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Effects of solvent medium on solubility. A linear free energy relationship treatment

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Linear relationships exist between the logarithms of the solubility equilibria of structurally closely related compounds, as they vary with changes in solvent or solvent composition in water and water-like solvents. The slope P_y of these linear free energy relationships quantitatively accounts for the direction and intensity of the relative solubility variations due to medium effects. Results obtained by applying the concept to series of both *p*-hydroxy- and *p*-aminobenzoic esters, and α-aminoacids, are presented. These results are explained by a simple model in terms of solute-solvent interactions.

Linear free energy relationships (LFER) are extrathermodynamic relationships of wide use in organic chemistry. Their systematic application to either equilibria and reaction rates, has been recognized as a powerful tool in the elucidation of structure-activity relationships as well as in the correlation of physical properties with the structure of organic compounds (Wells 1968; Shorter 1973). Much effort has gone into rationalizing the solubility of organic compounds. The Hildebrand theoretical approach (Hildebrand et al 1970), originally proposed for non-polar systems, has been extended with variable success to non-electrolytes in polar solvents by several workers (Restaino & Martin 1964; Yalkowsky et al 1975; Martin & Cartensen 1981).

Other empirical approaches, such as the recognition of a linear relationship in homologous series or organic compounds between the logarithms of aqueous solubilities and the molecular weight (Saracco & Spaccamela Marchetti 1960; Spaccamela Marchetti & Saracco 1960), or the composition of aqueous non-aqueous mixtures (Yalkowsky et al 1975) have been reported, as well as some work investigating dielectric constant solubility relationships (Paruta et al 1962 Paruta & Irani 1966).

An early attempt to compare solvent effects on solubility was reported by McMeekin et al (1935) and Cohn (1936) who compared the ratio of the solubility in ethanol to that in water for several aminoacids and related compounds. Recently (Anderson & Conradi 1980, an LFER has been applied to some solubility data of prostaglandin pro-drugs. However, a general treatment of the subject is not available in the literature. Therefore, a test of the applicability of LFER to solubility equilibria was the subject of this study.

THEORETICAL

Formulation of LFER in solubility equilibria

In a saturated solution of a solid compound A_x in a solvent *s* at constant pressure and temperature, the excess of solid is in equilibrium with A_x in solution. In the simplest situation, the concentration of A_x in solution is equal to the solubility of only one species. In more complicated situations, A_x exists in solution in more than one form as a result of ionization, tautomerism, dimerization, etc. Therefore, the apparent solubility S_{app} is the sum of the concentrations of all the species at equilibrium in a saturated solution, the least soluble species being that determining the solubility (Kramer & Flynn 1972), whose concentration is the specific solubility S_{sp}. Whatever the solubility measured, there will be a free energy change accompanying the process, which is related to the solubility equilibrium by

$$-2{\cdot}303\ RT \log S_x = \Delta G \qquad (1)$$

Consider a series of structurally related solutes (A_1, $A_2 \ldots A_n$) whose solubilities are measured in a set of solvents (s_1, $s_2 \ldots s_n$) as depicted in Table 1. The solvents in the set may be pure, or mixtures with regular variations in the proportions of their constituents.

The solubility data of Table 1 can be conveniently correlated by one of the following procedures:

i. Plotting the logarithms of the solubilities of one horizontal line in the Table against those of another.

Table 1. Block of solubilities S for a series of n substrates A in a set of n solvent s.

	Solvents			
Compounds	s_1	s_2	s_3	s_n
A_1	S_{11}	S_{12}	S_{13}	S_{1n}
A_2	S_{11}	S_{22}	S_{23}	S_{2n}
A_3	S_{31}	S_{32}	S_{33}	S_{3n}
A_n	S_{n1}	S_{n2}	S_{n3}	S_{nn}

ii. The correlation between two vertical columns instead of two lines offers an alternative way when the solvents are closely related.

