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Solubilities of mestanolone, methandienone, methyltestosterone, nandrolone and testosterone in homologous series of alkanes and alkanols

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Summary

The solubilities of mestanolone, methandienone, nandrolone and testosterone have been determined in the *n*-alkanes between C_7 and C_{16} and in *n*-alkanols between C_5 and C_{12}. The mole fraction solubilities in the alkanes increased rectilinearly with the carbon number of the solvent, indicating a progressively decreasing increment in free energy of mixing for each additional methylene group. The solubilities in the alkanols of all the steroids except nandrolone, followed a parabolic relationship with carbon number and with solubility parameter of the solvent, and approximately fitted regular solution theory predictions. Divergences between observed and predicted solubilities were explained in terms of an interaction between solute and solvent which invalidated the geometric mean assumption. The suggestion was supported by thermodynamic measurements. Nandrolone showed decreasing solubility with increasing solvent carbon number. Its behaviour fitted the theory suggested for the other steroids and was confirmed by the thermodynamic data.

Introduction

Much has been written about changes in solubility which occur when groups of solutes which form part of an homologous series are dissolved in a given solvent. The

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subject has been reviewed by Davis et al. (1974), who concluded that each additional methylene group contributed a constant increment to the excess free energy of mixing. In contrast, there is little to be found in which the properties of solutions in homologous series of solvents are compared. In a recent bioavailability study (James et al., 1980), the solubilities of methyltestosterone (17β-hydroxy-17α-methylandrost-4-en-3-one) were determined in homologous series of alkanes and alkanols, and as a result of the interesting results obtained, the investigation was extended to 4 other steroids, methandienone (17β-hydroxy-17α-methylandrosta-1,4-dien-3-one), mestanolone (17β-hydroxy-17α-methyl-5α-androstan-3-one), nandrolone (17β-hydroxyoestr-4-en-3-one) and testosterone (17β-hydroxyandrost-4-en-3-one). The results are presented below.

Materials and methods

Mestanolone, methandienone, methyltestosterone, nandrolone and testosterone of British Pharmacopoeia or Pharmaceutical Codex standard were recrystallized from absolute ethanol. Melting points agreed with published values. Alkanes and alkanols were obtained from BDH, and were used without further purification. All were claimed to be at least 98% pure, and had boiling points which agreed with the literature.

Determination of solubilities

Saturated solutions were prepared by continuously percolating a small volume of solvent through a plug of the crystalline solute. Preliminary experiments showed that 2 h at a temperature about 10°C in excess of the required value, followed by equilibration at the required temperature for 8 h was sufficient for saturation. Aliquots were removed, weighed and adjusted to volume with cyclohexane. Concentrations were determined from the UV extinction at the previously determined absorption maximum. Mestanolone was not a sufficiently powerful chromophore for this technique, and was therefore determined from the height of the carbonyl stretching peak at 1705 cm^{-1}, against pure solvent. A Beer's law relationship between peak height and concentration had been established previously.

Solubility parameters

Alkane solubility parameters were taken from James et al. (1976). Hoy (1970) published values for alkanols, and Small (1953), Rheineck and Lin (1968) and van Krevelen (1972) have listed group contributions for calculation of solubility parameters. The 4 sources yielded similar values for the alkanols, and the mean results were taken for this work.

Thermodynamic parameters

Solubilities of methandienone, methyltestosterone, nandrolone and testosterone were determined in alkanols at 20, 25, 30 and 35°C. Plots of log solubility against the reciprocal of temperature and against log temperature were rectilinear. Enthalpy

TABLE I

MOLE FRACTION SOLUBILITIES AT 25°C

(a) Alkanes – C_nH_{2n+2}	Mole fraction solubility ($\times 10^4$)							
Steroid	n = 6	7	8	9	10	11	12	16
Mestanolone	1.80(.03)	1.69(.04)	1.78(.19)	2.68(.11)	2.74(.24)	3.57(.22)	3.49(.58)	4.80(.32)
Methandienone	–	2.68(.01)	2.98(.01)	3.33(.01)	3.58(.02)	3.87(.01)	4.25(.01)	–
Methyltestosterone	2.44(.12)	2.99(.17)	3.47(.07)	3.71(.17)	4.02(.07)	4.64(.12)	4.69(.15)	5.86(.09)
Nandrolone	–	2.87(.22)	3.20(.01)	3.53(.03)	3.82(.01)	4.20(.02)	4.57(.02)	–
Testosterone	–	1.55(.01)	1.79(.03)	2.09(.03)	2.32(.00)	2.78(.00)	2.88(.00)	–

