CHEMOMETRIC ANALYSIS OF SUBSTITUENT EFFECTS. VII. INDUCTIVE EFFECT AS A BASIC SUBSTITUENT EFFECT. ISOEFFECT SUBSTITUENT CONSTANT

Oldrich PYTELA and Ales HALAMA

Department of Organic Chemistry,
University of Pardubice, 532 10 Pardubice, Czech Republic

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The paper deals with chemometric analysis of the inductive effect. The notion of inductive effect is discussed, and unambiguous definitions are given for the notions of triad: reaction centre–basic skeleton–substituent, and the therewith connected definitions of inductive effect. For a quantitative description of inductive effect 7 types of chemical models were selected including noncyclic compounds, cyclic, and bicyclic compounds, derivatives of quinuclidine, 3-substituted benzoic acids, sulfonamides and pyridines. Altogether 139 sets of experimental data from literature have been used including altogether 1 294 points (9.3 points per set, 5 points at least) reflecting substituent effects of 34 substituents. It has been found that for a standard model the dissociation of substituted bicycloalkanecarboxylic acids only is satisfactory, all the other models reflecting also the mesomeric effects to variable extent (up to 10%). A distinctly different substitution behaviour was observed with ^{19}F and ^{13}C NMR chemical shifts of 4-substituted 1-fluoro- or 1-methylbicyclo[2.2.2]octanes. The earlier suggested model of substituent effects based on different way of transmission of substituent effects (3 classes) has been used for separating the inductive and mesomeric effects: it is mathematically presented as a set of straight lines with the intersection point at the so-called isoeffect substituent constant. Using the modified method of conjugated deviations a chemometric scale has been created for the inductive effect σ_I^i which agrees very well with the conventional σ_I scales given in literature; the only differences were observed for F and CH=O substituents (which are overestimated and underestimated, respectively, in literature). In the context given the inductive effect appears as a fundamental quantity forming a basis for quantitative description of other effects transferred by electrons.

The interpretation of substituent effects based on the triad: reaction centre–basic skeleton–substituent seems to be generally accepted. There inevitably follows the question whether it is possible to quantitatively describe the interaction between reaction centre and substituent by means of a few independent additive quantities that describe a substantial part of the substituent effects within the validity range of the similarity principle. The question can, in principle, be answered positively[1–9], since it is possible to give a number of more or less successful solutions to the problem mentioned in the form of parameter scales and their modifications such as (σ_m, σ_p)[10,11], (σ_I, σ_R)[10,11] (σ_F, σ_χ, σ_α, σ_R)[6], (F, R)[11–13] (σ_l, σ_d, σ_e)[3], (ΔE^X, ΔC^X)[14,15], (σ^*, E_S)[16] and others. Obviously,

the scale of parameters published so far for describing the substituent parameters exceeds the number necessary for description of substituent effects in the above-mentioned sense[7], apparently they are variations of the same or very similar themes[17]. But there is no completely unambiguous answer to the question about the number of well separated elementary substituent effects described in the form of parameters with clear physico-chemical meaning. If we prefer such effects that are manifested to a substantial extent in most chemical compounds through the property measured, we clearly arrive at the classical Ingold classification[18] into inductive, mesomeric, and sterical effects without crossing this more or less qualitative limitation. Other classifications published[3,6] can be considered to be another, perhaps more precise and detailed, formulation of the same thing.

Even the inductive effect itself[1–11,19–23], which can be considered the most general and – at the same time – the least problematic manifestation of substituent effects, is sometimes viewed in various ways, which is best reflected in the term "the so-called inductive effect" used in introduction of an article on substituent effects (ref.[8], Chap. 2.2.4). The term "inductive effect" is usually adopted for all effects of substituent observed in the reaction centre with possible correction for other effects defined in some way[5,11,16,20,21]. However, often this term is used only for the effects transmitted by σ bonds (the so-called σ-inductive effect[1,5,7,10,22]). Other authors, on the other hand, stress the electrostatic nature of inductive effect[24], and their view is supported by the results of studies of angle independence of mutual positions of reaction centre and substituent[25]. It is also possible to encounter a view identifying the inductive effect with the field effect[11]. Attempts at surmounting this terminological confusion have led some authors to the necessity to formulate new quantities[3,6,14,15]. Therefore, it is possible to agree with the view that the notion "inductive effect" is suitably used without differentiating the way of its transmission[7], keeping in mind that this is a single, though complex, factor. A wide variety of chemical models have been used to quantitatively adjust the respective parameter, the most appropriate being those with rigid structure without multiple bonds (bicyclic compounds, adamantane derivatives). The nonuniformity in views of the basic skeleton for noncyclic aliphatic models has led to various scales for description of inductive effect (σ^*, σ_I, F and others) defined in principle for different substituents or processes. Substituent effects from *meta* position of aromatic nucleus were not used for the parametrization of inductive effect because of their observed dependence on σ_R constants which, of course, were determined by means of σ_I constants again. The interpretation of inductive effect as a combination of σ_m and σ_p constants[11] suffers from the same imperfection, because σ_p constants are a linear function of σ_m (refs[26–28]). The approaches mentioned resulted in a number of more or less similar parametric scales for quantitative description of inductive effect[3,6,11–13,16,17,29–31]. Although at present there is an extensive body of experimental data available, no large chemometric study has been published yet which would make it possible to evaluate

the extent of manifestation of inductive effect in various chemical models with the reaction centre defined in different ways. Therefore, the aim of the present paper is a chemometric analysis of inductive effect on a large set of data with the stress on general delimitation of the notion of inductive effect and its quantitative description.

