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Calculations of Dissociation Constants of Carboxylic Acids by Empirical and Quantum-Chemical DFT Methods

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Abstract—Dissociation constants of 15 carboxylic acids in water, methanol, and DMSO were calculated by empirical and quantum-chemical DFT methods. The maximal error of the empirical calculation was 1.4%. A comparative analysis of the results obtained was carried out.

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The interest to the old problem of calculating acidity (basicity) constants of organic compounds, which has been restored in the last two-three years, is caused by a rapid development of biological chemistry, biophysics, pharmacology, and allied sciences. Quantitative values of acid–base properties of biologically active substances in aqueous systems turned out to be demanded for the study and prediction of their pharmacological properties. It promoted the development of new methods of the experimental determination of dissociation constants (pK_a) of organic compounds for bioscreening [1, 2]. New models of calculating pK_a values were developed in parallel. In overwhelming majority these are QSPR methods using intermediate results of quantum-chemical calculations as descriptors. However the results of [3–18] point to the fact that the problem of the agreement between the calculated pK_a values and the experimental data is not solved finally. The main difficulty consists in a proper accounting for the effect of the medium (solvent). Numerous publications of the last years [19–29] and recent monographs [30–33] are devoted to the solution of this problem.

The quantum-chemical theoretical calculations of the protonation energy in a gas phase rather well agree with the experiment [34–39], whereas the error in the pK_a calculations in solutions up to the most recent time remains fairly large [40–44]. It can originate from the important role of the solvation of the acid molecule, proton, and the carboxylate ion prone to a specific solvation. Pal'm [45] once pointed out that the interaction with a solvent was the factor defining the pK_a value to a much greater extent than the protonation energy of the acid. These reasons were extended in [46] where it was concluded from a critical analysis of earlier works that empirical corrections should be introduced into calculated pK_a values for better agreement with the experiment.

Earlier we have advanced and developed an empirical method for calculation of certain physicochemical properties of organic compounds from the experimental data on the other properties. The method is based on the principle of free energy linearity in relation to the atomic composition and the assumption that for a certain pair of physicochemical properties X and Y in a certain series of compounds the deviations (δX and δY) of the experimental values of these properties X^{ex} and Y^{ex} linearly depend on the sums of atomic contributions to these values ($\Sigma g_i X_i$ and $\Sigma g_i Y_i$). This idea can be expressed by Eqs. (1) and (2).

$$\delta X = X^{ex} - \sum_i g_i X, \quad (1)$$

$$\delta Y = Y^{ex} - \sum_i g_i Y_i = a\delta X + b. \quad (2)$$

Here a and b are constant coefficients, g_i is the number of ith atoms in a molecule of the compound, and X_i and Y_i are the contributions of the ith atom to the corresponding experimental molecular parameter. However these expressions are not the unique mathematical model expressing the idea of the method, but only one of examples. It is important to note that the presence of a pronounced correlation between experimental X^{ex} and Y^{ex} is not indispensable for the application of the method.

We applied this method successfully to the calculations of polarizabilities, ionization potentials [47], and protonation energies [48] from the molecular volume and of one thermodynamic parameter from another [49] for a wide set of organic substances, and also for the calculation of pK_a values of 34 carboxylic acids depending on experimental properties of 11 solvents [50]. Unknown parameters were found by numerical methods and partially were selected manually.

We have compared [50] thus calculated data with pK_a values calculated by quantum chemistry methods within the last eight years. In 169 cases from 174 the agreement of the empirically calculated and experimental data was better than for analogous quantum-chemical data calculated in 19 papers of 24 publications under consideration.

To check the assumption on the better agreement of the results of empirical calculations with experimental data we decided to calculate pK_a by various methods for the same set of organic compounds in several solvents. For this purpose we have carried out our own quantum-chemical DFT calculations of pK_a for some carboxylic acids. To reduce the empirical method to the form more convenient for practical uses, we have modified it by excluding manual selection of parameters, i.e. all unknown parameters were found by numerical methods. According to our concept, joint searching for all empirical parameters related to acids and solvents can reveal certain trends and interrelations between them and properties of the objects under study and/or solvents.

