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SOLUTION THERMODYNAMICS OF SOME POTENTIALLY LONG-ACTING NORETHINDRONE DERIVATIVES II. SOLUTIONS IN 2,2,4-TRIMETHYLPENTANE (ISO-OCTANE)

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SUMMARY

A form of phase solubility analysis has been used to determine the solubilities in iso-octane of a number of potentially long-acting derivatives of norethindrone over the temperature range 5–55°C. From these data enthalpies of solution and, using a modification of the Flory–Huggins equation, the excess functions of free energy, enthalpy and entropy at infinite dilution have been calculated. The influence of molecular structure upon the excess free energy of solution at infinite dilution has been examined. The value of solubility data in iso-octane in predicting the solubilities of these compounds in solvents of pharmaceutical importance is discussed.

INTRODUCTION

The interaction of drug molecule with surrounding molecules can be characterized on the macroscopic scale by thermodynamic functions. Since the body is an isothermal, isobaric system, the natural thermodynamic function to employ is the chemical potential, μ. This itself cannot be measured, but changes in chemical potential are measurable, and so it is necessary to adopt a standard state.

The pure drug is the most accessible state, but it is usually a solid. Since one is generally interested in solution properties, the choice of the crystal as standard state introduces complexities in the free energy changes from solid to solution that result from the forms of crystal lattice. In particular there may be considerable differences between the crystal structures of compounds with similar molecular structures and pharmacological activities. The choice of the crystal as the standard state is thus appropriate for the

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study of solubility, but not for examination of detailed interactions between solute and solvent and of transfer of solute between phases.

The pure liquid is a suitable standard state for examining the effect of molecular structure on solubility, but there are experimental difficulties as the drug must exist in a metastable supercooled liquid at the temperature of interest for its thermodynamic activity to be measurable. This is the case for the norethindrone derivatives whose thermodynamic properties are described in this paper and whose free energies of fusion at room temperature have been measured (Lewis and Enever, 1979).

The interactions of a drug molecule with surrounding molecules in vivo are varied and complex since the medium may vary from adipose tissue, which is hydrophobic but contains some polar groups, to the mainly aqueous plasma. Protein binding may be by interaction of polar groups or by a non-specific hydrophobic 'bond'. Possible standard states are dilute solutions of the drug in water or in an organic solvent that approximates in hydrophobicity and proportions of polar groups to the adipose tissue – such as 1-octanol (Hansch and Dunn, 1972) or ethyl oleate (Chaudry and James, 1974). Another approach has been to choose as standard state the isolated non-interacting molecule (i.e. in a vapour at low pressure), but this state is of little general pharmaceutical interest and it is difficult to investigate in the case of non-volatile drugs. Rytting et al. (1972) suggested as a practical standard a dilute solution of the drug in a saturated hydrocarbon. Solvent–solute interactions are non-specific and partition coefficients between hydrocarbon and water will demonstrate the hydrophobic effect in these compounds. The work described here examines the thermodynamic relationships between three possible standard states (solid, liquid and dilute solution in a hydrocarbon solvent) prior to studying aqueous solutions of these steroids. Discussion of mechanisms of prolongation of action will then be possible using these data and the limited pharmacokinetic results that are available.

Measurements of the solubilities of norethindrone and 12 of its derivatives in 2,2,4-trimethylpentane (iso-octane) are reported here. Differences in chemical potential between the pure liquid and the dilute solution are calculated and excess enthalpies and entropies of solution derived using a simple model for the free energy of mixing.

The partial molar free energy of transfer of solute from the pure liquid to a solution in equilibrium with solute crystal is given by:

$$\Delta\mu^0 = \mu^0 - \mu^\ell = (\mu^0 - \mu^s) - (\mu^\ell - \mu^s) = -\Delta G^f \qquad (1)$$

where μ^0, μ^ℓ and μ^s are the chemical potentials of the solute in the saturated solution, the pure liquid and the crystals respectively, and ΔG^f is the molar free energy of fusion.

The change in partial molar free energy for a solution which is not saturated is given by:

$$\Delta\mu = \mu - \mu^\ell = RT \ln \frac{c}{c^0} - \Delta G^f \qquad (2)$$

provided the solution is very dilute and the solubility of the crystals is very low. Here c is the concentration of solute and c^0 is its solubility.

Equation 2 applies whatever the concentration scale employed and can be generalized for non-dilute solutions. $\Delta\mu$ is a free energy change between two real systems and is thus

directly measurable. Standard free energy changes, on the other hand, are concentration scale-dependent, as the standard states employed are defined according to the concentration scale chosen (Davis et al., 1974). In some cases the solution standard is a hypothetical solution of unit molar, molal or mole fraction concentration behaving as though it were infinitely dilute (Rytting et al., 1972).

