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Solvate Formation of Griseofulvin with Alkyl Halide and Alkyl Dihalides[1)]

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Six solvates of griseofulvin with alkyl halide and alkyl dihalides were isolated, and their crystallographic as well as physico-chemical properties were investigated by infrared spectroscopy, powder X-ray diffractometry, X-ray crystallographic analysis, thermogravimetry (TG) and differential scanning calorimetry (DSC). From the weight loss in TG curves, the combining ratios between the drug and the solvent were determined to be 1 : 1 except for that of griseofulvin 1-bromo-2-chloroethane solvate (drug : solvent = 1 : 0.8). The cell dimensions of griseofulvin bromoethane solvate and griseofulvin dibromomethane solvate were almost equal, and the solvates formed a new type of mixed crystal (substitutional solid solution).

From X-ray crystallographic analysis, it was elucidated that the molecular arrangement in the dichloroethane solvate crystal was the same as that in the chloroform solvate determined by Shefter *et al.*

Keywords——griseofulvin solvate; alkyl halide; alkyl dihalide; DSC curve; combining ratio; mixed crystal; X-ray analysis; cell dimension; crystal structure

In a series of studies on size reduction by way of solvate formation and subsequent desolvation, it was found that griseofulvin formed solvates with chloroform,[2,3)] benzene, or dioxane,[4)] cortisone acetate formed solvates with alcohols[5)] and sulfathiazole formed solvates with ketones.[6)] When the solvates are allowed to stand in air, they desolvate gradually and are ultimately converted to the original drugs in micronized form. In the case of sulfathiazole ketones solvates, the size of primary particles of the powder recovered after desolvation decreased as the molecular volume of the solvent component increased.

In this paper, therefore, six solvates of griseofulvin were isolated from corresponding solutions of alkyl halide and alkyl dihalides, and their physico-chemical properties were investigated prior to an examination of the effects of the solvent components on the size reduction.

Experimental

Materials——Griseofulvin was recrystallized from acetone. mp 220 °C. Reagent-grade dichloromethane (DCM), bromochloromethane (BCM), dibromomethane (DBM), bromoethane (BE), 1,1-dichloroethane (DCE), and 1-bromo-2-chloroethane (BCE) were used after distillation.

Preparation and Identification of Solvates——Griseofulvin was dissolved in a hot solvent under stirring and the solution was held at 4 °C until the corresponding solvate crystallized out. Identification of each solvate was done by means of infrared (IR) spectroscopy, X-ray powder diffractometry, differential scanning calorimetry (DSC), and thermogravimetry (TG). Further, in order to compare physico-chemical properties among solvates, griseofulvin chloroform solvate[2,3)] was also prepared and was identified by IR and X-ray powder diffractometry.

IR Spectroscopy——IR spectra were measured by the Nujol mull method using a Jasco IRA-1 grating IR spectrophotometer.

Simultaneous TG and DSC——Simultaneous measurements were carried out with a Thermoflex TG-DSC

machine (Rigaku Denki Co., Ltd.) using about 10 mg of a sample (heating rate, 5 C/min; nitrogen gas flow, 50 ml/min). Under open conditions, a solid sample pan was employed without a pan cover. Solvate crystals of samples were used without trituration in a mortar to avoid desolvation before measurements.

X-Ray Powder Diffractometry——A JDX 7F X-ray diffraction analyzer made by Japan Electron Optics Laboratory Co., Ltd. was used (Ni filter, CuK_α radiation, $\lambda = 1.542$ Å).

Determination of Combining Ratios of Solvates——Combining ratios of solvates were determined from weight decreases in the TG curves. However, since BCE solvate begin to desolvate during pretreatments before measurements, about 1 g of the freshly prepared solvate to which some solvent adhered was placed on the pan of a chemical balance at 27 °C, and the weightchange was read at intervals. From the time–weight curve thus obtained, the amount of combined bromochloroethane was determined.

Determination of Densities——Densities of solvates were determined by the flotation method using solvent mixtures of CCl_4, DCM, or DBM at 22 °C. Solvate crystals of about 2 mm in length were used as the sample.

Preparation of Mixed Crystal——Mixed crystals of the BE solvate and the DBM solvate were prepared by recrystallization from mixed solutions composed of different molar ratios of BE and DBM (BE:DBM = 0.25:0.75, 0.5:0.5, 0.75:0.25). The solutions were allowed to stand at 4 °C, and then the crystals which initially crystallized out were isolated and subjected to the analytical procedures. Identification of mixed crystals was done by means of IR, TG, powder X-ray diffractometry, nuclear magnetic resonance (NMR) spectroscopy, and elemental analysis.

