CHEMOMETRIC ANALYSIS OF SUBSTITUENT EFFECTS. XII. APPLICATION OF RELATIONSHIP BETWEEN 2- AND 4-SUBSTITUTION OF BENZENE RING TO STUDY *ortho* EFFECT IN SELECTED COMPOUNDS WITH DIFFERENT REACTION CENTRES

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Dedicated to Professor Otto Exner on the occasion of his 75th birthday in recognition of his outstanding contributions to the areas of physical organic chemistry and chemometrics.

Three model compounds have been selected to study the relationship between *ortho* and *para* substitution: benzoic acid, phenol, and aniline. Sixteen substituents have been chosen involving also those capable of potential interaction between *ortho* substituent and the reaction centre. For the combinations given, literature presents 25 pairs of data obtained by measuring a particular process for both the *ortho* and *para* substituted derivatives. The missing dissociation constants of 16 *ortho* substituted benzoic acids in water and ethanol and 16 *para* substituted benzoic acids in dimethyl sulfoxide and pyridine have been measured by potentiometric titration. The data matrices were submitted to analysis by the methods of projection of latent structures (PLS) and principal component analysis (PCA). It has been found that the substituent effects from *ortho* and *para* positions have the same character unless the *ortho* substituents interact with the reaction centre. Such interactions can change the experimentally found value by as much as 20% of its magnitude. The most significant interaction is a hydrogen bond formation. Out of the three models studied the most extensive interactions are present in benzoic acid, whereas almost none were observed in aniline. The capability of donation of electron pair to a hydrogen bond decreases in the substituent series $COCH_3 > SO_2CH_3 > NO_2$. The capability of donation of proton to a hydrogen bond with electron-pair donor decreases in the substituent series $OH > NHCOCH_3 \approx SH > NH_2 > SO_2NH_2$.

Key words: Substituent effects; *ortho* Effect; Dissociation constants; PLS; PCA; Benzoic acid; Phenol; Aniline; Chemometric.

The *ortho* and *para* positions of the aromatic nucleus are alternating positions and, therefore, it is justifiably presumed[1,2] that the substituent effect transferred by valence electrons from both positions is of identical nature,

differing only in its intensity. Therefrom it would follow that a quantitative description of substituent effect from the *ortho* position could easily make use of the parametrization valid for *para* position, which has already been standardised in various empirical correlation relations[3–5]. However, the situation is complicated by nonbonding interactions between the reaction centre and *ortho* substituent, which is usually referred to as "*ortho* effect" (for a survey see refs[1,2,6–10], see also series in refs[11–18]). The term "effect" is not quite precise since the *ortho* effect involves several effects, in particular hydrogen bond formation between certain atoms of the reaction centre and substituent[10], steric interaction between the solvated reaction centre and solvated substituent[19], changes in resonance interaction[20] and other less important factors[21]. The extent of operation of the effects mentioned specifically depends on the chemical structure of the reaction centre, its chemical neighbourhood, and the medium used[22]. The unique or even intimate character of these interactions cannot easily be predicted and, hence, also generally quantified. Despite that, there exist a number of more or less successful correlation relations appropriate for the description of substituent effects from the *ortho* position. The approach based on the Hammett equation was the least successful[23–27], due especially to the fact that this equation is an empirical relation without any description of the basis of the phenomenon. More success can be expected from the *a priori* correlation relations based on description of separated components of substituent effects[6,8,23,29–33] (inductive, mesomeric, steric) or on another principle[34–38], also with the use of the alternative interpretation of substituent effects (AISE) proposed by us[36,37]. In no case, however, we can avoid introducing additional effects by means of some other parameters describing the interaction of the reaction centre with the substituent through hydrogen bonding[10] or steric effects[32,39,40] or other ways[41,42]. However, the approaches mentioned are predominantly of a descriptive character, their aim usually being to obtain a close correlation relation, whereas the cause of the deviations observed (and hence the very basis of the *ortho* effect as such) is analysed only rarely.

The study of the *ortho* effect by means of substituents at the *para* position to the reaction centre has one advantage when compared with the approaches based on the above-mentioned physico-chemical or empirical models. Whereas the model describes only some (although undoubtedly substantial) parts of reality, experimental data encompass the entire reality. On the other hand, experimental data also contain information irrelevant to the causal description sought and, of course, are loaded with experimental error. Such irrelevant information can, in the case of the relationship

studied by us, involve the effect of medium, temperature *etc.*, despite the fact that such quantities are sometimes parametrized within the limits of correlation relations[41,42]. A correlation of experimental errors can result in misleading conclusions (an extreme example is the calculation of isokinetic temperature[43]). Suitable chemometrical procedures, however, can remove the unwanted information and thus obtain the required description of a certain relation or property. This approach was used in our previous papers dealing with the *ortho* effect[10,19], however, it has not been fully exploited yet in studies of relationhips between *ortho* and *para* substitution.

