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Empirical Conversion of pK_a Values between Different Solvents and Interpretation of the Parameters: Application to Water, Acetonitrile, Dimethyl Sulfoxide, and Methanol

Emanuele Rossini,[†,‡] Art D. Bochevarov,[§] and Ernst Walter Knapp*[,†]

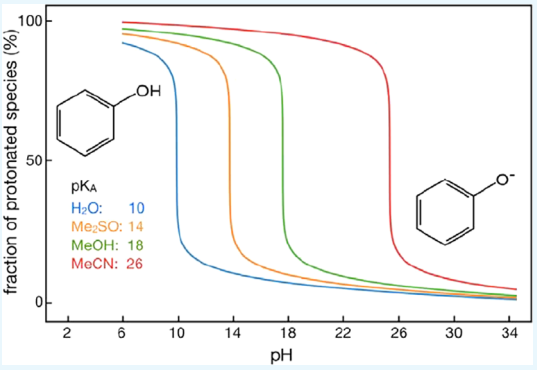
[†]Freie Universität Berlin, Institute of Chemistry and Biochemistry, Fabeck Strasse 36A, Berlin D-14195, Germany

[‡]Theoretical Biophysics, Max Planck Institute of Biophysics, Max-von-Laue-Strasse 3, Frankfurt a. M. 60438, Germany

[§]Schrödinger Inc, 120 West 45th Street, 17th floor, New York, New York 10036, United States

Supporting Information

ABSTRACT: An empirical conversion method (ECM) that transforms pK_a values of arbitrary organic compounds from one solvent to the other is introduced. We demonstrate the method's usefulness and performance on pK_a conversions involving water and organic solvents acetonitrile (MeCN), dimethyl sulfoxide (Me_2SO), and methanol (MeOH). We focus on the pK_a conversion from the known reference value in water to the other three organic solvents, although such a conversion can also be performed between any pair of the considered solvents. The ECM works with an additive parameter that is specific to a solvent and a molecular family (essentially characterized by a functional group that is titrated). We formally show that the method can be formulated with a single additive parameter, and that the extra multiplicative parameter used in other works is not required. The values of the additive parameter are determined from known pK_a data, and their interpretation is provided on the basis of physicochemical concepts. The data set of known pK_a values is augmented with pK_a values computed with the recently introduced electrostatic transform method, whose validity is demonstrated. For a validation of our method, we consider pK_a conversions for two data sets of titratable compounds. The first data set involves 81 relatively small molecules belonging to 19 different molecular families, with the pK_a data available in all four considered solvents. The second data set involves 76 titratable molecules from 5 additional molecular families. These molecules are typically larger, and their experimental pK_a values are available only in Me_2SO and water. The validation tests show that the agreement between the experimental pK_a data and the ECM predictions is generally good, with absolute errors often on the order of 0.5 pH units. The presence of a few outliers is rationalized, and observed trends with respect to molecular families are discussed.



INTRODUCTION

The acid dissociation constant K_a measures the strength of an acid in a solution. It is a key quantity for the functionality of molecules with variable protonation. For practical purposes, one uses the negative decadic logarithm of K_a, also known as pK_a. The determination of this quantity, performed in different protic and aprotic solvents, is particularly important for both applied and fundamental physicochemical sciences.[1−3]

The pK_a value also plays a central role in drug discovery. This value influences solubility, membrane permeability, clearance, and binding of a drug molecule to the target protein.[4−9] About two-third of the approved pharmaceutical compounds contain ionizable groups, usually in the pH range between 3 and 11 with a maximum at 8.5.[5] Before a drug can exercise its function in the living cell environment, it has to penetrate the cytoplasmic membrane, which is structurally composed of a lipid bilayer. The inside of such cell membranes is much less polar than water. Charged compounds are generally better soluble in water than in apolar solvents, whereas charge-neutral compounds are better soluble in apolar solvents. The lipophilicity is maximized for a protonation form with zero charge,[6] and therefore it is this form of a molecule that can penetrate the membrane most efficiently.

The pK_a value of a drug is important for passive renal tubular reabsorption.[10−12] Many drugs are either weak acids or bases. Their clearance and absorption behavior depends on urine pH that can vary from 4.5 to 8.0. Whereas weakly acidic drugs are reabsorbed from acidic urine, weakly basic drugs tend to be reinternalized in basic urine. Hence, by knowing the pK_a of the drug molecule, one can more effectively predict the clearance and its tubular reabsorption process as a function of pH. For all these reasons, the design of successful drug compounds could greatly benefit from a fast and accurate methodology to predict the pK_a of a molecule in apolar nonaqueous solvents.

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There are different approaches for computing or predicting the pK_a values ranging from empirical methods to ab initio methods. The latter employ quantum chemistry usually combined with electrostatics and occasionally also with molecular dynamics (MD). A recent work on proton solvation in different solvents[13] provides an overview of such pK_a computations for organic compounds. The empirical methods, on the other hand, relate their pK_a to specific features of titratable molecules like molecular structure, semiempirical molecular orbital theory, atomic charges, philicity, and others.[14−22]

It is demonstrated that converting the computed pK_a values of a set of 34 titratable compounds among the organic solvents acetonitrile (MeCN), dimethyl sulfoxide (Me_2SO), and tetrahydrofuran can be essentially performed with an additive shift parameter that depends only on the two solvents but not on the nature of the molecules.[23] For dimethyl sulfoxide (DMSO), it is demonstrated that the computed pK_a values agree very well with the measured values such that this conversion should be also valid among experimental pK_a values. These results suggest that for the mentioned organic solvents, only a solvent specific shift parameter is necessary, and that specific solute−solvent interactions have no influence on the pK_a values. In an earlier work,[24] the experimental pK_a values in water and methanol are compared for a much larger set of molecules. It is found that essentially an additive shift parameter is necessary for converting the pK_a values between the two solvents. However, it is necessary to use different values of the shift parameter for different groups of molecules. This may be partly due to the much larger set of considered molecules but also due the involvement of water, which has a stronger interaction with charged solutes.

