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REPORTER MOLECULES AS PROBES OF DNA CONFORMATION: STRUCTURE OF A CRYSTALLINE COMPLEX CONTAINING 2-METHYL-4-NITRO-ANILINE ETHYLENE DIMETHYLAMMONIUM HYDROBROMIDE -- 5-IODOCYTIDYLYL(3'-5')GUANOSINE

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2-Methyl-4-nitroaniline ethylene dimethylammonium hydrobromide forms a crystalline complex with the self-complementary dinucleoside monophosphate, 5-iodocytidylyl(3'-5')guanosine. The crystals are tetragonal, with a = b = 32.192 Å and c = 23.964 Å, space group $P4_32_12$. The structure has been solved to atomic resolution by Patterson and Fourier methods, and refined by full matrix least squares. 5-Iodocytidylyl(3'-5')guanosine molecules are held together in pairs through Watson-Crick base-pairing, forming an antiparallel duplex structure. Nitroaniline molecules stack above and below guanine-cytosine pairs in this duplex structure. In addition, a third nitroaniline molecule stacks on one of the other two nitroaniline molecules. The asymmetric unit contains two 5-iodocytidylyl(3'-5')guanosine molecules, three nitroaniline molecules, one bromide ion and thirty-one water molecules, a total of 160 atoms. Details of the structure are described.

In his series of classic studies, Gabbay (1-4) synthesized a large number of organic compounds that contain different aromatic ring systems linked to a variety of side chains to investigate their ability to bind to DNA. These molecules -- called "reporter" molecules -- were synthesized to study dynamic aspects of DNA structure and, in particular, to investigate the relationship between DNA breathing phenomena and drug intercalation. For this purpose, Gabbay synthesized three different classes of intercalators. The first -- called "partial" intercalators -- bind between partially unstacked base-pairs in DNA. Examples include several nitroaniline derivatives, aromatic polypeptides and steroidal diamines. The second -- correspond to "classic" intercalators -- molecules that, like ethidium and acridine orange, intercalate fully into DNA without necessitating the transient disruption of hydrogen bonds connecting base-pairs. Examples include a series of phenanthro-

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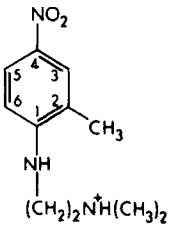

Figure 1. Chemical structure of the 2-methyl-4-nitroaniline ethylene dimethylammonium ion.

line and naphthylimide derivatives. The third -- which we call "breather" intercalators -- provide probes that relate DNA breathing motions with the intercalation process. These molecules contain bulky side chain substituents whose presence might be expected to interfere with the intercalation process (one example is N,N-[N-benzyl-N,N-dimethylethylammonium]-1,8,4,5-naphthyldiimide). For steric reasons, intercalation by this class of compounds must be preceded by the transient rupture of hydrogen-bonds connecting base-pairs -- events termed, DNA breathing. The ability of these compounds to intercalate into DNA provides convincing evidence that drug intercalation and DNA breathing are related phenomena.

Here, we describe the results of an X-ray crystallographic study of a complex containing 2-methyl-4-nitroaniline ethylene dimethylammonium hydrobromide (MNAED, shown in Figure 1) and 5-iodocytidylyl(3'-5')guanosine (iodoCpG). The structure is of interest since it demonstrates an unusual type of association between this reporter molecule and the nucleic acid component. Other interesting features of this crystal structure are presented.

Materials and Methods

2-Methyl-4-nitroaniline ethylene dimethylammonium hydrobromide (MNAED) was a gift from Professor Edward J. Gabbay, and was used without further purification. The dinucleoside monophosphate, cytidylyl(3'-5')guanosine (CpG), was purchased as the ammonium salt from Sigma Chemical Company and converted to the iodinated form using methods described previously (5). Deep yellow pyramidal shaped crystals were obtained by slow evaporation of equimolar mixtures of MNAED and iodoCpG. The crystal density was estimated by the floatation method to be 1.545 gm/cm^3.

