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Quantitative Structure–Property Relationship: XX.[1] Property–Property Correlation and Nonlinear Brønsted and Hammett Equations

I. B. Golovanov and S. M. Zhenodarova

Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Pushchino, Moscow oblast, Russia

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Abstract — A property–property correlation based on the previously suggested general expression for the quantitative structure–property relationship was obtained; it allows accurate estimation of many properties of organic compounds. Its connection with the Brønsted and Hammett equations was demonstrated.

In [2] we suggested a general structure–property relationship allowing estimation of various properties of organic compounds with a good accuracy from their structural characteristics. However, it is often necessary to estimate a certain property of a series of compounds when the relevant experimental data are insufficient but data on another property of these compounds are available. In this case, instead of a structure–property relationship, we can use a property–property relationship (see, e.g., [3]). Classical examples of such relationships are the Brønsted and Hammett equations. In this study we showed that the approach developed previously [2] can be applied to construction of a property–property relationship and analyzed its connection with the Brønsted and Hammett equations.

First and foremost, it should be noted that properties of compounds can be subdivided into (1) collective properties depending on intermolecular interactions of all the molecular fragments with the environment (boiling point, heat of vaporization, density, viscosity, etc.) and (2) local properties mainly determined by a certain group (reaction center) and adjacent fragments (reactivity, ionization constants, NMR chemical shifts, etc.).

In terms of the approach suggested in [2], a property of the first type of a molecule RX (R is an linear alkyl radical C_nH_{2n+1}, X is a functional group) can be described as follows:

$$P = \Sigma P_{ii} + \Sigma\Sigma P_{ij} + ... = P = \Sigma P_{ii+1} + \Sigma P_{ii+2} + ...,$$

where P is a property in question; P_{ii}, contribution of the ith fragment to property P (one-fragment or one-particle); and P_{ij}, contribution corresponding to interction of fragments i and j (two-fragment or two-particle). To simplify the reasoning, we neglect multiarticle contributions. Following [2], we denote one-fragment contributions P_{ii} as α_i, two-fragment contributions $P_{i,i+1}$ as β_i, etc. Since there are two kinds of atoms in a molecule RX, C atoms in fragment R and an X "atom" (functional group), we assume that $\alpha_X = \alpha_C + \alpha^*$; $\beta_{XC} = \beta_{CC} + \beta^*$; $\gamma_{XCC} = \gamma_{CCC} + \gamma^*$, etc. Assuming that R contains n C atoms, we can rewrite the expression for the property as follows:

$$P = (n + 1)\alpha + n\beta + n_\gamma\gamma + ... + \alpha^* + \beta^* + \gamma^* ... \quad (1)$$

Relationship (1) describes any collective property; by applying this equation to different properties P' and P'' of the same molecules RX, we obtain the difference $\Delta P = P' - P'' = (n + 1)(\alpha' - \alpha'') + n(\beta' - \beta'') + n_\gamma(\gamma' - \gamma'') + ... + (\alpha^{*\prime} - \alpha^{*\prime\prime}) + (\beta^{*\prime} - \beta^{*\prime\prime}) + (\gamma^{*\prime} - \gamma^{*\prime\prime}) + ... = (n + 1)\Delta\alpha + n\Delta\beta + n_\gamma\Delta\gamma + ... + \Delta\alpha^* + \Delta\beta^* + \Delta\gamma^*$. Hence, for P' we obtain

$$P' = P'' + (n + 1)\Delta\alpha + n\Delta\beta + n_\gamma\Delta\gamma + ... + \Delta\alpha^* + \Delta\beta^* + \Delta\gamma^* + ... \quad (2)$$

Thus, a property can be expressed through another property with introduction of corrections for the contributions corresponding to various interactions of the $1\cdots n$ type. Expression (2) is similar in the form to (1) but contains an additional term P''; at first glance, this equation offers no advantages, as, along with the contributions whose number is equal to the number of parameters in (1), it is necessary to know the property P'' for the whole series of molecules. However, the corrections decrease exponentially with increasing n, and in many cases it is sufficient to take into account

[1] For communication XIX, see [1].

