Linear Solvation Energy Relationships. Local Empirical Rules – or Fundamental Laws of Chemistry? A Reply to the Chemometricians

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Sjöström and Wold have suggested that, rather than being considered as combinations of fundamental effects, linear free energy relationships (LFERs) and linear solvation energy relationships (LSERs) should be regarded as local empirical models of similarity or locally valid linearizations of complicated relationships. In reply to the chemometricians, it is shown that hundreds of physicochemical properties and reactivity parameters of many diverse types are described by equations of the following forms: For solubility properties of multiple solutes in single solvents, or distribution between pairs of solvents,

$$XYZ = XYZ_0 + m\hat{V}_2/100 + s\pi^*=a(a_m)+b(b_m)$$

and for effects of multiple solvents on single indicators or combinations of reactants,

$$XYZ = XYZ_0 + h(\delta_H^2)+s\pi^*+a\alpha+b\beta,$$

where $$\hat{V}$$ is the solute molar volume, $$\delta_H$$ is the solvent Hildebrand solubility parameter, and $$\pi^*$$, $$\alpha$$, and $$\beta$$ are the solvatochromic parameters that scale solute and solvent dipolarity/polarizability, hydrogen bond donor acidity, and hydrogen bond acceptor basicity. Evidence is offered that, if the chemometricians are correct, the term local must be stretched to include every area in chemistry and many in biology, where physicochemical, biological, toxicological, and pharmacological properties depend on interactions between solutes and solvents.

In a paper in This Journal,2 whose title, “Linear Free Energy Relationships. Local Empirical Rules – Or Fundamental Laws of Chemistry?”, differs from the title of the present paper only in that the word Free replaces the word Solvation, Sjöström and Wold posed a set of questions and suggested a set of answers which are summarized in the following abstract, taken directly from their paper.

“Two fundamentally different interpretations of linear free energy relationships (LFERs) and the causes of the breakdowns of one term LFERs to more complex ones have been forwarded: (a) The classical interpretation of LFERs expressing combinations of “fundamental” effects, or (b) an interpretation where LFERs are looked at as empirical models of similarity.”
"In this review we argue against the classical interpretation (a). Instead we provide support for the second alternative (b) where LFERs are seen as locally valid linearizations of complicated relationships. The major argument is that the latter interpretation is scientifically preferable since it results in better predictions of new data from experimental facts. This is illustrated with data from organic reactivity and solvent effect studies."

Among the properties represented by Sjöström and Wold as *locally valid linearizations* were solvent effects on UV/visible spectra of some nitroaniline derivatives, which the authors of the present paper had unravelled, correlated and rationalized in terms of the *solvatochromic parameters*, $\pi^*$, $\alpha$, and $\beta$. The conclusion intended to be drawn from Sjöström and Wold's analysis was that all solvent dependent properties, similarly correlated by our *solvatochromic comparison method*, should similarly be regarded, not as analyses of solute/solvent interactions in terms of fundamental physicochemical properties of both the solutes and the solvents, as intended by the present authors, but rather as no more than *locally valid linearizations*. In the present paper we shall offer evidence that, if Sjöström and Wold are correct, the term *locally* must be stretched to include every area of chemistry, and many of biology, where physicochemical, biological, pharmacological, and toxicological properties depend on interactions between solutes and solvents.

