REPARAMETRIZATION AND/OR DETERMINATION OF HAMMETT, INDUCTIVE, MESOMERIC AND AISE SUBSTITUENT CONSTANTS FOR FIVE SUBSTITUENTS: $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$ AND $PO(OCH_3)_2$

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This work is dedicated to Professor Otto Exner on the occasion of his 80th birthday.

Ten *meta*- and *para*-substituted benzoic acids with substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$ and $PO(OCH_3)_2$ were synthesized. Dissociation constants of these acids were determined in five solvents (water, ethanol, methanol, *N*,*N*-dimethylformamide, dimethyl sulfoxide) at 25 °C. Dissociation constants of benzoic acid derivatives with other substituents H, CH_3, $NHCOCH_3$, OCH_3, F, Cl, Br, I, $COCH_3$, CN, NO_2, SO_2CH_3 were taken from the literature (calibration set). Substituent constants σ_m, σ_p, σ_I, σ_R, and σ^i for substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$, and $PO(OCH_3)_2$ were calculated by nonlinear and PLS (partial least-square method with latent variables) calibration in three correlation models using the calibration set. Nonlinear regression appears more suitable and more universal than PLS calibration. The advantage of nonlinear regression is its independence on possibly missing data in the given solvent, evaluation of precision (standard deviation), the accessibility of necessary software, and easy calculation. However, in contrast to PLS calibration, this procedure fails in calculation of substituent constants with description of properties of substituents (substituent constants σ_I, σ_R). The obtained values of substituent constants are in good agreement with those published in the literature.

Keywords: Dissociation constants; Benzoic acid; Substituent effects; Hammett equation; AISE; Quaternary ammonium salts; Sulfones; Phosphonates.

Substituent effects are still the subject of investigation as well as a necessary tool for study of mechanisms of organic reactions. In recent decades, original Hammett concept[1,2] was extended and completed by further approa-

ches based on the principle of similarity (e.g. lit.[3–11]). Correct evaluation of substituent constants describing properties of substituents is the basic requirement for application of these approaches. Old but so far important methods are based on critical compilation[12–14] of values obtained from experimental data; recently also a theoretical approach has been used[15–21]. Published values of substituent constants of basic substituents should be considered to be valid. On the other hand, this is not the case of other substituents[12–14]. The reason for this discrepancy is a small number of experiments and specificity of models or experimental conditions used for determination of substituent constants (e.g. solvent). The evaluation of experimental data is another important factor. It is suitable to apply methods using large sets of experimental data obtained under different conditions. This procedure allows extraction of the effect of a substituent as the only general factor[3,10,11] thus providing more precise quantitative determination of substituent constants. Unreliable values of substituent constants can cause incorrect interpretation of substituent effects on chemical processes.

This work is focused on determination or verification of the values of substituent constants σ_m, σ_p, σ_I, σ_R, and σ^i (see lit.[10,11]) for substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$, and $PO(OCH_3)_2$. This series represents less common substituents with interesting properties. $PO(OCH_3)_2$ is phosphorus analog of alkoxycarbonyl group. Substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, and $CH_2SO_2CH_3$ have no π electrons at the connecting atom and they could extend class of substituents with only inductive effect on reaction center. Number of substituents from this class with known substituent constants is still limited on alkyl or trifluoromethyl groups. In our case, we have met the problem of missing substituent constants of above mentioned substituents or their inaccuracy during studies of mechanism and substituent effect in the case of cleavage of alkanoates by oximes[22]. Oxime group represents after deprotonation powerful nucleophile readily attacking the ester function[23,24]; pyridinium oximes (e.g. 2-(hydroxyiminomethyl)-1-methylpyridinium iodide – 2-PAM) are used and studied as reactivators of phosphorylated acetylcholinesterase poisoned by organophosphorus inhibitors[23,25] or agents for hydrolysis of toxic organophosphates and phosphonates[26,27]. In the presented series, substituent constants σ_m, σ_p, σ_I, σ_R for substituents $N^+(CH_3)_3$, $CH_2\ N^+(CH_3)_3$, and $PO(OCH_3)_2$ (lit.[12–14] and references cited therein, lit.[28–30]) are known. The values for CH_2Py^+ and $CH_2SO_2CH_3$ and those of substituent constants σ^i for all the above-mentioned substituents have not been published. The second purpose of this work is verification of applicability of mathematic and statistic methods based on nonlinear regression (NLR) and PLS calibration[31]

(PLSC) for adjustment of substituent constants from large sets of experimental data.

EXPERIMENTAL

Temperature data were not corrected. TLC analyses were carried out on a Kieselgel 60 F_{254} (Merck Laboratory Chemicals). Column chromatography was performed on a Kieselgel 60 H (Merck Laboratory Chemicals). ^{1}H NMR spectra were recorded on a Varian Gemini 300 at 300.08 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard, coupling constants (*J*) are given in Hz. Elemental analyses (C, H, N) were performed on a Perkin–Elmer 240 analyser.

