Solubilities of testosterone propionate in non-polar solvents at 100°

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THE solubilities of the formate to valerate esters of testosterone in non-polar solvents at 25° were determined by James & Roberts (1968) who also compared them with ideal mole fraction solubilities (X_2), calculated from the equation,

$$-\ln.x_2 = \frac{\Delta H^F}{R}\left[\frac{T_M - 298}{298T_M}\right] \tag{1}$$

(Hildebrand & Scott 1962). ΔH^F is the heat of fusion of the solute and T_M the melting point. Changes in solubility as the homologous series is ascended were predicted by equation (1), but the individual experimental results did not agree with the calculated values. ΔH^F was calculated from the heat of fusion at the melting point, ΔH_M^F, by correcting for the differences in heat capacity of the solid and the supercooled liquid between T_M and T. The correction was estimated with a differential scanning calorimeter by extrapolating the liquid enthalpy line back to 25° and measuring the area between the extrapolation and the enthalpy line of the solid. The method was considered questionable, however, because it assumed that the enthalpy line of the supercooled liquid decreased linearly over the whole range of temperature. This theory is tested below by comparing the measured and calculated solubilities of testosterone propionate at a temperature just below its melting point, where the heat capacity correction is small and ΔH_M^F can be used for ΔH^F.

The solvents examined by James & Roberts (1968) had smaller molar volumes than the testosterone esters, and it was suggested that the difference in molar volume between solute and solvent could prevent the random distribution assumed by regular solution theory. Prediction of solubility would thus improve as the molar volume of the solvent approached that of the solute. The test is applied below by determining the solubility of testosterone propionate in a range of solvents.

EXPERIMENTAL

Volume fraction solubilities (ϕ_2) were calculated from the equation,

$$\phi_2 = \frac{X_2V_2}{X_1V_1 + X_2V_2} \tag{2}$$

where X is mole fraction solubility and V molar volume. The suffix 1 represents solvent, and 2 solute.

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Calculated mole fraction solubilities were obtained from the equation

$$-\ln X_2 = \frac{\Delta H^F}{R} \frac{(T_M - 373)}{373 T_M} + \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \tag{3}$$

where δ is solubility parameter (Hildebrand & Scott, 1962). ΔH_M^F (5·29 kcal mole^{-1}) taken from James & Roberts (1968), was substituted for ΔH_F.

Measured solubilities were determined using a method which has been described by Gordon & Scott (1952). Weighed quantities of solute and solvent were sealed in glass tubes, and the temperature at which solution occurred noted. Solubility at 100° was obtained from the plot of log solubility against log temperature by interpolation.

Solubility parameters and molar volumes were mainly from Hildebrand & Scott (1962). Molar volumes not quoted in this reference were determined from density measurements. The corresponding solubility parameters were calculated as $\left[\dfrac{\Delta H_v - RT}{V}\right]^{\frac{1}{2}}$ using molar heats of vaporisation (ΔH_v) from the equation,

$$\Delta H_V = -2950 + 23·7\, T_b + 0·020\, T_b^2 \tag{4}$$

(Hildebrand & Scott, 1950). Boiling points (T_b) were measured using a Perkin Elmer differential scanning calorimeter. Molar volume and solubility parameter of testosterone propionate were taken from James & Roberts (1968).

RESULTS AND DISCUSSION

Experimental solubilities are compared in Table 1 with those calculated from equation (3). The lack of agreement indicates that even when the value for heat of fusion is reliable, equation (3) does not predict the solubilities of testosterone esters in non-polar solvents. It also suggests, however, that even if the heat capacity correction were in error, it was only partly responsible for the poor agreement between experimental and calculated solubilities observed by James & Roberts (1968).

