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Structure of the DNA Complexing Agent Anthramycin

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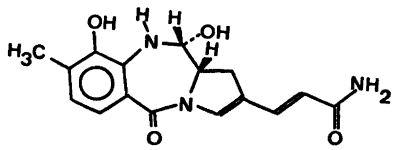
The crystal structure of the title compound has been determined by X-ray diffraction methods using 2477 observed reflections collected on an automated diffractometer at 110 K. The crystals are orthorhombic, space group $P\ 2_12_12_1$, with unit cell dimensions $a = 7.979(3)$ Å, $b = 13.525(5)$ Å, and $c = 16.222(6)$ Å. The structure was refined to a conventional R-factor of 0.048 for 1624 reflections with $\sin\theta/\lambda > 0.5$ Å^{-1}. The e.s.d. for bond lengths and angles not involving hydrogen atoms are 0.003 – 0.004 Å and 0.2°, respectively.

The molecule is twisted 40 – 50° from one end to the other along the long axis. A previously suggested pharmacophoric pattern is found to fit poorly to the present structure if the atoms showed to be important for the biological activity are to be included. It is suggested that the molecular twist may be of importance for the fit of the molecule into one of the grooves of DNA.

Anthramycin (5,10,11,11a-tetrahydro-9-hydroxy-11-methoxy-8-methyl-5-oxo-14-pyrrolo-[2,1-*c*][1,4]benzo-diazepine-2-acrylamide) with *S*-configuration in the 11a position has been



Scheme 1.

shown to exhibit a number of biological effects which have been correlated to its ability to interact with DNA.[1] The molecule does not show the usual structural features that have been associated with a tight binding to DNA.[1,4] The interaction has been extensively studied, and a number of observations concerning the binding mechanism have emerged.[2–5] There are thus indications of a covalent nature of bonding, that guanine-containing DNA in helical conformation is essential and that the binding capacity of DNA amounts to about one anthramycin molecule per ten base units. It has also been demonstrated that the DNA molecule gains in rigidity by the reaction, that this effect is not induced by intercalation,[5] and that the aromatic ring in anthramycin is inclined about 40° to the base pairs in the complex.

These facts may well indicate that the anthramycin molecule interacts with DNA by fitting into one of the grooves of the helical structure where it can bind to the guanine bases and stabilize the complex through hydrogen bonds.

A pharmacophoric geometric pattern has been suggested for a group of compounds, including anthramycin, showing antileukaemic activity.[6,7] In order to test this pattern and to study the mechanism of interaction with DNA, we have investigated the crystal structure of anthramycin methyl ether by X-ray methods. The methyl ether is readily hydrolyzed and converted to anthramycin and was chosen for the study because of its higher stability.

EXPERIMENTAL

A sample of anthramycin methyl ether monohydrate was given to us by Hoffmann-La Roche, Basel. The compound was in the form of light yellow needle-shaped crystals which could readily be cut to a size suitable for the X-ray experiments. The crystal selected was prismatic of dimensions $0.1 \times 0.2 \times 0.4$ mm^3. Data were collected on a SYNTEX $P\bar{1}$ four-circle diffractometer using graphite crystal monochromated Mo$K\alpha$ radiation ($\lambda = 0.71069$). The temperature at the crystal site was 110 K. Cell parameters were determined by a least-squares fit to the diffractometer settings for 15 general reflections. Intensity data were recorded using the $\theta/2\theta$ scanning mode; the scan speed (2θ)

