A note on the solubility of griseofulvin

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The solubility of griseofulvin in heptane, water and benzene over the temperature range 15–45° is reported together with the thermodynamic properties for solution of the antibiotic in these solvents.

AS part of a study on the rate of solution of griseofulvin, solubilities in various solvents were required. These are reported here together with data on the thermodynamics of solubility.

Experimental

Griseofulvin was recrystallized from ethanol and had m.p. 222°, assay by the method of the British Pharmacopoeia gave a purity of 99·7%. Analar benzene, stored over sodium had n_D^{20},1·5010 (1·5011). Fluka heptane ($\geqslant$99 mole %) stored over sodium had n_D^{20}, 1·3880 (1·3876). Literature values of the refractive index are from Timmermans (1965).

Solubility determinations. Preliminary solubility determinations, in which the saturated solution was freed from excess solute on 0·45 μ pore size Millipore filters, were poorly reproducible.

Filtration on a 5/3 sintered glass disk with the minimum of applied pressure gave the best results. A percolation apparatus was devised (Fig. 1) in which the solvent percolated through a plug of griseofulvin supported on a 5/3 sintered glass disk. After the solution had passed through the filter, it was transferred back to the left hand limb of the apparatus and allowed to percolate a second time, a portion being reserved for measurement of extinction. The process was repeated until the solution was saturated, shown by no further increase in extinction. The time for saturation depended on the solvent used, but was in general

Griseofulvin
Sintered disk
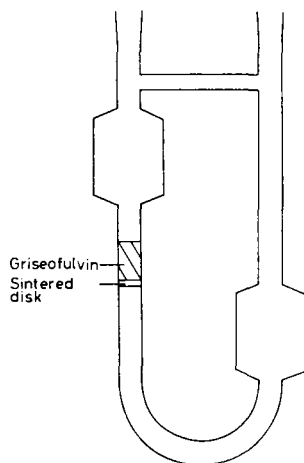
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5–6 days. The percolator was placed on a thermostat, controlled to $\pm 0.05°$.

The concentrations of griseofulvin in water and heptane were determined spectrophotometrically by diluting a known weight of the saturated solution with a known amount of ethanol and benzene respectively, and establishing a calibration curve in the ethanol–water and benzene–heptane mixture. In benzene, the solubility was large enough for the E (1%, 1 cm) to be measured directly. Beer's law was obeyed up to saturation. Extinctions were determined using a Uvispek at 296 mμ in water, 287 mμ in heptane, and 291 mμ in benzene.

Results and discussion

The solubility results expressed as molalities (m) are given in Table 1.

TABLE 1. SOLUBILITIES (MOLES/1000 G SOLVENT) OF GRISEOFULVIN IN HEPTANE, WATER AND BENZENE

Solvent	Temperature			
	15°	25°	35°	45°
Heptane ($m \times 10^5$)	0·82	1·49	2·84	5·38
Water ($m \times 10^5$)	1·83	2·45	3·51	6·14
Benzene ($m \times 10^2$)	2·63	3·81	5·14	6·78

In all solvents studied, the solubility increased with temperature. The results for water are in reasonable agreement with those of Bates, Gibaldi & Kanig (1966). The partial molal heats ($\Delta \bar{H}$) and entropies ($\Delta \bar{S}$) of solution are given in Table 2. $\Delta \bar{H}$ was obtained from graphs of log m vs $1/T$, and $\Delta \bar{S}$ by dividing $\Delta \bar{H}$ by T. The thermodynamic properties represent the energy change occurring when one mole of griseofulvin is dissolved in an infinite amount of saturated solution.

TABLE 2. THERMODYNAMIC PROPERTIES FOR SOLUTION OF GRISEOFULVIN IN HEPTANE, WATER AND BENZENE

		Heptane	Water	Benzene
20°	$\Delta \bar{H}$	10·9	5·1	5·4
	$\Delta \bar{S}$	37	17	18
30°	$\Delta \bar{H}$	11·6	6·5	5·5
	$\Delta \bar{S}$	38	22	18
40°	$\Delta \bar{H}$	12·4	10·0	5·2
	$\Delta \bar{S}$	40	32	17

$\Delta \bar{H}$ in kcal mole^{-1}, $\Delta \bar{S}$ in cal mole^{-1}deg^{-1}.

In the griseofulvin–heptane system, there is only a small variation of the thermodynamic properties with temperature.

$\Delta \bar{H}$ will include the heat necessary to rupture the bonds in the crystal of griseofulvin, as well as a contribution from heat of dilution, and any interaction with the solvent. In the case of heptane the last two factors

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probably make little contribution to $\Delta \overline{H}$. The positive $\Delta \overline{S}$ value indicates the greater disorder of the solute when dissolved over its state in the crystal. For griseofulvin in water, there is likely to be hydrogen bonding between solvent and solute molecules, a process which will tend to affect the overall heat change. $\Delta \overline{H}$ increases with temperature, and as it is known that the structuring of water decreases with temperature rise, the contribution to the heat term from solvent–solute interactions is likely to decrease also. At 40°, $\Delta \overline{H}$ for the griseofulvin–water system is not much less than that of the griseofulvin–heptane system. The increase of $\Delta \overline{S}$ with temperature may also reflect a decrease in the structuring effects of water.

In benzene, the saturation solubility is about one thousand times greater than in the other two solvents, which may introduce effects from heat of dilution in the dissolving process. Benzene is not a structured liquid like water, so strong interactions between solvent and solute are unlikely. There may be evidence for association of griseofulvin molecules in benzene, as both $\Delta \overline{H}$ and $\Delta \overline{S}$ are much lower than in the heptane system. No comment can be made on the change of these quantities with temperature, as the variation is within experimental error.

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References

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