Pharmaceutical Research, Vol. 8, No. 7, 1991

Research Article

A New Predictive Equation for the Solubility of Drugs Based on the Thermodynamics of Mobile Disorder

Paul Ruelle,[1] Catherine Rey-Mermet,[1] Michel Buchmann,[1] Hô Nam-Tran,[1] Ulrich W. Kesselring,[1,3] and P. L. Huyskens[2]

Received October 8, 1990; accepted February 19, 1991

The thermodynamics of mobile disorder rejects the static model of the quasi-lattice for liquids. Because of the perpetual change of neighbors, during the observation time of thermodynamics of the order of seconds, each molecule of a given kind in a solution has experienced the same environment and had at its disposal the same mobile volume. This domain is not localizable and not orientable. Each molecular group perpetually "visits" successively all parts of this domain. The highest entropy is obtained when the groups visit all the parts of the domain without preference. H-bonds are preferential contacts with given sites of the neighbors that cause deviations with respect to such "random" visiting, thereby decreasing the entropy. The quantitative development of these ideas leads to equations describing the effect of solvent–solvent, solute–solvent, and solute–solute hydrogen bonds on the chemical potential of the solute. A universal equation predicting the solubility of drugs in a given solvent is derived. The effect of H-bonds is governed not by "solubility parameters" but by stability constants from which the order of magnitude can be estimated. From the sole knowledge of the solubility of methylparaben in pentane, the method predicts correctly the order of magnitude of its solubility in 26 other solvents, including alcohols and water.

KEY WORDS: stability constants; hydrophobic effect; mobile order; solution thermodynamics; solubility; methylparaben.

INTRODUCTION

There is a need for a universal equation predicting the solubility of crystalline drugs in a given solvent. This solubility corresponds to the concentration of the solute in the solution for which the (differential) heat, needed for the dissolution, divided by the absolute temperature, equals the (differential) change of entropy.

For a crystalline substance, the heat of dissolution H_{dissol} always contains the heat of fusion H_{melt}, and it often also contains the heat of mixing H_{mix} of the fluidized solute with the solvent.

$$H_{dissolution} = H_{melt} + H_{mix} \quad (1)$$

H_{mix} may be positive or negative. The heat of fusion is independent of the solvent. The heat of mixing depends on the differences in the various energies of cohesion between molecules of solute and solvent. The differential heat of mixing is the derivative of the integral heat of mixing ΔH_{mix} with respect to the number of moles n_B of the solute.

Most predictive methods in the literature neglect entropy effects and focus only on the heat of mixing, thus considering the solutions as "regular." In general, they estimate the integral heat of mixing on the basis of the Scatchard–Hildebrand (1) equation, which can be written

$$\Delta H_{mix} = V \Phi_B \Phi_S (\delta_B - \delta_S)^2 \quad (2)$$

V is the total volume of the solution and Φ_B and Φ_S are the volume fractions of solute and solvent. In the original version the "solubility parameters" δ_B and δ_S correspond to the square root of the molar energy of vaporization of the substances in the pure liquid state divided by their molar volume.

The Scatchard–Hildebrand equation is based on two assumptions: (i) the hypothesis of the geometric mean (2)—the cohesive energy per unit volume between S and B is the geometric mean of the values for the pure substances; and (ii) the interactions between the molecules in the solution occur "at random" and there are no preferential contacts. These two assumptions can be considered as crude approximations for the cohesion forces of the dispersion type and also of the dipole–dipole type (3). *However, they contradict the very essence of hydrogen bonds.* H-bonds are preferential interactions (4) between a proton-donor site (the H-atom of the OH group, for instance) and a proton-acceptor site (the lone pair of electrons of a N-atom, for instance). An alcohol possesses both proton-donor and proton-acceptor sites but acetone has only acceptor sites. The energy of an

[1] Institute of Pharmaceutical Analysis, School of Pharmacy, University of Lausanne, B.E.P., CH–1015 Lausanne, Switzerland.
[2] Department of Chemistry, University of Leuven, Celestijnenlaan 200 F, B-3030 Heverlee, Belgium.
[3] To whom correspondence should be address.

0724-8741/91/0700-0840$06.50/0

H-bond between an alcohol and an acetone can by no means be equal to the geometric mean of that of the H-bond between two alcohol molecules and that between two acetone molecules because the last one simply does not exist!

The Scatchard–Hildebrand equation and the "hydrogen bond solubility parameter" (5) are inadequate for H-bonding since the heat of mixing is often negative (exothermic) when solute–solvent hydrogen bonds are formed. This is the case for a mixture of sulfuric acid and water. However, the Scatchard–Hildebrand expression is absolutely unable to lead to a negative value for ΔH_{mix}.

On the other hand, the preferential contacts originating from H-bonding modify the occupation of space by the different groups. Beside their energetic effect, H-bonds thus also have an influence on the entropy. As a consequence, solutions where they intervene can never be considered as "regular."

A model in the literature that takes entropic effects into account is the UNIQUAC (Universal Quasi Chemical) model of Abrams and Prausnitz (6). Excess free enthalpies of mixing are obtained via activity coefficients. The total activity coefficient is divided into a "combinatorial" and a "residual" part. The combinatorial contribution is only entropy-governed. It is obtained by the number of ways of forming a solution with molecules of which the size and the shape are given. The residual contribution is calculated from interaction parameters, which are either determined experimentally or obtained by adding interaction parameters of functional groups (UNIFAC).

THE MOBILE DISORDER IN LIQUIDS

The UNIQUAC theory, as all the others that can be found in the literature, considers a solution as a mixed crystal, with a fixed number z of neighbors for each molecule, but this does not quite correspond to the reality of liquids. Let us compare a pentane molecule in the liquid phase and in the crystal. In the crystal, all CH_3 groups form bilayers separated from each other by the zigzag chains of the CH_2 groups. The nearest neighbors of the CH_3 groups are exclusively CH_3 groups of neighboring molecules whereas the nearest neighbors of the CH_2 groups are exclusively similar groups of neighboring molecules.

In liquid pentane, one finds in an interval of time of 0.1 psec not only $CH_2 - -CH_2$ and $CH_3 - -CH_3$ contacts but also $CH_3 - -CH_2$ contacts. Moreover, the contacts always change, and for a "thermodynamic" observation time of 1 sec, each CH_3 group has experienced all possible contacts and situations. This holds for each group and for each kind of molecule in the solution. The number of nearest neighbors z always fluctuates around a value that is only an average. In a liquid solution, there does not exist anything that could resemble a "quasi-lattice," as considered, for instance, by the thermodynamics of Flory (7). The order "at short distance" that sometimes appears in the X-ray diffraction studies of liquid metals is only the consequence of the fact that all the atoms have the same radius, and does not imply any regularity in orientation.

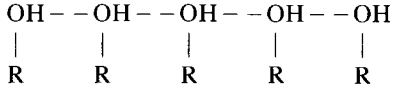
A correct thermodynamic treatment should take this perpetually changing character of the liquid state into account. It has to be based on stationary states of the molecules for the observation times of thermodynamics that are of the order of seconds and more. The molecular disorder in a liquid solution is thus not that of a mixed rigid crystal: it is a "mobile" disorder. This hypothesis is the basis of the thermodynamics of liquids (8) recently developed by Huyskens and Siegel.

