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CRYSTAL STRUCTURE ANALYSIS OF THE DESOLVATION OF THE CHLOROFORM SOLVATE OF GRISEOFULVIN

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SUMMARY

The crystal structures of the chloroform solvate and a non-solvated form of griseofulvin were determined by X-ray diffraction methods. There are substantial differences in the packing arrangements of the two forms. The chloroform molecules in the solvate are arranged in layers perpendicular to the *c*-axis. This dictates the direction which the solvent can exit from the crystal.

INTRODUCTION

Griseofulvin has been reported to form a chloroform solvate which upon heating converts to micronized anhydrous material (Sekiguchi et al., 1968). This suggests that a marked alteration in molecular packing of the materials takes place during the desolvation process. In order to gain insight into this process, X-ray diffraction studies were carried out on both the anhydrous form and chloroform solvate. With such information it is possible to map out the changes that take place on a molecular level and relate these to physical observations.

MATERIALS AND METHODS

Materials. Griseofulvin crystals which are non-solvated and solvated with chloroform were obtained by slowly evaporating ethylacetate and chloroform solutions of the compound, respectively. Griseofulvin U.S.P. (Ayerst Laboratories, Inc.) was used to prepare these solutions.

X-ray analysis. The pertinent crystallographic parameters for the two crystal forms determined from their X-ray diffraction patterns, along with their densities measured by means of flotation are listed in Table 1.

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TABLE 1

CRYSTALLOGRAPHIC PARAMETERS

Anhydrous form		Chloroform solvate
8.979 (4) Å	*a*	8.671 (2) Å
8.979 (4) Å	*b*	11.890 (2) Å
19.848 (7) Å	*c*	20.381 (4) Å
90°	$\alpha = \beta = \gamma$	90°
4	*z*	4($CHCl_3$: GRIS-1 : 1)
$P4_1$ (tetragonal)	Space group	$P\ 2_12_12_1$ (orthorhombic)
1.46 g/cm^3	D measured	1.45 g/cm^3
1.465 g/cm^3	D calc	1.493 g/cm^3
Octahedra, Needles	Habit	Tabular

TABLE 2

ATOMIC COORDINATES AND THEIR ESTIMATED STANDARD DEVIATIONS (IN PARENTHESES) × 10^4

Atom	Anhydrous form			Chloroform solvate		
	x/a	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
Cℓ	68 (3)	179 (2)	2532 (–)	−754 (2)	4118 (2)	−4335 (1)
O1	−1724 (5)	−2204 (4)	3188 (2)	−3389 (6)	5726 (4)	−4135 (2)
C2	−2328 (7)	−3530 (7)	3505 (3)	−4807 (8)	6345 (7)	−4029 (4)
O2	−78 (5)	−6256 (5)	1934 (2)	−7345 (6)	3120 (4)	−3991 (3)
C3	−1846 (7)	−4838 (7)	3048 (3)	−6110 (10)	5470 (7)	−4006 (4)
O3	−2551 (5)	−6125 (5)	3133 (3)	−7459 (6)	5683 (5)	−3940 (3)
C4	23 (7)	−4777 (7)	2036 (3)	−5835 (10)	3271 (7)	−4065 (3)
O4	1839 (5)	−1304 (5)	1493 (3)	2067 (7)	1908 (5)	−4290 (3)
C5	928 (7)	−3820 (8)	1672 (3)	−4744 (11)	2411 (7)	−4141 (4)
O5	−4598 (8)	−6009 (8)	4876 (4)	−6113 (13)	9682 (6)	−3831 (6)
C6	958 (7)	−2310 (7)	1814 (3)	−3225 (10)	2684 (7)	−4222 (4)
O6	−4586 (6)	−2554 (6)	3096 (3)	−4813 (8)	6574 (5)	−5164 (3)
C7	40 (8)	−1692 (7)	2316 (3)	−2654 (10)	3801 (7)	−4233 (4)
C8	−831 (7)	2653 (7)	2675 (3)	−3754 (10)	4605 (7)	−4151 (3)
C9	−880 (7)	4197 (7)	2554 (3)	−5313 (9)	4393 (7)	−4067 (4)
C10	74 (10)	−3641 (9)	4208 (4)	−4561 (14)	6229 (11)	−2786 (5)
C11	−6201 (10)	−2359 (9)	3104 (6)	−5042 (14)	7152 (11)	−5779 (5)
C12	803 (9)	−6877 (8)	1393 (4)	−7929 (11)	1984 (8)	−3954 (5)
C13	2767 (9)	−1867 (9)	960 (4)	−2518 (12)	727 (7)	−4344 (5)
C2′	−4007 (8)	−3391 (7)	3571 (4)	−5051 (10)	7117 (8)	−4608 (5)
C3′	−4718 (8)	−4198 (8)	4034 (4)	−5523 (12)	8181 (8)	−4547 (5)
C4′	−3945 (10)	−5112 (9)	4526 (4)	−5825 (13)	8663 (8)	−3903 (5)
C5′	−2296 (9)	4936 (9)	4597 (4)	−5807 (12)	7914 (8)	−3320 (5)
C6′	−1618 (8)	−3586 (8)	4222 (3)	−4597 (10)	6993 (8)	−3378 (4)
C				658 (14)	4747 (9)	−2744 (5)
Cℓ2				−1083 (4)	4058 (4)	−2580 (2)
Cℓ3				575 (6)	6137 (3)	2502 (2)
Cℓ4				2167 (4)	4030 (4)	2370 (2)

