CHEMOMETRIC ANALYSIS OF SUBSTITUENT EFFECTS. XI. SOLVENT EFFECTS ON DISSOCIATION OF 2,6-DISUBSTITUTED BENZOIC ACIDS

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Eleven symmetrically 2,6-disubstituted benzoic acids (with the following substituents: OCH_3, OC_2H_5, OC_3H_7, $OCH(CH_3)_2$, OC_4H_9, CH_3, F, Cl, Br, I, and NO_2) have been synthesized and their dissociation constants measured potentiometrically in methanol, ethanol, propan-1-ol, propan-2-ol, butan-2-ol, acetone, dimethyl sulfoxide, dimethylformamide, acetonitrile, pyridine, and 1,2-dichloroethane. The experimental data obtained have been analyzed from the point of view of solvent effects on acidity of the individual derivatives. Different behaviour found with benzoic acid and the disubstituted derivatives in protic solvents is due to changes in solvation. The different character of solvation of benzoic acid and the disubstituted derivatives depends on the type of substitution, being manifested only in 2,6-disubstituted benzoic acids. The graphical analysis has shown a distinct trend in the increase of magnitude of deviation of the point of benzoic acid in the series: propan-2-ol, butan-2-ol, propan-1-ol, ethanol, methanol. This order correlates with the steric demands of carbon chain of the alcohols used. The abnormal behaviour of benzoic acid in the dissociation in these alcohols as compared with that of its 2,6-disubstituted derivatives is due to the different extent of solvation of the reaction centre caused by steric hindrance. Against the expectation, benzoic acid appears to be a weaker acid in protic solvents, whereas its alkoxy derivatives are stronger acids. The solvation also minimizes the inductive effect of alkoxy groups in the symmetrically 2,6-disubstituted derivatives. In aprotic solvents the acidity of 2,6-dialkoxybenzoic acids is also increased, in this case as a result of sterically forced deviation of the reaction centre and/or the substituents out of the plane of benzene ring.
Key words: Substituent effects; *ortho* Effect; Solvation; Dissociation constants.

Our previous contributions dealt with the problem of *ortho* effect in the dissociation of monosubstituted[1] and disubstituted benzoic acids[2]. In the disubstituted acids we proved statistical insignificance of mutual interactions between the substituents and, hence, the additivity of substituent effects[2]. On the other hand, the interactions between solvents and the substituents turned out to be a significant factor. For this reason, the present paper is focused on the problem of solvent effects on the dissociation of symmetrically disubstituted benzoic acids. The symmetrically disubstituted derivatives were chosen to exclude the influence due different effects in *ortho* positions of the substituents present. The aim of the present communication is to give an integral self-contained set of pK_{HA} values of symmetrically 2,6-disubstituted benzoic acids (missing in the literature) and

subsequently to analyze the effects of the solvents used on the dissociation of selected derivatives.

The solvation of carboxylic and/or carboxylate group as a reaction centre belongs among the most significant effects affecting the acidity of the acids measured. Quantitatively the extent of solvation, and hence of stabilization of molecule, can be estimated from the magnitude of reaction constant in the Hammett relation: it is involved in this constant. The extent of solvation can absolutely be quantified *e.g.* by comparing the dissociation constants of substituted benzoic acids measured in organic solvents and in gas phase[3–5].

The proportion of stabilization of the base formed by substituents is generally lower in amphiprotic (protic) solvents (the ρ constant is near 1 for the dissociation of substituted benzoic acids), which is predominantly caused by efficient solvation of the conjugate base formed (neutral and protogenic solvents), or, as the case may be, by a better solvation of proton than that of the conjugate base (protophilic solvents). The stabilization of conjugate base of substituted derivatives is also aided by the solvation of substituents that can form hydrogen bonds[6]. A considerable role is played by the solvent in the solvation of substituted salicylic acids[7–11] and aminobenzoic acids[12]. Whereas in protic solvents the hydroxy groups present are significantly solvated, a formation of intramolecular hydrogen bond between OH (or NH_2) group and the reaction centre was observed in aprotic solvents[8,13]. The comparison of extent of solvation of benzoic acid derivatives by selected alcohols[14,15] and some aprotic solvents[8] is discussed in the papers quoted.