Chemicals

3-Methylbenzoic acid, 4-(bromomethyl)benzoic acid, methyl 3-methylbenzoate, methyl 4-(bromomethyl)benzoate, ethyl 3-bromobenzoate, ethyl 4-iodobenzoate, and dibenzoyl peroxide were obtained from Aldrich, sodium methanethiolate, *N*-bromosuccinimide, 4-(dimethylamino)benzoic acid, 3-(dimethylamino)benzoic acid, methyl iodide, anhydrous nickel chloride, and trimethyl phosphite were obtained from Fluka.

3-(Bromomethyl)benzoic acid (**1**). 3-Methylbenzoic acid (10 g, 73.4 mmol), *N*-bromosuccinimide (13 g, 73.4 mmol) and dibenzoyl peroxide (1.78 g, 7.3 mmol) were dissolved in 200 ml anhydrous tetrachloromethane. The reaction mixture was refluxed for 5 h, cooled and the remaining succinimide was filtered off. The solvent was evaporated and the crude product was purified by crystallization. Yield 6.85 g (63%), m.p. 150–154 °C (CCl_4) (lit.[32] 154–155 °C). ^{1}H NMR (DMSO-d_6): 4.77 s, 2 H (CH_2Br); 7.49 dd, 1 H, *J*(5,6) = *J*(5,4) = 7.7 (H-5); 7.68 d, 1 H, *J*(4,5) = 7.4 (H-4); 7.86 d, 1 H, *J*(6,5) = 7.7 (H-6); 8.01 s, 1 H (H-2).

General Procedure for Preparation of **2a** and **2b**

Compound **1** (2 g, 9.3 mmol) or 4-(bromomethyl)benzoic acid (2 g, 9.3 mmol) was dissolved in 50 ml of saturated solution of trimethylamine in acetone. The reaction mixture was stirred at ambient temperature for 1 h. Precipitated crystals were filtered off and purified by crystallization.

(3-Carboxybenzyl)trimethylammonium bromide (**2a**). Yield 1.42 g (56%), m.p. 216–218 °C (methanol–ether). For $C_{11}H_{16}BrNO_2 \cdot H_2O$ (292.2) calculated: 45.22% C, 6.21% H, 27.35% Br, 4.79% N; found: 44.98% C, 6.36% H, 27.18% Br, 4.76% N. ^{1}H NMR (DMSO-d_6): 3.07 s, 9 H ($N^+(CH_3)_3$); 4.69 s, 2 H (CH_2N^+); 7.62 dd, 1 H, *J*(5,4) = *J*(5,6) = 7.7 (H-5); 7.79 d, 1 H, *J*(4,5) = 6.6 (H-6); 8.05 d, 1 H, *J*(6,5) = 7.7 (H-4); 8.09 s, 1 H (H-2).

(4-Carboxybenzyl)trimethylammonium bromide (**2b**). Yield 1.61 g (63%), m.p. 242–246 °C (methanol–ether). For $C_{11}H_{16}BrNO_2 \cdot 0.5H_2O$ (291.2) calculated: 45.38% C, 5.89% H, 27.44% Br, 4.81% N; found: 45.10% C, 6.13% H, 27.28% Br, 4.85% N. ^{1}H NMR (DMSO-d_6): 3.06 s, 9 H ($N^+(CH_3)_3$)); 4.66 s, 2 H (CH_2N^+); 7.66 d, 2 H, *J*(2,3) = *J*(6,5) = 7.9 (H-2, H-6); 8.01 d, 2 H, *J*(3,2) = *J*(5,6) = 8.3 (H-3, H-5).

General Procedure for Preparation of **3a** and **3b** (lit.[33])

Compound **1** (2 g, 9.3 mmol) or 4-(bromomethyl)benzoic acid (2 g, 9.3 mmol) and pyridine (4 g, 25.3 mmol) were dissolved in 50 ml acetone. The reaction mixture was stirred at ambient temperature for 1 h, precipitated crystals were filtered off and purified by crystallization.

N-(3-Carboxybenzyl)pyridinium bromide (**3a**). Yield 0.61 g (56%), m.p. 172–173 °C (ethanol). For $C_{13}H_{12}BrNO_2$ (294.2) calculated: 53.08% C, 4.11% H, 27.16% Br, 4.76% N; found: 52.94% C, 4.17% H, 27.29% Br, 4.60% N. ^{1}H NMR (DMSO-d_6): 6.05 s, 2 H (CH_2N^+); 7.55 dd, 1 H, *J*(5,6) = *J*(5,4) = 7.6 (H-5); 7.85 d, 1 H, *J*(6,5) = 7.3 (H-6); 7.94 d, 1 H, *J*(4,5) = 7.6 (H-4); 8.13 s, 1 H (H-2); 8.20 dd, 2 H, *J*(5′,6′) = *J*(3′,2′) = 6.9 (H-3′, H-5′); 8.66 dd, 1 H, *J*(4′,5′) = *J*(4′,3′) = 7.4 (H-4′); 9.36 d, 2 H, *J*(6′,5′) = *J*(2′,3′) = 5.6 (H-2′, H-6′).