A direct consequence of this mobile character is that in a pure liquid, in the thermodynamic observation time, all the possibilities are equally distributed among all the molecules. Each molecule thus possesses the same number of possibilities $w_{\text{one molecule}}$ in the sense of Boltzmann. The entropy of a pure liquid can thus be written

$$S = k \ln (w_{\text{one molecule}})^N \tag{3}$$

where N is the number of molecules and k is Boltzmann's constant.

As a consequence, the H-bonded aggregates



that are temporarily formed in liquid ethanol and do not lead to real stationary wave functions, do not have a distinguishable "thermodynamic" identity. This is the reason why the classic "multicomponent" theory of H-bonding association of Kempter Mecke (9) and Prigogine (10) does not lead to correct predictions for the solubilities in alcohols and water.

The generalization of Eq. (3) for a liquid mixture of N_B molecules of the solute B and N_S molecules of the solvent S leads to

$$S = k \ln (w_{\text{one molecule B}})^{N_B} \cdot (w_{\text{one molecule S}})^{N_S} \tag{4}$$

As shown by Huyskens and Siegel (11), this equation deviates in principle from that of Boltzmann but agrees strictly with the definition of the entropy by Clausius.

OCCUPATION OF THE SPACE BY THE VARIOUS GROUPS OF A MOLECULE IN A LIQUID

The perpetual redistribution of the cohesion forces in a liquid makes that, for a "thermodynamic" interval of time (12), all the molecules of a given kind dispose of the same volume, equal to the total volume V of the liquid, divided by the number N_B of molecules of the same kind:

$$\text{Dom}B = V/N_B \tag{5}$$

The center of this domain perpetually moves. Moreover, the domain is not orientable with respect to external axes. This means that even for chain-like molecules, we have to consider this mobile part of the space as spherical!

All the groups of the molecule perpetually "visit" all the parts of the mobile domain. Let us take a given group of a neighboring molecule at the border of the domain as a "witness." This witness will see successively all the groups of the considered molecule, defiling in front of him.

The highest mobile disorder is obtained when the groups define pro rata of their volume fraction in the domain. This means that the groups visit all the parts of their domain without any preference. Preferential contacts lead to deviations with respect to this "random" visiting. This is espe-

cially the case when given groups of the molecule form H-bonds with active sites of the neighboring molecules. Such situation is characterized by a lower degree of disorder in the liquid. H-bonds in liquids are thus at the origin of a kind of "mobile" order (13).

ENTROPY OF PLACING IN LIQUID MIXTURES

In the dissolution of a crystalline substance the entropy of placing of the molecules in the solution plays an important role. In the crystal each molecule disposes only on one place and there is no entropy of placing. In contrast, in solution, the presence of the solvent molecules leads to the existence of an entropy of placing. It is important to recognize the real nature of this kind of entropy. In a mixed crystal, for instance, this entropy of placing results from the possibilities of exchange between the molecules of different kind. One obtains

$$S_{\text{exchange}} = -R(n_A \ln x_A + n_B \ln x_B) \quad (6)$$

where x_A and x_B are the mole fractions.

In a mixture of two gases the entropy of placing has the same expression but does not result from the exchange possibilities. It is the consequence of the enlargement of the volume each molecule has at its disposal compared to that before the opening of the cork between the two initial volumes containing the pure gases at the same pressure. It should be better called "entropy of expansion" and written in terms of volume-fractions:

$$S_{\text{expansion}} = -R\,(n_A \ln \Phi_A + n_B \ln \Phi_B) \quad (7)$$

In a liquid mixture the entropy of placing results among others from the exchange possibilities between the given molecule and the foreign molecules present in its domain. However, the entropy of placing is also an entropy of expansion because, for a liquid, and contrary to a gas, the presence of the molecules of a different kind is the only possibility to make the molecular domains larger. How to partake the two effects?

The entropy of placing can be written in a general expression:

$$\begin{aligned} S_{\text{placing}} &= S_{\text{exchange}} + S_{\text{expansion}} \\ &= -R\,(n_A \ln x_A^{(1-\alpha)} \Phi_A^{\alpha} \\ &\quad + n_B \ln x_B^{(1-\alpha)} \Phi_B^{\alpha}) \end{aligned} \quad (8)$$

Huyskens and Haulait-Pirson (14) have demonstrated from theoretical considerations based on the Einstein–Schmolukowski relation that the value of α equals ½. This can be experimentally demonstrated by comparing the predicted solubilities of solid alkanes in liquid alkanes.

This solubility in volume fraction Φ_B can be calculated from the equation

$$\begin{aligned} \ln \Phi_B &= -A + \alpha \Phi_B (V_B/V_S - 1) \\ &\quad + (1 - \alpha) \ln(\Phi_B + \Phi_S V_B/V_S) \end{aligned} \quad (9)$$

A is the molar free energy of melting divided by RT. This value is known from calorimetric measurements on the pure crystals. V_B and V_S are the molar volumes. The equation neglects here the heat of mixing (which is indeed very small owing to the chemical similitude between solute and solvent).

The data in Table I (15) allow comparison of the predictions with $\alpha = 1$ [Flory–Huggins expression (16)], $\alpha = 0$ (classical expression), and $\alpha = 0.5$ (Huyskens and Haulait-Pirson). The last value is the most adequate, although the first one is still of general use in the literature.

The equation of the entropy of placing of Huyskens and Haulait-Pirson does not introduce surface parameters that have to be more or less estimated, as is the case for the UNIQUAC theory. The agreement of the Huyskens–Haulait expression with the experimental values demonstrates that for the entropy of placing in the liquid phase, only the volume V_B plays a role, and not the shape of the molecules of the solute. In fact, all possible shape effects are averaged by the mobile character of the disorder in the liquid: the "thermodynamic" molecular domain in a liquid is a sphere!

THE REAL NATURE OF THE HYDROPHOBIC EFFECT

Liquid hydrocarbons are very scarcely soluble in water. Their solubilities decrease by a factor of 4 upon adding a supplementary CH_2 group. This low solubility is caused by the so-called "hydrophobic effect." In general, the authors attribute the hydrophobic effect to the necessity of breaking the H-bonded chains

OH– –OH– –OH– –OH– –OH– –OH

in order to create the cavity necessary for placing the hydrocarbon molecule. Other authors think that entering water necessitates the breaking of some special cohesion forces that should bind the molecules together in the pure hydrocarbon: the so-called "hydrophobic interactions" (17). However, both explanations are inadequate because the energy needed to bring a CH_2 group from its own phase into water is very low: only some 2 kJmol^{-1} (18). The hydrophobic effect is thus chiefly entropic.

The thermodynamics of the mobile disorder not only provides an explanation for the hydrophobic effect but also allows us to calculate this effect with precision. For the sake of simplicity, we consider first the alcohols because they form single H-bond chains. In ethanol, for instance, each hydroxyl proton is attached during 99% of the time to a neighboring oxygen atom that it follows in its walk through the liquid. Then, after 10^{-10} sec the H-bond is temporarily broken, and after a short time the hydroxyl proton follows a new oxygen atom. Hence the OH group renounces during 99% of the time its freedom of visiting its domain, Dom$A$, and resides in a small part v_o at the domain's border, where it participates in the H-bond chain with the neighbors. Of course, neither Dom$A$ nor v_o is fixed with respect to an external observer. However, the reduction of freedom corresponds clearly to the ratio v_o/Dom$A$. If, to a first approximation, we neglect the 1% of the time the hydroxyl group is free, the entropy of the "mobile" order in pure liquid ethanol is given by the expression

$$S_{\text{mobile}} = k \ln (v_o/\text{dom}A)^{N_A} \quad (10)$$

where N_A is the number of molecules.

