SUBSTITUENT EFFECTS ON THE BASE-CATALYSED HYDROLYSIS OF PHENYL ESTERS OF *ortho*-SUBSTITUTED BENZOIC ACIDS

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Fourteen model phenyl esters of 2-substituted benzoic acids were synthesised. Structures and purity of model compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as by HPLC and elemental analysis. Kinetics of base-catalysed hydrolysis of model phenyl esters occurring by the BAC2 mechanism were measured by UV spectrophotometry in 50% (v/v) aqueous dimethyl sulfoxide solutions at 25 °C under pseudo-first-order reaction conditions (c(NaOH) = 0.001–1.0 mol l^{-1}). Linear relation between J_{-}^{E} and log k_{obs} with the slope close to unity was found for all model compounds. Neither one-parameter nor multiparameter Hammett-type description of variability of experimental data obtained for phenyl esters of 2-substituted benzoic acids was found. Two groups (conjugating and non-conjugating) were created by division of *ortho*-substituents in *ortho*-position using the AISE theory, based on their interaction with the reaction centre.

Keywords: Esters; Benzoic acids; Base-catalysed hydrolysis; *ortho*-Effect; Substituent effects; Kinetics; Chemometrics; Hammett equation; AISE theory.

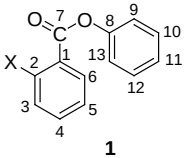
The substituent in an aromatic ring in *ortho*-position to a side chain containing the reaction centre manifests itself so differently and, in particular, so unsystematically – compared with substitutients in other ring positions – that this phenomenon has been referred to as the "*ortho*-effect" (ref.[1]). The *ortho*-effect involves all effects associated with specific interactions between an *ortho*-substituent and the reaction centre. The interactions are especially ascribed to those mediated by σ and π bonds of the molecular skeleton, those between the substituent and reaction centre due to of intramolecular hydrogen bonds, changes in resonance interactions, steric hindrance to the approach of the reagent to the reaction centre, hydrophobic interactions of the substituent and reaction centre, differences in solvation of the reaction centre due to changes in chemical environment, and, possibly, further less significant factors.

The extent of manifestation of those effects depends on the particular structure of the reaction centre, its chemical environment and medium. Quantitative description of the *ortho*-effect based on the similarity principle was less successful than in the cases of *meta*- and *para*-substituents. In principle, two approaches can be adopted: the first starts from the Hammett equation with the aim to propose universal substituent constants for the *ortho*-position[2–4]. Because of its numerous drawbacks, this approach ceased to be used. The other approach is based on separate description of inductive and mesomeric effects of a substituent and is associated with the extension of the equation by description of steric effects. The description is realised by means of multiparameter equations, of them the most frequently used[5–8] being Eq. (*1*):

$$\log k = \log k_0 + \rho_I\sigma_I + \rho_R\sigma_R + \psi\upsilon \ . \qquad (1)$$

Validity of Eq. (*1*) and similar relationships for substitution in *ortho*-position has been tested on a number of physical and chemical processes. However, the correlations obtained were mostly worse than those obtained by description of the effects from *meta*- and *para*-positions. A new approach to the problem of description of substituent effects irrespective of the position of substituents is represented by the AISE theory[9–11].

The aim of this study is to complete the description of substituent effects on the model of phenyl 2-substituted benzoates **1**, the main task being quantitative description of the *ortho*-effect using analogies between the *ortho*- and *para*-substitutions and modern mathematical-statistical methods.



1

1	X
a	H
b	CH_3
c	C_2H_5
d	CF_3
e	NO_2
f	NH_2
g	$N(CH_3)_2$
h	OCH_3
i	F
j	Cl
k	Br
l	I
m	SCH_3
n	SO_2CH_3

EXPERIMENTAL

Structure and purity of model compounds 1 were confirmed by using UV, ^{1}H and ^{13}C NMR spectroscopy (chemical shifts in ppm (δ-scale), coupling constants (*J*) in Hz), and by HPLC. Melting points were measured without correction by using a Kofler apparatus.

The substances not yet described in literature were also subjected to elemental analysis.

^{1}H and ^{13}C NMR spectra of model compounds **1** were measured in deuterated chloroform, scanned at 25 °C on an AMX 360 spectrometer (Bruker, 360.14 MHz, hexamethyldisiloxane, δ 0.05 ppm).

Syntheses of Phenyl 2-Substituted Benzoates

Model substances **1** were synthesised by the procedures described in our previous communication[12]: method *A* (ref.[13]), method *B* (ref.[14]) and method *C* (ref.[15]).

Phenyl benzoate (**1a**). Yield 48.3% (method *A*), m.p. 65–67 °C (ref.[16] 65–67 °C). ^{1}H and ^{13}C NMR spectra were in accord with the published data (ref.[17]).

