CHEMOMETRICAL ANALYSIS OF SUBSTITUENT EFFECTS. III. ADDITIVITY OF SUBSTITUENT EFFECTS IN DISSOCIATION OF 3,4-DISUBSTITUTED BENZOIC ACIDS IN ORGANIC SOLVENTS

Oldrich PYTELA, Jiri KULHANEK, Miroslav LUDWIG and Vaclav RIHA

Department of Organic Chemistry,
University of Chemical Technology, 532 10 Pardubice, The Czech Republic

Received May 17, 1993
Accepted July 2, 1993

Sixteen 3,4-disubstituted benzoic acids (with all combinations of CH_3O, CH_3, Cl/Br, and NO_2 substituents) have been synthesized and their dissociation constants measured in seven organic solvents (methanol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, 1,2-dichloroethane). The effect of disubstitution and the validity of additive correlation relationships based on the Hammett equation have been analyzed by means of the analysis of variance, comparison of overall residual standard deviations of correlation equations of additive and additive–multiplicative type, and application of the Hammett equation with internal (latent, defined in various ways) parameters and external (taken from literature) parameters describing the substituent effects. The effect of disubstitution has been found to be additive and describable – within the validity range of the substituent constants adopted – by applying the additivity principle without any additional correction for interactions between the two substituents. The same conclusion has been drawn from the comparison of overall residual deviations in correlation equations for mono- and disubstituted derivatives. The analysis of differences between the reaction constants of the Hammett equation applied to mono- and disubstituted benzoic acids has shown that in organic solvents the solvation of substituents makes various contributions. The substituent influence is stronger in polar aprotic solvents (acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile) than that in the protic, basic, and less polar ones in which the stabilization by hydrogen bond becomes important, the role of proton donor being played either by the solvent itself (methanol) or by its conjugated acid (pyridine) or by a molecule of the dissociating acid as a consequence of homoconjugation (1,2-dichloroethane).

In our earlier paper[1] dealing with the chemometrical analysis of substituent effects, the principle of substituent effects was analyzed on the basic model of benzoic acid. The dissociation of substituted benzoic acid was studied experimentally many times both in individual and mixed solvents. Most measurements were carried out in water (for a survey see ref.[2]). The dissociation constants in individual solvents were given for methanol[3 – 7], ethanol[3 – 5,7], 1-propanol[6 – 8], 1-butanol[4 – 6], 1,2-ethandiol[4 – 7], acetone[3], acetonitrile[3], dimethylformamide[3], dimethylacetamide[9], tetramethylenesulfone[3], dimethyl sulfoxide[7,10,11], and nitromethane[12]. Most of the measurements carried out, however, describe only the monosubstituted benzoic acids while less attention was paid to

the dissociation of disubstituted benzoic acids[9,13 – 17]. The effect of disubstitution was often studied by NMR spectroscopy[18 – 21] and less often by other methods[22,23]. A cognate phenomenon is the effect of substituents at a single reaction centre[24,25]. The quantitative description of disubstitution is based on the additive–multiplicative model, the nonadditivity of both substituents effects being usually corrected by adding a product term[17,21,26,27], and the relationship is referred to[27] as IFER (Interactive Free Energy Relationship). A more perfect model of mutual interaction of substituents and their interaction with the reaction centre has been described recently[26].

With regard to the given state of knowledge in the field of disubstitution of one nucleus, the aim of the present work is a chemometric analysis of effects of disubstitution and solvent upon the dissociation constants in a set of systematically selected 3,4-disubstituted benzoic acids.