TABLE 3

COORDINATES OF HYDROGEN ATOMS AND THEIR ESTIMATED STANDARD DEVIATIONS (IN PARENTHESES) × 10^3

Atom	Anhydrous form			Chloroform solvate		
	x/a	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
H (C5)	145 (8)	−410 (9)	137 (4)	−511 (8)	164 (6)	−403 (3)
H (C3′)	−586 (10)	−405 (10)	408 (5)	−573 (12)	853 (8)	−502 (4)
H1 (C5′)	−223 (7)	−441 (7)	517 (4)	−565 (7)	831 (5)	−283 (3)
H2 (C5′)	−186 (8)	−553 (8)	457 (4)	−700 (7)	747 (5)	−331 (3)
H (C6′)	−174 (10)	−272 (10)	448 (6)	−364 (8)	724 (6)	−336 (3)
H1 (C10)	−44 (7)	−471 (7)	399 (3)	−406 (10)	540 (7)	−289 (4)
H2 (C10)	63 (7)	−276 (7)	395 (3)	−448 (11)	653 (9)	−230 (5)
H3 (C10)	392 (8)	−359 (9)	471 (4)	−540 (9)	591 (7)	−271 (4)
H1 (C11)	−651 (7)	−168 (7)	366 (3)	−587 (9)	733 (7)	−579 (4)
H2 (C11)	−683 (9)	−334 (9)	295 (4)	−466 (11)	802 (8)	−558 (4)
H3 (C11)	−667 (8)	−194 (8)	272 (4)	−486 (6)	646 (5)	−611 (3)
H1 (C12)	61 (6)	−799 (6)	138 (3)	−898 (8)	198 (6)	−398 (3)
H2 (C12)	209 (13)	−656 (13)	141 (7)	−740 (8)	136 (5)	−368 (3)
H3 (C12)	61 (9)	−640 (8)	99 (4)	−778 (8)	183 (6)	−429 (3)
H1 (C13)	336 (9)	−257 (9)	131 (5)	−301 (11)	33 (8)	−458 (5)
H2 (C13)	206 (7)	−229 (7)	56 (3)	−150 (7)	37 (5)	−445 (3)
H3 (C13)	324 (12)	−122 (12)	81 (6)	−305 (14)	54 (9)	−381 (6)

X-ray intensity data for both forms were collected by the stationary counterstationary crystal technique using Ni filtered Cu K_2 radiation with balanced filters. The ranges of data collection were from 0 to 120° in *two theta* for the non-solvated form and from 0 to 110° for the chloroform solvate. This resulted in the measurement of 1404 and 1550 unique reflections for the non-solvated and solvated forms, respectively. The measured intensities were corrected for α_1—α_2 splitting, absorption and Lorentz-polarization effects. Of those reflections measured, 1183 for the non-solvated form and 1389 for the solvate had intensities significantly greater than their backgrounds.

The structures of the two materials were solved by direct methods using the program MULTAN (Germain et al., 1971). The structures were refined by least squares using a block diagonal approximation to the normal equations and difference electron density maps. The refined structures have R values (usual crystallographic reliability index) of 0.049 and 0.068 for the non-solvated and solvated forms, respectively. The positional parameters derived are listed in Table 2 and 3. A listing of the thermal parameters and structure factors can be obtained from the authors.