Phenyl 2-methylbenzoate (**1b**). Yield 77.7% (method *A*), b.p. 130–132 °C/133 Pa (ref.[18] 117–118 °C/0.6 Torr), n_D^{20} = 1.5723. ^{1}H NMR: 2.61 s, 3 H (CH_3); 7.13–7.23 m, 5 H (H-9, H-11, H-13, H-3, H-5); 8.10 d, 1 H (H-6); 7.31–7.37 m, 3 H (H-10, H-12, H-4). ^{13}C NMR: 21.64 (CH_3); 165.44 (C-7); 128.22 (C-1); 140.93 (C-2); 130.84 (C-3); 132.40 (C-4); 125.62 (C-5); 131.64 (C-6); 150.64 (C-8); 121.54 (C-9, C-13); 129.16 (C-10, C-12); 125.48 (C-11).

Phenyl 2-ethylbenzoate (**1c**). Yield 77.0% (method *A*), b.p. 135–137 °C/133 Pa, n_D^{20} = 1.5625. ^{1}H NMR: 1.21 t, 3 H (CH_3), *J* = 5.8; 3.02 q, 2 H (CH_2), *J* = 5.8; 7.14–7.25 m, 5 H (H-9, H-11, H-13, H-3, H-5); 8.06 d, 1 H (H-6); 7.46 t, 1 H (H-4); 7.33 t, 2 H (H-10, H-12), *J* = 6.2. ^{13}C NMR: 15.66 (CH_3); 27.49 (CH_2); 165.58 (C-7); 128.90 (C-1); 146.88 (C-2); 130.87 (C-3); 132.68 (C-4); 130.16 (C-5); 131.31 (C-6); 150.66 (C-8); 121.52 (C-9, C-13); 129.11 (C-10, C-12); 125.62 (C-11). For $C_{15}H_{14}O_2$ (226.3) calculated: 79.55% C, 6.19% H; found: 79.53% C, 6.25% H.

Phenyl 2-nitrobenzoate (**1e**). Yield 50.4% (method *A*), m.p. 45–46 °C (ref.[19] 50–52 °C). ^{1}H NMR: 7.96 d, 1 H (H-3); 7.61–7.71 m, 2 H (H-4, H-5); 7.83 d, 1 H (H-6); 7.12–7.27 m, 3 H (H-9, H-11, H-13); 7.40 t, 2 H (H-10, H-12), *J* = 6.1. ^{13}C NMR: 163.98 (C-7); 127.17 (C-1); 147.84 (C-2); 123.97 (C-3); 133.97 (C-4); 133.11 (C-5); 129.86 (C-6); 150.24 (C-8); 121.05 (C-9, C-13); 129.42 (C-10, C-12); 126.25 (C-11).

Phenyl 2-methoxybenzoate (**1h**). Yield 5.8% (method *A*), m.p. 48–50 °C (ref.[20] 57–58 °C). ^{1}H NMR: 3.90 s, 3 H (CH_3); 7.00–7.04 m, 2 H (H-3, H-5); 7.52 t, 1 H (H-4); 8.00 d, 1 H (H-6); 7.18–7.24 m, 3 H (H-9, H-11, H-13); 7.39 t, 2 H (H-10, H-12), *J* = 6.0. ^{13}C NMR: 55.75 (CH_3); 164.15 (C-7); 118.84 (C-1); 159.58 (C-2); 111.98 (C-3); 134.06 (C-4); 119.94 (C-5); 131.87 (C-6); 150.75 (C-8); 121.60 (C-9, C-13); 129.11 (C-10, C-12); 125.43 (C-11).

Phenyl 2-fluorobenzoate (**1i**). Yield 61.7% (method *A*), m.p. 72–74 °C (ref.[21] 70–71 °C). ^{1}H NMR: 7.58 d, 1 H (H-3); 8.09 t, 1 H (H-4); 7.18–7.28 m, 5 H (H-9, H-11, H-13, H-5, H-6); 7.42 t, 2 H (H-10, H-12), *J* = 5.9. ^{13}C NMR: 162.72 (C-7); 118.03 (C-1); 162.23 d (C-2), $^1J(^{13}C,^{19}F)$ = 261.48; 117.14 d (C-3), $^2J(^{13}C,^{19}F)$ = 22.19; 135.16 d (C-4), $^3J(^{13}C,^{19}F)$ = 9.06; 132.46 (C-5); 124.09 d (C-6), $^3J(^{13}C,^{19}F)$ = 3.89; 150.57 (C-8); 121.62 (C-9, C-13); 129.45 (C-10, C-12); 125.99 (C-11).

