

**KARL KAUPMEES**

Acidity and basicity in non-aqueous media:  
importance of solvent properties and  
purity



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## **KARL KAUPMEES**

Acidity and basicity in non-aqueous media:  
importance of solvent properties and  
purity



Institute of Chemistry, Faculty of Science and Technology, University of Tartu.

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## LIST OF ORIGINAL PUBLICATIONS

This thesis consists of five papers and the present review that is written based on the mentioned papers and uses some segments from the corresponding publications.

- I. Kaupmees, K.; Kaljurand, I.; Leito, I. Influence of water content on the acidities in acetonitrile. Quantifying charge delocalization in anions. *J. Phys. Chem. A*, **2010**, *114*, 11788–11793.
- II. Greb, L.; Tussing, S.; Schirmer, B.; Oña-Burgos, P.; Kaupmees, K.; Lõkov, M.; Leito, I.; Grimme, S.; Paradies, J. Electronic effects of triarylphosphines in metal-free hydrogen activation: a kinetic and computational study. *Chem. Sci.*, **2013**, *4*, 2788–2796.
- III. Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. On the Acidity and Reactivity of Highly Effective Chiral Brønsted Acid Catalysts: Establishment of an Acidity Scale. *Angew. Chem. Int. Ed.*, **2013**, *52*, 11569–11572.
- IV. Kaupmees, K.; Kaljurand, I.; Leito, I. Influence of water content on the basicities in acetonitrile. *J. Sol. Chem.*, **2014**, Accepted for Publication.
- V. Raamat, E.; Kaupmees, K.; Ovsjannikov, G.; Trummal, A.; Kütt, A.; Saame, J.; Koppel, I.; Kaljurand, I.; Lipping, L.; Rodima, T.; Pihl, V.; Koppel, I. A.; Leito, I. Acidities of strong neutral Brønsted acids in different media. *J. Phys. Org. Chem.*, **2013**, *26*, 162–170.

### Authors contribution

- Paper I.** Performed all experiments and computations. Main person responsible for planning and writing the manuscript.
- Paper II.** Planned all of the  $pK_a$  measurements and performed large part of them. Main person responsible for writing the part of the manuscript concerning the  $pK_a$  measurements.
- Paper III.** Performed all  $pK_a$  measurements. Main person responsible for planning and writing the manuscript.
- Paper IV.** Performed all experiments and computations. Main person responsible for planning and writing the manuscript.
- Paper V.** Performed some of the theoretical calculations. Contributed to the writing of the text.

## ABBREVIATIONS

|                    |  |
|--------------------|--|
| A                  | Basic form of a compound                                     |
| $A^\lambda$        | Absorbance   |
| AN                 | Acceptor number  |
| $\alpha$           | Empirical parameter for solvent HBA acidity                  |
| BPA                | BINOL-derived phosphoric acid diester                        |
| $\beta$            | Empirical parameter for solvent HBA basicity                 |
| COSMO-RS           | Conductor-like Screening Model for Real Solvents             |
| DCE                | 1,2-dichloroethane   |
| dma                | <i>N,N</i> -dimethylamino group                              |
| DMSO               | Dimethyl sulfoxide   |
| DN                 | Donor number   |
| EPA                | Electron pair acceptor                                       |
| EPD                | Electron pair donor  |
| $\epsilon_r$       | Relative permittivity  |
| $\epsilon^\lambda$ | Molar absorbance coefficient                                 |
| G                  | Gibbs free energy  |
| HA                 | Acidic form of a compound                                    |
| HBA                | Hydrogen bond acceptor                                       |
| HBD                | Hydrogen bond donor  |
| JINGLE             | Imides of sulfonic acid                                      |
| K                  | Equilibrium constant   |
| $\lambda$          | Wavelength   |
| MeCN               | Acetonitrile   |
| NTPA               | Mixed imide of phosphoric and trifluoromethanesulphonic acid |
| $pK_a$             | Negative logarithm of ionization constant                    |
| $pK_{ip}$          | Negative logarithm of ion-pair ionization constant           |
| pyrr               | <i>N</i> -pyrrolidino group                                  |
| S                  | Solvent  |
| ( $)_s$            | Solvent shell  |
| z                  | Charge of the species  |
| TfOH               | Trifluoromethanesulfonic acid                                |
| TMG                | <i>N,N,N',N'</i> -tetramethylguanidine group                 |
| WANS               | <i>Weighted Average Negative Sigma</i>                       |
| WAPS               | <i>Weighted Average Positive Sigma</i>                       |

## INTRODUCTION

Acidic and basic properties of compounds can influence processes in nearly all fields of chemistry and related sciences: from organic synthesis to chromatographic analysis, from biology to geology. The variety of environments for those applications is wide, from the classical aqueous solution to different non-aqueous solvents, the mixtures of solvents or even ionic liquids. In order to take into account the effects related to acidity and basicity, these properties must be reliably determined. Alongside the quantification of acid-base properties, possible environmental effects influencing these properties should also be accounted for.

This work examines the importance of solvent properties and purity on acid-base behavior on the example of several case studies. The importance of solvent's moisture content is specifically addressed on the example of acetonitrile. It is demonstrated that choosing suitable solvent is very important for acid-base studies and in certain cases the content of water – the most important impurity in solvents – can be critically important. In addition to quantifying the effect of water in solvent at low concentrations, suggestions concerning the experimental setup of  $pK_a$  measurements are given for minimizing its effect.

The behavior of several catalytic systems is rationalized on the basis of acid-base properties of the participating compounds. It is demonstrated that knowledge of acid-base properties of the molecules and ions participating in a catalytic process is essential for rationalizing the process. The carefully performed experiments reveal errors in literature  $pK_a$  values. Their origin is pointed out with additional experiments and the importance of knowledge of the usability limits of solvents is emphasized.

During the studies a gap was found in the selection of possible parameters for charge delocalization in ions. In order to rationalize the results and aid the interpretation two new parameters *Weighted Average Positive Sigma (WAPS)* for anions and *Weighted Average Negative Sigma (WANS)* for cations are proposed for that purpose. They seem to describe the charge delocalization well and in accordance with the chemical intuition.



# I. IN GENERAL

## I.1. Definition of acid-base equilibria

Modern chemistry uses mainly two theories to describe acids and bases: the Brønsted-Lowry theory and the Lewis theory. This work looks at acids and bases from the point of view of the Brønsted-Lowry theory, which defines acids as donors and bases as acceptors of proton. As the energy of the free proton is very high, it cannot be in “bare” form in solution and is therefore transferred to another molecule that acts as a base. In the case of pure solvents (eq 1) this is a solvent molecule. Although the product of proton transfer is in a simplified way written as  $\text{HS}^+$ , it is more realistic, that the proton is coordinated to at least two solvent molecules.<sup>1</sup>



The charge  $z = 0$  in case of acids and  $z = 1$  for bases. The Brønsted-Lowry theory also defines the conjugate acid-base pair – from an acid  $\text{HA}^z$  its conjugate base  $\text{A}^{z-1}$  is formed as a result of the ionization process. The basicity of a neutral base is defined using its conjugate acid, a cationic acid. This allows more convenient comparison of acidity and basicity data.

The equilibrium constant of equation 1 is expressed as:

$$K_a = \frac{a(\text{HS}^+) \cdot a(\text{A}^{z-1})}{a(\text{HA}^z)} \quad (2)$$

The activity of solvent  $a(\text{S})$  is counted within the  $K_a$  value because if dilute solutions are measured the solvent is in large excess and  $a(\text{S})$  can be considered constant.<sup>2</sup> The term equilibrium constant is not fully correct although universally referred to as one. Within a given solvent ( $K_a$  is solvent dependent)  $K_a$  depends on the temperature and ionic strength.<sup>3</sup> As these constants vary in several orders of magnitude the  $\text{p}K_a$ 's, the negative logarithms of  $K_a$ , are used to make the comparing more convenient:

$$\text{p}K_a = -\log K_a = -\log \frac{a(\text{HS}^+) \cdot a(\text{A}^{z-1})}{a(\text{HA}^z)} \quad (3)$$

The  $\text{p}K_a$  values are therefore the measure of acid-base strength, the lower the  $\text{p}K_a$  of an acid, the stronger it is. As the  $\text{p}K_a$  of a neutral base refers to its conjugate acid, the basicity increases along with the increase of  $\text{p}K_a$  values. The strength of the conjugate base is related to the strength of the acid – the stronger is the initial acid, the weaker base is its conjugate base.

Measuring the  $pK_a$  according to equation 3 is straightforward only in water (and few more solvents, such as methanol and ethanol), as the activity of  $H^+$  can be easily measured using a pH electrode. In non-aqueous media problems with electrode calibration and stabilization arise, making experiment difficult and unreliable unless very large efforts are made.<sup>4</sup> To eliminate the need for knowing the activity of hydrogen ion in a given solvent relative acidities of two acids or bases can be determined:



$$-\log K = \Delta pK_a = pK_a(HA_2) - pK_a(HA_1) = \log \frac{a(A_1^{z-1}) \cdot a(HA_2^z)}{a(HA_1^z) \cdot a(A_2^{z-1})} \quad (5)$$

If the measurements are carried out in dilute solutions, it can be assumed that the ratio of activity coefficients for neutral and ionic species is the same for both compounds.<sup>5</sup> This enables using equilibrium concentrations instead of activities:

$$-\log K = \Delta pK_a = pK_a(HA_2^z) - pK_a(HA_1^z) = \log \left[ \frac{[A_1^{z-1}] \cdot [HA_2^z]}{[HA_1^z] \cdot [A_2^{z-1}]} \right] \quad (6)$$

This approach avoids the need for measuring solution's pH, but brings in another limitation – as the ratios of equilibrium concentrations have to be known exactly, both species must be present in a quantity detectable with acceptable uncertainty. This means that the difference of  $pK_a$  values of the studied compounds must not exceed 2.5 units.

