Improved Procedures for Determining Second-derivative Cross-interaction Coefficients and for Establishing a Relationship between the Value and Reaction Type

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In a Hammett-type study of the second-derivative kinetic influences of dual substitution, one can use internally generated substituent constants, avoiding the need to choose from among the various substituent constant scales prior to statistical analysis; this method leads to a better, often considerably better, analysis than similar methods using external constants. It is shown that the Palm α values generated by this procedure can give a better classification of reaction type than the previously used uncalibrated ρ_{xy} values.

Multiple structural variations will, in the general case, result in non-additive substituent effects.[1] If a Hammett treatment is involved, a simple additivity of the $\rho\sigma$ terms requires that both of the individual plots, for variation of one substituent with the other kept unchanged, be linear and that the nature of the interaction between the two substituents does not change during reaction. If changes in the magnitude of the interaction between two substituents can be considered to be related to their Hammett σ values, then a term can be added to the Hammett equation involving a sensitivity (cross-interaction coefficient) towards the product of the σ values. Appreciable variation in the magnitude of the interaction between two or more substituents is to be expected in going to the transition state of nucleophilic substitution reactions, when the substituents are in the entering group, leaving group, or attached directly or indirectly to the site of the substitution other than within the leaving group [eqn. (1)]. Indeed, for such a system a

$$\mathrm{XN + YRLZ \longrightarrow XNRY + LZ} \qquad (1)$$

threefold structural variation of X, Y and Z is possible. The examples presented will be of this reaction, with variation in two of the X, Y and Z substituents.

Miller[2] presented general equations for dual [eqn. (2)] and

$$y = px + qxz + rz + s \qquad (2)$$

also threefold structural variations. For application of the Hammett equation to a kinetic study involving variation of two substituents, eqn. (2) can be expressed[3] as eqn. (3), where k_{ij} is

$$\log(k_{ij}/k_{\mathrm{HH}}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j + c \qquad (3)$$

the rate coefficient in the presence of substituents i and j and k_{HH} is the rate coefficient when $i = j = \mathrm{H}$, ρ_i, ρ_j and ρ_{ij} are first-derivative and second-derivative sensitivity parameters, controlling the magnitudes of the contributions to the linear free-energy relationship (LFER) from the three terms containing the Hammett substituent constants σ_i and σ_j and their product, and c is the intercept.

The sensitivity parameter ρ_{ij} has been called the cross-interaction constant[3,4] or (preferably) coefficient.[5,6] It has been suggested[3–7] that the sign and magnitude of the cross-interaction coefficient can be an extremely useful quantity in the establishment of a reaction mechanism. Lee has proposed that for an $\mathrm{S_N2}$ reaction the sign of the cross-interaction coefficient ρ_{XZ} is negative if the reaction series is intrinsic-barrier controlled and positive if it is thermodynamic-barrier controlled and that the magnitude of the cross-interaction coefficient involving two substituent sites is inversely proportional to the distance between them. Further, Lee has suggested that the cross-interaction coefficients can be used not only to characterize the structure of the transition state but also to evaluate changes resulting from structural changes in the reactants. Dubois, Ruasse and Argile[4] have pointed out that the magnitude of the second-derivative cross-interaction coefficients are to some extent determined by the first-derivative ρ values and relatively high ρ_{ij} values are observed only when the ρ_i and ρ_j values are also high. It is of interest in this context that Palm and Istomin[8] had earlier proposed an important variant of eqn. (2), where the parameter q is expressed as αpr, which, in the terminology of eqn. (3), is represented by eqn. (4). The coefficient α is a calibrated measure of the

$$\rho_{ij} = \alpha\rho_i\rho_j \qquad (4)$$

intensity of the interaction brought about by the electron-withdrawing and/or electron-supplying properties of the substituents i and j.

