value for 8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4] benzodiazepine (estazolam) was reported to be 2.84 from the UV absorption spectral change (23). Considering the structural difference mentioned, the estimated pKa value for triazolam, 1.52, is reasonable.

The bioavailability or the pharmacological effect of a drug would greatly depend on the formation rate in the cyclization reaction from the opened form to the closed form because only the cyclized 1,4-benzodiazepines possess pharmacological CNS activity (24), which are discussed in reports on diazepam (8) and desmethyldiazepam (12). The half-time of the forward reaction of I at pH 7.4, which was calculated to be 80.6 min (Fig. 5), indicates that much time is required to convert I into the closed form II, only if the *in vivo* reaction proceeds chemically.

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Extended Hildebrand Solubility Approach: Testosterone and Testosterone Propionate in Binary Solvents

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Abstract □ Solubilities of testosterone and testosterone propionate in binary solvents composed of the inert solvent, cyclohexane, combined with the active solvents, chloroform, octanol, ethyl oleate, and isopropyl myristate, were investigated with the extended Hildebrand solubility approach. Using multiple linear regression, it was possible to obtain fits of the experimental curves for testosterone and testosterone propionate in the various binary solvents and to express these in the form of regression equations. Certain parameters, mainly K and $\log \alpha_2$, were employed to define the regions of self-association, nonspecific solvation, specific solvation, and strong solvation or complexation.

Keyphrases □ Testosterone—extended Hildebrand solubility approach, solubility in binary solvents □ Solubility—extended Hildebrand solubility approach, testosterone and testosterone propionate in binary solvents □ Binary solvents—solubility of testosterone and testosterone propionate, extended Hildebrand solubility approach

Solute–solvent complexes of testosterone and testosterone propionate in binary solvents composed of cyclohexane with ethyl oleate, isopropyl myristate, and octanol have been reported previously (1). These solvents are pharmaceutically important; the first two are useful as solvents for steroid injectable preparations.

The calculated complexation constants (1) between the steroids and solvents were based on a previous method (2). The solute-mixed solvent systems are analyzed here with the extended Hildebrand solubility approach (3), an extension of the Hildebrand regular solution theory (4) which was introduced to allow the calculation of solubility of nonpolar and semipolar drugs in mixed solvents having a wide range of solubility parameters.

THEORETICAL

Solubility on the mole fraction scale, X_2, may be represented by the expression:

$$-\log X_2 = -\log X_2^i + \log \alpha_2 \qquad \text{(Eq. 1)}$$

where X_2^i is the ideal solubility of the crystalline solid, and α_2 is the solute activity coefficient in mole fraction terms. Scatchard (5) and Hildebrand and Scott (4) formulated the solubility equation for regular solutions in the form:

$$\log \frac{a_2^s}{X_2} = \log \alpha_2 = \frac{V_2 \phi_1^2}{2.303RT}(a_{11} + a_{22} - 2a_{12}) \qquad \text{(Eq. 2)}$$

where

$$\phi_1 = \frac{V_1(1 - X_2)}{V_1(1 - X_2) + V_2X_2} \qquad \text{(Eq. 3)}$$

The activity of the crystalline solid (a_2^s), taken as a supercooled liquid, is equal to X_2^i as defined in Eq. 1. Variable V_2 is the molar volume of the hypothetical supercooled liquid solute (subscript 2), ϕ_1 is the volume fraction of the solvent (subscript 1), R is the molar gas constant, and T is the absolute temperature of the experiment.

The terms a_{11} and a_{22} are the cohesive energy densities of solvent and solute, and a_{12}, referred to in other reports (3, 6) and elsewhere in this report as W, is expressed in regular solution theory as a geometric mean of the solvent and solute cohesive energy densities:

$$a_{12} = W = (a_{11}a_{22})^{1/2} \quad \text{(Eq. 4)}$$

The square roots of the cohesive energy densities of solute and solvent, called solubility parameters and given the symbol δ, are obtained for the solvent from the energy or heat of vaporization per cubic centimeter:

$$\delta_i = (a_{ii})^{1/2} = \left(\frac{\Delta E^v}{V_i}\right)^{1/2} \cong \left(\frac{\Delta H^v - RT}{V_i}\right)^{1/2} \quad \text{(Eq. 5)}$$