The solute and solvent properties, *solvatochromic parameters*, that have been used in these correlations are as follows: $\pi^*$, $\alpha$, $\beta$, $\delta$, $\delta_H^2$, $\omega$, $\omega_m$, $\beta_m$, $\delta_H$. A measure of solute or solvent dipolarity/polarizability. For "select solvents", nonprotonic aliphatic solvents with a single dominant bond dipole, $\pi^*$ values are proportional to molecule dipole moments. $\delta$, A "polarizability correction term". $\alpha$, A scale of hydrogen bond donor (HBD) acidities; applies to self-associating compounds when they are acting as solvents. $\beta$, A scale of hydrogen bond acceptor (HBA) basicities; applies to self-associating compounds when they are acting as solvents. $\omega$, An amphiprotic hydrogen bonding parameter, used for amphiprotic compounds in aqueous solution in place of $\beta$. For unsubstituted alkanols, $\omega = \beta_m$. $\delta_H$, The Hildebrand solubility parameter; $\delta_H^2$ measures the solvent's contribution to the cavity term. $\tilde{V}$, The solute molar volume, usually taken as the molecular weight divided by the liquid density at 25 °C. $\tilde{V}$ measures the solute's contribution to the cavity term. We use $\tilde{V}_{100}$ so that the cavity parameter should cover roughly the same range as the dipolarity/polarizability and hydrogen bonding parameters, which makes easier the evaluation of the contributions of the

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$\pi^*$, $\alpha$(1)

$\pi^*$, $\alpha$(1)

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* Series titles are: SCM, Solvatochromic Comparison Method; LSER, Linear Solvation Energy Relationships; SPPBM, Solubility Properties in Polymers and Biological Media.
three types of effects to the solubility property studied.

$\xi$, A coordinate covalency parameter used to correlate some basicity-dependent properties; $\xi$ reconciles the $\beta$ scale with the $pK_a$ scale.

We shall show that a large number of solubility and solvent dependent properties, $XYZ$, depend on three types of terms, eqn. (1), where a cavity term measures the free

$$XYZ = XYZ_0 + \text{cavity term} + \text{dipolar term} + \text{hydrogen bonding term}$$  \hspace{1cm} (1)

energy or enthalpy input required to separate the solvent molecules to create a suitably sized cavity for the solute; a dipolar term measures the exoergic effects of solute/solvent dipole-dipole, dipole-induced dipole, and mutually induced dipole interactions; and a hydrogen bonding term measures the exoergic effects of hydrogen bonding (or Lewis acid/base) complexation between the solute and the solvent. Using the convention that subscript 1 applies to the solvent and subscript 2 to the solute, eqn (1) with solvatochromic parameters appropriately included becomes:

$$XYZ = XYZ_0 + A(\delta_H^2) V_2/100 + B \pi^* + C a_1(\beta_m)_2 + D \beta_1(a_m)_2$$  \hspace{1cm} (2)

Eqn. (2) applies to biological media, such as blood and brain homogenate, and to polymer solvents, as well as to pure liquid solvents.

When effects of multiple solvents on a single solute or set of reactants are involved, correlations are expressed in terms of the solvatochromic parameters of the solvents, eqn. (3).

$$XYZ = XYZ_0 + h(\delta_H^2)_1 + s \pi^* + a a_1 + b \beta_1$$  \hspace{1cm} (3)

Conversely, when solubility properties of multiple solutes in single solvents, or distributions between pairs of solvents are involved, correlations are expressed in terms of the solvatochromic parameters of the solutes, eqn. (4)

$$XYZ = XYZ_0 + m V_2/100 + s \pi^* + b \beta(\text{or } \beta_m \text{ or } \omega)_2 + a a(\text{or } a_m)_2$$  \hspace{1cm} (4)

Where aromatic and aliphatic solutes or solvents are included in the same correlation, the $\delta$ parameter often needs to be used in conjunction with $\pi^*$. For certain types of “family dependent” basicity properties, the $\xi$ parameter needs to be used in conjunction with $\beta$.

In practice, most of the linear solvation energy relationships have been simpler than indicated by eqn. (3) and (4), because one or more of the terms have not been appropriate. Thus, if the $XYZ$ does not involve creation of a cavity or a change in cavity volume between states, the term in $(\delta_H^2)_1$ drops out of eqn. (3) and that in $V_2/100$ drops out of eqn. (4). If only non-HBD solvents are considered, the term in $a_1$ drops out of eqn. (3) and that in $\beta_2$ out of eqn. (4). Conversely, if solutes are not hydrogen bond donors or Lewis acids, the term in $\beta_1$ drops out of eqn. (3) and that in $a_2$ out of eqn. (4). As a result, most reported correlations have involved three or fewer terms.