Here, we introduce a fully empirical approach that converts the pK_a values known in aqueous solution to pK_a values of the same compound in other solvents. A key feature of our approach is the assignment of a titratable molecule to a specific family of titratable molecular groups. The molecular families of compounds follow the categorization scheme defined in ref 25. These families are selected according to the degree of homogeneity among the chemical functional groups characterizing their components, which can influence the pK_a values of their titratable groups. To convert a pK_a value between two solvents, one needs a single additive shift parameter for each molecular family and pair of solvents. Such families of titratable molecular groups are previously used in the context of empirical prediction of pK_a values in aqueous solvent,[25,26] and family-specific linear functions serve for interconversion between the estimated pK_a values.

Solvent molecules can either possess or not possess polar hydrogen atoms, and the corresponding solvents are called protic or aprotic, respectively. One of the most typical protic solvents is water, which involves only polar hydrogens. Acetonitrile (MeCN) and dimethyl sulfoxide (Me_2SO) constitute typical aprotic solvents. These are pharmacologically relevant solvents because they are of lower polarity and can therefore mimic the interior of the membranes, which need to be penetrated by drug molecules to reach their targets. On the other hand, methanol (MeOH) possesses both polar and nonpolar hydrogens and is therefore a solvent that is neither protic nor aprotic. Products of methanol oxidation are toxic in living cells. However, methanol can be considered as a model system that mimics the situation in a living cell consisting of a mixture of water with a high concentration of proteins and organic molecules that are neither protic nor aprotic.

In the present study, we consider two data sets. The first data set focuses on titratable compounds of small size, for which measured pK_a values are known in water and preferentially also in several of the considered three organic solvents. This data set is provided in Tables S1−S7 in the Supporting Information. It comprises 81 titratable compounds assigned to 19 different families (Figure 1). The 81 chosen titratable compounds are typical members of their molecular families. For this data set, 87 measured pK_a values are available in the three considered organic solvents. In 107 cases, where no measured pK_a values are available for some organic solvents, we compute them by the electrostatic transform method (ETM) using the measured pK_a values in other solvents.[27] To demonstrate the validity of the ETM, the pK_a values are computed in 35 cases and compared with the known measured pK_a values, yielding a root

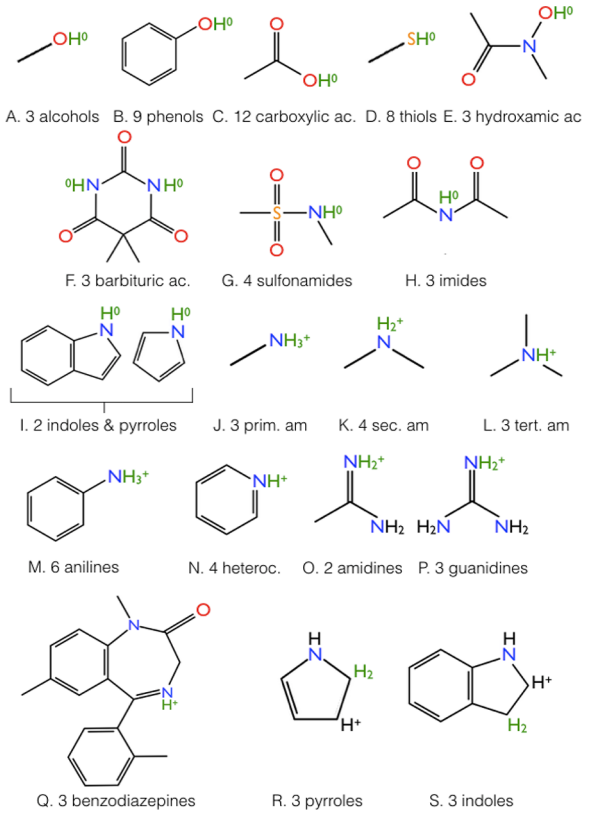

Figure 1. First data set of titratable molecules involves 81 molecules in nineteen different molecular families (A−S). The detailed data are listed in Tables S1−S7 of the Supporting Information. The number of molecules of a specific family is given after the one-letter family name. The molecules are displayed in the protonated state with titratable protons in green color, whereas the other polar hydrogens are displayed in black. For the families O and P only one resonance structure is shown, but, all displayed hydrogen atoms are equivalent and titratable. Nonpolar hydrogens are not displayed. For the families R and S protonation of the carbon atom C2 and C3, respectively, converts the double bond between the two carbon atoms to a single bond. As a consequence the excess positive charge is localizes at the carbon atom, which is not protonated. The formal charge localized at the titratable hydrogen is denoted as a superscript. Oxygen, nitrogen, and sulfur atoms are highlighted in red, blue, and yellow color, respectively.

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mean square deviation pK_a value (pK_a-RMSD) of 0.77 pH units.

We also provide the pK_a values in water obtained with the Jaguar pK_a prediction method (JPM),[28,29] which is based on the work of Friesner et al.[25] JPM assembles a reference pK_a value from gas phase and solution phase energies of protonated and deprotonated species, using the density functional theory B3LYP as implemented in Jaguar. The predicted pK_a value is obtained from the reference pK_a value with a linear regression scheme involving adjustable parameters for different molecular families. In the present work, the pK_a values in water obtained with the JPM are used as reference values for converting them to the pK_a values in the other solvents. The JPM predictions serve as a substitute for measured pK_a values in water because the pK_a values of the JPM are readily available for practically all different types of titratable molecules. The parameters of the presently proposed empirical conversion method (ECM) are determined by matching the pK_a values with 87 measured and 107 pK_a values computed with the electrostatic transform method (ETM). The quality of the ECM is evaluated by comparing the measured pK_a values and those computed with ETM, with the corresponding ones obtained through ECM.

The second data set involves 76 titratable compounds belonging to 5 different additional molecular families. These molecules are generally of larger size. Here, the measured pK_a values are mainly available in DMSO only. The corresponding pK_a values in DMSO are predicted with Jaguar whenever possible. The measured pK_a values in DMSO are used to compute the pK_a values in water through ETM. Subsequently, the measured and ETM pK_a values are used to establish the ECM for the five molecular families. The same operation is performed employing the measured pK_a values in DMSO and the pK_a values in water obtained with the JPM.[26] Here, the quality of the ECM is evaluated by comparing the ECM pK_a values in water with the corresponding ETM and JPM pK_a values.

