CHEMOMETRIC ANALYSIS OF SUBSTITUENT EFFECTS. VI. A STUDY OF *ortho* EFFECT IN DISSOCIATION OF 2,6-DISUBSTITUTED BENZOIC ACIDS

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Received December 12, 1994
Accepted January 23, 1995

Ten 2,6-disubstituted benzoic acids have been synthesized containing all possible combinations of the following substituents: CH_3, OCH_3, Cl, and NO_2. The dissociation constants of these acids have been measured by potentiometric titration in methanol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, and 1,2-dichloroethane. The experimental data obtained together with the p*K* values of 2-substituted benzoic acids in the same solvents have been analyzed from the point of view of *ortho* effect and additivity of disubstitution. The mutual interaction between substituents was found to represent only 0.12% of the variability due to substitution and to contribute to the overall variability of data less than the interaction between the substituent and solvent by a factor of about 13. The analysis of data by the method of multiple linear regression revealed a contribution of steric effects beside the effects transmitted through the aromatic skeleton. The 2- and 6-substituents effects are additive within the validity of the Hammett equation, and an addition of a multiplicative term describing interactions between the substituents is statistically insignificant. Nonlinear regression has been adopted in the additive model with multiplicative term to find the inner substituent constants including all the effects of substituents from *ortho* position: the term describing the interaction between 2- and 6-substituents is statistically insignificant in this model. An application of the method of conjugated deviations revealed two statistically significant latent variables. The first one explains 91.5% of the variability of data and is connected with the substituent effects transmitted through the aromatic skeleton. The second one explains 7.5% of variability of data and predominantly reflects the steric effects of substituents.

Previous papers of this series dealt with effects of disubstitution in the dissociation of 3,4- and 3,5-disubstituted benzoic acids[1,2] and with *ortho* effect in 2-substituted benzoic acids[3]. The additivity of effects was found in both above-mentioned cases of disubstitution[1,2]. The paper[3] dealing with *ortho* effect showed that dominant effects of *ortho* substituents are those transmitted through the aromatic skeleton to the reaction centre. In contrast to benzoic acids with substituents in other positions, the dissociation of *ortho* derivatives is markedly affected by the hydrogen bond between substituent and the carboxylate group and/or between the substituent and nondissociated carboxylic group[3]. The dissociation of 2,6-disubstituted benzoic acid, dealt with in the present

communication, involves both the problems: disubstitution and *ortho* effect; the complexity of this approach is probably responsible for the fact that this topic has not been paid sufficient attention so far. The dissociation constants of 2,6-disubstituted derivatives of benzoic acid were measured potentiometrically most often: 2,6-dichlorobenzoic acid in water[4–6], aqueous dimethyl sulfoxide[7], methanol, acetonitrile[8], and dimethylformamide[9], 2,6-dimethoxybenzoic acid in water[10,11] and in aqueous dioxane[12,13]. Also available are published dissociation constants of 2,6-dinitro- (ref.[6]), 2,6-dihydroxy- (refs[5,6]), 2,6-dimethyl- (refs[6,14]), 2,6-difluoro- (ref.[15]), and 2-halo-6-nitro- benzoic acids[6,16] and 6-substituted salicylic acids[6,17,18] in water. Spectrophotometry was adopted[19] for determining the relative strength of 2,6-disubstituted benzoic acids (with the combination of substituents Cl, OCH_3, and CH_3) in benzene[19]. The values of dissociation constants of most of the above-mentioned disubstituted benzoic acids together with the values of monosubstituted derivatives were used for verification of correctness of adjustment of new steric parameters[20,21], for studies of interactions between the substituents and reaction centre, and, at the same time, for studies of interactions between these substituents. Literature only describes the additivity of substituent effects for the 2,6-difluoro[15] and 2,6-dichloro[22–24] derivatives, whereas nonadditivity of substituent effects has been stated[16,22–24] for other currently used substituents (CH_3, OCH_3, NO_2) and their combinations. Additivity and nonadditivity, of course, are only relative terms which must be evaluated in the context of validity of the correlation equations used, the quality of the substituent constants adopted, and – last but not least – the precision of experiment. From this point of view, the conclusions could even be reversed in some of the papers mentioned.