THEORETICAL

A general model of influence of two substituents, A and B, presumes individual interactions of each substituent with the reaction centre and, at the same time, mutual interactions between the two substituents[26]. The resulting effect of substituents, as observed by means of the change in the Gibbs energy ΔG, can be expressed as follows:

$$\Delta G = \Delta G^0 + \alpha_A \sigma_A' + \alpha_B \sigma_B' , \qquad (1)$$

where ΔG^0 is the observed effect with standard substituents, α_A and α_B are sensitivity parameters, and σ_A', σ_B' are parameters describing the effect of substituents changed due to their mutual interactions. If we presume, in contrast to ref.[26], that not only the substituent A is affected by substituent B but also vice versa, then we can write Eqs (*2*) and (*3*) for the parameters σ_A' and σ_B', respectively,

$$\sigma_A' = \sigma_A(1 + \beta_B \sigma_B') \qquad (2)$$

$$\sigma_B' = \sigma_B(1 + \beta_A \sigma_A') , \qquad (3)$$

where σ_A and σ_B are parameters describing the substituent effects in a monosubstituted system, and β_A and β_B are the individual measures of contribution of the respective substituent to the change in properties of the other substituent. Equations (*2*) and (*3*) represent a set of equations for two unknowns, viz. σ_A' and σ_B'. After solving them and introducing into Eq. (*1*) we get the relation:

$$\Delta G = \Delta G^0 + \frac{\alpha_A \sigma_A + \alpha_B \sigma_B + (\alpha_A \beta_B + \alpha_B \beta_A)\ \sigma_A \sigma_B}{1 - \beta_A \beta_B \sigma_A \sigma_B} \ . \qquad (4)$$

If the interaction between substituents is neglected ($\beta_A = \beta_B = 0$), then Eq. (*4*) is reduced to the form (*5*)

$$\Delta G = \Delta G^0 + \alpha_A \sigma_A + \alpha_B \sigma_B \ . \qquad (5)$$

Equation (*4*) is often simplified by neglecting the product of parameters in the denominator (i.e. $\beta_A \beta_B \sigma_A \sigma_B << 1$), which gives Eq. (*6*)

$$\Delta G = \Delta G^0 + \alpha_A \sigma_A + \alpha_B \sigma_B + \alpha_{AB} \sigma_A \sigma_B \ . \qquad (6)$$

When describing the effect of disubstitution by means of the Hammett equation, we get the concrete form of Eq. (*7*) for Eq. (*5*),

$$\Delta G = \Delta G^0 + \rho_A \sigma_A + \rho_B \sigma_B = \Delta G^0 + \rho(\sigma_A + \sigma_B) \ , \qquad (7)$$

since in this case only a single reaction constant is considered regardless of the substituent positions (*meta*, *para*). An analogous generalization of Eq. (*4*), of course, presents no problems either.

EXPERIMENTAL

For the study of disubstitution we used the 3,4-disubstituted benzoic acids with all combinations of CH_3O, CH_3, Cl/Br, and NO_2 substituents. The acids were synthesized by known procedures or taken from the samples owned by our Department or were commercial samples. After the general operation of reprecipitation of the respective salt solutions the acids were further purified as specified in Table I (which also gives the physical data). The monosubstituted benzoic acids having the substituents CH_3O, CH_3, Cl, Br, and NO_2 at the 3 or 4 positions were adopted in the purity specified in our previous paper[3]. The solvents used were purified and dried before use (methanol[31], acetone[32], dimethylformamide[33], pyridine[32]). 1,2-Dichloroethane was pre-dried with calcium chloride and then rectified and dried over a molecular sieve 5A. Dimethyl sulfoxide (Fluka, for UV spectroscopy) and acetonitrile (Fluka, for UV spectroscopy) were used directly as the commercial products. The dissociation constants were measured potentiometrically using an RTS 622 apparatus (Radiometer, Copenhagen), the system of glass–calomel electrodes, and 0.1 M tetrabutylammonium hydroxide in absolute methanol as the titrant. Each titration was carried out three times using benzoic acid as the reference (methanol[34], acetone[35], dimethyl sulfoxide[36], dimethylformamide[37], acetonitrile[38], pyridine[39], 1,2-di-

chloroethane[40]). The experimental results were treated with the help of our own programs using a PC-AT computer.

RESULTS AND DISCUSSION

The average $\overline{pK}$ values of 3,4-disubstituted benzoic acids in methanol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, and 1,2-dichloroethane are given in Table II, those of 3- and 4-substituted benzoic acids in 1,2-dichloroethane and pyridine are in Table III.