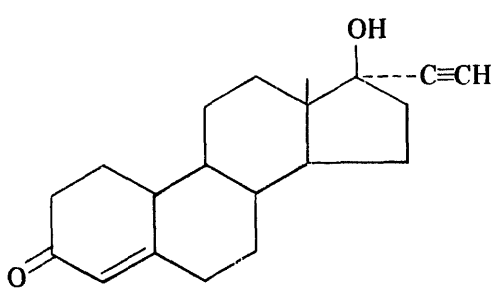
Free energy data for transfer of molecules between phases can be used to obtain evidence of the differences in the environment of the solute molecules between the phases. This applies to transfer of solute from pure solid, liquid or gas to the solution just as much as between two immiscible liquids. Since the chemical potential depends upon the dilution of the solute, it is advantageous to eliminate from the chemical potential that part of it which results from the entropy of dilution. There are a number of methods of attempting this and they depend ultimately on various statistical mechanical treatments of the mixing process. According to whichever method is used, a different entropy of dilution will be obtained and the result will be a different residual chemical potential change representing differences in solvation (Ben-Naim, 1978). It is this that is sometimes described as the standard free energy of a hypothetical system, or as an excess free energy ΔG^e. It is significant only in so far as the model for the entropy of dilution is correct. The measured change in chemical potential does not depend upon the model in any way.

MATERIALS AND METHODS

Materials

2,2,4-Trimethylpentane (iso-octane) Spectroscopy Grade obtained from B.D.H. Limited, Poole, England.

I Norethindrone (Serva Feinbiochemica)



II Norethindrone acetate (Serva Feinbiochemica)
III Norethindrone heptanoate (enanthate) (Schering A.G.)
IV Norethindrone dimethylpropionate
V Norethindrone trans-4-hexylcyclohexylcarboxylate
VI Norethindrone trans-3-(4-butylcyclohexyl)propionate
VII Norethindrone benzoate
VIII Norethindrone 4-biphenylcarboxylate
IX Norethindrone 4-cyclohexylbenzoate
X Norethindrone 6-(4-chlorophenyl)hexanoate

XI Norethindrone pentamethyldisiloxyl ether
XII Norethindrone 4-bicyclohexylcarboxylate
XIII Norethindrone 4-phenoxybenzoate

The structures and the sources of compounds IV–XI are given by Lewis and Enever (1979). Compounds XII and XIII were obtained through the World Health Organization from Dr. A. Shafiee, University of Tehran and Professor P.N. Natarajan, University of Singapore, respectively, who synthesized them.

Methods

Solubilities in 2,2,4-trimethylpentane were determined using phase solubility analysis. Known masses of solute and solvent were equilibrated at the required temperature for between 6 and 72 h depending on the solubility and the temperature. The excess solid was separated from the solution using cellulose acetate membranes. The concentration of the solute was determined by spectrophotometry in the case of all compounds with the exception of the heptanoate (III) and hexylcyclohexylcarboxylate (V), where it was determined by evaporating down a known mass of solution and weighing the residue. The concentration was then plotted against the solute mass per unit mass of solvent and the intercept of the linear plot on the concentration axis gave the solubility and the slope the degree of impurity (Mader and Grady, 1970).

The degree of impurity was checked by high precision liquid chromatography using a Partisil-10 octadecylsilyl bonded phase column. Many of the compounds are initially purified using silica column chromatography so it is necessary to use a different system to check the purity. The mobile phase used was methanol : water in various proportions between 65 : 35 and 80 : 20 by volume.

X-ray diffraction data were obtained with a Guinier camera, recording the patterns of the original crystals and the samples after equilibration with solvent in case there was any change in the crystal lattice. This precaution was considered important as steroids are known to exhibit polymorphism (Haleblian and McCrone, 1969). No such changes were observed.