Phenyl 2-chlorobenzoate (**1j**). Yield 43.9% (method *A*), m.p. 40–42 °C (ref.[22] 37 °C). ^{1}H NMR: 7.36–7.44 m, 4 H (H-10, H-12, H-3, H-5); 7.49 t, 1 H (H-4); 8.02 d, 1 H (H-6); 7.21–7.28 m, 3 H (H-9, H-11, H-13). ^{13}C NMR: 163.79 (C-7); 129.14 (C-1); 134.06 (C-2); 131.06 (C-3); 132.93

(C-4); 126.53 (C-5); 131.60 (C-6); 150.48 (C-8); 121.38 (C-9, C-13); 129.30 (C-10, C-12); 125.86 (C-11).

Phenyl 2-bromobenzoate (**1k**). Yield 38.9% (method *A*), b.p. 137–139 °C/133 Pa, n_D^{20} = 1.5997. ^{1}H NMR: 7.54 d, 1 H (H-3); 7.11–7.23 m, 5 H (H-9, H-11, H-13, H-4, H-5); 7.85 d, 1H (H-6); 7.30 t, 2 H (H-10, H-12), *J* = 6.0. ^{13}C NMR: 164.12 (C-7); 132.83 (C-1); 121.79 (C-2); 131.39 (C-3); 134.18 (C-4); 127.28 (C-5); 131.47 (C-6); 150.31 (C-8); 121.22 (C-9, C-13); 129.18 (C-10, C-12); 125.76 (C-11).

Phenyl 2-iodobenzoate (**1l**). Yield 52.4% (method *A*), b.p. 146–148 °C/133 Pa (ref.[23] 1.6326), n_D^{20} = 1.6310. ^{1}H NMR: 8.00–8.06 m, 2 H (H-3, H-6); 7.42 m, 3 H (H-10, H-12, H-4); 7.18–7.28 m, 4 H (H-9, H-11, H-13, H-5). ^{13}C NMR: 164.57 (C-7); 133.90 (C-1); 94.37 (C-2); 141.32 (C-3); 132.95 (C-4); 127.82 (C-5); 131.47 (C-6); 150.41 (C-8); 121.32 (C-9, C-13); 129.25 (C-10, C-12); 125.85 (C-11).

Phenyl 2-(trifluoromethyl)benzoate (**1d**). Yield 72.0% (method *B*), b.p. 106–108 °C/133 Pa, n_D^{20} = 1.5175. ^{1}H NMR: 7.76 d, 1 H (H-3); 7.52–7.63 m, 2 H (H-4, H-5); 7.92 d, 1 H (H-6); 7.19–7.26 m, 3 H (H-9, H-11, H-13); 7.40 t, 2 H (H-10, H-12), *J* = 6.0. ^{13}C NMR: 123.26 q (CF_3), $^1J(^{13}C,^{19}F)$ = 273.43; 165.09 (C-7); 126.72 q (C-1), $^3J(^{13}C,^{19}F)$ = 5.25; 128.75 q (C-2), $^2J(^{13}C,^{19}F)$ = 27.67; 126.72 (C-3); 131.76 (C-4); 131.57 (C-5); 130.45 (C-6); 150.50 (C-8); 121.19 (C-9, C-13); 129.44 (C-10, C-12); 126.11 (C-11). For $C_{14}H_9F_3O_2$ (266.2) calculated: 63.11% C, 3.38% H; found: 63.11% C, 3.31% H.

Phenyl 2-(methylsulfonyl)benzoate (**1n**). Yield 3.4% (method *B*), m.p. 108–110 °C. ^{1}H NMR: 3.33 s, 3 H (CH_3); 8.17 d, 1 H (H-3); 7.69–7.78 m, 2 H (H-4, H-5); 7.90 d, 1 H (H-6); 7.27–7.32 m, 3 H (H-9, H-11, H-13); 7.45 t, 2 H (H-10, H-12), *J* = 5.5. ^{13}C NMR: 44.85 (CH_3); 165.69 (C-7); 132.46 (C-1); 139.34 (C-2); 129.70 (C-3); 133.53 (C-4); 131.55 (C-5); 129.95 (C-6); 150.33 (C-8); 121.40 (C-9, C-13); 129.60 (C-10, C-12); 126.41 (C-11). For $C_{14}H_{12}O_4S$ (276.3) calculated: 60.80% C, 4.34% H, 11.58% S; found: 61.05% C, 4.52% H, 11.30% S.

Phenyl 2-(dimethylamino)benzoate (**1g**). Yield 94.2% (method *C*), m.p. 67–69 °C. ^{1}H NMR: 2.91 s, 6 H (CH_3); 6.96 d, 1 H (H-3); 7.37 m, 3 H (H-4, H-10, H-12); 6.86 t, 1 H (H-5); 7.90 d, 1 H (H-6); 7.16–7.22 m, 3 H (H-9, H-11, H-13).^{13}C NMR: 43.64 (CH_3); 166.11 (C-7); 119.17 (C-1); 152.93 (C-2); 116.73 (C-3); 132.84 (C-4); 118.39 (C-5); 132.09 (C-6); 150.94 (C-8); 121.55 (C-9, C-13); 129.28 (C-10, C-12); 125.48 (C-11). For $C_{15}H_{15}O_2N$ (241.3) calculated: 74.59% C, 6.22% H, 5.80% N; found: 74.38% C, 6.17% H, 5.91% N.