Aprotic solvents do not solvate well the conjugate base, which increases the effect of substituents on its stabilization (the ρ constant for dissociation of substituted benzoic acids[16] is greater than 2). In some cases, pyridine can form an exception[17], its conjugate acid being able to stabilize the anion formed. A low sensitivity to substitution was also observed in the dissociation of 2,6-disubstituted benzoic acids in little polar tetrahydrofuran[8]. The different affinity to the proton in protophilic and protophobic aprotic solvents has no substantial effect on the substitution sensitivity[18], which indicates a roughly identical extent of solvation of the proton being dissociated by protophilic and protophobic solvents. Hence the stabilization of conjugate base proceeds in similar ways in these two groups of aprotic solvents.

The inability of inert solvents to stabilize the charged particles formed in the dissociation of acids has the consequence of large effect of substituents on the stabilization of conjugate base manifested in a high value of the reaction constant in the Hammett equation. Rather surprising in this respect is 1,2-dichloroethane[17,19] in which the dissociation of substituted benzoic acids exhibits $\rho \approx 1.7$. This anomaly can probably be explained by the presence of a small amount of methanol, a distinctly more polar and protic solvent, in the nonpolar and inert 1,2-dichloroethane at the half-value of titration end point (the titration is carried out with methanolic tetrabutylammonium hydroxide).

EXPERIMENTAL

The symmetrically disubstituted benzoic acids containing the substituents OCH_3, OC_2H_5, OC_3H_7, $OCH(CH_3)_2$, OC_4H_9, CH_3, F, Cl, Br, I, and NO_2 were synthesized by known or partly modified procedures. 2,6-Dichlorobenzoic and 2,6-dimethylbenzoic acids were commercial products (Fluka). The identity of the acids was verified with the help of ^1H and ^{13}C NMR spectra and GC/MS. The purification methods after preliminary reprecipitation from the solution of the respective salt, the melting points and purity of the individual derivatives determined by HPLC are given in Table I.

Synthesis of 2,6-Diiodobenzoic Acid

A 500 ml three-necked flask equipped with a stirrer, separatory funnel and thermometer was charged with 2-amino-6-nitrobenzoic acid[20] (18.2 g, 0.1 mol), water (150 ml) and concentrated sulfuric acid (55 ml). The mixture was heated to 80 °C with stirring and then quickly cooled. The suspension formed was diazotized at 5 °C by adding a solution of sodium nitrite (6.9 g, 0.1 mol) in water (40 ml) within 30 min. After adding the last portion of the nitrite, the reaction mixture was stirred for another 60 min, whereafter the solution of diazonium salt was poured in a mixture of potassium iodide (31 g, 0.18 mol) and water (100 ml) during 10 min. The resulting mixture was boiled 1 h and then the excess iodide was removed by adding a small amount of dipotassium disulfite and the solution was cooled. The separated 2-iodo-6-nitrobenzoic acid was filtered off and recrystallized from water to give 22.4 g (76%) product melting at 184–189 °C (ref.[21] gives m.p. 188–189 °C).

TABLE I
Purification procedures, melting points and purity of the symmetrically 2,6-disubstituted benzoic acids used

Entry No.	Substituent	Purification procedure[a]	M.p., °C	M.p., ref.[21], °C	Purity[b], %
1	OCH_3[c]	W	187–189	188	100.0
2	OC_2H_5	E	130–132	132–134	98.9
3	OC_3H_7	F	55–59	54–56	98.6
4	$OCH(CH_3)_2$	C	104–106	107–108	99.0
5	OC_4H_9	P	81–84	82–84	98.2
6	CH_3[c]	W	115–116	115–116	100.0
7	F	W	157–158	157.5	99.1
8	Cl[c]	W	142–144	144	100.0
9	Br	T	145–148	150–151	97.7
10	I	S	184–187	–	99.6
11	NO_2[c]	W	201–202	202–203	97.3

