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# The mobile order solubility equation applied to polyfunctional molecules: The non-hydroxysteroids in aqueous and non aqueous solvents

P. Ruelle *, A. Farina-Cuendet, U.W. Kesselring

*Institut d'Analyse Pharmaceutique, Section de Pharmacie, Université de Lausanne, BEP, CH-1015, Lausanne, Switzerland*

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**Abstract**

The solubility equation for real solutions derived from the thermodynamics of mobile order in liquids is used to predict the solubility of non-hydroxysteroids in water and in common polar and nonpolar organic solvents. Strictly obtained on a thermodynamic basis, the model allows not only correct predictions of the solubilities from the knowledge of a limited number of characteristics of solutes and solvents, but also enables a better understanding of the solution process and of the factors that determine solubility. Some practical rules are derived which might help to orient the choice of a solvent for liquid pharmaceutical forms. © 1997 Elsevier Science B.V.

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## 1. Introduction

In pharmaceutical technology, the ability of estimating solubility is of importance to select solvent systems with adequate drug solubility, stability, and bioavailability for topical, oral or parenteral delivery. From the Hildebrand theories of ideal and regular solutions onwards, a remarkable improvement of solubility prediction for real solutions has been achieved with the mobile order theory stated by Huyskens and coworkers (Huyskens and Haulait-Pirson, 1985; Huyskens and Siegel, 1988; Huyskens, 1992). This theory constitutes the basis of a new thermodynamic treatment of the liquid state, and its quantitative development has led to a universal equation (Ruelle et al., 1991) to predict the solubility (in volume fraction) of liquid and solid compounds in apolar and polar solvents, whatever these are protic or not. By a correct description of the enthalpy and entropy of solution, the predictive equation accounts for all the contributions to the free energy change when a solute is dissolved in a

* Corresponding author. Fax: +41 21 6924505; e-mail address: paul.ruelle@iap.unil.ch


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solvent. In particular, thermodynamic expressions describing the influence of solvent–solvent, solute–solute and solute–solvent interactions on the chemical potential of the solute have been derived. Based on the knowledge at the molecular level of the physical phenomena that determine solubility as well as on the forces that operate between molecules in solution, such thermodynamic model provides better understanding of the solution behaviour, and also reveals the true dependence of the solubility on some molecular descriptors (molar volume, molar surface area) currently used in LSER or QSPR correlative models. Up to now, the mobile order-derived solubility model has been successfully applied to predict the solubility of low-polarity substances in single and binary solvent systems (Ruelle et al., 1992, 1994a; Ruelle and Kesselring, 1995, 1997a; Acree and Tucker, 1994; Zvaigzne et al., 1996; McHale et al., 1996), of water in hydrocarbons (Ruelle and Kesselring, 1996), of solid crystalline proton-acceptor substances in aprotic and protic solvents (Huyskens et al., 1994; Huyskens and Seghers, 1994; Ruelle and Kesselring, 1994; Ruelle et al., 1993; Ruelle and Kesselring, 1997b), and of alcohols in water (Ruelle and Kesselring, 1997c). In these works, essentially simple systems containing only one proton -acceptor or -donor functional group were considered. However, an important problem in the case of pharmaceutical drugs arises from the multiplicity of the possible acceptor or donor sites in the molecule. The objective of this paper is therefore to demonstrate that this particular aspect can also be accounted for by the mobile order thermodynamics, and that the mobile order-derived solubility equation can still be used to predict the solubility of polyfunctionnal drug molecules. As an illustration, we report the solubility predictions of 38 proton-acceptor steroids in 190 water and common organic solvents of differing polarities. Although chemically very similar, steroid hormones differ from one another by slight structural changes and the presence of a varying number of proton-acceptor sites that may modify solubility and induce physiogically dissimilar effects and potencies. From the comparison of the relative importance of the various contributions involved in the solubility calculation, the origin of the solubility of the steroids is analyzed allowing a deeper understanding into the solution process of these substances.

## 2. The solubility equation

If the solute (B) does not contain proton-donor functional group, its solubility, $\Phi_B$, can be calculated by means of the predictive slubility equation as the sum of five or three contributions according to whether the solvent (S) is proton donor or not.

1. Solubility in aprotic solvents:

$$\ln \Phi_B = A + B + D \quad (1)$$

2. Solubility in protic solvents:

$$\ln \Phi_B = A + B + D + F + O \quad (2)$$

Representing a particular physical phenomenon of the whole solution process, each term involved in Eqs. (1) and (2) has a thermodynamically well-defined expression and contributes favorably or unfavorably to the solubility.

'$A$' represents the fluidization of the solute or the ideal solubility. This contribution corresponds to the suppression of the collective forces which bind the solute molecules within their crystalline state. The fluidization term is a negative contribution independent of the solvent, and at the considered temperature is calculated from the knowledge of the molar enthalpy of fusion, $\Delta_m H$, and from the absolute melting temperature, $T_m$, of the pure crystalline substance.

$$A = -\frac{\Delta_m H}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) \quad (3)$$

In absence of available enthalpy of fusion of the steroids, their solute crystallinity contribution to the solubility is calculated from the equation proposed by Yalkowsky (Yalkowsky, 1979) requiring only the melting point in Kelvin of the compound.

$$A = -0.02278(T_m - 298.15) \quad (4)$$

'$B$' represents a correction factor for the entropy of mixing accounting for the difference in the sizes of the solvent and solute molecules in

solution. Accordingly, this term essentially depends on the ratio, $V_B/V_S$, between the molar volumes, and contributes positively to the solubility as far as $V_B$ is greater than $V_S$.

$$B = 0.5\Phi_S\left(\frac{V_B}{V_S} - 1\right) + 0.5\ln\left(\Phi_B + \Phi_S\frac{V_B}{V_S}\right) \quad (5)$$

'*D*' describes the changes in the non-specific cohesion forces (dispersion, induction, and dipole–dipole) when the fluidized pure solute is mixed with the solvent. This contribution is always negative, and can be represented by a Scatchard–Hildebrand equation based on the geometric mean of the cohesive energy density of B molecules surrounded by S molecules. This equation, which is essentially based on the assumption of random interactions in solution, is however no longer valid when preferential contacts are formed between the solute and the solvent, because these contacts modify the random distribution of the molecules. The effect of the new mode of distribution is actually accounted for by multiplying the Scatchard–Hildebrand expression by the fraction of time during which the solute is not bound to the solvent, i.e. during which the mixing can be considered to occur at random (Ruelle et al., 1994b). Using modified non-specific solubility parameters, $\delta'$, of the solute and of the solvent, the D contribution is expressed by:

$$D = -\frac{1}{\left(1.0 + \max(K_{Oi})\frac{\Phi_S}{V_S}\right)}\frac{\Phi_S^2 V_B}{RT}(\delta'_B - \delta'_S)^2 \quad (6)$$

'*F*' corresponds to the hydrophobic effect, and describes the negative influence of the solvent–solvent hydrogen-bonded chains on the solubility. This effect has been introduced in the frame of the mobile order theory and is quantitatively defined by Eq. (7) where $r_s$ represents the structuration factor of the solvent. At room temperature, the value of $r_s$ amounts to 0 for solvents which do not self-associate (hydrocarbons, esters, ethers, ketones, nitriles), approximately to one for solvents that form single H-bonded chains (alcohols), and to two for water and diols whose molecules are involved in double hydrogen-bonded chains.

$$F = r_s\Phi_S\frac{V_B}{V_S} \quad (7)$$

'*O*' expresses the effect on the solubility of the formation of hydrogen bonds between proton-donor solvents and the multiple proton-acceptor sites of the solute. Each particular proton-donor/proton-acceptor hydrogen bond is characterized by a standard stability constant, $K_{Oi}$, and contributes to increase the solubility. The overall *O* contribution is always positive, and is calculated to a fist approximation as the sum of the partial contributions that each proton-acceptor site brings about. Although the formation of a H-bond by a given active site weakens the strength of the other interaction sites, Eq. (8) assumes equal capacity for all the sites of the same nature.

$$O = \sum_i v_{Oi}\ln\left[1 + K_{Oi}\left(\frac{\Phi_S}{V_S} - v_{Oi}\frac{\Phi_B}{V_B}\right)\right] \quad (8)$$

In this equation, $i$ represents a particular type of solute–solvent interaction governed by $K_{Oi}$, whereas $v_{Oi}$ indicates the number of identical and independent active sites of type $i$ on the solute molecule.

