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Solubilities of Testosterone Propionate and Related Esters in Organic Solvents

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Abstract □ The solubility parameters of a range of saturated hydrocarbons were calculated from vapor pressures and heats of vaporization. Solubilities of testosterone propionate were determined in these solvents at 25° and yielded solute solubility parameters which varied from solvent to solvent. The solubility parameter of testosterone propionate was determined by several other methods, and support was found for the previously published figure of 9.5 cal^{1/2} cm^{-3/2}. The geometric mean coefficient (*l*₁₂) in saturated hydrocarbons was found to be a rectilinear function of the branching ratio (*r*). The mean *l*₁₂ of androstanolone and testosterone propionates was used to calculate the solubilities of other esters, giving good agreement with experimental results. IR data, presented as the sum of the shifts of the 3-keto and 17-ester carbonyl stretching frequencies in polar solvents, correlated rectilinearly with the geometric mean coefficients and the plot extrapolated to the *l*₁₂ value of *n*-hexane, calculated from the branching ratio plot. Attempts to predict solubilities of other esters in polar solvents using *l*₁₂ values achieved only limited success.

Keyphrases □ Testosterone propionate—related esters, solubility in various organic solvents □ Solubility—testosterone propionate and related esters in various organic solvents □ Hydrocarbons, saturated—solvents for testosterone propionate and related esters

The simplest model for a liquid solution is one where the solute and solvent have the same affinity for each other as they do for their own kind. Molecular distribution is then as random as can be permitted by molecular contact, and the solution is said to be ideal. Liquids that mix to form ideal solutions are mutually soluble in all proportions; but when the solute is a solid, solubility is limited because energy is necessary for liquefaction.

In real solutions, forces of intermolecular attraction are not uniform and like molecules tend to congregate together. When the solute and solvent have low polarities, thermal motion is sufficient to keep them randomly distributed, and solubility can be predicted (1) by:

$$-\ln X_2 = \frac{\Delta H_f}{R} \left[\frac{T_m - T}{T_m T} \right] + \frac{V_2 \phi_1^2 (\delta_1 - \delta_2)^2}{RT} \quad (\text{Eq. 1})$$

The first term on the right-hand side represents the natural logarithm of ideal solubility at temperature *T*; ΔH_f is the heat of fusion of the solute, and *T*_m is the melting point. The second term represents the contribution of 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. The term *V*₂ is the molar volume of the solute, and ϕ_1 is the volume fraction of the solvent.

Expansion of the $(\delta_1 - \delta_2)^2$ term gives the sum of the cohesive energy densities of solute and solvent minus twice their geometric mean, with the last term representing the energy gained in bringing the unlike molecules into contact. Cohesive energy has been equated with the energy of vaporization (1) and used to determine solubility parameters by:

$$\delta = \left[\frac{\Delta H^v - RT}{V} \right]^{1/2} \quad (\text{Eq. 2})$$

where ΔH^v represents heat of vaporization.

A solubility parameter of 9.5 cal^{1/2} cm^{-3/2} was obtained for testosterone propionate (2) by a modification of the Chertkoff and Martin technique (3); this figure was confirmed later (4). Efforts at predicting solubilities in nonpolar solvents have been unsuccessful, however, and a reaffirmation of the value was sought.

EXPERIMENTAL

Materials—Steroid alcohols¹ and testosterone propionate¹ were obtained from a commercial source. Methods of characterization and preparation of the remaining esters were described previously (5). Saturated hydrocarbons were purchased from various sources; purities were never less than 97%. Research grade cyclohexane² (minimum purity 99.99%) was used for vapor pressure determinations. Anisole and carbon tetrachloride were of reagent grade and were fractionally distilled before use. Solubilities in these solvents were determined using previously described techniques (2, 6), and the remaining solubilities were taken from the literature (2, 7) (Table I).

