CHEMOMETRIC ANALYSIS OF SUBSTITUENT EFFECTS. X. UNIFICATION AND REPARAMETRIZATION OF SUBSTITUENT CONSTANTS IN HAMMETT-TYPE EQUATIONS BY MEANS OF ALTERNATIVE INTERPRETATION OF SUBSTITUENT EFFECTS (AISE)

Oldrich PYTELA

Department of Organic Chemistry, University of Pardubice, 532 10 Pardubice, Czech Republic;
e-mail: pytela@hlb.upce.cz

The paper deals with evaluation of validity of substituent scales σ_m, σ_p, σ_p^0, σ_p^+, and σ_p^- in Hammett-type equations. Possible reasons of unreliability of these scales and conceivable ways of verification of individual substituent constants are discussed. On the basis of Alternative Interpretation of Substituent Effects (AISE) and four additional conditions, a regression nonlinear model has been suggested which includes the dependence of all above-mentioned substituent scales upon a single interpreting variable – the σ^i substituent constant. This model has been applied to the 32 most frequent substituents from each scale, i.e. altogether 160 substituent constants taken from literature. The optimization of 17 unknown regression parameters gave the residual standard deviation $s = 0.180$ and, after excluding 12 remote values, $s = 0.061$. The analysis of residua proved their standard and statistical appropriateness of the model. The agreement between literature values and predicted values of substituent constants was the best with the σ_m scale; on the other hand, the largest differences were encountered with the σ_p^+ scale. The found differences above a current reliability limit of substituent constants were due first to unreliability of some literature data and next to solvent effects and (in some cases) specific properties of substituents.

Key words: Substituent effects; Hammett equation; Alternative interpretation of substituent effects.

For chemists the substituent effects represent one of the means used in studies of electron density in a chemical system. It is a long time since the first formulation of the Hammett equation[1] which transformed the then more or less qualitative approach into a quantitative tool. Although other approaches have appeared (for reviews see refs[2–8]) since that time, the Hammett equation still belongs among the most significant correlation relations. In the field of quantitative relations between chemical structure and physico-chemical or biological properties as well as in studies of reaction mechanisms there exist a number of good reasons for preference of a simple correlation model of this sort irrespective of the relatively limited validity range and/or the worse fit of correlation. More complex and more sophisticated correlation equations can provide a greater number of relevant pieces of information which, however, require a greater number of experiments of higher precision.

The key problem of all correlation relations is their suitable parametrization. The parametrization of the Hammett equation for substituents at *meta* and *para* positions of benzene nucleus with respect to the reaction centre was dealt with in a number of papers[9–13] (reviews[2,14–16]). The most comprehensive critical compilation, undoubtedly, is that by Exner[11] giving also further types of substituent constants for use in the Hammett-type correlations. An extensive set of σ_m and σ_p constants can also be found in the work of Hansch et al.[12], and a critically compiled set was prepared by Shorter[13] for the IUPAC. In spite of the large amount of work carried out in this field one can agree with Exner's opinion[11] that published tables of substituent constants always represent a compromise between two wishes: to select reliable data only, and to present the maximum number of data. Although the term "constant" implies invariability, substituent constants are (due to their origin) statistically random variables. Hence they can be characterized by their mean value and measure of variability. The confidence interval given in literature varies from 0.024 to 0.087 for the 15 most common substituents[17–19]. Other sources give values of standard deviations corresponding to higher values of confidence intervals, e.g. Exner[16] 0.03, Shorter[13] 0.04, Hoefnagel and Wepster[20] 0.01 to 0.1. Also interesting in this context is the earlier study by vanBekkum et al.[21]. The above-mentioned variability characteristics seem to be high (about 10% of the extent of substituent constant values) but they – at least – reflect the precision of underlying experiments[13,22].

An unambiguous source of the variability observed in substituent constants lies in solvent effects affecting the primary experiments[2]. The medium-induced changes in substituent constants are considerable for some substituents[23–25]. This is not surprising with polar substituents having localized charges[23] (NO_2, SO_2CH_3, $COCH_3$, $NHCOCH_3$) or readily ionized substituents[23] (OH, SH, COOH), but the behaviour of bulky alkyl groups[20,24] (i-Pr, *t*-Bu) is surprising. In connection with the change in substituent constant depending on solvation of substituent there arises a question whether different sets of substituent constants should be created for individual types of media[23] or the Hammett equation should be extended by an additional term describing the solvent effects[24]. A third possibility (apparently a very practical one) is to simply neglect the corrections of substituent constants for solvent effects even at the price of lowered correlation fit. In this case the scale of substituent constants created by statistical treatment of results of a large set of experiments appears to be more suitable than a definition scale because it eliminates specific properties of individual solvents. An attractive possibility of adjustment of scale of substituent constants is presented by the results of gas-phase experiments which are quite numerous at present[26]. However, there the situation is not much better than that in solvents because other effects make themselves felt which are suppressed in solutions[4]. Hence, the application of the substituent constants obtained in gas phase to processes in solutions may be questionable. In contrast to solvents, the effect of another experimental factor, viz. temperature, is much lower[27].