As the ratio (v_o/Dom$A$) is smaller than one, the expression is negative. Let us now add pentane to ethanol. This will not affect the value v_o but will increase Dom$A$. As a consequence, the entropy of the "mobile order" of each ethanol

Table I. Experimental Solubilities Φ_{exp} (in Volume Fractions) of Solid *n*-Alkanes B in Fluid *n*-Alkanes and Cyclohexane at 25°C; Fluidization Constants *A*; Predicted Solubility Values Φ_B According to Eq. (9) with $\alpha = 0.0$, 1.0, and 0.5; Molar Volumes *V* ($cm^3\ mol^{-1}$) in the Liquid Phase (15)

Solute B	Solvent S	*A*	V_B	V_S	Φ_B $\alpha = 0$	Φ_B $\alpha = 1$	Φ_B $\alpha = 0.5$	Φ_{exp}
$C_{20}H_{42}$	$C_{15}H_{32}$	1.06	359.7	277.7	0.412	0.402	0.410	0.405
$C_{24}H_{50}$	C_8H_{18}	2.66	425.1	163.5	0.164	0.237	0.200	0.196
$C_{24}H_{50}$	$C_{10}H_{22}$	2.66	425.1	195.9	0.140	0.182	0.161	0.156
$C_{24}H_{50}$	$C_{12}H_{26}$	2.66	425.1	228.6	0.123	0.146	0.134	0.139
$C_{28}H_{58}$	C_5H_{12}	4.25	490.5	116.1	0.058	0.193	0.116	0.084
$C_{28}H_{58}$	C_6H_{14}	4.25	490.5	131.6	0.051	0.146	0.092	0.075
$C_{28}H_{58}$	C_7H_{16}	4.25	490.5	147.5	0.046	0.112	0.074	0.066
$C_{28}H_{58}$	$C_{10}H_{22}$	4.25	490.5	195.9	0.035	0.059	0.046	0.044
$C_{28}H_{58}$	$C_{12}H_{26}$	4.25	490.5	228.6	0.030	0.043	0.036	0.036
$C_{28}H_{58}$	$C_{16}H_{34}$	4.25	490.5	294.0	0.024	0.027	0.025	0.027
$C_{28}H_{58}$	C_6H_{12}	4.25	490.5	108.7	0.061	0.220	0.130	0.140
$C_{30}H_{62}$	C_6H_{14}	4.80	523.2	131.6	0.032	0.115	0.064	0.040
$C_{30}H_{62}$	$C_{10}H_{22}$	4.80	523.2	195.9	0.022	0.041	0.030	0.021
$C_{32}H_{66}$	C_5H_{12}	6.01	555.9	116.1	0.012	0.080	0.033	0.022
$C_{32}H_{66}$	C_6H_{14}	6.01	555.9	131.6	0.010	0.052	0.024	0.021
$C_{32}H_{66}$	C_7H_{16}	6.01	555.9	147.5	0.009	0.035	0.018	0.020
$C_{32}H_{66}$	$C_{10}H_{22}$	6.01	555.9	195.9	0.0069	0.0150	0.0102	0.0102
$C_{32}H_{66}$	$C_{12}H_{26}$	6.01	555.9	228.6	0.0059	0.0101	0.0078	0.0073
$C_{32}H_{66}$	C_6H_{12}	6.01	555.9	108.7	0.012	0.100	0.039	0.045
$C_{36}H_{74}$	C_5H_{12}	7.46	621.3	116.1	0.0031	0.0379	0.0110	0.0048
$C_{36}H_{74}$	C_6H_{14}	7.46	621.3	131.6	0.0027	0.0220	0.0079	0.0045
$C_{36}H_{74}$	C_7H_{16}	7.46	621.3	147.5	0.0024	0.0137	0.0058	0.0043
$C_{36}H_{74}$	C_8H_{18}	7.46	621.3	163.5	0.0022	0.0092	0.0045	0.0039
$C_{36}H_{74}$	$C_{10}H_{22}$	7.46	621.3	195.9	0.0018	0.0050	0.0030	0.0027
$C_{36}H_{74}$	$C_{12}H_{26}$	7.46	621.3	228.6	0.0016	0.0032	0.0028	0.0021
$C_{36}H_{74}$	$C_{15}H_{32}$	7.46	621.3	277.7	0.0015	0.0020	0.0016	0.0013

molecule will become still more negative. *This result is the essence of the hydrophobic effect.*

A straightforward calculation given in other papers (19) shows that the mobile order caused by the H-bonds between the alcohol molecules increases the chemical potential of the inactive solute, to a first approximation, by an amount

$$\mu_B{}^h = RT\,\Phi_A\,V_B/V_A \tag{11}$$

A similar expression holds for water, where, on account of the fact that the water molecules are involved in double chains, a factor of 2 appears:

$$\mu_B{}^h = 2\,RT\,\Phi_W\,V_B/V_W \tag{12}$$

An experimental test for the validity of these equations can be found in comparing the solubilities of alkanes that they predict in water and in the alcohols with the experimental values.

Neglecting to a first approximation the effect of the dispersion and dipole–dipole cohesion forces, the solubility of a solid alkane in an alcohol is predicted by the equation

$$\ln \Phi_B = -A - 0.5\,(1 - V_B/V_A)\Phi_A + 0.5\,\ln(\Phi_B + \Phi_A V_B/V_A) - \Phi_A V_B/V_A \tag{13}$$

The last term corresponds to the effect of the H-bonds between the alcohol molecules on the solubility of the solute. We call this term the "hydrophobic" term.

The only data needed for these predictions are the molar volumes of the alcohol and of the alkane and the "fluidization constant" obtained from the melting data. The results are given in Table II (19). The table also contains the values estimated from the classical "multicomponent" theory of the ideal associated solutions calculated with the association constants proposed by Wiehe and Bagley (20). The agreement of the values predicted by the mobile order theory with the experimental values is incomparably better. The values are still systematically overestimated, as a consequence of neglecting the effect of the other cohesion forces, but the order of magnitude is always correct.