Solubility Parameters—Nonpolar solvent solubility parameters, calculated from Eq. 2, are given in Table I. Some were obtained from published heats of vaporization (8); the remaining values were calculated from vapor pressures (9), corrected using (10):

$$\Delta H^v = \Delta H_{\text{app}}^v e^{-mT} \quad (\text{Eq. 3})$$

where ΔH^v represents the true heat of vaporization, ΔH_{app}^v is the experimental value at temperature *T*, and *m* is a constant. Polar solvent solubility parameters, taken from the literature (1), are

¹ Gifts from Organon Laboratories Ltd.

² British Drug Houses Ltd.

Table I—Solubilities and Related Data for Testosterone Propionate

Solvent	Mole Fraction Solubility, X_2	Solubility Parameter	Total Carbonyl Frequency Shift ^d , cm^{-1}
1. <i>n</i> -Pentane	0.003 ^b	7.05	—
2. <i>n</i> -Hexane	0.005 ^b	7.26	0
3. <i>n</i> -Heptane	0.0058	7.42	—
4. <i>n</i> -Octane	0.0081	7.54	—
5. <i>n</i> -Nonane	0.0074	7.65	—
6. <i>n</i> -Decane	0.0095	7.72	—
7. <i>n</i> -Undecane	0.0085	7.81	—
8. <i>n</i> -Dodecane	0.0112	7.86	—
9. <i>n</i> -Hexadecane	0.0100	7.99	—
10. Cyclopentane	0.007 ^b	8.11	—
11. Cyclohexane	0.012 ^b	8.19	0
12. <i>cis</i> -Decahydro-naphthalene	0.0170	8.58	—
13. <i>cis</i> -Hexahydroindan	0.0239	8.54	—
14. Methylcyclopentane	0.0107	7.95	—
15. Ethylcyclopentane	0.0131	7.95	—
16. Methylcyclohexane	0.0145	7.84	—
17. <i>n</i> -Propylcyclohexane	0.0100	7.94	—
18. Isopropylcyclohexane	0.0155	7.91	—
19. <i>n</i> -Butylcyclohexane	0.0141	7.94	—
20. <i>tert</i> -Butylcyclohexane	0.0153	7.77	—
21. Anisole	0.25 ^b	—	24.6
	0.251	—	—
22. Benzene	0.24 ^b	9.2 ^d	17.1
	0.260 ^c	—	—
23. Carbon disulfide	0.18 ^b	10.0 ^d	15.7
24. Carbon tetrachloride	0.16 ^b	8.6 ^d	14.7
	0.194	—	—
25. Chlorobenzene	0.27 ^b	9.5 ^d	22.8
26. Chloroform	0.35 ^b	9.2 ^d	43.4
27. 1,2-Dichloroethane	0.27 ^b	9.8 ^d	34.6
	0.294 ^c	—	—
28. <i>trans</i> -1,2-Dichloroethylene	0.32 ^b	9.0 ^d	34.1
29. <i>cis</i> -1,2-Dichloroethylene	0.30 ^b	9.1 ^d	35.5
30. Nitrobenzene	0.22 ^b	10.0 ^d	33.1
	0.220 ^c	—	—
31. Tetrahydro-naphthalene	0.20 ^b	—	16.8
32. Toluene	0.20 ^b	8.9 ^d	15.2
	0.199 ^c	—	—
Bicyclohexyl	0.0165	—	—
Cyclooctane	0.0181	—	—
Ethylcyclohexane	0.0110	—	—

^aTaken from Ref. 16. ^bTaken from Ref. 7. ^cTaken from Ref. 2. ^dTaken from Ref. 1.

given in Table I. Those of the solvent blends were calculated from the individual solvent values (11).

Determination of Vapor Pressures—The isoteniscope technique of Smith and Menzies (12) was adopted. Experimental details are given elsewhere (13). Readings were corrected for capillary depression (14) and temperature and reduced to sea level (15). Mean results, each of five readings, were: cyclohexane, $13.05 \pm 0.08 \text{ kNm}^{-2}$; saturated solution of testosterone propionate in cyclohexane, $11.60 \pm 0.07 \text{ kNm}^{-2}$; and saturated solution of androstanolone propionate in cyclohexane, $11.53 \pm 0.03 \text{ kNm}^{-2}$ ($p = 0.01$).