As it can be seen from the survey given, available literature lacks a set of dissociation constants of 2,6-disubstituted benzoic acids measured in various media and containing selected combinations of substituents which could be submitted to a complex analysis of disubstitution effect and *ortho* effect. The aim of the present work is to create and analyze such a set excluding (a priori – with respect to possible difficulties) the substituents capable of interaction with carboxylate group through hydrogen bond.

THEORETICAL

As already mentioned *ortho* substitution is connected with a significant possibility of operation of hydrogen bond between the reaction centre and substituent[3], but the factor of hydrogen bond causing difficulties in interpretation can be eliminated by a suitable choice of substituents. It can be claimed then that the variability of data is only due to the effects transmitted through the aromatic skeleton, to steric and solvation effects, and – to a lesser extent – to other possible effects. On the basis of such a choice, the analysis of substituent effects can be approached by the methods previously used[1–3], and the dissociation of 2,6-disubstituted benzoic acids can be correlated, after involving

the steric effects, with the help of equations of similar form as those for other derivatives[1,2]. Two basic approaches are usually adopted to describe *ortho* effect[3]. The first one starts from the Hammett equation with universal substituent constant, the second one consists in a separate description of inductive and mesomeric effects complemented by a description of steric interaction between the reaction centre and substituent. The inductive and mesomeric effects are usually described by σ_I and σ_R constants[25], the steric effects by the Charton υ constants[26] or the Taft E_s constants[27]. Presuming the additivity of inductive, mesomeric, and steric effects, we can write the correlation equation with the Charton υ constants e.g. as follows:

$$\log K = \log K_0 + \rho_I \Sigma\sigma_I + \rho_R \Sigma\sigma_R + \psi\Sigma\upsilon \quad , \qquad (1)$$

where log K is the logarithm of dissociation constant of the substituted derivative, log K_0 is the intercept, $\Sigma\sigma_I$ describes the total inductive effect of both substituents, $\Sigma\sigma_R$ describes the total mesomeric effect, and $\Sigma\upsilon$ describes the total steric effect. Presuming mutual interactions of substituents, one can rewrite Eq. (*1*) to the form (*2*).

$$\log K = \log K_0 + \rho_I \Sigma\sigma_I + \rho_R \Sigma\sigma_R + \psi\Sigma\upsilon + \rho_{II}\sigma_{I2}\sigma_{I6} + \rho_{RR}\sigma_{R2}\sigma_{R6} + \psi_{\upsilon\upsilon}\upsilon_2\upsilon_6 \qquad (2)$$

Another approach in terms of the modified Hammett equation[3] starts from a separate description of the effects transmitted through the aromatic skeleton and the extra-bond effects. In this case the correlation equation can be written as follows:

$$\log K = \log K_0 + \rho_o \Sigma\sigma_o^i + \rho_s \Sigma\sigma_s^i \quad , \qquad (3)$$

where $\Sigma\sigma_o^i$ describes the total effect of substituents transmitted through the aromatic skeleton from the *ortho* position, and $\Sigma\sigma_s^i$ describes the total steric effect. Presuming interactions between substituents, for Eq. (*3*) we obtain the following equation with the interaction terms:

$$\log K = \log K_0 + \rho_o \Sigma\sigma_o^i + \rho_s \Sigma\sigma_s^i + \rho_{oo}\sigma_{o2}^i\sigma_{o6}^i + \rho_{ss}\sigma_{s2}^i\sigma_{s6}^i \quad . \qquad (4)$$

A basically different approach to the description of disubstitution consists in application of the inner substituent constants σ_2 and/or σ_6 which involve all effects of the individual substituents except for their interaction

$$\log K = \log K_0 + \rho(\sigma_2 + \sigma_6) \,. \qquad (5)$$

If the interactions between substituents are taken into account, the Eq. (5) is extended to give the additive-multiplicative form (*6*).

$$\log K = \log K_0 + \rho(\sigma_2 + \sigma_6) + \rho_{26}\sigma_2\sigma_6 \qquad (6)$$

The main difference between the parameters describing the individual effects in the models (*1*) – (*4*) and in the models (*5*) and (*6*) lies in the fact that the first four models make use of outer parameters (which are adjusted for various processes, media, substrates), whereas the last two models adopt the inner parameters (adjusted from the data of the process interpreted).