METHODS

Basic Theory of pK_a Computation. Through the years, many different approaches have been developed for computing or predicting the pK_a value of a molecule in different solvents. Among these methods, there is a popular strategy based on the exploitation of a thermodynamic cycle that describes the process of proton dissociation.[30−33] In such a cycle, gas and solvent phases are considered. The gas-phase free energy of deprotonation (i.e., the proton affinity) is computed as

$$\Delta G_{gas}(A^-/AH) = G_{gas}(A^-) + G_{gas}(H^+) - G_{gas}(AH) \quad (1)$$

where $G_{gas}(M)$ is the gas-phase free energy of molecular species M. The gas-phase free energy of the proton in the standard state T = 298.15 K and 1 mol/L is given as[34,35]

$$G_{gas}(H^+) = H_{gas}(H^+) - TS_{gas}(H^+) + RT\ \ln(24.46)$$
$$= 1.48 - 7.76 + 1.89 = -4.39\ \text{kcal/mol} \quad (2)$$

The difference in solvation free energies of the deprotonated (A^- + H^+) and protonated (AH) molecular species given by

$$\Delta G_{solv}(A^-/AH) = G_{solv}(A^-) + G_{solv}(H^+) - G_{solv}(AH) \quad (3)$$

describes the influence of the solvent environment on the energetics of the protonation process. If the nonelectrostatic part of the binding free energy of a proton to a solute molecule does not depend on the particular solvent environment, which is often the case, the energetics of a protonation process in a solvent environment can be described as the sum of free energy differences in the gas-phase and solvent yielding with eqs 1 and 3

$$\Delta\Delta G_{prot}(A^-/AH) = \Delta G_{gas}(A^-/AH) + \Delta G_{solv}(A^-/AH) \quad (4)$$

According to a thermodynamic relation, the resulting free energy difference can be used to evaluate the pK_a value[31−33]

$$pK_a(AH) = \Delta\Delta G_{prot}(A^-/AH)/[k_B T\ \ln(10)] \quad (5)$$

Empirical pK_a Conversion Method (ECM). We seek a simple molecular family specific function g^f, with parameters to be optimized, that converts the pK_a value of a compound Y^f belonging to family f from solvent j (which, in the present case, is water) to one of the three considered organic solvents i

$$pK_a(Y^f, i) = g^f[pK_a(Y^f, j)] \quad (6)$$

This problem is related to the electrostatic transform method (ETM), which was recently introduced.[27] With the ETM, the measured or computed pK_a value of a titratable compound Y can be transformed from one solvent (j) to another (i) using only contributions from solvation energies of the two considered solvents according to the following relation

$$pK_a(Y, i) = pK_a(Y, j) + [k_B T\ \ln(10)]^{-1} \times [\Delta G_{solv}(Y, i) + G_{solv}(H^+, i) - \Delta G_{solv}(Y, j) - G_{solv}(H^+, j)] \quad (7)$$

The terms $\Delta G_{solv}(Y) = G_{solv}(Y^-) - G_{solv}(YH)$ in eq 7 are the electrostatically computed differences of solvation free energies (deprotonated minus protonated) of compound Y and $G_{solv}(U^+, i)$ together with $G_{solv}(H^+, j)$ are the free energies of proton solvation of the two solvents (i and j). In the following text, the energy differences $\Delta G_{solv}(Y, i) - \Delta G_{solv}(Y, j)$ are tabulated in pH units.

In the ETM methodology,[27] atomic partial charges of a molecule are determined by matching the electrostatic potential generated by the electronic wave function and the nuclear charges with the electrostatic potential from atomic point charges using the restrained electrostatic potential procedure.[36,37] The electronic wave function of the geometry optimized molecule is computed with the B3LYP functional in combination with the double-ζ basis set 6-31G. Finally, the electrostatic solvation energies of the protonated and deprotonated molecular species are computed by solving the Poisson equation with the program SOLVATE, from the program suit MEAD.[38,39]

The ETM works properly under the following three conditions: (1) variations in the molecular conformations in the environment that can be either a liquid or even the gas phase do no influence the pK_a value or do not even occur. (2) The charge pattern of protonated and deprotonated molecular species does not depend on the environment, i.e., the charge distribution is the same in the gas phase and different solvents. (3) The nonelectrostatic part of the energy difference between protonated and deprotonated molecular species does not depend on the environment, i.e., it is the same in gas phase or different solvents. Under these conditions, the ETM procedure has been proven to work with an accuracy of 0.7 pH units when

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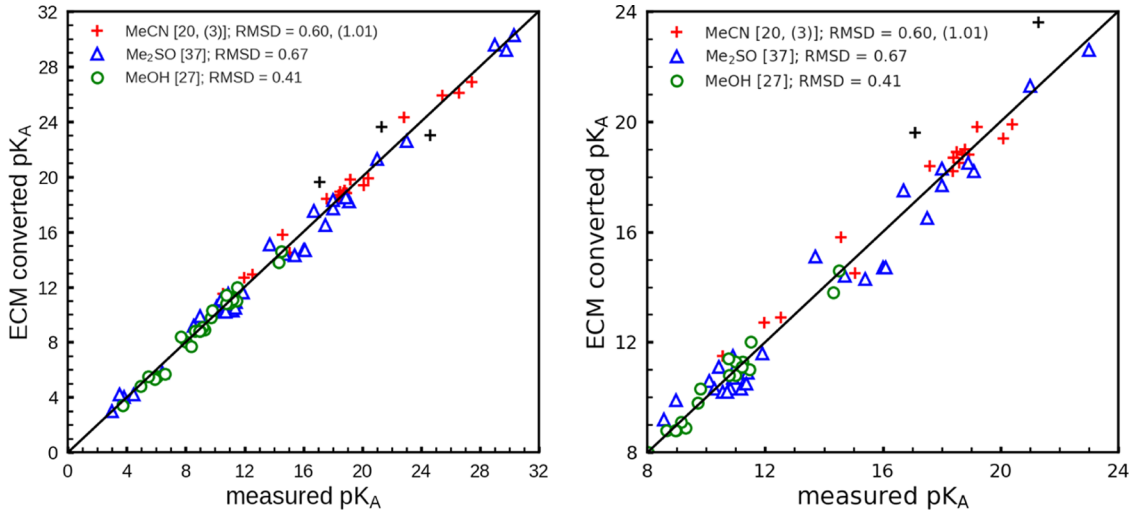

Figure 2. Correlation diagram for the empirical conversion method (ECM). ECM versus measured pK_a values are plotted for the first data set. The ECM pK_a values are evaluated according to eq 9 using the pK_a values in water obtained with the Jaguar pK_a prediction method (JPM)[28,29] as the basis. The three outliers for MeCN are denoted by black crosses (+). The numerical values of the pK_a are listed in Tables S1−S7 of the Supporting Information. The left part of the figure displays all of the data. The right part is a close-up that focuses on the center pH interval.

applied to transform pK_a values of compounds between water, MeCN, Me_2SO, and MeOH.[27] However, it should be noted that these conditions might not be satisfied for some titratable compounds considered in the present study.