From the foregoing, the solubility can be estimated on the basis of a limited number of intrinsic properties characterizing both the solute and solvent molecules. Regarding the steroids, all the physico-chemical parameters, i.e. the molar enthalpy and the temperature of fusion, the molar volume, the modified non-specific solubility parameter as well as the type and the number of proton-acceptor groups, needed to estimate their solubility are gathered in Table 1. It is important to mention that, in the case of the steroids which are solid at room temperature, the molar volume we have to consider is not that of the crystalline compound, but the volume of the fluidized substance in its hypothetical supercooled liquid state. These volumes have been estimated from the addition of group contributions (Ruelle et al., 1991; Huyskens et al., 1994). However, in the case of the estimation of the aqueous solubility, the values of the steroid molar volumes have been decreased by 15% to account for the contraction upon mixing resulting from the hydrogen bond formation between the various interactive sites on the solute and the water molecules. This proce-

Table 1
Physico-chemical properties of the steroids

| Solute[a] | $T_m^b$ (K) | $\Delta H_m$ (cal/mol) | $V_B$ (cm$^3$/mol) | $v_{O1}$ | $v_{O2}$ | $v_{O3}$ | Ref[c] |
|---|---|---|---|---|---|---|---|
| Testosterone formate | 398.00 | 4330.0 | 280.8 | 1 | 1 | 0 | James and Roberts (1968) |
| Testosterone acetate | 413.15 | 5380.0 | 307.1 | 1 | 1 | 0 | James and Roberts (1968) |
| Testosterone propionate | 393.15 | 5290.0 | 323.4 | 1 | 1 | 0 | James and Roberts (1968) |
| Testosterone butyrate | 382.15 | 6050.0 | 339.6 | 1 | 1 | 0 | James and Roberts (1968) |
| Testosterone valerate | 380.15 | 7400.0 | 355.8 | 1 | 1 | 0 | James and Roberts (1968) |
| Testosterone 17$\beta$-cypionate | 374.15 | | 399.2 | 1 | 1 | 0 | |
| Methyltestosterone acetate | 448.15 | 6129.0 | 327.1 | 1 | 1 | 0 | Roberts (1969) |
| Methyltestosterone propionate | 418.15 | 8149.0 | 343.4 | 1 | 1 | 0 | Roberts (1969) |
| Prasterone formate | 413.15 | | 280.8 | 1 | 1 | 0 | |
| Prasterone acetate | 440.15 | | 307.1 | 1 | 1 | 0 | |
| Prasterone propionate | 470.15 | | 323.4 | 1 | 1 | 0 | |
| Prasterone butyrate | 436.15 | | 339.6 | 1 | 1 | 0 | |
| Prasterone valerate | 393.15 | | 355.9 | 1 | 1 | 0 | |
| Norethindrone acetate | 480.00 | 6524.9 | 311.8 | 1 | 1 | 1 | Lewis and Enever (1979a) |
| Norethindrone heptanoate | 340.00 | 5162.5 | 397.0 | 1 | 1 | 1 | Lewis and Enever (1979a) |
| Norethindrone benzoate | 531.00 | 9918.7 | 366.8 | 1 | 1 | 1 | Lewis and Enever (1979a) |
| Norethindrone dimethylpropionate | 500.00 | 9034.4 | 373.8 | 1 | 1 | 1 | Lewis and Enever (1979a) |
| Progesterone | 403.25 | 5840.0 | 293.6 | 0 | 2 | 0 | Bernabei et al. (1974) |
| Ethynodiol diacetate | 399.15 | | 359.3 | 2 | 0 | 1 | |
| Medrogestone | 417.15 | | 311.6 | 0 | 2 | 0 | |
| Megestrol acetate | 488.15 | | 332.6 | 1 | 2 | 0 | |
| Cholesteryl acetate | 388.15 | | 462.3 | 1 | 0 | 0 | |
| Cholesteryl benzoate | 423.00 | | 517.3 | 1 | 0 | 0 | |
| Pregnenolone acetate | 423.15 | | 341.1 | 1 | 1 | 0 | |
| Stanolone formate | 415.15 | 6357.0 | 294.7 | 1 | 1 | 0 | Roberts (1969) |
| Stanolone acetate | 430.15 | 6647.0 | 321.0 | 1 | 1 | 0 | Roberts (1969) |
| Stanolone propionate | 394.15 | 5859.0 | 341.3 | 1 | 1 | 0 | Roberts (1969) |
| Stanolone butyrate | 364.15 | 5418.0 | 357.5 | 1 | 1 | 0 | Roberts (1969) |
| Stanolone valerate | 375.65 | | 373.8 | 1 | 1 | 0 | |
| Nandrolone propionate | 328.15 | | 303.4 | 1 | 1 | 0 | |
| Nandrolone butyrate | 346.15 | | 323.6 | 1 | 1 | 0 | |
| Nandrolone nonanoate | 313.15 | | 404.8 | 1 | 1 | 0 | |
| Nandrolone decanoate | 308.15 | | 421.1 | 1 | 1 | 0 | |
| Dydrogesterone | 442.15 | | 282.4 | 0 | 2 | 0 | |
| Deoxycorticosterone acetate | 430.00 | 7089.0 | 330.8 | 1 | 2 | 0 | Regosz et al. (1994) |
| Deoxycorticosterone pivalate | 476.15 | | 392.9 | 1 | 2 | 0 | |
| Dromostanolone propionate | 399.15 | | 361.2 | 1 | 1 | 0 | |
| 17$\alpha$-OH-progesterone caproate | 393.15 | | 399.6 | 1 | 2 | 0 | |

[a] $v_{O1}$ is the number of ester groups on the solute; $v_{O2}$ is the number of ketone groups on the solute; $v_{O3}$ is the number of alkyne groups on the solute; $\delta'_B$ for all steroids is equal to 20 MPa$^{1/2}$.
[b] Melting points of the steroids can be found either in the same references as the experimental solubility data were taken from, or they can be obtained from Hill and Makin (1991).
[c] Literature references for the enthalpy of fusion.

dure appears reasonably justified when one compares the calculated values with the partial molar volumes determined experimentally at infinite dilution in cyclohexane, ethanol, and water (Table 2). These last values were obtained in this work from high-precision densitometric measurements (Ruelle et al., 1996) carried out at 25°C on a DMA-58 vibrating tube density meter (Anton Paar, A-8054 Graz, Austria) capable of a precision reproducible to within $\pm 10^{-5}$ g/cm.