[a] Recrystallization from: C tetrachloromethane, E aqueous ethanol, P petroleum ether, W water, T toluene, F flash chromatography (silica gel, petroleum ether–diethyl ether 4 : 1), S reprecipitation. [b] HPLC (Separon SGW C 18, 150 × 3 mm, 60% aqueous methanol, 1% phosphoric acid, flow rate 1 ml min^{-1}, detector setting at 230 nm). [c] Ref.[2].

2-Iodo-6-nitrobenzoic acid (1.5 g, 5 mmol) was dissolved in acetic acid (20 ml) and the solution was treated with tin(II) chloride (4 g, 21 mmol) and concentrated hydrochloric acid (5 ml). The mixture was stirred at 50 °C 1 h, cooled, and the precipitated yellow amino acid was collected by filtration, washed with acetic acid, and dried. Yield 0.8 g (59%) 2-amino-6-iodobenzoic acid, m.p. 175–177 °C (ref.[21] gives m.p. 162 °C).

2-Amino-6-iodobenzoic acid (2.5 g, 9.5 mmol) was dissolved in a mixture of hot water (15 ml) and concentrated sulfuric acid (11 ml), cooled, and diazotized by adding a solution of sodium nitrite (2.5 g, 36 mmol) in water (15 ml) at 5 °C until positive reaction of nitrous acid. The solution of diazonium salt was stirred 20 min, filtered, the filtrate was poured in a solution of potassium iodide (6.2 g, 37 mmol) in water (20 ml), and the mixture was heated at 75 °C 30 min. After removing the excess potassium iodide with disodium disulfite, cooling, and reprecipitation, the yield of 2,6-diiodobenzoic acid was 0.15 g (4%), m.p. 184–187 °C. For $C_7H_4I_2O_2$ (373.9) calculated: 22.47% C, 1.08% H; found: 22.77% C, 1.06% H.

Potentiometric Measurements

The potentiometric titration was carried out on a Radiometer set consisting of an automatic burette ABU 93, controlling element TIM 90, and stirrer SAM 90. The volume of solution analyzed was 2 ml. The titration reagent was added dynamically, depending on the change of electric potential. During the titration, the sample was thoroughly stirred and argon free of carbon dioxide and saturated with vapours of the corresponding solvent was bubbled through. The samples were titrated in random order, each acid being titrated three times. The calibration of electrode system using benzoic acid as the standard was carried out after every 3 measurements. The measuring system involved a glass electrode G 240 B (Radiometer) and a modified calomel electrode K 4040 (Radiometer), the modification consisting in replacement of the inner aqueous solution of potassium chloride by the saturated methanolic solution of potassium chloride. The glass electrode was hydrated in 0.1 M HCl 12 h before the measurements in the individual solvents. In the cases of strong dehydration of the membrane and slow response of the electrode and/or shortening of the potential jump, the electrode was hydrated in the same way for a shorter period also during the measurements. If not used in the measurements, the glass electrode was kept in an aqueous buffer of pH 7.00. The titrator was connected to a PC AT 386 computer and using an evaluation programme the signal obtained was transformed to values of electric potential E (mV) of the individual samples at the half-value of titration end point. The pK_{HA} values of the 2,6-disubstituted benzoic acids were calculated from the potential E values measured for the individual acids and the E_0 values of the respective standards using Eq. (*1*).

$$pK_{HA} = pK_0 + (E - E_0)/59.16 \qquad (1)$$

RESULTS AND DISCUSSION

The values of differences ΔpK_{HA} of symmetrically 2,6-disubstituted benzoic acids and parent benzoic acid together with their standard deviations s measured in methanol (MeOH), ethanol (EtOH), propan-1-ol (PrOH), propan-2-ol (iPrOH), butan-2-ol (sBuOH), acetone (Ac), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), acetonitrile (AN), pyridine (Py), and 1,2-dichloroethane (DCE) are presented in Table II (the known pK_{HA} values of benzoic acid: methanol[22] 9.41, ethanol[23] 10.25, propan-1-ol[24] 8.60, propan-2-ol 10.71, acetone[25] 18.20, dimethyl sulfoxide[26] 11.00, *N*,*N*-dimethylform-