One can also derive an equation predicting the solubility of liquid alkanes in water (this can be done because the solubility of water in alkanes is also very low, which allows to take for the alkane in its own phase the chemical potential of the pure liquid alkane). In this case, there is no fluidization constant and one finds (21)

$$\ln \Phi_B = 0.5\,(V_B/18 - 1) + 0.5\,\ln(V_B/18) - 2\,V_B/18 \tag{14}$$

This equation is remarkable because it requires knowledge only of the molar volume of the alkane. It does not contain any adjustable parameter, not even a constant of nature. Nevertheless, as shown in Table III (22), it always predicts the correct order of magnitude of the solubilities, although they change by a factor 500. We cannot compare here the results with the predictions of the "multicomponent" theories of ideal association because these predict

Table II. Molar Volumes V_B and V_A ($cm^3\ mol^{-1}$), Fluidization Constant A, Experimental Solubilities $\Phi_{B\ exp}$ of Solid n-Alkanes in Alcohols at 25°C, and Solubilities (in Volume Fraction) Predicted by the Theory of Wiehe and Bagley, Φ_{BWB}, and by the Theory of the Mobile Order, Φ_{BHH} (19)

Solute	Solvent	V_B	V_A	A	Φ_{BWB}	$\Phi_{B\ exp}$	Φ_{BHH}
$C_{36}H_{74}$	1-Decanol	621.3	191.6	7.46	0.00024	0.00012	0.00012
$C_{23}H_{48}$	1-Pentanol	408.8	108.6	1.97	0.0596	0.0236	0.0263
$C_{23}H_{48}$	2-Butanol	408.8	92.4	1.97	0.0598	0.0194	0.0204
$C_{23}H_{48}$	1-Butanol	408.8	92.0	1.97	0.0598	0.0178	0.0204
$C_{32}H_{66}$	1-Hexanol	555.9	125.2	6.01	0.00102	0.00033	0.00034
$C_{28}H_{58}$	1-Pentanol	490.5	108.6	4.25	0.00590	0.00165	0.00193
$C_{23}H_{48}$	2-Propanol	408.8	76.9	1.97	0.0600	0.0094	0.0142
$C_{28}H_{58}$	1-Butanol	490.5	92.0	4.25	0.0592	0.0010	0.00139
$C_{23}H_{48}$	1-Propanol	408.8	75.1	1.97	0.0600	0.0103	0.0136
$C_{20}H_{42}$	Ethanol	359.7	58.7	1.06	0.1636	0.0172	0.0264
$C_{28}H_{58}$	1-Propanol	490.5	75.1	4.25	0.00594	0.00059	0.00086
$C_{23}H_{48}$	Ethanol	408.8	58.7	1.97	0.0603	0.0038	0.0070

complete miscibility of liquid alkanes with water! The agreement between the predicted values in Table III and the experimental values constitutes the most striking evidence for the correctness of the principles of the thermodynamics of the mobile disorder in liquids.

Table III. Experimental Solubilities $\Phi_{B\ exp}$ (in Volume Fractions) of Liquid Alkanes in Water at 25°C; Predicted Solubility Values $\Phi_{B\ calc}$ According to Eq. (14); Molar Volume V_B ($cm^3\ mol^{-1}$) of the Liquid Alkane (19)

Alkane	V_B	$\Phi_{B\ exp}$	$\Phi_{B\ calc}$
n-Pentane	116.1	$6.17\ 10^{-5}$	$9.88\ 10^{-5}$
n-Hexane	131.6	$1.59\ 10^{-5}$	$2.83\ 10^{-5}$
n-Heptane	147.5	$4.17\ 10^{-6}$	$7.97\ 10^{-6}$
n-Octane	163.5	$9.16\ 10^{-7}$	$22.10\ 10^{-7}$
n-Nonane	179.7	$2.38\ 10^{-7}$	$6.01\ 10^{-7}$
n-Decane	195.9	$1.71\ 10^{-7}$	$1.63\ 10^{-7}$
Cyclopentane	94.7	$2.13\ 10^{-4}$	$5.20\ 10^{-4}$
Methylcyclopentane	113.1	$5.61\ 10^{-5}$	$12.30\ 10^{-5}$
Propylcyclopentane	145.3	$2.63\ 10^{-6}$	$9.50\ 10^{-6}$
Cyclohexane	108.8	$7.83\ 10^{-5}$	$17.20\ 10^{-5}$
Methylcyclohexane	128.3	$1.96\ 10^{-5}$	$3.68\ 10^{-5}$
1-*cis*-2-Dimethylcyclohexane	141.6	$7.34\ 10^{-6}$	$12.80\ 10^{-6}$
1-*trans*-2-Dimethylcyclohexane	148.0	$5.08\ 10^{-6}$	$7.66\ 10^{-6}$
Cycloheptane	121.7	$3.70\ 10^{-5}$	$6.21\ 10^{-5}$
Cyclooctane	135.8	$9.55\ 10^{-6}$	$20.30\ 10^{-6}$
2-Methylbutane	117.4	$7.86\ 10^{-5}$	$8.73\ 10^{-5}$
2-Methylpentane	132.9	$2.17\ 10^{-5}$	$2.55\ 10^{-5}$
3-Methylpentane	130.6	$2.20\ 10^{-5}$	$3.07\ 10^{-5}$
2-Methylhexane	148.6	$3.75\ 10^{-6}$	$7.30\ 10^{-6}$
3-Methylhexane	146.7	$5.54\ 10^{-6}$	$8.50\ 10^{-6}$
3-Methylheptane	162.8	$1.12\ 10^{-6}$	$2.57\ 10^{-6}$
4-Methyloctane	179.1	$1.60\ 10^{-7}$	$6.31\ 10^{-7}$
2,2-Dimethylbutane	133.8	$3.48\ 10^{-5}$	$2.38\ 10^{-5}$
2,3-Dimethylbutane	131.2	$3.16\ 10^{-5}$	$2.92\ 10^{-5}$
2,2-Dimethylpentane	149.7	$7.61\ 10^{-6}$	$6.68\ 10^{-6}$
2,3-Dimethylpentane	145.0	$7.57\ 10^{-6}$	$9.73\ 10^{-6}$
2,4-Dimethylpentane	149.9	$6.95\ 10^{-6}$	$6.58\ 10^{-6}$
3,3-Dimethylpentane	145.4	$8.53\ 10^{-6}$	$9.43\ 10^{-6}$
2,2,4-Trimethylpentane	166.1	$2.72\ 10^{-6}$	$1.79\ 10^{-6}$
2,3,4-Trimethylpentane	159.8	$2.55\ 10^{-6}$	$2.98\ 10^{-6}$
2,2,5-Trimethylpentane	182.8	$7.65\ 10^{-7}$	$4.78\ 10^{-7}$

MORE REFINED TREATMENT

In the derivation of the simplified Eq. (10), we have neglected the 1% of the time an ethanol OH group is, from a thermodynamic point of view, noninserted in a chain with the neighbors. Although for this special purpose we did not need to know the fraction γ of time during which, according to the theory of the mobile disorder, the OH group "visits" its domain, this fraction plays an essential role in the quantitative treatment (23).

It should be emphasized that γ, although small, is never equal to zero: the order created by H-bonds has to be mobile, and the H-bonds in liquids must regularly be broken. As shown in previous publications, γ is directly related to the negative change of the free Gibbs energy of the system brought about by the H-bonds. One has

$$G^{hAA} = n_A\, RT \ln \gamma_A \tag{15}$$

In the case of the alcohols γ_A can be estimated to a first approximation from the ratio between the vapor pressure of the alcohol and that of the "homomorphous" hydrocarbon.

Huyskens and his co-workers (24) have shown that for substances that form single H-bonded chains, the fraction γ is given by the expression

$$1/\gamma_A = 1 + K_A \Phi_A / V_A \tag{16}$$

where K_A is the stability constant of the self-association H-bonds. For the primary alcohols, at room temperature, K_A is of the order of 5000 $cm^3\ mol^{-1}$ (25). For water, one has to take two association constants into account. One obtains

$$1/\gamma_w = (1 + K_{w1}\Phi_w/18 + K_{w2}K_{w1}(\Phi_w/18)^2) \tag{17}$$

K_{w1} is of the same order of magnitude as the association constant of the alcohols, but as shown by Huyskens, K_{w2} is markedly smaller (26) (of the order of 300 $cm^3\ mol^{-1}$ at 25°C).