(b) Alkanols – $C_nH_{2n+1}OH$	Mole fraction solubility ($\times 10^2$)					
Steroid	n = 5	6	7	8	9	10
Mestanolone	0.86(.08)	1.08(.09)	1.37(.22)	1.58(.04)	1.48(.14)	1.38(.05)
Methandienone	5.78(.02)	6.00(.09)	6.19(.05)	5.94(.07)	5.01(.02)	3.35(.03)
Methyltestosterone	3.99(.03)	4.24(.01)	4.25(.04)	4.21(.04)	3.84(.03)	3.65(.04)
Nandrolone	10.59(.03)	8.89(.03)	8.52(.04)	8.10(.04)	4.31(.05)	2.61(.05)
Testosterone	4.50(.01)	4.97(.01)	5.09(.01)	5.69(.01)	4.89(.02)	4.41(.00)

The figures in parenthesis represent confidence levels ($P = 0.01$).

of solution was calculated from the slopes of the first set of plots, and entropies of solution from the second (Hildebrand et al., 1970). Free energies of solution were obtained from the relationship, $\Delta H = \Delta G + T\Delta S$.

Results and discussion

The solubilities of the 5 steroids in the C_7 to C_{16} *n*-alkanes are shown in Table 1. They increase uniformly as the solvent homologous series is ascended, and are typical of the results obtained with the other steroids. A rectilinear relationship between the logarithms of mole fraction solubilities ($\ln X_2$) and carbon number (N) was anticipated, by analogy with the behaviour of solute homologous series, which give a constant excess free energy increment for each methylene group. However, the plots were curved, whereas perfect rectilinear relationships were obtained between mole fraction solubility and carbon number. The plots for methandienone are shown in Fig. 1, and are typical of all the alkane results. Linear regression analysis yielded Eqn. 1, which on rearrangement and substitution in the van't Hoff isochore gives Eqn. 2. ΔG^E is the excess free energy of mixing, R the gas constant and T temperature. Eqn. 2 indicates a progressively diminishing free energy increment as the homologous series is ascended.

$$X_2 = 3.144 \times 10^{-5} N + 4.638 \times 10^{-5} \quad (n = 7; r = 0.999; s = 3.5 \times 10^{-6}) \qquad (1)$$

$$\Delta G^E = -RT \ln(3.144 \times 10^{-5} N + 4.638 \times 10^{-5}) \qquad (2)$$

The excess free energy of mixing in regular solutions is given by Eqn. 3. V_2 is the molar volume of the solute, which is constant for the comparisons under considera-

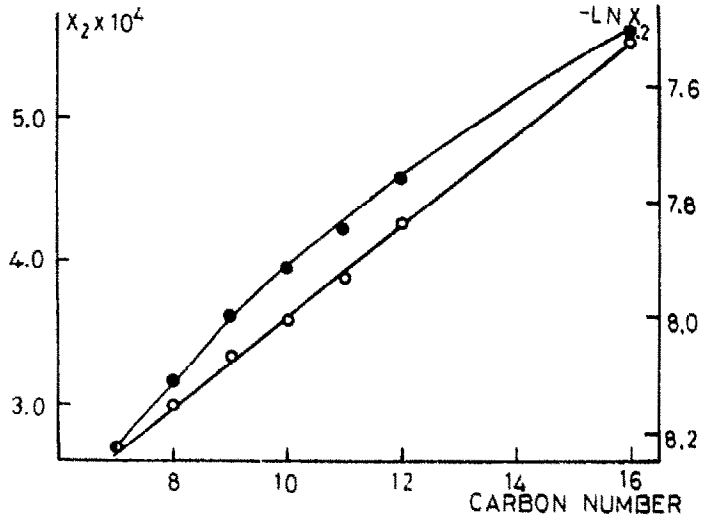

Fig. 1. Mole fraction solubilities of methandienone in *n*-alkanes at 25°C. Key: ○, X_2 against carbon number; ●, $-\ln X_2$ against carbon number.

tion, and ϕ_1 the volume fraction of the solvent; since X_2 is small, ϕ_1^2 can be approximated to unity. δ_1 and δ_2 are the solubility parameters of solvent and solute respectively, and are a function of the cohesive energy densities between like molecules in the solution (Hildebrand et al., 1970).

$$\Delta G^E = V_2\phi_1^2(\delta_1 - \delta_2)^2 \tag{3}$$

The solubility parameters of the alkanes under scrutiny are less than the values associated with 3-keto-17-hydroxy steroids (James et al., 1976). Since V_2, ϕ_1^2 and δ_2 are constant, Eqn. 3 represents the ascending side of a parabolic relationship between ΔG^E and δ_1. The characteristic curvature of a parabola indicates that the free energy increment for each additional methylene group in the alkanes decreases until $\delta_1 = \delta_2$, when $\Delta\Delta G^E_{CH_2} \rightarrow 0$. Several authors (Small, 1953; Hoy, 1970; Rheineck and Lin, 1968) have demonstrated that the solubility parameters of homologues decrease approximately rectilinearly with carbon number, so that Eqn. 3 gives support to the free energy changes inferred by Eqn. 2.