TABLE II

Values of differences ΔpK_{HA} of symmetrically 2,6-disubstituted benzoic acids and parent benzoic acid along with their standard deviations *s* measured in methanol, ethanol, propan-1-ol, propan-2-ol, butan-2-ol, acetone, dimethyl sulfoxide, *N*,*N*-dimethylformamide, acetonitrile, pyridine, and 1,2-dichloroethane at 25 °C

Entry No.	Substituent	$\Delta pK_{HA}/s$										
		MeOH	EtOH	PrOH	iPrOH	sBuOH	Ac	DMSO	DMF	AN	Py	DCE
1	OCH_3[a]	–0.84	–0.41	–0.33	0.10	–0.19	0.45	0.29	0.45	0.17	0.50	–0.33
		0.02	0.02	0.04	0.05	0.08	0.03	0.05	0.04	0.02	0.08	0.02
2	OC_2H_5	–0.36	–0.22	–0.07	0.38	0.14	0.68	0.38	0.70	0.27	0.58	0.07
		0.05	0.02	0.02	0.01	0.08	0.08	0.05	0.05	0.02	0.02	0.05
3	OC_3H_7	–0.22	–0.06	0.09	0.72	0.24	0.78	0.52	0.65	0.38	0.77	0.18
		0.03	0.06	0.05	0.04	0.09	0.02	0.09	0.09	0.02	0.03	0.02
4	$OCH(CH_3)_2$	–0.28	0.09	0.28	0.90	0.59	0.86	0.50	0.68	0.47	0.79	0.35
		0.01	0.03	0.06	0.09	0.08	0.02	0.06	0.05	0.05	0.04	0.07
5	OC_4H_9	–0.28	–0.06	0.13	0.77	0.41	0.80	0.45	0.63	0.43	0.72	0.31
		0.05	0.03	0.05	0.04	0.08	0.04	0.05	0.09	0.02	0.05	0.02
6	CH_3[a]	–0.84	–0.83	–0.77	–0.39	–0.63	–0.46	–0.36	–0.31	–0.39	–0.22	–0.58
		0.02	0.06	0.05	0.08	0.08	0.02	0.02	0.03	0.01	0.05	0.04
7	F	–2.02	–2.03	–2.02	–1.78	–2.11	–2.17	–2.41	–2.36	–2.40	–2.03	–2.23
		0.08	0.07	0.05	0.07	0.04	0.05	0.07	0.09	0.08	0.05	0.06
8	Cl[a]	–2.15	–2.22	–2.26	–2.00	–2.16	–2.52	–2.69	–2.56	–2.54	–1.86	–2.58
		0.03	0.04	0.05	0.05	0.05	0.05	0.06	0.03	0.06	0.06	0.04
9	Br	–2.27	–2.32	–2.29	–2.10	–2.33	–2.31	–2.39	–2.55	–2.66	–2.03	–2.41
		0.09	0.06	0.04	0.09	0.06	0.04	0.05	0.08	0.09	0.04	0.02
10	I	–2.12	–2.03	–2.13	–1.53	–1.99	–1.86	–2.25	–2.14	–2.43	–1.52	–2.03
		0.09	0.04	0.02	0.06	0.06	0.06	0.09	0.06	0.04	0.00	0.02
11	NO_2[a]	–2.92	–3.10	–3.17	–3.12	–3.49	–3.92	–4.28	–4.01	–4.03	–2.90	–3.72
		0.05	0.09	0.04	0.06	0.02	0.09	0.02	0.05	0.05	0.09	0.03

[a] Values taken from ref.[2].

amide[27] 12.27, acetonitrile[28] 20.70, pyridine[18] 9.80, 1,2-dichloroethane[29] 20.00). The standard deviations of repeated measurements varied within the range usual for titrations in non-aqueous media, *i.e.* 0.1 pK_{HA} units.

