Ortho EFFECT IN DISSOCIATION OF SUBSTITUTED *N*-PHENYLBENZENESULFONAMIDES

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Twenty-five 2,2′-disubstituted *N*-phenylbenzenesulfonamides (2-X-$C_6H_4SO_2NHC_6H_4$-Y-2′) were synthesised and their purity checked by elemental analysis. This set of model substrates involved all possible combinations of methoxy, methyl, hydrogen, chloro, and nitro substituents. The dissociation constants of the sulfonamides were determined by potentiometric titration in methanol, pyridine, dimethyl sulfoxide, *N*,*N*-dimethylformamide, acetone, and acetonitrile. The dissociation constants pK_{HA} obtained were correlated with various sets of substituent constants describing electronic and steric effects of the substituents, and the statistically treated data were used to discuss the contribution of the substituent effects in the dissociation and the difference between the effects transmitted from the two rings. A linear regression model explaining 99% of the variability of experimental data in all the solvents has been found and discussed. Moreover, the experimental data were also interpreted by the methods using latent variables, the principal component analysis (PCA) and conjugated deviation analysis (CDA), and two latent variables were shown to be statistically significant in the description of dissociation. The first obviously describes common action of electronic and steric effects of substituents; the other probably concerns a combined effect of substituent and solvent on the position of acid-base equilibrium.

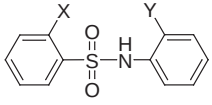
Keywords: Sulfonamides; Dissociation constants; *Ortho* effect; Chemometrics; Substituent effects; Solvent effects.

Ortho effect is a very interesting phenomenon in the theory of substituent effects because interactions between a reaction centre and *ortho* substituents are mediated not only by σ and π bonds of the benzene ring (as it is the case with *meta* and *para* substituents) but some further effects also become evident; among them, the most significant are steric effects and, as the case may be, formation of intramolecular hydrogen bond between the *ortho* substituent and reaction centre. *N*-Phenylbenzenesulfonamides **1** with *ortho* substituents in both rings are possible models for studying the *ortho* effect: determination of their dissociation constants in various organic sol-

vents provides - relatively easily - a large body of data that can be treated statistically to give information about effects operating in the dissociation of these compounds.

The mentioned model was chosen due to the presence of the two benzene rings: their respective *ortho* substituents affect the reaction centre in different ways because the distances from the reaction centre are different. In addition, formation of a hydrogen bond is possible between the acid hydrogen of the SO_2NH grouping and some of the substituents; some of the *ortho* substituents of the NHPh moiety can be directly conjugated with the reaction centre.

The dissociation of *N*-phenylbenzenesulfonamides with at least one substituent in the *ortho* position of one of the two rings almost has not been studied yet; if it was, then only within a series involving also substituents at the *meta* or *para* positions. In such cases, the values of dissociation constants of *ortho* derivatives were discussed only qualitatively, namely as an acidity increase or decrease in comparison with the corresponding *meta* and *para* substituted substrates. Potentiometric titration was used to find the dissociation constants of compounds of the 2-X-$C_6H_4SO_2NHC_6H_5$ and $C_6H_5SO_2NHC_6H_4$-Y-2′ types (X = NO_2, Y = CH_3, OCH_3, NO_2) in 72% aqueous ethanol[1,2], and compounds of the 4-R^1-3-R^2-$C_6H_3SO_2NHC_6$-2′-R^3-6′-R^4-3′-R^5-5′-R^6-4′-R^7 (R^3 and R^4 = CH_3 or Cl) in 50% aqueous ethanol[3]. Spectrophotometry was used to determine the dissociation constants of substances of the $C_6H_5SO_2NHC_6H_4$-Y-2′ type (Y = OCH_3, CH_3, CH_3OCO, Cl, Br, NO_2) in



1	X	Y	1	X	Y
a	H	H	**n**	OCH_3	Cl
b	H	CH_3	**o**	OCH_3	NO_2
c	H	OCH_3	**p**	Cl	H
d	H	Cl	**q**	Cl	CH_3
e	H	NO_2	**r**	Cl	OCH_3
f	CH_3	H	**s**	Cl	Cl
g	CH_3	CH_3	**t**	Cl	NO_2
h	CH_3	OCH_3	**u**	NO_2	H
i	CH_3	Cl	**v**	NO_2	CH_3
j	CH_3	NO_2	**w**	NO_2	OCH_3
k	OCH_3	H	**x**	NO_2	Cl
l	OCH_3	CH_3	**y**	NO_2	NO_2
m	OCH_3	OCH_3			

dimethyl sulfoxide[4], the values found being correlated with one of the proposed sets of σ_{ortho} constants.