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for non-hydrogen atoms. The anisotropic temperature factor is given by $\exp -2\pi^2 U_{11} a^{*2} h^2 + \ldots + 2U_{12} a^* b^* hk + \ldots)$.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	0.6902(3)	−0.1436(2)	0.6890(2)	0.0112(9)	0.0131(9)	0.0124(9)	0.0012(8)	−0.0008(8)	−0.0013(8)
C2	0.5447(3)	−0.1941(2)	0.6923(2)	0.0142(9)	0.0123(9)	0.0133(9)	0.0016(8)	0.0009(9)	−0.0014(8)
N3	0.4430(3)	−0.1597(2)	0.7568(2)	0.0128(9)	0.0121(10)	0.0133(9)	−0.0011(8)	0.0020(8)	−0.0026(8)
C4	0.2962(3)	−0.2055(2)	0.7787(2)	0.0123(9)	0.0123(10)	0.0160(9)	0.0013(8)	0.0027(8)	−0.0005(8)
C5	0.1869(3)	−0.1585(2)	0.8421(2)	0.0123(10)	0.0148(10)	0.0124(11)	0.0009(8)	0.0023(9)	−0.0026(8)
C6	0.0780(4)	−0.2272(2)	0.8823(2)	0.0170(11)	0.0138(11)	0.0169(11)	−0.0014(10)	0.0045(10)	0.0005(9)
C7	−0.0349(3)	−0.1966(2)	0.9424(2)	0.0189(10)	0.0190(11)	0.0181(9)	0.0017(9)	0.0064(9)	0.0017(8)
C8	−0.0509(3)	−0.0942(2)	0.9619(1)	0.0130(9)	0.0191(10)	0.0133(9)	0.0011(8)	0.0025(8)	−0.0002(8)
C9	0.0480(3)	−0.0256(2)	0.9196(1)	0.0112(10)	0.0133(10)	0.0135(9)	0.0016(8)	−0.0011(8)	−0.0025(8)
C10	0.1731(3)	−0.0552(2)	0.8612(2)	0.0122(10)	0.0134(9)	0.0111(9)	0.0013(8)	−0.0005(7)	0.0000(8)
N11	0.2621(3)	0.0241(2)	0.8279(1)	0.0176(9)	0.0113(10)	0.0241(9)	0.0008(8)	0.0079(8)	−0.0017(8)
C12	0.4108(3)	0.0214(2)	0.7787(2)	0.0137(9)	0.0131(10)	0.0129(9)	−0.0015(8)	0.0005(8)	−0.0039(8)
C13	0.5187(3)	−0.0704(2)	0.7961(2)	0.0116(9)	0.0144(10)	0.0111(9)	0.0016(8)	0.0002(8)	−0.0028(8)
C14	0.6956(3)	−0.0643(2)	0.7563(2)	0.0111(10)	0.0191(11)	0.0144(9)	0.0002(9)	0.0013(8)	−0.0059(8)
C15	0.8172(3)	−0.1638(2)	0.6270(2)	0.0122(9)	0.0156(10)	0.0136(10)	0.0024(8)	0.0011(7)	−0.0018(8)
C16	0.9706(4)	−0.1220(2)	0.6251(2)	0.0124(11)	0.0182(12)	0.0126(10)	0.0021(9)	−0.0009(9)	−0.0040(9)
C17	1.0877(5)	−0.1471(2)	0.5567(2)	0.0122(16)	0.0161(11)	0.0124(12)	0.0008(12)	−0.0012(12)	−0.0006(10)
N18	1.2472(3)	−0.1200(2)	0.5683(1)	0.0122(8)	0.0240(8)	0.0141(8)	−0.0025(7)	0.0007(8)	−0.0027(7)
O19	1.0415(3)	−0.1907(2)	0.4918(1)	0.0132(8)	0.0270(8)	0.0154(8)	0.0027(6)	−0.0024(7)	−0.0073(7)
O20	0.2577(3)	−0.2873(2)	0.7468(1)	0.0211(8)	0.0156(8)	0.0203(8)	−0.0050(7)	0.0083(6)	−0.0052(7)
C21	−0.1721(3)	−0.0598(2)	1.0279(1)	0.0174(8)	0.0237(10)	0.0182(8)	0.0022(8)	0.0087(7)	−0.0023(7)
O22	0.0331(3)	0.0763(2)	0.9327(1)	0.0119(8)	0.0148(8)	0.0186(8)	0.0029(7)	0.0003(7)	−0.0049(7)
O23	0.3769(3)	0.0206(2)	0.6909(2)	0.0179(2)	0.0137(9)	0.0149(10)	0.0023(8)	−0.0025(8)	−0.0015(8)
C24	0.3111(3)	0.1137(2)	0.6611(1)	0.0352(9)	0.0174(10)	0.0227(8)	0.0067(8)	−0.0059(7)	0.0028(8)
O25	0.7245(3)	0.1180(2)	0.9030(1)	0.0153(8)	0.0197(8)	0.0166(8)	0.0037(7)	0.0007(7)	0.0021(7)