The aim of the present work is to adopt the chemometrics tools in analysis of the relationships between *ortho* and *para* substitution in selected compounds with different types of reaction centre in various media and to explain the reasons for apparently anomalous behaviour of some *ortho* substituents.

THEORETICAL

What we are looking for with regard to the relationship between *ortho* and *para* substitution is such a description that will explain the maximum part of common information included in the data obtained for both *ortho* and *para* derivatives. Respecting this requirement, we can find a single vector u_{ortho} for the *ortho* position and a single vector t_{para} for the *para* position which are presumed to express the subtituent effects transferred by the bonding electrons. These two factors are connected by the following linear relationship

$$u_{ortho} = a\, t_{para} + h\,, \qquad (1)$$

where a and h are parameters. From the statistical point of view this is a regression dependence (with a certain inaccuracy, because t_{para} is not a non-random variable), u_{ortho} and t_{para} being a dependent and an independent variable, respectively. The vectors u_{ortho} and t_{para} in Eq. (*1*) can be of various types. In the simplest case, there are experimental results obtained for the respective pair of derivatives, but the interpretation can be distorted by internal correlation of the experimental conditions (*e.g.* medium). If we want to avoid this problem, we should work with the data sets (data matrices) obtained under the same conditions for the given pair of compounds, although generally under various experimental conditions. A suitable selection then allows a presumption that the information about experimental

conditions contained in the data are not mutually correlated. The vectors (latent variables) u_{ortho} and t_{para} obtained in this case by the method of projection of latent structures (PLS, a generalised regression between matrices[44]) will be loaded with information about experimental conditions to the minimum extent or not at all.

The common variability can also be looked for in the respective data matrices within the limits of individual substitution types. A suitable method here is the principal component analysis[45] (PCA), its result consisting in the latent variables describing the maximum common variability of columns of the given matrix by means of one or more vectors. The comparison of explained variability obtained by the PLS and PCA methods for a given matrix then gives information about the extent of common variability explained by the generalised regression relationship.

Generally, the vector t_{para} in Eq. (*1*) interprets only a part of information contained in the vector u_{ortho}, this part being the greater, the smaller are the interactions between the reaction centre and substituent which are not transmitted by the bonding electrons. The magnitude of variability not explained depends on the extent of different kinds of behaviour of the individual substituents as compared with the standard, *i.e.* the *para* substitution. The deviating substituents can be revealed with the use of indicator variables (value 1 for presumed deviating substituent, value 0 for others) which will extend Eq. (*1*). The regression model is looked for by means of multiple linear regression with leaving out statistically insignificant regression coefficients. The magnitude of the respective regression coefficient then directly represents the distance of the given substituent from the base line. Hence it is possible to propose a physico-chemical explanation of this phenomenon for statistically significantly deviating substituents.

EXPERIMENTAL AND CALCULATIONS

The preparation and properties of substituted benzoic acids, the procedure of titration for determination of their dissociation constants, and the purification of solvents used were described elsewhere[10,46]. 2-Acetylbenzoic acid was used as a commercial sample (Aldrich, 99% purity). 2-(Methylsulfonyl)benzoic acid was synthesised by a known method[47], m.p. 138–139 °C (ref.[47] gives m.p. 139–140 °C).

For the input data were used those given in this paper (Table I) along with those taken from the literature (for a survey see Table II). The data were treated by well known algorithms[44,45].

RESULTS AND DISCUSSION

Three typical chemical models have been chosen to study the relationship between *ortho* and *para* substitution in the selected compounds with various types of the reaction centre, *viz.* benzoic acid, phenol, and aniline. The choice of substituents respected the requirement of including ones in which a certain type of interaction with the reaction centre can be presumed in *ortho* position. Table I presents a survey of the substituents chosen in this way. The suitable data, which always included the measure-

TABLE I
The dissociation constants as pK_a and their standard deviations s_{pK} for selected 2- and 4-substituted benzoic acids in various solvents at 25 °C (W water, EtOH ethanol, DMSO dimethyl sulfoxide, Py pyridine)