EXPERIMENTAL

The *ortho* substituent effect was studied using 2,6-disubstituted benzoic acids with all possible combinations of the following substituents: OCH_3, CH_3, Cl, and NO_2. The respective acids were synthesized by known or partially modified procedures. 2,6-Dichlorobenzoic acid and

TABLE I
Methods of final purification, melting points, and purity (determined by liquid chromatography) of 2,6-disubstituted benzoic acids

No.	Substitution		Way of purification[a]	M.p., °C	M.p., °C ref.[28]	Purity[b]
	2-	6-				
1	CH_3	CH_3	w	115 – 116	115 – 116	100.0
2	CH_3	OCH_3	w	139 – 141	139	98.6
3	CH_3	Cl	w	103 – 104	110	98.6
4	CH_3	NO_2	t	151 – 152	151 – 153	99.0
5	OCH_3	OCH_3	w	187 – 189	188	100.0
6	OCH_3	Cl	w	139 – 141	141 – 142	98.8
7	OCH_3	NO_2	w	178 – 179	179 – 180	98.9
8	Cl	Cl	w	142 – 144	144	100.0
9	Cl	NO_2	t	161 – 165	160 – 165	100.0
10	NO_2	NO_2	w	201 – 202	202 – 203	97.3

[a] Recrystallization, w water, t toluene; [b] HPLC SEPARON SGX c18, 150 × 3 mm, 40% aqueous methanol.

2,6-dimethylbenzoic acid were commercial samples (Fluka). The identity of substrates was verified with the help of NMR and GC/MS. The purification methods after a pretreatment consisting in reprecipitation from the respective salt solutions, the melting points, and the purity of the individual derivatives (determined by means of liquid chromatography) are given in Table I. The dissociation constants of the above-mentioned benzoic acids were measured by potentiometric titrations in methanol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, and 1,2-dichloroethane. The methods of measurement of dissociation constants as well as those of drying

TABLE II

Mean values of dissociation constant $\overline{pK}$ and their standard deviations s of 2,6-disubstituted benzoic acids in methanol (MeOH), acetone (Ac), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (AN), pyridine (Py), and 1,2-dichloroethane (DCE) at 25 °C

No.	Substitution		$\overline{pK}$ and s						
	2-	6-	MeOH	Ac	DMSO	DMF	AN	Py	DCE
1	CH_3	CH_3	8.57	17.74	10.64	11.96	20.31	9.58	19.42
			0.02	0.02	0.02	0.03	0.01	0.05	0.04
2	CH_3	OCH_3	8.70	18.24	10.95	12.34	20.52	9.92	19.52
			0.03	0.02	0.02	0.02	0.06	0.05	0.08
3	CH_3	Cl	7.91	16.74	9.48	10.89	19.17	8.69	18.37
			0.01	0.06	0.07	0.07	0.04	0.05	0.03
4	CH_3	NO_2	7.56	16.13	8.85	10.13	18.63	8.23	17.88
			0.04	0.03	0.02	0.03	0.07	0.03	0.04
5	OCH_3	OCH_3	8.84	18.65	11.29	12.72	20.87	10.30	19.67
			0.01	0.03	0.05	0.04	0.02	0.08	0.02
6	OCH_3	Cl	8.06	17.24	9.76	11.24	19.33	9.09	18.51
			0.01	0.09	0.05	0.03	0.06	0.08	0.03
7	OCH_3	NO_2	7.65	16.65	9.16	10.65	18.98	8.52	18.01
			0.04	0.04	0.03	0.02	0.09	0.07	0.03
8	Cl	Cl	7.26	15.68	8.31	9.71	18.16	7.94	17.42
			0.03	0.05	0.06	0.03	0.06	0.06	0.04
9	Cl	NO_2	6.86	15.12	7.66	9.14	17.53	7.43	16.94
			0.03	0.07	0.00	0.04	0.09	0.08	0.06
10	NO_2	NO_2	6.49	14.28	6.72	8.26	16.67	6.90	16.28
			0.05	0.09	0.02	0.05	0.05	0.09	0.03

and purification of solvents are described elsewhere[1]. The experimental results were treated on a PC using our own programs[28].

RESULTS AND DISCUSSION

Table II presents the mean values of $\overline{pK}$ and their standard deviations *s* for 2,6-disubstituted benzoic acids in methanol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, and 1,2-dichloroethane. In all the cases the standard deviations of individual measurements varied within the limits given for titrations in nonaqueous media, i.e. 0.1 p*K* units.