A separate chapter in the problem of substituent effects deals with the substituents able of direct conjugation with the reaction centre[1,9,28,29]. The discussion of the question whether the introduction of new substituent constants, σ_p^- and σ_p^+, crosses the validity of the Hammett equation or, on the contrary, extends it[16] is a matter of definition. With regard to different extents of direct conjugation in various chemical systems it is more appropriate to consider the exalted substituent constants to be a sort of limit values. This of course urgently evokes the necessity of defining an opposite limit too, possibly represented by σ_p^0 and/or σ_p^n constants[21,30–33]. From practical point of view, the concept thus expressed definitely is much too complicated, but it is necessary for adjustment of values of substituent constants in the framework of other approaches. The reliability of exalted substituent constants given in literature[11,16,28,29,34,35] is undoubtedly lower than that of the basic substituent constants σ_p. The reason lies in the ambiguous formulation of the standard chemical model and the therewith connected extent of direct conjugation, larger extent of solvation of conjugated substituents[36] and, last but not least, small number of suitable experiments.

Verification of validity and/or possible correction of substituent constants in various correlation models can be carried out in several ways. As these relations are based on similarity and the effect of medium is significant, exact theoretical approaches can only be applied with certain limitations (see e.g. ref.[37]). This also holds good for quantum calculations[38–45] which can provide valuable information about the way of transmitting of substituent effect in particular molecules[46] but do not make it possible to take into account e.g. the effect of medium in a sufficient way. Another way lies in critical comparison of experimental data of a selected chemical system in terms of some correlation model[47,48]. In principle, this way has proved useful[11] and is still used[13]. Accumulation of a vast body of experimental data together with development of mathematical-statistical methods and increasing efficiency of computers make it possible to adopt chemometrical methods. An advantage of this approach is in its being more universal, a drawback is in its lacking the ability to give a sharp physico-chemical meaning of the parameter scales obtained. A suitable procedure is confrontation of results obtained on the basis of different principles[2–8]. However, the published correlations of the Hammett substituent constants with σ_I and σ_R substituent constants (e.g. ref.[2]) must be judged carefully due primarily to the method of calculation of the mesomeric substituent constants.

In earlier communications[8,49] of the present series we published a qualitatively new approach to description of substituent effects denoted as Alternative Interpretation of Substituent Effects (AISE). The method suggested starts from the idea that a substituent has only a single property described (in terms of quantitative description of substituent effects) by a single substituent constant, irrespective of type of the basic skeleton and position of substitution. The values of this constant were adjusted for 32 substituents with the help of chemometrical analysis of selected set of data. The different general

principle and independent adjustment of substituent scale makes it possible to verify the validity of the substituent constants used in the Hammett-type equations, which is the aim of the present communication.

THEORETICAL AND CALCULATIONS

According to the principles of Alternative Interpretation of Substituent Effects[8] (AISE) in orthogonal interpretation[49], the substituents are divided by the type of interaction with the basic skeleton into three classes. Class II substituents are defined as ones whose atom directly bound to the basic skeleton possesses nucleophilic character and is able of intramolecular nucleophilic interaction with the reaction centre. Analogously, class III includes the substituents whose atom directly bound to the basic skeleton possesses electrophilic character and is able of intramolecular electrophilic interaction with the reaction centre. Finally, class I includes the substituents that exhibit none of the above-mentioned properties. Mathematically, the AISE model is described by a family of straight lines with a single interpreting variable σ^i (Eq. (*1*)),

$$\log k = \log k_0 + \rho_I \delta_I(\sigma^i - \sigma_0^i) + \rho_N \delta_N(\sigma^i - \sigma_0^i) + \rho_E \delta_E(\sigma^i - \sigma_0^i) \ , \qquad (1)$$

where $\log k$ is logarithm of rate or equilibrium constant, $\log k_0$ is the same quantity at the point of intersection of the straight lines with σ_0^i coordinate (the so-called isosubstituent constant). The orthogonality of model (*1*) is given by the multiplication constants δ of the type of Kronecker's delta: they are equal to 1 if the substituent belongs to the given class, and to 0 if it does not. The respective reaction constants in Eq. (*1*) express the sensitivity to substituents of the first (ρ_I), second (ρ_N), or third class (ρ_E), and generally their relative magnitudes can vary[49]. The straight lines characterized by these reaction constants intersect in a single point σ_0^i different from the standard hydrogen point.

Validation of the substituents constants σ_m, σ_p, σ_p^-, and σ_p^+, and σ_p^0 in the Hammett equation can be carried out by means of AISE using the following postulates:

1. Equation (*1*) is valid individually also for the substituent constants of individual types, i.e.

$$\sigma = \sigma_0 + \rho_I \delta_I(\sigma^i - \sigma_0^i) + \rho_N \delta_N(\sigma^i - \sigma_0^i) + \rho_E \delta_E(\sigma^i - \sigma_0^i) \ . \qquad (2)$$

2. The straight lines formed by the class I substituents (the basic straight line, $\delta_I = 1$) must intersect for all the types of substituent constants in a single point $\sigma^i = 0$, and at

the same time it is $\sigma(\sigma^i = 0) = 0$. Therefrom, the relation $\sigma_0 = \rho_I \sigma_0^i$ follows for the intercept in Eq. (2).