Carboxylic acids were selected as subjects for the study as their pK_a were studied experimentally most systematically compared to other types of organic acids. As the consequence, the greatest array of reliably determined experimental pK_a values, which was used in [50], is available.

Technique of quantum-chemical calculations. In the present work the acid dissociation processes are considered as reactions of proton transfer from an acid molecule (HA) on a solvent molecule [51]. For aqueous solutions this process can be presented by Eq. (3), and for solutions in methanol and dimethyl sulfoxide, by Eqs. (4) and (5), respectively.

$$HA + H_2O \rightleftarrows A^- + H_3O^+, \quad (3)$$

$$HA + CH_3OH \rightleftarrows A^- + CH_3OH_2^+, \quad (4)$$

$$HA + (CH_3)_2SO \rightleftarrows A^- + (CH_3)_2SOH^+. \quad (5)$$

The calculations of electronic structure of the compounds were fulfilled by the DFT B3LYP method in the 6-31G** basis using the Jaguar 7.0 program complex [52]. Thermodynamic characteristics of the reactions were found in the calculations of normal vibration frequencies of the compounds on the basis of DFT force fields in harmonic approximation with the use of the following relations: $\Delta G^0 = \Delta H^0 - T\Delta S^0$ (T = 298 K) and $\Delta H^0 = \Delta E^{gas} + \Delta ZPE + \Delta H'$. Here ΔE^{gas} is a difference between total energies of systems: $\Delta E^{gas} = E_{tot}(H_3O^+) - E_{tot}(H_2O)$, $\Delta E^{gas} = E_{tot}(A^-) - E_{tot}(HA)$; ΔZPE is a difference between energies of zero vibration levels, ΔS^0 is a difference between standard entropies of formation, and $\Delta H'$ is a difference in energies corresponding to the molecular degrees of freedoms ($H' = E_{vibr} + E_{rot} + E_{trans} + RT$). The values of the dissociation constants were calculated by the formula $pK_a^{DFT} = \Delta G_{solv}/2.3RT$. Solvation energies of the compounds were calculated within the polarizable continuum model [53–56]. Acid dissociation constants of the compounds under consideration were obtained also with the use of "The pK_a Prediction Module" subprogram [52] ($pK_a^{DFT(PM)}$ values). The results of the DFT calculations for the reactions in aqueous media are given in Table 1.

Our analysis has shown that the basic difficulty in the calculation of pK_a values consists in correct estimation of the difference in the energies of the molecule and the anion, and also between their solvation energies, as the contributions of ΔZPE, $\Delta H'$, and ΔS^0 in ΔG^0 values are insignificant. For example, in the case of CH_3COOH they add up to 5.3 kJ mol^{-1} that changes the calculated pK_a value of 18.0 only by 0.9 logarithmic unities. The use of the more extended basis CC–PVTZ(–F)+ recommended in the Jaguar 7.0 program [52] instead of the standard 6-31G** basis set led to the decrease in the calculated pK_a value to 15.9. The solvation energies of charged particles A^- and H_3O^+ play a much greater role than the solvation energies of neutral molecules HA and H_2O, as they make a contribution to the ΔG_{solv} value greater by an order of magnitude. The solvation energy of the anion $E_{solv}(CH_3COO^-)$ (–321.4 kJ mol^{-1}) calculated in the present work proved to be close enough to the experimental value of 320.5 kJ mol^{-1} [57] that was not true for the solvation energy of the H_3O^+ cation (–418.3 instead of the experimental value 461.0 kJ mol^{-1}). The calculation of pK_a with the use of the data calculated in the CC–PVTZ(–F)$^+$ basis and the specified experimental solvation energies of the charged ions has reduced the pK_a value to 9.2, but has