TABLE 1. COMPARISON OF EXPERIMENTAL AND CALCULATED SOLUBILITIES OF TESTOSTERONE PROPIONATE IN VARIOUS SOLVENTS

	Molar volume of solvent (cm³)	Solubility parameter of solvent (cal½ cm³/²)	Mole fraction solubility at 100°		Measured volume fraction solubility at 100°
			Measured	Calculated	
Benzene	89	9·2	0·33	0·70	0·62
Cyclohexane	109	8·2	0·38	0·63	0·62
Naphthalene	123	9·9	0·40	0·69	0·61
Phenanthrene	158	9·8	0·56	0·69	0·70
Dekalin	156	7·9	0·41	0·54	0·57
Tetralin	135	9·5	0·47	0·68	0·66
Carbon disulphide	61	10·0	0·51	0·69	0·83
Chloroform	81	9·2	0·63	0·70	0·86
Carbon tetrachloride	97	8·6	0·56	0·69	0·79
Carbon tetrabromide	105	10·7	0·63	0·68	0·83

In regular solutions, forces of attraction between like molecules are overcome by thermal agitation, resulting in completely random distribution. When the difference between the molar volumes of solute and

solvent is large, however, geometrical considerations may demand a more ordered arrangement, resulting in a finite entropy of mixing, and a lower solubility than that predicted. If the observed solubility is low because of the entropy of mixing, arising in turn from the differences in molar volume of solute and solvent, theoretical prediction of solubility should improve as the molecular shape and size of the solvent approach those of the solute. Ratios of measured to calculated solubility of testosterone propionate in several solvents are plotted in Fig. 1, against molar volume of solvent, and show the anticipated improvement in prediction of solbility as the molar volume of the solvent increases. The hydrocarbon solvents gave a linear relation, extrapolating to theoretical solubility at a molar volume of 205 cc, while carbon disulphide, carbon tetrabromide, carbon tetrachloride and chloroform appeared to belong to a different series.
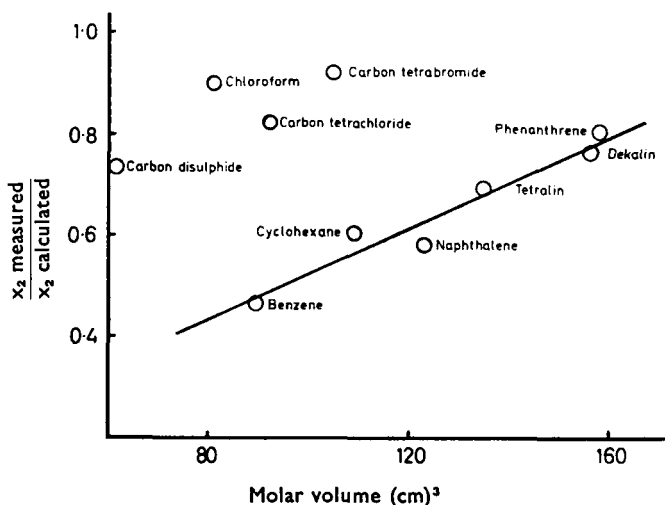

FIG. 1. Effect of molar volume of solvent on prediction of solubility.

Since there is a definite relation between molar volume of solvent and the accuracy with which the solubility of testosterone propionate can be predicted, the solubility parameter of 9·5 cal$^{\frac{1}{2}}$ cm$^{3/2}$, because it was determined from solubilities in solvents of varying molar volumes, is suspect. If the solubility parameter is in fact not 9·5 cal$^{\frac{1}{2}}$ cm$^{3/2}$, the correct value could bring all the results onto the same line. The solubility parameter giving the best straight line, fitting all the results, was calculated using an Elliott 803 electronic computer. The value obtained for all the results was 9·67 cal$^{\frac{1}{2}}$ cm$^{3/2}$ with a correlation coefficient of −0·19 while that for the hydrocarbon solvents alone was 9·50 cal$^{\frac{1}{2}}$ cm$^{3/2}$ with a correlation coefficient of 0·98. The two series must therefore be different, and the solubility parameter of 9·5 cal$^{\frac{1}{2}}$ cm$^{3/2}$ for testosterone propionate is confirmed.

SOLUBILITIES OF TESTOSTERONE PROPIONATE

Volume fraction solubilities are shown in Table 1. The values for the three halogen compounds and carbon disulphide are very similar, and those for the hydrocarbon solvents are also reasonably constant. It appears from this that the molecular proportions of solute and solvent which have been recorded as observed solubility at 100° are actually the limit at which the volume of solvent is no longer sufficient to maintain the system in the liquid state. The difference between the volume fractions for the two series suggests that, in the solvents examined, there are two types of orientation of solute molecules with respect to solvent molecules, one being more compact than the other.

References

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