Crystals were initially characterized by rotation and precession photographs using nickel filtered CuKα radiation, and the cell parameters then refined on a CAD-4 automatic diffractometer. Unit cell dimensions are: a = b = 32.192(10) Å and c = 23.964(8) Å, space group $P4_32_12$. Data were collected at low temperature (2° C) by the Molecular Data Corporation on a CAD-4 system out to a 2θ Bragg angle of 85°, using monochromatic CuKα radiation. A total of 4,942 unique reflections were collected, of which 2,002 were significantly above background (>3σI). Three standard reflections were monitored periodically during the course of data collection and no significant changes in intensity were observed. The data were corrected for Lorentz and polarization effects. In addition, absorption corrections were applied based on a series of ψ scans. Structure factors were put on

an absolute scale and the overall temperature factor estimated by Wilson's method. These were then converted into quasi-normalized structure factors using the method of Karle and Hauptman (6).

An (E^2-1) Patterson map was computed and this revealed the positions of two iodine atoms. A Fourier map based on these heavy atom positions showed another heavy peak, interpreted to be a bromide ion. Subsequent attempts to gain additional meaningful chemical information by Fourier methods were not successful. However, atomic superposition based on the positions of the heavy atoms gave about eighty peaks which, when combined with Fourier and sum-Fourier maps, eventually gave the complete structure. The asymmetric unit contains two iodoCpG molecules, three MNAED molecules and 31 water molecules, a total of 160 atoms. This was then refined by full matrix least squares, using rigid groups for purine and pyrimidine bases and phosphate groups. Isotropic temperature factors were used for light atoms, while anisotropic temperature factors were used for the heavy atoms. The final residual based on 2,002 observed reflections is 11.4%. Coordinates and temperature factors are shown in Table 1.

Results

Figures 2a and b show the complex viewed approximately parallel to and perpendicular to the guanine-cytosine base-pairs and MNAED molecules. IodoCpG forms a miniature Watson-Crick duplex, with two MNAED molecules stacking immediately above and below. This 2:2 structure possesses approximate 2-fold symmetry -- the bromide ion lying very close to this 2-fold axis. In addition, a third MNAED molecule stacks on MNAED(1) with its side chain oppositely oriented. The overall complex is electrically neutral. Each MNAED molecule carries a positive charge and these are counterbalanced by the negatively charged phosphate groups and bromide ion.

The conformation of the iodoCpG base-paired structure is of particular interest for several reasons. The separation between least squares planes of the base-pairs is 3.7 Å -- a distance considerably larger than the normal separation (3.4 Å). This reflects an unusual buckling present within each guanine-cytosine base-pair. Least squares planes computations indicate that guanine and cytosine rings form a dihedral angle of about 19° -- hydrogen bonds connecting base-pairs are therefore bent this amount. The sugar-phosphate backbone conformation is C3' endo (3'-5') C3' endo in iodoCpG(1) and C3' endo (3'-5') C2' endo in iodoCpG(2). The angular twist between the base-pairs is about 26° -- this is due in part to the mixed sugar puckering present in one of the two chains. Dihedral angles that define the overall conformation are summarized in Table 2.

Duplexes are related by 2-fold symmetry and are held together by hydrogen bonds (see Figures 3a and b). These involve the 2-amino- group and the N(3) ring nitrogen on one guanosine residue in the first duplex interacting with the O(2) carbonyl- and O(2)' hydroxyl- group on a cytidine residue in the second symmetry related duplex. In addition, the 2-amino- group of the other

Table 1. Final coordinates and isotropic temperature factors of MNAED-iodoCpG complex after least squares refinement. Occupancy factors for disordered water structure are indicated