N-(4-Carboxybenzyl)pyridinium bromide (**3b**). Yield 0.85 g (68%), m.p. 254–258 °C (ethanol) (lit.[27] 258 °C). ^{1}H NMR (DMSO-d_6): 6.02 s, 2 H (CH_2N^+); 7.63 d, 2 H, *J*(2,3) = *J*(6,5) = 8.3 (H-2, H-6); 7.95 d, 2 H, *J*(3,2) = *J*(5,6) = 8.3 (H-3, H-5); 8.20 dd, 2 H, *J*(5′,6′) = *J*(3′,2′) = 6.6 (H-3′, H-5′); 8.65 dd, 1 H, *J*(4′,5′) = *J*(4′,3′) = 7.7 (H-4′); 9.29 d, 2 H, *J*(6′,5′) = *J*(3′,2′) = 5.8 (H-2′, H-6′).

General Procedure for Preparation of **4a** and **4b** (lit.[34])

4-(Dimethylamino)benzoic acid (3 g, 18 mmol) or 3-(dimethylamino)benzoic acid (3 g, 18 mmol) and methyl iodide (7.66 g, 54 mmol) were dissolved in 50 ml of methanol and refluxed for 16 h. The solvent was evaporated and the crude product was purified by crystallization.

(3-Carboxyphenyl)trimethylammonium iodide (**4a**). Yield 3.05 g (55%), m.p. 188–192 °C (ethanol) (lit.[34] 258 °C). For $C_{10}H_{14}INO_2$ (307.1) calculated: 39.11% C, 4.59% H, 41.32% I, 4.56% N; found: 39.36% C, 4.51% H, 41.27% I, 4.46% N. ^{1}H NMR (DMSO-d_6): 3.64 s, 9 H ($N^+(CH_3)_3$); 7.75 dd, 1 H, *J*(5,6) = *J*(5,4) = 7.9 (H-5); 8.08 d, 1 H, *J*(4,5) = 7.7 (H-4); 8.25 d, 1 H, *J*(6,5) = 8.5 (H-6); 8.36 s, 1 H (H-2).

(4-Carboxyphenyl)trimethylammonium iodide (**4b**). Yield 1.95 g (35%), m.p. 212–215 °C (ethanol) (lit.[35] 238 °C). For $C_{10}H_{14}INO_2$ (307.1) calculated: 39.11% C, 4.59% H, 41.32% I, 4.56% N; found: 39.12% C, 4.80% H, 41.43% I, 4.41% N. ^{1}H NMR (DMSO-d_6): 4.64 s, 9 H ($N^+(CH_3)_3$); 7.79 d, 2 H, *J*(3,2) = *J*(5,6) = 9.1 (H-3, H-5); 8.01 d, 2 H, *J*(2,3) = *J*(6,5) = 9.1 (H-2, H-6).

Methyl 3-(Bromomethyl)benzoate (**5**) (lit.[36])

Methyl 3-methylbenzoate (12 g, 79.9 mmol), *N*-bromosuccinimide (14.22 g, 79.9 mmol) and dibenzoyl peroxide (1.78 g, 7.3 mmol) were dissolved in 200 ml dried tetrachloromethane. The reaction mixture was refluxed for 5 h, cooled and the remaining succinimide was filtered off. The solvent was evaporated and the crude product was purified by distillation under reduced pressure. Yield 10.2 g (56%), b.p.104 °C/27 Pa–106 °C/27 Pa (lit.[37] 98 °C/27 Pa–102 °C/27 Pa) ^{1}H NMR ($CDCl_3$): 3.92 s, 3 H (OCH_3); 4.52 s, 2 H (CH_2Br); 7.42 dd, 1 H, *J*(5,6) = *J*(5,4) = 7.7 (H-5); 7.59 d, 1 H, *J*(4,5) = 7.7 (H-4); 7.95 d, 1 H, *J*(6,5) = 7.7 (H-6); 8.06 s, 1 H (H-2).

General Procedure for Preparation of **6a** and **6b** (lit.[38])

To a solution of sodium methanethiolate (1.8 g, 25 mmol) in 50 ml of dried DMF cooled to 0 °C, compound **5** (5.5 g, 24 mmol) or methyl 4-(bromomethyl)benzoate (5.5 g, 24 mmol) was added and the reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was poured into 250 ml of water and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with water (2 × 100 ml) and dried with anhydrous magnesium sulfate. The solvent was evaporated and the crude product was purified by distillation under reduced pressure.

Methyl 3-[(methylsulfanyl)methyl]benzoate (**6a**). Yield 2.05 g (44%), b.p. 98 °C/119 Pa–100 °C/119 Pa. For $C_{10}H_{12}O_2S$ (196.1) calculated: 61.20% C, 6.16% H, 16.34% S; found: 60.98% C, 6.37% H, 16.24% S. ^{1}H NMR ($CDCl_3$): 1.98 s, 3 H (SCH_3); 3.69 s, 2 H (CH_2S); 3.91 s, 3 H ($COOCH_3$); 7.39 dd, 1 H, *J*(5,4) = *J*(5,6) = 7.4 (H-5); 7.51 d, 1 H, *J*(4,5) = 7.4 (H-4); 7.92 d, 1 H, *J*(6,5) = 7.7 (H-6); 7.96 s, 1 H (H-2).

