

**ANALYSIS OF SUBSTITUENT AND SOLVENT EFFECTS
ON DISSOCIATION OF N-PHENYLBENZENESULPHONAMIDES***

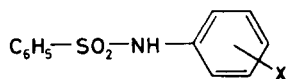
Miroslav LUDWIG, Oldřich PYTELA, Helena JAVŮRKOVÁ and Miroslav VEČEŘA

*Department of Organic Chemistry,
Institute of Chemical Technology, 532 10 Pardubice*

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The potentiometric titration in water, methanol, dimethyl sulphoxide, dimethylformamide, and acetonitrile has been used for determination of pK values of 13 N-arylbenzenesulphonamides. The validity of the Hammett and Yukawa-Tsuno models using several sets of substituent constants has been evaluated by the test to check adequacy of the regression function and by the factor analysis. It has been found that the substituent effects in solvents must be interpreted with regard to the experimental method used, solvent, set of the substituent constants, as well as the model equation ETR. The dependence of the Hammett reaction constants on the solvent has been analyzed and reveals a preferred stabilization of the conjugated base through hydrogen bonds. Direct conjugation of the reaction centre with the substituent and with different extent of the solvent-dependence with the 4-CN and 4-NO₂ derivatives have been observed.

The acid-base properties of the sulphonamides of the general formula



were studied in water¹ and in 50% (vol. %) aqueous ethanol²⁻⁴. As compared with the benzenesulphonamides studied earlier⁵⁻⁷, N-phenylbenzenesulphonamides are c. one order stronger acids in water⁵, which can be explained by the fact that the phenyl group is able to delocalize the electron pair in the conjugated base. In connection therewith a direct conjugation of the reaction centre with electron-acceptor substituents at positions 2 and/or 4 of the aniline part of the molecule can be expected.

The aim of this work is a study of solvent effects on substitution sensitivity of the title substrates and its possible interpretation in the terms of the Hammett equation using various sets of the substituent constants. Another aspect is a verification of the hypothesis about conjugation between the reaction centre and substituents by application of the Yukawa-Tsuno equation and an evaluation of the solvent effect on this phenomenon.

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EXPERIMENTAL

Synthesis of N-phenylbenzenesulphonamides. A solution of 4.5 g (0.025 mol) benzenesulphonchloride in 10 ml freshly distilled pyridine was cooled to -15°C and, with constant stirring, treated with a solution of 0.1 mol respective aniline in 200 ml pyridine. The reaction mixture was left to stand overnight and the separated solid was collected by filtration. Then it was dissolved in 40 ml 10% aqueous sodium hydroxide with addition of charcoal, and the solution was hot filtered and neutralized with 20% aqueous hydrochloric acid. The separated N-phenylbenzenesulphonamide was collected by suction, washed with water, and dried in air. The products were recrystallized from 50% aqueous ethanol. The yields of the syntheses related to the starting anilines are given in Table I along with experimental and published melting points.

The solvents were purified^{5,6} and the measurements, modification, and calibration of the electrodes⁶ were carried out by the described methods. The results were treated with an IQ 151 microcomputer and an EC 1033 computer according to our own programs.

RESULTS AND DISCUSSION

The dissociation constants of substituted N-arylbenzenesulphonamides determined by the potentiometric titration in water, methanol, dimethyl sulphoxide, dimethylformamide, and acetonitrile are summarized in Table II. The variability of dissociation constants determined in a single solvent is given by the variability due to experi-

TABLE I

The yields and melting points of the substituted N-arylbenzenesulphonamides $\text{X}-\text{C}_6\text{H}_4-\text{NH}-\text{SO}_2-\text{C}_6\text{H}_5$

X	Yield, %	M.p. (exp.), $^{\circ}\text{C}$	M.p. (lit.), $^{\circ}\text{C}$
H	65.6	109–110	108.5–109 ^a
3-CH ₃	53.8	93–94	95–96 ^b
4-CH ₃	81.9	121–122	120 ^c
3-CH ₃ O	63.4	80.5–82	82.5–83.5 ^d
4-CH ₃ O	81.5	93–94	95–96 ^e
3-CN	76.1	126–127.5	126.5–127 ^f
4-CN	86.6	172–173	175–176 ^g
4-Cl	61.1	121–121.5	120 ^h
4-Br	96.8	134–136	134 ⁱ
3-F ^j	37.9	99.5–100.5	—
3-CF ₃ ^k	39.1	85–89.5	—
3-NO ₂	58.1	134–135.5	136–137 ^l
4-NO ₂	61.6	137–139	139–140 ^l

