

Strengths of Acids in Acetonitrile

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Dedicated to the memory of Prof. Ilmar A. Koppel.

The equilibrium acidity scale (pK_a scale) in acetonitrile has been supplemented by numerous new compounds and new ΔpK_a measurements. It now contains altogether 231 acids – over twice more than published previously – linked by 569 ΔpK_a measurements and spans between the pK_a values of hydrogen iodide (2.8) and indole (32.57), covering close to 30 orders of magnitude. Measurement results acquired over the last 15 years were added to the scale and new least-squares treatment was carried out. The treatment yielded revised pK_a values for the compounds published previously, with the root mean square

difference between revised and previous values 0.04, demonstrating very good stability of the scale. Correlation equations were developed for estimating pK_a values for the studied types of compounds in water, DMSO, DMF, and 1,2-dichloroethane on the basis of pK_a values in acetonitrile. These equations enable predicting pK_a values with an average error around or less than 1 pK_a unit, which is a sufficient accuracy for many applications. The scale is expected to be a useful tool for the widest possible research areas in organic chemistry, electrochemical power sources, catalysis, etc.

Introduction

The pK_a values in different solvents are among the most important chemical parameters of any compound that is able to behave as an acid.^[1] The availability of pK_a data differs very much between different solvents. Expectedly, the largest body of pK_a data is available in water.^[2] Where the amount, diversity, and quality of the available pK_a data is concerned, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), and acetonitrile (MeCN) stand out from most other non-aqueous solvents.^[3–5] Especially notable is the monumental work of the Bordwell group,^[4] who have determined altogether more than 1000 pK_a values of neutral acids in DMSO solution.

Acetonitrile as a medium for acid-base studies has several favorable properties. Because of its high relative permittivity ($\epsilon_r = 36$) it favors the dissociation of ion pairs into free ions. Its very low autoprotolysis constant (estimated $pK_{a_{\text{auto}}}$ around or higher than 40^[6]) makes it a good differentiating solvent. Its basicity is very low for a dipolar aprotic solvent.^[1] As an example, the free energy of transfer of the proton from DMSO to MeCN is 15.7 kcal mol⁻¹,^[7] corresponding to more than 11 orders of magnitude of equilibrium constant. What is more,

acetonitrile has a low ability of anion solvation.^[8] These two properties put together make it useful for studies of strong acids. Additionally, acetonitrile is a useful solvent for non-aqueous electrochemistry, transparent for UV radiation down to 190 nm, and readily available in high purity.

Over the years, our group has measured the strengths of numerous acids in acetonitrile using a relative UV-Vis spectrophotometric measurement method. The first publication of this kind dates back to 1998 when an acidity scale spanning pK_a values from 3.8 to 16.7, i.e. to the range of about 13 pK_a units, was published.^[9] 8 years later, the scale was extended to a weaker acidity area up to pK_a value 28, now containing altogether 93 acids and covering essentially the whole acidity range that can be conveniently measured in acetonitrile.^[5] Over the years the pK_a values of numerous new compounds have been measured using the pK_a values of the acids from the scale. All new acids measured using the same method essentially became members of the scale themselves. The overall number of acids now is 231, with pK_a values ranging from 2.8 (HI) to 32.57 (indole). The values, however, are scattered among different publications. Also, the massive number of new relative measurements that have been performed (many of them under better conditions than the original values) justify the least-squares re-evaluation of the whole scale, in order to get more accurate values also for the compounds originally published in 1998 and in 2006. There are also whole families of compounds (aryl-triflyl-methanes, sulfonamides) with pK_a values in acetonitrile measured but not yet published.

Thus, the aim of the current work is to bring together all the ΔpK_a measurements carried out by us in acetonitrile over the years, assemble all of them into a single scale, and carry out the least-squares minimization procedure in order to get the best possible pK_a values for all the compounds on the scale. As a result, this scale will have a considerably larger number of

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compounds and involve many more overlapping ΔpK_a measurements making the whole scale more reliable.

Theoretical background

According to the Brønsted-Lowry definition, the acidity of a neutral acid HA in solvent S is defined by eq (1) and is expressed as the acid dissociation constant K_a (or more commonly as its negative logarithm, pK_a), according to eq (2).



$$pK_a = -\log \frac{a(A^-) \cdot a(SH^+)}{a(A)} \quad (2)$$

S is the solvent molecule and a is the activity of the corresponding species in solution. pK_a value depends strongly on the solvent. It is also important to consider the properties of the solvents to understand the possible side reactions that can occur in different solvents. In MeCN, since the solvent has modest anion solvating ability, some acids can undergo homo- or heteroconjugation processes and ion pairing. Some of these processes can be suppressed, but homoconjugation is the process we have quite often encountered.^[5]

Homoconjugation is the equilibrium process of formation of the homoconjugate complex – the hydrogen-bonded (HB) complex between a neutral acid and its anion according to eq (3). *Heteroconjugation* is the equilibrium process of formation of the heteroconjugate complex – the complex between the neutral and anionic forms of different compounds, defined by eq (4). In the present work, we evaluate K_{AHA} value where needed but our experimental conditions enable avoiding heteroconjugation (see the Experimental section).



In non-aqueous solvents, the measurements of the activity of solvated hydrogen ion $a(SH^+)$ are problematic, especially in solvents of low polarity. To exclude the necessity to measure the activity of solvated hydrogen ion $a(SH^+)$, the equilibrium between two acids HA_1 and HA_2 can be studied:



This equilibrium refers to the relative acidity of the two acids HA_1 and HA_2 which is expressed as ΔpK_a and is defined as follows:

$$\Delta pK_a = pK_a(HA_2) - pK_a(HA_1) = -\log \frac{a(HA_2) \cdot a(A_1^-)}{a(HA_1) \cdot a(A_2^-)} \quad (6)$$

As can be seen, the component $a(SH^+)$ does not appear in the eq (6). Assuming that the ratio of activity coefficients $f(HA)/$

$f(A^-)$ is the same for both species, then the eq (6) can be transformed into the following form:

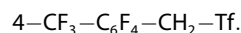
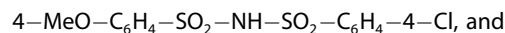
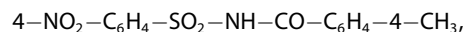
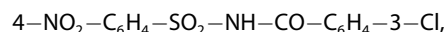
$$\Delta pK_a = pK_a(HA_2) - pK_a(HA_1) = -\log \frac{(HA_2) \cdot (A_1^-)}{(HA_1) \cdot (A_2^-)} \quad (7)$$

The species in square brackets are now equilibrium concentrations that can be measured directly. The simplification to use equilibrium concentrations can be made when relatively low concentrations can be used for measurements, which holds safely for UV-Vis spectrophotometric measurements.

