

Empirical Method for Consideration of Solvent Effect on the Dissociation Constants of Carboxylic Acids

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Received February 15, 2007

Abstract—An empirical method was used to calculate 363 dissociation constants of 33 benzoic and acetic acid derivatives in 11 solvents. The relative error in the calculations did not exceed 9.5%, and the average error was no higher than 3%. The calculated values were compared with those obtained by quantum-chemical and other methods for determination of acid dissociation constants in different solvents.

DOI: 10.1134/S1070428008010065

Solvent exerts a considerable effect on properties of organic molecules dissolved therein [1–3], which is clearly illustrated by variations in their UV, IR, and NMR spectra [1, 4, 5]. As a result, solvent inevitably affects the kinetic [6–9] and equilibrium parameters of chemical [10–15], biochemical [16, 17], and photochemical processes [17, 18]. Up to now, numerous parameters have been proposed to characterize solvent effect on properties of organic compounds. These parameters include physical constants (such as dielectric permittivity, dipole moment, refractive index, polarizability, etc.), parameters derived from physical constants, and empirical parameters [1, 3]. The latter become more and more popular in the recent years [3, 19]; they are related mainly to spectral parameters of solvatochromic indicators. The set of empirical parameters continuously broadens due to efforts made to build up a universal scale taking into account all specific features of solvents [3, 19, 20]. The problem concerning solvent effect in all the above aspects attracts growing researchers' interest, as follows from a large number of publications appeared in the past decade [2–22] and recent monographs [1, 23, 24].

Solvent effect on protonation–deprotonation equilibria, i.e., variation of basicity (acidity) constants in going from one solvent to another, remains so far an important problem. In the recent years, considerable progress was achieved in the calculations of acidity parameters (such as proton affinity ΔH_H and basicity ΔG) of molecules of many organic compounds in the gas phase [21, 25–29, 50–73]. Modern calculation methods are based on quantum-chemical approaches,

including newest modifications of Hartree–Fock approximation and density functional theory with continuously extending basis sets. In the past 5 years, the error in the calculation of the above acidity parameters for the gas phase was smaller than 1% [25, 30, 41, 44]. Therefore, it became possible to draw reliable relations between ΔH_H and structural parameters [31–33, 36] or other properties [27, 28, 30–37] and describe competing protonation processes involving multicenter molecules [27, 28, 34, 35] and gas-phase tautomeric proton-transfer equilibria [34, 37].

In order to pass from gas-phase acidities to pK_a in solution and estimate solvent effect on a quantitative level, a thermodynamic cycle (i.e., a set of elementary steps that characterize most appropriately the dissociation process in solution and species involved therein) is selected preliminarily. Energies corresponding to each elementary step are then calculated [38]. Here, an important problem is the calculation of the energies of solvation of undissociated and dissociated substrate, ΔG_s [39–49]. During the past decade, these quantities were usually calculated using various modifications of the polarizable dielectric continuum solvation model (PCM) [38–73] in combination with other methods, e.g., statistical thermodynamics [50] and electrostatic models [22]. Methods for determination of ΔG_s with account taken of solvent molecules in the explicit form were used only in [61, 64, 71]. The history of development, current state, and scope of application of the PCM were considered in [39, 40]. The most recent modification of this approach is conductor-like polarizable continuum model (CPCM) [41] which was used to

calculate pK_a values in [50–58]. The energies of deprotonation of molecules in solution are calculated from ΔG_s values in accordance with the selected thermodynamic cycle, and pK_a values are then determined using van't Hoff equation or its analogs with empirical coefficients [50, 56, 59–63]. For example, in the calculations of energies for a series of 50 compounds in water, the right part of the van't Hoff equation should be multiplied by a factor of 0.49 [50].

Only in [41, 54–58, 63–66] the calculations of pK_a were performed with account taken of variation of the substrate geometry in solution relative to the geometry of isolated molecule, while in [51, 54, 60, 67] the effect of solvent on the substrate geometry was considered only partially. In some cases, the substrate geometry was optimized with no account taken of solvent effect [40, 50, 52–54, 58, 59, 61, 62, 68–73]. Optimization of geometric parameters of carboxylic acid molecules in solution considerably enhances the accuracy of pK_a calculations [66]. For instance, the absolute error in the calculation of ionization constants (ΔpK_a) using geometric parameters of isolated molecules ranged from 0.4 to 0.97 log units, and the relative error (εpK_a), from 11 to 47%. After optimization of the substrate geometry for solution, the εpK_a values were less than 10% for a half of the examined substrates.

