N^4-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine. An X-Ray Diffraction Study of Chloroquine Diphosphate Hydrate

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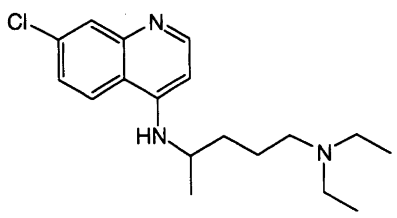
The crystal structure of N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine diphosphate hydrate has been determined at low temperature (150 K). The crystals are monoclinic, space group $P2_1/c$ with unit-cell dimensions: a = 9.719(3) Å, b = 16.813(4) Å, c = 15.659(2) Å and β = 105.16(2)°. Based on 3257 reflections with intensities larger than $3\sigma(I)$ the structure was refined to a conventional R-factor of 0.045 to give e.s.d.s in bond lengths and angles of 0.005 Å and 0.3°, respectively.

Two water molecules appear to be only partially present in their respective positions. Pairs of chloroquine molecules in relaxed conformations are connected through stacking interactions between quinoline moieties and phosphate-linked hydrogen bonds. It has been shown by X-ray powder diffraction methods, and thermal analysis combined with mass spectrometry, that chloroquine diphosphate hydrate loses water on being heated and recrystallizes in a modification characterized by a different unit cell and melting point.

Chloroquine, N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine, is used as an antimalarial agent. The mechanism of action may possibly rest on its ability to form a complex with nucleic acids[1,2] or through inhibition of incorporation of orthophosphates into nucleic acids of *Plasmodia*.[3] It has been suggested that the 1,4-diaminopentane side-chain in chloroquine interacts with the acidic phosphate groups of the nucleic acids.[4] The crystal structure of chloroquine phosphate monohydrate was reported in 1970[5] to be refined to an R-factor of 0.081. However, no coordinates were given and no later report of a detailed structure has been found in the literature. Furthermore, it appears that chloroquine phosphate may exist in two modifications of different melting point[6] (188 and 207 °C, respectively). Different batches of the compound will vary in the content of the different crystal modifications and this variation may cause problems when chloroquine phosphate is formulated into a pharmaceutical product. Variation in the content of different modifications may cause alterations in the dissolution rate of chloroquine phosphate as well as changes in the stability of the product.



On being heated in a closed ampoule to about 450 K, with one end of the ampoule being kept close to room temperature, as well as being heated in a stream of dry nitrogen to about 420 K, the substance appears to lose water and form a new modification. As a part of the study of the variables responsible for the transformation of chloroquine phosphate from one modification into the other, we have studied the compound by X-ray diffraction methods at low temperature, as well as by thermal analysis and mass spectrometry. However, whereas the phase with the lower melting point gives crystals suitable for X-ray analysis from an aqueous solution, good crystals of the second phase were more difficult to obtain and this modification was therefore investigated by X-ray powder diffraction methods.

Experimental

Colourless, needle-shaped crystals of the title compound were formed from an aqueous solution when acetone was added by diffusion at 20 °C. The crystals appeared to be stable and the melting point was found, by slow increments in the temperature, to be close to 450 K. The measured density of the compound was 1.40 g cm^{-3} and it was calculated to be 1.418 cm^{-3}. The relevant data for the single-crystal X-ray experiment are given in Table 1. Three test reflections were measured at regular intervals of 135 reflections during the intensity data collection. No loss of intensity was found during the experiment except for one single set of test reflections which indicated a significant dip

Table 1. Crystal and experimental data.

Compound	$C_{18}H_{26}ClN_3(PO_4)_2 \cdot (H_2O)$
Melting point/K	472
Diffractometer	SYNTEX P-1
Crystal size/mm	0.5×0.3×0.3
Radiation	Graphite cryst. monochromated Mo K_α (λ = 0.71069 Å)
Crystal system	Monoclinic
a/Å	9.719(3)
b/Å	16.813(4)
c/Å	15.659(2)
β/°	105.16(2)
V/Å^3	2469.8
T/K	150
Space group	$P2_1/c$ (No. 14)
M/D	527.57
Z	4
F(000)	1104
D_x/g cm^{-3}	1.418
μ (Mo K_β)/cm^{-1}	1.0
Scan mode	$\theta/2\theta$
Scan speed (2θ)/min^{-1}	4.0
Scan range (2θ)/°	$2\theta\alpha_1$ −0.8 to $2\theta\alpha_2$ +1.0
Maximum(sinθ/λ)/Å^{-1}	0.59
No. of independent measurements	4562
No. with $I > 3\sigma I$)	3254
Method of structure solution	Direct (MITHRIL)
No. of parameters refined	471
$R=\Sigma\|F_o-F_c\|/\Sigma F_o$	0.044
$R_w=[\Sigma w(F_o-F_c)^2/\Sigma wF_o^2]^{1/2}$	0.045
$S=[\Sigma w(F_o-F_c)^2/(n-m)]^{1/2}$	2.19

w is the inverse of the variance of the observed structure factors.