was from 1 to 2° min^{-1} depending on the intensity. All reflections with $\sin\theta/\lambda < 0.54$ $Å^{-1}$ were measured; reflections in the interval 0.54 $Å^{-1}$ $\sin\theta/\lambda < 0.76$ $Å^{-1}$ were measured only if a quick scan gave an intensity larger than a preset value. The scan range was from 0.7° below $2\theta(\alpha_1)$ to 0.9° above $2\theta(\alpha_2)$ and the background counts were taken for 0.35 of the scan time at each of the scan limits.

Out of the 2947 unique reflections recorded, 2477 with $I > 2.5\sigma(I)$ were retained for the structure analysis. The standard deviations for the intensities were calculated from $\sigma(I) = [C_T + (0.02C_N)^2]^{\frac{1}{2}}$ where C_T is the total number of counts and C_N is the scan count minus background count. The usual corrections were made for Lorentz and polarization effects, but no correction was made for absorption and extinction.

Scattering factors used were those of Doyle and Turner for O, N and C,[8] and of Stewart, Davidson and Simpson for H.[9] Description of the computer programs applied are given in Refs. 10 and 11. The quantity minimized in the least-squares calculations was $\sum w\Delta F^2$ where w is the inverse of the variance of the observed structure factors.

Table 2. Fractional atomic coordinates and B-values for hydrogen.

Atom	x	y	z	B
H2	0.510	−0.250	0.658	1.2
H6	0.091	−0.297	0.868	2.5
H7	−0.101	−0.244	0.970	2.5
H11	0.232	0.080	0.847	1.2
H12	0.475	0.086	0.789	1.2
H13	0.521	−0.077	0.856	1.2
H141	0.712	0.004	0.731	1.2
H142	0.779	1.080	0.794	1.2
H15	0.792	−0.209	0.582	1.2
H16	1.010	−0.074	0.668	1.2
H181	1.274	−0.087	0.612	2.5
H182	1.328	−0.127	0.523	2.5
H211	−0.198	−0.124	1.068	4.7
H212	−0.290	−0.037	1.002	4.7
H213	−0.140	−0.058	1.061	4.7
H22	−0.073	0.095	0.931	2.5
H241	0.289	0.105	0.603	4.7
H242	0.208	0.143	0.691	4.7
H243	0.396	0.170	0.669	4.7
H251	0.654	0.148	0.935	2.5
H252	0.739	0.151	0.862	2.5

CRYSTAL DATA

Anthramycin methyl ether monohydrate, $C_{17}H_{19}N_3O_4 \cdot H_2O$, orthorhombic.

$t = 18$ °C: $a = 7.979(3)$ Å; $b = 13.525(5)$ Å; $c = 16.222(6)$ Å; $V = 1750.6$ Å. $t = -163$ °C: $a = 7.968(3)$ Å; $b = 13.317(7)$ Å; $c = 16.071(9)$ Å; $V = 1705.3$ Å. $M = 347.37$; $Z = 4$; $F(000) = 736$; $\mu(\mathrm{Mo}K\alpha) = 1.1$ cm^{-1}; $D_x(t = 18$ °C$) = 1.318$ g cm^{-3}; $D_x(t = -163$ °C$) = 1.353$ g cm^{-3}. Space group $P\ 2_12_12_1$ (No. 19) from systematic absences.

STRUCTURE DETERMINATION

The structure was solved by direct methods using the program assembly MULTAN.[10] Phases were determined for 175 reflections with $E > 1.75$; an E-map revealed the positions for most of the non-hydrogen atoms, the rest were found by successive Fourier refinements. Positions of hydrogen atoms were calculated from stereo-chemical considerations after a preliminary least-squares refinement; the choice between two sets of hydrogen positions for the methyl group C(21) was made on the basis of B-values obtained after further refinements.