THEORETICAL

For the purpose of subsequent discussion it is necessary to formulate several basic notions. As already mentioned above, the description of substituent effects expressed by the triad: reaction centre–basic skeleton–substituent represents a generally accepted scheme. The first presumption which must be introduced in their delimitation is the different time-space (unambiguously with rigid molecules) or at least topological (with flexible molecules) localization of reaction centre, basic skeleton, and substituent in the given reaction series. The term time-space localization means stable in time or, on the other hand, time-averaged space arrangement in relation to the time of duration of the process investigated. The requirement of time-space localization instead of the usually considered topological localization is inevitable in order to avoid the problems connected e.g. with the geometrical isomers of rigid molecules[24,25] (another space localization – another reaction series), conformational isomers, discussions about the way of transmission[1,5,7,10,11,22,24] (through σ electrons or π electrons, through the space or through bonds), etc. The postulated requirement results in a certain reduction of validity range of inductive effect model, which, however, does not exclude a discussion of exceptions from the unambiguously defined basis.

A localized reaction centre is defined as an atom or bond between two atoms at which electron density is changed due to (so far not nearer specified) interaction with substituent, which is finally manifested in a quantitative change of result of a process measured at this centre. If there are more than one such centres in the molecule, completely equivalent during the whole process monitored (inclusive of the time-space localization), each such centre formally is a reaction centre. The observed quantitative result of the process measured is taken as a mean value of manifestations of this process on a statistical set of individual molecules. Obviously, a definition constructed like that excludes the cases in which the whole molecule is a reaction centre, but it naturally involves chemical reactions and equilibria, NMR and IR spectra, and some electrochemical processes.

The basic skeleton is defined as the part of molecule (excluding the reaction centre) which is constant within the whole reaction series (inclusive of the time-space arrangement). The general definition given is not restricted only to the bonds as imaginary connection lines of atoms but considers the whole space occupied by the molecule in the milieu of other molecules. It includes the obligatory aromatic and bicyclic systems, on the other hand, however, e.g. the term “side chain” (introduced as a consequence of aromatic nucleus postulated as the standard structure in the Hammett equation) loses its

meaning in this concept. Similarly, also the discussion connected e.g. with the definition of σ^* and σ_I substituent constants becomes superfluous. The basic skeleton mediates the transfer of effects between substituent and reaction centre. From the quantum-chemical point of view this process is more or less clear since the transfer of effects is mediated by molecular orbitals describing the spatially distinctly anisotropic distribution of individual electrons. Therefrom it can be deduced that an interaction between substituent and reaction centre is predominantly realized through electronic channels leading through places of the highest electron density. Such channels need not necessarily be identical with chemical bonds (topologically viewed usually as connecting lines between atoms) in complex molecules. Unreal can also be the approximate σ–π separation of molecular orbitals, which is obviously very acceptable for rigid planar molecules but does not fully apply to the interactions of such systems with those exhibiting only slight deviation from planarity. Probably an additional mechanism of transmission of effects between substituent and reaction centre is represented by electrostatic interaction mediated by electrostatic field[24], the basic skeleton can be viewed as dielectric in this case. It is also necessary to keep in mind the effect of polarization of skeleton[6] and solvent effects[32,33]. For the purpose of quantitative description, only one requirement concerning the basic skeleton must be taken into account, viz. that the properties of basic skeleton manifested in mediating the interaction between substituent and reaction centre must not depend on the substituent, at least not within the validity range of similarity principle. In our view of substituent effects the basic skeleton must exist (even if it was reduced to a single atom) in the chemical model.

The last component of triad – substituent – is that part of the molecule which is varied in the reaction series. Beside the above-mentioned requirements for time-space localization, another requirement is usually posed on substituent, viz. that of the minimum specific interactions with the reaction centre (such as sterical effect or hydrogen bonding). If these specific interactions are quantitatively describable, their existence presents no problems.

When explaining our approach to substituent effects we deliberately avoided any a priori specification of their physico-chemical nature. For interpretation of inductive effect on the basis of chemometric analysis it is most suitable to define it irrespective of the way of transmission, most appropriately as a single common factor describing mutual interactions between reaction centre and substituents on suitably chosen models fulfilling the above-given requirements. If there exist other factors with linearly proportional manifestations, they cannot be – without adopting further presumptions – only separated from the data (neither it is necessary), and they will be involved into a single parameter. The description of transmission of effects thus quantitatively expressed can then a posteriori be analyzed from the point of view of physico-chemical interpretation inclusive of additional separation of physico-chemically relevant effects.