in the intensities. Inspection of the intensity measurements close to this led to the rejection of three reflections [(7,14,−7)(7,14,−8)(7,14,−9)]. Corrections were made for Lorentz and polarization effects. Unit-cell dimensions were determined from diffractometer setting angles for 25 reflections. Standard deviations in the measured intensities were calculated as $\sigma(I) = [C_T + (0.02C_N)^2]^{1/2}$ where C_T is the total number of counts and C_N is the scan count minus the background count. The coordinates of all non-hydrogen atoms were determined by direct methods.[7] Refinements were performed by least-squares calculations using 3254 reflections. The calculation included refinements of the occupancy factors for the oxygen atoms at the position of the two disordered water molecules. The final least-squares calculation were performed with fixed population factors of 0.64 and 0.55 for O1 and O2, respectively, anisotropic temperature factors for all non-hydrogen atoms and with isotropic temperature factors for the hydrogen atoms. The hydrogen atoms of the two water molecules could not be located. Computer programs used are described in Refs. 8 and 9. The positional parameters are given in Table 2 and the list of thermal parameters and of structure factors may be obtained from the authors (A.M.).

Powder X-ray photographs of several batches of commercial chloroquine diphosphate were taken using a Guinier camera, (radiation: Cu $K_{\alpha 1}$ and Cr $K_{\alpha 1}$). All pho-

Table 2. Fractional coordinates of chloroquine diphosphate hydrate. Estimated standard deviations in parentheses.