^a Ref.⁸; ^b ref.³; ^c ref.⁹; ^d ref.¹⁰; ^e ref.¹¹; ^f ref.¹²; ^g ref.¹³; ^h ref.²; ⁱ ref.¹⁴; ^j for $\text{C}_{12}\text{H}_{10}\text{FNO}_2\text{S}$ (251.3) calculated: 5.58% N, 12.75% S; found: 5.85% N, 13.06% S; ^k for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}_2\text{S}$ (301.3) calculated: 4.65% N, 10.63% S; found: 4.56% N, 10.93% S; ^l ref.¹⁵.

mental error (the so-called pure error) and by that caused by substitution. The dispersion variances calculated from the pure error (Table III) shows that the pK measurements were loaded with usual error.

The variability caused by substitution can be interpreted by models given by the Hammett equation or the Yukawa-Tsuno equation accepting the possibility of

TABLE II

The pK values of the substituted N-phenylbenzenesulphonamides $X-C_6H_4-NH-SO_2-C_6H_5$ in water, methanol (MeOH), dimethyl sulphoxide (DMSO), dimethylformamide (DMF), and acetonitrile (AN) at 25°C

X	Water		MeOH		DMSO		DMF		AN	
H	8.24	8.16	12.01	12.01	13.56	13.50	13.77	13.47	22.64	22.51
	8.16	8.19	11.98	12.03	13.57	13.51	13.77	13.69	22.64	22.53
3-CH ₃	8.47	8.52	12.32	12.37	13.76	13.77	13.99	13.93	22.79	22.80
	8.48	8.45	12.35	12.32	13.50	13.80	13.94	13.88	22.69	22.65
4-CH ₃	8.62	8.60	12.37	12.43	13.76	13.94	14.25	14.22	22.78	22.42
	8.69	8.65	12.42	12.38	13.89	13.86	14.22	14.16	22.61	22.47
3-CH ₃ O	7.93	7.92	11.95	11.94	13.35	13.50	13.62	13.62	22.12	22.04
	8.01	7.98	11.94	11.93	13.40	13.65	13.60	13.54	22.17	22.02
4-CH ₃ O	9.10	8.85	12.45	12.42	14.23	14.28	14.72	14.55	22.95	22.81
	8.85	8.88	12.42	12.45	14.25	14.22	14.69	14.60	22.86	22.85
3-CN	7.18	7.20	10.71	10.76	11.37	11.39	11.32	11.42	20.72	20.63
	7.15	7.09	10.81	10.71	11.32	11.32	11.44	11.31	20.65	20.69
4-CN	6.70	6.80	10.39	10.35	10.90	10.97	10.77	10.92	20.48	20.16
	6.84	6.79	10.34	10.35	10.92	10.90	10.88	10.82	20.48	20.31
4-Cl	7.95	7.86	11.44	11.43	12.64	12.67	12.79	12.91	21.61	21.65
	7.90	7.92	11.49	11.47	12.64	12.72	12.78	12.68	21.63	21.55
4-Br	7.80	7.78	11.57	11.54	12.40	12.61	12.59	12.66	21.78	21.76
	7.75	7.82	11.56	11.57	12.61	12.69	12.64	12.67	21.75	21.66
3-F	7.58	7.58	11.27	11.24	12.30	12.37	12.48	12.44	21.17	21.39
	7.50	7.50	11.32	11.32	12.29	12.31	12.47	12.44	21.36	21.27
3-CF ₃	7.40	7.45	11.08	11.08	11.68	12.01	11.97	11.97	21.07	21.09
	8.38	7.29	11.10	11.07	12.03	12.10	11.97	11.83	20.94	21.12
3-NO ₂	6.89	6.90	10.51	10.52	11.12	11.19	11.07	11.12	20.29	20.33
	6.89	6.90	10.51	10.46	11.17	11.20	11.15	11.15	20.37	20.56
4-NO ₂	6.74	6.70	9.95	10.00	9.94	10.14	9.92	9.99	19.33	19.33
	6.78	6.76	9.98	9.83	10.12	10.25	10.02	9.92	19.23	19.35

