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

MORTIMER J. KAMLET and ROBERT W. TAFT

Naval Surface Weapons Center, White Oak Laboratory, Silver Spring, Maryland, 20910, U.S.A. and Department of Chemistry, University of California, Irvine, California 92717, U.S.A.

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,

$$XYZ = XYZ_0 + m\bar{V}_2/100 + s\pi^*_2 + a(\alpha_m)_2 + b(\beta_m)_2,$$

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

$$XYZ = XYZ_0 + h(\delta_H^2)_1 + s\pi^*_1 + a\alpha_1 + b\beta_1,$$

where $\bar{V}$ is the solute molar volume, δ_H is the solvent Hildebrand solubility parameter, and π^*, α, and β 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, π^*, α, and β.*[3-5] 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 solvatochromic parameters and equations. We now estimate, and will attempt to demonstrate in the present paper that, given a physicochemical, biological or toxicological property that is governed by a solute/solvent interaction, and given measured or estimated *solvatochromic parameters* of the solutes or solvents involved, there is a better than 80 % (possibly 90 %) likelihood that equations can be derived which will allow predictions of this property for new solutes or solvents. Further, more often than not, the precision of the prediction should be as good as or better than the usual precision of the experimental measurement (this is particularly true of toxicological properties). Further still, in marked contrast to the types of correlations suggested by Sjöström and Wold, the correlation equations will often contribute to detailed and quantitative *understandings* of the molecular interactions involved in the property studied.

The solute and solvent properties, *solvatochromic parameters,* that have been used in these correlations are as follows:[3-5]

π^*, A measure of solute or solvent dipolarity/polarizability. For "select solvents", nonprotonic aliphatic solvents with a single dominant bond dipole, π^* values are proportional to molecule dipole moments.[6]

δ, A "polarizability correction term".[7]

α, A scale of hydrogen bond donor (HBD) acidities; applies to self-associating compounds when they are acting as solvents.

α_m, Applies to self-associating compounds when they are acting as "monomer" solutes.

β, A scale of hydrogen bond acceptor (HBA) basicities; applies to self-associating compounds when they are acting as solvents.

β_m, Applies to self-associating compounds when acting as "monomer" solutes.

ω, An amphiprotic hydrogen bonding parameter, used for amphiprotic compounds in aqueous solution in place of β. For unsubstituted alkanols, $\omega \approx \beta_m$.

δ_H, The Hildebrand solubility parameter; δ_H^2 measures the solvent's contribution to the cavity term.

$\bar{V}$, The solute molar volume, usually taken as the molecular weight divided by the liquid density at 25 °C. $\bar{V}$ measures the solute's contribition to the cavity term. We use $\bar{V}/100$ 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

Table 1. Properties correlated with the solvatochromic parameters.

No.	Series,[a] Paper No.	Property correlated	Solvent (1) or solute (2) parameters	Ref.
1–2	SCM-1	UV/vis $\Delta\Delta\nu$, 4-nitrophenol, 4-nitroaniline	$\beta(1)$	27
3–4	SCM-1	log formation constants, phenol, 4-fluorophenol complexes with HBA bases	$\beta(2)$	
5	SCM-1	^{19}F NMR shifts, 4-fluorophenol	$\beta(2)$	
6–8	SCM-2	UV/vis, Brooker's merocyanine, Dimroth's betaine, $Fe(LL_2)(CN_2)$	$\alpha(1)$	28
9	SCM-2	Brownstein's S parameter, based on Kosower's Z	$\alpha(1)$	
10	SCM-2	Free energy of transfer between solvents, $Et_4N^+I^-$	$\alpha(1)$	
11	SCM-2	log k, t-butyl chloride solvolysis	$\alpha(1)$	
12–14	SCM-3	UV/vis, three 2-nitroaniline derivatives	$\beta(1)$	29
15–17	SCM-4	UV/vis, three N-alkyl-4-nitroaniline derivatives	$\beta(1)$	30
18–62	SCM-6	UV/vis, $p\to\pi^*$ and $\pi\to\pi^*$ transitions of 47 mainly nitroaromatic indicators	$\pi^*(1)$	31
	SCM-7	Solvent properly scales. Correlations involve *select solvents*	$\pi^*(1)$	6
63	SCM-7	Dipole moments	$\pi^*(1)$	
64	SCM-7	Brooker's χ_R, based on merocyanine UV/vis	$\pi^*(1)$	
65	SCM-7	Dimroth and Reinhardt's $E_T(30)$, based on betaine UV/vis	$\pi^*(1)$	
66	SCM-7	Lassau and Junger's log $k(Pr_3N+MeI)$	$\pi^*(1)$	
67	SCM-7	Walther's E_K, based on UV/vis of molybdenum tetracarbonyl complex	$\pi^*(1)$	
68	SCM-7	Knauer and Napier's A_N, based on notroxide ESR	$\pi^*(1)$	
69	SCM-7	Allerhand and Schleyer's G, based on IR	$\pi^*(1)$	
70	SCM-7	Taft's P, based on ^{19}F NMR	$\pi^*(1)$	
71	SCM-7	Brownstein's S, based on Kosower's Z	$\pi^*(1)$	
72–78	SCM-8	^{13}C NMR shifts of various ring carbons in $C_6H_5CF_3$, $C_6H_5CF_5$, C_6H_5Cl	$\pi^*(1)$	32
79–93	SCM-9	The $\alpha(1)$ scale, 25 data sets: 17 ^{13}C NMR, 7 UV/visible, 1 ^{31}P NMR	$\pi^*(1)$ of alcohols	33
94–95	LSER-1	IR, n-propyl and isobutyl chloride C–Cl stretch	$\pi^*, \alpha(1)$	34
96–97	LSER-1	IR, two alkanediols, O–H stretch	$\pi^*(1)$	
98–100	LSER-1	IR, hydrogen bonded O–H stretch, MeOH-ether, MeOH dimer, phenol-ether	$\pi^*(1)$	
101–103	LSER-1	IR, S=O stretch, dimethyl sulfoxide, diphenyl sulfoxide, $SOCl_2$	$\pi^*(1)$	
104–105	LSER-1	IR, P–O stretch, $POCl_3$, $Me_2HP=O$	$\pi^*(1)$	
106–108	LSER-1	IR, N–O stretch, 3 nitrile esters	$\pi^*(1)$	
109–114	LSER-1	IR, C=O stretch, 4 ketones, 1 ester, 1 amide	$\pi^*(1)$	
115–119	LSER-2	UV/vis, five aniline derivatives	$\pi^*(1)$	11
120	LSER-3	UV/vis, isoquinolinium ylid	$\pi^*, \beta(1)$	35
121	LSER-3	UV/vis, N,N-dimethylthiobenzamide-S-oxide	$\pi^*, \alpha(1)$	
122	LSER-3	UV/vis, 4-cyanoformyl-1-methylpyridinium oximate	$\pi^*, \alpha(1)$	
123	LSER-3	UV/vis, α-(p-dimethylaminophenylimino)acetoacetanilide	$\pi^*, \alpha(1)$	
124	LSER-3	UV/vis, 5,5-dimethylpyrroline-1-oxide	$\pi^*, \alpha(1)$	