Table 1. Energy characteristics of compounds (difference between total energies ΔE^{gas}, contributions to the free energy of systems *ZPE*, *H'*, S^0, and solvation energies E_{solv} in water), values of dissociation constants according to DFT calculations (pK_a^{DFT}, $pK_a^{DFT(PM)}$), and the experimental data (pK_a^{exp})

Compound (H_2O, H_3O^+)(HA, A^-)	ΔE^{gas}, kJ mol^{-1}	*ZPE*, kJ mol^{-1}	*H'*, kJ mol^{-1}	S^0, J mol^{-1} K^{-1}	E_{solv}, kJ mol^{-1}	pK_a^{DFT}	$pK_a^{DFT(PM)}$	pK_a^{exp}
H_2O		55.5	9.9	188.8	–34.5			
H_3O^+	–741.5	92.1	10.0	202.2	–418.3			
HCOOH		88.1	10.9	248.6	–30.3	16.9	2.9	3.80
$HCOO^-$	1512.7	54.1	10.3	238.3	–323.0			
CH_3COOH		160.8	14.3	284.9	–30.6	9.3	3.7	4.76
CH_3COO^-	1523.8	127.1	14.3	275.6	–321.4			
$CH_2ClCOOH$		138.7	16.5	321.5	–36.9	13.6	2.4	2.87
CH_2ClCOO^-	1452.1	105.8	15.7	312.2	–288.1			
$CHCl_2COOH$		114.5	19.0	345.4	–32.6	10.9	1.9	1.26
$CHCl_2COO^-$	1415.1	81.2	18.5	343.2	–260.6			
CCl_3COOH		86.8	22.1	372.7	–23.1	7.22	1.3	0.70
CCl_3COO^-	1384.0	53.1	21.9	376.4	–239.1			
PhCOOH		302.2	21.1	351.8	–28.1	18.9	4.0	4.20
$PhCOO^-$	1482.3	269.5	20.4	348.9	–278.3			
3-$MeOC_6H_4COOH$		386.6	28.1	412.6	–30.2	16.7	4.1	4.08
3-$MeOC_6H_4COO^-$	1480.0	353.8	27.5	414.5	–289.2			
3-MeC_6H_4COOH		373.3	25.7	388.6	–29.0	17.6	4.1	4.27
3-$MeC_6H_4COO^-$	1485.0	340.2	23.0	369.0	–291.0			
3-ClC_6H_4COOH		276.8	24.3	382.5	–26.6	15.5	3.8	3.83
3-$ClC_6H_4COO^-$	1455.4	244.1	23.5	377.9	–270.5			
3-BrC_6H_4COOH		274.9	25.0	396.0	–26.3	15.6	–	3.81
3-$BrC_6H_4COO^-$	1454.1	242.4	24.3	390.8	–268.7			
3-IC_6H_4COOH		274.3	25.4	404.1	–24.9	17.6	–	3.86
3-$IC_6H_4COO^-$	1454.4	241.9	24.6	398.2	–255.3			
3-$NO_2C_6H_4COOH$		308.5	27.8	413.2	–37.0	14.7	3.4	3.47
3-$NO_2C_6H_4COO^-$	1433.6	276.3	27.0	408.6	–263.2			
$PhCH_2COOH$		373.5	22.3	364.7	–16.7	16.5	4.6	4.31
$PhCH_2COO^-$	1483.4	342.9	24.3	393.6	–278.0			
EtCOOH		236.5	15.3	296.8	–28.2	20.3	4.2	4.87
$EtCOO^-$	1511.2	202.9	14.6	292.8	–298.3			
PrCOOH		310.3	20.7	345.0	–26.4	21.3	4.6	4.85
$PrCOO^-$	1509.2	277.4	20.1	344.9	–289.7			
t-BuCOOH		381.5	24.5	371.0	–26.3	20.4	4.5	5.03
t-Bu-COO^-	1498.8	348.9	23.4	360.1	–286.1			
$CyCH_2COOH$ [a]		557.5	26.1	388.5	–22.5	20.9	5.0	4.90
$CyCH_2OO^-$ [a]	1495.9	524.9	27.3	401.4	–272.4			

[a] Cy is cyclohexyl (hereinafter).

not led to the experimental value pK_a^{exp} 4.8. Thus it becomes obvious that the problem of overrating pK_a values calculated by the DFT method as compared to the experimental values is due to insufficient accuracy of the calculation of the energies of the molecule and its anion. This problem can be solved by using wider basis sets. It is rather difficult to find basis sets providing results adequate to the experimental data for the problems are connected with the calculation of a large array of the data on acidity of solutions in various solvents. Therefore a necessity arises to introduce calibration corrections to the calculated pK_a values.