No.	Substituent	2-Substituted benzoic acid				4-Substituted benzoic acid			
		W		EtOH		DMSO		Py	
		$\overline{pK_a}$	s_{pK}	$\overline{pK_a}$	s_{pK}	$\overline{pK_a}$	s_{pK}	$\overline{pK_a}$	s_{pK}
1	H[a]	4.21	–	10.25	–	11.00	–	9.80	–
2	CH_3	4.02	0.03	10.23	0.02	11.19	0.03	10.09	0.01
3	$COCH_3$	4.17	0.04	10.07	0.01	–	–	–	–
4	NH_2	4.87	0.01	10.94	0.03	12.23	0.04	11.18	0.03
5	$NHCOCH_3$	3.67	0.08	8.78	0.01	–	–	–	–
6	NO_2	2.85	0.06	8.27	0.01	9.32	0.07	8.15	0.01
7	OH	3.19	0.03	8.45	0.03	11.68	0.05	10.61	0.02
8	OCH_3	4.11	0.01	10.21	0.01	11.38	0.01	10.27	0.01
9	SH	–	–	8.48	0.11	–	–	–	–
10	SCH_3	3.89	0.06	10.08	0.03	–	–	–	–
11	SO_2CH_3	2.99	0.04	8.63	0.02	–	–	–	–
12	SO_2NH_2	3.14	0.06	8.51	0.01	9.90	0.02	8.84	0.02
13	F	3.60	0.06	9.52	0.03	10.63	0.05	9.46	0.02
14	Cl	3.23	0.02	9.08	0.02	10.35	0.03	9.22	0.02
15	Br	3.12	0.06	8.98	0.06	10.29	0.06	9.19	0.03
16	I	–	–	9.09	0.01	10.38	0.06	9.21	0.01

[a] The standard for titration, a value taken from literature.

TABLE II
The description of the process monitoreda and numbers of experimental points (*n*) at *ortho* and *para* positions of benzene ring

No.	Model compound and description of model process	n_{para}	n_{ortho}	Refs
1	BA, dissociation, water, titrimetrically	14	14	[b], 45
2	BA, dissociation, water, spectrophotometrically	9	9	48
3	BA, dissociation, water, titrimetrically, 7.75 m tetrabutylammonium bromide	9	9	49
4	BA, dissociation, 10% aqueous acetone	8	8	50
5	BA, dissociation, 25% aqueous acetone	8	8	50
	BA, dissociation, methanol	16	16	10, 45
7	BA, dissociation, ethanol	16	16	[b], 45
8	BA, reaction with diphenyldiazimethane, ethanol, 30 °C	5	5	51
9	BA, dissociation, acetone	15	16	10, 45
10	BA, dissociation, acetonitrile	13	16	10, 45
11	BA, dissociation, dimethylformamide	16	16	10, 45
12	BA, dissociation, pyridine	11	11	[b], 10
13	BA, dissociation, dimethylsulfoxide	11	11	[b], 10
14	BA, dissociation, gas phase	8	8	52
15	P, dissociation, water, titrimetrically	8	6	53
16	P, dissociation, water, spectrophotometrically	6	8	48
17	P, reaction with isopropyl methylphpsphonofluoridate, water	8	6	53
18	phenyl acetate, base-catalyzed hydrolysis, water	8	8	39
19	P, dissociation, gas phase	7	8	52
20	A, dissociation, spectrophotometrically	10	10	48
21	A, dissociation, spectrophotometrically, 20 °C	8	8	54
22	A, dissociation, spectrophotometrically, 25 °C	8	8	54
23	A, dissociation, spectrophotometrically, 30 °C	8	8	54
24	A, dissociation, spectrophotometrically, 35 °C	8	8	54
25	A, dissociation, spectrophotometrically, 40 °C	8	8	54

[a] BA benzoic acid, P phenol, A aniline, the pK_a and log *k* values have been used for the dissociations and reactions, respectively. [b] Table I.

ments of the same quantity for the *ortho* and *para* derivatives, were taken from our previous studies and from the literature. The missing dissociation constants of substituted benzoic acids in some solvents were measured the data being presented in Table I. Also completed were the values for 2-acetylbenzoic acid in methanol (pK_a = 9.32, s_{pK} = 0.04), acetone (pK_a = 17.80, s_{pK} = 0.02), acetonitrile (pK_a = 20.79, s_{pK} = 0.04), and dimethylformamide (pK_a = 11.68, s_{pK} = 0.02), and similarly for 2-methylsulfonylbenzoic acid in methanol (pK_a = 9.29, s_{pK} = 0.02), acetone (pK_a = 16.21, s_{pK} = 0.02), acetonitrile (pK_a = 18.92, s_{pK} = 0.01), and dimethylformamide (pK_a = 10.42, s_{pK} = 0.04). A survey of the experimental data series used is given in Table II. The data were treated by the above-mentioned PLS and PCA methods, and the obtained values of explained variability are presented in Table III. For the purpose of more detailed analysis, the data concerning benzoic acids were processed separately for different media (protic solvents, aprotic solvents, gas phase), and similarly divided were also the data concerning phenols (liquid and gas phases). Table III includes a number of significant pieces of information.