From Eqs. (14) and (15) one deduces immediately the effect of the self-association of the alcohol on the chemical potential of an inert solute. One finds

$$\mu_B^{hAA}/RT = [(K_A\Phi_A/V_A)/(1 + (K_A\Phi_A)/V_A)]\ \Phi_A V_B/V_A = r_A\, \Phi_A\, V_B/V_A \tag{18}$$

where r_A is practically equal to one [which corresponds to

Eq. (10)]. A similar derivation for water leads to a factor r_w practically equal to 2.

THE H-BOND ACTIVE SITES IN PHARMACEUTICAL DRUGS

Drug molecules display, in general, several sites that are active for H-bonding. Some molecules have only proton-acceptor sites (e.g., caffeine). However, when the molecules exhibit proton-donor sites they generally possess also acceptor sites. Further, when sites of the same nature are connected via delocalized electrons, the competition renders some of them inactive. For instance, Zeegers-Huyskens and her co-workers (27) have shown by infrared measurements that in caffeine, where one finds in principle eight acceptor sites, only three sites are active: one lone pair on each oxygen atom and one lone pair on the imino nitrogen atom (Scheme I).

The most important acceptor sites are the lone pairs of the oxygen atoms and of the nitrogen atoms, whereas the most important proton-donor sites are the OH, SH, and NH hydrogen atoms.

Solvents also may have only acceptor sites as, for instance, ketones, esters, ethers, and tertiary amines. However, in general, solvents with donor sites also possess acceptor sites: they are "amphiphilic." Examples are water and the alcohols. As a result, in order to form an H-bond with alcohols or water, the acceptor sites of a drug have to compete with the acceptor sites of the amphiphilic solvent. In contrast, the OH group of a drug DOH is not a real competitor for the association bonds of an alcohol ROH because it can insert itself in the chains:

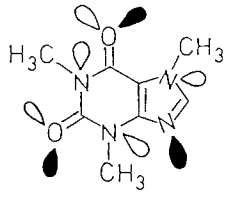
```
OH--OH--OH--OH--OH--OH--OH--OH--OH
|   |   |   |   |   |   |   |   |
R   R   R   D   R   R   R   R   R
```

When dealing with the effects of the H-bonds formed by the drugs it is therefore advisable to treat separately the two kinds of sites that we designate schematically by the symbols "OH" (amphiphilic) and "O" (only proton acceptor).

EFFECT OF PROTON-ACCEPTOR SITES OF THE DRUG ON ITS SOLUBILITY IN PROTON-DONOR SOLVENTS

An "O" site "visits" its domain and is thus not involved in H-bonding with the acidic solvent during a fraction γ_B of the time. According to Eq. (15) the reduction of the free energy of the system, caused by the solvent–solute H-bonds, is thus

$$G^{hSB} = n_B RT \ln \gamma_B \tag{19}$$



Scheme I. Caffeine.

γ_B depends on the concentration of the active proton-donor sites of the solvent. When the concentration of the O sites in the solution remains much lower than that of the donor sites of the solvent, the fraction γ_B is given to a good approximation by the expression

$$1/\gamma_B = 1 + K_{SB}\Phi_S/V_S \tag{20}$$

K_{SB} is the stability constant of the solvent–solute H-bonds. The effect of the SB hydrogen bonds on the chemical potential of the solute in the given circumstances is then given by

$$\mu_B^{hSB}/RT = -\ln (1 + K_{SB}\Phi_S/V_S) \tag{21}$$

The solubility of a solid ketone in an alcohol is predicted as

$$\ln \Phi_B = -A - 0.5 (1 - V_B/V_S)\Phi_S + 0.5 \ln(\Phi_B + \Phi_S V_B/V_S) - r_S\Phi_S V_B/V_S + \ln(1 + K_{SB}\Phi_S/V_S) \quad (\text{with } r_S = 1) \tag{22}$$

The value of K_{SB} can be calculated from the experimental solubility and from the fluidization constant determined by calorimetry. A similar equation can be used for determining the K_{SB} constants of the liquid ethers or esters in water, using $A = 0$ and $r_S = 2$. These values are only approximate because Eq. (20) neglects the effect of the other forces. Examples of such determinations (28) are given in Table IV.

In principle, the stability constants depend on both the acceptor and the solvent. However, one sees from these data that in a given family the constants remain similar to each other. For the predictions one can therefore use a standard value for a given type of bond. On the other hand, one observes a strong difference between the constants for the alcohols and those for water. This is due to the competition effect. The constant K_{SB} appearing in Eq. (20) is not that K_{SB}° which one should find when diluting the associated solvent in an inert one so as to suppress the self-association bonds. One can write

$$K_{SB} = [K_{SB}^\circ/(K_{SB}^\circ + K_A^\circ)] \cdot K_{SB}^\circ \tag{23}$$

In the case of water one has to take for K_A° the second K_{w2} of water. Furthermore, water is more acidic than the alcohols.

EFFECT OF THE H-BONDS FORMED BY THE AMPHIPHILIC GROUPS OF THE DRUGS ON THEIR SOLUBILITY

"OH" sites have more complicated effects than "O" sites; for the following reasons:

(1) They lead to the formation of self-association H-bonded chains between the drug molecules in the liquid state. These H-bonds are characterized by the stability constant K_{BB}
(2) With proton-acceptor solvents, they form H-bonds that can be treated with a K_{BS} constant in the same way as the O sites.
(3) With amphiphilic solvents, they insert themselves in the solvent chains, with a double positive influence on the solubility: (a) the hydrophobic effect is re-

Table IV. Stability Constants K_{SB} ($cm^3\ mol^{-1}$) of Solvent–Solute H-Bonds Derived from the Experimental Solubilities $\Phi_{B\ exp}$ at 25°C; Molar Volume V_B ($cm^3\ mol^{-1}$); Fluidization Constant A

Solute B	V_B	A	Solvent	$\Phi_{B\ exp}$	K_{SB}
$C_{18}H_{38}CO$	337.1	2.63	1-Propanol	0.0318	155
			1-Butanol	0.0389	155
			1-Octanol	0.0451	155
$C_{20}H_{42}CO$	369.7	3.51	Ethanol	0.0068	140
			1-Propanol	0.0131	205
			1-Butanol	0.0160	205
Me-isoBuether	118.5	0.0	Water	0.0150	2700
Me-secBuether	118.5	0.0	Water	0.0210	3600
Di-nProp. ether	139.5	0.0	Water	0.0034	3700
Ethylpropionate	115.5	0.0	Water	0.0190	2700
Butylacetate	132.5	0.0	Water	0.0007	4200
Ethylbutyrate	132.5	0.0	Water	0.0067	3500
Isobutylacetate	134.2	0.0	Water	0.0057	4000

duced and (b) the drug molecules are stabilized in the chains.

