The Analysis of Substituent Effects for Reactions not following the Hammett Relation

By **T. Marek Krygowski** and **W. Ronald Fawcett**,* Guelph-Waterloo Centre for Graduate Work in Chemistry (Guelph Campus), Department of Chemistry, University of Guelph, Guelph, Ontario, Canada

An extended Hammett equation based on separation of the enthalpic and entropic contributions to the total substituent effect is applied to systems where substituent–reaction site interactions are strong and non-uniform in nature, and therefore, the classical Hammett relation is not obeyed. Enthalpic and entropic substituent constants (σ_H and σ_S) are defined from independently determined values of standard enthalpy and entropy for the reference Hammett reaction in water. The extended equation $Q = Q_0 + \rho_H\sigma_H + \rho_S\sigma_S$ was found to describe successfully substituent effects for a collection of systems containing *ortho*-substituents and/or strong substituent–reaction site interactions. The results of analysing 42 selected sets of equilibrium and kinetic data are summarized and discussed.

WOLD[1] has recently shown on the basis of a mathematical analysis of similarity models that the Hammett equation and other one-parameter representations of linear free energy relationships (l.f.e.r.) are most justified for reaction series in which variation in substituent and reaction site nature are small. Although the magnitude of the permitted variation is difficult to define quantitatively, the conclusion agrees with those reached earlier by Leffler and Grunwald,[2] and by Hansen and Hepler,[3] namely, that an l.f.e.r. exists if substituent–reaction site interactions are not too strong and uniform in nature.

When substituent–reaction site interactions are stronger, for example, in the ionization of phenols or for electrophilic substitution to the benzene ring, either the substituent constants must be changed[4] or a two-parameter equation must be used.[5,6] In the latter case, the equation used most often involves separation of the substituent effect into inductive and resonance contributions.[7-9] Taft and his colleagues[10] have recently re-examined the inductive–resonance treatment taking into account different possible interactions between the substituent X and the reaction site Y. They concluded that four scales for the resonance parameter σ_R are needed to account for the observed variation in the substituent effect. Although this work is of great importance in the development of an understanding of the blend of resonance and inductive contributions to the overall substituent effect, it is subject to criticism on the basis of statistical analyses.[11] Thus, the inductive–resonance analysis is subject to the shortcoming that the parameters used, particularly for the resonance contribution,[5] are not very precise because of experimental and model difficulties. Model difficulties are due to the problem of selecting a standard reaction which defines the given substituent constants for a unique mechanism of interactions between the substituent and the reaction site.

Another problem associated with this type of analysis is due to the fact that a substituent effect observed in solution also reflects solute–solvent interactions and thus, may not simply be a reflection of electrical interaction between substituent and reaction site. An example of the effect of solute–solvent interactions is provided by the anomalous order of amine basicity in solution[12,13] compared with its gas-phase basicity.[14-16] Thus, a more general analysis of substituent effects would be based on separation of intra- and inter-molecular effects. The intramolecular interaction between substituent and reaction site in an isolated molecule results in a rearrangement of electronic charge which can be interpreted in terms of inductive, resonance, and steric effects. In solution, intermolecular interactions between the substituted molecule and solvent molecules depend on the electronic charge distributions in contiguous molecules and on their orientations with respect to one another. Obviously, intra- and inter-molecular interactions are connected in a complex way, no simple analysis of substituent effects on this basis being available. However, for ionization processes it is well known[17] that the enthalpic contributions to the substituent effect are composed of both intra- and intermolecular interactions whereas the entropic contributions are chiefly related to intermolecular interactions. In an effort to reveal the relative importance of intra- and intermolecular effects, we[18] have suggested an alternative