EXPERIMENTAL

Syntheses of Intermediates and Model Substances

The model substances were prepared by reactions of the corresponding 2-substituted benzenesulfonyl chlorides with 2-substituted anilines[5]. The reaction yields are given below. The respective benzenesulfonyl chlorides were obtained by decomposition of benzenediazonium salts in acetic acid saturated with sulfur dioxide in the presence of Cu_2Cl_2 (ref.[6]). The purity of all the sulfonamides prepared was checked by elemental analysis using an automatic analyser EA 1108 (Fisons).

N-Phenylbenzenesulfonamides of General Formula 2-X-$C_6H_4SO_2NHC_6H_4$-Y-2′

1a: Yield 49%, m.p. 105-107 °C (ref. [4] 107-109 °C). **1b**: Yield 86%, m.p. 119-121 °C (ref. [4] 124-126 °C). **1c**: Yield 51%, m.p. 82.5-83.5 (ref. [4] 85-86 °C). **1d**: Yield 83%, m.p. 125-126 °C (ref.[4] 129-130 °C). **1e**: Yield 62%, m.p. 96-96.5 °C (ref. [4] 99-101 °C). **1f**: Yield 35%, m.p. 132-133.5 °C (ref. [7] 136 °C). **1g**: Yield 41%, m.p. 113-115 °C (ref. [8] 134 °C). **1h**: Yield 48%, m.p. 102.5-103.5 °C. For $C_{14}H_{15}NO_3S$ (277.3) calculated: 60.63% C, 5.45% H, 5.05% N, 11.56% S; found: 60.11% C, 5.51% H, 5.98% N, 11.29% S. **1i**: Yield 36%, m.p. 76-77 °C. For $C_{13}H_{12}ClNO_2S$ (281.8) calculated: 55.42% C, 4.29% H, 4.97% N, 11.38% S; found: 55.08% C, 4.35% H, 5.82% N, 11.12% S. **1j**: Yield 33%, m.p. 95.5-98 °C. For $C_{13}H_{12}N_2O_4S$ (292.3) calculated: 53.42% C, 4.14% H, 9.58% N, 10.97% S; found: 53.48% C, 4.23% H, 9.82% N, 10.52% S. **1k**: Yield 58%, m.p. 154.5-156 °C (ref. [9] 161 °C). **1l**: Yield 59%, m.p. 144-145 °C. For $C_{14}H_{15}NO_3S$ (277.3) calculated: 60.63% C, 5.45% H, 5.05% N, 11.56% S; found: 60.64% C, 5.41% H, 5.42% N, 10.87% S. **1m**: Yield 28%, m.p. 94-95 °C. For $C_{14}H_{15}NO_4S$ (293.3) calculated: 57.32% C, 5.15% H, 4.77% N, 10.93% S; found: 57.47% C, 5.18% H, 5.20% N, 10.06% S. **1n**: Yield 31%, m.p. 116.5-117.5 °C. For $C_{13}H_{12}ClNO_3S$ (297.8) calculated: 52.44% C, 4.06% H, 4.70% N, 10.77% S; found: 52.33% C, 4.10% H, 5.01% N, 10.23% S. **1o**: Yield 53%, m.p. 120.5-121.5 °C. For $C_{13}H_{12}N_2O_5S$ (308.3) calculated: 50.65% C, 3.92% H, 9.09% N, 10.40% S; found: 50.67% C, 3.99% H, 9.35% N, 9.90% S. **1p**: Yield 52%, m.p. 141.5-143 °C. For $C_{12}H_{10}ClNO_2S$ (267.7) calculated: 53.84% C, 3.76% H, 5.23% N, 11.97% S; found: 53.78% C, 3.75% H, 5.25% N, 11.07% S. **1q**: Yield 45%, m.p. 119-121 °C. For $C_{13}H_{12}ClNO_2S$ (281.8) calculated: 55.42% C, 4.29% H, 4.97% N, 11.38% S; found: 55.57% C, 4.42% H, 4.96% N, 10.31% S. **1r**: Yield 43%, m.p. 91-92 °C. For $C_{13}H_{12}ClNO_3S$ (297.8) calculated: 52.44% C, 4.06% H, 4.70% N, 10.77% S; found: 52.34% C, 4.02% H, 4.73% N, 9.70% S. **1s**: Yield 38%, m.p. 89-90 °C. For $C_{12}H_9Cl_2NO_2S$ (302.2) calculated: 47.70% C, 3.00% H, 4.64% N, 10.61% S; found: 47.72% C, 2.87% H, 4.67% N, 9.76% S. **1t**: Yield 34%, m.p. 125.5-126.5 °C. For $C_{12}H_9ClN_2O_4S$ (312.7) calculated: 46.09% C, 2.90% H, 8.96% N, 10.25% S; found: 45.98% C, 2.80% H, 8.97% N, 9.43% S. **1u**: Yield 22%, m.p. 110-111 °C (ref. [10] 114-115 °C). **1v**: Yield 69%, m.p. 133-134 °C (ref. [5] 137-138 °C). **1w**: Yield 64%, m.p. 87.5-88.5 °C (ref. [5] 91-92 °C). **1x**: Yield 65%, m.p. 143-144 °C (ref. [5] 147-148 °C). **1y**: Yield 34%, m.p. 139-140 °C. For $C_{12}H_9N_3O_6S$ (323.3) calculated: 44.58% C, 2.81% H, 13.00% N, 9.92% S; found: 44.39% C, 2.88% H, 13.07% N, 10.25% S.

