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Correlations and predictions of solvent effects on reactivity: some limitations of multi-parameter equations and comparisons with similarity models based on one solvent parameter

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ABSTRACT: Three recent publications on multi-parameter correlations of solvent effects on solvolytic reactivity are re-examined, by considering 'similarity' and/or 'analogy'. Systematic errors due to compensation effects and to comparisons between dissimilar processes are found. Models for solvent nucleophilicity involving dissimilar spectroscopic processes (e.g. β or B parameters) give insensitive measures of low nucleophilicity. From qualitative considerations based on structural similarities, it is predicted that the sensitivities to changes to solvent polarity for solvolyses of chloroalkanes should be in the order: 1-adamantyl (**3**) > 2-methyl-2-adamantyl (**1**) > *t*-butyl (**2**). The predictions are confirmed quantitatively by simple linear free-energy relationships and similarity models, involving correlations with Y_{Cl} (based on solvolyses of 1-chloroadamantane) or $E_{\mathrm{T}}(30)$ (based on solvatochromism). Multi-parameter correlations, indicating that solvolyses of **1** show a low sensitivity to both solvent polarity and electrophilicity, and also a negative sensitivity to solvent nucleophilicity, are shown to be unreliable. Large errors are also evident in recent KOMPH2 calculations. Conclusions are supported by comparing several multi-parameter treatments of solvolyses of 4-methoxyneophyl tosylate, for which there is a reliable set of kinetic data and a generally accepted mechanism. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: solvolysis; kinetics; tertiary halides; similarity models; multi-parameter correlations

INTRODUCTION

Reasoning based on analogies is frequently applied to qualitative considerations of organic reaction mechanisms, and the reasoning can also be extended quantitatively to reaction kinetics using 'similarity models'[1,2] and linear free energy relationships (LFER), alternatively referred to as 'quantitative analogy models'.[1b] The concept of similarity models has evolved slowly over decades,[3a] beginning with applications of the Brønsted and Hammett equations;[3b] although usually expressed as relationships between rate constants and equilibrium ionization constants, closer 'similarity' can be claimed because changes in equilibrium constants reflect mainly changes in rates of ionization (because rates of the reverse reactions are very similar).[4] Consequently, typical Brønsted and Hammett plots could be regarded as similarities between two rate processes, rather than between a rate process and an equilibrium process.

Another early example of similarity is the correlation for various solvents of X-H IR stretching frequencies (proportional to energies) for a wide range of solutes (e.g. HCl, MeOH, $PhNH_2$) with the N-H stretching frequencies of pyrrole in the same solvent.[2c,5] In an influential review chapter, the importance of similarity in LFER was re-emphasised,[1a] and the Brønsted coefficient was later referred to as a 'similarity coefficient';[6] this terminology was adopted in a recent text for all LFER of the general formula, $\Delta G = a\,\Delta G_{\mathrm{s}} + c$, where ΔG_{s} refers to a standard process, ΔG (or log k) refers to a process under investigation and a is the similarity coefficient.[7]

Initially, only a small number of similarity models were investigated (e.g. ionization constants of benzoic acids gave empirical parameters for aromatic substituent effects (σ[3b]), and solvolyses of *t*-butyl chloride gave a parameter referred to as solvent ionizing power (Y[8]). Subsequently, additional model processes were used to define other important parameters [(e.g. σ^*,[9] σ^+,[10] Z,[11] and $E_{\mathrm{T}}(30)$[12,13]], and a proliferation of parameters was gathering momentum. As a wide range of parameters is now available for correlations, appropriate choices can be based on analogy or similarity. Some of the problems associated with the proliferation of 'fundamental' parameters then become opportunities because a wider range of similarity models become available (a closer similarity model is then more likely).

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Reflecting the great diversity of organic reactions, equations were also introduced capable of showing blends of behaviour (e.g. *r*, blending between σ and σ^+,[14] or *Q*, blending between S_N2 and S_N1 solvolyses[15]). Multiparameter equations correlating solvent effects were also investigated,[16–18a] and a fundamental debate later ensued on whether LFERs were local empirical rules (i.e. similarity models) or fundamental laws of chemistry.[1a,19] Further details of the extensive background and many aspects omitted in the above brief introduction are given elsewhere.[1,2,7,19a]

Multiple linear regression is a very versatile procedure, especially for interpreting solvent effects,[16–18a] and its popularity has increased owing to the ready availability of statistical packages for PCs. Ideally, interpretations based on linear regression using relatively simple comparisons should not conflict with interpretations based on multiple linear regressions: for example recent multi-parameter correlations for the competing reaction channels for solvolyses of benzoyl chloride and substituted derivatives,[20a,b] are in satisfactory agreement with previous work using single-parameter similarity models;[20c,d,e] the correlations were sufficiently precise to reveal mechanistic changes, and there is independent support from substituent effects and variations in product selectivities.[20e,f]

Until recently, there also appeared to be broad agreement that the rates of solvolyses of tertiary haloalkanes depended mainly on 'solvent polarity', and that the response to solvent nucleophilicity was small but significant for *t*-butyl chloride.[21] However, two recent studies using multiple linear regressions have claimed a negative dependence of rates on solvent nucleophilicity,[22,23] implying a need for revision of accepted mechanisms. It was also argued that 'uses of simple solvolytic correlations may be invalid even for similar types of substrates for example tertiary haloalkanes'.[23] Another recent paper,[24a] re-emphasises earlier claims[24b] that solvolyses of haloalkanes show variations in responses to solvent electrophilicity *rather than* nucleophilicity.

Our aim is to investigate the causes of the diverse interpretations.[21–24] Continuing the role of solvolytic reactions as a testing ground for new developments in physical organic chemistry, we draw more general conclusions about the reliability of predictions of rate constants based either on simple similarity models or on multiple linear regressions. Analysis of the magnitudes of errors will play an important role.