Activity coefficients were calculated from the relative lowering of vapor pressure of cyclohexane, and solubility parameters were calculated by equating the natural logarithm of the result with the heat of mixing term in Eq. 1. The process yielded solubility parameters of 10.33 and $10.41 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ for androstanolone and testosterone propionates, respectively.

Ideal Solubilities—The values for testosterone esters were taken from James and Roberts (2). The remainder were calculated from heats of fusion, measured³ and corrected for the heat capacity of the supercooled liquid (2) when necessary.

Miscellaneous Data—Solvent molar volumes were taken from Hildebrand *et al.* (1) when available, and the other values were calculated from published densities (15). Refractive indexes also were obtained from the literature (15). Molar volumes, 294 liters for testosterone propionate and 296 liters for androstanolone propionate, were those determined by Bowen (7). Volume fraction concentrations were calculated using a published procedure (2).

Geometric mean coefficients (l_{12}) were calculated by substituting observed solubilities in Eq. 6. A solubility parameter of $9.5 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ was assumed for testosterone propionate for these calculations, and those of the other esters were calculated from it using Hoy's constants (10). Spectral results were obtained using procedures described elsewhere (16, 17) (Table I).

DISCUSSION

Determination of Solubility Parameters—Hansen (18) considered that the calculation of solubility parameters from Eq. 2 was oversimplified when applied to polar solvents and split up the "overall" solubility parameter (δ) into dispersion (δ_d), polar (δ_p), and hydrogen-bonding (δ_h) components, as defined by:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (\text{Eq. 4})$$

Several lists of these parameters have been compiled (*e.g.*, 18, 19), but all are based on "volumes of solubility" and suitable only for semiquantitative predictions.

More precise figures can be employed by considering saturated hydrocarbons only, in which polar and hydrogen-bonding contributions are zero. The overall solubility parameter is then defined by Eq. 2 and can be calculated precisely from vapor pressures or heats of vaporization. Solubility parameters were not available in the literature for all of the saturated hydrocarbons examined here. Moreover, the rule of Hildebrand and Scott (20) frequently gave results at variance with published figures, throwing doubt on its reliability for evaluating unknown solubility parameters. The solubility parameters calculated from heats of vaporization compared favorably with those from other sources, when available, indicating that the hitherto unpublished solubility parameters obtained in this way would be reliable.

There still remained several saturated hydrocarbon solvents for which solubility parameters were required. Keller *et al.* (21) correlated the solubility parameters of 96 hydrocarbons with the Lorentz-Lorentz function $(n^2 - 1)/(n^2 + 2)$ and obtained a good rectilinear relationship. Since refractive indexes (n) were available for the unknown solvents (15), an attempt was made to calculate solubility parameters by this means. The straight-chain hydrocarbons showed excellent correlation; but when cyclic and branched-chain hydrocarbons were included, considerable scatter resulted. The overall standard deviation about the best rectilinear relationship was $0.24 \text{ cal}^{1/2} \text{ cm}^{-3/2}$.

The method, therefore, appears suitable for predicting solubility parameters of straight-chain hydrocarbons, but results for the compounds for which solubility parameters were required in this work could be regarded only as approximate. Therefore, it was decided to use our own solubility parameters for nonpolar solvents, calculated from heats of vaporization and vapor pressures, and to consider only the solvents for which data were available.

The solubility parameter of testosterone propionate was calculated for each nonpolar solvent by substituting observed solubilities for X_2 in Eq. 1. Considerable variation was observed. The normal paraffins, for example, indicated that testosterone propionate had a solubility parameter between 9.9 and 10.0, while the solubility in cyclohexane gave a value of $10.4 \text{ cal}^{1/2} \text{ cm}^{-3/2}$, which was confirmed by vapor pressure measurements.

Solubility parameters of nonvolatile solutes have been determined by plotting solubilities in a range of solvent blends against a solvent blend solubility parameter (3). Each plot went through a maximum, and the corresponding solubility parameter was equated to that of the solute. Similar procedures yielded a solubility parameter of $9.5 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ for testosterone propionate (2, 4). Polar solvents are normally required for this method, because of the limited solubility parameter range of nonpolar solvents. The method was repeated with testosterone propionate, using a large range of polar solvents.