				Ref.
125–126	LSER-3	ESR nitrogen hyperfine splitting constants, two nitroxides	π^*, $\alpha(1)$	
127–129	LSER-3	log k, 2-thiophenesulfonyl chloride with three anilines	π^*, $\alpha(1)$	36
130	LSER-3	log k, benzylation of aniline	π^*, $\alpha(1)$	
131	LSER-3	Fluorescence lifetime, Rose Bengal dye	π^*, $\alpha(1)$	
132	LSER-3	UV/vis absorption intensity, N-salicylidenebutylamine	π^*, $\alpha(1)$	
133	LSER-3	Koppel and Palm's E parameter	π^*, $\alpha(1)$	
134–136	LSER-4	UV/vis, two betaines, one bis(cyano)iron(II) complex	π^*, $\alpha(1)$	
137	LSER-4	UV/vis, (n-Hex)$_4$N$^+$I$^-$/trinitrobenzene complex	π^*, $\alpha(1)$	
138	LSER-4	UV/vis, tropylium iodide charge transfer band	π^*, $\alpha(1)$	
139–140	LSER-4	log k, t-butyl chloride solvolysis, two temperatures	π^*, $\alpha(1)$	
141	LSER-4	log k, t-butyl-o-phenylthioperbenzoate thermal decomposition	π^*, $\alpha(1)$	
142	LSER-4	^{19}F NMR shifts, 4-fluoro-2-picoline	π^*, $\alpha(1)$	
143	LSER-4	Free energy of transfer between solvents of Et$_4$N$^+$I$^-$	π^*, $\alpha(1)$	
144	LSER-4	Gutmann's AN scale, based on ^{31}P NMR shifts of Et$_3$P–O	π^*, $\alpha(1)$	
145	LSER-4	Kosower's Z scale, based on UV/vis on 4-carbethoxypyridinium iodide	π^*, $\alpha(1)$	
146	LSER-5	IR, $\Delta\nu$(O–H, free minus H-bonded), phenol/HBA complex, CCl$_4$	$\beta(2)$	37
147	LSER-5	IR, $\Delta\nu$(O–H, free minus H-bonded), 4-fluoropenol, CCl$_4$	$\beta(2)$	37
148	LSER-5	IR, $\Delta\nu$(O–H, free minus H-bonded), MeOH, CCl$_4$	$\beta(2)$	38
149	LSER-5	IR $\Delta\nu$(OH, free minus H-bonded), MeOD, pure base solvent	$\beta(2)$	
150	LSER-6	Free energy of transfer between solvents, Et$_4$N$^+$I$^-$	π^*, $\delta(1)$	39
151	LSER-6	log k, n-Pr$_3$N+MeI	π^*, $\delta(1)$	
152	LSER-6	log k, t-butyl peroxyformate thermal decomposition	π^*, $\delta(1)$	
153	LSER-7	Gutmann's Acceptor Number, AN	π^*, $\alpha(1)$	
154	LSER-7	Gutmann's Donor Number, DN, based on ΔH_f of SbCl$_5$ complexes	$\beta(2)$	12
155	LSER-8	NMR shifts, ^{19}F, 5-fluoroindole/HBA complexes, CCl$_4$	π^*, $\beta(2)$	
156–159	LSER-8	NMR shifts, ^{1}H, fluorodinitromethane, t-butanol, phenol, thioacetamide	π^*, $\beta(1)$	
160–162	LSER-8	NMR shifts, ^{1}H and ^{13}C coupling constants of CHCl$_2$	π^*, $\beta(1)$	
163–165	LSER-8	^{119}Sn–C–^{XY} coupling constants of three polyalkyltin compounds	π^*, $\beta(1)$	
166	LSER-8	NMR shifts, ^{13}C, carbonyl carbon of acetone	π^*, $\alpha(1)$	
167	LSER-8	NMR shifts, ^{15}N, pyridine	π^*, $\alpha(1)$	
168–169	LSER-8	NMR shifts, ^{15}N, and ^{29}Si of 1-methylsilatrane	π^*, $\alpha(1)$	
170–174	LSER-9	Gas/liquid partition coefficients, toluene, MeNO$_2$, MeCOEt, dioxane and EtOH solutes	π^*, β, α, $\beta(1)$	40
175	LSER-10	UV/visible fluorescence spectra, 7-dimethylamino-4-methylcuomarin	π^*, $\alpha(1)$	41
176	LSER-10	UV/visible fluorescence spectra, 7-amino-4-methyl coumarin	π^*, α, $\beta(1)$	
177	LSER-10	UV/visible fluorescence spectra, potassium 2-(toluidino-6-naphthalenesulfonate	π^*, α, $\beta(1)$	
178–183	LSER-11	^{15}N NMR shifts, HCONHMe, HCONMe$_2$, CH$_3$CONMe$_2$, CH$_3$CONMe$_2$, HCONH$_2$, HCONHMe, (E)- and (Z)-HCONH–Bu–t	π^*, α, $\beta(1)$	42
184	LSER-12	UV/vis, Brooker's merocyanine	$\pi^*(1)$	7
185	LSER-12	UV/vis, Dimroth and Reichardt's betaine	π^*, $\delta(1)$	