Potentiometric Titrations

The dissociation constants of sulfonamides (pK_{HA}) at 25 °C in methanol (MeOH), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), acetone (Me_2CO), acetonitrile (AN), and pyridine (Py) were determined by potentiometric titration using an automatic apparatus Titralab 3 (Radiometer), the electrodes and experimental arrangement being the same as in the previous studies[11-13]. Each measurement was repeated three to four times. The solvents used were purified in standard way.

RESULTS AND DISCUSSION

Table I summarises the mean values of dissociation constants in the form of pK_{HA} along with the corresponding standard deviations for the individual compounds and solvents.

The experimental data obtained were subjected to statistical treatment. All the pK_{HA} values were used in calculations of multiple linear regression, and the mean pK_{HA} values were treated with the methods working with latent variables (PCA (ref.[14]) and CDA (ref.[15])).

Evaluation of Measured Data by Multiple Linear Regression

The explaining variables in the multiple linear regression were represented by various combinations of sets of substituent constants separately treating the electronic and steric effects. The electronic effects were described by the following series of substituent constants: σ_o^i (ref.[16]), σ_p (ref.[17]), and σ_R together with σ_I (ref.[18]). The steric effects were described by the following substituent constants: σ_S^i (ref.[16]) and υ (ref.[18]). The regression parameters ρ_{ef} were calculated simultaneously for both groups of substituents (X and Y) from Eq. (*1*), where σ_{ef} are the substituent constants (selected for the regression) describing the respective substituent effect.

$$pK_{HA} = pK_0 + \sum \rho_{ef}^X \sigma_{ef}^X + \sum \rho_{ef}^Y \sigma_{ef}^Y \qquad (1)$$

Based on the values of residual standard deviation and the magnitude of explained variability, the best model is that including the σ_I, σ_R, and σ_S^i constants. This model explains the total variability of data as follows (residual standard deviation and solvent are given in parentheses): 98.6% (0.134, MeOH), 99.0% (0.158, DMSO), 99.0% (0.170, DMF), 99.4% (0.136, Py), 99.6% (0.112, Me_2CO), 99.2% (0.136, AN). However, a more detailed analysis of this model shows a certain heterogeneity of the reaction constants