Analysis of Effect of Disubstitution by Means of Analysis of Variance

One of the approaches to analysis of the effect of disubstitution is the decomposition of variability of data by means of the analysis of variance – in our case with three factors: solvent, 2-substituent, 6-substituent. The model chosen, involving the interactions, gave the decomposition of variability given in Table III. The given values of sum of squares *S* corresponding to the individual factors and their combinations are comparable with

TABLE III

The factors followed (Sol solvent, SUBX substitution at 2- and 3-positions, SUBY substitution at 4-, 5-, and 6-positions), sums of squares *S*, degrees of freedom ν (the same for all the cases), values of *F* criterion, and critical values of Fisher–Snedecor distribution F_{crit} at the significance level $\alpha = 0.05$ in the model of analysis of variance with interactions

Factors	$S_{3,4}$	$S_{3,5}$	$S_{2,6}$	$F_{2,6}$	ν	F_{crit}
Sol	6 922.7	6 821.0	6 799.0	$4.36 . 10^5$	6	2.14
SUBX	114.0	135.4	187.1	$2.40 . 10^4$	3	2.64
SUBY	175.8	135.4	187.1	$2.40 . 10^4$	3	2.64
Sol + SUBX	4.8	5.4	6.5	$1.39 . 10^2$	18	1.65
Sol + SUBY	5.2	5.4	6.5	$1.39 . 10^2$	18	1.65
SUBX + SUBY	0.7	0.3	0.5	$1.94 . 10^1$	9	1.92
Sol + SUBX + SUBY	1.2	1.5	0.5	3.79	54	1.39
Residual	0.650	0.670	0.582		224	
Total	7 225.1	7 105.0	7 188.0		335	

the values found for 3,4- (ref.[1]) and 3,5-disubstituted benzoic acids[2] (see Table III) for which the validity of additivity of effects within the limits of the Hammett equation was proved[1,2]. According to expectation, the significant factors are those of solvent, 2- and 6-substituents, the interaction terms being significant too. The interactions between 2- and 6-substituents represent 0.12% as compared with the variability due to substitution and contribute to total variability 13 times less than the substituent–solvent interactions. From these results it unambiguously follows that the error due to neglecting the interaction between substituents is less than that caused by the approximate validity of the correlation equations used at the given accuracy of measurements (0.051 p*K* units).

Analysis of Effects of Disubstitution by Regression Analysis

Models (*1*) – (*4*) were used to analyze the substituent effects by regression analysis. Before the calculation, the data of Table II were extended by the values of 2-substituted benzoic acids containing the same substituents and measured in the same solvents[3]. The substituent constants used for Eqs (*1*) and (*2*) were σ_I, σ_R taken from ref.[25] and the steric constants υ from ref.[26]; those for Eqs (*3*) and (*4*) were the parameters suggested in ref.[3]. Table IV compares the regression parameters and statistical characteristics of the models (*1*) – (*4*). For Eq. (*1*) the regression coefficient of the steric constant υ was statistically insignificant in all the solvents except methanol and acetone. This fact indicates either a rather unsuitable adjustment of the steric parameters υ or a manifestation of some further effect which scales the steric effect. In the present case a likely reason is the solvation of reaction centre by the protic methanol. The results of regression analysis of relation (*2*) lead to the same conclusions: the product terms – except the interaction between inductive effects of substituents – are statistically insignificant in methanol. The negative value of regression coefficient ρ_{II} indicates a lowered interaction between the substituents and reaction centre due obviously to the steric hindrance to resonance caused by the solvated carboxylate group. In model (*3*), which is based on a separate description of effects transmitted through aromatic skeleton and steric effects, both the regression coefficients of the parameters σ_o^i and σ_s^i were statistically significant in all the solvents (Table IV). This clearly documents the fact that application of various correlation equations with different parametrization can lead to different conclusions – about the significance of steric effect in this particular case. The addition of additive-multiplicative term (Eq. (*4*)) was statistically insignificant in all the cases, which confirms the conclusion about the negligible extent of interactions between the individual effects for the substituents used. The residual standard deviations given in Table IV show that the model with the σ_o^i and σ_s^i substituent constants appears to be better, due probably to the better description of steric effects.