INPUT DATA AND THEIR TREATMENT

Table I presents a survey of selected data sets from literature. Only chemical reactions and dissociation equilibria were chosen for model processes for chemometric analysis of inductive effect. The NMR chemical shifts of ^{19}F in 4-substituted 1-fluorobicyclo[2.2.2]octanes[34] and of ^{13}C in analogous 4-substituted 1-methylbicyclo[2.2.2]octanes[35] were used for comparison only. For chemical models were chosen only substituted cyclic compounds with one or more cycles (Table I, groups A, B, C), *meta* substituted benzoic acids and their analogues (group D), *meta* substituted benzenesulfonamides (group E), 3-substituted pyridines (group F), and some other compounds containing an sp^3 carbon bridge (group G). Deliberately chosen were such chemical models and processes which involved formation of a negative (first of all groups A, D, G) or positive charge (first of all groups B, C, F) at the reaction centre. At the same time, the models chosen contain a more or less rigid nonaromatic (predominantly groups A, B, C) or rigid aromatic basic skeleton (predominantly groups D, E, F). Also included are compounds with flexible or partially flexible skeleton (group G). On the basis of preliminary calculations we excluded – in the first phase of analysis – such substituents which undergo the same type of process as the reaction centre itself (OH, SH, COOH in the dissociation equilibria). The minimum number of substituents in each data series was 5, the numbers for the individual data series are given in Table I. The data were processed by the method of conjugated deviations[26,36] (CDA) using the below-given modifications and by multiple regression analysis using our own programs on a PC type computer.

RESULTS AND DISCUSSION

Analysis of Individual Types of Chemical Models

The individual groups of chemical models given in Table I were treated separately by the method of conjugated deviations and the results are given in Table II for 2 latent variables. From data of Table II it is obvious that the similarity principle is very well fulfilled except for the heterogeneous group G, the agreement being comparable with the validity range of the Hammett equation ($s = 0.188$, $V = 96.9\%$ when using $\sigma_{m,p}$; $s = 0.161$, $V = 97.7\%$ on the 1st latent variable[26]). But the models chosen are not fully identical, as it is seen from the comparison of individual statistical characteristics with results of treatment of the whole set. This non-homogeneity is still more marked when characterizing the mutual bonds between the 1st latent variables by means of pair correlation coefficients (Table III). The closest bonds are in the pairs of groups: A–B, D–E, D–F, E–F, and E–G. The first two relations are not surprising because the models are chemically cognate, on the other hand, the similarity in behaviour of benzenesulfonamides (E) and pyridines (F) with compounds containing a methylene bridge (G) was not expected. At the same time there is obvious little close correlation between the standard models A and B and further models with aromatic or heteroaromatic nuclei. A closer inspection of mutual relations shows that the similarity level strongly depends on the extent of similarity of distinct $+M$ substituent effects (NH_2, $NHCH_3$, $N(CH_3)_2$, OCH_3), the $-M$ substituent effects being also partially manifested (NO_2, CH_3SO_2, COOR). The extent of operation of mesomeric effect, which is the obvious cause of the results given,

TABLE I
Selected sets of experimental data (*n* is number of substituents used in calculation)

No.	Processes and data sets	*n*	Ref.
	A. Dissociation equilibria of substituted mono- and polycyclic compounds (pK_a)		
1	4-Substituted cyclohexanecarboxylic acids, water, 24.91 °C	7	3
2	4-Substituted cyclohexanecarboxylic acids, 50% methanol, 24.91 °C	6	3
3	4-Substituted cyclohexanecarboxylic acids, 50% ethanol, 24.91 °C	6	3
4	3-Substituted bicyclo[1.1.1]pentane-1-carboxylic acids, 50% (v/v) ethanol, 25 °C	7	38
5	3-Substituted bicyclo[2.2.2]octane-1-carboxylic acids, 50% (v/v) ethanol, 25 °C	7	39
6	3-Substituted bicyclo[2.2.2]octane-1-carboxylic acids, 80% (w/w) MCS, 25 °C	7	39
7	4-Substituted bicyclo[2.2.2]octane-1-1carboxylic acids, gas phase, $\delta\Delta G^0$	7	40
8	4-Substituted bicyclo[2.2.2]octane-1-carboxylic acids, 50% (w/w) ethanol, 25 °C	9	41
9	4-Substituted bicyclo[2.2.2]octane-1-carboxylic acids, 50% (w/w) ethanol, 25 °C	12	42
10	3-Substituted adamantane-1-carboxylic acids, 50% ethanol, 25 °C	8	3
11	6-Substituted spiro[3.3]heptane-2-carboxylic acids, 50% (w/w) ethanol, 25 °C	6	3
	B. Dissociation equlibria and reactions of substituted quinuclidines (pK_a, log *k*)		
12	2-Substituted quinuclidinium perchlorates, water, 0.1 M KCl, 25 °C	8	43
13	3-Substituted quinuclidinium perchlorates, water, 0.1 M KCl, 25 °C	7	43
14	3-Substituted quinuclidinium perchlorates, water, 25 °C	6	44
15	4-Substituted quinuclidinium perchlorates, water, 0.1 M KCl, 25 °C	7	43
16	4-Substituted quinuclidinium perchlorates, water, 0.1 M KCl, 25 °C	21	45
17	4-Substituted quinuclidinium perchlorates, water, 25 °C	21	46
18	4-Substituted quinuclidinium perchlorates, water, 25 °C	7	44
19	4-Substituted quinuclidines, 5% (v/v) ethanol, 25 °C	8	47
20	4-Substituted quinuclidines, 50% (w/w) ethanol, 25 °C	8	47
21	Reactions of 4-substituted quinuclidines with methyl iodide in methanol, 25 °C	7	47
22	Reactions of 4-substituted quinuclidines with methyl iodide in methanol, 25 °C	19	3
	C. Solvolyses of substituted bicyclic compounds (log *k*)		
23	Solvolysis of 1-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	48
24	Solvolysis of 1-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	48
25	Solvolysis of 4-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	5	49
26	Solvolysis of 4-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	5	49
27	Solvolysis of 5-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	49
28	Solvolysis of 5-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	49