Lee[3] and Shpan'ko, Litvinenko, and co-workers[5,7] favour the use of eqn. (3) to arrive at ρ_{ij} values, a technique which automatically also gives ρ_i and ρ_j values. However, Dubois, Ruasse and Argile[4] have favoured the use of increment quotients [eqn. (5)] on the grounds that this technique avoids

$$(\rho_i - \rho_{\mathrm{H}}) = \rho_{ij}\sigma_i \text{ or } (\rho_j - \rho_{\mathrm{H}}) = \rho_{ij}\sigma_j \qquad (5)$$

artificial optimizations resulting from statistical treatments of multiple regression, which were recommended only 'as a last resort'. The two expressions of eqn. (5) require Hammett treatment of data involving variation of $j(i)$ with $i(j)$ as a fixed substituent to give $\rho_i(\rho_j)$ values, the deviation of this quantity from ρ_{H} [determined for $i(j) = \mathrm{H}$] can be used to calculate the ρ_{ij} value [eqn. (5)]. Lee[3b] has countered with the argument that accurate determinations of ρ_{ij} are essential and it is necessary to be able objectively to assess the accuracy and reliability of the determined ρ_{ij} values and, in this regard, the increment quotient method 'leaves much to be desired'.

However, both of the above techniques for analysing rate data, so as to arrive at cross-interactions coefficient values, involve the use of externally generated Hammett substituent constants and this has several unsatisfactory features.

Traditional Hammett substituent constants are based on the equilibrium ionization of substituted benzoic acids in water at 25 °C, and this will be a poor model for the usual kinds of system involved in studies of cross-interaction coefficients.[9] Reactions are almost invariably carried out in mixed or non-aqueous solvents (methanol, acetonitrile, or an aromatic solvent is frequently used), and they are often carried out at temperatures considerably removed from 25 °C. In addition to possible variation of substituent constants with solvent and temperature changes, it is frequently necessary to decide whether the original σ scale would be better replaced by σ^- or σ^+ scales;[10] for example, Dubois, Ruasse and Argile[4] have used all three scales during their calculations and Lee *et al.*[3b,11] have reported that benzyl systems are better analysed using σ^+ values. Further, many of the analysed systems involve substituted anilines as nucleophiles, where it has been shown[12] that strongly electron-withdrawing *para*-substituents require values intermediate between the σ and σ^- values.[13,14] A fourth possible problem is that there is, for some substituents, ambiguity concerning the numerical σ value.[15] For example, one system we have reanalysed includes the *m*-CN substituent[16] and σ values have been tabulated[10] of 0.56,[17] 0.68,[18] and 0.61.[19]

Application of the similarity model approach[20] suggests that the ideal situation for assessing the importance of a contribution which makes only a minor contribution to the overall LFER, such as the term [within eqn. (3)] governing cross-interaction, would be if external standards could be avoided.[21] Exner[22] has pointed out that, in this type of analysis, constants can be defined by the correlated data themselves, with the advantage that attention is then focused on the interaction of substituents and the disadvantage that any consideration of controlling factors must be abandoned or postponed.

We report a technique for analysis of the rate coefficients obtained in a study of the influence of dual substitution which allows one to assess the importance of cross-correlation without recourse to external substituent constants. The quantity obtained is the calibrated cross-interaction coefficient α, as defined by Palm and Istomin,[8] which can be converted into the usually quoted cross-interaction coefficient by use of eqn. (4). Although the objections raised above will apply to the determination of ρ_i and ρ_j, the $\rho_i\rho_j$ value is used only as a normalization coefficient, introduced after the completion of statistical analysis, and hence after the extent of cross-interaction has been determined.

Data sets usually include as subsets the situations where j = H and i is varied and where i = H and j is varied. These subsets can be used internally to define $\sigma_i^{\text{in}} = \log(k_{i\text{H}}/k_{\text{HH}})$ and $\sigma_j^{\text{in}} = \log(k_{\text{H}j}/k_{\text{HH}})$. It is, of course, necessary that the variation of both of the substituents i and j lead to reasonably large changes in the rate coefficient. These internal substituent constants can be incorporated within eqn. (3) to give eqn. (6).

$$\log(k_{ij}/k_{\text{HH}}) = \rho_i^{\text{in}}\sigma_i^{\text{in}} + \rho_j^{\text{in}}\sigma_j^{\text{in}} + \rho_{ij}^{\text{in}}\sigma_i^{\text{in}}\sigma_j^{\text{in}} + c \qquad (6)$$