X-Ray Crystallographic Analysis——The intensity measurements were undertaken on a Rigaku AFC4 automated four-circle diffractometer with graphite-monochromated CuK_α radiation ($\lambda = 1.54184$ Å).

Determination of Cell Dimensions: A solvate crystal with dimensions of *ca.* $0.5 \times 0.5 \times 0.5$ mm^3 was put into a glass capillary together with the small amount of solvent to prevent desolvation, then the capillary was closed hermetically. The cell dimensions were obtained by the least squares method using about 20 reflections within the range of $15° < 2\theta < 25°$.

Determination of Crystal Structure: The structure was determined only for the DCE solvate, which was relatively stable in air compared with other solvates. A crystal ($0.2 \times 0.3 \times 0.5$ mm^3) placed in a hermetically closed glass capillary was used for the measurement. The reflections within the range of $\theta \leqq 65$ were collected with the 2θ–ω scan technique (scan speed, 8 °/min; scan width, $0.8 + 0.5 \tan\theta$). The intensities were corrected for the Lorenz and polarization factors, but no correction was applied for absorption or extinction. One thousand five hundred and twenty-two independent reflections with $|F_O| > 3\sigma(F_O)$ were used for the structure determination. The calculations were carried out on a HITAC M280H computer at the computer center of the University of Tokyo, using the UNICS III program system.[7] The atomic scattering factors were taken from International Tables for X-Ray Crystallography, Vol. IV.[8]

Results and Discussion

Crystallographic Properties of Solvates

As shown in Fig. 1, when griseofulvin was recrystallized from DCM, BCM, DBM, BE, DCE or BCE, crystals of the six solvates were easily isolated as quadrangular prisms, or lods. Griseofulvin also crystallized out as octahedra from acetone, as shown in Fig. 2. Therefore, it is clear that the crystal habits of qriseofulvin and its solvates are different. The cell dimensions obtained by X-ray analysis are shown in Table I. No X-ray analysis was carried out for the BCE solvate because of its low stability in air. The cell dimensions of griseofulvin and its chloroform solvate are from the reported data.[9,10]

The DCM, BCM, DBM, and BE solvates belong to the triclinic system, having about the same cell dimensions, while the DCE solvate and the chloroform solvate belong to the orthorhombic system and also have similar values of the cell dimensions.

Those solvate crystals desolvated gradually on exposure to air, and became opaque while retaining original crystal shapes of solvates. The crystals changed into agglomerates of primary particles of griseofulvin when all the solvent components were released.

Combining Ratios of Solvates

Simultaneous TG-DSC measurements were carried out under open conditions, as shown in Fig. 3. Two endothermic peaks were found in the DSC curve of each solvate. The first one at lower temperature is ascribed to desolvation of the solvent component, while the peak at about 220 °C is assigned to melting of griseofulvin. In the simultaneous TG runs, the weight

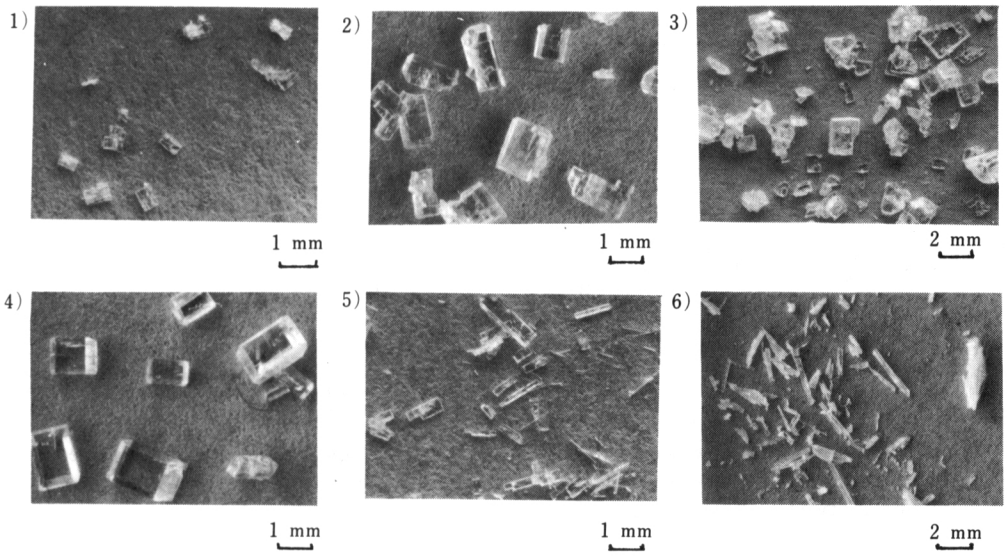

Fig. 1. Shapes of the Solvate Crystals

1), DCM; 2), BCM; 3), DBM; 4), BE; 5), DCE; 6), BCE.