Analysis of Solvation Effects by Means of Analysis of Variance

In order to analyze the effects of individual solvents on the substituent–solvent interaction we carried out the analysis of variance separately on the pK_{HA} set of symmetrically substituted 2,6-dialkoxybenzoic acids determined in protic solvents (MeOH, EtOH, PrOH, iPrOH, sBuOH) and on the pK_{HA} set of the same derivatives measured in aprotic media (Ac, DMSO, DMF, AN, Py, DCE). This is a situation involving two factors and interaction: the first factor is represented by the solvent and the second by the substituent. Before the calculation, the set was centered by subtracting the pK_{HA} value of benzoic acid from the pK_{HA} values of substituted derivatives. The decomposition of variability according to this model is given in Table III. The value of *F* criterion for substitution indicates an approximately twofold effect of substituents on the dissociation in alcohols as compared with that in aprotic solvents at comparable accuracy of the measurements (the aprotic solvents 0.050 pK_{HA} units, the protic solvents 0.053 pK_{HA} units). This higher sensitivity of dissociation to substituents in protic solvents is caused by different extent of specific solvation of the individual alkoxy groups by the alcohols used, which results in a changed magnitude of their inductive effect. The conclusion just stated is confirmed also by the increased value of *F* criterion for the solvent–substituent interaction in the pK_{HA} set of dialkoxy derivatives measured in alcohols as contrasted by the corresponding quantities obtained in aprotic medium,

TABLE III

The factors monitored (Sol solvent, Sub substitution), sums of squares *S*, degrees of freedom *n*, values of *F* criterion and critical values of Fisher–Snedecor distribution F_{crit} at the significance level $\alpha = 0.05$ in the model of analysis of variance with interactions (the pK_{HA} set of symmetrically substituted 2,6-dialkoxybenzoic acids)

Factors	Aprotic solvent				Protic solvent			
	S	*n*	*F*	F_{crit}	*S*	*n*	*F*	F_{crit}
Sol	3.97	5	318	2.37	7.42	4	658	2.56
Sub	1.42	4	144	2.53	3.22	4	286	2.56
Sol + Sub X	0.39	20	8	1.75	0.42	16	9	1.85
Residual	0.15	60			0.14	50		
Total	5.95	89			11.20	74		

which is statistically significant in both the cases. As the value of this factor is statistically significant also for the other derivatives[2], it can be stated that the solvent–substituent interaction plays a significant part in the dissociation of 2,6-disubstituted benzoic acids.

Analysis of Solvation Effects of Protic Solvents

In order to find out the effects of the selected solvents on the behaviour of individual derivatives of benzoic acid in the dissociation, we analyzed the experimental data graphically. When plotting the values of differences of dissociation constants of symmetrically 2,6-disubstituted benzoic acids and parent benzoic acid in aprotic solvents (Ac, DMSO, DMF, AN, Py, DCE) against the corresponding quantities in methanol (Fig. 1) we can see a deviation of the point belonging to the parent benzoic acid (solid circles) from the expected linear dependence. As this is the substance used for the standardization of the pK_{HA} values of all the other derivatives measured, the result mentioned cannot be due to a gross experimental error. Since methanol differs in its properties from aprotic solvents, it can be presumed that the deviation of the point of benzoic acid is caused by this very solvent. For confirmation of this thesis we plotted