TABLE I
Mean values of dissociation constants in the form of pK_{HA} and their standard deviations (*s*) of substituted *N*-phenylbenzenesulfonamides of general formula 2-X-$C_6H_4SO_2NHC_6H_4$-Y-2′

Comp.	MeOH	DMSO	DMF	Py	Me_2CO	AN
1a	13.26 (0.09)	12.01 (0.05)	13.25 (0.04)	10.00 (0.06)	19.95 (0.08)	22.50 (0.03)
1b	13.43 (0.12)	11.84 (0.11)	12.96 (0.04)	10.03 (0.18)	19.98 (0.10)	22.65 (0.05)
1c	13.75 (0.04)	12.28 (0.06)	13.73 (0.09)	11.13 (0.12)	21.23 (0.03)	23.49 (0.11)
1d	12.40 (0.08)	10.34 (0.11)	11.54 (0.03)	8.98 (0.02)	18.67 (0.01)	21.38 (0.01)
1e	11.20 (0.01)	8.72 (0.14)	9.95 (0.06)	7.29 (0.03)	17.22 (0.01)	20.14 (0.06)
1f	13.29 (0.05)	11.97 (0.07)	13.12 (0.05)	10.10 (0.02)	19.87 (0.06)	22.49 (0.07)
1g	13.49 (0.08)	11.78 (0.05)	13.04 (0.06)	9.85 (0.02)	19.77 (0.11)	22.45 (0.09)
1h	13.88 (0.10)	12.14 (0.11)	13.42 (0.04)	11.02 (0.07)	21.16 (0.08)	23.56 (0.07)
1i	12.40 (0.04)	10.04 (0.09)	11.42 (0.06)	8.82 (0.03)	18.50 (0.04)	21.27 (0.03)
1j	11.22 (0.02)	8.35 (0.12)	9.56 (0.04)	7.15 (0.02)	17.03 (0.02)	20.07 (0.03)
1k	13.79 (0.10)	12.61 (0.12)	13.95 (0.09)	11.54 (0.02)	21.50 (0.19)	23.77 (0.11)
1l	13.96 (0.05)	12.51 (0.16)	13.78 (0.07)	11.31 (0.19)	21.56 (0.14)	23.82 (0.08)
1m	14.06 (0.06)	12.81 (0.21)	14.82 (0.12)	12.96 (0.01)	23.21 (0.12)	25.15 (0.06)
1n	13.21 (0.07)	11.14 (0.01)	12.73 (0.04)	10.26 (0.04)	20.41 (0.03)	22.75 (0.04)
1o	12.61 (0.06)	9.76 (0.10)	11.36 (0.05)	8.91 (0.03)	19.15 (0.02)	21.73 (0.01)
1p	13.01 (0.08)	11.48 (0.15)	12.79 (0.04)	9.94 (0.04)	19.62 (0.07)	22.19 (0.05)
1q	13.11 (0.07)	11.18 (0.06)	12.51 (0.04)	9.67 (0.06)	19.52 (0.07)	22.13 (0.03)
1r	13.62 (0.04)	11.79 (0.06)	13.32 (0.19)	10.86 (0.08)	20.99 (0.06)	23.23 (0.02)
1s	12.01 (0.04)	9.64 (0.08)	10.85 (0.06)	8.45 (0.03)	18.12 (0.01)	20.86 (0.04)
1t	10.96 (0.01)	8.08 (0.08)	9.11 (0.14)	6.74 (0.03)	16.76 (0.02)	19.69 (0.06)
1u	12.14 (0.13)	10.43 (0.02)	11.69 (0.06)	8.86 (0.03)	18.50 (0.03)	21.21 (0.05)
1v	12.39 (0.07)	10.21 (0.08)	11.52 (0.04)	8.79 (0.02)	18.56 (0.03)	21.30 (0.03)
1w	12.91 (0.09)	10.78 (0.09)	12.34 (0.02)	9.83 (0.02)	19.87 (0.06)	22.28 (0.04)
1x	11.08 (0.05)	8.53 (0.04)	9.74 (0.10)	7.31 (0.04)	17.01 (0.01)	19.81 (0.02)
1y	10.04 (0.01)	6.90 (0.08)	8.32 (0.13)	5.57 (0.06)	15.48 (0.07)	18.46 (0.03)