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only a few corrections corresponding to "short-range" interactions.

Using relationship (1) for describing a property of different compounds RX and RY (X and Y are different functional groups) and assuming, as previously, that $\alpha_Y = \alpha_C + \alpha^{**}$, $\beta_{YC} = \beta_{CC} + \beta^{**}$, and $\gamma_{YCC} = \gamma_{CCC} + \gamma^{**}$, we obtain for the difference $\Delta P = P_{RX} - P_{RY}$: $\Delta P = (\alpha^* - \alpha^{**}) + (\beta^* - \beta^{**}) + (\gamma^* - \gamma^{**}) + \ldots = \Delta\alpha^* + \Delta\beta^* + \Delta\gamma^* + \ldots$ For P_{RX}, we obtain

$$P_{RX} = P_{RY} + \Delta\alpha^* + \Delta\beta^* + \Delta\gamma^* + \ldots \quad (3)$$

Relationship (3) is similar to (2), and all the above reasonings are valid for it. The same expression describes a correlation between different properties of different compounds RX and RY.

To make relationships (2) and (3) practically useful, we should make additional approximations. We showed previously that various properties of any organic compounds RX (R is a linear alkyl radical C_nH_{2n+1}, X is a functional group) [4] or linear molecules A_n [5] can be described with a simple function of n containing a small number of parameters:

$$P = k_1 + k_2\sqrt{n} + k_3/\sqrt{n}.$$

For their branched isomers, the following expression is valid [6]:

$$P = k_1 + k_2\sqrt{n} + k_3/\sqrt{n} + \delta.$$

Here δ is the correction for branchings and interactions between them. In this case, expression (2) takes the form

$$P' = P'' + \Delta k_1 + k_2\sqrt{n} + k_3\sqrt{n} + \Delta\delta. \quad (2^*)$$

In P' and P'', the corrections for branchings and interactions between them are taken into account similarly; therefore, Eq. (2*) can be rewritten as

$$P' = k_1 + k_2P'' + k_3\sqrt{n}\ . \quad (4)$$

Here the parameters k_2 and k_3 differ in the sense from those in the above relationships. We assumed that the last two contributions in (2*) are relatively small and can be approximately taken into account by introducing the parameter k_2.

Similarly, Eq. (3) can be rewritten as follows:

$$P_{RX} \approx k_1 + k_2P_{RY} + k_3\sqrt{n}\ . \quad (5)$$

If we neglect the term $k_3n^{1/2}$, then Eqs. (4) and (5) actually express the Brønsted relationship, a prototype of the majority of correlation equations and a particular case of the linear free energy relationship [7, 8] underlying other relationships commonly used for describing correlations of local properties.

A property of the second kind, a local property of fragment X in RX, can be described as follows:

$$P_{X(RX)} = P_X + \Sigma P_{Xi} + \Sigma P_{lk}^* = \alpha_X + m\beta_{XC} + n\gamma_{XCC} + \ldots + n^*g^*_{CCC} + \ldots$$

Here α_X is the contribution of fragment X to a property; β_{XC}, contribution corresponding to interaction of fragment X with the adjacent C atom (1···2 interaction); γ_{XCC}, contribution corresponding to interaction of fragment X with the next C atom (1···3 interaction), etc.; γ^*_{CCC} is the contribution corresponding to 1···3 interaction in fragment R, responsible for the nonadditive effect of R on P_X. Apparently, in this case also a property of molecules RX can be expressed through another property in the same way as different properties of molecules RX and RY can be expressed through each other.