Instead of Eq. (18) for the hydrophobic effect of an alcohol, one obtains

$$\mu_B^{hSS}/RT = \Phi_S\,(r_S\,V_B/V_S - n_{OH}) \qquad (18')$$

where n_{OH} denotes the number of amphiphilic sites in the molecule of the drug. On the other hand, the hydrogen bonds between the drug molecules reduce their chemical potential by an amount

$$\mu_B^{hBB}/RT = -\ln(1 + K_{BB}\Phi_B/V_B) \qquad (24)$$

for one OH site. If thus one brings the molecule of the drug from its own pure phase in an "inactive" solvent, the effect of the B–B hydrogen bonds on the solubility will correspond to

$$-\Delta\ln\,\Phi_B = \ln(1 + K_{BB}/V_B) - \ln(1 + K_{BB}\Phi_B/V_B) \qquad (25)$$

In an amphiphilic solvent this amount reduces to

$$-\Delta\ln\,\Phi_B = \ln(1 + K_{BB}/V_B) - \ln(1 + K_{ins}(\Phi_S/V_S + \Phi_B/V_B)) \qquad (26)$$

where K_{ins} is the insertion constant of the amphiphilic group of the drug in the chains of the solvent. To a first approximation one can take K_{BB} and K_{ins} as equal to each other.

In a proton-acceptor solvent the equation has to be replaced by

$$-\Delta\ln\,\Phi_B = \ln(1 + K_{BB}/V_B) - \ln(1 + K_{BS}\Phi_S/V_S + K_{BB}\Phi_B/V_B) \qquad (27)$$

In this case K_{BS} and K_{BB} differ in general from each other. It should be noted that, in principle, the equations above hold only when Φ_S/V_S is sufficiently larger than Φ_B/V_B.

INFLUENCE OF THE CHANGES IN THE DISPERSION AND DIPOLE–DIPOLE INTERACTIONS ON THE SOLUBILITY OF DRUGS

This effect can be treated in the usual way with the "solubility parameter." However, we use in this method not the solubility parameters of Hildebrand but modified values that were determined from the experimental solubilities of solid *n*-alkanes in the various solvents (29).

The effect brings about a reduction of the solubility that can be written

$$-\Delta(\ln\,\Phi_B)^{dd} = \Phi_S^2\,V_B\,(\delta_B' - \delta_S')^2/(RT) \qquad (28)$$

(dd for dispersion + dipole–dipole).

Table V provides a list of the modified solubility parameters δ_s' of various solvents together with their molar volume V_S at 25°C.

A GENERAL EQUATION FOR THE PREDICTION OF THE SOLUBILITY OF DRUGS IN PURE SOLVENTS

From the above considerations we can deduce the following predictive equation for the solubility Φ_B of the drug, in volume fraction. It may contain six terms:

$$\ln\,\Phi_B = -A + B - D - F + O - OH \qquad (SO)$$

A is the fluidization term. It is calculated from the molar heat of fusion ΔH_{melt} and from the equilibrium melting temperature T_m of the pure crystalline drug.

$$A = \Delta H_{melt}\,(1/T - 1/T_m)/R \qquad (S1)$$

When the crystals undergo a transition at the temperature T_{trans} between T and T_m, a second term of the same form with the molar transition heat ΔH_{trans} and T_{trans} is added.

B is a correction term for the placing entropy resulting from the difference in the molar volumes of solvent and solute. The molar volume of the solute is not that of the pure crystalline substance but that of the dissolved solute, which is in general a few percent larger.

Molar volumes of the solute in solution are at best estimated by adding group contribution G_{vi} for the various groups constituting the molecule. A nonexhaustive list is given in Table VI. These group contributions were calculated to fit at best the experimental molar volumes of the solvents of Table V and those of other liquids.

$$B = 0.5\,\Phi_S(V_B/V_S - 1) + 0.5\,\ln(\Phi_B + \Phi_S V_B/V_S) \qquad (S2)$$

D describes the effect of the change in the dispersion and in the dipole–dipole interactions. At the present stage it

Table V. Molar Volume V_S and Modified Nonspecific Solubility Parameter δ_S' of Various Solvents at 25°C (28,29)

Solvent	V_S (cm^3 mol^{-1})	δ_S' (MPa$^{1/2}$)
Alkanes		
n-Pentane	116.1	14.18
n-Hexane	131.6	14.56
n-Heptane	147.5	14.66
n-Octane	163.5	14.85
n-Nonane	179.7	15.07
n-Decane	195.9	15.14
n-Dodecane	228.6	15.34
n-Tetradecane	260.3	15.49
n-Pentadecane	277.7	15.56
n-Hexadecane	294.1	15.61
n-Heptadecane	310.7	15.67
Cyclohexane	108.8	15.43
Isooctane	166.1	14.00
Aromatic hydrocarbons		
Benzene	89.4	18.95
Toluene	106.9	18.10
p-Xylene	123.9	17.30
Ethylbenzene	123.1	18.02
Mesitylene	139.6	17.00
m-Xylene	123.2	17.20
Halohydrocarbons		
CH_2Cl_2	64.5	20.53
$CHCl_3$	80.7	18.77
CCl_4	97.1	17.04
CH_2ClCH_2Cl	78.8	20.99
n-C_4H_9Cl	105.0	18.57
$Cl_2C_6H_4$	113.1	18.77
Ethers		
Diethylether	104.8	19.50
Dipropylether	141.8	18.30
Dibutylether	170.3	17.40
Tetrahydrofurane	81.4	19.30
Dioxane	85.8	20.89
Esters		
Methylformate	62.1	22.96
Methylacetate	79.8	21.71
Ethylacetate	98.5	20.79
Butylacetate	132.5	19.73
Hexylacetate	165.8	19.17
Ethylpropionate	115.5	20.05
Ketones		
Acetone	74.0	22.16
Methyletylketone	90.2	22.10
Diethylketone	106.4	20.28
Methylisobutylketone	125.8	20.02
Diisopropylketone	140.4	19.45
Didecylketone	369.8	17.27
Nitroderivative		
Nitroethane	71.8	22.44
Alcohols		
Methanol	40.7	19.25
Ethanol	58.7	17.81
1-Propanol	75.1	17.29
1-Butanol	92.0	17.16
1-Pentanol	108.6	16.85
1-Hexanol	125.2	16.40
1-Heptanol	141.9	16.39
1-Octanol	158.3	16.38
1-Decanol	191.6	16.35
2-Propanol	76.9	17.60
2-Butanol	92.4	16.60
Diols and water		
1,2-Propanediol	73.7	19.10
Ethanediol	56.0	19.90
Water	18.1	20.50

seems not yet necessary to separate it into two terms, as some authors do.

$$D = \Phi_S^2 V_B (\delta_B' - \delta_S')^2/(RT) \quad \text{(S3)}$$

F describes the effect of the hydrogen-bonded chains of the solvent (hydrophobic effect). For the alcohols and for water it can be written

$$F = \Phi_S(r_S V_B/V_S - n_B) \quad \text{(S4)}$$

r_S equals one for the alcohols and two for water. More exact values can be used for the alcohols, based on the equation

$$r_A = (K_A\Phi_A/V_A)/(1 + K_A\Phi_A/V_A) \quad (29)$$

O corresponds to the positive effect of the H-bonds between the O sites of the drug and the proton-donor solvents.