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	0.0920	0.4318	-0.1049	6.5		42	I5 C2	0.0110	0.3935	0.2872	6.8	
2	N1 C1	0.1555	0.3155	-0.1129	6.2		43	N1 C2	0.0927	0.2916	0.3051	4.9	
3	C2 C1	0.1626	0.3021	-0.0559	8.4		44	C2 C2	0.1038	0.2764	0.2525	4.5	
4	O2 C1	0.1800	0.2689	-0.0498	4.9		45	O2 C2	0.1290	0.2485	0.2447	4.9	
5	N3 C1	0.1486	0.3284	-0.0173	4.1		46	N3 C2	0.0876	0.2974	0.2085	7.1	
6	C4 C1	0.1271	0.3639	-0.0256	7.7		47	C4 C2	0.0625	0.3312	0.2146	6.6	
7	N4 C1	0.1143	0.3847	0.0169	5.7		48	N4 C2	0.0480	0.3507	0.1686	4.6	
8	C5 C1	0.1205	0.3753	-0.0843	9.7		49	C5 C2	0.0518	0.3451	0.2680	7.2	
9	C6 C1	0.1355	0.3509	-0.1242	2.7		50	C6 C2	0.0655	0.3236	0.3119	5.0	
10	C1'C1	0.1787	0.2939	-0.1578	7.1		51	C1'C2	0.1062	0.2620	0.3518	4.7	
11	C2'C1	0.1561	0.2537	-0.1763	8.5		52	C2'C2	0.1514	0.2716	0.3689	4.0	
12	C3'C1	0.1311	0.2726	-0.2274	8.8		53	C3'C2	0.1442	0.3026	0.4166	6.5	
13	C4'C1	0.1606	0.3035	-0.2525	4.8		54	C4'C2	0.1050	0.2856	0.4440	7.4	
14	O1'C1	0.1835	0.3202	-0.2043	5.6		55	O1'C2	0.0799	0.2682	0.3989	7.3	
15	C5'C1	0.1418	0.3386	-0.2855	11.5		56	C5'C2	0.0800	0.3182	0.4764	6.8	
16	O5'C1	0.1168	0.3611	-0.2513	10.9		57	O5'C2	0.0711	0.3533	0.4421	10.8	
17	O2'C1	0.1849	0.2244	-0.1960	6.4		58	O2'C2	0.1693	0.2343	0.3906	8.7	
18	O3'C1	0.1148	0.2414	-0.2613	6.5		59	O3'C2	0.1776	0.3078	0.4524	5.6	
19	P1	0.0676	0.2244	-0.2610	9.9		60	P2	0.2161	0.3376	0.4402	6.1	
20	O1 P1	0.0375	0.2565	-0.2434	13.0		61	O1 P2	0.2025	0.3745	0.4109	8.5	
21	O2 P1	0.0648	0.2046	-0.3159	15.5		62	O2 P2	0.2376	0.3402	0.4950	7.9	
22	O5'G1	0.0672	0.1891	-0.2145	9.3		63	O5'G2	0.2433	0.3131	0.3963	7.9	
23	C5'G1	0.0962	0.1551	-0.2149	9.9		64	C5'G2	0.2596	0.2742	0.4115	5.4	
24	C4'G1	0.0972	0.1326	-0.1607	7.6		65	C4'G2	0.2811	0.2546	0.3615	6.1	
25	C3'G1	0.0531	0.1268	-0.1347	12.9		66	C3'G2	0.3176	0.2818	0.3444	12.2	
26	C2'G1	0.0467	0.1241	-0.0715	5.6		67	C2'G2	0.2998	0.3085	0.2964	11.2	
27	C1'G1	0.1033	0.1574	-0.0694	5.8		68	C1'G2	0.2682	0.2783	0.2730	6.6	
28	O1'G1	0.1180	0.1618	-0.1246	5.0		69	O1'G2	0.2527	0.2546	0.3161	5.8	
