Acta Chemica Scandinavica B 35 (1981) 537–554

Linear Free Energy Relationships. Local Empirical Rules – Or Fundamental Laws of Chemistry?

MICHAEL SJÖSTRÖM and SVANTE WOLD

Research Group for Chemometrics, Institute of Chemistry, Umeå University, S-901 87 Umeå, Sweden

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 experimental facts. This is illustrated with data from organic reactivity and solvent effect studies.

In organic chemistry it is easy to make small modifications in a studied process. For example, a reaction can be investigated in different solvents, at different temperatures, pressures *etc.*, or it can be modified by changing a substituent on a reactant. Similarly, other "properties" of compounds such as NMR spectra are often studied by slightly modifying the compounds or their environment.

In the late nineteenth and early twentieth centuries, examples were found where data measured on series of reactions involving compounds perturbated in the same way showed approximate linear relationships to each other. Historically, the earliest example is the relationship between the narcotic effect of a series of drugs and their partition coefficient.[1] The first really chemical example was the Brönsted relation[2] between the catalytic power and the acid/base strength of a series of compounds. In 1935 numerous approximate relations had been reported between pairs of processes modified in the same way. The relations then best investigated were those of rate and/or equilibrium data of series of *meta-* and *para-*substituted benzene derivatives.[3]

Based on these findings, Hammett formulated a relation for the reactivity of substituted benzene derivatives[4,5] which originally took the form shown in eqn. (1).

$$y_k = y_0 + \rho\sigma_k \tag{1}$$

Here y_k is the logarithmic rate or equilibrium constant of the substituted benzene derivative (index k for substituent) and y_0 that of the unsubstituted derivative. This relation, later called the Hammett equation, quantifies the effect of the substituents by constants σ and the sensitivity of the reaction to the substituents by another constant ρ. The latter is specific of the reaction and reaction conditions. The substituent parameter scale was originally defined from substituted benzoic acids in water as in eqn. (2).

$$\sigma_k = \log K_k/K_0 \tag{2}$$

Eqn. (1) is not an exact model but is preferably written as a statistical model with deviations, residuals (ε), as in eqn. (3).

$$y_{ik} = \alpha_i + \rho_i\sigma_k + \varepsilon_{ik} \tag{3}$$

Here the residuals ε describe the non-modelled part of the data y_{ik}. They are due to errors of measurement and imperfections in the model. The latter are, as in all models, an unavoidable consequence of the fact that models are simplifications of a complicated reality. In fortunate cases the models describe 90 – 99 % of the variability

0302-4369/81/080537-18$02.50

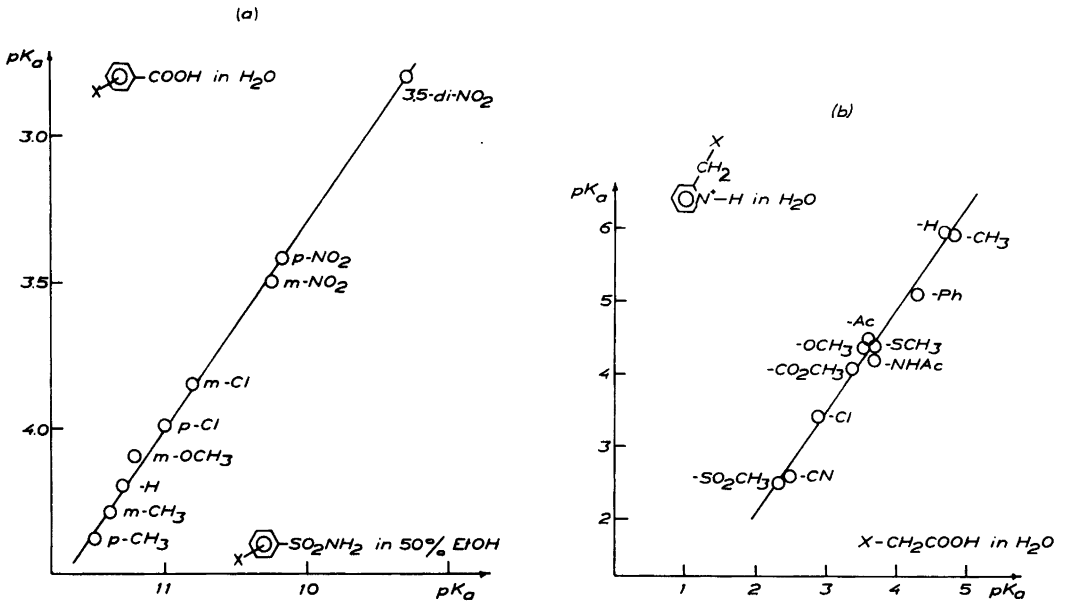
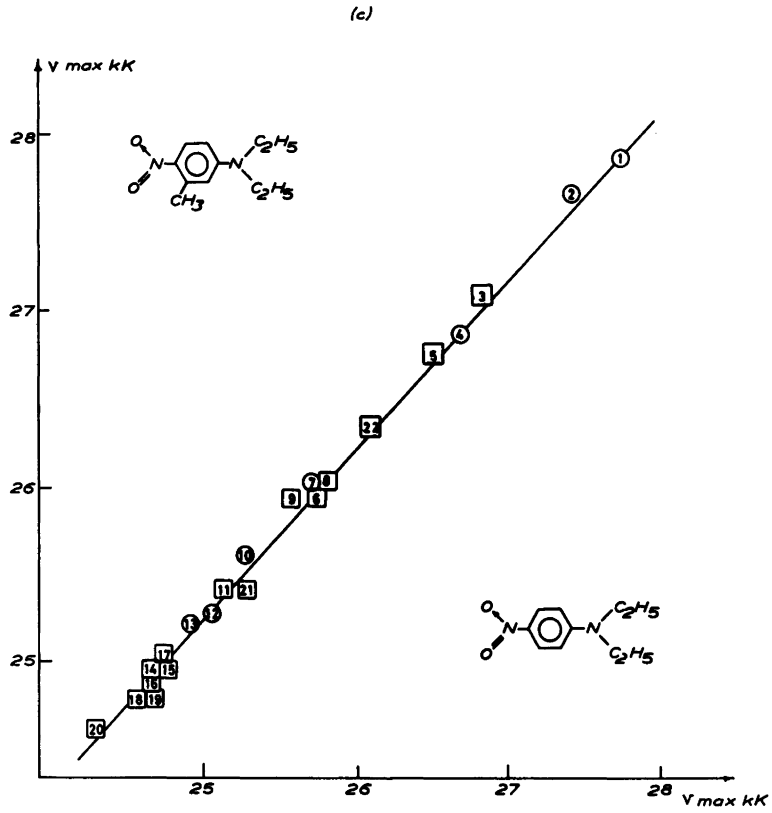


Fig. 1. Series of measurements on chemical phenomena perturbated in the same way often show an approximate linear relation to each other. This indicates that model (3) gives a good description of the measurements. (*a*) A substituent scale, denoted σ^0, has been estimated from these and a large number of other reaction series of *meta* and *para* substituted benzene derivatives. Data from Refs. 10–12. (*b*) Another substituent scale, σ_I, can be estimated from measurements on these and similar aliphatic systems. Data from Refs. 13 and 14.

(standard deviation) of the data in a series. One unresolved question is how much of the data variability the model is expected to describe in ideal and "average" practical cases. Noticable is also that in contrast to model (1), model (3) assumes that the data of the unsubsrituted benzene derivative contain model and measurement errors. This means that in eqn. (3) we have $\alpha_i = y_{i0} - \varepsilon_{io}$ if $\sigma = 0$ for the unsubstituted benzene derivative.

Quantitative models like the Hammett equation are usually called linear free energy relationships (LFERs) since they describe linear relationships between logarithms of rate and/or equilibrium constants. However, quantitative models like (3) are not restricted to describe differences in free energies, but can describe any type of measurements on a process if certain assumptions are fulfilled. We shall therefore use the name extrathermodynamic relationships (ETRs) henceforth. The requirements for the applicability of ETRs will be discussed in a subsequent section. For exhaustive reviews dealing with ETRs, see Refs. 6, 7 and 8*a*. In Figs. 1a–c some examples are given of series of measurements that each is well described by a one-term ETR.

When the model errors become larger, see Figs. 2a–c for examples, one usually wants to decrease their size the either limiting the domain of the model or by inclusion of more terms. The latter leads to the multiple terms ETRs (eqn. (5)) of which the dual substituent parameter (DSP) model is the simplest case, eqn. (4).