Table 2
Experimental vs calculated molar volume ($cm^3$/mol) of steroids[a]

| Steroid | $V_{increment}$ | $\bar{V}_{cyclohexane}$ | $\bar{V}_{ethanol}$ | $\bar{V}_{water}$ |
|---|---|---|---|---|
| Testosterone propionate | 323.4 | 314.6 (−2.7) | 304.8 (−5.7) | — |
| Norethindrone acetate | 311.8 | 309.0 (−0.9) | 293.5 (−5.9) | — |
| Prasterone acetate | 307.1 | 296.5 (−3.4) | — | — |
| Progesterone | 293.6 | 286.2 (−2.5) | 279.5 (−4.8) | — |
| Prednisolone | 282.6 | — | 263.0 (−6.9) | 235.0 (−16.8) |

[a] In parentheses are given the percentage differences between experimental and calculated molar volumes $\frac{\bar{V}-V_{increment}}{V_{increment}}\times 100$.

Concerning the solvents, their molar volume and their modified non-specific solubility parameter can be found in some of our previous papers (Ruelle et al., 1993, 1994a), except for the five following solvents whose values are given hereafter: ethyl oleate (356.9 $cm^3$/mol, 17.69 $MPa^{1/2}$), isopropyl myristate (317.0 $cm^3$/mol, 17.83 $MPa^{1/2}$), benzyl benzoate (189.8 $cm^3$/mol, 18.5 $MPa^{1/2}$), benzyl alcohol (103.8 $cm^3$/mol, 17.0 $MPa^{1/2}$) and cyclohexene (101.4 $cm^3$/mol, 17.0 $MPa^{1/2}$).

Finally, the solubility predictions in alcohols or in water still require the knowledge of the stability constants, $K_{Oi}$ characteristic of the particular solute–solvent associations. Assuming that the interaction of a given functional group like ester or ketone on the solute with a proton-donor solvent is independent of the molecular environment, we actually use standard stability constants. The values of these constants (Table 3) were previously calculated from experimental solubilities of monofunctional systems (Ruelle et al., 1993; Ruelle and Kesselring, 1997b).

Table 3
Solute–solvent standard stability constants, $K_{Oi}$, at 25°C

| Solute | Solvent | $K_{Oi}$ $cm^3$/mol |
|---|---|---|
| Ester | Alcohol | 110.0 |
| | Water | 3500.0 |
| Ketone | Alcohol | 170.0 |
| | Water | 5000.0 |
| Triple bond C≡C | Alcohol | 0.0 |
| | Water | 80.0 |

## 3. Results and discussion

Using the physico-chemical parameters characterizing the steroids, the solvents, and their interactions, we have calculated the solubility of 38 non-hydroxysteroids in 190 solvents according to Eq. (1) or Eq. (2). The results as well as the corresponding experimental data are presented in Tables 4 and 5 together with the values of the various contributions involved in the solubility predictions. The agreement between the observed and predicted solubilities (Fig. 1) illustrates the quality of the prediction. The predictive ability of the model is furthermore characterized by the ratio of the calculated to experimental solubility, $\Phi_B^{calc}/\Phi_B^{exp}$, given in the fifth column of Tables 4 and 5. Irrespective to the complexity of the solute and of its interactions with the solvent, 174 out of the 190 predicted values, i.e. 89% of the results show a solubility ratio between 0.1 and 10.0 (105 results have a ratio in the range of 0.5–2.0) and 16 ratios are beyond these limits. The discrepancies between the experimental and calculated solubilities can partly be attributed either to the lack of known values of melting enthalpies, or to the uncertainties of both the liquid molar volumes and modified non-specific solubility parameters of the steroids. Another source of error may also result from the use of standard values of the association constants instead of using particular values depending on both the solute and solvent interacting molecules. Nevertheless, the results on the whole clearly demonstrate the good predictive ability of the mobile order-derived solubility

Table 4
Experimental and calculated solubility of the nonhydroxy-steroids at 25°C, and *A*, *B*, *D*, *F* and *O* contributions to the solubility (part 1)

