Ortho EFFECT IN DISSOCIATION OF BENZOIC ACIDS WITH ELECTRON-ACCCEPTOR SUBSTITUENTS USING THE AISE THEORY; RELATION TO *Para* SUBSTITUTION AND SOLVENT

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Received April 2, 2002
Accepted May 16, 2002

Potentiometric titration at 25 °C has been used to measure the dissociation constants of 2- and 4-substituted benzoic acids with electron-acceptor substituents in methanol, *N*,*N*-dimethylformamide, acetonitrile, and acetone. But for a few exceptions, no significant differences have been found between the dissociation constants measured and those given in literature. Using the measured pK_a values, those of 3-substituted derivatives taken from literature (measured in the same solvents) and those of 3- and 4-substituted derivatives measured in water, the so far missing substituent constants σ^i of NO and CH_3SO substituents have been determined by Alternative Interpretation of Substituent Effects (AISE). The previously published relationships and the σ^i constants have been used to calculate the σ_m and σ_p constants for the given substituents and compare them with literature. The agreement was the better, the more reliable the corresponding Hammett substituent constant was. Using a non-linear regression model, we have analysed the structure of matrix of pK_a values of ten 2-X-benzoic acids (X is electron-acceptor substituent) measured in the given organic solvents and in water. It has been found that in non-aqueous solvents the conjugate base of benzoic acid is stabilised by intramolecular hydrogen bond if X is COOH and SO_2NH_2 or electrostatic force if X is CH_3SO. On the other hand, in water the carboxylate group is out of the plane of the benzene ring due to interaction between the solvated reaction centre and substituent, this being the case with all the substituents except for X = CHO, CH_3CO, NO, and CN. In all the solvents used, intramolecular ring closure takes place between the carboxylate group and substituent X = CH_3CO, CHO, and NO, this phenomenon being the most important in water.

Keywords: Dissociation constants; Benzoic acid; *Ortho* effect; Latent variable; Chemometrics; Substituent effects; AISE.

The AISE theory[1,2] (Alternative Interpretation of Substituent Effects), which has been used in the present communication, is based on the idea that a substituent possesses a single characteristic described by σ^i constant, and this is transmitted to the reaction centre in three different ways depending on the interaction type in the triad reaction centre–basic skeleton–

doi:10.1135/cccc20020596

substituent. For interpretation it is essential whether or not the substituent contains π electrons at the atom connecting it to the basic skeleton. If not, then the substituent belongs to group *I* and operates only through its basic effect described by the substituent constant σ^i. In principle, this effect is identical with the inductive effect. The substituent of group *II* has a lone electron pair on the atom connecting it to the basic skeleton, which roughly corresponds to a combination of *I* and +*M* effects. These substituents are internal nucleophiles, and their characteristics are again described by the single substituent constant σ^i. The last group, *III*, which is dealt with in the present study, includes internal electrophiles having a multiple polarized bond between the first and the second atom (counting from the atom bonded to the basic skeleton, second atom is more electronegative)[3]. This effect roughly corresponds to a combination of *I* and –*M* effects. Group *III* includes substituents such as RCO, COOH, COOR, $CONR^1R^2$, CN, NO, NO_2, RSO, RSO_2, $SO_2NR^1R^2$ and the like. The substituents NO and RSO also carry a free electron pair at the first atom, hence they could be also considered substituents of group *II*. However, the free electron pair is orthogonal to the multiple bond, and any conformation enabling involvement of the multiple bond in conjugation is more favourable than that enabling conjugation with the free electron pair; hence these substituents behave as group *III* substituents. Evaluation of substituent effects using AISE results in finding the point of intersection and the slopes of a family of three lines describing the dependence of the quantity measured with substituent constant σ^i for the three types of substitution.