(*c*) In the same way as substituent effects can be quantified by substituent scales, solvent effects can be quantified by empirical solvent scales, for example estimated from the solvatochromic shift from these and other indicators. (○, non hydrogen bonding (NHB) solvents and □, hydrogen bond acceptor (HBA) solvents). The solvents are; 1, hexane; 2, cyclohexane; 3, dibutyl ether; 4, carbon tetrachloride; 5, diethyl ether; 6, dioxane; 7, trichloroethylene; 8, ethyl acetate; 9, tetrahydrofuran; 10, anisole; 11, triethyl phosphate; 12, 1,2-dichloroethane; 13, dichloromethane; 14, *N*,*N*-dimethylacetamide; 15, pyridine; 16, *N*,*N*-dimethylformamide; 17, hexamethylphosphoramide; 18, γ-butyrolactone; 19, *N*-methylpyrrolidone; 20, dimethylsulfoxide; 21, ethyl chloroacetate; 22, *N*,*N*-dimethylbenzylamine. Data from Ref. 15.

$$y_{ik} = \alpha_i + \rho_{i1}\sigma_{1k} + \rho_{i2}\sigma_{2k} + \varepsilon_{ik} \quad (4)$$

$$y_{ik} = \alpha_i + \sum_{a=1}^{A} \rho_{ia}\sigma_{ak} + \varepsilon_{ik} \quad (5)$$

Different interpretations of ETRs

Two fundamentally different interpretations of ETRs and the causes of the breakdowns of one-terms ETRs to more complex ones have been forwarded: (a) The classical interpretation as ETRs expressing combinations of "fundamental" effects or (b) an interpretation where ETRs are looked at as empirical models of similarity (EMS).

These two interpretations are historically coupled to the possibilities to statistically relate model (5) to measured data. Before the age of computers, the only way open was to derive the parameters from a standard series where a single component model, as eqn. (3), was adequate and thereafter interpret deviations from the single component model in terms of a second component. The Yukawa-Tsuno extension of the Hammett equation provides a good example of this approach as discussed below.

With computers and statistical data analytic methods of multivariate data – principal components (PC) and factor analysis – model (5)

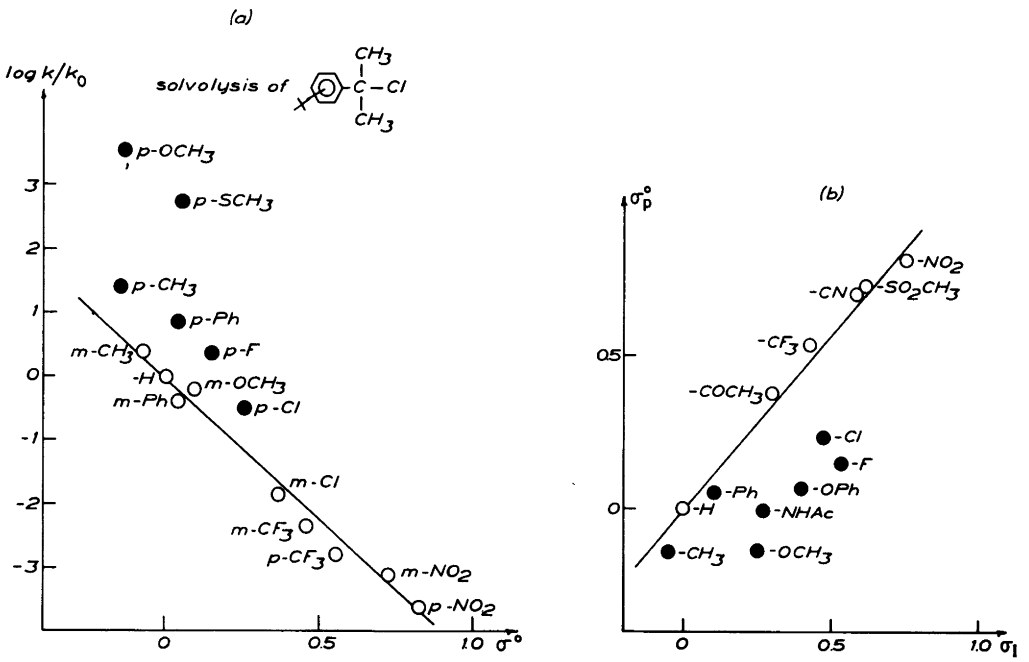
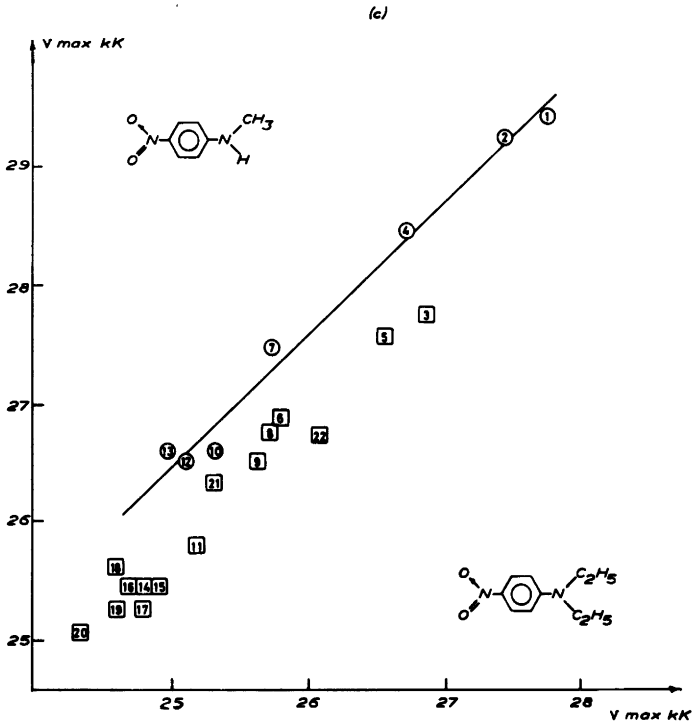


Fig. 2. Examples of breakdowns of simple ETRs. (*a*) For reactions with an electron deficient reaction center, like in solvolysis of substituted *t*-cumyl chlorides, the *para* donor substituents deviate strongly when plotted against the σ^0 scale. Data from Refs. 9, 16 and 17. (*b*) Aliphatic and aromatic substituent constants are poorly correlated to each other. Thus substituent constants from aliphatic systems are not applicable to aromatic reactivity. For the deviating donor substituents, ●, a resonance scale σ_R^0 is defined which is considered to

can be related directly to a matrix (table) of measured data (possibly transformed to logarithms and thereafter perhaps scaled). The data analysis immediately provides information about the adequate number of product terms, A, in eqn. (5) needed to give the model optimal predictive properties. Moreover, the "substituent scales" σ_{ak} ($a = 1, 2, \ldots, A$) are obtained directly from the data analysis together with the "sensitivity parameters", the loadings $*\rho_{ia}$. Reaction series (i) and/or substituents (k) which show appreciable deviations from the model – outliers – are pointed out by the analysis. Measures of fit between model and data are obtained in the usual way as residual standard deviations (RSD).

The mathematics of fitting PC and factor models to a matrix of chemical data is well described elsewhere [18-23] and we shall not repeat the details here. We just note that today with these data analysis methods we are in a situation where we objectively can judge the adequacy of an ETR of a given complexity on a given data set; judge objectively without making assumptions about a single term model fitting part of the data set. The data set used for the evaluation of the ETR can be part of, or the whole data set used to calculate the model parameters. Alternatively, the evaluation set can be a different data set on which one then tests the "transferability" of the model.

*The statistical term loading refers to the fact that the parameters σ_{ak} are calculated as linear combination of the variables y_{ik}. The "weight" or loading ρ_{ia} expresses the influence of variable i in this linear combination.



operate together with the inductive effect. Similarly other resonance scales σ_R, σ_R^+, σ_R^-, are defined to deal with other types of deviations, see for example eqn. (11). Data from Refs. 9 and 13.

(*c*) In this plot one of the indicators (*N*-methyl-4-nitroaniline) has hydrogen bond donor (HBD) properties, in contrast to the indicators in Fig. 1c. Solvents with HBA properties (□) deviate from the approximate linear behaviour of the NHB (○) solvents. Data from Ref. 15.

Classical interpretation

The traditional interpretation is that a one-term ETR expresses the influence of a "fundamental effect" which is universally present in chemical reactions (at least organic ones*). Deviations from this ETR are interpreted as due to new "effects" in addition to the old effect. This interpretation of ETRs predominates in the literature and we will here just give some typical examples.

Reactivity models. The Hammett equation, eqn. (3) above, is a single term ETR describing a single "effect" influencing "normal" aromatic reactions. The interpretation of this "effect" varies, see for instance Refs. 18 and 24. In many reaction series, the points corresponding to *para* donor substituents deviate from the simple one-term model. In the Yukawa-Tsuno relation,[25] eqn. (6), a new substituent scale is introduced to deal with the deviating *para* donors in reaction series with an electron deficient reaction center, see Fig. 2a.

$$\log k_k/k_0 = \rho(\sigma^0 + r\Delta\sigma_R^+) \qquad (6)$$

The substituent constants $\Delta\sigma_R^+$ were defined as the difference between the σ^+ and the σ^0 scales, where the σ^+ scale was defined from the solvolysis of *t*-cumyl chlorides in acetone – water (90 %). Thus for the *para* donors we can interpret this equation as if a σ^0 "effect" is present with the same sensitivity, ρ-value, as for the *para* acceptors and *meta* substituents. Then for the *para* donors, an additional

* We note that ETRs are increasingly used also in inorganic chemistry, see for instance Ref. 8*b*.

resonance effect is considered to operate in parallel with the σ^0-effect.