Atom	*x*	*y*	*z*	U_{eq}/Å^2 [a]
Cl1	0.35891(9)	0.08041(5)	0.21662(5)	0.027
P1	0.98273(9)	0.13795(5)	0.22419(6)	0.021
P2	1.05010(10)	−0.10989(5)	0.25505(6)	0.024
O11	0.8604(2)	0.1793(1)	0.2501(2)	0.024
O12	1.0754(3)	0.2004(1)	0.1907(2)	0.031
O13	1.0808(2)	0.0993(1)	0.3098(2)	0.026
O14	0.9361(2)	0.0749(1)	0.1538(2)	0.026
O21	1.0409(2)	−0.0683(1)	0.1637(1)	0.024
O22	1.1815(2)	−0.1671(1)	0.2673(2)	0.026
O23	0.9157(2)	−0.1580(1)	0.2480(2)	0.034
O24	1.0838(3)	−0.0490(1)	0.3281(2)	0.038
O1	0.3834(5)	0.0189(3)	0.4208(3)	0.068
O2	0.3311(6)	0.1850(4)	0.4035(4)	0.077
N1	0.7013(3)	0.0980(2)	0.0221(2)	0.019
N2	0.3848(3)	0.1184(2)	−0.2117(2)	0.021
N3	0.1556(3)	−0.1317(2)	−0.4151(2)	0.022
C1	0.7331(3)	0.1014(2)	−0.0554(2)	0.021
C2	0.6322(3)	0.1107(2)	−0.1335(2)	0.020
C3	0.4863(3)	0.1140(2)	−0.1352(2)	0.018
C4	0.4506(3)	0.1089(2)	−0.0512(2)	0.018
C5	0.3087(3)	0.1087(2)	−0.0420(2)	0.020
C6	0.2814(3)	0.1006(2)	0.0388(2)	0.021
C7	0.3950(4)	0.0928(2)	0.1148(2)	0.022
C8	0.5347(3)	0.0943(2)	0.1099(2)	0.020
C9	0.5622(3)	0.1007(2)	0.0273(2)	0.018
C10	0.4141(3)	0.1246(2)	−0.2990(2)	0.023
C11	0.4308(4)	0.2112(2)	−0.3227(2)	0.029
C12	0.2958(4)	0.0827(2)	−0.3677(2)	0.024
C13	0.2895(4)	−0.0062(2)	−0.3533(2)	0.025
C14	0.1728(4)	−0.0434(2)	−0.4249(2)	0.022
C15	0.0212(4)	−0.1577(2)	−0.4824(2)	0.026
C16	−0.0161(4)	−0.2438(2)	−0.4741(3)	0.037
C17	0.2853(4)	−0.1799(2)	−0.4156(2)	0.029
C18	0.3231(5)	−0.1806(3)	−0.5029(3)	0.058
H1	0.828(3)	0.099(2)	−0.055(2)	0.015(8)
H2	0.661(3)	0.114(2)	−0.183(2)	0.026(8)
H5	0.233(3)	0.117(2)	−0.092(2)	0.033(9)
H6	0.187(3)	0.102(2)	0.046(2)	0.018(8)
H8	0.607(3)	0.087(2)	0.165(2)	0.020(8)
H11	0.772(3)	0.089(2)	0.071(2)	0.035(9)
H21	0.302(3)	0.125(2)	−0.213(2)	0.04(1)
H31	0.144(3)	−0.140(2)	−0.456(2)	0.030(9)
H101	0.500(3)	0.093(2)	−0.297(2)	0.019(8)
H111	0.506(3)	0.237(2)	−0.281(2)	0.030(9)
H112	0.338(3)	0.243(2)	−0.330(2)	0.031(9)
H113	0.446(3)	0.216(2)	−0.384(2)	0.04(1)
H121	0.309(3)	0.093(2)	−0.429(2)	0.017(8)
H122	0.208(3)	0.106(2)	−0.367(2)	0.026(9)
H131	0.268(3)	−0.019(2)	−0.298(2)	0.018(8)
H132	0.382(3)	−0.030(2)	−0.354(2)	0.026(9)
H141	0.183(3)	−0.037(2)	−0.483(2)	0.018(8)
H142	0.080(3)	−0.022(2)	−0.428(2)	0.033(9)
H151	0.034(3)	−0.145(2)	−0.536(2)	0.04(1)
H152	−0.054(4)	−0.122(2)	−0.471(2)	0.04(1)
H161	−0.018(4)	−0.257(2)	−0.412(2)	0.05(1)
H162	−0.105(4)	−0.256(2)	−0.514(2)	0.05(1)
H163	0.048(4)	−0.277(2)	−0.495(2)	0.04(1)
H171	0.362(3)	−0.156(2)	−0.370(2)	0.014(8)
H172	0.267(3)	−0.235(2)	−0.399(2)	0.024(9)
H181	0.346(4)	−0.128(2)	−0.519(2)	0.04(1)
H182	0.410(4)	−0.214(2)	−0.497(2)	0.06(1)
H183	0.247(5)	−0.207(3)	−0.555(3)	0.10(2)
HO12	1.081(5)	0.246(3)	0.212(3)	0.10(2)
HO13	1.085(5)	0.049(3)	0.307(3)	0.09(1)
HO21	1.013(4)	−0.027(2)	0.166(2)	0.04(1)
HO22	1.166(4)	−0.213(2)	0.264(2)	0.05(1)
H881	0.370(9)	0.024(5)	0.413(6)	0.09(3)
H991	0.25(3)	0.16(2)	0.40(2)	0.4(1)

[a] $U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

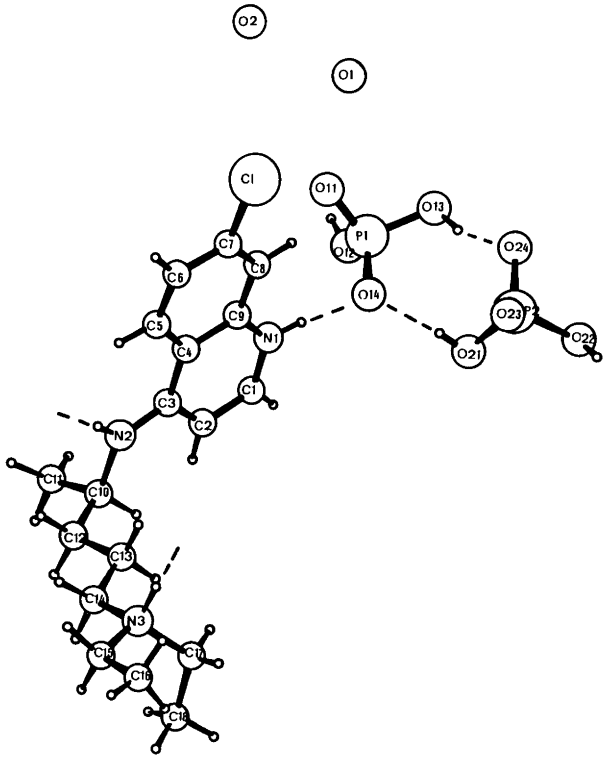


Fig. 1. PLUTO plot of the chloroquine diphosphate hydrate structure.