3. For a given type of substituent constant, the straight lines formed by substituents of classes II and III intersect the basic straight line in a single point with the coordinate $\sigma = \sigma_0^i$. The σ_0^i values are different[49] for individual types of substituent constants.

4. The basic straight lines for all substituent constants from *para* position are the same, hence it is $\rho_I(\sigma_p) = \rho_I(\sigma_p^0) = \rho_I(\sigma_p^+) = \rho_I(\sigma_p^-)$.

At these conditions, the validation of the above-mentioned substituent constants leads to nonlinear regression with a single interpreting variable, σ^i, and 17 unknown parameters (slope ρ_I for *meta* substitution, slope ρ_I for *para* substitution, 5 values of points of intersection σ_0^i, 5 values of slopes ρ_N, and other 5 values of slopes ρ_E corresponding to substituents of the classes II and III). The number of unknown parameters seems to be high, but of course most of them are mutually orthogonal (the orthogonal AISE model) and their optimization presents no problems.

For the validation we selected the 32 most common substituents with σ^i values published earlier[8]. The values of substituent constants σ_m and σ_p were primarily taken from the set recommended by IUPAC (ref.[13]), those of σ_p^0, σ_p^+, and σ_p^- were taken from Exner's book[16], and the missing data were taken from other publications[11,12]. For optimizing the 17 unknowns we used the least squares treatment with the objective function S given in Eq. (3).

$$S = \sum_{k=1}^{N} (\sigma_k^{\text{lit}} - \sigma_k)^2 = \text{minimum} \ , \qquad (3)$$

where σ_k^{lit} is the substituent constant for the k-th substituent taken from literature, σ_k is the corresponding value determined from Eq. (2) respecting the above conditions *1–4*. The estimates of standard deviations were obtained by usual way from the covariance matrix of parameters (see e.g. ref.[50]). The residual standard deviation s was calculated from the residual sum of squares S (Eq. (3)) for the optimum parameters. The calculations were carried out using our own programs.

RESULTS AND DISCUSSION

Nonlinear Regression and Regression Diagnostics

The nonlinear regression with regression function (2) respecting the above-mentioned side conditions was applied to 160 substituent constants (5 types). On the basis of analysis of residua involving the analysis of deviating points and normality, the following constants were gradually eliminated from the original set: $\sigma_p^+(\text{NHCH}_3)$, $\sigma_p^+(\text{N(CH}_3)_2)$, $\sigma_p^+(\text{SH})$, $\sigma_p(\text{SH})$, $\sigma_p(\text{SCH}_3)$, $\sigma_p^+(\text{C}_6\text{H}_5)$, $\sigma_p(\text{OCOCH}_3)$, $\sigma_p(\text{OC}_6\text{H}_5)$,

$\sigma_p^+(CH_3)$, $\sigma_p^+(CH_2CH_3)$, $\sigma_p^+(CH(CH_3)_2)$, and $\sigma_p^+(CH_2C_6H_5)$, i.e. 7.5% of data. After this modification, the classical residua had the arithmetic mean of –0.010 and the median of –0.009, i.e. values near to zero. The test of hypothesis of Normal distribution of residua $L(\hat{e})$ recommended for regressions[51] had the criterion value of 0.67, the critical value for the significance level of $\alpha = 0.05$ being 5.99. Hence the hypothesis of normality of residua was not rejected. The statistical characteristics given confirm the suitable non-linear model used for the interpretation of data.

The residual standard deviation s had the value of 0.180 for all the 160 substituent constants, and it decreased to 0.061 after elimination of the 12 above-mentioned constants. In regression models, the residual standard deviation includes both the error of the model and that of the experiment. In an extreme case, the whole residual standard deviation is given by the error of model (2), in reality, however, it must be less with regard to the precision of adjustment of substituent constants[13,16–21]. Therefrom it follows that the validity of model is at least comparable with that of the Hammett equation[16].

The regression parameters obtained by optimization after elimination of remote points are given in Table I together with the respective standard deviations; graphically, the interpretation of substituent scales using the most significant regression straight lines is represented in Figs 1–3. The isosubstituent constants σ_0^i of the substituent constants σ_m and σ_p are almost the same, having the magnitude usual for benzoic acids[49]. A somewhat higher value of isosubstituent constant for σ_p^0 scale indicates elimination of conjugation of electron-deficit carbon atom of carboxyl group with aromatic nucleus, which is in accordance with the definition of this substituent scale. According to a former investigation[49], the lower value of isosubstituent constant is characteristic of chemical models with electron deficit, on the other hand a higher one indicates systems with electron excess at the reaction centre. The found values of isosubstituent constant obtained for the σ_p^+ and σ_p^- scale confirm this conclusion. The larger slope of basic