RESULTS AND DISCUSSION

Kinetic data were either assembled directly or calculated from published data, as described in the footnotes to tables. All statistical calculations were performed using Microsoft Excel. Some of the calculations reported by other research groups[23,24a] were repeated, and the results agreed (except for a different definition of the correlation coefficient in Ref. 24a).

Estimates of errors

The correlations which led to the above quotation[23] are based on the KAT equation (1),[19c,21d] in which logarithms of rate constants (*k*) are related to the following solvent properties: solvent dipolarity and polarizability (π^*), hydrogen-bond donor acidity or electrophilicity (α), hydrogen-bond acceptor basicity or nucleophilicity (β) and the Hildebrand solubility parameter (δ_H). Multiple linear regression (e.g. using Excel) gives optimised values of the coefficients *s*, *a*, *b*, and *h*, as well as for the intercept log k_0 term, which refer to solvolyses in cyclohexane ($\pi^* = \alpha = \beta = 0.00$), if ${\delta_H}^2$ is excluded. As values of k_0 are not usually known reliably (or not known at all), log k_0 becomes a fifth freely adjustable parameter.

$$\log\ k = \log\ k_0 + s\pi * + a\alpha + b\beta + h\delta_H^2 \qquad (1)$$

In addition to typically quoted statistical results, Excel shows the upper and lower limits for the values of optimised variables (slopes/coefficients and intercepts) for a 95% confidence level; these are typically about two to three times greater than the standard errors.[25] Even then, errors are underestimated, because it is assumed that there are no errors in the independent/explanatory variables. Additional uncertainties may arise if rate data at one temperature are correlated with solvent parameters determined at a different temperature. In practice, the value of a particular solvent parameter will not be known exactly and uncertainties could be large: for example two values of β for water are 0.18[23] to 0.50.[26] Comparing independent data for six protic solvents (water, MeOH, EtOH, *n*-PrOH, *i*-PrOH, and *n*-BuOH), average absolute deviations are: π^* (0.02), α (0.06), and β (0.09).[23,26] Relatively large uncertainties (10–20%) in absolute values of KAT parameters have been quoted,[27] and sources of the uncertainties are discussed elsewhere.[28]

Responses of solvolyses to solvent polarity

Results from Eqn. (1) for a range of protic and aprotic solvents for 2-methyl-2-chloroadamantane (**1**), and *t*-butyl chloride (**2**) are summarised in Table 1. Values for coefficients are quoted with the precision stated in the original papers,[21d,23] but we have added the standard errors for solvolyses of **1**.

Considering the standard errors, the values for the parameters in Table 1 are quoted to an optimistic precision, for example the predicted value of log k_0 for solvolyses of **1** in cyclohexane is quoted as −5.409, and the possible range of −6.33 to −4.49 (at 95% confidence) should be accessible experimentally; attempts were made

Table 1. KAT correlations (Eqn 1) for solvolyses of 2-chloro-2-methyladamantane (**1**), and 2-chloro-2-methylpropane/*t*-butyl chloride (**2**) in protic and aprotic solvents

	2-Me-2-AdCl (**1**)[a]		*t*-BuCl (**2**)[b]	
Parameter	Value	Standard error	Value	Standard error
log k_0	-5.409	0.42	-14.60	0.29
s (π^*)	2.219[c,d]	0.35	5.10	0.37
a (α)	2.505[c,d]	0.12	4.17	0.11
b (β)	-1.823[c,d]	0.24	0.73	0.21
$100h$			0.48	0.07
r	0.996		0.997	

[a] Based on kinetic data for 10 protic and 5 aprotic solvents at 60 °C (Ref. 23).

[b] Based on kinetic data for 11 protic and 10 aprotic solvents at 25 °C (Ref. 21d).

[c] Recalculating the data point for water at 60 °C, using our value (footnote d) of $k = ca.\ 0.7\ \mathrm{s}^{-1}$ at 25 °C (extrapolation based on Eqn (2), Refs. 21a and 29), and assuming $\Delta H^{\neq} = 23$ kcal/mol (Refs. 21a and 30), gives $k = ca.\ 47\ \mathrm{s}^{-1}$ (in contrast to the published calculated value of $0.57\ \mathrm{s}^{-1}$); the revised correlation is then $\log k = -7.3\ (\pm 1.1) + 4.2\ (\pm 0.9)\ \pi^* + 3.0\ (\pm 0.3)\ \alpha - 1.4\ (\pm 0.7)\ \beta$ ($r = 0.975$), that is a greater response to π^* and α; if the β term is omitted, $\log k = -9.3\ (\pm 0.7) + 5.5\ (\pm 0.8)\ \pi^* + 3.4\ (\pm 0.3)\ \alpha$ ($r = 0.965$).

[d] Comparing published rate data (Ref. 23) for solvolyses of 2-chloro-2-methyladamantane (**1**) in aqueous ethanol ($k \times 10^4/\mathrm{s}^{-1}$) at 25 °C with data from two independent groups (Refs. 29 and 31) indicates overestimates in highly ethanolic media and underestimates in more aqueous media: 80% [$10^4 k = 1.45$ (Ref. 23), 0.64 (Ref. 31)]; 70% [3.63 (Ref. 23), 2.45 (Ref. 31)]; 50% [29.5 (Ref. 23), 34.0 (Ref. 31)]; 40% [51 (Ref. 23), 118 (Ref. 29)]; extrapolation of the older data (Refs. 29 and 31), which is assumed to be more reliable, *versus* Y_{Cl} (Eqn (2) gives $k = ca.\ 0.7\ (\pm 0.3)\ \mathrm{s}^{-1}$ for water, *ca.* 15-fold faster than the published value of $4.73 \times 10^{-2}\ \mathrm{s}^{-1}$, obtained by similar extrapolations *versus* Y (Ref. 23).