TABLE I
(*Continued*)

No.	Processes and data sets	*n*	Ref.
29	Solvolysis of 6-*endo*-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	10	50
30	Solvolysis of 6-*endo*-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	51
31	Solvolysis of 6-*exo*-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	14	52
32	Solvolysis of 6-*exo*-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	13	52
33	Solvolysis of 7-*anti*-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	53
34	Solvolysis of 7-*anti*-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	6	53
35	Solvolysis of 7-*anti*-substituted 2-*exo*-norbornyl *p*-toluenesulfonates, 97% (w/w) TFE, 70 °C	6	54
36	Solvolysis of 7-*anti*-substituted 2-*endo*-norbornyl *p*-toluenesulfonates, 97% (w/w) TFE, 70 °C	6	54
37	Solvolysis of 2-substituted bicyclo[2.2.2]octyl *p*-nitrobenzenesulfonates, 80% (v/v) ethanol, 70 °C	7	55
38	Solvolysis of 3-substituted bicyclo[2.2.2]octyl *p*-nitrobenzenesulfonates, 80% (v/v) ethanol, 70 °C	7	55
39	Solvolysis of 4-substituted bicyclo[2.2.2]octyl *p*-nitrobenzenesulfonates, 80% (v/v) ethanol, 70 °C	6	55
40	Solvolysis of 6-*exo*-substituted 2-*exo*-bicyclo[2.2.2]octyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	5	56
41	Solvolysis of 6-*exo*-substituted 2-*endo*-bicyclo[2.2.2]octyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	5	56
42	Acid catalyzed hydrolysis of 3-substituted nortricyclanes, 1 M $HClO_4$, 348.2 K	5	57
43	Solvolysis of 3-substituted 1-adamantyl *p*-toluenesulfonates, 80% (v/v) ethanol, 70 °C	9	58
44	Solvolysis of 3-substituted 1-adamantyl *p*-toluenesulfonates, 97 (w/w) TFE, 70 °C	6	54
45	Solvolysis of 4^e-substituted 2^e-adamantyl *p*-nitrobenzenesulfonates, 80% (v/v) ethanol, 70 °C	8	59
	D. Dissociation equilibria of *meta* substituted benzoic acids and cognate compounds (pK_a)		
46	*meta* Substituted benzoic acids, gas phase, $\delta\Delta G$, 600 K	8	60
47–92	46 Sets of *meta* substituted benzoic acids, water	–	26
93	Protonation of *meta* substituted benzoic acids, H_2SO_4	9	61
94	Equilibrium 3-X–C_6H_4–CO_2CH_3 + C_6H_5–$C(OCH_3)OH^{(+)}$, gas phase, $\delta\Delta G$, 343 K	10	62
95	Equilibrium 3-X–C_6H_4–$COCH_3$ + C_6H_5–$C(CH_3)OH^{(+)}$, gas phase, $\delta\Delta G$, 343 K	10	62
96	3-X–C_6H_4–$CONH$–$N^{(+)}(CH_3)_3$, water, 25 °C	8	63

TABLE I
(*Continued*)