For linear molecules RX, the local properties depending on n vary more steeply than the collective properties, and in many cases the influence of the fifth and more remote neighbors can be neglected (attenuation of the inductive effect). Therefore, for estimating local properties, we can assume $P = k_1 + k_2/(n + 1)^{k_3}$. Here n is the number of C atoms in fragment R. The unity is added to define the length of a molecule by the number of "heavy" fragments (taking into account the contribution of X) and to avoid problems in the case of R = H when $n = 0$. The parameter k_3 was determined by using the latter relationship for reproducing the pK_a values and ^{13}C NMR chemical shifts of carboxylic acids. With different sets of data, this parameter appears to be different; since in what follows it is necessary to use the same relationship for different properties, we chose $k_3 = 4$, which allows estimation of various properties with a good accuracy. The parameter $k_3 = 2$, often used in correlation equations, gives less accurate results in our case. Thus, to estimate local properties, we will use the relationship

$$P = k_1 + k_2/(n + 1)^4. \quad (6)$$

In Table 1 we give as example the pK_a values for a series of carboxylic acids RCOOH and log rate constants of base hydrolysis of their methyl esters $RCOOCH_3$ (in water at 15°C), calculated by (6); it is seen that this relationship well reproduces the available experimental data.

The ^{13}C NMR chemical shifts of the C^α atoms in

Table 1. Log ionization constants of carboxylic acids RCOOH and rate constants of base hydrolysis of their methyl esters $RCOOCH_3$, calculated by (6)

R	pK_a		ln k	
	experiment [9]	calculation[a]	experiment [10]	calculation[a]
H	3.70	3.70	1.32	1.33
CH_3	4.76	4.78	–1.01	–1.11
C_2H_5	4.88	4.84	–1.06	–1.24
C_3H_7	4.83	4.85	–1.30	–1.27
C_4H_9	4.83	4.85	–1.35	–1.27
C_5H_{11}	4.84	4.85	–1.36	–1.27
C_6H_{13}	4.89	4.85	–1.36	–1.28
		r 0.9980[b]		r 0.9942[b]
		s 0.0299		s 0.1153

[a] k_1 4.8542 ± 0.0124, k_2 –1.1552 ± 0.0327 (for pK_a) and k_1 –1.2768 ± 0.4770, k_2 2.6052 ± 0.1260 (for ln k). [b] At k_3 = 2, r 0.9856, s 0.0792 (for pK_a) and r 0.9940, s 0.1169 (for ln k).

Table 2. ^{13}C NMR chemical shifts of the C^{α} atoms in alcohols ROH and carboxylic acids RCOOH[a]

R	ROH		RCOOH	
	experiment [9]	calculation[b]	experiment [10]	calculation[b]
CH_3	49.3	49.0	21.1	20.5
C_2H_5	57.3	59.7	27.8	31.8
C_3H_7	63.9	61.5	36.3	33.7
C_4H_9	61.7	62.0	34.1	34.2
C_5H_{11}	62.1	62.2	34.5	34.4
C_6H_{13}	62.2	62.2	35.1	34.4
		r 0.9594		r 0.9299
		s 1.7101		s 2.4239

[a] Here and hereinafter, the chemical shifts are given in ppm relative to TMS. [b] Calculated by relationship (6), k_1 62.3187 ± 0.8181, k_2 –213.5402 ± 31.3843 (for ROH) and k_1 34.5390 ± 1.1596, k_2 –224.8460 ± 44.4845 (for RCOOH).

alcohols and carboxylic acids, calculated in the same approximation, are given in Table 2. It is seen that the experimental data are reproduced with a reasonable accuracy (within the framework of approach [2], the accuracy can be improved by increasing the number of parameters, but here we discuss other problems).

Using approximation (6), we can obtain an expression relating P' and P'':

$$P' = k_1 + k_2P'' + k_3/(n + 1)^4. \quad (7)$$

It is an analog of (4) for collective properties, etc. All the above reasonings concerning (4) and (5) will be valid for (7).

