

## Solubility behaviour of griseofulvin in fatty acids

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The solubility of griseofulvin in the straight-chain alkanolic acids from C<sub>2</sub> to C<sub>22</sub> and in the C<sub>4</sub> and C<sub>5</sub> alkanolic acids branched at C-2 was measured at various temperatures. The enthalpy of fusion of griseofulvin, measured by differential scanning calorimetry, was 39.39 kJ mol<sup>-1</sup> at the melting point (495.15 K) and 36.95 kJ mol<sup>-1</sup> at 373.15 K. The standard Gibbs free energy ( $\Delta G^\circ$ ), standard enthalpy ( $\Delta H^\circ$ ) and standard entropy ( $\Delta S^\circ$ ) of solution were calculated at 373.15 K, from the van't Hoff plot of the temperature dependence of the mole fraction solubility in terms of the pure supercooled liquid solute as the standard state. With increasing chain length of the alkanolic acid solvents,  $\Delta G^\circ$  increased in parallel with the increase in pK<sub>a</sub> of the acids in water, suggesting that the solubility behaviour involves specific solute-solvent proton interactions, while  $\Delta H^\circ$  and  $\Delta S^\circ$  fluctuated but tended to decrease in parallel with the corresponding decreases in their enthalpies and entropies of ionization, respectively. The fluctuations in  $\Delta H^\circ$  and  $\Delta S^\circ$  may be attributed to the different solid adducts containing griseofulvin and the solvent. An observed non-linear (logarithmic) decrease in solubility with decreasing molality of the carboxyl group in the liquid solvent on ascending the homologous series is attributed to the disturbing influence of the hydrocarbon chains on the specific solute-solvent hydrogen bonding. Chain-branching of the solvent at C-2 gave a reduced solubility of griseofulvin and higher  $\Delta G^\circ$ ,  $\Delta H^\circ$  and  $\Delta S^\circ$  values compared with the corresponding straight chain acid.

Griseofulvin is an antifungal antibiotic having a very low solubility in water and also in hydrocarbons (Elworthy & Lipscomb 1968). These low solubilities probably arise from the extraordinarily high stability of the crystal lattice of the drug which is reflected in its high melting point (218–224 °C, Martindale 1977) and the absence of polymorphic transitions. This stable crystal lattice can, however, be broken down by solvents capable of forming relatively strong hydrogen-bonded complexes with the drug. Since the griseofulvin molecule contains four ether oxygen atoms and two carbonyl oxygen atoms, it is appreciably soluble in the presence of hydrogen donors with which it is capable of undergoing specific interactions (Higuchi et al 1969). Specific interactions between griseofulvin and the straight chain alkanolic acids, C<sub>1</sub>–C<sub>9</sub>, give rise to crystalline solvates and amorphous inclusion compounds (Abougela & Grant 1979; Grant & Abougela 1981). Since alkanolic acids are generally regarded as safe additives, they may be of value in the processing and formulation of griseofulvin.

The present study examines the thermodynamics of solubility of griseofulvin in various straight chain

and C-2 branched alkanolic acids, in which the drug is appreciably soluble, in order to broaden our understanding of the role of specific interactions in the solubility behaviour of drugs.

### MATERIALS AND METHODS

#### Materials

Griseofulvin was a gift from ICI Limited, Pharmaceuticals Division. The batch used consisted of very angular crystals with a specific surface area of 308 m<sup>2</sup> kg<sup>-1</sup> and a volumetric median diameter of 57.5 μm (Hansford et al 1980). The sample gave a single sharp transition in differential thermal analysis at the melting point (220–224 °C) and was reported by the manufacturers to contain at least 99% griseofulvin.

The fatty acids used were reported by the suppliers to give assays of at least 99%. BDH Chemicals Ltd, supplied the following acids: formic, propanoic, n-pentanoic, n-heptanoic, n-decanoic and n-octadecanoic. Sigma London Ltd, provided the following acids: n-butanoic, n-hexanoic, n-octanoic, n-nonanoic, n-undecanoic, n-dodecanoic, n-hexadecanoic, n-eicosanoic and n-docosanoic. Fisons Ltd supplied acetic acid, Eastman Chemicals Ltd provided (±)-2-methylbutanoic acid and Koch-Light Ltd supplied trimethylacetic acid and 2-methylpropanoic acid.