A common feature of group *III* substituents is that they are polar and, at the same time, the differences between their substituent constants are small. If they are connected to the basic skeleton near the reaction centre (*e.g.* in *ortho* position in the benzene ring), then there an intramolecular interaction with this centre often arises. The polarity of these substituents results in their increased solvation in polar and protic solvents and, consequently, in a change of the influence of the substituent on the reaction centre (see ref.[4] and references therein). We have shown in one of our papers[5] that steric effects between the reaction centre and *ortho* substituent in an isolated molecule are generally overestimated: in reality these are interactions between their solvation spheres. If the solvation is only weak, then steric interactions from *ortho* position are mostly negligible unless the substituent is exceptionally bulky even without solvation (*e.g.* $–C(CH_3)_3$). A sterically enforced deviation of carboxyl group out of the aromatic ring plane leads to an acidity increase of the respective carboxylic acid due to the loss of conjugation between the carbonyl group and aromatic system and, hence, the loss of cross-conjugation.

As a consequence of differences between individual substituent constants of group *III* substituents the correlations show not only an inaccurate determination of substituent constants but also other anomalies, which can thus be detected and analysed. The most significant intramolecular interaction between a substituent and a nearby reaction centre on the basic skeleton is the formation of hydrogen bond[6–9] and steric interaction due to solvation spheres[5]. In certain combinations of chemical structures of the reaction centre and substituent, a chemical bond can be formed with concomitant ring closure[10–13]. In addition, all the intramolecular interactions mentioned are affected by solvent effects[14,15], which we consider an essential but, unfortunately, often neglected fact.

Benzoic acids traditionally are a standard (even though not the most appropriate) chemical model for quantitative evaluation of substituent effects, and their dissociation reactions are standard chemical processes measured on this model. Consequently, detailed knowledge of the nature of effects of individual substituents on the reaction centre is essential, particularly if the substituent is in such a specific position as the *ortho* position in the benzene ring is (for a review, see, *e.g.*, refs[6–8]). Any analysis and interpretation of potential interactions between the substituent and reaction centre in benzoic acids carrying electron-acceptor substituents in *ortho* position can make use of a comparison with the effect of the same substituent in *para* position and of various manifestations of the above-mentioned effects operating in dissociations in solvents of different types. Undoubtedly, water is an exceptional solvent[16]; however, the largest number of dissociation constants were measured just in water. Other frequently used solvents are mixtures of water with organic solvents, and the smallest body of data is that including measurements in media of individual non-aqueous solvents. Table I gives a survey of literature dissociation constants (pK_a) of benzoic acids with selected electron-acceptor substituents in position 2 and 4 measured in water and organic solvents. From the table it is evident, that water really is the most frequent solvent, the nitro group being the most frequent substituent. Avoiding “problematic” electron-acceptor substituents is logical but, as a consequence, there are few pieces of information for any reliable description of their properties. Clearly, exceptions[24] also exist.

Analyses of underlying factors of substituent effects use *inter alia* methods with latent variables (*e.g.*, see refs[6,40]): most often the principal component analysis and less frequently other methods. The principal component analysis[41] is one of the basic methods of analysis of experimental data in chemistry. However, its application to this purpose is associated with two problems. The first problem follows from the matrix definition of current algorithms (*e.g.*, iterative algorithm NIPALS for PCA; see ref.[41]) for calculation of latent variables. Therefore, there must be no elements absent from

TABLE I
pK_a values of substituted benzoic acids with selected electron-acceptor substituents X in water (W), methanol (MeOH), *N*,*N*-dimethylformamide (DMF), acetonitrile (AN) and acetone (Me_2CO) from literature