By contrast, Tran and Colvin [54] showed that geometry optimization for solution gives no essential gain in the calculation accuracy. A combination of the Langevin dipole model and PCM in 6 versions was used to calculate pK_a values of acetic, orthophosphoric, and mono-, di-, and trifluoroacetic acids and 4 nucleobases. Although εpK_a for all 9 substrates exceeded 30% (the lowest relative accuracy among the data published in the past decade), an acceptable correlation ($r = 0.92$) between the experimental and calculated pK_a values was obtained for all substrates.

An alternative approach to calculation of pK_a values with account taken of solvation is based on the use of cluster models involving molecules in the nearest solvate shell in the explicit form [56, 61, 62, 70–72] and geometric parameters of such clusters [61, 71, 72]. These models were applied both in combination with PCM [56, 70] and without the latter [61, 62, 71, 72].

Calculations of pK_a values were performed for both chemically different [50, 54, 62, 68–70, 72, 73] and structurally related compounds [40, 51, 52, 53, 55, 57–61, 63, 64, 66, 67]. Some series were isolated from a large group [52, 54, 56, 61, 65, 71, 73]. While studying complex structures, conformational behavior and

tautomerism were taken into account [41, 51, 53, 57, 58, 60, 69] by averaging tautomer energies in different ways or excluding structures that were shown to be energetically unfavorable by preliminary calculations. The relative deviation of the calculated energies of solvation from the experimental values ($\varepsilon \Delta G_s$) ranges from 10 to 40%. As a result, the relative error in the calculation of pK_a is 5 to 40%. The errors did not exceed 10% for more than half of the calculated pK_a values (sometimes calculated by different methods for the same substrate) only in [50, 51, 55, 56, 61, 63, 67, 71, 73].

A good accuracy in the calculation of pK_a values was achieved due to joint application of quantum-chemical methods and QSPR approach implying calculated or experimental parameters as descriptors (ΔG_s for molecules, anions, or a proton, ΔH_H) or their combinations [50, 56, 61, 63].

Apart from water, the most popular medium for assay of methods involving solvent effects is dimethyl sulfoxide (DMSO) [44, 68, 72, 73].

Thus the existing methods for the calculation of pK_a values with account taken of solvent effect are based on complex and resource-consuming quantum-chemical procedures that are characterized by appreciable errors.

In this paper we demonstrate the possibility of using the empirical procedure proposed by us previously [74–76] for the calculation of dissociation constants of some organic compounds in various solvents on the basis of experimental parameters of the substrates and solvents. The use of exclusively experimental data is the main difference between our procedure and empirical QSPR method which relates experimental molecular parameters to other parameters of molecules or molecular fragments, calculated by quantum-chemical methods (mostly semiempirical), via multiparameter equations. In particular, QSPR calculations of dissociation constants involved charges on the carbonyl oxygen atoms of an acid and its anion and differences in their HOMO energies, calculated by the AM1 method [77]. The correlation coefficient was as poor as 0.88; it corresponded to an average relative error of about 10–15%.

Our method is based on the linear Gibbs energy relationship principle [78] with account taken of atomic contributions to a given molecular parameter. Refinement of that principle originates from the assumption that any molecular parameter may be represented as the sum of contributions of atoms consti-

tuting the given molecule. Obviously, unlike other parameters (such as electronic, rotational, and vibrational quantum numbers, configuration, etc.), just the formula of a molecule, ion, or radical can be determined experimentally before any chemical reaction.