to determine the value, but it was reported to be 'extremely slow at temperatures up to 100 °C'.[23] Even allowing for large uncertainties, there appear to be significant differences between the values of the s, a and b parameters for **1** and **2** (Table 1). Solvolyses of **2** appear to be more sensitive to π^*, α and β than **1**, and solvolyses of **1** have a negative sensitivity to β. Surprisingly, it is predicted that the rate constant for solvolysis of **1** in cyclohexane (at 60 °C) is 10^9-fold greater than that for **2** (at 25 °C), whereas in ethanol at 50 °C, the rate ratio **1**/**2** is only 20-fold.[23,30]

The greater sensitivity of **2** (compared with **1**) to solvent polarity based on π^* and α (Table 1) is the opposite of that expected from our published data,[29] based on a modified Grunwald–Winstein (GW) equation (2) in which logarithms of rate constants (k) relative to solvolyses in 80% ethanol/water (k_0) are related to an adjustable parameter (m), a residual term (c, often close to 0.00), and Y_{Cl} (referred to as the solvent ionizing power, that is 'polarity'), defined by $m = 1$ for solvolyses of 1-chloroadamantane (**3**) at 25 °C (Table 2).[21a,32] *In protic solvents, the order of* m *values (a measure of the sensitivity to solvent polarity) is* **3** > **1** > **2**, *as might be expected qualitatively from structural similarities.*

$$\log (k/k_0) = mY_{\mathrm{Cl}} + c \qquad (2)$$

Table 2. Slopes of correlations of rate constants for solvolyses of **1**–**4** in protic solvents using one term Eqns (2) and (3) for solvent polarity

	Y_{Cl} (Eqn 2)[a]		$E_{\mathrm{T}}(30)$ (Eqn 3)[b]	
Substrate	m	r	m_{30}	r
1	0.90 ± 0.02[c]	0.998	0.42 ± 0.05[d]	0.956
			(0.32 ± 0.05)[e]	0.915
2	0.75 ± 0.01[f]	0.997	0.35 ± 0.04[g]	0.956
3	1.00[h]		0.65 ± 0.07[i]	0.975
4	j		0.20 ± 0.03[k]	0.944

[a] Y_{Cl} values from Refs. 21a and 32.

[b] $E_{\mathrm{T}}(30)$ values from Refs. 18b and 33.

[c] For 80, 70, 50 and 40% v/v ethanol/water, 97% w/w trifluoroethanol (TFE)/water and 97% hexafluoroisopropanol (HFIP)/water at 25 °C (Refs. 29 and 31), with no significant deviations shown by the latter two less nucleophilic solvents.

[d] For nine protic solvents at 25 °C, $c = -26.7 \pm 2.7$, s.d. = 0.74; solvents: TFE ($\log k = -1.4$), 97% HFIP (0.24), ethane-1,2-diol (-3.84), extrapolated data for MeOH (-4.51), EtOH (-5.60), *n*-PrOH (-5.22), *i*-PrOH (-5.72), and *n*-BuOH (-5.01) (Ref. 23), and revised data for water (Table 1, footnote d), but omitting data for acetic acid because the activation parameters are very unusual.

[e] Using the original data at 60 °C (Ref. 23) for 10 protic solvents ($c = -20.0 \pm 2.8$); adding data for 5 aprotic solvents to the 10 protic solvents at 60 °C (Ref. 23) gave $m_{30} = 0.25 \pm 0.05$, $c = -15.6 \pm 1.7$, s.d. = 0.82, $r = 0.906$.

[f] For a range of aqueous acetone, ethanol and methanol mixtures (10–80% v/v) at 25 °C (Ref. 21a); a two-parameter equation for a wider range of solvents and allowing for changes in solvent nucleophilicity gives $m = 0.86 \pm 0.02$, $r = 0.993$ (Ref. 21e).

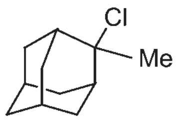
[g] For 11 protic solvents at 25 °C, $c = -24.8 \pm 2.0$, s.d. = 0.70 (kinetic data from Ref. 21d); adding 10 aprotic solvents at 25 °C (Ref. 21d) gave $m_{30} = 0.34 \pm 0.02$, $c = -23.8 \pm 0.8$, s.d. = 0.59, $r = 0.980$; a plot for these and additional data is given in Ref. 33.

[h] By definition.

[i] For six solvents (water, MeOH, EtOH, TFE, HFIP and AcOH) at 25 °C (Ref. 21a) ($c = -36.0 \pm 4.3$, s.d. = 0.84).

[j] A correlation with Y_{OTs} is required (Refs. 34a and 34b).

[k] For six protic solvents at 75 °C, $c = -13.4 \pm 2.0$, s.d. = 0.39 (kinetic data from Refs. 34a and 35a); extrapolations collated in Ref. 36 (revising data for AcOH to $\log k = -2.77$ and omitting data for formic acid); including nine aprotic solvents at 75 °C (data from Ref. 35a) gave $m_{30} = 0.20 \pm 0.01$, $c = 13.5 \pm 0.6$, s.d. = 0.41, $r = 0.977$, $n = 15$.