The plot of solubility against the solvent solubility parameter showed considerable scatter, which could not be resolved into any

³ Perkin-Elmer differential scanning calorimeter.

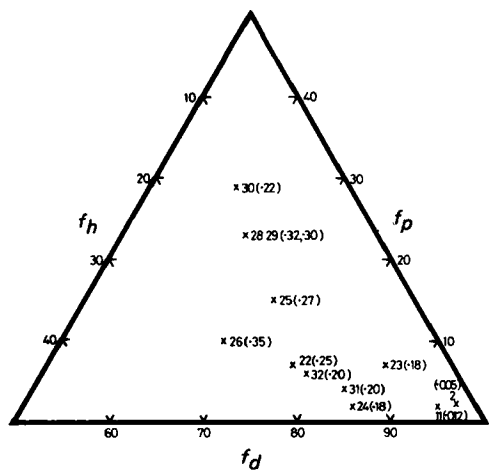


Figure 1—Triangular solubility plot for testosterone propionate. Solvents are numbered in the manner indicated in Table I. Figures in parentheses represent mean solubilities.

simple relationship and was attributed to variation in the shapes and sizes of the solvent molecules (22). To overcome this objection, studies were made on binary mixtures of nitrobenzene and toluene, which have similar shapes and molar volumes but different solubility parameters. The plot went smoothly through a maximum and indicated a solubility parameter for testosterone propionate in the region of $9.5 \text{ cal}^{1/2} \text{ cm}^{-3/2}$. A first derivative plot gave the precise value of $9.59 \text{ cal}^{1/2} \text{ cm}^{-3/2}$.

Plots without maxima were obtained when the procedure was repeated using blends of 1,2-dichloroethane with *cis*- and *trans*-1,2-dichloroethylenes, however. The reason for this result cannot be stated with certainty, but the fact that testosterone propionate forms some 1:2 complexes with 1,2-dichloroethane and chloroform through its 3-keto carbonyl group and only 1:1 complexes with the dichloroethylenes and aromatic solvents (16) may well be significant. It appears, therefore, that the answer obtained from this procedure is dependent on what solvents are used in the blends. Even with a range of different solvents, the results can be biased if a large proportion of the solvents react with the solute in a particular way, different from the rest. The result obtained with the nitrobenzene-toluene blends probably is reliable, because these two solvents are known to complex with testosterone propionate in a similar manner (16, 17).

Supporting evidence for the figure of 9.5 is available from sources not dependent on solubility data. The boiling point of testosterone propionate was determined by differential scanning calorimetry (7). Application of the Hildebrand and Scott (20) rule yielded a heat of vaporization of $23.03 \text{ kcal mole}^{-1}$, which gave a solubility parameter of $8.74 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ when substituted into Eq. 2. More realistic solubility parameters were obtained by adding 0.6 unit to those calculated from the heats of vaporization (23). A value of $9.34 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ was obtained by applying this correction to testosterone propionate, in fair agreement with that calculated from solubilities, considering the empirical nature of the derivation.

Another method for determining solubility parameters is expressed by (24):

$$\delta = \sqrt{\frac{\sum G}{V}} \quad (\text{Eq. 5})$$

where G is the partial molar attraction constant, and V is the molar volume. Insertion of G values from a recent compilation (10) in Eq. 5 gave a solubility parameter of $9.50 \text{ cal}^{1/2} \text{ cm}^{-3/2}$. Thus, although neither method was expected to give accurate results, they both provide independent supporting evidence that the solubility parameter is in the region of $9.5 \text{ cal}^{1/2} \text{ cm}^{-3/2}$.