Properties Correlated. At the time of the present writing, there are published, in the press, or in preparation, three series of papers involving correlations by eqn. (3) and (4):

(a) The Solvatochromic Comparison Method (SCM), Parts 1–9; (b) Linear Solvation Energy Relationships (LSER), Parts 1–32; and (c) Solubility Properties in Polymers and

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Biological Media (SPPBM), Parts 1–6. Representative among the properties we have correlated are the following, which are given together with the usual measures of statistical goodness of fit. The sample from among the many properties reported (vide infra) is intended to illustrate the scope and diversity of the correlations.

(a) **Molar solubilities in water**, \( S_w \), and the very nearly equivalent quantity, \( S_g/K_{gw} \), of 93 liquid aliphatic non-HBD and weak HBD solutes,\(^8\) where \( S_g \) is the molar concentration in the saturated vapor at 25 °C \( (S_g = P_{atm}/24.5) \), and \( K_{gw} \) is the gas/water partition coefficient of the solute at 25 °C, eqn. (5).

\[
\log S_w = \log \left( \frac{S_g}{K_{gw}} \right) = 0.55 - 3.36 \bar{Y}_2/100 + 0.46 \pi^* + 5.23 \beta_2
\]
\( n = 93, \ r = 0.9944, \ sd = 0.144 \) \hspace{1cm} (5)

(b) **Molar solubilities in blood**, \( S_b \), of 23 non-HBD aliphatic and aromatic solutes,\(^9\) where \( S_b \) is determined from \( S_g/K_{gb} \), the experimental property measured being \( K_{gb} \), the gas/blood partition coefficient. The correlation is given by eqn. (6).

\[
\log S_b = \log \left( \frac{S_g}{K_{gb}} \right) = 0.81 - 2.61 \bar{Y}_2/100 - 0.13 \pi^* + 3.18 \beta_2
\]
\( n = 25, \ r = 0.978, \ sd = 0.16 \) \hspace{1cm} (6)

We have suggested that equations of similar form for solubilities in lipid and tissue homogenates can serve toward improved predictions and understanding of blood/lipid, blood/tissue, tissue/lipid, and tissue/tissue distributions of pharmacologically and toxicologically active solid and liquid solutes and, indeed, **potentially total equilibrium distributions throughout the body**.\(^9\)

(c) **Free Energies of transfer between solvents of tetrathlammonium chloride** dissociated ions, \( \Delta G_i^0 \). Unlike the previous examples, the correlation is given in terms of solvent properties, eqn. (7).\(^10\)

\[
\Delta G_i^0 = 36.31 + 0.0682(\bar{\delta}_H^2)_{1} - 45.3 \pi^* - 24.1 a_1 \text{ kcal/mol}
\]
\( n = 18, \ r = 0.996, \ sd = 0.6 \text{ kcal/mol} \) \hspace{1cm} (7)

(d) **UV/visible spectra of 3,5-dinitroaniline**.\(^11\) Solvent effects on \( \nu_{\max} \) are given by eqn. (8).

\[
\nu_{\max} = 27.57 - 1.357 \pi^* - 2.815 \beta_1 (\times 10^3 \text{ cm}^{-1})
\]
\( n = 32, \ r = 0.996, \ sd = 0.10 \times 10^3 \text{ cm}^{-1} \) \hspace{1cm} (8)

(e) **tert-Butyl chloride solvolysis/heterolysis rates** in 23 non-HBD and HBD solvents are well correlated by eqn. (9). The statistically significant term in \( (\bar{\delta}_H^2)_{1} \) is a consequence of the fact that there are negative volumes of activation ranging from –2 to –40 cc/mol for this reaction, depending on the solvent.

\[
\log k(\text{Bu'Cl}) = -15.25 + 0.0039(\bar{\delta}_H^2)_{1} + 6.03 \pi^* + 4.23 a_1 + 1.01 \beta_1
\]
\( n = 23, \ r = 0.9952, \ sd = 0.36 \) \hspace{1cm} (9)

We will report the details of these interesting new findings in a soon to be forthcoming paper.

