3'-5')guanosine (ellipticine-iodoCpG) and 3,5,6,8-tetramethyl-N-methyl phenanthrolinium-5-iodocytidylyl(3'-5')guanosine (TMP-iodoCpG). These are isomorphous crystals and therefore demonstrate common intercalative geometries. We describe these in detail in this paper.

A preliminary account of this work has already been presented at the American Crystallographic Association Meetings at the University of Oklahoma, Norman, Oklahoma (Jain, Bhandary & Sobell, 1978) and at the University of Hawaii, Honolulu, Hawaii (Bhandary, Jain & Sobell, 1979).

2. Materials and Methods.

Ellipticine and 3,5,6,8-tetramethyl-N-methyl phenanthrolinium were gifts

from Dr. Kurt Kohn, National Institutes of Health, and from Dr. Edward Gabbay, The University of Florida at Gainsville, respectively, and were used directly. The dinucleoside monophosphate, cytidylyl(3'-5')guanosine, was obtained as the ammonium salt from Sigma Chemical Company and then iodinated using the procedure we have described previously (Tsai et al., 1977). Plate-like crystals of both complexes were obtained by slow evaporation over several days of equimolar mixtures of ellipticine (or TMP) and 5-iodocytidylyl(3'-5')guanosine (see Fig. 3) adjusted to pH 5.5 in aqueous solution containing a few drops of ethanol and methanol. These crystals were initially characterized from precession photographs using Ni-filtered CuKα radiation, and the unit cell dimensions then refined by least squares using 12 independent reflections measured on a Picker FACS-1 automatic diffractometer.

The ellipticine-iodoCpG crystals are monoclinic, $P2_1$, with $\underline{a}$ = 13.88 ± 0.02 Å, $\underline{b}$ = 19.11 ± 0.03 Å, $\underline{c}$ = 21.42 ± 0.03 Å, β = 105.4 ± 0.4 . The TMP-iodoCpG crystals are isomorphous to these, with $\underline{a}$ = 13.99 ± 0.02 Å, $\underline{b}$ = 19.12 ± 0.03 Å, $\underline{c}$ = 21.31 ± 0.03 Å, β = 104.9 ± 0.4 . Single crystals of the ellipticine-iodoCpG complex measuring 0.08 mm x 0.06 mm x 0.04 mm were mounted with some mother liquor in 0.5 mm quartz capillaries; larger crystals of the TMP-iodoCpG complex could be obtained (0.11 mm x 0.16 mm x 0.33 mm), and these were mounted with mother liquor in 0.5 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 angle of 60 for the ellipticine structure and 70 for the TMP structure. Of the 1669 and 2513 reflections theoretically accessible, 1191 and 1409 reflections were considered to be significantly above background (i.e., 1.5σ) in the ellipticine and TMP structures, respectively, and used for the analyses. These were corrected for the Lorentz

and polarization factors; however, absorption effects were ignored. The structure factors were put on an absolute scale and the overall temperature factors estimated by the Wilson (1942) method. These were then converted into quasi-normalized structure factors (Karle and Hauptman, 1953).

An (E^2-1) Patterson function was calculated for the ellipticine-iodoCpG structure using all the reflections and this gave the position of both iodine atoms. Using this information a Patterson superposition function was calculated and this revealed the possible positions of both guanine-cytosine base-pairs. Phases calculated from this partial structure were used in a sum-function Fourier synthesis to generate additional information. The complete structure was eventually developed using Fourier, sum function Fourier and difference Fourier methods. This includes two iodoCpG molecules, two ellipticine molecules, 16 water molecules and 2 methanol molecules, a total of 140 atoms. Two cycles of full matrix least squares were then carried out using 1191 observed reflections. The positional shifts were damped to 60%, while the isotropic temperature shifts were damped to 30%; iodine atoms, however, were allowed full shifts for both positional and temperature parameters. The refinement converged rapidly to 21.1%. At this stage, a final Fourier and sum-Fourier was calculated and these were reinterpreted in terms of chemical structures of iodoCpG molecules and ellipticine molecules. This gave a final residual of 21.5% on 1191 observed reflections.

The TMP-iodoCpG structure was deduced to be isomorphous with the ellipticine-iodoCpG structure since the (E^2-1) Patterson functions were almost identical. An initial Fourier map was computed using the phases based on the positions of two iodoCpG molecules from the ellipticine structure. This gave the positions of both TMP molecules. Refinement and additional structural information was accomplished with several cycles of Fourier, sum-Fourier and difference Fourier syntheses

interleaved with several cycles of full matrix least squares using 1409 observed reflections and the damping scheme described above, except that both iodine atoms were refined anisotropically with full shifts. At this time, it was observed that most atoms in the stacked TMP molecules had unrealistically high temperature factors and a difference Fourier synthesis was therefore computed leaving out this TMP molecule. This clearly indicated two possible orientations for this stacked TMP molecule with equal probability (see Fig. 4). The final structure contains two iodoCpG molecules, two TMP molecules, 17 water molecules and 2 methanol molecules, a total of 141 atoms. This gave a final residual of 14.1% on 1409 observed 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 x, y and z coordinates of light atoms lie between 0.04 A and 0.05 A in the ellipticine-iodoCpG complex and between 0.02 A and 0.04 A in the TMP-iodoCpG complex. This results in standard deviations for bond lengths between light atoms of about $\pm$ 0.10 A, and for bond angles of about $\pm$ 5.0 in the ellipticine structure, and about $\pm$ 0.06 A and $\pm$ 3.6 for the TMP structure. The enhanced accuracy of the TMP-iodoCpG analysis probably reflects the quality and quantity of the diffraction data available.

(a) Drug-nucleic acid intercalative binding.

Figures 5-12 show the ellipticine-iodoCpG and TMP-iodoCpG complexes viewed approximately parallel and perpendicular to the planes of guanine-cytosine base-pairs and drug molecules. Both structures are very similar

to each other and to the ethidium-iodoUpA and ethidium-iodoCpG structures described previously (Tsai et al., 1977; Jain et al., 1977). They also are quite similar to the acridine orange-iodoCpG and 9-aminoacridine-iodoCpG complexes described in the accompanying papers (Reddy et al., 1979; Sakore et al., 1979). Each contains a 2:2 ellipticine (or TMP) -iodoCpG complex and involve two drug molecules interacting with two dinucleoside monophosphates. 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 near identity of the ellipticine- and TMP- iodoCpG structures is particularly interesting in view of the completely different chemical structures of these drugs. Ellipticine is an asymmetric structure having an extended conjugated ring system, whereas TMP is very nearly 2-fold symmetric and has a smaller conjugated system. The different stacking patterns that are observed between these drug molecules and guanine-cytosine base-pairs argues that van der Waals stacking interactions are relatively unimportant in determining the intercalative nucleotide geometry in these structures. We will return to this point later.

(b) Sugar-phosphate conformation and double-helix unwinding.

Table 3 summarizes the torsional angles that define the sugar-phosphate conformations in these structures. In both structures, iodocytidine ribose sugar residues are best described as C3' endo, while guanosine ribose sugar residues are C2' endo. In each case, the conformation around the C4'-C5' bond is gauche-gauche. The glycosidic torsional angles (denoted χ) fall in the low anti range for iodocytidine residues and in the high anti range for guanosine residues.

The torsional angles describing the sugar-phosphate conformations in this structure give rise to a characteristic twist angle between base-pairs above and below the intercalative ellipticine (or TMP) molecules. This value is estimated to be 10-12 in both structures and this leads to the unwinding observed for double-helical nucleic acid polymers at the immediate site of drug intercalation (i.e., estimated to be about -26 for ethidium-DNA binding (Wang, 1974)). We have not attempted to relate base-pairs above and below the ellipticine (or TMP) molecules by a helical screw operation; this reflects our fundamental realization that drug intercalation gives rise to a helical screw axis dislocation in DNA and in RNA (Sobell et al., 1977a, b).

Stereo- pairs of the ellipticine- and TMP- intercalative geometries are shown in Figures 13 and 14.

(c) Crystal lattices.

Figures 15-18 show the ellipticine- and TMP- iodoCpG crystal structures viewed down the a and b axes. Ellipticine (or TMP) -iodoCpG complexes form sandwich-like hydrophobic stacks along the a axis, and this leaves hydrophillic channels containing water structure extending in the same direction. Both structures are heavily hydrated -- water molecules forming hydrogen bonds to hydrophillic groups on the sugar-phosphate chains and base-pairs of nucleoside monophosphate residues. In addition, there is considerable water-water hydrogen bonding. The water structure differs somewhat in these two structures -- this probably reflects the differences in chemical structures and physical properties of the ellipticine and TMP molecules.

Relevant hydrogen bonding contacts are summarized in Table 4.

4. Discussion.

Figures 19 and 20 compare structural information obtained from X-ray analyses of six different drug-nucleic acid crystalline complexes. In addition to the com-

plexes described here, acridine orange -iodoCpG, ethidium -iodoCpG and -iodoUpA, and the platinum containing organometallic intercalator complex, 2-hydroxyethane--thiolate-2,2',2"-terpyridine-platinum (II) -dCpG complexes are shown (Reddy et al., 1979; Jain et al., 1977; Tsai et al., 1977; Wang et al., 1978). It is clear that there is a remarkable similarity in the sugar-phosphate backbone geometries in these structures -- and that, therefore, the stereochemistry of drug intercalation into these RNA- and DNA- like self-complementary dinucleotide sequences is relatively insensitive to the exact nature of the intercalative drug or dye.

If one uses the information obtained from these model studies to understand the stereochemistry of drug intercalation into DNA and RNA, a common structural feature emerges: each sugar-phosphate chain contains the mixed sugar puckering pattern C3' endo (3'-5') C2' endo at the immediate site of drug intercalation. Thus, drug intercalation into B DNA would require the coordinate conversion (related across a 2-fold axis) of two C2' endo sugar residues into C3' endo conformations, whereas, with RNA, drug intercalation would require the opposite to happen (i.e., two C3' endo sugar residues would have to convert to C2' endo conformations).

These concepts form major postulates in our models to understand drug-DNA (and -RNA) binding and, in addition, have led us to propose the precise nature of dynamic DNA structure that leads to drug intercalation (Sobell et al., 1976; Sobell et al., 1977a, b; Sobell et al., 1978; Lozansky et al., 1979). According to these concepts, drug intercalation is preceded by the transient formation of a second DNA structure, β kinked DNA. This structure -- an inelastically deformed DNA structure that contains an alternating pattern of sugar puckering down the sugar-phosphate backbone with the concommitant partial unstacking of alternate base-pairs -- arises due to a specific normal mode oscillation in DNA structure excited through Brownian motion of solvent molecules. Further normal mode oscillations in this β

kinked structure during its lifetime give rise to the stereochemistry required for mono- and bis- functional drug intercalation.

More generally, we have proposed that different regions of DNA could have two discrete structures that coexist at equilibrium. That is, at any given temperature, DNA may consist of Watson-Crick B DNA regions and other regions that are permanently β kinked. Here, β kinked DNA corresponds to a second order phase transition in the polymer -- different regions of DNA undergoing this transition at different temperatures. We have suggested these multiply-kinked premelted regions to be promoters (Sobell et al., 1978; Lozansky et al., 1979).

Similar lines of reasoning can be advanced to understand drug intercalation into double helical RNA and to understand the possible nature of viral RNA promoters.

The technique of molecular cocrystallization has provided an opportunity to obtain detailed structural information about a large number of drug interactions with nucleic acid components. For the most part, these studies have concentrated on crystalline complexes between drugs and self-complementary ribo- and deoxyribodinucleoside monophosphates. It is clear that additional information with longer oligonucleotides would be valuable -- we are therefore continuing our efforts along these lines.

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Table 4. Hydrogen bonding distances observed in the ellipticine- and TMP- iodoCpG crystal structures.

ellipticine-iodoCpG			
Atoms	Distance (A)	Atoms	Distance (A)
OW1 - OW4 (1)	3.05		
OW1 - N4C2 (1)	3.00		
OW1 - O2'C (2)	3.26		
OW2 - OW8 (1)	2.70		
OW2 - O5'C (3)	3.28		
OW3 - OW15 (1)	2.43		
OW3 - O6G2 (1)	2.52		
OW3 - N7G2 (1)			

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FIGURE CAPTIONS:

Figure 1. Chemical structure of ellipticine.

Figure 2. Chemical structure of 3,5,6,8-tetramethyl-N-methyl phenanthrolinium.

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

Figure 4. Illustration to show the two different orientations observed for the stacked TMP molecule (TMP(2)) in the TMP-iodoCpG crystal structure. These two orientations occur with equal probability and reflect statistical disorder in the crystal. (a) stacking patterns of TMP(2) molecules on guanine-cytosine base-pairs, viewed from the top (i.e., compare with Fig. 8). (b) stacking patterns of TMP(2) molecules on guanine-cytosine base-pairs, viewed from the bottom.

Figure 5. A portion of the ellipticine-iodoCpG crystal structure viewed approximately parallel to the planes of the guanine-cytosine base-pairs and ellipticine molecules showing bond distances of sugar-phosphate chains. IodoCpG molecules are drawn with dark solid bonds; intercalative ellipticine molecules (ellipticine(1)) and stacked ellipticine molecules (ellipticine(2)) have been drawn with light open bonds.

Figure 6. Same as Fig. 5, but showing bond angles of sugar-phosphate chains.

Figure 7. Illustration of the ellipticine-iodoCpG structure viewed perpendicular to the planes of the guanine-cytosine base-pairs and ellipticine molecules, showing bond distances of base-pairs and ellipticine molecules. See text for discussion.

