SOLUBILITIES OF TESTOSTERONE, METHYLTESTOSTERONE AND NANDROLONE IN ALKANOLS

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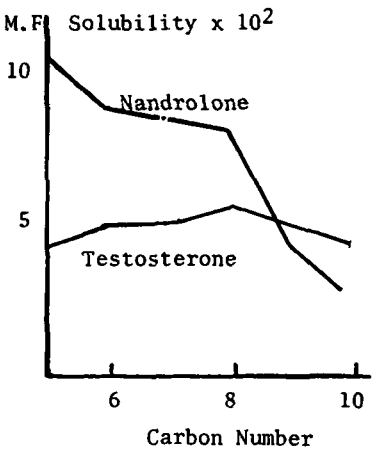
The activity coefficients (γ) of non-electrolytes in dilute regular solutions are given by Eq. 1, where A is a constant, dependent on the solute, and δ_1 and δ_2 are solubility parameters of solvent and solute respectively. When $\delta_1=\delta_2$,

$$\gamma = \exp.A(\delta_1-\delta_2)^2 \qquad (1)$$

the activity coefficient reduces to unity, the solution is ideal, and the solubility maximal. Solubilities of testosterone in the C_5 to C_{10} normal alkanols, whose solubility parameters decrease progressively from 11.1 to 8.8 $cal^{\frac{1}{2}}cm^{-3/2}$, passed through a maximum at C_8 (Fig. 1), suggesting that testosterone has the same solubility parameter as octanol (10.3). This is less than the calculated value (10.7). Furthermore, methyltestosterone does not have the same solubility parameter as testosterone, and yet it gave a similar plot of solubility against carbon number, with a maximum at C_8. However, nandrolone solubilities decreased progressively from C_5 to C_{10}, suggesting a solubility parameter higher than 11.1. The calculated result is 11.3, in agreement with regular solution theory.

The major weakness of regular solution theory is that it assumes the cohesive energy density between solute and solvent is the geometric mean of that between like molecules. If the solute and solvent molecules can pack together into a compact form, cohesive energy density will then be greater than that predicted by the geometric mean, and the entropy of mixing less than ideal, with a resulting enhanced solubility. Thermodynamic parameters of solution in alkanols were measured for methyltestosterone, nandrolone and testosterone. The testosterone entropies went through a minimum at C_7, suggesting a favoured orientation with heptanol, but when combined with enthalpies, gave Gibbs free energies which were minimal at octanol, in line with the observed solubilities. Methyltestosterone gave a similar result. Nandrolone entropies and free energies increased progressively with increasing solvent molecular weight, supporting the solubility profile shown in Fig. 1. The carbonyl group of testosterone hydrogen bonds with the hydroxyl hydrogen of octanol. Courtald models show that the octyl chain can fit closely along the β face of testosterone and methyltestosterone, with its terminal methyl group falling just short of the 17-hydroxyl group. It is suggested that this compact configuration is the reason for the solubility maximum and for the observed pattern of thermodynamic parameters. Increasing chain length beyond octanol, brings hydrocarbon groups in contact with 17-OH, and beyond the peripheri of the steroid. The absence of the 19-methyl group from nandrolone upsets the fit, and solubilities follow the regular pattern.



Similar solubility maxima have been observed with the parabens (Restaino & Martin 1964) and bromacids (Coutinho 1944). Courtald models indicate that their results fit the above suggestion.

Restaino, F.A. & Martin, A.N. (1964) J. Pharm. Sci. 53, 636-639.
Coutinho, H. (1944) Soap, Perfumery, Cosmetics, 914-926.

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