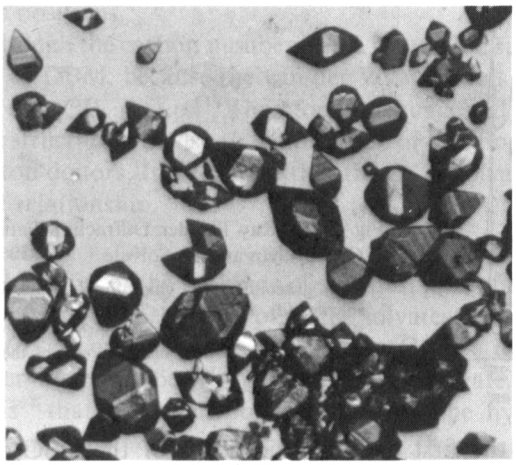

Fig. 2. Crystals of Griseofulvin (× 60)

TABLE I. Cell Dimensions of Griseofulvin and Its Solvates

Crystal	Crystal system	*a*	*b*	*c*	$\alpha^{a)}$	β	γ
		(Å)			(°)		
Gris.	Tetragonal	8.967 (2)	8.967 (2)	19.904 (9)	90	90	90
DCM solvate	Triclinic	11.776 (5)	11.819 (6)	8.640 (4)	111.44 (3)	90.00 (3)	66.69 (3)
BCM solvate	Triclinic	11.754 (5)	11.908 (6)	8.648 (4)	111.18 (3)	89.99 (3)	66.41 (3)
DBM solvate	Triclinic	11.825 (9)	12.015 (10)	8.679 (5)	111.28 (5)	89.69 (5)	65.44 (5)
BE solvate	Triclinic	11.819 (5)	12.009 (6)	8.693 (3)	111.19 (4)	89.91 (5)	65.67 (4)
DCE solvate	Orthorhombic	11.895 (1)	20.720 (3)	8.720 (12)	90	90	90
Chloroform solvate	Orthorhombic	11.890 (2)	20.380 (4)	8.671 (2)	90	90	90

a) The values of angles for triclinic crystals were rounded off to two decimal places.

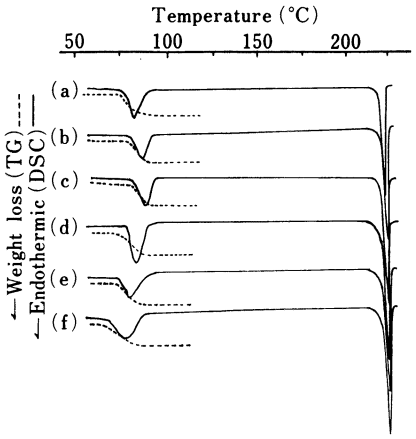

Fig. 3. Simultaneous TG-DSC Curves of the Solvates under Open Conditions

(a), DCE; (b), DCM; (c), BCM; (d), DBM; (e), BE; (f), BCE.

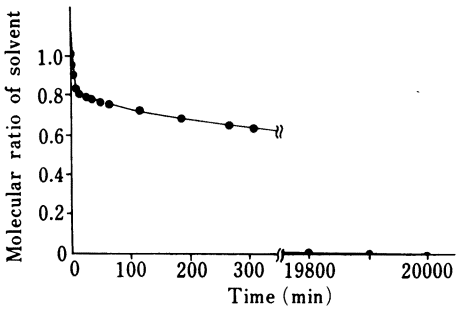

Fig. 4. Weight Decrease Curve of Griseofulvin BCE Solvate at 27 °C under Atmospheric Pressure

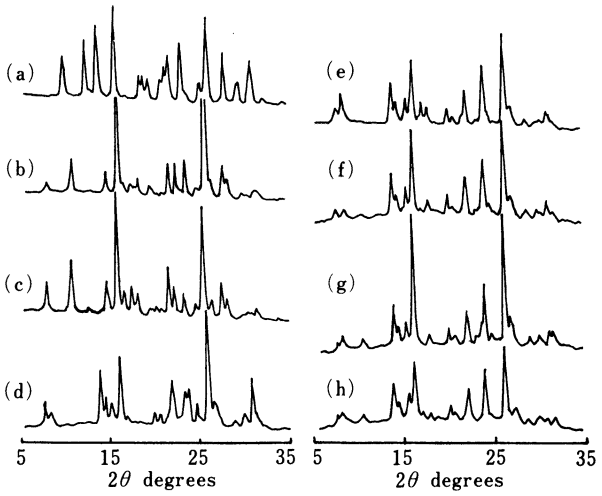

Fig. 5. X-Ray Powder Diffraction Patterns of Griseofulvin and Its Solvate

(a), griseofulvin; (b), chloroform solvate; (c), DCE solvate; (d), BCE solvate[a]; (e), DCM solvate; (f), BCM solvate; (g), DBM solvate; (h), BE solvate.