Methods

Compounds and pK_a measurement method

The origin of the compounds published by us earlier, as well as the pK_a measurement methods, can be found from the following references: [5,10–27]. The most comprehensive method description is given in ref [5]. Indoxyl acetate, nitro-substituted phenols, sulfonamides, sulfonic acids, bis-(2,4,6-trinitrophenyl)-amine were purchased from commercial sources and were used as received. 3,5-F₂-C₆H₃-CH₂-Tf was a kind gift from the laboratory of Prof. Masaaki Mishima. Synthesis of the following compounds are described in SI:

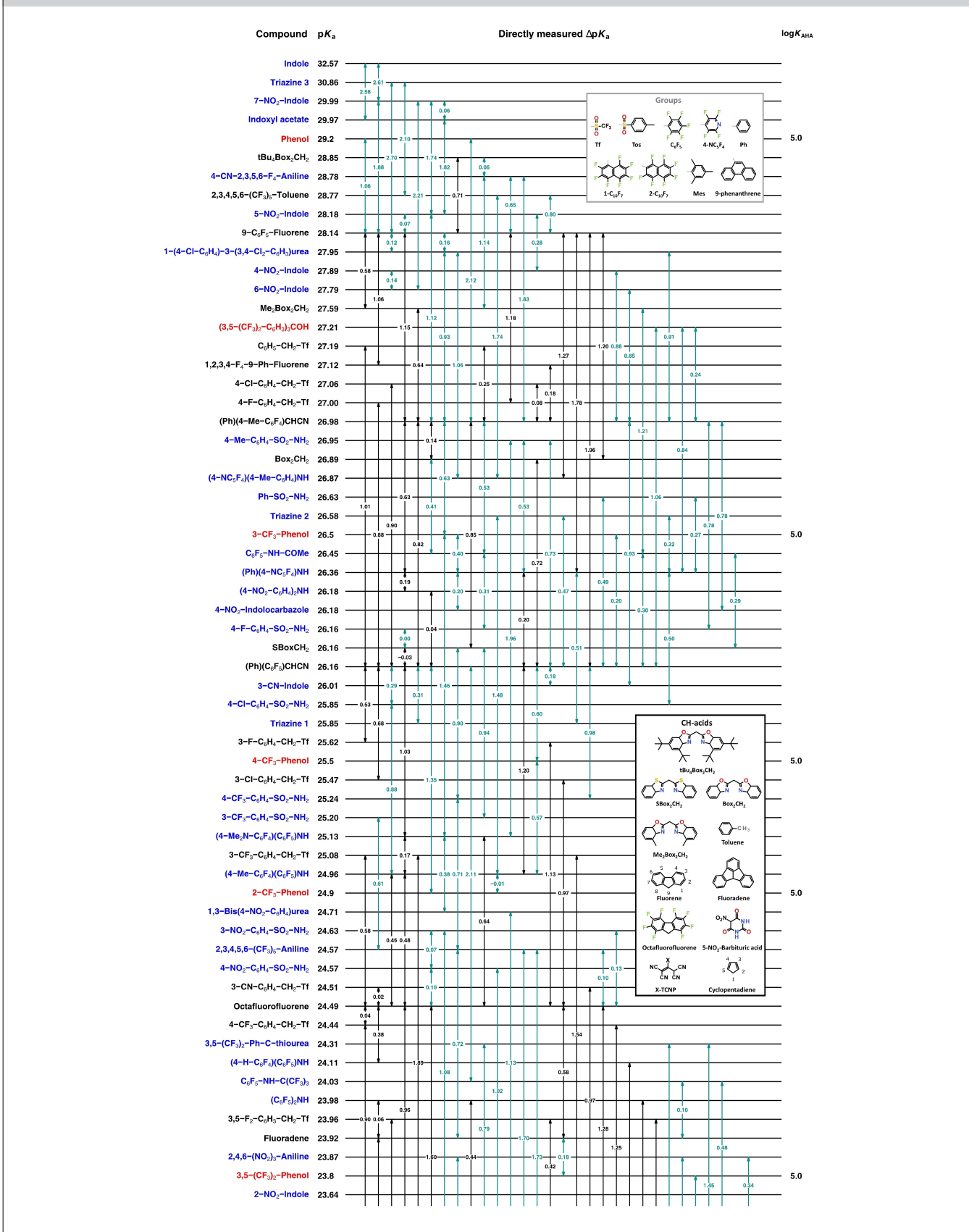


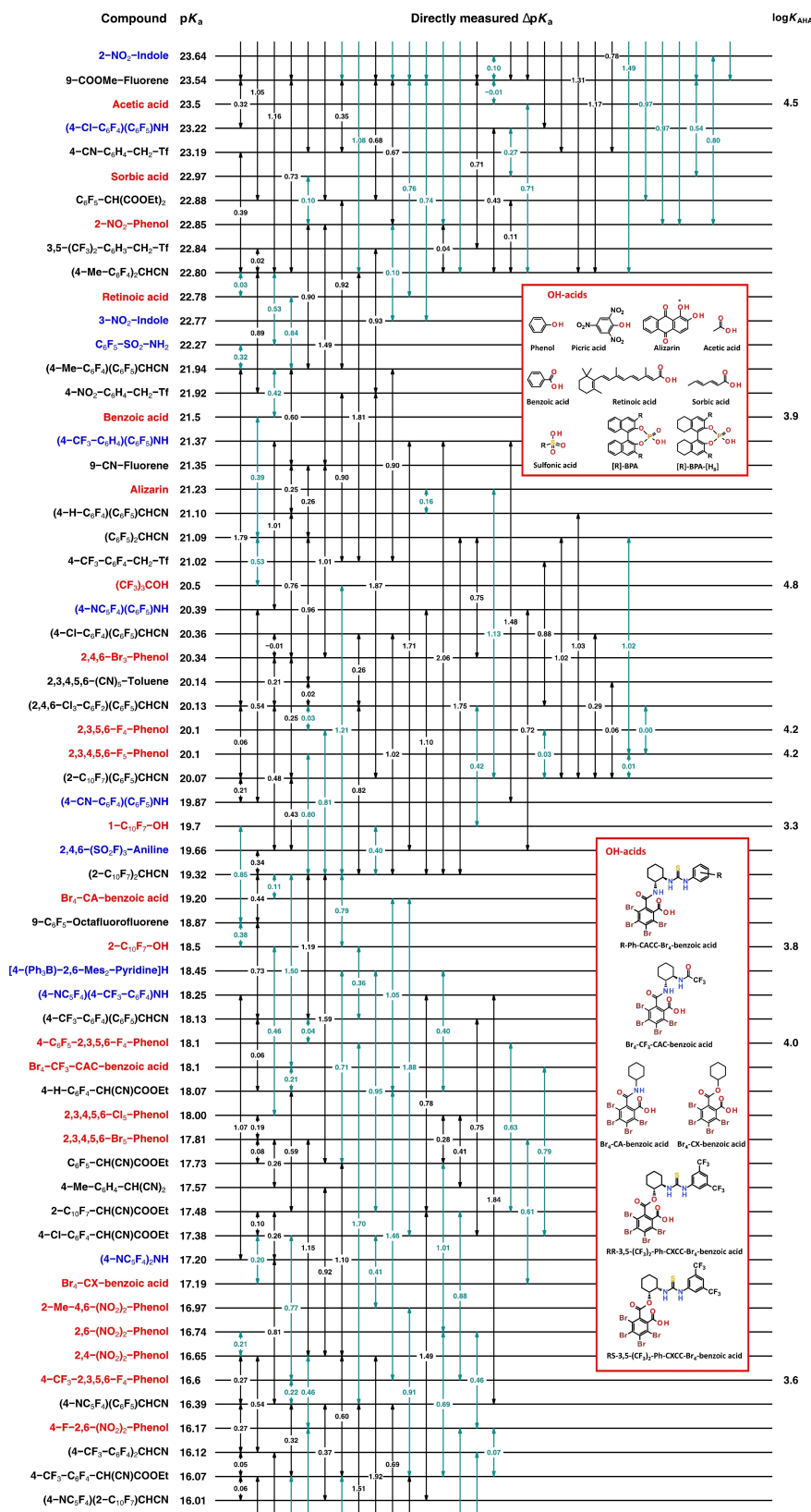
Compiling the acidity scale

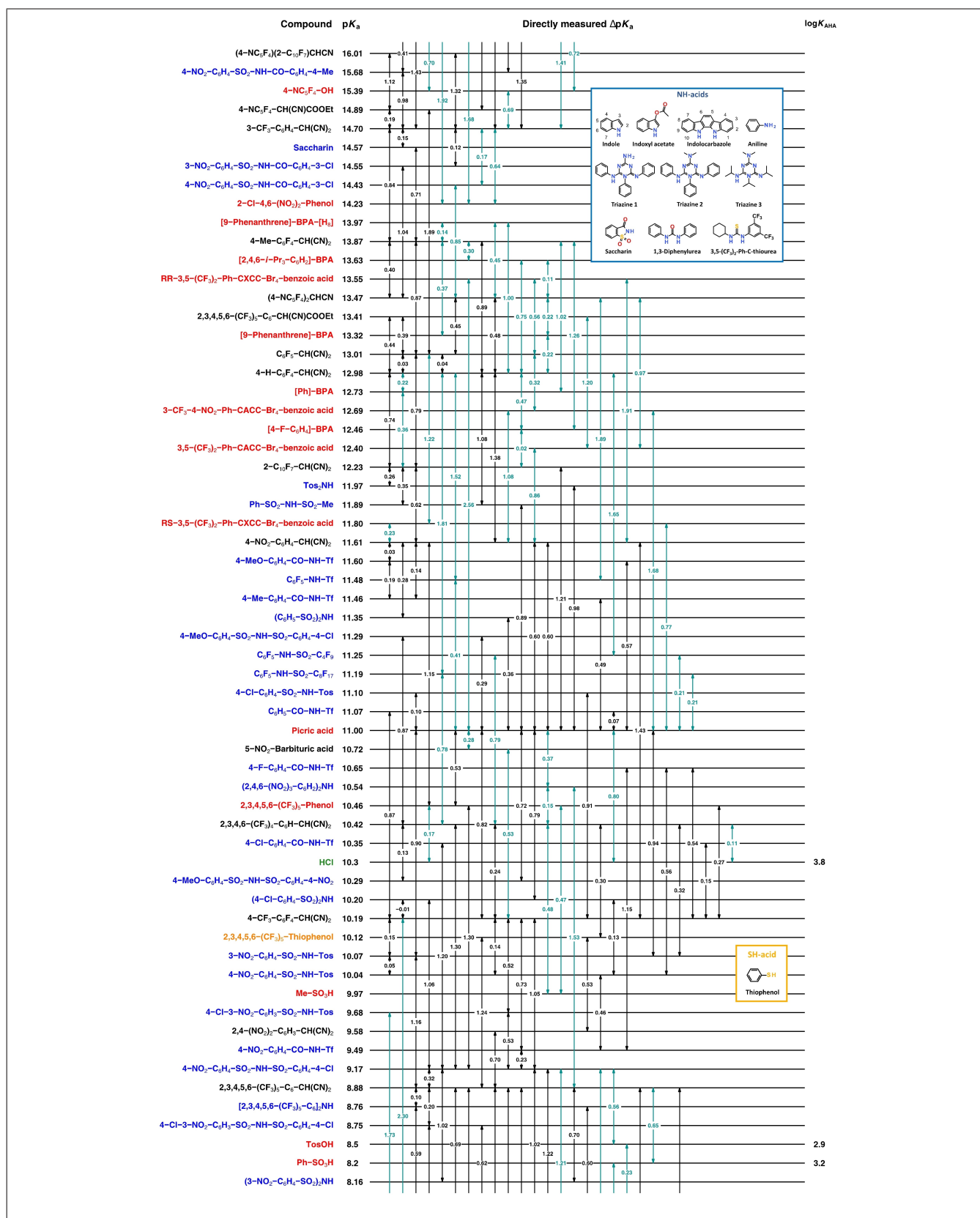
In order to obtain the acidity scale (Table 1) with the most reliable pK_a values possible, the acids were divided into two groups based on the reliability of the corresponding ΔpK_a measurements and handled in such a way as to give more weight to more reliable results. The reliable compounds ("backbone" acids) were selected on the basis of the following preferable properties (listed in approximate order of importance):