Fig. 1 shows an example of the former procedure. The following general equation accounts for the correlation obtained

$$\log S_y = P_y \log S_x + C \quad (2)$$

Where P_y is the slope and C the intercept; S_y and S_x are the solubility data of the vertical and horizontal axis respectively.

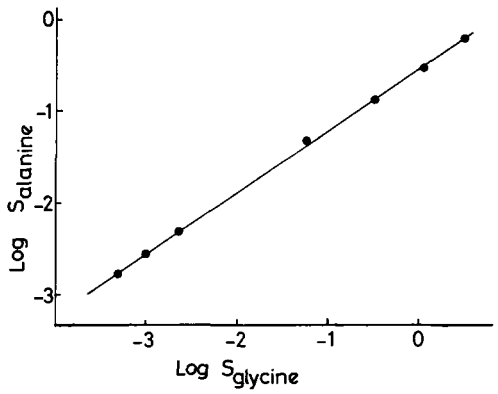

FIG. 1. Typical LFER plot. Correlation in ethanol–water mixtures. Ethanol proportions (from left to right) 1·0, 0·95, 0·74, 0·50, 0·24, 0·10 and 0·0.

Equation 2 has the typical form of an LFER. The meaning and properties of such an LFER will be explored in the following sections.

MATERIALS AND METHODS

Solubility determinations. A stoppered test tube containing an excess of solid substrate and the appropriate solvent was kept at least 24 h in a constant temperature bath at 25 °C with adequate shaking. Samples were taken with a small diameter tube having a piece of sintered glass in its extreme to avoid contamination with the solid. To assure that equilibration was reached, in some experiments a second sample was taken 4 h later. An analytical u.v.-spectrophotometric procedure to measure ester concentration was used. Samples were adequately diluted with ethanol to determine their absorbances at γ_{max}.

Substrates: methyl and propyl *p*-hydroxybenzoic esters were both commercial products which were recrystalized from ethanol–water before use.

Solvents: ethanol (Merk) and cyclohexane (Mallinkrodt) both analytical grade. n-Octanol (Sigma) was purified by distillation according to James & Mehdizadeh (1981).

RESULTS AND DISCUSSION

Correlation of some representative collections of data in water and water-like solvents

In a first step, to test the applicability of equation 2, some collections of data were taken from the literature and appropriately correlated.

Because solvent changes produce variations in the solubility equilibrium of the substrates and a concomitant change in the free energy (eqn 1) the larger the solubility variation, the better the test about the validity of equation 2. From this point of view the first two series correlated represent favourable situations, because both involve large changes in solubility in moving from one pure solvent to the other. This is indicated by $\Delta\log S_y$, which is the difference between the log solubilities in the two pure solvents. Values are given in Table 2. Another important point in the correlation of solubility data deals with the selection of the unit of concentration to be used. Because from initial analysis any unit appears to have relevant advantages, some collections of data were comparatively correlated using different units (molar fraction, molality and mol kg^{-1} soln). The results showed that the quality of the correlations appears to be independent of the units used. Then, molality was arbitrarily selected to express solubilities and will be used throughout the paper.

Lastly, the solubility variation of the lower molecular weight member of a series ($\Delta\log S_x$) was always taken as the horizontal coordinate.

i. *p*-Aminobenzoic esters in water–propylene glycol mixtures

Good solubility data are available for the series of ethyl, butyl, hexyl and octyl esters in water-propylene glycol mixtures at 37 °C (Yalkowsky et al 1975). The solubility increase when water is replaced by propylene glycol is about 10^2 times for the ethyl and 10^5 times for the octyl ester. As is apparent from