The strategy to transform pK_a values from one environment to another is also performed for titratable residues in proteins.[40−50] In this case, the pK_a values are transformed from aqueous solution to the corresponding protein environment, which is represented by the atomic point charges embedded in a low dielectric medium. The accuracy of the computed pK_a values in proteins is typically in the range of 1 pH unit or above, where one critical source of error is the uncertainty in the atomic coordinates of the protein model. This is particularly the case if the protein model is solely based on the crystal structures. Alternating the protein crystal structures by modeling[51,52] or molecular dynamics (MD) simulations[53] helps reduce the pK_a-RMSD, which for MD simulations is significantly below 1 pH unit.

Empirical schemes have already been used for converting measured pK_a values between different solvents. They were applied to a set of phenols (Ph) using multiplicative (A = 1.68) and additive (B = 9.80) parameters[54] converting the pK_a values from water (WAT) to acetonitrile (ACN) according to

$$\mathrm{p}K_a(\mathrm{Ph, ACN}) = A \times \mathrm{p}K_a(\mathrm{Ph, WAT}) + B \quad (8)$$

A linear transformation is also used to convert approximately computed pK_a values for water[25,29,55−57] and acetonitrile[40] into pK_a values comparable to experiment. Thereby, the parameter A compensates mainly for deficiencies of the quantum chemically computed energies and the electrostatic solvation energies, whereas the additive parameter B accounts mainly for the lack or insufficient accuracy of vibrational energies, entropy, and proton solvation energy.[27]

The ETM and its eq 7[27] demonstrates that no multiplicative factor like A in eq 8 is necessary to convert pK_a values between different solvents, if the pK_a value of the reference solvent is precise. In other work, it is demonstrated that the pK_a values can be converted between different organic solvents with eq 8 with a multiplicative factor A close to unity.[23,24] Therefore, we advocate the use of the simplified linear function

$$\mathrm{p}K_a(Y^f, i) = \mathrm{p}K_a(Y^f, j) + \Delta\mathrm{p}K_a{}^f(i, j) \quad (9)$$

to convert the pK_a value of a compound Y^f belonging to the molecular family f from the solvent j to the solvent i. Test computations show no detectable improvement if the more general linear function, eq 8, was used.

The validity of the electrostatic transform method (ETM) requires that the molecular conformation and the atomic partial charges be the same in gas phase and solutions. In contrast, the empirical conversion method (ECM), eq 9, is more general and can account for such dependencies as well as for solvent-dependent shifts in the electronic energies, if they are the same for the considered molecular family. The accuracy of the ECM depends on the appropriate choice of the molecular families and can be improved by using more molecular families.

RESULTS AND DISCUSSION

First Data Set of Titratable Molecules. Let us begin with an application of our method to the first data set of titratable molecules, shown in Figure 1. Our empirical conversion method (ECM) will be used to transform the pK_a values from water to three organic solvents: acetonitrile (MeCN), dimethyl sulfoxide (Me_2SO), and methanol (MeOH). As reference pK_a values in water, we use the pK_a values computed with the Jaguar pK_a prediction method (JPM), alternatively referred to as simply Jaguar. The pK_a values computed with Jaguar apply a semiempirical scheme where an approximate "raw" pK_a value is converted by a linear function with adjustable parameters that depend on a molecular family. These reference pK_a values are used to optimize the parameters $\Delta\mathrm{p}K_a^f$ of eq 9. For comparison, we also provide the corresponding experimental pK_a values in water. The deviation between the measured pK_a values in water and those predicted by Jaguar varies for the 19 different molecular families of the first data set, but is on the average less than 0.5 pH units for the considered titratable molecules. However, for some families in some solvents, it can be larger. Detailed data are given in Tables S1−S7 of the Supporting Information.

In this study, the ECM, eq 9, is established for 81 titratable compounds of the first data set represented by the nineteen

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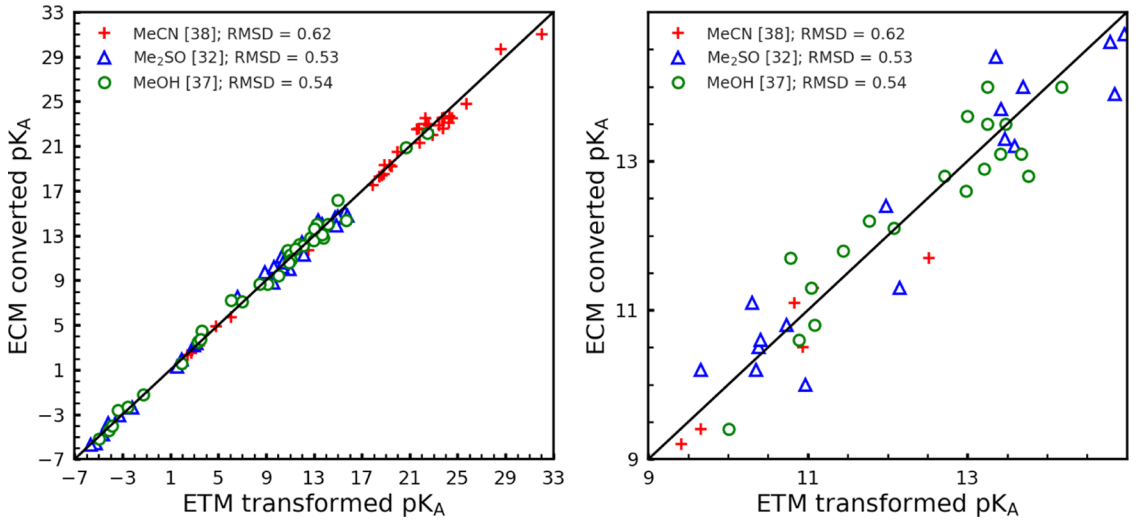