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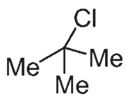

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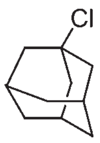


3

Of the many possible scales of solvent polarity,[37] we also investigated correlations involving $E_{\mathrm{T}}(30)$, based on changes in the solvent effects of a betaine dye.[12,13,18b,33] Although, as a non-kinetic process there is not a close similarity to solvolysis, $E_{\mathrm{T}}(30)$ is a leading indicator of solvent polarity and has the advantage that aprotic solvents could be included. Data for solvolyses of **1**–**3** in protic solvents at 25 °C are correlated using Eqn. (3) (Table 2), to allow direct comparisons with m values (Eqn. (2); only short temperature extrapolations were required for solvolyses of **1**. *As expected, correlations* *based on* Eqn (3) *are not as precise as those based on* Eqn (2), *but the* m_{30} *values for* **1** *are the same or higher than those for* **2**, *strongly supporting the above conclusion based on* Eqn (2).

$$\log\ k = m_{(30)}\ E_{\mathrm{T}}(30) + c \qquad (3)$$

To avoid debates[21–24] about mechanisms of solvolyses of chloroalkanes **1–3**, data for solvolyses of 4-methoxyneophyl tosylate (**4**) have been included in Table 2.[34,35] The agreed[34,35] solvolysis mechanism for **4** involves ionization and rearrangement with anchimeric assistance by the 4-methoxyphenyl group through a transition state in which positive charge is highly delocalised (so m_{30} is very low, Table 2).

Unlike bridgehead substrates such as **3**, the availability of methyl groups in **1** and **2** could lead to elimination, and this may complicate the correlations. Also the experimental kinetic data for solvolyses of **1** and **2** in aprotic solvents are not as reliable as those for protic solvents; results may be affected by: (i) the presence of traces of polar impurities such as water; (ii) greater temperature extrapolations;[38] (iii) assumed activation energies; also correlations with gas-phase data have been used to predict 'observed' rates for some of the slower solvolyses (e.g. solvolyses of **2** in THF and EtOAc—Ref. 39a). Despite these uncertainties, inclusion of data for both protic and aprotic solvents for solvolyses of **1**, **2** and **4** show no significant changes in slopes or intercepts (Table 2, footnotes e, g and k), but the correlations for **1** are less 'robust' (with larger errors) than for **2** and **4** (e.g. see the various calculated values of the intercept *c*).

However, one reason that the correlations for **1** using Eqn (3) (Table 2) are not greatly affected by inclusion of the five aprotic solvents is because the span of $E_{\mathrm{T}}(30)$ values is small (4.1 kcal/mol), compared with the range of protic solvents (14.7 kcal/mol).[18b,33] Data for the 2-bromo-derivative of **1** in a wider range of aprotic solvents do show a change in slope from aprotic to protic solvents, consistent with a mechanistic change.[22] Unexpectedly, the response to changes in solvent polarity is greater in the aprotic solvents, but the kinetic data are questionable because they were calculated from exceedingly low extents of reaction.[22]

Unreliable kinetic data also appear to have contributed to the unexpected results for solvolyses of **1**.[23] A large error in a rate constant for a polar solvent such as water exerts leverage in the correlation, and when the published correlation at 60 °C using Eqn (1) is repeated with our revised estimate for water (Table 1, footnote d), the sensitivity to π^* and α increases about 50% (see Table 1, footnote c). Data for acetic acid showed unexpectedly high values (especially for an aliquot procedure), and very unusual activation parameters.[23]

The reliability of Eqn (1) was investigated further by truncation to Eqn (4) (the bβ term is small). Data for solvolyses of **2** and **3** in protic media at 25 °C, have previously been correlated with π^* and α (Eqn (4),[39b] and comparisons with solvolyses of **1** and with $E_{\mathrm{T}}(30)$ in the same solvents can now be made (Table 3).

Table 3. Correlations using Eqn (4) for solvolyses of **1–4** in protic solvents at 25 °C[a]

Substrate	*s*	*a*	*r*	*n*
1[b]	4.97 ± 1.04	4.31 ± 0.54	0.976	9
(**1**	3.27 ± 0.32	3.97 ± 0.17	0.997	9)[c]
2[d,e]	8.38 ± 1.57	2.86 ± 0.63	0.967	7[f]
3[d,g]	9.67 ± 2.58	4.95 ± 1.04	0.957	7[f]
4[h]	2.74 ± 0.72	2.37 ± 0.29	0.979	7[f]
$E_{\mathrm{T}}(30)$[i]	14.9 ± 2.3	8.28 ± 1.17	0.978	9[j]

[a] Errors shown are standard errors.

[b] Kinetic data from Table 2, footnote d; log $k_{\mathrm{o}} = -11.4 \pm 0.8$.

[c] For the same nine solvents but at 60 °C, and with the original data reported in Ref. 23; log $k_{\mathrm{o}} = -8.64 \pm 0.24$.

[d] Data from Ref. 39b.

[e] Log $k_{\mathrm{o}} = -9.2 \pm 1.3$.

[f] The same solvents are studied for all three correlations with $n = 7$, see footnote h.

[g] Log $k_{\mathrm{o}} = -12.1 \pm 2.2$.

[h] Log $k_{\mathrm{o}} = -9.3 \pm 0.6$; data from Refs. 34a and 35a, solvent (log *k*): water (−3.45), MeOH (−5.29), EtOH (−5.75), TFE (−3.49), HFIP (−2.59), AcOH (−5.27), formic acid (−3.08).

[i] Intercept 36.6 ± 1.7.

[j] For the same nine protic solvents as for **1**.

$$\log k = \log k_0 + s\pi^* + a\alpha \qquad (4)$$

Correlations for solvolyses of **1**, using Eqn (4) and either our 25 °C data set or the original data at 60 °C, give higher coefficients for responses to polarity (*s* and *a*) than those obtained using Eqn (1), but the standard errors are relatively large. It appears that the anomalously low response to solvent polarity, predicted by Eqn (1), is related to the unexpected negative coefficient (*b*) to β (Eqn 1). The opportunity for unreliable results is emphasised by a correlation of the sum of $(\pi^* + \alpha)$ with β which has a negative slope (−1.4) and a respectable correlation coefficient ($r = 0.966$) for 6 of the 7 solvent data set (Table 3, excluding formic acid); for the 15 solvent data set (Table 1)[23] including aprotic solvents, $r = 0.64$. *Consequently, if the correct response to* β *is that it is negligible, a false response to* β *could be computed, and a false negative response will lead simultaneously to an anomalously low response to solvent 'polarity'* $(\pi^* + \alpha)$.

