SOLVENT EFFECT IN DISSOCIATION OF SUBSTITUTED BENZENESULPHONAMIDES IN DIMETHYLFORMAMIDE, DIMETHYL SULPHOXIDE, AND ACETONITRILE*

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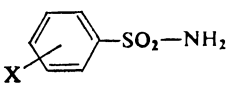
Dissociation constants of fifteen substituted arenesulphonamides of general formula $XC_6H_4.SO_2NH_2$ (or $X_2C_6H_3SO_2NH_2$) have been measured by potentiometric titration in dimethylformamide, dimethyl sulphoxide, and acetonitrile. The Hammett substitution correlations have been calculated and interpreted for these media. The pK_{HA} values measured and the results published earlier for methanol, ethanol, and water have been treated by multiple linear regression using the published set of the parameters characterizing solvents and by factor analysis using the short cycle and the target testing method.

Acid-base properties of benzenesulphonamides *I* were studied in amphiprotic solvents – water[1,2], methanol[1], ethanol[1], and 50% (w/w) ethanol[3-5]. In these media, substituent effects were also evaluated[1-5], and an attempt was made to describe quantitatively the solvent effects[1] which was, however, restricted to one type of solvents only, *viz.* the amphiprotic ones. In constrast to these solvents, dipolar aprotic



I

solvents are characterized by low solvation ability due especially to their unability to form hydrogen bonds involving the hydrogen atom of solvent. The dissociation of weak acids is then connected with formation of conjugates of the type HA_2^- and/or higher types $[A(HA)_n]^-$ (refs[6-9]). If the possibility of formation of the conjugates type HA_2^- is included into the relations describing the dissociation, the following relation is obtained[7]:

$$[\mathrm{ACID}]\,K_{HA}^2 - \{[\mathrm{ACID}] + [\mathrm{SALT}] + K_{HA_2}\text{-}([\mathrm{ACID}] - [\mathrm{SALT}])^2\}a_{H^+}fK_{HA} + a_{H^+}^2 f^2[\mathrm{SALT}] = 0\,, \qquad (1)$$

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where $f = f_{A^-} = f_{HA_2^-}$, [ACID] and [SALT] are actual concentrations of the acid and its conjugated base, respectively, and K_{HA} and $K_{HA_2^-}$ are equilibrium constants of dissociation of the acid and of formation of the homoconjugate, respectively. From Eq. (*1*) it can be seen that, without knowing the homoconjugation constant, the dissociation constant can only be determined in the half-neutralization point. For the measurements in dipolar aprotic solvents the calibration of the system of electrodes is of great importance. In principle, the following four possibilities can be considered: *a*) The calibration with buffers containing the same amounts of the acid and its completely dissociated salt, the pK_{HA} in the given medium being known[8,10–12]. *b*) The calibration using the Henderson–Hasselbalch equation and mixed solutions of acids and their salts with unequal concentrations of the components (the acids used must not undergo homoconjugation in the given medium)[13]. *c*) The calibration according to Eq. (*1*) with the use of buffers composed of acids and salts of various ratios, the pK_{HA} and $pK_{HA_2^-}$ being known[14]. *d*) The calibration with very diluted solutions of an acid whose complete dissociation in the given medium is presumed[15]. The first method is not very precise, because in dipolar aprotic solvents the capacity of buffers exhibits a deep local minimum just in the point of half neutralization[6,7,14]. The method (*c*) is depreciated by relatively inaccurate determination of $K_{HA_2^-}$ in these media. The last method given is considerably exacting both experimentally and with respect to fulfilling the starting prerequisities. The method (*b*) seems to be the most accurate, being not loaded with the errors mentioned. It is, however, necessary to use acids which are unequivocally without homoconjugation, *i.e.* acids whose pa_H depends linearly on log ([ACID]/[SALT]) with the slope of $-1{\cdot}0$ (refs[6,7,16]). Especially used are nitrophenols with nitro group in one or both *ortho* positions and other possible groups in the remaining positions.

The aim of the present communication is determination of dissociation constants of substituted benzenesulphonamides by potentiometric titration in dipolar aprotic solvents – dimethylformamide, dimethyl sulphoxide, and acetonitrile – and description of substituent and solvent effects with involvement of previous results[1] of the measurements in amphiprotic solvents, and interpretation of the relations obtained.