No.	Processes and data sets	*n*	Ref.
	E. Dissociation equilibria of *meta* substituted benzenesulfonamides (pK_a)		
97	*meta* Substituted benzenesulfonamides, 25% methanol, 25 °C	7	64
98	*meta* Substituted benzenesulfonamides, 50% methanol, 25 °C	7	64
99	*meta* Substituted benzenesulfonamides, 75% methanol, 25 °C	7	64
100	*meta* Substituted benzenesulfonamides, 90% methanol, 25 °C	7	64
101	*meta* Substituted benzenesulfonamides, methanol, 25 °C	7	65
102	*meta* Substituted benzenesulfonamides, ethanol, 25 °C	7	65
103	*meta* Substituted benzenesulfonamides, 25% acetone, 25 °C	7	64
104	*meta* Substituted benzenesulfonamides, acetone, 25 °C	7	64
105	*meta* Substituted benzenesulfonamides, 1,2-DCE, 25 °C	7	64
106	*meta* Substituted benzenesulfonamides, AN, 25 °C	7	66
107	*meta* Substituted benzenesulfonamides, Py, 25 °C	7	64
108	*meta* Substituted benzenesulfonamides, TMS, 25 °C	7	64
109	*meta* Substituted benzenesulfonamides, DMSO, 25 °C	7	66
110	*meta* Substituted benzenesulfonamides, 25% DMF, 25 °C	7	64
111	*meta* Substituted benzenesulfonamides, 50% DMF, 25 °C	7	64
112	*meta* Substituted benzenesulfonamides, 75% DMF, 25 °C	7	64
113	*meta* Substituted benzenesulfonamides, DMF, 25 °C	7	66
	F. Dissociation of substituted pyridines (pK_a)		
114	Equilibrium 3-X–$PyH^{(+)}$ + Py, gas phase, $\delta\Delta G$, 25 °C	13	67
115	Equilibrium 3-X–$PyH^{(+)}$ + Py, water, $\delta\Delta G$, 25 °C	13	67
116	3-Substituted pyridinium ions, water, 25 °C	17	68
117	3-Substituted pyridines, water, 0 °C	6	69
118	3-Substituted pyridines, water, 25 °C	9	70
119	3-Substituted pyridines, water, 37 °C	6	69
120	3-Substituted pyridines, $\delta\Delta G$, water, 25 °C	15	71
121	3-Substituted pyridines, nitromethane, 25 °C	7	72
	G. Dissociation equlibria and reactions of other model compounds (pK_a, log *k*)		
122	4-XCH_2–C_6H_4–CO_2H, 80% (w/w) MCS, 25 °C	8	3
123	3-X–C_6H_4–CH_2CO_2H, 10% ethanol, 25 °C	10	73
124	3-X–C_6H_4–CH_2CO_2H, 50% ethanol, 25 °C	11	73
125	3-X–C_6H_4–CH_2CO_2H, 75% ethanol, 25 °C	12	73
126	4-X–C_6H_4–CH_2CO_2H, 10% ethanol, 25 °C	11	73
127	4-X–C_6H_4–CH_2CO_2H, 50% ethanol, 25 °C	16	73
128	4-X–C_6H_4–CH_2CO_2H, 75% ethanol, 25 °C	16	73
129	4-X–C_6H_4–$C(CH_3)_2CO_2H$, 50% ethanol, 25 °C	10	74

TABLE I
(*Continued*)

No.	Processes and data sets	*n*	Ref.
130	3-X–C_6H_4–CH=$CHCO_2H$, 50% ethanol, 25 °C	6	75
131	$RCH_2NH_3^{(+)}$, water, 25 °C	6	3
132	3-(XCH_2)-Substituted pyridines, water, 25 °C	15	76
133	4-(XCH_2)-Substituted pyridines, water, 25 °C	14	77
134	Reaction of X–CH_2CO_2H with Ph_2CN_2, methanol, 30 °C	8	3
135	Reaction of X–CH_2CO_2H with Ph_2CN_2, ethanol, 30 °C	8	3
136	Reaction of X–CH_2CO_2H with Ph_2CN_2, t-BuOH, 30 °C	8	3
137	Reaction of X–CH_2CO_2H with Ph_2CN_2, DMSO, 30 °C	8	3
138	Reaction of 3-(XCH_2)-substituted benzoic acids with Ph_2CN_2, 40% ethanol, 0.1 M NaCl, 25 °C	9	78
139	Reaction of 2-(XCH_2)-substituted benzoic acids with Ph_2CN_2, 40% ethanol, 0.1 M NaCl, 25 °C	9	78

TABLE II
Overall standardized residual standard deviations *s* (ref.[25]), total explained variability *V*, overall coefficients of multiple correlation *R*, and degrees of freedom ν obtained by the method of conjugated deviations with the data sets of Table I