29	O2'G1	0.0838	0.0882	-0.0583	12.8		70	O2'G2	0.3317	0.3217	0.2576	17.3	
30	O3'G1	0.0352	0.0891	-0.1536	11.2		71	O3'G2	0.3520	0.2586	0.3261	13.2	
31	N1 G1	0.0958	0.2567	0.0961	4.1		72	N1 G2	0.1794	0.3081	0.0952	4.1	
32	C2 G1	0.1152	0.2197	0.0917	6.1		73	C2 G2	0.2072	0.2763	0.1036	4.3	
33	N2 G1	0.1345	0.2045	0.1365	3.2		74	N2 G2	0.2148	0.2506	0.0621	3.1	
34	N3 G1	0.1157	0.1959	0.0446	4.3		75	N3 G2	0.2269	0.2692	0.1524	4.5	
35	C4 G1	0.0947	0.2148	0.0029	3.5		76	C4 G2	0.2186	0.2958	0.1905	11.6	
36	C5 G1	0.0741	0.2515	0.0030	5.1		77	C5 G2	0.1904	0.3305	0.1684	8.5	
37	C6 G1	0.0733	0.2757	0.0513	5.5		78	C6 G2	0.1689	0.3391	0.1340	4.5	
38	O6 G1	0.0568	0.3097	0.0610	5.8		79	O6 G2	0.1428	0.3651	0.1243	3.9	
39	N7 G1	0.0540	0.2588	-0.0469	4.4		80	N7 G2	0.1888	0.3559	0.2363	8.3	
40	C8 G1	0.0648	0.2252	-0.0771	3.2		81	C8 G2	0.2146	0.3354	0.2699	7.7	
41	N9 G1	0.0901	0.1974	-0.0505	5.9		82	N9 G2	0.2327	0.3004	0.2447	7.3	
		MNAED MOLECULE(1)							MNAED MOLECULE(2)				
83	C1 D1	-0.0180	0.2327	0.0943	7.3		99	C1 D2	0.2422	0.4133	0.1069	4.4	
84	C2 D1	0.0024	0.1928	0.0964	6.2		100	C2 D2	0.2677	0.3796	0.0968	6.3	
85	C3 D1	0.0213	0.1806	0.1436	5.2		101	C3 D2	0.2692	0.3614	0.0425	5.1	
86	C4 D1	0.0182	0.2085	0.1896	3.7		102	C4 D2	0.2459	0.3770	0.0001	4.5	
87	C5 D1	0.0002	0.2469	0.1894	6.7		103	C5 D2	0.2194	0.4118	0.0071	3.2	
88	C6 D1	-0.0193	0.2606	0.1412	7.4		104	C6 D2	0.2166	0.4305	0.0597	5.8	
89	C7 D1	0.0026	0.1651	0.0434	7.2		105	C7 D2	0.2950	0.3636	0.1434	7.3	
90	N4 D1	0.0398	0.1946	0.2417	6.3		106	N4 D2	0.2469	0.3580	-0.0564	8.8	
91	NO1D1	0.0581	0.1614	0.2436	9.4		107	NO1D2	0.2721	0.3299	-0.0615	11.3	
92	NO2D1	0.0366	0.2177	0.2830	9.5		108	NO2D2	0.2276	0.3734	-0.0943	11.2	
93	N8 D1	-0.0364	0.2466	0.0403	6.6		109	N8 D2	0.2379	0.4317	0.1573	7.5	
94	C9 D1	-0.0408	0.2852	0.0331	6.8		110	C9 D2	0.2147	0.4699	0.1680	6.6	
95	C10D1	-0.0378	0.3261	0.0203	4.4		111	C10D2	0.1676	0.4657	0.1802	10.1	
96	N11D1	-0.0146	0.3204	-0.0273	7.1		112	N11D2	0.1627	0.4408	0.2274	8.4	