TABLE III
The explained variability in data matrices for *para* and *ortho* derivatives in per cent and comparison of deviating substituents

Set[a]	PLS		PCA		Deviating substituents[b]
	para	*ortho*	*para*	*ortho*	
1–14	97.152	87.775	97.724	89.256	(+)$COCH_3$>SO_2CH_3>NO_2, (–)OH>SH>$NHCOCH_3$>NH_2
1–8	98.828	91.632	99.144	92.372	(+)$COCH_3$, (–)OH>$NHCOCH_3$>SH
9–13	99.172	98.516	99.464	98.834	(+)$COCH_3$>SO_2CH_3>NO_2, (–)OH>SH> >$NHCOCH_3$>NH_2>SO_2NH_2>OCH_3
14	100.000	44.000	100.000	100.000	(–)OH>NH_2
15–19	98.001	82.293	98.604	83.340	(+)$COCH_3$>NO_2
15–18	97.454	89.906	98.437	91.459	(+)$COCH_3$>NO_2
19	100.000	92.621	100.000	100.000	–
20–25	99.936	99.946	99.998	99.992	–

[a] According to Table II. [b] In the regression according to Eq. (*1*) obtained by means of indicator variables: (+) and (–) mean increase and decrease in experimental value, respectively.

First of all, from the values of the explained variability obtained by the PCA method for *para* substitution it can be inferred that the effect of substituent on the reaction centre is only slightly affected by the solvent, the effect being, of course, less in aprotic solvents (sets 9–13) than in protic ones (sets 1–8) and, at the same time, the effects are different in different types of media (sets 1–14 and 15–18, 19). The values of explained variability by the PLS and PCA methods differ only insignificantly, the differences being less than 1%. Therefrom it can be deduced that virtually the whole information contained in the data obtained for the *para* derivatives is used for explanation of behaviour of the *ortho* derivatives. This is a very important finding since the t_{para} vector then only includes the information about the substituent effect on the reaction centre and obviously nothing else.

The values of the explained variability obtained by the PCA method for *ortho* substitution, as compared with *para* substitution, are not so homogeneous any more. Again the above-mentioned trend in behaviour of solvents is obvious, the differences, however, are marked, wherefrom it can be concluded that the contribution of the solvent used to the interaction of the reaction centre with solvent is significant. This conclusion agreed with our previous statement about steric interactions between the solvated reaction centre and the solvated substituent[19]. Also the differences in the values of the explained variability by the PLS and PCA methods are greater than those of the *para* derivatives. This is particularly the case with the measurements in gas phase, where the intramolecular interaction makes itself felt, without any stabilising effect of solvent, in the strongest way. If we neglect the gas phase data, the found differences are given by a specific behaviour of the respective *ortho* derivatives which is not associated with the transfer of substituent effects *via* the valence electrons. This finding will be dealt with in the following paragraphs describing the individual model compounds.

Benzoic Acid

Although benzoic acid is a standard model for studying substituent effects, it is not the best model for *ortho* substitution, due to the hydroxyl group with acidic hydrogen capable of forming strong hydrogen bonds with *ortho* substituents having a free electron pair on the first atom (counted from the aromatic nucleus) or even the second atom (thanks to conformational flexibility of the carboxylic group). Another potential source of "complications" is the free electron pairs at the carbonyl oxygen atom in carboxylic group; these can be suitable donors for hydrogen bond formation with substitu-

ents having a relatively acidic hydrogen at the first or even the second atom (counted from the aromatic nucleus).