TABLE I
Regression parameters and their standard deviations obtained by optimization according to Eq. (2) at the conditions specified in Theoretical and Calculations without excluded remote points (see the text)

Constant	σ_0^i	ρ_I	ρ_N	ρ_E
σ_m	0.531 ± 0.152	1.195 ± 0.050	1.555 ± 0.164	1.175 ± 0.146
σ_p	0.535 ± 0.032	1.359 ± 0.027	3.042 ± 0.164	1.160 ± 0.117
σ_p^0	0.695 ± 0.106	1.359 ± 0.027	2.074 ± 0.161	1.267 ± 0.085
σ_p^+	0.479 ± 0.013	1.359 ± 0.027	5.035 ± 0.205	1.087 ± 0.132
σ_p^-	1.466 ± 0.415	1.359 ± 0.027	1.628 ± 0.100	1.028 ± 0.128

straight line ρ_I for *para* substitution, as compared with that for *meta* position, is a well-known phenomenon, and the found ratio of $\rho_I(para)/\rho_I(meta) = 1.14$ is identical with the popular value given by Exner[52]. From the comparison of slopes of straight lines ρ_N expressing the sensitivity to intramolecular nucleophilicity follows an equivocal and expected dominance of the σ_p^+ scale. In this context noteworthy is the marked contribution of nucleophilic interaction from *meta* position expressed by the difference between ρ_N and ρ_I – slope of the basic straight line (Fig. 1). The lower nucleophilic sensitivity of σ_p^0 scale as compared with that of σ_p scale (Table I) is connected with the magnitude of isosubstituent constant. The slopes ρ_E expressing the sensitivity to intramolecular electrophilicity of substituent can be denoted as close, except for the value for σ_p^0 scale. The reasons of the anomaly found are not obvious.

Comparison of Literature Substituent Constant with those Predicted by AISE

The substituent constants σ_m and σ_p from two literature sources[13,16] and those predicted by the nonlinear regression at the above-mentioned conditions are presented in Table II, and their relation is graphically represented in Figs 1 and 2. The agreement between the original and predicted scales of substituent constants from *meta* position (Fig. 1) can be considered good. Greater differences are most frequently encountered with ionizable substituents, such as NH_2, $N(CH_3)_2$, OH, and SH. Whereas for amino group the predicted value of substituent constant lies somewhere in the middle among the literature data, the predicted electron-acceptor abilities of groups able of deprotonation are lower. The differences are undoubtedly due to the media in which the primary experiments were carried out. For adjusting the substituent constant of CHO group there are obviously not enough reliable experimental data: even the critical IUPAC study[13] presents
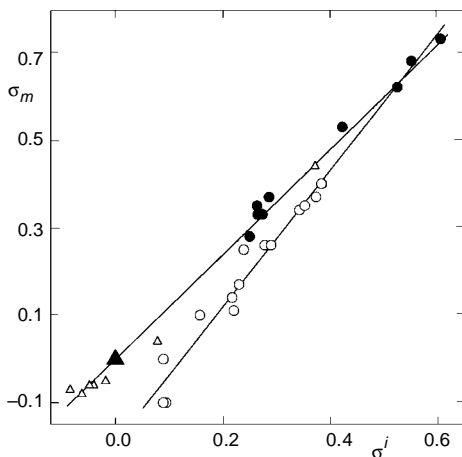

FIG. 1
Dependence of substituent constants σ_m on substituent constants σ^i; the regression straight lines correspond to $\rho_I(\sigma_m) = \rho_E(\sigma_m)$ ($\triangle$,●) and $\rho_N(\sigma_m)$ (○). The symbol ▲ denotes the definition position of hydrogen

the resulting value obtained as an average of very much differing values. With the C_6H_5 substituent the situation is probably similar.

The agreement between the literature values and predicted values of σ_p is not so good (Table II, Fig. 2). First of all, there is a puzzling discrepance between the values of alkyl groups, even so in the case of methyl group itself which represents one of the basic substituents. As there is agreement in the primary experiments concerning CH_3 group, the reason must be somewhere else. The first likely interpretation is enhanced level of conjugation (hyperconjugation) of methyl (alkyl) groups with aromatic nucleus characterized by the difference between the substituent constants from *meta* and *para* positions. However, the small dependence on the magnitude and branching of alkyl group is strange. The second, less likely reason can be the above-discussed solvation effects[20,24]. On the other hand, solvation is undoubtedly the cause of the found difference between substituent constants of substituents that readily form hydrogen bonds with solvent, such as $CONH_2$, $NHCOCH_3$, OH, $OCOCH_3$, and SH substituents. The last two groups mentioned are even denoted as electron acceptors in literature, which is little likely. Obviously distinctly underestimated in literature is the electron-donor nature of SCH_3 group. The substituent constant of OC_6H_5 group is entirely unreliable, which was also known to the author of the work[13] used for comparison. The predicted value of substituent constant of CHO group is closest to the newest experimental results[24], whereas the value from critical compilation of IUPAC is affected by the calculation of an average value involving older and maybe less reliable data[13]. A traditional problem is the substituent constant of fluorine substituent. Like with alkyl substituents, obviously also here an additional positive mesomeric effect of fluorine is operating, maybe also as a result of conjugation with carboxylic group in the standard model.