Methyl 4-[(methylsulfanyl)methyl]benzoate (**6b**). Yield 3.1 g (72%), b.p. 115 °C/39 Pa–119 °C/39 Pa (lit.[32] 122 °C/79 Pa–124 °C/79 Pa). ^{1}H NMR ($CDCl_3$): 1.97 s, 3 H (SCH_3); 3.69 s, 2 H (CH_2S); 3.90 s, 3 H ($COOCH_3$); 7.37 d, 2 H, *J*(3,2) = *J*(5,6) = 7.9 (H-3, H-5); 7.98 d, 2 H, *J*(2,3) = *J*(6,5) = 8.2 (H-2, H-6).

General Procedure for Preparation of **7a** and **7b** (lit.[38])

To a solution of **6a** (1.8 g, 9 mmol) or **6b** (1.8 g, 9 mmol) in 10 ml glacial acetic acid 5.2 ml of 30% hydrogen peroxide were added. The reaction mixture was refluxed for 1 h and the flask contents were poured into 100 ml cold water. Precipitated crystals were filtered off, washed with water and purified by crystallization.

Methyl 3-[(methylsulfonyl)methyl]benzoate (**7a**). Yield 1.52 g (73%), m.p. 120–121 °C (ethyl acetate). For $C_{10}H_{12}O_4S$ (228.3) calculated: 52.62% C, 5.30% H, 14.05% S; found: 52.57% C, 5.56% H, 13.86% S. ^{1}HNMR (DMSO-d_6): 2.12 s, 3 H (SO_2CH_3); 3.93 s, 3 H ($COOCH_3$); 4.29 s, 2 H (CH_2SO_2); 7.51 dd, 1 H, *J*(5,4) = *J*(5,6) = 7.7 (H-5); 7.66 d, 1 H, *J*(4,5) = 7.4 (H-4); 8.07 m, 2 H (H-2, H-6).

Methyl 4-[(methylsulfonyl)methyl]benzoate (**7b**). Yield 1.44 g (69%), m.p. 161–163 °C (ethyl acetate) (lit.[38] 162–164°C). ^{1}H NMR (DMSO-d_6): 2.78 s, 3 H (SO_2CH_3); 3.92 s, 3 H ($COOCH_3$); 4.30 s, 2 H (CH_2SO_2); 7.49 d, 2 H, *J*(3,2) = *J*(5,6) = 8.2 (H-3, H-5); 8.06 d, 2 H, *J*(2,3) = *J*(6,5) = 7.9 (H-2, H-6).

General Procedure for Preparation of **8a** and **8b** (lit.[38])

Ester **7a** (1.04 g, 4.6 mmol) or **7b** (1.04 g, 4.6 mmol) dissolved in 25 ml of ethanol was added to 10 ml 1 M sodium hydroxide. The reaction mixture was stirred at ambient temperature for 3 h. Ethanol was evaporated and pH was adjusted to 1 using 1 M hydrochloric acid. The resulting precipitate was collected by filtration, washed with cold water and purified by crystallization.

3-[(Methylsulfonyl)methyl]benzoic acid (**8a**). Yield 0.61 g (63%), m.p. 214–217 °C (ethanol). For $C_{10}H_{12}O_4S$ (214.0) calculated: 50.46% C, 4.70% H, 14.97% S; found: 50.19% C, 4.87% H, 14.69% S. ^{1}H NMR (DMSO-d_6): 2.91 s, 3 H (SO_2CH_3); 4.59 s, 2 H (CH_2SO_2); 7.52 dd, 1 H, *J*(5,4) = *J*(5,6) = 7.4 (H-5); 7.63 d, 1 H, *J*(4,5) = 7.4 (H-4); 7.93 d, 1 H, *J*(6,5) = 7.7 (H-6); 7.99 s, 1 H (H-2).

4-[(Methylsulfonyl)methyl]benzoic acid (**8b**). Yield 0.69 g (71%), m.p. 250–254 °C (ethanol) (lit.[38] 249–253 °C). ^{1}H NMR (DMSO-d_6): 2.91 s, 3 H (SO_2CH_3); 4.57 s, 2 H (CH_2SO_2); 7.52 d, 2 H, J(3,2) = J(5,6) = 8.3 (H-3, H-5); 7.95 d, 2 H, J(2,3) = J(6,5) = 8.2 (H-2, H-6).

General Procedure for Preparation of **9a** and **9b** (lit.[39])

To a stirred suspension of anhydrous nickel chloride (0.16 g, 1.3 mmol) in ethyl 3-bromobenzoate (5.81 g, 25.3 mmol) or ethyl 4-iodobenzoate (6.98 g, 25.3 mmol) trimethyl phosphite (3.62 g, 29.2 mmol) at 150 °C was dropped. The reaction mixture was heated for 1 h, cooled and then pure products were obtained by column chromatography (dichloromethane–methanol, 100:2)

Ethyl 3-(dimethoxyphosphoryl)benzoate (**9a**). Yield 3.9 g (60%). For $C_{11}H_{15}O_5P$ (258.2) calculated: 51.17% C, 5.86% H, 12.00% P; found: 50.93% C, 5.93% H, 11.82% P. ^{1}H NMR ($CDCl_3$): 1.29 t, 3 H, J(2′,1′) = 7.1 ($OCH_2C\mathbf{H}_3$); 3.67 d, 6 H, $^3J_{HP}$ = 11.1 (OCH_3); 4.28 q, 2 H, J(1′,2′) = 7.0 ($OC\mathbf{H}_2CH_3$); 7.46 m, 1 H (H-5); 7.87 ddt, 1 H, J_{HP} = 12.9, J(4,5) = 7.6, J(4,2) = J(4,6) = 1.3 (H-4); 8.12 dd, J(6,5) = 7.6, J_{HP} = J(6,2) = J(4,2) = 1.2 (H-6); 8.34 d, 1 H, J_{HP} = 12.9 (H-2).