calculated (Table II). The first thing to be noticed is a negative value of ρ_I^X in MeOH and DMSO and a positive value in Py, Me_2CO, and AN. A positive value of the constant means that electron-withdrawing (-I type) substituents decrease the acidity. This is only possible if the substituent does not affect the reaction centre by polarisation of σ bonds but directly through space. However, the fact that the constant is negative in some solvents and positive in others may also be due to the small number of substituents investigated or, as the case may be, to some relations between the explaining variables. A potential inadequacy of the model is also indicated by the statistical insignificance of the constant in DMF, which alone is surprising. In the model discussed, the statistically significant constants are ρ_S^X and ρ_S^Y which quantify the steric effects of substituents. Both these constants are negative in all the solvents. Hence, the sterically more demanding substituents increase the acidity. In this case, entropy effects can play a role, *e.g.* a greater change in solvation of the species present on both sides of the dissociation equilibrium and carrying bulky substituents. It is also possible to discuss the differences between the substituent effects transmitted to the reaction centre from the two different rings, and the manifestation of individual effects coming from one of the rings. For this purpose it is helpful to calculate some ratios of the reaction constants (Table III). The ratios ρ_R^X/ρ_I^X and ρ_R^Y/ρ_I^Y expressing the relative magnitudes of mesomeric and inductive effects in each of the rings are characterised by an extensive scattering of values. The

TABLE II
Reaction constants and their standard deviations (*s*) obtained by regression of pK_{HA} values *versus* substituent constants σ_I, σ_R, and σ_S^i

Solvent	ρ_I^X	ρ_I^Y	ρ_R^X	ρ_R^Y	ρ_S^X	ρ_S^Y
MeOH	-0.77 (0.13)	-1.84 (0.13)	-2.63 (0.13)	-3.78 (0.32)	-1.91 (0.28)	-3.12 (0.27)
DMSO	-0.43 (0.15)	-2.30 (0.15)	-4.32 (0.14)	-5.29 (0.15)	-4.37 (0.32)	-5.91 (0.32)
DMF	N[a]	-2.10 (0.16)	-4.77 (0.13)	-6.10 (0.15)	-5.19 (0.16)	-6.63 (0.34)
Py	0.82 (0.13)	-1.26 (0.13)	-6.28 (0.14)	-6.80 (0.13)	-6.82 (0.28)	-7.24 (0.28)
Me_2CO	1.19 (0.13)	-0.54 (0.13)	-7.18 (0.13)	-7.52 (0.12)	-8.10 (0.28)	-8.83 (0.28)
AN	0.54 (0.13)	-0.72 (0.13)	-5.76 (0.12)	-6.21 (0.12)	-6.23 (0.28)	-7.10 (0.28)

[a] N denotes a statistically insignificant parameter.

lowest and not very differing values are those found in methanol, whereas those found in the other solvents considerably differ, it seems that these values result from a specificity of this mathematical model rather than they reflect real properties of the system. The ρ_R^Y/ρ_R^X values are greater than unity in all the solvents. The sensitivity of the dissociation to mesomeric effect of substituents Y is thus stronger than that of X substituents (as expected). The same statement regarding the ratio ρ_R^Y/ρ_R^X is also true for the ρ_S^Y/ρ_S^X ratio, which compares the steric effects of substituents in both the positions. Again, the values of the ρ_I^Y/ρ_I^X considerably differ and are difficult to discuss. In conclusion, it can be stated that this model cannot be considered good (despite its ability to describe the overall variability of data to a considerable extent) because the values of regression coefficients obtained from multiple linear regression are hard to interpret. This can be caused by the above-mentioned narrow selection of substituents or by involvement too many variables in the regression, which were in addition, adjusted in entirely different ways.