a) Measured with a small amount of the solvent because of low stability.

decreased in the temperature ranges of the first endothermic peaks of the DSC curves. Combining ratios between griseofulvin and corresponding solvent molecules calculated from the weight decreases were 1 : 1 except for that of the BCE solvate. In the case of the BCE solvate, the values fluctuated between 0.75 and 0.81 owing to desolvation during pretreatments for TG-DSC runs. For this reason, the combining ratio was measured precisely by the use of a chemical balance as shown in Fig. 4. At the initial time of measurement, the weight decreased rapidly because of evaporation of the solvent attached to the crystal surfaces, and after that, decreased gradually owing to release of the combined solvent; after 2000 min, the weight became constant. Thus, the molecular ratio was determined to be 1 : 0.8 (griseofulvin : BCE).

Powder X-Ray Diffractometry

Figure 5 shows the powder X-ray diffraction patterns of the six kinds of solvates, griseofulvin and its chloroform solvate. The DCM, BCM, DBM, and BE solvates gave almost the same diffraction patterns. Similar patterns were also obtained with respect to the DCE solvate and the chloroform solvate. That is to say, as was expected, when the cell dimensions

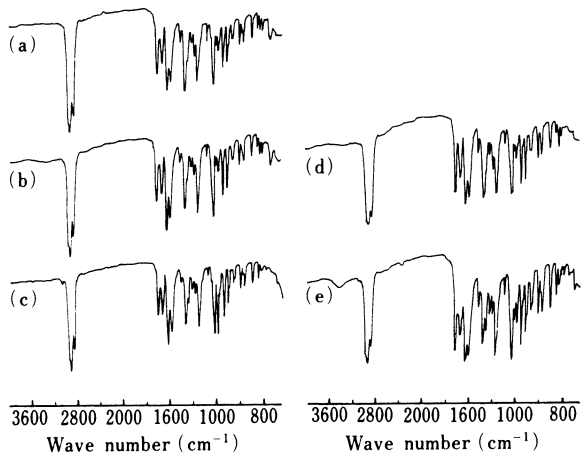

Fig. 6. IR Spectra of the Solvates
(a), DCM; (b), BCM; (c), DBM; (d), BE; (e) BCE.

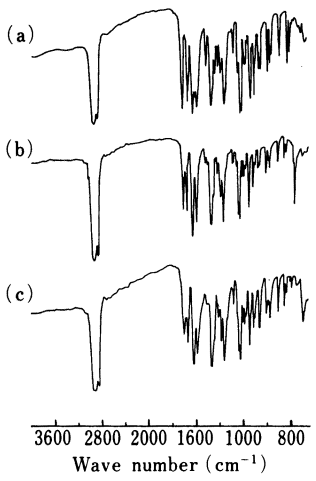

Fig. 7. IR Spectra of Griseofulvin and Its Solvates
(a), griseofulvin; (b), chloroform solvate; (c), DCE solvate.

of two solvates are almost the same, the X-ray diffraction peaks of the crystals also appear in similar positions.

Though the carbon number in BE is two, the size of the molecule is near to that of DCM, BCM, or DBM, because the van der Waals radius of a Br atom or Cl atom is similar to the size of the $-CH_3$ group.[11] Therefore, it is suggested that those solvates have not only the same crystal structure, but also the same mode of bonding because the molecules of solvents behave as proton donors. It is thought that the DCE solvate and the chloroform solvate also have a similar relationship.

IR Spectra

IR spectra of the six kinds of solvates, griseofulvin and its chloroform solvate are shown in Figs. 6 and 7. The spectra of all the solvates were similar to that of griseofulvin, though the peak at 1720 cm^{-1}, which is ascribed to $>C=O$ stretching in the benzofuran ring, was shifted to lower wave number. In the chloroform solvate, it was proved by X-ray crystallographic analysis[9] that hydrogen bonding between the hydrogen in chloroform molecule and the oxygen in the $>C=O$ group occurred, and thus the peak of the $>C=O$ stretching was shifted to lower wave number.[2] Therefore, it is thought that the DCE solvate, having cell dimensions similar to those of the chloroform solvate, is also stabilized by hydrogen bonding.

Mixed Crystal of Solvates

The solvents BE and DBM have good miscibility, and further, from the results of X-ray analysis, it was found that there is a close similarity in the cell dimensions of the BE solvate and the DBM solvate. Therefore, we attempted to isolate mixed crystals by recrystallization from a mixed solvent of BE and DBM.