$$0 = \ln(1 + K_{SB}\Phi_S/V_S) \quad \text{(S5)}$$

The OH term describes the effect of the amphiphilic

Table VI. Group Contributions G_{vi} (cm^3 mol^{-1}) of Groups to the Molar Volume of Liquids at 25°C

Group	G_{vi}	Group	G_{vi}
$-CH_3$	25–32[a]	$-S-$	12.3
$>CH_2$	16.5	$>N-H$	7
$>CH_2$ (cycl)	18	$-NH_2$	17.5
$-\overset{|}{C}-H$	9	$>N$	0
$-\overset{\|}{C}-H$	13.2	$>N$ (arom)	6
$-\overset{|}{C}-H$ (arom)	14.9	$-NO_2$	22.3
$-C\equiv CH$	34.2	$>C=O$	10
$-\overset{|}{C}-$	0	$-\overset{\|}{C}(=O)-H$	13.1
$-F$	17	$-\overset{\|}{C}(=O)-O-H$	28
$-Cl$	24.3	$-\overset{\|}{C}(=O)-O-$	21
$-Br$	28	$>S=O$	10
$-I$	31	$-C\equiv N$	20.6
$-O-H$	9	$-SO$	7
$-S-H$	27		
$-O-$	8		
$-\overset{|}{C}-$ (arom)	5.5		

[a] 32 at the end of chains, 29 in the vicinity of another CH_3, 25 when connected with a group of delocalized electrons.

group OH of the drug [with the exception of the reduction of the hydrophobic term that already appears in Eq. (S4)].

$$OH = \ln(1 + K_{BB}/V_B) - \ln(1 + K_{OH}\Phi_S/V_S + K_{BB}\Phi_B/V_B) \quad (S6)$$

In this equation K_{OH} is equal to K_{BS} in proton-acceptor solvents, to K_{ins} (approximately K_{BB}) in amphiphilic solvents, and to zero in the others.

WHAT CHARACTERISTICS OF THE DRUG HAVE TO BE KNOWN OR ESTIMATED TO APPLY THE METHOD?

One needs the following:

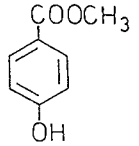
(1) the melting point T_m of the crystalline drug and the molar heat of fusion ΔH_{melt}, in order to calculate the fluidization constant A;
(2) the formula of the drug in order to calculate its molar volume V_B in solution from the group contributions in Table VI;
(3) the active amphiphilic "OH" sites and the order of magnitude of their self-association constants K_{BB} ($= K_{insertion}$) and of their complexation constants K_{BS} with ethers, ketones, esters, or other proton-acceptor solvents;
(4) the active "O" sites and the order of magnitude of their stability constants K_{SB} with the alcohols and with water; and
(5) the modified solubility parameter δ_B' of the drug—this can be fitted from one experimental solubility in a solvent that does not form H-bonds with the drug.

APPLICATION: METHYL *p*-HYDROXYBENZOATE

The melting point of methylparaben is 399.65 K. Its molar heat of fusion, determined by differential scanning calorimetry (30), is 22,600 J mol^{-1}. This leads to a fluidization constant A of 2.32 at 25°C (Scheme II).

From Table VI one deduces from the group contributions a molar volume V_B of 133 cm^3 mol^{-1}. Other values cited in the literature (30) lead to a density of 1.29 g cm^{-3}. This seems to us much too high, compared with liquids of analogous chemical composition. Paraben displays one active OH site, namely, the phenolic OH group. For K_{BB} (and K_{ins}) we take the arbitrary value of 5000 cm^3 mol^{-1} because it is the order of magnitude of the association constants of primary alcohols and phenols. As this OH group is rather acidic, we take the same value for K_{BS}.

Methylparaben displays one O site, namely, one of the lone pairs of the carbonyl oxygen atom of the ester group. The other lone pairs are inactive. We do not yet have determinations of K_{SB} for such a group attached to an aromatic ring. We therefore take for the prediction the mean values of the data in Table IV. This means 170 cm^3 mol^{-1} for the alcohols and 3500 cm^3 mol^{-1} for water.



Scheme II. Methylparaben.

In order to estimate the modified solubility parameter of the drug for the nonspecific cohesion forces, we take one experimental solubility, namely, that in *n*-pentane. Martin *et al.* (30) have found a value Φ_B of 7.22 10^{-5} at 25°C. For this solvent the terms F and O vanish. With K_{BB} = 5000 cm^3 mol^{-1} one calculates from the experimental solubility a value δ_B' of 22.5 MPa$^{1/2}$.

From this sole experimental data and using stability constants roughly estimated on a basis that has nothing to do with paraben, we predict the solubilities of methylparaben in some 26 solvents and compare them in Table VII with the experimental values. It must be emphasized that this is really a prediction and not a fitting of 26 experimental values with a series of adjustable parameters. Further, it must be borne in mind that if only rough orders of magnitude are used for the various stability constants, we can expect to find only orders of magnitude for the solubilities. Nevertheless, although the predicted values can sometimes be four or five times too high or too low, the agreement between the predicted values and the experimental ones that range over five orders of magnitudes is remarkable. A prediction of a solubility of methylparaben of 0.9 vol% in water, based only on the physical characteristics of the solute and on its solubility in pentane, is not a bad estimation when the experimental value is about 0.2%. And this is one of the worst cases.

The reason for this success is that the method utilizes correct thermodynamic equations. An equation such as that used by Beerbower *et al.* (31) on the basis of "donor" and "acceptor" parameters δ_a and δ_b, although fundamentally more correct than the equations with "hydrogen-bond parameters," neglects entropy effects. This equation is of the form

$$\ln \alpha_B = A\,[C_1(\delta_{dB} - \delta_{dS})^2 + C_2(\delta_{pB} - \delta_{pS})^2 + 2C_3(\delta_{aB} - \delta_{aS})(\delta_{bB} - \delta_{bS}) + C_0$$

where α_B is the activity coefficient of the solute and

$$A = V_B \Phi_S^2/RT$$

In the last equation the term Φ_S^2 is the consequence of an assumption of random contacts. Such hypothesis contradicts the very essence of H-bonds that are preferential contacts.

The entropy effects are more or less artificially included in the eight coefficients (D_0 to D_7) that are needed by such an equation to fit a set of experimental solubilities, but the mathematical form is inadequate. The formation of stoichiometric cohesion bonds, such as H-bonds but also ion–ligand bonds in aqueous solutions, has to be treated by means of stability constants and concentrations of active sites. The values A, B, D, F, O, and OH appearing in Table VII have a direct physical interpretation in the frame of the thermodynamics of the mobile order. One can write Eq. (S0) in the form

$$\Phi_B = e^{-A}e^{B}e^{-D}e^{-F}e^{O}e^{-OH} \quad (S0)$$

When all the values A, B, etc., are zero, Φ_B is equal to one and B would be miscible in all proportions in the solvent.

- e^{-A} is the so-called "ideal solubility" of the drug.

