

CHEMOMETRICAL ANALYSIS OF SUBSTITUENT EFFECTS.

V. *ortho* EFFECT

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The dissociation constants of nineteen *ortho* substituted benzoic acids have been determined in eight organic solvents (methanol, ethanol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, 1,2-dichloroethane). The correlation between the σ_1 , σ_R , and ν constants were unsuccessful due to neglecting the description of intramolecular hydrogen bond effect. The method of conjugated deviations has been applied to the results obtained and to those given in literature for *ortho* substituted benzoic acids (the dissociation constants, the reaction with diphenyldiazomethane, 33 sets), and values of three types of substituent constants have been determined for 29 substituents. The first of these substituent constants, σ_o^i , describes the electronic effects and was adjusted with the application of the isoparameter relation (σ_o^i as a function of σ_m^i) suggested in previous communications. This constant (after excluding the substituents NHCOCH_3 and OCOCH_3) correlates very well ($R = 0.993$) with the σ_1 and σ_R constants. The second substituent constant, σ_{HG}^i , describes the interaction of the reaction centre (the oxygen atom of carboxylate anion) with the substituent, and it has non-zero values for the substituents OH, SH, NH_2 , NHCH_3 , NHCOCH_3 , COOH, CONH_2 , and SO_2NH_2 . The third substituent constant, σ_s^i , describes the steric effects and is not significantly related to any of the known quantities of this type. The set given was tested together with the triad of σ_1 , σ_R , and ν on the definition set and on a set extended by other 28 sets of processes with *ortho* substituted compounds. On the whole, the set of substituent constants suggested explains 94.6% of variability of data, whereas only 66.0% are explained with the use of σ_1 , σ_R , and ν constants. Moreover, the tests have shown that the σ_o^i constant is not suitable for interpretations of processes involving direct conjugation between the reaction centre and substituent.

Our previous papers of this series dealt with the chemometrical analysis of the principles of substituent effects^{1,2} and the effect of disubstitution^{3,4} excluding the substituents at 2 position with respect to the side chain with reaction centre. This type of substitution compared with substitution at other positions is characterized by manifestations as specific as to obtain a special name of "*ortho* effect" (for a survey see refs⁵⁻⁹). The term "effect" is not quite correct since the *ortho* effect involves several effects connected with the interactions between substituent and reaction centre. Beside the changes in interactions mediated by σ and π bonds of the skeleton they involve a possible formation of hydrogen bond between substituent and reaction centre, changes in resonance interaction, and steric hindrance to the approach of reagent to the reaction

centre as a consequence of steric effects, different solvation of (first of all) the reaction centre due to changes in the chemical environment, hydrophobic interactions and, perhaps, also other less significant factors. The extent of operation of the above-mentioned effects depends specifically upon the structure of the reaction centre and its chemical environment¹⁰. For this reason, the application of similarity principle to a quantitative description of *ortho* effect appears to be less successful than that to the substitutions at other positions. Two basic approaches are usually adopted^{6,7,9}.

The first and older of them starts from the Hammett equation with the aim of suggesting universal substituent constants for this type of relation and its modifications^{8,11-15}. In accordance with the facts that there are several types of interactions between reaction centre and substituent and that their manifestations are variable, this approach showed variable success^{6,7,15,16} even when adopting the most common "well-behaved" substituents. An interesting (although also expected) result is the possibility of application of the Hammett substituent constants σ_p to a rough correlation of substituent effects from *ortho* position. Because of its drawbacks, this principle was not studied and used any further.

The second approach is based on a separate description of inductive and mesomeric effect of substituents^{7,17-20} with usual extension involving the steric effects due to the interactions between reaction centre and substituent^{5,7,11,19-22}. In this case, the correlation equation has the forms (1) and (2) for the application of the Taft¹¹ steric constants E_s (and their modifications) and the steric constants υ by Charton^{21,22}, respectively.

$$\Delta G = \Delta G^0 + \rho_I \sigma_I + \rho_R \sigma_R + \delta E_s \quad , \quad (1)$$

$$\Delta G = \Delta G^0 + \rho_I \sigma_I + \rho_R \sigma_R + \psi \upsilon \quad . \quad (2)$$

According to refs^{23,24}, the E_s^o constant designed for the correlation of *ortho* effect does not describe the steric effects only, but also the electronic ones. Similarly, literature²⁵ also presents a discussion of the relation between the steric effects described by the υ parameter and the electronic effects. In reality, the relation (nonorthogonality) between the parameters describing the steric effects and those describing the electronic effects can be real, e.g. as a consequence of the steric inhibition of resonance. It is even likely that the two types of effects cannot at all be separated without orthogonal transformation. As a consequence, however, the resulting parameters can lose their physical meaning and the respective correlation equations can lose their interpretation ability. On the other hand, however, a multicollinearity (usually resulting from a small number of points) in the regressions according to Eqs (1) and (2) can – without the statistical analysis – lead to quite meaningless results. The validity of the relations (1), (2), and

similar ones^{26,27} for the substitution at *ortho* position was extensively tested using various types of chemical and physical processes^{17,22,27–34}. The significance of these studies is limited by the number of substituents used, however, anyway the correlations were less close than those describing the effects from *meta* and *para* positions²⁷.