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*Determination of solubility*

The solubility of griseofulvin in each of the liquid alkanolic acids was determined at a variety of temperatures using a modification of the 'synthetic method' (Gordon & Scott 1952). The temperature was measured at which each of various mass fractions of griseofulvin (0.01 to 0.05) just became soluble in each solvent. For this purpose 7 to 8 g of the solvent were mixed with 0.01 mass fraction of griseofulvin in a boiling tube which was surrounded by a paraffin bath. The paraffin bath was heated by an electrical hotplate under which there was fitted a magnetic stirrer so that magnetic followers in the mixture and in the paraffin could be rotated together to establish thermal equilibrium. Nitrogen gas was very slowly passed through to prevent oxidation while heating. Under these conditions evaporation of the solvent was negligible. While heating at a constant rate of about 0.5 to 1.0 °C min<sup>-1</sup> the temperature was noted at which the last crystal of solute just dissolved in the molten solvent. This temperature was within 0.5–1 °C of the true equilibrium solubility temperature for the entire contents of the tube on account of the following observations: (a) the temperature was increased very slowly, (b) agitation was very rapid, (c) the temperatures were reproducible within 0.5 to 1.0 °C (Table 1).

The solubility of griseofulvin at each temperature was expressed as molality ( $m_2$ , moles of griseofulvin kg<sup>-1</sup> of solvent) or as mole fraction ( $x_2$ ).

The molality scale was chosen by Elworthy & Lipscomb (1968), the standard state being a

hypothetical solution of unit molality whose properties correspond to an infinitely dilute solution at the defined temperature. The mole fraction scale is commonly encountered (e.g. Hildebrand et al 1970; Yalkowsky 1981) for which the standard state is the pure supercooled liquid solute at a defined temperature. The solubility,  $m_2$  or  $x_2$ , when interpolated or extrapolated to 373.15 K, were respectively designated the standard molal solubility  $m_2^\circ$ , or the standard mole fraction solubility,  $x_2^\circ$ . The respective standard Gibbs free energies of solution,  $\Delta G_m^\circ$  or  $\Delta G_x^\circ$ , according to each of these concentration scales, were calculated as follows:

$$\Delta G_m^\circ = -RT \ln m_2^\circ \quad (1)$$

$$\Delta G_x^\circ = -RT \ln x_2^\circ \quad (2)$$

The temperature dependence of  $x_2$  was treated by plotting  $\ln x_2$  against  $1/T$ , where  $T$  is the absolute temperature. According to the van't Hoff (1886) isochore written in the form

$$\ln x_2 = -\frac{\Delta H_x^\circ}{R} \cdot \frac{1}{T} + C_m \quad (3)$$

the slope affords  $\Delta H_x^\circ$ , the *apparent* molar enthalpy of solution (Hollenbeck 1980), where  $R = 8.3144 \text{ J K}^{-1} \text{ mol}^{-1}$ . The intercept,  $C_m = \Delta S_x^\circ/R$ , affords  $\Delta S_x^\circ$ , the apparent molar entropy of solution. Interpolation or extrapolation to the standard temperature, namely 373.15 K (= 100 °C), afforded  $x_2^\circ$  and hence  $\Delta G_x^\circ$  from equation (2). This choice of temperature enables the solubility of griseofulvin in all the various alkanolic acids to be compared without the need for extensive extrapolation and represents the best compromise for the various solvents.

Table 1. Equilibrium solubility temperatures °C<sup>-1</sup> for solid griseofulvin in various liquid alkanolic acids over the concentration range 0 to 5% (w/w) griseofulvin.