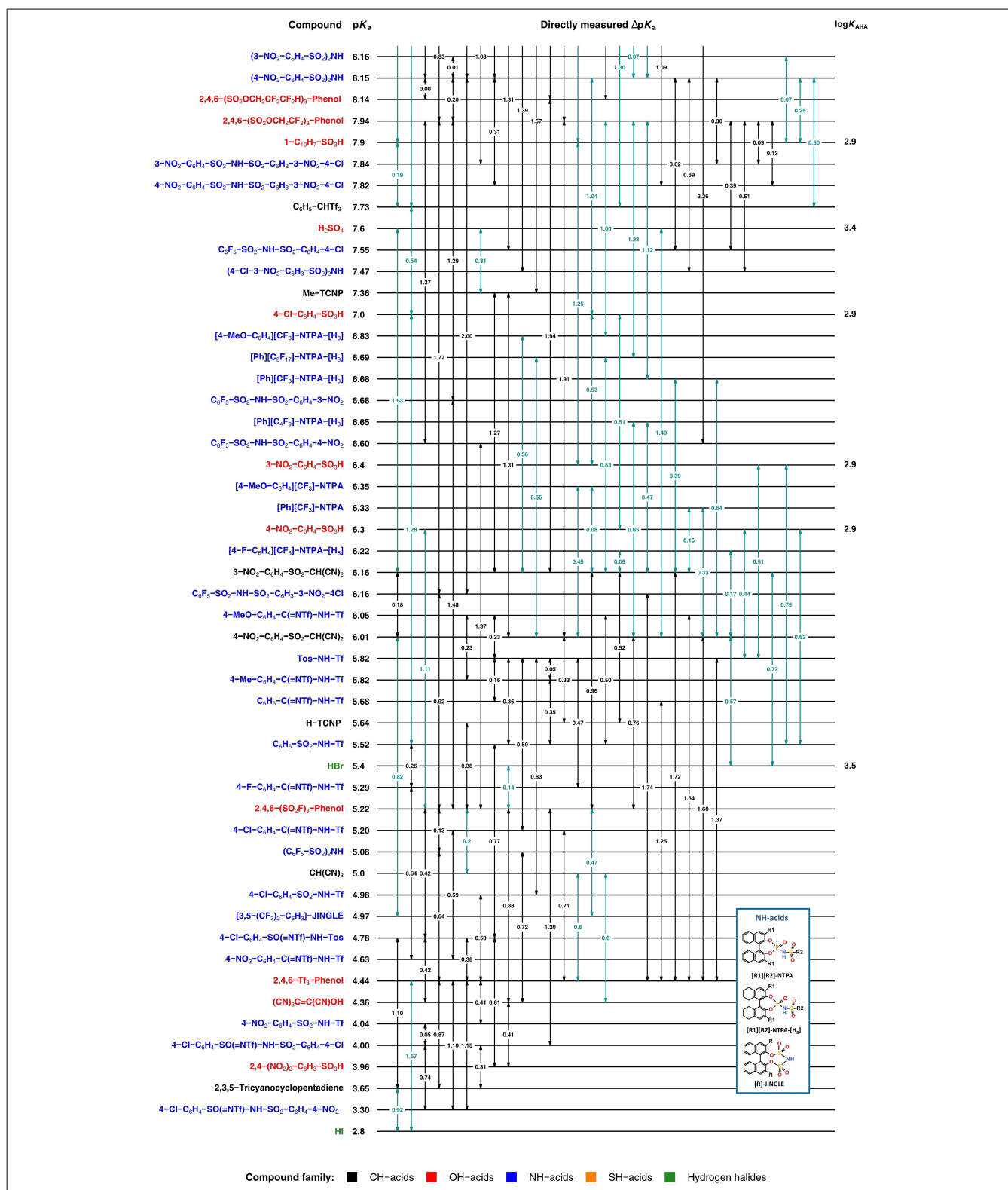
- They have convenient UV-Vis spectral properties: absorption in the range above ca 230 nm and considerably different spectra of the neutral and anion, leading to a prominent change in the UV-Vis spectrum during the titration with the basic (deprotonation of the acid) or acidic (protonation of conjugate base) titrant. As a generalization, in such compounds, the acidity center is directly attached to an aromatic or other pi-electron system (arylacetonitriles, (di)arylamines, (di)arylmethanes, phenols, fluorenes, etc) or is part of such a system. As is demonstrated in ref [5], in the case of the ΔpK_a

Table 1. Revised equilibrium acidity scale in acetonitrile. The scale in continuous form, as well as the data in tabulated form complete with CAS numbers and formulas of compounds, are presented in the SI.









measurement between two backbone acids the ΔpK_a value can be calculated from spectral data only, without the need for accurate concentrations of compounds and with minimal influence of possible impurities. This greatly enhances the accuracy of the obtained ΔpK_a values. Weighing data was

only used for adjusting concentrations into a range suitable for UV-Vis spectrophotometry and for minor volume corrections, not for calculating concentrations.

- Their ΔpK_a measurement results obtained against different compounds are self-consistent, i.e. lead to similar pK_a values.

• They do not undergo homo- or heteroconjugation. These processes (especially homoconjugation) have been quite extensively studied and a solid amount of homoconjugation constant data is available in the literature.^[3,8] The generalization that can be made is that homo- and heteroconjugation reactions are negligible if the acid under question is not a strong HB donor and its anion does not have a strongly localized charge. According to these criteria, the information from literature, and our observations, homoconjugation ability is first of all the property of OH acids and is essentially absent with CH and NH acids. In UV-Vis spectrophotometric pK_a measurements homoconjugation can be experimentally observed in two ways: (1) distortions in spectra (i.e. the spectrum of partially deprotonated acid cannot be presented as a linear combination of the spectra of the neutral and the anion) and (2) significant drift is observed in the pK_a values of a measurement series. According to our experimental observations, almost all carboxylic acids undergo homoconjugation, as well as phenols that do not have bulky or HB acceptor substituents in ortho position. Sulfonic acids also undergo homoconjugation, although to a lesser extent. All acids that demonstrably undergo homoconjugation were left out of the “backbone” group, as well as some for which homoconjugation possibility was implicitly evident from irregularities in the spectrophotometric titration data or inconsistency of the ΔpK_a measurement results. Thus, preferably, CH and NH acids were used. Only a few OH acids were designated into backbone acids.

