DISSOCIATION OF SUBSTITUTED BENZENESULPHONAMIDES IN WATER, METHANOL AND ETHANOL

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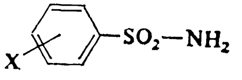
Thirteen monosubstituted arylsulphonamides ($XC_6H_4SO_2NH_2$) and two 3,4-disubstituted arylsulphonamides ($X_2C_6H_3SO_2NH_2$) have been synthetized and their dissociation constants have been measured by potentiometric titration in water, methanol, and ethanol. The Hammett substitution dependences have been calculated for all the media, and changes in the reaction constants due to transition from water to alcohols are discussed in confrontation with analogous dependences of benzoic acids. The reaction constant ϱ found in methanol is lower than that in water. The dissociation constants have been treated mathematically by the method of the principal components and by multiple linear regression.

Within the acid-base concept, the sulphonamides *I* represent N-acids. In this respect, literature provides data on their dissociation constants measured in water[1] and in 50% ethanol[2-4]. Values of these dissociation constants (for X = H it is $pK_A = 10{\cdot}00$ in water at 20°C, and $pK_A = 11{\cdot}34$ in 50% ethanol at 25°C) indicate low acidity of these substrates: they are weaker acids than the corresponding benzoic acids by 6 orders of magnitude (*cf.* benzoic acid, $pK_A = 4{\cdot}20$ in water at 25°C (ref.[6]) and $pK_A = 5{\cdot}72$ in 50% ethanol at 25°C (refs[7,8])) or even benzenesulphonic acid ($pK_A = 2{\cdot}55$ in water at 25°C (ref.[5])). On the contrary, sensitivity to the substituent effects is roughly the same in the two series as indicated by comparison of the reaction constants found for sulphonamides ($\varrho = 1{\cdot}06$ (ref.[1]), $\varrho = 0{\cdot}88$ (ref.[9]), water, 20°C; $\varrho = 1{\cdot}41 \pm 0{\cdot}04$ (refs[2,3]), $\varrho = 1{\cdot}45 \pm 0{\cdot}02$ (ref.[2]), 50% ethanol, 25°C) with those of benzoic acids ($\varrho = 1{\cdot}000$, water, 25°C; $\varrho = 1{\cdot}48$ (ref.[7]), $\varrho = 1{\cdot}52$ (ref.[8]), $\varrho = 1{\cdot}46$ (ref.[10]) 50% ethanol, 25°C).



I

The potentiometric method with glass indication electrode represents the most usual way for measurements of dissociation constants in aqueous-organic and selected organic solvents. This method was also used for the measurement of the dissociation constants of sulphonamides in water and in 50% ethanol which belong to amphiprotic polar solvents; methanol and ethanol, which were used by us, fall in the same category[11,12]. Dissociation of acids in these media can be described by the equation

$$\mathrm{HA} + \mathrm{SH} \rightleftharpoons \mathrm{SH}_2^+ + \mathrm{A}^- , \qquad (1)$$

where HA and SH represent acid and the respective solvent, resp. Salts of the acids are quantitatively dissociated in diluted solutions in amphiprotic solvents, and if a conventional or working pa_H scale is determined, then the Henderson–Hasselbalch equation also holds in these solvents

$$\mathrm{p}K_\mathrm{A} = \mathrm{p}a_\mathrm{H} - \log\left(a_{\mathrm{H}^-}/a_\mathrm{HA}\right), \qquad (2)$$

where $\mathrm{p}K_\mathrm{A}$ means negative logarithm of the dissociation constant of acid HA in the given solvent, $\mathrm{p}a_\mathrm{H}$ is the proton activity in the same solvent, and a_HA and a_A-stand for activities of the acid and its conjugated base, respectively. If the activities are expressed as products of molar concentrations and molar activity coefficients (from the Debye–Hückel equation[13]), then

$$\mathrm{p}a_\mathrm{H} = \mathrm{p}K_\mathrm{A} - \log\left([\mathrm{HA}]/[\mathrm{A}]\right) + \log \gamma . \qquad (3)$$

The last term of Eq. (*3*) can be neglected (at low concentrations of the components in the solvent) with respect to accuracy of the measurement, and Eq. (*3*) without the last term represents then the basis of the working $\mathrm{p}a_\mathrm{H}$ scale: it is used for determination of $\mathrm{p}K_\mathrm{A}$ of the acids measured with the help of standards with known $\mathrm{p}K_\mathrm{A}$ (*e.g.*, benzoic acid and its substitution derivatives) in the given solvent. The measurements of dissociation constants in aqueous–organic or purely organic solvents are complicated considerably by homoconjugation (association of the acid and its conjugated base). This phenomenon has not yet been described in literature for amphiprotic polar solvents, and we also did not consider it in our work.