Table 2. *a*. r is the regression coefficient, δ_{sl} is the standard deviation of the slope and δ_y is the standard deviation of the points from the regression line in the y-direction. *b*. Solubility data of Yalkowsky et al (1975). Ethyl ester data were taken as horizontal coordinate. The six points correlated correspond to the following proportions of water in the mixture: 0·0, 0·2, 0·4, 0·6, 0·8 and 1·0. *c*. Data from Weast (1976). Glycine solubility data were taken as horizontal coordinate. The points quoted correspond to the following proportions of ethanol: 0·0, 0·1, 0·25, 0·5, 0·74, 0·95 and 1·0. *d*. Datum at 1·0 ethanol not available. *e*. Datum at 0·1 ethanol not available. *f*. Data of Alexander et al (1977). Methyl ester data as horizontal coordinate. The set of alkanols is constituted by the first four homologues plus hexanol, octanol and decanol.

Compound	Slope	Intercept	r[a]	δ_{sl}[a]	δ_y[a]	$\Delta\log S_y$	Points
1. Alkyl *p*-aminobenzoate esters in water–propylene glycol mixtures at 37 °C [b]							
Butyl	1·73	2·82	0·993	0·163	0·100	3·26	6
Hexyl	2·05	3·12	0·994	0·180	0·110	3·97	6
Octyl	2·47	3·88	0 995	0·197	0·120	4·84	6
2. α-Amino acids in water–ethanol mixtures at 25 °C [c]							
DL-Alanine	0·855	−0·128	0·997	0·030	0·110	−3·28	7
DL-Valine	0·666	−0·561	0·999	0·011	0·038	−2·57	7
DL-Leucine	0·480	−1·39	0·995	0·025	0·067	−1·59	6[d]
DL-Aspartic	0·801	−1·70	0·999	0·023	0·058	−2·60	5[d,e]
L-Glutamic	0·819	−1·66	0·989	0·060	0·205	−3·40	6[e]
DL-Serine	1·02	−0·869	0·999	0·010	0·024	−3·25	5[d,e]
DL-Tyrosine	0·335	−2·82	0·990	0·028	0·070	−1·04	5[d,e]
3. Alkyl *p*-hyroxybenzoate esters in a set of seven n-alkanols at 25 °C [f]							
Ethyl	0·753	0·117	0·998	0·018	0·010	−0·48	7
Propyl	0·617	0·201	0·992	0·035	0·020	−0·40	7
Butyl	0·441	0·392	0·993	0·018	0·010	−0·30	7

Table 2, linear relationships corresponding to equation 2 were obtained for every member of the series in the whole range of water–propylene glycol mixtures. The regression parameters indicate a high quality of linear correlation.

ii. α-Aminoacids in water–ethanol mixtures

α-Amino acids are water-soluble compounds. On replacing water by ethanol, the solubility decreases by an average factor of 10^3. Unlike *p*-aminobenzoic esters, which in aqueous solution are almost completely in their neutral form, α-amino acids exist as an equilibrium among several forms, mainly zwitterion, acidic and basic. Therefore, the quantities plotted are apparent solubilities (S_{app}). Moreover, the data belong to racemic compounds giving rise to a more complex system than that with *p*-aminobenzoic acid esters.

Good linear correlations were obtained with the homologous series alanine, valine and leucine over the whole range of ethanol–water mixtures. Glycine solubility data were used as the horizontal coordinate. The relationships are shown in Table 2. The higher the molecular weight (MW) of the second amino acid coordinate, the lower the slope P_y of the glycine-second amino acid regression. Fig. 2 shows that P_y is linearly related with MW_y. Table 2 also shows that dicarboxylic amino acids (aspartic and glutamic) and amino acids with, in addition, an hydroxylic group (serine, tyrosine) were found to correlate equally well with glycine solubility data. However the slopes obtained do not follow the pattern $P_y - MW_y$ exhibited by glycine homologues. This point will be further discussed.

iii. *p*-Hydroxybenzoic esters in a series of n-alkanols

Solubility data of the series of methyl to butyl esters in a set of seven n-alkanols are available (Alexander et al 1977). Their correlation according to equation 2 is also reported in Table 2.