During the final stages of refinement, the absolute configuration of the molecule was determined by making use of anomalous scattering of chlorine. The stereochemistry observed in both crystals was in agreement with that established by chemical means (MacMillan, 1959).

Microscopic examination. Crystals of the chloroform solvate were examined microscopically before and during desolvation. Selected crystals were heated in an oven at 82—87°C for varied periods of time and photographed.

RESULTS AND DISCUSSION

A comparison of the overall features of the molecular structures of griseofulvin obtained for each crystals form is illustrated in Fig. 1. In general, the molecule was not

TABLE 4

BOND ANGLES [a]

Atom–Atom–Atom			Angle (°)	
			Anhydrous	Chloroform
C2	O1	C8	107.6	107.6
O1	C2	C3	105.3	106.5
O1	C2	C6′	105.6	106.3
O1	C2	C2′	109.9	108.2
C2′	C2	C3	113.0	109.4
C3	C2	C6′	113.3	113.4
C2′	C2	C6′	109.3	112.7
C2	C3	O3	123.6	125.1
C2	C3	C9	105.4	104.1
C9	C3	O3	131.0	130.8
C5	C4	C9	119.2	118.3
O2	C4	C9	115.9	116.3
C5	C4	O2	124.9	125.4
C4	O2	C12	117.1	118.5
C4	C5	C6	120.9	119.4
C5	C6	C7	121.2	124.1
C5	C6	O4	124.5	124.0
C7	C6	O4	114.3	111.9
C6	O4	C13	116.6	117.2
C6	C7	Cl	123.3	123.2
C6	C7	C8	117.2	114.3
C8	C7	Cl	119.4	122.5
C7	C8	O1	122.8	121.6
C7	C8	C9	123.5	124.8
C9	C8	O1	113.7	113.6
C8	C9	C3	107.4	108.2
C8	C9	C4	118.0	119.1
C2	C6′	C5′	107.7	110.1
C2	C6′	C10	113.1	112.9
C5′	C6′	C10	112.1	112.6
C6′	C5′	C4′	115.2	112.1
C5′	C4′	O5	119.6	119.4
C5′	C4′	C3′	118.5	118.9
C3′	C4′	O5	121.9	121.7
C4′	C3′	C2′	122.9	120.8
C3′	C2′	C2	119.3	123.1
C3′	C2′	O6	128.1	126.3
C2	C2′	O6	112.2	110.6
C2′	O6	C11′	117.0	119.4

[a] Average e.s.d. in bond angles is 0.5°.