It is seen from the figure that, despite the overestimated calculated pK_a values, as a whole they reflect a trend in the variation of the experimental value in the series of acids under study. Using the idea proposed in [46], we have carried out linear approximation (6).

$$pK_a^{DFTapp} = apK_a^{DFT} + b. \quad (6)$$

The resulting coefficients a and b were used for the calculation of the approximated pK_a^{DFT} values. Correlation parameters are given in Table 2.

Empirical method. The choice of carboxylic acids, for which pK_a were calculated by the empirical method, corresponded to a series of compounds, for which the quantum-chemical calculations (Table 1) were performed. Acids considerably differing in structures were deliberately selected for the calculations. Thus, the array of pK_a value for 15 acids in 3 solvents, i.e. 45 values, of which 6 were unknown, was treated.

In the previous works on the pK_a calculations for carboxylic [50] and NH-acids [58] we applied successfully modified Eq. (2) to calculate dissociation constant pK_a^{jk} of a certain acid (to which a number k was assigned) in a solvent (to which a number j was assigned).

$$pK_a^{jk} = a_k(X_j^{ex} - X_k\Sigma g_{ij}X_i) + Y_j + b_k. \quad (7)$$

Here a_k and b_k are empirical parameters, X_i is the contribution of the ith atom to the experimental molecular parameter of a solvent, g_{ij} is the number of the ith atoms in the jth molecule of the solvent, X_k is a scale factor at the sum of atomic contributions to the numerical value of the solvent parameter X^{ex}. The coefficient Y_j is accepted as a constant of the jth solvent (though it also includes a characteristic of the object in a latent form).

The application of Eq. (7) was expedient, as large arrays of experimental pK_a values of 33 carboxylic acids in 11 solvents [50] and of 24NH-acids in 8 solvents [58] were treated, a significant number of experimental values being absent. In the first case 115 parameters were required for the evaluation of 363 pK_a values, and 98 of them were unknown.

As in the present work we dealt with a much smaller data array (only 45 pK_a values), the number of empirical parameters necessary for the calculation of pK_a values by Eq. (7) exceeds the number of values to be calculated. If we designate the number of acids as K, the number of solvents as J, and the number of atoms included in the consideration as I, in this case it turns out that $3K + J + I = 52$ parameters are necessary for the calculation of 45 pK_a values of 15 acids in 3 solvents with the atoms C, H, O, and S. It is obvious that it is senseless to apply Eq. (7) for treating data arrays of a great number of acids in a small number of solvents. Therefore we have reduced Eq. (7) to form (8) with the aim to decrease the number of empirical parameters, especially of those related to acids.

Table 2. Parameters of correlations in Eq. (6) for reducing pK_a^{DFT} values to pK_a^{DFTapp} for various media

Medium	a	b	R
Water	0.3168	–1.453	0.964
Methanol	0.4605	–0.6746	0.936
DMSO	0.6978	+3.030	0.913

$$pK_a^{jk} = a_k X_j^{ex} - c_k X_j + Y_j + b_k. \quad (8)$$

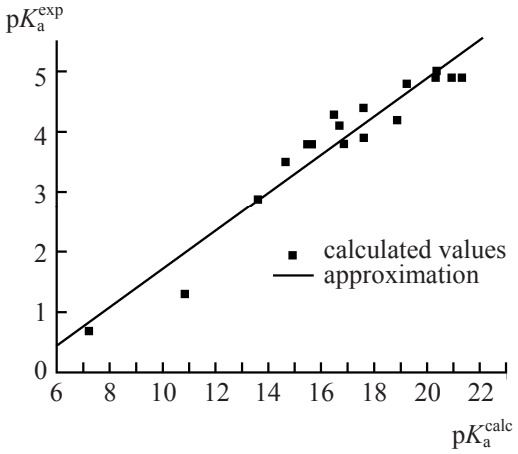
Here X_j are empirical parameters of a solvent, which represent function (9) of atomic contributions.