97	C12D1	-0.0448	0.3187	-0.0769	14.6		113	C12D2	0.1230	0.4292	0.2371	6.7	
98	C13D1	0.0011	0.3625	-0.0368	7.6		114	C13D2	0.1778	0.4545	0.2811	12.5	
						MNAED MOLECULE(3)							
115	BR	0.0287	0.4440	0.0902	8.5		124	NO1D3	-0.0579	0.0929	0.0928	21.5	
116	C1 D3	-0.0240	0.1151	0.2914	7.2		125	NO2D3	-0.0976	0.1447	0.1177	21.8	
117	C2 D3	-0.0081	0.0866	0.2511	13.9		126	N8 D3	-0.0060	0.1091	0.3584	18.7	
118	C3 D3	-0.0239	0.0876	0.1978	16.7		127	C9 D3	-0.0296	0.1168	0.4122	34.0	
119	C4 D3	-0.0544	0.1187	0.1831	15.4		128	C10D3	-0.0061	0.1321	0.4649	28.3	
120	C5 D3	-0.0687	0.1460	0.2221	10.7		129	N11D3	0.0371	0.1276	0.4550	26.3	
121	C6 D3	-0.0532	0.1447	0.2747	14.4		130	C12D3	0.0584	0.1381	0.5049	41.4	
122	C7 D3	0.0230	0.0535	0.2647	6.4		131	C13D3	0.0482	0.1550	0.4110	38.0	
123	N4 D3	-0.0729	0.1185	0.1254	16.3								
						SOLVENT MOLECULE ATOMS							
132	OW1	0.4770	0.3924	0.4768	27.7		147	OW14R	0.3275	0.3275	0.5000	21.0	0.50
133	OW2	-0.0812	0.2009	0.5092	17.6		148	OW15A	-0.0781	0.2363	0.6100	7.9	0.60
134	OW3	0.4347	0.2994	0.3159	17.3		149	OW15B	-0.0557	0.2541	0.6538	5.9	0.40
135	OW4	-0.1105	0.2823	0.8391	18.8		150	OW16A	0.1239	0.4155	0.4178	19.1	0.60
136	OW5	0.3263	0.4860	0.3938	22.4		151	OW16B	0.1394	0.4318	0.4619	27.5	0.40
137	OW6	-0.0301	0.2338	0.8173	21.3		152	OW17A	0.2870	0.0078	0.3671	8.5	0.35
138	OW7	0.4002	0.1258	0.4143	19.9		153	OW17B	0.3278	0.0279	0.3576	15.1	0.30
139	OW8	0.0105	0.0289	0.0471	27.6		154	OW17C	0.3582	0.0423	0.3803	6.0	0.35
140	OW9	0.1101	0.1519	0.6342	13.2		155	OW18A	-0.0257	0.3853	0.7993	10.7	0.40
141	OW10	0.2315	0.0201	0.4555	27.6		156	OW18B	0.0297	0.3393	0.8134	10.2	0.60
142	OW11	0.1562	0.2594	0.5817	19.1		157	OW19A	0.0966	0.4731	0.3715	18.0	0.50
143	OW12	0.1753	0.1862	0.2955	10.9		158	OW19B	0.4263	0.0199	0.4618	23.9	0.50
144	OW13A	-0.1292	0.1173	0.6663	10.8	0.50	159	OW20A	0.0285	0.4653	0.7497	9.3	0.50
145	OW13B	-0.1012	0.1477	0.6431	12.0	0.50	160	OW20B	-0.0145	0.4813	0.6789	17.0	0.50
146	OW14A	-0.1254	0.1820	0.7512	12.7	0.50							