If ion pair acidities/basicities are studied, then the equilibrium between two compounds is:



$$\Delta pK_{ip} = \log \frac{[HB^+ A_1^{z-1}] \cdot [HA_2^z]}{[HA_1^z] \cdot [HB^+ A_2^{z-1}]} \quad (8)$$

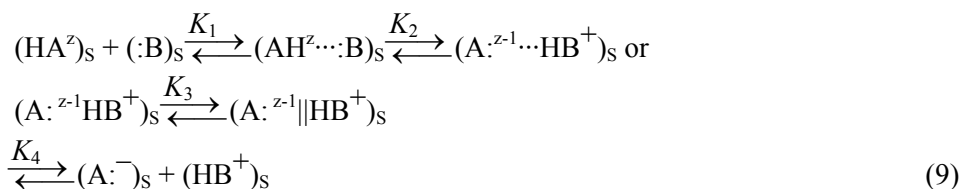
Where  $HB^+$  indicates a protonated base. As this methodology only describes the ionization part of the full reaction associated with acidity/basicity (equation 9) the dissociation segment ( $K_d = K_3 \cdot K_4$ ) must be determined by another measurement or by estimating if  $\Delta pK_a$  values are desired.<sup>6</sup>

## 1.2. Influence of the solvent

In order to influence the acid-base equilibria, a compound must first dissolve in the solvent. From that point on solvent affects several processes: dissociation, aggregation *etc.*

From equation 1 it can be seen that in condensed media solvent takes part in the ionization as a base or as an acid, meaning that both acidity and basicity of the solvent itself are relevant when interpreting these ionization reactions. The more detailed description of acidity and basicity of different solvents is given in future sections. One should also note that the reactions describing acidity and basicity are somewhat different. In case of acidity a cation and an anion are formed from a neutral molecule – charged species are created in the solution. In the case of basicity no charged species are created nor destroyed.

Equation 1 presents a very simplified view of the proton transfer reaction and reflects the situation only in polar solvents (and at low concentrations). In more detailed terms the transfer of proton from one species to another can be broken down into four steps<sup>2</sup>:



B indicates a base, in case of simple ionization reaction in solvent S, a solvent molecule is considered as a base.  $K_1$  describes the formation of a hydrogen bonded complex.  $K_2$  describes the transfer of proton, resulting in hydrogen bonded complex of ionized species or an ion pair. In the third step, characterized by  $K_3$ , solvent molecules come between the ionized species producing a solvent separated ion pair. In the final, fourth step, full dissociation of the ion pair occurs. The overall product of the equilibrium constants of individual steps is the  $K_a$

$$K_a = K_1 \cdot K_2 \cdot K_3 \cdot K_4 \tag{10}$$

The value of  $K_2$  is defined first of all by the acid and base strengths of  $\text{HA}^z$  and B. The values of  $K_3$  or  $K_4$  are determined by the properties of the ions (their size and extent of charge delocalization) as well as the properties of the solvent.  $K_3$  depends first of all on the ability of the solvent to (specifically) solvate the ionized species.  $K_4$  correlates well with the solvent polarity (in terms of dielectric constant): the lower the polarity, the lower also the dissociation to free solvated ions.

If the solvating power of the solvent is low and the ionized species are quite small and therefore the charge is not well delocalized or hidden, side reactions may occur. These side reactions involve association processes to aid the charge

delocalization and can be divided into three: homoassociation, heteroassociation and selfassociation.<sup>2</sup> As solvents have different abilities to solvate anions and cations, association processes may be favored for one charge type. In the case of acetonitrile, the main solvent used in this work, the anions of Brønsted acids tend to homo- and heteroassociate more than the protonated forms of Brønsted bases.<sup>7</sup>

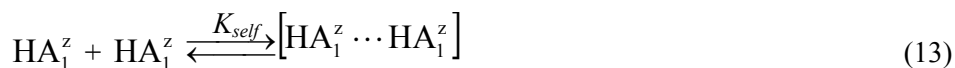
Homoassociation occurs when neutral and ionic species of the same substance form a complex:



If the species forming a complex are from different substances the process is called heteroassociation



Formation of a complex can also occur when both species are neutrals of the same substance. This is selfassociation:



All of these association processes can be characterized by equilibrium constants and must be either avoided or taken into account when determining  $pK_a$  values. Aggregation processes can also involve more than two molecules, depending on the nature of the solvent, solutes and their concentrations. To suppress the formation of aggregates, measurements in dilute solutions are recommended.

Along with the mentioned conjugation processes ion pairing is also considered as a side process. In equation 9 ion pairing was discussed as a result of incomplete dissociation. This is the case for acids, where cations and anions are formed that are strongly attracted to each other, either electrostatically or via hydrogen bond. Ion pairs can also be, and usually are, formed between solutes of different origin. During experiments this is mainly caused by different titrants introduced in the solution in order to change the equilibrium of the conjugate acid-base pair.<sup>6</sup>

If a mixed solvent is used then its composition can also be a major factor influencing the equilibrium. Although the solvent mixture might be homogeneous in the macroscopic scale, the composition of the solvent shell is usually not.<sup>2,8</sup> If the solvent shell differs in composition from the bulk solvent mixture two distinct possibilities arise. (1) If the solvent shell contains molecules of all solvents, but not in the same mole ratio as the bulk mixture it is called preferential solvation. (2) If the preference of one solvent component proceeds

to extremity and the solvent shell is composed by the molecules of only one solvent component the solvation is selective.

The properties of solutes in condensed media are the combination of the intrinsic properties of the solute molecule and the supportive effect of the solvent molecules, more precisely the molecules in close proximity, in the solvent shell of the solute. If the solvent shell is changed, the observed physicochemical properties of the solute in a given media may also change depending on the gain in the solvation energy. Therefore significant changes in physicochemical properties can be observed if the additive, that is capable of selectively or even preferentially solvating the solute molecules, is present even in small quantities.

Although solvents are often referred to as pure, they contain almost always impurities, making them mixed solvents. If the concentration of impurities is very low and do not influence the properties of solvents to observable amount, referring to them as pure is justified.

### 1.2.1. Characterization of solvents

Before discussing different solvents for studies of acid-base equilibria, one should be acquainted with parameters describing them. Depending on the method used, several physical and chemical characteristics should be considered. Among the most common are boiling point, transparency, stability against both the environment (oxygen) and studied compounds, viscosity, hygroscopicity *etc.* In order to describe the interactions between solvent and solute molecules three groups of properties should be considered: polarity, polarizability and acidity/basicity.<sup>2</sup>

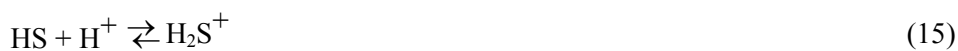
One of the first characteristics of solvents taught to young chemists is the polar-apolar scale, „like dissolves like“. Although polarity is perhaps the most important property of a solvent and seems to be easily understandable at first sight, chemists have still not agreed upon a definition to date. Reichardt for instance defines polarity as the sum of all molecular properties responsible for all the interaction forces between the solvent and the solute molecules.<sup>2</sup> Just like with definitions, there is no single good parameter available for quantifying solvent polarity. If solvents are looked at as a bulk, the relative permittivity  $\epsilon_r$  is often used. Relative permittivity of a solvent describes its ability to reduce the Coloumbic forces between charged particles in a solution by changing the orientation of dipoles of its molecules. Based on the  $\epsilon_r$  values the polar-apolar scale can be quantitatively divided – solvents with  $\epsilon_r$  above 40 are considered polar, the ones with  $\epsilon_r < 20$  are apolar or even inert if  $\epsilon_r$  approaches 1, if  $20 < \epsilon_r < 40$  a solvent is of medium polarity.

If the close proximity of solute molecule is considered, the relative permittivity of the solvent no longer serves as an adequate measure of polarity because solvent molecules are not as free to orient themselves in the solvation shell. Several empiric parameters have been proposed to describe this other side of polarity that measure a solvent dependent parameter in a previously defined

standard system. Probably the most known is the ET<sub>30</sub>, that measures polarity based on the spectral shifts of a molecular probe between solvents.<sup>2</sup>

Dispersion interactions are the main contributors to solvation energy, especially in the case of neutral molecules. Dispersion interactions arise from the correlated fluctuations in the electron clouds of two neighboring molecules. The ease, by which the electron cloud can be distorted from its normal shape, is different for every substance. This dependence is named polarizability and is measured by refractive index. The higher the polarizability of a molecule, the easier it is to deform its electron cloud and the higher is the possibility for favorable interactions. Solvents with high polarizability tend to be good solvators for species with high polarizability, like anions and molecules with large conjugated  $\pi$  electron systems.