Besides the relations mentioned, other correlations have been suggested, based on other types of processes and other principles. The thermodynamic principle of separation of enthalpy and entropy components of substituent effects was successful in correlations with several basic substituents³⁵. The application of ¹³C NMR chemical shifts³⁶ to the description of *ortho* effects is less useful since the relations are complicated by additional specific properties of the quantities correlated. A position weight factor was suggested to correct the specifics of *ortho* substitution in the Swain–Lupton equation²⁶ but the improvement attained was not significant³⁷. The same can be stated about the extension by steric density³⁷ which term denotes another parameter from the series of parameters describing the steric effects. On the other hand, an interesting description of steric effects could be obtained by means of the Ω_s constant based on a projection of electronic shell of atoms of substituent on the surface of a sphere³⁸, however, the values are only published for alkyls.

Relatively few experimental studies^{14,15,39–51} and other works^{5–9,11,17,20,22–24,34,52,53} can be found in literature dealing with more or less successful quantitative evaluation of the *ortho* effect, the majority of them being restricted to an only narrow selection of well-tried substituents. An exception is a series of communications (refs^{42,43} and the preceding ones) dealing with the reaction of diphenyldiazomethane with *ortho* substituted benzoic acids in a number of protic and aprotic solvents. The application of Eq. (2) was only successful in the cases not involving the substituents able to form a hydrogen bond with the conjugated base⁵³ (COOH, OH, SH, NH₂, NHCH₃, NHCOOCH₃) or those forming hydrogen bonds with the nondissociated acid (CH₃O, C₂H₅O, OCOCH₃) and some others (NO₂). These studies showed that the variety of effects denoted as *ortho* effect is greater, involving – beside the electronic and steric effects of substituents – at least the formation of hydrogen bond and solvation effects as well. The formation of hydrogen bond between reaction centre and substituent in some cases undoubtedly can be the dominant effect preventing any successful application of correlation methods. This problem is usually circumvented by excluding such substituents from correlation, which, however, does not solve the problem. No attempt at introduction of quantitative description of formation of intramolecular hydrogen bond has been made yet. Certain doubts are also connected with the quantitative evaluation of the steric effects. The lack of dependence of experimental data upon parameters describing steric effects need not necessarily indicate a nonoperation of these effects^{17,41,50}; the reason can equally well lie in an unsuitable parametrization and selection of substituents. The trouble is in that the correlation with reliable substituent parameters usually involve such a small number of substituents that they are statistically worthless, and –

on the other hand – reliable parameters are not available for any greater set of substituents, and therefore the physico-chemical interpretation is of little value.

In the context of the analysis given, the aim of the present communication is to contribute to the delimitation of the phenomenon of *ortho* effect and to separate description of its dominant components in the experimental field and – using the chemometric methods – in the theoretical area as well. In the experimental field we focused our attention to the determination of dissociation constants of *ortho* substituted benzoic acids with common and deliberately chosen substituents in several organic solvents. The chemometric analysis was focused on the verification of Eq. (2) using both original and literature data, and first of all on a quantitative description of *ortho* effect based on a treatment of extensive data set taken from literature using the methods with latent variables.

EXPERIMENTAL

The 2-substituted benzoic acids used were synthesized by current procedures or were commercial products. They were purified by reprecipitation from their respective salt solutions and subsequent recrystallizations. Their identity was verified by their melting points which agreed with literature data^{54–60}. The purity was verified by the liquid chromatography using a Spectra Physics apparatus (mobile phase 40% aqueous methanol, column length 25 cm, packed with SPH Eriosorb ODS 10 μm). The procedures of purification and drying of solvents and of the potentiometric titrations are described elsewhere³.

RESULTS AND DISCUSSION

Evaluation of Measured Dissociation Constants of 2-Substituted Benzoic Acids by Correlation Equations

The data of Table I were submitted to a regression analysis using Eq. (2) with the parameters σ_1 and σ_R taken from the Exner monograph⁶¹ and with the parameters ν given in ref.⁴². The equation (1) was not adopted because of the small number of known values of E_s parameter. The multiple correlation coefficients obtained by the regression were very low (the best one in methanol, $R = 0.70$), on the other hand, the respective residual deviations were too great. For the data measured in acetone, dimethylformamide, and pyridine, Eq. (2) was statistically insignificant, in the other cases the only statistically significant dependence was that on σ_1 . The analysis of residua for all the solvents revealed – as outliers – the data for OH substituent, and after they were excluded, the situation repeated for NHCOCH_3 group. In both the cases the substituent is able to form an intramolecular hydrogen bond with the carboxylate anion. But even with these substituents excluded, the correlations were not much close, e.g. for methanol the correlation coefficient of the dependence on σ_1 and σ_R (without the statistically insignificant dependence on ν) was $R = 0.949$.