As in [74–76], the sought quantity (in the given case, pK_a^{jk} value of some acid denoted as k in some solvent denoted as j) was determined using the linear form of Eq. (1):

$$\delta pK_a^{jk} = a\delta X_{jk} + b, \quad (1)$$

where a and b are constants. The quantity δpK_a^{jk} is linearly related to the dissociation constant through the parameter Y_j :

$$\delta pK_a^{jk} = pK_a^{jk} - Y_j. \quad (2)$$

The experimental solvent parameter ($X_{\text{exp},j}$) minus atomic contributions was determined using Eq. (3):

$$\delta X_{\text{exp},j} = X_{\text{exp},j} - X_k \sum_i g_{ij} X_i. \quad (3)$$

Here, g_{ij} is the number of i th atoms in a j th solvent molecule, X_i is the contribution of i th atom to the molecular solvent parameter, and X_k is a dimensionless coefficient. The principal difference from the procedure described in [74–76] is that Eqs. (1)–(3) relate to each other similar molecular parameters of different compounds rather than different molecular parameters of the same compound. Therefore, Eqs. (2) and (3) were reduced to bilinear form as follows: the coefficient Y_j was assumed to be a constant of j th solvent, and the coefficient X_k at atomic contributions to the

solvent parameter was assumed to be a constant of k th acid. As molecular parameters of solvent we preliminarily tested molecular volume, dipole moment, reciprocal dielectric permittivity, polarizability, Dimroth–Reichardt solvatochromic parameter E_T^{30} , and molecular proton affinity (gas-phase enthalpy of protonation ΔH_H). Rough calculations showed that better results were obtained with the use of the two latter parameters. In these cases, the physical sense of atomic contributions X_i , in contrast to [74–76], becomes unobvious. For example, a contribution of an atom to non-additive solvent parameter E_T^{30} *a fortiori* makes no sense. Therefore, atomic contributions to solvent parameters were fitted empirically. The experimental ΔH_H values for atoms and molecules were taken from the NIST database [79], and E_T^{30} values, from [1, 80].

Although numerous experimental pK_a values of structurally different compounds (carboxylic acids, amines, phenols, CH acids, NH acids) in various solvents are available [81–113], combination of the data obtained in different studies into a single set for further processing and analysis is not appropriate for the following reasons:

(1) Different methods were used to determine pK_a values (spectrophotometry, potentiometry, conductometry). The two latter cannot be applied to determination of pK_a values in weakly polar media [85];

(2) Different mathematical models were used in the calculation of pK_a values from the data of experimental measurements and in data processing;

(3) Experimental studies were generally performed on large series of substrates and a limited number of solvents, and the substrate series were specific in each case;

(4) The acid dissociation constant in weakly polar aprotic solvents makes no rigorous physical sense, while constants for formation of ion pairs with proton transfer (that are measured experimentally) depend on the selected base [93, 100, 106–111].

As a result, pK_a values for the same substrate in the same solvent, determined by different authors, may differ by 5 log units. Therefore, as basis experimental data set we selected pK_a values of substituted benzoic [81] and acetic acids [82] in 12 and 5 polar solvents, respectively, which were supplemented by recent data [83]. In addition, pK_a values for methanol and ethanol [97] were used. All measurements were performed by the potentiometric method, and the results were processed uniformly.

Table 1. Empirical solvent parameters Y_j for ΔH_H and E_T^{30} selected as experimental solvent parameters

Solvent no. (j)	Solvent	Y_j	
		$X_{\text{exp}} \equiv \Delta H_H$	$X_{\text{exp}} \equiv E_T^{30}$
1	Acetonitrile	15.41	57.8
2	Acetone	13.62	44.4
3	DMF	5.35	41.4
4	DMSO	5.82	33.2
5	Propylene carbonate	11.90	66.1
6	Water	4.28	23.8
7	Methanol	8.70	28.9
8	Formamide	0.60	37.8
9	Benzonitrile	11.60	77.9
10	Nitromethane	11.80	61.2
11	Ethanol	9.60	27.2

Table 2. Coefficients for the calculation of pK_a using ΔH_H and E_T^{30} as experimental solvent parameter, numbers of solvents N , and maximal relative errors $\max(\varepsilon pK_a)$