tographs were identical, and the *d*-values as well as the intensities agree with values calculated[10] on the basis of the present structure determination of the hydrate and with the *d*-values listed in the literature.[4] The conversion of one modification into another was studied by means of thermal analysis at heating rates varying between 0.3 and 10 K min^{-1} and by mass spectrometry. Use of a Redcroft ST 758 DSC/MS instrument with heating (3 K min^{-1}) in a dry nitrogen stream at 0.1 MPa confirmed that only water is expelled and thermogravimetric analysis using a METTLER 300 DSC system indicated that the amount of water expelled is about 1 mol of water per mole of chloroquine phosphate hydrate. The water-free form is characterized by a melting point of 480 K (on rapid heating higher temperatures are observed) and an X-ray powder photograph as listed in Table 6 and appears to be distinctively different from that of the hydrate.

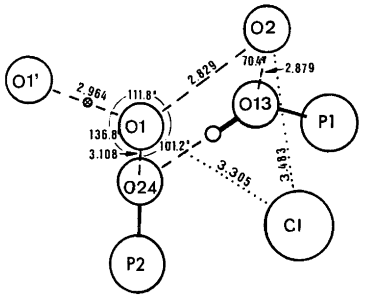


Fig. 2. Hydrogen bonding of the disordered water molecules.

Table 3. Bond lengths (Å) and angles (°) in chloroquine diphosphate hydrate.

Cl1–C7	1.732(4)	P1–O11	1.521(3)
P1–O12	1.561(3)	P1–O13	1.569(3)
P1–O14	1.511(3)	P2–O21	1.574(3)
P2–O22	1.570(3)	P2–O23	1.516(3)
P2–O24	1.506(3)		
N1–C1	1.331(5)	N1–C9	1.377(4)
N2–C3	1.340(5)	N2–C10	1.471(5)
N3–C14	1.506(5)	N3–C15	1.512(5)
N3–C17	1.502(5)	C1–C2	1.361(5)
C2–C3	1.412(5)	C3–C4	1.447(5)
C4–C5	1.423(5)	C4–C9	1.417(5)
C5–C6	1.367(5)	C6–C7	1.402(5)
C7–C8	1.380(5)	C8–C9	1.391(5)
C10–C11	1.523(5)	C10–C12	1.526(5)
C12–C13	1.515(5)	C13–C14	1.507(5)
C15–C16	1.506(6)	C17–C18	1.506(6)
O11–P1–O12	110.0(2)	O11–P1–O13	107.7(2)
O11–P1–O14	114.2(2)	O12–P1–O13	106.9(2)
O12–P1–O14	108.4(2)	O13–P1–O14	109.4(2)
O21–P2–O22	103.5(2)	O21–P2–O23	109.1(2)
O21–P2–O24	109.7(2)	O22–P2–O23	109.9(2)
O22–P2–O24	108.4(2)	O23–P2–O24	115.5(2)
C1–N1–C9	121.2(3)	C3–N2–C10	123.9(3)
C14–N3–C15	108.2(3)	C14–N3–C17	114.6(3)
C15–N3–C17	114.4(3)	N1–C1–C2	122.6(3)
C1–C2–C3	120.4(3)	N2–C3–C2	121.3(3)
N2–C3–C4	121.3(3)	C2–C3–C4	117.3(3)
C3–C4–C5	124.1(3)	C3–C4–C9	118.9(3)
C5–C4–C9	117.0(3)	C4–C5–C6	121.5(3)
C5–C6–C7	119.7(3)	Cl1–C7–C6	119.3(3)
Cl1–C7–C8	119.5(3)	C6–C7–C8	121.2(3)
C7–C8–C9	119.0(3)	N1–C9–C4	119.5(3)
N1–C9–C8	118.9(3)	C4–C9–C8	121.6(3)
N2–C10–C11	110.7(3)	N2–C10–C12	109.2(3)
C11–C10–C12	112.2(3)	C10–C12–C13	113.7(3)
C12–C13–C14	110.5(3)	N3–C14–C13	114.6(3)
N3–C15–C16	113.7(3)	N3–C17–C18	114.4(4)