No.	LSER	Description	Parameters	Ref.
186	LSER-12	^{19}F NMR shifts, 4-fluoronitrosobenzene	π^*, $\delta(1)$	43
187	LSER-12	ESR, di-t-butylnitroxide	π^*, $\delta(1)$	
188	LSER-12	IR, P–O stretch, dimethyl methylphosphonate	π^*, $\delta(1)$	
189	LSER-12	UV/vis fluorescence, N,N-dimethyl-4-(2,6-dichloro-1,3,5-triazinyl)anilane	π^*, $\delta(1)$	44
190	LSER-12	UV/vis absorption, same compound	$\pi^*(1)$	
191	LSER-13	Hildebrand solubility parameter, δ_H	$\pi^*(1)$	
192–206	LSER-13	Free energies of solution of 15 non-dipolar solutes	$\delta(1)$	45
207	LSER-14	IR, $\Delta\nu$(O–H), phenol/HBA complexes	$\beta(2)$	14
208	LSER-14	IR, $\Delta\nu$(C–I), cyanogen iodide/HBA complexes	$\beta(2)$	
209–210	LSER-14	Enthalpies and free energies of formation, I$_2$/HBA complexes	$\beta(2)$	
211	LSER-14	Enthalpies of formation, 4-fluorophenol complexes	$\beta(2)$	
212	LSER-14	^{19}F NMR shifts, 5-fluoroindole complexes	$\beta(2)$	
213–215	LSER-15	log k, t-BuCl, t-BuBr, t-BuI solvolyses	π^*, $\alpha(1)$	46
216	LSER-16	Formation constant, diphenylamine/HBA complex, CCl$_4$	π^*, $\beta(2)$	
217	LSER-16	Formation constant, 4-bromoaniline/HBA complex, CCl$_4$	μ, $\beta(2)$	
218	LSER-16	Formation constant, 5-fluoroindole/HBA complex, CCl$_4$	μ, $\beta(2)$	
219	LSER-16	Formation constant, CHCl$_3$/HBA	μ, $\beta(2)$	
220	LSER-16	Formation constant, trifluoroethanol/HBA	μ, $\beta(2)$	
221	LSER-16	Formation constant, tri-n-butylammonium ion/HBA complex in o-C$_6$H$_4$Cl$_2$	μ, $\beta(2)$	
222–225	LSER-17	ESR, α^H(COCH$_3$), α^H(3,5), α^H(2) and α^H(6) of 4-acetyl-1-methyldihydropyridyl	π^*, $\alpha(1)$	47
226–227	LSER-17	ESR, diphenyl and di-p-anisylnitroxide	π^*, $\alpha(1)$	
228–230	LSER-17	Enthalpies of transfer between solvents of three alkynes	π^*, $\beta(1)$	
231–232	LSER-17	UV/vis absorption and fluorescence spectra of a merocyanine	π^*, $\delta(1)$	
233–235	LSER-17	log k, DABCO with phenethyl chloride, bromide, and iodide	π^*, $\delta(1)$	
236	LSER-18	UV/vis, 4-nitrophenoxide ion	π^*, δ, $\alpha(1)$	
237–277	LSER-19	Free energies of solution and of transfer of 41 solutes ranging in size and dipolarity from H$_2$ to Me$_4$N$^+$Cl$^-$	π^*, $\delta_H(1)$	48
278–279	LSER-20	2-nitrophenol, N-methyl-2-nitroaniline	π^*, $\beta(1)$	49
280	LSER-21	π^* Parameter correlated with functions of the refractive index and bulk dielectric constant		
281	LSER-22	UV/vis, W(CO)$_4$(phenanthrene)	$\pi^*(1)$	50
282–283	LSER-22	NMR, ^{77}Se shifts of Me$_2$Se, and ^{125}Te shifts of Me$_2$Te	π^*, $\delta(1)$	51
284	LSER-23	ΔG_f(aq BH$^+$), which is linear with pK_a	β, $\xi(2)$	3
285	LSER-24	UV/vis, 4-aminobenzenethiyl free radical	π^*, δ, $\beta(1)$	52
286	LSER-25	log k, 4-aminobenzenethiyl with styrene	π^*, δ, $\beta(1)$	
287–302	LSER-27	UV/vis, fifteen 2- and 4-substituted aniline derivatives	π^*, $\beta(1)$	53
	LSER-27	Additional solvent property scales, *select solvents*, see also 63–71	$\pi^*(1)$	54
302	LSER-27	Snyder's P' scale of solvent chromatographic strength	$\pi^*(1)$	
303	LSER-27	Dong and Winnick's Py scale, from pyrene fluorescence	$\pi^*(1)$	
304	LSER-27	Swain's "Basity" scale, B	$\pi^*(1)$	