Acid	$X_{\text{exp}} \equiv \Delta H_H$					$X_{\text{exp}} \equiv E_T^{30}$				
	a	b	X_k	$\max(\varepsilon pK_a)$	N	a	b	X_k	$\max(\varepsilon pK_a)$	N
PhCOOH	0.0349	-23.6	16.2	7.5	11	0.499	-54.5	-5.73	5.2	11
2-O ₂ NC ₆ H ₄ COOH	0.0345	-25.0	23.0	7.2	6	0.521	-57.9	-5.44	6.0	6
3-O ₂ NC ₆ H ₄ COOH	0.0302	-21.0	19.8	5.7	11	0.548	-58.3	-5.15	5.4	11
4-O ₂ NC ₆ H ₄ COOH	0.0298	-20.8	19.7	5.7	11	0.551	-58.5	-5.14	5.3	11
3-BrC ₆ H ₄ COOH	0.0328	-22.5	17.9	5.2	11	0.523	-56.4	-5.42	5.1	11
4-BrC ₆ H ₄ COOH	0.0332	-22.6	17.4	6.0	11	0.515	-55.8	-5.52	5.1	11
3-IC ₆ H ₄ COOH	0.0331	-22.7	16.4	6.5	10	0.517	-56.0	-5.57	5.4	10
4-IC ₆ H ₄ COOH	0.0329	-22.4	16.5	6.7	10	0.517	-55.9	-5.57	5.7	10
3-ClC ₆ H ₄ COOH	0.0319	-21.9	18.2	5.5	11	0.530	-56.8	-5.36	5.1	11
4-ClC ₆ H ₄ COOH	0.0328	-22.4	17.6	6.3	11	0.519	-56.0	-5.48	5.1	11
3-MeC ₆ H ₄ COOH	0.0359	-24.1	15.3	8.5	11	0.487	-53.7	-5.90	5.0	11
4-MeC ₆ H ₄ COOH	0.0351	-23.7	15.8	7.4	11	0.495	-54.2	-5.80	5.1	11
3-MeOC ₆ H ₄ COOH	0.0349	-23.8	15.2	7.1	10	0.495	-54.4	-5.85	5.8	10
4-MeOC ₆ H ₄ COOH	0.0368	-24.6	14.6	7.6	10	0.480	-53.0	-6.05	5.7	10
3-NCC ₆ H ₄ COOH	0.0344	-23.4	27.5	4.7	6	0.530	-57.0	-5.14	7.6	6
3-AcC ₆ H ₄ COOH	0.0338	-22.9	25.0	6.2	6	0.529	-56.8	-5.29	5.5	6
3-MeSO ₂ C ₆ H ₄ COOH	0.0323	-22.1	25.8	5.0	6	0.544	-58.0	-5.14	5.5	6
4-H ₂ NSO ₂ C ₆ H ₄ COOH	0.0339	-23.2	25.0	4.9	6	0.531	-57.1	-5.28	5.3	6
2-OHC ₆ H ₄ COOH	0.0294	-19.0	29.3	5.5	5	0.561	-58.1	-5.05	5.3	5
<i>o</i> -C ₆ H ₄ (COOH) ₂	0.0210	-15.5	16.5	6.3	5	0.642	-65.4	-5.17	5.9	5
2-AcOC ₆ H ₄ COOH	0.0371	-25.7	22.1	7.1	5	0.497	-55.5	-5.82	4.6	5
2-ONC ₆ H ₄ COOH	0.0300	-20.2	34.9	8.6	5	0.556	-58.5	-4.74	8.3	5
2-MeSOC ₆ H ₄ COOH	0.0301	-21.0	26.7	4.7	5	0.558	-59.4	-5.18	4.6	5
AcOH	0.0402	-26.3	23.0	9.0	9	0.477	-52.4	-5.52	7.5	9
ClCH ₂ COOH	0.0319	-22.5	24.2	4.1	9	0.541	-58.3	-5.02	3.3	9
Cl ₂ CHCOOH	0.0254	-19.8	24.2	9.4	9	0.594	-63.3	-4.74	8.7	9
EtCOOH	0.0457	-30.5	8.4	7.4	6	0.423	-49.5	-7.71	8.7	6
PrCOOH	0.0414	-27.2	15.7	3.5	6	0.456	-51.2	-6.47	2.9	6
<i>t</i> -BuCOOH	0.0412	-26.9	15.7	3.1	6	0.458	-51.2	-6.44	3.2	6
<i>cyclo</i> -C ₆ H ₁₁ CH ₂ COOH	0.0383	-25.1	15.9	4.3	6	0.480	-52.7	-6.13	1.9	6
PhOCH ₂ COOH	0.0349	-24.2	23.3	5.4	7	0.516	-56.4	-5.25	4.8	7
Ph ₂ CHCOOH	0.0360	-24.4	18.8	2.2	6	0.506	-55.2	-5.63	5.1	6
PhCH ₂ COOH	0.0387	-25.7	21.7	9.3	7	0.483	-53.2	-5.65	8.7	7