With the universal applicability of "effects" it follows that the classical "inductive effect" can be defined by data measured on aliphatic systems as well as by data measured on aromatic systems. However, poor correlations are found between the inductive effect defined from aliphatic systems, and aromatic substituent constants like σ_m^0 and σ_p^0 (or σ_p, σ_p^+, σ_p^-), see Fig. 2b. The poor correlations are usually interpreted as due to the influence of a mesomeric (resonance) effect in the benzene system which operates in addition to the inductive effect (σ_I). Furthermore, it is assumed that the blend of the mesomeric and inductive effects is different in the *meta* and *para* positions. Thus it has been proposed that the inductive effect directly can be extracted from σ_m and σ_p constants by finding the best choice of constants $a-d$ in eqns. (7) and (8).[26]

$$\sigma_p = a\sigma_I + b\sigma_R \tag{7}$$

$$\sigma_m = c\sigma_I + d\sigma_R \tag{8}$$

Usually, however a and c are taken to be unity[27-30] due to the assumed structural similarities between the bicyclo[2.2.2]octanecarboxylic acids, used to anchor the σ_I scale, and the benzene system. The resonance scale is then calculated from eqn. (7) with b equal to unity and d estimated to 0.33.

Inductive σ_I-constants have also been calculated directly from ^{19}F NMR shifts of *meta* and *para* substituted fluorobenzenes,[30,31] as in eqns. (9) and (10).

$$\sigma_I = -\delta_m/7.1 + 0.084 \tag{9}$$

$$\sigma_R^0 = (\delta_m - \delta_p)/29.5 \tag{10}$$

Ehrenson *et al.*[24] have proposed that together with a supposedly universal inductive effect, a mesomeric substituent effect ($\bar{\sigma}_R$) is operating with "limited generality" as in eqn. (11). Ehrenson *et al.* propose four different mesomeric scales for different types of reactions.

$$\log k/k_0 = \rho_I\sigma_I + \rho_R\bar{\sigma}_R \tag{11}$$

The choice of mesomeric scale $\bar{\sigma}_R$ is dependent on the reaction type, these scales being calculated from a two-term model with an "inductive scale" fixed at previously defined values.

The approach by Swain and Lupton[32] is another effort to define separate effects by the analysis of different data sets conforming to one-term ETRs. In this approach, any substituent constant σ from a one-term ETR is supposed to consist of a field effect (F) and a resonance effect (R) as in eqn. (12). The field effect F was calculated from σ_m and σ_p according to eqn. (13).

$$\sigma = fF + rR \tag{12}$$

$$F = a\sigma_m + b\sigma_p \tag{13}$$

The constants a and b were estimated from σ' values defined by data measured on the rigid bicyclo[2.2.2]octanecarboxylic acids. By setting R

$$\sigma' = a\sigma_m + b\sigma_p \tag{14}$$

equal to zero for $-N(CH_3)_3^+$ in eqn. (15) α was estimated at 0.56. The resonance term R for the other substituents were then calculated from eqn. (15).

$$\sigma_p = \alpha F + R \tag{15}$$

Solvent effect models. Kamlet *et al.*[33] have found that a one-term ETR well can describe the solvatochromic shifts of non-hydrogen bond donor (non-HBD) indicators, see Fig. 1c. Hence, the effect of the solvents is quantified by a one-term ETR, eqn. (16), with the solvent scale denoted by π^*.

$$\nu_{ik} = \nu_{i0} + s_i\pi_k^* + \varepsilon_{ik} \tag{16}$$

This one-term ETR no longer holds if hydrogen bond donor (HBD) indicators are considered, since hydrogen bond acceptor (HBA) solvents, like acetone, show strong deviations from a one-term ETR, see Fig. 2c. The one-term ETR is then extended to a two-term ETR, eqn. (17). The new solvent scale, β_k, describes the deviating HBA solvents, while the sensitivity, s_i, is kept at the same value as in eqn. (17) for the non-hydrogen bonding (NHB) solvents.[34]

$$\nu_{ik} = \nu_{i0} + s_i\pi_k^* + b_i\beta_k + \varepsilon_{ik} \tag{17}$$

Eqn. (16) is sometimes further extended with a third solvent scale. This (eqn. (18)) is introduced to

$$\nu_{ik} = \nu_{i0} + s_i\pi_k^* + a_i\alpha_k \tag{18}$$

deal with solvents with hydrogen bond donor and acceptor (HBA – D) properties, like ROH solvents, in combination with indicators with HBA properties.[35,36] A general equation [eqn. (19)] is

$$v_{ik} = v_{i0} + s_i\pi_k^* + b_i\beta_k + a_i\alpha_k \quad (19)$$

also formulated, to deal with all three types of interactions.[33]

ETRs as empirical models of similarity (EMS)

In the second interpretation of ETRs, which goes back to Polanyi diagrams[37] of chemical kinetics, and has been refined by Leffler and Grundwald,[38] Palm[39] and most recently by Wold and Sjöström,[18,40] ETRs are interpreted as approximate models with local validity only. According to this interpretation one model is formulated for the reactions of substituted benzene derivatives, another model for open chain aliphatic reactions, possibly a third for the reaction of alicyclic compounds, a fourth for naphthalenes and so on. For solvent effects one model applies for non-HBD indicators, a second for HBD indicators. By statistical analysis one can investigate how far a given model can be applied: one might, for instance, find that indeed the same model applies to aliphatic and alicyclic reactivity. The important point of this second interpretation is that a given ETR is not necessarily universally valid. The substituent scales cannot for certain be used for all types of reactions, they might not map universal "effects". This philosophy rests on the data analytical possibilities given by principal components (PC) and factor analysis. By means of these methods one can indeed objectively judge the applicability of a given ETRs, as shown below.

It is noted that each of the ETRs examples above is consistent also with this second interpretation. According to Popper, the discrimination between these two views must therefore be based on an evaluation of the practicality, *i.e.*, quantitative performance, of models derived from either view.

Summary of introduction

In this presentation we will discuss the differences and empirical evidences for and against the two lines of interpretation. The choice between the two interpretations is in our view strongly connected with the reasons for using ETRs in particular applications. Those who use ETRs for the retrospective rationalization of chemical reactivity are likely to favour the first line of interpretation. Those who are more interested in the use of ETRs as a practical tool of prediction and classification, might prefer the second. In the long run we believe that the interpretation which leads to the most correct predictions will also be the more scientifically correct. With Feyerabend[41] we note, however, that the choice between the conflicting scientific models is at least partly based on irrational arguments.

LFERS AS LOCALLY VALID LINEARIZATIONS OF COMPLICATED FUNCTIONAL RELATIONS

We shall here argue that mathematical models having the form of eqn. (5) arbitrarily well can approximate data measured on ensembles of similar processes (objects, samples, systems). With processes we here mean chemical reactions or equilibria.

The argument is based on identifying the measured data with a continuous function in two vector variables followed by a differentiation of the function and a grouping of the terms in the resulting Taylor expansion. Mathematically the arguments are trivial, but the consequences are profound. Eqn. (5) can be used to describe any data observed on a class of similar "objects" regardless of whether the objects are chemical reactions, complicated chemical samples or biological individuals and regardless of whether the data are kinetic, thermodynamic, spectroscopic, or express product distributions or concentrations of constituents in the objects. A corollary of the mathematical derivation below is that any variable measured on an ensemble of sufficiently similar objects is correlated to any other variable measured on the same objects; the correlations being better the closer the similarity between the objects. Together, these consequences are important for the philosophy of chemistry; it is always possible to construct empirical models valid locally for similar objects or processes, but the relation between the variables measured on similar objects have no more fundamental meaning than being indicators of similarity.

Now the derivation. We consider an ensemble

(S_{ik}) of similar chemical systems obtained by slightly modifying (perturbing) the system S_0 in two distinct ways, for instance modifying the reaction center (i) and the substituent (k). We now make one measurement y on each modified system. We describe formally these measurements as a function F plus small "errors of measurements" ε, eqn. (19).

$$y_{ik} = F(z_i, x_k) + \varepsilon_{ik} \tag{19}$$

The function F is constructed in such way that all changes in the measurements y induced by the first modification i, let's say reaction center, are described as caused by changes of a vector variable Z in F. Analogously, all changes in y induced by the second modification k, say change of substituent, are described as caused by changes of another vector variable X. Though the function F may be very complicated and the vector variables Z and X may contain many elements, this formalism is in accordance with physical and chemical theory. Thus quantum theory represents any observable y as a solution of an operator equation, which makes y have function like behaviour. Classical thermodynamics is based on continuity properties of observables, *i.e.*, a function-like behaviour.

We note that although the influences of the two modifications are separated in different vector variables this description includes all types of interaction between the two modifications. In simple cases such interactions might be described by simple cross terms zx; in more complicated cases by more involved functional relationships between elements in vector variables.

In chemical language the two vector variables contain as elements microscopic (non-observed)[42] variables such as changes in charge distribution, dipole interactions, solvation, orbital energies, *etc.*, that we like to use to "explain" the variation of a measurement y between one reaction and another or one compound and another. The crucial point of this derivation is that we need not "know" these microscopic variables; it is sufficient to postulate the existance of such variables and that they have certain continuity properties.