Figure 3. Correlation diagram for the empirical conversion method (ECM). ECM pK_a values are plotted versus with the electrostatic transform method (ETM)[27] computed pK_a values for the first data set. The ECM pK_a values are evaluated according to eq 9 using the pK_a values in water obtained with the Jaguar pK_a prediction method (JPM)[28,29] as the basis. The ETM uses the measured pK_a values in water for the transformation to other solvents. The numerical values of the pK_a are listed in Tables S1−S7 of the Supporting Information. The left part of the figure displays all of the data. The right part is a close-up that focuses on the center pH interval.

Table 1. Parameters that Shift pK_a Values from Water to MeCN, Me_2SO, and MeOH for the First Data Set of Nineteen Molecular Families as Depicted in Figure 1[a]

		ΔpK_a, eq 9, relative to water			$[\Delta pK_a]$, eq 11, relative to water without proton solvation		
No.	molecular family	MeCN	Me_2SO	MeOH	MeCN	Me_2SO	MeOH
A 3	alcohols[b]	13.20			13.27		
B 9	phenols	16.30	7.90	4.00	8.08	7.97	3.71
C 12	carboxylic acids	15.50	7.20	5.00	7.28	7.27	4.71
D 8	thiols	12.70	3.70	2.20	4.48	3.77	1.91
E 3	hydroxamic acids	15.00	6.60	5.00	6.78	6.67	4.71
F 3	barbituric acids	15.40	6.50	4.70	7.18	6.57	4.41
G 4	sulfonamides	12.80	4.50	4.20	4.58	4.57	3.91
H 3	imides	15.00	5.70	4.10	6.78	5.77	3.81
I 2	indoles and pyrroles N	14.20	5.80	5.40	5.98	5.87	5.11
J 3	primary amines	7.70	−0.50	0.30	−0.52	−0.43	0.01
K 4	secondary amines	7.90	0.20	0.20	−0.32	0.27	−0.09
L 3	tertiary amines	8.30	−0.40	0.20	0.08	−0.33	−0.09
M 6	anilines	6.80	−0.70	0.80	−1.42	−0.63	0.51
N 4	heterocycles	7.70	−1.00	0.30	−0.52	−0.93	0.01
O 2	amidines	9.90	1.80	1.20	1.68	1.87	0.91
P 3	guanidines	9.50	1.40	0.60	1.28	1.47	0.31
Q 3	benzodiazepines	7.30	−0.60	−0.30	−0.92	−0.53	−0.59
R 3	pyrroles (C-2 prot.)	6.60	−1.50	−0.30	−1.62	−1.43	−0.59
S 3	indoles (C-3 prot.)	6.90	−1.10	−0.30	−1.32	−1.03	−0.59
	first group B−I	14.70	6.00	4.20	6.48	6.07	3.91
	second group J−S	7.80	−0.30	0.30	−0.42	−0.23	0.01

[a]The first column denotes the family by single letter code and gives the number of compounds considered for this family. The first three columns with numbers list the shift of pK_a values (ΔpK_a) in MeCN, Me_2SO, and MeOH relative to the values in water. In the last three columns, the contributions from the proton solvation energies (in pH units: 8.22, −0.07, and 0.29 for MeCN, Me_2SO, and MeOH, respectively) were subtracted from ΔpK_a yielding $[\Delta pK_a]$, eq 11. The last two lines contain the pK_a shift parameters, if only two groups of families are considered as described in text. [b]No experimental pK_a values are available in MeCN and MeOH and the electrostatic transform method (ETM) fails to yield proper values.

different molecular families from Figure 1. The additive parameters ΔpK_a^f are optimized by fitting the pK_a values of the ECM to the measured benchmark pK_a values for the three organic solvents using the predicted JPM pK_a values in water as a basis. For pure Me_2SO, the measured pK_a values are available for many organic compounds (37 for the considered set of titratable compounds).[58] However, there are fewer measured pK_a values available for the pure solvents of MeCN (23 for the

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considered set of titratable compounds) and MeOH (27 for the considered set of titratable compounds). In the two latter solvents, the pK_a measurements are often performed in mixtures with water. However, the pK_a values measured in mixtures with water may be biased by water molecules clustering around the polar atoms of the titratable groups. Hence, such measurements are not considered for the set of benchmark pK_a values.

For seven molecular families [barbituric acids (F), imides (H), amidines (O), guanidines (P), benzodiazepines (Q), pyrroles C (R), and indoles C (S)], the measured pK_a values are not available in any of the three considered organic solvents. Therefore, to enlarge the database of benchmark pK_a values for the first data set and obtain a more representative set of known pK_a values for the three organic solvents, the ETM[27] is applied. The accuracy of this method is generally high and allows optimizing the parameters on a larger set of benchmark pK_a values to convert the pK_a values between the three organic solvents. However, the ETM has a limited range of applicability, as discussed above. Therefore, we apply it to small molecules, where the gas-phase geometry is the same as in solutions. We also make sure that the computed atomic partial charges determined in vacuum are appropriate for the solution phase.

In Figure 2, the ECM pK_a values are plotted versus the measured values. The pK_a-RMSD values are 0.60, 0.67, 0.41 pH units for 20 (excluding 3 outliers), 37, and 27 measured pK_a values in acetonitrile, dimethyl sulfoxide, and methanol, respectively. In Figure 3, the ECM pK_a values are displayed versus the pK_a values computed with the ETM[27] that uses the measured pK_a values in water for the transformation to the other solvents. In this case, the pK_a-RMSD values are 0.62, 0.53, 0.54 pH units for 38, 32, 37 transformed pK_a values in acetonitrile, dimethyl sulfoxide, and methanol, respectively. Hence, the pK_a-RMSD values between empirically converted pK_a values and pK_a values obtained with the ETM are nearly as small as the pK_a-RMSD values between empirically converted and experimental pK_a values, which demonstrates the quality of the pK_a values obtained with ECM.