The coefficients a_k , b_k , X_k , and Y_j were determined by minimization of the sum of the squared relative deviations of the calculated values from the experimental (denoted with superscript "exp") ionization constants of k th acid in the selected solvent series:

$$E_k = \sum_j \left[\frac{pK_a^{\text{exp},jk} - pK_a^{jk}}{pK_a^{\text{exp},jk}} \right]^2 \quad (4)$$

Analysis of the results performed in [76] showed that a high correlation coefficient r for two parameters does not necessarily ensure low error in the calculation of one parameter from the other. For example, at $r = 0.9$, the relative deviation of calculated values from the experimental ones can attain 30%, which makes the correlation unsuitable for practical use.

As in [76], the minimum condition was written as

$$\frac{\partial \sum_k E_k}{\partial a_k} = \frac{\partial \sum_k E_k}{\partial b_k} = \frac{\partial \sum_k E_k}{\partial X_k} = \frac{\partial \sum_k E_k}{\partial Y_k} = 0 \quad (5)$$

for any j and k . However, numerical solution of a system consisting of 110 equations was unsuccessful, and the number of equations was reduced by exclusion of the solvent parameters Y_j . The condition implying minimal sum of the squared relative deviations of

the calculated dissociation constants from the experimental values for k th acid in all solvents became as follows:

$$\frac{\partial \sum_k E_k}{\partial a_k} = \frac{\partial \sum_k E_k}{\partial b_k} = \frac{\partial \sum_k E_k}{\partial X_k} = 0. \quad (6)$$

Using Eq. (6), all coefficients X_k , a_k , and b_k were determined. The program for the calculation of X_k , a_k ,

Table 3. Calculated (using ΔH_{H} and E_{T}^{30} as experimental solvent parameters) and experimental $\text{p}K_{\text{a}}$ values of some substituted benzoic acids

Acid	Solvent	$\text{p}K_{\text{a,exp}}$	$X_{\text{exp}} \equiv \Delta H_{\text{H}}$		$X_{\text{exp}} \equiv E_{\text{T}}^{30}$	
			$\text{p}K_{\text{a}}$	$\varepsilon \text{p}K_{\text{a}}, \%$	$\text{p}K_{\text{a}}$	$\varepsilon \text{p}K_{\text{a}}, \%$
PhCOOH	Acetonitrile	20.57	19.9	-3.5	21.6	5.2
	Acetone	18.15	17.1	-6.0	17.5	-3.5
	DMF	12.46	12.0	-3.5	12.2	-2.4
	DMSO	11.64	11.1	-4.7	11.2	-4.1
	Propylene carbonate	19.56	19.1	-2.3	19.4	-0.9
	Water	4.20	4.11	-2.2	4.16	-1.0
	Methanol	9.42	9.87	4.8	9.80	4.1
	Formamide	6.27	6.73	7.4	6.14	-2.2
	Benzonitrile	20.91	20.8	-0.7	21.7	3.7
	Nitromethane	17.73	16.9	-4.8	17.8	0.4
4-O ₂ NC ₆ H ₄ COOH	Ethanol	10.25	10.7	4.2	10.8	5.0
	Acetonitrile	19.04	18.7	-1.6	20.6	5.3
	Acetone	16.46	15.7	-4.8	15.6	-5.0
	DMF	10.55	10.3	-2.6	10.4	-1.4
	DMSO	9.61	9.32	-3.1	9.41	-2.1
	Propylene carbonate	17.89	17.9	-0.1	17.6	-1.6
	Water	3.43	3.36	-2.1	3.40	-0.8
	Methanol	8.29	8.77	5.7	8.61	3.8
	Formamide	5.23	5.40	3.2	5.13	-2.0
	Benzonitrile	19.38	19.6	1.2	20.1	3.6
4-MeOC ₆ H ₄ COOH	Nitromethane	16.23	15.9	-1.8	16.3	0.5
	Ethanol	9.04	9.43	4.3	9.34	3.3
	Acetonitrile	21.05	20.3	-3.7	22.2	5.5
	Acetone	18.75	17.6	-5.9	18.3	-2.4
	DMF	13.11	12.7	-3.0	12.9	-1.9
	DMSO	12.19	11.8	-2.7	11.9	-2.0
	Propylene carbonate	20.00	19.5	-2.4	19.9	-0.3
	Water	4.49	4.44	-1.2	4.49	0.0
	Methanol	9.79	10.4	5.9	10.4	5.7
	Formamide	6.71	7.23	7.7	6.46	-3.7
	Benzonitrile	21.40	21.1	-1.6	22.1	3.0
	Nitromethane	18.15	17.2	-5.4	18.2	0.4