guanosine residue in the first duplex hydrogen bonds to the furanose ring oxygen on its symmetry related counterpart. A total of six hydrogen bonds connect these symmetry related duplexes.

Figure 4 shows a projection of the structure down the c axis. Bromide ions and iodine atoms cluster together around the 4-fold screw axis, forming

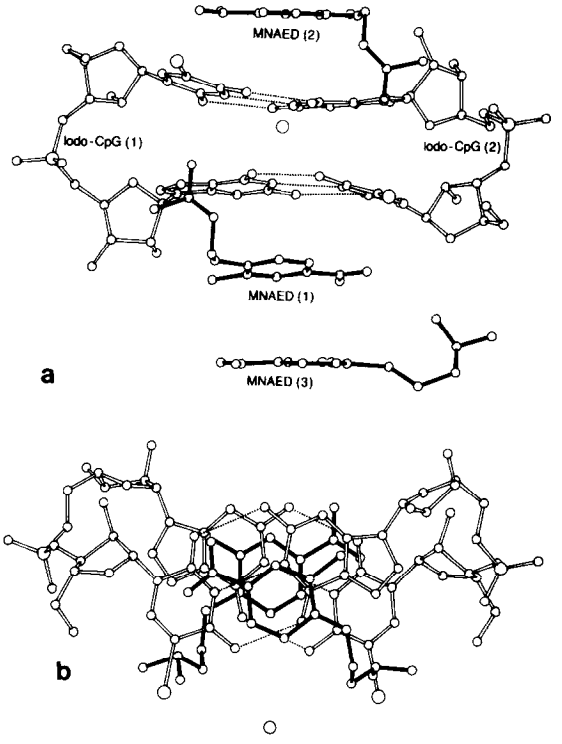

Figure 2. A portion of the MNAED-iodoCpG complex viewed approximately parallel to (a) and perpendicular to (b) base-pairs and MNAED molecules.

Table 2. Torsional angles describing the conformations of the sugar-phosphate chains in the MNAED-iodoCpG crystalline complex

Torsional Angle	iodoCpG(1)	iodoCpG(2)
O1'C-C1'C-N1C-C6C	13	12
O1'G-C1'G-N9G-C8G	49	77
O5'C-C5'C-C4'C-C3'C	61	53
C5'C-C4'C-C3'C-O3'C	80	79
C4'C-C3'C-O3'C-P	221	200
C3'C-O3'C-P-O5'G	273	283
O3'C-P-O5'G-C5'G	305	299
P-O5'G-C5'G-C4'G	165	175
O5'G-C5'G-C4'G-C3'G	42	63
C5'G-C4'G-C3'G-O3'G	89	143
C4'C-O1'C-C1'C-C2'C	8	6
O1'C-C1'C-C2'C-C3'C	-27	-27
C1'C-C2'C-C3'C-C4'C	37	36
C2'C-C3'C-C4'C-O1'C	-34	-34
C3'C-C4'C-O1'C-C1'C	17	18
C4'G-O1'G-C1'G-C2'G	- 7	-22
O1'G-C1'G-C2'G-C3'G	-20	33
C1'G-C2'G-C3'G-C4'G	36	-30
C2'G-C3'G-C4'G-O1'G	-40	20
C3'G-C4'G-O1'G-C1'G	31	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.

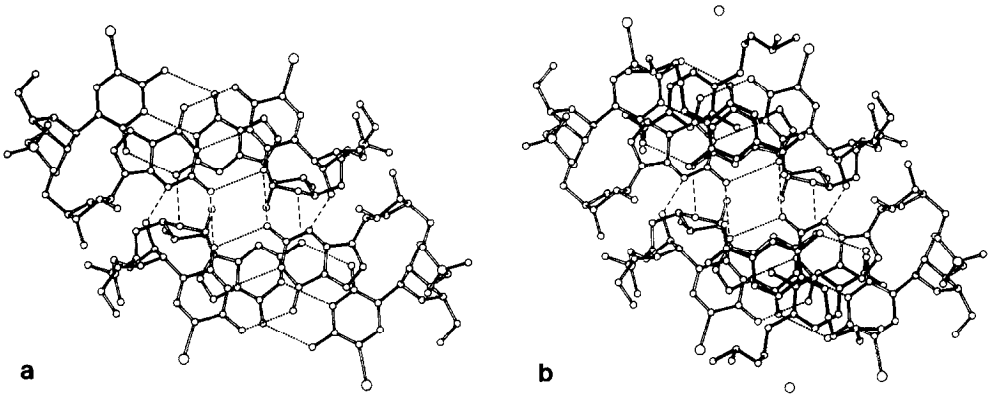

Figure 3. Hydrogen bonding between 2-fold symmetry related iodoCpG duplexes (a) and these duplexes with stacked MNAED molecules shown above and below (b). See text for discussion.