The analysis of effect of disubstitution can be carried out at different levels of generality and from various points of view. The first step may consist in the decomposition of variability of data by means of the analysis of scatter and evaluation of contributions of individual effects. This approach has its advantage in the fact that it is not necessary

TABLE I
Final purification procedures and physical constants of 3,4-disubstituted benzoic acids

Position		Method of purification[a]	M.p., °C	M.p.[b], °C
3	4			
H	H	e	121 – 122	122
CH_3	CH_3	e	165 – 166	166
CH_3	OCH_3	e	196 – 198	196 – 197
CH_3	Cl	e	209 – 211	209 – 210
CH_3	NO_2	a, t	215 – 216	215 – 216[c]
OCH_3	CH_3	a, t	157 – 159	156
OCH_3	OCH_3	a, s	180 – 182	181 – 182
OCH_3	Cl	e	214 – 215	215 – 216
OCH_3	NO_2	a	208 – 211	208 – 211[d]
Br	CH_3	a	204 – 205	204
Br	OCH_3	a	215 – 218	218 – 219
Cl	Cl	a, s	207 – 208	208 – 209
Cl	NO_2	w	182 – 184	183 – 184
NO_2	CH_3	a	189 – 190	190 – 191
NO_2	OCH_3	a	193 – 195	195 – 196
NO_2	Cl	a, s	183 – 184	183
NO_2	NO_2	a	165 – 166	165

[a] Crystalization (e ethanol, a acetic acid, t toluene, w water), s sublimation; [b] ref.[28] if not otherwise stated; [c] ref.[29]; [d] ref.[30].

TABLE II

Average dissociation constants $\overline{pK}$ and their standard deviations *s* for 3,4-disubstituted benzoic acids in methanol (MeOH), acetone (Ac), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (AN), pyridine (Py), and 1,2-dichloroethane (DCE)

Position		$\overline{pK}$ and *s*						
3	4	MeOH	Ac	DMSO	DMF	AN	Py	DCE
H	H	9.41	18.20	11.00	12.27	20.70	9.80	20.00
CH_3	CH_3	9.63	18.71	11.46	12.70	21.05	10.19	20.43
		0.01	0.04	0.04	0.09	0.05	0.09	0.08
CH_3	OCH_3	9.81	19.01	11.71	12.84	21.29	10.32	20.76
		0.01	0.06	0.08	0.04	0.08	0.04	0.04
CH_3	Cl	9.12	17.59	10.54	11.70	20.27	9.52	19.89
		0.02	0.04	0.01	0.01	0.01	0.05	0.04
CH_3	NO_2	8.54	16.55	9.48	11.03	19.21	8.90	18.90
		0.04	0.07	0.11	0.01	0.10	0.01	0.16
OCH_3	CH_3	9.49	18.32	11.06	12.39	20.76	9.94	20.34
		0.05	0.05	0.08	0.09	0.10	0.01	0.10
OCH_3	OCH_3	9.54	18.59	11.40	12.65	20.95	10.08	20.49
		0.02	0.02	0.04	0.03	0.04	0.09	0.09
OCH_3	Cl	8.98	17.39	10.39	11.58	20.02	9.29	19.52
		0.02	0.05	0.02	0.02	0.09	0.02	0.04
OCH_3	NO_2	9.28	16.21	9.22	10.33	18.77	8.42	18.61
		0.01	0.04	0.07	0.03	0.04	0.02	0.02
Br	CH_3	9.06	17.59	10.30	11.49	20.03	9.34	19.62
		0.02	0.03	0.01	0.01	0.04	0.02	0.01
Br	OCH_3	9.27	17.82	10.61	11.83	20.38	9.74	19.84
		0.01	0.03	0.03	0.07	0.06	0.05	0.07
Cl	Cl	8.64	16.70	9.60	10.79	19.42	8.94	19.02
		0.01	0.03	0.03	0.03	0.02	0.06	0.08
Cl	NO_2	8.09	15.78	8.61	10.07	18.28	8.03	18.37
		0.05	0.03	0.11	0.04	0.04	0.02	0.07
NO_2	CH3	8.61	16.75	9.45	10.93	19.36	9.00	19.17
		0.01	0.01	0.05	0.05	0.04	0.04	0.04
NO_2	OCH_3	8.83	17.04	9.85	11.18	19.51	9.20	19.31
		0.00	0.05	0.04	0.05	0.04	0.05	0.08
NO_2	Cl	8.24	15.98	8.74	9.98	18.57	8.26	18.28
		0.01	0.04	0.07	0.02	0.05	0.06	0.09
NO_2	NO_2	7.44	15.07	7.88	9.07	17.50	7.45	17.76
		0.02	0.03	0.05	0.03	0.04	0.09	0.09