TABLE I

Average dissociation constants \overline{pK} and their standard deviations s for 2-substituted benzoic acids in methanol (MeOH), isopropyl alcohol (isoPrOH), acetone (Ac), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (AN), pyridine (Py), and 1,2-dichloroethane (DCE)

Substituent	\overline{pK}/s							
	MeOH	isoPrOH	Ac	DMSO	DMF	AN	Py	DCE
H	9.41	10.68	18.20	11.00	12.27	20.70	9.80	20.00
CH ₃	9.31	10.71	18.39	11.07	12.42	20.77	9.87	20.05
	0.00	0.13	0.00	0.00	0.06	0.05	0.04	0.09
COOH ^a	7.70	7.78	14.33	7.12	8.37	15.82	6.00	–
	0.02	0.08	0.05	0.08	0.09	0.05	0.09	
COOCH ₃	8.47	9.83	17.39	10.09	11.41	19.65	9.06	–
	0.08	0.10	0.04	0.08	0.07	0.07	0.14	
NH ₂	10.02	11.27	18.58	11.22	12.63	20.93	9.90	20.41
	0.00	0.10	0.04	0.02	0.05	0.13	0.12	0.07
NHCH ₃	10.02	11.10	18.28	10.85	12.28	20.82	9.74	20.35
	0.04	0.09	0.05	0.05	0.10	0.06	0.11	0.13
NHCOCH ₃	8.29	9.05	15.79	8.63	9.63	18.53	7.48	18.61
	0.03	0.10	0.07	0.10	0.15	0.02	0.06	0.08
NO ₂	7.58	8.62	15.91	8.66	9.92	18.16	7.75	17.83
	0.01	0.13	0.05	0.11	0.04	0.04	0.06	0.10
OH	7.93	8.60	14.81	8.12	8.47	17.62	6.62	17.72
	0.03	0.11	0.04	0.04	0.08	0.06	0.06	0.15
OCH ₃	9.24	10.88	18.94	11.21	12.66	21.24	10.10	20.77
	0.04	0.02	0.12	0.06	0.08	0.04	0.14	0.01
OCOCH ₃	8.92	10.41	17.69	10.40	11.75	20.13	9.03	19.49
	0.02	0.03	0.13	0.03	0.08	0.04	0.11	0.07
SH	8.49	8.52	14.04	7.42	7.55	17.41	5.89	17.24
	0.01	0.04	0.01	0.05	0.21	0.04	0.12	0.08
SCH ₃	9.09	10.70	17.97	10.71	12.07	20.36	9.36	19.85
	0.08	0.01	0.06	0.08	0.04	0.06	0.00	0.10
SCOCH ₃	8.43	9.72	17.08	9.72	11.11	19.38	8.62	18.84
	0.03	0.02	0.06	0.04	0.05	0.08	0.03	0.07
SO ₂ NH ₂	7.82	8.58	15.44	8.13	9.33	17.73	7.20	17.52
	0.01	0.06	0.03	0.09	0.09	0.02	0.03	0.04
F	8.67	10.12	17.44	10.15	11.44	19.79	9.02	19.22
	0.00	0.08	0.01	0.05	0.08	0.03	0.14	0.04
Cl	8.22	9.54	17.01	9.70	11.00	19.26	8.72	18.84
	0.02	0.11	0.07	0.08	0.03	0.03	0.06	0.09
Br	8.13	9.48	16.84	9.64	10.98	19.28	8.80	18.72
	0.03	0.10	0.04	0.04	0.05	0.02	0.15	0.09
I	8.24	9.50	16.98	9.76	11.02	19.21	8.73	18.85
	0.03	0.12	0.10	0.07	0.06	0.02	0.13	0.07

^a Corrected for the statistical factor.

Separation and Quantitative Description of Substituent Effects in ortho Position

The failure of application of correlation (2) to the data of Table I due to neglecting the description of hydrogen bond showed the necessity of extension and/or modification of the said relation, including the separation and quantitative description of the individual effects. For this purpose we selected from literature 64 data series with at least eight values involving experimental results with compounds bearing *ortho* substituents with respect to the side chain with the reaction centre. From the selection were excluded spectral characteristics (NMR chemical shifts and IR wavenumbers due to their specificity), and, on the other hand, equilibrium and kinetic processes were preferred. The large range of properties of the solvents used in selected experiments made it possible to eliminate specific solvation effects during the statistical treatment. The obtained data set was then analyzed by the method of conjugated deviations^{1,62} which represents one of the methods of investigation of data by means of latent variables. On the basis of the calculation, we used for the next treatment only the sets with significant contribution to the construction of latent variables (the modelling power⁶³ of at least 0.3 at the first latent variable). The description of 61 selected sets and 8 sets from Table I is presented in Table II, the other sets were excluded from the further treatment. The selected sets were further arranged according to the type of process and according to the criterion whether the process involves the O–H bond cleavage in carboxyl group of benzoic acid (subsets A and B) or not (the rest). This classification was carried out to eliminate the effect of structure of skeleton as an element which – according to the model suggested in the previous communications^{1,2} – can be projected into the respective substituent constants. After a preliminary treatment, the substituents SH and COOH were excluded from data of Table II because of their anomalous behaviour.