When comparing the differences between the literature values and predicted values of the σ_p^0 substituent constant (Table III, Fig. 3), we may again be interested in the
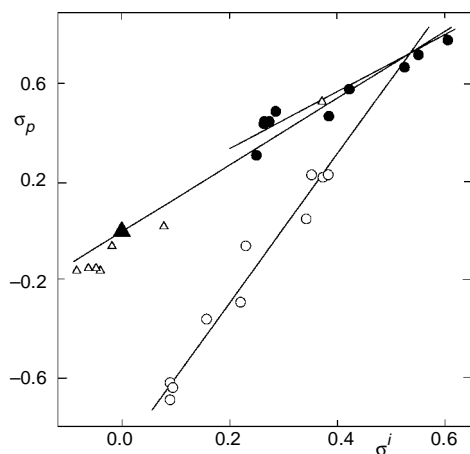

FIG. 2
Dependence of substituent constants σ_p on substituent constants σ^i; the regression straight lines correspond to $\rho_I(\sigma_p)$ ($\triangle$) $\rho_N(\sigma_p)$ ($\bigcirc$) and $\rho_E(\sigma_p)$ ($\bullet$). The symbol $\blacktriangle$ denotes the definition position of hydrogen

TABLE II
Values of substituent constants taken from literature[13,16] (if not otherwise stated), values of substituent constants predicted with the use of the optimized parameters in Table I and their difference Δ for σ_m and σ_p scales

Substituent	σ_m				σ_p			
	ref.[13]	ref.[16]	AISE	Δ	ref.[13]	ref.[16]	AISE	Δ
Class I								
H	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CH_3	–0.06	–0.06	–0.05	–0.01	–0.16	–0.14	–0.05	–0.11
CH_2CH_3	–0.06	–0.08	–0.06	0.00	–0.15	–0.13	–0.07	–0.08
$CH(CH_3)_2$	–0.08	–0.08	–0.07	–0.01	–0.15	–0.13	–0.08	–0.07
$C(CH_3)_3$	–0.07	–0.09	–0.10	0.03	–0.16	–0.15	–0.11	–0.05
C_6H_5		0.04	0.09	–0.05		0.02	0.11	–0.08
$CH_2C_6H_5$		–0.05	–0.02	–0.03		–0.06	–0.02	–0.04
CF_3	0.44	0.46	0.44	0.00		0.53	0.51	0.02
Class II								
NH_2	0.00	–0.09	–0.05	0.05	–0.62	–0.57	–0.63	0.01
$NHCH_3$		–0.10[a]	–0.05			–0.64[a]	–0.62	
$N(CH_3)_2$		–0.10	–0.05	–0.05	–0.69	–0.63	–0.63	–0.06
$NHCOCH_3$	0.17	0.14	0.17	0.00	–0.06	–0.09	–0.20	0.14
OH	0.10	0.13	0.05	0.05	–0.36	–0.38	–0.42	0.06
OCH_3	0.11	0.10	0.15	–0.04	–0.29	–0.28	–0.23	–0.06
OC_6H_5	0.26	0.25	0.24	0.02	–0.32	0.14[b]	–0.06	
$OCOCH_3$		0.26	0.26	0.00		0.16[b]	–0.02	
SH	0.25	0.25	0.18	0.07		0.15[b]	–0.17	
SCH_3		0.14	0.15	–0.01	0.01	0.00[b]	–0.24	
F	0.34	0.34	0.34	0.00	0.05	0.06	0.14	–0.09
Cl	0.37	0.37	0.39	–0.01	0.22	0.22	0.24	–0.02
Br	0.40	0.37	0.41	–0.01	0.23	0.22	0.27	–0.04
I	0.35	0.34	0.36	–0.01	0.23	0.21	0.17	0.05

TABLE II
(*Continued*)

Substituent	σ_m				σ_p			
	ref.[13]	ref.[16]	AISE	Δ	ref.[13]	ref.[16]	AISE	Δ
				Class III				
CN	0.62	0.62	0.63	−0.01	0.67	0.71	0.71	−0.04
CHO	0.40	0.41	0.46	−0.06	0.47	0.47	0.55	−0.08
COCH$_3$	0.37	0.36	0.35	0.02	0.49	0.47	0.44	0.05
CONH$_2$		0.28	0.30	−0.02	0.31	0.31	0.40	−0.09
COOH	0.35	0.35	0.32	0.03	0.44	0.44	0.41	0.03
COOCH$_3$	0.33	0.35	0.33	0.00	0.45	0.44	0.42	0.03
COOC$_2$H$_5$	0.33	0.35	0.32	0.01	0.45	0.44	0.41	0.04
NO$_2$	0.73	0.71	0.72	0.01	0.78	0.81	0.81	−0.03
SO$_2$CH$_3$	0.68	0.68	0.66	0.02	0.72	0.73	0.75	−0.03
SO$_2$NH$_2$	0.53	0.53	0.51	0.02	0.58	0.58	0.60	−0.02