to formulate a concrete correlation equation, which – at the same time – is also its drawback because the individual correlation relationships cannot be mutually compared. The second step may consist in the verification of statistical significance of the models (*4*) and/or (*6*) as compared with that of the model (*5*) not including the interactions: in our case this is possible only for the model (*6*). Two approaches can be chosen for this purpose: independent statistical tests for the individual solvents or a single statistical test for all the solvents at the same time. In the former case it is necessary to determine by optimization the values σ_A, σ_B, and, as the case may be, α_{AB} under the presumption that $\alpha_A = \alpha_B = 1$, in the latter case – on the other hand – it is necessary to use a suitable method with latent variables to determine σ_A, σ_B common for all the solvents, and to determine by regression the values α_A, α_B, and, as the case may be, α_{AB}. It is obvious that the two results can differ (though not fundamentally). In accordance with the line of interpretation throughout this paper, we restricted the tests to the second type of testing. The third step is the evaluation of additivity in terms of the model of the Hammett equation (*7*). In this case it is possible to use an "internal" parametrization based on the treatment of data of Table II or an "external" one based on other experiments or tabulated values.

TABLE III
Average dissociation constants $\overline{pK}$ and their standard deviations *s* for 3- and 4-substituted benzoic acids in pyridine (Py) and 1,2-dichloroethane (DCE)

Substituent	$\overline{pK}$ and *s*			
	meta derivatives		*para* derivatives	
	Py	DCE	Py	DCE
H	9.80	20.00	9.80	20.00
CH_3	10.05 0.13	20.29 0.04	10.13 0.03	20.35 0.06
OCH_3	9.59 0.24	20.09 0.09	10.42 0.07	20.53 0.04
Br	8.93 0.05	19.48 0.07	9.29 0.06	19.82 0.14
Cl	8.99 0.00	19.46 0.14	8.87 0.02	19.90 0.17
NO_2	8.23 0.03	18.75 0.09	8.15 0.21	19.22 0.06

Analysis of Effect of Disubstitution by Analysis of Variance

The data of Table II represent a set in a form of a matrix whose every element is a mean value of three measurements. The result of each measurement possesses – with respect to the standard state – the variability composed of the solvent effect, the 3-substituent effect, the 4-substituent effect, the effect of possible interactions between the given factors, and the experimental error. Obviously, this is a model of analysis of variance with interactions, which gave the decomposition of variability given in Table IV. As expected, the significant factors are the basic ones, however, the statistical significance of interaction terms is interesting too. It is noteworthy that the mutual interactions between substituents contribute less (roughly by the factor of seven) than the interactions between solvent and substituent to the overall variability, the effect of solvent upon the 4-substituent being somewhat greater than that upon the 3-substituent. The higher solvent sensitivity of *para* substituents seems to be a fairly general phenomenon[41]. As the interactions between the substituents form about 0.5% of the variability due to substitution (Table IV), they can be neglected, and it can be stated that in these models the effect of 3,4-disubstitution is additive. For comparison we also give the magnitude of experimenmtal error which is $5.39 \cdot 10^{-2}$ p*K* units for the set analyzed by us.