X	pK_a(2-X)	pK_a(4-X)
CHO	4.55[a](W)	3.69[b](W), 3.75[c](W), 3.77[d](W), 6.43[e](MeOH)
CH_3CO	4.13[f](W), 4.13[g](W)	3.74[b](W), 3.72[c](W), 3.70[g](W), 3.74[h](W), 8.72[i](MeOH), 8.75[h](MeOH), 11.40[h](DMF), 19.69[h](AN), 17.28[h](Me_2CO)
COOH	2.95[j](W), 7.70[k](MeOH), 8.37[k](DMF), 15.82[k](AN), 14.33[k](Me_2CO)	3.47[l](W), 8.25[h](MeOH), 11.21[h](DMF)
$COOCH_3$	3.18[m](W), 8.57[m](MeOH), 8.47[k](MeOH), 11.41[k](DMF), 19.95[k](AN), 20.00[m](AN), 17.39[k](Me_2CO)	3.74[h](W), 8.75[h](MeOH), 8.82[m](MeOH), 11.40[k](DMF), 19.69[h](AN), 19.70[m](AN), 17.28[h](Me_2CO)
CN	3.08[n](W), 3.10[i](W)	3.53[b](W), 3.51[o](W), 3.50[h](W), 8.34[i](MeOH), 8.36[h](MeOH), 10.77[h](DMF), 19.23[h](AN), 16.74[h](Me_2CO)
NO		3.27[p](W)
NO_2	2.17[g](W), 2.20[q](W), 2.17[r](W), 2.14[s](W), 7.58[k](MeOH), 9.90[t](DMF), 9.92[k](DMF), 18.16[k](AN), 15.91[k](Me_2CO)	3.43[b](W), 3.43[g](W), 3.46[q](W), 3.45[v](W), 3.40[h](W), 8.30[v](MeOH), 8.30[w](MeOH), 8.23[h](MeOH), 10.60[t](DMF), 10.58[h](DMF), 18.70[v](AN), 18.95[h](AN), 16.43[h](Me_2CO)
CH_3SO	3.10[x](W)	3.66[x](W)
CH_3SO_2	2.53[x](W)	3.52[y](W), 3.48[h](W), 8.37[i](MeOH), 8.36[h](MeOH), 10.84[h](DMF), 19.24[h](AN), 16.82[h](Me_2CO)
SO_2NH_2	2.68[z](W), 7.82[k](MeOH), 9.33[k](DMF), 17.73[k](AN), 15.44[k](Me_2CO)	3.52[z](W), 3.63[h](W), 8.49[i](MeOH), 8.55[h](MeOH), 11.28[h](DMF), 19.56[h](AN), 16.90[h](Me_2CO)

References: [a] 17, [b] 18, [c] 19, [d] 20, [e] 21, [f] 11, [g] 22, [h] 23, [i] 24, [j] 25, [k] 6, [l] 26, [m] 27, [n] 28, [o] 29, [p] 30, [q] 31, [r] 32, [s] 33, [t] 34, [v] 35, [w] 36, [x] 37, [y] 38, [z] 39.

the matrix of analysed data (the matrix of manifest variables). This requirement is considerably restrictive, but it can be circumvented using a procedure suggested by Exner[42], which can be also applied to incompletely filled matrices. The other problem follows from the current practice of exploratory analysis consisting in isolation of a valid number of latent variables and subsequent mathematical operations with them. The analysis of substituent effects based on the methods with latent variables is based on the presumption that the latent variables calculated describe the basic effects of substituents and can be physico-chemically interpreted in this way. This need not generally be the case: sometimes this is true only after certain subsequent mathematical operations, sometimes the postulated basic effects cannot be isolated at all. The approach given does not make it possible to isolate latent variables in a given structure *a priori* (similar to confirmatory procedures in factor analysis[43]) and thus to verify the accordance between the physico-chemical model suggested and the experimental data. No suitable procedures for modelling patterned structure of the matrix of latent variables have been suggested or applied so far.

The aim of this paper is to provide the missing experimental values of dissociation constants in non-aqueous organic solvents, to determine the missing substituent constants of some electron-acceptor substituents in terms of AISE, and to interpret the underlying factors of potential intramolecular interaction in dissociation of 2-substituted benzoic acids with selected electron-acceptor substituents.