direct conjugation of the reaction centre with the substituents. The part of variability which is not reflected by the model is called the lack of fit. Obviously, the lack of fit will depend (beside the model itself) on the (standard) parametrization used. As it has already been shown on the model of dissociation of benzoic acids, the substituent constant of the Hammett equation is affected by the experimental medium used, in this case by solvent¹⁷. Table III summarizes the dispersion variances calculated from the lack of fit for the Hammett model (except the 4-CN and 4-NO₂ substituents) with application of the substituent constants by Exner¹⁶ and those calculated from the dissociation constants of benzoic acids measured in methanol, ethanol, acetonitrile, dimethylformamide, sulpholane, and acetone (σ_{F6}), in water (σ_w), and in all

TABLE III

The dispersion variances and degrees of freedom for the pure error and the lack of fit of the substitution models with various substituent constants (σ_{Ex} , ref.¹⁶; σ_w , σ_{F6} , σ_{F7} , ref.¹⁷) in the individual solvents

Solvent ^a	$10^2 s_S^2(\sigma_{Ex})$	$10^2 s_R^2(\sigma_{Ex})$	$10^2 s_S^2(\sigma_w)$	$10^2 s_S^2(\sigma_{F6})$	$10^2 s_S^2(\sigma_{F7})$	$10^2 s_R^2$
The model by Hammett (except X = 4-CN, 4-NO ₂)						
Water	2.7678	0.3610	3.0602	6.6858	7.2442	0.2846
MeOH	4.8998	0.1320	4.6802	2.4435	2.9419	0.0723
DMSO	9.0902	0.9335	7.6391	1.5108	2.1073	0.9127
DMF	7.0939	0.5962	6.1364	1.1901	2.2499	0.4779
AN	10.472	0.8151	10.173	7.7805	8.1026	0.7413
The model by Yukawa-Tsuno ^b						
Water	3.0584	0.3418	—	7.2091	7.4690	0.2767
MeOH	4.4905	0.1594	—	2.1993	2.6610	0.1096
DMSO	9.7388	0.9253	—	1.8034	2.6418	0.9075
DMF	8.2681	0.5586	—	1.5607	2.8722	0.4576
AN	16.404	0.8930	—	11.281	12.260	0.8326
Model	$n_S(\sigma_{Ex})$	$n_R(\sigma_{Ex})$	$n_S(\sigma_w)$	$n_S(\sigma_{F6})$	$n_S(\sigma_{F7})$	n_R
Hammett	8	34	33	33	33	9
Yukawa-Tsuno	9	40	39	39	39	10

^a For explanation of the abbreviations see Table II; ^b the $\sigma_p^- - \sigma_p$ values used were taken from ref.¹⁶.

the solvents mentioned (σ_{F7}), ref.¹⁷. From the data given it follows that the substituent constants by Exner are suitable for interpretation of substituent effects on the dissociation constants of N-arylbenzenesulphonamides in water and methanol, whereas the σ_{F6} set is suitable in the other cases. Hence, the properties of substituents are affected by solvent but the differences are not large enough to affect the interpretation of the parameters of the Hammett equation using the standard substituent constants.