The values of the empirical pK_a shift parameters ΔpK_a^f that appear in eq 9 are listed in Table 1 for the nineteen considered molecular families. They describe the family (f) specific shifts of the pK_a values in water to obtain the pK_a values in the other three organic solvents. For MeCN the shift parameters of the pK_a values (ΔpK_a^f) are systematically larger by about 8 pH units compared to the corresponding values for Me_2SO. This is due to the difference in proton solvation energies relative to the value in water. The proton solvation energies are −255.1, −266.4, and −265.9 kcal/mol for MeCN, Me_2SO, and MeOH, respectively.[13] They correlate with the pK_a values that these solvent molecules have in aqueous solution.[13] In water the corresponding proton solvation energy determined by matching computed and measured pK_a values for a suitable set of titratable organic molecules is −266.3 kcal/mol.[13] This value is slightly lower than the consensus value of −265.9 kcal/mol.[59,60] The differences of the proton solvation energies relative to the value in water are 11.2, −0.1, and 0.4 kcal/mol for MeCN, Me_2SO, and MeOH, respectively. Converting these energy values into pH units by means of eq 5, we obtain at T = 298 K the values 8.22, −0.07, and 0.29 for MeCN, Me_2SO, and MeOH, respectively. These values where subtracted from the pK_a shift parameter ΔpK_a^f yielding the values in the last three columns of Table 1. They show the contributions to the pK_a shift parameter $[\Delta pK_a]$ relative to water, which are due to the solvation energy differences of the deprotonated and protonated molecular species. According to eq 7, the solvation energy difference corresponding to the pK_a shift between water and another solvent (solv) is given by

$$\Delta\Delta G_{solv}(A^-/AH) = [G_{solv}(A^-) - G_{solv}(AH)] - [G_{water}(A^-) - G_{water}(AH)] \quad (10)$$

The corresponding contribution to the pK_a shift relative to water without the contribution from proton solvation is

$$[\Delta pK_a] = \Delta\Delta G_{solv}(A^-/AH)/[k_B T \ln(10)] \quad (11)$$

The nineteen molecular families of the first data set, Figure 1, can be split into two groups. The molecules of the first group (A–I) possess a neutrally charged titratable group in the protonated state with a single proton attached to oxygen, sulfur, or nitrogen atoms. The molecules of the second group (J–Q) possess a positively charged titratable group in the protonated state with a proton attached to nitrogen or an additional proton attached to carbon.

For the first group of nine molecular families (A–I), the values of solvation energy differences $\Delta\Delta G_{solv}(A^-/AH)$ [defined by eq 10] and consequently also $[\Delta pK_a]$ (defined by eq 11 and listed in Table 1) are significantly positive. This indicates that deprotonation in one of the three considered organic solvents is energetically less favorable than in water. This is due to the fact that in the negatively charged deprotonated state, the molecules are better solvated in the protic solvent water than in the aprotic solvents acetonitrile and dimethyl sulfoxide. Because methanol is neither protic nor aprotic, the corresponding values of $[\Delta pK_a]$ are less positive for methanol.

For the other ten molecular families (J–S) belonging to the second group of families, the $[\Delta pK_a]$ values are generally close to zero, yielding shift parameters ΔpK_a that depend mainly on the proton solvation energy. These molecular families have two common features. (i) In the protonated state, they have a positively charged titratable group. (ii) The titratable atom is either nitrogen or carbon to which several hydrogen atoms are attached (except for tertiary amines, family K), and so they possess generally less polar titratable groups than the molecules of the first group of molecular families. Therefore, the solvation energies of these molecules differ less between protic and aprotic solvents than for molecules belonging to the first group.

Simplified pK_a Prediction Model that Ignores Detailed Molecular Family Dependencies. In contrast to the pK_a prediction model that requires the use of nineteen molecular families for applying the electrostatic conversion method (ECM) to the first data set, a very approximate scheme may use just two different sets of molecular families. However, one cannot dispense with the dependence on the solvent because the pK_a shift parameters $[\Delta pK_a]$ are systematically larger for MeCN than for Me_2SO and MeOH. The first set involves the families B to I, where the pK_a shift parameters are generally large (Table 1). What is common about these titratable compounds is that their titratable group is charge neutral in the protonated state. The family of alcohols (A) is excluded because for them, the necessary ΔpK_a values (albeit available only for Me_2SO) are considerably larger than for other compounds. This difference may correlate with the fact that the ETM fails to provide proper pK_a values for this family. A reason for this failure could be solvent-specific interactions that are not included in an electrostatic continuum model of the

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solvent. The second set comprises the molecular families J−S (Table 1). Here, the pK_a shift parameters [ΔpK_a] are small for all three organic solvents. These compounds are similar in that their titratable group is positively charged in the protonated state and involves a nitrogen or carbon atom to which several hydrogen atoms are attached in the protonated state. The corresponding values of the pK_a shift parameters are listed in the last two lines of Table 1. The overall pK_a-RMSDs for all three considered organic solvents are 1.37 and 0.96 for the first and second set of molecular families, respectively, which is reasonably small to serve as a rough approximation.