The free energy of fusion of compounds XII and XIII was obtained by differential scanning calorimetry as described in a previous paper for the other compounds (Lewis and Enever, 1979). Enthalpies of fusion, $\Delta H^f(T)$, were measured from 260 K to the melting temperature, T_m. The free energy of fusion is then given by:

$$\Delta G^f(T_0) = \int_{T_0}^{T_m} \frac{\Delta H^f(T)\, dT}{T^2} \qquad (3)$$

RESULTS AND DISCUSSION

The solubilities of all the compounds are plotted as $\log_{10}\phi$, where ϕ is the mass fraction, against T^{-1}, in Figs. 1and 2. Where the saturated solutions are dilute ($\phi < 10^{-3}$) these plots are linear. Above this concentration deviations from linearity are observed. The linear plots for the lower solubilities indicate a constant molar enthalpy of solution

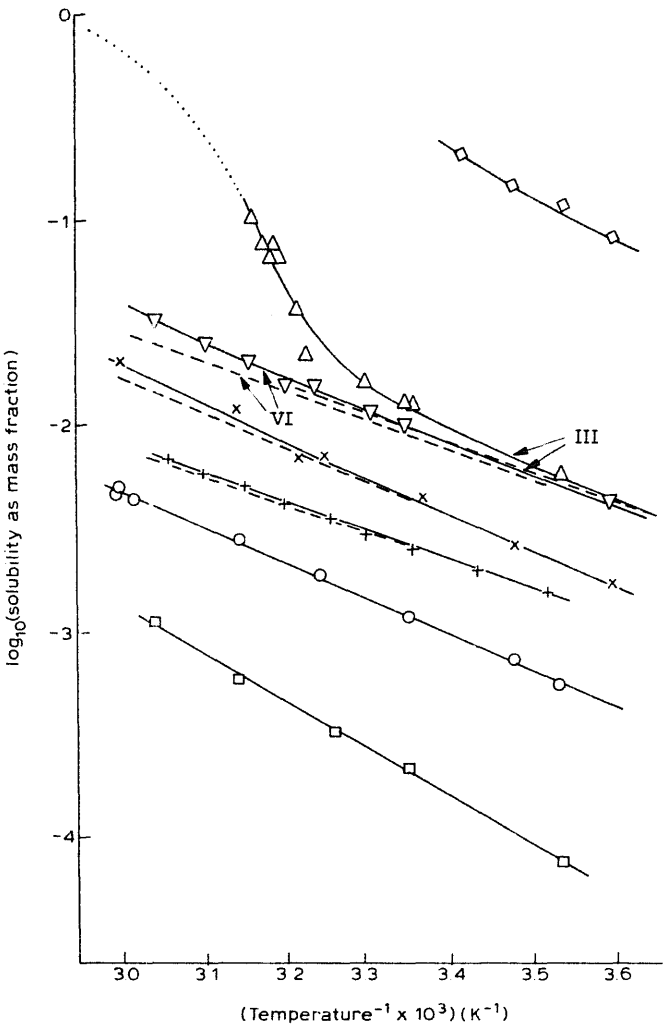


Fig. 1. Relation between $\log_{10}$ (solubility in iso-octane) and reciprocal of absolute temperature for aliphatic derivatives of norethindrone. - - - - - -, calculated log γ^{∞} values; · · · · · ·, extrapolation according to Eqns. 8 and 11. Key: ○, norethindrone acetate (II); △, norethindrone heptanoate (III): □, norethindrone dimethylpropionate (IV); ×, norethindrone trans-4-hexylcyclohexylcarboxylate (V); ▽, norethindrone trans-3-(4-butylcyclohexyl)propionate (VI); ◇, norethindrone pentamethyldisiloxyl ether (XI); +, norethindrone 4-bicyclohexylcarboxylate (XII).

within experimental error

$$\Delta\bar{H} = \frac{-R\,\partial \ln \phi}{\partial(1/T)} \tag{4}$$

where $\Delta\bar{H}$ is the partial molar enthalpy of transfer of the solute from the crystal to the dilute solution. Regression analysis of the $\log \phi$ vs T^{-1} plots produced slightly better