EXPERIMENTAL

Synthesis of the model substances and preparation of the titrating agent are described in the previous communication[1].

Purification of solvents: Dimethyl sulphoxide and acetonitrile were purified according to Kolthoff[17,18]. Dimethylformamide was repeatedly distilled in vacuum in the presence of fused powdered potassium hydroxide. Traces of alkalis were removed by two subsequent vacuum distillations, and the solvent was dried by keeping over activated molecular sieve for 14 days.

Preparation of tetrabutylammonium nitrophenoxides: Picric acid, 2,4-dinitrophenol, and 2,6-dinitrophenol were dissolved in methanol. The solutions were neutralized with 0·1 mol l^{-1} tetra-

butylammonium hydroxide solution on phenolphthalein. The mixture was evaporated, and the evaporation residue was recrystallized from a 10 : 1 heptane–ethanol mixture.

Potentiometric measurements of the dissociation constants: The dissociation constants were determined by potentiometric titration with an TRS-622 apparatus (Radiometer, Copenhagen). The completely hydrated glass electrode was used as the indication electrode, and when its response was slowed down, the hydration with 0·1 mol l^{-1} hydrochloric acid was repeated. The glass electrode was calibrated before each measurement series, and if not used, it was kept immersed in an aqueous buffer of pH 7·00. Calomel electrode with saturated methanolic solution of potassium chloride was used as the reference electrode.

The electrode system was calibrated with the use of buffers prepared from 2,4-dinitrophenol (pK_{HA}: acetonitrile 16·00, dimethylformamide 6·34, refs[8,11,16]), 2,6-dinitrophenol (pK_{HA}: dimethyl sulphoxide 4·9, acetonitrile 16·45, dimethylformamide 6·18, refs[8,11,13,16]), picric acid (pK_{HA}: acetonitrile 11·00, dimethylformamide 3·65, refs[8,11,16]), and their tetrabutylammonium salts with the concentration ratios [ACID]/[SALT] = 1 000, 100, 10, 1, 0·1, 0·01, 0·001. The maximum concentration of the component present in excess was $5 . 10^{-3}$ mol l^{-1}. The calibration straight line of potential (in mV) *vs* pa_H exhibited the theoretical slope[7] of (59 ± ± 1) mV per one pa_H unit. The proper titration of sulphonamides (initial concentration $5 . . 10^{-3}$ mol l^{-1}) was carried out with the use of 0·1 mol l^{-1} tetrabutylammonium hydroxide solution in methanol. The titration agent was added by means of an automatic burette ABU-12 (Radiometer, Copenhagen) at a rate of 0·2 μl s^{-1}, and the solution was temperated at (25·0 ± ± 0·1) °C and argon was bubbled through it during the titration. Each titration was repeated 3–4 times.

Mathematical treatment of the results: The pK_{HA} values of the sulphonamides were determined from the titration curves by means of the half-neutralization point. All the values measured in a given solvent were used for calculation of the Hammett relation of the dissociation of the sulphonamides (the σ constants were taken from ref.[20]). Along with the results published earlier[1] for water, methanol, and ethanol, the present results were used for evaluation of the dependence of pK_{HA} on solvent and substitution by means of multiple linear regression. The results were treated further by target testing in factor analysis.

RESULTS AND DISCUSSION

The dissociation constants of substituted benzenesulphonamides were measured by potentiometric titration in dimethylformamide, dimethyl sulphoxide, and acetonitrile, and are given in Table I in the form of pK_{HA} along with their standard deviations. The treatment of the results by means of the Hammett equation gave the pK^0_{HA} and ϱ values given in Table II. The reaction constants ϱ are almost the same for all the three dipolar aprotic solvents used, which indicates similar character of solvation of the conjugated base. When compared with amphiprotic solvents (Table III), the dipolar aprotic solvents appear to be less solvating, which is reflected in increased sensitivity to substituent effects due obviously to inability of formation of hydrogen bonds. Benzenesulphoamides exhibit lower sensitivity to substituent effects in the solvents studied than benzoic acids which represent O-acids (ϱ, 25°C: dimethylformamide −2·36, dimethyl sulphoxide −2·48, acetonitrile −2·40, ref.[19]). This phenomenon, which has already been observed with amphiprotic solvents[1], can

TABLE I

Dissociation constants of substituted benzenesulphonamides in dimethylformamide, dimethyl sulphoxide and acetonitrile determined by potentiometric titration at 25°C