Hansen (18) evaluated component solubility parameters (Eq. 4), using three-dimensional solubility diagrams, which were difficult to interpret. Teas (25) simplified the approach by using triangular diagrams, giving "areas" rather than "volumes" of solubility, defined in terms of functions of each component, such as the dispersive force function (f_d), equal to $100 (\delta_d^2/\delta^2)$. The technique is applied to testosterone propionate in Fig. 1. The area of maximum

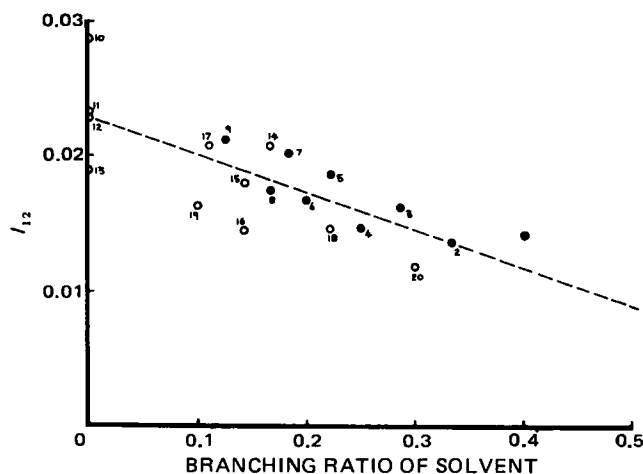


Figure 2—Relationship between geometric mean coefficient and branching ratio. Solvents are numbered in the manner indicated in Table I.

solubility indicates that a good solvent for testosterone propionate requires hydrogen-bonding and polar contributions of at least 10 on the Teas scale. If these contributions are too high, solvating ability will be reduced, as demonstrated by the solubilities in ethanol and water (2) and in nitrobenzene.

Chloroform appears to possess the optimum qualities; but in view of its complexing behavior, the significance of the result was regarded with suspicion and its position was ignored. The remainder of the points followed a logical pattern, with an area of maximum solubility in the region of $f_d = 65$, $f_p = 20$, and $f_h = 15$. The ideal characteristics could not be located precisely, because of the dearth of suitable solvents in this area. However, approximate component solubility parameter contributions suitable for solvent selection, assuming an overall value of $9.5 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ ($615 \text{ J}^{1/2} \text{ m}^{-3/2}$), are $\delta_d = 7.3 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ ($500 \text{ J}^{1/2} \text{ m}^{-3/2}$), $\delta_p = 4.2 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ ($270 \text{ J}^{1/2} \text{ m}^{-3/2}$), and $\delta_h = 3.7 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ ($240 \text{ J}^{1/2} \text{ m}^{-3/2}$).

Solubilities in Nonpolar Solvents—Hildebrand and Dymond (26) observed that solubilities in hydrocarbons depend on the degree of branching in the solvent molecule, which they assessed as a branching ratio (r), the number of methyl groups divided by the total number of carbon atoms. Hildebrand *et al.* (1) introduced an empirical coefficient (l_{12}) to improve the practicability of the geometric mean, extending Eq. 1 to Eq. 6:

$$-\ln X_2 = \frac{\Delta H_f}{R} \left[\frac{T_m - T}{T_m T} \right] + \frac{V_2 \phi_1^2}{RT} [(\delta_1 - \delta_2)^2 + 2l_{12} \delta_1 \delta_2] \quad (\text{Eq. 6})$$

A plot of l_{12} for testosterone propionate against the branching ratio is shown in Fig. 2. Least-squares analysis indicated a good rectilinear correlation (correlation coefficient = 0.822, $F_{1,18} = 37.4$, and $\alpha 0.001 = 15.38$) with a slope of 0.604. A similar plot and slope (0.664) were obtained with androstanolone propionate.

Table II—Observed and Calculated Solubilities in Cyclohexane

	Mole Fraction Solubility		
	Observed	Calculated	
		Eq. 1	Eq. 6
Androstanolone:			
Formate	0.003	0.010	0.002
Acetate	0.007	0.012	0.003
Butyrate	0.022	0.037	0.024
Nandrolone:			
Formate	0.009	0.027	0.007
Acetate	0.037	0.113	0.041
Propionate	0.084	0.424	0.156
Testosterone:			
Formate	0.004	0.039	0.009
Acetate	0.004	0.028	0.006
Butyrate	0.014	0.097	0.018
Valerate	0.018	0.088	0.017

