

The effect of temperature on the solubilities of testosterone propionate in low polarity solvents

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The solubilities of testosterone propionate have been determined between 25 and 100° in 15 solvents and compared with theoretical values obtained from regular solution theory. Entropy considerations show that solvent-solute interactions occur in some solvents, increasing the solubility and resulting in deviations from regular solution behaviour. "Regular solutions" are obtained only in saturated hydrocarbon solvents, and the solubility is more accurately predicted as the temperature approaches the melting point, and as the molar volumes of solvent approach that of the solute.

It is seldom possible to predict the extent to which a particular solute will dissolve in a particular solvent. Regular solutions (Hildebrand & Scott, 1962) are an exception. In these, the mol fraction solubility (x_2) of a solid solute can be calculated from the equation,

$$-\ln x_2 = \frac{\Delta H^F}{R} \left[\frac{T_M - T}{T_M T} \right] + \frac{V_2 \phi_1^2}{RT} (\delta_1 - \delta_2)^2 \dots \dots (1)$$

The first term represents ideal solubility, and is derived from a consideration of the energy required to liquify the solid at temperature T . ΔH^F is the heat of fusion and T_M the melting point; V_2 the molar volume of the solute and ϕ_1 the volume fraction of the solvent. The second term represents the heat of mixing which is assessed in terms of the solubility parameters, δ_1 and δ_2 , the square roots of the cohesive energy densities of solvent and solute respectively. Expansion of the squared term thus gives the sum of the cohesive energy densities of solvent and solute minus twice their geometric mean, which is placed equal to the energy gained in bringing the unlike molecules into contact.

The use of equation (1), in an attempt to predict the solubilities of the lower testosterone esters (James & Roberts, 1968), led to poor agreement between experimental and predicted results and it was suggested that this was due either to the method of obtaining ΔH^F , or to the large difference between molar volumes of solute and solvent preventing random distribution. It has already been shown (Bowen & James, 1968) that the former was not the cause of the discrepancy and the second hypothesis is tested in this paper by measuring solubilities in a larger number of solvents and over a range of temperatures.

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EXPERIMENTAL

Testosterone propionate, a gift from Organon Laboratories Ltd, was used without further purification. Organic solvents were fractionally distilled and their purities checked by refractive index and density determinations.

Determination of solubilities. Solubilities below 60° were determined by the U tube method (James & Roberts, 1968) and at higher temperatures by the capillary tube method (Bowen & James, 1968).

At the lower end of the temperature range 40–70° many solubilities could not be determined by the capillary tube method because of slow rates of solution and the U-tube method was unsuitable at the higher end of the range because of the volatility of the solvents. Extrapolation of results from one method formed a continuous line with the others.

DISCUSSION

Provided the solution is dilute, or the solubility parameters of solute and solvent are similar, the entropy change of a solid forming a regular solution in a liquid is given by

$$\bar{S} - S^s = \frac{R \cdot d \ln x_2}{d \ln T} \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

(Hildebrand, 1952), where x_2 represents mol fraction solubility at temperature T. S^s is the entropy of the solid solute and \bar{S} the partial entropy of the solute in solution. $\bar{S} - S^s$ is therefore the sum of the entropies of fusion and dilution. Entropies of solution of testosterone propionate were investigated by plotting log mol fraction solubility against log temperature. Two types of behaviour were observed; entropies of solution were independent of temperature with the aliphatic hydrocarbons, but increased with increasing temperature with the other solvents. Typical plots are shown in Fig. 1. Entropies of solution were obtained from the slopes of the straight lines, or from the tangents to the curves at the temperatures of interest.

The theoretical entropy change on dispersing a liquid solute in a solvent is given by

$$\bar{S} - S^o = - R \ln x_2 \quad \dots \quad \dots \quad \dots \quad \dots \quad (3)$$

derived from a consideration of the number of possible configurations in a random distribution. S^o is the entropy of the liquid solute, so that $\bar{S} - S^o$ represents the entropy of dilution.