TABLE IV
Investigated factors (solvent Sol, *meta* substitution P3, *para* substitution P4), sums of squares *S*, degrees of freedom ν, values of *F* criterion, and critical values of Fisher–Snedecor distribution F_{crit} at significance level $\alpha = 0.05$ in model of analysis of variance with interactions

Factors	*S*	ν	*F*	F_{crit}
Sol	6 922.7	6	$3.98 \cdot 10^5$	2.14
P3	114.0	3	$1.31 \cdot 10^4$	2.64
P4	175.8	3	$2.02 \cdot 10^4$	2.64
Sol + P3	4.8	18	$9.11 \cdot 10^1$	1.65
Sol + P4	5.2	18	$1.00 \cdot 10^2$	1.65
P3 + P4	0.7	9	$2.78 \cdot 10^1$	1.92
Sol + P3 +P4	1.2	54	7.79	1.39
Residual	0.650	224	–	–
Total	7 225.1	335	–	–

Analysis of Effect of Disubstitution by Means of Additive–Multiplicative Relationships

The data of Table II were treated by the method of conjugated deviations[42], two latent variables being looked for satisfying the relationships (*5*) and (*6*) in the first and the second cases, respectively. In both cases the values of latent variables were averaged in the course of calculation so as the first and the second latent variables could express the σ values from the positions 3 and 4, respectively. By Eq. (*5*) 99.20% variability of data was explained, the summary residual deviation[42], expressed as the square root of quotient of residual sum of squares of nonstandardized data of Table II and the respective number of degrees of freedom, was $s = 1.13 \cdot 10^{-1}$. By Eq. (*6*) it was possible to interpret 99.51% of variability of data, which corresponds to a summary residual deviation $s = 1.09 \cdot 10^{-1}$. The test of the hypothesis of equality of residual variances of both correlation relationships gave the value of criterion $F(64,40) = 1.07$. On the basis of comparison with the critical value $F_{0.975} = 1.79$ we can state that the hypothesis is not rejected at the significance level of $\alpha = 0.05$. Hence the mutual influence between substituents is statistically unprovable and their effects are additive.

Analysis of Effect of Disubstitution in Hammett Equation

The evaluation of additivity or nonadditivity of substituent effects in the sense of Eq. (*7*) depends on the quantitative description of effects of individual substituents. In the first approximation, the term $(\sigma_A + \sigma_B)$ can be replaced by the first latent variable of the matrix given in Table II. This latent variable implicitly involves the effect of disubstitution within the set of solvents used. Due to different origins and modules of p*K* scales the calculation requires the application of standardized matrix (the average of the respective column is subtracted from each element, and the result is divided by the standard deviation). The first latent variable calculated by the CDA method[1,42] described 99.35% of variability of data, the summary residual deviation being $8.57 \cdot 10^{-2}$. This latent variable describes the additivity of data regardless of the solvent used and represents the lowest possible value of residual standard deviation in models with one substituent constant (latent variable). The result is comparable with the analogous calculation for monosubstituted benzoic acids[43] (*s*: *meta* 0.10, *para* 0.11, *meta*, *para* 0.09).

In order to be able to analyze the additivity of disubstitution by means of the "internal" substituent constants, we created data matrices from the earlier p*K* values of monosubstituted benzoic acids[3] and data of Tables II and III: the rows of these matrices corresponded with the substitution at 3 and 4 positions, respectively (substituents H, CH_3, OCH_3, Cl/Br, NO_2) and the columns were formed by the benzoic acid substituted at the positions 4 and 3, respectively (substituents H, CH_3, OCH_3, Cl/Br, NO_2) and the individual solvents (35 columns altogether). The calculation of the first latent variable by the CDA method in both matrices gave the vectors t_3 and t_4 of the latent variables

describing the substituent effects from the positions 3 and 4, respectively, regardless of the substituent at the positions 4 and 3, respectively, and the solvent used. These vectors were used for interpretation of data of Table II with the help of the modified equation (*7*) in the form of Eq. (*8*),

$$\Delta G = \Delta G^0 + \rho(t_3 + \kappa t_4) , \qquad (8)$$

where κ is the proportionality parameter adjusted by optimization so as to minimize the overall residual deviation in the data matrix of Table II. The value of this deviation was $9.66 . 10^{-2}$ for 99.05% of interpreted variability of data. The difference between the statistical characteristics in this calculation and those in the calculation with one latent variable represents the error introduced as the consequence of the approximation by additive model (not regarding the solvent effect). It is obvious that the introduction of this approximation is acceptable with the data analyzed, the two values of residual standard deviation being even statistically equivalent ($F = 1.27$, $F_{0.975}(88,88) = 1.52$).