Figure 8. Same as Fig. 7, but showing bond angles of base-pairs and ellipticine molecules.

Figure 9. A portion of the 3,5,6,8-tetramethyl-N-methyl phenanthrolinium (TMP) - iodoCpG crystal structure viewed approximately parallel to the planes of the guanine-cytosine base-pairs and TMP molecules showing bond distances of sugar-phosphate chains. IodoCpG molecules are drawn with dark solid bonds; intercalative TMP molecules (TMP(1)) and stacked TMP molecules (TMP(2)) have been drawn with light open bonds. Only one of two statistically disordered orientations for this stacked TMP molecule has been shown.

Figure 10. Same as Fig. 9, but showing bond angles of sugar-phosphate chains.

Figure 11. Illustration of the TMP-iodoCpG structure viewed perpendicular to the planes of the guanine-cytosine base-pairs and TMP molecules, showing bond distances of base-pairs and TMP molecules. See text for discussion.

Figure 12. Same as Fig. 11, but showing bond angles of base-pairs and TMP molecules.

Figure 13. Stereo- pairs of ellipticine-iodoCpG intercalative binding.

FIGURE CAPTIONS: (continued)

Figure 14. Stereo- pairs of TMP-iodoCpG intercalative binding.

Figure 15. A lattice picture of the ellipticine-iodoCpG crystalline complex drawn down the a crystallographic direction to show relations between columns of ellipticine-iodoCpG complexes and the surrounding water structure.

Figure 16. A lattice picture of the TMP-iodoCpG crystalline complex drawn down the a crystallographic direction to show relations between columns of TMP-iodoCpG complexes and the surrounding water structure. The isomorphous nature of the ellipticine- and TMP- iodoCpG structures is apparent.

Figure 17. View of ellipticine-iodoCpG structure down the b crystallographic direction. For simplicity, water structure has been ommitted in this Figure.

Figure 18. View of TMP-iodoCpG structure down the b crystallographic direction. Water structure has been omitted for clarity. See text for discussion.

Figure 19. Illustration to compare intercalative geometries observed in RNA and DNA-like dinucleoside monophosphates and different intercalative drug molecules. (a) ellipticine-iodoCpG (b) TMP-iodoCpG (c) acridine orange-iodoCpG. See text for discussion.

Figure 20. Illustration to compare intercalative geometries observed in RNA and DNA-like dinucleoside monophosphates and different intercalative drug molecules (a) ethidium-iodoUpA (b) ethidium-iodoCpG (c) terpyridine platinum(II)-dCpG. See text for discussion.

Table 1. Final coordinates and temperature factors obtained from the ellipticine-iodoCpG crystal structure analysis.

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	1.0093	0.2906	0.4196	5.0	42	I5 C2	0.2146	0.2500	-0.0298	3.1
2	N1 C1	1.0170	0.5087	0.3914	6.1	43	N1 C2	0.2155	0.4705	-0.0462	4.2
3	C2 C1	0.9707	0.5184	0.3251	5.4	44	C2 C2	0.2628	0.4951	0.0154	3.0
4	O2 C1	0.9608	0.5796	0.3039	3.6	45	O2 C2	0.2727	0.5592	0.0237	5.9
5	N3 C1	0.9377	0.4631	0.2884	1.6	46	N3 C2	0.2950	0.4493	0.0630	1.6
6	C4 C1	0.9431	0.3991	0.3127	1.6	47	C4 C2	0.2882	0.3808	0.0531	8.6
7	N4 C1	0.9036	0.3457	0.2757	5.2	48	N4 C2	0.3297	0.3364	0.0998	9.1
8	C5 C1	0.9901	0.3875	0.3817	1.6	49	C5 C2	0.2420	0.3551	-0.0103	6.6
9	C6 C1	1.0249	0.4439	0.4167	5.6	50	C6 C2	0.2069	0.4009	-0.0576	9.2
10	C1'C1	1.0524	0.5714	0.4307	2.1	51	C1'C2	0.1647	0.5249	-0.0980	1.6
11	C2'C1	0.9661	0.6047	0.4498	1.9	52	C2'C2	0.2444	0.5546	-0.5546	9.0
12	C3'C1	0.9863	0.5736	0.5190	12.7	53	C3'C2	0.2410	0.5031	-0.1751	6.1
13	C4'C1	1.0986	0.5744	0.5445	2.1	54	C4'C2	0.1318	0.4896	-0.2054	11.6
14	O1'C1	1.1314	0.4485	0.4864	1.6	55	O1'C2	0.0891	0.4937	-0.1496	13.2
15	C5'C1	1.1420	0.5234	0.5962	3.5	56	C5'C2	0.1042	0.4206	-0.2400	1.8
16	O5'C1	1.1007	0.4554	0.5796	3.9	57	O5'C2	0.1531	0.3646	-0.2009	10.9
17	O2'C1	0.9773	0.6784	0.4528	4.7	58	O2'C2	0.2224	0.6233	-0.1466	3.7
18	O3'C1	0.9419	0.6167	0.5620	1.9	59	O3'C2	0.2920	0.5433	-0.2104	4.7
19	P1	0.8296	0.6056	0.5724	4.6	60	P2	0.3779	0.5218	-0.2439	3.8
20	O1 P1	0.8207	0.6498	0.6280	5.6	61	O1 P2	0.3627	0.5588	-0.3067	8.9
21	O2 P1	0.8067	0.5300	0.5764	6.5	62	O2 P2	0.3916	0.4450	-0.2456	8.0
22	O5'G1	0.7608	0.6340	0.5020	4.0	63	O5'G2	0.4751	0.5511	-0.1877	7.3
23	C5'G1	0.7384	0.7044	0.4914	10.5	64	C5'G2	0.4824	0.6238	-0.1580	11.3
24	C4'G1	0.6311	0.7197	0.4568	2.4	65	C4'G2	0.5884	0.6482	-0.1289	7.3
25	C3'G1	0.5624	0.7010	0.5014	12.5	66	C3'G2	0.6546	0.6350	-0.1745	6.3
26	C2'G1	0.5158	0.6344	0.4743	2.1	67	C2'G2	0.7142	0.5694	-0.1472	4.3
27	C1'G1	0.5169	0.6388	0.4066	12.6	68	C1'G2	0.7217	0.5763	-0.0744	10.3
28	O1'G1	0.6000	0.6777	0.4001	4.6	69	O1'G2	0.6357	0.6104	-0.0698	1.6
29	O2'G1	0.4179	0.6198	0.4825	9.8	70	O2'G2	0.8087	0.5649	-0.1609	10.6
30	O3'G1	0.4867	0.7534	0.4957	8.3	71	O3'G2	0.7186	0.6921	-0.1758	12.8
31	N1 G1	0.3697	0.4967	0.1941	1.6	72	N1 G2	0.8485	0.4906	0.1593	2.9
32	C2 G1	0.3791	0.5694	0.2023	3.8	73	C2 G2	0.8480	0.5570	0.1346	1.6
33	N2 G1	0.3469	0.6097	0.1507	3.8	74	N2 G2	0.8821	0.6094	0.1759	1.6
34	N3 G1	0.4205	0.5983	0.2617	7.4	75	N3 G2	0.8137	0.5708	0.0708	6.1
35	C4 G1	0.4464	0.5493	0.3084	1.6	76	C4 G2	0.7816	0.5125	0.0355	1.6
36	C5 G1	0.4378	0.4787	0.3047	4.4	77	C5 G2	0.7810	0.4462	0.0545	2.1
37	C6 G1	0.3963	0.4472	0.2419	11.7	78	C6 G2	0.8177	0.4296	0.1234	3.5
38	O6 G1	0.3855	0.3845	0.2317	5.3	79	O6 G2	0.8208	0.3741	0.1497	12.5
39	N7 G1	0.4724	0.4476	0.3662	7.5	80	N7 G2	0.7467	0.4004	0.0028	2.1
40	C8 G1	0.5037	0.5013	0.4036	1.6	81	C8 G2	0.7233	0.4432	-0.0477	8.3
41	N9 G1	0.4896	0.5635	0.3731	11.4	82	N9 G2	0.7441	0.5112	-0.0312	3.6
		ELLIPTICINE(1)						ELLIPTICINE(2)			
83	C1 E1	0.7740	0.3955	0.4078	13.5	102	C1 E2	-0.0402	0.3763	-0.0275	1.6
84	C2 E1	0.7848	0.4642	0.4286	12.6	103	C2 E2	-0.0480	0.4465	-0.0491	5.0
85	C3 E1	0.7532	0.5179	0.3855	10.4	104	C3 E2	-0.0126	0.5003	-0.0059	1.6
86	C4 E1	0.7111	0.5061	0.3200	5.5	105	C4 E2	0.0310	0.4873	0.0605	12.5
87	C5 E1	0.6987	0.4382	0.2968	9.8	106	C5 E2	0.0396	0.4201	0.0824	1.6
88	C6 E1	0.7316	0.3823	0.3431	1.6	107	C6 E2	0.0034	0.3637	0.0373	1.6
89	N7 E1	0.6746	0.5551	0.2667	12.5	108	N7 E2	0.0718	0.5364	0.1123	1.6
90	C8 E1	0.6369	0.5135	0.2067	1.6	109	C8 E2	0.1093	0.4946	0.1726	2.6
91	C9 E1	0.6507	0.4449	0.2240	3.1	110	C9 E2	0.0915	0.4255	0.1563	2.5
92	C10E1	0.5942	0.5339	0.1447	12.7	111	C10E2	0.1537	0.5146	0.2366	2.2
93	C11E1	0.5783	0.6114	0.1270	12.5	112	C11E2	0.1743	0.5905	0.2528	12.4
94	C12E1	0.5631	0.4847	0.0951	7.8	113	C12E2	0.1840	0.4657	0.2838	12.7
95	C13E1	0.5751	0.4124	0.1077	5.1	114	C13E2	0.1677	0.3940	0.2710	6.9
96	C14E1	0.6208	0.3935	0.1756	1.6	115	C14E2	0.1190	0.3745	0.2033	6.0
97	C15E1	0.6366	0.3147	0.1937	3.9	116	C15E2	0.0995	0.2961	0.1858	4.2
98	C16E1	0.5202	0.5034	0.0309	1.9	117	C16E2	0.2288	0.4837	0.3473	2.0
99	C17E1	0.4912	0.4576	-0.0169	1.9	118	C17E2	0.2577	0.4372	0.3952	13.7
100	N18E1	0.5030	0.3829	-0.0051	8.1	119	N18E2	0.2422	0.3635	0.3837	11.2
101	C19E1	0.5458	0.3643	0.0594	1.6	120	C19E2	0.1971	0.3450	0.3204	3.1
				SOLVENT MOLECULE ATOMS							
121	OW1	0.9096	0.1898	0.2827	6.0	131	OW11	0.0109	0.2590	0.8062	12.0
122	OW2	0.3008	0.2300	0.8045	13.1	132	OW12	0.9448	0.4309	0.6314	13.9
123	OW3	0.4083	0.2825	0.3087	15.5	133	OW13	0.5583	0.2813	0.8062	8.0
124	OW4	0.7416	0.1874	0.3499	14.8	134	OW14	0.5423	0.3379	0.5976	3.6
125	OW5	0.3308	0.1888	0.0263	3.9	135	OW15	0.5083	0.3250	0.4125	12.8
126	OW6	0.0585	0.2245	0.6626	12.2	136	OW16	0.6250	0.3187	0.7125	8.0
127	OW7	0.3750	0.4012	0.5000	5.7	137	OME1	0.7576	0.2064	0.5375	19.7
128	OW8	0.3582	0.2313	0.6939	10.4	138	CME1	0.7833	0.2600	0.5025	11.8
129	OW9	0.8147	0.4215	0.7285	7.4	139	OME2	0.7083	0.2375	0.8900	1.2
130	OW10	0.3291	0.3901	0.6025	8.1	140	CME2	0.7750	0.2388	0.9525	7.7

Table 2. Final coordinates and temperature factors obtained from the TMP-iodoCpG crystal structure analysis.