[a] Value from ref.[11]. [b] Values from literature not included in the regression.

alkyls. According to the 4th postulate given in Theoretical, the basic straight lines for *para* substitution are identical, which agrees with the AISE concepts. Obviously on the basis of similar consideration, also the literature values of σ_p^0 and σ_p substituent constants of alkyl substituents[16] are mentioned as identical. As in the normal σ_p^0 substituent
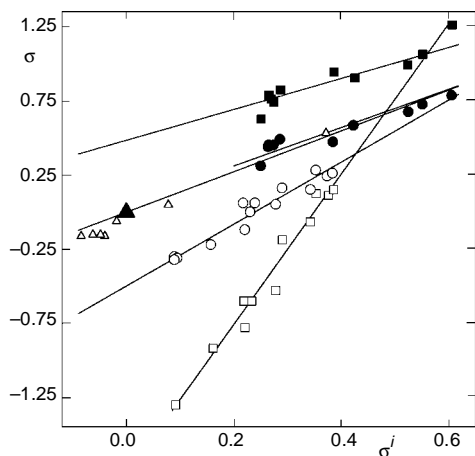

FIG. 3
Dependence of substituent constants σ_p^0, σ_p^+, and σ_p^- on substituent constants σ^i; the regression straight lines correspond to $\rho_I(\sigma_p^0)$ (Δ), $\rho_N(\sigma_p^0)$ (○), $\rho_E(\sigma_p^0)$ (●), $\rho_N(\sigma_p^+)$ (□), and $\rho_E(\sigma_p^-)$ (■). The symbol ▲ denotes the definition position of hydrogen

TABLE III
Values of substituent constants taken from literature[16] (if not otherwise stated), values of substituent constants predicted with the use of the optimized parameters in Table I and their differences Δ for σ_p^0, σ_p^+ and σ_p^- scales

Substituent	σ_p^0			σ_p^+			σ_p^-		
	ref.[16]	AISE	Δ	ref.[16]	AISE	Δ	ref.[16]	AISE	Δ
Class I									
H	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CH_3	–0.16	–0.05	–0.11	–0.31[d]	–0.05		–0.16	–0.05	–0.11
CH_2CH_3	–0.15	–0.07	–0.08	–0.30[d]	–0.07		–0.15	–0.07	–0.08
$CH(CH_3)_2$	–0.15	–0.08	–0.07	–0.28[d]	–0.08		–0.15	–0.08	–0.07
$C(CH_3)_3$	–0.16	–0.11	–0.05	–0.26	–0.11	–0.15	–0.16	–0.11	–0.05
C_6H_5	0.05	0.11	–0.06	–0.18[d]	0.11		0.08	0.11	–0.03
$CH_2C_6H_5$	–0.06	–0.02	–0.04	–0.27[d]	–0.02		–0.06	–0.02	–0.04
CF_3	0.53	0.51	0.02	0.53	0.51	0.02	0.62	0.51	0.11
Class II									
NH_2	–0.30	–0.31	0.01	–1.30	–1.31	0.01	–0.30	–0.25	–0.05
$NHCH_3$	–0.31[a]	–0.30		–1.81[b,d]	–1.29		–0.31[a]	–0.24	
$N(CH_3)_2$	–0.32	–0.31	–0.01	–1.70[d]	–1.31		–0.32	–0.25	–0.07
$NHCOCH_3$	0.00	–0.02	0.02	–0.60	–0.60	0.00	0.00	–0.02	0.02
OH	–0.22	–0.17	–0.05	–0.92[c]	–0.97	0.05	–0.22	–0.14	–0.08
OCH_3	–0.12	–0.04	–0.08	–0.78	–0.65	–0.13	–0.12	–0.04	–0.08
OC_6H_5	0.05	0.08	–0.03	–0.53	–0.36	–0.17	0.05	0.06	–0.01
$OCOCH_3$	0.16[a]	0.10		–0.19[b]	–0.30	0.11	0.16[a]	0.08	
SH	0.06	0.00	0.06	–0.03[b,d]	–0.56		0.06	–0.01	0.07
SCH_3	0.06[a]	–0.05		–0.60	–0.67	0.07	0.06	–0.04	0.10
F	0.15	0.21	–0.06	–0.07	–0.03	–0.04	0.15	0.16	–0.01
Cl	0.24	0.28	–0.04	0.11	0.12	–0.01	0.24	0.21	0.03
Br	0.26	0.30	–0.04	0.15	0.17	–0.02	0.26	0.23	0.03
I	0.28	0.24	0.04	0.13	0.02	0.11	0.28	0.18	0.10

TABLE III
(*Continued*)