Ethyl 4-(dimethoxyphosphoryl)benzoate (**9b**). Yield 4.62 g (71%). For $C_{11}H_{15}O_5P$ (258.2) calculated: 51.17% C, 5.86% H, 12.00% P; found: 50.09% C, 5.94% H, 11.91% P. ^{1}H NMR ($CDCl_3$): 1.36 t, 3 H, J(2′,1′) = 7.1 ($OCH_2C\mathbf{H}_3$); 3.74 d, 6 H, $^3J_{HP}$ = 12.9 (OCH_3); 4.21 q, 2 H, J(1′,2′) = 7.0 ($OC\mathbf{H}_2CH_3$); 7.84 dd, 2 H, $^3J_{HP}$ = 12.9, J(3,2) = J(5,6) = 8.3 (H-3, H-5); 8.09 dd, 2 H, $^4J_{HP}$ = 3.8, J(2,6) = J(3,5) = 8.3 (H-2, H-6).

General Procedure for Preparation of **10a** and **10b** (lit.[40])

To ester **9a** (1.5 g, 5.8 mmol) or **9b** (1.5 g, 5.8 mmol) dissolved in 25 ml ethanol sodium hydroxide (0.23 g, 5.8 mmol) in 10 ml water was added. The reaction mixture was stirred at ambient temperature for one week, ethanol was evaporated and pH was adjusted to 1 using 0.01 M hydrochloric acid. The separated oil was extracted with benzene (3 × 20 ml) and combined organic layers were dried with anhydrous magnesium sulfate. The solvent was evaporated and crude products were purified by crystallization.

3-(Dimethoxyphosphoryl)benzoic acid (**10a**). Yield 0.46 g (34%), m.p. 122–124 °C (benzene, petroleum ether) (lit.[41] 124.5–125.5 °C). ^{1}H NMR (DMSO-d_6): 3.63 d, 6 H, $^3J_{HP}$ = 11.1 (OCH_3); 7.67 m, 1 H (H-5); 7.92 dd, 1 H, J_{HP} = 12.6, J(4,5) = 7.6 (H-4); 8.19 m, 2 H (H-2, H-6).

4-(Dimethoxyphosphoryl)benzoic acid (**10b**). Yield 0.65 g (49%), m.p. 115–118 °C (benzene, petroleum ether) (lit.[41] 116–117 °C). ^{1}H NMR (DMSO-d_6): 3.74 d, 6 H, $^3J_{HP}$ = 11.1 (OCH_3); 7.91 dd, 2 H, $^3J_{HP}$ = 13.2, J(3,2) = J(5,6) = 8.5 (H-3, H-5); 8.19 dd, 2 H, $^4J_{HP}$ = 3.8, J(2,6) = J(3,5) = 8.3 (H-2, H-6).

Determination of Dissociation Constants

Dissociation constants of compounds **2**–**4**, **8**, and **10** (as pK_a) at 25 °C in water (W), methanol (MeOH), ethanol (EtOH), *N*,*N*-dimethylformamide (DMF), and dimethyl sufoxide (DMSO) were determined by potentiometric titration using an automatic titrator Titralab 3 (Radiometer) under the same experimental conditions and using the same electrodes as in previous works[42–44].

Calculation of Substituent Constants

Procedures used were based on the prediction of unknown substituent constants by means of correlation relations between logarithm of dissociation constants *meta*- and *para*-substituted benzoic acids in selected solvents (water, methanol, ethanol, *N*,*N*-dimethylformamide, dimethyl sulfoxide) and known substituent constants. The calibration set of substituents with known and valid substituent constants included H, CH_3, $NHCOCH_3$, OCH_3, F, Cl, Br, I, $COCH_3$, CN, NO_2, SO_2CH_3. The substituents were chosen depending on accessibility of all values of dissociation constants of corresponding *meta*- and *para*-benzoic acid derivatives in relevant solvents. The values of dissociation constants were taken from the literature[8,45,46]. Substituent constants for group of substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$, and $PO(OCH_3)_2$ were evaluated using the procedures described below.

Equation (*1*) was used for prediction of Hammett substituent constants σ_m and σ_p by nonlinear regression

$$\log K_{jk} = \log K_{0,j} + \rho_j \sigma_k \,, \tag{1}$$

where indexes *j* and *k* are the number of solvent used for measurement of dissociation constants and the number of substituent (numbered independently in position *meta* and *para*), respectively. Values of log K_{jk} are logarithms of experimental values of dissociation constants of subtituted benzoic acid derivatives in a given solvent, log $K_{0,j}$ values are unknown intercepts, ρ_j are unknown reaction constants in the Hammett equation for given solvent, and σ_k are Hammett substituent constants. Unknown parameters in Eq. (*1*) were optimized minimizing the sum of squares *S* using Eq. (*2*).

$$S = \sum_{jk} (\log K_{jk}^{\text{exp}} - \log K_{jk}^{\text{pred}})^2 = \min \tag{2}$$

Analogously to the previous case, Eq. (*3*) was used for prediction of substituent constants σ_I and σ_R by nonlinear regression.

$$\log K_{jk} = \log K_{0,j} + \rho_{I,j} \sigma_{I,k} + \rho_{R,j} \sigma_{R,k} \,, \tag{3}$$

where $\rho_{I,j}$ and $\rho_{R,j}$ are reaction constants (the same meaning of symbols as in Eq. (*1*)). Optimization was made by minimization of the function *S* in Eq. (*2*).