X	Dimethylformamide			Dimethyl sulphoxide			Acetonitrile		
	pK_{HA}		$\overline{pK}_{HA}$ $s_{pK_{HA}}$	pK_{HA}		$\overline{pK}_{HA}$ $s_{pK_{HA}}$	pK_{HA}		$\overline{pK}_{HA}$ $s_{pK_{HA}}$
H	17·11	16·94	17·06	15·40	15·03	15·16	24·58	24·61	24·61
	17·14		0·11	15·04		0·21	24·63		0·03
4-CH_3	17·50	17·41	17·36	15·74	15·54	15·58	24·95	24·77	24·82
	17·18		0·16	15·47		0·14	24·93	24·63	0·15
3-CH_3	17·34	17·13	17·22	15·46	15·27	15·39	24·70	24·60	24·64
	17·19	17·23	0·09	15·45		0·11	24·73	24·54	0·09
3,4-$(CH_3)_2$	17·68	17·36	17·45	15·92	15·77	15·81	25·12	24·90	25·02
	17·51	17·24	0·19	15·74		0·10	25·06	24·96	0·09
4-Cl	16·66	16·57	16·58	14·69	14·67	14·66	23·98	23·91	23·98
	16·50	16·57	0·07	14·62		0·04	24·03	24·00	0·05
3-Cl	16·18	16·24	16·21	14·43	14·42	14·46	23·77	23·86	23·80
	16·11	16·29	0·08	14·54		0·07	23·82	23·76	0·05
3,4-Cl_2	15·84	15·87	15·85	14·03	14·16	14·11	23·32	23·16	23·29
	15·82	15·85	0·02	14·15		0·07	23·40	23·27	0·10
4-NO_2	15·48	15·45	15·49	13·85	13·89	13·91	22·95	22·95	22·88
	15·54	15·47	0·04	14·03	13·88	0·08	22·95	22·78	0·09
3-NO_2	15·67	15·40	15·52	13·86	13·96	13·95	23·02	22·92	22·95
	15·58	15·43	0·12	14·05	13·92	0·08	22·99	22·87	0·07
3-OCH_3	17·10	16·96	17·00	15·12	15·19	15·15	24·49	24·42	24·48
	16·97	16·96	0·07	15·13		0·04	24·54		0·06
4-OCH_3	17·68	17·31	17·48	16·13	15·80	15·88	25·12	24·99	25·07
	17·55	17·39	0·17	15·70		0·22	25·14	25·10	0·10
4-Br	16·34	16·37	16·41	14·67	14·57	14·61	24·04	23·91	24·04
	16·38	16·55	0·09	14·59		0·05	24·14	24·07	0·10
4-F	16·57	16·63	16·67	15·04	14·88	14·96	24·12	24·09	24·19
	16·68	16·80	0·10	14·96		0·08	24·27	24·27	0·10
3-CF_3	16·09	16·11	16·01	14·13	14·21	14·27	23·56	23·58	23·53
	15·87	15·95	0·11	14·47		0·18	23·46		0·06
3-CN	15·68	15·57	15·70	13·95	14·09	14·07	23·15	23·13	23·23
	15·72	15·82	0·10	14·18		0·12	23·26	23·39	0·12

be explained by decreased ability of sulphonyl group to transmit electronic effects from the substituent to the reaction centre, as compared with this ability of carbonyl group. The solvent effect on the dissociation equilibrium as a whole is reflected in the pK^0_{HA} values of the Hammett relations. However, these values are affected by the working scales used which can be mutually somewhat shifted. In spite of this fact, Table III shows that, out of the aprotic dipolar solvents discussed, the dissociation into ions is greatest in dimethyl sulphoxide which can, in this respect, be compared with amphiprotic solvents, the lowest dissociation being observed in acetonitrile. Obviously, the proton stabilization plays decisive role in determining this order. The solvent effect on the dissociation equilibrium can be expressed quantitatively by means of the parameters suggested for description of solvent effects[21] due

TABLE II

Parameters of the Hammett relation for dissociation of substituted benzenesulphonamides in dimethylformamide (DMF), dimethyl sulphoxide (DMSO), and acetonitrile (AN) at 25°C