When the solubility parameters and the geometric mean are introduced into Eq. 2, the expression becomes:

$$\log \alpha_2 = A(\delta_1{}^2 + \delta_2{}^2 - 2\delta_1\delta_2) = A(\delta_1 - \delta_2)^2 \quad \text{(Eq. 6)}$$

where

$$A = \frac{V_2\phi_1{}^2}{2.303RT} \quad \text{(Eq. 7)}$$

By substituting Eq. 6 into Eq. 1, one obtains:

$$-\log X_2 = -\log X_2{}^i + A(\delta_1 - \delta_2)^2 \quad \text{(Eq. 8)}$$

which is the Hildebrand–Scatchard solubility equation (4) for a crystalline solid compound of solubility parameter δ_2 dissolved in a solvent of solubility parameter δ_1. Equation 8 may be referred to as the regular solution equation; the term regular solution will be defined. The ideal solubility term is ordinarily expressed in terms of the heat of fusion of the crystalline solute at its melting point:

$$-\log X_2{}^i \cong \frac{\Delta H_m{}^f}{2.303RT}\frac{T_m - T}{T_m} \quad \text{(Eq. 9)}$$

although this is an approximation that disregards the molar heat capacity difference ΔC_p of the liquid and solid forms of the solute. An approximation involving the entropy of fusion, $\Delta S_m{}^f$, was introduced (7) as:

$$-\log X_2{}^i \cong \frac{\Delta S_m{}^f}{R}\log\frac{T_m}{T} \quad \text{(Eq. 10)}$$

to partially correct for the failure to include ΔC_p in Eq. 9, and this form of log ideal solubility is employed in the current report. Equations 9 and 10 are approximations, and currently it has not been determined which is more appropriate for use in solubility analysis.

The Hildebrand–Scatchard equation (Eq. 8) may be used to estimate solubility only for relatively nonpolar drugs in nonpolar solvents which adhere to regular solution requirements. The molar volumes of the solute and solvent should be approximately the same, and the solution should not expand or contract when the components are mixed. Dipole–dipole and hydrogen bonding interactions are absent from regular solutions, with only physical forces being present. In such a system the mixing of solvent and solute results in a random arrangement of the molecules. The entropy in a regular solution is the same as that in an ideal solution, and therefore, the entropy of mixing is zero. Only the enthalpy of mixing has a finite value and it is always positive.

In most solutions encountered in pharmacy, interactions and selective ordering of molecules occur; these systems are referred to as irregular solutions. In pharmaceutical solutions, the geometric mean rule (Eq. 4) is too restrictive, and Eq. 6 or 8 ordinarily provides a poor fit to experimental data in irregular solutions. Instead, $\delta_1\delta_2$ is replaced in Eq. 6 by $W = a_{12}$, which is allowed to take on values as required to yield correct mole fraction solubilities:

$$-\log X_2 = -\log X_2{}^i + A(\delta_1{}^2 + \delta_2{}^2 - 2W) \quad \text{(Eq. 11)}$$

It is not possible at this time to determine W by recourse to fundamental physical chemical properties of solute and solvent. It has been found, however, for drugs in binary solvent mixtures (3, 6, 8) that W may be regressed in a power series on the solvent solubility parameter:

$$W_{calc} = C_0 + C_1\delta_1 + C_2\delta_1{}^2 + C_3\delta_1{}^3 + \ldots \quad \text{(Eq. 12)}$$

A reasonable estimate, W_{calc}, is obtained by this procedure, and when W_{calc} is substituted in Eq. 11 for W, mole fraction solubilities in polar binary solvents are obtained ordinarily within ≤20% of the experimental results. Log α_2/A may also be regressed directly on powers of δ_1, bypassing W and obviating the need for δ_2. The estimated solubility, X_2, with this method is identical to that obtained with W_{calc} except for rounding-off errors. The entire procedure, referred to as the extended Hildebrand solubility approach (3), may be conducted by using a polynomial regression program and carrying out the calculations on a computer. It is useful to include a statistical routine which provides R^2, Fisher's F ratio, and a scatter plot of the residuals. Terms of the polynomial (*i.e.*, powers of δ_1) are added sequentially and the values of R^2 and F, together with the appearance of the residual scatter plot, indicate when the proper degree of the polynomial has been reached. A well-known polynomial program using multiple regression analysis, SPSS (9), is convenient for this purpose.

Parameters for Solute–Solvent Interaction—The activity coefficient of the solute, α_2, may be partitioned into a term, α_V, for physical or van der Waals (dispersion and weak dipolar) forces and a second term, α_R, representing residual and presumably stronger solute–solvent interactions (Lewis acid-base type forces). In logarithmic form:

$$\log \alpha_2 = \log \alpha_V + \log \alpha_R \quad \text{(Eq. 13)}$$

According to this definition of log α_2, Eq. 11 may be written:

$$(\log \alpha_2)/A = (\delta_1 - \delta_2)^2 + 2(\delta_1\delta_2 - W) \quad \text{(Eq. 14)}$$

where

$$(\log \alpha_V)/A = (\delta_1 - \delta_2)^2 \quad \text{(Eq. 15)}$$

and

$$(\log \alpha_R)/A = 2(\delta_1\delta_2 - W) \quad \text{(Eq. 16)}$$

Hildebrand *et al.* (10) introduced a parameter, l_{12}, to account for deviations from the geometric mean. In terms of W, l_{12} may be written:

$$W = (1 - l_{12})\delta_1\delta_2 \quad \text{(Eq. 17)}$$

Therefore, the second right-hand term of Eq. 14, representing the residual activity coefficient, is:

$$(\log \alpha_R)/A = 2l_{12}\delta_1\delta_2 \quad \text{(Eq. 18)}$$

and the modified equation for solubility of a drug in binary polar solvents becomes:

$$-\log X_2 = -\log X_2{}^i + A(\delta_1 - \delta_2)^2 + 2A(l_{12})(\delta_1\delta_2) \quad \text{(Eq. 19)}$$