The acid-base properties of solvents can be looked at several angles. The autoprotolysis constant ( $K_{\text{auto}}$ ) combines both the acidic (14) and basic (15) properties of a solvent.



$$K_{\text{auto}} = a(\text{S}^-) \cdot a(\text{H}_2\text{S}^+) \quad (17)$$

As the solvents are very different in respect to one another, the  $\text{p}K_{\text{auto}}$  values are used. In a solvent HS the strongest acid is  $\text{H}_2\text{S}^+$  and the strongest base  $\text{S}^-$ , all acids stronger than  $\text{H}_2\text{S}^+$  are levelled at the strength of  $\text{H}_2\text{S}^+$  and are fully deprotonated, the analogy goes also for bases – bases stronger than  $\text{S}^-$  are levelled at its strength and are fully protonated. The range of  $\text{p}K_{\text{a}}$  values measurable in a solvent is therefore limited by the autoprotolysis constant. The larger is the  $\text{p}K_{\text{auto}}$ , the wider is the span of acidities/basicities realizable in a given solvent. The  $\text{p}K_{\text{auto}}$  of water is 14, meaning that as a broad generalization acidities and basicities in water can be measured between  $\text{p}K_{\text{a}}$  values of 0 and 14 with conventional methods.

Depending on whether a solvent molecule has acidic hydrogen atoms or not, solvents can be classified as protic or aprotic. If a solvent molecule has both significant acidic and basic properties (reactions 14 and 15 can be experimentally observed) then the solvent is called amphiprotic. If a solvent has high  $\text{p}K_{\text{auto}}$ , it is a differentiating solvent, which is a desirable quality in acid-base studies. For many solvents one property (acidic or basic) dominates over the other. For example MeCN is more basic than acidic. If a solvent is acidic and lacks of basic character, it is protogenic, and a solvent with basic properties, but negligible acidic properties can be referred to as a protophilic solvent. One should already realize that protogenic solvents are levelling for strong bases and

are therefore usually used for the studies of acids with strong or moderate strength and weak bases. Protophilic solvents on the other hand are suitable for studies of strong and medium strength bases as well as weak acids.

Acidity and basicity of a solvent are strongly correlated to hydrogen bond donating (HBD) and accepting (HBA) ability, respectively, as the formation of a hydrogen bond is the first step in equation 9. The HBD and HBA are very important concerning the specific solvation via hydrogen bonds – HBD solvents tend to solvate anions very well, whereas HBA solvents solvate cations very well. There are several parameters for quantitatively describing HBD and HBA.<sup>2</sup> The most often used are the  $\alpha$  and  $\beta$  scales, respectively, proposed by Kamlet, Abboud and Taft.<sup>9</sup>

Specific solvation does not only include the interaction via hydrogen bonding but also via electron pair donor (EPD) – electron pair acceptor (EPA) interaction. EPD and EPA describe the Lewis basicity and acidity of the solvent, determining its ionizing power. The higher the ability to donate or accept electron pairs, the more easily ions are formed from neutral molecules. EPD and EPA are usually described by donor (*DN*) and acceptor (*AN*) numbers by Gutmann and coworkers.<sup>10,11</sup>

### 1.2.2. Media for p*K*<sub>a</sub> measurements

The acid-base properties of a molecule in the condensed phase are influenced by two distinct set of factors: the molecular structure of the compound and the properties of the medium (solvent). The molecular structure determines the intrinsic acidity or basicity and can be studied either experimentally in the gas phase or computationally. The solvent properties modify the intrinsic acidity and basicity significantly. Acetic acid, for example, is a very weak acid in the gas phase (341.1 kcal mol<sup>-1</sup>)<sup>12</sup> compared to picric acid (299.0 kcal mol<sup>-1</sup>, from Publication V): the difference is around 30 orders of magnitude. In water the p*K*<sub>a</sub> values of these acids are much closer: 4.76<sup>13</sup> and 0.40<sup>13</sup>, respectively, differing by slightly more than 4 orders of magnitude. The p*K*<sub>a</sub> measurements in condensed media are carried out, because most of the “practical chemistry” takes place in solutions and the computational approaches of p*K*<sub>a</sub> determination are still very much less accurate than experiments. The acidity-basicity data in different solvents, as well as in the gas phase, complement each other.

If one should list the characteristics of an ideal solvent for p*K*<sub>a</sub> studies, the list should contain the following: sufficiently polar to aid the dissociation into free ions; very high autoprotolysis constant, low basicity and acidity; transparent to widen the choice of analytical methods; easy to purify; stable towards strong acids and strong bases; not very viscous. Unfortunately there is no ideal solvent and different solvents have to be used. To combine aspects of different solvents, sometimes mixtures of multiple solvents are used.

In the present work three solvents are used:

Acetonitrile (MeCN) is considered to be a rather polar ( $\epsilon_r = 35.94$ )<sup>2</sup> aprotic solvent, meaning it dissolves reasonably well both polar and apolar compounds

and enables dissociation of ion pairs into free ions after ionization, so that  $pK_a$  values corresponding to eq 1 can be studied. MeCN is a weak HBD and EPD ( $DN = 14.1^{10}$   $\beta=0.31^{14}$ ) and moderate HBA and EPA ( $AN = 18.9^2$ ;  $\alpha=0.19^{14}$ ). It can specifically solvate cations to some extent, but the solvation of anions is limited to van der Waals interactions – first of all dispersion forces and ion-dipole interactions.<sup>2</sup> That results in the formation of homo- and heteroassociates in the case of acids having small molecular size and with localized charge in their anions.<sup>15</sup> The differentiating ability ( $pK_{\text{auto}} = 33.3\text{-}44$ )<sup>16,17</sup> is quite good enabling measurements in a wide range of  $pK_a$  values. MeCN is suitable for measurements of both acids and bases: acids of medium and high strength, bases with medium and low strength. In the superbasic region ( $pK_a$ 's over 32) it starts to oligomerize (which partly explains the very huge uncertainty of its autoprotolysis constant) and the basicity of its molecule hinders its use in the superacidic region, so that the  $pK_a$  values of *e.g.*  $\text{CF}_3\text{SO}_2\text{OH}$  and perfluorinated sulfonyl imides are not measurable in MeCN.

1,2-dichloroethane (DCE) is a non-polar ( $\epsilon_r = 10.36$ )<sup>2</sup> solvent, meaning that only ion-pair acidities can be measured experimentally. Its autoprotolysis constant is very high and quantitatively unknown because no detectable ionization can be observed (any ionization detected is caused by impurities). Thus, theoretically DCE enables measurements of  $pK_a$  values in a very wide range. Both HBD and HBA capabilities of DCE are very low ( $\alpha=0.00$   $\beta=0.00$ ).<sup>14</sup> Its Lewis acidity is low ( $AN=16.7^2$ ) and Lewis basicity non-existent ( $DN=0$  by definition<sup>10</sup>). DCE has been used due to these properties for acidity measurements of superacidic compounds<sup>6</sup> and is used to measure the  $pK_a$  values of very weak bases in this work.

Dimethyl sulfoxide (DMSO) is a highly polar ( $\epsilon_r = 46.45$ )<sup>2</sup> solvent with  $pK_{\text{auto}} = 33.3^2$ . It is a rather basic solvent ( $DN = 29.8^{10}$ ;  $\beta=0.76^{14}$ ) that is mainly used for studies of acids, especially for the weaker region of acidity scale. Along with MeCN, DMSO is one of the most often used solvent for acid-base measurements, as they both are sufficiently polar to dissolve and aid the dissociation of compounds of different properties. They complement each other: DMSO is more suitable for studying weak acids, MeCN is more suitable for studying strong acids. Both these media are widely used for  $pK_a$  measurements and are also the media of choice for other fields of chemistry where the determined  $pK_a$ 's are directly put in practice.

For comparison, water and the gas phase are also characterized below.

Water is definitely the most popular solvent for studying acid-base properties of compounds, the  $pK_a$  values for aqueous media are often needed and a very large amount of aqueous  $pK_a$  data<sup>18,19</sup> is available. Importance of water arises from its role in biological systems and analytical chemistry (HPLC, UV-Vis spectroscopy as well as electrochemistry). The environmental aspect along with the low cost makes water the first choice of solvent (if possible) for industrial processes. Water is a very polar solvent ( $\epsilon_r=78.36^2$ ) and  $pK_a$  values corresponding to eq 1 are measured. Water is a protic solvent with strong acidic and basic properties and thus a high tendency to autoprotolyse ( $pK_{\text{auto}}=14.00^2$ ).



Water is best known for hydrogen bonding, both as a donor ( $\alpha=1.17$ ) and an acceptor ( $\beta=0.18$ ). Water is also a good EPA and EPD solvent ( $AN = 54.8^{11}$   $DN=18^{10}$ ). Water is widely used for  $pK_a$  measurements, but the levelling effect due to the autoprotolysis hinders the measurements of strong acids and bases. Also the high polarity of the solvent means that less polar compounds may not dissolve enough to carry out  $pK_a$  measurements.

Gas phase is a medium, that is ideally inert ( $\epsilon_r=1$  by definition), as there is no solvent, the true intrinsic properties of molecules can be measured. There is no levelling effect and the acidity of almost every hydrogen-containing compound (and basicity of any compound) can be at least in theory studied in gas phase. Although there are also no solubility problems, there are limits caused by the volatility of compounds, as they have to be vaporized for experiments. The absence of solvent molecules makes the theoretical calculations much more accurate so that the acidity and basicity in the gas phase can be studied computationally with high accuracy.