In order to secure a link to the standard chemical model of benzoic acid, the subsets A and B from Table II were only used for the proposal of correlation relation and the respective parametrization. The application of the method of conjugated deviations^{1,62} to these data showed that at least four latent variables were statistically significant⁶², the first latent variable explaining 92.9% of the variability of data, the first two 98.2%, the first three 98.8%. As compared with the similar calculation for *para* substituted derivatives¹, the measures of explained variability by the individual latent variables are different (the first 87.9%, the first two 99.0%). The result is surprising because at the *ortho* position one can presume a greater number of various factors than at the *para* position, and hence also a smaller possibility of their description by one quantity however complex from the physico-chemical point of view. In this case the reason may lie in the greater homogeneity of experimental data in the sets according to Table II as compared with the data of the cited paper¹. From the data given about the explained variability it is obvious that with respect to the precision of experiment the two first latent variables only are worth interpreting meaningfully. Their mutual relation expressed by the position of substituents in the plane formed by these latent variables is

TABLE II

Selected sets of experimental data of *ortho* substituted compounds at 25 °C (if not otherwise stated) and numbers *n* of experimental points

No.	Process and data sets	<i>n</i>	Ref. ^a
A Dissociation of substituted benzoic acids (p <i>K</i>)			
1	Gas phase, 600 °C, $\Delta\Delta G$	8	64
2	Water	9	65
3	Water	8	66
4	Water, tetrabutylammonium bromide	10	67
5	50% Ethanol	9	15
6	10% Acetone	8	66
7	25% Acetone	8	66
8	50% Dimethyl sulfoxide	9	68
9	65% Dimethyl sulfoxide	10	68
10	85% Dimethyl sulfoxide	11	68
11	Methanol	17	A
12	Methanol	8	69
13	Ethanol	8	69
14	Isopropyl alcohol	17	A
15	Isopropyl alcohol	8	69
16	1-Butanol	8	69
17	Glycol	8	69
18	Acetone	17	A
19	Dimethyl sulfoxide	17	A
20	Dimethylformamide	17	A
21	Acetonitrile	17	A
22	Pyridine	17	A
23	1,2-Dichloroethane	17	A
B Reaction of substituted benzoic acids with diphenyldiazomethane (log <i>k</i> ₂)			
24	Methanol	27	42
25	Ethanol	27	42
26	2-Methyl-1-propanol	27	42
27	2-Butanol	27	42
28	1-Pentanol	27	42
29	2-Methyl-2-butanol	27	42
30	Cyclopentanol	27	42
31	Benzyl alcohol	27	42
32	2-Phenylethanol	27	42
33	3-Phenyl-1-propanol	27	42
34	2-Methoxyethanol	27	42
35	Acetone	26	43
36	Ethyl acetate	25	43
37	Dimethylacetamide	21	43

TABLE II
 (Continued)

No.	Process and data sets	<i>n</i>	Ref. ^a
B Reaction of substituted benzoic acids with diphenyldiazomethane (log <i>k</i> ₂)			
38	Dimethylformamide	18	43
39	Dimethyl sulfoxide	19	43
40	Nitrobenzene	24	43
41	Chlorobenzene	23	43
C Other dissociation and chemical equilibria (p <i>K</i> if not otherwise stated)			
42	Arylphosphoric acids, p <i>K</i> ₁ , water	11	45
43	Arylphosphoric acids, p <i>K</i> ₂ , water	11	45
44	Arenesulfonic acids, p <i>K</i> ₁ , water	10	70
45	Arenesulfonic acids, p <i>K</i> ₂ , water	10	70
46	Aryloxyacetic acids, water	9	71
47	Substituted benzamides, water, HClO ₄	9	72
48	Substituted phenols, gas phase 600 K, Δ <i>ΔG</i>	9	64
49	Substituted phenols, water	8	73
50	Substituted phenols, water, 0.1 M KCl	9	74
51	Substituted phenols, water, 0.1 M KCl	9	75
52	Substituted anilines, water	8	76
53	Substituted anilines, water	13	77
54	Substituted phenylhydrazines, water	9	78
55	Aryltetrazoles, 50% ethanol	8	79
56	Protonated substituted benzoic acids, water	12	80
57	Addition of OH ⁻ to substituted benzaldehydes, log <i>K</i> , water	11	81
D Other chemical reactions (log <i>k</i>)			
58	Acid catalyzed hydrolysis of substituted benzamides, water	15	48
59	Acid catalyzed hydrolysis of substituted benzamides, water–dioxane 1 : 1	15	48
60	Base catalyzed hydrolysis of aryl diethylphosphates, water	8	74
61	Hydrolysis of aryl acetates, water	12	41
62	Hydrolysis of aryl <i>N</i> -methylcarbamates, 10% ethanol, 37 °C	12	82
63	Base catalyzed hydrolysis of aryl <i>N,N</i> -dimethylcarbamates, water, 0.9 M NaOH	10	41
64	Base catalyzed hydrolysis of ethyl arylacetates, 85.4% ethanol, 24.8 °C	9	83
65	Hydrolysis of methyl benzoates, 56% acetone	9	84
66	Hydrolysis of methyl benzoates, 80% methanol	9	85
67	Substituted iodobenzenes plus phenyl radical	12	86
68	Oxidation of substituted benzylamine with <i>N</i> -chlorosuccinimide, water, pH 10.6	10	46
E Other processes			
69	Arylferrocenes, <i>E</i> _{1/4} , acetonitrile, 25 °C	12	39