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	0.9998	0.2953	0.4248	10.0	42	I5 C2	0.2223	0.2500	-0.0297	8.2
2	N1 C1	1.0220	0.5162	0.3975	8.1	43	N1 C2	0.2245	0.4742	-0.0470	9.5
3	C2 C1	0.9830	0.5301	0.3322	9.8	44	C2 C2	0.2626	0.4999	0.0147	4.4
4	O2 C1	0.9810	0.5906	0.3112	14.0	45	O2 C2	0.2735	0.5635	0.0226	9.4
5	N3 C1	0.9482	0.4760	0.2921	6.7	46	N3 C2	0.2876	0.4540	0.0647	6.0
6	C4 C1	0.9488	0.4114	0.3130	9.9	47	C4 C2	0.2820	0.3869	0.0553	7.3
7	N4 C1	0.9163	0.3588	0.2730	9.2	48	N4 C2	0.3130	0.3421	0.1037	6.9
8	C5 C1	0.9904	0.3954	0.3831	4.7	49	C5 C2	0.2425	0.3587	-0.0096	9.6
9	C6 C1	1.0250	0.4504	0.4214	8.5	50	C6 C2	0.2151	0.4048	-0.0575	4.4
10	C1'C1	1.0615	0.5776	0.4419	9.4	51	C1'C2	0.1783	0.5245	-0.1019	6.8
11	C2'C1	0.9733	0.6101	0.4552	7.4	52	C2'C2	0.2551	0.5555	-0.1244	6.0
12	C3'C1	0.9750	0.5812	0.5245	8.1	53	C3'C2	0.2592	0.5131	-0.1831	11.3
13	C4'C1	1.0853	0.5763	0.5532	8.8	54	C4'C2	0.1511	0.4944	-0.2084	13.1
14	O1'C1	1.1291	0.5602	0.5005	9.9	55	O1'C2	0.1126	0.4883	-0.1523	8.4
15	C5'C1	1.1084	0.5194	0.6045	10.2	56	C5'C2	0.1390	0.4242	-0.2455	8.1
16	O5'C1	1.1199	0.4573	0.5780	14.0	57	O5'C2	0.1978	0.3674	-0.2107	13.4
17	O2'C1	0.9732	0.6834	0.4540	10.3	58	O2'C2	0.2407	0.6281	-0.1405	12.5
18	O3'C1	0.9286	0.6246	0.5620	9.2	59	O3'C2	0.2934	0.5501	-0.2297	7.2
19	P1	0.8210	0.6063	0.5638	11.8	60	P2	0.3946	0.5281	-0.2401	9.9
20	O1 P1	0.7993	0.6472	0.6176	14.1	61	O1 P2	0.4133	0.5658	-0.2958	14.8
21	O2 P1	0.8042	0.5308	0.5662	12.8	62	O2 P2	0.3996	0.4505	-0.2435	11.2
22	O5'G1	0.7594	0.6333	0.4945	13.6	63	O5'G2	0.4713	0.5552	-0.1748	12.3
23	C5'G1	0.7365	0.7056	0.4887	15.0	64	C5'G2	0.4780	0.6306	-0.1609	4.9
24	C4'G1	0.6291	0.7167	0.4620	10.2	65	C4'G2	0.5760	0.6542	-0.1343	6.9
25	C3'G1	0.5661	0.7007	0.5091	13.4	66	C3'G2	0.6462	0.6386	-0.1757	9.0
26	C2'G1	0.5171	0.6314	0.4870	13.7	67	C2'G2	0.7054	0.5749	-0.1448	5.8
27	C1'G1	0.5130	0.6365	0.4158	11.2	68	C1'G2	0.7053	0.5930	-0.0764	7.2
28	O1'G1	0.5897	0.6737	0.4063	7.8	69	O1'G2	0.6189	0.6201	-0.0728	10.1
29	O2'G1	0.4258	0.6202	0.5011	14.7	70	O2'G2	0.8039	0.5699	-0.1541	12.0
30	O3'G1	0.4938	0.7531	0.5084	14.5	71	O3'G2	0.7126	0.6963	-0.1767	13.5
31	N1 G1	0.3801	0.4950	0.2017	6.3	72	N1 G2	0.8436	0.4879	0.1487	3.7
32	C2 G1	0.3872	0.5671	0.2089	4.6	73	C2 G2	0.8410	0.5576	0.1299	7.4
33	N2 G1	0.3532	0.6063	0.1568	7.7	74	N2 G2	0.8733	0.6058	0.1750	5.0
34	N3 G1	0.4249	0.5978	0.2673	7.4	75	N3 G2	0.8045	0.5764	0.0675	7.7
35	C4 G1	0.4527	0.5513	0.3158	4.8	76	C4 G2	0.7734	0.5221	0.0280	6.8
36	C5 G1	0.4478	0.4809	0.3147	5.7	77	C5 G2	0.7759	0.4534	0.0406	6.1
37	C6 G1	0.4076	0.4461	0.2513	3.8	78	C6 G2	0.8152	0.4314	0.1084	11.1
38	O6 G1	0.3998	0.3845	0.2375	9.1	79	O6 G2	0.8200	0.3722	0.1306	7.0
39	N7 G1	0.4827	0.4522	0.3754	6.3	80	N7 G2	0.7395	0.4124	-0.0140	9.5
40	C8 G1	0.5129	0.5066	0.4123	6.3	81	C8 G2	0.7119	0.4613	-0.0617	5.6
41	N9 G1	0.4949	0.5681	0.3801	10.0	82	N9 G2	0.7319	0.5272	-0.0389	6.1
						3,5,6,8-TETRAMETHYL N-METHYL PHENANTHROLINIUM (1) & (2)					
83	N1 T1	0.5649	0.3682	0.1137	9.2	112	C11T2	0.1135	0.4955	0.1792	10.9
84	C2 T1	0.5256	0.3662	0.0512	9.4	113	C12T2	0.1499	0.4584	0.2389	5.9
85	C3 T1	0.4998	0.4266	0.0100	7.2	114	C13T2	0.1431	0.3852	0.2380	7.3
86	C4 T1	0.5180	0.4897	0.0371	8.9	115	C14T2	0.0699	0.4598	0.1210	10.3
87	C5 T1	0.5881	0.5620	0.1378	9.8	116	CC3T2	0.2561	0.3530	0.4183	9.5
88	C6 T1	0.6322	0.5649	0.2002	14.4	117	CC5T2	0.0966	0.2693	0.1775	13.7
89	C7 T1	0.6928	0.5022	0.3071	8.7	118	CC6T2	0.0219	0.3453	0.0588	13.3
90	C8 T1	0.7127	0.4425	0.3387	15.1	119	CC8T2	-0.0005	0.6148	0.0049	16.5
91	C9 T1	0.7000	0.3781	0.3041	7.2	120	CN10T2	0.1659	0.6001	0.2391	15.2
92	N10T1	0.6522	0.3784	0.2429	14.0	121	N1T2'	0.0348	0.3668	0.0724	6.1
93	C11T1	0.6312	0.4371	0.2071	4.3	122	C2T2'	-0.0035	0.3583	0.0095	1.7
94	C12T1	0.5840	0.4320	0.1393	13.3	123	C3T2'	-0.0319	0.4162	-0.0350	6.8
95	C13T1	0.5606	0.4968	0.1029	7.6	124	C4T2'	-0.0159	0.4806	-0.0115	3.6
96	C14T1	0.6522	0.5031	0.2379	10.4	125	C5T2'	0.0483	0.5605	0.0844	10.5
97	CC3T1	0.4518	0.4160	-0.0605	14.4	126	C6T2'	0.0837	0.5686	0.1470	16.8
98	CC5T1	0.5605	0.6300	0.0986	12.2	127	C7T2'	0.1452	0.5152	0.2572	17.6
99	CC6T1	0.6554	0.6359	0.2354	14.6	128	C8T2'	0.1655	0.4545	0.2948	17.1
100	CC8T1	0.7599	0.4427	0.4144	11.3	129	C9T2'	0.1525	0.3898	0.2647	13.9
101	CN10T1	0.6293	0.3135	0.2061	16.0	130	N10T2'	0.1147	0.3861	0.2020	6.0
102	N1 T2	0.1890	0.4971	0.2927	15.0	131	C11T2'	0.0903	0.4413	0.1622	11.2
103	C2 T2	0.2221	0.4617	0.3473	26.4	132	C12T2'	0.0500	0.4306	0.0939	13.6
104	C3 T2	0.2172	0.3890	0.3520	16.8	133	C13T2'	0.0267	0.4923	0.0542	7.5
105	C4 T2	0.1781	0.3507	0.2977	13.8	134	C14T2'	0.1068	0.5096	0.1895	8.3
106	C5 T2	0.1012	0.3498	0.1775	20.5	135	CC3T2'	-0.0784	0.4007	-0.1073	5.0
107	C6 T2	0.0667	0.3850	0.1225	2.5	136	CC5T2'	0.0258	0.6259	0.0413	12.2
108	C7 T2	0.0328	0.4998	0.0649	9.7	137	CC6T2'	0.1047	0.6413	0.1769	8.9
109	C8 T2	0.0392	0.5709	0.0668	11.8	138	CC8T2'	0.2091	0.4612	0.3700	12.5
110	C9 T2	0.0852	0.6037	0.1250	8.6	139	CN10T2'	0.0951	0.3171	0.1698	12.1
111	N10T2	0.1194	0.5659	0.1782	14.0						
						SOLVENT MOLECULE ATOMS					
140	OW1	0.8900	0.4035	0.7104	23.2	151	OW12	0.6790	0.2692	0.8400	21.4
141	OW2	0.7417	0.2242	0.4762	24.2	152	OW13	0.7176	0.2419	0.9653	21.0
142	OW3	0.3192	0.3266	0.7216	22.7	153	OW14	0.7165	0.1975	0.3483	15.0
143	OW4	0.0203	0.1635	0.1318	23.6	154	OW15	0.8723	0.1866	0.2760	14.7
144	OW5	0.0446	0.2538	0.7885	16.7	155	OW16	0.9001	0.4052	0.5965	14.4
145	OW6	0.1784	0.0163	0.2718	21.9	156	OW17	0.3250	0.1937	0.3225	23.4
146	OW7	0.4861	0.0938	0.3712	21.8	157	OME1	0.7500	0.2437	0.0812	33.9
147	OW8	0.5004	0.2941	0.3825	23.3	158	CME1	0.8583	0.2375	0.0938	23.7
148	OW9	0.5053	0.2613	0.7356	24.1	159	OME2	0.0288	0.2570	0.6499	23.6
149	OW10	0.5948	0.3927	0.7930	15.2	160	CME2	0.1333	0.2562	0.6500	17.8
150	OW11	0.6323	0.4652	0.5586	21.1						

Table 2. (continued).

Temperature factors shown for iodine atoms are the equivalent isotropic temperature 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	0.1654	0.0867	0.1046	-0.0031	-0.0086	0.0243
I5C2	0.1466	0.0887	0.0668	0.0000	0.0241	0.0000

Table 3. Torsional angles describing conformations of sugar-phosphate chains in ellipticine- and TMP- iodoCpG crystalline complexes.

		ellipticine-iodoCpG		TMP-iodoCpG	
Torsional Angle*	Greek symbol	I-CpG(1)	I-CpG(2)	I-CpG(1)	I-CpG(2)
O1'C-C1'C-N1C-C6C	χ	25	14	22	13
O1'G-C1'G-N9G-C8G	χ	80	74	86	69
O5'C-C5'C-C4'C-C3'C	ψ	36	34	82	35
C5'C-C4'C-C3'C-O3'C	ψ'	91	104	93	95
C4'C-C3'C-O3'C-P	ϕ'	199	234	203	212
C3'C-O3'C-P-O5'G	ω'	285	258	278	285
O3'C-P-O5'G-C5'G	ω	281	315	283	303
P-O5'G-C5'G-C4'G	ϕ	212	194	219	206
O5'G-C5'G-C4'G-C3'G	ψ	65	47	71	55
C5'G-C4'G-C3'G-O3'G	ψ'	145	141	141	143
C4'C-O1'C-C1'C-C2'C	τ_0	7	14	4	3
O1'C-C1'C-C2'C-C3'C	τ_1	-30	-36	-27	-27
C1'C-C2'C-C3'C-C4'C	τ_2	31	30	25	26
C2'C-C3'C-C4'C-O1'C	τ_3	-41	-37	-36	-36
C3'C-C4'C-O1'C-C1'C	τ_4	13	10	14	16
C4'G-O1'G-C1'G-C2'G	τ_0	-26	-23	-24	-31
O1'G-C1'G-C2'G-C3'G	τ_1	31	29	31	33
C1'G-C2'G-C3'G-C4'G	τ_2	-39	-42	-42	-45
C2'G-C3'G-C4'G-O1'G	τ_3	18	21	21	21
C3'G-C4'G-O1'G-C1'G	τ_4	3	0	4	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 the ellipticine- and TMP- iodoCpG crystal structures.

ellipticine-iodoCpG

Atoms	Distance (Å)	Atoms	Distance (Å)
OW1 - OW4 (1)	3.05	OW11 - O5'C1 (3)	2.84
OW1 - N4C2 (1)	3.00	OW11 - N2G1 (4)	3.19
OW2 - OW8 (1)	2.70	OW12 - O5'C2 (5)	2.73
		OW12 - O2P2 (1)	2.73
OW3 - OW15 (1)	2.43		
OW3 - O6G2 (1)	2.52	OW13 - OW16 (1)	2.53
		OW13 - OME2 (1)	2.50
OW4 - O1P1 (2)	2.88		
		OW14 - OW16 (1)	2.45
OW6 - O2C2 (4)	2.89	OW14 - O3'G2 (4)	2.51
OW6 - O2'C2(4)	2.54		
		OW15 - N7G2 (1)	2.54
OW7 - OW10 (1)	2.45	OW15 - O3'G2 (4)	2.40
OW7 - OW14 (1)	2.95		
		OME1 - O2'G2 (4)	2.88
OW8 - O1'G2(4)	2.46		
		OME2 - N2G2 (4)	2.64
OW9 - OW12 (1)	3.10		
OW10 - OW14(1)	3.15		

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

TMP-iodoCpG

Atoms	Distance (Å)	Atoms	Distance (Å)
OW1 - OW16 (1)	2.51	OW7 - OW17 (1)	2.94
OW1 - OW6 (2)	2.43	OW7 - O2'G2 (5)	2.73
		OW7 - O1P2 (4)	2.45
OW2 - OW14 (1)	2.71		
		OW8 - O3'G1 (5)	2.44
OW3 - O5'C2 (3)	2.61	OW8 - N7G1 (1)	3.03
OW3 - O2P2 (3)	2.64	OW8 - OW17 (1)	3.12
OW3 - OW9 (1)	2.83		
		OW9 - OW10 (1)	2.93
OW4 - O2'G2 (4)	2.98	OW9 - OW12 (1)	2.85
OW5 - OME2 (1)	2.91	OW10 - O2P2 (3)	2.86
OW5 - N2G2 (5)	3.08	OW10 - OW12 (1)	2.85
OW6 - O2'G2 (4)	2.78	OW11 - O2P1 (1)	2.68

Table 4. (continued)

Atoms	Distance (Å)	Atoms	Distance (Å)
OW12 - OW13 (1)	2.64	OW17 - O1P1 (5)	2.57
OW12 - N2G1 (5)	3.15	OW17 - O3'G2 (4)	3.02
OW13 - OME1 (3)	2.40	OME1 - O6G2 (1)	2.75
		OME1 - O2'C2 (4)	2.53
OW14 - OW15 (1)	2.98		
OW14 - O1P2 (4)	3.14	OME2 - O2'C1 (5)	2.62
OW15 - O2'C2 (4)	3.12		
OW16 - O2P1 (1)	2.74		

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

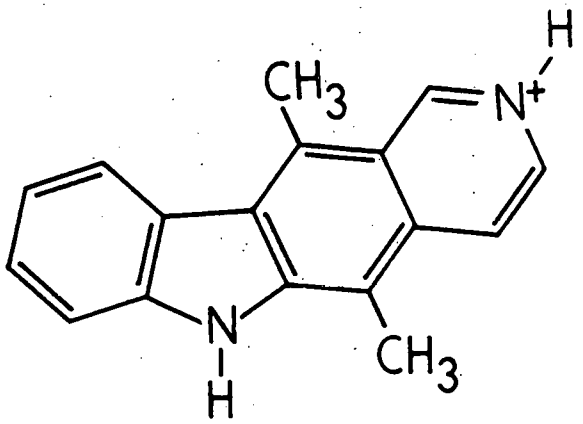


Figure 1.