Until now, we assumed that R is a hydrocarbon radical C_nH_{2n+1}. Let us now consider the case when R contains a heteroatom Y which can be located in various positions relative to X. To describe the effect of Y on the properties of X, we assume $\alpha_Y = \alpha_C + \alpha_Y^*$ and make a correction to a property for the introduction of a heteroatom Y into a position separated from X by n_Y bonds, in accordance with (6): $\Delta P_Y = \alpha_Y^*/n_Y^4$. When several heteroatoms Y are introduced, it is nec-

Table 3. Boiling points, heats of vaporization (ΔH_v), dielectric constants (ε), and surface tension (γ) of saturated hydrocarbons and of their hydroxy and chloro derivatives [12]

R	bp, °C			$\Delta H_{vap}(RCH_3)$, kJ mol^{-1}	ε(ROH) (25°C)	γ(ROH), dyne cm^{-1} (25°C)
	RCH_3	RIOH	RCl			
CH_3	–88.6	64.7	–24.0	14.69	32.66	22.07
C_2H_5	–42.1	78.3	12.7	19.04	24.30	21.97
C_3H_7	–0.5	97.2	46.8	22.44	20.10	23.32
C_4H_9	36.1	117.7	77.8	25.79	17.10	24.93
C_5H_{11}	68.7	137.3	108.2	28.85	13.90	25.36
C_6H_{13}	98.5	157.6	135.0	31.77	13.30	25.81
C_7H_{15}	125.7	176.5	159.0	34.41	12.10	26.40
C_8H_{17}	150.8	195.2	181.5	36.91	10.34	27.10
$(CH_3)_2CH$	–11.7	82.3	35.4	21.30	18.30	20.93
$(CH_3)_2CHCH_2$	27.9	107.7	68.7	24.69	17.70	19.00
$(CH_3)_3C$	9.5	82.4	50.7	22.74	10.90	17.71

Table 4. Mutual coefficients correlation of the compound properties given in Table 3

Property	T_b (RCH_3)	T_b (ROH)	T_b (RCl)	$\Delta H_{vap}(RCH_3)$	ε(ROH)	γ(ROH)
$T_b(RCH_3)$	1	0.9717	0.9989	0.9987	–0.8516	0.6662
T_b(ROH)		1	0.9815	0.9815	–0.7079	0.7894
T_b(RCl)			1	0.9998	–0.8283	0.6946
$\Delta H_{vap}(RCH_3)$				1	–0.8279	0.6967
ε(ROH)					1	–0.2753
γ(ROH)						1

Table 5. Boiling points, dielectric constants, and surface tension of aliphatic alcohols ROH

R	T_b, °C			ε(25°C)			γ(25°C), dyne cm^{-1}		
	experiment [12]	this work		experiment [12]	this work		experiment [12]	this work	
		a	b		a	b		a	b
CH_3	64.7	46.3	60.6	32.66	26.90	31.76	22.07	19.65	22.63
C_2H_5	78.3	73.5	77.8	24.30	23.28	24.74	21.97	20.97	21.88
C_3H_7	97.2	97.7	100.3	20.10	20.03	20.89	23.32	22.16	22.69
C_4H_9	117.7	119.1	121.6	17.10	17.17	18.03	24.93	23.20	23.73
C_5H_{11}	137.3	138.1	141.0	13.90	14.63	15.60	25.36	24.13	24.73
C_6H_{13}	157.6	155.5	159.0	13.30	12.31	13.49	25.81	24.98	25.72
C_7H_{15}	176.5	171.4	175.3	12.10	10.18	11.51	26.40	25.76	26.57
C_8H_{17}	195.2	186.1	190.1	10.34	8.22	9.59	27.10	26.48	27.32
$(CH_3)_2CH$	82.3	91.2	82.7	18.30	20.90	18.00	20.93	21.84	20.05
$(CH_3)_2CHCH_2$	107.7	114.3	108.7	17.70	17.81	15.91	19.00	22.97	21.80
$(CH_3)_3C$	82.4	103.6	79.8	10.90	19.25	11.16	17.71	22.45	17.47
r		0.9717	0.9889		0.8516	0.9889		0.6662	0.9389
s		10.8002	1.1008		3.6572	1.1008		2.4310	1.1896