THEORETICAL

In the first part of this paper we have mentioned some problems associated with application of the methods with latent variables to evaluation and interpretation of substituent effects, particularly with regard to the physico-chemical meaning of the latent variables obtained. This problem can be solved using the ModLaV (Modelling of Latent Variables) algorithm suggested by us. Its name reflects the possibility of real modelling the structure of the matrix of latent variables (score matrix) on the basis of physico-chemical hypotheses. It is also possible to test the validity of these hypotheses and to select the most appropriate one. The algorithm suggested can use the following quantities as latent variables: the regression latent variables given by the vectors of explaining variables (the same as in linear regression), the classic latent variables calculated according to PCA algorithms, or combined latent variables. The last type of latent variables is the most versatile in the ModLaV algorithm and makes it possible to set in advance the values of chosen elements of the latent variable vector, to completely exclude chosen elements of the latent variable vector from calculation or, on the other hand, to add the values of missing elements of the latent variable vector containing a part of explaining variables. The basis of calculation by the ModLaV algorithm is the iterative NIPALS algorithm modified by Exner[42]. Before the calculation it is necessary to determine the number of latent variables and create the structure of matrix of latent variables (score matrix). The structure of the latent matrix is given by the required values of elements and by the symbols determining whether or not a given element should be calculated or excluded from the calculation. In each iteration of the calculation, the element of latent variable is either calculated or corrected according to the pattern structure. In the cases of regression and combined latent variables, both the origin and the scale are given by explaining variables, whereas the values of classic latent variable are normalised into the interval of $\langle 0,1 \rangle$. The statistical characteristics of decomposition are identical with those obtained from the PCA method[41].

EXPERIMENTAL AND CALCULATIONS

Synthesis of 2- or 4-Substituted Benzoic Acids

The synthesis of model substances were carried out by known or modified procedures – 4-acetylbenzoic acid[44], 2-methoxycarbonylbenzoic acid[45], 4-methoxycarbonylbenzoic acid[46], 2-cyanobenzoic acid[47], 2-nitrosobenzoic acid[48], 4-nitrosobenzoic acid[49], 2- and 4-methylsulfinylbenzoic acid[50], 2- and 4-methylsulfonylbenzoic acid[51]. Unknown 4-(*N*,*N*-dimethylaminocarbonyl)benzoic acid was synthesised by modification of Braun and Kaiser method[52] in 64% yield. It was identified by ^{1}H NMR (360 MHz, DMSO-d_6) δ: 2.88 (s, 3 H), 3.00 (s, 3 H), 7.51 (d, J = 8.0 Hz, 2 H), 7.99 (d, J = 8.0 Hz, 2 H); and by elemental analysis, calculated: 62.17% C, 5.74% H, 7.25% N; found: 62.19% C, 5.68% H, 7.30% N (m.p. 169–172 °C). Derivatives with substitutions 2-CHO, 4-CHO, 2-CH_3CO, 4-CN, 2-NO_2 and 4-NO_2 were commercial chemicals.

Measurements of Dissociation Constants

Purification of the used solvents, potentiometric titration, and evaluations of dissociation constants were described in our previous papers[53]. The measurements were carried out at 25 °C and repeated three times with each compound.

Mathematical-Statistical Treatment of Data

The data were processed using our own program involving moduli for variance analysis, linear and non-linear regressions, analysis of latent variables by PCA algorithm[42], CDA algorithm[54], and the above-described ModLaV algorithm. The data were always standardised before the calculation of latent variables.

RESULTS AND DISCUSSION

pK_a *Values and Comparison with Literature*

The values of measured dissociation constants (as pK_a) of 2- and 4-substituted benzoic acids in water, methanol, *N*,*N*-dimethylformamide, acetonitrile, and acetone are presented in Table II along with other values taken from literature. The residual standard deviation from repeated measurements of pK_a calculated by the analysis of variance with two factors (substituent, solvent) was 0.060 units. The difference between the values found by us and those taken from literature (Tables I and II) is unambiguously the largest with the pK_a values of 4-formylbenzoic acid in methanol (2.51 units), and the value is obviously a mistake. The other fairly significant differences between the pK_a values given in literature and those obtained by us (substituents 2-NO_2, 4-NO_2, 4-CH_3CO, 2-$COOCH_3$, 4-$COOCH_3$ in acetonitrile, 4-CN, 4-NO_2 in *N*,*N*-dimethylformamide, and 4-NO_2, 4-CH_3SO_2 in methanol) are not considered fundamental in measurements of dissociation constants in organic solvents. The application of literature data for pK_a in the calcula-

TABLE II
pK_a values of 2- and 4-X-substituted benzoic acids measured in water (W), methanol (MeOH), *N*,*N*-dimethylformamide (DMF), acetonitrile (AN) and acetone (Me_2CO) at 25 °C