Another measure of approximation is represented by the application of "external" parameters to the description of substituent effects. For this purpose we chose the model of the Hammett equation (*7*) with the parametrization σ^i (ref.[1]) and σ_{Ex} (ref.[44]). The calculation according to Eq. (*7*) with the parametrization σ^i gave the residual standard deviation $s = 1.01 . 10^{-1}$ (98.99% interpreted variability), that with σ_{Ex} gave $s = 1.30 . 10^{-1}$ (98.42% interpreted variability). As expected, the introduction of general external substituent constants results in a worse fit of the correlation, the somewhat lower successfulness of σ_{Ex} being due to the parametrization for water as the solvent, whereas measurements in various media were adopted in constructing σ^i constants. The validity of the additive model of substituent constants with the application of the σ^i set has been confirmed because the residual standard deviation in comparison with the value for the internal vector of substituent constants turns out to be comparable ($F = 1.39$, $F_{0.975}(88,105) = 1.51$), whereas the opposite conclusion is arrived at for the σ_{Ex} set ($F = 2.30$). In conclusion of this section it can be stated that the additive model (*7*) is generally valid, a possible nonadditivity being ascribable to the set of substituent constants used.

For verifying just the dependence upon the substituent constants we carried out a comparison between the accuracy of validity of the Hammett equation for monosubstitution and disubstitution using always the same scale of substituent constants. The calculation adopted a matrix formally identical with that given in Table II, the substituents at 4 and 3 positions, respectively, being replaced by hydrogen. The values of the overall residual standard deviation for the substitution at 3 position were $s = 1.02 . 10^{-1}$ and $1.07 . 10^{-1}$ for the scales of σ^i and σ_{Ex}, respectively, the analogous values for substitution at 4 position being $s = 9.70 . 10^{-2}$ and $9.70 . 10^{-2}$. Now the hypothesis can be

tested whether or not the scatters for mono- and disubstitution are comparable. For the substitution at 3 position the obtained values of test criterion were $F = 0.98$ and 1.48 for σ^i and σ_{Ex} substituent constants, respectively, the corresponding values for the substitution at 4 position being $F = 1.08$ and 1.80, respectively. As the critical range of this test is $F_{0.975} = (0.68, 1.48)$, the hypothesis of equality is rejected only for σ_{Ex} in 4 substitution, and the decision about validity of this hypothesis cannot be carried out at the given significance level of $\alpha = 0.05$ for substitution in 3 position. Hence we have arrived at a similar conclusion as in the comparison of overall residual standard deviations with internal and external parametrizations.

On the basis of the analysis carried out it can at least be stated that the additive models of disubstitution are valid within the validity range of the Hammett equation with the parametrization for the medium used. A certain role can be played also by the respecting of the relationship between the substitutions at 3 and 4 positions within the σ^i scale[1]. The application of more complex models of the type (*4*) is meaningless for the dissociation equilibria, the interaction effects observed in the studies of disubstitution using NMR spectroscopy[26] can be caused by specific effects of the method used.

Analysis of Solvent Effects

Table V presents the reaction constants and corresponding statistical characteristics in the Hammett equation for dissociation constants of sixteen disubstituted benzoic acids in seven organic solvents. The comparison with the reaction constants for monosub-

TABLE V

Reaction constants ρ, their standard deviations s_ρ, residual standard deviations *s*, and correlation coefficients *r* in Hammett equation with parametrizations $\Sigma\sigma^i$ (ref.[1]) and $\Sigma\sigma_{Ex}$ (ref.[38]) for dissociation constants of 3,4-disubstituted benzoic acids (repeated analyses, $n = 48$) in organic solvents (for symbols see Table II)