The factor analysis[14,15] and the analysis of the principal components[14,15] (which make it possible to interpret the changes in pK, the reaction constant of the dissociation, and other quantities with changes in solvent) proved useful for evaluation of solvent effects on the dissociation equilibria.

The aim of our work was to measure the dissociation constants of the substituted benzenesulphonamides in water, methanol, and ethanol, and to interpret the results obtained from the point of view of solvent effects on the dissociation constants and sensitivity to substituents as compared with the reference benzoic acids which represent an example of well-studied O-acids.

EXPERIMENTAL

Preparation of the Substituted Benzenesulphonyl Chlorides

A1 (a modified procedure of ref.[16]): 65 ml chlorosulphuric acid was added drop by drop to 0·25 mol of the substituted benzene with cooling at 0°C (in the case of nitrobenzene the mixture had to be heated slightly, whereas anisole had to be dissolved in 100 ml chloroform, and the mixture was cooled at −10°C). When the evolution of hydrogen chloride ceased, the mixture was left to stand 2 h at room temperature, and then it was poured onto crushed ice. The separated solid was collected by suction (in the case of the 4-methoxy derivative, the chloroform layer formed after addition of ice was separated, and chloroform was evaporated) and used immediately for further preparations.

A2 (ref.[17]): Mixture of 0·25 mol substituted aniline and 85 ml concentrated hydrochloric acid was cooled to 0°C, and a solution of 20 g sodium nitrite in 40 ml water was added thereto drop by drop so that the temperature did not exceed 5°C. Cuprous chloride (7 g) was dissolved in 200 ml glacial acetic acid, and the solution was saturated with sulphur dioxide gas with cooling below 10°C for 2 h. Then the above diazonium salt solution was added, and the mixture was left to stand at room temperature 2 h. The excess sulphur dioxide was removed by bubbling air through the solution, and the product was extracted with benzene. The extract was shaken with 1 mol l^{-1} sodium hydrogen carbonate solution, then with water, dried with calcium chloride, and benzene was evaporated under reduced pressure.

Preparation of the Substituted Benzenesulphonamides

0·25 mol of the substituted benzenesulphonyl chloride was dissolved in the minimum amount of acetone, and the solution was added to 500 ml concentrated aqueous ammonia with stirring. The separated solid was collected by suction, and the filtrate was neutralized to obtain further portion of the product. In the case of the 4-fluoro derivative, the filtrate had to be concentrated, filtrated by suction, and the solid was extracted with acetone, whereafter the solvent was evaporated. The raw product was reprecipitated from its solution in sodium hydroxide by addition of hydrochloric acid, then it was dried and recrystallized. Purity of the derivatives prepared was checked by titration in dimethylformamide, in which solvent the titration curves were sufficiently developed. The determined purity was above 99% with all the compounds. Table I gives the preparation procedures, yields, and melting points.

Determination of the Dissociation Constants

Preparation of the titration reagent: solution of 0·1 mol l^{-1} tetrabutylammonium hydroxide in methanol was used.

B1: 3 g silver nitrate was dissolved in 5 ml water and treated with 5·5 ml 4 mol l^{-1} NaOH solution in carbonate-free water. The precipitate formed was washed with 75 ml boiling water and 30 ml methanol. Tetrabutylammonium bromide (3·5 g) was dissolved in 10 ml methanol, and the solution was cooled to −5°C. The air above the solution in the flask was removed by nitrogen gas, the hydrated silver oxide was added thereto, the flask was closed and left in cooling bath 1 h with intermittent shaking. Then the content of the flask was filled to 100 ml with methanol, and, after 15 min standing, the undissolved portions were removed by filtration through fine sintered glass filter.