Let us now study the behaviour of function F in a small area $Z+\Delta Z$, $X+\Delta X$. In particular, we consider the case when the perturbation due to the second modification ΔX is very small. In such case all elements in X vary linearly with respect to each other and the elements in ΔX, Δx_s can all be described as multiples of a single variable t (Fig. 3). Thus eqn. (19) reduces to eqn. (20).

$$y_{ik} = F(Z,t) + \varepsilon_{ik} \tag{20}$$

Let us now Taylor expand this function around the point (Z_0, t_0). The indices p and r denote the elements in the vector variable Z.

$$F(Z,t) = F_{00} + \sum_r F'_r \Delta z_r + F'_t + \sum_p \sum_r F''_{pr} \Delta z_p \Delta z_r +$$

$$\sum_r F''_{rt} \Delta z_r \Delta t + F''_{tt} \Delta t^2 + \text{cubic terms and higher} \tag{21}$$

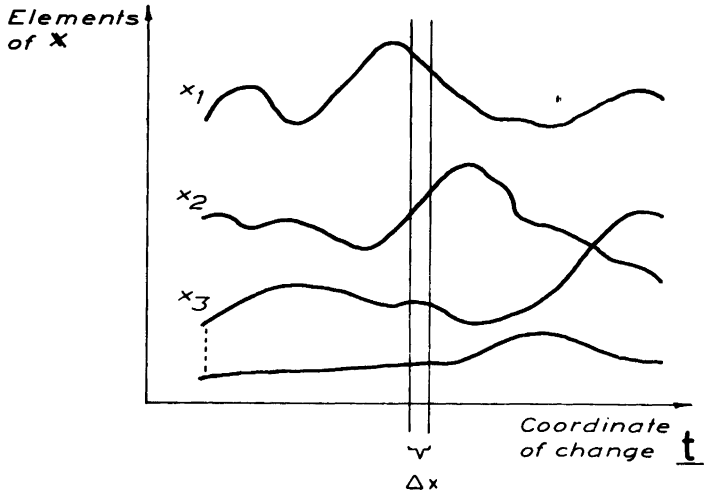


Fig. 3. When the change in Δt in the coordinate t is sufficiently small, the elements in the vector X vary linearly with each other.

This can be rearranged to eqn. (22) where $R(3)$ and $R'(3)$ denote the remainder with cubic and higher terms.

$$F(Z,t) = F_{00} + \sum_r F'_r \Delta z_r + \sum_p \sum_r F''_{pr} \Delta z_p \Delta z_r +$$

$$\Delta t[1 + (1/F'_t)\sum_r F''_{rt} \Delta z_r] F'_t +$$

$$\Delta t^2[1 + (1/F'_t)\sum_r F''_{rt} \Delta z_r] F''_{tt} -$$

$$\Delta t^2[\sum_r F''_{rt} \Delta z_r] F''_{tt}/F'_t + R(3) =$$

$$F_{00} + \sum_r F'_r \Delta z_r + \sum_r \sum_p F''_{pr} \Delta z_p \Delta z_r +$$

$$[1 + (1/F'_t)\sum_r F''_{rt} \Delta z_r][F'_t \Delta t + F''_{tt} \Delta t^2] + R'(3) =$$

$$f(Z) + g(Z)h(t) + R'(3) \qquad (22)$$

Identifying Z with i and t with k we get the one-term ETR [eqn. (3)] where now ε_{ik} includes the remainder $R'(3)$.

Since $R'(3)$ can be made arbitrarily small by making ΔZ and Δt sufficiently small, this proves that a one-term ETRs, eqn. (3), describes any data observed on sufficiently similar processes or objects.

One important point concerns the size of $g(Z)$ in eqn. (22); *i.e.*, ρ in eqn. (3). In the way the parameters scales ρ and σ are defined, F' is set constant (the same "σ" scale is used in all reaction series, the "sensitivity" is expressed by "ρ"). Hence a large ρ-value corresponds to a large $\sum F''_{rt} \Delta z_r$. This term also appears in $R'(3)$. Hence one would expect this to be larger for large ρ-values than for small ρ-values. Indeed this was found by Sjöström and Wold;[9,17] see further section "Behaviour of LFERs in practice".

We can now continue the derivation by splitting $R'(3)$ into terms containing only ΔZ_r times other terms containing only Δt and in the same way show that eqn. (4) with $A = 2$ is a general similarity model of cubic approximation power and so on. This was done in Ref. 40 and we will not tire the chemically minded reader with these mathematical arguments. We just note that eqn. (5) has the same approximation properties for tables (matrices) of data $Y = (y_{ik})$ as polynomials have for bivariate data (y_k, x_k). Provided that the objects k are in some way "similar", the model can approximate data measured on the objects. The greater the dissimilarity between the objects k, the more terms are needed in the model to reach a given approximation power. We note also that a special use of eqn. (4) is the quaratic model of eqn. (23). This is the first "breakdown" of the one term model (3) as the diversity increases between the objects in the "class".

$$y_{ik} = \alpha_i + \rho_{i1}\sigma_k + \rho_{i2}\sigma_k^2 + \varepsilon_{ik} \qquad (23)$$

In conclusion, the present derivation predicts the following behaviour of ETRs. In particular, points 4 and 6 are in contrast to the classical ETRs interpretation. They provide criteria which can be tested on chemical data.

1. For a given class of similar processes of objects modified in two ways, eqn. (5) can approximate data measured on the objects.

2. The simplest model corresponding to the closest similarity between the objects is the one-term ETR, eqn. (3). When the diversity increases slightly, a quadratic model (23) is applicable; *i.e.* curvature is an indication of moderate breakdown of the one-term ETR.

3. For sufficiently similar processes or objects, any measured variable i is linearly correlated to any other measured variable j.

4. The greater the diversity between the objects and/or processes, the more terms are needed in the similarity model. For a given model the fit gets worse when the diversity increases.

5. If the diversity between the objects is too large, the model collapses; *i.e.* the σ_{ak}-values contain little or no predictive information.

6. The loading ρ_i should be related to the residual RSD for processes within a class.

DATA ANALYSIS AND CRITERIA FOR GOODNESS OF FIT BETWEEN MODEL AND DATA

When relating a model like eqn. (5) to a data set we have two different situations.

A. Fitting model (5) to a matrix (table) of measured data Y. The data may be unscaled or scaled to unit variance for each series in the case the variability in the series differs appreciably. The analysis involves two problems.

(1) The estimation of the adequate number of product terms, components, A. This is done by cross-validation[43] (CV) in the following sequential procedure. We start with the model with $A = 0$ and

evaluate the significance of the first component ($A = 1$) in the following way: Part of the data – matrix elements selected in a pseudo-random fashion – are kept out of the data matrix and the one component model fitted to the remaining incomplete data matrix. The resulting parameters ρ_{il} and σ_{lk} are then used to calculate "predicted" values for the kept out matrix elements. The sum of the squared differences between the predicted values and the actually observed values for the kept out elements is formed. This sum is called PRESS (prediction sums of squares). Then the data matrix is restored. Other elements are then kept out, the model parameters estimated, predictions calculated for the kept out elements and the squared differences between prediction and observed values for kept out elements are added to the previous PRESS. The process is repeated until each element in the data matrix has been kept out once and only once. The PRESS now measures the prediction error of the one component model. If PRESS is smaller than the residual sum of squares (RSS) for the zero component model (corrected for the number of degrees of freedom) the one component model is significant. One then fits the one component model to the complete data matrix, forms the residuals and proceeds with the testing of the next component. This is done in the same way but now one tests whether the residuals can be modelled with a one-component model or not. Finally one arrives at a component which is non-significant and the CV procedure stops.

The CV procedure rests on two properties of the PC model.

(i) The components are orthogonal to each other and can therefore be "peeled off" and thereby evaluated one after another.

(ii) The one component PC model can be estimated also for incomplete data matrices.

The CV procedure thus gives information about which number of components, A, gives model (5) the best predictive properties. We note that the CV procedure usually leads to fewer components than other evaluation procedures:[43] the predictive performance is harder on a model than the degree of retrospective fit.

(2) Calculations of parameters α_i, ρ_{ia} and σ_{ak}. Once the adequate number of components, A, has been determined by the CV procedure, the determination of the values of the α_i, σ_{ak} and ρ_{ia} ($a = 1, 2, ..., A$: $i = 1, 2..., M$ and $k = 1, 2, ..., N$) which give the model the best fit to the data in the least squares sense is numerical routine accomplished with any statistical standard package. This analysis also gives values of the reisudals ε which can be used to evaluate the fit of the series (i) or a "substituent" (k).

We note that the parameter vectors (σ_{ak}) are orthogonal to each other. Hence, if one wishes to relate the resulting σ_{ak}-values (in case $A > 1$) to a preconceived scale, say s_k, this is done by "rotation" of the different σ_{ak}-vectors. The coefficients in this rotated combination is simplest determined by linear regression.