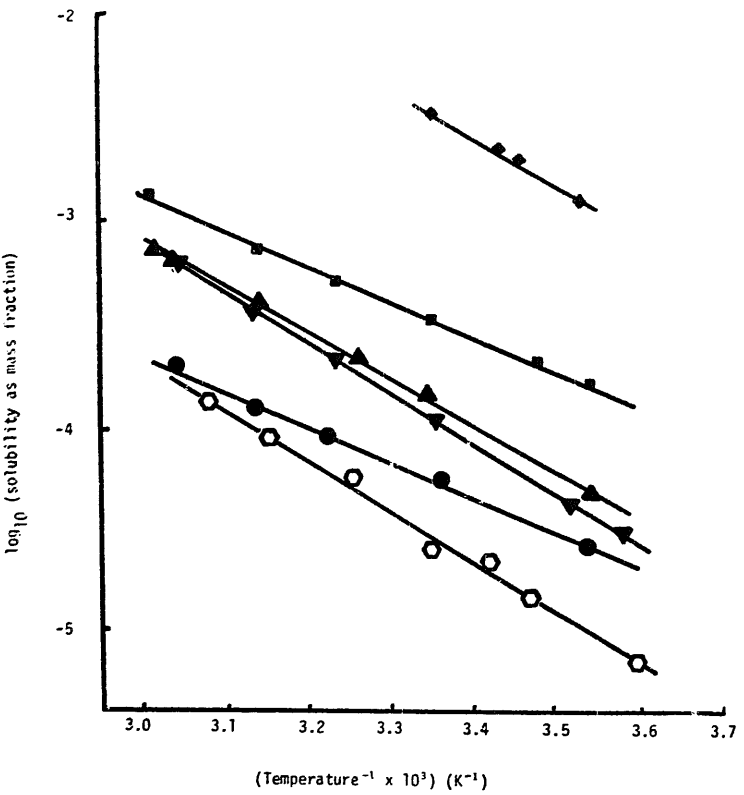


Fig. 2. Relation between $\log_{10}$ (solubility in iso-octane) and reciprocal of absolute temperature for norethindrone and its aromatic derivatives. Key: ○, norethindrone (I); ●, norethindrone benzoate (VII); ▲, norethindrone 4-biphenylcarboxylate (VIII); ■, norethindrone 4-cyclohexylbenzoate (IX); ▼, norethindrone 6-(4-chlorophenyl)hexanoate (X); ◆, norethindrone 4-phenoxybenzoate (XIII).

results than linear regression of log ϕ against log T which gave

$$\Delta\bar{H} = T\,\Delta\bar{S} = RT\frac{\partial \ln \phi}{\partial \ln T} \tag{5}$$

To obtain the enthalpy of solution of these compounds which have higher solubilities, in general those esters with aliphatic side chains, corrections must be made and the activity coefficient at infinite dilution obtained. Equation 2 is generalized for all concentrations of solute and the activity coefficient γ is defined here relative to the solid by

$$\mu - \mu^s = RT \ln \phi\gamma \tag{6}$$

At infinite dilution $\gamma \rightarrow \gamma^\infty$. Log γ^∞ is useful in a number of ways. Firstly it can be used as a basis for discussion of the interaction of a solute molecule with surrounding solvent

molecules and it can be differentiated to give the enthalpy of solution at infinite dilution.

$$\Delta\bar{H} = \frac{\partial \ln \gamma^{\infty}}{\partial(1/T)} \tag{7}$$

Secondly, it can be used as a basis for prediction of solubility in other solvents using regular solution theory (Hildebrand et al., 1970) and, using partition data and the thermodynamics of functional groups, the solubility in water can be predicted (Yalkowsky et al., 1972).

In order to correct the data for non-ideal-dilute behaviour a model must be chosen. In this paper a form of the Flory–Huggins equation (Flory, 1952) is used

$$\mu - \mu^{s} = RT \ln \phi - RT(r-1)(1-\phi) + \Delta G^{f} + \Delta G^{e} \tag{8}$$

where r is the ratio of the molecular mass of solute to that of the solvent. This equation has been used instead of the more familiar mole fraction equation because the molecules are large – considerably larger than the solvent molecules – and it is anticipated that in future work norethindrone derivatives and other molecules of still higher molecular weight will be investigated. Both the Flory–Huggins equation and the mole fraction equation have one important disadvantage. The statistical mechanical theories on which they are derived assume a lattice structure for which there is no evidence, and they also assume constant volume (Guggenheim, 1951). An expansion term is therefore included in ΔG^{e}.

For moderately dilute solutions the simple Eqn. 9 suffices

$$\Delta G^{e} = \Delta G^{e\infty}(1-\phi)^{2} \tag{9}$$

and so from Eqns. 6, 8 and 9 $\log \gamma^{\infty}$ can be calculated, i.e.

$$RT \ln \gamma^{\infty} = \{-RT[\ln \phi + (r-1)(\phi - \phi^{2})] - \Delta G^{f}(2\phi - \phi^{2})\}\{1-\phi\}^{-2} \tag{10}$$

and $(-\log \gamma^{\infty})$ calculated according to Eqn. 10 is plotted against T^{-1} for norethindrone bicyclohexylcarboxylate, butylcyclohexylpropionate and hexylcyclohexylcarboxylate in Fig. 1. Enthalpies for solution calculated according to Eqn. 7 are listed in Table 1.