| Solute | Solvent | $\Phi_B^{calc}$ | $\Phi_B^{exp}$ | $\Phi_B^{calc}/\Phi_B^{exp}$ | *A* | *B* | *D* | *F* | *O* | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| Testosterone formate | Cyclohexane | 0.88 E−01 | 0.11 E−01 | 8.1 | −1.067 | 1.167 | −2.526 | | | e |
| | Benzene | 0.65 E+00 | 0.55 E+00 | 1.2 | −1.067 | 0.653 | −0.015 | | | b |
| | Toluene | 0.58 E+00 | 0.41 E+00 | 1.4 | −1.067 | 0.598 | −0.071 | | | b |
| | Nitrobenzene | 0.60 E+00 | 0.47 E+00 | 1.3 | −1.067 | 0.611 | −0.057 | | | b |
| | 1,2-dichloroethane | 0.69 E+00 | 0.62 E+00 | 1.1 | −1.067 | 0.699 | −0.011 | | | b |
| | $CHCl_3$ | 0.68 E+00 | 0.68 E+00 | 1.0 | −1.067 | 0.694 | −0.018 | | | b |
| | Isopropyl myristate | 0.23 E+00 | 0.37 E−01 | 6.1 | −1.067 | −0.090 | −0.317 | | | c |
| | Ethyl oleate | 0.19 E+00 | 0.47 E−01 | 4.1 | −1.067 | −0.189 | −0.393 | | | c |
| | Ethanol | 0.49 E+00 | 0.10 E−00 | 4.8 | −1.067 | 1.503 | −0.057 | −2.441 | 1.348 | b |
| | Water | 0.11 E−03 | 0.33 E−05 | 31.9 | −1.067 | 7.383 | −0.000 | −26.373 | 10.895 | b |
| Testosterone acetate | Cyclohexane | 0.43 E−01 | 0.11 E−01 | 4.0 | −1.471 | 1.376 | −3.041 | | | e |
| | Isooctane | 0.91 E−02 | 0.37 E−02 | 2.5 | −1.471 | 0.726 | −3.952 | | | d |
| | Benzene | 0.56 E+00 | 0.40 E+00 | 1.4 | −1.471 | 0.909 | −0.027 | | | b |
| | Toluene | 0.47 E+00 | 0.31 E+00 | 1.5 | −1.471 | 0.841 | −0.126 | | | b |
| | Nitrobenzene | 0.49 E+00 | 0.34 E+00 | 1.4 | −1.471 | 0.858 | −0.101 | | | b |
| | 1,2-dichloroethane | 0.60 E+00 | 0.53 E+00 | 1.1 | −1.471 | 0.973 | −0.020 | | | b |
| | $CHCl_3$ | 0.59 E+00 | 0.61 E+00 | 1.0 | −1.471 | 0.967 | −0.032 | | | b |
| | Isopropyl myristate | 0.15 E+00 | 0.23 E−01 | 6.4 | −1.471 | −0.027 | −0.425 | | | c |
| | Ethyl oleate | 0.12 E+00 | 0.29 E−01 | 4.2 | −1.471 | −0.127 | −0.510 | | | c |
| | Ethanol | 0.30 E−00 | 0.83 E−01 | 3.6 | −1.471 | 2.183 | −0.097 | −3.688 | 1.853 | b |
| | Water | 0.12 E−04 | 0.19 E−05 | 6.2 | −1.471 | 8.044 | −0.000 | −28.839 | 10.895 | b |
| Testosterone propionate | *n*-pentane | 0.15 E−01 | 0.83 E−02 | 1.8 | −1.300 | 1.387 | −4.288 | | | a |
| | *n*-hexane | 0.22 E−01 | 0.12 E−01 | 1.8 | −1.300 | 1.156 | −3.697 | | | a |
| | *n*-heptane | 0.20 E−01 | 0.13 E−01 | 1.6 | −1.300 | 0.971 | −3.571 | | | a |
| | *n*-octane | 0.23 E−01 | 0.16 E−01 | 1.4 | −1.300 | 0.813 | −3.306 | | | a |
| | *n*-nonane | 0.27 E−01 | 0.13 E−01 | 2.0 | −1.300 | 0.677 | −3.005 | | | a |
| | *n*-decane | 0.26 E−01 | 0.16 E−01 | 1.6 | −1.300 | 0.563 | −2.925 | | | a |
| | *n*-undecane | 0.26 E−01 | 0.13 E−01 | 2.1 | −1.300 | 0.455 | −2.790 | | | a |
| | *n*-dodedane | 0.27 E−01 | 0.16 E−01 | 1.7 | −1.300 | 0.371 | −2.682 | | | a |
| | *n*-hexadecane | 0.28 E−01 | 0.11 E−01 | 2.5 | −1.300 | 0.224 | −2.508 | | | a |
| | Cyclohexane | 0.50 E−01 | 0.35 E−01 | 1.4 | −1.300 | 1.465 | −3.159 | | | a |
| | Decaline | 0.44 E+00 | 0.34 E−01 | 12.8 | −1.300 | 0.530 | −0.049 | | | a |
| | Methylcyclohexane | 0.45 E−01 | 0.36 E−01 | 1.2 | −1.300 | 1.175 | −2.974 | | | a |
| | *t*-Butylcyclohexane | 0.51 E−01 | 0.28 E−01 | 1.8 | −1.300 | 0.706 | −2.378 | | | a |
| | Cyclohexene | 0.51 E+00 | 0.16 E+00 | 3.2 | −1.300 | 0.685 | −0.001 | | | e |
| | Cyclooctane | 0.74 E−01 | 0.42 E−01 | 1.7 | −1.300 | 1.062 | −2.368 | | | a |
| | $CS_2$ | 0.73 E+00 | 0.54 E+00 | 1.3 | −1.300 | 0.987 | −0.002 | | | a |
| | $CCl_4$ | 0.53 E+00 | 0.39 E+00 | 1.4 | −1.300 | 0.918 | −0.253 | | | a |
| | Chlorobenzene | 0.59 E+00 | 0.54 E+00 | 1.1 | −1.300 | 0.770 | −0.006 | | | a |
| | $CHCl_3$ | 0.65 E+00 | 0.69 E+00 | 0.9 | −1.300 | 0.891 | −0.024 | | | b |
| | 1,2-dicloroethane | 0.63 E+00 | 0.63 E+00 | 1.0 | −1.300 | 0.878 | −0.040 | | | b |
| | *t*-1,2-diclethylene | 0.65 E+00 | 0.66 E+00 | 1.0 | −1.300 | 0.914 | −0.040 | | | a |
| | *c*-1,2-diclethylene | 0.66 E+00 | 0.65 E+00 | 1.0 | −1.300 | 0.918 | −0.029 | | | a |
| | Nitrobenzene | 0.56 E+00 | 0.47 E+00 | 1.2 | −1.300 | 0.802 | −0.078 | | | a |
| | Benzene | 0.62 E+00 | 0.56 E+00 | 1.1 | −1.300 | 0.843 | −0.021 | | | a |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Toluene | 0.54 E+00 | 0.43 E+00 | 1.3 | −1.300 | 0.789 | −0.098 | | | a |
| | Tetraline | 0.49 E+00 | 0.37 E+00 | 1.3 | −1.300 | 0.606 | −0.011 | | | a |
| | Anisole | 0.54 E+00 | 0.48 E+00 | 1.1 | −1.300 | 0.685 | −0.001 | | | a |
| | Isopropyl myristate | 0.18 E+00 | 0.25 E−01 | 4.4 | −1.300 | 0.016 | −0.409 | | | c |
| | Ethyl oleate | 0.15 E+00 | 0.42 E−01 | 3.4 | −1.300 | −0.081 | −0.500 | | | c |
| | Ethanol | 0.33 E+00 | 0.14 E−00 | 2.4 | −1.300 | 2.197 | −0.095 | −3.672 | 1.772 | b |
| | Propanol | 0.30 E+00 | 0.15 E−00 | 2.0 | −1.300 | 1.753 | −0.181 | −3.007 | 1.537 | f |
| | Butanol | 0.27 E+00 | 0.15 E−00 | 1.8 | −1.300 | 1.433 | −0.237 | −2.553 | 1.362 | f |
| | Water | 0.44 E−05 | 0.11 E−05 | 4.2 | −1.300 | 8.454 | −0.000 | −30.376 | 10.895 | b |
| Testosterone butyrate | Cyclohexane | 0.30 E−01 | 0.40 E−01 | 0.7 | −1.636 | 1.588 | −3.459 | | | e |
| | Benzene | 0.54 E+00 | 0.54 E+00 | 1.0 | −1.636 | 1.054 | −0.032 | | | b |
| | Toluene | 0.45 E+00 | 0.44 E+00 | 1.0 | −1.636 | 0.990 | −0.149 | | | b |
| | Nitrobenzene | 0.47 E+00 | 0.38 E+00 | 1.2 | −1.636 | 1.006 | −0.119 | | | b |
| | 1,2-dicloroethane | 0.58 E+00 | 0.59 E+00 | 1.0 | −1.636 | 1.121 | −0.023 | | | b |
| | $CHCl_3$ | 0.57 E+00 | 0.68 E+00 | 0.8 | −1.636 | 1.117 | −0.038 | | | b |
| | Isopropyl myristate | 0.13 E+00 | 0.41 E−01 | 3.1 | −1.636 | 0.061 | −0.492 | | | c |
| | Ethyl oleate | 0.10 E+00 | 0.49 E−01 | 2.1 | −1.636 | −0.044 | −0.587 | | | c |
| | Ethanol | 0.19 E−00 | 0.86 E−01 | 2.3 | −1.636 | 2.718 | −0.128 | −4.661 | 2.069 | b |
| | Water | 0.10 E−05 | 0.40 E−06 | 2.6 | −1.636 | 8.860 | −0.000 | −31.901 | 10.895 | b |
| Testosterone valerate | Cyclohexane | 0.14 E−01 | 0.52 E−01 | 0.3 | −2.251 | 1.707 | −3.747 | | | e |
| | Benzene | 0.40 E+00 | 0.45 E+00 | 0.9 | −2.251 | 1.400 | −0.056 | | | b |
| | Toluene | 0.30 E+00 | 0.32 E+00 | 0.9 | −2.251 | 1.300 | −0.254 | | | b |
| | Nitrobenzene | 0.32 E+00 | 0.33 E+00 | 1.0 | −2.251 | 1.326 | −0.206 | | | b |
| | 1,2-dicloroethane | 0.45 E+00 | 0.51 E+00 | 0.9 | −2.251 | 1.500 | −0.042 | | | b |
| | $CHCl_3$ | 0.44 E+00 | 0.63 E+00 | 0.7 | −2.251 | 1.494 | −0.069 | | | b |
| | Isopropyl myristate | 0.65 E−01 | 0.22 E−01 | 3.0 | −2.251 | 0.111 | −0.591 | | | c |
| | Ethyl oleate | 0.53 E−01 | 0.38 E−01 | 1.4 | −2.251 | −0.003 | −0.687 | | | c |
| | Ethanol | 0.81 E−01 | 0.40 E−01 | 2.0 | −2.251 | 3.191 | −0.159 | −5.568 | 2.279 | b |
| | Water | 0.18 E−06 | 0.23 E−06 | 0.8 | −2.251 | 9.262 | −0.000 | −33.414 | 10.895 | b |
| Testosterone 17$\beta$-cypionate | Benzene | 0.57 E+00 | 0.63 E+00 | 0.9 | −1.731 | 1.202 | −0.033 | | | c |
| | Toluene | 0.48 E+00 | 0.60 E+00 | 0.8 | −1.731 | 1.154 | −0.157 | | | c |
| | Nitrobenzene | 0.50 E+00 | 0.44 E+00 | 1.1 | −1.731 | 1.166 | −0.126 | | | c |
| | 1,2-dichloroethane | 0.61 E+00 | 0.66 E+00 | 0.9 | −1.731 | 1.263 | −0.024 | | | c |
| | $CHCl_3$ | 0.60 E+00 | 0.79 E+00 | 0.8 | −1.731 | 1.261 | −0.039 | | | c |
| | Isopropyl myristate | 0.12 E+00 | 0.56 E−01 | 2.2 | −1.731 | 0.216 | −0.584 | | | c |
| | Ethyl oleate | 0.98 E−01 | 0.60 E−01 | 1.6 | −1.731 | 0.104 | −0.700 | | | c |
| Me-Testosterone acetate | Isooctane | 0.99 E−03 | 0.17 E−02 | 0.6 | −3.462 | 0.823 | −4.279 | | | g |
| | Cyclohexane | 0.44 E−02 | 0.83 E−02 | 0.5 | −3.462 | 1.548 | −3.509 | | | e |
| | $CHCl_3$ | 0.18 E+00 | 0.34 E+00 | 0.5 | −3.462 | 1.880 | −0.134 | | | e |
| | Water | 0.40 E−06 | 0.17 E−05 | 0.2 | −3.462 | 8.545 | −0.000 | −30.718 | 10.895 | h |
| Me-Testosterone propionate | Cyclohexane | 0.25 E−02 | 0.23 E−01 | 0.1 | −3.947 | 1.649 | −3.699 | | | e |
| | $CHCl_3$ | 0.13 E+00 | 0.38 E+00 | 0.4 | −3.947 | 2.083 | −0.158 | | | e |
| | Water | 0.79 E−07 | 0.98 E−06 | 0.1 | −3.947 | 8.954 | −0.000 | −32.254 | 8.954 | h |