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empirical division of the substituent effect. Accordingly, the property Q varies with substituent as in equation (1) where σ_H and σ_S are the enthalpic and

$$Q = Q_0 + \rho_H\sigma_H + \rho_S\sigma_S \qquad (1)$$

entropic substituent constants, ρ_H and ρ_S, the corresponding reaction constants, and Q_0, the value of Q for the unsubstituted compound. The substituent constants are defined by equations (2) and (3) where

$$\sigma_H = -\delta\Delta H^0/2.303RT \qquad (2)$$

$$\sigma_S = \delta\Delta S^0/2.303R \qquad (3)$$

$\delta\Delta H^0$ and $\delta\Delta S^0$ are the changes in the standard enthalpy and entropy of reaction with substituent X for process (4). The results of analysing data by equation (1) were

$$XC_6H_4CO_2H + PhCO_2^- \rightleftharpoons XC_6H_4CO_2^- + PhCO_2H \qquad (4)$$

compared with results obtained using the classical Hammett equation (5) where $\sigma = -\delta\Delta G^0/2.303RT$ is the

$$Q = Q_0 + \rho\sigma \qquad (5)$$

standard substituent constant, ρ, the reaction constant, and $\delta\Delta G^0$, the change in the standard free energy of the above reaction with substituent.

In a previous paper,[18] 31 sets of data for the ionization constants of aromatic acids were successfully analysed using equation (1), the results being used to discuss the relative importance of inductive and resonance effects for the systems considered. However, only *meta*- and *para*-substituents were considered. On the basis of the original experimental data, it has been customary to assume that $\delta\Delta H^0$ is proportional to $\delta\Delta S^0$ and to discuss the theoretical basis of linear free energy relationships accordingly.[19] However, it is clear from the recent data of Matsui *et al.*[20] that the linear relationship does not hold for *p*-methoxy, *p*-methyl, and *p*-hydroxy substituents. It is important to emphasize that the entropy and enthalpy data were obtained independently so that the deviations cannot be considered artificial.[21]

The chief purpose of the present paper is to extend the enthalpy–entropy separation of the substituent effect to reaction series with strong and non-uniform substituent–reaction site interactions. In this regard, reaction series with *ortho*-substituents are generally found not to follow the simple Hammett relation.[22] Other non-Hammett reaction series not necessarily containing *ortho*-substituents are also considered. Since the isokinetic relationship does not hold when substituent–reaction site interactions are strong and non-uniform[23] and therefore, the Hammett relation is not valid,[21] application of the enthalpy–entropy separation equation is particularly advantageous.

Interpretation of σ_H and σ_S.—Values of the enthalpic and entropic substituent constants calculated from available values of ΔH^0 and ΔS^0 are summarised in Table 1. With the exception of *o*-nitro-, *o*-iodo-, *o*-chloro-, and *o*-hydroxy-benzoic acids,[24] the data were obtained using calorimetric values of ΔH^0.[20,25] On plotting σ_S against σ_H it can be seen that there is no simple relationship between these parameters. Thus, when *ortho*-substituents are included in a reaction series, the isoequilibrium relationship is not obeyed.

TABLE 1

Summary of σ parameters

Substituent *	σ	σ_H	f_H †	σ_S	f_S †
H	0.000	0.000		0.000	
o-NO_2 [18]	2.01	2.54	0.82	−0.53	0.18
m-NO_2	0.744	−0.198	0.17	0.942	0.83
p-NO_2	0.780	−0.236	0.18	1.016	0.82
m-Br	0.394	−0.051	0.10	0.446	0.90
p-Br	0.224	−0.029	0.10	0.253	0.90
o-Cl [18]	1.32	1.89	0.77	−0.57	0.23
m-Cl	0.371	−0.066	0.13	0.437	0.87
p-Cl	0.220	−0.095	0.23	0.315	0.77
m-F	0.341	−0.081	0.16	0.422	0.84
o-I [18]	1.34	2.45	0.68	−1.12	0.32
m-I	0.350	−0.059	0.12	0.409	0.88
p-I	0.209	0.023	0.11	0.186	0.89
o-OH [18]	1.23	−0.65	0.26	1.89	0.74
m-OH	0.127	−0.037	0.18	0.164	0.82
p-OH	−0.377	−0.191	0.51	−0.186	0.49
o-CH_3 [18]	0.33	1.10	0.59	−0.77	0.41
m-CH_3	−0.048	0.029	0.27	−0.077	0.73
p-CH_3	−0.158	−0.103	0.65	−0.055	0.35
o-CH_3O [19]	0.11	1.25	0.53	−1.14	0.47
m-CH_3O	0.113	0.045	0.39	0.068	0.61
p-CH_3O	−0.280	−0.359	0.81	0.079	0.19