For acceptable data sets, the internally generated ρ_i^{in} and ρ_j^{in} values should be very close to unity and, indeed, any appreciable deviation from unity can be taken as evidence for an inconsistent data set or a miscalculation. It follows that the generated ρ_{ij}^{in} value will be identical with the previously defined α value, which has been considered[5,8] as the best measure of interaction intensity. The ρ_i and ρ_j values needed to convert, using eqn. (4), the ρ_{ij}^{in} values to ρ_{ij} values can be determined as the slopes of plots of σ_i^{in} against σ_i and σ_j^{in} against σ_j or, more accurately, by application of eqn. (3).

To illustrate the use of this approach, we present an analysis of a very recently reported study of solvolyses of 5-(Y)-substituted indan-2-yl (Z)-benzenesulfonates in aqueous ethanol and aqueous methanol.[23] Our calculations are in full agreement with the ρ_Y, ρ_Z and ρ_{YZ} parameters previously calculated using eqn. (3) and presented, without any consideration of error limits, by Lee and co-workers[23] in their Table 6. An extension of this analysis shows, however, that the reported correlation coefficients (0.9949–0.9988) are only marginally higher than those (0.9937–0.9985) obtained after omission of the $\rho_{ij}\sigma_i\sigma_j$ term (governing cross-interaction) from the calculation. Further, the six ρ_{ij} values are in five instances associated with large standard errors and (in parentheses) rather high probabilities that the $\rho_{ij}\sigma_i\sigma_j$ term is not statistically significant; as one goes down the table: $-0.31 \pm 0.15(0.08)$, $-0.27 \pm 0.16(0.15)$, $-0.15 \pm 0.10(0.15)$, -0.33 ± 0.08 (0.01), -0.23 ± 0.13 (0.11) and -0.28 ± 0.20 (0.20).

The evidence for a significant cross-interaction term is much more convincing if the calculations are carried out using internally generated σ_i^{in} and σ_j^{in} substituent constants (Table 1). Five of the analyses show considerably improved probabilities and correlation coefficients, and the sixth (for 30% ethanol) is only very marginally worse. The two highest (> 0.05) associated probability values are for the more aqueous solvents; it is possible that, for these solvents, substrate solubility could be a problem.[24]

As a second example (Table 2), we have reanalysed, with inclusion of error analysis, the reported study of sixteen reactions of substituted anilines or *N*,*N*-dimethylanilines with 2-methylallyl arenesulfonates in acetonitrile.[25] Cross-interaction coefficients, which are associated with an only marginally acceptable probability value when calculated using eqn. (3), have probability values of $\leqslant 0.0001$ when calculated according to eqn. (6).

We also present details of our analyses of two systems studied by Shpan'ko, Litvinenko, and co-workers: reactions of $\text{XC}_6\text{H}_4\text{NH}_2$ with $\text{YC}_6\text{H}_4\text{CH}_2\text{Br}$ in 1 mol dm^{-3} dimethyl sulfoxide in nitrobenzene at 40.0 °C,[16] and of $\text{XC}_6\text{H}_4\text{NH}_2$ with $\text{YC}_6\text{H}_4\text{COCl}$ in chlorobenzene at 25.0 °C.[5] For the first reaction, an overall correlation coefficient of 0.998 (n = 16) is associated with values of -1.40 ± 0.04 for ρ_X, 0.22 ± 0.04 for ρ_Y, and -0.57 ± 0.07 for ρ_{XY}.[16] Our present calculation in terms of internally generated σ_X and σ_Y values gives an overall correlation coefficient of 0.9993 and a Palm α value of 1.84 ± 0.22, corresponding to a ρ_{XY} value (multiplying by the previously determined[16] ρ_X and ρ_Y values) of -0.57 ± 0.07. Similarly, for the second reaction, an overall correlation coefficient of 0.998 (n = 23) is associated with values of -3.23 ± 0.05 for ρ_X, 0.88 ± 0.05 for ρ_Y, and -0.57 ± 0.08 for ρ_{XY}.[5] Our present calculation leads to an overall correlation coefficient of 0.9994 and a Palm α value of 0.196 ± 0.017, corresponding to a ρ_{XY} value of -0.56 ± 0.05.