[a] a, James et al., 1976; b, James and Roberts, 1968; c, Roberts, 1969; d, Rytting et al., 1989; e, Bowen, 1969; f, Ruelle et al., 1993; g, Higuchi et al., 1979; h, Bowen et al., 1970; i, Reynolds, 1993; j, Gennaro, 1985; k, Lewis and Enever, 1979b; l, Bernabei et al., 1974; m, Yalkowsky et al., 1983; n, Regosz et al., 1994; o, Lau and Sutter, 1974; p, Myrdal et al., 1995; q, Bar et al., 1984; r, Pal and Moulik, 1984; s, Budavari, 1989; t, Chaudry and James, 1974.

Table 5
Experimental and calculated solubility of the nonhydroxy-steroids at 25°C, and *A*, *B*, *D*, *F* and *O* contributions to the solubility (part 2)

| Solute | Solvent | $\Phi_B^{calc}$ | $\Phi_B^{exp}$ | $\Phi_B^{calc}/\Phi_B^{exp}$ | *A* | *B* | *D* | *F* | *O* | Ref[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Prasterone formate | Cyclohexane | 0.13 E−01 | 0.67 E−02 | 2.0 | −2.620 | 1.250 | −2.960 | | | h |
| | $CHCl_3$ | 0.27 E+00 | 0.28 E+00 | 1.0 | −2.620 | 1.415 | −0.090 | | | e |
| | Water | 0.22 E−04 | 0.11 E−04 | 2.1 | −2.620 | 7.383 | −0.000 | −26.375 | 10.895 | h |
| Prasterone acetate | Cyclohexane | 0.61 E−02 | 0.10 E−02 | 0.6 | −3.235 | 1.423 | −3.284 | | | h |
| | $CHCl_3$ | 0.20 E+00 | 0.29 E+00 | 0.7 | −3.235 | 1.720 | −0.122 | | | e |
| | Water | 0.20 E−05 | 0.91 E−05 | 0.2 | −3.235 | 8.044 | −0.000 | −28.840 | 10.895 | h |
| Prasterone propionate | Cyclohexane | 0.28 E−02 | 0.17 E−01 | 0.2 | −3.918 | 1.527 | −3.481 | | | h |
| | $CHCl_3$ | 0.12 E+00 | 0.30 E+00 | 0.4 | −3.918 | 1.966 | −0.152 | | | e |
| | Water | 0.32 E−06 | 0.66 E−05 | 0.05 | −3.918 | 8.454 | −0.000 | −30.376 | 10.895 | h |
| Prasterone butyrate | Cyclohexane | 0.58 E−02 | 0.29 E−01 | 0.2 | −3.144 | 1.622 | −3.634 | | | h |
| | $CHCl_3$ | 0.24 E+00 | 0.31 E+00 | 0.8 | −3.144 | 1.836 | −0.120 | | | e |
| | Water | 0.23 E−06 | 0.64 E−05 | 0.04 | −3.144 | 8−860 | −0.000 | −31.901 | 10.895 | h |
| Prasterone valerate | Cyclohexane | 0.15 E−01 | 0.44 E−01 | 0.3 | −2.164 | 1.706 | −3.737 | | | h |
| | $CHCl_3$ | 0.46 E+00 | 0.36 E+00 | 1.3 | −2.164 | 1.447 | −0.064 | | | e |
| | Water | 0.20 E−06 | 0.62 E−05 | 0.03 | −2.164 | 9.264 | −0.000 | −33.425 | 10.895 | h |
| Norethindrone acetate | Isooctane | 0.55 E−03 | 0.79 E−03 | 0.7 | −4.172 | 0.753 | −4.082 | | | g |
| | Acetone | 0.90 E−01 | 0.19 E+00 | 0.5 | −4.172 | 2.146 | −0.038 | | | i |
| | Dioxane | 0.87 E−01 | 0.31 E+00 | 0.3 | −4.172 | 1.815 | −0.083 | | | j |
| | Diethyl ether | 0.56 E−01 | 0.48 E−01 | 1.2 | −4.172 | 1.458 | −0.167 | | | j |
| | Ethanol | 0.15 E−01 | 0.84 E−01 | 0.2 | −4.172 | 2.953 | −0.152 | −5.233 | 2.391 | j |
| | Water | 0.30 E−05 | 0.42 E−05 | 0.7 | −4.172 | 8.162 | −0.000 | −29.282 | 12.585 | g |
| Norethindrone heptanoate | Water | 0.19 E−06 | 0.51 E−07 | 3.6 | −1.073 | 10.286 | −0.000 | −37.293 | 12.585 | k |
| Norethindrone benzoate | Water | 0.29 E−08 | 0.65 E−08 | 0.4 | −7.341 | 9.536 | −0.000 | −34.453 | 12.585 | k |
| Norethindrone diMepropion | Water | 0.58 E−08 | 0.26 E−07 | 0.2 | −6.156 | 9.709 | −0.000 | −35.105 | 12.585 | k |
| Progesterone | *n*-octane | 0.69 E−02 | 0.33 E−02 | 2.1 | −2.569 | 0.686 | −3.098 | | | l |
| | Isooctane | 0.33 E−02 | 0.21 E−02 | 1.6 | −2.569 | 0.667 | −3.823 | | | l |
| | *n*-octanol | 0.52 E−01 | 0.48 E−01 | 1.1 | −2.569 | 0.702 | −0.692 | −1.760 | 1.346 | m |
| | Water | 0.14 E−04 | 0.94 E−05 | 1.5 | −2.569 | 7.707 | −0.000 | −27.580 | 11.250 | n |
| Ethynodiol diacetate | Heptane | 0.53 E−02 | 0.18 E−01 | 0.3 | −2.301 | 1.158 | −4.089 | | | o |
| | $CHCl_3$ | 0.43 E+00 | 0.48 E+00 | 0.9 | −2.301 | 1.528 | −0.071 | | | i |
| | Diethtyl ether | 0.33 E+00 | 0.21 E+00 | 1.6 | −2.301 | 1.294 | −0.096 | | | i |
| | Ethanol | 0.50 E−01 | 0.59 E−01 | 0.8 | −2.301 | 3.318 | −0.226 | −5.817 | 2.023 | i |
| | Water | 0.52 E−06 | 0.12 E−05 | 0.4 | −2.301 | 9.349 | −0.000 | −33.746 | 12.230 | o |
| Medrogestone | Water | 0.35 E−05 | 0.14 E−05 | 2.4 | −2.711 | 8.159 | −0.000 | −29.271 | 11.250 | p |
| Megestrol acetate | $CHCl_3$ | 0.90 E−01 | 0.52 E+00 | 0.2 | −4.328 | 2.092 | −0.168 | | | i |
| | Ethanol | 0.42 E−01 | 0.16 E−01 | 2.7 | −4.328 | 3.085 | −0.156 | −5.428 | 3.657 | i |