The above argument would be valid for any combination of π^* and α, and the sum of the two is simply an illustration of the possibility of unreliable results from optimisations. Another example is the prediction[40a] that solvolyses of methyl tosylate show a negative response to anion-solvating tendency (acity, i.e. electrophilicity); the antithesis, a more positive response to solvent cation-solvating tendency (basity, i.e. nucleophilicity), makes much more chemical sense (e.g. compare entries 1, 2, 5, and 11 in Table VI of Ref. 40a); several other anomalous predictions have been calculated.[40b] A variation on Eqn (1) has been developed (codename KOMPH2, discussed later),[24a] in which solvatochromic parameters are avoided; this shows an analogous negative response to hydrogen-bond donation (i.e. electrophilicity) in correlations with the solvent nucleophilicity parameter N_{OTs}, based on solvolyses of methyl tosylate. Also, several 'correlations without causality' were recognised by the negative coefficients in the term for solvent basicity,[24a] a preferable alternative to proposals[22,23] of unusual mechanisms.

Separation of electrostatic and electrophilic effects

There is a long-standing debate about whether rates of solvolyses of **3** show a greater response to hydrogen-bond donation (solvent electrophilicity) than solvolyses of **2**,[21a,24] and this was given prominence in the title of a recent paper.[24a] It is suggested[24] that a greater response to electrophilic effects for **3** has been incorrectly[21a] attributed to a greater response to solvent nucleophilicity for **2** (strongly electrophilic solvents are weak nucleophiles,[21d] and this led to the incorrect assignments noted above). *Importantly, more recent work*[21b–21j]*has strengthened the evidence*[21a,29]*that data for* ***2*** *can be explained by changes in solvent nucleophilicity*, in combination with a term for solvent polarity. Comparisons of chloroalkanes with dimethylsulfonium salts, for which the response to solvent polarity is very low, are particularly significant.[21c]

Now, we examine critically the evidence for a recent alternative interpretation.[24a] We will discuss how the above results (Tables 1–3) allow further insights into the problems which arise when attempting to separate the electrostatic and electrophilic contributions to observed rates of solvolyses.

Single scales of solvent polarity [(e.g. Y, Y_{X}, or $E_{\mathrm{T}}(30)$] may be regarded as combinations of π^* and α (Eqn (4);[26,39b,41] Y_{X} values are based on adamantyl-X substrates, where X is the leaving group.[32] As there are only seven data points and three adjustable parameters, the standard errors are so large that the values of the coefficients s and a could be the same for Y and Y_{Cl}; for example values of $a = 2.86$ for Y and 4.95 for Y_{Cl} (Table 3) are the same within 95% confidence (*ca.* 2–3 × standard error), and the large uncertainty in the value of a (2.86) for Y is further supported by the value of 4.17 obtained from Eqn (1), Table 1. A suitably cautious interpretation of trends in a for various Y_{X} scales was given,[39b] recognising that KAT correlations involving only protic solvents are far less reliable.[21d]

A less cautious interpretation of similarly limited data was recently published using KOMPH2.[24a] For illustration, we have recalculated some of the results after truncating KOMPH2 to avoid the incorrect β term noted above;[24a] in Eqn (5), the natural log of the rate constant is related to the three solvent parameters, bulk dielectric constant/relative permittivity (ϵ_{r}), a measure of hydrogen-bond donation (α'), and cohesive energy density (CED), by optimising x_1, x_2, x_3, and c.

$$\ln\ k = x_1\ [(\varepsilon_{\mathrm{r}} - 1)/(2\varepsilon_{\mathrm{r}} - 1)] + x_2\ \alpha' + x_3\ \mathrm{CED} + c \tag{5}$$

The results (Table 4) again show large standard errors, in part because of the small number of input data when the four adjustable parameters were optimised. Despite the large uncertainties, it was concluded[24a] that solvolyses of 1-chloroadamantane (**3**) showed a significantly greater dependence on α' than solvolyses of *t*-butyl chloride (**2**). The same trend was observed for corresponding dimethyl sulfonium salts (Table 4),[24a] with solvolyses of 1-Ad $\mathrm{SMe_2^+}$ showing a small positive response to changes in solvent electrophilicity (α'), and solvolyses of *t*-$\mathrm{BuSMe_2^+}$ showing a small negative response; the negative sign of the coefficient in α' was judged to be 'remarkable'.[24a]

The mechanistic (or any other) explanation for the difference in sign of response to α' for the two sulfonium salts was recognised as 'not obvious'.[24a] It is not

Table 4. Correlations of rate constants for solvolyses of 1-adamantyl and *t*-butyl substrates using truncated KOMPH2 (Eqn 5)

Parameter (substrate)	1-AdCl (**3**)[a]	*t*-BuCl (**2**)[b]	1-AdS$^+$Me$_2$[c,d]	*t*-BuS$^+$Me$_2$[c,e]
x_1 (ϵ_{r} term)	57.1 ± 29.2	44.9 ± 20.4	0.9 ± 4.4	−1.3 ± 4.3
x_2 (α' term)	72.0 ± 13.9	44.0 ± 9.7	5.0 ± 1.8[f]	−11.0 ± 1.8[f]
x_3 (CED term)	12.6 ± 4.3	11.7 ± 3.0	0.2 ± 0.6	0.4 ± 0.6
c	−47.6 ± 12.7	−36.0 ± 8.8	−0.6 ± 2.0	5.2 ± 1.9
r	0.970	0.970	0.837	0.961
n	7	7	8	8

[a] Results and data (Y_{Cl} at 25 °C) correspond to Eqn 12 of Ref. 24a, with standard errors added.