$$X_j = \sum_i g_{ij} X_i. \quad (9)$$

The coefficient b_k in Eq. (8) was calculated analytically as a function of empirical parameters (X_j, Y_j, a_k, c_k) and experimental values. By analogy to works [50, 58], parameters of this equation were found by solving Eqs. (10), (11).

$$\frac{\partial E}{\partial a_k} = \frac{\partial E}{\partial c_k} = \frac{\partial E}{\partial X_j} = \frac{\partial E}{\partial Y_j} = 0, \quad (10)$$

$$E = \sum_{j=1}^{J}\sum_{k=1}^{K} \varepsilon_{jk}^2 = \sum_{j=1}^{J}\sum_{k=1}^{K}\left(\frac{pK_a^{expjk} - pK_a^{jk}}{pK_a^{expjk}}\right)^2. \quad (11)$$



Correlation of the values calculated by DFT method (pK_a^{calc}) and the experimental values (pK_a^{exp}) for carboxylic acids in water.

The value of E represents the sum of squares of the relative deviations ε_{jk} of the calculated pK_a^{jk} values from the experimental pK_a^{exjk} values. However, unlike the previous work [50], here all unknown parameters were found by numerical methods excluding the labor-consuming empirical selection. As a result we obtained analytical ($\varepsilon_{jk}^{max} < 10^{-7}$) solution of the system, however it required $2K + 2J = 36$ parameters that did not correspond to the task in view. In this connection we have obtained simplified Eq. (12) from Eq. (7) with the analogous analytical dependence of b_k [Eq. (13)] on unknown parameters X_j, Y_j, and c_k.

$$pK_a^{jk} = X_j^{ex} - c_k X_j + Y_j + b_k, \quad (12)$$

$$b_k = \frac{1}{J}(\sum_j pK_a^{exjk} - c_k \sum_j X_j - \sum_j X_j^{ex} - \sum_j Y_j) \quad (13)$$

The substitution of expression (13) in Eq. (12) has allowed us to reduce the number of unknown parameters to 21 at a good (ε_{jk}^{max} <1.4%) correctness of the calculation [Eq. (14)].

$$pK_a^{jk} = X_j^{ex} - X_j^{ex} - c_k(X_j - X_j) + Y_j - Y_j + pK_a^{expk}. \quad (14)$$

A bar above a symbol designates an average of three values related to the solvents under consideration.

On the basis of the application of this method to NH-acids [58] we have chosen the Dimrot–Reichardt solvatochromic parameter (E_T^{30}) and molecular volume (V_M) as the solvent molecular parameters.

When a set of equations was solved numerically, we substituted for missing pK_a values approximate values calculated in view of the trend to the variation of experimental pK_a values in the series of solvents under study, which is similar for the majority of acids. Formic and trichloroacetic acids were not included in the calculations, as reliable pK_a values for them were obtained only for water, which has not allowed us to include them in the set of Eqs. (10), (11). The experimental values of E_T^{30} for the solvents under study were taken from the monographs [32, 59] and the value of V_M, from the monograph [59].