| | Water | 0.33 E−04 | 0.13 E−05 | 25.0 | −4.328 | 8.683 | −0.000 | −31.237 | 16.519 | p |
| Cholesteryl acetate | Acetone | 0.59 E+00 | 0.60 E−01 | 9.9 | −2.050 | 1.640 | −0.113 | | | q |
| | Methanol | 0.33 E−02 | 0.23 E−02 | 1.4 | −2.050 | 6.376 | −0.028 | −11.321 | 1.306 | q |
| | Ethanol | 0.93 E−02 | 0.69 E−02 | 1.4 | −2.050 | 4.434 | −0.307 | −7.802 | 1.049 | q |
| | 2-propanol | 0.21 E−01 | 0.11 E−01 | 0.5 | −2.050 | 3.371 | −0.774 | −5.946 | 0.881 | q |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cholesteryl benzoate (30°C) | Benzene | 0.42 E+00 | 0.16 E+00 | 2.6 | −2.844 | 2.053 | −0.076 | | | r |
| | Toluene | 0.30 E+00 | 0.15 E+00 | 2.0 | −2.844 | 2.000 | −0.365 | | | r |
| | $CCl_4$ | 0.22 E+00 | 0.19 E+00 | 1.1 | −2.844 | 2.425 | −1.093 | | | r |
| | Ethyl acetate | 0.39 E+00 | 0.14 E−01 | 27.6 | −2.844 | 1.944 | −0.048 | | | r |
| | Methanol | 0.79 E−03 | 0.18 E−03 | 4.3 | −2.844 | 7.121 | −0.031 | −12.700 | 1.308 | r |
| | Ethanol | 0.26 E−02 | 0.27 E−03 | 9.9 | −2.844 | 4.983 | −0.341 | −8.789 | 1.054 | r |
| | Propanol | 0.40 E−02 | 0.26 E−02 | 1.6 | −2.844 | 3.895 | −0.608 | −6.860 | 0.899 | r |
| Pregnenolone acetate | Benzene | 0.26 E+00 | 0.20 E+00 | 1.3 | −2.848 | 1.597 | −0.082 | | | s |
| | $CCl_4$ | 0.12 E+00 | 0.45 E−01 | 2.7 | −2.848 | 1.683 | −0.926 | | | s |
| | $CHCl_3$ | 0.30 E+00 | 0.34 E+00 | 0.9 | −2.848 | 1.730 | −0.103 | | | s |
| | Acetone | 0.30 E+00 | 0.25 E−01 | 12.0 | −2.848 | 1.892 | −0.245 | | | s |
| | Ethyl acetate | 0.24 E+00 | 0.70 E−01 | 3.4 | −2.848 | 1.465 | −0.050 | | | s |
| | Benzyl benzoate | 0.85 E−01 | 0.77 E−01 | 1.1 | −2.848 | 0.639 | −0.259 | | | s |
| | Dioxane | 0.28 E+00 | 0.16 E+00 | 1.7 | −2.848 | 1.639 | −0.056 | | | s |
| | Ethanol | 0.47 E−01 | 0.23 E−01 | 2.0 | −2.848 | 3.152 | −0.159 | −5.537 | 2.337 | s |
| | Isopropanol | 0.43 E−01 | 0.19 E−01 | 2.3 | −2.848 | 2.372 | −0.414 | −4.245 | 1.986 | s |
| | Benzyl alcohol | 0.44 E−01 | 0.96 E−01 | 0.5 | −2.848 | 1.673 | −0.441 | −3.143 | 1.627 | s |
| Stanolone formate | Cyclohexane | 0.81 E−02 | 0.82 E−02 | 1.0 | −3.024 | 1.343 | −3.139 | | | e |
| | $CHCl_3$ | 0.22 E+00 | 0.35 E+00 | 0.6 | −3.024 | 1.602 | −0.111 | | | e |
| | Water | 0.57 E−05 | 0.14 E−05 | 4.1 | −3.024 | 7.734 | −0.000 | −27.679 | 10.895 | h |
| Stanolone acetate | Cyclohexane | 0.46 E−02 | 0.20 E−02 | 2.3 | −3.443 | 1.510 | −3.442 | | | e |
| | $CHCl_3$ | 0.18 E+00 | 0.37 E+00 | 0.5 | −3.443 | 1.844 | −0.133 | | | e |
| | Water | 0.62 E−06 | 0.94 E−06 | 0.7 | −3.443 | 8.392 | −0.000 | −30.144 | 10.895 | h |
| Stanolone propionate | Pentane | 0.40 E−02 | 0.88 E−02 | 0.5 | −2.409 | 1.504 | −4.627 | | | e |
| | Hexane | 0.57 E−02 | 0.15 E−01 | 0.4 | −2.409 | 1.267 | −4.028 | | | e |
| | Cyclohexane | 0.12 E−01 | 0.47 E−02 | 2.6 | −2.409 | 1.623 | −3.603 | | | e |
| | Decaline | 0.18 E+00 | 0.49 E−01 | 3.7 | −2.409 | 0.817 | −0.111 | | | e |
| | Cyclohexene | 0.18 E+00 | 0.20 E+00 | 0.9 | −2.409 | 1.515 | −0.840 | | | e |
| | $CHCl_3$ | 0.39 E+00 | 0.39 E+00 | 1.0 | −2.409 | 1.537 | −0.078 | | | e |
| | Water | 0.43 E−06 | 0.61 E−06 | 0.7 | −2.409 | 8.901 | −0.000 | −32.055 | 10.895 | h |
| Stanolone butyrate | Cyclohexane | 0.27 E−01 | 0.68 E−02 | 3.9 | −1.657 | 1.698 | −3.666 | | | e |
| | $CHCl_3$ | 0.58 E+00 | 0.44 E+00 | 1.3 | −1.657 | 1.157 | −0.038 | | | e |
| | Water | 0.30 E−06 | 0.44 E−06 | 0.7 | −1.657 | 9.302 | −0.000 | −33.569 | 10.895 | h |
| Stanolone valerate | Cyclohexane | 0.22 E−01 | 0.94 E−02 | 2.3 | −1.765 | 1.801 | −3.874 | | | e |
| | $CHCl_3$ | 0.57 E+00 | 0.45 E+00 | 1.3 | −1.765 | 1.248 | −0.042 | | | e |
| | Water | 0.86 E−07 | 0.30 E−06 | 0.3 | −1.765 | 9.709 | −0.000 | −35.105 | 10.895 | h |
| Nandrolone propionate | Cyclohexane | 0.19 E+00 | 0.20 E−01 | 9.1 | −0.683 | 1.177 | −2.177 | | | a |
| Nandrolone butyrate | Ethyl oleate | 0.23 E+00 | 0.30 E+00 | 0.8 | −1.093 | −0.073 | −0.311 | | | t |
| | Water | 0.54 E−05 | 0.40 E−06 | 1.3 | −1.093 | 8.460 | −0.000 | −30.398 | 10.895 | t |
| Nandrolone nonanoate | Ethyl oleate | 0.70 E+00 | 0.38 E+00 | 1.8 | −0.342 | 0.040 | −0.060 | | | t |
| | Water | 0.42 E−07 | 0.77 E−06 | 0.06 | −0.342 | 10.478 | −0.000 | −38.022 | 10.895 | t |