TABLE I

The way of preparation and the physical constants of the studied substrates $XC_6H_4SO_2NH_2$ and $C_2C_6H_3SO_2NH_2$

X	Preparation of $ArSO_2Cl$ crystallization	Yield %	M.p., lit. m.p., exp., °C
H	A1 water, toluene	25	[a]150 —150·5 151 —152
4-CH_3	— ethanol–water, toluene	95	[a]135·5—136 136 —137
3-CH_3	A2 toluene	55	[b]108 108 —109
3,4-$(CH_3)_2$	A1 toluene	30	[a]143 —144 143·5—144
4-Cl	A1 ethanol–water, toluene	50	[c]142 —143 144 —145·5
3-Cl	A2 toluene	40	[b]148 147 —148
3,4-Cl_2	A1 toluene	45	[c]134 —135 134 —136
4-NO_2	A2 toluene	30	[b]180 179 —170
3-NO_2	A1 ethanol–water	30	[d]167 —168 165 —167
3-OCH_3	A2 toluene	45	[b]128 128·5—129
4-OCH_3	A1 benzene	25	[e]110 —111 110 —111
4-Br	A1 ethanol–water	40	[c]161·5 162 —163·5
4-F	A1 toluene	60	[c]124 —125 123·5—125
3-CF_3	A2 toluene	85	[f]121 —122·5 122 —122·5
3-CN	A2 ethanol–water	40	[g]151 —152 152 —154

[a] Ref.[22], [b] ref.[3], [c] ref.[16], [d] ref.[2], [e] ref.[23], [f] ref.[24], [g] ref.[25].

B2: A column of anion exchange resin was transferred to OH cycle by washing with 10% sodium hydroxide solution and then with methanol. Tetrabutylammonium bromide (3·5 g) was dissolved in 100 ml methanol, and the solution was left to flow slowly through the prepared ion exchange column.

Methods for purification of the solvents: Methanol and ethanol were purified by the Lund–Bjerrum method[12,18].

The potentiometric measurements: The potentiometric titration with 0·1 mol l^{-1} tetrabutylammonium hydroxide solution in methanol was carried out with an RTS-622 (Radiometer Copenhagen) apparatus. As the indication electrode we used a glass electrode which was freshly hydrated before the measurements in organic solvents and, between the measurements, kept in the given solvent. The saturated calomel electrode served as the reference electrode: it was filled with the saturated solutions of potassium chloride in methanol and lithium chloride in ethanol for the measurements in methanol and ethanol, respectively. The temperature was kept at 25 ± 0·1°C. The initial concentrations of the benzenesulphonamides were $5 \cdot 10^{-3}$ mol l^{-1}. The titration reagent was added by means of an automation burette ABU 12 at a rate of 1 μl s^{-1}, and argon was bubbled through the solution during the measurement. Each titration was repeated 3—4 times.

Calculation of the dissociation constants: On the basis of Eq. (*3*) and the non-substituted benzoic acid as the standard in the two non aqueous solvents we derived a working pa_H scale in the form of calibration straight line (dependence of pa_H *vs* voltage in mV of the cell glass electrode-S.C.E). For calculation of the calibration straight line we used 20 points of the linear section of titration curve of benzoic acid in the corresponding solvent and the pK_0 values (9·41 and 10·25 for methanol[6,19] and ethanol[6,20], resp.). The slope of the dependence obtained agreed with the theoretical value of 59 mV/pa_H with the accuracy of 2 mV/pa_H. The calibration was carried out twice a day. Using the calibration straight line and Eq. (*3*) we determined the pK_A value of a given sulphonamide as the arithmetic mean of the values obtained for 20 various readings of the titration reagent near the half-neutralization point. The titrations in water and methanol (and also ethanol — in the cases of electron-donor substituents) did not give well-developed titration curves for the substrates studied (titrations of weak acids in solvents with low autoprotolysis constant). In these cases we determined the equivalence point from the weighings.

Treatment of the results: For the repeated experiments the dissociation constants in the form of pK_A were averaged (the remote points being not involved in the calculation according to ref.[21]), and the standard deviation was calculated. For calculation of the Hammett equation in the individual solvents we used all the measured pK_A values and the σ constants from ref.[9], the averaged values were used as the input data for the treatment by the method of the principal components and the factor analysis.