TABLE IV
Regression parameters and statistical characteristics in models (*1*) – (*4*) applied to data of Table II

Relation	Solvent						
	MeOH	Ac	DMSO	DMF	AN	Py	DCE
(*1*)							
ρ_1	1.13	2.10	2.69	2.54	2.58	1.87	2.54
ρ_R	–	2.55	1.87	2.02	1.81	1.51	1.32
Ψ	0.60	1.41	–	–	–	–	–
R	0.942	0.974	0.960	0.955	0.941	0.948	0.917
s	0.294	0.312	0.375	0.395	0.446	0.314	0.500
(*2*)							
ρ_1	1.89	2.10	2.69	2.54	2.58	1.87	2.54
ρ_R	1.15	2.55	1.87	2.02	1.81	1.51	1.32
Ψ	1.04	1.41	–	–	–	–	–
ρ_{II}	–1.12	–	–	–	–	–	–
ρ_{RR}	–	–	–	–	–	–	–
Ψ_{vv}	–	–	–	–	–	–	–
R	0.989	0.974	0.960	0.955	0.941	0.948	0.917
s	0.136	0.312	0.375	0.395	0.446	0.314	0.500
(*3*)							
ρ_o	0.71	1.30	1.30	1.31	1.25	0.97	1.06
ρ_s	1.43	0.95	1.13	0.85	1.15	0.69	1.73
R	0.975	0.968	0.988	0.981	0.972	0.979	0.960
s	0.194	0.340	0.211	0.261	0.312	0.203	0.352
(*4*)							
ρ_o	0.71	1.30	1.30	1.31	1.25	0.97	1.06
ρ_s	1.43	0.95	1.13	0.85	1.15	0.69	1.73
ρ_{oo}	–	–	–	–	–	–	–
ρ_{ss}	–	–	–	–	–	–	–
R	0.975	0.968	0.988	0.981	0.972	0.979	0.960
s	0.194	0.340	0.211	0.261	0.312	0.203	0.352

Analysis of Effects of Disubstitution by Means of Inner Substituent Constants

An approach different from both previous ones is the analysis of disubstitution with the help of inner substituent constants which are adjusted only from the data of the process interpreted. This method has the advantage that the analysis results are independent of the parametrization adopted and depend only on the model chosen. The nonlinear regression of the models (*5*) and (*6*) using data of Table II gave the values of inner substituent constants (the optimized parameters) from *ortho* position for the model (*5*): CH_3 = 0.103, OCH_3 = –0.059, Cl = 0.660; for the model (*6*): CH_3 = 0.111, OCH_3 = –0.051, Cl = 0.664. By definition, the values for H and NO_2 were 0.000 and 1.000, respectively. The calculated residual standard deviations are s = 0.205 and 0.196 for the models (*5*) and (*6*), respectively. On the basis of the test of hypothesis of agreement of residual standard deviations of models (*5*) and (*6*) with the value of the criterion F = 1.094 and the critical value $F_{0.95}(158,151)$ = 1.305, we do not reject the hypothesis tested at the significance level α = 0.05. Hence the addition of the additive-multiplicative term is not significant, and the interaction of substituents does not make itself felt.

Separation of Substituent Effects and Analysis of Disubstitution Effects by Means of Latent Variables

The fact that the steric effect makes itself felt beside the effects transmitted through the aromatic skeleton has the consequence that it is necessary to separate and possibly quantify the individual effects. That is why the data of Table II extended by the pK values of 2-substituted benzoic acids[3] were submitted to the analysis by the method of conjugated deviations[29] (CDA, the method with latent variables). The first latent variable explained 98.6% of the total variability, the first two 99.5%, the first three 99.8%. The addition of the third latent variable was not statistically significant. The first latent variable, when correlated with the constants σ_I and σ_R, gave the correlation coefficient R = 0.947; when using the substituent constants σ_o^i (ref.[3]) as the explaining variables, the correlation was improved to the value of r = 0.962. The second latent variable, when correlated with the Charton steric constants υ (ref.[25]), gave the correlation coefficient r = 0.642; with the steric constants σ_s^i (ref.[3]) it was r = 0.545. From the above-mentioned correlation coefficients it follows that the calculation carried out in the standard way fails in giving a proper separation of the effects transmitted through the aromatic skeleton from the steric effects. Therefore, the calculation was modified by introducing a description of the effects transmitted through the aromatic skeleton as the first latent variable in the form[30]