A mixed crystal (solid solution) is formed when the constituent atoms of molecules as well as the molecular volumes are similar, for example, dextrorotatory and levorotatory substances such as *d*-carboxime and *l*-carboxime, or *m*-chloronitrobenzene and *m*-fluoronitrobenzene,[12] *etc.*

Figure 8 shows the shape of mixed crystals recrystallized from an equimolar mixture of BE and DBM. The NMR spectrum (Fig. 9), showed a triplet at 1.6 ppm, a quartet at 3.4 ppm and a singlet at 5.1 ppm, ascribable to the resonances of the $-CH_3$ and $-CH_2-$ protons of BE,

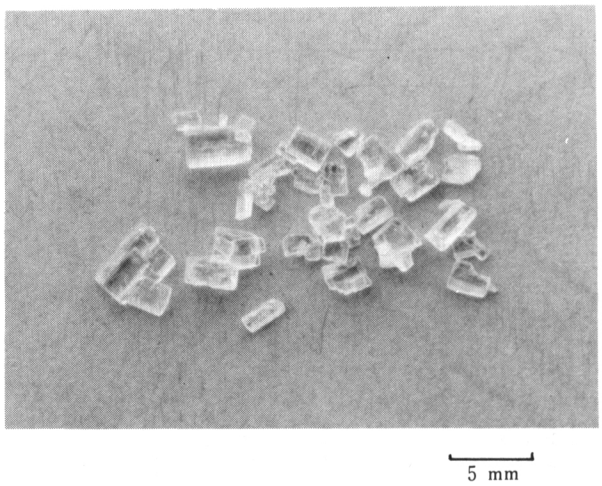

Fig. 8. Mixed Crystals of BE Solvate and DBM Solvate

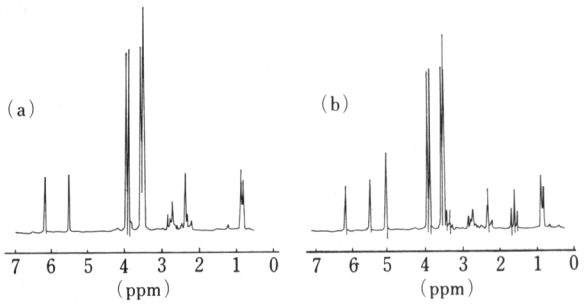

Fig. 9. NMR Spectra of Griseofulvin and Mixed Crystal in $CDCl_3$

(a), griseofulvin; (b) mixed crystals recrystallized from an equimolar mixture of BE and DBM.

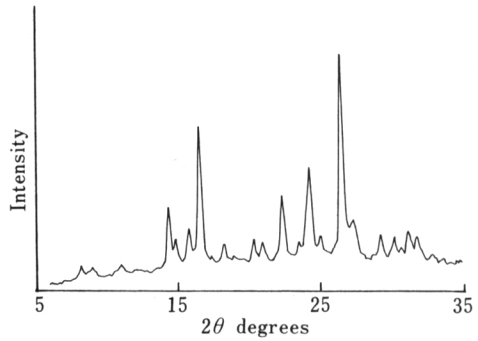

Fig. 10. X-Ray Diffraction Pattern of Mixed Crystals Recrystallized from an Equimolar Mixture of BE and DBM

TABLE II. Densities of the DBM Solvate, the BE Solvate and Their Mixed Crystals

Solvate	Density (g/cm^3)
DBM	1.700
BE25%[a)]	1.633
BE50%[a)]	1.596
BE75%[a)]	1.554
BE	1.485

a) BE25% means that the mixed crystal was prepared from a mixture of 25% BE and 75% DBM.

and $-CH_2-$ protons of DBM, respectively. Therefore, it is apparent that the mixed crystal could be prepared by recrystallization. The powder X-ray diffraction pattern of the crystals is shown in Fig. 10. The X-ray diffraction pattern was the same as that of the BE solvate or the DBM solvate, and hence, it is suggested that the mixed crystals have the same cell dimensions as the BE solvate or the DBM solvate.

Tables II and III show the densities of the mixed crystals, and the results of elemental analysis of the crystals isolated from mixed solvents of different molar ratios of BE and DBM (BE : DBM = 0.25 : 0.75, 0.5 : 0.5, 0.75 : 0.25). The values of density became smaller with increasing ratio of BE in the solvent, while the fraction of carbon obtained by elemental analysis increased with increasing ratio of BE. The compositions of BE and DBM calculated

Table III. Results of Elemental Analysis for the DBM Solvate, the BE Solvate and Their Mixed Crystals

Crystal	C (%)		H (%)	
	Calcd	Found	Calcd	Found
DBM	41.05	41.07	3.64	3.48
BE25%[a]		43.05		3.92
BE50%[a]		45.11		4.07
BE75%[a]		46.66		4.35
BE	49.42	49.45	4.81	4.66

a) BE25% means that the mixed crystal was prepared from a mixture of 25% BE and 75% DBM.