* Except where noted, the thermodynamic data were obtained from ref. 15. † f_H and f_S are fractional substituent constants and are defined by the equations $f_H = |\sigma_H|/(|\sigma_H| + |\sigma_S|)$ and $f_S = |\sigma_S|/(|\sigma_H| + |\sigma_S|)$; when multiplied by 100 they simply express the percentage of enthalpic and entropic contribution to the total substituent effect.

The treatment proposed to this paper agrees with theoretical considerations[1-3] according to which deviations from the Hammett equation and isoequilibrium relationship are for substituents which do not interact uniformly with the reaction site. The two-parameter equation proposed here seems to be a convenient extension of the l.f.e.r. in which all substituents may be considered. None of the existing two parameter extensions of the Hammett equation have been applied to *ortho*-substituted compounds in a simple way. Fujita and Nishioka[26] have proposed a general equation for

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substituent effects but the analysis involves four parameters and thus is not as useful as that proposed here.

It may be assumed that σ_S accounts mainly for intermolecular contributions to the measured substituent effect whereas σ_H reflects both inter- and intra-molecular effects. As a consequence ρ_S values may be taken as a measure of solute–solvent interactions whereas ρ_H is less sensitive to these effects. σ_H and σ_S depend on intramolecular interactions in a complex way [18,27] which cannot be resolved at present. On the other hand, the inductive and resonance parameters, σ_I and σ_R, are assumed to represent intramolecular properties. Since they are based on experimental measurements in solution, they obviously also reflect intermolecular interactions to an unknown extent.

RESULTS AND DISCUSSION

The results of analysing thermodynamic and kinetic data for 42 reaction series including *ortho*-substituted compounds are presented in Tables 2—4. The constants ρ_S, ρ_H, and ρ were determined by fitting the experimental data to equations (1) and (5) using standard regression analysis, r_P and r_L being the correlation coefficients for planar [equation (1)] and linear regression [equation (5)], respectively. In order to assess the relative contributions of the entropic and enthalpic effects to the total explained variation, normalised partial regression coefficients $\bar{\rho}_S$ and $\bar{\rho}_H$ were calculated as described previously ($\bar{\rho}_S + \bar{\rho}_H = 100$).[18,27]

TABLE 2

Application of the enthalpy–entropy separated and normal Hammett equations to the analysis of ionization equilibrium constant data for *ortho*-, *meta*-, and *para*- substituted benzoic acids