ΔG^{e} for norethindrone heptanoate (III) has a more complex form and Eqn. 9 does not describe its solubility adequately. Without an extensive series of measurements of vapour pressures over a wide range of concentrations and temperatures the form of dependence of ΔG^{e} on temperature and composition cannot be fixed unambiguously. For this compound the solubilities are considerably higher than those of all other derivatives except norethindrone pentamethyldisoloxyl ether, and this is probably the reason for its atypical behaviour. An equation of a form introduced by Scatchard and Harmer (1935) is used here

$$\Delta G^{e} = \Delta G^{e\infty}(1 - \Gamma\phi)(1-\phi)^{2} \tag{11}$$

Γ is assumed independent of temperature over the range at which it is an important factor

TABLE 1

SOLUBILITIES OF NORETHINDRONE DERIVATIVES IN ISO-OCTANE AT 25°C AND ENTHALPIES OF SOLUTION CALCULATED FROM EQUATION 7 TOGETHER WITH ASSOCIATED CORRELATION COEFFICIENTS

Compound	Log solubility ($\log \phi$)	Enthalpy of solution ($\Delta\bar{H}$ kJ mol^{-1})	r^2
Norethindrone (I)	−4.52	46.8	0.994
Norethindrone acetate (II)	−2.92	33.2	0.998
Norethindrone heptanoate (III)	−1.96	(26.3)	–
Norethindrone dimethylpropionate (IV)	−3.69	45.2	0.996
Norethindrone trans-4-hexylcyclohexylcarboxylate (V)	−2.33	30.2	0.986
Norethindrone trans-3-(4-butylcyclohexyl)propionate (VI)	−2.03	26.5	0.995
Norethindrone benzoate (VII)	−4.22	31.2	0.998
Norethindrone 4-biphenyl carboxylate (VIII)	−3.86	40.4	0.983
Norethindrone 4-cyclohexylbenzoate (IX)	−3.47	32.4	0.998
Norethindrone 6-(4-chlorophenyl)hexanoate (X)	−3.96	46.3	0.999
Norethindrone pentamethyldisiloxyl ether (XI)	−0.94	21.6	0.926
Norethindrone 4-bicyclohexylcarboxylate (XII)	−2.57	25.3	0.980
Norethindrone 4-phenoxybenzoate (XIII)	−2.52	41.7	0.985

(300–315 K). Taking $\Gamma = 2.0$, $(-\log \gamma^{\infty})$ and $(-\log \gamma)$ for the saturated solution have been calculated and are plotted in Fig. 1.

Using Eqns. 8, 9 and 11, values of $\Delta G^{e\infty}$, the excess partial molar free energy of solution in iso-octane of each compound, were calculated. The results are plotted in Fig. 3 against the absolute temperature T. Values of ΔG^{f} had been obtained previously as functions of temperature by measurement of the molar heat capacities of both crystals and the supercooled liquid down to room temperature (Lewis and Enever, 1979). Below the glasss transition temperature extrapolated values of ΔC_p were used to calculate ΔG^{f} (crystal → liquid).

For norethindrone (I) itself and its hexylcyclohexylcarboxylate ester (V) it was not possible to calculate ΔG^{f} at room temperature as the liquid did not supercool. ΔG^{f} was estimated by assuming $\Delta G^{f} \sim 0.75\, \Delta H^{f}_{m}\, (1 - T/T_m)$ from comparison with data for the other compounds which supercooled. This was thought to give a reasonable enough estimate for $\Delta G^{e\infty}$, but it was not sufficiently accurate to be differentiated to obtain the excess enthalpy and entropy.

$\Delta H^{e\infty}$ and $\Delta S^{e\infty}$ can be derived from $\Delta G^{e\infty}$ as follows:

$$\frac{\partial\, \Delta G^{e\infty}}{\partial T} = -\Delta S^{e\infty} \tag{12}$$

$$\frac{\partial\, \Delta G^{e\infty}/T}{\partial \frac{1}{T}} = \Delta H^{e\infty} \tag{13}$$