Table 5 (Continued)

| Solute | Solvent | $\Phi_B^{calc}$ | $\Phi_B^{exp}$ | $\Phi_B^{calc}/\Phi_B^{exp}$ | *A* | *B* | *D* | *F* | *O* | Ref[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Nandrolone decanoate | Ethyl oleate | 0.80 E+00 | 0.49 E+00 | 1.6 | −0.228 | 0.035 | −0.026 | | | t |
| | Ethanol | 0.78 E+00 | 0.50 E+00 | 1.6 | −0.228 | 1.116 | −0.024 | −1.592 | 0.477 | i |
| | Water | 0.15 E−07 | 0.55 E−06 | 0.03 | −0.228 | 10.879 | −0.000 | −39.547 | 10.895 | t |
| Dydrogestone | $CHCl_3$ | 0.17 E+00 | 0.31 E+00 | 0.5 | −3.280 | 1.605 | −0.120 | | | i |
| | Acetone | 0.17 E+00 | 0.51 E−01 | 3.3 | −3.280 | 1.777 | −0.289 | | | i |
| | Diethyl ether | 0.11 E+00 | 0.45 E−02 | 24.6 | −3.280 | 1.213 | −0.134 | | | i |
| | Methanol | 0.61 E−01 | 0.22 E−01 | 2.8 | −3.280 | 2.549 | −0.129 | −4.515 | 2.586 | i |
| Deoxycorticosterone acetate | Acetone | 0.16 E+00 | 0.14 E−01 | 11.1 | −3.669 | 2.151 | −0.348 | | | i |
| | Ethanol | 0.83 E−01 | 0.36 E−01 | 2.3 | −3.669 | 2.956 | −0.147 | −5.170 | 3.536 | i |
| | Water | 0.69 E−04 | 0.66 E−05 | 10.5 | −3.669 | 8.639 | −0.000 | −31−070 | 16.519 | n |
| Deoxycorticosterone pivalate | $CHCl_3$ | 0.16 E+00 | 0.24 E+00 | 0.6 | −4.055 | 2.361 | −0.171 | | | j |
| | Diethyl ether | 0.93 E−01 | 0.15 E−02 | 68.8 | −4.055 | 1.872 | −0.194 | | | i |
| | Methanol | 0.27 E−01 | 0.59 E−02 | 4.6 | −4.055 | 5.331 | −0.017 | −9.393 | 4.522 | j |
| | Ethanol | 0.36 E−01 | 0.21 E−02 | 16.9 | −4.055 | 3.681 | −0.186 | −6.456 | 3.679 | j |
| Dromostanolone propionate | $CHCl_3$ | 0.43 E+00 | 0.44 E−01 | 9.9 | −2.301 | 1.532 | −0.071 | | | j |
| | Diethyl ether | 0.33 E+00 | 0.48 E−01 | 7.0 | −2.301 | 1.299 | −0.096 | | | j |
| | Ethanol | 0.74 E−01 | 0.32 E−01 | 2.3 | −2.301 | 3.263 | −0.163 | −5.700 | 2.292 | j |
| 17α-OH-Progesterone caproate | $CHCl_3$ | 0.50 E+00 | 0.70 E+00 | 0.7 | −2.164 | 1.532 | −0.051 | | | i |
| | Diethyl ether | 0.40 E+00 | 0.85 E−01 | 4.7 | −2.164 | 1.336 | −0.061 | | | i |
| | Ethanol | 0.25 E+00 | 0.85 E−01 | 3.0 | −2.164 | 3.003 | −0.136 | −5.079 | 3.005 | i |

[a] See footnote to Table 4 for details of references.

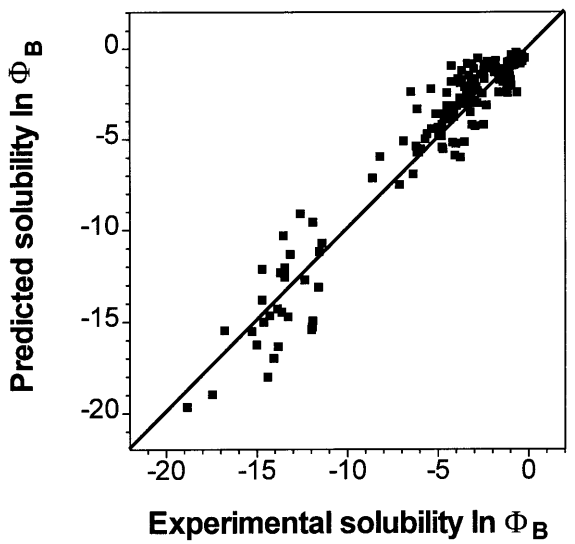


Fig. 1. Predicted versus experimental solubility (volume fraction) of non-hydroxysteroids.

model from which the order of magnitude of the solubility spanning over eight orders of magnitude can in most cases correctly be predicted. Besides its remarkable predictive character, more information can be learned from the present thermodynamic model concerning the origin of the solubility and the nature of the solution process. In particular, the analysis of the relative importance of the different terms contributing to the solubility and of their evolution with respect to solvent or solute properties lead to express some practical rules which might be very useful in pharmaceutical technology for the choice of a suitable dosage form or delivery system for a drug. Furthermore, the understanding of the factors that govern solubility would help the pharmaceutivcal chemist to incorporate desirable formulation, biopharmaceutical and distributive properties into a drug.