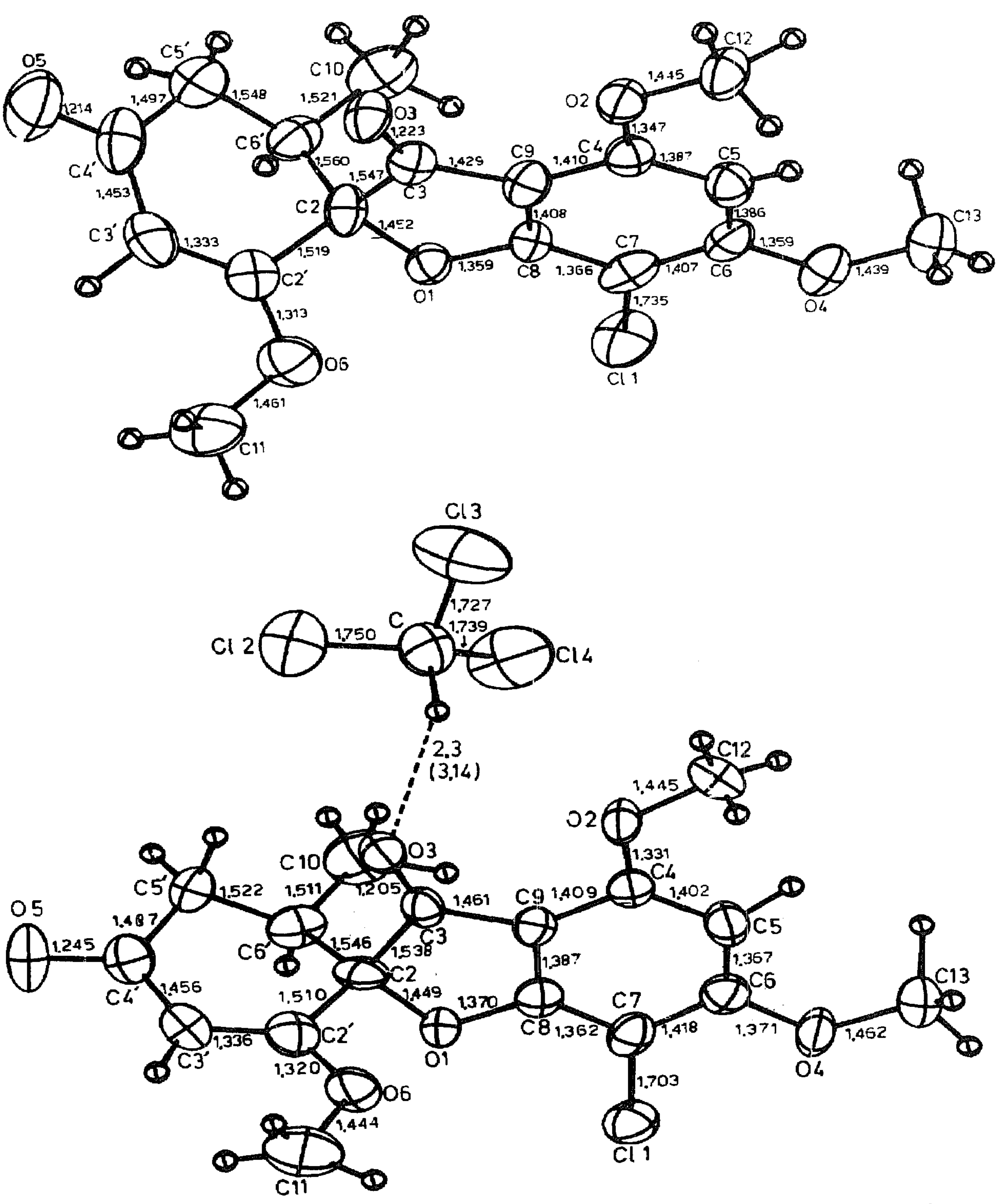

Fig. 1. A general view of the griseofulvin molecule found in the chloroform solvate (top) and the non-solvated crystals (bottom). Bond lengths are noted, their e.s.d. are of the order of ±0.01 Å.

TABLE 5

SOME PERTINENT TORSION ANGLES

Atom–Atom–Atom–Atom				Torsion angle (°)	
				Anhydrous	Chloroform
O1	C8	C9	C3	−2.5	1.7
C8	O1	C2	C6′	112.5	119.3
O1	C2	C6′	C5′	176.8	163.9
C2	C6′	C5′	C4′	−44.2	−53.3
C6′	C5′	C4′	C3′	10.3	35.6
C5′	C4′	C3′	C2′	11.2	−8.2
C4′	C3′	C2′	C2	5.9	0.3
C3′	C2′	C2	C6′	−41.9	−20.1
C2′	C2	C6′	C5′	58.6	45.6
C2	C2′	O6	C11′	179.1	177.8
C5	C4	O2	C12	−1.4	3.0
C5	C6	O4	C13	1.7	6.3