The variable W may be related to the geometric mean, $\delta_1\delta_2$, by the introduction of a proportionality constant, K (11), such that:

$$W = K(\delta_1\delta_2) \quad \text{(Eq. 20)}$$

From Eqs. 17 and 20:

$$(1 - l_{12}) = W/(\delta_1\delta_2) = K \quad \text{(Eq. 21)}$$

or

$$l_{12} = 1 - K \quad \text{(Eq. 22)}$$

The extended Hildebrand solubility expression (Eq. 11) may now be written:

$$-\log X_2 = -\log X_2{}^i + A(\delta_1 - \delta_2)^2 + 2A(1 - K)\delta_1\delta_2 \quad \text{(Eq. 23)}$$

By employing Eq. 20 to replace W of Eq. 11, another form of the extended Hildebrand equation is obtained:

$$-\log X_2 = -\log X_2{}^i + A(\delta_1{}^2 + \delta_2{}^2 - 2K\delta_1\delta_2) \quad \text{(Eq. 24)}$$

or, with Eq. 17:

$$-\log X_2 = -\log X_2{}^i + A[\delta_1{}^2 + \delta_2{}^2 - 2(1 - l_{12})\,\delta_1\delta_2] \quad \text{(Eq. 25)}$$

It was found (12) that a plot of l_{12} against a branching ratio, r, provided a good linear correlation for testosterone in a number of branched hydrocarbon solvents.

Variable K was employed (11) to describe the dissolving power of solvents for polyacrylonitrile, and it was concluded that the solvent action of organic solvents on the polymer solute was determined "by a very delicate balance between the various intermolecular forces involved." Solvent power could not be explained alone in terms of dipolar interaction and hydrogen bonding; it depended rather on whether dipolar and hydrogen bonding energies for the solvent–polymer contacts were a few percentage points less than, equal to, or greater than the sum of the solvent–solvent and polymer–polymer interaction energies. The same conclusions can be reached for steroids in the various solvents in the present study and are elaborated.

The various extended solubility equations (Eqs. 11, 24, and 25) are equivalent, and the deviation of polar (or nonpolar) systems from regular solution behavior may be expressed in terms of $(\log \alpha_2)/A$, $(\log \alpha_R)/A$, W, l_{12}, or K. Any one of the parameters may be regressed on a polynomial in δ_1 to obtain values of solubility, X_2. These quantities may also be regressed against the volume fraction or percent of one of the solvents in the mixture or against the mean molar volume of the binary solvent mixture (3). Volume percents and mean molar volumes of chloroform in mixtures of cyclohexane and chloroform are given in Table I. The $X_{2(\mathrm{calc})}$ values may be converted to molal solubility units and, if densities of the solutions are available, to molar or gram per milliliter concentration.

Solubility Parameters for Crystalline Solids—It is not possible to obtain solubility parameters of crystalline drugs by vaporization using Eq. 5, because many organic compounds decompose above their melting points. Instead, it has been shown (13) that the solubility parameter of solid drugs can be estimated from the point of maximum solubility in a binary solvent such as ethyl acetate and ethyl alcohol. The solubility parameter of the solute must lie between the δ values of the two solvents for this technique to be successful. In a regular solution, when:

$$\log X_2 = \log X_2{}^i \qquad \text{(Eq. 26)}$$

the system represents an ideal solution, and the maximum solubility is obtained, excluding specific solvation effects. When a pure solvent or solvent mixture is found that yields a peak in the solubility profile for a regular solution, δ_1 is assumed to equal δ_2, and the final term of Eq. 8 becomes zero, then Eq. 26 holds.