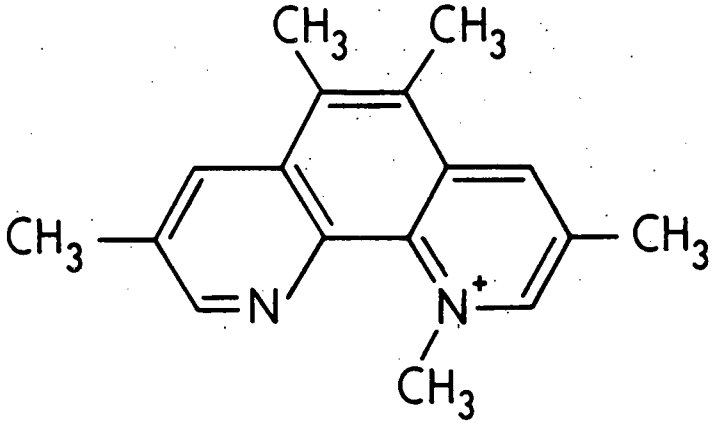


Figure 2.

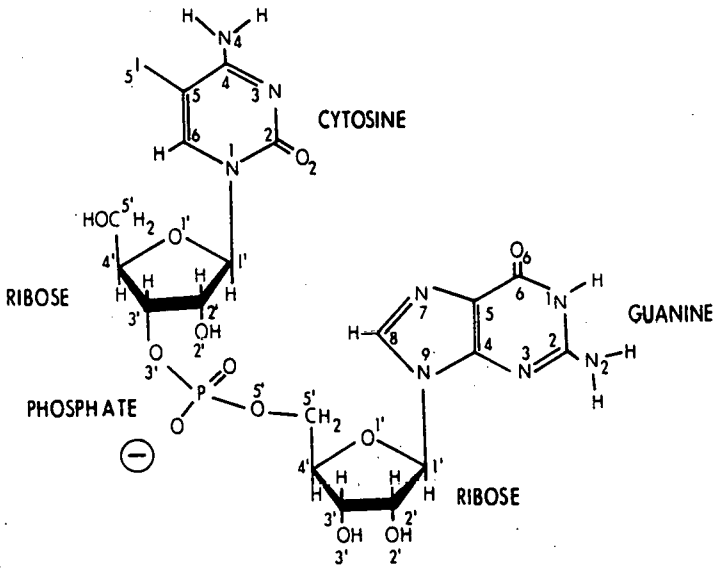
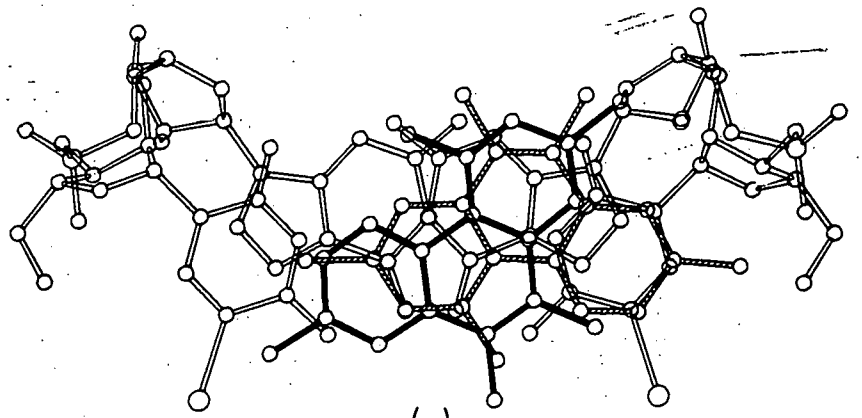
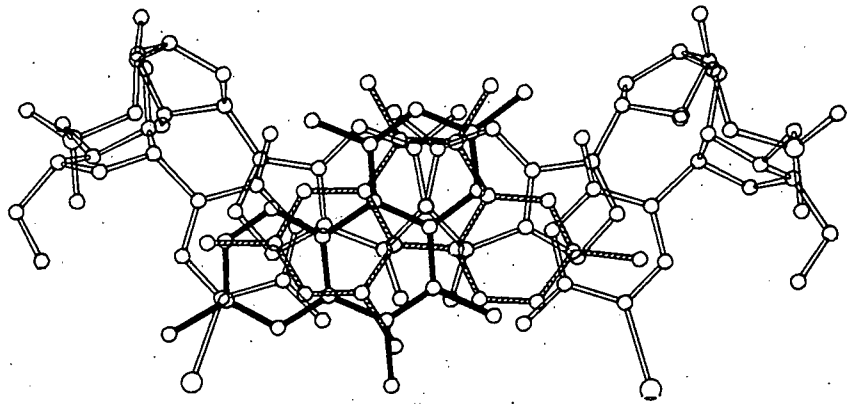


Figure 3.



(a)



(b)

Figure 4.

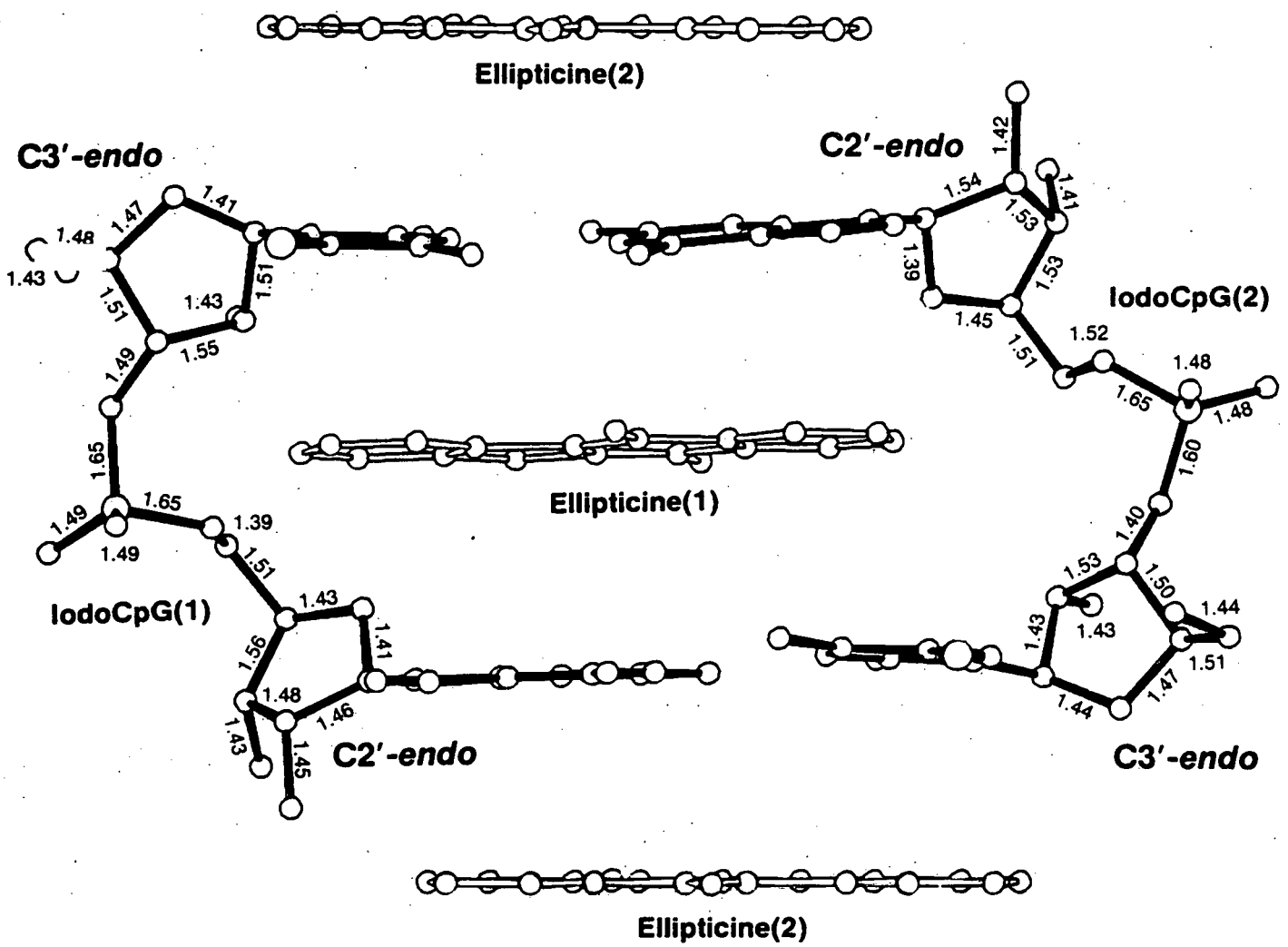

Ellipticine(2)
C3′-endo
C2′-endo
IodoCpG(2)
Ellipticine(1)
IodoCpG(1)
C2′-endo
C3′-endo
Ellipticine(2)

Figure 5.