^a A means that the data originate from Table I of this paper (the data for SH and COOH substituents were not used).

represented in Fig. 1. The order of substituents according to the first latent variable roughly corresponds (with exception of OH and NHCOCH_3) to their electronic substituent parameters described e.g. by the constant σ_p (the correlation coefficient $r = 0.975$). Hence the physico-chemical meaning of the first latent variable is more or less clear. The same can be said about the second latent variable where one extreme is represented by the substituents OC_2H_5 , C_4H_9 , and SO_2CH_3 , and the other by NH_2 , NHCH_3 , NHCOCH_3 , SH , and OH . According to the character of the substituents given it can be stated that they are substituents able of formation of intramolecular hydrogen bond with the carboxylate anion^{53,87} (NHCOCH_3 , SH , and OH) or with the undissociated carboxylic group⁸⁷ (OC_2H_5) or substituents sterically demanding (C_4H_9 and SO_2CH_3). According to their location the NH_2 and NHCH_3 substituents belong to the first type⁸⁷. In this context it must be repeated that we presume a statistical elimination of specific solvation effects with regard to the method adopted for the treatment and to great variety of solvents used. As the second variable is a complex one, it cannot be used as a general tool for a correlation analysis of data.

The analysis given makes it possible to postulate the conditions at which the individual factors can be quantitatively separated. If the substituent effects are dominant, the substitution model suggested in the previous papers^{1,2} can be used as the first postulate. This model is based on the relation (3) in the form

$$\Delta G_o = \Delta G_{\text{iso}}^0 + \rho_{\text{iso}} [\sigma_o^{i0} + (I + \delta\Delta M) (\sigma_m^i - \sigma_m^{i0})] , \quad (3)$$

where ΔG is the Gibbs energy of a process, ρ_{iso} is the reaction constant, and the expression in square brackets represents the substituent constant from *ortho* position ex-

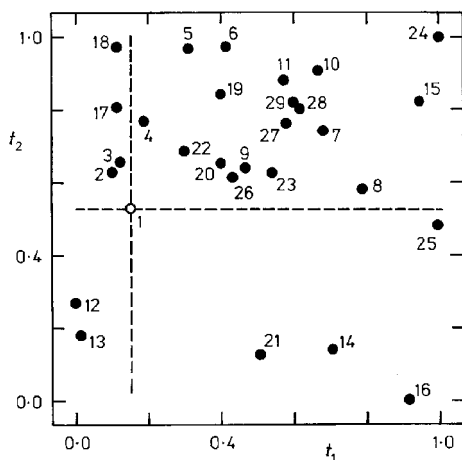


FIG. 1

Distribution of substituents in the plane formed by the first (t_1) and the second (t_2) latent variables obtained by treating the data of sets A and B of Table II by the method of conjugated deviations; for the numbers of substituents see Table III

pressed as a function of the substituent constant σ_m^i from *meta* position. The substituents are divided into three classes – those without a mesomeric effect ($\delta\Delta M = 0$), those with $+M$ effect ($\delta\Delta M_{II} > 0$), and those with $-M$ effect ($\delta\Delta M_{III} < 0$). Geometrically expressed, the substituents lie on three straight lines intersecting at a point with the coordinates σ_m^{i0} and σ_o^{i0} . With the use of Eq. (3) it is possible – when simultaneously optimizing the unknown parameters σ_o^{i0} , σ_m^{i0} , I , $\delta\Delta M_{II}$, and $\delta\Delta M_{III}$ – to eliminate, from the data, the variability corresponding to the substituent effect and express it as the first latent variable. The second postulate represents a delimitation of hydrogen bond. The following groups are suggested as ones able of formation of hydrogen bond: CONH_2 , COOH , NH_2 , NHCH_3 , NHCOCH_3 , OH , SH , and SO_2NH_2 . When constructing the second latent variable, this fact can be expressed by the additional condition of agreement of values of the latent variable for the other substituents. The other latent variables can be isolated in normal way^{62,63}.

The described procedure with application of the method of conjugated deviations^{1,62} was applied to the data set of Table II with the selection of substituents given in Table III. The parameters σ_o^{i0} , σ_m^{i0} , I , $\delta\Delta M_{II}$, and $\delta\Delta M_{III}$ of Eq. (3) were optimized for the

TABLE III

Values of σ_{HB}^i and σ_{S}^i parameters and optimized values of σ_o^i parameters according to Eq. (3) referred to unit reaction constants for dissociation of 2-substituted benzoic acids in water at 25 °C; σ_m^i values were taken from ref.² and from optimization (see text) for substituents CONH_2 (0.280), COOH (0.391), NHCH_3 (-0.135), OH (0.135), OC_2H_5 (0.100), OC_6H_5 (0.252), SCH_3 (0.146), SCOC_3 (0.388)