Solvent	Parametrization $\Sigma\sigma^i$				Parametrization $\Sigma\sigma_{Ex}$			
	ρ	s_ρ	$s \cdot 10^2$	*r*	ρ	s_ρ	$s \cdot 10^2$	*r*
MeOH	1.25	0.02	5.63	0.996	1.21	0.02	6.24	0.995
Ac	2.20	0.03	11.4	0.995	2.13	0.04	14.3	0.992
DMSO	2.15	0.04	12.3	0.994	2.07	0.05	16.0	0.989
DMF	2.09	0.04	14.9	0.990	2.01	0.05	18.9	0.984
AN	2.10	0.02	7.53	0.998	2.03	0.03	10.1	0.996
Py	1.59	0.03	8.72	0.994	1.54	0.03	9.55	0.993
DCE	1.70	0.04	12.2	0.990	1.64	0.04	14.2	0.987

stituted benzoic acids[3] (ρ: methanol 1.47, acetone 2.29, dimethylformamide 2.27, acetonitrile 2.05) shows substantial differences only for methanol and, perhaps, dimethylformamide. Further data for the reaction constant in methanol vary in a certain interval (ρ (number of substituents)[ref.]: 1.41 ± 0.07 (19)[45]; 1.39 ± 0.05 (16)[46]; 1.38 (13)[47]; 1.34 (13)[48]), the value found by us being always significantly lower than the lowest value given. The result can be explained by the saturation effect of substituents (the real additive substituent constant is lower than that used) or by solvation differences (in protic solvents) between a single substituent and a pair of adjacent substituents (the individual solvated nitro group is a stronger electron acceptor; with respect to decreased solvation extent in the case of disubstitution the real substituent constant is lower than that used). The interaction between substituent and solvent undoubtedly takes place, which is indicated by the results of analysis of variance (Table IV). With regard to the fact that in aprotic solvents there are no differences between the reaction constants for monosubstitution and disubstitution, the second explanation is more likely. The differences between the reaction constants in various solvents indicate that the extent of participation of substituent stabilization depends on the ability of solvent to solvate the conjugated base by a hydrogen bond. In this respect even pyridine represents no exception, its conjugated acid being able to act in this way. Surprisingly, the little polar 1,2-dichloroethane exhibits a relatively small value of reaction constant. One of the reasons can consist in the application of the titrant dissolved in methanol (in the equivalence point this means the presence of a 2.5% solution of methanol in 1,2-dichloroethane), which can result in preferred solvation of the conjugated base. However, without the titrant in methanol the glass electrode exhibits no response. Another possible explanation consists in the existence of homoconjugates of the conjugated base with undissociated acid (which are currently present in solvents of this type), in which the acid bound by hydrogen bond has a similar effect as a solvating protic solvent.

REFERENCES

1. Pytela O.: Collect. Czech. Chem. Commun. *59*, 159 (1994).
2. Pytela O.: Collect. Czech. Chem. Commun. *59*, 381 (1994).
3. Ludwig M., Baron V., Kalfus K., Pytela O., Vecera M.: Collect. Czech. Chem. Commun. *51*, 2135 (1986).
4. Elliott J. H., Kilpatrick M.: J. Phys. Chem. *45*, 454, 466, 472 (1941).
5. Kilpatrick M., Elanes R. D.: J. Am. Chem. Soc. *65*, 586, 589 (1943).
6. Weiner P. H.: J. Am. Chem. Soc. *95*, 5845 (1973).
7. Exner O., Kalfus K.: Collect. Czech. Chem. Commun. *41*, 569 (1976).
8. Elliott J. H.: J. Phys. Chem. *46*, 221 (1942).
9. Petrov S. I., Bykova L. N., Karaseva L. A., Kvasha N. M.: Org. React. (Tartu) *14*, 17 (1977).
10. Kalfus K., Vecera M.: Collect. Czech. Chem. Commun. *37*, 3607 (1972).
11. Lebed V. I., Makurina V. I., Gorodnyanskii D. L., Kitaeva I. M.: Zh. Fiz. Khim. *1990*, 2242.