The results reported in Table 2 show that equation 2 can be successfully applied to solubility data. P_y is the ratio of the responses of the solubility equilibria

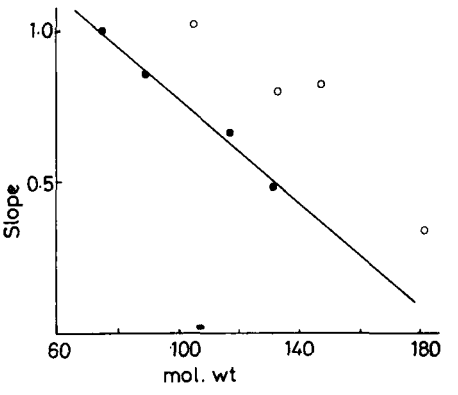

FIG. 2. Plot of slope P_y against the MW of the amino acids. (●) normal members: from left to right glycine, DL-alanine, DL-valine and DL-leucine. (○) amino acids having an additional hydrophilic group: from left to right DL-serine, DL-aspartic, L-glutamic and DL-tyrosine.

of compounds A_y and A_x both subjected to the same environmental changes, i.e.

$$P_y = \frac{\log S_y^a - \log S_y^b}{\log S_x^a - \log S_x^b} = \frac{\Delta \log S_y}{\Delta \log S_x} \qquad (3)$$

In equation 3 the superscript a corresponds to the solubility in a solvent of more lipophilic character than that of b.

The medium effect parameter P_y appears to be quite sensitive to the introduction of a structural change in a solute. The analysis of P_y values of the homologous series reported in Table 2 shows that an homologous A_y of higher MW than that of the reference homologue affords a slope P_y steeper than one when $\Delta \log S$ is positive but lower than one when $\Delta \log S$ is negative. Lines a and b in Fig. 3 show the $+\Delta$'s and $-\Delta$'s situations respectively.

To obtain information on this behaviour over a wide range of solvent lipophilicities, methyl and propyl *p*-hydroxybenzoic esters were selected as model compounds and they were used as A_x and A_y respectively. These esters have been extensively used in solubility research and there are considerable data on their solubility in different solvents, some of which were used in addition to those herein determined.

The solubility data reported in Table 3 cover solvents with a wide range of lipophilicity going from water at one extreme to n-octanol diluted with cyclohexane at the other.

Table 3. Solubility of methyl and propyl *p*-hydroxybenzoic esters.

Solvent		$\log S_{Me}$	$\log S_{Pr}$	LV	π'_y
water[a]		−1·841	−2·687	−1·841	0·000
Ethanol–water	6·5%	−1·772	−2·526	−1·772	0·092
,,	13·3%	−1·487	−2·157	−1·487	0·176
,,	33·0%	−0·654	−1·023	−0·654	0·477
,,	38·0%	−0·471	−0·777	−0·471	0·540
,,	80·0%	0·336	0·183	0·336	0·699
Ethanol[a]		0·374	0·434	0·930	0·906
Propanol[a]		0·288	0·384	1·016	0·942
Butanol[a]		0·236	0·340	1·068	0·950
Hexanol[a]		0·129	0·257	1·175	0·974
Octanol[a]		−0·0149	0·169	1·319	1·030
Octanol–cyclohexane	60·0%	−0·378	−0·150	1·682	1·074
,,	20·0%	−0·692	−0·332	1·996	1·206
,,	10·0%	−1·012	−0·621	2·316	1·237

[a] Solubility data of Alexander et al (1978) and (1977) for water and pure n-alkanols respectively.

Going from water to ethanol through a series of ethanol–water mixtures, the solubilities of both esters increase to reach a maximum at pure ethanol. Further increases in solvent lipophilicity result in a progressive decrease in solubility.