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(f) $^{15}$N NMR shifts of 1-methyilsilatrane. $^{12}$ Solvent effects are well correlated by eqn. (10). The correlation equation differs slightly from that reported earlier because of minor changes in the solvatochromic parameters.

$$^{15}\text{N NMR } \delta = 0.04 + 8.0(\pi^* - 0.20\delta) + 2.9\beta_1 \text{ ppm}$$
$$n=16, \ r=0.9906, \ sd=0.42 \text{ ppm.}$$

(g) Adsorption coefficients on Pittsburgh CAL activated carbon, $\bar{a}=\lim_{C\to 0} X/C$, where $X$ is the amount adsorbed on carbon (mg/g) and $C$ is the equilibrium concentration of the solute in aqueous solution; $\bar{a}$ represents the infinite dilution partition coefficient between the adsorbed and solution phases.$^{13}$ The correlation is given by eqn. (11).

$$\log \bar{a} = -1.93 + 3.06\bar{V}/100 + 0.56\pi^* - 3.20\beta_2$$
$$n=37, \ r=0.974, \ sd=0.19$$

(h) Formation constants of “hydrogen bonded” complexes of 4-bromoaniline with a series of HBA bases are well correlated in terms of the $\pi^*$ and $\beta$ values of the bases,$^{14}$ eqn. (12). The solvent is CCl$_4$. The major dependence on $\pi^*$ is a consequence of the fact that there are important contributions of dipole/dipole interactions to the formation constants of these “hydrogen bonded” complexes.

$$\log K_f = 1.17 + 1.23\pi^* + 0.72\beta_2$$
$$n=8, \ r=0.986, \ sd=0.06$$

(i) Inhibition of bioluminescence of Photobacterium Phosphorem in response to toxicants, the basis for the Beckmann “Microtox” test, which is widely used to screen potential industrial pollutants.$^{15}$ The property correlated is the 5 minute bacterial EC$_{50}$ (the concentration causing 50% inhibition of bioluminescence), expressed in mol/l, eqn. (13). Again, as with most of the correlations described here, the standard deviation of the correlation compares favourably with the precision of the experimental measurements.

$$\log \text{EC}_{50} = 7.27 - 4.27\bar{V}/100 - 2.10\pi^* + 5.54\beta_2 - 1.62(a_m)$$
$$n=36, \ r=0.990, \ sd=0.25.$$  

(k) HPLC capacity factors, $k'$, on an octadecylsilane column, with a mobile phase comprising 55/45-methanol/aqueous phosphate buffer.$^{15}$ The correlation is given by eqn. (14).

$$\log k' = -0.24 + 1.52\bar{V}/100 - 0.59\pi^* - 1.95\beta_2$$
$$n=28, \ r=0.991, \ sd=0.07.$$
comprises a list of not yet but (hopefully) soon to be published correlations, and Table 3 gives a cross-section of correlations by eqn. (3) and (4) that have been published by other workers.

It can seen that the XYZ properties in eqn. (3) and (4) have included: (a) positions and intensities of maximal absorption in IR, ESR, NMR, and UV/visible absorption and fluorescence spectra and NMR coupling constants; (b) formation constants and enthalpies of formation of hydrogen bonded complexes; (c) pKₐ; (d) solubilities of various type solutes in chemical solvents and biological tissues and fluids; free energies of solution and of transfer between solvents; (e) logarithms of reaction rate constants, equilibrium constants, and fluorescence lifetimes; (f) toxicity and narcosis effects on a variety of aquatic organisms, bacteria, and fungi; (g) HPLC and GLC capacity factors and retention indexes; (h) adsorption properties on various type adsorbants; etc.

Indeed, we are hard pressed to find a property which is governed by a solute/solvent interaction, and which has not been or can not be correlated, rationalized, and predicted using the present type of methodology if only the solvatochromic parameters are known or can be estimated, and on this basis we address again the question first posed by Sjöström and Wold.