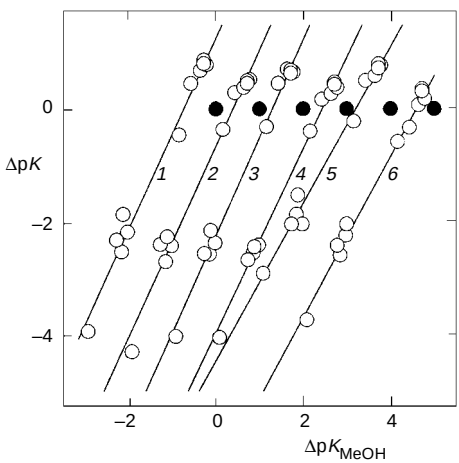

FIG. 1
Dependences of ΔpK_{HA} values of 2,6-disubstituted benzoic acids in aprotic solvents (straight lines: *1* Ac, *2* DMSO, *3* DMF, *4* AN, *5* Py, *6* DCE) on ΔpK_{HA} in methanol; solid circles denote ΔpK_{HA} of benzoic acid (to be better seen the individual straight lines are shifted by one pK_{HA} unit to the right)

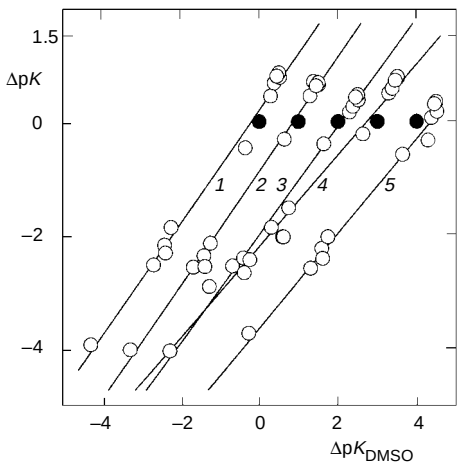

FIG. 2
Dependences of ΔpK_{HA} values of 2,6-disubstituted benzoic acids in aprotic solvents (straight lines: *1* Ac, *2* DMF, *3* AN, *4* Py, *5* DCE) on ΔpK_{HA} in dimethyl sulfoxide; solid circles denote ΔpK_{HA} of benzoic acid (to be better seen the individual straight lines are shifted by one pK_{HA} unit to the right)

in mutual dependences the ΔpK_{HA} values of 2,6-disubstituted benzoic acids measured only in aprotic solvents. In contrast to the above-mentioned results concerning methanol, no deviation of the point for disubstitution of 2-H, 6-H takes place. A clear example is the dependences of ΔpK_{HA} of 2,6-disubstituted benzoic acids in aprotic solvents on the same quantities in dimethyl sulfoxide given in Fig. 2. Thus the presumption of specific effect of methanol as a protic solvent on the behaviour of the individual derivatives was unambiguously confirmed.

For finding out the effect of substitution on the different character of solvation of the 2,6-disubstituted derivatives and unsubstituted benzoic acid in methanol we analyzed the data for 3,4- (ref.[16]) and 3,5-disubstituted benzoic acids[19] in a similar way to that used for the 2,6-disubstituted benzoic acids (the derivatives with combinations of the substituents CH_3, OCH_3, Cl, NO_2 (ref.[2])). As it can be seen from the dependences of ΔpK_{HA} of these derivatives in dimethyl sulfoxide on the same quantities in methanol (Fig. 3, dependences *1* and *2*), no deviation can be observed for the unsubstituted benzoic acid in contrast to the 2,6-derivatives (Fig. 3, dependence *3*). This fact agrees with the findings by Chantooni and Kolthoff[15] concerning an analogous behaviour of benzoic acid in the dissociation and of some of its 3,4- and 3,5-disubstituted derivatives. Hence it can be stated that the different character of solvation of benzoic acid and its disubstituted derivatives depends on the type of substituents, being only manifested in the 2,6-disubstituted benzoic acids.