The compounds not meeting the above-mentioned requirements were classified into the group of less reliable (“secondary”) acids. Then, the following two-step approach was used for assigning the pK_a values to the acids:

- (1) The “backbone” of the scale was built using reliable ΔpK_a measurements of “backbone” acids. Their pK_a values were fixed by the least-squares minimization procedure (explained below) using the measured ΔpK_a values between these compounds, whereby the pK_a values of all of them were allowed to vary, except picric acid ($pK_a = 11.00$), which is the primary reference compound for the whole scale. The corresponding measurements are shown as black arrows in Table 1.
- (2) The “backbone acids” are then used as secondary reference acids for assigning pK_a values to the “secondary” acids with less reliable ΔpK_a values. This was done by using the same least-squares minimization procedure, but this time the pK_a values of backbone acids were fixed and only pK_a values of the secondary acids were allowed to change. The measurements of secondary acids are denoted as green arrows in Table 1.

In the case of acids that undergo homoconjugation during measurements, homoconjugation was corrected for by using estimated K_{AHA} values, as explained in ref [5]. Heteroconjugation of such compounds was avoided by choosing reference acid unable to participate in heteroconjugation.

The obtained acidity scale is presented in Table 1. Every double-headed arrow in Table 1 refers to one titration experiment and the corresponding ΔpK_a value is an average of

individual ΔpK_a values calculated for each of 5–20 additions of titrant, by one or several (whenever applicable) ΔpK_a calculation methods (described in ref [5]). The ΔpK_a values obtained from measurements between compounds with good UV-Vis spectral properties are more reliable, since due to the relative nature of the measurement method the influence of several uncertainty sources – weighing small amounts of compounds, their purity, impurities in compounds and solvent, incl. water, etc – will partially or fully cancel out. In particular, the relative measurement method can be considered robust regarding the water content of solutions: the influence of trace amounts of water is largely negated by the nature of the method, as demonstrated in ref [28].

The absolute pK_a values for individual compounds were found by the least-squares minimization procedure as follows:

$$SSD = \sum_{i=1}^{n_m} \{ \Delta pK_a^i - [pK_a(HA_2)] - [pK_a(HA_1)] \}^2 \rightarrow \min \quad (8)$$

where SSD , the minimized parameter, is the sum of squared deviations between the directly measured acidity difference between acids HA_1 and HA_2 (ΔpK_a^i) over all the n_m titration series and the difference between the assigned absolute pK_a values for the same acids $pK_a(HA_1)$ and $pK_a(HA_2)$. The absolute pK_a values for all compounds were assigned using two consecutive minimization procedures as described above.

The precision and consistency of each of the minimization steps can be assessed using the consistency standard deviation s :

$$s = \sqrt{\frac{SSD}{n_m - n_c}} \quad (9)$$

where n_m is the total number of ΔpK_a measurements in that step and n_c is the number of pK_a values assigned during that step.

Creating and validating the predictive equations

The pK_a data in water, DMSO, DMF, and DCE, as well as the GA values, were critically selected and are presented in the SI together with sources (Table S1).

In the case of DMSO, values from the Bordwell group were preferred. DMSO data from other groups were critically evaluated for consistency and experimental details, especially the pK_a values of reference compounds used for calibration. Three sets of data sources were observed. The first set^[4,21,29–42] is consistent with Bordwell’s data: all these works use pK_a values for reference compounds that are the same or similar to those observed by the Bordwell group. Another set of data^[43–47] was corrected to make them consistent with the Bordwell data. The third set is composed of three strong acids HCl, HBr, and HI with negative pK_a values in DMSO, which the Bordwell method is unable to measure. The pK_a values for those compounds were taken from ref [48].

The acidity data in DMF was critically evaluated, analogously to DMSO. The data from works [43,49–57] was found consistent, or the need for correction could not be identified.

In the case of DCE, values from ref [58] (obtained using the highly reliable ladder approach and corrected for ion-pairing) were used. It should be noted that the values obtained in that work correspond to essentially pure DCE, whereas any polar impurities (first of all, water) may lower the pK_a values dramatically.

For the gas phase data, experimental data was preferred; calculated values were used in few cases where no experimental values were available.

The equations were developed in a similar manner to ref [59]. Simple structure-based descriptors (e.g. numbers of atoms and various functional groups, see the SI for the full list) were computed for the studied compounds. Considering the relatively small number of acids in the data subsets, to reduce the overfitting 10% of the randomly selected values were repeatedly removed and the remaining data then used for selecting descriptors. The few most frequently chosen sets of descriptors were considered for the final equation. The ultimate equation coefficients were calculated based on the full data set. The equations were validated using the “leave one out” approach.^[59]

Results

The Revised and Updated Acidity Scale in Acetonitrile

The revised and updated acidity scale is presented in Table 1. It contains currently 231 acids from a large number of families (see Figure 1), which are interconnected with 569 relative acidity measurements. The consistency standard deviation obtained from measurements with “backbone” acids is 0.03 pK_a units, which can be considered good. The consistency standard deviation of the measurements involving “secondary” compounds is 0.10 pK_a units.

When comparing the pK_a values in the current scale with those published earlier – first of all in ref [5] and the strong acids revised in ref [11] — then two distinct regions emerge. In the pK_a region between 9 and 33 the differences between the currently reevaluated and previously published values are small: mostly between –0.02 to 0.02 pK_a units. Differences with both signs occur, although in the region above pK_a 22 the newly revised values tend to be by few hundredths of pK_a units higher than the previous ones. The biggest deviation (+0.07) from previous values in this region is displayed by 2,3,4,5,6-(CF₃)₅-toluene. However, its previous pK_a value was published with just one decimal place. In the region below pK_a 9, the new values are on an average by –0.03 pK_a units lower. Two big discrepancies stand out in this region: 3-nitro- and 4-chlorobenzenesulfonic acids, by –0.27 and –0.23 pK_a units, respectively. The significant discrepancies with these two acids are due to their challenging nature (unsuitable spectral properties and homoconjugation).

All in all, one can conclude that except for the two above-mentioned sulfonic acids, the differences between the current

and earlier published values are insignificant for almost all possible applications.