Group	The 1st latent variable				The 2nd latent variable			
	s	*V*, %	*R*	*v*	*s*	*V*, %	*R*	*v*
A	0.181	98.1	0.991	33	0.164	99.2	0.996	18
B	0.095	99.4	0.997	78	0.056	99.9	0.999	49
C	0.178	97.8	0.989	90	0.168	98.5	0.992	68
D	0.180	97.3	0.986	407	0.136	98.6	0.993	357
E	0.154	98.2	0.991	78	0.101	99.3	0.997	66
F	0.174	98.0	0.990	49	0.050	99.9	0.999	31
G	0.267	94.9	0.974	107	0.155	98.9	0.994	69
A–G	0.234	95.4	0.977	930	0.172	97.7	0.988	834

can be estimated from the pair correlation coefficients given in Table III. Their graphical representation (Fig. 1) shows a typical form of a family of three straight lines already observed for the dependence between the substituents constants σ_m and σ_p (refs[26,27]). The basic, middle straight line is formed by substituents without mesomeric effect, whereas substituents having a free electron pair at the atom adjacent to the basic skeleton lie on the second straight line, and those with polarized multiple bond between the first and the second atoms (with respect to the basic skeleton) form the third straight line. The existence of the described type of dependence in the data analyzed supports the correctness of the model of substitution effects suggested earlier[26,27,37] based on a single substituent effect and on different ways of transmission of this effect to the reaction centre.

TABLE III
Sample correlation coefficients *r* between the 1st latent variables calculated for groups A – G

Group	A	B	C	D	E	F
B	0.990	–	–	–	–	–
C	0.968	0.905	–	–	–	–
D	0.962	0.917	0.975	–	–	–
E	0.950	0.933	0.980	0.997	–	–
F	0.958	0.901	0.982	0.989	0.999	–
G	0.973	0.931	0.954	0.975	0.991	0.980

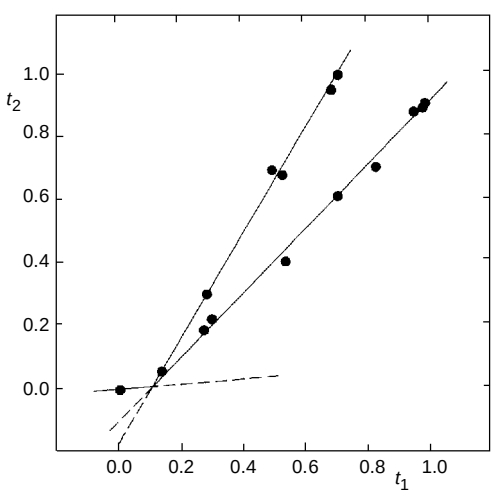

FIG. 1
Dependence of the 1st latent variable calculated from data of group C (Table I) upon the 1st latent variable calculated from data of group B; for numbers see Table IV

Separation of Inductive Effect from Mesomeric Effect

For separation of inductive from mesomeric effect in data of Table I we used the model of substituent effects in the form:

$$\Delta G = \Delta G^0_{\mathrm{iso}} + \rho_I(1 + \delta\Delta M)(\sigma_I^i - \sigma_I^{i0}) \,, \qquad (1)$$

where ΔG is the quantitative result of measurement, $\Delta G^0_{\mathrm{iso}}$ is intercept, ρ_I is reaction constant, $\rho_I\delta\Delta M$ is slope of straight line with the value of 0 for substituents not interacting by mesomeric effect (class I) and a different, non-zero value for substituents with $+M$ effect (class II) or $-M$ effect (class III), σ_I^i is substituent constant characterizing the inductive effect, and σ_I^{i0} is the value of σ_I constant at the point of intersection of the straight lines. The quantity σ_I^{i0} in fact represents the "isoeffect substitution constant" since all the effects considered are identically manifested at this value. This quantity has a universal value identical for all the series. From mathematical point of view, Eq. (*1*) leads to a model with triple linear regression with unknown parameters $\Delta G^0_{\mathrm{iso}}$ as its intercept, and ρ_I and two values of $\rho_I\delta\Delta M$ for substituents of classes II and III as its slopes. If the data do not include substituents of classes II or III, the triple regression is reduced to a lower dimension.

The model (*1*) can also be applied as one with latent variables (σ_I^i values as the 1st latent variable) provided the mentioned unknown parameter σ_I^{i0} is optimized to the maximum interpreted variability. This procedure was implemented into the algorithm of the method of conjugated deviations[26,36] and applied to data of Table I. In the first phase, the data for dissociable substituents OH, SH, COOH were excluded from the calculation, their inclusion did not lead to convergency of calculation. For the initial estimate of the 1st latent variable we used the 1st latent variable obtained by calculation on the A and B sets, the other two variables were fixed to the 1st latent variable according to Eq. (*1*). In the case of absence of substituent of a particular type from the data, the model (*1*) was reduced to a lower dimension automatically by the program. The optimization of σ_I^{i0} parameter to the maximum interpreted variability gave the 1st latent variable which was transformed to σ_I scale[3,7] by means of regression. The resulting σ_I^i values are given in Table IV, the optimized value is $\sigma_I^{i0} = 0.537$ after recalculating to the standard σ_I scale. As a very similar value of $\sigma_{\mathrm{m}}^{i0} = 0.595$ was found for the point of intersection of the family of straight lines of the dependences of σ_{p} vs σ_{m} (ref.[27]), it seems probable that this value could possess a fairly general validity.