Special attention in this work was given to a balance of summands X_j^{ex}, $c_k X_j$, and Y_j in Eq. (12). Absolute values of X_j^{ex}, $c_k X_j$, and Y_j were found within the limits from 0.001 to 50, and the ratio of X_j^{ex} to $c_k X_j$, within the limits from 0.1 to 10 in magnitude. The scale factor c_k was set positive. When the specified conditions are violated the basic idea of the method is not realized. If the ratio of X_j^{ex} to $c_k X_j$ exceeds 10, atomic contributions X_i are also practically insignificant, and if it is less than 0.1 X^{ex} values become insignificant. We have considered the sense of the scale factor c_k in detail in [49]. Solvent parameters Y_j and X_j and atomic contributions X_i are given in Table 3. By virtue of the fact that there are only three X_j values, and four atoms composing the solvents, one of atomic contributions could be selected arbitrarily. The atomic contribution of oxygen was taken to be zero ($X_0 = 0$).

The values of c_k and maximal errors of the calculations are given in Table 4. Owing to negative values of the coefficient c_k in the case of $X^{ex} \equiv V_M$, despite the low error of the calculation ($\varepsilon_{j\,k}^{max} < 1.4\%$), we have given preference to the results obtained on the basis of $X^{ex} \equiv E_T^{30}$. The values of c_k are not constant, but in the case of $X^{ex} \equiv E_T^{30}$ they slightly differ for various objects except for propionic and trichloroacetic acids.

The $pK_a^{emp}(X^{ex} \equiv E_T^{30})$ values most properly calculated by the empirical method for water, methanol, and DMSO are given in Tables 5–7, respectively, in comparison with experimental data (pK_a^{exp}) and the values calculated by the quantum-chemical method (pK_a^{DFT}, pK_a^{DFTapp}) together with relative deviations $\varepsilon pK_a^{DFTapp}$ and εpK_a^{emp} for both methods.

It is seen from Tables 5–7 that the relative error of the pK_a calculation by the empirical method ($\varepsilon^{max} <$ 1.4%) is less than that of the quantum-chemical DFT method ($\varepsilon^{max} >$ 50%). It confirms the regularity revealed earlier [50, 58] when comparing with the published results of quantum-chemical calculations for the last 8 years. Nevertheless, indisputable advantage of the DFT method with the approximating accepted in

Table 3. Parameters Y_j and X_j of solvents and X_i of atoms

Solvent	Y_j		X_j		Atom	X_i	
	$X^{ex} \equiv V_M$	$X^{ex} \equiv E_T^{30}$	$X^{ex} \equiv V_M$	$X^{ex} \equiv E_T^{30}$		$X^{ex} \equiv V_M$	$X^{ex} \equiv E_T^{30}$
Water	25.74	–5.79	0.14	0.93	C	–0.108	–0.821
Methanol	–18.91	13.92	–0.26	–1.82	H	0.052	0.394
DMSO	8.17	6.87	0.13	0.89	S	–0.298	–2.267

the present work is the clear physical sense of the input data for the calculation and the presence of only two empirical coefficients in Eq. (6). The approximated pK_a^{DFTapp} values (R = 0.964) correlate with the experiment better than the values calculated by "The pK_a Prediction Module" subprogram [52] (R = 0.940).

This work clearly shows that the proposed empirical method gives good results (as to the calculation error) on treating various arrays of experimental data, but for the work with small arrays (a small number of solvents) it should be refined.

The low error of the calculations of small arrays of experimental data by the empirical method is reached at the cost of a great many empirical parameters, namely 21 coefficients for the calculation of 45 pK_a^{ex} values. A positive side of the empirical method is the fact that calculation Eq. (12) formally corresponds to the principle of polylinearity [45] in the description of functional dependences on several parameters.

The comparison of columns in Table 4 shows that the use of the solvent experimental parameter V_M provides the same calculation error as E_T^{30}.

We can consider the small c_k variation for various carboxylic acids at a good calculation accuracy as an indication of the fact that these coefficients can be a quantitative measure of similarity of the objects within the limits of this empirical method.