The least-squares refinements included positional parameters for all atoms, anisotropic thermal parameters for the heavier atoms and isotropic thermal parameters for hydrogen atoms; the latter were constrained to three B-values common for groups of hydrogen atoms. The refinements using all 2477 observations lead to a conventional R-factor of 0.043, $R_w = 0.039$ and $S = (\sum w\Delta F^2/n-m)^{\frac{1}{2}} = 1.69$. In order to avoid the influence of bonding electrons on the bond distances, the refinement of the parameters of the heavy atoms was repeated using the 1624 data with $\sin\theta/\lambda > 0.5$ $Å^{-1}$; this resulted in a slightly poorer R-value (0.048) and a better goodness-of-fit ($S = 1.14$). The parameters obtained in this way are listed in Tables 1 and 2 and were applied for the

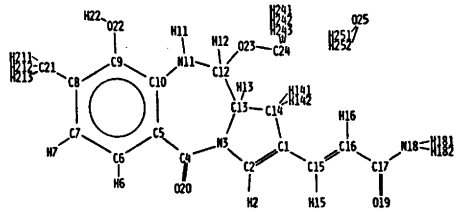


Fig. 1. Schematical drawing of anthramycin with numbering of atoms.

calculation of structural data used in the discussion. Tables of observed and calculated structure factors are available from the authors.

An analysis of the molecular motions in terms of rigid body vibrations resulted in insignificant changes in interatomic distances.

DESCRIPTION OF THE STRUCTURE

The asymmetric unit including one molecule of water is schematically drawn in Fig. 1 where the numbering of the atoms is also given. Structural data are listed in Table 3.

Table 3. Structural data for anthramycin.

Bond length (Å)

C1 – C2	1.342(4)
C1 – C14	1.513(3)
C1 – C15	1.447(3)
C2 – N3	1.396(3)
N3 – C4	1.366(3)
N3 – C13	1.475(3)
C4 – C5	1.480(3)
C4 – O20	1.242(3)
C5 – C6	1.418(4)
C5 – C10	1.413(3)
C6 – C7	1.383(4)
C7 – C8	1.403(4)
C8 – C9	1.386(4)
C8 – C21	1.508(4)
C9 – C10	1.426(3)
C9 – O22	1.378(3)
C10 – N11	1.380(4)
N11 – C12	1.428(3)
C12 – C13	1.520(4)
C12 – O23	1.437(3)
C13 – C14	1.552(3)
C15 – C16	1.345(4)
C16 – C17	1.482(4)
C17 – N18	1.336(3)
C17 – O19	1.250(3)
O23 – C24	1.428(4)

Average values

C – H	0.97
N – H	0.89
O – H	0.85

Bond angle (°)

C2 – C1 – C14	110.2(2)
C2 – C1 – C15	122.7(2)
C14 – C1 – C15	127.1(2)
C1 – C2 – N3	111.6(2)
C2 – N3 – C4	123.0(2)
C2 – N3 – C13	110.1(2)
C4 – N3 – C13	126.9(2)
N3 – C4 – C5	119.6(2)
N3 – C4 – O20	119.8(2)
C5 – C4 – O20	120.6(2)
C4 – C5 – C6	113.8(2)
C4 – C5 – C10	127.4(2)
C6 – C5 – C10	118.7(2)
C5 – C6 – C7	121.9(3)
C6 – C7 – C8	120.1(3)
C7 – C8 – C9	118.6(2)
C7 – C8 – C21	120.7(3)
C9 – C8 – C21	120.7(2)
C8 – C9 – C10	122.7(2)
C8 – C9 – O22	121.6(2)
C10 – C9 – O22	115.7(2)
C5 – C10 – C9	117.9(2)
C5 – C10 – N11	128.3(2)
C9 – C10 – N11	113.8(2)
C10 – N11 – C12	128.6(2)
N11 – C12 – C13	112.9(2)
N11 – C12 – O23	112.9(2)
C13 – C12 – O23	106.4(2)
N3 – C13 – C12	109.6(2)
N3 – C13 – C14	103.8(2)
C12 – C13 – C14	113.4(2)
C1 – C14 – C13	103.5(2)
C1 – C15 – C16	125.2(2)
C15 – C16 – C17	119.8(2)
C16 – C17 – N18	115.8(2)
C16 – C17 – O19	122.7(2)
N18 – C17 – O19	121.6(3)
C12 – O23 – C24	113.2(2)