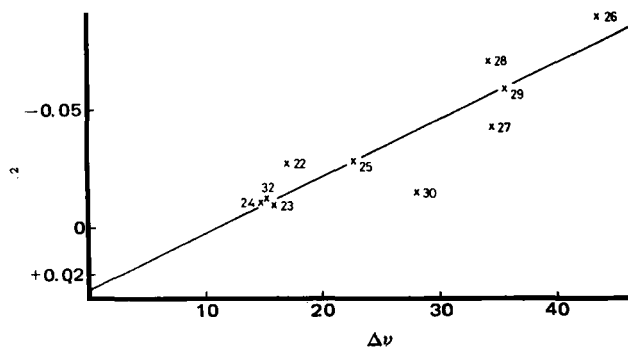


Figure 3—Relationship between carbonyl stretching frequency shift and geometric mean coefficient. Solvents are numbered in the manner indicated in Table I.

Ascent of the androstanolone and testosterone ester homologous series involves only small changes in molecular structure. Since l_{12} depends on the stereochemistry of the solute and solvent, it would be anticipated that the l_{12} for the propionate would be similar to those of adjacent esters. Table II shows solubilities of the lower androstanolone, nandrolone, and testosterone esters in cyclohexane, together with solubilities calculated using Eqs. 1 and 6. The mean l_{12} (0.022) for androstanolone and testosterone propionates was used in Eq. 6. An improvement was obtained by consideration of l_{12} ; most predictions were good and, in all cases except that of androstanolone acetate, were significantly better than those in which the geometric mean was not corrected.

The terms δ_2 and l_{12} are interdependent; one can be set at any value, provided the other is adjusted to fit it. It appears that l_{12} would be a comparatively easy term to estimate in nonpolar solvents. It is suggested that, in view of the difficulties in obtaining solubility parameters for nonvolatile solutes, an arbitrary standard solubility parameter be used as the basis of a solubility parameter scale for steroids.

Testosterone propionate is a suitable standard substance, since it is readily available and comparatively inert. The figure of $9.5 \text{ cal}^{1/2} \text{ cm}^{-3/2}$ is probably a good estimate of the solubility parameter of testosterone propionate. Solubility parameters of other steroids can be calculated from this value by using the procedures described by Small (24) and Hoy (10). The l_{12} values of key compounds, calculated from solubilities in a range of nonpolar solvents, could then be used as the basis of a scheme for estimating l_{12} values of other solutes, in the same way as was demonstrated with testosterone propionate.

Solubilities in Polar Solvents—While the three-component solubility parameter concept used here provides a means of selecting suitable solvents for testosterone propionate and similar compounds, the approach breaks down when applied to the prediction of solubilities in polar solvents because the observed values are in excess of ideal values while those predicted by Eq. 1 cannot exceed the ideal. It has been suggested that the high observed solubilities arise because complexation between solvent and solute gives a cohesive energy density between them greater than that predicted by the geometric mean assumption (22). Since the factor l_{12} corrects the differences between the solute to solvent cohesive energy densities and those predicted by the geometric mean (1), it should be influenced by complexing effects.

A plot of total carbonyl frequency shift, as an indicator of complexation, against l_{12} is illustrated in Fig. 3. The correlation is good, considering that l_{12} values represent small differences between large numbers. Solubility parameters were not available for anisole and tetrahydronaphthalene, which were, therefore, not included in the plot. A significant feature of this plot is that the linear regression line extrapolates to 0.025 at a frequency shift of zero, in good agreement with the l_{12} for *n*-hexane obtained from solubility data (Fig. 2). Scatter about the line could be due to steric effects for which a correcting factor, analogous to the r value of the saturated hydrocarbons, is difficult to assign.

Attempts to predict solubilities of other esters by substituting l_{12} values of testosterone propionate in Eq. 6 were disappointing. The limited success is probably due to the assumption that the es-

ters interact identically with the solvent, which is an oversimplification. IR measurements, in fact, suggest significant ester to ester variation in complex stability. A three-variable treatment, in which the shifts induced by changing both ester and solvent are correlated with l_{12} , might achieve more success.

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