Table 4. Experimental^a and calculated^b pK_a values of acids in some solvents

Acid	DMSO	Propylene carbonate	H ₂ O	MeOH	HCONH ₂	PhCN	MeNO ₂	EtOH
PhCOOH	11.6	19.6	4.2	9.4	6.3	20.9	17.7	10.3
2-O ₂ NC ₆ H ₄ COOH	8.4	18.4/17.0	2.2	7.6	5.5/4.1	20.9/19.5	16.2/15.6	8.0/8.4
3-O ₂ NC ₆ H ₄ COOH	9.7	18.2	3.5	8.3	5.4	19.4	16.4	9.2
4-O ₂ NC ₆ H ₄ COOH	9.6	17.9	3.4	8.3	5.2	19.4	16.2	9.0
3-BrC ₆ H ₄ COOH	10.7	18.9	3.8	8.9	5.9	20.3	17.1	9.7
4-BrC ₆ H ₄ COOH	11.1	19.1	4.0	9.1	6.0	20.6	17.4	9.9
3-IC ₆ H ₄ COOH	10.8	18.8	3.9	8.9	5.8	20.2	17.0	10.3/10.3
4-IC ₆ H ₄ COOH	10.9	19.0	4.0	9.0	5.9	20.2	17.2	10.4/10.5
3-ClC ₆ H ₄ COOH	10.6	18.8	3.8	8.8	5.8	20.1	17.0	9.8
4-ClC ₆ H ₄ COOH	11.1	19.1	4.0	9.1	6.0	20.5	17.3	9.9
3-MeC ₆ H ₄ COOH	12.1	19.9	4.4	9.7	6.5	21.3	18.0	10.7
4-MeC ₆ H ₄ COOH	11.8	19.7	4.3	9.5	6.4	21.0	17.8	10.5
3-MeOC ₆ H ₄ COOH	11.4	19.3	4.1	9.3	6.1	20.7	17.5	10.7/10.8
4-MeOC ₆ H ₄ COOH	12.2	20.0	4.5	9.8	6.7	21.4	18.2	11.3/11.4
3-NCC ₆ H ₄ COOH	9.3	20.5/18.8	3.5	8.5	7.2/5.7	23.6/21.6	18.3/17.4	8.8/9.3
3-AcC ₆ H ₄ COOH	9.8	20.1/18.6	3.7	8.8	7.1/5.7	22.8/21.2	17.9/17.2	9.3/9.8
3-MeSO ₂ C ₆ H ₄ COOH	9.3	19.7/18.0	3.5	8.5	6.6/5.3	22.3/20.6	17.5/16.7	9.0/9.4
4-H ₂ NSO ₂ C ₆ H ₄ COOH	9.7	20.0/18.3	3.6	8.5	6.9/5.5	22.7/20.9	17.8/16.9	9.2/9.6
2-HCOC ₆ H ₄ COOH	9.7/10.3	20.4/18.4	4.5	9.2	7.3/6.1	23.1/20.9	18.5/17.2	9.7/10.3
<i>o</i> -C ₆ H ₄ (COOH) ₂	7.7/8.4	15.0/12.3	3.0	7.7	3.0/2.5	15.9/13.2	13.6/11.7	8.9/9.3
2-AcOC ₆ H ₄ COOH	10.0/10.3	19.8/18.2	3.2	8.5	6.9/5.0	22.4/20.4	17.4/16.6	9.2/9.9
2-ONC ₆ H ₄ COOH	8.5/9.0	20.6/18.7	3.6	7.9	7.1/5.9	24.0/21.9	18.6/17.4	8.3/8.8
2-MeSOC ₆ H ₄ COOH	8.6/9.1	18.8/16.8	3.1	7.9	5.8/4.6	21.3/19.1	16.8/15.6	8.5/9.1
AcOH	12.5	20.4	4.8	9.6	9.1/7.5	25.2/24.7	21.3	10.3
ClCH ₂ COOH	8.9	17.9	2.9	7.8	5.7/5.0	21.0/20.8	16.6	8.5
Cl ₂ CHCOOH	5.9	15.6	1.3	6.3	2.8/2.8	17.2/17.3	12.6	7.1
EtCOOH	15.5	20.5	4.9	11.6/11.7	8.4/6.1	21.2/20.4	17.4/17.7	12.9/13.6
PrCOOH	12.8	20.8	4.9/4.9	10.9/11.0	8.6/6.8	23.1/22.5	18.5/18.7	11.7/12.2
<i>t</i> -BuCOOH	12.9	20.9	5.0/5.0	11.1/11.1	8.8/7.0	23.2/22.6	18.7/18.9	11.9/12.4
<i>cyclo</i> -C ₆ H ₁₁ CH ₂ COOH	12.6	20.4	4.9	10.8/10.8	8.1/6.7	22.4/22.0	18.1/18.4	11.7/12.0
PhOCH ₂ COOH	9.7	18.5	3.2	8.6/8.5	6.6/5.5	22.1/21.7	18.0	9.0/9.1
Ph ₂ CHCOOH	10.9	19.5	3.9	9.6/9.5	7.1/5.9	21.7/21.4	17.4/17.5	10.3/10.4
PhCH ₂ COOH	11.7	20.0	4.3	9.9/9.9	8.3/6.8	23.9/23.4	20.7	10.4/10.7