Solvent acid	Mass fraction, w, of griseofulvin				
	0.01	0.02	0.03	0.04	0.05
Acetic (C <sub>2</sub> )	19	24	28	30	32
Propanoic (C <sub>3</sub> )	38	42.5	45	47	49
Butanoic (C <sub>4</sub> )	45	54	59.5	63.5	67
Pentanoic (C <sub>5</sub> )	60	75.5	85	92.5	99
Hexanoic (C <sub>6</sub> )	77.5	85	89.5	93	93.5
Heptanoic (C <sub>7</sub> )	86	96	102	106.5	110
Octanoic (C <sub>8</sub> )	99	109.5	116	121	125
Nonanoic (C <sub>9</sub> )	102	113	120	125	128.5
Decanoic (C <sub>10</sub> )	105	125	137.5	147	155
Undecanoic (C <sub>11</sub> )	110	127	137.5	146	152
Dodecanoic (C <sub>12</sub> )	119.5	134.5	143	151	156.5
Hexadecanoic (C <sub>16</sub> )	142	155	163	168.5	173
Octadecanoic (C <sub>18</sub> )	120	136	146	153	159
Eicosanoic (C <sub>20</sub> )	132	146	155	161	166
Docosanoic (C <sub>22</sub> )	140	161	173.5	182.5	189.5
2-Methyl- propanoic (C <sub>4</sub> )	78	86	90.5	94	97
(±)-2-Methyl- butanoic (C <sub>5</sub> )	90	102	109	114.5	119
Trimethyl- acetic (C <sub>5</sub> )	104	116	123	128.5	133
Formic (C <sub>1</sub> , data less accurate)	8	10	11	12	13

*Differential scanning calorimetry*

A Perkin-Elmer differential scanning calorimeter model DSC-2 was used to determine the thermal data for the fusion of griseofulvin. For these purposes 5 to 20 mg of sample were heated at a rate of 2.5 °C min<sup>-1</sup>, the setting for the rate of energy absorption being 10 mcal s<sup>-1</sup> (41.84 mJ s<sup>-1</sup>). Using indium as the calibrating standard substance, the enthalpy of fusion,  $\Delta H_m^f$ , of griseofulvin at its melting point ( $T_m = 495.15 \text{ K} = 222 \text{ °C}$ ) was found to be 39.39 kJ mol<sup>-1</sup>.

Using sapphire as the standard and the procedure described by James & Roberts (1968), we found  $\Delta C_p$ , the difference between the heat capacity of the solid and that of the supercooled liquid, to be 20.03 J K<sup>-1</sup> mol<sup>-1</sup> for griseofulvin between the standard state temperature ( $T = 373.15 \text{ K} = 100 \text{ °C}$ ) and  $T_m$ .

The enthalpy of fusion,  $\Delta H_T^f$ , of griseofulvin at  $T = 373.15$  K was calculated from  $\Delta H_m^f$  and  $\Delta C_p$  by means of Kirchhoff equation in the form:

$$\Delta H_T^f = \Delta H_m^f - \Delta C_p (T_m - T) \quad (4)$$

Substitution of the state numerical values affords  $\Delta H_T^f = 36.95$  kJ mol<sup>-1</sup> for griseofulvin.

#### Calculation of the ideal solubility at 373.15 K

The ideal mole fraction solubility,  $x_2$  (ideal), of a solid is given by:

$$\ln x_2(\text{ideal}) = \frac{-\Delta H_m^f}{R} \left( \frac{T_m - T}{T T_m} \right) + \frac{\Delta C_p}{R} \left( \frac{T_m - T}{T} \right) - \frac{\Delta C_p}{R} \ln \left( \frac{T_m}{T} \right) \quad (5)$$

where  $R$  is the gas constant (8.3144 J K<sup>-1</sup> mol<sup>-1</sup>) and the other quantities have been defined above. This equation (Hildebrand & Scott 1962) assumes that  $\Delta C_p$  is independent of temperature which is normally an excellent approximation. Insertion of the numerical values stated above for the standard temperature of 373.15 K yields  $x_2^*(\text{ideal}) = 0.0487$ .