With a sufficient reliability of the calculation results, an essential barrier to the further evolution of

Table 4. Coefficients c_k for the calculation of pK_a using V_M and E_T^{30} and maximal relative errors of the calculation

Acid	c_k (V_M)	ε_{jk}^{max}, %	c_k (E_T^{30})	ε_{jk}^{max}, %
C_6H_5COOH	–2.77	1.4	1.18	1.4
3-$NO_2C_6H_4COOH$	–5.96	1.4	1.33	1.4
3-BrC_6H_4COOH	–4.15	0.5	1.25	0.5
3-IC_6H_4COOH	–4.13	0.1	1.25	0.1
3-ClC_6H_4COOH	–4.58	0.3	1.27	0.3
3-MeC_6H_4COOH	–2.48	1.3	1.16	1.3
3-$MeOC_6H_4COOH$	–3.06	1.1	1.19	1.1
CH_3COOH	–2.22	1.3	1.18	1.3
$ClCH_2COOH$	–6.60	0.9	1.38	1.0
$Cl_2CHCOOH$	–9.71	0.5	1.53	0.5
EtCOOH	5.14	0.3	0.88	0.3
PrCOOH	–1.62	0.1	1.12	0.1
t-BuCOOH	–1.74	0.1	1.13	0.1
$CyCH_2COOH$	–2.12	0.1	1.16	0.1
$PhCH_2COOH$	–3.02	0.0	1.22	0.0

Table 5. Calculated[a] values of pK_a in water and their relative deviations εpK_a from experimental pK_a^{exp} values

Acid	pK_a^{exp}	pK_a^{DFT}	pK_a^{DFTapp}	$\varepsilon pK_a^{DFTapp}$, %	$pK_a^{DFT(PM)}$	$\varepsilon pK_a^{DFT(PM)}$, %	pK_a^{emp}	εpK_a^{emp}, %
PhCOOH	4.20	18.9	4.52	7.6	4.0	4.8	4.24	1.1
3-NO_2PhCOOH	3.47	14.7	3.19	7.9	3.4	2.0	3.43	1.2
3-BrPhCOOH	3.81	15.6	3.49	8.5	–	–	3.82	0.4
3-IPhCOOH	3.86	17.6	4.13	6.9	–	–	3.86	0.1
3-ClPhCOOH	3.83	15.5	3.45	9.9	3.8	0.8	3.82	0.3
3-MePhCOOH	4.27	17.6	4.12	3.5	4.1	4.0	4.31	1.0
3-MeOPhCOOH	4.08	16.7	3.84	5.9	4.1	0.5	4.11	0.8
CH_3COOH	4.76	19.3	4.65	2.4	3.7	22	4.71	1.1
$CH_2ClCOOH$	2.87	13.6	2.86	0.3	2.4	16	2.85	0.7
$CHCl_2COOH$	1.26	10.9	1.98	57	1.9	51	1.26	0.3
EtCOOH	4.87	20.3	4.99	2.5	4.2	14	4.86	0.3
PrCOOH	4.85	21.3	5.30	9.3	4.6	5.2	4.85	0.1
t-BuCOOH	5.03	20.4	5.01	0.5	4.5	11	5.03	0.1
$CyCH_2COOH$	4.90	20.9	5.18	5.7	5.0	2.0	4.90	0.1
$PhCH_2COOH$	4.31	16.5	3.77	12	4.6	6.7	4.31	0.0
HCOOH	3.80	16.9	3.89	2.3	2.9	24	–	–
CCl_3COOH	0.70	7.22	0.83	19	1.3	86	–	–

[a] pK_a^{DFT} are pK_a values based on DFT calculations of the present work, pK_a^{exp} are experimental values taken from the references in [50], pK_a^{DFTapp} are pK_a^{DFT} values found from linear dependence (6), $pK_a^{DFT(PM)}$ are values calculated using "The pK_a Prediction Module" subprogram [52], pK_a^{emp} are values calculated by the empirical method at $X^{ex} \equiv E_T^{30}$, $\varepsilon pK_a^{DFTapp}$ are relative deviations of pK_a^{DFTapp} from pK_a^{exp}, $\varepsilon pK_a^{DFT(PM)}$, relative deviations of $pK_a^{DFT(PM)}$ from pK_a^{exp}, and εpK_a^{emp}, relative deviations of pK_a^{emp} from pK_a^{exp}.