^a Single value per cell.^b Two values separated by slash per cell; the first corresponds to ΔH_{H} as solvent parameter, and the second, to E_{T}^{30} .

and b_k from known values of X_i and Y_j was given in [114]. The optimal atomic contributions X_i to any of the two selected molecular solvent parameters were found by random search within the range from -5 to $+5$. The solvent parameters Y_j were found in parallel in a similar way (within the range from -100 to $+100$) until several their combinations were obtained for

which the maximal value of εpK_a was lower than 50%. One of the sets of X_i thus obtained was assumed to be constant, and Y_j values were varied in such a way that E_k be minimal. If this condition was not met, a new set of X_i was selected. The contributions X_i of C, H, O, N, and S atoms are -1.97 , 1.75 , -2.30 , -2.85 , and -0.76 , respectively. The optimal solvent parameters Y_j are

Table 5. Comparison of the results of quantum-chemical calculations of pK_a with those obtained in the present work

Solvent	Calculation method ^a	Substrates	Number of compounds ^b	Number of pK_a values matching the condition $\epsilon pK_a < 10\%$	Z_1^c	Z_2^d	Reference
Water	CPCM, QSPR	Various substrates	64 (64)	42 ^e	4 (4)	0	[50]
Water	CPCM	Carboxylic acids	6 (183)	115 ^e	3 (54)	0	[51]
Water	CPCM	Acids	28 (56)	10	9 (18)	1	[52]
Water	CPCM	Carboxylic acids	6 (27)	15	2 (8)	1	[53]
Water	CPCM	Chloroacetic acids, nucleotides	9 (60)	0	1 (1)	0	[54]
Water	CPCM	Phenols	20 (40)	36 ^e	0	0	[55]
Water	CPCM, cluster, QSPR	Acids, phenols, pyridinium salts	64 (64)	53 ^e	15 (15)	2	[56]
Water	CPCM	Tetrazoles	9 (144)	38	0	0	[57]
Water	CPCM	Imidazoles	36 (36)	9	0	0	[58]
Water	PCM, QSPR	Imidazoles	4	0	0	0	[60]
Water	Cluster, QSPR	Halogen-substituted phenols	35 (62)	61 ^e	0	0	[61]
Water	Cluster, QSPR	Acids, phenols, alcohols	57 (57)	11	0	0	[62]
Water	PCM, QSPR	Carboxylic acids	16 (32)	17 ^e	5 (10)	0	[63]
Water	PCM	Acids, alcohols, thiols	14 (14)	5	4 (4)	0	[65]
Water	PCM	Carboxylic acids	8 (16)	4	4 (8)	0	[66]
Water	PCM	Acids	7 (7)	4 ^e	4 (4)	0	[67]
Water, DMSO, MeCN	PCM	Acids, phenols, amines	8 (144)	23	2 (36)	0	[68]
Water	PCM	Amines, imines, heterocycles	25 (72)	18	0	0	[69]
Water	PCM, cluster	Different substrates	17 (17)	5	1 (1)	0	[70]
Water	Cluster	Phenols, imidazole, methanol	5 (16)	11 ^e	0	0	[71]
DMSO	Cluster	Various substrates	106 (212)	98	4 (8)	0	[72]
DMSO	PCM	Acids, alcohols, amides, imines	42 (42)	28 ^e	2 (2)	0	[73]