305	LSER-27	Gutmann's Acceptor Number scale, AN	$\pi^*(1)$	55
306	LSER-27	Schmid's log ε_B	$\pi^*(1)$	
307	LSER-27	Swain's "Acity", scale, A	$\pi^*,\ \alpha(1)$	56
308	LSER-28	Swain's "Basity", scale, B	$\pi^*(1)$	
309–315	LSER-29	Free energies of transfer between solvents of $R_4N^+I^-$, and Br^- ion pairs	$\pi^*,\ \alpha,\ \delta(1)$	5
316–321	LSER-29	Free energies of transfer between solvents of $R_4N^+X^-$ dissociated ions	$\pi^*,\ \alpha,\ \delta(1)$	
322–328	LSER-30	log k of seven S_N2 reactions of neutral and anionic nucleophiles	$\pi^*,\ \alpha(1)$	8
329–331	LSER-30	log k of reactions of CH_3I with Cl^-, Br^-, and I^-	$\alpha(1)$	
332	LSER-31	Solubilities of liquid aliphatic non-HBD solutes in water	$\bar{V},\ \pi^*,\ \beta(2)$	57
332a.	LSER-31	Solubilities of liquid aliphatic alcohols in water	$\bar{V},\ \pi^*,\ \beta_m(2)$	
333	LSER-32	$\Delta\nu$(O–H), phenol/HBA complex, CCl_4	$\beta,\ \xi(2)$	
334	LSER-32	ΔH_f, BF_3/HBA complex	$\beta,\ \xi(2)$	
335	LSER-32	pK_a	$\beta,\ \xi^*(2)$	
336	LSER-32	$\Delta\nu$(C–I), ICN complex	$\beta,\ \xi(2)$	
337	LSER-32	$\Delta\nu$(O–D), MeOD complex in pure base solvent	$\pi^*,\ \xi(1)$	
338–339	LSER-32	ΔH_f and ΔG_t of I_2/HBA complexes	$\pi^*,\ \xi(2)$	
340–343	LSER-32	ΔH_f of HBA complexes with phenol, 4-fluorophenol, n-BuOH, and CH_3CH_2OH	$\pi^*,\ \xi(2)$	
344	LSER-32	ΔH_f pf $4\text{-}F\text{-}C_6H_4SO_3^-BH_4^+$ ion pair	$\pi^*,\ \xi(2)$	
345	LSER-32	^{19}F NMR shift of above ion pair	$\pi^*,\ \xi(2)$	
346	LSER-33	Adsorption coefficient from aqueous on to activated carbon	$\bar{V},\ \pi,\ \beta(2)$	15
347	SPPBM-1	Critical temperatures	$R_G(2)$	58
348–352	SPPBM-1	Solubilities in brain, blood, plasma, muscle, and oil, non-dipolar solutes	$R_G(2)$	
353–357	SPPBM-2	Solubilities in oil, human fat, silicone rubber, rubber, olive oil	$R_G(2)$	
358	SPPBM-4	Octanol/water partition coefficients, aliphatic non-HBD solutes	$\bar{V},\ \pi^*,\ \delta,\ \beta(2)$	59
358a.	SPPBM-5	Above correlation expanded to include alcohol and aromatic solutes	$\bar{V},\ \pi^*,\ \delta,\ \beta(2)$	60
359	SPPBM-5	Cyclohexane/water partition coefficients of aliphatic non-HBD solutes	$\bar{V},\ \pi^*,\ \delta,\ \beta(2)$	61
360	SPPBM-6	Solubility of non-HBD solutes in blood	$\bar{V},\ \pi^*,\ \delta,\ \beta(2)$	
371	SPPBM-6	Et_2O/H_2O partition coefficients of aliphatic and aromatic HBA and HBD solutes	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	9
372	SPPBM-7	HPLC capacity factors of aromatic HBA and non-HBA solutes	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	62
373	SPPBM-7	QSAR, Inhibition of bioluminescence of *Photobacterium phosphorem* (the Beckmann Microtox test)	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	
374	SPPBM-7	QSAR, Toxicity to Fathead Minnow, *Pimephalas promilas*	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	
375	SPPBM-7	QSAR, Minimum toxic dose to the Madison 517 fungus	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	
376	SPPBM-7	QSAR, Tadpole Narcosis	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	
377	SPPBM-7	QSAR, Minimum blocking concentration to inhibit frog muscle activity	$\bar{V},\ \pi^*,\ \delta,\ \beta,\ \alpha_m(2)$	

three types of effects to the solubility property studied.

ξ, A coordinate covalency parameter used to correlate some basicity-dependent properties; ξ reconciles the β 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

$$XYZ = XYZ_o + \text{cavity term} + \text{dipolar term} + \text{hydrogen bonding term} \tag{1}$$

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:

$$XYZ = XYZ_o + A(\delta_H^2)_1 \bar{V}_2/100 + B\pi^*_1 \pi^*_2 + C\alpha_1(\beta_m)_2 + D\beta_1(\alpha_m)_2 \tag{2}$$

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).

$$XYZ = XYZ_o + h(\delta_H^2)_1 + s\pi^*_1 + a\alpha_1 + b\beta_1 \tag{3}$$

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)

$$XYZ = XYZ_o + m\bar{V}_2/100 + s\pi^*_2 + b\beta(\text{or } \beta_m \text{ or } \omega)_2 + a\alpha(\text{or } \alpha_m)_2 \tag{4}$$

Where aromatic and aliphatic solutes or solvents are included in the same correlation, the δ parameter often needs to be used in conjunction with π^*.[7] For certain types of "family dependent" basicity properties,[3,5] the ξ parameter needs to be used in conjunction with β.

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 $\bar{V}_2/100$ drops out of eqn. (4). If only non-HBD solvents are considered, the term in α_1 drops out of eqn. (3) and that in β_2 out of eqn. (4). Conversely, if solutes are not hydrogen bond donors or Lewis acids, the term in β_1 drops out of eqn. (3) and that in α_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*

Table 2. Properties correlated with the solvatochromic parameters, but not yet written up.

No.	Property correlated	Solvent (1) or solute (2) parameters
1–10	Solvent/water partition coefficients of 10 phenols	π^*, $\beta(1)$
11–18	Solvent/water partition coefficients of 8 carboxylic acids	π^*, $\beta(1)$
19–24	Solvent/water partition coefficients of 6 alkanols	π^*, $\beta(1)$
25–48	HPLC retention indexes of aromatic non-HBD solutes, 4 stationary and 6 mobile phases	$\bar{V}$, π^*, $\beta(2)$
49–53	GLC Kovats retention indexes of large numbers of solutes on five stationary phases	$\log P_{atm}$, π^*, δ, $\alpha_m(2)$
54	QSAR, Effects of solutes in chick embryo hatching	$\bar{V}$, π^*, β, $\alpha_m(2)$
55	QSAR, Precipitation nucleoprotein, liver, sheep, 40 °C	$\bar{V}$, π^*, β, $\alpha_m(2)$
56	QSAR, I_{100}, succinate oxidase, muscle, bovine, 40 °C	$\bar{V}$, π^*, β, $\alpha_m(2)$
47–85	$\log k$, 29 Menschutkin and other nucleophilic substitution rates	π^*, $\beta(1)$
86	$\log k$, t-butyl chloride solvolysis (including cavity term)	δ_H, π^*, α, $\beta(1)$
87	Solubilities of nondipolar and dipolar solutes in molten polystyrene	R_G, $\mu(2)$
88–92	Solubilities of nondipolar and weakly dipolar solutes in polydimethylisoxane, poly-*cis*-isoprene, alethon-14, ethyl cellulose, and polyethyl methacrylate	$R_G(2)$
93–95	Solubilities in non-HBD and HBD solvents, hydrocortisone, naphthalene, methyl p-hydroxybenzoate	δ_H, π^*, δ, $\beta(1)$

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).

$$\log S_w \simeq \log (S_g/K_{gw}) = 0.55 - 3.36\bar{V}_2/100 + 0.46\pi^*_2 + 5.23\beta_2 \tag{5}$$
$$n=93, \ r=0.9944, \ sd=0.144$$

(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).

$$\log S_b \simeq \log (S_g/K_{gb}) = 0.81 - 2.61\bar{V}_2/100 - 0.13\pi^*_2 + 3.18\beta_2 \tag{6}$$
$$n=25, \ r=0.978, \ sd=0.16$$