### 1.2.3. Acetonitrile-water mixtures

Water and acetonitrile are miscible in all proportions above 272 K (-1 °C)<sup>20</sup>. The structure of the mixture depends strongly on relative concentrations of the two co-solvents. In water-rich mixtures the individual MeCN molecules are solvated by water molecules via hydrogen bonding, as the O-H $\cdots$ O bonds are replaced by O-H $\cdots$ N.<sup>21</sup> This means that MeCN molecules fit in the cavities of structured water molecules. Upon addition of acetonitrile, the cavities are no longer sufficient to host the MeCN molecules, so that the structure becomes micro heterogeneous with two domains.<sup>22</sup> The hydrogen-bonded network in water is broken down into smaller self-associated regions.<sup>21</sup> MeCN molecules also undergo the self-association process. Hydrogen bonding between MeCN and water molecules takes place on the interface of these micro domains.<sup>21</sup> At higher concentrations of acetonitrile, there are no longer sufficient amounts of water molecules available to form hydrogen bonded domains, so they are limited to small clusters consisting of few molecules (or even single water molecules), that are in turn hydrogen bonded by MeCN molecules.<sup>21,22</sup>

$pK_a$  values of both acids and bases are higher in acetonitrile compared to water. The changes are not linear over different fractions of MeCN/H<sub>2</sub>O content and changes in opposite direction are reported for bases<sup>23</sup> at higher mole fractions of water. This behavior in  $pK_a$  values is universal in mixtures of water and an organic solvent.<sup>23,24</sup> As the multicomponent solvent mixtures, among them acetonitrile-water, are relevant in many fields of chemistry, the  $pK_a$  values in them have also been studied quite extensively.<sup>23,24,25</sup> However, acetonitrile-water mixtures, where water content is very low, have not gained as much attention. The  $pK_a$  dependence of picric acid, as the anchor for the acidity scale in acetonitrile, has been studied systematically at impurity levels of water and found not to be influenced significantly by small amounts of water.<sup>26</sup> Based on chemical intuition, there are assumptions, that in the case of  $pK_a$  values of acids,

addition of water in acetonitrile should in one hand influence (*i.e.* increase the acidic strength of) weaker acids more than stronger acids and on the other hand the effect should generally be greater on OH acids compared to NH and CH acids.<sup>15</sup> The anions of OH acids tend to be smaller and therefore have more concentrated charge than their NH and CH acid analogs if acids with similar strength are considered (acids **A5**, **A6** and **A8** in Section 3.3), making their anions more open to selective or preferential solvation.

### **I.3. Methods for acid-base studies**

Over the past hundred years, that  $pK_a$  values have been measured quantitatively, a wide variety of techniques have been used. If a change of a solution property, that is sensitive to pH, can be measured by an analytical method, then this property can be used in  $pK_a$  measurements. Among them are various electrochemical, spectrometric and chromatographic methods.<sup>3</sup> Depending on the nature of solutes and solvents, the combination of several methods may also be used.<sup>3</sup>

Electrochemical methods, especially potentiometry, are the most commonly used methods among acid-base chemists. Potentiometry is probably the easiest method to use in aqueous media but is often also used in non-aqueous media.<sup>4</sup> The accuracy of potentiometry largely relies on the accuracy of calibration of the electrodes and the stability of their behavior. This is easy to achieve in water, but often problematic in non-aqueous media.<sup>27</sup> It is problematic to measure potentiometrically  $pK_a$  values in solutions with either high or low activity of  $H^+$ .<sup>3</sup> As the method measures only the changes in potential during titration and the species of studied compounds are not directly observed, significant errors may occur.

The possible spectrometric methods used for  $pK_a$  measurements include UV-Vis, infrared, nuclear magnetic resonance, fluorescence *etc.*<sup>3</sup> These methods use the differences in spectra of the neutral and ionized species (in case of UV-Vis and fluorescence spectroscopy a chromo-/fluorophore is needed) and the results are calculated from the observed changes in spectra as a response to changes of the acidity of the solution. The general advantage of spectrometric methods is that they enable directly observing both the neutral and ionized species separately and give information if a competing equilibrium is affecting the measurements (side processes usually affect the spectra).

In this work UV-Vis spectrophotometry is used. This technique enables measurements in very dilute solutions minimizing the possibility of side processes. Besides the already mentioned need for substances, that have different UV-Vis spectra in neutral and ionized form, UV-Vis spectroscopy also requires the usage of solvents transparent in the UV-Vis region used for measurements. Details of the used spectrophotometric method are given below.

Alongside experimental techniques, mankind has also intensely developed methods to computationally predict  $pK_a$  values.<sup>28</sup> From the classical additive

methods of substituent effects of Hammett and Taft equations<sup>29,30,31</sup> to more complex quantitative structure activity relationships (QSAR) models, we have reached to the era of computational methods capable of predicting the  $pK_a$  values with reasonable accuracy. This reasonable accuracy is achieved through parametrization and correlations with experimental data.<sup>28</sup> The computational methods are faster and cheaper compared to the experimental methods. They enable predicting the  $pK_a$  values of compounds, that haven't even been synthesized yet, making it a usable tool for screening.

Calculation of properties in the gas phase only needs the calculation of the Gibbs free energy of all the species involved in the reaction. In the case of ionization of an acid HA, the conformers of two species, HA and  $A^-$ , are needed. For the Gibbs free energy of  $H^+$  the experimental value is usually used.

In the solution the interactions with the solvent molecules in the solvent shell have to be calculated in addition. In order to calculate these interactions correctly all possible orientations and positions of solvent molecules as well as the solute molecules have to be taken into account. This is a very complex task and several approximations are made in order to arrive at a reasonable computation time. The solvent surrounding the solute molecule is often handled as a continuum, characterized by its permittivity  $\epsilon$ , so that only the interaction with the continuum has to be calculated.<sup>32</sup> These models are referred to as Continuum Solvation Models (CSM) and there are several modifications of them (CPCM<sup>33</sup>, SMD<sup>34</sup> etc).<sup>28,32</sup>

In this study the Conductor-like Screening Model for Real Solvents (COSMO-RS)<sup>35</sup> is used. COSMO-RS calculation consists of quantum chemical COSMO calculation, that is also a modification of CSM,<sup>36</sup> and a statistical thermodynamics part.<sup>35</sup> The COSMO part consists of calculating the geometry and energy in a virtual conductor  $\epsilon_r = \infty$ . As a result also a detailed data on the shape of the molecular cavity is calculated and the polarization charge densities are mapped onto the cavity surface, yielding the  $\sigma$ -surface. The  $\sigma$ -surfaces of all solutes and solvent molecules are then used in the statistical thermodynamics calculation, where the relative concentrations of each species can be taken into account. This enables calculations in various solvent mixtures, which is a huge advantage of COSMO-RS, which is the reason why it was chosen for this work. It has been shown that COSMO-RS is able to calculate the  $pK_a$  values of acids and bases in different solvents, among which are also acetonitrile and water, with, in best scenarios, an average error of 1  $pK_a$  unit.<sup>35,37,38</sup>

## 2. EXPERIMENTAL SETUP AND COMPUTATIONAL ASPECTS

In the previous sections we have established that it is possible to measure the relative difference in acidities excluding the need for knowing the pH of the solution, equations 6 and 8. This approach in combination with UV-Vis spectrophotometric titration method results in a “pure” spectrophotometric method, without the need for measurement of pH and, in case of compounds having different spectra in acid and base forms, also knowledge of exact concentrations. It also allows the elimination of several possible errors of different origin (impurities, instrumental *etc*), as the errors are the same for both compounds. The method is based on titrating first the solutions of pure compounds with strong acid and/or base and recording the spectra of neutral and ionic species. From the intermediate spectra of these titration series, the influence of spectrally active impurities, as well as possible side processes can be determined. The titration is repeated with the solution containing both compounds with the emphasis not only on the spectra of acidic and basic forms, but also on the intermediate spectra, in which the net absorbance is caused by absorbance of four species (eq 4), at different ionization level. The ionization level is defined as

$$\alpha = \frac{[A^{z-1}]}{[HA^z] + [A^{z-1}]} = \frac{[A^{z-1}]}{c(\text{HA})} \quad (18)$$

The ionization levels are calculated from spectra for both compounds and are the basis for  $\Delta pK_a$  calculations

$$\Delta pK_a = \log \frac{[A_1^{z-1}] \cdot [HA_2^z]}{[HA_1^z] \cdot [A_2^{z-1}]} = \log \frac{[A_1^{z-1}] \cdot (c_2 - [HA_2^z])}{(c_1 - [HA_1^z]) \cdot [A_2^{z-1}]} = \log \frac{c_1}{c_1 - [HA_1^z]} \cdot \frac{c_2}{[A_2^{z-1}]} = \log \frac{\alpha_1(1 - \alpha_2)}{\alpha_2(1 - \alpha_1)} \quad (19)$$

Where  $c_1$  and  $c_2$  refer to the analytical concentrations of studied compounds. The titrants used have to be transparent in the analytical wavelengths and at least one of the compounds measured must have difference in spectra of neutral and ionic species. If both compounds exhibit spectral properties, they cannot be identical.

In part 3.3 of the thesis, the influence of water in impurity level on acid-base properties of the compounds is studied. In order to observe the changes in relative acidity/basicity caused by small amounts of water, the measurement was repeated in four solvents with water content approximately up to 10, from 30 to 70, 1000 and 10000 ppm. Best commercially available UV-grade acetonitrile has water content in around from 30 to 70 ppm level and this has been used in this study and previously in building acidity<sup>6,15,39</sup> and basicity<sup>41-45</sup>

ladders. The higher water concentrations were achieved by adding additional water gravimetrically whereas the lowest was obtained by drying the solvent over molecular sieves.