It can be seen that our correlations are only marginally improved over those previously reported based on use of eqn. (3) and, in particular, the values and standard errors (probabilities of the second-derivative term not being statistically significant of <0.0001) associated with the ρ_{XY} coefficients are essentially identical. The very good statistical analyses[5,16] using external substituent constants within eqn. (3) is associated with the range of σ values being considerably larger than in the two studies considered in Tables 1 and 2 and, also, the Ukranian workers restricted themselves to *meta*-substituents, which are well known to vary less in value with changes in reaction system than *para*-substituents.[10]

In a recent review,[3a] a table of ρ_{XY} values has been presented, calculated for fourteen nucleophilic substitution reactions in methanol as the solvent, using externally determined Hammett substituent constants within eqn. (3). The reactions are of the type where the leaving group is unchanged

Table 1 Correlation, using eqn. (6), of the specific rates of solvolysis of a series of 5-(Y)-substituted indan-2-yl (Z)-benzenesulfonates at 45.0 °C[a]

Solvent	ρ_Y^{in}	ρ_Z^{in}	$\rho_{YZ}^{in\ b-d}$	c	r^e
80% EtOH	1.00 ± 0.06	1.02 ± 0.02	0.29 ± 0.08 (0.006)	−0.01 ± 0.03	0.9992
	1.11 ± 0.07	0.95 ± 0.02		0.02 ± 0.05	0.9979
50% EtOH	1.00 ± 0.04	1.00 ± 0.02	0.22 ± 0.05 (0.003)	0.01 ± 0.02	0.9995
	1.10 ± 0.05	0.93 ± 0.02		0.03 ± 0.04	0.9984
30% EtOH	0.99 ± 0.05	1.00 ± 0.03	0.11 ± 0.08 (0.189)	0.01 ± 0.04	0.9986
	1.03 ± 0.05	0.97 ± 0.02		0.03 ± 0.04	0.9983
MeOH	0.97 ± 0.04	0.98 ± 0.02	0.29 ± 0.06 (0.001)	0.00 ± 0.02	0.9993
	1.06 ± 0.06	0.90 ± 0.03		0.02 ± 0.05	0.9971
80% MeOH	0.95 ± 0.04	1.02 ± 0.02	0.18 ± 0.05 (0.010)	0.00 ± 0.02	0.9994
	1.02 ± 0.04	0.96 ± 0.02		0.02 ± 0.04	0.9985
50% MeOH	0.90 ± 0.08	0.99 ± 0.05	0.20 ± 0.11 (0.117)	0.02 ± 0.07	0.9963
	0.96 ± 0.08	0.93 ± 0.03		0.04 ± 0.07	0.9949

[a] Rate data from ref. 23; values are quoted with associated standard errors. [b] When no entry in this column, the $\rho_{YZ}^{in}\sigma_Y^{in}\sigma_Z^{in}$ term has been omitted from the correlation equation. [c] These values can be converted into ρ_{YZ} values by multiplying by ρ_Y^H and ρ_Z^H (contained in ref. 23). [d] Values in parentheses are the probabilities that the $\rho_{YZ}^{in}\sigma_Y^{in}\sigma_Z^{in}$ term is not statistically significant. [e] Correlation coefficient.