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 tetramethylammonium chloride* dissociated ions, ΔG_t°. Unlike the previous examples, the correlation is given in terms of *solvent* properties, eqn (7).[10]

$$\Delta G_t^\circ \text{ (from methanol)} = 36.31 + 0.0682(\delta_H^2)_1 - 45.3\pi^*_1 - 24.1\alpha_1 \text{ kcal/mol} \tag{7}$$
$$n=18, \ r=0.996, \ sd=0.6 \text{ kcal/mol}$$

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

$$\nu_{max} = 27.57 - 1.357\pi^*_1 - 2.815\beta_1 \ (\times 10^3 \text{ cm}^{-1}) \tag{8}$$
$$n=32, \ r=0.996, \ sd=0.10 \times 10^3 \text{ cm}^{-1}$$

(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 $(\delta_H^2)_1$ 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.

$$\log k(\text{Bu}^t\text{Cl}) = -15.25 + 0.0039(\delta_H^2)_1 + 6.03\pi^*_1 + 4.23\alpha_1 + 1.01\beta_1 \tag{9}$$
$$n=23, \ r=0.9952, \ sd=0.36.$$

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

Table 3. Physicochemical properties correlated with the solvatochromic parameters by other authors.

No.	Ref.	Properties correlated	Solvent (1) or solute (2) parameters
1	63	Fluorescence spectra of 5-(dimethylamino)-1-naphthalenesulfonamide derivative	π^*, α, β(1)
2–3	64	Integrated intensities of IR stretching modes of Et$_3$SiH and Et$_3$GeH complexes with HBA bases in heptane solution	β(2)
4	65	^{15}N NMR shifts of benzonitrile	π^*, α(1)
5,6	66	Formation constants of Br$_3^-$ and I$_3^-$ ions	π^*, α, β(1)
10–17	67	UV/visible spectra of 10 4-diethylaminoazobenzene derivatives.	π^*(1)
18	68	^{13}C NMR shifts of the carbonyl carbon of N,N-dimethylbenzamide	π^*, α(1)
19	69	Isomerization rates of cis-[Pt(PEt$_3$)$_2$(m-MeC$_6$H$_4$)Cl]	α(1)
20	70	Free energies of transfer between solvents of tetraphenylarsonium tetraphenylboride	π^*, α(1)
21–23	71	Reaction rates of S,S-dimethyl-, S-methyl-S-phenyl-, and S,S-diphenyl-N-tosylsulfilimine with benzenethiol	α(1)
24	72	UV/visible spectrum of phenol blue	π^*, α(1)
25–26	73	Tautomerism of some hydroxy and mercaptopyridines	π^*, α(1)
27–36	74	UV/visible spectra of 10 azobenzene derivatives.	$f(\varepsilon)$, α, β(1)
37	75	^{15}N NMR shifts of pyridine	π^*(1)
38–43	76	UV/vis absorption and fluorescence spectra of 3 coumarin dyes	π^*, δ, α(1)
44	77	Solvent effects on pK of 1-[2,4-dinitrophenyl)azo]-4-naphthol	π^*, β(1)
45	78	Association constants of alcohols with pyridine-N-oxide in c-C$_6$H$_{12}$	α(2)
46–52	79	Rates of seven nucleophilic substitution reactions of octahedral rhodium(III) complexes	π^*, α(1)
53	80	$E_{\frac{1}{2}}$ in electrode reaction of (tetraphenylporphorin)Ru(CO) complex	β(1)
54	81	Catalysis of n-butylaminolysis of a sultone in toluene solvent	π^*, pK$_{HB}$(2)
55–56	82	ESR of 1-methyl-4-acetopyridyl free radical; UV/vis of p-aminobenzenethiyl free radical	π^*, δ, α(1)
57	83	Syndiotacticity of N-vinylcarbazole polymer	π^*(1)
58–59	84	Tautomerism of 2-phenyl-1,3-indanedione; UV/vis of phenindione methyl ether	β(1)
60	85	Fourth derivative spectrum of AcTyrOEt (UV/vis)	π^*, α, β(1)
70–71	87	UV/of some styryl-merocyanines	π^*, α, β(1)
72–74	88	UV/vis of some M(CO$_4$)(diimine) derivs., M=Cr, Mo, W.	π^*(1)
75–77	89	UV/vis of some anthraquinone derivatives	π^*, α, β(1)
78–79	90	Tautomerism of t-butyl 2-picolyl and t-butyl quinaldyl ketones	π^*, δ, α(1)

80–84	91	Fluorescence spectra of four thiabendazole homologues	π^*, α, $\beta(1)$
85–92	92	UV/vis spectra of 8 additional aminoacridine derivatives	π^*, α, $\beta(1)$
93–94	93	cis–trans isomerization and UV/vis of 4-(diethylamino)-4'-nitroazobenzene	π^*, $\alpha(1)$
95–103	94	Nine absorption and fluorescence spectra of 1-aryl-4-(p-dimethyl-aminophenyl)-cycloheptatriene derivatives	π^*, $\alpha(1)$
104–111	95	Eight absorption and fluorescence spectra of miscellaneous indicators	π^*, $\alpha(1)$
112–117	96	Absorption and emission spectra of three aryl-1,2-diazapines	π^*, $\alpha(1)$
118	97	Redox reaction of bis(N,R-2,6-pyridinedicarboxaldimine)cobalt(II)	$\beta(1)$
119	98	Enthalpies of solution of 10 miscellaneous solutes	$\pi^*(1)$, $\pi^*(2)$
120	99	Solubility of 2-phenyl-1,3-indanedione	π^*, $\beta(1)$
121	100	Oxidative dimerization of styrene	$\pi^*(1)$
122	101	Reaction of anthracene/pyrene with ozone	π^*, $\delta(1)$
123–124	102	UV/visible spectra of three ruthenium(II) ammine complexes	$\beta(1)$
125	103	Transesterification of butyl chloroacetate by sec-butyl orthotitanate	π^*, δ_H, $E(1)$
126	104	UV/visible spectrum of [Mo(CO)$_4$(4,4'-Me$_2$-bpy)]	$\pi^*(1)$
127–129	105	Absorption and fluorescence spectrum and fluorescence quantum yield of triphenyl-1,3,4-oxadiazoline	$\pi^*(1)$
130–8	106	Absorption and fluorescence spectra and photophysical desactivation behavior of some dialkylaniline derivatives	π^*, $\alpha(1)$
139	107	Blue shifts of I$_2$ complexes with pyridine derivatives	$\beta(2)$
140–144	108	Multiple bands in the electronic spectra of 9-cyano- and 9-benzoyl-10-anthryloxy anion	π^*, α, $\beta(1)$
145–146	109	cis-trans-isomerism of 4'-nitro- and 4'-methoxy-4-diethylaminoazobenzene	π^*, $\delta(1)$
147	110	Formation constants of hydrogen bonded complexes with monomeric water	$\beta(1)$
148–154	111	^{13}C and ^{19}F NMR shifts of Cl$_2$FCH, Cl$_3$CH, CCl$_3$CCl$_2$H, and Cl$_2$=CHCl	$\beta(1)$
155	112	Reaction of benzyl chloride with triphenylphosphine	π^*, $\alpha(1)$
156–158	113	Fluorescence spectra of methyl 1-, 2-, and 9-anthroates	π^*, $\alpha(1)$
159	114	Reaction of 1-naphthalenesulfonyl chloride with pyridine	π^*, $\alpha(1)$