[a] Calculation by relationship (9) k_1 98.0383 ± 3.6323, k_2 0.5837 ± 0.0473 (*for* T_b); k_1 19.9916 ± 1.2300, k_2 –0.0780 ± 0.0160 (for ε); k_1 22.1749 ± 0.8176, k_2 0.0285 ± 0.0106 (for γ). [b] Calculation by relationship (4*), k_1 334.9096 ± 26.1464, k_2 1.5721 ± 0.1100, k_3 –153.0186 ± 14.8893 (for T_b); k_1 100.5572 ± 8.4383, k_2 0.2582 ± 0.0355, k_3 –45.9231 ± 4.8053 (forε); k_1 71.7257 ± 9.1187, k_2 0.2353 ± 0.0384, k_3 –28.2444 ± 5.1927 (for γ).

essary to make corrections for their interaction γ_{YCY}. Then, the expression for the property will be

$$P = k_1 + k_2/(n + 1)^4 + \Sigma\alpha^*/n_Y^4 + \Sigma\gamma_{YCY}. \quad (8)$$

It is quite probable that relationship (7) between different properties P' and P'' will remain the same in this case also, because the effects from introduction of a heteroatom are manifested similarly in properties of the same type.

Both collective and local properties of RX molecules are nonlinear with respect to *n*; therefore, the Brønsted and Hammett equations linking these properties should be nonlinear. Equations (4), (5), and (7) are full analogs of the Brønsted and Hammett equations, but they reproduce more accurately the correlations between the properties of both the same and different compounds.

To confirm the above reasonings, let us consider specific examples. Some collective properties of saturated hydrocarbon molecules are given in Table 3, and the coefficients of correlation between these properties, in Table 4. The boiling points of all these compounds well correlate with the enthalpies of vaporization, so that it is possible to estimate with a good accuracy the properties of compounds using linear relationships (of the Brønsted or Hammett type) with the properties of other compounds. For the dielectric constant (ε) and surface tension (γ), the correlation coefficients are considerably lower, but in these cases also fairly accurate estimates can be made by taking into account nonlinear contributions. In Table 5 we give as example the boiling points, dielectric constants, and surface tension of aliphatic alcohols, esti-

Table 6. Distribution factors of aliphatic alcohols ROH in the system octanol–water ($\log P$) and between the gas phase and water ($\log L^w$)

R	$\log P$		$\log L^w$		
	experiment [13]	calculation[b]	experiment [14]	calculation	
				a	b
H	–1.38	–1.52	4.64	3.83	4.48
CH_3	–0.77	–0.79	3.74	3.98	3.91
C_2H_5	–0.31	–0.23	3.67	3.85	3.67
C_3H_7	0.25	0.32	3.57	3.75	3.44
C_4H_9	0.88	0.83	3.46	3.52	3.35
C_5H_{11}	1.56	1.35	3.35	3.37	3.23
C_6H_{13}	2.03	2.12	3.23	3.19	3.15
C_7H_{15}	2.72	2.65	3.09	3.00	3.09
$(CH_3)_2CH$	0.05	0.18	3.48	3.52	3.61
$(CH_3)_2CHCH_2$	0.76	0.69	3.30	3.46	3.40
$(CH_3)_3C$	0.35	0.54	3.28	3.34	3.48
r		0.9948		0.7229	0.9448
s		0.1298		0.3035	0.1472

[a] Calculation by relationship (10), k_1 –2.6361± ±0.1157, k_2 1.0211±0.0348 (for $\log P$) and k_1 5.6869±0.6938, k_2 1.2739± 0.4059 (for $\log L^w$). [b] Calculation by relationship (4**), k_1 4.1962±0.4320, k_2 –0.9475±0.4492, k_3 –1.0980±0.1996.