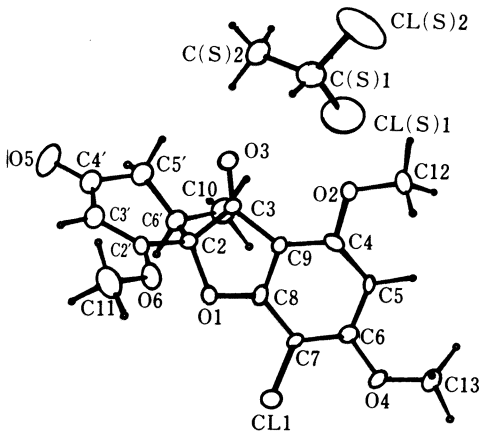

Fig. 11. ORTEP Drawing of Griseofulvin DCE Solvate

Table IV. Molecular Volumes of DCM, BCM, DBM, BE, DCE and Their Solvates

	Solvent		Solvate	
	Density[a] (g/cm^3)	Molecular volume (cm^3/mol)	Density[a] (g/cm^3)	Molecular volume (cm^3/mol)
DCM	1.326	64.3	1.437	304.6
BCM	1.991	64.8	1.574	306.3
DBM	2.495	69.7	1.700	309.8
BE	1.456	74.9	1.485	310.9
DCE	1.175	84.3	1.410	320.4

a) At 20 °C.

Table V. Crystal Data of Griseofulvin DCE Solvate

$C_{17}H_{17}ClO_6 \cdot C_2H_4Cl_2$
$M_r = 451.73$
Orthorhombic
Space group = $P2_12_12_1$
$a = 11.895$ (1) Å
$b = 20.720$ (3) Å
$c = 8.720$ (12) Å
$V = 2147$ (3) Å^3
$D_m = 1.410$ g/cm^3
$D_c = 1.397$ g/cm^3
$Z = 4$

from the carbon contents of the crystals were 32,52, and 70 mol% with respect to the original mixed solutions, respectively. Thus, the compositions of BE and DBM in the mixed crystal depend on the molar ratio of BE and DBM in the mixed solvents.

Judging from the standpoint of the molecular volumes of solvents and solvates, as shown in Table IV, the molecular volumes of the two solvates are extremely similar, though those of the solvents are somewhat different. From the above results, it is considered that the two solvates form a mutually substitutional solid solution in which molecules in the crystal lattice are substituted with molecules of the other kind depending upon the molar ratio of solvent.

We know of no previous report on mixed crystals of solvates. Nevertheless, it appears that mixed crystals of two solvates (a new type of substitutional solid solution) can be prepared simply by recrystallization, presumably because selective solvation does not occur in the mixed solution.

Determination of Crystal Structure of the DCE Solvate

The structure was solved by the direct method, using MULTAN.[13] All the nonhydrogen atoms were located from the *E*-map generated using 288 reflections with $|E| \geqq 1.5$ and subsequent difference Fourier synthesis. The structure was refined by the block-diagonal least-squares method initially using isotropic temperature factors and finally anisotropic ones with the following weighting scheme: $w = 1/(0.8 + 0.1 \times |F_O|^2)$ when $|F_O| < 10$ and $w = 1/$

TABLE VI. Coordinates ($\times 10^4$) with the Estimated Standard Deviations in Parentheses and Isotropic Thermal Parameters (Å^2) for Non-hydrogen Atoms

Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
CL1	4125 (2)	4337 (1)	5796 (3)	3.84	C9	4402 (8)	4075 (5)	10362 (12)	2.71
O1	5732 (5)	4124 (4)	8413 (8)	3.00	C10	6213 (12)	2792 (7)	9618 (20)	5.86
O2	3113 (6)	3993 (4)	12360 (8)	3.66	C11	7179 (13)	5724 (7)	10090 (20)	6.40
O3	5704 (6)	3933 (4)	12465 (9)	3.89	C12	1982 (10)	3992 (7)	12940 (15)	4.35
O4	1900 (6)	4316 (4)	7128 (9)	4.18	C13	732 (10)	4389 (7)	7546 (16)	4.71
O5	9671 (8)	3823 (7)	11188 (17)	8.82	C2′	7125 (8)	4585 (6)	10074 (13)	3.37
O6	6581 (6)	5137 (4)	9838 (10)	4.02	C3′	8212 (10)	4525 (7)	10553 (17)	4.80
C2	6365 (8)	4013 (5)	9833 (12)	3.29	C4′	8679 (11)	3878 (9)	10878 (19)	6.11
C3	5477 (8)	3993 (5)	11121 (12)	2.91	C5′	7898 (11)	3315 (7)	10840 (17)	4.88
C4	3286 (9)	4072 (5)	10795 (13)	2.96	C6′	6981 (10)	3383 (7)	9652 (17)	3.95
C5	2398 (7)	4125 (5)	9826 (13)	2.69	CL(S)1	4039 (7)	2303 (3)	12889 (7)	12.45
C6	2681 (8)	4239 (5)	8245 (13)	2.92	CL(S)2	3765 (9)	2627 (4)	15975 (10)	17.62
C7	3782 (8)	4229 (5)	7693 (12)	2.80	C(S)1	4652 (12)	2758 (10)	14392 (23)	6.08
C8	4628 (7)	4151 (5)	8766 (12)	2.57	C(S)2	5958 (15)	2493 (7)	14502 (17)	8.98