RESULTS AND DISCUSSION

Table II gives the dissociation constants of the substituted benzenesulphonamides in water, methanol, and ethanol (in the form of p*K*) along with the standard deviations. The p*K* values in water agree well with the literature data[1,9]. Generally, the p*K* value increases (the acidity decreases) in the series water, methanol, ethanol, the most distinct difference being between water and the alcohols. This dependence can be easily quantified by means of four parameters suggested[26] for description of solvent effects: AP, BP, EP, and PP describing acidity, basicity, electrostatic

TABLE II

The dissociation constants of the sulphonamides $XC_6H_4SO_2NH_2$ and $X_2C_6H_3SO_2NH_2$

X	Water			Methanol			Ethanol		
	pK_A		$\overline{pK_A}$ s_{pK_A}	pK_A		$\overline{pK_A}$ s_{pK_A}	pK_A		$\overline{pK_A}$ s_{pK_A}
H	9·35	9·44	9·41	14·45	14·46	14·48	15·78	15·72	15·75
	9·43		0·05	14·52	14·50	0·03	—	—	0·04
4-CH_3	9·60	9·60	9·61	14·36	14·42	14·44	—	—	—
	9·65	9·60	0·03	14·54	—	0·09	—	—	—
3-CH_3	9·50	9·51	9·51	14·37	14·44	14·44	15·94	15·91	15·95
	9·51	9·52	0·01	14·42	14·53	0·07	15·01	—	0·05
3,4-$(CH_3)_2$	9·56	9·65	9·62	14·51	14·48	14·50	16·16	16·28	16·17
	9·60	9·68	0·05	—	—	0·02	16·07	—	0·1
4-Cl	9·23	9·23	9·23	14·22	14·29	14·27	15·37	15·28	15·33
	9·22	9·23	0·01	14·31	14·27	0·04	—	—	0·06
3-Cl	9·08	9·03	9·04	14·29	14·11	14·23	15·32	15·35	15·34
	9·03	9·02	0·03	14·29	—	0·1	—	—	0·02
3,4-Cl_2	8·93	8·94	8·94	14·06	14·14	14·12	14·97	14·83	14·89
	8·95	—	0·01	14·15	14·12	0·04	14·87	—	0·08
4-NO_2	8·56	8·60	8·63	13·86	13·90	13·92	14·62	14·68	14·68
	8·66	8·71	0·06	13·95	13·99	0·06	14·75	—	0·07
3-NO_2	—	—	—	13·98	13·95	13·98	14·75	14·69	14·68
	—	—	—	13·99	—	0·02	14·58	—	0·09
3-OCH_3	9·40	9·35	9·39	14·31	14·39	14·35	15·67	15·59	15·63
	9·40	9·40	0·03	—	—	0·35	—	—	0·06
4-OCH_3	9·68	9·64	9·65	14·40	14·51	14·47	16·01	15·98	16·05
	9·63	9·65	0·02	14·52	—	0·06	16·16	—	0·01
4-Br	—	—	—	14·31	14·21	14·27	15·46	15·32	15·39
	—	—	—	14·28	—	0·05	—	—	0·1
4-F	9·37	9·35	9·34	14·33	14·52	14·41	—	—	—
	9·32	9·33	0·02	14·42	14·36	0·08	—	—	—
3-CF_3	8·98	8·98	8·98	14·22	14·29	14·27	15·16	15·30	15·23
	8·98	8·99	0·01	14·31	14·27	0·04	—	—	0·1
3-CN	8·90	8·81	8·84	14·02	14·00	14·02	14·83	14·83	14·78
	8·82	8·84	0·04	14·01	14·04	0·02	14·68	—	0·09

action, and polarizability of the solvent, respectively. Moreover, if the calculation involves the substitution (described by the Hammett substituent constants σ) and the solvent effect on the reaction constant ϱ in the Hammett equation in the form of the products σAP, σBP, σEP, σPP, then the results of Table II can be expressed by linear regression of the 9th degree. When applied to the three solvents studied, the treatment showed (within experimental error) a linear dependence between the parameters BP and EP, the electrostatic action being decreased with increasing basicity when going from water to ethanol. So the two effect cannot be differentiated statistically, and, therefore, the linear regression of the 8th degree was calculated always excluding one of the mentioned two parameters. If the parameter BP was used, then the regression equation predicted an increase in pK with increasing basicity of solvent, which is physically meaningless. On the other hand, the application of the EP parameter indicates an increase in pK with decreasing ability of the solvent to stabilize electrostatically the ions formed. After exclusion of insignificant coefficients (by the Student t-test) and recalculation we get Eq. (*4*).