Medium	ρ_S	ρ_H	$\Delta\rho_S$	r_P	ρ	r_L	n
Water [20,24,25]	1.00	1.00	0.0	1.000	1.000	1.000	22
33.2% Ethanol–water [28]	1.21 ± 0.05	0.92 ± 0.04	7 ± 2	0.991	0.94 ± 0.08	0.943	16
52.4% Ethanol–water [28]	1.32 ± 0.07	0.98 ± 0.05	7 ± 2	0.987	0.93 ± 0.10	0.929	16
73.4% Ethanol–water [28]	1.37 ± 0.08	0.99 ± 0.05	8 ± 3	0.984	0.96 ± 0.11	0.918	16
84.5% Ethanol–water [28]	1.26 ± 0.14	0.82 ± 0.08	10 ± 5	0.945	0.77 ± 0.13	0.851	16
Ethanol [28]	1.40 ± 0.08	1.09 ± 0.07	6 ± 3	0.979	1.14 ± 0.011	0.932	17
Methanol [28]	1.22 ± 0.07	1.02 ± 0.05	5 ± 3	0.980	1.02 ± 0.08	0.954	20
n-Butanol [29]	1.18 ± 0.08	0.96 ± 0.06	5 ± 3	0.966	0.96 ± 0.09	0.931	20
Ethylene glycol [29]	1.11 ± 0.05	0.93 ± 0.04	4 ± 2	0.984	0.93 ± 0.06	0.960	21
26.5% Dioxan–water [30]	1.16 ± 0.03	0.96 ± 0.02	5 ± 1	0.997	0.97 ± 0.22	0.966	17
43.5% Dioxan–water [30]	1.22 ± 0.04	0.92 ± 0.03	7 ± 2	0.990	0.92 ± 0.09	0.922	20
73.4% Dioxan–water [30]	1.27 ± 0.13	0.9 ± 0.1	8 ± 5	0.930	0.91 ± 0.14	0.841	20
31.7% Dimethyl sulphoxide (DMSO)–water [31]	1.12 ± 0.02	0.94 ± 0.02	4 ± 1	0.998	0.93 ± 0.06	0.983	10
41.5% DMSO–water [31]	1.36 ± 0.12	0.99 ± 0.08	8 ± 4	0.979	0.97 ± 0.14	0.927	10
51.2% DMSO–water [31]	1.27 ± 0.06	0.94 ± 0.04	7 ± 2	0.994	0.92 ± 0.11	0.945	10
61.2% DMSO–water [31]	1.39 ± 0.09	0.96 ± 0.06	9 ± 3	0.986	0.93 ± 0.14	0.910	11
73.5% DMSO–water [31]	1.52 ± 0.10	1.02 ± 0.07	10 ± 3	0.984	0.98 ± 0.16	0.889	11
80.4% DMSO–water [31]	1.8 ± 0.2	1.1 ± 0.1	11 ± 7	0.944	1.04 ± 0.2	0.834	11
86.4% DMSO–water [31]	1.8 ± 0.1	1.2 ± 0.1	10 ± 4	0.979	1.1 ± 0.2	0.884	11
91.0% DMSO–water [31]	1.9 ± 0.1	1.2 ± 0.1	10 ± 4	0.976	1.2 ± 0.2	0.885	11
95.5% DMSO–water [31]	2.0 ± 0.2	1.3 ± 0.1	10 ± 5	0.967	1.3 ± 0.3	0.878	11
Gas phase [32]	8.5 ± 0.8	5.0 ± 0.6	14 ± 5	0.952	5.6 ± 1.3	0.765	16

TABLE 3

Application of the enthalpy-entropy separated and normal Hammett equations to ionization constants of polysubstituted phenols in *N*-methylacetamide–water mixtures [33]

wt% *N*-Methyl acetamide in water	ρ_S	ρ_H	$\Delta\rho_S$	r_P	ρ	r_L	n
0.0	2.9 ± 0.3	1.7 ± 0.1	4 ± 3	0.988	1.6 ± 0.2	0.906	11
9.15	3.0 ± 0.3	1.8 ± 0.1	5 ± 4	0.982	1.5 ± 0.3	0.857	10
27.2	3.4 ± 0.3	2.0 ± 0.1	6 ± 4	0.983	1.6 ± 0.4	0.849	10
45.1	3.6 ± 0.3	2.0 ± 0.1	5 ± 4	0.987	1.9 ± 0.3	0.890	11
66.2	3.9 ± 0.3	2.2 ± 0.1	5 ± 3	0.988	2.0 ± 0.3	0.892	11
75.6	3.9 ± 0.3	2.3 ± 0.1	5 ± 3	0.988	2.1 ± 0.3	0.893	11
85.1	4.0 ± 0.7	2.4 ± 0.1	4 ± 4	0.987	2.2 ± 0.4	0.893	11

The quantity reported in the Tables, $\Delta\bar{\rho}_S(\Delta\bar{\rho}_H = -\Delta\bar{\rho}_S)$ is the difference between the normalized entropic partial regression coefficient for the given reaction and that for the reference Hammett reaction on the basis of the same set of substituents; it is an estimate of the excess entropic contribution for the given reaction compared

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to the reference reaction (4) and may be regarded as a measure of the departure of the reaction from normal Hammett behaviour.