Table 2 Correlation, using eqn. (3) and eqn. (6), of the second-order rate coefficients for reaction of $XC_6H_4NH_2$ and $XC_6H_4N(CH_3)_2$ with 2-methylallyl (Z)-benzenesulfonates in acetonitrile at 45.0 °C[a]

Amine	ρ_X	ρ_Z	$\rho_{XZ}{}^{b,c}$	c	r^d
$XC_6H_4NH_2$	−1.87 ± 0.07	1.48 ± 0.03	0.39 ± 0.17 (0.043)	−0.04 ± 0.05	0.9978
	−1.79 ± 0.07	1.45 ± 0.04		−0.04 ± 0.05	0.9969
$XC_6H_4N(CH_3)_2$	−2.37 ± 0.07	1.64 ± 0.03	0.36 ± 0.17 (0.050)	0.02 ± 0.05	0.9985
	−2.29 ± 0.07	1.62 ± 0.04		0.02 ± 0.05	0.9980
Amine	ρ_X^{in}	ρ_Z^{in}	$\rho_{XZ}^{in\ b,c,e}$	c	r^d
$XC_6H_4NH_2$	1.01 ± 0.02	1.01 ± 0.01	−0.143 ± 0.025 (0.000)	0.00 ± 0.02	0.9997
	0.96 ± 0.02	1.00 ± 0.02		0.00 ± 0.04	0.9988
$XC_6H_4N(CH_3)_2$	1.01 ± 0.01	1.01 ± 0.01	−0.095 ± 0.015 (0.000)	0.01 ± 0.02	0.9998
	0.98 ± 0.02	1.00 ± 0.01		0.01 ± 0.03	0.9993

[a] Rate data from ref. 25; values are quoted with associated standard errors. [b] When no entry in this column, the cross-interaction term has been omitted from the correlation equation. [c] Values in parentheses are the probabilities that the cross-interaction term is not statistically significant. [d] Correlation coefficient. [e] Multiplying by $\rho_X\rho_Z$ leads to ρ_{XZ} values of 0.40 ± 0.07 and 0.37 ± 0.06.

and the varying X-substituent is within an aromatic ring present in the nucleophile and the varying Y-substituent is within an aromatic ring attached directly or indirectly to the reaction centre. The reactions were divided into three classes: ρ_{XY} values of −0.62 to −0.78 (seven reactions), −1.67 and −1.07 (two reactions) and −0.22 to −0.66 (five reactions). Inspection shows that reactions of varying type fall into each class.

The first class contains reactions of ring-substituted anilines with ring-substituted benzyl bromides, benzyl chlorides, benzyl benzenesulfonates, benzenesulfonyl chlorides and benzoyl chlorides, and also the reaction of substituted thiophenoxide ions with ring-substituted benzyl chlorides. The second class consists of the reactions of ring-substituted anilines with substituted benzoyl and benzenesulfonyl fluorides. The third class consists of reactions of ring-substituted benzylamines, benzoate ions, and cinnamate ions with ring-substituted benzyl bromides, benzenesulfonyl chlorides and benzenesulfonyl fluorides. Indeed, many of the reactions grouped together on the basis of the ρ_{XY} value appear to have very little in common, other than being nucleophilic substitutions.

We find that a much more logical division of the reactions follows from a consideration in terms of the Palm α values, and the α_{XY} values are tabulated, in four groupings, in Table 3. The four reactions having negative α_{XY} values (−1.28 to −0.72) involve attack of a primary amine on a series of ring-substituted benzylic derivatives. In particular attacks by either aniline or benzylamine now fall into the same class. Previously the lower ρ_{XY} values for attack by benzylamines led to these reactions falling into a different classification than for attack by anilines. Similarly, in the third grouping of Table 3, values of 0.71 and 1.19 are for attack upon substituted benzenesulfonyl fluorides of ring-substituted anilines and benzylamines, respectively. Treatments in terms of α_{XY} do not require any additional consideration of the approximate fall-off factor of 2.4 to 2.8 for an extra intervening carbon. Lee found it necessary to make use of this factor several times in his reviews;[3] with use of α_{XY} values, rather than ρ_{XY} values, the fall-off is automatically and accurately taken into account through the incorporation [eqn. (4)] of ρ_X and ρ_Y values.

The second grouping, five reactions with α_{XY} values of from 0.14 to 0.34, consists of reactions of ring-substituted anilines or benzylamines with substituted benzoyl chlorides, benzoyl fluorides or benzenesulfonyl chlorides. The fourth and final grouping, three reactions with α_{XY} values from 1.45 to 1.84, involves the three anionic nucleophiles included in the compilation in reaction with ring-substituted benzenesulfonyl or benzyl chlorides.