Irrespective to the nature of the solvent, the fluidization term ($A$), i.e. the removal of the solute from its crystal lattice, always represents a barrier, the height of which is inversely related to the solubility. This contribution is particularly important, and may be the dominant factor when the solubility has to be estimated in non-associated solvents. Once the melting has occured, the solute

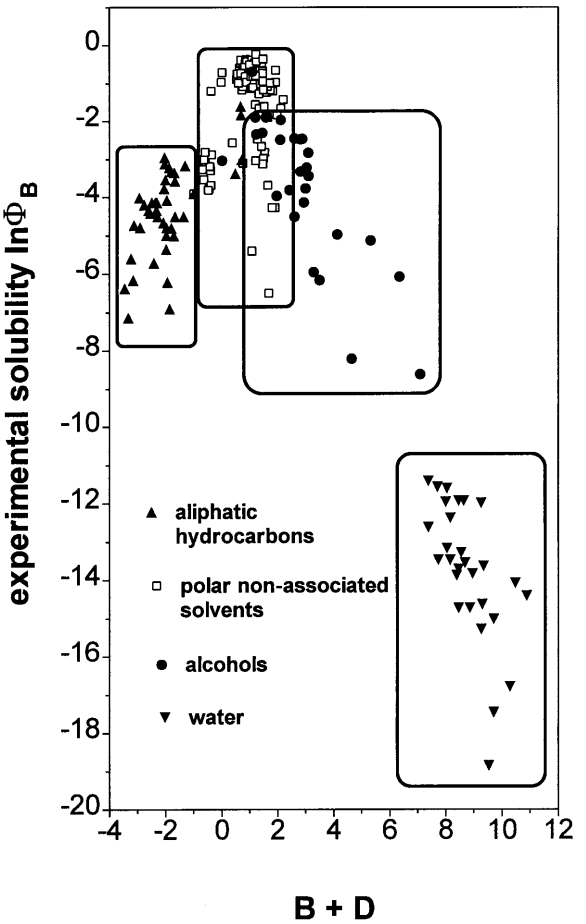


Fig. 2. Logarithm of the volume fraction solubility of non-hydroxysteroids versus the $B+D$ balance of the exchange entropy correction and the change of the nonspecific cohesion forces upon mixing.

forms an homogeneous solution with the solvent following the solvation process the enthalpic and entropic contributions of which determine the overall non-crystalline solubility. According to the relative importance of these contributions, the solvents can be grouped into four categories (Fig. 2).

1. In aliphatic hydrocarbons, the sum of the $B$ and $D$ contributions is generally negative, and the absolute value of the $B/D$ ratio is lower than one. In these solvents, the solubility of the steroids is thus mainly ruled by the change in the non-specific solute–solvent interactions

($D$ term) due to the large difference of the modified non-specific solubility parameters between the solvents ($13 < \delta'_S < 16$) and the steroids ($\delta'_B = 20$). Playing against solubilization, this endothermic effect reduces the solubility and allows to explain why non-hydroxysteroids are less soluble in aliphatic hydrocarbons than in the aromatics or in the polar non-interacting solvents of similar volume.

2. In aromatic hydrocarbons and in polar non-associated solvents (halogenated hydrocarbons, ethers, esters, ketones), the addition of $B$ and $D$ contributions is positive and the absolute value of the $B/D$ ratio is greater than one. The solubility of the steroids in these solvents thus essentially depends on the correction factor for the exchange entropy ($B$ term). This term generally favours dissolution, and its influence on the solubility is as important as the molar volume of the solute is greater than that of the solvent. In this class of solvents, the steroid solubilities are 10–100 times greater than in the first class. However, a closer look at the individual values of $B$ and $D$ contributions shows that the larger steroid solubilities in the present class does not result from an increase of the $B$ term, but rather originates from the $D$ contribution decrease related to the closeness of the modified non-specific solubility parameter of the solute and solvent molecules.
3. In the third category of solvents, i.e. the alcohols, the sum of the $B$ and $D$ terms favours the solubility. Although in these solvents, the exothermic formation of specific steroid–alcohol H-bonds ($O$ term) contributes along with the $B + D$ positive effect to increase the solubility, the solubility values remain generally lower than those observed in ether, ester or ketone solvents. The reason is that, in alcohols, the main contribution to the solubility is the hydrophobic effect ($F$ term) which hardly disfavours the non-crystalline part of the solubility in proportions depending on the solute/solvent molar volume ratio, $V_B/V_S$. As a result, the solubility values of the non-hydroxysteroids in alcohols are relatively comparable to those observed in the aliphatic hydrocarbons.
4. The fourth category of solvents is represented by water. In water, the solubilities of the steroids are the lowest although the positive $B$ contributions are greater than in the other solvent classes, and the negative $D$ contributions are close to zero. In fact, the steroid aqueous solubilities are predominantly dependent on the hydrophobic effect ($F$ term). Their large hydrophobicities are due to the smallness of the water molar volume with respect to that of the steroid molecules. The huge loss of the mobile order entropy of the water molecules can never be recovered by the exothermic energy gained by the solute–solvent specific interactions ($O$ term). A direct consequence of the hydrophobic effect is that any increase of the molar volume of the steroid which normally promotes its solubility in non-associated solvents will lessen it in alcohols and water.

## 4. Conclusion

Based on the knowledge of a small number of properties of solutes and solvents, the mobile order-derived solubility equation enables correct quantitative predictions of the solubilities of steroids displaying several proton-acceptor sites in common organic solvents including water. On the basis of the relative non-crystalline solubility contributions, the solvents can be classified into four categories of decreasing solubility. The in-depth analysis then provides useful conclusions regarding the solubility of the steroids.

1. The solubility increases whenever the fluidization of the steroid is lessened. In practice, one can seek to replace an original compound with one of similar properties, but characterized by lower melting temperature and/or enthalpy of fusion.
2. Among non-associated solvents of similar molar volumes, the best dissolving solvent for a given steroid will be the one showing the modified non-specific solubility parameter as close as that of the steroid. Such behaviour expresses the old empirical principle ‘like dissolves like’.

3. Similarly, if two or more non-associated solvents are characterized by similar differences of their modified non-specific solubility paremeters with that of a given steroid, then the solvent with the small molar volume will dissolve the large amount of that steroid.
4. In self-associated solvents, the higher solubilities will be observed for the steroid–solvent systems presenting the smaller values of the molar volume ratio, $V_B/V_S$.
5. Given two or more non-hydroxysteroids of similar volumes, the non-crystalline part of their solubility in amphiphilic solvents will essentially differ by the number of their proton-acceptor sites: the greater the number of these active sites, the larger the solubility.

Concluding, we dispose of a thermodynamical model allowing a priori predictions of solubility of steroids with reasonable accuracy not only in water, but also in apolar or polar associated or non-associated solvents. Such model could therefore be used to test rapidly and before any experimentation the dissolving power of solvents for a given solute at a fixed temperature, hence could serve to orient the choice of a solvent for liquid oral, topical or parenteral pharmaceutical forms.

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