The alkanol solubilities can also be explained in terms of regular solution theory. Solubilities in the C_5 to C_{12} *n*-alkanols are shown in Table 1, and all but one can be seen to pass through a solubility maximum in the region of heptanol or octanol. The solubility of a solid solute in a solvent with which it forms a regular solution is given by Eqn. 4, in which a_2 represents ideal solubility and A is equal to $V_2\phi_1^2/RT$.

$$-\ln X_2 = -\ln a_2 + A(\delta_1 - \delta_2)^2 \tag{4}$$

Expansion of the bracketed term yields Eqn. 5, which is the equation for a parabola

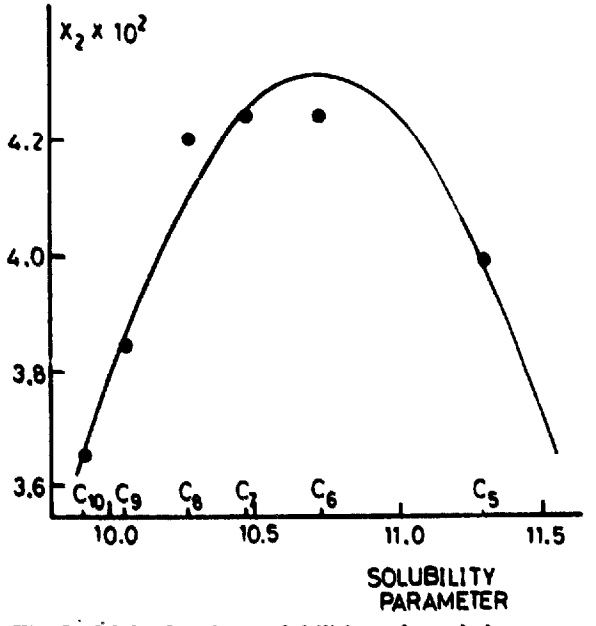

Fig. 2. Mole fraction solubilities of methyltestosterone in *n*-alkanols at 25°C. The continuous line represents the predicted results.

relating $\ln X_2$ to δ_1, since all the other terms in the equation are constant. The alkanol solubilities were introduced into a binomial curve fitting program, and the methyltestosterone results gave Eqn. 6.

$$-\ln X_2 = -\ln a_2 + A\delta_2^2 - 2A\delta_1\delta_2 + A\delta_1^2 \quad (5)$$

$$-\ln X_2 = 31.50 - 5.292\delta_1 + 0.2469\delta_1^2 \quad (n = 6;\ r = 0.972;\ s = 0.018) \quad (6)$$

The graph of Eqn. 6 is superimposed on the observed solubilities in Fig. 2, and there is reasonable agreement between calculated and measured results. Differentiation of Eqn. 6, and placing the result equal to zero, gives a solute solubility parameter of 10.7 H, which suggests that hexanol is the best solvent of the alkanols examined; but the experimental results indicate the solubility is greatest in heptanol. Furthermore, Eqn. 6 gives a symmetrical parabola, whereas the observed solubilities follow a skewed distribution, with the result that while the predicted solubilities are reasonably accurate, the overall profile is displaced.

The major weakness of Eqn. 4 is that it assumes that the cohesive energy density between a solute molecule and a solvent molecule is the geometric mean of the cohesive energy densities between two solute molecules and between two solvent molecules. Cohesive energy falls off with approximately the sixth power of the distance of separation, so that if the conditions cause the solute and solvent molecules to pack together in a particularly compact form, they could approach each other more closely than they are able to approach their own kind. Only a small reduction in the distance of separation is required to bring about a large increase in cohesive energy, with the result that the cohesive energy density between solute and solvent will be greater than the value estimated by the geometric mean assumption. A theory which fits this situation is illustrated in Fig. 3. It is known that the alkanol hydroxyl group hydrogen bonds with the 3-keto steroid group (James and Mehdizadeh, 1981). If the alkyl chain of the alkanol lies along the β-face of the steroid, where there is ample scope for attraction by dispersion forces, octanol is of such a length that its end-methyl group falls just short of the 17-hydroxy function of the steroid. If the alkyl chain is extended, as in nonanol, the alkyl chain comes within the range of the hydroxyl group, with resulting repulsion and increasing disorder.

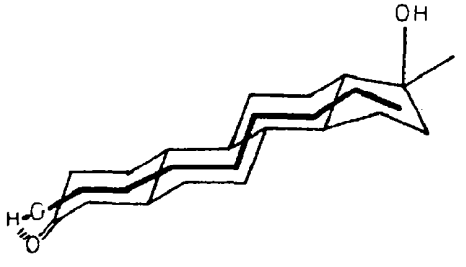

Fig. 3. Postulated interaction between octanol and testosterone. The thick line represents the alkyl chain of octanol lying along the β-face of the steroid.