$$\begin{gathered} \mathrm{p}K_\mathrm{A} = (18{\cdot}72 \pm 0{\cdot}07) - (4{\cdot}04 \pm 0{\cdot}06)\,\mathrm{AP} - (4{\cdot}82 \pm 0{\cdot}29)\,\mathrm{EP} + \\ + (3{\cdot}77 \pm 0{\cdot}26)\,\sigma - (2{\cdot}50 \pm 0{\cdot}14)\,\sigma\mathrm{AP} - (16{\cdot}43 \pm 0{\cdot}89)\,\sigma\mathrm{BP} \qquad (4) \\ n = 134\,; \quad R = 0{\cdot}9996\,; \quad s^2 = 5{\cdot}90\,.\,10^{-3} \end{gathered}$$

As it is seen from the second and the third terms of Eq. (*4*) the solvent – besides electrostatic stabilization of the ions formed by the dissociation – suppresses this dissociation by transfer of its own protons to the conjugated base of the substrate. A similar change of the absolute magnitude of pK with a change in solvent can be found with the reference benzoic acids, although benzenesulphonamides and benzoic acids differ in acidity by about 5 orders of magnitude (for benzoic acid pK = 4·20 (water, 25°C) (ref.[6]), 9·41 (methanol, 25°C) (ref.[6,19]), 10·25 (ethanol, 25°C) (ref.[6,20]).

The linear regression between the pK values given in Table II and the Hammett substituent constants gives the equations which are summarized in Table III. The

TABLE III

The constants of the Hammett relation for dissociation of sulphonamides

Solvent	pK_0	$s_{\mathrm{p}K_0}$	ϱ	s	r	n	s
Water	9·43	0·01	−0·96	0·02	−0·989	50	0·048
Methanol	14·39	0·01	−0·52	0·04	−0·903	51	0·083
Ethanol	15·77	0·03	−1·45	0·05	−0·980	33	0·112

reaction constants ϱ do not show any unambiguous increase which is usually observed on going from water to organic solvents. This finding does not correspond to the results obtained for benzoic acids (ϱ = 1·00, water, 25°C, ϱ = 1·38 (ref.[27]), 1·36 (ref.[28]), 1·54 (ref.[29]), methanol. 25°C; ϱ = 1·67 (ref.[27]), 1·72 (ref.[28]), ethanol, 25°C). As the sensitivity to substituents in a given solvent is given by the ability of this solvent to stabilize the conjugated base of the substrate, the increase in the reaction constants ϱ along the solvent series methanol–water–ethanol (for benzenesulphonamides) and water–methanol–ethanol (for benzoic acids) is due to decreasing stabilization ability in the mentioned series of solvents. It can be expected that – out of the properties of solvents which affect the sensitivity to substitution – their accidities and basicities will make themselves felt preferably. The dominant effect is that of the basicity (the parameters normed), its increase being accompanied by increasing sensitivity to substituents. Basic solvents have affinity to the proton of the substrate, which results in higher localization of electrons in the conjugated base and, hence, in a higher sensitivity to substituents. If the sensitivity to substituents expressed by the reaction constant ϱ is compared for the benzenesulphonamides and benzoic acids in water and ethanol, then the benzenesulphonamides appear (in spite of their lower acidity) to be less sensitive to substituents, which is obviously due to better solvation

TABLE IV

The target testing of the first two main components on the unit vector and the Hammett substituent constants

X	Prediction[a]	Test	Prediction
H	1·011	0·00	0·14
4-CH_3	0·995	−0·14	−0·20
3-CH_3	0·999	−0·06	−0·12
3,4-$(CH_3)_2$	0·998	−0·20	−0·27
4-Cl	1·002	0·22	0·29
3-Cl	1·002	0·37	0·35
3,4-Cl_2	1·002	0·59	0·59
4-NO_2	0·993	0·81	0·70
3-NO_2	0·996	0·71	0·69
3-OCH_3	0·999	0·10	0·08
4-OCH_3	0·997	−0·28	−0·23
4-Br	0·995	0·22	0·20
4-F	1·006	0·06	0·13
3-CF_3	1·010	0·46	0·51
3-CN	0·995	0·62	0·61

[a] The testing vector contains all 1·000 values.

stabilization of the sulphonamide group as compared with the carboxylic group The different substitution sensitivity in methanol could be connected with its increased acidity and probably with different specific solvation of the two substrates.