(f) *^{15}N NMR shifts of 1-methylsilatrane.*[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.

$$^{15}\text{N NMR } \delta = 0.04 + 8.0(\pi^*_1 - 0.20\delta) + 2.9\beta_1 \text{ ppm} \tag{10}$$
$$n = 16, \ r = 0.9906, \ sd = 0.42 \text{ ppm}.$$

(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).

$$\log \bar{a} = -1.93 + 3.06\bar{V}_2/100 + 0.56\pi^*_2 - 3.20\beta_2 \tag{11}$$
$$n = 37, \ r = 0.974, \ sd = 0.19$$

(h) *Formation constants of "hydrogen bonded" complexes of 4-bromoaniline* with a series of HBA bases are well correlated in terms of the π^* and β values of the bases,[14] eqn. (12). The solvent is CCl_4. The major dependence on π^* is a consequence of the fact that

$$\log K_f = 1.17 + 1.23\pi^*_2 + 0.72\beta_2 \tag{12}$$
$$n = 8, \ r = 0.986, \ sd = 0.06$$

there are important contributions of dipole/dipole interactions to the formation constants of these "hydrogen bonded" complexes.

(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/1, 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.

$$\log EC_{50} = 7.27 - 4.27\bar{V}_2/100 - 2.10\pi^*_2 + 5.54\beta_2 - 1.62(\alpha_m)_2 \tag{13}$$
$$n = 36, \ r = 0.990, \ sd = 0.25.$$

(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).

$$\log k' = -0.24 + 1.52\bar{V}_2/100 - 0.59\pi^*_2 - 1.95\beta_2 \tag{14}$$
$$n = 28, \ r = 0.991, \ sd = 0.07$$

In addition to the above ten rather diverse types of properties of solutes and solvents, we have assembled in Table 1 a list of the hundreds of additional correlations which we have published in the SCM, LSER, and SPPBM series of papers mentioned earlier. Table 2

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) pK_a; (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 funghi; (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 workers [16-24] 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, [3,5] and expect soon to relate the α scale to pK_a, and the ξ 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 *semi*empirical 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

---

* 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 Kupfer 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 n^{th} principal components. Thus, $s\pi^*$ stands for solvent polarity, $m\bar{V}$ for molar volume, α for hydrogen bond acidity, β for hydrogen bond basicity; by way of contrast θ_1, θ_2, θ_3, and θ_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 $\Delta G_s = -0.5$ 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 α of water is greater than α of the nonaqueous components of blood, the dependence on β 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 θ_1, θ_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[26] have reported free energies and enthalpies for the gas phase equilibria; $K^+ + L \rightleftarrows K^+(L)$. We have found that for the aliphatic ligands, Me_2SO, DMA, DMF, Me_2CO, MeCN, Et_2O, Me_3N, n-$PrNH_2$ and H_2O,** their data are well correlated by eqn. (15) and (16). These equations tell us that charge/

$$\Delta G = (4.5 \pm 1.2) + (12.6 \pm 1.2)\pi^* + (10.7 \pm 2.0)\beta \text{ kcal/mol} \tag{15}$$
$$n = 9, \ r = 0.983, \ sd = 1.1 \text{ kcal/mol}$$

$$\Delta H = (9.0 \pm 1.5) + (13.4 \pm 1.5)\pi^* + (14.9 \pm 2.4)\beta \text{ Kcal/mol} \tag{16}$$
$$n = 9, \ r = 0.981, \ sd = 1.3 \text{ kcal/mol}$$

---

* 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" π^* 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 π^* and α 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.
2. Sjöström, M. and Wold, S. *Acta Chem. Scand. B 35* (1981) 537.
3. Kamlet, M.J., Abboud, J.-L.M., Abraham, M.H. and Taft, R.W. *J. Org. Chem. 48* (1983) 2877.
4. Kamlet, M.J., Abboud, J.-L.M. and Taft, R.W. *Prog. Phys. Org. Chem. 13* (1981) 485.
5. Taft, R.W., Abboud, J.-L.M., Kamlet, M.J. and Abraham, M.H. *J. Solution Chem. 14* (1985) 153.
6. Abboud, J.-L.M., Kamlet, M.J. and Taft, R.W. *J. Am. Chem. Soc. 99* (1977) 8325.
7. Taft, R.W., Abboud, J.-L.M. and Kamlet, M.J. *J. Am. Chem. Soc. 103* (1981) 1080.
8. Taft, R.W., Abraham, M.H., Doherty, R.M. and Kamlet, M.J. *Nature 313* (1985) 384.
9. Kamlet, M.J., Doherty, R.M., Abraham, M.H. and Taft, R.W. *Science. Submitted.*
10. Taft, R.W., Abraham, M.H., Doherty, R.M. and Kamlet, M.J. *J. Am. Chem. Soc. 107* (1985) 3105.
11. Kamlet, M.J., Jones, M.E., Taft, R.W. and Abboud, J.-L.M. *J. Chem. Soc. Perkin Trans. 2* (1979) 342.
12. Taft, R.W. and Kamlet, M.J. *Org. Magn. Reson. 14* (1980) 485.
13. Kamlet, M.J., Doherty, R.M., Abraham, M.H. and Abboud, J.-L.M. *Carbon. Submitted.*