Second Data Set of Titratable Molecules. The second data set involves 76 titratable molecules from 5 specific families (Figure 4). It is of high interest to know the pK_a values of these

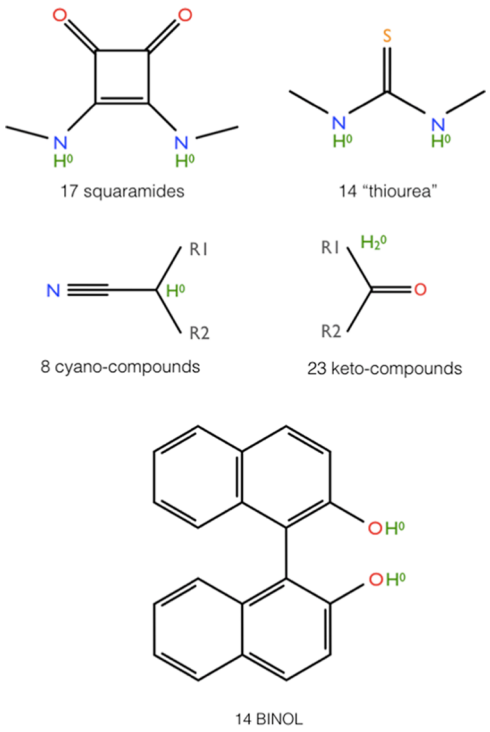

Figure 4. The second data set of titratable molecules involves 76 molecules in 5 different molecular families displayed in the protonated state. The detailed data are listed in Tables S8−S12 of the Supporting Information. The number of molecules of a specific family is given before the family name. Titratable hydrogens carry the formal charge zero for all five families and are shown in green. Oxygen, nitrogen, and sulfur atoms are highlighted in red, blue, and yellow, respectively.

compounds in water. Unfortunately, experimental pK_a values for this data set are scarce and practically only available for DMSO. The majority of these molecules are of larger size and are more flexible than the molecules from the first data set. Therefore, the pK_a values computed with the electrostatic transform method (ETM) are not necessarily as reliable as for the first data set. But the ETM is nevertheless a practical tool to obtain estimates of the pK_a values in water. In addition to ETM, the Jaguar prediction scheme is also applied for obtaining the pK_a values in water. Both sets of pK_a values in water are used to establish alternative ECM for the pK_a values in water. For two families (cyano- and keto-compounds), the Jaguar prediction scheme is applicable in DMSO. A comparison of these predicted pKa values with the measured pK_a values yielded pK_a-RMSD of 1.32 and 1.85 pH units for the families of cyano- and keto-compounds, respectively. However, it should be noted that the Jaguar prediction scheme for DMSO is still in preliminary stage of development and needs to be improved. Detailed data are listed in Tables S8−S12 of the Supporting Information. The correlation diagram between ECM (converted) and ETM (transformed) pK_a values is shown in Figure 5 for all five molecular families of the second data set. If the outliers are discarded, then the pK_a-RMSDs differ by less than 0.8 pH units.

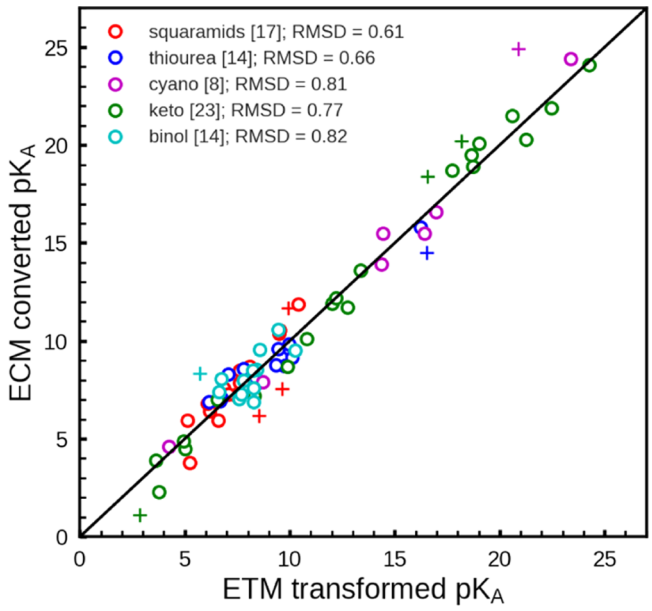

Figure 5. Correlation diagram for the empirical conversion method (ECM). ECM (converted) pK_a values are plotted versus the electrostatic transform method (ETM)[27] computed pK_a values for the second data set. The latter are based on measured pK_a values in DMSO. The ECM pK_a values are evaluated according to eq 9 using preliminary pK_a values in DMSO obtained with the Jaguar pK_a prediction method (JPM)[28,29] as the basis. The number of compounds for the individual molecular families is given in the rectangular brackets. Outliers where the pK_a values differ by more than 1.5 pH units are denoted with "+". The numerical values of the pK_a are listed in Tables S8−S12 of the Supporting Information.

The titratable groups in the molecules of the second data set carry for all five molecular families zero formal charge (Figure 4). For the molecular families squaramides, thiourea, and BINOL, the titratable hydrogen is attached to nitrogen or oxygen. These molecular families are therefore analogous to the families A−I of the first data set (Figure 1), where the values of [ΔpK_a], eq 11, are significantly larger than zero. Because the proton solvation energy is nearly the same for water and DMSO, the shift parameters ΔpK_a involving also proton solvation are nearly equal to the shift parameters [ΔpK_a] without proton solvation. Hence, for the same reason as described before, we expect significantly positive values of the shift parameters, ΔpK_a. This is indeed the case (see Table 2).

The other two molecular families of cyano- and keto-compounds have the titratable hydrogen attached to carbon atom. They should therefore be analogous to the molecular families R and S of the first data set, where the [ΔpK_a] parameters are close to zero. But, for the cyano- and keto-compounds, the pK_a shift parameter ΔpK_a adopts values above 6 pH units. Hence, the deprotonated cyano- and keto-

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Table 2. Parameters Shifting pK_a Values from Water to Me_2SO for the Second Data Set Consisting of Five Molecular Families as Depicted in Figure 4[a]

		ΔpK_a, eq 9, relative to water	
No.	molecular family	based on ETM	based on JPM
17	squaramides	4.60	4.50
14	thiourea-compounds	3.70	1.40
8	cyano-compounds	6.40	6.00
23	keto-compounds	6.30	6.20
14	BINOL-compounds	2.40	2.60

[a]The first column gives the number of compounds considered for the corresponding molecular family. The last two columns contain the values of the pK_a shift parameter ΔpK_a. They convert the pK_a values from water to Me_2SO according to eq 9. In this application, the shift parameters are determined by converting the measured pK_a values in Me_2SO to the corresponding values in water. The third column contains the values of ΔpK_a obtained by using the pK_a values in water that were computed with the electrostatic transform method (ETM), whereas in the last column ΔpK_a are obtained using the pK_a values in water computed with the Jaguar pK_a prediction method (JPM).

compounds must be much more polar than the deprotonated indoles and pyrroles (molecular families R and S). In the latter case, the carbon atoms are part of an aromatic ring system, which may be responsible for lower polarity of the deprotonated state of these compounds. However, another difference is the formal charge of the titratable group in the protonated state. This charge is positive for the molecular families R and S of the first data set, but neutral for the cyano- and keto-compounds of the second data set, which is in analogy to the molecular families A–I of the first data set. Therefore, the cyano- and keto-compounds are indeed more polar in the deprotonated state than the deprotonated pyrroles and indoles of the molecular families R and S, which explains the large values of the pK_a shift parameters ΔpK_a.