In an irregular solution, these relations do not hold exactly as in a regular solution. Equation 24 may be written as:

$$\frac{1}{A}(\log X_2{}^i - \log X_2) = \frac{\log \alpha_2}{A} = \delta_1{}^2 + \delta_2{}^2 - 2K\delta_1\delta_2 \qquad \text{(Eq. 27)}$$

The partial derivative of $(\log \alpha_2)/A$ then is taken with respect to δ_1 and the result set equal to zero to obtain the value of δ_2 at the peak in the solubility profile:

$$\left[\frac{\partial(\log \alpha_2/A)}{\partial(\delta_1)}\right]_{\delta_2} = 2\delta_1 - 2K\delta_2 = 0 \qquad \text{(Eq. 28)}$$

$$\delta_1 = K\delta_2 \qquad \text{(Eq. 29}a\text{)}$$

or, from Eq. 5 and the corresponding equation for the solute:

$$a_{11} = K^2 a_{22} \qquad \text{(Eq. 29}b\text{)}$$

Thus, $\delta_1 \neq \delta_2$ at the maximum in the solubility curve, but rather is equal to $K\delta_1$ (11). In irregular solutions, K is slightly greater than unity (~1.01) when solvation occurs between the solute and solvent; K is slightly less than unity (~0.98) when the species of the solution self-associate; and $K = 1.00$ when the solution is regular. As pointed out (11), a very small change in K can bring about large changes in solvent action; this phenomenon is considered in another report (8). Since K is nearly unity, even for highly solvated solutions, δ_2 is almost equal to δ_1 at the point of peak solubility in the system. This gives the researcher a good method for estimating solubility parameters of crystalline drugs. A differentiation method was introduced to obtain this value more precisely (12). Methods for calculating the solubility parameters of solid drugs, involving a regression of $(\log \alpha_2)/A$ on δ_1 in a second degree power series, have been introduced (14, 15). Satisfactory values of $\delta_2{}^2$ and K are obtained[1] by use of the coefficients of the polynomial in moderately polar systems, but the technique is inadequate for highly irregular solutions. Another approach was introduced (16) to calculate δ_2 of solid compounds. Solubility parameters for solutes may also be obtained by a group contribution method (17).

EXPERIMENTAL

The solubility analyses of testosterone and testosterone propionate in solvent mixtures (*i.e.*, cyclohexane–chloroform, cyclohexane–octanol, cyclohexane–isopropyl myristate, and cyclohexane–ethyl oleate) were reported earlier (1), and the reported values were used in this study.

[1] The K value reported in Ref. 15 is constant over the range of solvent solubility parameters used. It differs from K introduced in the extended Hildebrand solubility approach which has a different value for each solvent used. The term in Ref. 15 should properly be differentiated from K by use of another symbol, such as κ, kappa.

Table I—Testosterone in Chloroform–Cyclohexane at 25° [a]

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Volume, % $CHCl_3$	δ_1	V_1	A	$\log \alpha_2$	$\frac{\log \alpha_2}{A}$	$\frac{\log \alpha_{2(\mathrm{calc})}}{A}$ [b]	W	W_{calc} [c]	K	l_{12}	$\frac{\log \alpha_R}{A}$	X_2	$X_{2(\mathrm{calc})}$	Percent Error
0	8.19	108.8	0.1863	2.458	13.194	12.714	86.347	86.586	0.9672	0.0328	5.849	0.000253	0.000311	−22.9
2	8.21	108.3	0.1862	2.232	11.987	11.916	87.113	87.149	0.9734	0.0266	4.572	0.000426	0.000439	−3.1
4	8.23	107.7	0.1860	2.070	11.129	11.138	87.706	87.703	0.9777	0.0223	4.002	0.000618	0.000616	0.3
6	8.25	107.1	0.1857	1.880	10.124	10.378	88.373	88.247	0.9827	0.0173	3.103	0.000957	0.000859	10.2
8	8.27	106.6	0.1853	1.712	9.239	9.638	88.982	88.783	0.9871	0.0129	2.323	0.00141	0.00119	15.6
10	8.29	106.0	0.1849	1.611	8.713	8.916	89.412	89.309	0.9895	0.0105	1.897	0.00178	0.00163	8.4
20	8.38	103.2	0.1807	1.049	5.805	5.884	91.614	91.575	1.0030	−0.0030	−0.545	0.00649	0.00628	3.2
30	8.48	100.4	0.1677	0.537	3.202	2.899	93.760	93.911	1.0143	−0.0143	−2.655	0.0211	0.0237	−12.3
40	8.57	97.6	0.1387	0.100	0.721	0.516	95.767	95.870	1.0252	−0.0252	−4.708	0.0577	0.0616	−6.8
50	8.67	94.8	0.1096	−0.147	−1.341	−1.842	97.662	97.910	1.0334	−0.0334	−6.319	0.102	0.116	−13.7
60	8.76	92.0	0.0788	−0.351	−4.454	−3.743	100.001	99.645	1.0473	−0.0473	−9.034	0.163	0.143	12.3
70	8.86	89.2	0.0705	−0.394	−5.589	−5.657	101.448	101.483	1.0505	−0.0505	−9.748	0.180	0.182	−1.1
80	8.95	86.4	0.0606	−0.448	−7.393	−7.242	103.157	103.077	1.0574	−0.0574	−11.204	0.204	0.200	2.0
90	9.05	83.6	0.0549	−0.475	−8.652	−8.898	104.685	104.805	1.0612	−0.0612	−12.080	0.217	0.224	−3.2
100	9.14	80.8	0.0487	−0.506	−10.390	−10.334	106.368	106.342	1.0677	−0.0677	−13.484	0.233	0.232	0.4