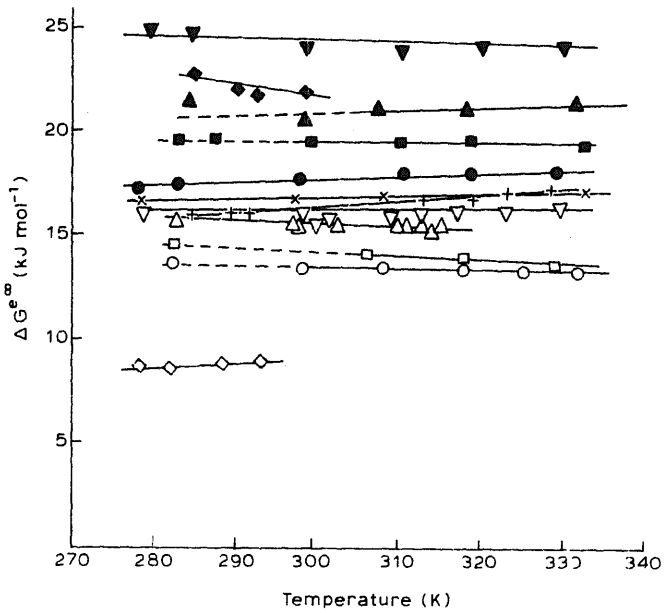


Fig. 3. Relation between excess free energy of solution at infinite dilution in iso-octane ($\Delta G^{e\infty}$) and temperature for the aliphatic and aromatic derivatives of norethindrone. Key: as in Figs. 1 and 2.

It is assumed that both of these are constant because the method of determining enthalpy and entropy from the variation of free energy with temperature is insufficiently precise for determining variation in enthalpy. $\Delta H^{e\infty}$ is unlikely to be constant bearing in mind the increase in volume of the system with temperature, and there is evidence of a decrease with temperature in the enthalpy of mixing of some hydrocarbons (Orwoll and Flory, 1967). Since ΔH^f increased with temperature for the norethindrone derivatives (Lewis and Enever, 1979) and the heat of solution, ΔH^s, is constant to a good approximation (Table 1), ΔH^e apparently decreases with temperature. This is not conclusive evidence for such a decrease if the entropy of solution (from crystals to the saturated solution) is assumed constant; $\Delta\bar{S} = \Delta\bar{H}/T$ = constant, i.e. $\Delta\bar{H}$ increases proportionally with temperature, $\Delta H^{e\infty}$ is still calculated to decrease with temperature.

Values of $\Delta H^{e\infty}$ and $\Delta S^{e\infty}$ were calculated by Eqns. 12 and 13 and the results are shown, together with associated standard deviations, in Table 2. In the case of norethindrone (I) and norethindrone hexylcyclohexylcarboxylate ester (V), ΔH^e was calculated by estimating ΔH^f from similar data and subtracting it from $\Delta\bar{H}$ (Table 1). These results are therefore less dependable.

In the case of norethindrone cyclohexylbenzoate (IX) and norethindrone biphenylcarboxylate (VIII), long extrapolations of ΔC_p had been used to obtain ΔG^f below the glass transition temperature. It was suggested (Lewis and Enever, 1979) that such data, more than 30–50 degrees below T_g, should not be differentiated and therefore $\Delta H^{e\infty}$ and $\Delta G^{e\infty}$ have been determined for these compounds using only the data above 298 K.

It can be seen that the major part of ΔG^e is enthalpic in nature although the entropic component is not negligible. These systems thus behave as regular solutions (Hildebrand et al., 1970), as has been previously observed for testosterone esters (James et al., 1976).

TABLE 2

EXCESS THERMODYNAMIC FUNCTIONS AT INFINITE DILUTION FOR THE STEROID DERIVATIVES AT 25°C TOGETHER WITH ASSOCIATED STANDARD DEVIATIONS OF THE MEASUREMENTS

Compound	$\Delta G^{e\infty}$ (kJ mol^{-1})	$\Delta H^{e\infty}$ (kJ mol^{-1})	$\Delta S^{e\infty}$ (J K^{-1} mol^{-1})
Norethindrone (I)	17.0 ± 1.0	(19.00) [a]	(6.7) [a]
Norethindrone acetate (II)	13.65 ± 0.06	14.64 ± 0.36	3.2 ± 1.1
Norethindrone heptanoate (III)	15.70 ± 0.18	17.40 ± 1.80	6.0 ± 6.0
Norethindrone dimethylpropionate (IV)	14.00 ± 0.30	17.22 ± 2.19	10.80 ± 8.10
Norethindrone trans-4-hexylcyclohexyl-carboxylate (V)	16.90 ± 0.5	(16.6) [a]	(1.0) [a]
Norethindrone trans-3-(4-butylcyclohexyl) propionate (VI)	16.25 ± 0.16	11.71 ± 1.17	−15.50 ± 3.60
Norethindrone benzoate (VII)	17.90 ± 0.10	12.90 ± 0.40	−16.60 ± 1.33
Norethindrone 4-biphenylcarboxylate (VIII)	20.85 ± 0.10	14.10 ± 1.60	−21.00 ± 5.50
Norethindrone 4-cyclohexylbenzoate (IX)	19.60 ± 0.06	19.50 ± 0.04	−0.10 ± 1.20
Norethindrone 6-(4-chlorophenyl)hexanoate (X)	24.40 ± 0.25	26.10 ± 1.50	4.30 ± 5.10
Norethindrone pentamethyldisiloxylether (XI)	9.25 ± 0.25	6.00 ± 3.80	−25.60 ± 18.30
Norethindrone 4-bicyclohexylcarboxylate (XII)	16.40 ± 0.06	7.35 ± 0.39	−30.50 ± 1.32
Norethindrone 4-phenoxybenzoate (XIII)	22.00 ± 0.26	36.50 ± 2.84	48.06 ± 17.00

[a] Liquid steroids do not supercol. Excess enthalpies have been estimated by subtracting estimated values of ΔH^f (T) from $\Delta \bar{H}$ in Table 1.