^a PCM stands for polarizable continuum model, CPCM stands for conductor-like polarizable continuum model, cluster denotes the model taking into account geometric parameters of the solvate-solvent complex, and QSPR stands for the quantitative structure-property relationship.

^b The number of pK_a values calculated by different methods is given in parentheses.

^c The number of acids for which pK_a values were calculated in the present work and in the corresponding referenced study; the total number of pK_a values calculated for these acids by different methods is given in parentheses.

^d The number of pK_a values (see note ^c) for which the relative error was lower than in the present work.

^e The number of pK_a values matching the condition $\epsilon pK_a < 10\%$, which exceeds the half of the total number of calculated values.

listed in Table 1. The coefficients X_k , a_k , and b_k for $X_{\text{exp}} = \Delta H_H$ and $X_{\text{exp}} = E_T^{30}$ are given in Table 2.

The different numbers of solvents for different acids is explained by the available experimental data. The set of acids was selected taking into account that five or more experimental dissociation constant in different solvents be available for each acid. A large dis-

persion of Y_j values for $X_{\text{exp}} = \Delta H_H$ as compared to $X_{\text{exp}} = E_T^{30}$ corresponds to more significant correlation between pK_a and E_T^{30} , while no correlation between pK_a and ΔH_H exists.

The solvent parameter Y_j and oxygen contribution X_O were found to affect ϵpK_a most strongly. Although the coefficients a and b are not similar for all 33 acids

(as might be expected; Table 2), they have comparable values and the ratio a_k/b_k is relatively constant.

The pK_a values were calculated by Eq. (7) that directly follows from Eqs. (1)–(3):

$$pK_a^{jk} = a_k \left[X_{\text{exp},j} - X_k \sum_i g_{ij} X_i \right] + Y_j + b_k. \quad (7)$$

The calculated pK_a values are given in [114] together with the experimental data. Table 3 compares the pK_a values calculated by Eq. (7) with the experimental values for three benzoic acids. We calculated pK_a values of acids in solvents for which no experimental data were given in [81–83, 97] (Table 4). The pK_a values of all 33 acids in acetonitrile ($j = 1$), acetone ($j = 2$), and dimethylformamide ($j = 3$) were reported in [81–83, 97].

Comparison with the results of quantum-chemical calculations. In the present work we calculated 530 pK_a values, and the relative deviation from the corresponding experimental data [81–83, 97] did not exceed 9.5%. Our results allowed us to define the accuracy criterion for calculation methods at a level of 10% relative error (ΔpK_a). Among the results of quantum-chemical calculations of pK_a values of organic compounds in different solvents, published in the past decade, the best agreement with the experimental data was achieved in [55]. The above criterion was met for 36 of 40 pK_a values calculated for 20 substituted phenols in water. The use of a combination of different methods gave the best results in [61]: 61 of 62 calculated values for 35 halogen-substituted phenols in water matched the proposed criterion. Different calculation methods are compared in Table 5. It is seen that, among 173 pK_a values calculated in [50–73], deviation from the experimental data for only four values is lower than that obtained in the present work.

Although the average error in the calculation of pK_a from the enthalpies of protonation of solvents is slightly greater than in the calculations from the parameter E_T^{30} (3.0 against 2.8%), we cannot still prefer the latter. The numerical part of the proposed empirical method should be updated with a view to eliminate random search for atomic contributions X_i and solvent parameters Y_j . For example, the fact that X_i values are similar regardless of the solvent parameter used in the calculations (ΔH_H or E_T^{30}) is likely to indicate wide potential of the calculation procedure rather than physical relation between these parameters.

The authors are grateful to Prof. I.V. Tselinskii for helpful discussion.

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