For a more detailed investigation of character of solvation of the diad reaction centre–substituent in protic solvents, the set of dissociation constants of symmetrically 2,6-disubstituted benzoic acids in the above-mentioned solvents was completed by the measurements in ethanol, propan-1-ol, butan-2-ol, and propan-2-ol. By plotting the differences ΔpK_{HA} of 2,6-disubstituted benzoic acids and parent benzoic acid in acetonitrile on the analogous quantities in alcohols we obtained the dependences depicted in

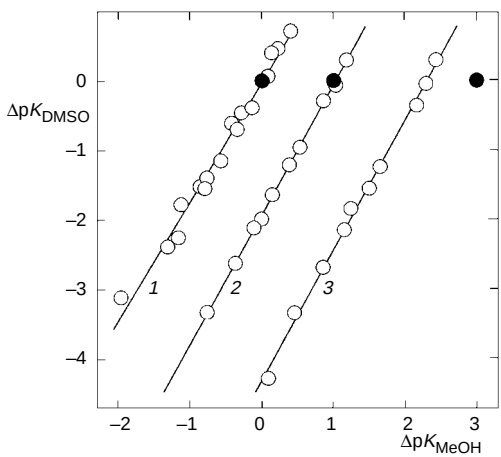

FIG. 3
Dependences of ΔpK_{HA} values of disubstituted benzoic acids (straight lines: *1* 3,4-disubstituted, *2* 3,5-disubstituted, *3* 2,6-disubstituted) in dimethyl sulfoxide on ΔpK_{HA} of these derivatives in methanol; solid circles denote ΔpK_{HA} of benzoic acid (to be better seen the individual straight lines are shifted by one or two pK_{HA} units to the right)

Fig. 4 (the regression straight lines were only calculated for the substituents unable of formation of intramolecular hydrogen bond). Practically identical dependences were obtained by plotting the ΔpK_{HA} obtained also in the remaining aprotic solvents against the respective quantities in alcohols. From Fig. 4 we can see a clear trend in the magnitude of deviation of the point of benzoic acid in the series: propan-2-ol, butan-2-ol, propan-1-ol, ethanol, methanol. This order correlates with the steric demands of carbon chain of the alcohols used. On the basis of the given correlation it can be claimed that the abnormal behaviour of benzoic acid in dissociation in these alcohols is due to the different extent of solvation of its reaction centre and the reaction centres of disubstituted derivatives, which is a consequence of the steric hindrance to the approach of solvent forced by the substituents present. Due to this phenomenon, propan-2-ol (as contrasted with the other alcohols) shows the least specific solvation and its effect on the acids measured is similar to that of the aprotic solvents. The fact described is also confirmed by the value of differences of the classical residua e_K of benzoic acid from the regression straight lines in the above-mentioned dependences (Table IV). The regression straight lines were only calculated for the substituents unable of forming an intramolecular hydrogen bond. Whereas the greatest deviation value is observed for the measurement in methanol, the deviation for the measurement in propan-2-ol can be neglected with regard to the accuracy of measurement (0.05 pK_{HA} units). The lower values of deviations of benzoic acid from the regression straight line obtained for 1,2-dichloroethane are caused by the application of methanolic solution of titration agent in the potentiometric determination of the dissociation constants in this solvent[17].

It is surprising to find that benzoic acid turns out to be a weaker acid than expected, whereas their alkoxy derivatives appear to be stronger acids. A probable explanation of this artefact is a deviation of COO^- group out of the plane of benzene ring which is connected with a more intense solvation. Another possible explanation can be a forma-

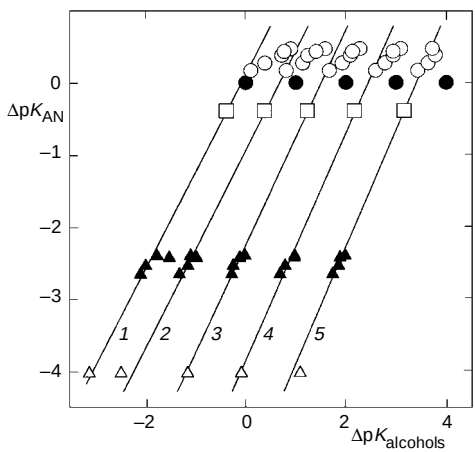

FIG. 4
Dependences of ΔpK_{HA} values of symmetrically 2,6-disubstituted benzoic acids in acetonitrile on ΔpK_{HA} values of these derivatives in alcohols (straight lines: *1* propan-2-ol, *2* butan-2-ol, *3* propan-1-ol, *4* ethanol, *5* methanol), ● benzoic acid, ❍ 2,6-dialkoxybenzoic acids, ❒ 2,6-dimethylbenzoic acid, ▲ 2,6-dihalogenobenzoic acids, Δ 2,6-dinitrobenzoic acid (to be better seen the individual straight lines are shifted by one pK_{HA} unit to the right)