Table 6. Calculated and experimental values of pK_a in methanol and their relative deviations[a]

Acid	pK_a^{exp}	pK_a^{DFT}	pK_a^{DFTapp}	pK_a^{emp}	$\varepsilon pK_a^{DFTapp}$, %	εpK_a^{emp}, %
PhCOOH	9.42	22.4	9.64	9.29	2.3	1.4
3-NO_2PhCOOH	8.34	20.1	8.58	8.46	2.9	1.4
3-BrPhCOOH	8.91	20.8	8.90	8.86	0.1	0.5
3-IPhCOOH	8.91	20.5	8.77	8.90	1.6	0.1
3-ClPhCOOH	8.83	20.8	8.90	8.86	0.8	0.3
3-MePhCOOH	9.48	22.6	9.73	9.36	2.7	1.3
3-MeOPhCOOH	9.26	21.5	9.23	9.16	0.4	1.1
CH_3COOH	9.63	24.9	10.8	9.76	12	1.3
$CH_2ClCOOH$	7.80	18.7	7.94	7.87	1.8	1.0
$CHCl_2COOH$	6.30	14.8	6.14	6.27	2.5	0.5
EtCOOH	–	24.3	10.5	9.95	–	–
PrCOOH	–	25.0	10.8	9.90	–	–
t-BuCOOH	–	24.1	10.4	10.1	–	–
$CyCH_2COOH$	–	24.9	10.8	9.95	–	–
$PhCH_2COOH$	–	23.4	10.1	9.35	–	–
HCOOH	–	22.2	9.55	–	–	–
CCl_3COOH	–	11.7	4.71	–	–	–

[a] See Table 5.

Table 7. Calculated and experimental values of pK_a in DMSO and their relative deviations[a]

Acid	pK_a^{exp}	pK_a^{DFT}	pK_a^{DFTapp}	pK_a^{emp}	$\varepsilon pK_a^{DFTapp}$, %	εpK_a^{emp}, %
C_6H_5COOH	11.6	12.2	11.5	11.7	0.7	0.7
3-NO_2PhCOOH	9.71	9.78	9.85	9.63	1.5	0.8
3-Br-PhCOOH	10.7	10.6	10.4	10.8	2.7	0.3
3-I-PhCOOH	10.8	10.7	10.5	10.8	3.0	0.0
3-ClPhCOOH	10.6	10.6	10.4	10.6	1.4	0.2
3-MePhCOOH	11.8	12.8	11.9	11.9	0.9	0.6
3-MeOPhCOOH	11.4	12.1	11.5	11.5	0.4	0.6
CH_3COOH	12.5	14.4	13.1	12.4	4.9	0.6
$CH_2ClCOOH$	8.85	7.91	8.55	8.79	3.4	0.6
$CHCl_2COOH$	5.94	5.08	6.57	5.96	10.7	0.4
EtCOOH	15.5	13.9	12.7	15.5	18	0.2
PrCOOH	12.8	14.8	13.3	12.8	4.2	0.1
t-BuCOOH	12.9	14.6	13.3	12.9	2.5	0.1
$CyCH_2COOH$	12.6	15.0	13.5	12.6	6.8	0.1
$PhCH_2COOH$	11.7	13.6	12.5	11.7	7.3	0.0
HCOOH	–	11.9	11.3	–	–	–
CCl_3COOH	–	1.80	4.29	–	–	–

[a] See Table 5.

the empirical method is the unclear physical sense of atomic contributions to solvent parameters X_i and of solvent empirical parameters Y_j. We have not yet found simple relations between values of atomic contributions and experimental molecular properties of a solvent or of atoms composing it. It is possible that the determination of such empirical dependences will help to disclose the physical sense of the specified parameters. We think that the most promising way in this direction is the analysis of large arrays of various in

structure organic compounds and revealing criteria of similarity among the parameters calculated for them. Such approach was successfully applied in [60] to the determination of physical sense of the universal parameters offered by the authors and describing simultaneously inductive and steric effects of substituents.

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