Selected torsional angles (°)

C9 – C10 – N11 – C12	169.3	C5 – C4 – N3 – C2	– 173.8
C10 – N11 – C12 – C13	– 27.8	C5 – C4 – N3 – C13	6.9
N11 – C12 – C13 – C14	– 168.7	C4 – N3 – C2 – C1	– 173.1
N11 – C12 – O23 – C24	69.7	N3 – C2 – C1 – C14	– 0.6
N11 – C12 – C13 – N3	75.8	C2 – C1 – C15 – C16	– 173.8
C12 – C13 – C14 – C1	– 111.0	C14 – C1 – C15 – C16	7.9
C13 – C14 – C1 – C15	173.7	C1 – C15 – C16 – C17	– 178.4
C6 – C5 – C4 – O20	21.3	C15 – C16 – C17 – N18	– 166.4
C6 – C5 – C4 – N3	– 156.8	C15 – C16 – C17 – O19	13.8

The molecule is composed of a six-membered aromatic ring and a five-membered ring, both fused to a seven-membered ring, and an acrylamide side chain. The phenyl ring is planar, all displacements out of the least-squares plane through the six atoms being less than 0.03 Å; the substituent atoms are situated within 0.10 Å from this plane. There are significant variations in the C–C distances within the benzene ring [from 1.383 to 1.426 Å] as well as in the bond angles. The bond lengths and angles involving the substituents C21 and O22 are quite normal, including the difference in external angles at C9.

Only two of the atoms in the seven-membered ring appear to be sp^3 hybridized, *i.e.* C12 and C13, both atoms are chiral centres giving rise to epimeric isomers. For the atoms N3, C4, C5, C10 and N11, the sum of the bond angles are within 1° of 360°, thus indicating sp^2 hybridization. The conformation of the ring may be described as that of a twisted boat, somewhat flattened because of the sp^2 hybridized state of five of the atoms.

From the torsional angles given in Table 3 it may be seen that C12 and N3 are situated above the plane of the aromatic ring as viewed in Fig. 1 and that C13 is situated still further above the plane; the N3–C13 bond forms an angle of 28° with this plane.

The rather short C10–N11 bond length [1.380 Å] indicates some double bond character and may explain the increase in the bond lengths C9–C10 and C5–C10 as well as the decrease in the C5–C10–C9 angle relative to the values normally found in a benzene ring.

It may also be seen from the torsion angles in Table 3 that the chain of atoms from C4 to C16 is nearly planar but with a right-handed twist of 6–7° at each of the single bonds. The near planarity would be expected for the conjugated system including the "peptide" bond C4–N3.

The atoms N3, C2, C1 and C14 of the five-membered ring are strictly co-planar, whereas the fifth atom, C13, is situated above the plane, giving the ring an envelope conformation.

The bonds of each of the atoms in the side-chain, C15, C16 and C17, are coplanar; the chain is nearly planar with a small right-handed twist about each of the bonds C1–C15, C15–C16 and C16–C17. The dimensions of the amido group appear to be normal.[12,13]

A stereoscopic view of the packing of the anthramycin molecules in the crystal is shown in Fig. 2. There are four potential hydrogen donor atoms (O22, O25, N11 and N18) and five hydrogen acceptors (O19, O20, O22, O23 and O25) for hydrogen bonding. With the exception of N11 all are used for hydrogen bonding between molecules in the crystals; relevant distances and angles are given in Table 4.