14. Kamlet, M.J., Dickinson, C., Gramstad, T. and Taft, R.W. *J. Org. Chem. 47* (1982) 4971.
15. Kamlet, M.J., Doherty, R.M., Abraham, M.H. and Taft, R.W. *Am. Chem. Soc. Submitted.*
16. Abboud, J.-L.M., Guiheneuf, G., Essfar, M., Taft, R.W. and Kamlet, M.J. *J. Phys. Chem. 88* (1984) 4414.
17. Bekarek, V. *J. Phys. Chem. 85* (1981) 722.
18. Bekarek, V. and Jurina, J. *Collect. Czech. Chem. Commun. 47* (1982) 1060.
19. Abboud, J.-L.M. and Taft, R.W. *J. Phys. Chem. 83* (1979) 412.
20. Ehrenson, S. *J. Am. Chem. Soc. 103* (1981) 6036.
21. Kolling, O.W. *Trans. Kans. Acad. Sci. 84* (1981) 32.
22. Brady, J.E. and Carr, P.W. *J. Phys. Chem. 86* (1982) 3053.
23. Brady, J.E. and Carr, P.W. *Anal. Chem. 54* (1982) 1751.
24. Abboud, J.-L.M., Taft, R.W. and Kamlet, M.J. *J. Chem. Soc. Perkin Trans. 2* (1985) 815.
25. Kupfer, M. and Abraham, W. *J. Prakt Chem. 325* (1983) 95.
26. Sunner, J. and Kebarle, P. *J. Am. Chem. Soc. 106* (1984) 6135.
27. Kamlet, M.J. and Taft, R.W. *J. Am. Chem. Soc. 98* (1976) 377.
28. Taft, R.W. and Kamlet, M.J. *J. Am. Chem. Soc. 98* (1976) 2886.
29. Yokoyama, T., Taft, R.W. and Kamlet, M.J. *J. Am. Chem. Soc. 98* (1976) 2886.
30. Kamlet, M.J., Kayser, E.G., Jones, M.E., Abboud, J.-L.M., Eastes, M.H. and Taft, R.W. *J. Phys. Chem. 82* (1978) 2477.
31. Kamlet, M.J., Abboud, J.-L.M. and Taft, R.W. *J. Am. Chem. Soc. 99* (1977) 6027.
32. Chawla, B., Pollack, S.K., Lebrilla, C.B., Kamlet, M.J. and Taft, R.W. *J. Am. Chem. Soc. 103* (1981) 6924.
33. Chawla, B., Fujio, M., Simanyi, L., Pollack, S.K., Fong, C.W., Grant, H.G., Kamlet, M.J. and Taft, R.W. *J. Am. Chem. Soc. To be published.*
34. Kamlet, M.J. and Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* (1979) 337.
35. Kamlet, M.J. and Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* (1979) 349.
36. Taft, R.W. and Kamlet, M.J. *J. Chem. Soc. Perkin Trans. 2* (1979) 1723.
37. Kamlet, M.J., Solomonovici, A. and Taft, R.W. *J. Am. Chem. Soc. 101* (1979) 3734.
38. Kamlet, M.J., Hall, T.N., Boykin, J. and Taft, R.W. *J. Org. Chem. 44* (1979) 2577.
39. Taft, R.W., Pienta, N.J., Kamlet, M.J. and Arnett, E.M. *J. Org. Chem. 46* (1981) 661.
40. Kamlet, M.J., Taft, R.W., Carr, P.W. and Abraham, M.H. *J. Chem. Soc. Faraday Trans. 1, 78* (1982) 1689.
41. Kamlet, M.J., Dickinson, C. and Taft, R.W. *Chem. Phys. Lett. 77* (1981) 69.
42. Kamlet, M.J., Dickinson, C. and Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* (1981) 353.
43. Kamlet, M.J., Carr, P.W., Taft, R.W. and Abraham, M.H. *J. Am. Chem. Soc. 103* (1981) 6062.
44. Taft, R.W., Gramstad, T. and Kamlet, M.J. *J. Org. Chem. 47* (1982) 4557.
45. Abraham, M.H., Taft, R.W. and Kamlet, M.J. *J. Org. Chem. 47* (1982) 4971.
46. Kamlet, M.J. and Taft, R.W. *Pol. J. Chem. 55* (1981) 1337.
47. Abboud, J.-L.M., Taft, R.W. and Kamlet, M.J. *Bull. Chem. Soc. Jpn. 55* (1982) 603.
48. Abraham, M.H., Kamlet, M.J. and Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* (1982) 923.
49. Kamlet, M.J. and Taft, R.W. *J. Org. Chem. 47* (1982) 1734.
50. Abboud, J.-L.M., Taft, R.W. and Kamlet, M.J. *J. Phys. Chem. 88* (1984) 4414.
51. Taft, R.W. and Kamlet, M.J. *Inorg. Chem. 22* (1983) 250.
52. Fong, C.W., Taft, R.W. and Kamlet, M.J. *J. Org. Chem. 48* (1983) 832.
53. Yokoyama, T., Taft, R.W. and Kamlet, M.J. *Aust. J. Chem. 36* (1983) 701.
54. Abboud, J.-L.M., Taft, R.W. and Kamlet, M.J. *J. Chem. Res.* (1984) 98.
55. Taft, R.W., Abboud, J.-L.M. and Kamlet, M.J. *J. Org. Chem. 49* (1984) 2001.
56. Taft, R.W., Abraham, M.H., Doherty, R.M. and Kamlet, M.J. *J. Am. Chem. Soc. 107* (1985) 3105.
57. Kamlet, M.J., Gal, J.F., Maria, P.C. and Taft, R.W. *J. Chem. Soc. Perkin Trans. 2. In press.*
58. Abraham, M.H., Kamlet, M.J., Taft, R.W. and Weathersby, P.K. *J. Am. Chem. Soc. 105* (1983) 6797.