[a] Parameters: $\Delta H_m{}^f$ = 6190 cal/mole; T_m = 427.2°K, δ_2 = 10.9 (cal/cm^3)$^{1/2}$; V_2 = 254.5 cm^3/mole; $X_2{}^i$ = 0.07264; $-\log X_2{}^i$ = 1.1388. [b] Equation 33. [c] Equation 32.

RESULTS

Testosterone in Cyclohexane–Chloroform—The solubilities of testosterone at 25° in mixtures of cyclohexane and chloroform are found in Table I. The $\Delta H_m{}^f$ value for testosterone is 6190 cal/mole and T_m is 427.2°K. The $-\log X_2{}^i$ value is 1.1388 ($X_2{}^i$ = 0.07264), and δ_2 is 10.90 (cal/cm^3)$^{1/2}$. The solubility parameter for cyclohexane is 8.19 and for chloroform is 9.14. The molar volume of testosterone is 254.5 cm^3/mole (12). The log activity coefficients are calculated using the expression:

$$\log \alpha_2 = \log X_2{}^i - \log X_2 \qquad \text{(Eq. 30)}$$

The values of W for the various mixtures are obtained directly from the solubility data, using a rearranged form of Eq. 11:

$$W = \tfrac{1}{2}\left[\delta_1{}^2 + \delta_2{}^2 - \frac{\log (X_2{}^i/X_2)}{A}\right]$$

$$= \tfrac{1}{2}\left[\delta_1{}^2 + \delta_2{}^2 - (\log \alpha_2)/A\right] \qquad \text{(Eq. 31)}$$

Also included in Table I are the calculated values of $(\log \alpha_2)/A$ and W obtained by regressing $(\log \alpha_2)/A$ and W on δ_1 in a third degree polynomial:

$$W = -3298.82 + 1084.56\delta_1 - 116.904\delta_1{}^2 + 4.26742\delta_1{}^3 \qquad \text{(Eq. 32)}$$

$$n = 15, R^2 = 0.999, F = 6702, F(3, 11, 0.01)^2 = 6.22$$

and:

$$\frac{\log \alpha_2}{A} = 6716.38 - 2169.12\delta_1 + 234.809\delta_1{}^2 - 8.53485\delta_1{}^3 \qquad \text{(Eq. 33)}$$

$$n = 15, R^2 = 0.998, F = 2352, F(3, 11, 0.01) = 6.22$$

The observed mole fraction solubilities, and the calculated values (obtained with Eqs. 30 and 33), together with percent differences between calculated and observed solubilities, are given in Table I. Variables K, l_{12}, and $(\log \alpha_R)/A$ were also regressed on δ_1 and the equations are:

$$K = -41.1320 + 13.7685\delta_1 - 1.50351\delta_1{}^2 + 0.0549512\delta_1{}^3 \qquad \text{(Eq. 34)}$$

$$n = 15, R^2 = 0.997, F = 1476, F(3, 11, 0.01) = 6.22$$

$$l_{12} = 42.1320 - 13.7685\delta_1 + 1.50351\delta_1{}^2 - 0.0549512\delta_1{}^3 \qquad \text{(Eq. 35)}$$

$$n = 15, R^2 = 0.997, F = 1476, F(3, 11, 0.01) = 6.22$$

and:

$$\frac{\log\alpha_R}{A} = 918.478\delta_1 - 300.154\delta_1{}^2 + 32.7765\delta_1{}^3 - 1.19794\delta_1{}^4 \qquad \text{(Eq. 36)}$$

$$n = 15, R^2 = 0.997, F = 1476, F(4, 10, 0.01) = 5.99$$

Since $K = 1 - l_{12}$ from Eq. 21 and $(\log \alpha_R)/A = 2l_{12}\delta_1\delta_2$ from Eq. 18, any one of the regression equations for K, l_{12}, and $(\log \alpha_R)/A$ can be obtained from the others. For example, replacing K in Eq. 34 by $(1 - l_{12})$ yields Eq. 35 for l_{12}. It is seen that the only differences are in the constant terms, −41.1320 in Eq. 34 and +42.1320 in Eq. 35, and the change in sign of each coefficient. Equation 36 for $(\log \alpha_R)/A$ is observed to take on an interesting form: no constant term exists and the polynomial is carried to the fourth rather than the third power.