The test to check the adequacy of the regression function can show whether or not the model given can interpret – within the experimental error – the variability found. Let the variability given by experimental error (the pure error) be expressed by Eq. (1)

$$S_R = \sum_{i=1}^m \sum_{j=1}^{n_i} (y_{ji} - \bar{y}_i)^2, \quad (1)$$

where y_{ji} is the experimental value of dependent variable, \bar{y}_i means the selection arithmetic mean from experimental values of the dependent variable at the same value of the independent variables, m stands for the number of groups of different independent variables, and n_i is the number of values in the individual groups. If

$$n = \sum_{i=1}^m n_i, \quad (2)$$

then the variability expressed by S_R has $(n - m)$ degrees of freedom. The regression function will express that part of variability which can be described by Eq. (3)

$$S_V = \sum_{i=1}^m (y_i - \bar{y}) n_i, \quad (3)$$

where y_i means the regression estimate of the value of the dependent variable. S_V has k degrees of freedom, k being the regression multiplicity. Since the overall variability of the dependent variable is given by Eq. (4)

$$S_T = \sum_{i=1}^m \sum_{j=1}^{n_i} (y_{ji} - \bar{y})^2, \quad (4)$$

the part not explained by the regression (the lack of fit) can be expressed by the formula (5)

$$S_S = S_T - S_V - S_R = \sum_{i=1}^m (\bar{y}_i - y_i) n_i \quad (5)$$

with $(m - k - 1)$ degrees of freedom. By means of the Fischer F -test it can be

determined whether or not the dispersion variance corresponding to the lack of fit is greater than that calculated from the pure error (*cf.* Eq. (6))

$$F = (n - m) S_S / ((m - k - 1) S_R). \quad (6)$$

If this hypothesis is valid, then the model used or its parametrization do not sufficiently interpret the variability of experimental data. By application of Eq. (6) on the best set of substituent constants from Table III in the Hammett model we obtain the following F values: water 7.67, methanol 33.80, dimethyl sulphoxide 1.66, dimethylformamide 2.49, acetonitrile 10.50; $F_{crit} = 2.23$. Thus in most solvents the model used does not reflect the variability to a sufficient extent. The reason obviously lies not only in the approximative validity of the Hammett equation (as a relation with empirical parameters) but also in the concentration dissociation constants used. If the validity of the Hammett equation is claimed to have the standard deviation 0.06 in the dissociation constants¹⁶, then this value is exceeded in our case as it is shown by the standard deviations calculated from the lack of fit for the standard σ constants by Exner¹⁶: $s(\text{water}) = 0.17$, $s(\text{MeOH}) = 0.22$, $s(\text{DMSO}) = 0.30$, $s(\text{DMF}) = 0.27$, $s(\text{AN}) = 0.32$. Hence, when using non-thermodynamic dissociation constants in correlations with substituent constants, we must expect an additional error reflecting the non-ideality of behaviour of the solutes. This statement can be documented with the dissociation constants of the same¹ or cogate compounds (sulphonamides⁷) where similar results were obtained, whereas the spectral estimation of pK of N_1 -arylsulphanilamides¹⁹ leads to much closer dependences in the terms of the Hammett equation.

The factor analysis²⁰ represents another point of view from which the substituent effects can be interpreted. By treating the data (without 4-CN and 4-NO₂) reflecting only the substituent effects (*i.e.* after subtracting the pK value of the non-substituted compound) we found that the first factor includes 98.68% of the common variability. The score vector corresponding to this factor correlates with the substituent constants by Exner with the correlation coefficient $r = 0.995$. Within the limits of validity the factor found can be interpreted as a factor describing the substitution sensitivity of the title substrates during their dissociation. The communality expresses the share of the variability of common information in the overall variability of the variable, *i.e.* solvent in this case. The following communalities h^2 were found by the calculation with one factor: water 0.9666, methanol 0.9905, dimethyl sulphoxide 0.9923, dimethylformamide 0.9942, acetonitrile 0.9800. As according to the theory of factor analysis²⁰ the overall variability is given as a sum of the communality, specificity, and mean square, it is possible to determine the specificity, if the last quantity — the mean square — is known, *e.g.*, from the covariance analysis of the pure error. The following specificities b^2 were obtained for the individual solvents: water 0.003, methanol 0.008, dimethyl sulphoxide 0.001, dimethylformamide 0.003, acetonitrile