Equation (2) then gives  $\Delta G_x^\circ(\text{ideal}) = 9.376$  kJ mol<sup>-1</sup>. Now  $\Delta H_x^\circ(\text{ideal}) = \Delta H_T^f = 36.95$  kJ mol<sup>-1</sup>, therefore  $\Delta S_x^\circ(\text{ideal}) = 73.9$  J K<sup>-1</sup> mol<sup>-1</sup>.

## RESULTS AND DISCUSSION

### Influence of solvent carbon number on solubility behaviour

The excess free energy, which is given by

$$\Delta G^E = \Delta G_x^\circ - \Delta G_x^\circ(\text{ideal}) \quad (6)$$

is negative for acetic, propanoic and n-butanoic acid (Fig. 1(a)), suggesting specific solute-solvent interactions in which the proton-donating carboxyl group of the fatty acid forms a hydrogen bond with one of the basic (lone-pair donating) oxygen atoms of the griseofulvin molecule. This mechanism accounts for the existence of griseofulvin-fatty acid solvates (Abougela & Grant 1979; Grant & Abougela 1981) and readily explains why the presence of a proton donor, such as a phenol, increases the solubility of the proton acceptor, griseofulvin, in non-polar solvents, such as carbon tetrachloride (Higuchi et al 1969).

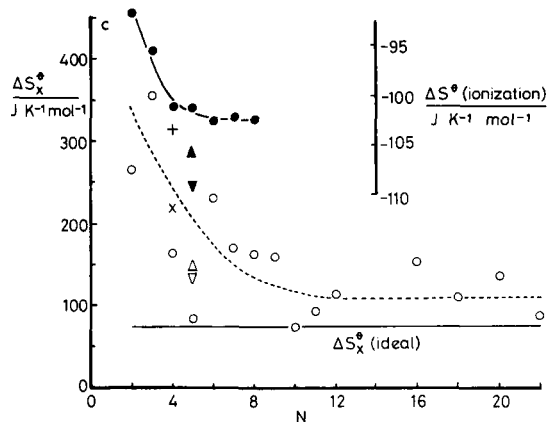
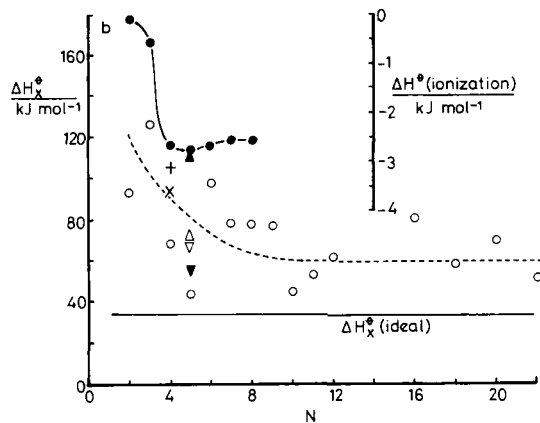
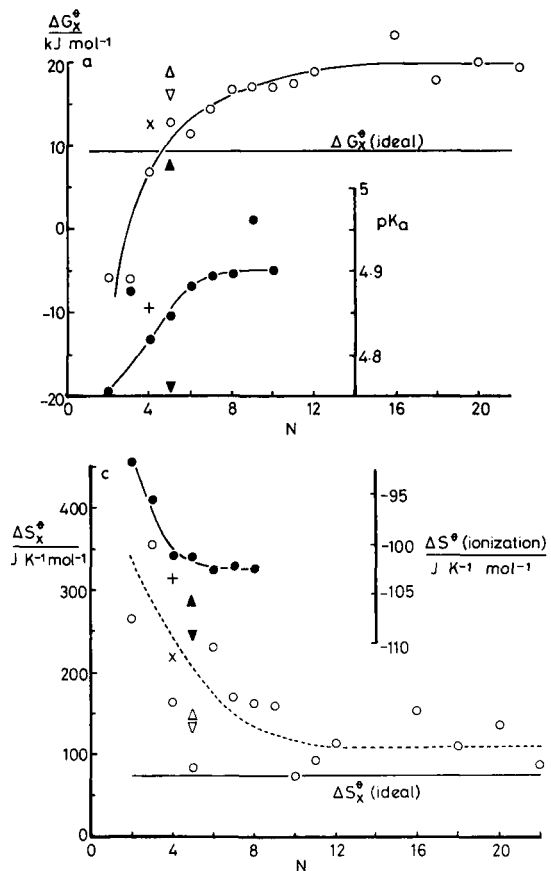