Linear regressions with other combinations of substituent constants describing electronic and steric effects of substituents gave substantially worse results with regard to the calculated statistical characteristics. Moreover, regression parameters expressing the manifestations of steric effects are statistically insignificant in many cases; hence it is impossible to unambiguously claim that the dissociation is really sterically affected by the substituents.

The multiple linear regressions involving only those sets of substituent constants that describe the electronic effects of substituents will give infor-

TABLE III
Various ratios of reaction constants obtained by regression of pK_{HA} values *versus* the substituent constants σ_I, σ_R, and σ_S^i

Solvent	ρ_S^Y/ρ_S^X	ρ_I^Y/ρ_I^X	ρ_R^Y/ρ_R^X	ρ_R^X/ρ_I^X	ρ_R^Y/ρ_I^Y
MeOH	1.63	2.39	1.44	3.42	2.05
DMSO	1.35	5.35	1.22	10.05	2.30
DMF	1.28	-	1.28	-	2.90
Py	1.06	-1.54	1.08	-7.66	5.40
Me_2CO	1.09	-0.45	1.05	-6.03	-13.93
AN	1.14	-1.33	1.08	-10.67	8.63

mation about the extent of manifestation of these effects in the dissociation of model compounds. Table IV summarises the correlation coefficients and residual standard deviations calculated in these regressions.

The values of correlation coefficients *R* given in Table IV show that a large part of data variability can be explained with the help of the substituent constants describing the electronic effects of substituents. Nevertheless, the unexplained part of them is by no means negligible and must be ascribed to other effects. The average explained variability for each medium shows the extent to which the pK_{HA} values are affected by electronic effects of substituents and what part of total variability is due to other effects (and, of course, to experimental error). If for each solvent the used models are arranged in the order of magnitude of residual standard deviation, it becomes clear that the choice of a set of substituent constants describing the electronic effects of substituents for the purpose of explanation of overall variability of data is not immaterial (this conclusion is based on the Friedman test). The average order expressing the success of a model using particular substituent constants is as follows: σ_p 1.16, σ_o^i 2.33, and σ_I, σ_R 2.5. These data make it clear that the largest part of overall variability is described by the model using the σ_p constants, there being no difference between the remaining two models. In the models using the σ_p and σ_o^i constants as explaining variables, it is possible to observe (as could be expected) a larger effect on the pK_{HA} value of the substituents Y, which is ex-

TABLE IV
Correlation coefficients and residual standard deviations calculated from the regression of pK_{HA} values *versus* various sets of substituent constants describing electronic effects

Solvent	σ_p		σ_o^i		σ_I and σ_R	
	R	*s*	*R*	*s*	*R*	*s*
MeOH	0.967	0.278	0.958	0.311	0.956	0.325
DMSO	0.965	0.422	0.974	0.364	0.961	0.451
DMF	0.959	0.473	0.958	0.480	0.946	0.551
Py	0.950	0.536	0.929	0.632	0.939	0.594
Me_2CO	0.930	0.664	0.902	0.779	0.919	0.724
AN	0.943	0.507	0.920	0.596	0.929	0.571

pressed by a greater absolute value of ρ^Y constant as compared with ρ^X constant (Table V). These constants are lowest in methanol, which corresponds with the fact that methanol solvates well the anion formed in the dissociation, and thus decreases the need for stabilisation of the anion by dispersing the charge over the molecule; such dispersing process is considerably affected by electronic effects of substituents. The reaction constant ρ_p^X can be compared with the reaction constant ρ_1, which quantifies the substituent effect on the dissociation constant value of *meta* and *para* substituted benzenesulfonamides[11-13], while the reaction constant ρ_p^Y can be compared with ρ_2 found for the dissociation processes of *N*-phenylbenzenesulfonamides substituted in *meta* and *para* positions of the aniline ring[19]. The values of these reaction constants are summarised in Table V giving also the reaction constant ratios ρ_p^Y/ρ_p^X and ρ_o^Y/ρ_o^X, which express how many times the dissociation is more sensitive to electronic effects of Y substituents those of X substituents. The ρ_1 value found in methanol is questionable because it is low compared with the other ρ_1 constants; neglecting it, we can claim that the corresponding constants are more or less identical. We can see that the ρ_o^Y/ρ_o^X ratio for individual solvents is somewhat higher than the ρ_p^Y/ρ_p^X ratio, and the order of solvents arranged according to magnitude of these ratios remains the same.