[b] Results and data (Y at 25 °C) correspond to Eqn (4) of Ref. 24a, with a revised data point for water and standard errors added.

[c] Input data ($\ln k \times 10^6$) from Ref. 24a; correlations including a small β term are in Eqns 14 and 17 of Ref. 24a.

[d] At 70.4 °C; kinetic data from Ref. 21c.

[e] At 50 °C; kinetic data from Refs. 21c and 42.

[f] Almost identical slopes are obtained if the rate data are correlated simply with the α' term (Eqns 15 and 18) of Ref. 24a.

reasonable for two very similar solvolyses to show opposite responses to changes in solvent electrophilicity. A more plausible interpretation is that the responses to solvent electrophilicity for t-BuSMe$_2^+$ and 1-Ad SMe$_2^+$ are the same within statistical uncertainties, and are close to zero. This alternative viewpoint implies that the true errors in the coefficients (not simply the standard errors quoted) are so large that the correlations using Eqn (5) (Table 4) are unreliable.

Also, the surprising prediction based on the intercept that t-BuSMe$_2^+$ would react at 50 °C 'about 100'-times faster than 1-Ad SMe$_2^+$ at 70 °C in the gas phase was noted to be incorrect.[24a] The 'explanation'[24a] may be unnecessary because the errors are very large. Nevertheless, it was proposed that the intercept referred to high dielectric media, implying that there would be a non-linear correlation if data points for low dielectric media and the gas phase are added to the same plot. If correlations were indeed non-linear, further advantages of Hammett and GW correlations become apparent because the reference points (H for substituents and 80% ethanol/water for solvents) are usually close to the middle of the range of data under investigation. Correlations may then be more reliable because they assess directly a small perturbation from the centrally located reference substituent or solvent.

It is assumed[24a] that the electrostatic and electrophilic effects have been separated completely (i.e. without cross-contamination), despite clear acceptance[24a] of the evidence (noted above) that false, negative coefficients for β' can be obtained from KOMPH2 correlations. In KOMPH2 (Eqn (5) the π^* term is replaced by a function of ϵ_r, a bulk solvent property relevant to the separation of ions (i.e. dissociation). The description of Y values as 'ionizing power' is carefully chosen to distinguish it from 'dissociating power' because formation of contact ion pairs (or related transition states) is the rate-determining step in many solvolytic reactions of alkyl substrates.[35] Macroscopic solvent properties such as ϵ_r have long been regarded as inappropriate for the microscopic events leading to solvolysis transition states.[43]

Parameters for solvent nucleophilicity (*N*)

Early studies of solvolyses in solvents of very low N (e.g. TFA,[44] sulphuric acid,[45a] and fluorosulfonic acid[45b]) showed enhanced structural effects due to weaker cation-solvation, which led to increased electron demand from the organic residue. Later, quantitative scales were developed (Table 5), and extensive kinetic data were obtained conveniently in alcohols of low N (e.g. 2,2,2-trifluoroethanol (TFE), hexafluoroisopropanol (HFIP) and others[47]). Research up to 1996 has been reviewed,[48] including: (i) examples of successful correlations combining Y and N; (ii) other parameters for cation-solvation by electron-pair donation (e.g. donor number and basity).

Table 5. Comparison of parameters for solvent nucleophilicity (*N*) and hydrogen-bond donation (basicity, β) for 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP)

	Value for various solvents			
Parameter	97% HFIP	TFE	97% TFE	EtOH
N_{OTs}[a]	−4.27	−3.0	−2.79	0.00
N_T[b]	−5.26	−3.93	−3.3	0.37
N_1[c]	(−1.2)[d]	+1.23	1.8	7.44
β or β_1[e]	0.0	0.0		0.77
β'[f]	0.00	0.0203		0.1203
β_2[g]	0.03	0.18		0.44
B[h]	(0.85)[i]	(1.3)[i]		2.81

[a] Based on pseudo first-order rate constants for S_N2 solvolyses of methyl tosylate at 50 °C, corrected for solvent ionizing power (Ref. 46a).

[b] Based on pseudo first-order rate constants for S_N2 solvolyses of S-methyldibenzthiophenium triflate at 25.1 °C (Ref. 46b).

[c] Based on pseudo first order rate constants for reactions of benzhydrylium cations with solvent at 20 °C (Ref. 46c).

[d] Based on a correlation with N_T (Ref. 46c), but other kinetic data for cations confirm large rate differences between TFE and HFIP (see Table 6 of Ref. 46d).

[e] The original β values of solvents (Ref. 39) may be referred to as β_1; they are based on UV data for suitable pairs of indicators (e.g. nitroaromatic alcohols and ethers).

[f] Based on free energies of transfer of potassium ions, with two correction terms (Ref. 24a).

[g] Basicity of monomers; a solute property determined in dilute solution from equilibria involving reference hydrogen-bond donors (Ref. 46e).

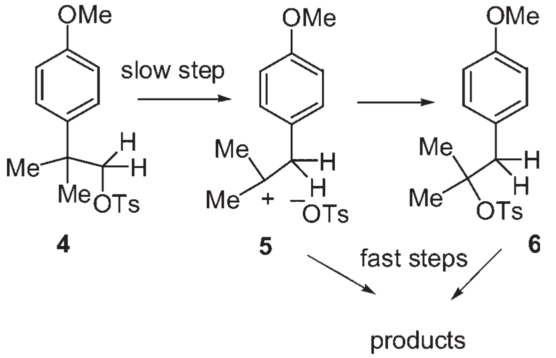
[h] Based on changes in MeOD IR stretching frequencies (Ref. 22); values for protic solvents cannot be determined directly because of exchange, and then values may be obtained from changes in PhOH stretching frequencies in dilute solutions (Ref. 46f), so they are not properties of the bulk solvent; unexpectedly, values for methanol and acetone are almost identical.