Fig. 1. Influence of carbon number,  $N$ , of the alkanolic acids on each standard thermodynamic quantity of solution for griseofulvin solubility (open symbols) and on the corresponding quantity for proton ionization in water at 25 °C (from Christensen et al 1970, full symbols). Thus, (a) relates  $\Delta G_x^\circ$  and  $pK_a$  to  $N$ ; (b) relates  $\Delta H_x^\circ$  and  $\Delta H^\circ(\text{ionization})$  to  $N$ ; (c) relates  $\Delta S_x^\circ$  and  $\Delta S^\circ(\text{ionization})$  to  $N$ . — Reliable and - - - approximate regression lines;  $\circ$  solubility behaviour and  $\bullet$  ionization behaviour of straight chain alkanolic acids;  $\times$  solubility behaviour and  $+$  ionization behaviour of 2-methylpropanoic acid;  $\nabla$  solubility behaviour and  $\blacktriangledown$  ionization behaviour of ( $\pm$ )-2-methylbutanoic acid;  $\triangle$  solubility behaviour and  $\blacktriangle$  ionization behaviour of trimethylacetic acid.

With increasing number of carbon atoms,  $N$ , among the straight chain alkanolic acids, the solubility at a given temperature tends to decrease (Table 1) and  $\Delta G_x^\circ$  tends to increase (Fig. 1(a)). In alkanolic acids of  $N \geq 5$ ,  $\Delta G^E$  is positive, tending towards  $10 \text{ kJ mol}^{-1}$ . The gradient of the tangent to the curve in Fig. 1(a) represents the methylene group contribution of the solvent to  $\Delta G_x^\circ$ , and this is not constant but decreases and virtually vanishes for  $N \geq 8$ . This trend probably reflects the increasing disturbance to the griseofulvin-carboxyl group interactions by the longer hydrocarbon chains and the partial replacement of these interactions by weaker dispersion forces between the hydrocarbon chains and the griseofulvin molecule. This explanation is supported by the parallel decrease in the proton-donating ability of the fatty acids, as measured by the increase of  $\text{pK}_a$  with increasing chain length (Fig. 1(a)) ( $\text{pK}_a$  data from Dippy 1938; Christensen et al 1970; Weast 1980).

If the solubility of griseofulvin in the fatty acids were determined solely by the concentration of carboxyl groups in the solvent milieu, such that the hydrocarbon chains were merely acting as an inert diluent, then the standard molal solubility,  $m_2^\circ$ , would increase linearly with increasing molality of the carboxyl group,  $m(\text{COOH}) = 1000/M_1$ , in the solvent, of molecular weight  $M_1$ , on descending the homologous series of alkanolic acids. That this is not the case is apparent from the linear relationship that is observed between  $m(\text{COOH})$  and a logarithmic function of solubility, which may be expressed as  $\Delta G_m^\circ$  according to equation (1), as shown in Fig. 2. Thus, the hydrocarbon chains play a significant role in actively reducing the specific solubilizing interaction between the basic griseofulvin molecule and the proton-donating carboxyl group on ascending the homologous series of straight chain alkanolic acids.

With increasing  $N$ , both  $\Delta H_x^\circ$  and  $\Delta S_x^\circ$  tend to decrease towards their ideal values, although in an irregular manner resembling an alternation, seen in Fig. 1(b), (c). These rough decreases provide support for the increasing influence of non-specific dispersion forces and the decreasing influence of specific hydrogen bonding interactions as the hydrocarbon component increases in the solvent milieu. This explanation is further buttressed by the parallel decreases in  $\Delta H^\circ$  and  $\Delta S^\circ$  for ionization of the alkanolic acids in water at  $25^\circ \text{C}$  (Fig. 1(b), (c) from Christensen et al 1970).