The effects of molar volumes on entropies of solution were tested by plotting entropies obtained from equation (2) against those calculated from equation (3). A typical result is shown in Fig. 2, the points were widely scattered and regression analysis gave low correlation coefficients and negative intercepts on the $d \log x_2 / d \log T$ axis, indicating negative entropies of fusion. In contrast, the points for the saturated aliphatic hydrocarbons gave good straight line plots, extrapolating to positive entropies of fusion, which agreed reasonably well with those obtained calorimetrically.

A similar situation has been observed by Hildebrand & Glew (1956), who determined the entropies of solution of iodine in a series of solvents. Their line, corresponding to that of the saturated hydrocarbon solvents in Fig. 2, was followed by the violet iodine solutions, which are known to be regular. All their other points lay below this line, and represented brown solutions, in which iodine is known to be

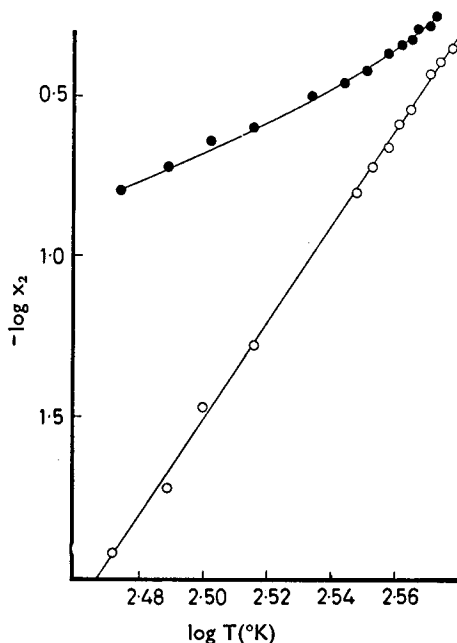


FIG. 1. Determination of entropies of solution: ○ cyclohexane; ● carbon tetrachloride.

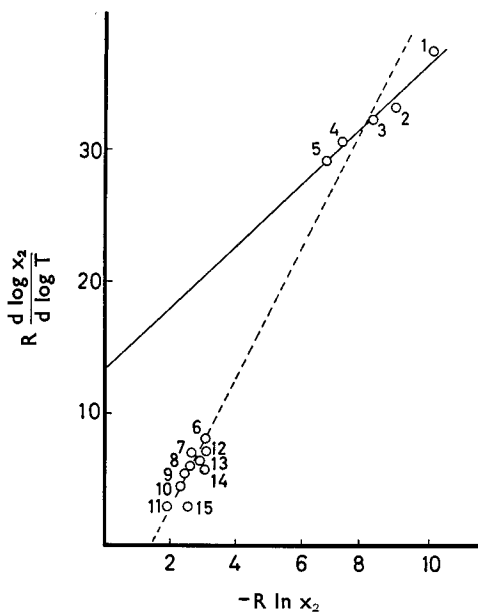


FIG. 2. Entropies of soln of testosterone propionate at 40°; 1, n-pentane (116); 2, n-hexane (132); 3, cyclopentane (95); 4, cyclohexane (109); 5, decalin (153); 6, carbon tetrachloride; 7, nitrobenzene; 8, benzene; 9, 1,2-dichloroethane; 10, *cis*- and *trans*-1,2-dichloroethylene; 11, chloroform; 12, carbon disulphide; 13, tetralin; 14, toluene; 15, chlorobenzene. - - - Regression on all points. — Regression on saturated hydrocarbons only. Figures in brackets are molar volumes.

complexed. Analogy suggests that the saturated hydrocarbon solutions of testosterone propionate are regular and that the diminished entropy in the other solvents may be due to complex formation.

The order in which the saturated aliphatic hydrocarbon solvents occur on their regression line was independent of molar volume, indicating that entropy of solution is not related to the relative molar volumes of solute and solvent and that random distribution is not prevented when the steroid molecules are much larger than those of the solvent.