TABLE V

Comparison of the reaction constants ρ_p^X and ρ_p^Y with the reaction constants ρ_1, ρ_2, ρ_o^X, and ρ_o^Y. The ρ_1 and ρ_2 constants were obtained by regression of pK_{HA} values *versus* substituent constants σ_m and σ_p for *meta* and *para* substituted benzenesulfonamides (ρ_1) and *meta* and *para* substituted *N*-phenylbenzenesulfonamides ($C_6H_5SO_2NHC_6H_4$-Y, constant ρ_2)

Solvent	ρ_1	ρ_p^X	ρ_o^X	ρ_2	ρ_p^Y	ρ_o^Y	ρ_1/ρ_2	ρ_p^Y/ρ_p^X	ρ_o^Y/ρ_o^X
MeOH	-0.52	-1.49	-0.90	-2.11	-2.27	-1.44	4.05	1.52	1.60
DMSO	-1.91	-2.00	-1.23	-3.28	-3.47	-2.23	1.72	1.74	1.81
DMF	-2.03	-2.10	-1.27	-3.69	-3.60	-2.29	1.81	1.71	1.80
Py	-2.06	-2.19	-1.30	-	-3.44	-2.14	-	1.57	1.64
Me_2CO	-2.22	-2.42	-1.43	-	-3.58	-2.22	-	1.47	1.55
AN	-2.10	-2.15	-1.27	-2.70	-3.05	-1.90	1.28	1.41	1.49

Evaluation of Measured Data by Methods with Latent Variables

For the purpose of analysis of substituent effects by these methods, we compiled two matrices (XY and YX) out of the average pK_{HA} values. Both of them were then standardised and subjected to calculation by principal component analysis[14] (PCA) and conjugate deviation analysis[15] (CDA).

First, a square matrix 5 × 5 was constructed for each solvent, the rows representing the pK_{HA} values of sulfonamide groups with constant X substituent and columns representing those of sulfonamides with constant Y substituent. These square matrices were arranged side-by-side, which resulted in a final XY matrix of 5 rows and 30 columns. The YX matrix was constructed by ordering the transposed matrices side-by-side. Both resulting matrices were 100% full.

The statistical characteristics show that the variability of both source matrices can be sufficiently described by two latent variables. In both types of calculation, the first latent variable explains 97.45 and 98.42% of variability of data in the XY and YX matrices, respectively. The variability explained by the second latent variable is slightly different in the two types of calculation. The PCA method gives 2.13 and 1.29% for XY and YX matrices, respectively, the CDA method gives 1.19 and 1.00% for XY and YX matrices, respectively. For both source matrices, it holds true that the values of the vector of the first latent variable decrease from methoxy group to nitro group (Table VI), the order approximately corresponding to the polar effects of the substituents. Hence it can be presumed that the first latent vari-

TABLE VI
Vectors of latent variables isolated from PCA and CDA calculations on XY and YX matrices

X and Y	XY-PCA		XY-CDA		YX-PCA		YX-CDA	
	t_1	t_2	t_1	t_2	t_1	t_2	t_1	t_2
H	0.562	0.859	0.559	0.858	0.769	0.000	0.791	0.000
CH_3	0.529	1.000	0.526	1.000	0.759	0.052	0.780	0.049
OCH_3	1.000	0.000	1.000	0.000	1.000	1.000	1.000	1.000
Cl	0.394	0.579	0.393	0.581	0.391	0.379	0.400	0.377
NO_2	0.000	0.056	0.000	0.056	0.000	0.603	0.000	0.602