For prediction of substituent constants σ^i according to AISE (lit.[10,11]) by nonlinear regression, Eq. (*4*) was applied.

$$\log K_{jk} = \log K_{0,j} + \rho_{I,j} \delta_{I,k} (\sigma_k^i - \sigma_0^i) + \rho_{N,j} \delta_{N,k} (\sigma_k^i - \sigma_0^i) + \rho_{E,j} \delta_{E,k} (\sigma_k^i - \sigma_0^i) \,, \tag{4}$$

where $\rho_{I,j}$, $\rho_{N,j}$, and $\rho_{E,j}$ are reaction constants, symbols δ are multiplying constants which assume the values 1 or 0 depending on the type of interaction of substituent with reaction center (I, substituents with inductive effect only; N, internal nucleophiles; E, internal ele-

ctrophiles), and σ_0^i is an unknown parameter in the AISE theory. The meaning of symbols is the same as in Eq. (*1*). Optimization was made by minimization of the function *S* in Eq. (*2*).

For prediction of substituent constants by PLS calibration[31], decomposition of matrixes ***X*** and ***Y*** in the first step was realized using Eqs (*5*) and (*6*)

$$\boldsymbol{X} = \boldsymbol{T}\boldsymbol{P}^{\mathrm{T}} + \boldsymbol{E} \,, \tag{5}$$

$$\boldsymbol{Y} = \boldsymbol{U}\boldsymbol{Q}^{\mathrm{T}} + \boldsymbol{F} \,, \tag{6}$$

with defined relation between matrixes ***T*** and ***U***:

$$\boldsymbol{U} = \boldsymbol{T}\boldsymbol{A} + \boldsymbol{H} \,. \tag{7}$$

In Eqs (*5*)–(*7*), ***X*** is the matrix of log K_a values (calibration set of substituents, in rows are substituents, in columns are solvents used in the measurements), ***Y*** means the matrix of substituent constants (rows represent substituents, two columns represent a pair of known Hammett substituent constants σ_m, σ_p or a pair of known substituent constants σ_I, σ_R), ***T*** and ***U*** are matrixes of latent variables (score), ***A*** is the diagonal matrix describing relation between latent variables, ***P*** and ***Q*** are loading matrixes; remaining symbols are residual matrixes.

Matrix $\boldsymbol{Y}^{\boldsymbol{c}}$ (in rows are substituents, two columns represent a pair of unknown Hammett substituent constants σ_m, σ_p or a pair of unknown substituent constants σ_I, σ_R) was calculated using Eq. (*8*) with calculated matrixes ***P***, ***A*** and ***Q***, and matrix $\boldsymbol{X}^{\boldsymbol{c}}$ of measured values of log K_a (in rows are substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$, and $PO(OCH_3)_2$, in columns are solvents used in measurements).

$$\boldsymbol{Y}^{\mathrm{c}} = [(\boldsymbol{P}^{\mathrm{T}}\boldsymbol{P})^{-1}\boldsymbol{P}^{\mathrm{T}}(\boldsymbol{X}^{\boldsymbol{c}})^{\mathrm{T}}]^{\mathrm{T}}\boldsymbol{A}\boldsymbol{Q}^{\mathrm{T}}. \tag{8}$$

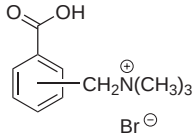
All calculations were carried out using standard algorithms[31] and the own OPstat program.

RESULTS AND DISCUSSION

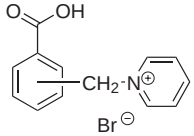
Syntheses and Acidity of Substituted Benzoic Acids

For determination of substituent constants, 3- and 4-substituted benzoic acids **2**–**4**, **8**, and **10** were synthesized. Quaternary salts **2** and **3** were prepared by reaction of corresponding (bromomethyl)benzoic acids with trimethylamine or pyridine, anilinium salts **4** by quaternization of (dimethylamino)-benzoic acids with methyl iodide. Compounds **8** were synthesized starting from corresponding methyl (bromomethyl)benzoate by substitution with

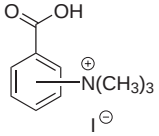
sodium methanethiolate followed by oxidation with hydrogen peroxide and hydrolysis of ester function. Compounds **10** were prepared from ethyl 3-(bromomethyl)benzoate or ethyl 4-(iodomethyl)benzoate by reaction with trimethyl phosphite followed by hydrolysis of carboxylate ester.