DISCUSSION

One of the reasons for the present structure determination was to test the triangular pharmacophoric pattern proposed for anthramycin

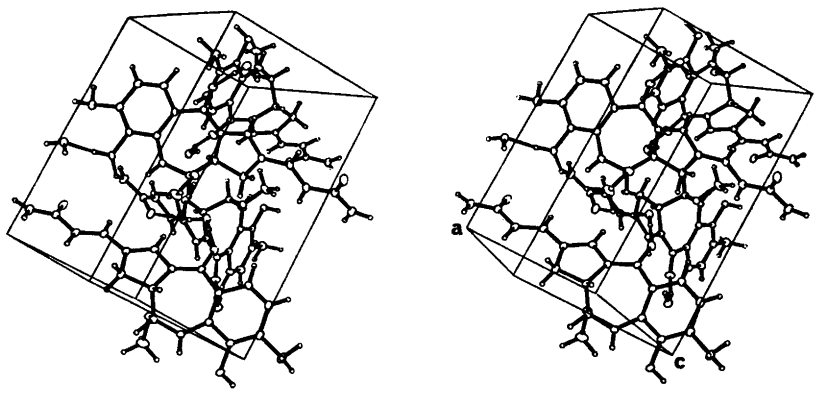


Fig. 2. Stereoscopic view of the packing of anthramycin molecules in the crystal. The *a* and *c* axes are pointing upwards from the paper plane.

Table 4. Hydrogen bonds between donor atoms (D) in the molecule given in Table 1 to acceptor atoms (A) in surrounding molecules.

D	A	Equiv. pos.	D–A (Å)	D–H (Å)	H–A (Å)	∠DHA (°)
N18	O22	$\frac{1}{2}-x$, $2-y$, $\frac{1}{2}+z$	2.859	0.974	1.947	158.7
N18	O23	$x-1$, y, z	2.909	0.852	2.084	162.7
O22	O25	$x+1$, y, z	2.569	0.886	1.702	165.4
O25	O19	$\frac{1}{2}-x$, $2-y$, $z-\frac{1}{2}$	2.736	0.867	1.890	166.7
O25	O20	$1-x$, $y-\frac{1}{2}$, $\frac{1}{2}-z$	2.723	0.806	1.928	168.9

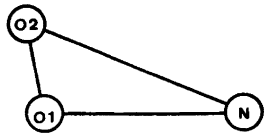


Fig. 3. The pharmacophoric triangle, *cf.* Table 5.

and similar compounds.[6] This pattern is reproduced in Fig. 3, and the results are compared to the proposed values as well as to results from other investigations in Table 5.

For anthramycin the triangle of importance for its biological activity is assumed to be the atoms N18(N), O23(O1) and O22(O2). It appears from the found values that the fit to the proposed pattern is rather poor for the present compound. Another possibility for the choice of triangle in anthramycin, consists of the atoms N18, O20 and O23 where the distances are 7.45 Å (N–O1), 8.71 Å (N–O2) and 4.36 Å (O1–O2). Even if this seems to be in better agreement with the proposed pattern, the atom O22 is excluded from the pharmacophor, and this atom is shown[1] to be important for the activity of the compound. It has been shown, however, that the mechanism of biological action may vary for the different compounds containing the pharmacophoric triangle;[14] thus, the triangle may be of importance for some common mechanism involved in the action, *e.g.* in transport.

Another interesting feature in the structure of anthramycin is the twist about the long axis of the relatively flat molecule.

The absolute configuration of anthramycin has been shown to be the one illustrated in Scheme 1 where C13 (11a-position) has the *S* configuration for the biologically active form. The rapid epimerisation at C12 leaves the absolute configuration at this atom of less importance for the biological activity,[1] whereas the *S* configuration at C13 is imperative. It is interesting to note that the configuration at this point determines whether the twist along the molecule is left- or right-handed.

It follows from the discussion of the conformational angles that the active form has a right-handed twist along the entire molecule amounting to about 45° from the phenyl ring

Table 5. Interatomic distances (A) in various molecules with reference to the pharmacophoric triangle (see text).