a helical columnar arrangement in the z direction. MNAED molecules cluster around a 2-fold screw axis, themselves related by additional 2-fold rotational symmetry along the diagonal. Hydrogen bonded pairs of 3:2 MNAED-iodoCpG complexes pack together in a zig-zag fashion in the crystalline lattice. The complex is heavily hydrated with water molecules hydrogen bonded to sugar

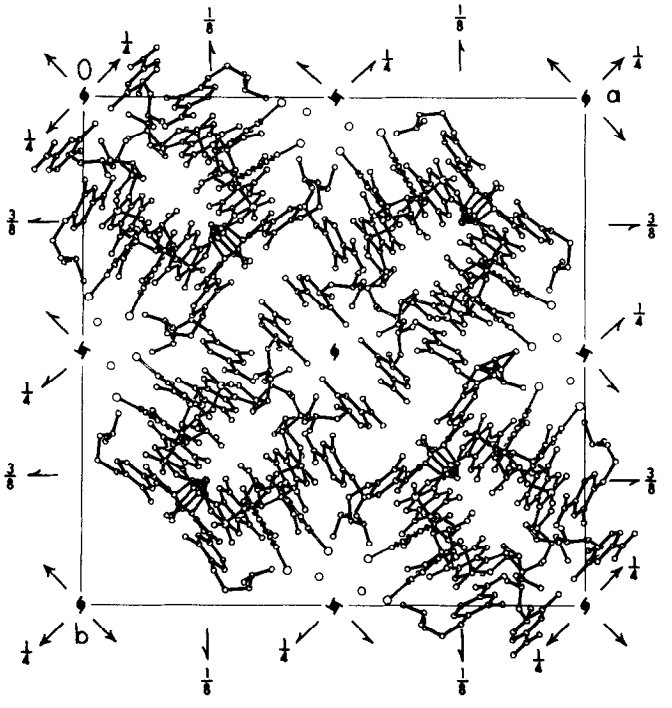

Figure 4. Lattice figure showing the crystal structure of the MNAED-iodoCpG complex viewed down the c axis. For simplicity, water structure is omitted. See text for discussion.

hydroxyl- groups and phosphate oxygen atoms. Additional hydrogen bonds form between water molecules and other hydrophillic groups on base-pairs and MNAED molecules.

Discussion

2-Methyl-4-nitroaniline ethylene dimethylammonium hydrobromide is one in a series of nitroaniline reporter molecules synthesized by Gabbay that intercalate -- either partially or fully -- into DNA structure. This class of molecules is of particular interest, since they resemble naturally occuring aromatic amino- acids such as tyrosine and phenylalanine. Their ability to intercalate into DNA raises the possibility that aromatic side chains in proteins might also intercalate when binding to DNA (7-9).

Recent experimental evidence indicates the presence of nuclease hypersensitive sites in eukaryotic DNA, many of these located at 5' ends of genes (10,11). These same sites are sensitive to cleavage by a 1,10-phenanthroline-copper(I) complex, a known intercalating agent. These data suggest the existence of an altered DNA conformation in these regions recognized by nucleases and intercalators by a common intercalative mechanism (12).

The current study was carried out to investigate the ability of 2-methyl-4-nitroaniline ethylene dimethylammonium hydrobromide to intercalate -- either partially or fully -- into the self-complementary dinucleoside monophosphate, iodoCpG. Although intercalation in the classic sense has not been observed, this nitroaniline derivative stacks above and below base-pairs in the miniature Watson-Crick type duplex structure. The absence of intercalation could reflect the smaller stacking energies associated with the aromatic ring system in MNAED and the base-pairs, along with other factors determining the energetics of the complex. We have repeatedly observed that molecules containing larger conjugated ring systems form intercalation complexes with this same dinucleoside monophosphate (13-15). It is possible that longer oligonucleotides would provide better model systems to study the interaction of MNAED with DNA, and we are pursuing this further at the present time.

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