B. Evaluating the fit of a given σ_{ak}-scale to one reaction series (i). The data analytic problem now is one of multiple regression[44] since the σ_{ak}-scales are fixed. Only the parameters α_i and ρ_{ia} are estimated. To have a criterion of the goodness of fit which is easy to use and which corresponds to the predictive properties of the model we also here use the cross validation criterion. This is now done by keeping aside part of the observations (say every third value), fitting the model to the remaining data. We obtain from the resulting α_i and ρ_{ia} values and the predetermined σ_{ak} values predicted values for the kept out observations. The sums of squared differences between these predictions and the actual values of the kept out points are formed (PRESS). Then another part of the observations is kept out and so on until each point has been kept out once. The resulting PRESS is then a measure of predictive performance of the model on the given series. Below we refer to this method as the CMREG method (cross-validated multiple regression). The squared root of PRESS divided by n (n observations in the reaction series) can then be compared with the standard deviation around the mean (SDM) of the data in the series. The percent of unexplained standard deviation in the data for a series when fitted to a given σ_{ak} scale is then obtained by multiplying $(\text{PRESS}/n)^{1/2}/\text{SDM}$ with 100, which we will refer to as %UNEX SDM.

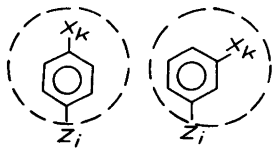
BEHAVIOUR OF ETRs IN PRACTICE

Hammett equation

The most prominent example at present of a large body of data that well can be described by a simple similarity model as eqn. (3), is the rate and equilibrium constants of *meta* and *para* substituted aromatic systems. Thus this type of data is well

suited to study the behaviour of chemical data in general, and to study the breakdown of simple ETRs.

In the Hammett equation *meta* and *para* substituents are treated as separate objects in the same model. In our view, this is rationalized most easily if we see a substituent, or any other discrete part of the molecule corresponding to the subscript k, in terms of a core and a shell, as in Scheme 1. In the



Scheme 1.

core, any number of variables may operate in any complex way, despite a regular behaviour outside the shell. In the case of the Hammett equation, we observe the "effects" of the substituent X-Ph in the reaction part. Since a one-component ETR is valid, the "effects" evidently can be approximated by a change of a single variable t; the reaction center lies outside the shell.

An extensive statistical analysis has been done on a large body of data that follows the Hammett equation ($\sim$60 substituents and $\sim$60 reactions).[9] Thus the body of data was described by model (3). Some features in the behaviour of the data have been found that can be taken as clear indicators in favour of the EMS interpretation.

Model errors. In a plot of the residual standard deviation RSD for each series against their ρ-values a linear relation is seen (Fig. 4). The enhanced RSD values cannot be due to increasing errors of measurements since the given error of measurements is much smaller and show no dependence on ρ. Hence, we interprete the increase of RSD with ρ as increasing model errors. This is expected as a consequence of the EMS approach as discussed above.

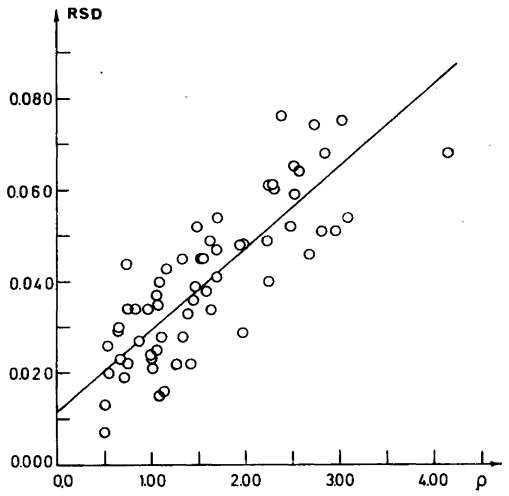


Fig. 4. The residual standard deviation (RSD) is found to be a function of ρ in the statistical analysis of the Hammett equation. The error of measurements should not show a dependence of ρ.

Curvature. If the variation of the elements in Z or in X is large over the experimental width, terms

Table 1. Some examples of reaction series showing a significant curvature (P = 0.05) to the σ^0 scale.

Series[a]	Linear model $y=a+b(\sigma^0)+e$			Curved model $y=a'+b'(\sigma^0)+c'(\sigma^0)^2+e$				
	a	b	RSD	a'	b'	c'	RSD	F[b]
1	−0.048	1.64	0.10	0.051	−2.40	1.05	0.05	27.7
2	−3.69	−2.26	0.18	−3.59	−3.66	1.94	0.06	47.6
3	−0.068	−4.42	0.17	0.024	−5.43	1.46	0.13	6.7

[a] The reaction series are; *1*, solvolysis of benzyl chlorides, 50% EtOH; data from Ref. 45 (substituents: −H, *m*-CH_3, *m*-Cl, *m*-CF_3, *m*-F, *m*-NO_2, *p*-NO_2, *m*-OCH_3, 3,4-di-CH_3, 3,5-di-CH_3, 3,5-di-OCH_3); *2*, solvolysis of benzyl tosylates, 56% acetone; data from Refs. 46 and 47 (substituents: −H, *m*-CH_3, *m*-F, *m*-Cl, *m*-Br, *m*-I, *p*-NO_2); *3*, cleavage of aryltrigermanates, H_2O, CH_3COOH; data from Ref. 48 (substituents: −H, *m*-CH_3, *m*-F, *m*-Cl, *m*-Br, *m*-CF_3, *p*-CF_3, *p*-CO_2CH_3, *m*-COOH, *m*-NO_2, *p*-NO_2, *m*-OCH_3). [b] With this F-test the residual variance (RSD^2) of the linear model is compared with the residual variance (RSD^2) of the curved model. In all the cases the linear models give significantly larger (P = 0.05) residual variances compared to the curved model.

from $R(3)$ must also be considered. As earlier shown $R(3)=g(Z)h^2(X)+R(4)$. If $R(4)$ is small, this term is included in the residuals, but a moderate curvature is expected when the width of the substituent effects increases (ρ is large for a series) or if the variations in the elements in Z is large, as for a reaction series with moderately changing reaction mechanism. In Table 1 we give some examples of reaction series that show curvature when fitted to the earlier mentioned σ^0 scale. For the solvolysis of benzyl tosylates Hammond *et al.*[49,50] have investigated the mechanism thoroughly by changing temperature, solvent composition and by adding anions such as Cl^- and NO_2^- to the solvolysis medium. The results from these investigations support a systematic variation in a single mechanism. This is consistent with the EMS interpretation of this curvature.

ANALYSIS OF SUBSTITUENT EFFECTS IN ALIPHATIC AND AROMATIC REACTIVITY

With the approaches that are reviewed in the introduction [eqns. (7)–(10) and (12)–(15)] it is possible to extract substituent constants from aromatic reactivity that are quite similar to aliphatic substituent constants. These findings have formed the basis for the assumption of the existence of a universal inductive effect, present in aliphatic as well as aromatic reactivity. Thus it should be possible to extract this universal inductive effect from aliphatic as well as from aromatic reactivity. To investigate if this is possible we have collected five series of data (see Table 2) that can be considered as aliphatic series since the substituents are attached to sp^3 hybridized carbons. Eleven substituents were chosen for which measurements were available for all series.

A PC–CV analysis showed that a one-component model was adequate to describe the systematic variation within the data set. To determine the predictive ability among the series, we delected series *1* and extracted a one-component model from the remaining four series. The resulting substituent parameter scale was then used to predict the measurements of the deleted series with the approach described above as the CMREG method.

The standard deviation of the prediction errors PRESS of series *1*, can now be compared with the standard deviation around the mean of the data in the series denoted %UNEX SDM. As seen in Table 2, 13% of the standard deviation in series *1* is unexplained by the substituent scale from series *2* –*5*. The same scheme is then followed to predict each of the series *2* – *5*. The mean values of %UNEX SDM, denoted MEAN %UNEX SDM, for series *1* –*5* is 12% as long as substituent scales from

Table 2. Prediction ability of aliphatic and aromatic substituent scales, S(IA) and S(IIA), respectively, expressed as %UNEX SDM (see text), tested on p*K* in water of 5 series of aliphatic compounds.