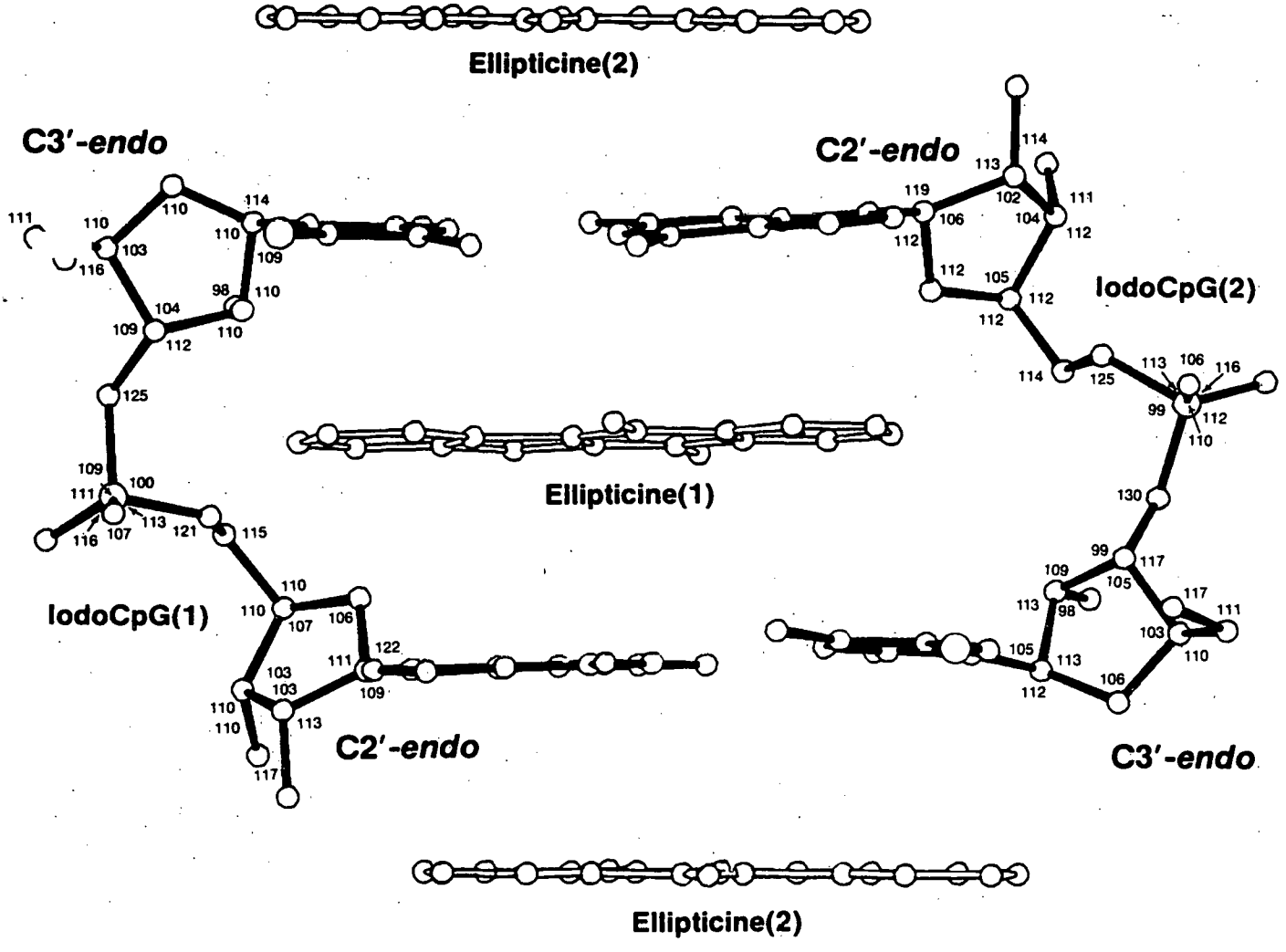
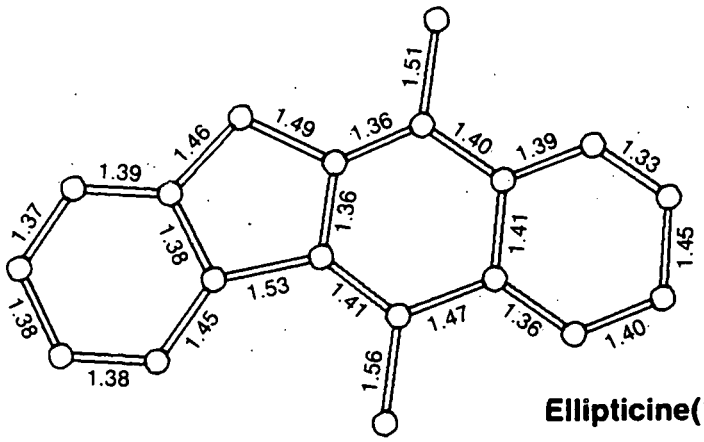
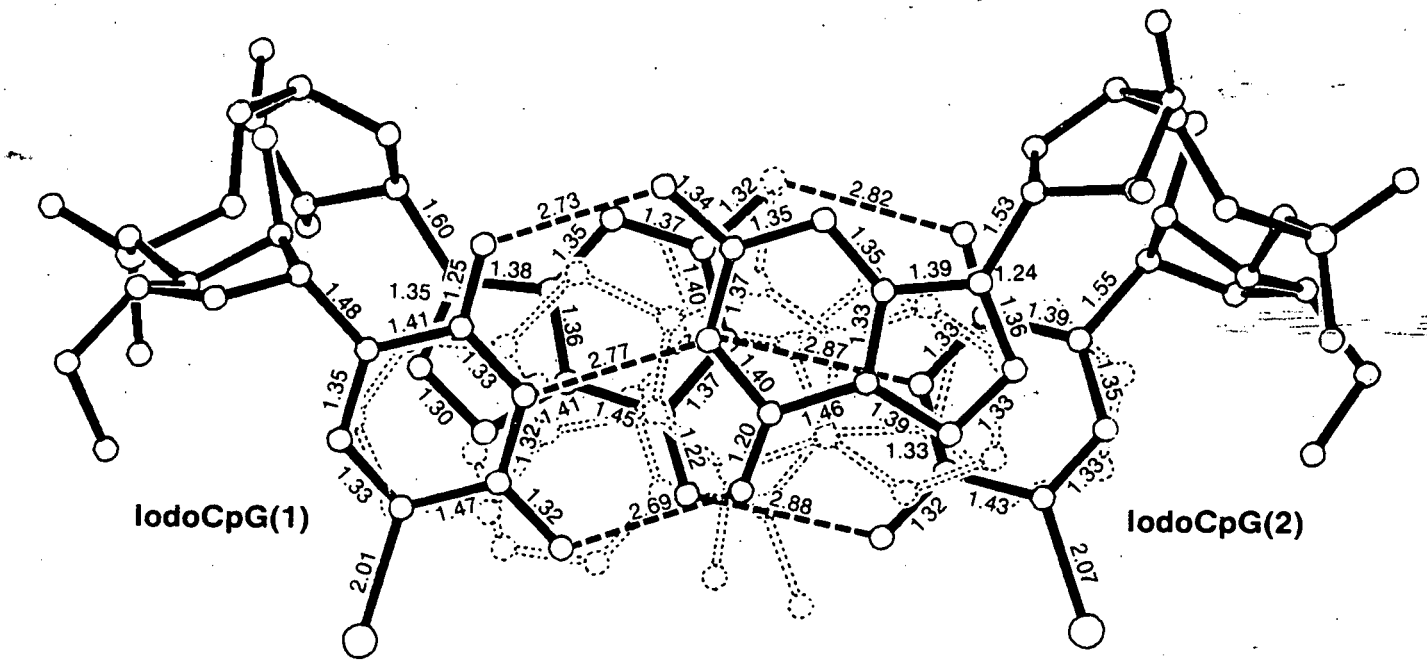
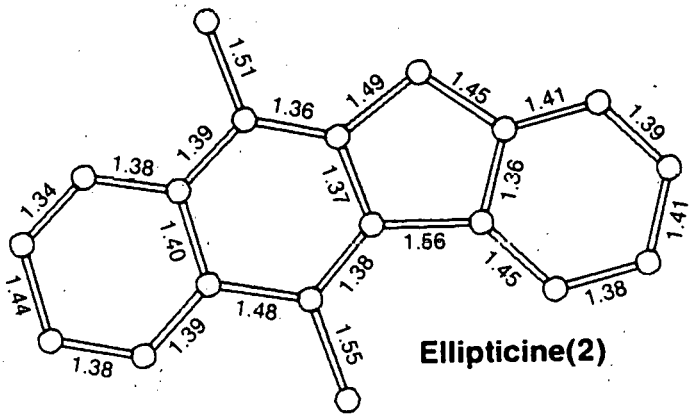

Ellipticine(2)
C3′-endo
C2′-endo
IodoCpG(2)
Ellipticine(1)
IodoCpG(1)
C2′-endo
C3′-endo
Ellipticine(2)

Figure 6.







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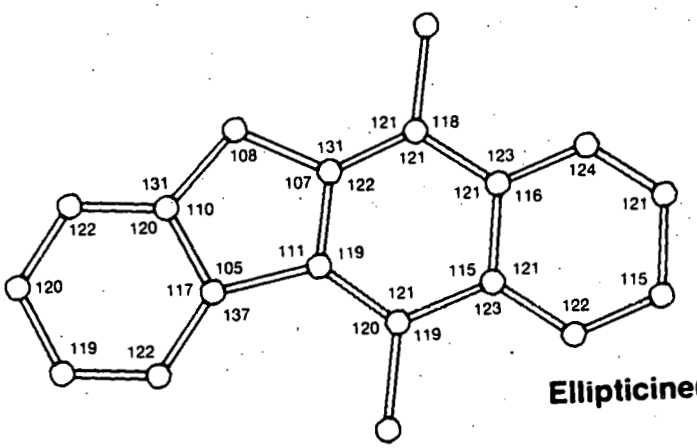

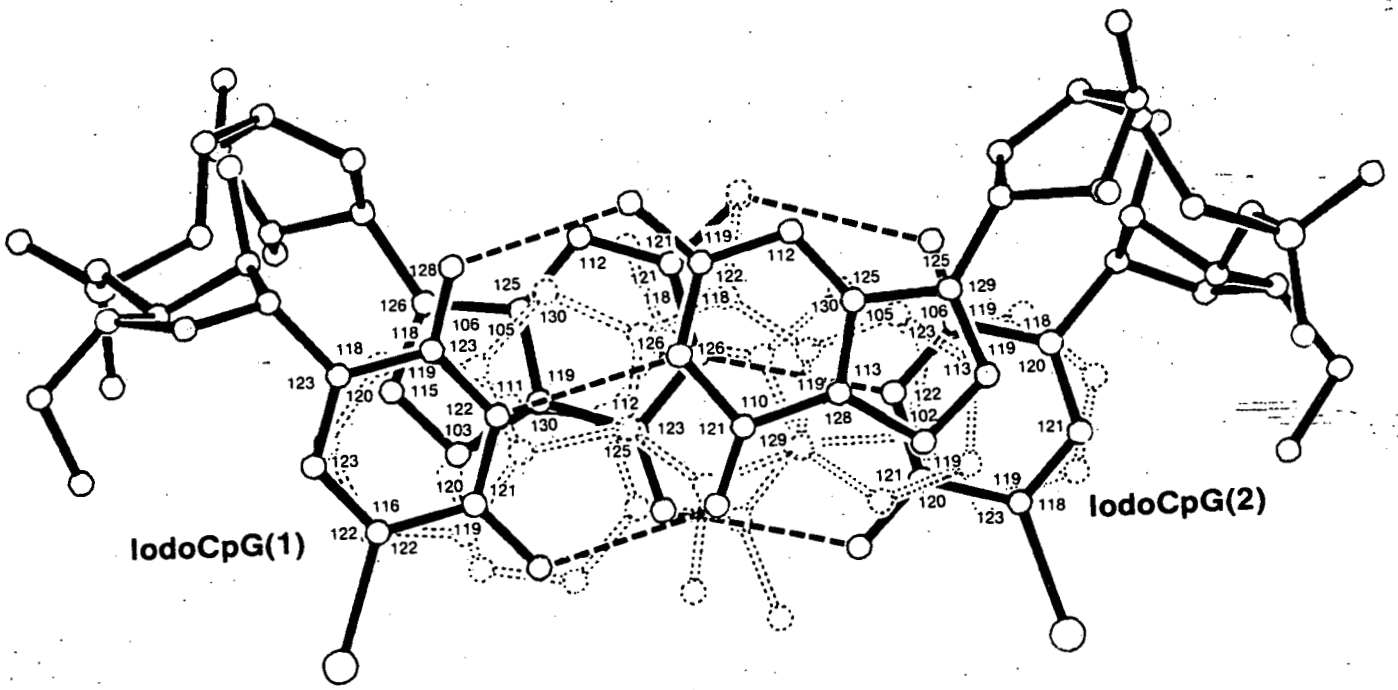

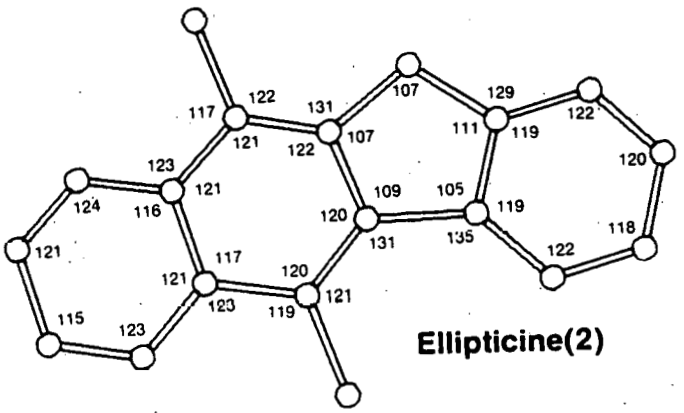

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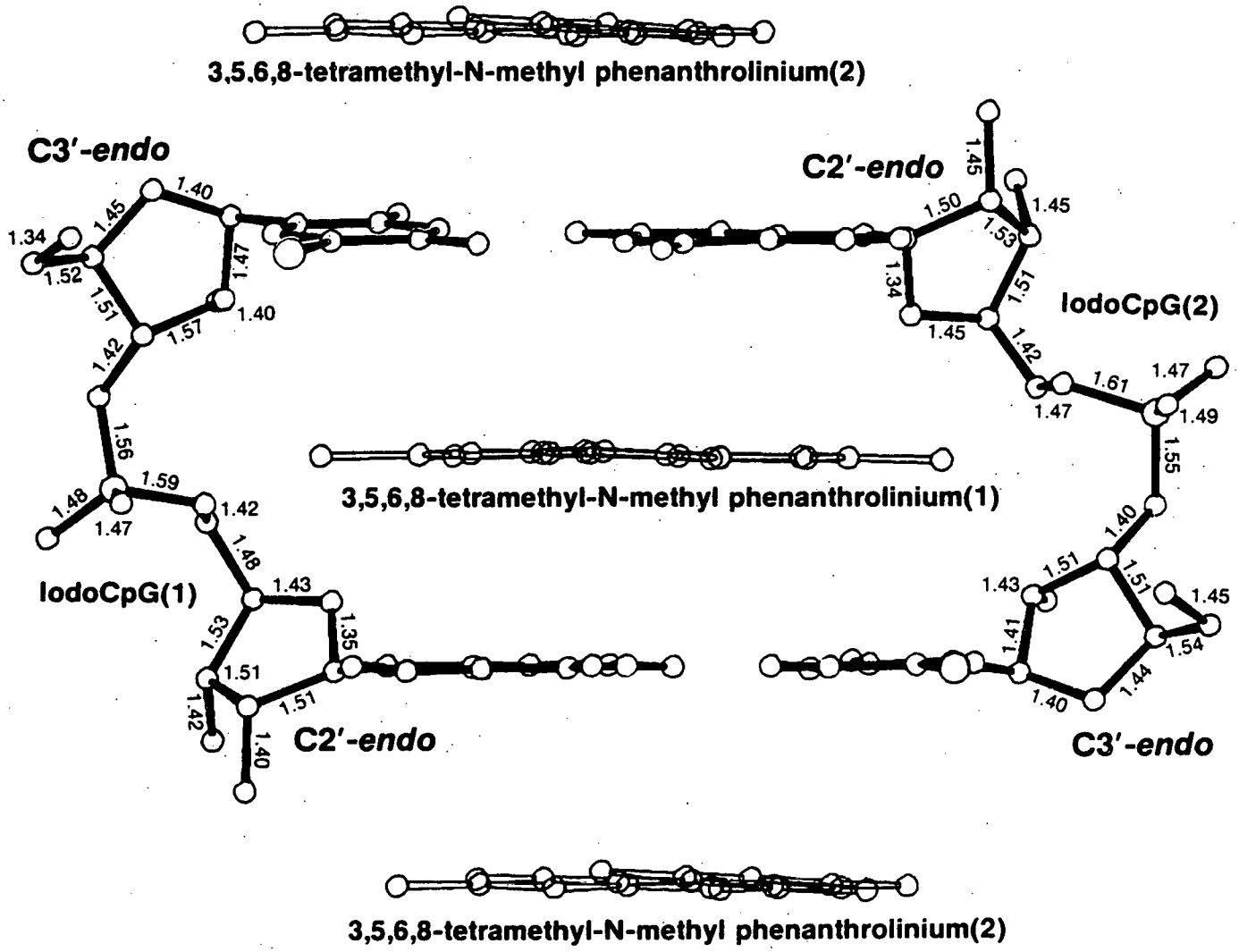

3,5,6,8-tetramethyl-N-methyl phenanthrolinium(2)
C3′-endo
C2′-endo
IodoCpG(2)
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(1)
IodoCpG(1)
C2′-endo
C3′-endo
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(2)

Figure 9.