12. Kozatchenko A. G., Matrosov E. I., Kabatchnik M. I.: Izv. Akad. Nauk SSSR, Ser. Khim. *1976*, 2440.
13. Hoefnagel A. J., Hoefnagel M. A., Wepster B. M.: J. Org. Chem. *43*, 4720 (1978).
14. Hoefnagel A. J., Wepster B. M.: J. Chem. Soc., Perkin Trans. 2 *1989*, 977.
15. Shorter J., Stubbs F. J.: J. Chem. Soc. *1949*, 1180.
16. Peltier D., Kerdavid M.: Compt. Rend. *243*, 2086 (1956).
17. Kalfus K., Kroupa J., Vecera M., Exner O.: Collect. Czech. Chem. Commun. *40*, 3009 (1975).
18. Holik M.: Magn. Reson. Chem. *9*, 491 (1977).
19. Lynch B. M.: Can. J. Chem. *55*, 541 (1977).
20. Bromilov J., Brownlee R. T. C., Craik D. J., Sadek M., Taft R. W.: J. Org. Chem. *45*, 2429 (1980).
21. Shorter J. in: *Similarity Models in Organic Chemistry, Biochemistry and Related Fields* (R. I. Zalewski, T. M. Krygowski and J. Shorter, Eds), p. 93. Elsevier, Amsterdam 1991.
22. Istomin B. I., Boranskii V. A.: Zh. Obshch. Khim. *1983*, 954.
23. Rodante F., Ceccaroni G., Fantauzzi F.: Thermochim. Acta *1983*, 295.
24. Exner O.: Collect. Czech. Chem. Commun. *41*, 1516 (1976).
25. Lee I., Shim C. S., Chung S. Y., Kim H. Y., Lee H. W.: J. Chem. Soc., Perkin Trans. 2 *1988*, 1919.
26. Holik M.: Magn. Reson. Chem. *30*, 189 (1992).
27. Dubois J.-E., Ruasse M.-F., Argile A.: J. Am. Chem. Soc. *106*, 4840 (1984).
28. *Dictionary of Organic Compounds*. Chapman and Hall, New York 1982.
29. Muler E.: Chem. Ber. *42*, 430 (1909).
30. Froelicher V., Cohen J. B.: J. Chem. Soc. *119*, 1428 (1921).
31. Safarik L., Stransky Z.: *Odmerna analyza v organickych rozpoustedlech*. SNTL, Praha 1982.
32. Keil E. et al.: *Laboratorni technika organicke chemie*. CSAV, Praha 1963.
33. Pitra J., Vesely Z., Kavka P.: *Laboratorni uprava chemikalii a pomocnych latek*. SNTL, Praha 1981.
34. Kolthoff I. M., Guss L. S.: J. Am. Chem. Soc. *60*, 2516 (1938).
35. Foltin M., Majer P.: Collect. Czech. Chem. Commun. *43*, 95 (1978).
36. Barnes K. K., Mann C. K.: Anal. Chem. *36*, 2502 (1964).
37. Ritchie C. D., Uschold R. E.: J. Am. Chem. Soc. *90*, 2821 (1968).
38. Kolthoff I. M., Chantooni M. K., Bhownik S.: J. Am. Chem. Soc. *88*, 5430 (1966).
39. Mukherjee L. M., Schultz R. S.: Talanta *19*, 707 (1972).
40. Bos M., Dahmen E. A. M. F.: Anal. Chim. Acta *63*, 185 (1973).
41. Pytela O., Ludwig M.: J. Chim. Phys. *89*, 1567 (1992).
42. Pytela O.: Collect. Czech. Chem. Commun. *55*, 42 (1990).
43. Ludwig M., Wold S., Exner O.: Acta Chem. Scand. *46*, 549 (1992).
44. Exner O.: *Correlation Analysis of Chemical Data*. Plenum, New York 1988.
45. Koppel I. A., Karelson M. M.: Org. React. *42*, 985 (1975).
46. Nummert V., Palm V.: Org. React. *63*, 292 (1980).
47. Charton M., Charton B. I.: J. Org. Chem. *33*, 3872 (1968).
48. Exner O., Kalfus K.: Collect. Czech. Chem. Commun. *41*, 569 (1976).

Translated by J. Panchartek.