0.011. These values reflect the behaviour specificity of the compounds titrated in the individual solvents.

Table III summarizes the lack of fit obtained by the covariance analysis of all the substituted derivatives titrated according to the Yukawa-Tsuno model. The results show that, except water, the substitution is better described by application of the σ_{F6} constants¹⁷. Even in this case, the experimental data are not sufficiently interpreted within the experimental accuracy, as it is seen in the values of the F criterion according to Eq. (6): water 26.05, methanol 20.07, dimethyl sulphoxide 1.99, dimethylformamide 3.41, acetonitrile 13.55 ($F_{crit} = 2.08$). The term with dual constants is statistically significant in all the solvents except water. The values for the r parameter of the Yukawa-Tsuno equation (with σ values of ref.¹⁶) in methanol (0.39),

TABLE IV

The regression coefficients, their standard deviations, correlation coefficients r and overall standard deviations s in the Hammett equation for dissociation of the substituted N-phenylbenzenesulphonamides (without 4-CN and 4-NO₂) in various solvents (the σ constants used were taken from ref.¹⁶)

Solvent ^a	pK ₀	s _{pK₀}	ρ	s _{ρ}	r	s	n
Water	8.29	0.02	1.99	0.05	0.989	0.091	11
MeOH	12.02	0.02	2.11	0.05	0.988	0.102	11
DMSO	13.46	0.03	3.28	0.08	0.988	0.158	11
DMF	13.68	0.03	3.69	0.07	0.993	0.135	11
AN	22.32	0.03	2.70	0.08	0.981	0.163	11

^a For explanation of the abbreviations see Table II.

TABLE V

The calculated differences $\Delta\sigma_p$ for N-(4-cyanophenyl)benzenesulphonamide and N-(4-nitrophenyl)benzenesulphonamide in various solvents^a

Substituent	$\Delta\sigma_p$				
	ref. ¹⁶	MeOH	DMSO	DMF	AN
4-CN	0.28	0.17	0.21	0.21	0.04
4-NO ₂	0.44	0.38	0.69	0.73	0.82

^a For explanation of the abbreviations see Table II.

dimethyl sulphoxide (0.42), dimethylformamide (0.39), and acetonitrile (0.55) indicate direct conjugation of the reaction centre with *para* substituents. The absence of this effect in water is interesting, because in literature the direct conjugation is unambiguously claimed for N₁-arylsulphanilamides¹⁹ (spectral determination), and somewhat ambiguous results were found with N-arylbenzenesulphonamides¹ (titrimetric determination).

The reaction constants obtained from the Hammett equation (without the 4-CN and 4-NO₂ derivatives; the σ values from ref.¹⁶) are given in Table IV and indicate different extent of stabilization of the conjugated base in the individual solvents. As compared with the cognate benzenesulphonamides^{5,6}, the solvents order is somewhat different being unambiguously coincident with the order of parameters describing the solvent acidity in various solvent scales, as *e.g.* $E_T(30)$ (ref.²¹), α (ref.²²), ACITY (ref.²³), E (ref.²⁴), AP (ref.²⁵), but not with the parameter AN (ref.²⁶). Hence, the stabilization of free electron pair of the conjugated base is predominantly due to formation of hydrogen bonds between the reaction centre and solvent, nevertheless, the stabilization by solvent through sulphonyl group is not excluded either. The different behaviour of benzenesulphonamides is obviously given by different extent of solvation of the reaction centre proper and of the transmission pathway, *i.e.* the sulphonyl group.

Table V summarizes the values of $\Delta\sigma_p$ differences of the 4-CN and 4-NO₂ derivatives calculated from the regression coefficients from Table IV and from average pK constants (Table II). From the Table V it follows that the conjugation of substituent with the reaction centre is affected by solvent more strongly in the case of the 4-NO₂ derivative than with 4-CN derivative. This result is obviously due to the greater number of terminal atoms and higher polarizability of nitro group. Also significant can be the solvation of the reaction centre: Nitro group will probably be more sensitive than cyano group to this solvation. Such explanation is derived from different behaviour of nitro and cyano groups in the saturation effect of substituted diphenylamines²⁷. As compared with standard literature data (Table V), 4-CN group shows a weaker effect and 4-NO₂ group shows roughly the same or larger effect. Quite abnormal differences $\Delta\sigma_p$ were found in acetonitrile (Table V). This solvent is obviously exceptional in the series used, which is indicated by both the specificities determined from the factor analysis and detailed studies of structure and interactions in its solutions²⁸.

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