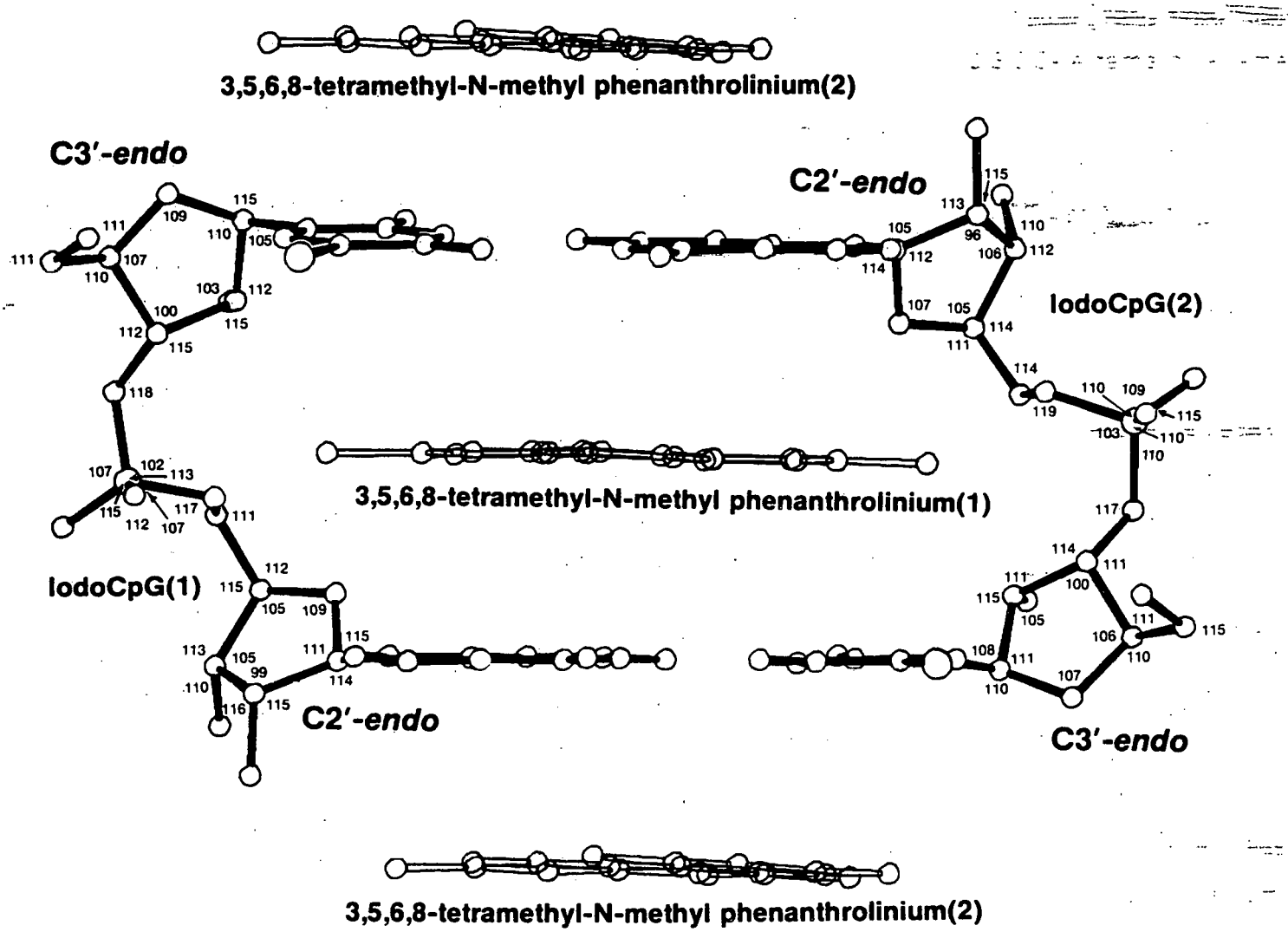
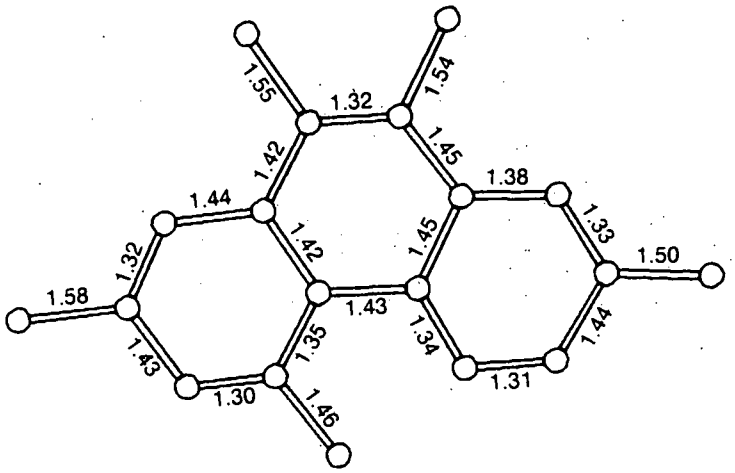
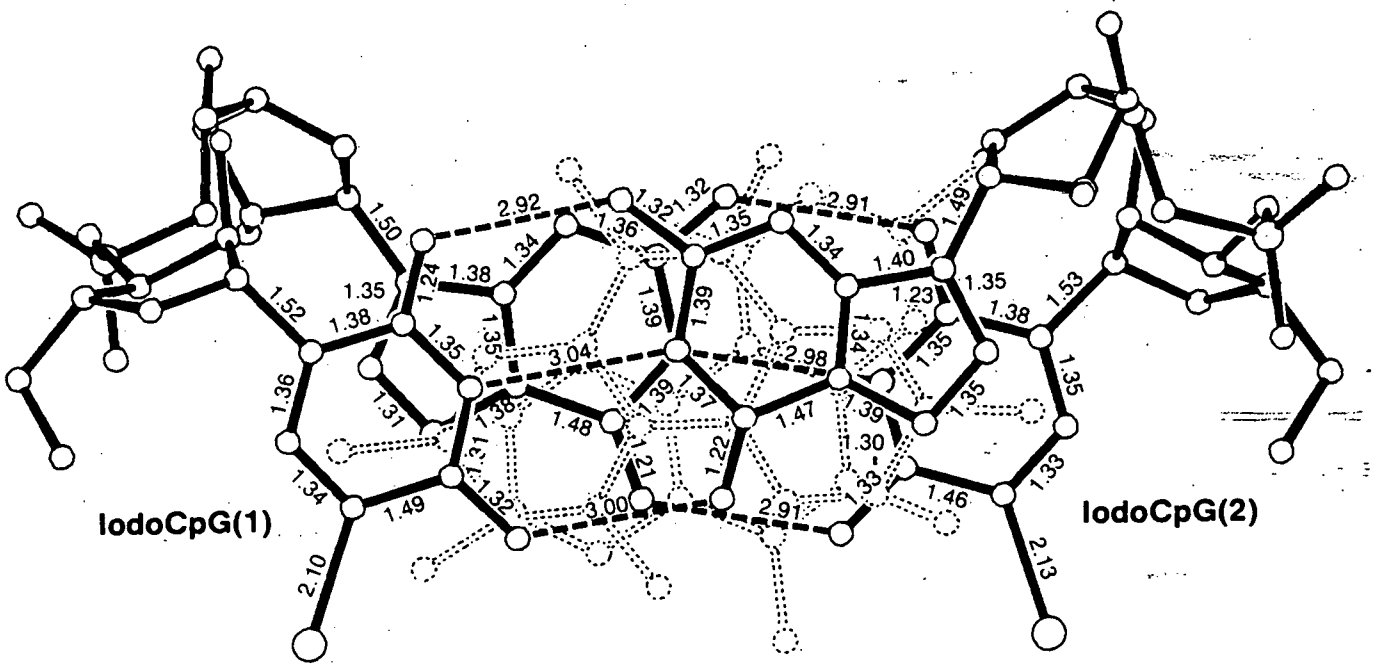
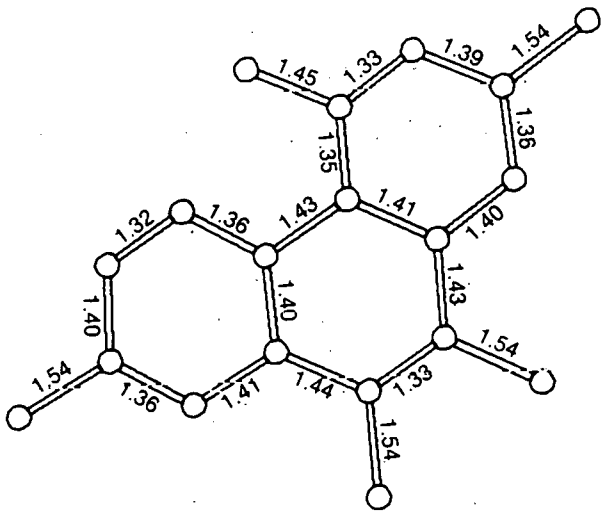

3,5,6,8-tetramethyl-N-methyl phenanthrolinium(2)
C3′-endo
C2′-endo
IodoCpG(2)
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(1)
IodoCpG(1)
C2′-endo
C3′-endo
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(2)

Figure 10.



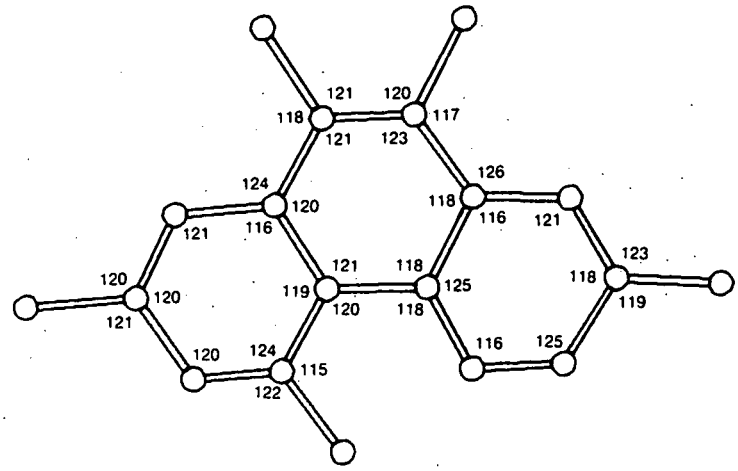
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(1)



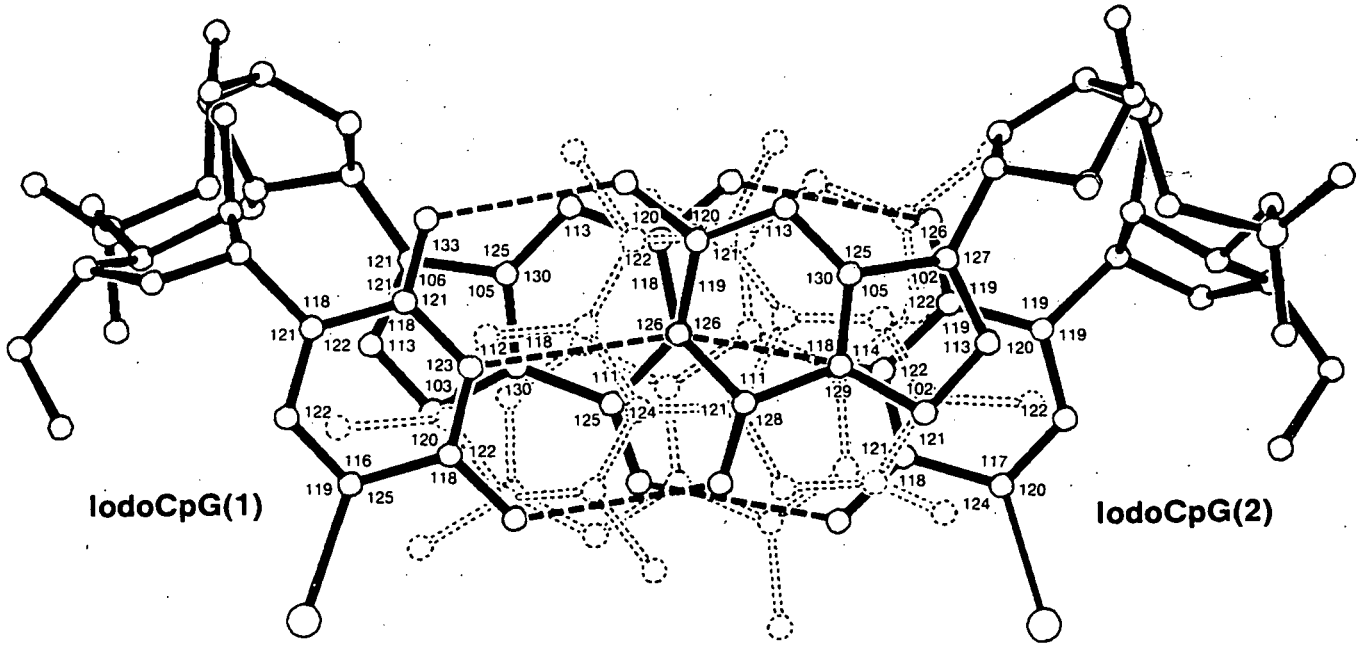


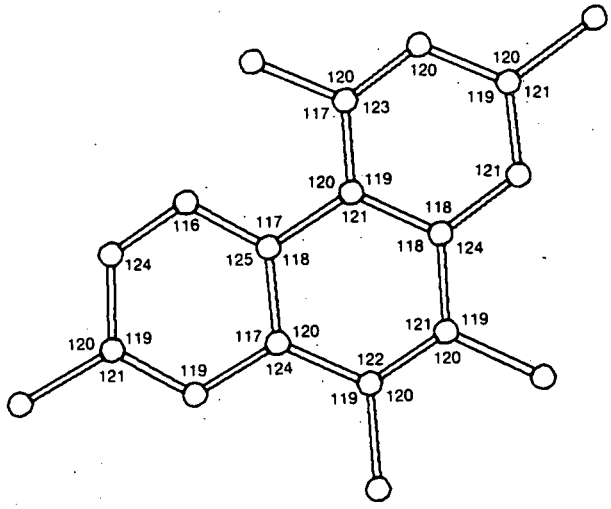
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(2)

Figure 11.