Once the calculated value for one of these parameters is obtained from the regression equation, it may be substituted in the appropriate expression given earlier to obtain $X_{2(\text{calc})}$. For example, $l_{12(\text{calc})}$ for testosterone solubility in 50% chloroform–50% cyclohexane (v/v) ($\delta_1 = 8.67$) is obtained with Eq. 35:

$$l_{12(\text{calc})} = 42.1320 - 13.7685(8.67) + 1.5035(8.67)^2$$

$$-0.0549512(8.67)^3 = -0.0362$$

Then, from the second right hand term of Eq. 25:

$$\frac{\log \alpha_2}{A} = \delta_1{}^2 + \delta_2{}^2 - 2(1 - l_{12})\delta_1\delta_2 = (8.67)^2 + (10.9)^2$$

$$- 2(1 + 0.0362)\,(8.67)\,(10.9) = -1.8691$$

[2] $F(3, 11, 0.01)$ is the tabulated F value with p degrees of freedom in the numerator and n-p-1 degrees of freedom in the denominator, where $p = 3$ is the number of independent variables and $n = 15$ is the total number of samples. The value 0.01 signifies that the F ratio is compared with the tabular value obtained at the 99% level of confidence.

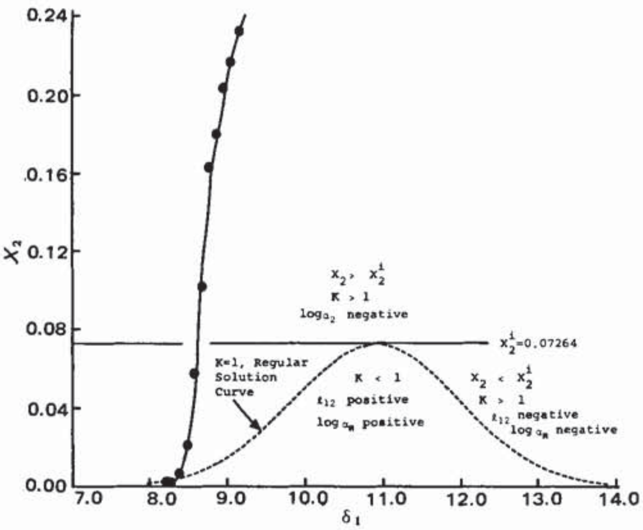

Figure 1—*Mole fraction solubility of testosterone ($\delta_2 = 10.9$) at 25° in cyclohexane and chloroform. Key: (●) experimental points; (—) solubility calculated by extended Hildebrand solubility approach; (- - - -) solubility curve calculated using regular solution theory.*

where the solubility parameter of testosterone is 10.9 $(cal/cm^3)^{1/2}$. Log $X_2{}^i$ is equal to −1.1388 for testosterone at 25°, and A from Table I is 0.1096 at 50% by volume chloroform. Continuing with Eq. 25, one obtains:

$$-\log X_2 = 1.1388 + (0.1096)(-1.8691) = 0.9340$$

$$X_{2(\text{obs})} = 0.102$$

$$X_{2(\text{calc})} = 0.116\ (-13.7\%\ \text{error})$$

Variables K, l_{12}, and log α_R are three different means of expressing deviation from regular solution behavior. Log α_R (Column 12, Table I) is a measure of the residual activity coefficient due to dipolar interactions between solvent and solute, inductive effects, and hydrogen bonding. Variables K and l_{12} are also used to represent solution irregularities. When log α_R is negative, l_{12} (Column 11) becomes negative and K (Column 10) becomes greater than unity, indicating that X_2 is greater than the mole fraction solubility in a regular solution. As observed in Table I, this effect occurs at 20% chloroform in cyclohexane. Above this concentration of chloroform, it may be assumed that the predominant factor promoting the solubility of testosterone is solvation of the drug by chloroform, most probably in this case through hydrogen bonding. At 50% chloroform in cyclohexane, the interaction between testosterone and chloroform has increased sufficiently to elevate the drug solubility above the ideal mole fraction solubility, $X_2{}^i = 0.0726$. At this point the total logarithmic activity coefficient, log α_2, as well as log α_R, is negative, indicating the beginning of strong solvation. It is suggested that the term complexation is appropriate for interactions between solute and solvent when $X_2 \gg X_2{}^i$, observed in Table I for testosterone in pure chloroform.