The values of σ_I^i constants for dissociable substituents (OH, SH, COOH) were adjust additionally by calculation using the method of conjugated deviations with fixed optimum values for other substituents. The comparison of standard deviations of substituent constants in Table IV for dissociable and nondissociable substituents indicates a

great variability of substituent effect for dissociable substituents, which is particularly obvious with carboxyl and less so with hydroxyl groups.

The variability of data of Table I was explained with application of model (*1*) with three latent variables to 97.51%, the overall residual standard deviation on standardized data was $s = 0.189$. The three latent variables obtained by standard calculation by the method of conjugated deviations explained 98.40% variability of data, $s = 0.151$, for the remaining data see Table II. Although the difference of less than 1% is statistically significant, from the standpoint of similarity principle the interpreted variability is sufficient and comparable with results of similar studies[79–82].

Proportion of Mesomeric Effect in Individual Chemical Models

Using Eq. (*1*) with σ_I^i substituent constants and $\sigma_I^{i0} = 0.537$, and including the substituents according to Table IV (which is identical with ref.[27], only CF_3 being placed into group I), we can verify the extent of mesomeric contribution of a substituent relative to the reaction centre in the individual chemical models of Table I. The quantity δ assumes the value of 1 if the substituent belongs to the group; if not, then $\delta = 0$. The first latent variable obtained by the method of conjugated deviations from group A depends only on σ_I^i constant with correlation coefficient $r = 0.993$. As the group A represents a standard chemical model, this result confirms a correct adjustment of the σ_I^i scale (the mesomeric effect is not manifested). The first latent variable determined with the group B correlates according to Eq. (*1*) with the correlation coefficient $R = 0.995$; besides the dependence upon σ_I^i with the partial correlation coefficient $r_I = 0.995$, however, there is also a significant dependence on the term $\delta\Delta M_{II}\sigma_I^i$ (the substituents with free electron pair at the first atom from the basic skeleton) with the partial correlation coefficient $r_{II} = 0.747$, which is little as compared with r_I value. Analogous situations are encountered with the other groups: C ($R = 0.981$, $r_I = 0.978$, $r_{II} = 0.809$, 89.02%/7.19%), D ($R = 0.996$, $r_I = 0.996$, $r_{II} = 0.956$, 89.02%/10.25%), E ($R = 0.998$, $r_I = 0.998$, $r_{II} = 0.976$, 93.05%/6.62%), F ($R = 0.995$, $r_I = 0.994$, $r_{II} = 0.949$, 99.04%/8.74%), G ($R = 0.987$, $r_I = 0.987$, $r_{II} = 0.844$, 97.49%/6.22%). Noteworthy is the high proportion of mesomeric effect at *meta* position in dissociation of benzoic acids (group D), even though it is lower than the value given in literature[8] viz. 30–50%. Interesting is the practically insignificant correlation of ^{19}F chemical shifts of 4-substituted 1-fluorobicyclo[2.2.2]octanes[34] in cyclohexane ($R = 0.757$, $r_I = 0.665$, $r_{II} = 0.602$, 57.29%/24.25%), in deuteriochloroform ($R = 0.808$, $r_I = 0.741$, $r_{II} = 0.638$, 65.32%/23.86%) and in dimethylformamide ($R = 0.790$, $r_I = 0.740$, $r_{II} = 0.567$, 62.42%/17.77%) and that of ^{13}C chemical shifts of 4-substituted 1-methylbicyclo- [2.2.2]octanes[35] in deuteriochloroform ($r = 0.625$). A contribution of another type of transmission of substituent effects proportional to σ_I^i in the case of ^{19}F chemical shifts represents a substantial part of the amount explained by σ_I^i constant, the remaining effects being not reflected at all. Obviously, the substituent scales based on NMR chemical shifts should be adopted very carefully.

Comparison of σ_I^i Scale with Other Scales for Description of Inductive Effect

The model (*1*) with σ_I^i values from Table IV was used for interpretation of σ_I substituent constant scale taken from two sources[3,7] and σ_F scale taken from ref.[11]. Application of σ_I constants from Exner's monograph[7] gave the dependence (*2*)

$$\sigma_I = (0.571 \pm 0.017) + (1.004 \pm 0.043)(\sigma_I^i - \sigma_I^{i0}) - (0.145 \pm 0.049)_{II}(\sigma_I^i - \sigma_I^{i0}) \quad (2)$$

$$n = 33,\ s = 0.045,\ R = 0.973\ .$$

The subscript II at the brackets in the second term of Eq. (*2*) symbolizes that the regression coefficient applies to the substituents of class II; the regression coefficient

TABLE IV
Classification of substituents into groups, values of σ_I^i constants and their standard deviations *s* (according to ref.[26]) obtained by the method of conjugated deviations according to model (*1*) with data of Table I