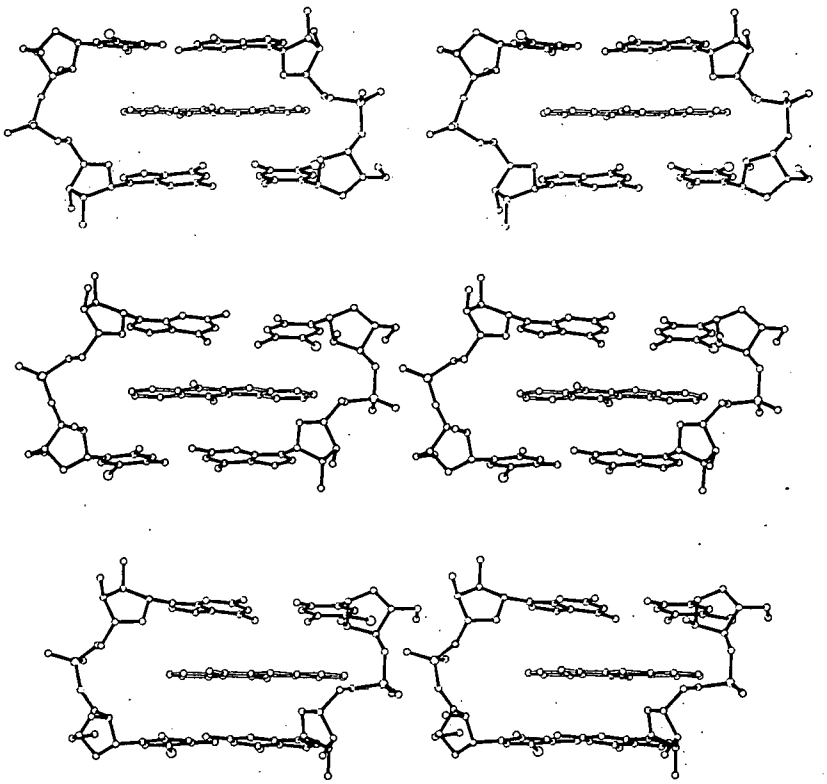
3,5,6,8-tetramethyl-N-methyl phenanthrolinium(1)





3,5,6,8-tetramethyl-N-methyl phenanthrolinium(2)

Figure 12.



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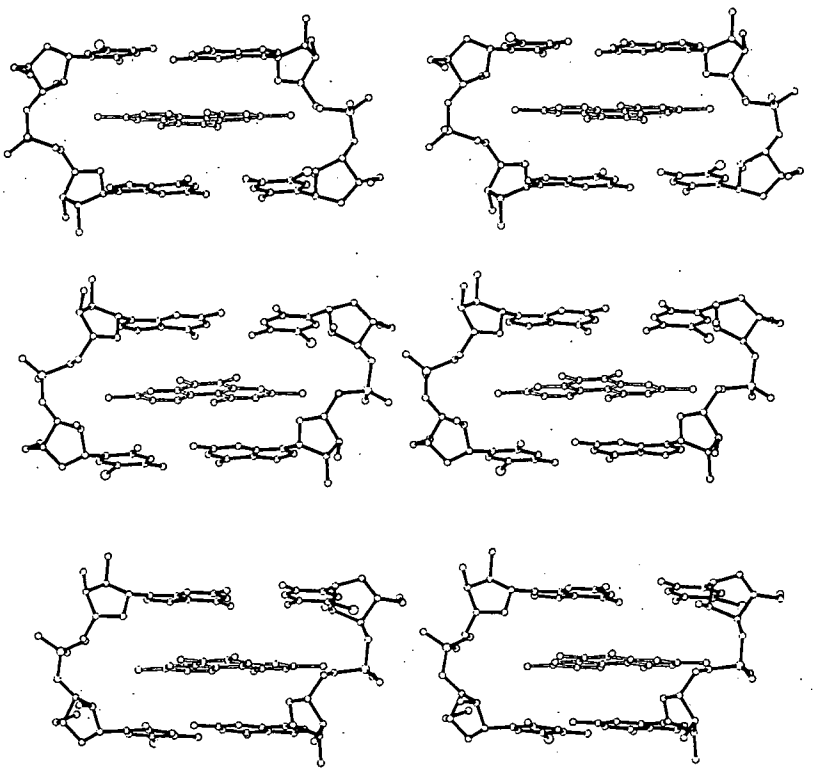

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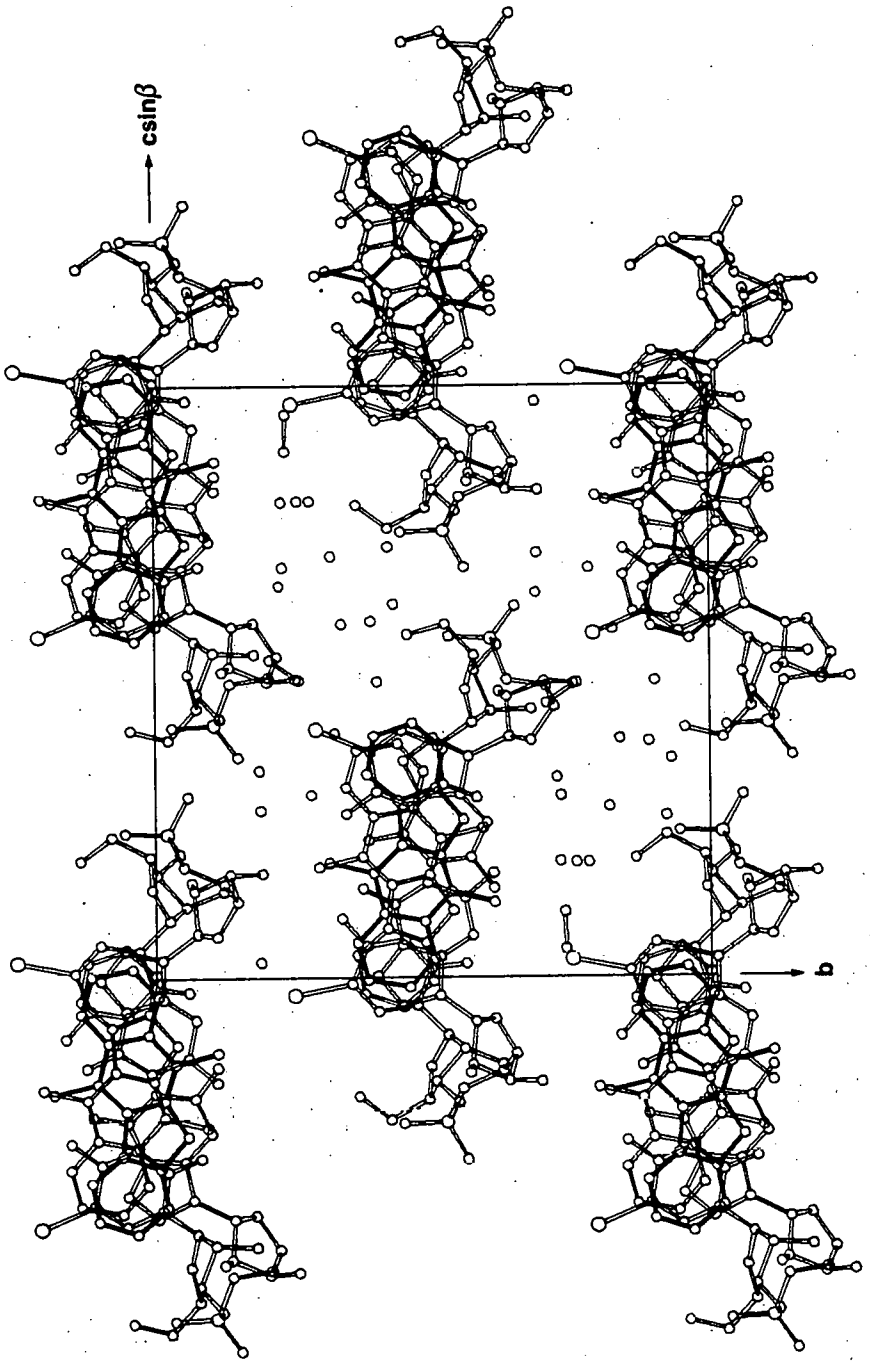

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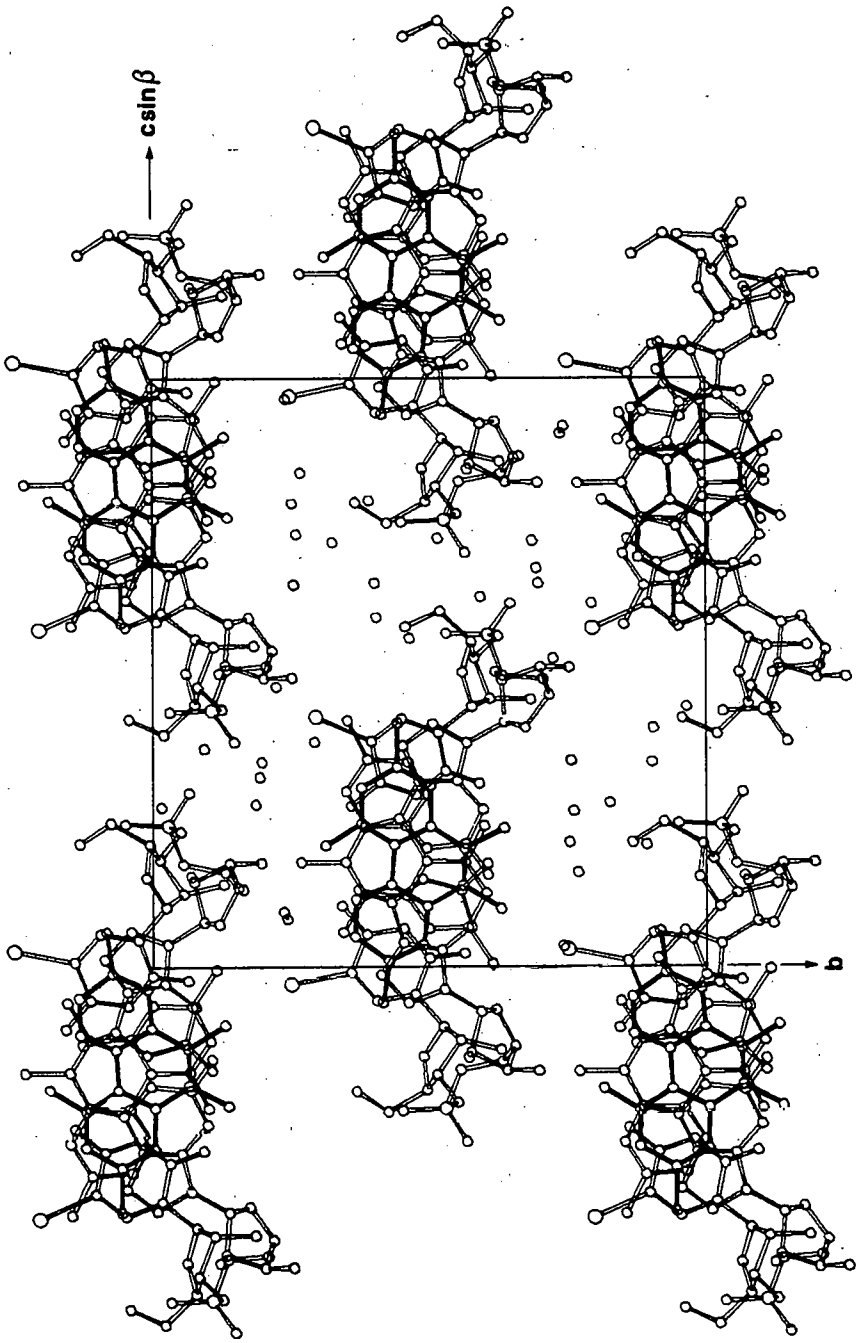


Figure 16.