X	pK_a(2-X)					pK_a(4-X)				
	W	MeOH	DMF	AN	Me_2CO	W	MeOH	DMF	AN	Me_2CO
CHO	4.50	9.19	11.21	20.38	17.39	3.72[a]	8.94	11.19	19.74	17.10
CH_3CO	4.13[a]	9.28	11.68	20.51	17.67	3.73[a]	8.84	11.38	19.95	17.32
COOH	2.95[a]	7.70[a]	8.37[a]	15.82[a]	14.33[a]	3.47[a]	8.25[a]	11.21[a]	–	–
$COOCH_3$	3.18[a]	8.47	11.33	19.78	17.34	3.74[a]	8.84	11.45	19.91	17.37
$CON(CH_3)_2$	–	–	–	–	–	–	9.00	11.83	20.55	17.83
CN	3.10[a]	8.15	10.37	19.07	16.65	3.51[a]	8.49	11.02	19.34	16.69
NO	3.64	7.89	10.54	19.57	16.88	3.27[a]	8.40	10.98	19.25	17.76
NO_2	2.17[a]	7.59	9.96	18.54	15.98	3.43[a]	8.36	10.80	19.08	16.42
CH_3SO	3.10[a]	7.94	10.04	18.74	15.95	3.66[a]	8.77	11.41	19.79	17.17
CH_3SO_2	2.53[a]	7.87	10.31	18.89	16.42	3.50[a]	8.49	10.99	19.28	16.66
SO_2NH_2	2.68[a]	7.82[a]	9.33[a]	17.73[a]	15.44[a]	3.58[a]	8.52[a]	11.28[a]	19.56[a]	16.90[a]

[a] Table I.

tions of latent variables always led to lower values of the explained variability of data, hence our results are more consistent from the viewpoint of the purposes of this communication.

Verification of AISE Principle and Determination of σ^i Constants. Comparison with Hammett Substituent Constants

In terms of AISE, the selected substituents belong to group *III* of the so-called internal electrophiles. In connection with previous parametrisation[1,3], the σ^i values of all the substituents of this type given in Table II were determined except for $CON(CH_3)_2$, NO and CH_3SO substituents. In order to determine the missing σ^i values, we applied the ModLaV algorithm to the matrix of manifest variables formed by the pK_a values of 4-substituted derivatives from Table II complemented by the pK_a values of 3-substituted derivatives taken from literature[23] measured in the same solvents and the values of 3- and 4-substituted derivatives measured in water[25]. Three latent variables were used as explaining variables in the score matrix. The first latent variable was a combined one and involved σ^i values taken from literature[1,3], the remaining two latent variables was classic latent variables. Substituent $CON(CH_3)_2$ was excluded from further calculation for missing experimental data in any solvents. The calculation provided a decomposition in which the first latent variable explained 91.99% of variability of the matrix of manifest variables, the second explained 4.97% (96.96% if cumulated), and the third 2.22% (99.18% if cumulated). The addition of the second and third variable is statistically nonsignificant[54] ($F(19,20) = 2.07$, $F_{0.95}(19,20) = 2.14$; $F(19,1) = 0.72$, $F_{0.95}(19,1) = 247.69$). The analysis of score matrix showed significant differences between the experimental and predicted pK_a values of 4-formyl- and 4-acetylbenzoic acids in water and particularly in methanol (pK_a was higher than expected), whereas no anomalies were found in the other solvents. Repeated measurements confirmed the pK_a values originally measured in methanol, hence the differences are not one to experimental error. From what has been said it follows that in these solvents there obviously proceeds base-catalysed formation of hydrate and/or hemiacetal, and thus a substantial change in the quality of a substituent takes place. Also the derived Hammett substituent constants should be assessed with respect to the above-mentioned fact, as pointed out by Shorter in a critical compilation[26]. Therefore, the pK_a values of 4-formyl- and 4-acetylbenzoic acids in water and methanol were excluded from the matrix of manifest variables, and the calculation was repeated with two latent variables. It was found that after this modification the first latent variable explains 93.91% and the second 3.76% (97.67% if cumulated) of variability of the matrix of manifest variables. The addition of the second latent variable is statistically insignificant in this case ($F(19,20) = 1.69$, $F_{0.95}(19,20) = 2.14$). Hence the variability of data is described by a single latent variable which represents the substituent effect without any solvent effects. The calculated σ^i constants obtained by the ModLaV algorithm are: $\sigma^i(NO) = 0.578$ and $\sigma^i(CH_3SO) = 0.326$. The existence of a single statistically significant latent variable formed predominantly by the previously determined[1,3] substituent constants σ^i confirms their correctness as well as the validity of the AISE principle for the substituent type studied.