Description and discussion

The molecular structure is depicted in Fig. 1 where the numbering of the atoms is also indicated. Bond lengths and angles are given in Table 3. The compound appears to exist as a hydrate in the crystal, the water molecules partly populating two positions. The geometry around the partly occupied water sites does not allow for more than one hydrogen bond from each water molecule and thus the loosely bonded water molecules may easily escape from the structure. This may explain why the water positions are only partly populated and is in agreement with the results of the mass spectrometric masurements which indicate only one water molecule per molecule of chloroquine diphosphate.

The geometry of this part of the structure is given in Fig. 2. The water-free modification of chloroquine diphosphate is stable in a dry atmosphere, but takes up water in humid air at room temperature, again forming a hydrate. During heating of the hydrate, melting occurs in the same temperature region as the dehydration. Slow heating allows for

Table 4. The geometry of the hydrogen bonds in chloroquine diphosphate hydrate. E.s.d.s in A····D distances: 0.003 Å and in distances involving H, 0.04 Å.

A	D	A····D	A····H	D–H	D–H····A	H····A–P
O11	O22 (2−*x*,1/2+*y*,1/2−*z*)	2.616	1.83	0.79	174.8	120.9
O11	N3 (1−*x*,−*y*,−*z*)	2.748	1.79	0.97	165.4	106.4
O23	O12 (2−*x*,*y*−1/2,1/2−*z*)	2.560	1.72	0.84	176.9	122.6
O24	O13 (*x*,*y*,*z*)	2.510	1.69	0.84	164.1	121.9
O23	N2 (1−*x*,−*y*,−*z*)	2.903	2.12	0.81	164.7	131.5
O14	O21 (*x*,*y*,*z*)	2.603	1.86	0.75	171.6	122.5
O14	N1 (*x*,*y*,*z*)	2.673	1.79	0.93	168.3	118.6

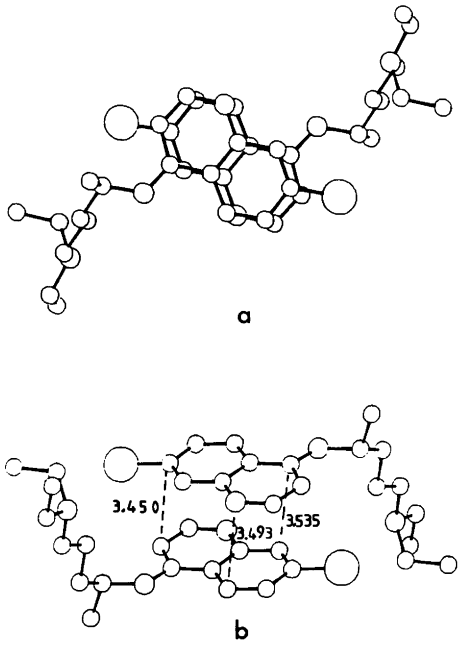


Fig. 3. Stacking of the aromatic ring system.

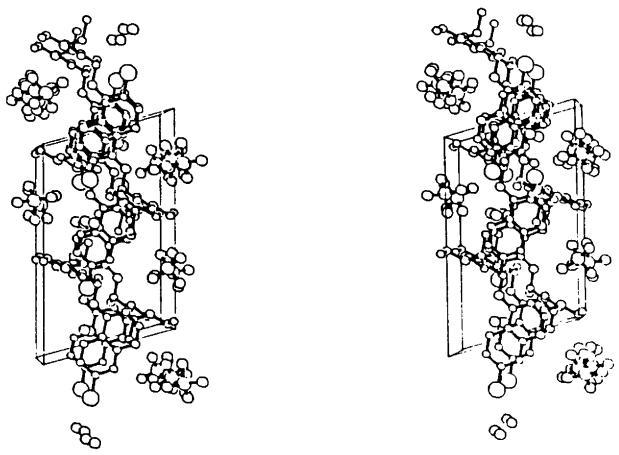


Fig. 4. PLUTO stereo plot of the structure.

Table 5. Some torsion angles in chloroquine phosphate.