Comparing the values of the shift parameters for the molecular families of the second data set by using the ETM or the JPM pK_a values in water, we obtain practically the same values except for the thiourea compounds (Table 2). This general agreement demonstrates the reliability of the computed pK_a values in water. However, for thiourea, the shift parameters deviate by 2.3 pH units, which is considerable. Unfortunately, no measured pK_a values in water are available for thiourea compounds to resolve this discrepancy. These deviations may be connected with the sulfur atomic radii of 2.00 and 2.18 Å used in water and DMSO,[13,27] respectively, which have not yet been tested sufficiently carefully.

For cyano- and keto-compounds, the measured pK_a values in water are available in a few cases. We also found the measured pK_a values in water for four different keto-compounds (Table S10 of the Supporting Information). Except for cyclobutanone, the measured pK_a values agree well with the corresponding values obtained by ETM and JPM, supporting our approach to establish the empirical conversion method (ECM) with the pK_a values in water obtained with ETM and JPM. For cyano-compounds, we found only two measured pK_a values. These are 25.0[61] and 11.2[62] for CH_3CN and $CH_2(CN)_2$, respectively (Table S10 of the Supporting Information). These values deviate considerably from 20.89 and 4.25 computed with ETM or 19.23 and 7.96 obtained with JPM, respectively. Interestingly, the ECM pK_a values for CH_3CN in water are 24.90 and 25.30, if based on the ETM or JPM pK_a values in water, respectively. Hence, the ensemble of molecules considered for the family of cyano-compounds makes sure that the ECM estimate of the pK_a value of CH_3CN is appropriate. However, this is not the case for the pK_a value of $CH_2(CN)_2$, where the pK_a values in water estimated with ECM are 4.60 and 5.00, if based on the ETM or JPM pK_a values in water, respectively. According to the measured pK_a values of $CH_2(CN)_2$ in DMSO (11.2) and water (11.0), which are practically equal, $[CH(CN)_2]^-$ should solvate equally well or even better (because $CH_2(CN)_2$ is aprotic as is DMSO) in DMSO than in water. On the other hand, the measured pK_a values of CH_3CN in water (31.3) and DMSO (25.0) suggest that $[CH_2CN]^-$ solvates better in water than in DMSO. Hence, the measured pK_a value of $CH_2(CN)_2$ in water being practically equal to the value in DMSO is not very plausible.

SUMMARY

The empirical pK_a conversion method (ECM) predicts the pK_a values of titratable compounds in organic solvents using known pK_a values in water. The concept of the ECM, which uses a molecular family dependent parameterization, seems to work also for large and even flexible molecules. This indicates that the dependencies of pK_a values on molecular conformations and interactions of the titratable group with other functional molecular groups within the solute molecule are moderate at least for the molecules studied in this work. The ECM procedure uses a single additive shift parameter. It is explained why an additional multiplicative shift parameter is not useful. Two data sets of titratable molecules are considered. The first data set involves 19 different molecular families with 81 different titratable compounds. Molecular family and solvent-specific additive pK_a shift parameters ΔpK_a are evaluated relative to the pK_a values in water, which, in their turn, are obtained with the Jaguar pK_a prediction method (JPM)[28,29] for the solvents acetonitrile, dimethyl sulfoxide, and methanol (Table 1). The additive pK_a shift parameters are optimized using 87 measured and 107 pK_a values that are computed with the electrostatic transform method (ETM).[27] The ETM may also be very useful in extending the ECM of the present work to other solvents where the database of measured pK_a values is small. By combining the pK_a shift parameters ΔpK_a of Table 1 additively, pK_a values can be converted between arbitrary pairs of solvents involving water, DMSO, acetonitrile, and methanol. The average accuracy of the ECM pK_a values is found to be about 0.5 pH units. The agreement between the measured and the ETM computed pK_a values demonstrates the usefulness of this method, which can be employed to enlarge the database of known pK_a values for different solvents.

An analysis of the additive parameters shifting the water pK_a value of a molecule to the corresponding values in other solvents reveals that there are two categories of molecules: very polar molecules involving preferentially titratable oxygen and nitrogen with a single hydrogen attached and less polar molecules involving either titratable nitrogen with several hydrogens attached or carbon atoms. The first category involves molecules with solvation energies that disfavor deprotonation in aprotic organic solvents compared to water. The molecules from the second category have solvation energy differences between protonated and deprotonated species, which are about the same in water and different organic solvents.

The second data set of titratable molecules involves five molecular families with 76 molecules. Most of these molecules

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are considerably larger than the molecules of the first data set. Here, the measured pK_a values are available essentially only for DMSO. The pK_a shift parameters between water and DMSO are optimized by using computed pK_a values in water obtained with ETM or JPM. These two sets of shift parameters agreed well except for the family thiourea demonstrating the validity of the ECM for the other four families (Table 2). In the few cases where the measured pK_a values in water are available, the computed pK_a values agree with the corresponding measured values except in one case (the keto-compound cyclobutanone) where the measured pK_a value is doubtful.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01895.

Detailed data of measured and computed pK_a values shown in Figures 2, 3, and 5 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: knapp@chemie.fuberlin.de (E.W.K.).

ORCID

Art D. Bochevarov: 0000-0002-0376-8432

Ernst Walter Knapp: 0000-0002-2858-0460

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

MeCN, acetonitrile; Me_2SO (DMSO), dimethyl sulfoxide; ECM, empirical conversion method; ETM, electrostatic transform method; JPM, Jaguar pK_a prediction method; MD, molecular dynamics; pK_a-RMSD, pK_a root mean square deviation; RESP, Restrained Electrostatic Potential

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