Solubility behaviour depends on the intermolecular interactions both in the solution phase and in the solid state. Since griseofulvin forms different

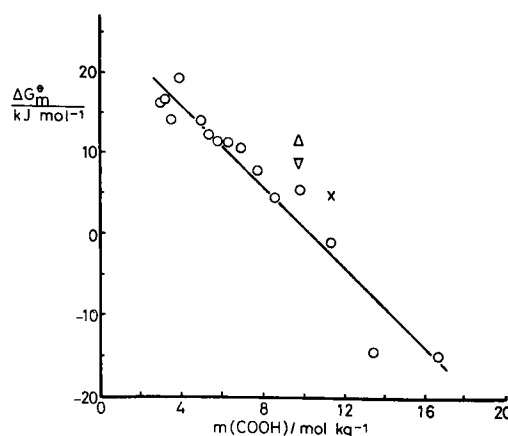


Fig. 2. Relationships between  $\Delta G_m^\circ$ , the molality-based standard free energy of solution of griseofulvin in each alkanolic acid at  $373.15 \text{ K}$  calculated from equation (1), and  $m(\text{COOH})$ , the molality of the carboxyl groups in each pure liquid alkanolic acid. — Line of linear regression for the straight chain alkanolic acids  $\circ$ ;  $\times$  2-methylpropanoic acid;  $\nabla$  ( $\pm$ )-2-methylbutanoic acid;  $\triangle$  trimethylacetic acid.

solvates, classified as Types I and II, with the various straight chain alkanolic acids except propanoic acid (Abougela & Grant 1979; Grant & Abougela 1981), the variability of  $\Delta H_x^\circ$  and  $\Delta S_x^\circ$  can be attributed to the unique dependence of the activity of each solid form on the precise structure of its crystal lattice. In support of this explanation, alternations in the solubility behaviour of cholesterol in the  $n$ -alkanols have been attributed by Flynn et al (1979) to solvent-induced crystalline changes in the solid cholesterol. The abnormally high  $\text{pK}_a$  value for propanoic acid may be associated with its inability to form a solvate with griseofulvin. With this exception, however, the interactions in solution, which are reflected in the ionization behaviour, tend to change smoothly from one fatty acid to the next (Fig. 1(a), (b), (c)). This effect will make the solubility behaviour less sensitive than expected to the sharp distinctions among the solid phases.

#### Formic acid as a solvent for griseofulvin

The solubility data and the thermodynamic quantities for formic acid followed the same trend as for the other acids, but had higher numerical values than expected, thus:  $\Delta G_x^\circ = -53 \text{ kJ mol}^{-1}$ ;  $\Delta H_x^\circ = 225 \text{ kJ mol}^{-1}$ ;  $\Delta S_x^\circ = 745 \text{ J K}^{-1} \text{ mol}^{-1}$ . These abnormally high values can be attributed to formic acid's stronger hydrogen bonding with griseofulvin as a result of its stronger acidic properties which are reflected in the following quantities for ionization:

$pK_a = 3.752$  at  $25^\circ\text{C}$  (Harned & Embree 1934);  $\Delta H^\circ = -0.335 \text{ kJ mol}^{-1}$ ;  $\Delta S^\circ = -72.8 \text{ J K}^{-1} \text{ mol}^{-1}$ .