Substituent	σ_p^0			σ_p^+			σ_p^-		
	ref.[16]	AISE	Δ	ref.[16]	AISE	Δ	ref.[16]	AISE	Δ
				Class III					
CN	0.67	0.73	–0.06	0.67	0.70	–0.03	0.99	1.02	–0.03
CHO	0.47	0.55	–0.08	0.47	0.55	–0.08	0.94	0.88	0.06
COCH$_3$	0.49	0.43	0.06	0.49	0.44	0.05	0.82	0.78	0.04
CONH$_2$	0.31	0.38	–0.07	0.31	0.40	–0.09	0.62	0.74	–0.12
COOH	0.44	0.40	0.04	0.44	0.42	0.02	0.78	0.76	0.02
COOCH$_3$	0.45	0.41	0.04	0.45	0.43	0.02	0.74	0.77	–0.03
COOC$_2$H$_5$	0.45	0.40	0.05	0.45	0.42	0.03	0.74	0.76	–0.02
NO$_2$	0.78	0.83	–0.05	0.78	0.79	–0.01	1.25	1.11	0.14
SO$_2$CH$_3$	0.72	0.76	–0.04	0.72	0.73	–0.01	1.05	1.05	0.00
SO$_2$NH$_2$	0.58	0.60	–0.02	0.58	0.59	–0.01	0.89	0.92	–0.03

[a] Estimate. [b] Values taken from ref.[12]. [c] Values taken from ref.[11]. [d] Values from literature not included in the regression.

constants the effect of conjugation of reaction centre with aromatic nucleus should be eliminated, the σ_p^0 values of alkyl groups should be proportional (say with a factor of 1.14) to the substituent constants from *meta* position. In reality, however, this is not the fact, and the electron-donor character of alkyl groups, expressed in the value of σ_p^0 substituent constant (and similarly σ_p), seems to be overestimated. Similar situation is encountered with the series of class II substituents having mesomeric effects. In contrast to the σ_p scale, a relatively good agreement was observed with the substituents NHCOCH$_3$, OC$_6$H$_5$, OCOCH$_3$, and SH. This, however, cannot be stated about OCH$_3$ group. Probably, the effect of mesomeric conjugation with reaction centre is not fully eliminated in this case. Among the class III substituents the deviating ones include CHO and CONH$_2$, the reasons of the differences found being obviously identical with those in the σ_p scale.

The differences between the literature values and predicted values of σ_p^+ substituent constants are the highest out of all the scales discussed (Table III, Fig. 3). Probably there are several reasons. The first reason is the small number of reliable experiments applicable to the adjustment of substituent constants. The second reason (connected with the first one) is the variable measure of direct conjugation of the reaction centre with substituent in various chemical models. A far from negligible reason is that of the

effect of medium, especially solvation[53], in the model experiments. From the point of view of application of the AISE approach, there can even be some other exceptional effects operating. The reasons mentioned result in such differences between the literature values as e.g. those found with the pairs NH_2 and $N(CH_3)_2$ or SH and SCH_3. If we exclude the deviating points, the straight line delimiting the behaviour of the class III substituents is unambiguously defined (Fig. 3).

An especially interesting feature of the last scale studied is the behaviour of the electron-acceptor substituents (Table III, Fig. 3). The differences found with CF_3 group (which belongs to class I in the terms of AISE) are obviously due to hyperconjugation. The deviations observed with $CONH_2$ and NO_2 substituents can be ascribed to specific solvation. In the first case, a partial transfer of hydrogen to solvent (in the form of hydrogen bond) will decrease the electron-acceptor nature of the substituents, whereas in the second case the opposite process will increase the same property. The solvent polarity cannot be neglected either.

In conclusion it can be stated that the scale of basic substituents used in the Hammett-type equations can be quantitatively described on the basis of Alternative Interpretation of Substituent Effects. The found differences between literature data and predicted values exceeding the current measure of reliability of substituent constants are probably due first to unreliability of some literature data and next to solvent effects and (in some cases) specific properties of substituents.

REFERENCES

1. Hammett L. P.: J. Am. Chem. Soc. *59*, 96 (1937).
2. Shorter J. in: *Similarity Models in Organic Chemistry, Biochemistry and Related Fields* (R. I. Zalewski, T. M. Krygowski and J. Shorter, Eds), Chap. 2. Elsevier, Amsterdam 1991.
3. Ehrenson S., Brownlee R. T. C., Taft R. W.: Prog. Phys. Org. Chem. *10*, 1 (1973).
4. Taft R. W., Topsom R. D.: Prog. Phys. Org. Chem. *16*, 1 (1987).
5. Swain C. G., Unger S. H., Rosenquist N. R., Swain M. S.: J. Am. Chem. Soc. *105*, 492 (1983).
6. Charton M.: Prog. Phys. Org. Chem. *13*, 120 (1981).
7. Drago R. S., Dadmun A. P.: J. Am. Chem. Soc. *116*, 1792 (1994).
8. Pytela O.: Collect. Czech. Chem. Commun. *60*, 1502 (1995).
9. Jaffe H. H.: Chem. Rev. *53*, 191 (1953).
10. McDaniel D. H., Brown H. C.: J. Org. Chem. *23*, 240 (1958).
11. Exner O. in: *Correlation Analysis in Chemistry: Recent Advances* (J. Shorter and N. B. Chapman, Eds), Chap. 10. Plenum, New York 1978.
12. Hansch C., Leo A., Taft R. W.: Chem. Rev. *91*, 165 (1991).
13. Shorter J.: Pure Appl. Chem. *66*, 2451 (1994).
14. Palm V. A.: *Osnovy kolichestvennoi teorii organicheskikh reaktsii*, 2nd ed., Chaps 4, 5. Khimiya, Leningrad 1977.
15. Shorter J.: *Correlation Analysis of Organic Reactivity*, Chap. 3. Wiley, Chichester 1982.