Series[a]	S(IA)[b]	S(IIA)[c]				
	$A=1$	$A=1$	$A=2$	$A=3$	$A=4$	$A=5$
1	13	59	19	20	23	26
2	9	63	19	19	21	20
3	9	57	17	20	21	20
4	12	64	17	18	24	32
5	16	54	17	13	16	21
SPRESS[d]	0.63	14.1	1.18	1.30	1.87	1.79
F=SPRESS/0.63[e]		*22.4*	*1.87*	*2.06*	*2.96*	*2.84*

[a] The series are: *1*, α-X-2-methylpyridinium ions (data, Ref. 14): *2*, α-X-3-methylpyridinium ions (data, Ref. 14): *3*, α-X-4-methylpyridinium ions (data Ref. 14): *4*, 4-X-quinuclidines (data, Ref. 51): *5*, X-acetic acids (Ref. 13). The substituents –X are in all cases: –H, $-CH_3$, –Ph, –CN, –Ac, $-CO_2CH_3$, –NHAc, $-OCH_3$, $-SCH_3$, $-SO_2CH_3$, –Cl. [b] The substituent scales used for prediction were calculated from four series among series *1* – *5* and thus the predicted series was not used in the derivation of the S(IA)-values used for prediction. [c] S(IIA), where calculated from σ_m^0, σ_p^0, F, R, $\sigma_I^{0\,F-NMR}$, $\sigma_R^{0\,F-NMR}$. Data from Refs. 9, 27, 31 and 52. [d] SPRESS $=\sum_{i=1}^{5}$ PRESS, *i.e.* the sum of the squared prediction errors for series *1* –*5*. [e] With this F-test, SPRESS of the aromatic substituent scales, used to predict the aliphatic series, is compared with SPRESS of the aliphatic substituent scales (=0.63). The F-values in italics are significant on the 95% level. Thus, overall the aromatic substituent constants give significantly worse prediction of pK of aliphatic compounds compared to substituent scales from aliphatic series.

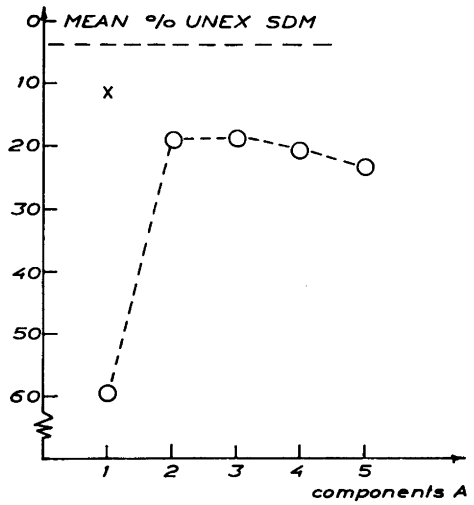


Fig. 5. Mean percentage of unexplained standard deviation (MEAN %UNEX SDM) in data of different substituent scales when applied to p*K* of five series of aliphatic compounds. ×: Substituent scales from aliphatic systems. ○: Substituent scales from aromatic systems. Broken line indicates the estimated errors of measurements in relation to the mean of SDM of the series used.

aliphatic data is used for prediction, see Table 2 and Fig. 5.

From the classical point of view, aromatic substituent scales should contain the same universal inductive effect. To investigate this we have extracted the systematic information from a data set where for each substituent the aromatic substituent scales σ_m^0, σ_p^0, F, R $\sigma_R^{0\,F-NMR}$, $\sigma_I^{0\,F-NMR}$ are given. With this organization of the data matrix, we now investigate the complexity of the interaction between the substituent and aromatic moiety, see Scheme 2.

A 5-component model was needed to describe the systematic part in the data according to CV. The predictive properties of the five substituent scales were investigated with the CMREG approach in the same way as the substituent scales from aliphatic data. In this case a linear combination of the two or three first components gave the best prediction of the aliphatic series, see Table 2 and Fig. 5 for the results. The results clearly show that aromatic reactivity contain predictive information of the behaviour of aliphatic systems. However, even if one of the series is somewhat better predicted with aromatic substituent constants, the overall prediction ability of the aromatic substituent scales was significantly worse compared to the aliphatic substituent scales. This is shown by the *F* test* in Table 2 where the variances of the overall prediction errors, SPRESS, with the two types of substituent scales are compared.

We also note the gaps between the predictive errors and the errors of measurements (see Fig. 4). These gaps can, if we accept the EMS approach be explained as the existance of model errors and thus a consequence of the approximate nature of the models applied. The gaps and the overall worse prediction of aliphatic reactivity using scales from aromatic reactivity are difficult to explain from the classical point of view.

Summary of aliphatic–aromatic substituent analysis

1. An aliphatic data set containing 5 series, 11 substituents was well described by a one-component model. On an average, models from aliphatic data predicted 88% of the SDM in aliphatic data.

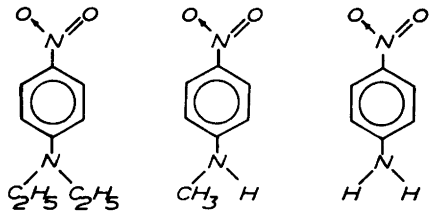
2. A data matrix consisting of the values of 6 aromatic substituent scales for the same 11 substituents needed a 5-component model. The best combination of these scales had a predictive ability of 82% of the SDM of the aliphatic data set, significantly less than the 88% of the scales extracted from the aliphatic data set.

ANALYSIS OF SOLVENT EFFECTS

In analogy to the analysis of aliphatic and aromatic data, we have investigated the behaviour of solvatochromic shift of indicators. From the excellent data of Kamlet *et al.* it has been possible to form a complete data set consisting of solvatochromic shifts of 16 indicators in 15 solvents of hydrogen bond acceptor (HBA) type.

The indicators are of two types: non-hydrogen bond donor (non-HBD) indicators typified by I and hydrogen bond donor (HBD) types. The HBD indicators are of two types with one and two

* The *F*-test measures the significance of the difference between two variances. In the present case the test is used to compare the prediction errors of two different scales.



I *II* *III*

Scheme 2.

hydrogens accessible for hydrogen bonds, typified by II and III, see Scheme 2, and Figs. 1c and 2c.

A PC–CV analysis of the shifts of the 7 non-HBD indicators (I) showed that a one-component model was sufficient to describe the systematic part in the data. With the aim of investigating the predictive power among the non-HBD indicators, indicators *1* and *2* were deleted. A PC–CV analysis was repeated on the remaining data set with measurements of 5 indicators and a one-component model was sufficient to describe the systematic part in the data. The CMREG approach was then used to investigate the predictive information in the solvent scale determined from indicators *3–7* on the solvatochromic shifts of indicators *1* and *2*. Solvent scales were thereafter calculated from indicators *1*, *2*, *4–7* and then finally *1–4*. The predictive properties of these scales were investigated on indicators *3* and *4* and on indicators *5–7*. The results are presented in Table 4 and in Fig. 6 and the origins of the solvent scales are presented in Table 3. On an average, 13% of the standard deviations (SDM) in the series were unexplained by the calculated solvent scales.

PC models were also extracted from the solvatochromic shift of HBD indicators *8–14* (set IV) and from the subsets II and III, see Table 3. Two components were needed to describe the systematic part in the data set. Some further components were also determined, however. The solvent scales were then used to predict the behaviour of indicators *1–7* with the CMREG method. As seen from the results presented in Table 4 and Fig. 6 the overall predictive ability of the solvent scales from HBD indicators is significantly lower than that of the solvent scales derived from the non-HBD indicators.

Summary of solvent effect analysis

1. Non-HBD indicators (I) are well modelled with a one-component model. On an average, models from non-HBD indicators predict 87% of the SDM in the data of the non-HBD indicators.

2. HBD indicators (set II, III, IV) need two-components models. These predict 78, 65 and 80%, respectively, of the SDM in set I.

3. The scales extracted from set II, III and IV have a prediction ability on set I, which is significantly less than the scales from set I.

DISCUSSION

a. General

The scope of this review is to provide evidence for the non-generality (non-transferability) of

Table 3. The origins of solvent scales used to predict the solvent effects of non-HBD indicators.

Solvent scales[a]	Components *A*[b]	Indicators[c]	Predicted series[c]
T(IA)	1(2)	*3–7*	*1, 2*
T(IA)	1(2)	*1, 2, 5–7*	*3, 4*
T(IA)	1(2)	*1–4*	*5–7*
T(IIA)	2(3)	*8–11*	*1–7*
T(IIIA)	2(4)	*12–16*	*1–7*
T(IVA)	2(4)	*8–16*	*1–7*

[a] Solvents in all cases; 3, 5, 6, 8 – 11, 14 – 21 for numbering of solvents see Fig. 1c. [b] Numbers of significant components in eqn. (5) according to CV and within parenthesis the number of calculated components. [c] Indicators; *1*, 4-nitroanisole; *2*, *N*,*N*-diethyl-3-nitroaniline; *3*, 4-methoxy-β-nitrostyrene; *4*, *N*,*N*-diethyl-4-nitroaniline; *5*, *N*,*N*-dimethyl-4-aminobenzophenone; *6*, *N*,*N*-3,5-tetramethyl-4-nitroaniline; *7*, *N*,*N*-diethyl-3-methyl-4-nitroaniline; *8*, *N*-methyl-4-nitroaniline; *9*, *N*-ethyl-4-nitroaniline; *10*, *N*-isopropyl-4-nitroaniline; *11*, *N*-ethyl-3-nitroaniline; *12*, 3,5-dimethyl-4-nitroaniline; *13*, 4-aminobenzophenone; *14*, 3,5-dinitroaniline; *15*, 3-nitroaniline; *16*, 4-nitroaniline. Data from Refs. 15, 33, 34, 53 and personal communication from Dr. M. J. Kamlet.

Table 4. Prediction ability of various solvent scales, T(XA)[a] tested on ν_{max} of 7 indicators of non-HBD type and in 15 HBA solvents. The prediction ability of a solvent scale T(XA) is expressed as %UNEX SDM (see text).