Examination of the correlation coefficients for the linear and planar fits to the data summarized in Tables 2—4 reveals that the two-parameter equation is significantly better than the classical Hammett equation. For the planar fit, all reported correlation coefficients are greater than 0.9, more than 75% of the examples giving values of $R_p > 0.95$. Thus, the enthalpy–entropy relationship accounts for at least 80% and often >90% of the observed variation in the given experimental parameter. On the other hand, the correlation coefficient for the classical Hammett equation is <0.9 in more than 75% of the cases considered. This point is further emphasized when the statistical parameter F is calculated from the parameters reported in Tables 2—4. Comparison of the value of F calculated for a given regression using relationship (6) where n is

$$F = r^2(n - k - 1)/(1 - r^2)k \qquad (6)$$

the number of data points and k the number of independent variables, with tabulated values of F allows one to determine the significance level of a given regression. According to this test, the proposed enthalpy–entropy separation relationship is significant at the 99% level for the data considered. In comparing the present results with those obtained using the traditional two-parameter equations based on separation of inductive and resonance effects,[7-9] it should be kept in mind that the latter regressions are performed separately for *ortho*-, *meta*-, and *para*-substituents. Thus, the degrees of freedom $(n - k - 1)$ in these analyses will be considerably less since fewer data points are considered in each fit. Accordingly, r_P for any one of these fits would have to be considerably higher in order to achieve the significance level reported here.

TABLE 4

Application of the enthalpy–entropy separated and normal Hammett equations to selected kinetic data

Reaction	ρ_S	ρ_H	$\Delta\tilde{\rho}_S$	r_P	ρ	r_L	n
Alkylation of phenylacetic acid with diazodiphenylmethane in methanol [34,35,*]	0.28 ± 0.02	0.17 ± 0.01	12 ± 4	0.969	0.13 ± 0.03	0.789	13
Reaction (1) in ethanol [34,35,*]	0.33 ± 0.03	0.19 ± 0.02	14 ± 5	0.962	0.14 ± 0.04	0.708	13
Reaction (1) in 2-methylpropan-1-ol [34,35,*]	0.35 ± 0.05	0.22 ± 0.03	12 ± 6	0.935	0.17 ± 0.04	0.752	13
Reaction (1) in propan-1-ol [34,35,*]	0.40 ± 0.03	0.22 ± 0.02	14 ± 4	0.970	0.16 ± 0.05	0.675	13
Reaction (1) in 2-methylpropan-2-ol [34,35,*]	0.53 ± 0.05	0.26 ± 0.03	18 ± 5	0.961	0.16 ± 0.08	0.531	13
Reaction (1) in 2-methylbutan-2-ol [34,35,*]	0.63 ± 0.05	0.31 ± 0.03	18 ± 5	0.966	0.19 ± 0.10	0.516	13
Solvolysis of phenylacetyl chlorides in aqueous acetone [36,*]	−5.0 ± 0.5	−3.3 ± 0.4	10 ± 5	0.935	−3.0 ± 0.7	0.741	14
Alkaline hydrolysis of ethyl benzoates in aqueous ethanol [37,*]	2.1 ± 0.2	0.9 ± 0.1	21 ± 5	0.972	0.8 ± 0.4	0.566	11
Reaction of benzophenones with hydroxylamine in buffered aqueous methanol [38]	0.36 ± 0.06	1.1 ± 0.1	−24 ± 9	0.933	0.3 ± 0.1	0.764	10
Esterification of benzoic acids with cyclohexanol (*meta*- and *para*-derivatives only) [39,†]	0.48 ± 0.07	1.1 ± 0.2	−19 ± 8	0.943	0.5 ± 0.1	0.854	11
Cleavage of $XC_6H_4Ge(C_2H_5)_3$ in acidified aqueous ethanol [40,*]	−5.0 ± 0.5	−3.6 ± 0.6	8 ± 6	0.965	−5.3 ± 0.7	0.912	13
Alkali cleavage of $XC_6H_4Sn(CH_3)_3$ in aqueous methanol [41,*]	1.6 ± 0.2	0.8 ± 0.2	16 ± 9	0.910	0.6 ± 0.3	0.509	13
Decomposition of diazoacetophenones in aqueous dioxans [42]	−1.43 ± 0.05	−2.1 ± 0.1	−7 ± 2	0.996	−1.41 ± 0.08	0.985	11

* The reaction series includes *ortho*-substituents. † A satisfactory fit was not obtained when *ortho*-derivatives were included.