The variation in observed solubility, as a function of calculated regular solubility, with temperature is shown in Fig. 3. Calculated solubilities were obtained using the integrated heat of fusion. This method appeared to be the better method for calculating regular solubilities since it gave straight lines or smooth curves, whereas the plots using mean heats of fusion were irregular. In all the solvents examined the experimental values approached the calculated values as the temperature increased. The solvents could be divided into the same two groups, in one group the ratio of experimental solubility to calculated solubility increased linearly with temperature, and in the other the ratio decreased uniformly, but not linearly with increasing temperature.

Although the entropy results indicate that the solvents in the first of the above groups form regular solutions of testosterone propionate, this appears to be contradicted by the fact that the observed solubilities are lower than those anticipated for regular solutions. Hiraoko & Hildebrand (1963) demonstrated that solvents containing substituted methyl groups did not obey the normal linear relation when mol fraction solubilities of iodine were plotted against the square of solubility parameter differences. Shinoda & Hildebrand (1965) showed that the solutions gave regular entropy plots and concluded that the solubility parameter did not give a correct measure of attractive forces between the iodine and the methyl groups, the geometric mean being too high an estimate of the intermolecular attraction between solute molecules and solvent molecules. It is probable that, in solutions which otherwise behave regularly, the solubilities of testosterone propionate are low for the same reason. When the molar volume of the solvent is significantly less than that of testosterone propionate, solvent molecules will be unable to approach solute molecules as closely as their own kind. The result will be a lower cohesive energy between solute and solvent than predicted by the geometric mean assumption, and a lower solubility than anticipated. This difference will diminish as the molar volume of the solvent approaches that of the solute, the geometric mean will become a better estimate of cohesive energy between solvent and solute and the observed solubility will approach the calculated value. Fig. 3 illustrates this because the straight lines occur in order of solvent molar volume. A similar argument can be advanced for the effect of temperature on the regular solutions, shown in Fig. 3. Translational molecular motion increases with temperature and opposes close molecular packing. Steric effects therefore become less important as the temperature increases, with a resulting increase in the reliability of the geometric mean and in the observed solubility.

It has been suggested that the entropy results indicate complexation between the solvents of the second group and testosterone propionate. Complexation affects the geometric mean in the opposite way to that outlined above. Attractive forces between unlike molecules are now greater than those between like molecules, and the cohesive energy is greater than that given by the geometric mean. The result is

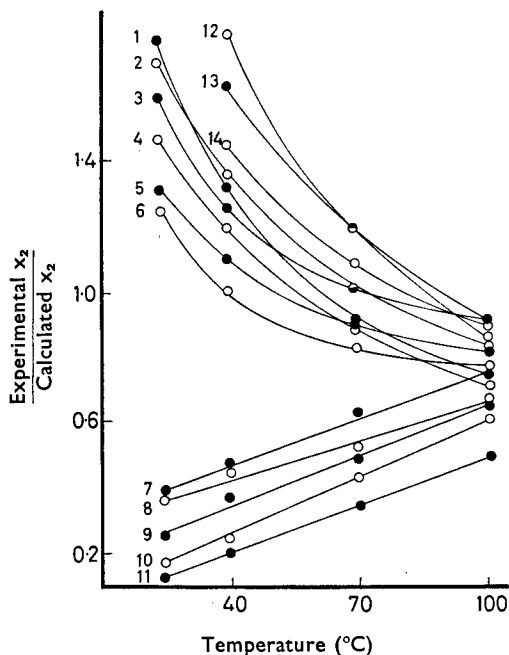


FIG. 3. Variation of experimental/calculated solubilities of testosterone propionate with temperature; 1, chlorobenzene; 2, benzene; 3, nitrobenzene; 4, tetralin; 5, carbon tetrachloride; 6, carbon disulphide; 7, decalin (153); 8, n-hexane (132); 9, n-pentane (116); 10, cyclohexane (109); 11, cyclopentane (95); 12, chloroform; 13, *cis*- and *trans*-1,2-dichloroethylene; 14, 1,2-dichloroethane. Figures in brackets are molar volumes.

that the solubilities are higher than those calculated for regular solutions, as is shown in Fig. 3. Complexation would be expected to decrease with increasing temperature, accounting for the fall in solubility observed in Fig. 3.

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