Much work on the solution thermodynamics of complex molecules has been based on the assumption that the thermodynamic functions can be calculated by assuming constant contributions for each of the groups comprising the molecule (Davis et al., 1974). This is an approximation and it appears to be more valid when applied to the excess free energy than to the enthalpy and entropy, a common result of a simple thermodynamic theory (Hildebrand et al., 1970). Another reason for non-additivity of enthalpy data may be the general inaccuracy of the results obtained by differentiation of free energy data. In many cases, solubilities are so low that it is not possible to obtain the enthalpy by the direct calorimetric method, which, whenever possible, is to be preferred. It has been shown (Krug et al., 1976) that in many cases so called enthalpy–entropy compensation is a result of random scatter in the original free energy data and in such circumstances linear regression may show a value of r^2 very close to unity but $(\partial H/\partial S)$ very close to the harmonic mean of the range of temperature of the experimental results. Analysis of the results presented here has shown a weak correlation ($r^2 = 0.54$) between ΔH^e and ΔS^e with a slope equal to 315 K showing that such correlation was most likely a result of scatter in the solubility data.

Fig. 3 shows the excess free energies of these norethindrone esters of aromatic carboxylic acids to be higher than the excess free energies of the aliphatic esters. Of these,

norethindrone acetate (II) and dimethylpropionate (IV) have the lowest excess free energies of solution. The surface of the 2,2,4-trimethylpentane solvent consists mainly of methyl groups so they can be expected to interact with the methyl and t-butyl gropus on these steroids in a very similar manner to their interactions with other solvent molecules.

Addition of methylene groups increases $\Delta G^{e\infty}$. (Comparison of the heptanoate (III) and acetate (II) data suggests an increment of 0.4 kJ per methylene group, but more data are needed for a definite conclusion.) Addition of a cyclohexyl group results in an increase of between 0.6 and 1.25 kJ in ΔG^{e}, but its effect is strongly dependent on its position in the alkyl chain as can be seen by comparison of the values for the hexylcyclohexylcarboxylate (V) and butylcyclohexyl propionate (VI).

The biphenylcarboxylate ester (VIII) is considerably less soluble than the benzoate (VII) – the difference in $\Delta G^{e\infty}$ being 3.3 kJ. The larger value of $\Delta G^{e\infty}$ for these aromatic compounds is probably more a result of strong intermolecular forces in the pure liquid steroid rather than weak forces between solute and solvent. If the chemical potentials of the solutes in hydrocarbon solution were compared with the chemical potentials of the solute vapours the relative free energy charges would most likely be very different.

The excess free energy term for the phenoxybenzoate derivative (XIII) is also higher than for aromatic derivatives not containing a polar group. In spite of the very low free energy of fusion and low melting point, its solubility is lower than that of non-aromatic compounds of considerably higher melting point.

The excess free energy of norethindrone chlorophenylhexanoate (X) is considerably higher than that of the other aromatic derivatives and must be attributed to the effect of the halogen substituent. However this effect is considerably larger than expected by comparison with other data (Davis, 1973a) and it is hoped to carry out further investigation as related compounds become available.

Norethindrone pentamethyldisiloxyl ether (XI) was the only ether studied. Its low excess free energy is probably a result of weak intermolecular forces in the liquid (being an ether rather than an ester) and the methyl groups on the side chain interacting nearly ideally with iso-octane.

Norethindrone has a larger value of $\Delta G^{e\infty}$ than its aliphatic esters, the result of strong bonding in the pure liquid in which hydrogen bonding plays a part. From data available in the literature the effect on the excess free energy of solution of substituting a hydroxyl group for a hydrogen atom (Davis, 1973b) is an increase of 2.3 kJ mol^{-1}.