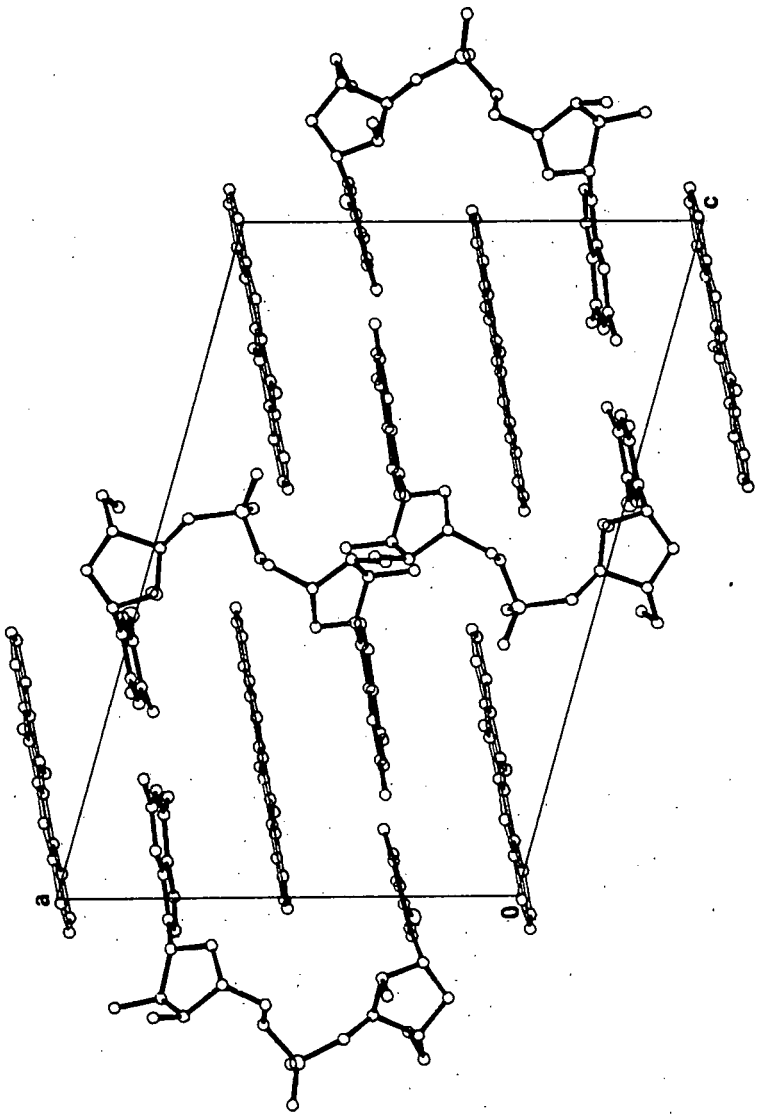
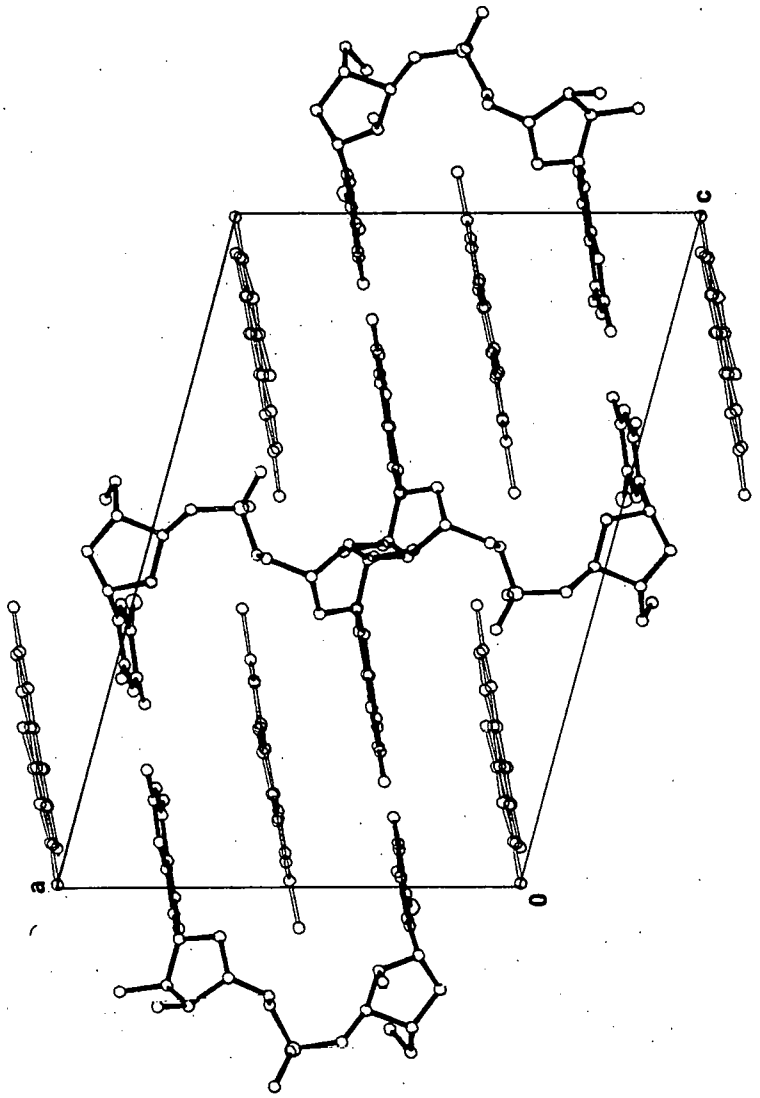


Figure 17.



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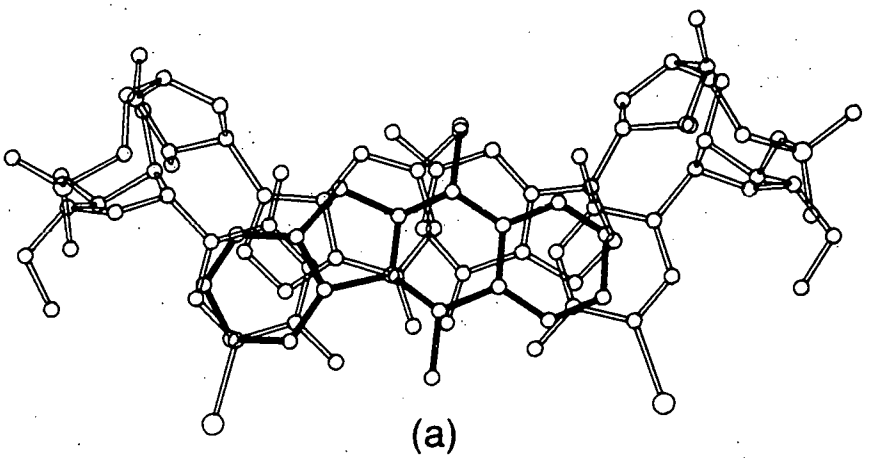
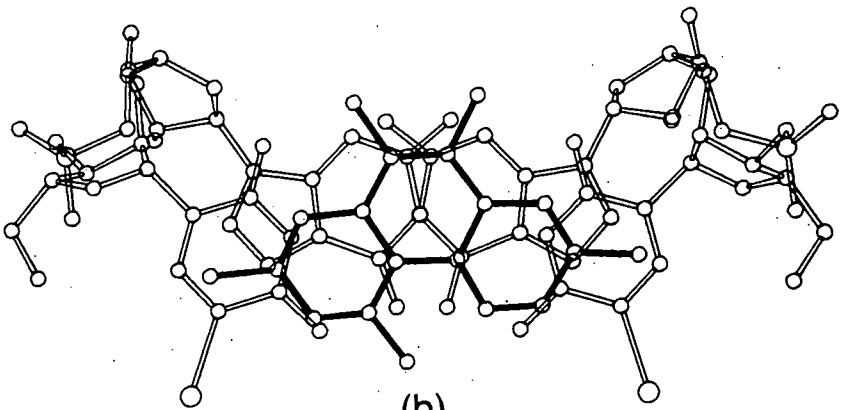
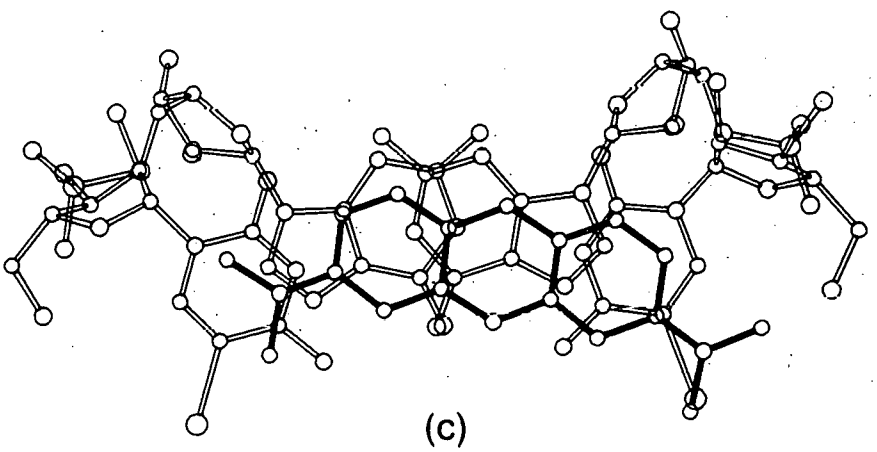


(a)



(b)



(c)

Figure 19.

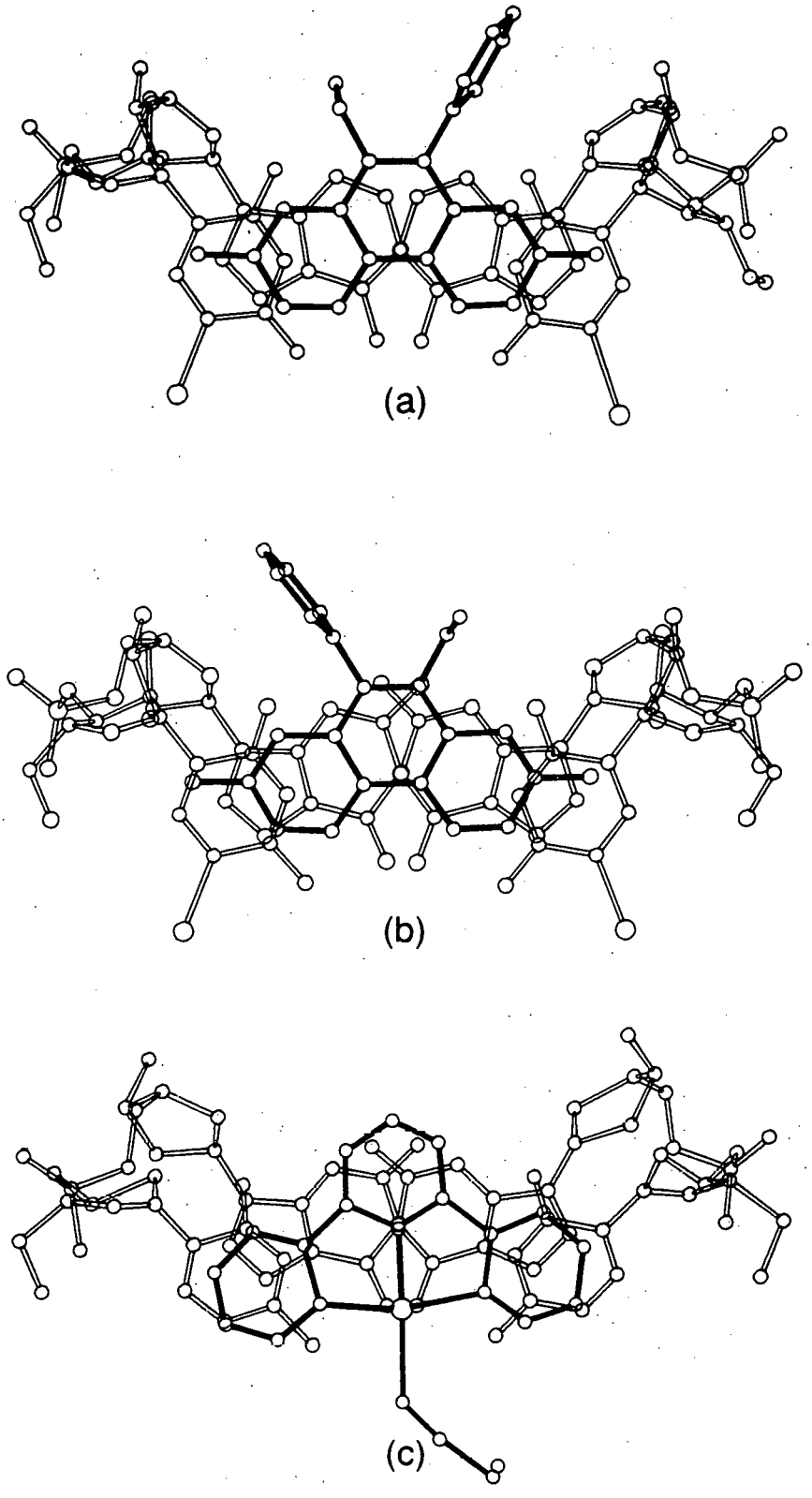


Figure 20.