An important comparison in practice is between pK_a values of neutral acids to pK_{aH} values of neutral bases (pK_a values of the respective cationic acids) from ref [59]. The pK_a scales of neutral and cationic acids have been developed/measured separately. The reason is that when a neutral acid AH is measured against a cationic acid BH⁺ then the assumption of constant activity coefficient ratio – see explanations to eqs (6) and (7) – breaks down. As a result, for obtaining ΔpK_a it is necessary to evaluate the activity coefficients of the species, which in turn invokes the need to know the ionic composition of the solution, thereby introducing additional uncertainty into the results. Nevertheless, ΔpK_a measurements between neutral acids of the current scale and cationic acids in the scale of ref [59] have been performed for estimating their comparability.^[60] The conclusion reached was that the scales are compatible with a standard uncertainty of ca 0.1 pK_a units^[60] (i.e. the discrepancy is below 0.2 pK_a units in ca 95% of cases). This is suitable for most practical applications. True, since the time of ref [60] both scales have been revised, but the differences between the values in original and revised scales have typically been well below 0.1 pK_a units.

Conversion of Acidity Data between Solvents

In many practical cases acids have known pK_a values in some solvent(s) but for the task at hand pK_a values in a different solvent are needed.^[61] At the same time, for many applications approximate values are sufficient. For this purpose, simple linear conversion equations were created that enable predicting pK_a values in water, DMSO, DMF, and 1,2-dichloroethane (DCE), as well as gas-phase acidities on the basis of acetonitrile pK_a values and very simple structure-based descriptors. The general model is:

$$pK_a(\text{medium X}) = a + b \cdot pK_a(\text{MeCN}) + \sum_{i=1}^n (c_i \cdot D_i) \quad (10)$$

where $D_1 \dots D_n$ are the descriptor values and a , b , $c_1 \dots c_n$ are equation coefficients. The equations created for different compound types are listed in Table 2. The additional descriptors enable improving the prediction ability compared to simple linear regression (see Figure 2).

The correlation between pK_a values in MeCN and DCE is very good even if different acid families are considered jointly. Me-TCNP and H-TCNP are the strongest outliers (by about 5 pK_a units). Good estimates of DCE pK_a values can be calculated with simple correlation equations, not including any additional descriptors. However, the included acids are not especially diverse, so predictions for non-represented types of compounds may fail (see warnings below). The overall correlation between MeCN and DMSO pK_a values is somewhat inferior to that of DCE. However, when some additional descriptors and within-family relationships are used then good DMSO pK_a estimates are possible. The correlations for water and the gas phase are



Figure 1. Overview of the types and acidity ranges of the studied compounds in acetonitrile and, where available, water, DMSO, DMF, DCE, and the gas phase (GA values in kcal mol⁻¹ are shown on the secondary x-axis on top).

expectedly of lower quality. Interestingly, between-solvent correlations for OH acids occasionally appear better than those for CH acids, although chemical intuition would suggest the opposite. This may be related to the considerable structural similarity of the OH acids included in correlations. For instance, most phenols are either nitro-, halo-, or CF₃-substituted and at least one of the nitro groups is always in ortho-position to the acidity center.

Regarding the accuracy of the predicted pK_a values, the following should be stressed:

(1) The accuracy depends on the quality of the correlation itself. This is first of all expressed by columns *S* and *u* in Table 2, which depend on the quality of the data involved in correlations. All the MeCN data have been obtained with

the same relative method (which enables minimizing several uncertainty sources), with multiple overlapping measurements, have been characterized by the consistency standard deviations of the ladder and can thus be considered very reliable. The pK_a values in other solvents come from different groups, were obtained using different methods and occasionally different reference points. Efforts were made to include only reliable values and in some cases, literature values were corrected (see the Experimental section). However, at least part of the scatter in correlations can be due to the quality of the data.

(2) The quality of predictions is also dependent on the number of compounds involved in the correlation and the range of their pK_a values (columns “*N*” and “pK_a(MeCN) range” in

Table 2. Equations for conversion of acidity data from acetonitrile to other media. Standard errors are given in parentheses. *N* – number of compounds used in regression; *S* – standard error of regression.

Eq. No	Compounds included	<i>N</i>	Equation ^[a]	<i>S</i>	<i>R</i> ²	<i>u</i> ^[b]	<i>pK</i> _a (MeCN) range
Water							
1.1	All available	47	$pK_a(H_2O) = pK_a(MeCN) \cdot 0.72(0.03) + nC \cdot 0.45(0.05) + nON \cdot 0.19(0.05) - X-CO \cdot 1.6(0.5) - 12.0(0.6)$	1.2	0.961	1.4	2.8...32.6
1.2	OH acids (18 phenols, 3 carboxylic acids, 1 alcohol)	22	$pK_a(H_2O) = pK_a(MeCN) \cdot 0.55(0.01) - X-CO \cdot 2.2(0.2) + nC \cdot 0.13(0.04) + MW \cdot 0.0017(0.0007) - 6.5(0.5)$	0.3	0.994	0.3	4.4...29.2
1.3	NH acids	15	$pK_a(H_2O) = pK_a(MeCN) \cdot 0.70(0.02) - nS \cdot 2.9(0.2) - nH \cdot 0.24(0.06) - 3.9(0.4)$	0.3	0.995	0.4	10.5...32.6
DMSO							
2.1	All available	75	$pK_a(DMSO) = pK_a(MeCN) \cdot 0.94(0.02) + nHBD \cdot 1.1(0.2) + X-SO_2 \cdot 1.8(0.3) - X-H \cdot 0.8(0.3) - 10.7(0.5)$	1.1	0.969	1.2	2.8...32.6
2.2	CH acids	27	$pK_a(DMSO) = pK_a(MeCN) \cdot 0.78(0.03) + nS \cdot 1.4(0.3) - X-CN \cdot 0.6(0.3) - 8.0(0.7)$	0.7	0.979	0.9	7.7...28.8
2.3	NH acids (mainly diarylamines and sulfonamides)	24	$pK_a(DMSO) = pK_a(MeCN) \cdot 1.00(0.02) + X-SO_2 \cdot 2.0(0.2) + nN \cdot 0.3(0.1) - 12.6(0.6)$	0.4	0.991	0.5	14.6...32.6
2.4	OH acids (16 phenols/naphthols, 5 other acids)	21	$pK_a(DMSO) = pK_a(MeCN) \cdot 0.87(0.02) - nNO_2 \cdot 1.0(0.1) + nCF_3 \cdot 0.37(0.09) - 8.0(0.6)$	0.5	0.992	0.6	10.5...29.2
DMF							
3.1	All available	22	$pK_a(DMF) = pK_a(MeCN) \cdot 0.91(0.03) - 7.6(0.6)$	0.9	0.982	0.9	10.2...32.6
3.2	Phenols	7	$pK_a(DMF) = pK_a(MeCN) \cdot 0.95(0.01) - 9.5(0.3)$	0.2	0.999	0.2	11.0...29.2
3.3	Aromatic sulfonamides	7	$pK_a(DMF) = pK_a(MeCN) \cdot 0.77(0.02) - 3.5(0.6)$	0.05	0.995	0.06	24.6...27.0
DCE							
4.1	All available	47	$pK_a(DCE) = pK_a(MeCN) \cdot 1.10(0.03) + 32.6(0.4)$	1.2	0.973	1.2	2.8...23.5
4.2	CH acids, excl TCNP acids ^c	27	$pK_a(DCE) = pK_a(MeCN) \cdot 1.05(0.01) + 33.5(0.2)$	0.3	0.997	0.3	3.6...23.5
4.3	Aromatic sulfonimides	9	$pK_a(DCE) = pK_a(MeCN) \cdot 1.03(0.03) + 32.8(0.2)$	0.2	0.995	0.2	3.3...10.0
Gas phase (GA values in kcal mol ⁻¹)							
5.1	All available	101	$GA = pK_a(MeCN) \cdot 1.15(0.06) - nHal \cdot 1.31(0.09) - nSON \cdot 2.2(0.1) - nCN \cdot 3.6(0.4) - X-Aryl \cdot 2.9(0.6) + 310.2(1.5)$	3.1	0.953	3.3	2.8...32.6
5.2	CH acids	44	$GA = pK_a(MeCN) \cdot 1.10(0.07) - MW \cdot 0.066(0.006) - nN \cdot 4.1(0.5) + Ortho \cdot 2.7(0.3) + nH \cdot 0.7(0.2) + 307.7(2.7)$	2.0	0.969	2.3	5.0...28.8
5.3	NH acids (mainly diarylamines and sulfonimides)	32	$GA = pK_a(MeCN) \cdot 1.08(0.08) + nH \cdot 1.6(0.1) - nC \cdot 1.5(0.2) - nSON \cdot 1.6(0.2) - nCF_3 \cdot 2.6(0.4) + 307.7(2.8)$	1.8	0.989	2.6	5.0...32.6
5.4	OH acids (14 phenols/naphthols, 7 other acids)	21	$GA = pK_a(MeCN) \cdot 2.2(0.1) + X-CO \cdot 11.6(2.0) + X-SO_2 \cdot 8.9(2.6) - nC \cdot 0.6(0.2) + 278.6(3.0)$	3.0	0.974	3.8	4.0...29.2