Table 4 reports the results obtained by applying equations 2_1 and 2_2 to each of the two sets of data

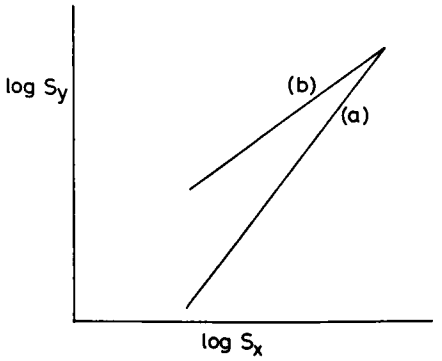

FIG. 3. Expected LFER plot for a pair of solutes which pass through a solubility maximum (MSC) when they move from the first to the last solvent condition.

which are delimited by the maximum solubility condition (MSC). In both cases a good quality of linear correlation is obtained.

For ethanol–water mixtures

$$\log S_{y_1} = P_{y_1} \log S_{x_1} + C_1 \qquad (2_1)$$

For alkanols and ethanol–cyclohexane mixtures

$$\log S_{y_2} = P_{y_2} \log S_{x_2} + C_2 \qquad (2_2)$$

By appropriately plotting both equations a plot like that of Fig. 3 should be obtained. The point where lines 2_1 and 2_2 have the same value correspond to the MSC. Their vertical and horizontal coordinates yield log MSC_y and log MSC_x respectively.

To explain the experimental results, a simple model in terms of solute-solvent interactions was developed.

Table 4. Correlation according with equations 2_1 and 2_2 of solubility data of table 3.

		P_y	C	r	Points
For ethanol–water mixtures	(2_1)	1·318	−0·204	0·999	6
For alkanols and octanol–cyclohexane mixtures	(2_2)	0·758	0·161	0·999	8

The model of the maximum solubility condition (MSC)

For the purposes of the present discussion both a molecule of solute or solvent can be considered as formed by a lipophilic component and n-hydrophilic groups. Then the relative extent of the solubility will depend on the lipophilic-hydrophilic balance of both solute and solvent.

For a solute A_x in a given solvent system, there will be a real or hypothetical condition where an optimum solute-solvent interaction occurs. Such a condition corresponds to the MSC. Solubility should

decrease as the system is going away from the MSC owing to solvent changes.

Consider an increase in the lipophilicity of a solvent by introducing a bigger R portion in an homologous solvent series or by increasing the proportion of the more lipophilic component of a mixture. The response of A_x to this change in the solubility equilibrium can be either, an increase in solubility ($+\Delta\log S_x$) when the change approaches the system to the MSC, or a decrease in it ($-\Delta\log S_x$) when the system is going away from the MSC. These changes are represented in Fig. 4 by a horizontal displacement from left to right.

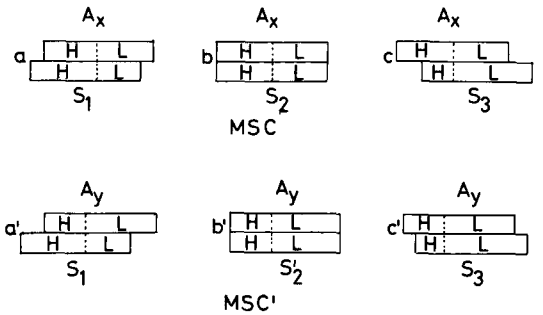

FIG. 4. Diagram of the MSC model. For every condition the upper and lower rectangles represent solute and solvent respectively. A solvent change is represented by an horizontal shift and a structural variation of the solute by a vertical one. H and L mean hydrophilic and lipophilic portions respectively. Their respective areas have no real meaning.

It is reasonable to assume that the intensity of the response of a solubility equilibrium to medium changes (MCH) becomes weaker as the system is approaching the MSC (at MSC the infinitesimal solubility variation $dS_x/d(MCH)$ approaches zero). Consider now the introduction of a structural change in A_x by increasing its lipophilic portion. This change is represented in Fig. 4 by a vertical displacement.