No.	Substituent	σ_o^i	σ_{HB}^i	σ_{S}^i	No.	Substituent	σ_o^i	σ_{HB}^i	σ_{S}^i
1	H	0.000	0.000	0.000	16	OH	-0.088	0.695	0.392
2	CH ₃	-0.150	0.000	0.133	17	OCH ₃	-0.211	0.000	0.257
3	C ₂ H ₅	-0.188	0.000	0.189	18	OC ₂ H ₅	-0.186	0.000	0.212
4	isoC ₃ H ₇	-0.195	0.000	0.393	19	OC ₆ H ₅	0.240	0.000	0.356
5	<i>tert</i> -C ₄ H ₉	-0.209	0.000	0.756	20	OCOCH ₃	0.405	0.000	0.143
6	C ₆ H ₅	0.074	0.000	0.603	21	SH	0.372	0.000	-0.032
7	CF ₃	0.909	0.000	0.239	22	SCH ₃	-0.057	0.000	0.466
8	CN	1.234	0.000	0.070	23	SCOC ₃	0.627	0.000	0.350
9	CONH ₂	0.697	-0.060	0.043	24	SO ₂ CH ₃	1.218	0.000	0.677
10	COOH	0.852	0.116	0.083	25	SO ₂ NH ₂	1.002	0.376	-0.109
11	COOR	0.745	0.000	0.203	26	F	0.425	0.000	0.198
12	NH ₂	-0.788	0.153	0.235	27	Cl	0.576	0.000	0.430
13	NHCH ₃	-0.830	0.183	0.233	28	Br	0.596	0.000	0.489
14	NHCOCH ₃	-0.104	0.520	0.322	29	I	0.554	0.000	0.521
15	NO ₂	1.400	0.000	0.288					

maximum isolated variability after the first three latent variables. The values σ_m^i were taken from ref.², the missing data for the substituents iso-C₃H₇, CONH₂, COOH, NHCH₃, OH, OC₂H₅, OC₆H₅, SCH₃, SCOCH₃ were estimated from σ_m and then also optimized for the maximum isolated variability. When using the optimized values, the first latent variable explained 59.8% of variability, the first two 91.3%, the first three 97.4%, and the first four 98.7%. From a comparison with the direct calculation by the method of conjugated deviations (three latent variables 98.8%, vide supra) it can be seen that it was possible to express, in a structured way, almost the same measure of variability. An idea about properties of substituents in the space of the first three latent variables can be got from Figs 2 and 3. From Fig. 2 it is obvious that a dominant formation of hydrogen bond (the second latent variable) is shown by the substituents OH, NHCOCH₃, SO₂NH₂ and partially SO₂CH₃. An apparently opposite effect is shown by CONH₂. From the distribution of substituents over the area determined by the first and the third latent variables (Fig. 3) it can be deduced that the third latent variable

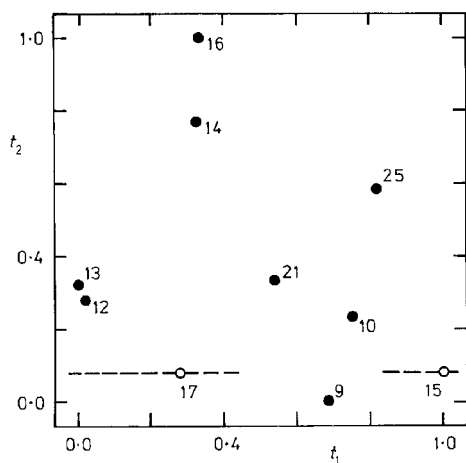


FIG. 2

Distribution of the substituents forming intramolecular hydrogen bonds in the plane formed by the first (t_1 , electronic effects) and the second (t_2 , hydrogen bond effects) latent variables obtained by treating the data of sets A and B of Table II by the method of conjugated deviations at the condition of agreement of t_2 for the other substituents (dashed line); for the numbers of substituents see Table III

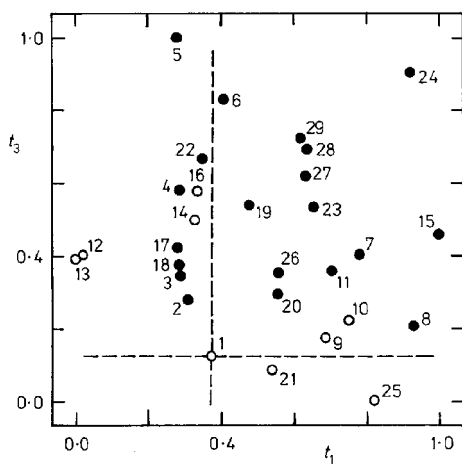


FIG. 3

Distribution of substituents in the plane formed by the first (t_1 , electronic effects) and the third (t_3 , steric effects) latent variables obtained by treating the data sets A and B from Table II by the method of conjugated deviations at the condition of agreement of t_2 for the substituents forming no intramolecular hydrogen bond (the substituents with anomalous behaviour are denoted with empty circles, see text); for the numbers of substituents see Table III