[a] Descriptors: *nC*, *nH*, *nN*, *nS* – numbers of C, H, N, and S atoms in the molecule, respectively; *nON* – total number of O and N atoms; *nSON* – total number of S, O, and N atoms; *nHal* – number of halogen atoms; *nCF*₃ – number of trifluoromethyl groups (terminal –CF₃ in perfluoroalkyl chain does not count); *nCN*, *nNO*₂ – total number of nitro and cyano groups in the molecule, respectively; *X-H*, *X-CO*, *X-SO*₂, *X-CN* – numbers of hydrogens, carbonyl, sulfonyl and cyano groups attached directly to the acidity center, respectively; *X-Aryl* – number of aryl substituents at the acidity center (0 if the acidity center is part of the aromatic cycle, e.g. in indole; 2 for fluorene; 3 for fluoradene); *nHBD* – number of hydrogen bond donors (N–H, O–H, Hal–H); *MW* – molar weight [au]; *Ortho* – number of non-hydrogen substituents in ortho- or peri- position to the acidity center (0 if not applicable, e.g. for imides). [b] Root mean square error of the leave-one-out test. Can be used as an estimate of standard uncertainty of prediction for compounds with a similar structure to those used for creating the equations, but not included in the training data. [c] The TCNP acids deviate strongly. Predictions by equation 4.2 are ca. 5 *pK*_a units higher than the corresponding experimental values.

Table 2). The larger the number and the wider the spread of the *pK*_a values the better. Regarding the number of acids involved, a warning is due regarding the correlations

between DMF and MeCN. Although the quality parameters are very good, the correlations were created using a small