Phenyl 2-(methylsulfanyl)benzoate (**1m**). Yield 64.3% (method *C*), m.p. 83–85 °C. ^{1}H NMR: 2.46 s, 3 H (CH_3); 7.28 d, 1 H (H-3); 7.53 t, 1 H (H-4); 7.19–7.26 m, 4 H (H-9, H-11, H-13, H-5); 8.23 d, 1 H (H-6); 7.39 t, 2 H (H-10, H-12), *J* = 6.0. ^{13}C NMR: 15.52 (CH_3); 164.67 (C-7); 107.68 (C-1); 144.46 (C-2); 124.37 (C-3); 133.03 (C-4); 123.44 (C-5); 131.84 (C-6); 150.64 (C-8); 121.73 (C-9, C-13); 129.34 (C-10, C-12); 125.77 (C-11). For $C_{14}H_{12}O_2S$ (244.3) calculated: 68.78% C, 4.91% H, 13.10% S; found: 68.45% C, 5.12% H, 13.25% S.

Synthesis of Phenyl 2-Aminobenzoate **1f** (ref.[24])

A solution of 10 g (0.062 mol) isatoic anhydride (4*H*-3,1-benzoxazine-2(1*H*),4-dione) in 1,4-dioxane (200 ml) was treated with 5.8 g (0.062 mol) phenol and 0.2 g (0.004 mol) powdered KOH at 50 °C. The solution was slowly heated to 100 °C until the evolution of CO_2 ceases. The mixture was cooled and treated with water (300 ml). The separated phenyl 2-aminobenzoate **1f** was collected by suction and recrystallised from aqueous methanol. The yield was 8 g (60.5%), m.p. 64–65 °C (ref.[25], m.p. 63–65 °C). ^{1}H NMR: 5.74 s, 2 H (NH_2); 6.65–6.71 m, 2 H (H-3, H-5); 7.31 t, 1 H (H-4); 8.06 d, 1 H (H-6); 7.16 d, 2 H (H-9, H-13), *J* =

6.5; 7.40 t, 2 H (H-10, H-12), J = 6.1; 7.24 t, 1 H (H-11), J = 5.7. ^{13}C NMR: 166.65 (C-7); 109.50 (C-1); 150.64 (C-2); 116.27 (C-3); 134.69 (C-4); 116.66 (C-5); 131.42 (C-6); 151.01 (C-8); 121.84 (C-9, C-13); 129.30 (C-10, C-12); 125.62 (C-11).

Kinetic Measurements

Kinetic measurements were carried out under the same conditions as those used for phenyl 4-substituted benzoates described in detail elsewhere[12]. The observed rate constants obtained by non-linear regression using an optimisation program are presented in Table I.

RESULTS AND DISCUSSION

Evaluation of Calculation Method of Catalytic Rate Constants

The logarithms of catalytic rate constant, log k_{cat}, were obtained by the procedure described in our previous communication[12]. This procedure resulted in the intercept values of the log k_{obs} *vs* J_-^E dependence corresponding to differences in logarithms of catalytic rate constants $\Delta\log k_{cat} = (\log k_{cat}^X - \log k_{cat}^H)$. The intercepts in the dependences of log k_{obs} *vs* acidity function J_-^E are given in Table II for the model compounds investigated.

Evaluation of Substituent Effects

Description of Substituent Effects by Hammett-Type Relationships

For the description of substituent effects in *ortho*-position we subjected to regression analysis the differences of logarithms of rate constants $\Delta\log k_{cat}^{ortho}$ and various independent variables describing electronic, steric or, as the case may be, specific (hydrogen bond) properties of substituents – σ_I, σ_R, σ^*, σ_0^i, σ_{HB}^i, σ_S^i and υ (refs[26–32]).

The only statistically significant correlations were those of the differences in logarithms of catalytic rate constants $\Delta\log k_{cat}^{ortho}$ with σ_I, σ^* or σ_0^i constants, *i.e.* constants describing the inductive effects of substituents. Figure 1 gives a diagram of the dependences of $\Delta\log k_{cat}^{ortho}$ *vs* σ_I.