Local empirical rules or fundamental laws of chemistry? In addition to the above correlations, at least five groups of workers¹⁶-²⁴ have related the π* scale and the δ “correction factor” to more fundamental dipolarity and polarizability properties of the solutes and solvents, expressed in terms of functions of the refractive index and the dielectric constant or dipole moment. In addition, we have related the β scale,⁵ and expect soon to relate the α scale to pKₐ, and the ζ parameter has been shown to follow the ordering of relative electronegativities of the hydrogen bond acceptor atoms.⁵

On the basis of the above, in view of the fact that for non-self-associating compounds the solvatochromic parameters serve equally well to correlate properties of both solutes and solvents, and in the light of the number and diversity of the properties correlated by eqn. (3) and (4), we feel that we can safely address the following reply to the Umeå chemometricians. If our linear solvation energy relationships are “local empirical rules” or “locally valid linearizations”, then the term “local” must encompass the very large neighborhood that includes a major proportion of the properties in chemistry and biology that depend on solute/solvent interactions.

Indeed, it is not unfair to challenge Sjöström and Wold to support their assessment of linear free and linear solvation energy relationships (which we consider as facile as it is unwarranted) by citing some types of physicochemical properties or reactivity parameters that are outside of this neighborhood.* If the LSERs and LFERs are, indeed, no more than “empirical models of similarity”, then the chemometricians would perform a very real service to the physical organic chemists by informing them of what criteria would need to be met by our equations to escape this pejorative assessment. Is semiempirical or (dare we say it) fundamental beyond our grasp? The ball, now, chemometricians, is in your court. We encourage the group at Umeå and other chemometricians to join with us in a spirited dialogue on this subject. A controversy that generates sufficient heat can sometimes also shed some light. (We are grateful that the referees and editor have allowed the preceding

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* Understanding, of course, that the solvatochromic equations are not intended to be used mindlessly, but rather that one should take into account such additional effects as may be operative for the specific XYZ studied, such as solvent viscosity in fluorescence relaxation processes, as demonstrated by Kuper and Abraham.²⁵

paragraph to pass unscathed. There was great pleasure in writing it.)

Is the goal improved predictions or improved understandings? We wish also to take issue with Sjöström and Wold’s statement that their interpretation is “scientifically preferable since it results in better predictions of new experimental facts”. If the chemometricians believe that improved predictions are the main purpose of LFERs and LSERs, they fail to understand either the purpose or the main utility of such correlations, which are in improved understandings of the underlying phenomenology. If one compares their contributions to better understandings, the substituent parameters in LFERs and the solvatochromic parameters in LSERs convey far more information that Sjöström and Wold’s first, second, third, fourth, and nth principal components. Thus, \( s^* \) stands for solvent polarity, \( mV \) for molar volume, \( a \) for hydrogen bond acidity, \( b \) for hydrogen bond basicity; by way of contrast \( \theta_1 \), \( \theta_2 \), \( \theta_3 \), and \( \theta_4 \) bring no physical property to mind.

Thus, also, from eqn. (5) we learn that the major factors influencing solubilities of organic nonelectrolytes in water are the opposing endoergic influence of solute molar volume and the exoergic influence of solute HBA basicity, with solute dipolarity/ polarizability playing only a secondary exoergic role. Given a solute whose solvatochromic parameters are not known, e.g., diethylpropionamide, we can estimate from a general knowledge of chemistry and from related compounds that \( \bar{V}/100 = 1.394 \), \( \pi^* = 0.80 \), \( \beta = 0.78 \); hence, \( \log S_w = 0.37 \). This amounts to \( \Delta G = -0.5 \) kcal/mol, which can be broken down into a cavity term of \( +6.4 \) kcal/mol, a hydrogen bonding term of \( -5.6 \) kcal/mol, a dipolarity term of \( -0.5 \) kcal/mol, and an intercept of \( -0.75 \) kcal/mol. * It is not immediately evident to us how one might arrive at so straightforward and understandable a prediction using Sjöström and Wold’s principal components.