In a previous paper[55] we analysed the Hammett substituent constants by AISE. Using the relationships given there and the newly determined substituent constants σ^i, we calculated the following values of the Hammett substituent constants: $\sigma_m(NO) = 0.68$ (0.49, ref.[56]; 0.62, ref.[57]), $\sigma_p(NO) = 0.67$ (0.65, ref.[56]; 0.91, ref.[57]), $\sigma_m(CH_3SO) = 0.38$ (0.50, ref.[58]; 0.52, ref.[57]), $\sigma_p(CH_3SO) = 0.38$ (0.48, ref.[58]; 0.49, ref.[57]). Thus the predicted values of the Hammett substituent constants neither fully agree with, nor substantially contradict, the literature data, and a good agreement can be stated for the more reliable Hammett substituent constants.

Description of Ortho Effect and Separation of Individual Effects

Analysis of the underlying factors of the *ortho* effect in the dissociation of 2-substituted benzoic acids was based on the pK_a values given in Table II. The analysis started from the presumption that manifestations of potential intramolecular interactions between substituent and reaction centre is different in individual solvents[5,6] and manifests itself in a number of latent variables higher than 1. This presumption proved to be justified. The PCA method provided three statistically significant latent variables. The addition of the second latent variable is statistically significant[58] ($F(15,15) = 3.96$, $F_{0.95}(15,15) = 2.40$), the addition of the third latent variable cannot be tested statistically due to the insufficient number of degrees of freedom. The first latent variable has explained 83.88% and the second 12.88% (96.76% if cumulated) of the variability of the source data. Therefrom it can be inferred that the dissociation of benzoic acids containing electron-acceptor substituents is affected by three different substituent effects associated with the solvent change. Similar results were also obtained by the method of conjugated deviations (CDA), the statistical significance of values of loadings here indicating a division of the solvents used into aprotic (DMF, AN, Me_2CO) and protic (W, MeOH).

A comparison of pK_a values of *ortho* and *para* substituted derivatives shows interesting differences in the values of dissociation constants. Benzoic acids containing substituents such as $COOCH_3$, CN, NO_2, CH_3SO, and SO_2NH_2 in *ortho* position are – irrespective of solvent – more acidic than the benzoic acids having the same substituents in *para* position. Quite the opposite is true of the benzoic acids containing CHO and CH_3CO substituents, and the behaviour of NO substituted benzoic acids depends on the solvent. There are two possible reasons for the enhanced acidity of *ortho* substituted benzoic acids compared with the *para* counterparts. The first is associated with the –*I* effect, which weakly operates from *para* position. The other reason is the sterically enforced deviation of carboxylic group out of the plane of aromatic ring, which is associated with an acidity increase of the respective benzoic acid due to loss of conjugation between carbonyl group and aromatic ring and, consequently, loss of cross-conjugation. Hence, the electron delocalisation in carboxylate group becomes more important in the stabilisation of reaction centre. Thus, *e.g.*, the pK_a value of 2-*tert*-butylbenzoic acid is lower than that of the *para* isomer by 0.78 units in water, whereas the corresponding difference is 0.48 in 95% aqueous dimethyl sulfoxide[37]. The acidity lowering of *ortho* substituted benzoic acids compared with the *para* isomers having the CHO, CH_3CO, and obviously also NO substituents is probably due to intramolecular ring closure, which was described for the first two substituents mentioned[10,13].