able describes just these properties of substituents. In order to support this presumption, we carried out linear regression of the vector of the first latent variable obtained by the PCA and CDA calculations *versus* all the types of the above-discussed substituent constants describing electronic effects of substituents. The results are similar for the latent variables obtained from both types of calculation; therefore, we will present here only the results for the latent variables obtained by PCA calculation. It was found that the vector of the first latent variable of both the XY and YX matrices correlates best with the σ_p constants (XY: s = 0.151, R = 0.931; YX: s = 0.090, R = 0.979), which is in accordance with the above-mentioned finding: the linear regression of pK_{HA} values *versus* those substituent constants that are supposed to reflect only the electronic substituent effects gives the best results just for the σ_p constants. However, the calculated statistical characteristics show that the dependences obtained are not very close, which is particularly true for the vector of the first latent variable of the XY matrix. At first sight, we can notice, *e.g.*, that the value for methyl group in the vector of the first latent variable of both source matrices is lower than that expected for the variable reflecting solely the electronic substituent effects. This can be explained by potential operation of the steric effect in the formation of this latent variable. From this point of view, it is interesting that the $\boldsymbol{t}_1$ vector of the YX matrix (*i.e.*, the Y substituents) correlates with the σ_p substituent constants better than the $\boldsymbol{t}_1$ vector of the XY matrix (X substitu-

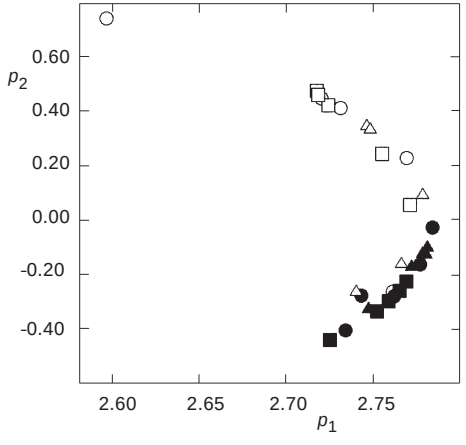


FIG. 1

Position of points in the space of loads from the PCA calculation for the XY source matrix: ❍ methanol, ❑ dimethyl sulfoxide, Δ dimethylformamide, ● pyridine, ■ acetone, ▲ acetonitrile

ents) does. In this case, quite the opposite could have been anticipated since the Y substituents are closer to the reaction centre, and their steric effects should thus be stronger. This fact could be explained by deviation of the ring plane making the substituent more distant from the reaction centre and the steric effect lower. The deviation would also weaken the direct conjugation with the reaction centre and thus improve the correlation with the σ_p substituent constants.

For a better understanding of the influences operating in the creation of the second latent variable, which is statistically significant with both the source matrices, it is helpful to construct the space of loads in which each column of the source matrix is characterised by one point. Figures 1 and 2 show that the points are dislocated in the space of loads in such a way as to form two branches. It is the sign of the p_2 value which determines to which branch a point will belong. If the points in the figures are denoted with individual solvents, it can be seen that in both figures one branch is formed by the MeOH, DMSO, and DMF solvents and the other by Py, Me_2CO, and AN. The properties of substituents probably determine the behaviour of solvents in the dissociation and their division into two groups according to the similarity of this behaviour. This can be presumed on the basis of the fact that the location of a point in the space of loads depends not only on the solvent but also on substitution. This substituent-solvent interconnection is apparently reflected in the second latent variable.

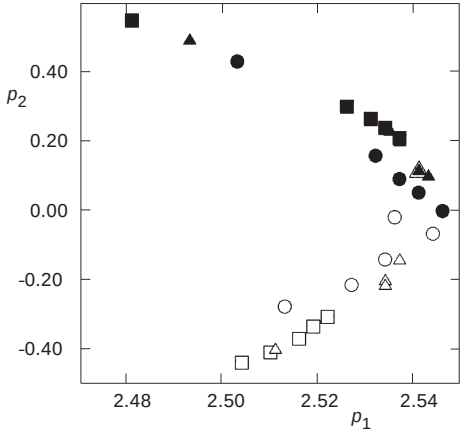


FIG. 2
Position of points in the space of loads from the PCA calculation for the YX source matrix; for symbols see Fig. 1

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