Solvent	pK^0_{HA}	$s(pK^0_{HA})$	ϱ	s_ϱ	r	n	s
DMF	17·00	0·02	−2·03	0·06	−0·979	58	0·143
DMSO	15·24	0·04	−1·91	0·10	−0·989	47	0·173
AN	24·52	0·02	−2·10	0·04	−0·988	57	0·113

TABLE III

The pK^0_{HA} and ϱ values of substituted benzenesulphonamides in various solvents obtained by three methods

Solvent	Hammett[b]		Equation (2)[b]		Factor. analysis[c]	
	pK^0_{HA}	ϱ	pK^0_{HA}	ϱ	pK^0_{HA}	ϱ
Water[a]	9·43	−0·96	9·45	−0·96	9·43	−0·96
Methanol[a]	14·39	−0·52	14·41	−0·51	14·39	−0·50
Ethanol[a]	15·77	−1·45	15·65	−1·37	15·75	−1·44
Dimethyl-formamide	17·00	−2·03	17·09	−2·09	17·02	−2·08
Dimethyl sulphoxide	15·24	−1·91	15·19	−1·87	15·26	−2·01
Acetonitrile	24·52	−2·10	24·51	−2·10	24·52	−2·14

[a] The data of ref.[1]; [b] calculated from the pK_{HA} values; [c] calculated from the $\overline{pK}_{HA}$.

to acidity (AP), basicity (BP), electrostatic effects (EP), and weak interactions (PP). If the calculation involves also the substituent by means of the σ constant and the respective interactions (σAP, σBP, σEP, σPP), then the description leads to linear regression of the 9th order. The treatment of the results of Table I along with the pK_{HA} values of benzenesulphonamides measured in amphiprotic solvents[1] gave the equation:

$$pK_{HA} = (27{\cdot}39 \pm 0{\cdot}05) - (4{\cdot}67 \pm 0{\cdot}04)\,AP - (19{\cdot}86 \pm 0{\cdot}08)\,BP - (18{\cdot}21 \pm 0{\cdot}20)\,EP - (4{\cdot}49 \pm 0{\cdot}15)\,\sigma - (0{\cdot}77 \pm 0{\cdot}11)\,\sigma AP + (1{\cdot}83 \pm 0{\cdot}20)\,\sigma BP + (7{\cdot}31 \pm 0{\cdot}56)\,\sigma EP + (3{\cdot}22 \pm 0{\cdot}14)\,\sigma PP\,, \qquad (2)$$

where $R = 0{\cdot}9996$, $s^2 = 0{\cdot}016$, $n = 296$, the term PP is statistically insignificant. Equation (2) enables both description of solvent effect on the dissociation itself and calculation of the reaction constants ϱ expressing the sensitivity to substituents. Table III shows that the calculated ϱ values are, in principle, identical with the results obtained from the Hammett equation. In addition to it, Eq. (2) makes it possible to evaluate solvent effect on the substituent sensitivity. As the parameter scale used is standardized and orthogonal, it is possible to deduce from Eq. (2) that the dominant effect is that on electrostatic stabilization of the conjugated base (the σEP term), the lesser roles being played by the weak interactions and solvent basicity (the σPP and σBP terms, respectively). All the effects mentioned will make themselves felt by lowering of sensitivity to substituents, because they have opposite sign to that of σ. Besides the ϱ constants also the pK^0_{HA} values can be determined from Eq. (2), and they also agree well with results of simple Hammett treatment (Table III). As it follows from Eq. (2), the dominant effect on the dissociation equilibria of benzenesulphonamides is that of basicity and electrostatic action of solvent which decrease the pK_{HA} values (negative sign) and, hence, shift equilibrium in favour of dissociation. This result supports the idea of and acid-base dissociation in which formation of hydrogen bonds with basic cantres of the solvent stabilizes the proton, and the ions formed simultaneously are stabilized by increased relative permittivity of the medium. Although the pK_{HA} values are expressed in relative working scales, the close correlation (expressed by the value of the coefficient R of multiple correlation) between pK_{HA} values and the parameters describing the solvents and obtained by the factor analysis from most varied types of measurements indicates connection between the individual working scales and, hence, possibility of comparison of the dissociation constants in different solvents.