In a subsequent review,[3b] four reactions in which a carbonyl group is inserted between the Y-substituent and the reaction

Table 3 Classification of nucleophilic substitution reactions,[a] in methanol as solvent, on the basis of the value for the second-derivative Palm α value

Class[b]	Reaction	T/°C	α_{XY}[c]
I	$XC_6H_4NH_2 + YC_6H_4CH_2Cl$	35.0	−1.28
I	$XC_6H_4NH_2 + YC_6H_4CH_2OSO_2C_6H_5$	35.0	−0.89
I	$XC_6H_4NH_2 + YC_6H_4CH_2Br$	35.0	−0.88
III	$XC_6H_4CH_2NH_2 + YC_6H_4CH_2Br$	45.0	−0.72
I	$XC_6H_4NH_2 + YC_6H_4COCl$	35.0	0.14
III	$XC_6H_4CH_2NH_2 + YC_6H_4SO_2Cl$	35.0	0.19
II	$XC_6H_4NH_2 + YC_6H_4COF$	55.0	0.31
I	$XC_6H_4NH_2 + YC_6H_4SO_2Cl$	25.0	0.32
I	$XC_6H_4NH_2 + YC_6H_4SO_2Cl$	35.0	0.34
II	$XC_6H_4NH_2 + YC_6H_4SO_2F$	45.0	0.71
III	$XC_6H_4CH_2NH_2 + YC_6H_4SO_2F$	45.0	1.19
III	$XC_6H_4CO_2^- + YC_6H_4SO_2Cl$	30.0	1.45
III	$XC_6H_4CH{=}CHCO_2^- + YC_6H_4SO_2Cl$	30.0	1.59
I	$XC_6H_4S^- + YC_6H_4CH_2Cl$	20.0	1.84

[a] The fourteen reactions of Table 2 of ref. 3(*a*). [b] As presented in Table 2 of ref. 3(*a*). [c] $\alpha_{XY} = \rho_{XY}/\rho_X\rho_Y$ [see eqn. (4)], with the three ρ values taken from Table 2 of ref. 3(*a*).

centre, also with methanol as the solvent, have been presented. These reactions involve a series of phenacyl bromides ($YC_6H_4COCH_2Br$) or benzenesulfonates in reaction with a series of ring-substituted anilines or benzylamines. The α_{XY} values, calculated as in Table 3, are all negative and small in magnitude: −0.10, and −0.09 for the reactions with the anilines and −0.15 and −0.08 for the reactions with the benzylamines, respectively. Again, similar reactions, previously placed in two different classes on the basis of appreciable differences in ρ_{XY} values,[3b] give almost identical α_{XY} values and nucleophilic attacks by anilines and benzylamines are grouped together.

Conclusions

Second-derivative cross-interaction coefficients can be obtained as the calibrated Palm α values by use of internally generated substituent constants, without the need to choose among the various external Hammett scales of substituent values. The α_{ij} values obtained in the presence of substituents i and j will be more precise than the corresponding ρ_{ij} values obtained using external σ values, frequently appreciably more precise. If desired, the α_{ij} values can be converted into ρ_{ij} values by multiplying by both of the ρ_i and ρ_j values. Since the Palm α values are to be considered as *calibrated* second-derivative cross-interaction coefficients, it is not surprising that groupings based on α_{XY} values, for eighteen previously tabulated nucleophilic substitution reactions, are considerably more logical than when based, as previously,[3a,b] on ρ_{XY} values.

It must, however, be emphasized that many more reactions and solvents need to be considered before any classifications (groupings of reactions) based on α_{XY} (or ρ_{XY}) values can be considered to be well established. However, the improved classification of the fourteen reactions listed in Table 3 and of the four additional reactions studied in the presence of an intervening carbonyl group, discussed in the text, can be considered as extremely promising and as indicating that further investigation will be worthwhile. We are currently investigating the extent to which the treatment developed in this article can be extended to analyses of threefold structural variation.[2,26]

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