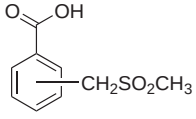
Position	
3	**2a**
4	**2b**



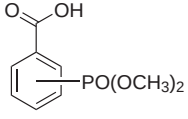
Position	
3	**3a**
4	**3b**



Position	
3	**4a**
4	**4b**



Position	
3	**8a**
4	**8b**



Position	
3	**10a**
4	**10b**

Dissociation constants (pK_a) of benzoic acids **2**–**4**, **8**, and **10** were measured in water, methanol, ethanol, *N*,*N*-dimethylformamide, and dimethyl sulfoxide. The obtained data are summarized in Table I.

Hammett Substituent Constants

The values of substituent constants σ_m and σ_p given in Table II were obtained using nonlinear regression and PLS calibration by the procedures described in Experimental. Computation by nonlinear regression fast converged to minimum thus giving evidence about suitability of the correlation model. The residual standard deviation in nonlinear regression according to Eq. (*1*) calculated by Eq. (*2*) using residual sum of squares was s = 0.130 for a set of 174 experimental values of log K_a. This value is comparable with obviously precision of potentiometric determination of dissociation constants in nonaqueous solvents. Therefore, model (*1*) can be considered to be valid. In PLS calibration, two latent variables in matrix ***X*** (cali-

bration set of log K_a values) explained 99.55% of overall variability and all variability in matrix ***Y*** (values of substituent constants σ_m and σ_p). Thus, calibration can be considered to be good enough for prediction of unknown substituent constants.

A comparison of calculated substituent constants with those obtained by other methods shows a very good agreement in the scope of data published in the literature. The calculated Hammett substituent constants for $CH_2SO_2CH_3$ group are comparable with those for $CH_2SO_2C_6H_5$ (σ_m = 0.15, σ_p = 0.17, lit.[53]). Similarly, the electron-withdrawing effect of CH_2Py^+ is practically the same as in the case of $CH_2N^+(CH_3)_3$ keeping in mind accuracy of the obtained results. Values of σ_p are comparable, with the exception of $PO(OCH_3)_2$, with corresponding values of σ_m showing the dominating influence of the inductive effect.

Substituent Constants σ_I *and* σ_R

Substituent constants σ_I and σ_R calculated by nonlinear regression using Eq. (*3*) show high intercorrelation (very slow convergence of the optimiza-

TABLE I
Mean values of $p\bar{K}_a$ of substituted benzoic acids and their standard deviations *s* (in parentheses) calculated from three to eight repeated measurements in water (W), methanol (MeOH), ethanol (EtOH), *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO)

Substituent	Solvent				
	W	MeOH	EtOH	DMF	DMSO
3-$N^+(CH_3)_3I^-$	3.45 (0.05)	7.73 (0.03)	8.05 (0.01)	10.33 (0.08)	9.36 (0.09)
4-$N^+(CH_3)_3I^-$	3.58 (0.04)	7.99 (0.03)	8.49 (0.01)	10.46 (0.09)	9.79 (0.08)
3-$CH_2N^+(CH_3)_3Br^-$	3.77 (0.06)	8.32 (0.07)	8.82 (0.06)	11.15 (0.11)	10.03 (0.14)
4-$CH_2N^+(CH_3)_3Br^-$	3.74 (0.04)	8.43 (0.08)	8.96 (0.08)	11.13 (0.09)	10.17 (0.09)
3-$CH_2Py^+Br^-$	3.84 (0.06)	8.37 (0.02)	8.82 (0.08)	11.22 (0.10)	10.37 (0.08)
4-$CH_2Py^+Br^-$	3.71 (0.03)	8.52 (0.10)	9.14 (0.03)	11.31 (0.07)	10.24 (0.11)
3-$CH_2SO_2CH_3$	4.09 (0.04)	9.17 (0.06)	9.86 (0.04)	11.87 (0.04)	10.50 (0.09)
4-$CH_2SO_2CH_3$	4.13 (0.05)	9.22 (0.07)	9.95 (0.06)	11.97 (0.04)	10.74 (0.08)
3-$PO(OCH_3)_2$	3.85 (0.06)	8.75 (0.05)	9.51 (0.01)	11.37 (0.10)	10.14 (0.07)
4-$PO(OCH_3)_2$	3.64 (0.06)	8.65 (0.04)	9.33 (0.04)	11.15 (0.05)	10.14 (0.04)

tion process) probably due to the way of setting substituent constants σ_m and σ_p. For successful optimization it was necessary (with the exception of substituent $PO(OCH_3)_2$) to define value of substituent constant $\sigma_R = 0$. Under this condition, values of σ_I and σ_R (Table III) were obtained using the procedure described in Experimental. These values were obtained also by PLS calibration (Table III). Small values of σ_R obtained by PLS calibration confirm validity of their omission in calculations by nonlinear regression.