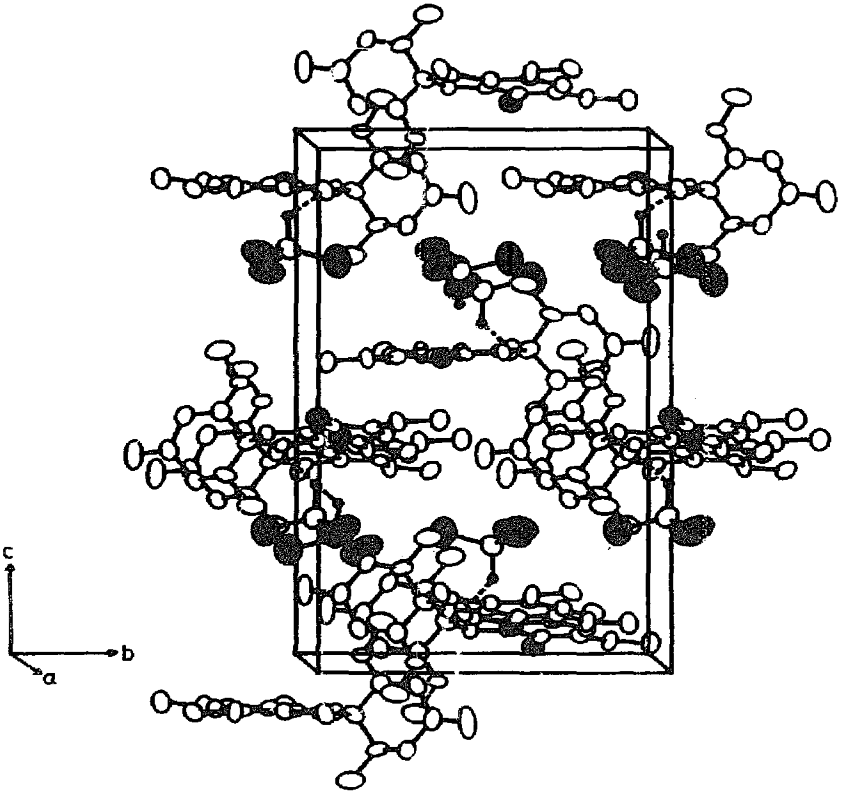

Fig. 2. Packing diagram for chloroform solvate. Chlorine atoms are shaded.

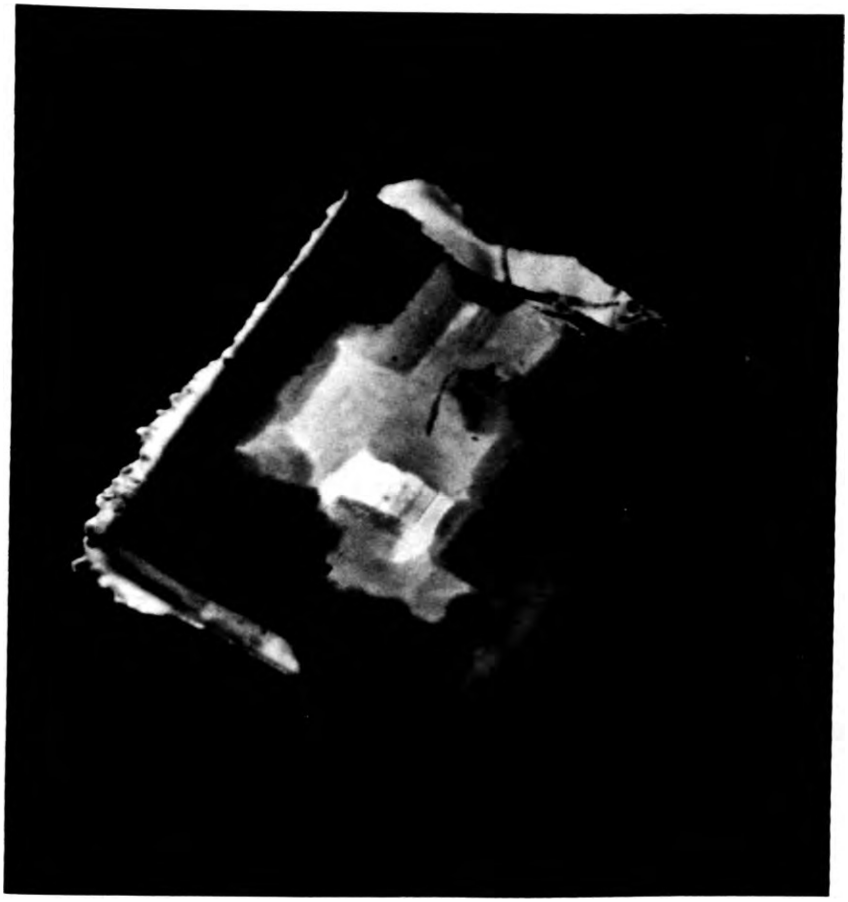

Fig.3. A crystal of the chloroform solvate after partial desolvation. The (001) direction is perpendicular to the photomicrograph.

found to be substantially altered in the two crystal environments. The bond lengths and angles (listed in Table 4) are not significantly different from each other. These bonding parameters are also in general agreement with those reported for 5-bromogriseofulvin (Brown and Sim, 1963). Significant differences, however, exist in the conformation of the molecule in the two crystal environments (see Table 5). These differences are greatest in certain regions of the molecules where the energy barriers to rotation about a bond are relatively soft. There is little doubt that the observed differences in torsion angles are a result of the molecule being in markedly different crystal environments. It should be pointed out that though these differences are significant, the overall characteristics of the molecule in the two structures are not dramatically different.