TABLE VII. Bond Lengths in Griseofulvin DCE Solvate with the Estimated Standard Deviations in Parentheses

Atom	Length (Å)	Atom	Length (Å)
CL1–C7	1.72 (1)	O1–C2	1.47 (1)
O1–C8	1.35 (1)	O2–C4	1.39 (1)
O2–C12	1.44 (1)	O3–C3	1.21 (1)
O4–C6	1.36 (1)	O4–C13	1.45 (1)
O5–C4′	1.22 (2)	O6–C11	1.42 (2)
O6–C2′	1.33 (1)	C2–C3	1.54 (1)
C2–C2′	1.50 (2)	C2–C6′	1.50 (2)
C3–C9	1.45 (1)	C4–C5	1.36 (1)
C4–C9	1.38 (1)	C5–C6	1.43 (2)
C6–C7	1.40 (1)	C7–C8	1.38 (1)
C8–C9	1.43 (2)	C10–C6′	1.53 (2)
C2′–C3′	1.36 (1)	C3′–C4′	1.48 (2)
C4′–C5′	1.49 (2)	C5′–C6′	1.51 (2)
CL(S)1–C(S)1	1.77 (2)	C(S)1–CL(S)2	1.76 (2)
C(S)1–C(S)2	1.65 (2)		

$((F_O)+0.1\times|F_O|^2)$ when $|F_O|\geqq 10$. The final R value was 0.103. The hydrogen atoms were fixed computationally on the basis of stereochemical and geometrical considerations.

Tables V and VI show the crystallographic parameters, the final atomic coordinates and isotropic thermal parameters. An ORTEP[14] drawing of the DCE solvate is shown in Fig. 11. Bond lengths and bond angles of the griseofulvin molecule are not appreciably different from those previously reported[10,16] (Tables VII and VIII). Also, the distances of C(S)1 to O3 and of O3 to H attached to C(S)1 are 3.2 and 2.3 Å, respectively. Therefore, the hydrogen atom attached to C(S)1 in DCE interacts weakly by hydrogen bonding with the carbonyl group at C3, as in the griseofulvin chloroform solvate.[9] Also, it is apparent from the isotropic thermal parameters that significantly higher thermal motion of DCE molecules occurred in the crystal lattice.

Figure 12 shows that the DCE molecules in the crystal are situated in layers perpendicular to the b-axis. Shefter *et al.*[9] observed that the plane of desolvation in the chloroform solvate was perpendicular to the b-axis[16] because the chloroform molecules lie in

TABLE VIII. Bond Angles in Griseofulvin Molecule with the Estimated Standard Deviations in Parentheses

Atom	Angle (°)	Atom	Angle (°)
C2–O1–C8	108.3 (7)	C6–C7–C8	116.8 (9)
O1–C2–C3	105.4 (7)	C8–C7–CL1	119.5 (7)
O1–C2–C6′	107.3 (9)	C7–C8–O1	124.0 (9)
O1–C2–C2′	107.7 (9)	C7–C8–C9	122.4 (8)
C2′–C2–C3	109.3 (9)	C9–C8–O1	113.6 (8)
C3–C2–C6′	112.7 (9)	C8–C9–C3	107.0 (8)
C2′–C2–C6′	113.9 (9)	C8–C9–C4	116.7 (9)
C2–C3–O3	123.8 (9)	C2–C6′–C5′	111.1 (10)
C2–C3–C9	105.6 (8)	C2–C6′–C10	114.0 (10)
C9–C3–O3	130.6 (9)	C5′–C6′–C10	111.8 (11)
C5–C4–C9	125.2 (10)	C6′–C5′–C4′	113.1 (12)
O2–C4–C9	114.3 (9)	C5′–C4′–O5	122.4 (16)
C5–C4–O2	120.5 (9)	C5′–C4′–C3′	118.1 (11)
C4–O2–C12	119.0 (9)	C3′–C4′–O5	119.6 (11)
C4–C5–C6	115.5 (8)	C4′–C3′–C2′	119.9 (15)
C5–C6–C7	123.4 (9)	C3′–C2′–C2	122.7 (12)
C5–C6–O4	123.2 (9)	C3′–C2′–O6	125.9 (11)
C7–C6–O4	113.3 (9)	C2–C2′–O6	111.3 (8)
C6–O4–C13	119.3 (9)	C2′–O6–C11	117.8 (9)
C6–C7–CL1	123.6 (8)		