If the system is placed left of the MSC, the change on the one hand moves it from (a) to a lesser overlapping condition (a'); on the other, the MSC moves from (b) to (b'). Note that the relative weight of the lipophilic portion in (b') is raised in both solute and solvent. The overall effect is a withdrawal of the system from the previous MSC. Consequently, a stronger response of the solubility equilibrium of higher homologues to medium changes ($P_y > 1$) is expected. This conclusion is in agreement with the experimental results.

If the system is placed to the right of the MSC, then an increase in the lipophilic portion of the solute will shift the system toward the MSC through the changes (c) to (c') and (b) to (b'). Therefore, a weaker respone of higher homologues to medium changes ($P_y < 1$) is expected. This behaviour is clearly observed with glycine homologues in ethanol–water mixtures (Fig. 2).

Reasoning in the same way, the introduction to an α-amino acid of an additional hydrophilic group such as a carboxylic group (aspartic and glutamic acids) or a hydroxylic group (serine, tyrosine) moves the system away from the previous MSC. Consequently, slopes steeper than those expected for a glycine homologue of the same MW are predicted. As can be seen in Fig. 2, slopes higher by about 0·3 are found with amino acids having an additional hydrophilic group.

Lastly, the results quoted in Table 4 (*p*-hydroxybenzoic esters) are successfully explained in terms of the MSC model. Evidently, as a result of its greater lipophilic portion the solubility of the propyl ester increases faster and decreases more slowly than that of the methyl ester.

The relationship with partition coefficients (PC)

Although of a more complex nature than solubility equilibria, the partition of organic substrates between two immiscible solvents has received attention mainly in connection with the relationship between structure and biological activity of drugs (Hansch & Dunn 1972).

There is much evidence that PCs are of additive-constitutive character. The additivity was established for a wide variety of groups (Leo et al 1971; Flynn 1971; Davis et al 1974) mainly in the system n-octanol-water. Thus, equation 4 relates the PCs of two structurally closely related compounds A_y and A_x both measured in the same pair of solvents.

$$\pi_y = \log PC_y - \log PC_x \qquad (4)$$

In a given system of solvents π_y is a constant for each functional group, i.e. for an homologous series of substrates, π_y is linearly related by MW_y. The meaning of π_y has also been extensively discussed from thermodynamic (Flynn 1971) and extra-thermodynamic (Leo et al 1971) points of view.

Assuming that the phases involved in a partition equilibrium are completely inmiscible and that the concentration of substrate is approaching is solubility in each phase, a conceptual connection with medium effects on solubility is readily obtainable. Then, equation 4 may be re-written as follows:

$$\pi'_y = \log \frac{S_y^a}{S_y^b} - \log \frac{S_x^a}{S_x^b} = \Delta\log S_y - \Delta\log S_x \qquad (5)$$

The superscripts a and b refer to the two partitioning solvents.

π'_y may also be regarded as the expected PC parameter which is obtained by considering a PC as a ratio between the solubility of the substrate in the two partitioning solvents.

General relationship between P and π'_y

Combining equations 3 and 5

$$\pi'_y = P_y \Delta\log S_x - \Delta\log S_x \quad (6)$$

Equation 6 states the relationship among P_y, π'_y and $\Delta\log S_x$. Table 5 shows the properties of both P_y and π'_y when a structural variation is introduced in a reference compound by increasing either its lipophilic or hydrophilic portions. As it is apparent from the Table, the sign of π'_y depends only on the nature of the strutural change regardless of the sign of $\Delta\log S_x$.

Table 5. Relationship among π'_y, P_y and $\Delta\log S_x$.

Series type	π'_y	P_y	$\Delta\log S_x$
A_y has a bigger lipophilic portion than A_x	>0	>1	>0
	>0	<1	<0
A_y has a bigger hydrophilic portion than A_x	<0	>1	<0
	<0	<1	>0

On the other hand, P_y depends on both the nature of the structural change and the effect of the solvent variation on the solubility of the substrate series, that is on $\Delta\log S$. This difference between the properties of P_y and π'_y will be used in a complementary way.