C5–C4–C3–N2	−0.5(3)
C9–C4–C3–N2	177.2(5)
C13–C12–C10–N2	−65.0(3)
C2–C3–N2–C10	−3.4(3)
C4–C3–N2–C10	179.3(5)
C11–C10–N2–C3	−88.1(4)
C12–C12–N2–C3	147.9(4)
C13–C14–N3–C15	171.1(4)
C16–C15–N3–C14	−174.7(4)
C13–C14–N3–C17	−60.0(3)
C18–C17–N3–C14	−67.4(4)
C16–C15–N3–C17	56.3(4)
C18–C17–N3–C15	58.4(4)
C11–C10–C12–C13	171.9(4)
C10–C12–C13–C14	−178.5(4)
C12–C13–C14–N3	−178.5(4)

more-or-less complete transformation into the water-free modification before much of the hydrate melts and the presence of the dehydrated form is then confirmed by the endothermic peak at the melting point for this modification. Rapid heating, however, prevents the dehydration and recrystallization; the hydrate melts and the peak corresponding to the second melting point is diminished. As the removal of water from larger crystals is more time consuming, thorough crushing of the samples before heating enhances dehydration. This was confirmed by experiments. The varying speed of water elimination under different conditions and from samples of different crystal sizes is suggested to be the reason for the different behaviour of different samples of chloroquine diphosphate hydrate when it is formed into tablets. However, phosphate groups exist as univalent diprotonated anions; the hydrogen atoms take part in hydrogen-bonded chains of phosphate groups along the screw axes (0, *y*, 1/4 and 0, *y*, 3/4). In this way the phosphate chains form a paling between the layers of organic molecules as indicated in Fig. 4.

The two amino groups (N1 and N3) of the organic cation are protonated. The hydrogen atoms are involved in hydrogen bonds to phosphate groups as described in Table 4. Pairs of organic moieties are coupled by stacking interactions between the aromatic ring systems as depicted in Fig. 3 and by phosphate groups through hydrogen bonds. Connections between the paired organic moieties appear to exist only through the phosphate chains.

Table 6. X-Ray powder diffraction data of chloroquine diphosphate (dehydrated).

d	I/I_1	d	I/I_1
11.48	31	4.559	28
8.66	71	4.354	28
7.77	73	4.305	100
7.20	14	4.104	42
7.016	16	3.913	35
5.195	27	3.789	8
4.906	18	3.773	42
4.758	14	3.498	48
4.687	11	3.108	22

The chloroquine molecule exists in a relaxed conformation in the crystal. Each of the six-membered rings are planar within the accuracy of the structure determination, but these two planes form an angle of 2.5°. The chain C10–C12–C13–C14–N3 is almost planar, the deviations being less than 0.015 Å and the out-of-plane distance to C15 and C16 are 0.210 Å and 0.380 Å, respectively. The plane forms an angle of 100° with the plane of the quinoline ring system, and it is interesting to note that this angle is close to that found between the aromatic part and the sugar moiety in a nucleotide. The torsion angle about the C3–N2 bond is such as to bring the C10 atom close to the plane of the aromatic part of the molecules as expected for an sp^2 hybridized N2 atom. Furthermore, the torsion angle about the N2–C10 bond is such that the aromatic part is in the most relaxed position relative to the side chain. The relevant conformational angles are given in Table 5. The geometry of the hydrogen bonding is given in Table 4. The hydrogen bonds are indicated in Fig. 5, which shows a stereo view of the molecular packing as seen along the z-axis.

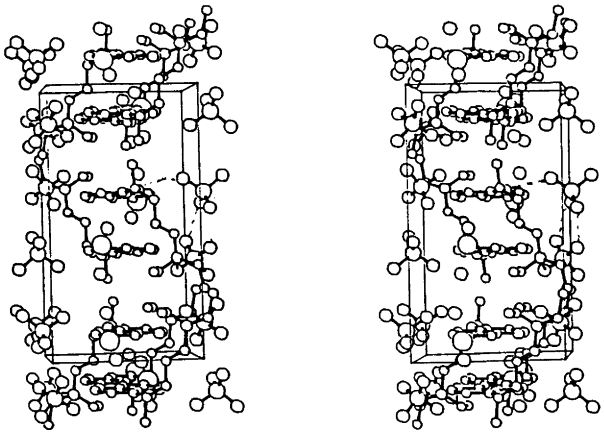


Fig. 5. Stereo plot of the structure along *c*.

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