A more detailed picture of substituent effect in *ortho* substituted benzoic acids can be obtained from the dependence of logarithm of dissociation constant on substituent constants σ^i. This dependence found in dimethylformamide is given in Fig. 1 (the dependences for acetonitrile and for acetone are practically identical), and that found in water is given in Fig. 2 (the dependence for methanol is analogous). From Fig. 1 it is obvious at first sight that substituents COOH, $SOCH_3$, and SO_2NH_2 are exceptional in their distinct acidity-enhancing effect and substituents CHO, CH_3O and NO create own class (see below). The reason obviously lies in the formation of intramolecular hydrogen bond between the acid hydrogen of the substituent and carboxylate group, which results in stabilisation of the latter. This effect has already been observed in benzoic acids[6–8]. A potential change in the group undergoing dissociation in the case of SO_2NH_2 substituent ($COOH \rightarrow SO_2NH_2$) is not likely because sulfonamides are several pK_a units less acidic[59,60]. The CH_3SO group probably stabilize carboxylate anion by electrostatic force between oxygen and positive charged sulfur. The stabilisation of carboxylate anion by intramolecular hydrogen bond or by electrostatic interaction is negligible compared with the solvation stabilisation by water molecules; however, the same is not true of methanol, as shown in Fig. 1. On the other hand, Fig. 2 shows different effects of CHO, CH_3CO and NO substituents, which manifest themselves much less in aprotic solvents. The different behaviour observed is obviously due to ring closure with carboxylate anion group, which was described earlier for the first two substituents[10–13] and is probable for last substituent[61].

CN group holds a special position among the substituents studied. With regard to its shape, size, and potential way of solvation, this substituent

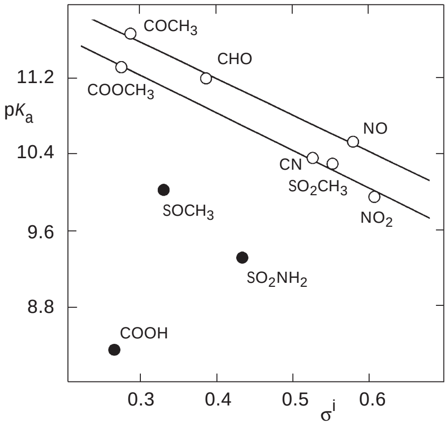

FIG. 1
Dependence of pK_a values of 2-X-benzoic acids in dimethylformamide at 25 °C on substituent constants σ^i

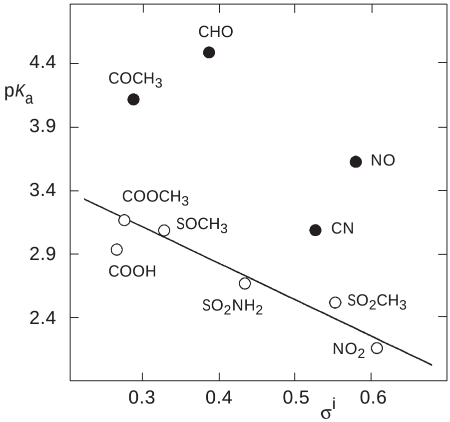

FIG. 2
Dependence of pK_a values of 2-X-benzoic acids in water at 25 °C on substituent constants σ^i

does not much affect the *ortho*-standing carboxylic or carboxylate group in any of the solvents used. From comparison of the different location of pK_a values of the cyano derivative in Figs 1 and 2 it follows that substituents $COOCH_3$, CN, NO_2, and CH_3SO_2, and obviously also CHO, CH_3CO, and NO in aprotic solvents do not show strong steric interactions. Planar substituents may be twisted from the plane of the benzene ring and decreased by it steric hindrance. The reason is that the solvation of carboxylate anion is rather weak in these solvents, and, therefore, the steric interactions with *ortho*-standing substituents are small. A similar result was obtained with 2-alkoxybenzoic acids[5]. On the other hand, a considerable solvation of carboxylate anion in water causes a sterically enforced deviation of carboxylate group associated with better resonance stabilisation and higher acidity of the respective acid. This effect can be observed with all rather bulky substituents.

The authors are indebted to the Ministry of Education, Youth and Sports of the Czech Republic for financial support (research project CIMSM 253 100001).

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