Table VII. Experimental (30,32–34) and Predicted [Eq. (S0)] Solubilities (in Volume Fraction) of Methylparabene at 25°C[a]

Solvent	$\Phi_{B\,exp}$	$\Phi_{B\,pred}$	r_s	K_{SB}	K_{OH}	B	D	F	O	OH
Hexane	$7.78\ 10^{-5}$	$8.82\ 10^{-5}$	0	0	0	0.01	3.38	0.00	0.00	3.65
Heptane	$7.48\ 10^{-5}$	$8.59\ 10^{-5}$	0	0	0	−0.10	3.30	0.00	0.00	3.65
Isooctane	$5.04\ 10^{-5}$	$4.31\ 10^{-5}$	0	0	0	−0.21	3.88	0.00	0.00	3.65
Nonane	$7.84\ 10^{-5}$	$10.00\ 10^{-5}$	0	0	0	−0.28	2.96	0.00	0.00	3.65
Decane	$8.21\ 10^{-5}$	$9.86\ 10^{-5}$	0	0	0	−0.35	2.91	0.00	0.00	3.65
Benzene	$5.32\ 10^{-3}$	$2.20\ 10^{-3}$	0	0	0	0.44	0.67	0.00	0.00	3.57
CCl_4	$1.38\ 10^{-3}$	$0.75\ 10^{-3}$	0	0	0	0.34	1.60	0.00	0.00	3.62
Acetone	$3.05\ 10^{-1}$	$2.62\ 10^{-1}$	0	0	5,000	0.53	0.00	0.00	0.00	−0.45
Diethylether	$1.04\ 10^{-1}$	$1.04\ 10^{-1}$	0	0	5,000	0.23	0.39	0.00	0.00	−0.21
Dipropylether	$2.95\ 10^{-2}$	$3.64\ 10^{-2}$	0	0	5,000	−0.06	0.88	0.00	0.00	0.06
Dibutylether	$2.10\ 10^{-2}$	$1.61\ 10^{-2}$	0	0	5,000	−0.23	1.35	0.00	0.00	0.24
Dioxane	$3.13\ 10^{-1}$	$3.15\ 10^{-1}$	0	0	10,000	0.35	0.06	0.00	0.00	−0.88
Ethylacetate	$1.64\ 10^{-1}$	$1.50\ 10^{-1}$	0	0	5,000	0.28	0.11	0.00	0.00	−0.26
Butylacetate	$1.33\ 10^{-1}$	$0.70\ 10^{-1}$	0	0	5,000	0.00	0.36	0.00	0.00	−0.00
Hexylacetate	$9.56\ 10^{-2}$	$3.80\ 10^{-2}$	0	0	5,000	−0.20	0.55	0.00	0.00	0.20
Methanol	$3.19\ 10^{-1}$	$4.75\ 10^{-1}$	1	170	5,000	0.99	0.16	1.19	1.16	−0.77
Ethanol	$2.85\ 10^{-1}$	$2.73\ 10^{-1}$	1	170	5,000	0.79	0.62	0.92	1.13	−0.64
1-Propanol	$2.36\ 10^{-1}$	$1.54\ 10^{-1}$	1	170	5,000	0.58	1.04	0.65	1.07	−0.49
1-Butanol	$2.01\ 10^{-1}$	$1.03\ 10^{-1}$	1	170	5,000	0.37	1.23	0.40	0.98	−0.33
1-Pentanol	$1.81\ 10^{-1}$	$0.65\ 10^{-1}$	1	170	5,000	0.20	1.50	0.21	0.90	−0.19
1-Hexanol	$1.55\ 10^{-1}$	$0.38\ 10^{-1}$	1	170	5,000	0.06	1.85	0.06	0.84	−0.06
1-Heptanol	$1.40\ 10^{-1}$	$0.30\ 10^{-1}$	1	170	5,000	−0.06	1.88	−0.06	0.77	0.06
1-Octanol	$1.19\ 10^{-1}$	$0.25\ 10^{-1}$	1	170	5,000	−0.16	1.91	−0.16	0.72	0.16
1-Decanol	$0.63\ 10^{-1}$	$0.18\ 10^{-1}$	1	170	5,000	−0.33	1.96	−0.30	0.63	0.35
1,2-Propanediol	$1.58\ 10^{-1}$	$0.94\ 10^{-1}$	2	340	5,000	0.64	0.51	2.36	1.64	−0.54
Water	$1.98\ 10^{-3}$	$8.77\ 10^{-3}$	2	3,500	5,000	4.14	0.21	13.58	5.26	−1.96

[a] Properties of the solute: $V_B = 133\ cm^3\ mol^{-1}$; $\delta_B' = 22.5\ MPa^{1/2}$; $K_{BB} = 5{,}000\ cm^3\ mol^{-1}$; $A = 2.32$; $n_{OH} = 1$. Properties of the solvents: see V_S and δ_S' in Table V.

• e^B is the correction factor, related to the disorder of placing, for the inequality of the molar volumes of solute and solvent. For the case under consideration it is important only when the solvent molecule is markedly smaller than that of the solute: for acetone (1.70), for 1,2-propanediol (1.87), and for the lower alcohols and for water, it reaches 62.8.

• e^{-F} is the factor due to the solvent–solvent H-bonds. It is equal to 1 for solvents without H-bonding association. For the others it is generally lower than one except when the molar volume of the solvent exceeds that of the drug. It is especially low for water, 0.0000013, and this justifies the name "hydrophobic" that we have used for the effect of solvent–solvent H-bonds, in the same way that "Spa," a watering place in Belgium, designates a resort with mineral springs.

These three factors are known with precision.

• e^{-D} is the reduction factor due to the changes in the nonspecific cohesion forces. It is especially low for the alkanes, where it seems to be of the order of 0.04. However, this value depends on the estimation of K_{BB} and this is thus only an order of magnitude.

• e^O is a factor describing the effect of the H-bonds in which the ester group is involved. In fact, according to the theory of the mobile disorder, the ratio $(e^O - 1)/e^O$ is the fraction of the time the ester group of a paraben molecule is involved in H-bonding with the solvent. For the lower alcohols this gives an order of 66% of the time. For water it should be 99%. As the used stability constants K_{SB} are only rough estimations, the real values may markedly differ from these figures.

• e^{OH} is a factor of the order of 0.025 when the OH group of paraben has no occasion to form H-bonds with the solvent. However, when this is well the case the factor may become greater than one. This means that the self-association bonds between the molecules of solute, which have to be broken in order to dissolve it in the first solvents, are overcompensated by the addition or insertion bonds the drug forms with the latter solvents. From the data in Table VII one deduces that the OH group of paraben is from a thermodynamic point of view "free of H bonding" and thus noninserted in the solvent chains during a fraction of time of 2% in the lower alcohols and 0.3% in water. Again, the figures are only orders of magnitude.

CONCLUSION

The thermodynamics of mobile disorder leads to new equations that allows a correct prediction of the order of magnitude of the solubility of drugs in pure solvents. Contrary to the methods based on the "solubility parameters" (even those utilizing donor and acceptor parameters), which do not take account of preferential contacts and entropy effects, the present treatment is based, for H-bonds, on stability constants and on concentrations of the active sites, which allows us to take the important entropy effects into account.

The further development of the method will consist in

finding ways to predict the individual values of these stability constants K_{BB}, K_{SB}, K_{BS}, K_{ins}, etc., on the basis of only the formula of solute and solvent. Another important problem to be studied is the competition of several active sites, as they often appear in pharmaceutical drugs.

ACKNOWLEDGMENT

The authors are grateful to the Swiss National Science Foundation (FNRS) for partial financial support (Grant 3100-26565-89).

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