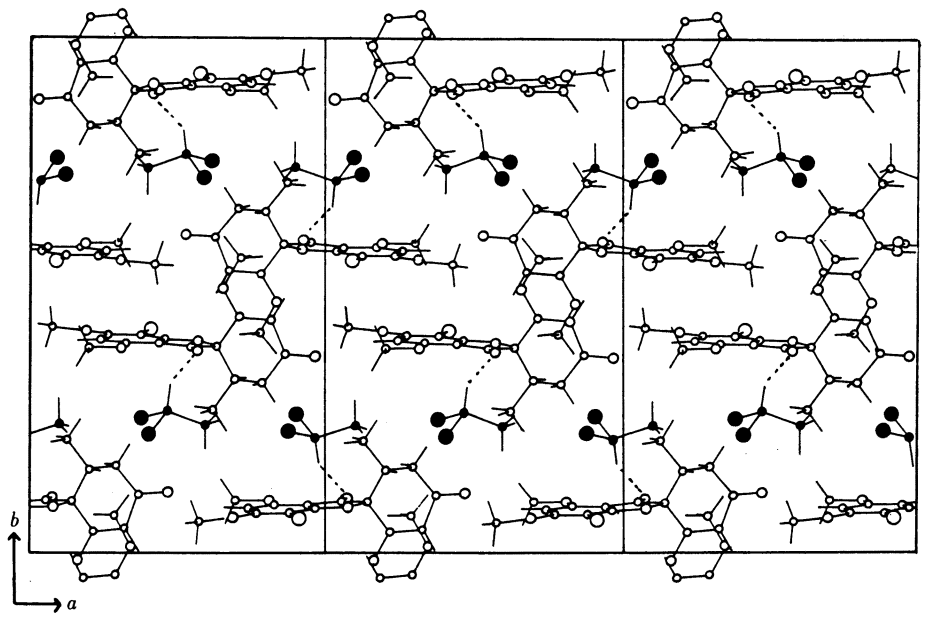

Fig. 12. Packing Diagram for Griseofulvin DCE Solvate

: DCE molecule

layers perpendicular to the *b*-axis of the crystal. Thus, it is thought that the DCE solvate also desolvates in the direction perpendicular to the *b*-axis. However, as has been reported in the previous paper,[17] because the nuclei of desolvation are preferentially formed at localized spots such as scratches, cracks, or lattice discontinuities on the crystal, the direction of

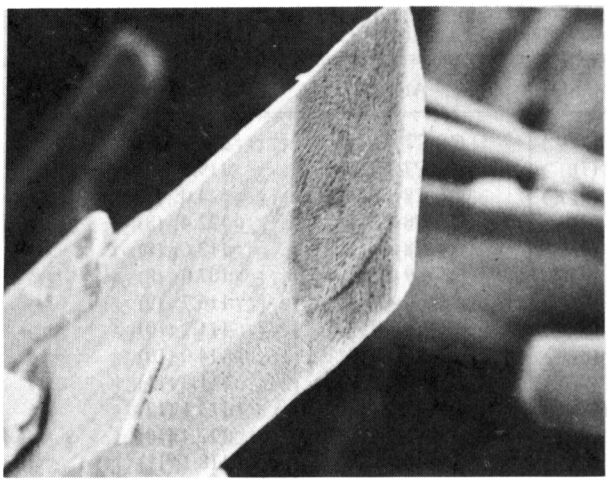

Fig. 13. Scanning Electron Microphotograph of Griseofulvin Recovered from Its DCE Solvate (× 700)

desolvation for real crystals may not always be the same. The SEM photograph in Fig. 13 shows that primary particles were uniformly formed in desolvated products without showing series of parallel cracks in any particular direction.[18)]

Conclusion

Six kinds of griseofulvin solvates were isolated from corresponding alkyl halide and alkyl dihalide solutions. The DBM solvate and the BE solvate formed a new type of mixed crystal (substitutional solid solution). This implies that selective solvation dose not occur in the mixed solution.

From the X-ray crystallographic analysis, the arrangement of molecules in the DCE solvate crystal is the same as that in the chloroform solvate, and further, it was concluded that hydrogen bonding is responsible for the solvate formation.

References and Notes

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