	Ref.	N–O1	N–O2	O1–O2
Proposed dimensions	6	7.08±0.56	8.62±0.38	3.35±0.65
Anthramycin		7.457	11.621	4.818
Camptothecin	15	5.495	7.706	2.656
Demecolcine	16	7.117	7.265	2.697
Vincristine	17	7.43	8.01	3.00
Cycloheximide	18	5.427	8.225	3.113
(2 conformers)	18	5.391	7.754	2.727

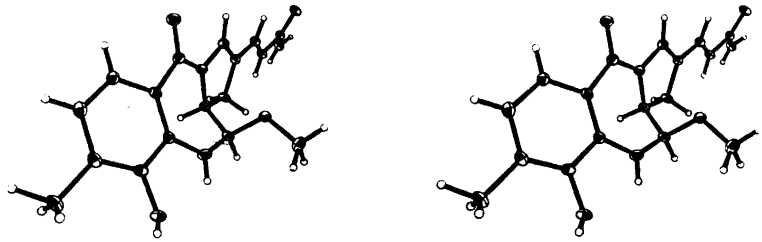


Fig. 4. Stereoscopic drawing of the biologically active form of anthramycin.

to the amido group. This is illustrated stereoscopically in Fig. 4.

It may be noted that for a molecule of about 14 Å length like the present one to fit into one of the grooves of helical DNA a right-handed twist of about 40° along the molecule is needed. This mechanism of DNA-anthramycin complex formation would facilitate the interaction with guanine and would account for the stiffening of the DNA molecule, the dependence of a proper DNA conformation for the complex formation and may also give the angle of 40° between the aromatic ring in anthramycin and the DNA base pairs indicated from the electric dichroism experiments. Also, in a DNA where 25 % of the bases are guanine there may be expected to be on average three bases between guanine molecules. In the interaction mechanism indicated above the anthramycin molecule will cover at least five bases and thus block a mean number of two guanine molecules. The result would be an anthramycin to base proportion of 1:8.

Based on the above considerations a complex formation by a fit of anthramycin into one of the DNA helical grooves appears reasonable.

REFERENCES

1. Kohn, K. W. *Antibiotics 3* (1975) 3.
2. Bates, M., Kuenzig, W. and Watson, W. B. *Cancer Res. 29* (1969) 29.
3. Kohn, K. W. and Spears, C. L. *J. Mol. Biol. 51* (1970) 551.
4. Kohn, K. W., Glaubiger, D. and Spears, C. L. *Biochim. Biophys. Acta 361* (1974) 288.
5. Glaubiger, D., Kohn, K. W. and Charney, E. *Biochim. Biophys. Acta 361* (1974) 303.
6. Zee-Cheng, K. Y. and Cheng, C. C. *J. Pharm. Sci. 59* (1970) 1630.
7. Cheng, C. C. *Pharmacological Basis of Cancer Chemotherapy, 27. Am. Symp. on Fundamental Cancer Res. 1974*, Williams & Wilkins, Baltimore 1975.
8. Doyle, P. A. and Turner, P. S. *Acta Crystallogr. A 24* (1968) 390.
9. Stewart, R. F., Davidson, E. R. and Simpson, W. T. *J. Chem. Phys. 42* (1965) 3175.
10. Germain, G., Main, P. and Woolfson, M. M. *Acta Crystallogr. A 27* (1971) 368.
11. Groth, P. *Acta Chem. Scand. 27* (1973) 1837.
12. Denne, W. A. and Small, W. H. *Acta Crystallogr. B 27* (1971) 1094.
13. Lodell, J. and Post, B. *Acta Crystallogr. 7* (1954) 559.
14. Adamson, R. H. *Pharmacology and the Future of Man. Proc. 5th Int. Congr. Pharmacol. San Francisco 1972*, Karger, Basel 1973, p. 402.
15. McPhail, A. T. and Sim, G. A. *J. Chem. Soc. B* (1968) 923.
16. Margulis, T. N. *J. Am. Chem. Soc. 96* (1974) 899.
17. Moncrief, J. W. and Lipscomb, W. N. *Acta Crystallogr. 31* (1966) 322.
18. Sayres, J., Schindler, D. and Sundaralingam, M. *J. Am. Chem. Soc. 99* (1977) 3848.

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