The lipophilic variable (LV)

The interpretation of a plot like that of Fig. 3 presents some difficulty because of its own complex nature. Therefore, in order to gain clarity in the presentation of the results a definition of a new variable which could be used as horizontal coordinate in LFER plots was attempted. In this way a possible choice of a lipophilic variable (LV) for a particular series in a given set of solvents may be obtained by the following definition: $\log S_x$ goes up or down linearly and with unitary slope as LV is increasing. The values of LV using methyl *p*-hydroxybenzoate as reference were calculated through equations 7_1 and 7_2.

$$LV_1 = \log S_{x_1} \text{ (in ethanol–water mixtures)} \quad (7_1)$$

$$LV_2 = 2\log MSC_x - \log S_{x_2} \text{ (in alkanols and octanol–cyclohexane mixtures)} \quad (7_2)$$

The value of $\log MSC_x$ (0·652) was calculated from equations 2_1 and 2_2 as described below.

The LV values calculated are quoted in Table 3 and they are used as the horizontal coordiante in Fig. 5. It shows the variations of the solubilities of both esters due to the increasing lipophilicity of the solvents. It is evident that, as a result of its bigger lipophilic portion, the solubility of propyl paraben (A_y) increases faster and decreases slower than that of methyl-paraben (A_x).

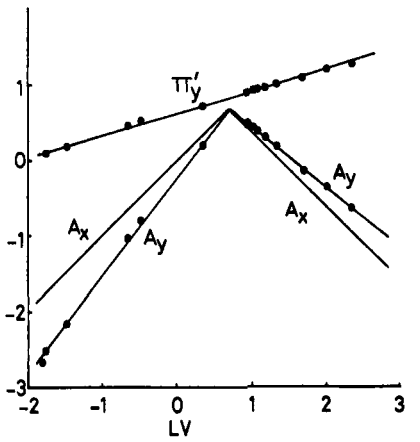

FIG. 5. Plot showing the relationship between π_y and LV (upper line) and the variation of the log solubilities of propyl (A_y) and methyl (A_x) p-hydroxybenzoates as LV is increasing.

Medium effects on π'_y

Fig. 5 also shows the variation of π'_y in the whole range of lipophilicity. As expected, regardless of whether the solubilities of the esters increase or decrease, π'_y increases continuously with increasing lipophilicity–affording the following relationship with LV.

$$\pi'_y = 0{\cdot}293(LV) + 0{\cdot}618 \quad r = 0{\cdot}996,\ n = 13 \quad (8)$$

π'_y can also be calculated from the solubility data of the reference compound and the medium effects parameters P_{y_1} and P_{y_2}. Thus, introducing equations 7_1 and 7_2 into 2_1 and 2_2 respectively and combining with equation 5, π'_y for a given ΔLV may be calculated by the following relationship

$$\pi'_y = \pi'_{y_1} + \pi'_{y_2} = P_{y_1}(\log MSC_x - LV_1) - (\log MSC_x - LV_1) + P_{y_2}(\log MSC_x - LV_2) - (\log MSC_x - LV_2) \quad (9)$$

The additive-constitutive character of π_y (and hence of π'_y) has been already pointed out, it is here shown that it is linearly related to LV. Because of these

properties π_y' itself may be regarded as a fundamental lipophilic variable (FLV) useful to quantitatively characterize the lipophilic ability of a wide spectrum of solvents. The definition of π_y' as a FLV extends the original concept of the lipophilic parameter.

CONCLUSIONS

A better understanding of medium effects on solubility is an important subject in many areas of pharmaceutical sciences. The present LFER treatment appears to be successful with the solute series reported here. However, further systematic work is necessary to understand the real scope of this approach.

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