Table 7. Log ionization constants of carboxylic acids RCOOH and rate constants of base hydrolysis of their methyl esters $RCOOCH_3$, calculated from the ^{13}C NMR chemical shifts of the carbonyl carbon atoms in the acids

R	δ_C^{carb} [11]	pK_a		$\ln k$	
		experiment [9]	calculation	experiment [10]	calculation
CH_3	177.2	4.76	4.70	–1.01	–0.85
C_2H_5	180.4	4.88	5.09	–1.06	–1.50
C_3H_7	179.6	4.83	4.72	–1.30	–1.10
C_4H_9	179.7	4.83	4.72	–1.35	–1.11
C_5H_{11}	180.1	4.84	4.84	–1.36	–1.25
C_6H_{13}	180.2	4.89	4.87	–1.36	–1.29
$ClCH_2$	173.8	2.83	2.90	1.47	1.01
Cl_2CH	169.7	1.30	1.43	2.87	2.67
Cl_3C	167.1	0.65	0.53	3.37	3.69
r			0.9977		0.9890
s			0.1356		0.3369

[a] Calculation by relationship (7*), k_1 –54.9521± ±1.6775, k_2 0.3319±0.0095, k_3 13.4732±2.4210 (for pK_a) and k_1 67.3717±4.1661, k_2 –0.3810±0.0236, k_3 –11.3270±6.0128 (for $\ln k$).

mated from the boiling points of hydrocarbons using relationships (9) and (4*).

$$P_{ROH} = k_1 + k_2 T_b^{RCH_3}, \quad (9)$$

$$P_{ROH} = k_1 + k_2 T_b^{RCH_3} + k_3\sqrt{n}\ . \quad (4^*)$$

Table 5 shows that, when the nonlinear contribution is taken into account [relationship (4*)], the estimation accuracy is considerably improved.

In Table 6 we give the properties of alcohols, calculated using relationships (10) and (4**) between the analogous properties of alcohols and isoelectronic hydrocarbons (here we consider not only linear but also branched molecules):

$$P_{ROH} = k_1 + k_2 P_{RCH_3}, \quad (10)$$

$$P_{ROH} = k_1 + k_2 P_{RCH_3} + k_3\sqrt{n}\ . \quad (4^{**})$$

In the case of the distribution factors ($\log P$) in the octanol–water system, estimates of a good accuracy can be obtained with linear relationship (10), whereas for the distribution factors between the gas phase and water ($\log L^w$) good accuracy is attained only when taking into account the nonlinear contribution. Thus, when taking into account the nonlinear contribution, it is possible to calculate properties of compounds from the data on collective properties of compounds of another series.

Let us then consider local properties of organic compounds such as, e.g., ^{13}C NMR chemical shifts of the carbonyl carbon atom in carboxylic acids RCOOH, ionization constants of these acids, and rate constants of base hydrolysis of their methyl esters $RCOOCH_3$. It is natural to assume that the ^{13}C NMR chemical shifts of the carbonyl carbon atom (δ_C^{carb}) characterize the electron distribution in the COO groups, which also governs, to certain extent, the ionization constants (pK_a) and chemical reactivity ($\ln k$) of carboxy derivatives. Therefore, we can assume that the pK_a values of carboxylic acids or $\ln k$ values for the base hydrolysis of their methyl esters can be described by relationship (7), which has the following form in this specific case:

$$P = k_1 + k_2\delta_C + k_3/(n+1)^4. \quad (7^*)$$

The data obtained using (7*) are given in Table 7; they show a good agreement with the experiment.