59. Abraham, M.H., Kamlet, M.J., Taft, R.W., Doherty, R.M. and Weathersby, P.K. *J. Med. Chem. In press.*
60. Kamlet, M.J., Abraham, M.H., Doherty, R.M. and Taft, R.W. *J. Am. Chem. Soc. 106* (1984) 464.
61. Taft, R.W., Abraham, M.H., Famini, G.R., Doherty, R.M. and Kamlet, M.J. *J. Pharm. Sci. In press.*
62. Kamlet, M.J., Abraham, M.H. and Taft, R.W. *J. Am. Chem. Soc. Submitted.*
63. Shea, K.J., Okahata, Y. and Dougherty, T.K. *Macromolecules 17* (1984) 296.
64. Khorshev, S.Y., Tsvetkova, V.L. and Egorochkin, A.N. *J. Organomet. Chem. 264* (1984) 169.
65. Kolling, O. *Anal. Chem. 56* (1984) 430.
66. Bienvenue, E., Msika, R. and Dubois, J.-E. *J. Chim. Phys. Phys.-Chim. Biol. In press.*
67. Marcandalli, B., Bubini-Paglia, E. and Pelliciardi-Di Liddo, L. *Gazz. Chim. Ital. 111* (1981) 187.
68. Fong, C.W. and Grant, H.G. *Org. Magn. Reson. 14* (1980) 147.
69. Romeo, R., Minniti, D. and Lanza, S. *Inorg. Chem. 19* (1980) 3663.
70. Kolling, O. *Anal. Chem. 52* (1980) 987.
71. Dell'Erba, C., Guanti, G., Garbarino, G., Novi, M. and Poluzzi Corallo, G. *Tetrahedron 37* (1981) 795.
72. Kolling, O. *Anal. Chem. 53* (1981) 54.
73. Beak, P., Covington, J.B. and White, J.M. *J. Org. Chem. 45* (1980) 1347.
74. Mustroph, H. and Ebberlein, J. *J. Prakt.' Chem. 322* (1980) 305.
75. Kolling, O. *Anal. Chem. 51* (1979) 1324.
76. Jones, G., Jackson, W.R., Kanoktanaporn, S. and Halpern, A.M. *Optics Commun. 33* (1980) 315.
77. Abate, L., Longo, M.L., Maccarone, E. and Torre, M. *Gazz. Chim. Ital. 110* (1980) 527.
78. Frange, B., Abboud, J.-L.M., Benamou, C. and Bellon, L. *J. Org. Chem. 47* (1982) 4553.
79. Peloso, A. *J. Chem. Soc. Dalton Trans.* (1982) 2141.
80. Kadish, K.M. and Chang, D. *Inorg. Chem. 21* (1982) 3614.
81. Ciuffarin, E., Isola, M. and Leoni, P. *Tetrahedron Lett. 2* (1981) 2131.
82. Kolling, O. *Anal. Chem. 55* (1983) 143.
83. Terrell, D.R. and Evers, F. *J. Polym. Sci. 20* (1982) 2529.
84. Pipkin, J.D. and Stella, V.J. *J. Am. Chem. Soc. 104* (1982) 6672.
85. Padros, E., Morros, A., Manosa, J. and Dunach, M. *Eur. J. Biochem. 127* (1982) 117.
86. Marty, A. and Viallet, P. *J. Photochem. 29* (1982) 213.
87. Abd-El-Mottaleb, M.S.A. *Z. Naturforsch. Teil A 37* (1982) 1353.
88. Manuta, D.M. and Lees, A.J. *Inorg. Chem. 22* (1983) 3825.
89. Fain, V.Y., Kliot, L.Y., Ivanov, Y.V. and Zaitsev, B.E. *Org. React. 20* (1983) 467.
90. Roussel, R., Oteyza de Guerrero, M., Spegt, P. and Galin, J.C. *J. Heterocycl. Chem. 19* (1982) 785.
91. Tway, P.C. and Cline Love, L.J. *Chem. Phys. Lett. 87* (1982) 204.
92. Marty, A. and Viallet, P. *C. R. Acad. Sci. (Paris) 296* (1983) 343.
93. Schange, K.S., Mattox, T.F. and Whitten, D.G. *J. Org. Chem. 48* (1983) 2808.
94. Abraham, W., Kupfer, N. and Kreysig, D. *J. Prakt. Chem. 324* (1982) 753.
95. Kupfer, M. and Abraham, W. *J. Prakt. Chem. 325* (1983) 95.
96. Abraham, W., Kupfer, M., Buck, K. and Kreysig, D. *Z. Naturforsch. Teil A 36* (1981) 1213.
97. Zhu, T., Su, C.H., Lemke, B.K., Wilson, L.J. and Kadish, K.M. *Inorg. Chem. 22* (1983) 2527.
98. Fuchs, R. and Stephenson, W.K. *J. Am. Chem. Soc. 105* (1983) 5159.
99. Pipkin, J.D. and Stella, V.J. *Int. J. Pharmaceutics 14* (1983) 263.
100. Yatsimirsky, A.K., Ryabov, A.D., Zogorodnikov, V.P., Sakodinskaya, I.K., Kavatskaya, O.I. and Berozin, I.V. *Inorg. Chim. Acta 48* (1981) 163.
101. Pryor, W.A., Gleicher, G.J. and Church, D.F. *J. Org. Chem. 48* (1983) 4198.
102. Curtis, J.C., Sullivan, B.P. and Meyer, T.J. *Inorg. Chem. 22* (1983) 224.

103. Uri, A. and Tuulmets, A. *Org. React.* *20* (1983) 578.
104. Connor, J.A. and Overton, C. *Inorg. Chim. Acta 65* (1983) L1.
105. Czongar, C., Socher, R. and Tomaschewski, G. *J. Prakt. Chem. 324* (1982) 246.
106. Kupfer, M. and Abraham, W. *Monatsh. Chem. 114* (1983) 513.
107. Nicolet, P. and Laurance, C. *Chim. Phys. Phys.-Chim. Biol. 81* (1984).
108. Hamanoue, K., Nikajima, K., Amano, M., Hidaka, T., Nakayama, T. and Teranishi, H. *Polymer Photochem. 3* (1983) 407.
109. Marcandalli, B., Pellicciardi-Di Liddo, L., Di Fede, C. and Bellobono, I.R. *J. Chem. Soc. Perkin Trans. 2* (1984) 589.
110. Coetzee, J.F. and Hussam, A. *J. Solution Chem.* (1982) 395.
111. Ueji, S., Nakamura, M., Kitadani, M. and Sera, A. *Bull. Chem. Soc. Jpn. 55* (1982) 1665.
112. Maccarone, E., Perrini, G. and Torre, M. *Gazz. Chim. Ital. 112* (1982) 25.
113. Werner, T.C. and Lyon, D.B. *J. Phys. Chem. 86* (1982) 933.
114. Lee, I., Uhm, T.S., Sung, D.D. and Yeom, G. *Daehon Hwahok Hwoejee 27* (1983) 1.