The solvent effect on the dissociation constants was also studied by the factor analysis (or analysis of the principal components)[14,15,20]. Application of the method of the main components to the data of Table II and with the help of the IND critetion by Malinowski[14] and the 3-σ misfit-test for $\sigma = 0{\cdot}1$ (the maximum s_{pK} in Table II) gave the two necessary factors for interpretation of the variance of the source Table II. In accordance with ref.[14] we identified by the target testing the first factor with pK_0 and the second factor with the substitution sensitivity (ϱ) in the sense of Eq. (5).

$$pK^i = pK_0^i \,.\, 1 + \varrho^i\sigma\,, \quad i = H_2O,\ CH_3OH,\ C_2H_5OH\,, \tag{5}$$

where the first testing vector only contains 1's (the unity vector) and the second contains the Hammett substituent constants[9]. The calculation showed that the missing data in Table II affect considerably the results of the target testing, and, therefore, these missing data were complemented by target transformation[14] in four iteration steps, the starting data being assessed from the Hammett equations (Table III)

TABLE V

The target testing of the first main component of the data modified according to Eq. (6) on the Hammett substituent constants for incomplete and the completed data

X	Test	Prediction[a]	Prediction[b]
H	0·00	0·00	0·00
4-CH_3	−0·14	−0·05	−0·15
3-CH_3	−0·06	−0·12	−0·11
3,4-$(CH_3)_2$	−0·20	−0·26	−0·25
4-Cl	0·22	0·29	0·27
3-Cl	0·37	0·34	0·33
3,4-Cl_2	0·59	0·60	0·57
4-NO_2	0·81	0·82	0·78
3-NO_2	0·71	0·61	0·74
3-OCH_3	0·10	0·09	0·08
4-OCH_3	−0·28	−0·21	−0·20
4-Br	0·22	0·21	0·25
4-F	0·06	0·02	0·06
3-CF_3	0·46	0·40	0·39
3-CN	0·62	0·70	0·67

[a] The incomplete data, [b] the completed data, see the text.

for the individual solvents. The results of the target testing p_0 the last iteration are summarized in Table IV from which it is clear that the unit test is fulfilled excellently, whereas the test for the Hammett substituent constants predicts – for some substituents – different results from the testing values. The target transformation gave a matrix containing the vector pK_0 (water 9·43, methanol 14·39, ethanol 15·78) and the vector of the reaction constants ϱ (water −0·95, methanol −0·52, ethanol −1·46), the errors in the factor loadings 0·014 and 0·043 at the first and the second vectors, resp. These results show excellent agreement with those obtained by application of the Hammett equation to the individual solvents (Table III).

For a more accurate evaluation of the substitution alone, the data of Table II were modified according to Eq. (*6*)

$$\Delta pK = pK - pK_0 , \qquad (6)$$

pK_0 being taken from Table III (results of the target transformation can equally be used). The analysis of the principal components showed – as expected – one main component necessary for description of variance of the matrix ΔpK without interpretation of experimental errors. The calculation was carried out both for the data with missing values and for those with the complemented values in the same way as described above. Table V gives the results of the target testing for the two treatments. After the target transformation was carried out, the following ϱ values were obtained in the first case: water −0·76, methanol −0·53, ethanol −1·46, the error in the factor loadings 0·079, whereas with the use of the added data $\varrho = -0{\cdot}95$ (water), −0·53 (methanol), −1·46 (ethanol), the error in the factor loadings 0·032. Comparison of these results with those given for the target transformation of the original matrix and Table III shows mutual agreement in methanol and ethanol, whereas in water the results of the data treatment after modification according to Eq. (*6*) without addition of the missing data are different, though 2 values are missing as in the case of ethanol. The errors in the factor loadings are distinctly smaller with the completed matrices due probably partially to the fact that the completion is carried out by the target transformation on the same vectors (*e.g.* the substituent constants) as the final target testing. From the analysis carried out it is seen that the treatment of the incomplete matrices can (ethanol) but need not (water) lead to correct predictions or even interpretations.

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