No. of indicator	T(IA)		T(IIA)			T(IIIA)				T(IVA)			
	$A=1$	$A=2$	$A=1$	$A=2$	$A=3$	$A=1$	$A=2$	$A=3$	$A=4$	$A=1$	$A=2$	$A=3$	$A=4$
1	15	15	24	21	19	51	35	37	37	39	21	19	20
2	18	19	33	30	34	60	44	49	46	48	30	34	23
3	18	22	34	28	29	62	38	42	44	50	23	23	23
4	9	8	27	16	17	56	27	27	29	44	13	14	13
5	17	19	34	25	24	62	45	54	56	50	24	17	22
6	8	9	27	17	17	57	30	33	32	44	14	13	13
7	11	13	24	16	17	57	26	26	25	44	13	14	11
SPRESS[b]	0.70	0.78	3.24	1.74	1.90	11.6	4.21	5.40	5.48	7.91	1.44	1.43	1.18
F=SPRESS/0.70[c]		1.11	*4.63*	*2.49*	*2.71*	*16.5*	*6.0*	*7.71*	*7.82*	*11.3*	*2.05*	*2.04*	*1.69*

[a] The origins of the solvent scales and the used solvents are given in Table 3. [b] SPRESS = $\sum_{i=1}^{7}$ PRESS *i.e.* the sum of the squared prediction errors for indicators *1* – 7. [c] With this F-test, SPRESS of the solvent scales from indicators with HBD properties, used to predict the behaviour of the non-HBD indicators, is compared with SPRESS (=0.70) of the solvent scales T(I1) from the non-HBD indicators. The F-values in italics are significant on the 95% level. Thus in these cases the used T(XA) scale gives significantly inferior prediction compared to the T(I1) scales.

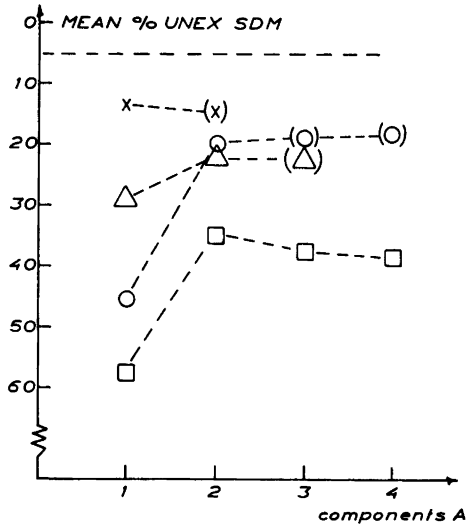


Fig. 6. Mean percentage of unexplained standard deviation (MEAN %UNEX SDM) of different solvent scales, when applied to indicators of non HBD type. ×, solvent scales from NHB indicators (type 1); △, solvent scales from HBD indicators of type II; □, solvent scales from HBD indicators of type III; ○, solvent scales from HBD indicators of type II and III together, data set IV; Broken line, see Fig. 5.

chemical "effects" and their quantitative models (ETRs). We favour an interpretation of these models as being local linearizations of very complicated relationships; the full complexity of which we can never, not even in principle, grasp. Even if the models are not generally applicable, they are still most useful both for "applied" work in, say, chemical reactivity and structure-biological activity studies as well as for the basic understanding of organic chemistry.

The reason for our strong emphasis on the local validity of ETRs is our belief (empirically founded) that a failure to understand this non-generality of organic chemical models leads to very a confusing picture and apparently contradictory results in the quantitative investigation of organic reactivity.

Above we have shown that aromatic reactivity *partly* can be transferred to aliphatic reactivity and the reverse. However, the predictive precision of models derived in one area (say aromatic reactivity) and applied in another area (say aliphatic reactivity) is significantly lower than the predictive precision of models derived from reactions in the same area as those studied.

In the same way, we have shown that the predictive properties of solvent effects models are more precise for indicators of the same type as those for

which the models are "calibrated" and significantly less precise for less similar indicators.

This property of local validity of ETRs is rather easy to understand in terms of perturbation theory but is not consistent with the idea that the same "effects" operate everywhere in organic chemistry.

b. Scope of ETRs

We can now discern two different main objectives with ETRs. The first (and simplest to discuss) is the use of ETRs to predict the behaviour of chemical compounds in various reaction systems, for instance their reactivity in a given step in a synthetic scheme or their biological activity *versus* some biological test system. For this "empirical" use of ETRs the interpretation of the models is not of primary interest. Rather, one desires good predictive properties in a given application.

Since the predictive precision is better when the ETR is derived from the behaviour of systems similar to the one studied, there should be little controversy regarding the preferability of the "statistical" approach in this context. Exner[8] has stated that the best approach to a precise prediction of reactivity is the plotting of one series against another. We note that principal components analysis is a generalization of this approach where, instead, a series is "plotted" against components summarizing a battery of similar series. Thus parameters derived statistically give more precise predictions in the domain of applicability of the model because "random" fluctuations in individual series have been smoothed out.

This does not mean that large deviations for the "normal behaviour" can be overlooked in a statistical derivation of substituent parameters. On the contrary, the statistical approach is the only one where the level of unacceptable deviations can be specified and deviations exceeding this level detected.

The second objective is more central to organic chemistry and concerns the use of ETRs to "understand" organic reactivity. We note that the philosophy of science with Gödel, Bohr and Heisenberg gave up hope of being able to understand "how things really are". Instead the only thing a scientist can do now is to construct models of greater or less generality. Thus the battle over the interpretation of ETRs is not whether the "effects" are "true" or not – a philosophically meaningless question – but rather about their range of applicability. Thus the traditional interpretation of ETRs can be said to regard the models as being of general scope (within organic chemistry) while the present interpretation regards them as considerably less general.

Also, even if we were to accept the general scope of ETRs, we think that the least one has to do is to verify this generality of the "effects". The efforts of a rigorous analysis of reactivity data strongly indicate that "effects" are not generally valid.

However, many analyses have been made with limited range of substituents and reactions. The results of such analysis often are interpreted as supporting the generality of ETRs in their uncomplicated form. A good example of this is our recent analysis of the influence of alkyl groups on aliphatic reactivity[54] where the statistical results show that one needs to postulate at least three "effects" even with this limited range of reactions and substituents. DeTar,[55] analyzing a subset of the same set of data, finds a simpler (one component) model after deleting data that were not consistent with this idea. The resulting arguments are, in our view, hardly constructive. Different models can be evaluated only when they are applied to the same level of statistical rigour.

An interesting example is seen in a recent analysis of acidity function data.[56] In this investigation it was shown that a two-component model is needed to adequately describe the carefully measured data set. When restricting the range of the solvent variation, various one-component models are adequate. Each of these is a local linearization of the more complicated two-component model needed for the full data set.

The arguments concerning the two different ways of interpreting ETRs are, in our view, unnecessarily confused due to the inability to keep apart on the one hand statistical significance of the model and on the other hand chemically exhaustive fit to a model (*i.e.* a fit that explains fully the systematic part of the data). There is no doubt that data measured on a class of aliphatic reactions contain a component which is significantly correlated to data measured on aromatic reactions. However, we and others have shown that this correlation is not as good as that obtained with a component derived from aromatic reactions. Thus the "aliphatic" reactivity parameters do not give an exhaustive fit in aromatic reactions – the model is not perfectly transferable

between aliphatic and aromatic reactions. Moreover, the difference in fit between aliphatic and aromatic substituent scales varies between aromatic reactions in a difficult-to-predict manner; it is not so that, say, 80% of the inductive "aliphatic" effect is transferable to aromatic systems.

In this context it is perhaps worthwhile to discuss the results of Taft and Grob,[57] which by many are cited as support for the classical ETRs interpretation. In their analysis they plot the difference in pK_a between 4-substituted pyridines and 4-substituted quinuclidines against σ_R^+ and obtain a straight line apparently indicating an "isolated resonance" effect. When looking into this example, however, one finds that σ_R^+ is defined as the difference between σ^+ (aromatic) and σ_I (aliphatic). The latter (σ_I) is derived from 4-substituted bicyclooctanecarboxylic acids and similar systems.[24] Now, 4-substituted quinuclidines are very similar to 4-substituted bicyclooctanes. Hence we would expect that the pyridines are modelled by a σ^+ type of scale and the quinuclidines by a σ_I (aliphatic) scale. If we now subtract the two nonrelated models from each other we, of course, still get straight lines without any physical meaning even if we rename $\sigma^+ - \sigma_I$ as σ_R^+. The difference between two straight lines remains a straight line even if the two original lines are completely unrelated to each other. Hence we conclude that the Taft-Grob example is no support for the classical ETRs interpretation.