## 2.1. Methods of calculation of $pK_a$ values from experimental data

The basis of every UV-Vis analysis is the Lambert-Beer law.

$$A_X^\lambda = [X] \varepsilon_X^\lambda \quad (20)$$

where the absorbance  $A_X^\lambda$  of the solution of species X in a layer of unit thickness at wavelength  $\lambda$  is determined by the equilibrium concentration of X and its molar absorbance coefficient  $\varepsilon^\lambda$  at given wavelength, assuming the absorbance of the pure solvent has been taken into account. If the solution of two acids is considered, where both are partially dissociated, the absorbance of the solution is the sum of the absorbances of four species:

$$A^\lambda = [\text{HA}_1^z] \varepsilon_{\text{HA}_1^z}^\lambda + [\text{A}_1^{z-1}] \varepsilon_{\text{A}_1^{z-1}}^\lambda + [\text{HA}_2^z] \varepsilon_{\text{HA}_2^z}^\lambda + [\text{A}_2^{z-1}] \varepsilon_{\text{A}_2^{z-1}}^\lambda \quad (21)$$

Introducing the ionization levels (equations 18 and 19) into the equation results after regrouping in a following formula

$$A^\lambda - c_1 \varepsilon_{\text{HA}_1^z}^\lambda - c_2 \varepsilon_{\text{HA}_2^z}^\lambda = \alpha_1 c_1 (\varepsilon_{\text{A}_1^{z-1}}^\lambda - \varepsilon_{\text{HA}_1^z}^\lambda) + \alpha_2 c_2 (\varepsilon_{\text{A}_2^{z-1}}^\lambda - \varepsilon_{\text{HA}_2^z}^\lambda) \quad (22)$$

Let us introduce the relative concentrations, which are defined as the ratio of compound's concentration in the mixture and the concentration in the solution of pure compound.

$$c_1^{\text{rel}} = \frac{c_1}{c_{1\text{pure}}} \quad (23)$$

Previously the importance of border forms was emphasized, these border forms allow the calculation of concentration of the substance in the solution based on the Lambert-Beer law. For instance if the solution of pure acid  $\text{HA}_1^z$  is considered and it is fully in ionic form ( $[\text{HA}_1^z] = 0$ ):

$$A^\lambda = [\text{A}_1^{z-1}] \varepsilon_{\text{A}_1^{z-1}}^\lambda = c_{1\text{pure}} \varepsilon_{\text{A}_1^{z-1}}^\lambda \quad (24)$$

Combining the equation 22, 23 and 24 gives

$$A^\lambda - c_1^{\text{rel}} A_{\text{HA}_1^\lambda}^\lambda - c_2^{\text{rel}} A_{\text{HA}_2^\lambda}^\lambda = \alpha_1 c_1^{\text{rel}} (A_{\text{A}_1^{\lambda-1}}^\lambda - A_{\text{HA}_1^\lambda}^\lambda) + \alpha_2 c_2^{\text{rel}} (A_{\text{A}_2^{\lambda-1}}^\lambda - A_{\text{HA}_2^\lambda}^\lambda) \quad (25)$$

Which can be used in two parameter linear regression model when

$$(A_{\text{A}_1^{\lambda-1}}^\lambda - A_{\text{HA}_1^\lambda}^\lambda) = x_1 \quad \text{and} \quad (A_{\text{A}_2^{\lambda-1}}^\lambda - A_{\text{HA}_2^\lambda}^\lambda) = x_2$$

The ionization ratios of both compounds can be obtained from the regression analysis and  $\Delta pK_a$  can be calculated according to equation 19. The linear regression analysis can be carried out with or without an intercept giving two calculation methods. It should be noted, that the calculation of  $\Delta pK_a$  does not use any other input data than the normalized spectra of pure compounds and mixture and the relative concentrations.

Alternatively the ionization ratios can be calculated utilizing the isosbestic points (wavelength at which both neutral and ionic species have the same molar absorptivity) or regions in spectra, where only one of the compounds absorbs light. This allows ascribing the changes in the spectra of mixture of two compounds to one of the compounds and therefore calculation of the ionization ratio of that compound.

$$\alpha_1 = \frac{A_{\text{A}_1^{\lambda-1}}^\lambda - A^\lambda}{A_{\text{A}_1^{\lambda-1}}^\lambda - A_{\text{HA}_1^\lambda}^\lambda} \quad (26)$$

If ionization ratios can be calculated for both compounds, an independent method can be achieved for calculating the  $\Delta pK_a$ .

Not all compounds have suitable chromophores or the changes in spectra upon protonation or deprotonation are very small, which makes the above described calculation methods inapplicable. In these cases the ionization ratio of one compound must be obtained from the spectra according to equation 26. Knowing the concentration of the first compound, concentration of the added titrant and the ionization ratio of the first compound allows the calculation of amount of titrant used for ionization of the second compound, which in turn lets us calculate the ionization ratio of the second compound and the calculation of  $\Delta pK_a$ . The concentrations of both compounds and titrants must be accurately known, meaning that larger amounts of compounds along with lower titrant concentrations are needed to minimize the errors of weighing.

As already mentioned earlier side processes can occur depending on the chemical nature of studied compounds and solvent used. In the case of acid pairs **g**, **h**, and **i** in section 3.3 one of the acids in pairs (compounds **A12**, **A13** and **A14**, respectively) is prone to homoassociate. All of mentioned acids do not have sufficient spectral properties, so that the calculation method based on the

concentrations had to be modified. The homoassociation equilibria (equation 11) can be taken into account knowing that

$$K_{\text{homo}} = \frac{[\text{HA}^z \cdots \text{A}^{z-1}]}{[\text{HA}^z][\text{A}^{z-1}]} \quad (27)$$

In the previous method  $[\text{HA}^z]$  and  $[\text{A}^{z-1}]$  values could be easily calculated using the concentrations and knowing the amount of acidic or basic titrants added. The same scheme can be used here, but the obtained values correspond to apparent concentrations:

$$[\text{HA}^z]_{\text{app}} = [\text{HA}^z] + [\text{HA}^z \cdots \text{A}^{z-1}] \text{ and } [\text{A}^{z-1}]_{\text{app}} = [\text{A}^{z-1}] + [\text{HA}^z \cdots \text{A}^{z-1}] \quad (28)$$

If equations 27 and 28 are combined quadratic equation is formed

$$([\text{HA}^z \cdots \text{A}^{z-1}])^2 + \left( [\text{HA}^z]_{\text{app}} + [\text{A}^{z-1}]_{\text{app}} + \frac{1}{K_{\text{homo}}} \right) [\text{HA}^z \cdots \text{A}^{z-1}] + [\text{HA}^z]_{\text{app}} + [\text{A}^{z-1}]_{\text{app}} = 0 \quad (29)$$

From which the concentration of homoassociate complex can be found

$$[\text{HA}^z \cdots \text{A}^{z-1}] = \frac{[\text{HA}^z]_{\text{app}} + [\text{A}^{z-1}]_{\text{app}} + \frac{1}{K_{\text{homo}}} + \sqrt{\left( [\text{HA}^z]_{\text{app}} + [\text{A}^{z-1}]_{\text{app}} + \frac{1}{K_{\text{homo}}} \right)^2 - 4[\text{HA}^z]_{\text{app}}[\text{A}^{z-1}]_{\text{app}}}}{2} \quad (30)$$

Knowing the  $[\text{HA}^z \cdots \text{A}^{z-1}]$  allows the calculation of the true concentration of  $[\text{HA}^z]$  and  $[\text{A}^{z-1}]$  and therefore also the calculation of ionization ratio and  $\Delta\text{p}K_a$ . Experimental standard deviation  $s(\Delta\text{p}K_a)$  in Table 4 was calculated over the range of  $\Delta\text{p}K_a$  values obtained during  $n$  titration experiment points (generally 8 to 20 values), where both of the acids were generally dissociated more than 5% and less than 95% according to eq 31.

$$s(\Delta\text{p}K_a) = \sqrt{\frac{\sum_{i=1}^n (\Delta\text{p}K_{a,i} - \overline{\Delta\text{p}K_a})^2}{(n-1)}} \quad (31)$$

In section 3.2 a basicity scale is constructed in DCE. In order to get assigned  $\text{p}K_{\text{ip}}$  values for the bases, one of the base was taken as the reference point (anchor compound) and its  $\text{p}K_{\text{ip}}$  considered to be zero, the sum of squares (SS) of differences between estimates of assigned  $\text{p}K_{\text{ip}}$  values and the experimentally measured  $\Delta\text{p}K_{\text{ip}}$  values were minimized, allowing the changing of all the assigned  $\text{p}K_{\text{ip}}$  values except the one, that was taken as an anchor compound.

This was done according to the following equation

$$SS = \sum_{i=1}^{n_m} \left\{ \Delta pK_{ip}^i - \left[ pK_{ip}(\text{HA}_2) - pK_{ip}(\text{HA}_1) \right] \right\}^2 \rightarrow \min \quad (32)$$

Where  $n_m$  is the number of measurements.

## 2.2. Computations

If equilibrium constants are desired the computations operate on the basis of Gibbs free energy: every reaction can be characterized by the Gibbs free energy change of the reaction, which can be calculated as the difference of Gibbs free energies of products and substrates, in the case of acid ionization (eq 1):

$$\Delta G_{\text{ion}} = G_{\text{A}^-} - G_{\text{HA}} - (G_{\text{SH}^+} - G_{\text{S}}) \quad (33)$$

The equilibrium constants can be calculated using the following relationship between  $K$  and  $\Delta G$ :

$$\Delta G = -RT \ln K \quad (34)$$

Where  $R$  is the universal gas constant,  $T$  is the temperature.