The correlations with other constants (or with combinations of electronic, steric and specific substituent constants) were statistically insignificant. There have been used following combinations of explaining variables for our calculations:

• $\Delta\log k_{cat}^{ortho}$ *vs* σ_I (σ^* or σ_0^i), σ_R and υ (or σ_S^i) – parameters calculated for substituent constants σ_R and υ (or σ_S^i) were statistically insignificant,

TABLE I
Observed rate constants $k_{obs} \cdot 10^4$ (in s^{-1}) for base-catalysed hydrolysis of model phenyl esters **1** at various concentrations of sodium hydroxide in 50% (v/v) aqueous dimethyl sulfoxide at 25 °C

Compound	*c*(NaOH), mol l^{-1}																		
	0.001	0.002	0.003	0.005	0.01	0.02	0.03	0.05	0.06	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
1a	3.75	8.51	13.7	27.0	41.6	83.9	137	241	283	533	968	1370	1450	1520					
1b				4.16	8.01	16.5	23.1	41.6	51.0	78.5	172	237	302	380	483	503	566	580	682
1c					3.51	7.44	11.1	17.6	19.5	34.0	71.4	107	111	150	152	172	188	224	247
1d				6.45	11.3	26.1	39.5	69.1	75.4	143	274	391	358	500	645	698	823	813	1040
1e					3.30	6.96	10.9	16.5	20.5	30.2	67.1	94.8	127	139	188	215	185	259	277
1f										2.69	5.40	8.17	10.4	12.1	16.6	16.7	22.3	23.3	30.0
1g	19.0	41.1	66.1	137	256	554	851	1370	1610	2890									
1h				5.19	10.2	20.6	33.7	57.6	67.5	93.9	229	363	470	651	761	884	902	1080	1130
1i	15.1	33.4	50.9	106	188	426	638	1050	1200	2070									
1j	6.90	11.3	18.0	46.9	91.7	196	306	503	584	959	2070								
1k	4.78	10.1	14.7	33.0	61.5	132	200	351	414	644	1310	1850							
1l		6.21	6.62	20.6	39.4	86.5	142	238	252	433	853	1170	1260	1730					
1m				6.11	11.5	26.4	40.8	73.1	81.7	162	269	403	502	844					
1n		3.01	4.43	10.7	20.0	47.9	71.1	117	146	232	494	738	900	1240					

• $\Delta\log k_{cat}^{ortho}$ *vs* σ_0^i, σ_{HB}^i and σ_S^i – parameters obtained for substituent constants σ_{HB}^i and σ_S^i were statistically insignificant.

The somewhat surprising finding that *ortho*-substituents affect the reaction rate only by their inductive and not by mesomeric effects can be explained by imperfect coplanarity of the molecule and the substituent and, consequently, interruption of conjugation between the benzene ring and reaction centre. In such case, the electronic effects of substituents can only be transmitted over the σ bonds or through field.

It has also been confirmed that the formation of intramolecular hydrogen bond is not represent a dominant factor in the base-catalysed hydrolysis of model *ortho*-substituted phenyl esters.

TABLE II
Intercepts (a_0) in the dependence of log k_{obs} on the acidity function J_-^E relative to the unsubstituted substrate (*N*, number of measurements; *r*, correlation coefficient; *s*, residual standard deviation)

Compound	Substituent	*N*	a_0	*r*	*s*
1a	H	14	0.000	0.9981	0.056
1b	CH_3	16	–0.765	0.9994	0.025
1c	C_2H_5	15	–1.171	0.9981	0.038
1d	CF_3	16	–0.590	0.9981	0.045
1e	NO_2	10	0.766	0.9992	0.031
1f	NH_2	15	–1.164	0.9987	0.033
1g	$N(CH_3)_2$	10	–2.221	0.9961	0.030
1h	OCH_3	16	–0.598	0.9991	0.033
1i	F	10	0.649	0.9993	0.029
1j	Cl	11	0.299	0.9984	0.049
1k	Br	12	0.146	0.9995	0.027
1l	I	13	–0.065	0.9964	0.074
1m	SCH_3	11	–0.522	0.9983	0.042
1n	SO_2CH_3	13	–0.309	0.9994	0.032

From a plot of the dependence of $\Delta\log k_{cat}^{ortho}$ *vs* σ_I (see Fig. 1) it is obvious that seven points lie approximately on a straight line, the distant points belonging to the group I and group III of substituents according to the AISE theory. The points lying on the straight line belong to group II with the only exception of the $N(CH_3)_2$ substituent. For the substituents of group II (except for $N(CH_3)_2$) we obtained a correlation equation (*2*):

$$\Delta\log k_{cat}^{ortho} = -(1.993 \pm 0.081) + (4.792 \pm 0.204)\sigma_I, \qquad (2)$$

$$N = 7,\ r = 0.9955,\ s = 0.064,$$

the proportion of explained variability is 99.10%.