#### *Influence of chain branching of the solvent*

Among the  $C_4$  and  $C_5$  alkanolic acids chain branching at C-2 (adjacent to the carboxyl group) increases the endothermicity of  $\Delta H_x^\circ$  and makes  $T\Delta S_x^\circ$  more positive, but to a smaller extent, so that  $\Delta G_x^\circ$  becomes more endergonic (Fig. 1(a), (b), (c)) and the solubility decreases. Since the chain branching was arranged to occur at C-2, it is expected to exert both an electronic and a steric influence on proton donation and hydrogen bonding. Since, however, the water molecule and the hydrated proton are much smaller than the griseofulvin molecule, the steric effect on the solubility will be much greater than on ionization in water. For this reason the thermodynamics of griseofulvin solubility and of ionization in water are sometimes affected differently by chain branching at C-2. For example, ( $\pm$ )-2-methylbutanoic acid has lower values of  $pK_a$  and  $\Delta H^\circ$  for ionization than has n-pentanoic acid, but confers higher values of  $\Delta G_x^\circ$  and  $\Delta H_x^\circ$  for the solubility of griseofulvin.

Because of thermodynamic compensation phenomena, n-pentanoic acid appears to give almost ideal values of  $\Delta G_x^\circ$ ,  $\Delta H_x^\circ$  and  $\Delta S_x^\circ$  (Fig. 1(a), (b) and (c)), but chain-branching of pentanoic acid produces deviations from ideality.

#### *Conclusion*

Specific interactions, particularly solute-solvent hydrogen bonding, appear to exert a greater effect than non-specific dispersion forces in accounting for the solubility behaviour of griseofulvin in the lower fatty acids. With the higher fatty acids, the increasing length of the hydrocarbon chain appears increasingly to disrupt this specific interaction. This disruption, which evidently changes the nature of solid griseofulvin-fatty acid solvates (Abougela & Grant

1979; Grant & Abougela 1981), takes place more gradually in solution than in the solid state.

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#### REFERENCES

- Abougela, I. K. A., Grant, D. J. W. (1979) *J. Pharm. Pharmacol.* 31: Suppl.: 49P
- Christensen, J. J., Slade, M. D., Smith, D. E., Izatt, R. M., Tsang, J. (1970) *J. Am. Chem. Soc.* 92: 4164-4167
- Dippy, J. F. J. (1938) *J. Chem. Soc.* 1938: 1222-1227
- Elworthy, P. H., Lipscomb, F. J. (1968) *J. Pharm. Pharmacol.* 20: 790-792
- Flynn, G. L., Shah, Y., Prakongpan, S., Kwan, K. H., Higuchi, W. I., Hofmann, A. F. (1979) *J. Pharm. Sci.* 9: 1090-1097
- Gordon, L. J., Scott, R. L. (1952) *J. Am. Chem. Soc.* 74: 4138-4140
- Grant, D. J. W., Abougela, I. K. A. (1981) *J. Pharm. Pharmacol.* 33: 619-620
- Hansford, D. T., Grant, D. J. W., Newton, J. M. (1980) *J. Chem. Soc. Faraday Trans. I*, 76: 2417-2431
- Harned, H. S., Embree, N. D. (1934) *J. Am. Chem. Soc.* 56: 1042-1044
- Higuchi, T., Richards, J. H., Davis, S. S., Kamada, A., Hou, J. P., Nakano, M., Nakano, N. I., Pitman, I. H. (1969) *J. Pharm. Sci.* 58: 661-671
- Hildebrand, J. H., Prausnitz, J. M., Scott, R. L. (1970) *Regular and Related Solutions*, Van Nostrand Reinhold, New York, N.Y., pp 22-26, 212-213
- Hildebrand, J. H., Scott, R. L. (1962) *Regular Solutions*, Prentice Hall Inc., New Jersey, pp 20-23
- Hollenbeck, G. R. (1980) *J. Pharm. Sci.* 69: 1241-1242
- James, K. C., Roberts, M. (1968) *J. Pharm. Pharmacol.* 30: 709-714
- Martindale (1977) *The Extra Pharmacopoeia*, 27th Edition. Edited by A. Wade and J. E. F. Reynolds. The Pharmaceutical Press, London, pp 634-637
- van't Hoff, J. H. (1886) *Arch. Néerl.* 20: 239-302.
- Weast, R. C. (1980) *Handbook of Chemistry and Physics*, 61st Edition, CRC Press, Inc., Boca Raton, Florida
- Yalkowsky, S. H. (1981) *J. Pharm. Sci.* 70: 971-973