The relationship between  $K_a$  and Gibbs free energy change of reaction is:

$$\Delta G_{\text{ion}} = -RT \ln K_a + RT \ln [S] \quad (35)$$

The need for  $RT \ln [S]$  comes from the  $\Delta G$  definition equation (eq 33), where the  $G$  of solvent molecules is given, but absent in the  $K_a$  definition equation at dilution limit (eq 2) as it is considered constant.

The  $pK_a$  is therefore

$$pK_a = \frac{\Delta G}{RT \ln(10)} + \frac{G(\text{HS}^+) - G(\text{S})}{RT \ln(10)} - \log [S] \quad (36)$$

The  $\Delta G$  is here referred to as the energy difference between ionic and neutral form ( $\Delta G = G(\text{A}^-) - G(\text{HA})$ ). The experimental approach used in this work involves measurement of relative acidity/basicity (i.e. acidity/basicity difference) of two compounds ( $pK_a$ ), this approach is applicable also here, avoiding the need for calculating the energy of solvated proton.



$$\Delta pK_a = \frac{\Delta G_A}{RT \ln(10)} + \frac{G(\text{HS}^+) - G(\text{S})}{RT \ln(10)} - \log[\text{S}] - \left( \frac{\Delta G_B}{RT \ln(10)} + \frac{G(\text{HS}^+) - G(\text{S})}{RT \ln(10)} - \log[\text{S}] \right) = \quad (37)$$

$$= \frac{\Delta G_A}{RT \ln(10)} - \frac{\Delta G_B}{RT \ln(10)} = \frac{1}{RT \ln(10)} (\Delta G_A - \Delta G_B)$$

In this study computations were made to supplement the observations made from the results of the experiments, where the effect of water content of the solvent on the acidities and basicities was studied. COSMO-RS is only one of the few computational methods capable of calculation in solvent mixtures.<sup>46</sup> In previous section it was already mentioned that COSMO-RS uses two step computation protocol<sup>35</sup>:

As the first step, full geometry optimization and energy calculation at DFT BP TZVP level with the RI approximation and applying the COSMO continuum solvation model was carried out for all species of eq 4 and solvent molecules using the Turbomole V 6.2 or V 6.3 software package<sup>47</sup>. Different starting geometries were used, based on common chemical knowledge of the species involved. For most species, several conformers corresponding to different local energy minima were found. These were all taken into account by statistical weighting inherent in the COSMO-RS procedure. The default convergence criteria of Turbomole were used (wavefunction convergence: max difference  $10^{-6}$  Hartree; geometry convergence: max gradient  $|dE/dxyz|$   $10^{-3}$  Hartree/Bohr). This first computation step yields for every conformer the following data: (1) the geometry of the conformer, (2) detailed data on the shape of the molecular cavity, (3) the polarization charge densities mapped onto the cavity surface (the sigma profile) and (4) the total electronic energy of the species submerged into a virtual conductor ( $\epsilon_r = \infty$ ).

As the second step the COSMO-RS calculation was carried out on all species using the above listed data as input data with the COSMOtherm software package Version C2.1, Release 01.10 and Version C3.0, Release 13.01<sup>48</sup>. COSMO-RS calculation takes into account the interactions between the species of eq 4 and the solvent/medium molecules, as well as between the solvent molecules themselves (the implicit solvation model is used). The solvent composition is input as it was in the experiment (i.e. including the concentration of water in the solvent). Zero concentrations of the species of eq 4 are used. This way the interactions between the species and the solvent components are taken into account, but not the interactions between the species themselves. This situation corresponds well to the reality of very low concentrations used in the experiments. Both van der Waals interactions (electrostatic interactions, such as dipole-dipole, ion-dipole, *etc* and dispersion forces) and hydrogen bonds (in the implicit way) are taken into account. The interactions are quantified via statistical counting and averaging of energies of pairwise interactions of molecular surface segments using the polarization charge density maps of the species created in the first step taking into account the concentrations of the respective species in the solution.<sup>35</sup> Terms accounting for

vibrational contributions to the  $G$  are also added in this step. This is done implicitly, as these are represented through the experimental data used for parametrization of the method. The energetics of these interactions are calculated at 298 K using a statistical thermodynamics procedure whereby also the conformers of all the interacting species are taken into account and statistically weighted based on their relative stabilities.<sup>35</sup> This way the entropy effect of the same species present in multiple conformers is also accounted for. As a result, a  $G$  value is found for every species. From the  $G$  values of the species the  $\Delta pK_a$  is found.

### 2.2.1. WAPS and WANS parameters

In previous sections it was already mentioned, that the effect of water on ions through preferential solvation is influenced by the charge delocalization in the ions. The concept of charge delocalization in ions seems to be insufficiently quantified as it is used only at qualitative level. There are different well-known approaches, that involve partial charges on atoms in molecules and ions,<sup>32,50</sup> but prior to Publication I, there was no quantitative parameter available that would characterize the charge distribution in an ion as a whole. At the same time in numerous situations – especially in interactions, such as ion-aggregation, hydrogen bonding between neutrals and ions, *etc* – it is the extent of charge delocalization of the ion as the whole that plays role.

The need to quantitatively describe the charge delocalization in anions in order to interpret the experimental results lead to the definition of a parameter for quantifying charge delocalization – Weighted Average Positive Sigma (*WAPS*).<sup>1</sup> It utilizes the sigma profile – distribution of charge density ( $\sigma$ ) on molecular surface<sup>35</sup> – obtained from the COSMO calculation. *WAPS* is defined as weighted mean of positive sigma values divided by the ion surface area:

$$WAPS = \frac{\int_{\sigma=0}^{\infty} \sigma \cdot p(\sigma) d\sigma}{A \int_{\sigma=0}^{\infty} p(\sigma) d\sigma} \quad (38)$$

Where  $\sigma$  is the polarization charge density on the ions surface,  $p(\sigma)$  is the probability function of  $\sigma$  and  $A$  is the surface area of the anion. The surface segments with negative charge are (due to definition of  $\sigma$ ) characterized by positive sigma values.

Analogous to the *WAPS* parameter, describing charge delocalization in anions, *WANS* (Weighted Average Negative Sigma) parameter can be defined to describe the charge delocalization in cations:

$$WANS = \frac{\int_{\sigma=-\infty}^0 \sigma \cdot p(\sigma) d\sigma}{A \int_{\sigma=-\infty}^0 p(\sigma) d\sigma} \quad (39)$$

The smaller is the value of *WAPS* or *WANS*, respectively, the more delocalized is the charge in the ion. A charge in an ion is considered to be “localized” if the *WAPS/WANS* value is above 4.5 as proposed in Publications I and IV.

### 2.3. Instruments and chemicals

Preparations of all solutions and titration experiments were done in MBraun UniLab glovebox in the atmosphere of argon (concentration of O<sub>2</sub> and H<sub>2</sub>O less than 1 ppm). Before each measurement from 1 to 2 ml of stock solutions (ca 10<sup>-3</sup> M) of both acids were prepared gravimetrically by using analytical balance into small glass vials with PTFE lined caps. For titration experiments the solutions of acids were further diluted to ca 10<sup>-5</sup> M range directly into the 3.5 ml spectrophotometrical UV-grade quartz PTFE lined screw capped cuvette. Perkin Elmer UV-Vis spectrometer Lambda 40 with external sample compartment, which was situated in the glovebox and was connected to the spectrometer with quartz fiber optic light guides, was used for acquiring spectral data. For pairs **h** and **i** Ocean Optics HR2000+ spectrometer with Micropack DH-2000 light source, Sony ILX-511 detector and Quantum Northwest TLC 50F™ sample compartment was used, the temperature of the sample compartment was set to 25°C using Quantum Northwest TC 125™ temperature controller. Spectra of both neutral and ionic form were registered and as well as several spectra (ca 5 for pure acids and up to 20 to 30 for mixture of acids) of mixtures which contained both neutral and the ionic forms. The spectral data are processed in MS Excel using the calculation methods described in section 2.1

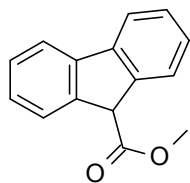
For the measurements, where the influence of water content was observed, the chemicals, measurement method, equipment and conditions were kept the same as in the previous studies<sup>6,15,41,42,45</sup> in our research group, where the  $\Delta pK_a$  values were first measured. The only difference was the water content of the solvent. Commercially available MeCN (Romil, >99.9 %, *Super Purity Solvent*, far UV) was used for preparation of solutions for the data points up to around 0.01% (100 ppm) of water. For obtaining the lowest possible water content MeCN was kept on molecular sieves (Riedel de Haën, average pore size 3Å) for at least 12 hours. This resulted trace water at few ppm level. Deionized water from Purite Analyst HP or Millipore Advantage a10 was gravimetrically added by syringe to the acetonitrile used for preparation of all solutions to get higher concentrations of water and its content was determined for pure solvent and titrated solutions by coulometric Karl Fischer titration (Mettler Toledo DL32)

after each experiment run using DM 143-SC diaphragmaless indicator electrode, Riedel deHäen Hydranal<sup>®</sup> Coulomat AD reagent solution and the following instrument settings: mix time 10 s, drift was kept at 3–5  $\mu\text{g}/\text{min}$ , iodine generation speed was lower in dryer solvents and higher in wetter solvents. For measuring, the electrode polarization current was set to 2  $\mu\text{A}$  and end point voltage to 100mV. The solvents with increased water content were individually made for each of the acid/base pair titration experiments. The same experimentally determined water content was later used in COSMO-RS calculation to exactly match the experimental conditions. For the investigation of phosphane bases DCE (Romil, >99.9 %, *Super Purity Solvent*, far UV) and MeCN were both used as solvents because of the solubility problems and due to the solvent limit of MeCN making the measurement of weakest bases impossible. Both solvents were dried on 3Å molecular sieves to minimize the effect of water.