The residual standard deviation in nonlinear regression according to Eq. (*1*) calculated from Eq. (*2*) using residual sum of squares was $s = 0.134$ for the set of 174 experimental values of dissociation constants, conse-

TABLE II
Values of substituent constants σ_m and σ_p obtained using Eq. (*1*) or PLS calibration by Eq. (*8*); comparison with data from the literature

Substituent	σ_m			σ_p		
	NLR	PLSC	Literature	NLR	PLSC	Literature
$N^+(CH_3)_3$	0.99 ± 0.05	0.97	0.99[a] (W)	0.89 ± 0.04	0.96	0.96[a](W)
			0.88[b]			0.82[b]
			1.02[c] (50% EtOH)			0.88[c] (50% EtOH)
						0.72[d] (W, log *k*)
			1.03[e] (W)			0.98[e] (W)
			1.02[e] (10% EtOH)			0.94[e] (10% EtOH)
			1.13[e] (50% EtOH)			0.99[e] (50% EtOH)
			1.23[e] (75% EtOH)			1.03[e] (75% EtOH)
			0.99[f] (W)			0.96[f] (W)
			0.88[g]			0.82[g]
$CH_2N^+(CH_3)_3$	0.61 ± 0.04	0.61		0.57 ± 0.04	0.61	0.44[d] (W, log *k*)
			0.68[e] (W)			0.67[e] (W)
			0.69[e] (10% EtOH)			0.68[e] (10% EtOH)
			0.82[e] (50% EtOH)			0.73[e] (50% EtOH)
			0.92[e] (75% EtOH)			0.78[e] (75% EtOH)
			0.40[g]			0.44[g]
CH_2Py^+	0.55 ± 0.04	0.57		0.50 ± 0.04	0.54	
$CH_2SO_2CH_3$	0.19 ± 0.04	0.20		0.10 ± 0.04	0.10	
$PO(OCH_3)_2$	0.41 ± 0.04	0.43	0.42[h] (50% EtOH)	0.50 ± 0.04	0.49	0.53[h] (50% EtOH)
			0.34[i] (^{19}F NMR)			0.43[i] (^{19}F NMR)

[a] Lit.[47], [b] lit.[3], [c] lit.[48], [d] lit.[49], [e] lit.[30], [f] lit.[8], [g] lit.[13], [h] lit.[41], [i] lit.[50]

quently slightly more higher than in model (*1*). The explained variabilities in PLS calibration were similar to calculation according to model (*1*). From these finding results the fact that models (*1*) and (*3*) are of the same statistical significance for interpretation of experimental data. Differences between the calculated substituent constants and known values obtained by other procedures (see Table III) are higher than in the case of Hammett constants. That is in particular the case of charged substituent $N^+(CH_3)_3$ and also $PO(OCH_3)_2$, where the mesomeric effect seems to be underestimated.

Substituent Constant σ^i in AISE Theory

Due to non-additive character of Eq. (*4*), only nonlinear regression can be used for setting unknown values of substituent constant σ^i. The calculation converged fast to a minimum thus pointing to a suitable model without intercorrelations between parameters. The calculated values σ^i for substituents are: $N^+(CH_3)_3$ 0.788 ± 0.035, $CH_2N^+(CH_3)_3$ 0.501 ± 0.024, CH_2Py^+ 0.450 ± 0.023, $CH_2SO_2CH_3$ 0.138 ± 0.025, and $PO(OCH_3)_2$ 0.407 ± 0.019; residual standard deviation was s = 0.134 for a set of 174 experimental values of dissociation constants.

TABLE III
Values of substituent constants σ_I and σ_R obtained by nonlinear regression using Eq. (*3*) and PLS calibration using Eq. (*8*); comparison with literature data

Substituent	σ_I			σ_R		
	NLR	PLSC	Literature	NLR	PLSC	Literature
$N^+(CH_3)_3$	0.94 ± 0.03	0.91	0.73[b]	0[a]	0.03	
			0.61, 0.59[c]			
			0.99[d] (NMR)			–0.08[d] (NMR)
			1.07[e]			
$CH_2N^+(CH_3)_3$	0.60 ± 0.03	0.54		0[a]	0.08	
CH_2Py^+	0.54 ± 0.03	0.53		0[a]	0.03	
$CH_2SO_2CH_3$	0.18 ± 0.03	0.22	0.21[f] (IR)	0[a]	0.06	0.09[f] (IR)
$PO(OCH_3)_2$	0.27 ± 0.08	0.31	0.35[g]	0.26 ± 0.11	0.22	0.18[g]
						0.19[h]
			0.16[d] (NMR)			0.06[d] (NMR)
			0.32[e]			0.17[e]

[a] Arbitrary, [b] lit.[51], [c] lit.[30], [d] lit.[13], [e] lit.[8], [f] lit.[52], [g] lit.[41], [h] lit.[50]

Conclusion

Substituent constants σ_m, σ_p, σ_I, σ_R, and σ^i for substituents $N^+(CH_3)_3$, $CH_2N^+(CH_3)_3$, CH_2Py^+, $CH_2SO_2CH_3$, and $PO(OCH_3)_2$ in three correlation models were calculated by two different mathematical methods using a large set of experimental data and calibration set. The predicted values of substituent constants calculated by two methods are practically indistinguishable. It was found that nonlinear regression is more suitable and more universal than PLS calibration. The advantages of nonlinear regression are: independence on variate experimental data from one solvent, possibility of estimation of precision of substituent constants (standard deviation), availability of software and easy calculation. On the other hand, nonlinear regression fails for calculation of constants with additive description of substituents (σ_I and σ_R) in contrast to PLS calibration. The calculated values correspond with those cited for the same substituents in the literature.

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