The position of deviating points corresponding to H, CH_3 and C_2H_5 substituents in Fig. 1 might indicate that, besides the inductive effect, which is very similar with these three substituents, their steric effects probably also operate in the base-catalysed hydrolysis of the model substances. This interpretation agrees with differences of logarithms of catalytic rate constants decreasing in the order H > CH_3 > C_2H_5. This hypothesis is also be supported by the position of the points corresponding to the NH_2 and $N(CH_3)_2$

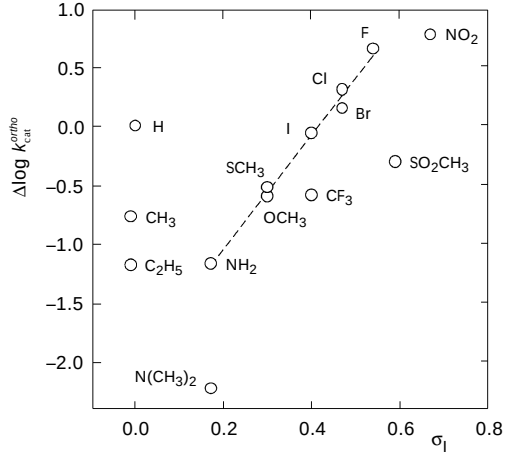


FIG. 1

Dependence of differences in logarithms of catalytic rate constants on substituent constants, $\Delta\log k_{cat}^{ortho}$, *vs* σ_I, in base-catalysed hydrolysis of phenyl 2-substituted benzoates in 50% (v/v) aqueous dimethyl sulfoxide at 25 °C

substituents: as in the previous case, these two substituents also differ very slightly in their inductive effects, but the difference in reaction rates between the respective two substrates is rather large. However, in multiple linear regression of $\Delta\log k_{cat}^{ortho}$ against σ_I and υ (or σ_S^i) constants, the explaining variable describing steric effects was statistically insignificant. Therefore, another guideline in analysis of *ortho*-substituent effects could be found in the above-mentioned differences between the substituents of individual groups (as classified according to AISE), associated with specific interactions between the substituent and reaction centre.

Description of Substituent Effects by AISE Theory

In order to verify the relationship describing the substituent effects from *ortho*-position by the AISE theory, we used the kinetic data obtained for the model compounds containing all three groups of substituents. Group I included H, CH_3, C_2H_5 and CF_3; group II included F, Cl, Br, I, NH_2, $N(CH_3)_2$, OCH_3, SCH_3; group III included NO_2 and SO_2CH_3.

The values of σ^i substituent constants are given in ref.[28]. Optimisation by the AISE theory gave correlation equation (*3*):

$$\Delta\log k_{cat}^{ortho} = -(0.591 \pm 0.309) + (0.313 \pm 1.211)[\sigma^i - (0.240 \pm 0.049)] + \\ + (6.842 \pm 1.271)[\sigma^i - (0.240 \pm 0.049)] + (2.537 \pm 1.059)[\sigma^i - \\ - (0.240 \pm 0.049)], \qquad (3)$$

$$N = 14,\ r = 0.8662,\ s = 0.424.$$

The proportion of variability explained by the AISE theory including all the above-mentioned substituents is 75.03%, but the ρ_I and ρ_E parameters are statistically insignificant. Hence, in comparison with the AISE model describing *para*-substituted model substances[12], the proportion of explained variability is much lower and the residual standard deviation is much higher. The $\Delta\log k_{cat}^{ortho}$ value predicted by this model was the same for the NH_2 and $N(CH_3)_2$ substituents, being also the same for the group of H, CH_3, and C_2H_5, and almost the same for the group of halogen substituents. Clearly, the experimental values of $\Delta\log k_{cat}^{ortho}$ distinctly decrease with increasing steric demands of the substituents. Therefore, the model was ex-

tended by a further explaining variable describing the steric demands of substituents.

After adding an explaining variable describing steric properties of substituents, we obtained a correlation in the form Eq. (*4*):

$$\Delta\log k_{\mathrm{cat}}^{ortho} = (0.615 \pm 0.432) + (2.195 \pm 0.881)[\sigma^{\mathrm{i}} - (0.303 \pm 0.045)] + \\ + (7.967 \pm 0.869)[\sigma^{\mathrm{i}} - (0.303 \pm 0.045)] + (2.530 \pm 1.029)[\sigma^{\mathrm{i}} - \\ - (0.303 \pm 0.045)] - (1.479 \pm 0.322)\upsilon, \qquad (4)$$

$$N = 14,\ r = 0.9640,\ s = 0.270.$$

The explained variability was 92.94% of total variability, the most deviating substituents being NH_2 and $N(CH_3)_2$. Some optimised parameters (ρ_I and ρ_E) are statistically insignificant, hence a mere addition of another explaining variable describing steric properties of substituents does not seem sufficient for description of the *ortho*-effect in the hydrolysis of model substances **1**.