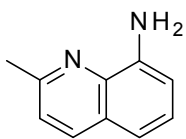
TfOH (Aldrich, 99+%) was used for preparation of the acidic titrant, commercial superbasic phosphazenes *t*-BuP<sub>1</sub>(pyrr) (Fluka, >98%) and EtP<sub>2</sub>(dma) (>98%) depending on the strength of acids to be measured were used for preparation of the basic titrants in MeCN. In DCE TfOH was found to be too weak to protonate the acids studied so the CF<sub>3</sub>SO(=NTf)NHTf as acidic titrant<sup>49</sup> had to be used.

In the studies of effect of water content, the compounds were the same as in previously published acidity<sup>6,15</sup> and basicity<sup>41,42,45</sup> scales, the origin of compounds is described therein. The origin of chiral acid catalysts (BINOL-phosphoric acids; NTPA (N-triflylphosphoramidate); sulfurylimides (JINGLE, BINOL-bis(sulfurylimide)) and phosphane base catalysts (mainly fluoro and chloro substituted triphenylphosphanes) is described in Publications II and III, respectively.

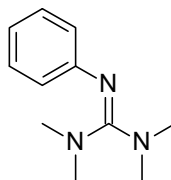
In the  $\text{p}K_{\text{a}}$  determination experiments each  $\text{p}K_{\text{a}}$  value was obtained by measuring the acid under question in reference to 2 or 3 different reference acids and the assigned  $\text{p}K_{\text{a}}$  (in Table 1 and Table 3) is the average over the  $\text{p}K_{\text{a}}$  values obtained from the individual measurements.



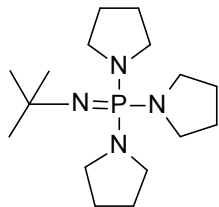
9-COOMe  
Fluorene



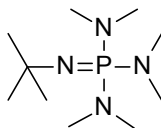
2-methyl-8-  
quinolineamine



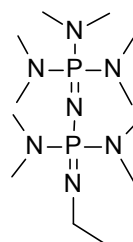
PhTMG



*t*-BuP<sub>1</sub>(pyrr)



*t*-BuP<sub>1</sub>(dma)



EtP<sub>2</sub>(dma)

**Figure 1.** Structures of some of the compounds in order to help interpret the names and abbreviations.

### 3. RESULTS

Knowing the limits and properties of solvents is very important when choosing the solvent for  $pK_a$  measurements.

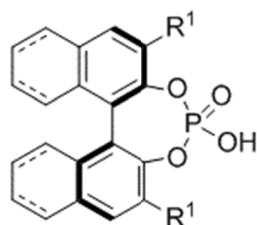
The first two parts of the Results section is focused on the  $pK_a$  determination experiments of two sets of compounds: chiral Brønsted acid catalysts – BINOL-phosphoric acids; NTPA (N-triflylphosphoramidate); sulfurylimides (JINGLE, BINOL-bissulfurylimide) – and phosphane bases as a part of Frustrated Lewis Pair (FLP) catalyst system. The two compound groups are similar in the sense that both have quite low  $pK_a$  values, very near, or in the case of some phosphanes even below, the limit of MeCN (set by the basicity of the solvent). Knowing the limits of MeCN has led to involving besides MeCN also DCE for  $pK_a$  measurements of phosphanes. In the case of chiral acid catalysts choosing MeCN as the solvent revealed serious errors in previously published  $pK_a$  values of similar compounds determined in DMSO. The reasons behind the differences, both from the point of view of solvent properties as well as experimental setup are discussed.

In the third part the influence of MeCN purity with respect to water content is studied and the effect of low water concentration is quantified for acids and bases with varying properties. The resulting suggestions for experimental setup based on the gained knowledge are presented in the fourth part of the results section.

#### 3.1. $pK_a$ measurements of acid catalysts

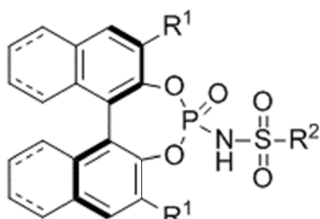
There is increasing interest in highly efficient metal-free Brønsted acid organocatalysts<sup>51</sup>, especially in the field of asymmetric catalysis. Perhaps the best known are the chiral 1,1'-bi-2-naphthol (BINOL)-derived phosphoric acid diesters and analogues. They are used *e.g.* for transfer hydrogenations as well as various addition reactions to aldimines and ketimines. As the application of these catalysts involves basic substrates, the activation of more challenging (*i.e.* less basic) substrates needs more acidic catalysts. Therefore, the more acidic chiral BINOL-derived *N*-triflylphosphoramidates (NTPAs)<sup>52,53</sup> and bis(sulfuryl)imide<sup>54</sup> based catalysts have been introduced.

Although the catalytic activity of these catalysts is related to acidity of the compounds<sup>52</sup>, very little was known about their exact  $pK_a$  values. This inspired the measurement of the  $pK_a$  values of these very important compounds with the aim of help to fine tune the catalysts. The  $pK_a$  values of a selection of representatives (Figure 2) of the mentioned organocatalysts' families were measured.



type A (BPA) BINOL-phosphoric acid

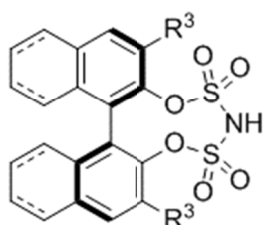
- 1:  $R^1 = \text{Ph}$   
 2:  $R^1 = 4\text{-F-C}_6\text{H}_4$   
 3:  $R^1 = 2,4,6\text{-}(i\text{Pr})_3\text{C}_6\text{H}_2$   
 4:  $R^1 = 9\text{-phenanthryl}$   
 5-[H<sub>8</sub>]:  $R^1 = 9\text{-phenanthryl}$



type B (NTPA)

*N*-triflylphosphoramidate

- 6:  $R^1 = \text{Ph}, R^2 = \text{CF}_3$   
 7-[H<sub>8</sub>]:  $R^1 = \text{Ph}, R^2 = \text{CF}_3$   
 8-[H<sub>8</sub>]:  $R^1 = \text{Ph}, R^2 = \text{C}_4\text{F}_9$   
 9-[H<sub>8</sub>]:  $R^1 = \text{Ph}, R^2 = \text{C}_8\text{F}_{17}$   
 10:  $R^1 = 4\text{-MeOC}_6\text{H}_4, R^2 = \text{CF}_3$   
 11-[H<sub>8</sub>]:  $R^1 = 4\text{-MeOC}_6\text{H}_4, R^2 = \text{CF}_3$   
 12-[H<sub>8</sub>]:  $R^1 = 4\text{-FC}_6\text{H}_4, R^2 = \text{CF}_3$



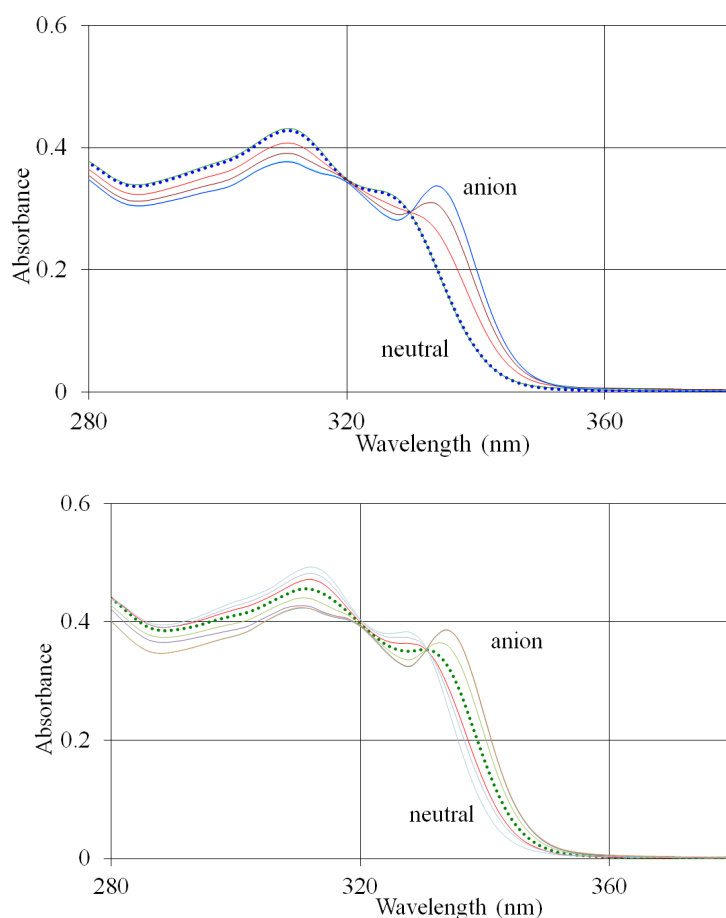
type C (JINGLE)

- 13:  $R^3 = 3,5\text{-}(\text{CF}_3)_2\text{C}_6\text{H}_3$   
 BINOL-bis(sulfuryl)imide

**Figure 2.** Types of chiral Brønsted acid organocatalysts. [H<sub>8</sub>] denotes 5,6,7,8-tetrahydronaphthyl rings.

The  $pK_a$  values of these compounds proved quite difficult to measure. Because the acidity centers of these compounds are quite distant from the aromatic system, the molar absorbance coefficients (and thus the spectra) of the neutrals and anions are very similar in the case of all of these compounds, meaning that the changes in spectra upon protonation/deprotonation are very small. Figure 3 shows the best spectra, with the largest changes upon deprotonation, out of all studied compounds, for comparison see also Figure 6, image on the left. This affects the performance of methods used for calculation of  $pK_a$  values from the spectra that rely on the changes in spectra. Due to the limited choice of reference acids (and their spectral properties relative to studied compounds) in the investigated  $pK_a$  region, the measurements of these acids as “invisible” acids proved impossible. The original list of compounds was much wider than the final list of compounds with  $pK_a$  values successfully measured (13 compounds).