The various parameters, and the manner in which they may be used to express self-association ($K < 1$), nonspecific solvent effects or regular solution ($K \cong 1$), weak solubilization ($K > 1$ and $X_2 < X_2{}^i$), and complexation or strong solubilization ($K > 1$ and $X_2 > X_2{}^i$), are depicted in Fig. 1 for testosterone in a mixture of chloroform and cyclohexane. As the real or irregular solubility line crosses the regular solution line at the lower left side of Fig. 1, K changes from <1.0 to >1.0. Then, as the irregular solution line crosses the ideal solubility line, K remains >1.0, X_2 becomes greater than $X_2{}^i$, and log α_2 becomes negative. At 100% chloroform, log $\alpha_2 = -0.506$, which means that the ratio of X_2 to $X_2{}^i$ is ~3:1. The curve for testosterone propionate in chloroform–cyclohexane (not shown) is similar to Fig. 1 for testosterone, demonstrating complexation between the steroid ester and chloroform >30% by volume chloroform in the chloroform–cyclohexane mixture.

Testosterone Propionate in Mixed Solvents—The solubilities of the steroidal ester, testosterone propionate, at 25° in octanol–cyclohexane, ethyl oleate–cyclohexane, and isopropyl myristate–cyclohexane are plotted in Figs. 2–4 as a function of the solubility parameter of the mixed solvent. The logarithmic ideal solubility of testosterone propionate, log $X_2{}^i$, is −0.81356 at 25°; $X_2{}^i = 0.15362$. The solubility parameter, δ_2, and

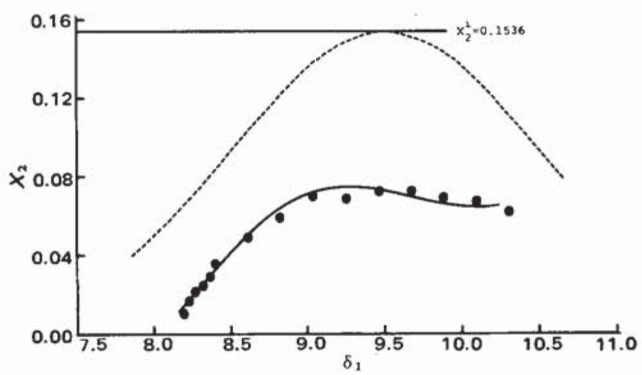

Figure 2—*Mole fraction solubility of testosterone propionate ($\delta_2 = 9.5$) at 25° in cyclohexane and octanol. Key: (●) experimental points; (—) solubility calculated by extended Hildebrand solubility approach; (---) solubility curve calculated using regular solution theory.*

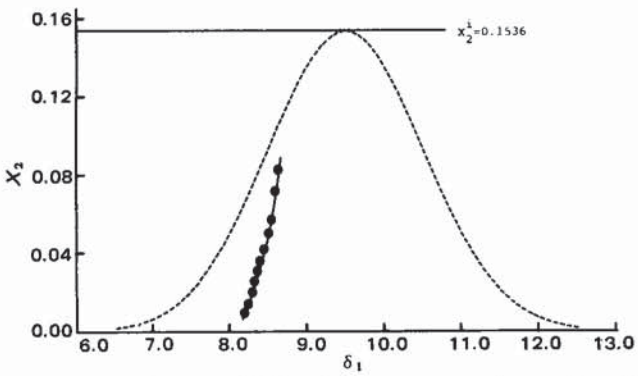

Figure 3—*Mole fraction solubility of testosterone propionate ($\delta_2 = 9.5$) at 25° in cyclohexane and ethyl oleate. Key: (●) experimental points; (—) solubility calculated by extended Hildebrand solubility approach; (---) solubility curve calculated using regular solution theory.*

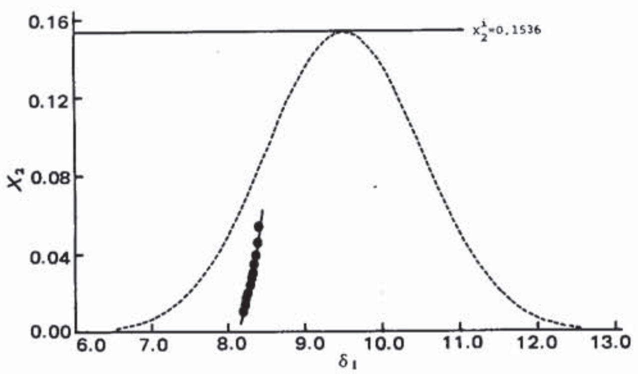

Figure 4—*Mole fraction solubility of testosterone propionate ($\delta_2 = 9.5$) at 25° in cyclohexane and isopropyl myristate. Key: (●) experimental solubility; (—) solubility calculated by extended Hildebrand solubility approach; (---) solubility curve calculated using regular solution theory.*

the molar volume, V_2, of testosterone propionate are, respectively, 9.5 $(\text{cal/cm}^3)^{1/2}$ and 294.0 cm^3/mole. The solubility parameter is 8.19 for cyclohexane, 10.30 for octanol, 8.63 for ethyl oleate, and 8.85 for isopropyl myristate.

Use of the extended Hildebrand solubility approach to calculate solubilities yields good results for these systems as observed by the fit of the calculated line to the points in Figs. 2–4.