As another example, in comparing solubilities in water and blood, we conclude that, since the nonaqueous components of blood have lower Hildebrand solubility parameters than water, the dependence on \( \bar{V}/100 \) is smaller in eqn. (6) than in eqn. (5). Since \( a \) of water is greater than \( a \) of the nonaqueous components of blood, the dependence on \( b \) is smaller in eqn. (6) than in eqn. (5). Thus, we relate coefficients of solvatochromic parameters of the solutes to the complementary solvatochromic parameters of the solvents. This hardly seems possible with \( \theta_1 \), \( \theta_2 \), etc.

A further example which has very recently come to our attention does not even involve the condensed phase, but rather extends the term local to include ion-molecule reactions in the gas phase. Sunner and Kebarle have reported free energies and enthalpies for the gas phase equilibria; \( K^+ + L \rightleftharpoons K^+(L) \). We have found that for the aliphatic ligands, Me₂SO, DMA, DMF, Me₂CO, MeCN, Et₂O, Me₂N, n-PrNH₂ and H₂O,** their data are well correlated by eqn. (15) and (16). These equations tell us that charge/

\[
\Delta G = (4.5 \pm 1.2) + (12.6 \pm 1.2) \pi^* + (10.7 \pm 2.0) \beta \text{ kcal/mol}
\]

\( n = 9, r = 0.983, sd = 1.1 \text{ kcal/mol} \)  

\[
\Delta H = (9.0 \pm 1.5) + (13.4 \pm 1.5) \pi^* + (14.9 \pm 2.4) \beta \text{ Kcal/mol}
\]

\( n = 9, r = 0.981, sd = 1.3 \text{ kcal/mol} \)

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* We shall show in a future paper that, in a more detailed analysis, one must take into account a term which involves the process of separating the single solute molecule from the bulk liquid solute. This term is partially included in the intercept, and partially in the cavity and dipolarity dependences.

** Aromatics are excluded to exclude variable polarizability effects. We use a "monomer" \( \pi^* \) value of 0.45 for water.

dipole interactions contribute as much to the formation free energies and enthalpies as do the Lewis acid/base interactions which involve the sharing by potassium ion of the ligand lone electron pair.

Hundreds of such examples abound among the correlations assembled in Tables 1-3. These were published, not because they led to improved predictability, but because they led to improved understanding. Further, these examples go against the core of the Wold-Sjöström reasoning, which is that they are "locally valid linearizations of complicated relationships". Rather than being complicated, they show by way of contrast that, if multiple effects are correctly unravelled, the more we learn about solute/solvent interactions, the simpler to understand become the relationships. Simple additivity of free energy of enthalpy-dependent terms seems usually to explain interactions in a highly satisfactory manner.

In conclusion, we wish to point out that the information in Tables 1-3 can serve some further purposes beyond that of supporting our rebuttal of Sjöström and Wold. First, to workers newly involved with LSER's, they can serve as convenient guides to a data base which can be used for both example and comparison. (How, for example do the dependences on solvent $\pi^*$ and $\alpha$ values compare for nucleophilic substitution reactions of charged and uncharged nucleophiles?). Second, to the toxicology-pharmacology community they demonstrate that there is nothing particularly different or unusual about interactions of chemical solutes with biological solvents. The same solute parameters that govern solubility in water also govern solubility in blood. The same parameters that correlate UV/visible, IR, NMR, and ESR spectra can also determine the minimum toxic dose for Madison 517 fungus (Table 1, No. 375) or LC50 for the fathead minnow (Table 1, No. 374). HPLC and GLC retention indexes can probably be used to estimate parameters that determine effectiveness of candidate pharmaceuticals. Finally, they show that, when all solute/solvent interactions are properly accounted for, the entire data base, involving thousands of measurements, fits into a comprehensive, mutually supporting framework of properties and interactions which, taken together, describe and define the field of linear solvation energy relationships.

REFERENCES

1. Part 35 in the Linear Solvation Energy Relationship series.


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