16. Exner O.: *Correlation Analysis of Chemical Data*. Plenum, New York 1988.
17. Sjostrom M., Wold S.: Chem. Scr. *6*, 114 (1974).
18. Sjostrom M., Wold S.: Chem. Scr. *9*, 200 (1976).
19. Wold S., Sjostrom M.: Ref.[11], Chap. 1.
20. Hoefnagel A. J., Wepster B. M.: J. Am. Chem. Soc. *95*, 5357 (1973).
21. vanBekkum H., Verkade P. E., Wepster B. M.: Rec. Trav. Chim. Pays-Bas *78*, 815 (1959).
22. Kortum G., Vogel W., Andrussov K.: *Dissociation Constants of Organic Acids in Aqueous Solutions*. Butterworths, London 1961.
23. Pytela O., Ludwig M., Vecera M.: Collect. Czech. Chem. Commun. *51*, 2143 (1986).
24. Hoefnagel A. J., Wepster B. M.: J. Chem. Soc., Perkin Trans. 2 *1989*, 977.
25. Hoefnagel A. J., Wepster B. M.: Collect. Czech. Chem. Commun. *55*, 119 (1990).
26. Lias S. G., Liebman J. F., Levin R. D.: J. Phys. Chem. Ref. Data *13*, 695 (1984).
27. Matsui T., Ko H. C., Hepler L. G.: Can. J. Chem. *52*, 2906 (1974).
28. Brown H. C., Okamoto Y.: J. Am. Chem. Soc. *80*, 4979 (1958).
29. Stock L. M., Brown H. C.: Adv. Phys. Org. Chem. *1*, 35 (1963).
30. Taft R. W., Lewis I. C.: J. Am. Chem. Soc. *80*, 2436 (1958).
31. Taft R. W., Lewis I. C.: J. Am. Chem. Soc. *81*, 5343 (1959).
32. Taft R. W.: J. Phys. Chem. *64*, 1805 (1960).
33. Yukawa Y., Tsuno Y., Sawada M.: Bull. Chem. Soc. Jpn. *45*, 1198 (1972).
34. Zollinger H., Wittwer C.: Helv. Chim. Acta *39*, 347 (1955).
35. Fisher A., Leary G. J., Topsom R. D., Vaughan J. J.: J. Chem. Soc., B *1966*, 782.
36. Fujio M., McIver R. T., Taft R. W.: J. Am. Chem. Soc. *103*, 4017 (1981).
37. Cyranski M., Krygowski T. M.: Pol. J. Chem. *69*, 1088 (1995).
38. Kuthan J., Danihel I., Skala V.: Collect. Czech. Chem. Commun. *43*, 447 (1978).
39. Danihel I., Kuthan J.: Collect. Czech. Chem. Commun. *44*, 873 (1979).
40. Danihel I., Kuthan J.: Collect. Czech. Chem. Commun. *45*, 2201 (1980).
41. Bohm S., Kuthan J.: Int. J. Quantum Chem. *26*, 21 (1984).
42. Gilliom R. D., Beck J.-P., Purcell W. P.: J. Comput. Chem. *6*, 437 (1985).
43. Krygowski T. M., Hafelinger G.: J. Chem. Res., Synop. *1986*, 348.
44. Topsom R. D.: Prog. Phys. Chem. *16*, 125 (1987).
45. Monaco R. R., Gardiner W. C.: J. Phys. Org. Chem. *8*, 629 (1995).
46. Exner O., Friedel Z.: Prog. Phys. Org. Chem. *19*, 259 (1993).
47. Reis J. C. R., Segurado M. A. P., De Oliveira J. D. G.: J. Phys. Org. Chem. *8*, 5 (1995).
48. Reis J. C. R., Segurado M. A. P., De Oliveira J. D. G.: J. Phys. Org. Chem. *8*, 671 (1995).
49. Pytela O.: Collect. Czech. Chem. Commun. *61*, 704 (1996).
50. Bard Y.: *Nonlinear Parameter Estimation and Programing*. IBM Scientific Center, New York 1967.
51. Jarque C. M., Bera A. K.: Int. Stat. Rev. *55*, 163 (1987).
52. Exner O.: Collect. Czech. Chem. Commun. *31*, 65 (1966).
53. Grunwald E., Winstein S.: J. Am. Chem. Soc. *70*, 846 (1948).