The effect of solvent on the Hammett reaction is illustrated by the results summarized in Table 2. It is apparent that the classical substituent constants defined on the basis of free energy changes for this reaction in water do not describe the variation in equilibrium constants observed in the gas phase, that is, in a solvent free system. An equally poor result is obtained when a linear fit between the equilibrium constants and σ_S is attempted (r_L 0.686); however, addition of the enthalpy parameter results in an acceptable fit (r_P 0.952). For this system, both reaction constants are large with the entropic contribution predominant ($\Delta\tilde{\rho}_S$ 14). In all cases ρ_S is larger than ρ_H, variation in the latter quantity with solvent being much smaller. As noted previously,[18] the reaction constant ρ_S increases with decrease in solvent acidity. This trend is apparent both with solvent mixtures of varying composition and with pure solvents; in the latter case, a correlation between ρ_S and the

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Dimroth–Reichardt acidity parameter E_T [43] is observed. Thus, an increase in solute–solvent interactions results in less variation in acidity with substituent nature. It can be argued that the anions involved in the Hammett reaction are chiefly responsible for variation in solute–solvent interactions with solvent. However, solvent interactions at the substituent site must also be considered. Thus, water which is both a good Lewis acid and base will interact with both electron-withdrawing and -repelling substituents; this will result in a less pronounced substituent effect. If a solvent is a stronger acid or base, one type of substituent will interact more strongly with the solvent so that a simple linear correlation between ρ_S and solvent acidity is not observed.

The results of analysing ionization constant data for polysubstituted phenols in various aqueous *N*-methylacetamide solutions are summarized in Table 3. In this case the extended Hammett equation is written as (7)

$$Q = Q_0 + \rho_H \sum_k \rho_{H,k} + \rho_S \sum_k \sigma_{S,k} \tag{7}$$

where $\sigma_{H,k}$ and $\sigma_{S,k}$ are the enthalpic and entropic substituent constants for the *k*th substituent on a given reactant. A significant improvement in the fit is observed when results for equation (7) are compared with those obtained using the classical Hammett equation. Again, one finds that the entropic reaction constant increases with decrease in solvent acidity, a reflection of the fact that an anion is involved in the reaction.

The results of analysing substituent effects for kinetic data, most of which cannot be described by the Hammett equation, are summarized in Table 4. The success of the proposed enthalpy–entropy separated equation is striking, correlation coefficients >0.9 being obtained in all cases. The data for the reaction of substituted phenylacetic acids with diazodiphenylmethane in six pure solvents show a marked departure from Hammett behaviour, the value of $\Delta\bar{\rho}_S$ being >10 in all cases. In addition the entropic reaction constant increases with decrease in solvent acidity as estimated by the parameter E_T. This is probably due to an increase in sensitivity to intramolecular inductive effects with decrease in solute–solvent interactions but may also be related to the fact that the reaction mechanism involves proton transfer as the rate-determining step.[44]

A large range of values of $\Delta\bar{\rho}_S$ is found for the data summarized in Table 4, from 21 for the alkaline hydrolysis of ethyl benzoates to -24 for the reaction between benzophenones and hydroxylamine. Negative values of $\Delta\bar{\rho}_S$ are expected for reactions with a strong electrophilic character. If the activated complex is positively charged, electron-donating substituents will interact strongly with the reaction site; these substituents are enthalpy controlled (except for *o*-OH) so that the enthalpic reaction constant increases and $\Delta\bar{\rho}_S$ becomes negative.

In conclusion, the proposed extended Hammett equation based on separation of enthalpic and entropic effects appears to offer a very good empirical description of substituent effects for systems in which large deviations from the simple Hammett equation are expected. Although a simple interpretation of the derived parameters is difficult to offer, a more detailed analysis would be facilitated if more data were available for processes in both the gas phase and in solution. Finally, it is clear that a complete analysis of substituent effects must consider intra- and inter-molecular effects separately.

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