As seen by comparing the regular solution curve (calculated using Eq. 8) with the extended Hildebrand solubility line (calculated using Eq. 11, 24, or 25), the observed solubilities are smaller than those predicted for a regular solution over most of the range of δ_1 values of the mixed solvents, as contrasted to the chloroform–cyclohexane mixture. At no composition of mixed solvent do the solubilities exceed the ideal solubility, as observed earlier in chloroform–cyclohexane (Fig. 1). The regression equations used to calculate solubilities in these systems are:

Octanol–Cyclohexane Mixtures (Fig. 2):

$$\frac{\log \alpha_2}{A} = 1142.47 - 356.237\delta_1 + 37.0357\delta_1^2 - 1.28137\delta_1^3 \quad \text{(Eq. 37)}$$

$$n = 15, R^2 = 0.965, F = 101, F(3, 11, 0.01) = 6.22$$

Ethyl Oleate–Cyclohexane Mixtures (Fig. 3):

$$\frac{\log \alpha_2}{A} = 27888.99 - 9867.80\delta_1 + 1164.77\delta_1^2 - 45.8617\delta_1^3 \quad \text{(Eq. 38)}$$

$$n = 11, R^2 = 0.999, F = 2589, F(3, 7, 0.01) = 8.45$$

Isopropyl Myristate–Cyclohexane Mixtures (Fig. 4):

$$\frac{\log \alpha_2}{A} = 157348.62 - 56738.3\delta_1 + 6821.48\delta_1^2 - 273.439\delta_1^3 \quad \text{(Eq. 39)}$$

$$n = 11, R^2 = 0.999, F = 3970, F(3, 7, 0.01) = 8.45$$

Nonlinear Regression—The solubility of testosterone in octanol–cyclohexane and in ethyl oleate–cyclohexane are plotted in Figs. 5 and 6. The extended Hildebrand solubility approach with polynomial regression, used with success for the other systems, failed to provide a satisfactory fit of the data, as shown by the dotted lines in Figs. 5 and 6.

The polynomial regression method contains potential numerical difficulties which show themselves only in certain applications. The source of these difficulties may be seen by recognizing that to date the extended

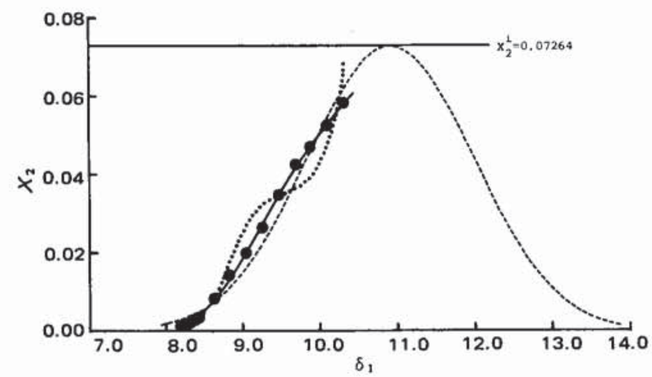

Figure 5—*Mole fraction solubility of testosterone ($\delta_2 = 10.9$) at 25° in cyclohexane and octanol. Key: (●) experimental points; (—) extended Hildebrand solubility curve based on NONLIN polynomial regression; (. . . .) extended Hildebrand solubility curve based on ordinary polynomial regression; (- - - -) regular solution curve.*

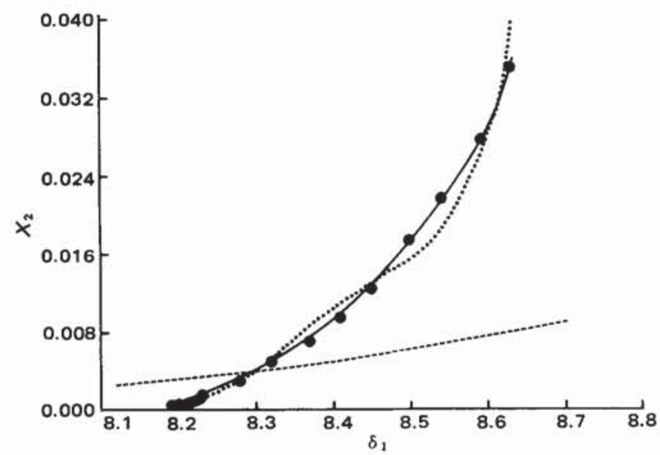

Figure 6—*Mole fraction solubility of testosterone ($\delta_2 = 10.9$) at 25° in cyclohexane and ethyl oleate. Key: (●) experimental points; (—) extended Hildebrand solubility curve based on NONLIN polynomial regression; (·····) extended Hildebrand solubility curve based on ordinary polynomial regression; (---) regular solution curve.*

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