predominantly reflects the steric effects. The figure shows obvious structural similarities of some substituents ($\text{CH}_3\text{O} - \text{CH}_3\text{S}$, $\text{CH}_3\text{O} - \text{C}_2\text{H}_5\text{O} - \text{C}_6\text{H}_5\text{O}$, $\text{OCOCH}_3 - \text{SCOCH}_3$) expressed by their close positions. Perhaps surprisingly great appear to be the halogens Cl, Br, and I, and, on the other hand, NO_2 group appears to be small (it may be rotated). Unexpected locations are observed with OH and NHCOCH_3 groups (they appear somewhat bigger) and with COOH group (it appears somewhat smaller). An unequivocally small value of the third latent variable is encountered with SH and SO_2NH_2 groups. This can be either an artefact due to the procedure of separation of effects or another coupled effect. When plotting the substituents in the plane formed by the second and the third latent variables, the above-mentioned problematic substituents lie at two unequivocally defined straight lines with opposite slopes. The first group is formed by the substituents NHCH_3 , NH_2 , NHCOCH_3 , and OH which show – in the order given – increasing acidity of hydrogen and slightly increasing value of the third latent variable. This can be a result of intramolecular hydrogen bond fixing the carboxylate group in a certain position, which is connected with certain steric demands. The second group is formed by the groups COOH, SH, and SO_2NH_2 whose acidity, in the order given, decreases with concomitant relatively distinct decrease in the value of the third latent variable describing steric effects. A probable explanation is a formation of dimers in the nondissociated state which are decomposed after dissociation of the carboxylic group. Hence, in this case the effect of intermolecular hydrogen bond is operating which can be significant in aprotic solvents. Although the fourth isolated latent variable describes only a fraction of total variability, a possibility of interpretation of a random error seems improbable, because the highest values are exhibited by the substituents OC_2H_5 , OCH_3 , and OC_6H_5 . As these are substituents able of formation of intramolecular hydrogen bond with undissociated carboxylic group⁸⁷, the fourth latent variable obviously describes this little significant effect.

The results given show that it was possible to successfully separate the individual factors determining the *ortho* effect. In order to create a relation to the scales used, the latent variables were transformed to obtain the slope one for the dependence of $\log K_a$ of *ortho* substituted benzoic acids in water upon all the explaining variables. The constants obtained in this way were denoted as σ_0^i (electronic effects, the term in square brackets in Eq. (3)), σ_{HB}^i (effects of hydrogen bond), and σ_{S}^i (steric effects), and the corresponding values are given in Table III for 32 substituents. The effect described by the above-discussed fourth latent variable is not considered as significant as to be necessary to express it explicitly.

A usual procedure of suggesting empirical parameters involves a definition of their relation to the parameters already used. The relation of the substituent constant σ_0^i to the analogous parameters from *meta* and *para* positions^{1,2} is given by the definition relation (3). The correlation with the parameters σ_1 and σ_{R} is good ($R = 0.985$) and – after elimination of the extreme points corresponding to the substituents NHCOCH_3 and

OCOCH₃ – excellent ($R = 0.993$). The parameter $\sigma_{\text{HB}}^{\text{i}}$ has no classic parallel, as far as we know. Steric effects are described in literature by various parameters, and the closeness of their correlation with the parameter $\sigma_{\text{S}}^{\text{i}}$ is generally low and it decreases in the order: S^0 (ref.⁸⁸, $r = 0.744$), E_{S} (AMD) (ref.⁵⁰, $r = 0.663$), ν (ref.⁴², $r = 0.553$), SD (ref.³⁷, $r = 0.217$).

The standardization of latent variables simultaneously enabled a determination of standardized value of parameters in Eq. (3). The value $I = 1.95$ is greater by a factor of 1.72 than the corresponding value from *para* position (1.135, ref.²). The values of $\delta\Delta M_{\text{II}} = 2.87$ and $\delta\Delta M_{\text{III}} = 1.36$ are surprisingly in the multiple almost equally greater than the same values from *para* position (1.734 and 0.845, respectively²), i.e. by a factor of 1.6. As the values $\delta\Delta M$ for *ortho* and *para* positions were obtained independently, and also independently they were optimized for the individual classes of substituents, this represents an argument in favour of a more general validity of Eq. (3) and models derived therefrom^{1,2}. Hence the proportionality of interaction of substituents having $+M$ and $-M$ effects with identical reaction centre is the same in *ortho* and *para* positions. Moreover, from the facts given it follows that the electronic effects in *ortho* position, as compared with those in *para* position, make themselves felt more strongly, the component of inductive effect being increased more distinctly. Consequently, the constants σ_{p} cannot fully be used for interpretation of electronic effects from *ortho* position.