[i] Extrapolated from a correlation of B with N_{OTs} (Ref. 22).

Various relatively stable carbocations such as 4-methoxybenzyl react rapidly with HFIP (at 20 °C, $k = 3 \times 10^2\,s^{-1}$) and more rapidly with TFE (at 20 °C, $k = 4 \times 10^6\,s^{-1}$).[46d] These and other data[46d] provide relatively direct measures of N,[46c] and support other N scales (Table 5) showing that TFE is significantly more nucleophilic than HFIP. *The identical β values of zero for TFE and HFIP show that β is not a reliable guide to N.*

Also, β' values for HFIP and formic acid are zero, whereas N_{OTs} and N_T values show that HFIP is much less nucleophilic than formic acid. Although some of the weakly nucleophilic solvents are so acidic that the substrate may be protonated,[49b] the observation of stable cations in very weakly nucleophilic media shows that significantly less nucleophilic media are available.[49b] Values of β and β' of zero refer to media of 'zero' nucleophilicity (cyclohexane and the gas phase, respectively). As β and β' values for HFIP are also zero (Table 5), *these scales lack sensitivity in regions of low N.*

When β or β' values for aprotic and protic solvents are compared, even more surprising results are apparent; for example DMSO, DMF and acetone have higher β' values than ethanol;[24a] nitromethane has a higher β value than



Scheme 1. Mechanism of solvolysis of 4-methoxyneophyl tosylate (4)[35]

water;[23] β and β' are determined from model processes which do not involve formation of covalent bonds (see footnotes to Table 5), and they do not appear to be reliable similarity models for nucleophilicity.

The original β parameter is a property of the solvent, and may be referred to as β_1. A solute property (β_2, obtained from monomeric species) does show differences between HFIP and TFE (Table 5). Improvements in experimental methods have also led to revised β_1 values, which also show lower values for HFIP than TFE.[50] The results alleviate some of the above criticisms of the original β values, whilst highlighting uncertainties in the solvent parameters which are not included in the calculations of standard errors (Tables 1–4).

Although the main sources of data for the B parameter are based on changes in H-O and D-O stretching frequencies from IR (Table 5, footnote h), data for TFE and HFIP are derived from a correlation with N_{OTs} (Table 5), so there is a connection to nucleophilicity. *However, various correlations still reveal examples of negative dependences on B*,[22,36] *even for solvolyses of* ***4***. According to the accepted mechanism (Scheme 1), ion pair return from the first intermediate, a rearranged ion-pair (**5**) would give a very reactive tertiary tosylate (**6**), so the observed rate of solvolysis of **4** is determined by the rate of ionisation.[35] Consequently, any solvation effect which aids ionisation, including nucleophilic solvation of partially positive carbon atoms (if any), will enhance the rate of solvolysis.

If the negative dependence on B were explained by nucleophilic solvation of a cationic intermediate, prior to the rate-determining step,[22,23] significant 'return' from the cationic intermediate is implied. Generalising, equations[22] predicting a negative dependence on nucleophilicity for solvolyses of **4** are not credible. In other cases a negative dependence on B is more plausible, for example for reactions between benzoic acid and diazodiphenylmethane, the proposed explanation was nucleophilic solvation of the acid prior to the rate-determining step.[46f]

Evidence that solvolyses of **1**–**3** do not involve appreciable ion pair return has been discussed previously.[21a,29] In addition to an explanation involving ion pair return,[23] the negative dependence on β for solvolyses of **1** was also explained as follows: 'solvents with stronger hydrogen bond basicity would slow the reaction because the solvent could compete with the chloride for stabilisation of the carbocation'.[23] This explanation may be relevant to solvolyses in aprotic media, but hydrogen bond donation to chloride would be expected to be dominant in protic media. Although, mechanistic explanations of a negative dependence on β for solvolyses of **1**–**3** may be unconvincing, mechanistic evidence alone does not require a zero or positive dependence on β.

Consequently, solvolyses of **4** are of particular significance because the mechanism in generally accepted (Scheme 1). Also, the kinetic data set for **4** are from two reliable sources,[34a,35a] and include seven protic and nine aprotic solvents at 75 °C, so it is one of the best available for comparing various multi-parameter correlations. Results using KAT (Eqn (1) are given in Eqn (6) (s.d. = 0.29, $r = 0.991$, $n = 15$, formic acid excluded), and using KOMPH2 are given in Eqn (7) (s.d. = 0.43, $r = 0.983$, $n = 16$); although they have opposite signs, the *coefficients for β or β′ are not significantly different from zero*, in accord with the accepted reaction mechanism (Scheme 1),[35] Therefore, the published correlations[22,36] using B in combination with other parameter such as refractive index, are anomalous.

$$\begin{aligned}\log\ k_4 &= 4.14(\pm 0.38)\pi^* + 2.72\ (\pm 0.15)\alpha \\ &\quad + 0.93\ (\pm 0.41)\beta - 8.63\ (\pm 0.38) \qquad (6)\end{aligned}$$

$$\begin{aligned}\log\ k_4 &= 13.0\ (\pm 2.9)[(\varepsilon_{\mathrm{r}} - 1)/(2\varepsilon_{\mathrm{r}} - 1)] \\ &\quad + 10.3\ (\pm 1.6)\alpha' - 0.9\ (\pm 2.9)\beta' \\ &\quad + 1.6\ (\pm 0.8)\mathrm{CED} - 11.3\ (\pm 1.2) \qquad (7)\end{aligned}$$