TABLE 2

THERMODYNAMIC PARAMETERS OF SOLUTION IN ALKANOLS $C_nH_{2n+1}OH$

	Steroid n =	5	6	7	8	9	10
Methandienone	ΔH (kJ·mol^{-1})	21.54	20.98	20.54	21.12	21.54	25.24
	ΔS (J·mol^{-1}·deg^{-1})	69.94	68.00	66.56	68.42	69.70	81.61
	ΔG (J·mol^{-1})	698	716	705	731	769	920
Methyltestosterone	ΔH	26.53	25.20	25.49	24.38	25.67	25.26
	ΔS	85.92	81.61	82.44	78.99	83.08	81.60
	ΔG	926	880	923	841	912	943
Nandrolone	ΔH	7.52	7.63	8.64	8.73	9.20	13.75
	ΔS	24.46	24.70	28.12	28.12	29.84	44.75
	ΔG	231	269	260	356	308	415
Testosterone	ΔH	23.70	22.03	21.92	22.39	22.31	24.01
	ΔS	76.75	71.28	70.99	72.61	72.21	77.67
	ΔG	829	789	765	752	791	864

This idea was tested by constructing Coultald models. The octanol model fitted readily onto the β-face of the testosterone model, with its hydroxyl hydrogen-bonding with the 3-keto oxygen, and the terminal methyl falling just short of the 17-hydroxyl hydrogen. With nonanol the terminal methyl group came into contact with the hydroxyl group.

A model of this sort requires that the most stable combination should have the highest cohesive energy and the lowest entropy of formation, characterized by the lowest enthalpy and entropy of solution. Thermodynamic parameters are given in Table 2, and show that the free energies of solution of methyltestosterone and testosterone are minimal at octanol, in line with the observed solubilities. The lowest free energy for methandienone occurs at heptanol, again in line with the observed solubilities. It appears from this that the shorter quinonoid A ring of methandienone brings the end methyl group of octanol too close to the 17-hydroxy group.

Nandrolone did not appear to behave in the same way as the other solutes. The variation in solubility as the alkanol homologous series was ascended is shown in Fig. 4, solubilities decreased progressively from C_5 to C_{10}, suggesting that the maximum in the parabola for this compound corresponded with a solubility parameter greater than 11.3 H (for pentanol). The thermodynamic parameters, shown in Table 2, supported this observation. Enthalpies, entropies and free energies of solution all increased uniformly as the alkanol homologous series was ascended, indicating a progressive decrease in solubility. However, regression analysis predicted that the line drawn in Fig. 4 was the best-fitting parabola for the results, giving a solubility maximum corresponding to a solubility parameter of 11.0 H. The stereo-

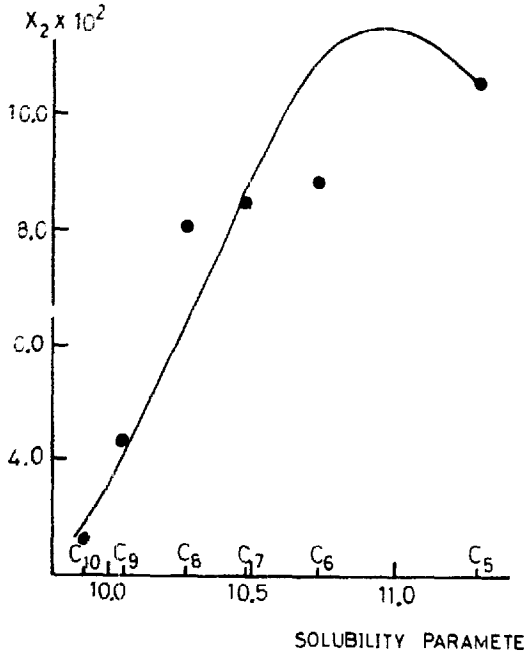

Fig. 4. Mole fraction solubilities of nandrolone in *n*-alkanols at 25°C. The continuous line represents the predicted results.

chemistry of the nandrolone molecule fits these observations. Courtald models indicated that the absence of the 19-angular methyl group leaves a cavity in the surface of the nandrolone molecule, with the result that the alkanols do not fit as closely along the β-face, as with the other steroids.

Whatever relationship applies to the nandrolone results, it is clear that the best solvent is lower down the alkanol homologous series than the best solvent for the remainder of the steroids examined. It may therefore be concluded that while regular solution theory will give an approximate idea of the solubility profiles of steroids in homologous series of alkanols, the precise answers depend on factors additional to those upon which Eqn. 4 is based.

Acknowledgements

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