No.	Substituent	Group	σ_I^i	*s*	No.	Substituent	Group	σ_I^i	*s*
1	H	I	0.000	0.002	18	$COOC_2H_5$	III	0.265	0.001
2	CH_3	I	–0.040	0.002	19	NH_2	II	0.089	0.002
3	CH_3CH_2	I	–0.048	0.002	20	$NHCH_3$	II	0.094	0.004
4	$CH(CH_3)_2$	I	–0.062	0.001	21	$N(CH_3)_2$	II	0.089	0.003
5	$C(CH_3)_3$	I	–0.084	0.001	22	$NHCOCH_3$	II	0.230	0.001
6	C_6H_5	I	0.078	0.003	23	NO_2	I	0.606	0.003
7	$CH_2C_6H_5$	I	–0.018	0.001	24	OH	II	0.157	0.014
8	$CH{=}CH_2$	I	0.049	0.002	25	OCH_3	II	0.220	0.002
9	CH_2CN	I	0.161	0.001	26	OC_6H_5	II	0.278	0.001
10	CH_2CN	I	0.075	0.002	27	SH	II	0.239	0.004
11	CH_2Cl	I	0.147	0.002	28	SCH_3	II	0.217	0.003
12	CF_3	I	0.372	0.002	29	SO_2CH_3	III	0.551	0.002
13	CH=O	III	0.385	0.001	30	SO_2NH_2	I	0.423	0.000
14	$COCH_3$	III	0.286	0.001	31	F	II	0.249	0.002
15	CN	I	0.525	0.002	32	Cl	II	0.374	0.002
16	COOH	III	0.264	0.050	33	Br	II	0.384	0.002
17	$COOCH_3$	III	0.274	0.002	34	I	II	0.353	0.001

for substituents of class III was statistically insignificant. Deviating points were found with F, CH=O, and OC_6H_5 substituents, and Eq. (*3*) was obtained after excluding them

$$\sigma_I = (0.578 \pm 0.008) + (1.009 \pm 0.019)(\sigma_I^i - \sigma_I^{i0}) - (0.101 \pm 0.021)_{II}(\sigma_I^i - \sigma_I^{i0}) \quad (3)$$

$$n = 30,\ s = 0.019,\ R = 0.995\ .$$

Equations (*2*) and (*3*) confirm a close dependence between our and the standard scale, on the other hand, however, the significant regression coefficient at the term describing the mesomeric effect of substituents having a free electron pair at the first atom from the basic skeleton indicates a certain contribution of this effect in the interpreted σ_I scale. This contribution, however, represents only 0.79% of the total explained variability of 99.01%, i.e. the value is negligible. The underestimated value of substituent constant for formyl group and, on the other hand, the overestimated value for fluorine substituent have already been stated with the σ_p substituent constant in an earlier paper of this series[27], which indicates identical primary sources used in construction of parametric scales.

The same conclusions also follow from the interpretation of σ_I scale taken from Charton's paper[3]. Equation (*4*) describes the dependence without correction for deviating points and Eq. (*5*) after excluding the F, CH=O, and OC_6H_5 substituents.

$$\sigma_I = (0.589 \pm 0.016) + (1.029 \pm 0.041)(\sigma_I^i - \sigma_I^{i0}) - (0.103 \pm 0.045)_{II}(\sigma_I^i - \sigma_I^{i0}) \quad (4)$$

$$n = 33,\ s = 0.042,\ R = 0.977\ ,$$

$$\sigma_I = (0.593 \pm 0.009) + (1.030 \pm 0.024)(\sigma_I^i - \sigma_I^{i0}) - (0.064 \pm 0.027)_{II}(\sigma_I^i - \sigma_I^{i0}) \quad (5)$$

$$n = 30,\ s = 0.024,\ R = 0.993\ .$$

Also in this case the indicated proportion of mesomeric contribution 0.31% of total explained variability 98.53% is negligible.

Finally, the scale *F* given in a review by Hansch, Leo, and Taft[11] was interpreted. The results are expressed in Eq. (*6*), and – after excluding the CH=O, $CH_2C_6H_5$, OH, NH_2, and $NHCH_3$ substituents – in Eq. (*7*).

$$F = (0.571 \pm 0.018) + (0.962 \pm 0.048)(\sigma_I^i - \sigma_I^{i0}) \qquad (6)$$

$$n = 33,\ r = 0.964,\ s = 0.050\ ,$$

$$F = (0.572 \pm 0.012) + (0.942 \pm 0.033)(\sigma_I^i - \sigma_I^{i0}) \qquad (7)$$

$$n = 28,\ r = 0.984,\ s = 0.033\ .$$

The closeness of correlation is somewhat less than that in the preceding two substituent scales but the agreement is still relatively good. In this case no other type of transmission of substituent effects was indicated.

On the basis of the results given it can be stated that chemometric methods have been successful in application to a large set of experimental data and separating the scale that describes the inductive effect, and – at the same time – in confirming the validity of the model of substituent effects based on different types of transmission of these effects depending on type of substituent[26,27].

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