General implications

The most well-established single-parameter relationships for substituent or solvent effects (e.g. Hammett or Grunwald–Winstein equations) involve quantitative comparisons of relative effects[39b]—small deviations from a centrally located reference points (e.g. substituent H, or solvent 80% ethanol-water) for similar processes. Multiple parameter correlations play an important role in *refining* single parameter correlations: for example from detailed studies of many solvolytic reactions, it is possible to devise reliable multi-parameter equations to correlate solvolytic reactivity (Eqn (8), in which a term for ionising power (Y_{X}) can be combined with terms for solvent nucleophilicity (N_{T}, Table 5) and aromatic ring solvation (I)—for example for solvolyses of **4**.[34b] In Eqn (8), the main effect is usually due to the Y_{X} term, and the other terms refine the calculation. As Eqn (8) is designed specifically for solvolytic reactions, it may not be reliable when applied to other reaction types. Even when applied to solvolyses, caution is required: for example rates of solvolyses of **4** correlate 'well' with Y_{OTs} and N_T,[34b] but the dependence on N_T is negative (i.e. incorrect or spurious).

$$\log(k/k_0) = mY_X + lN_T + hI + c \qquad (8)$$

Equation (8) is a refinement of Eqn (2), both correlating solvent effects relative to 80% ethanol/water, and it is designed to provide accurate correlations empirically. Other equations (such as Eqns (1 and 5) have the more ambitious aim of relating solvent effects to a distant reference point (e.g. the gas phase or a non polar solvent), so the responses to each parameter should be absolute rather than relative.[21d] An improved understanding of the underlying phenomena (including the nature of the transition state[39b]) is the main aim of such multi-parameter correlations:[19c] for example the relatively robust KAT correlation for solvolyses of **2**, showing a significant sensitivity to β (Table 1).[21d] Absolute responses of **3** to α may be greater than for **2** (Table 3),[39b] but responses relative to 80% ethanol may not be (see Discussion of electrophilic effects in Ref. 51).

However, based on the detailed information available about solvolytic reactions (e.g. Tables 1–5), which reveal some large errors, we infer that considerable caution is needed in the interpretation of multi-parameter equations. A useful test of reliability is a comparison of the predicted rate constant for the reference state (the 'hidden' parameter) with the experimental result or with the prediction from another model.[21g] It is recognised[21i] that extensive sets of accurate data (preferably at 25 °C) are required; for example from a range of experimental techniques (e.g. NMR), and temperatures extrapolations (e.g. to obtain data in high polarity media such as water); also data for 'new' solvents (e.g. tertiary fluorinated alcohols[47]) could be obtained. Unfortunately, increasing the range of data, also increases the chances of mechanistic changes.

A recent criticism of the multi-parameter LFER approach re-emphasised the 'defect' of strong co-linearity between parameters measuring electrophilicity and nucleophilicity.[21j] As an alternative way to improve mechanistic understanding, monohydrates of chloroalkanes were investigated using density functional theory (DFT) [(B3LYP/6-31G(d)] and the polarizable continuum solvation model.[21j] 'Fair' agreement with experimental data was obtained for MeCl, *t*-BuCl, and 1-AdCl, and nucleophilic solvent assistance was found for hydrolyses of *t*-BuCl. Quantum-mechanical treatment of additional solvent molecules would improve this approach (e.g. as second water molecule to deprotonate partially the water nucleophile). A recent DFT calculation for solvolysis of acetyl chloride included up to six methanol molecules.[52]

CONCLUSIONS

Organic chemist's concepts of analogy or 'similarity' are useful in establishing and interpreting results of linear free energy relationships. Great caution is required if results of multi-parameter correlations *contradict* rather than *refine* the results of single parameter correlations and/or other mechanistic evidence, especially if dissimilar processes are involved. Several recent mechanistic explanations of results from multi-parameter equations for solvent effects[22–24a] are unreliable because both random and systematic errors have been underestimated. We reiterate cautionary comments[21d] about relying on 'excellent' correlation coefficients (e.g. for solvolyses of *t*-butyl bromide in protic solvents, Eqn M in Ref. 21d shows $r = 1.000$, and an incorrect negative dependence on β).

If, the response to one parameter is small compared with the inaccuracies due to inadequacies of the model of solvation and/or errors in the other parameters (e.g. a small response to β or N, compared with polarity, polarizability, and electrophilicity parameters for solvolyses of tertiary substrates), the 'improvement' in the correlation by adding a β term could be spurious and may be due to *any* combination of the other terms, not just simple co-linearity (e.g. $-\beta$ correlating with α); the unexpected results for solvolyses of **1**[23] are due in part to a correlation of $-\beta$ with $(\pi^* + \alpha)$ for some protic solvents. Similarly, examples of various weakly nucleophilically assisted solvolyses were reviewed recently; the claims[22] of a negative dependence on B (even for solvolyses of **4**) and the associated new ion-pair mechanism for solvolyses are unreliable.

Whilst solvatochromic parameters are useful, none of the correlations using them (Eqns (1), (3), and (4), Tables 1–3) to correlate solvolysis rates of chloalkanes are as precise as those based on the closer similarity models (Eqns (2 and 8); solvent nucleophilicity is not well modelled by spectroscopic measurements (e.g. β is insensitive to solvents of low N, Table 5). KOMPH2 (Eqn (5), Table 4)[24a] avoids solvatochromic parameters, but reliability is sacrificed because bulk rather than microscopic solvent properties are incorporated. Also, for the specific case[24a] discussed above, the number of experimental data is small compared with the number of freely-adjustable coefficients. Another alternative, combining solvatochromic parameters with bulk solvent properties [(e.g. $E_T(30)$ with functions of dielectric constant and/or refractive index)][21g] requires cautious further evaluation.

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