The chloroform molecules in the solvate crystals are involved in hydrogen bonding. The chloroform hydrogen interacts weakly with the carbonyl function at C_3. The H to O distance is only slightly smaller than the sum of the van der Waals radii of the two atoms. The weak attachment of the chloroform to the griseofulvin is also reflected in the signifi-

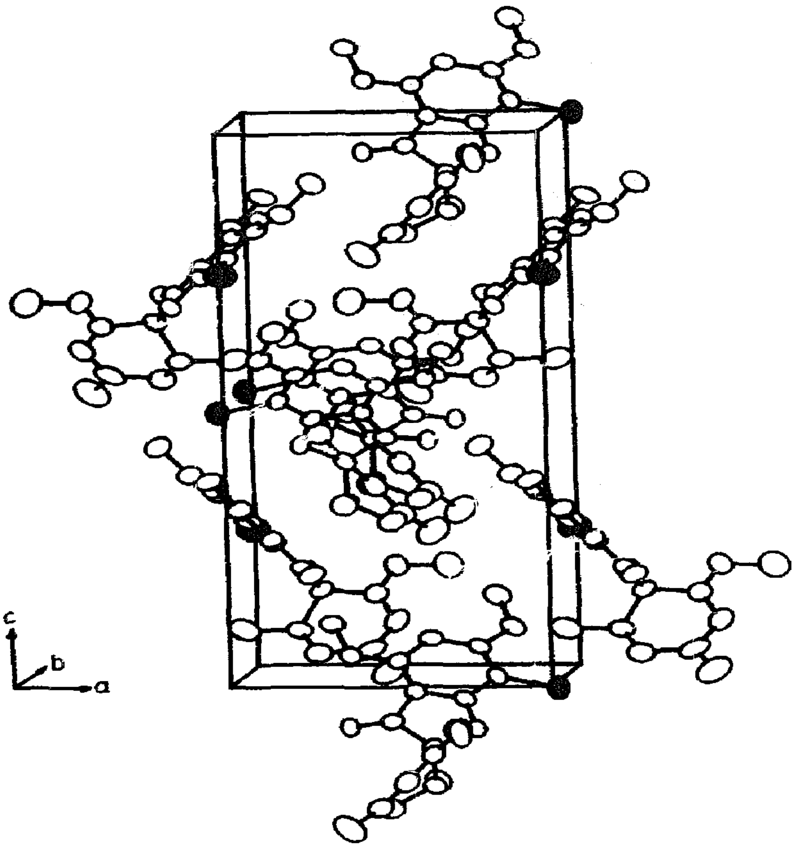

Fig. 4. Packing diagram for non-solvated crystals.

cantly higher thermal motion for the solvent atoms.

The chloroform molecules lie in layers perpendicular to the *c*-axis of the crystal (see Fig. 2). It is, therefore, reasonable to expect that during the desolvation process the chloroform molecules should exit from those crystal faces which are not perpendicular to the *c*-axis, i.e. the direction of loss will be in the *a*–*b* plane. Fig. 3 is a photomicrograph taken of a crystal during the desolvation process. The opaqueness, which is a sign of desolvated material, progresses in a planar manner from the crystal surfaces towards the center of the crystal. In all cases observed the plane of desolvation was perpendicular to the *c*-axis. The rate at which desolvation proceeded was observed to differ at different levels in the crystal. This is clearly evident in the photomicrograph of a single crystal which has undergone partial desolvation. The upper surface of the crystal in this figure is the (001) face.

The desolvation process converts a single crystal of solvate to a composite of small anhydrous crystals, as reported by Sekiguchi et al. (1968). The packing arrangement of the molecules in the non-solvated crystal is illustrated in Fig. 4. This arrangement is markedly different from that found in the solvate. The griseofulvin molecules lie along a 4-fold screw axis in this form, i.e. they form a helical pattern. The desolvation process requires substantial reorganization of the packing, to the extent that many regions will nucleate separately and form small crystals of the anhydrous form.

During the course of this investigation it was observed that griseofulvin sublimed near its melting point. The habit of the sublimed material is acicular, whereas the non-solvated crystals obtained by solvent recrystallization are distorted octahedra. The 4-fold screw axis (*c*-axis) lies along the needle axis, which means that the growth from the vapor is principally a helical layering of the molecules. Recrystallization from solution permits a much greater degree of lateral growth of the helical packing of the molecules.

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