A further complication with the classical interpretation is the choice of standard series. The dilemma is, which of the series is best suited to describe a "fundamental effect". How large deviations can be tolerated before another "effect" is postulated? Does an investigated series contain all or just some (which) of previously postulated effects. This approach inevitably leads to an ever-increasing number of scales, each of which is claimed to be superiour in some respect. This proliferation has now gone rather far and presently there are more than 20 scales to choose among to describe polar and resonance effects of a substituent. The user of ETRs thus has a formidable problem to choose among available models. Also one has the problem of chance correlation due to the large number of possibilities to select scales and combinations thereof in a given application. To quote Bordwell [58] in a recent effort to analyze the behaviour of substituted nitroalkanes with the battery of scales available: "the variety of parameters used to correlate the acidity data for nitroalkanes and the variety of ways in which these parameters have been combined has led to a complex and confusing picture, to say the least".

We also note that the "effects" described by various scales in ETRs are inconsistent with quantum mechanics since a $\sigma - \pi$ separation is possible only in planar molecules. Even in these $\sigma - \pi$ polarization still operates and at least 7 effects may operate according to Katritzky,[59] even if we adopt a very simplified picture based on one electron orbitals.

c. Conclusion

We conclude that also for the understanding of organic reactivity, *i.e.* the central domain of physical organic chemistry, the classical interpretation of ETRs as generally applicable models is counterproductive. We don't want, however, to dismiss the use of substituent scales. We just want to emphasize their local validity and the difficulties encountered when one starts to combine scales derived from different data sets. Thus σ^+ certainly is a good scale for certain aromatic reactions. The combination of σ^+ with, say, σ^0 for series deviating from both σ and σ^+ to the Yukawa-Tsuno equation is maybe valid, but is in our view a less than optimal way to estimate parameters.

Acknowledgements. This project is supported by grants from the Swedish Natural Science Research Council. We are also grateful to Dr. Mortimer J. Kamlet for the access to unpublished solvatochromic shift measurements.

REFERENCES

1. Overton, E. *Vierteljahrsschr. Naturforsch. Ges. Zuerich 44* (1899) 88.
2. Brönsted, J. N. and Pedersen, K. *Z. Phys. Chem. 108* (1924) 185.
3. Hammett, L. P. *Chem. Rev. 17* (1935) 125.
4. Hammett, L. P. *J. Am. Chem. Soc. 59* (1937) 96.
5. Hammett, L. P. *Trans. Faraday Soc. 34* (1938) 156.
6. Hammett, L. P. *Physical Organic Chemistry*, McGraw-Hill, New York 1940, Chapter 7.
7. Jaffe, H. H. *Chem. Rev. 53* (1953) 191.
8. a. Exner, O. In Chapman, N. B. and Shorter, J., Eds., *Advances in Linear Free Energy Relationships*, Plenum, London 1972, Chapter 1; b. Chipperfield, J. R. *Ibid.* Chapter 7.

9. Sjöström, M. and Wold, S. *Chem. Scr. 9* (1976) 200.
10. Dippy, J. F. J. *Chem. Rev. 25* (1939) 151.
11. Dippy, J. F. J. and Hughes, S. R. C. *Tetrahedron 19* (1963) 1527.
12. Dauphin, G., Kergomard, A. and Verschambre, H. *Bull. Soc. Chim. Fr.* (1967) 3395.
13. Charton, M. *J. Org. Chem. 29* (1964) 1223.
14. Fischer, A., King, M. J. and Robinson, F. P. *Can. J. Chem. 56* (1978) 3059, 3068 and 3072.
15. Minesinger, R. R., Jones, M. E., Taft, R. W. and Kamlet, M. J. *J. Org. Chem. 42* (1977) 1929.
16. Brown, H. C. and Okamoto, Y. *J. Am. Chem. Soc. 79* (1957) 1913.
17. Brown, H. C., Okamoto, Y. and Unukai, T. *J. Am. Chem. Soc. 80* (1958) 4964, 4969.
18. Wold, S. and Sjöström, M. In Chapman, N. B. and Shorter, J., Eds., *Correlation Analysis in Chemistry*, Plenum, London 1978, Chapter 1.
19. Harman, H. H. *Modern Factor Analysis*, 2nd Ed., Univ. Chicago Press, Chicago 1967.
20. Weiner, P. H. *CHEMTECH* (1977) 321.
21. Wold, S. and Sjöström, M. In Kowalski, B. R., Ed., *Chemometrics; Theory and Application*, A.C.S., Series No. 52, Washington 1977, Chapter 12.
22. Wold, S. *Pattern Recognition 8* (1976) 127.
23. Jöreskog, K. G., Klovan, J. E. and Reyment, R. A. *Geological Factor Analysis*, Elsevier, Amsterdam 1976.
24. Ehrenson, S., Brownlee, R. T. C. and Taft, R. W. In Streitwieser, A., Jr. and Taft, R. W., Eds., *Physical Organic Chemistry*, Wiley, New York 1973.
25. Yukawa, Y. and Tsuno, Y. *Bull. Chem. Soc. Jpn. 32* (1959) 971.
26. Exner, O. In Chapman, N. B. and Shorter, J., Eds., *Correlation Analysis in Chemistry*, Plenum, London 1978, Chapter 10.
27. Taft, R. W. and Lewis, I. C. *J. Chem. Soc. 80* (1958) 2436.
28. Taft, R. W. and Lewis, I. C. *J. Am. Chem. Soc. 81* (1959) 5343.
29. Taft, R. W. *J. Phys. Chem. 64* (1960) 1805.
30. Taft, R. W., Ehrenson, S., Lewis, I. C. and Glick, R. E. *J. Am. Chem. Soc. 81* (1959) 5352.
31. Taft, R. W., Price, E., Fox, I. R., Lewis, I. C., Andersen, K. K. and Davis, G. T. *J. Am. Chem. Soc. 85* (1963) 3146.
32. Swain, C. G. and Lupton, E. C., Jr. *J. Am. Chem. Soc. 90* (1968) 4328.
33. Kamlet, M. J., Abboud, J. L. and Taft, R. W. *J. Am. Chem. Soc. 99* (1977) 6027.
34. Taft, R. W. and Kamlet, M. J. *J. Am. Chem. Soc. 98* (1976) 377.
35. Taft, R. W. and Kamlet, M. J. *J. Am. Chem. Soc. 98* (1976) 2886.
36. Taft, R. W. and Kamlet, M. J. *J. Chem. Soc. Perkin Trans. 2* (1979) 1723.
37. Horiuti, J. and Polanyi, M. *Acta Physicochim. U.R.S.S. 2* (1935) 505.
38. Leffler, J. E. and Grundwald, E. *Rate and Equilibria of Organic Reactions*, Wiley, New York 1963, p. 128.
39. Palm, V. A. *Osnovy Kolichestvennoi Teorii organicheskikh Reaktskii*, Izdatelstvo Khimiya, Leningrad 1967: German translation, *Grundlagen der Quantitativen Theorie Organischer Reaktionen*, Akad. – Verlag, Berlin 1971.
40. Wold, S. *Chem. Scr. 5* (1974) 97.
41. Feyerabend, P. K. *Against Method*, NLB, London 1975.
42. Wold, S. In Jöreskog, K. G. and Wold, H., Eds., *Systems Under Indirect Observation*, North-Holland, Amsterdam 1981.
43. Wold, S. *Technometric 20* (1978) 397.
44. Davis, O. L. and Goldsmith, P. L. *Statistical Methods in Research and Production*, 4th Ed., Longman Group, London 1980.
45. Fuchs, R. and Carlton, D. M. *J. Am. Chem. Soc. 85* (1963) 1041.
46. Fany, F. T., Kochi, J. K. and Hammond, G. S. *J. Am. Chem. Soc. 8* (1958) 563.
47. Kochi, J. K. and Hammond, G. S. *J. Am. Chem. Soc. 75* (1953) 3445.
48. Eaborn, C. and Pande, R. C. *J. Chem. Soc.* (1961) 5082.
49. Hammond, G. S., Peloquin, J., Fany, F. T. and Kochi, J. K. *J. Am. Chem. Soc. 82* (1960) 433.
50. Hammond, G. S., Reeder, C. E., Fany, F. J. and Kochi, J. K. *J. Am. Chem. Soc. 80* (1958) 568.
51. Grob, C. A., Schaub, B. and Schlageter, M. G. *Helv. Chim. Acta 63* (1980) 57.
52. Hansch, C., Leo, A., Unger, S. H., Kim, K. H., Nikaitani, D. and Lien, E. J. *J. Med. Chem. 16* (1973) 1207.
53. Kamlet, M. J., Jones, M. E., Taft, R. W. and Abboud, J.-L. *J. Chem. Soc. Perkin Trans. 2* (1979) 342.
54. Sjöström, M. and Wold, S. *J. Chem. Soc. Perkin Trans. 2* (1979) 1274.
55. DeTar, D. F. *J. Org. Chem. 45* (1980) 5166.
56. Edward, J. T., Sjöström, M. and Wold, S. *Can. J. Chem. In press.*
57. Taft, R. W. and Grob, C. A. *J. Am. Chem. Soc. 96* (1974) 1236.
58. Bordwell, F. G., Bartmess, J. E. and Hautala, J. A. *J. Org. Chem. 43* (1978) 3095.
59. Katritzky, A. R. and Topsom, R. D. *J. Chem. Educ. 48* (1971) 427.

Received June 9, 1981.