Table 8. Log rate constants of base hydrolysis of methyl esters of carboxylic acids $RCOOCH_3$ and dissociation constants of carboxylic acids RCOOH, calculated by different methods

R	ln *k*				pK_a	
	experiment [10]	calculation			experiment [9]	calculation[a]
		a	b	c		
H	1.32	0.10	1.34	1.33	3.70	3.70
CH_3	–1.01	–1.13	–1.12	–1.12	4.76	4.76
C_2H_5	–1.06	–1.27	–1.33	–1.25	4.88	4.82
C_3H_7	–1.30	–1.21	–1.28	–1.27	4.83	4.83
C_4H_9	–1.35	–1.21	–1.29	–1.27	4.83	4.83
C_5H_{11}	–1.36	–1.22	–1.30	–1.28	4.84	4.83
C_6H_{13}	–1.36	–1.28	–1.36	–1.28	4.89	4.83
$(CH_3)_2CH$	–1.36	–1.25	–1.32	–1.27	4.86	4.83
$ClCH_2$	1.47	1.11	1.03	1.41	2.83	2.76
Cl_2CH	2.87	2.88	2.78	2.93	1.30	1.37
Cl_3C	3.37	3.63	3.53	3.35	0.65	0.63
$HOCH_2$	0.00	–0.04	–0.10	0.02	3.82	3.64
CH_3OCH_2	0.20	0.29	0.22	0.00	3.53	3.65
$C_2H_5OCH_2$	–0.08	018	0.10	–0.01	3.63	3.66
$C_3H_7OCH_2$	–0.06	0.14	0.06	–0.01	3.66	3.66
$C_4H_9OCH_2$	–0.06	0.14	0.06	–0.01	3.66	3.66
$CH_3O(CH_2)_2$	–1.07	–0.78	–0.86	–1.03	4.46	4.60
$CH_3O(CH_2)_3$	–1.12	–1.04	–1.11	–1.20	4.68	4.76
r		0.9716	0.9941	0.9981		0.9983
s		0.3596	0.1707	0.1044		0.0835

[a] Calculation by relationship (11), k_1 4.3855 ± 0.2865, k_2 –1.1589 ± 0.0706. [b] Calculation by relationship (7**), k_1 4.2773 ± 0.1367, k_2 –1.1522 ± 0.0335, k_3 1.3231 ± 0.1766. [c] Calculation by relationship (8*), k_1 –1.2817 ± 0.0360, k_2 2.6110 ± 0.1112, α_{Cl} 42.5481 ± 1.3035, γ_{ClCl} –1.1168 ± 0.0915, α_O 20.3370 ± 0.9550 (for ln *k*) and k_1 4.8319 ± 0.0288, k_2 –1.1290 ± 0.0890, α_{Cl} –32.9147 ± 1.0426, γ_{ClCl} 0.6561 ± 0.0732, α_O –18.7839 ± 0.7639 (for pK_a).

We calculated the log rate constants of base hydrolysis of methyl esters of carboxylic acids from the ionization constants of the acids using (11) and (7**):

$$\ln k = k_1 + k_2 pK_a. \quad (11)$$

$$\ln k = k_1 + k_2 pK_a + k_3/(n + 1)^4. \quad (7^{**})$$

The results (Table 8) show that, when the nonlinear contribution is taken into account, the accuracy of estimating ln *k* is considerably improved. In accordance with (7**), for such calculations it is necessary to know three parameters (k_1, k_2, and k_3) and the experimental value of pK_a for each example.

We found that ln *k* and pK_a can be fairly accurately estimated using directly the approach suggested in [2] [Eq. (8)]. For the available experimental data (R contains several chlorine atoms arranged similarly relative to the ester or carboxy group, or an oxygen atom in different positions relative to this group), Eq. (8) can be written as follows:

$$P = k_1 + k_2/(n + 1)^4 + n_{Cl}\alpha^*_{Cl}/n^4_{Cl} + m\gamma_{ClCl} + n_O\alpha^*_O/n^4_O. \quad (8^*)$$

The sense of all the contributions was explained when deriving Eq. (8); *P* is ln *k* or pK_a. The results obtained with Eq. (8*) (its use requires only the knowledge of the molecular structure and contributions corresponding to the molecular fragments) are given in Table 8; they are well consistent with the experiment.

Thus, the above examples show that the general expression for the structure–property relationship, suggested in [2], not only allows estimation of various properties of organic compounds of various classes,

but also shows connection with the previously suggested approaches, extending the concepts developed in them.

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