tion of intramolecular hydrogen bond between hydrogen atom of alcohol and oxygen atom of alkoxy group. This could make the alkoxy group a weaker electron donor as compared with hydrogen substituent, and the subsequent increase in stabilization of conjugate base leads to increased acidity of the respective dialkoxy derivative.

Differences in the extent of solvation and their influence on substituent effects are also indicated by the arrangement of points of dialkoxy derivatives in Fig. 4. In methanol the solvation suppresses the manifestations of inductive effect of individual alkoxy groups to such an extent that the difference in acidities of individual derivatives is slight (the points lie at the regression straight line). A quite opposite situation is encountered with propan-2-ol, where the solvation is restricted to the minimum by steric interactions between the substituents and carbon chain of the alcohol with concomitant more distinct manifestation of inductive effect of alkyls in alkoxyl groups (deviation of points from the regression straight line). For the remaning alcohols the positions of points of alkoxy derivatives is a resultant of operation of both effect. These results are confirmed by the conclusions about the effects of protic solvents on the properties of alkoxy groups made on the basis of analysis of variance.

Analysis of Solvent Effects of Aprotic Solvents

The above discussion about dialkoxy derivatives concerns the behaviour of these acids in protic solvents. On the other hand, the behaviour of the same derivatives in aprotic media is indicated by the arrangement of the points in the coordinate axis. Against expectations, the alkoxy derivatives do not appear much weaker acids than benzoic acid despite the positive mesomeric effect of their alkoxy groups. From this fact it can be concluded that the reaction centre (carboxylic group) and/or the substituents are steri-

TABLE IV
Classical residuals e_K for benzoic acid and mean values of this characteristic $\bar{e}_K$ in the dependences of ΔpK_{HA} in aprotic solvents on the corresponding values in alcohols

Alcohol	e_K						$\bar{e}_K$
	Ac	DMSO	DMF	AN	Py	DCE	
MeOH	0.60	0.65	0.67	0.60	0.75	0.48	0.63
EtOH	0.54	0.62	0.63	0.57	0.71	0.43	0.58
PrOH	0.49	0.55	0.58	0.50	0.67	0.36	0.53
sBuOH	0.31	0.40	0.41	0.34	0.48	0.18	0.35
iPrOH	0.02	0.14	0.16	0.10	0.21	–0.10	0.09

cally forced out of the plane of benzene ring[14,30]. Hence the effect mentioned does not influence the stability of conjugate base by mesomeric effect of substituent[5], *i.e.* no decrease in acidity of the derivatives discussed occurs in our case. An analogous effect can be observed when comparing the pK_{HA} values of 2-methoxybenzoic acid[1] and the sterically demanding 2,6-dimethoxy derivatives in the aprotic solvents mentioned. With the same values for the standard, the 2,6-disubstituted derivative appears in dimethyl sulfoxide (pK_{HA} of the 2-substituted and 2,6-disubstituted derivatives are 11.21 and 11.29, respectively), *N*,*N*-dimethylformamide (12.66, 12.72), and pyridine (10.10, 10.30) to be an only slightly weaker acid than the monosubstituted derivative. In acetone (18.94, 18.65), acetonitrile (21.24, 20.87), and 1,2-dichloroethane (20.77, 19.67) 2,6-dimethoxybenzoic acid becomes even more acidic than the monosubstituted derivative. From the facts given follows such a dominant role of steric effect of methoxy groups in the 2,6-disubstituted derivative in aprotic medium that the influence of mesomeric effect on the reaction centre is minimized.

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