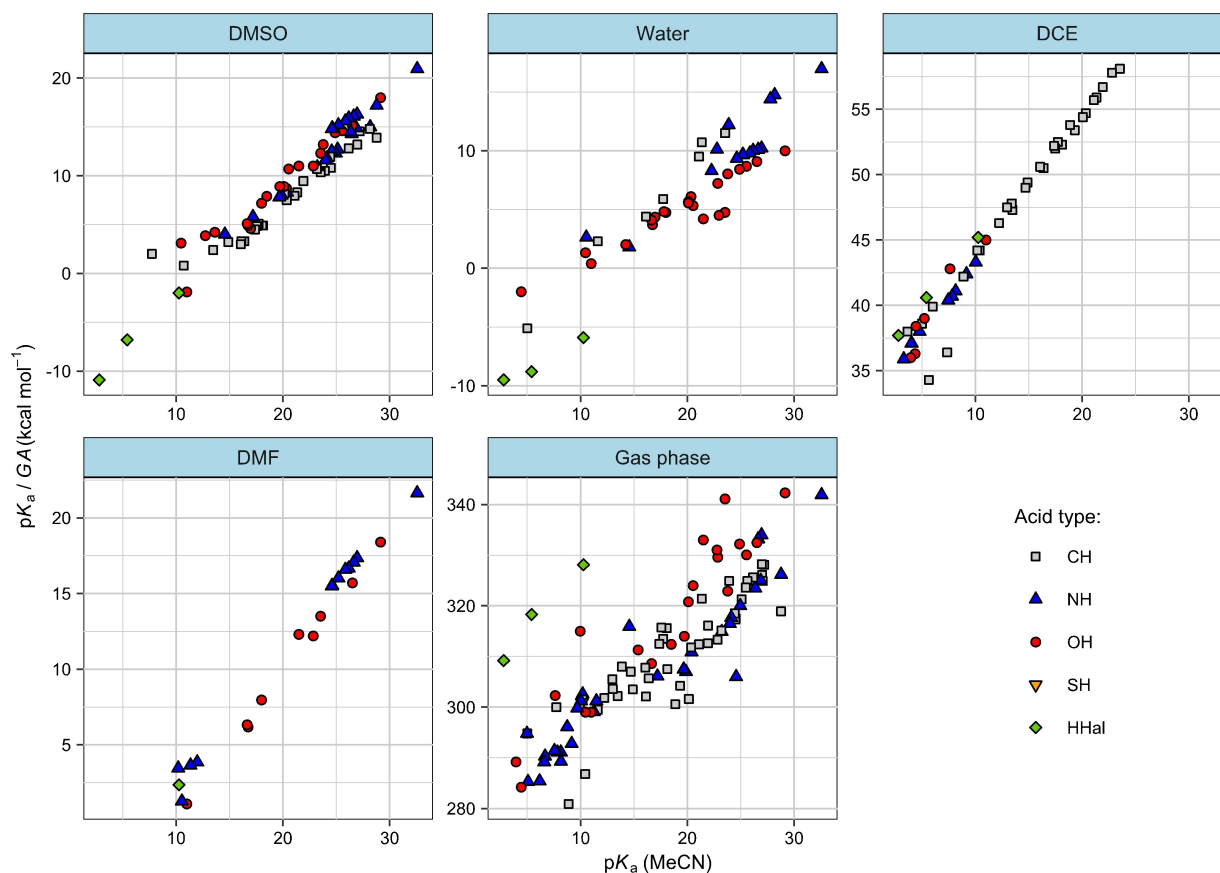


Figure 2. Correlations between the acidity values in acetonitrile and other media. Acidity data in tabulated form is available in the SI.

number of compounds, which decreases the reliability of the predictions.

- (3) A very important but difficult to quantify aspect is the similarity between the compounds for which the predictions are made and the compounds used for creating the conversion equations. The families of acids for which data are available in specific solvents can be seen from Figure 1 and the exact compounds together with their acidities in different media are presented in Table S1 in the SI. Obviously, the more similar are the compounds to those used for creating the equations, the better is the quality of the predictions. This is especially worth stressing in the case of the general equations. As can be seen, within-family equations usually work better than the general equations ("All available" in Table 2). Although all available data were included in creating them, the diversity of acids is still somewhat limited. For example, the large majority of acids measured in DCE are CH or NH acids and only a very small number are OH acids – mostly phenols and sulfonic acids. So, it cannot be expected that e.g. carboxylic acid pK_a values in DCE can be predicted within standard uncertainty quoted in the table (1.2 pK_a units) with the presented correlation equation between DCE and MeCN, even though the quality of the correlation is very good.

Summary and outlook

The pK_a values of 231 acids ranging from hydrogen iodide (2.8) to indole (32.57) form a self-consistent pool of acidity data in acetonitrile. Over the years these values have been used by numerous groups in diverse fields ranging from organo-,^[62,63] photoredox-,^[64,65] and electrocatalysis,^[66–68] to computational chemistry,^[69,70] and from coordination^[71–73] and supramolecular chemistry,^[74] to drug design^[75–77] and biomass valorization.^[78,79] We expect this usage to continue and widen, as more pK_a values are available.

Moreover, the simple to use prediction equations presented here enable estimating pK_a values in DMSO, DMF, 1,2-dichloroethane, and water, as well as gas-phase acidities on the basis of acetonitrile pK_a values. The standard uncertainties of prediction in the case of similar compounds are in a number of cases below 1 pK_a unit, which we consider very good, given the simplicity of prediction. This transfer possibility between solvents is expected to further enhance the usefulness of the MeCN pK_a scale.

Supporting Information

The synthesis and characterization data, tabulated full pK_a and GA data (in acetonitrile, DMSO, DMF, water, gas phase), details related to conversion equations, and full one-page acidity scale in acetonitrile are available as Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Acetonitrile • Acidity • Non-aqueous solvents • pK_a values • Solvent effects

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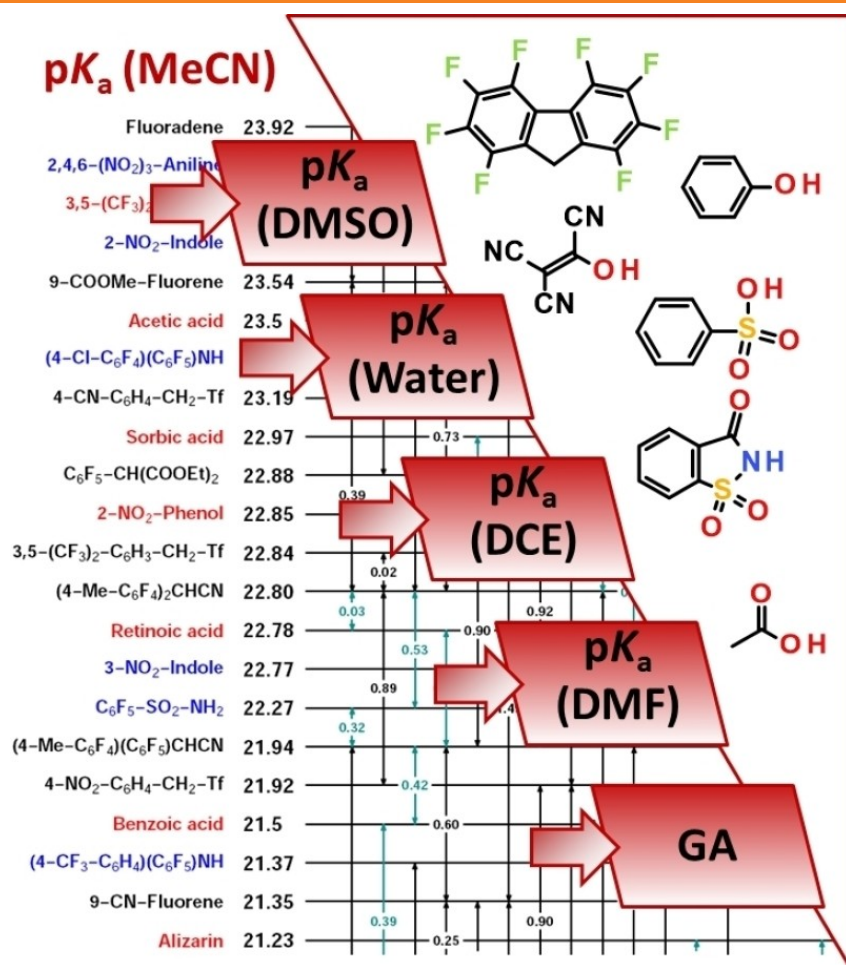
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FULL PAPERS



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1 – 14

Strengths of Acids in Acetonitrile



Revised pK_a scale, containing 231 acids and spanning almost 30 orders of magnitude of acidities in

acetonitrile, one of the most useful solvents for non-aqueous acid-base chemistry, is presented.