Therefore, the substituent effects from *ortho*-position were analysed on the basis of the following consideration:

Group I (substituents H, CH_3, C_2H_5, CF_3) are, due to the absence of a free electron pair, unable to form any nucleophilic conjugation with the reaction centre. The Gibbs energy of reactants can then – in accordance with the AISE theory – be expressed by Eq. (*5*):

$$\delta G_{1,\mathrm{NC}} = \delta G_{0,\mathrm{NC}} + \rho_{1,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}), \qquad (5)$$

where the NC subscript denotes a non-conjugated substrate and I stands for the inductive effect.

Group IIA substituents are capable of nucleophilic conjugation with the reaction centre and the Gibbs energy change is described by Eq. (*6*):

$$\delta G_{2,\mathrm{C}} = \delta G_{0,\mathrm{C}} + \rho_{2,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}) + \rho_{2,\mathrm{N}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}) = \delta G_{0,\mathrm{C}} + (\rho_{2,\mathrm{I}} + \rho_{2,\mathrm{N}})(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}), \qquad (6)$$

where subscript C denotes a conjugated substrate and subscript N stands for nucleophilic conjugation with the reaction centre.

Group IIB substituents do not exhibit intramolecular conjugation with the reaction centre, which could be due to such a deviation of the substituent from planar arrangement as to make any conjugation impossible. The Gibbs energy is described by Eq. (*7*):

$$\delta G_{2,\mathrm{NC}} = \delta G_{0,\mathrm{NC}} + \rho_{2,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}), \qquad (7)$$

the meaning of symbols being the same as in the preceding equations.

Group IIA include halogen, methoxy and NH_2 substituents, whereas group IIB contained OCH_3, SCH_3 and $N(CH_3)_2$.

Group III substituents (NO_2 and SO_2CH_3) did not exhibit intramolecular conjugation with the reaction centre either, which again could be due to deviation of the substituent from planar arrangement. The Gibbs energy can then be described by Eq. (*8*):

$$\delta G_{3,\mathrm{NC}} = \delta G_{0,\mathrm{NC}} + \rho_{3,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}). \qquad (8)$$

In the process of formation of the activated complex, probably all the substituents irrespective of their nature operate through their steric effects, no conjugation being possible. The reason lies in the changed hybridisation ($sp^2 \rightarrow sp^3$) at the carbonyl carbon atom. Hence the Gibbs energy of the activated complex can be described by the following equations:

$$\delta G_1^{\neq} = \delta G_0^{\neq} + \rho_{1,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}) + \rho_S \upsilon, \qquad (9)$$

$$\delta G_2^{\neq} = \delta G_0^{\neq} + \rho_{2,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}) + \rho_S \upsilon, \qquad (10)$$

$$\delta G_3^{\neq} = \delta G_0^{\neq} + \rho_{3,\mathrm{I}}(\sigma^{\mathrm{i}} - \sigma_0^{\mathrm{iso}}) + \rho_S \upsilon. \qquad (11)$$

The difference between the Gibbs energies of the activated complex, $\delta G^{\neq}$, and of the ground state, δG, is expressed by the difference in logarithms of

catalytic rate constants, $\Delta\log k_{cat}^{ortho}$. Then it is possible to write for substituents of all groups:

$$\Delta\log k_{cat}^{ortho} = \log k_0 + \rho_{1,I}\delta_I(\sigma^i - \sigma_0^{iso}) + (\rho_{2,I} + \rho_{2,N})\delta_{IIA}(\sigma^i - \sigma_0^{iso}) + \\ + \rho_{2,I}\delta_{IIB}(\sigma^i - \sigma_0^{iso}) + \rho_{3,I}\delta_{III}(\sigma^i - \sigma_0^{iso}) + \rho_S\upsilon, \quad (12)$$

where $\rho_{1,I}$, $\rho_{2,I}$, $\rho_{2,N}$ and $\rho_{3,I}$ are the reaction constants corresponding to the substituents of the individual groups, δ_I, δ_{IIA}, δ_{IIB} and δ_{III} being Kronecker delta, which assumes discrete values of 1 or 0 depending on whether the substituent belongs or does not belong to the given group, respectively. The iso-effect σ_0^{iso} is given by the point of intersection of four straight lines of the $\Delta\log k_{cat}^{ortho}$ *vs* σ^i dependence.

Optimisation of seven parameters then gave the correlation equation (*13*) in the following form:

$$\Delta\log k_{cat}^{ortho} = (0.516 \pm 0.148) + (2.122 \pm 0.349)[\sigma^i - (0.275 \pm 0.016)] + \\ + (6.195 \pm 0.502)[\sigma^i - (0.275 \pm 0.016)] + (11.135 \pm 0.883)[\sigma^i - \\ - (0.275 \pm 0.016)] + (2.534 \pm 0.373)[\sigma^i - (0.275 \pm 0.016)] - (1.439 \pm 0.142)\upsilon, \quad (13)$$

$$N = 14,\ r = 0.9934,\ s = 0.124,$$

the explained variability amounting to 98.69%.