Application of other parameters for description of solvent effects gives no such close correlations. So *e.g.* the dependence of pK_{HA} of the substituted benzenesulphonamides (at the same conditions as those used for Eq. (2)) on the parameters suggested by Palm and Koppel[22] is expressed by the equation:

$$pK_{HA} = (55{\cdot}20 \pm 1{\cdot}20) - (0{\cdot}89 \pm 0{\cdot}01)\,E - (0{\cdot}023 \pm 0{\cdot}002)\,B - \\ - (80{\cdot}3 \pm 5{\cdot}2)\,(n^2 - 1)/(n^2 + 1) + (0{\cdot}082 \pm 0{\cdot}025)\,\sigma E + \\ + (0{\cdot}0092 \pm 0{\cdot}0042)\,\sigma B - (14{\cdot}38 \pm 3{\cdot}76)\,\sigma(n^2 - 1)/(n^2 + 1)\,, \qquad (3)$$

where $R = 0{\cdot}9787$, $s^2 = 0{\cdot}920$, $n = 296$, and the statistically insignificant terms are $(\varepsilon - 1)/(2\varepsilon + 1)$, $\sigma(\varepsilon - 1)/(2\varepsilon + 1)$, and σ. The Eq. (3), in which E describes acidity of the solvent (in 10^1), B is basicity of the solvent (in 10^2), and n means refractive index (the magnitude of the fraction $(n^2 - 1)/(n^2 + 1)$ being in 10^{-1}), is not so easily interpreted as Eq. (2). At any rate it can be stated that the calculation showed insignificance of the term $(\varepsilon - 1)/(2\varepsilon + 1)$ which describes electrostatic action of the solvent, and this conclusion disagrees with results of Eq. (2). Of course, it is possible that the electrostatic action of solvent is included implicitely in some other parameter, because the used set of parameters is not orthogonal.

Description of the effects of medium on the dissociation of benzenesulphonamides by means of the parameters E_T suggested by Reichardt and Dimroth[23] gives unsatis-

TABLE IV

Target testing of the first two factors on the unity vector (the unity test) and the Hammett substituent constants

X	Prediction[a]	σ Test	Prediction of σ
H	1·0104	0·00	0·10
4-CH_3	0·9956	−0·14	−0·19
3-CH_3	0·9999	−0·06	−0·08
3,4-$(CH_3)_2$	0·9987	−0·20	−0·25
4-Cl	1·0000	0·22	0·26
3-Cl	1·0072	0·37	0·44
3,4-Cl_2	0·9990	0·59	0·56
4-NO_2	0·9865	0·81	0·60
3-NO_2	0·9901	0·71	0·61
3-OCH_3	0·9976	0·10	0·02
4-OCH_3	0·9939	−0·28	−0·31
4-Br	1·0077	0·22	0·35
4-F	1·0066	0·06	0·21
3-CF_3	1·0122	0·46	0·58
3-CN	0·9937	0·62	0·56

[a] The unity test.

factory results, because it does not reflect the solvent effect on the reaction constant, as it follows from the equation:

$$pK_{HA} = (39{\cdot}77 \pm 1{\cdot}40) - (0{\cdot}46 \pm 0{\cdot}03)\, E_T - (1{\cdot}58 \pm 0{\cdot}56)\, \sigma\,, \qquad (4)$$

where $R = 0{\cdot}708, s^2 = 10{\cdot}73$, $n = 206$, and the statistically insignificant term is σE_T.

The treatment of mean values $\overline{pK}_{HA}$ from Table I and the corresponding quantities given in the previous communication[1] for amphiprotic solvents by the factor analysis with addition of the missing positions by the short cycle method[24] provided two necessary factors for description of the source matrix of the experimental data. Using the method of target transformation[24], they were transformed by means of the unity vector and the vector of tabulated σ constants[20] into the vectors pK^0_{HA} and ϱ given in Table III. Comparison with other data in this Table shows a good agreement of the results of factor analysis with those obtained by other methods and thus confirms the correctness of the model used for interpretation of variability of the source matrix. From Table IV we can arrive at the same conclusion (the table summarizes comparisons between the testing and predicted values of the model parameters along the rows of the source matrix). A large difference between the tested and the predicted values can only be observed with the 4-nitro derivative, smaller discrepances are encountered with the 4-fluoro, 4-bromo, and 3-trifluoromethyl derivatives. The results found can be interpreted either by different behaviour of the individual substitution derivatives of benzenesulphonamide in the solvents used (probably the 4-nitro derivative, according to the large difference in the unity test), or by unsuitable testing substituent constant (4-fluoro and 3-trifluoromethyl).

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