$$\sigma_o = \sigma_o^{i0} + (I + \delta\Delta M)(\sigma_m^i - \sigma_m^{i0}) \quad , \qquad (7)$$

where σ_o is the substituent constant from *ortho* position[3] expressed as a function of the substituent constant σ_m^i from *meta* position. The other latent variables were constructed without any limiting conditions. The first latent variable describing the effects transmitted through the aromatic skeleton explained 91.5% of the total variability, the second latent variable explained 7.5%. For comparison with the monosubstituted benzoic acids[3]: the first latent variable explained 59.8% of total variability (the effects transmitted through the aromatic skeleton), the second latent variable 31.5% (the effect of intramolecular hydrogen bond), and the third latent variable 6.1% (steric effects). It can be seen that the contribution of steric effects in both cases is similar and non-negligible. This result casts doubt on the previous statement[31] that *ortho* effect can satisfactorily be described by means of the inductive and mesomeric effects. The regression of the newly calculated second latent variable with steric parameters resulted in improving the correlation between the second latent variable and the steric constants υ to a value of $r = 0.793$, the respective improvement being to $r = 0.620$ for σ_s^i constants. Although the correlation is little close (due probably to perceptible manifestation of intramolecular hydrogen bond in alkoxy derivatives), it can be presumed that the second latent variable predominantly reflects the steric effects. A clear picture of this fact is presented in Fig. 1 giving the individual derivatives located in the coordinate system of the first (the effects transmitted through the aromatic skeleton) and the second latent variables. Whereas the points in the axis of the first latent variable are dislocated according to expectation, it is possible to state several interesting facts about some substituents in the axis of the second latent variable describing the steric effect. In contrast to literature data, sterically the most demanding substituent is chlorine in the 2,6-dichloro derivative, and, on the other hand, the least demanding one is methoxy group in the 2-methoxy derivative. The former result could

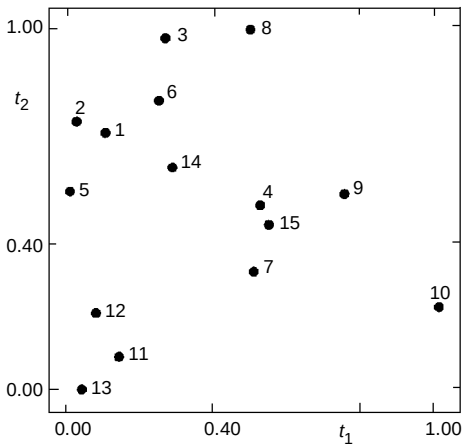

FIG. 1
Dislocation of substituents in the plane of the first (t_1) and the second (t_2) latent variables calculated by the method of conjugated deviations from data of Table II and values of 2-substituted benzoic acids[3]. For numbers of substituents see Table II; further derivatives: 11 2-H-6-H, 12 2-H-6-CH_3, 13 2-H-6-OCH_3, 14 2-H-6-Cl, 15 2-H-6-NO_2

have been be expected with respect to the rigid nature of chlorine substituent. However, the position of methoxy group is surprising since it appears sterically less demanding than hydrogen substituent. This artefact is probably due to formation of intramolecular hydrogen bond between hydrogen of nondissociated carboxylic group and oxygen of methoxy group, which makes this derivative a weaker acid than expected. This bond is not manifested in the 2,6-dimethoxybenzoic acid because of the out-of-plane deviation of the reaction centre by two adjacent bulky OCH_3 groups. Another interesting phenomenon showed in Fig. 1 is the position of 2,6-dinitro derivative which indicates a low manifestation of steric effect in this combination of substituents. The fact can only be interpreted by the deviations of nitro groups, reaction centre, or all three of them simultaneously. This statement is also supported by the results of calculation of the second latent variable by the CDA method with adjusted separation of steric effects as the second latent variable. For the substitution constants we used the υ values[26] for both the nitro groups: out-of-plane deviated and nondeviated. With the value $\upsilon = 0.35$ for deviated nitro group the second latent variable explained 4.9% of data variability, with $\upsilon = 1.39$ for nondeviated nitro group the second latent variable became statistically insignificant.

This research was sponsored by the Grant Agency of the Czech Republic, grant No. 203/94/0122.

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