The optimum classification of substituents into individual groups was carried out on the basis of stepwise shifting substituents from one group to another and concomitant monitoring the significance of regression parameters and comparisons of magnitude of residual standard deviation for the individual dependences.

Relation Between ortho- and para-Substitution

Looking for analogy between substitution in *ortho*- and *para*-positions appears to be a logical consequence – in the studies of *ortho*-effect – of the fact that these two positions are alternating. Therefore, the "*ortho*-effect" was of-

ten defined as a difference between the behaviour of *ortho*- and *para*-substituted derivatives, as expressed by a measured quantity[33].

By comparing differences of the logarithms of catalytic rate constants, $\Delta\log k_{cat}^{ortho}$ and $\Delta\log k_{cat}^{para}$, it was found that the *ortho*-substituted phenyl esters are hydrolysed more slowly than their *para*-substituted counterparts, the only exception being phenyl 2-fluorobenzoate. The same anomaly was observed in hydrolysis of *ortho*-substituted ethyl benzoates in 84.8% (w/w) ethanol[34]. This behaviour can be interpreted by the low steric demand of the fluorine substituent[33], because in this case the hydrolyses of phenyl 2-fluorobenzoate and phenyl 4-fluorobenzoate proceeded at the same rate.

The correlation of differences in logarithms of catalytic rate constants, $\Delta\log k_{cat}^{ortho}$ *vs* $\Delta\log k_{cat}^{para}$, leads to similar dislocation of points to that in the case of the $\Delta\log k_{cat}^{ortho}$ *vs* σ_I dependence (see Fig. 1). Therefore, the correlation was extended by a term describing steric properties of substituents.

The two-parameter correlation (having the difference between logarithms of catalytic rate constants, $\Delta\log k_{cat}^{ortho}$, as the dependent variable, and the difference in logarithms of catalytic rate constants, $\Delta\log k_{cat}^{para}$, and the Charton steric constants υ as the explaining variables) gave the relationship whose graph is presented in Fig. 2. In this figure we can see a division of the points into two approximately linear dependences. The first is formed by the so-called conjugating substituents (classified in to group IIA accord-

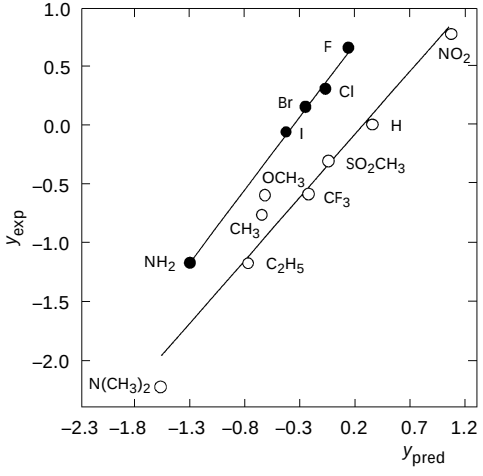


FIG. 2

The relation between experimental values $\Delta\log k_{cat}^{ortho}(y_{exp})$ and predicted values $\Delta\log k_{cat}^{ortho}(y_{pred})$

ing to the AISE theory) and the other by non-conjugating substituents belonging to groups I, IIB and III. The observed linear dependences can be described by the following correlations:

$$\Delta\log k_{\mathrm{cat}}^{ortho} = (0.895 \pm 0.076) + (0.883 \pm 0.032)\,\Delta\log k_{\mathrm{cat}}^{para} - (1.840 \pm 0.141)\upsilon, \quad (14)$$

$$N = 5,\ r = 0.9987,\ s = 0.050,$$

the explained variability being 99.46%. The other dependence valid for the so-called non-conjugating substituents has the form:

$$\Delta\log k_{\mathrm{cat}}^{ortho} = (0.083 \pm 0.165) + (0.763 \pm 0.078)\,\Delta\log k_{\mathrm{cat}}^{para} - (1.554 \pm 0.281)\upsilon, \quad (15)$$

$$N = 7,\ r = 0.9749,\ s = 0.229,$$

with explained variability being 95.05%.

From Fig. 2 it can also be seen that the most deviating point corresponds to the OCH_3 substituent, which lies at the borderline between conjugating and non-conjugating substituents. However its behaviour with respect to the reaction centre can be denoted as ambivalent. Its reclassification to conjugating substituents in terms of substituent effects from the *ortho*-position by the AISE theory caused an increase in residual standard deviation, lowering of the explained variability, and making some parameters in the optimisation statistically insignificant.

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