The consequences of possible interactions are depicted very clearly for data sets 1–13 in Fig. 1 giving the individual substituents plotted in u_{ortho} and t_{para} coordinates. From the picture it can be seen that substituents with a polarised multiple bond and a terminal atom with free electron pair form a hydrogen bond with OH group of carboxylic group and thus stabilise the non-dissociated form. The result is an acidity decrease and pK_a increase or lowering of the respective rate constant. The extent to which this effect is manifested decreases with decreasing polarity of the multiple bond, *i.e.* from acetyl to nitro group. On the other hand, substituents capable of providing an acidic hydrogen for the formation of a hydrogen bond with free electron pairs at oxygen atoms of the carboxylic group facilitate splitting off of the proton and stabilise the conjugated base. The result is an acidity increase and hence pK_a decrease or increase in the respective rate constant. As a hydrogen bond is formed most readily if the hydrogen atom is bound to an oxygen atom, the strongest effect can be observed with the hydroxyl group. To a lesser extent the above-mentioned interaction makes itself felt with the sulfanyl group, and it depends on acidifying groups in the case of N–H groupings (the acetylamino group being a stronger proton donor than the amino group itself).

The division of the substituents into two categories was also indicated statistically by means of indicator variables, and the results being given in Table III for the individual media. From the data of Table III it follows that a greater extent of intramolecular interaction *via* the hydrogen bond can be observed in aprotic solvents. This finding is understandable since these sol-

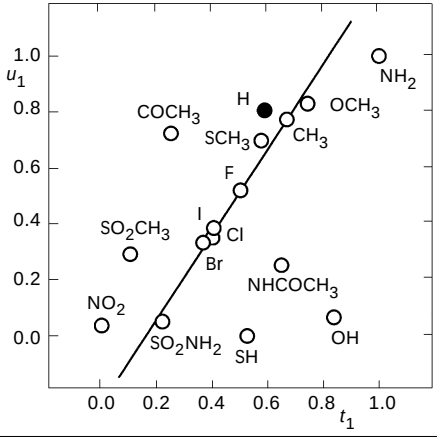

FIG. 1
Location of substituents in the plane of latent variables u_{ortho} and t_{para} for data sets 1–13, the straight line is from the regression with the use of indicator variables

vents do not stabilise the reaction centre by solvation, which makes other ways of stabilisation more important. A comparison with experiments carried out in gas phase is not quite justified since here the proton is split off from other reaction centres[52].

Phenol

As compared with benzoic acid, phenol is a less complex model since the structure of its reaction centre is simpler. An interaction through hydrogen bonding, can especially be expected with such *ortho* substituents as have a polarised multiple bond between the first and the second atoms from the aromatic nucleus and free electron pairs at the terminal atom. The resulting manifestations will be similar to those described for benzoic acids. In addition, some of the substituents can participate in direct conjugation with the reaction centre, thus forming thus polar structures. This is connected with stronger manifestations of individual solvation, which can be documented by the increased non-homogeneity of data expressed by the differences in the explained variability by the PLS and PCA methods given in Table III. As expected the deviating substituents are nitro and acetyl groups, the latter due to strong polarisation of the C=O bond, and the former for the same reason as a consequence of direct conjugation of the reaction centre with the substituent. The substituent effect of the methylsulfonyl group has not been evaluated due to lack of data.

Aniline

Compared to the previous chemical models, aniline is the simplest. The free electron pair at the nitrogen atom is involved in conjugation with the aromatic nucleus and, as the case may be, with suitable substituents participating in direct conjugation, too. Due to that, its spatial orientation excludes a potential nonbonding interaction with simple *ortho* groups. This statement is unambiguously confirmed by the values of explained variability obtained by the PLS and PCA methods summarised in Table III. This conclusion, however, has another fundamental consequence. The whole of the present work is based on the presumption given above, namely that the substituent effect transferred by bonding electrons is identical in nature from either position and only differs in its intensity. The results given support this presumption unless, of course, neither nonbonding interactions nor hydrogen bond interactions are present.

Summary and Generalisation of Results

In the above parts we have discussed the results obtained for selected chemical models with the application of statistical methods enabling a description of fundamental bonds between and inside the data sets. The results given can be summarised in the following way:

1. If neither nonbonding interactions nor hydrogen bond interactions make themselves felt, then there exists high correlation between the substituent effects from *ortho* and *para* positions of benzene ring. This conclusion is of statistical nature and is independent of the way of description of substituent effects. The extent of mutual influence of substituent from *ortho* and *para* position on the reaction centre cannot be determined in this way.

2. If a hydrogen bond can be formed between atoms of the reaction centre and substituent at *ortho* position to it, then the result is significant changes (up to 15% of the differences as compared with the *para* positions) in the results of the process investigated. The magnitude and character of the changes are specific for the interacting groups of atoms, they can be chemically described, but they cannot be generally quantified.

3. Nonbonding effects and therewith connected manifestations of little solvated substituents at *ortho* position, in comparison with *para* position, were not identified.

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