The above data show the effect of various aromatic and aliphatic groups on the excess thermodynamic functions of solution. It is evident that, for aliphatic derivatives, differences in solubility are mainly a result of differences in crystal lattice energies. However, with the aromatic derivatives, the excess free energies are high, and strongly influence the solubility in iso-octane. The pure unsaturated hydrocarbon is not a typical hydrophobic solvent and, in particular, it has different properties from the type of solvent commonly used in formulation of the drug in an oleaginous vehicle for injection as has been used for norethindrone heptanoate.

In some cases there may be difficulty in dissolving the steroid in such a vehicle, and then a knowledge of the excess free energy of solution in hydrocarbon may be of assistance. The simplest theory to apply is the method of regular solutions (Hildebrand et al., 1970). From the data given solubility parameters can be calculated. Solubility param-

eters are normally determined using the mole fraction equation assuming ideal entropy of mixing:

$$\mu - \mu^{\varrho} = RT \ln x_2 + V_2(\delta_1 - \delta_2)^2(1 - \phi_2)^2 \quad (14)$$

where x_2 is the mole fraction of solute of molar volume V_2 and solubility parameter δ_2, and δ_1 is the solubility parameter of the solvent. Equation 14 is used here in preference to Eqn. 8 since it has been used in the past to define solubility parameters. The solubility parameters calculated for the steroid derivatives are shown in Table 3 together with literature values for some solvents used in the formulation of parenteral injections. In calculation of the values for the steroids a value of 16.8 $MPa^{1/2}$ has been used for the solubility paremeter of iso-octane, a value derived from solubility data rather than the heat of vapourisation to allow for the anomalous behaviour of alkanes (Hildebrand et al., 1970).

The solubility parameters for the steroids lie in the range 19.8 to 22.6 $MPa^{1/2}$, but, apart from a low value for the pentamethyldisiloxyl ether (XI), the differences between them, although significant, are not obviously related to differences in the structures of

TABLE 3

SOLUBILITY PARAMETERS OF NORETHINDRONE AND ITS DERIVATIVES AND OF SOME SOLVENTS USED IN PARENTERAL FORMULATIONS

Compound	Solubility parameter (δ) [b]	
	($Cal^{1/2}$ $cm^{-2/3}$)	($MPa^{1/2}$)
Silicones, e.g. dimethylpolysiloxanes	5–6	10.2–12.3
Esters of long chain fatty acids, e.g. ethyl oleate, isopropyl myristate, fixed oils	8.3–9.6	16.9–19.6
Norethindrone (I)	10.9	22.2
Norethindrone acetate (II)	10.7	21.9
Norethindrone heptanoate (III)	10.8	22.0
Norethindrone dimethylpropionate (IV)	10.7	21.9
Norethindrone trans-4-hexylcyclohexylcarboxylate (V)	10.6	21.6
Norethindrone trans-3(4-butylcyclohexyl)propionate (VI)	10.4	21.3
Norethindrone benzoate (VII)	10.9	22.2
Norethindrone 4-biphenylcarboxylate (VIII)	10.8	22.0
Norethindrone 4-cyclohexylbenzoate (IX)	10.4	21.3
Norethindrone 6-(4-chlorophenyl)hexanoate (X)	11.1	22.6
Norethindrone pentamethyldisiloxyl ether (XI)	9.7	19.8
Norethindrone 4-bicyclohexylcarboxylate (XII)	10.4	21.2
Norethindrone 4-phenoxybenzoate (XIII)	10.8	22.1
Alcohols and polyhydric alcohols, e.g. benzyl alcohol	12.1	24.8
1,3-butylene glycol	11.6	23.7
propylene glycol	12.6	25.8
glycerol	16.5	33.8
Water	23.4 [a]	47.9 [a]

[a] Value uncertain.

[b] Calculated using a value 0.8 g cm^{-3} for the densities of the liquid steroids.

the compounds. Comparison of the values with those of the solvents listed will act as a guide to the choice of solvent for the steroids. In the absence of specific interactions, the best solvent would have a similar solubility parameter to that of the compound under investigation. These figures can only provide an approximate indication of relative solubility, as the solubility parameter in its simplest form does not allow for molecular polarities and hydrogen bonding, although allowance can be made for these at the cost of the theory's simplicity (Barton, 1975). Such interactions would be expected to occur with these keto-steroids and hydrogen-bonding solvent systems. Indeed, chloroform appears to behave in this manner and dissolves all the compound easily.

The reverse considerations apply to the choice of a medium for microcrystalline suspensions of these derivatives. Difficulties do arise in preparing suspensions from the more soluble, low melting point, aliphatic norethindrone esters. A medium with a solubility parameter much greater or much lower than that of the compound is advisable, and in some cases may be very difficult to achieve, particularly as additives to the medium often increase the solubility of the drug.

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