Application to Further Experimental Data Compared with Correlation Relations Used

According to the principle of construction of latent variables, the derived parameters for description of *ortho* effect represent the explaining variables in the empirical correlation equation

$$\Delta G = \Delta G^0 + \rho_{\text{o}}\sigma_{\text{o}}^{\text{i}} + \rho_{\text{HB}}\sigma_{\text{HB}}^{\text{i}} + \rho_{\text{S}}\sigma_{\text{S}}^{\text{i}} . \quad (4)$$

The success of this relation in the interpretation of the dissociation constants measured by us (Table I) is compared with that of Eq. (2) in Table IV, and it is obvious that Eq. (4) is more advantageous than Eq. (2). The magnitudes of respective reaction constants ρ_{o} with regard to the solvent used show similar relations as those for *meta* and *para* substitutions⁸⁹. The sensitivity to formation of hydrogen bond expressed by the coefficient ρ_{HB} is smaller in protic solvents due probably to the formation of intermolecular hydrogen bonds to the detriment of the intramolecular ones. The steric effects are manifested most strongly in acetonitrile whereas in pyridine and 1,2-dichloroethane they are not at all indicated. In the second case, the dissociation is probably connected

TABLE IV

Regression parameters and statistical characteristics of dependences of logarithms of dissociation constants of 2-substituted benzoic acids from Table I vs substituent constants according to Eq. (4)

Solvent	ρ_0	ρ_{HB}	ρ_S	s	R
MeOH	1.169 ± 0.051	1.668 ± 0.143	1.141 ± 0.175	0.119	0.989
isoPrOH	1.311 ± 0.064	2.904 ± 0.177	0.993 ± 0.217	0.147	0.989
Ac	1.446 ± 0.087	4.665 ± 0.242	1.239 ± 0.296	0.201	0.988
DMSO	1.355 ± 0.070	4.027 ± 0.194	0.931 ± 0.238	0.161	0.990
DMF	1.446 ± 0.066	5.091 ± 0.182	1.226 ± 0.223	0.152	0.994
AN	1.537 ± 0.079	4.125 ± 0.220	1.152 ± 0.269	0.183	0.989
Py	1.208 ± 0.065	4.257 ± 0.182	0.806 ± 0.222	0.151	0.991
DCE	1.437 ± 0.090	3.067 ± 0.250	0.755 ± 0.305	0.207	0.981

TABLE V

Comparison of residual standard deviations s from regressions according to Eqs (2) and (4) on data sets from Table II

Data set	$s_{(2)}$	$s_{(4)}$	Data set	$s_{(2)}$	$s_{(4)}$	Data set	$s_{(2)}$	$s_{(4)}$
1	–	1.395	24	0.244	0.055	47	–	–
2	0.368	0.158	25	0.251	0.045	48	4.426	2.609
3	0.480	0.214	26	0.250	0.050	49	0.185	0.220
4	–	0.080	27	0.279	0.046	50	0.203	0.230
5	–	0.047	28	0.238	0.054	51	0.511	0.692
6	–	0.167	29	0.350	0.097	52	0.081	0.285
7	–	0.134	30	0.276	0.050	53	0.089	0.195
8	0.071	0.122	31	0.276	0.060	54	0.370	0.140
9	0.166	0.155	32	0.284	0.041	55	0.186	0.147
10	–	0.156	33	0.284	0.044	56	–	–
11	0.538	0.119	34	0.334	0.057	57	0.274	0.243
12	0.430	0.050	35	0.696	0.242	58	0.347	–
13	0.461	0.080	36	0.734	0.258	59	0.341	–
14	0.750	0.147	37	0.512	0.175	60	0.038	0.117
15	0.439	0.084	38	0.452	0.149	61	0.041	0.137
16	0.414	0.109	39	0.417	0.193	62	0.238	0.439
17	0.430	0.056	40	0.561	0.105	63	0.094	0.234
18	–	0.201	41	0.706	0.166	64	0.093	0.199
19	0.916	0.161	42	0.164	0.138	65	0.201	0.236
20	–	0.152	43	0.160	0.248	66	1.084	0.724
21	0.977	0.183	44	0.139	0.119	67	0.149	0.219
22	–	0.151	45	0.132	0.218	68	0.462	0.438
23	0.809	0.207	46	0.042	0.042	69	0.019	0.016

with no distinct change in steric environment as a consequence of formation of associates with the shared proton.

An overall comparison of validity of the correlation equations (2) and (4) is represented by the residual standard deviations (see Table V) of the applications to the experimental data of Table II. From Table V it follows that – out of the 69 sets given – there was at least one statistically significant regression parameter in 58 and 65 cases when using Eqs (2) and (4), respectively. The average explained variability was 66.0% and 94.6% for Eqs (2) and (4), respectively. The relation (4) was unequivocally more successful than Eq. (2) when using the definition data sets, whereas in other cases the opposite was true. As the substituent effects are the dominant ones, the quality of their description is clearly crucial. In Eq. (2) the substituent effects are described by two parameters with separated inductive and mesomeric components, whereas in Eq. (4) they are described in an integrated way using a single parameter adjusted for the reaction centres without direct conjugation with substituent. As most processes given in sections B, C, D of Table II do not fulfil this condition of nonconjugation, the suggested constant σ_0^+ was unsuccessful in describing the substituent effects in contrast to the combination of the constants σ_I and σ_R . As small a change as the replacement of this constant by σ_p^- in Eq. (4) leads e.g. in the case of dissociation of anilines to values of residual standard deviation comparable with that of Eq. (2) (set 52, $s = 0.151$, set 53, $s = 0.096$).

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