Many of the compounds were not successfully measured due to (1) insufficient solubility in MeCN, (2) no clear spectrum of neutral or anionic form could be achieved, (3) unexpected changes in spectra in the case of over titration, (4) abnormal shifts in isosbestic points. The reasons 2-4 indicate that unwanted side processes are taking place or impurities with similar spectra and  $pK_a$  values are present in the solution. The shift of the isosbestic point was not contiguous, but rather two specific isosbestic points were observed. As the compounds were very pure (as indicated by their mass spectra) the conclusion can be made that other possible equilibria were present in the solution for some of the compounds. Some of these processes were reversible, some were not. As these impurities and/or side processes were impossible to take into account or correct, the affected compounds were left aside and only compounds with clear and fully interpretable spectra were used.



**Figure 3.** Spectra of compound 3 in MeCN (left) and DMSO (right).



The results of the  $pK_a$  measurements are presented in Table 1 along with catalytic properties characterized by rate constants of Nazarov cyclization reaction.

**Table 1.** Results of  $pK_a$  measurements.

| Compound;<br>Substituents   | Assigned<br>$pK_a$ | $-\log(k_1)$     |                  |
|---|--------------------|------------------|------------------|
|   |                    | LLS <sup>a</sup> | NLS <sup>b</sup> |
| <b>5</b> -[H <sub>8</sub> ]; R <sup>1</sup> = 9-phenathrene   | 14.0               | 5.55             | 5.55             |
| <b>3</b> ; R <sup>1</sup> = 2,4,6-( <i>i</i> Pr) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>                          | 13.6               |                  |                  |
| <b>4</b> ; R <sup>1</sup> = 9-phenathrene   | 13.3               |                  |                  |
| <b>1</b> ; R <sup>1</sup> = Ph  | 12.7               | 5.35             | 5.36             |
| <b>2</b> ; R <sup>1</sup> = 4-F-C <sub>6</sub> H <sub>4</sub>   | 12.5               |                  |                  |
| <b>11</b> -[H <sub>8</sub> ]; R <sup>1</sup> = 4-MeO-C <sub>6</sub> H <sub>4</sub> ; R <sup>2</sup> = CF <sub>3</sub> | 6.9                |                  |                  |
| <b>9</b> -[H <sub>8</sub> ]; R <sup>1</sup> = Ph; R <sup>2</sup> = C <sub>8</sub> F <sub>17</sub>                     | 6.8                | 3.73             | 3.72             |
| <b>7</b> -[H <sub>8</sub> ]; R <sup>1</sup> = Ph; R <sup>2</sup> = CF <sub>3</sub>                                    | 6.7                |                  |                  |
| <b>8</b> -[H <sub>8</sub> ]; R <sup>1</sup> = Ph; R <sup>2</sup> = C <sub>4</sub> F <sub>9</sub>                      | 6.7                | 3.60             | 3.60             |
| <b>10</b> ; R <sup>1</sup> = 4-MeO-C <sub>6</sub> H <sub>4</sub> ; R <sup>2</sup> = CF <sub>3</sub>                   | 6.4                | 3.33             | 3.32             |
| <b>6</b> ; R <sup>1</sup> = Ph; R <sup>2</sup> = CF <sub>3</sub>  | 6.4                |                  |                  |
| <b>12</b> -[H <sub>8</sub> ]; R <sup>1</sup> = 4-F-C <sub>6</sub> H <sub>4</sub> ; R <sup>2</sup> = CF <sub>3</sub>   | 6.3                |                  |                  |
| <b>5</b> -[H <sub>8</sub> ]; R <sup>1</sup> = 9-phenathrene   | 14.0               | 5.55             | 5.55             |
| <b>13</b> R <sup>3</sup> = 3,5-(CF <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                         | 5.2                |                  |                  |

<sup>a</sup> LLS – linearized least squares method; <sup>b</sup> NLS – nonlinear least squares method.

These acids can be classified by their acidity centers into three groups: **A** – BINOL-derived phosphoric acid diesters (BPAs) with  $pK_a$  values in the range of 12-14, **B** – mixed imides of phosphoric and triflic acid (NTPAs) with  $pK_a$  values in the range of 6–7, and **C** – imides of sulfonic acids (JINGLES) with  $pK_a$  values around 5. The  $pK_a$  ranges observed for these groups agree with the general structure-acidity trends in MeCN.<sup>15,37,55</sup>

The nature of the acidity center has the strongest influence on the acidities of the catalysts studied, increasing in the order **A** (BPAs) < **B** (NTPAs) < **C** (JINGLES). The next important influencing factor is the aromatic or aliphatic nature of the bi-naphthalene outer rings. This influence can be seen in the pairs **4** and **5**-[H<sub>8</sub>], **10** and **11**-[H<sub>8</sub>], **6** and **7**-[H<sub>8</sub>], bringing the average acidifying influence of aromatization of the second aromatic ring to 0.5  $pK_a$  units. The acidity increases in the row **11**-[H<sub>8</sub>], **7**-[H<sub>8</sub>], **12**-[H<sub>8</sub>] as well as in the row **3**, **4**, **1**, **2** is as expected from the electronic properties of the substituents R<sup>1</sup> (Figure 2). It must be noted that the influence of substituent R<sup>1</sup> is more important in the group **A** than it is in the group **B**. This can be interpreted in terms of delocalization of the negative charge in the anionic form of the acid: the more concentrated it is on the acidity center, the more effect the substituent has. In group **B** the charge is largely delocalized on the perfluoroalkanesulfonyl group. This phenomenon is also responsible for the much larger  $pK_a$  difference

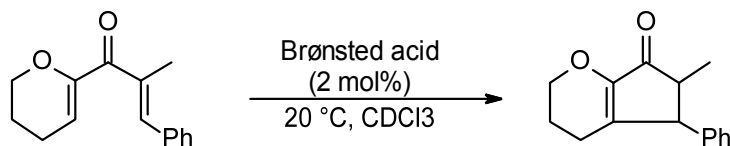
between compound **1** and 4-toluenesulfonic acid (4.2  $pK_a$  units) than between **6** and TosNHTf (0.5  $pK_a$  units) and can also be extended to the above mentioned aromatic nature of the outer bi-naphthalene backbone.

The members of group **B**, which differ only in the length of the perfluoroalkyl chain, have almost equal acidities. Although the perfluoroalkyl chain is closer to the acid center than the  $R^1$  substituents they influence the negative charge of the anions only through an inductive effect.

Type **C** catalyst **13** is the most acidic and differs in acidity from type **B** by one order of magnitude.

As mentioned above, the relationship between the acidity of a catalyst and its catalytic activity has been observed empirically. As concrete  $pK_a$  values for a number of acidic catalysts had been measured, the measurement of catalytic activity followed with the aim of establishing the relation between acidity and catalytic activity. The catalytic activity measurements were carried out by our partners at RWTH Aachen University and the data treatment was carried out by the author [see Publication III] and hereby a brief description is given.

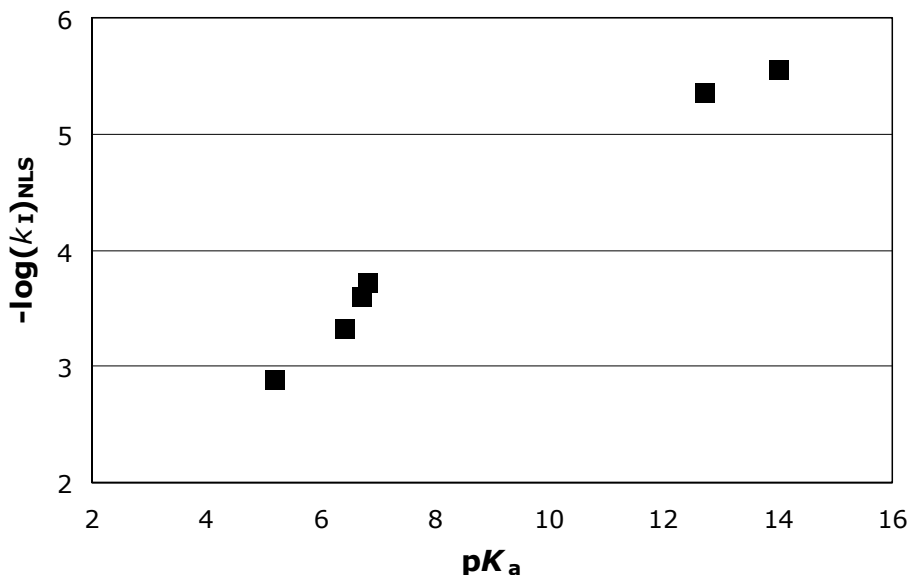
As a model reaction the Nazarov cyclization of dienone (Figure 4) was chosen. This reaction is particularly suitable as the corresponding product, the neutral cyclopentenone, does not contain basic sites, which bind the Brønsted acids or form ion-pairs leading to different catalyst concentrations or catalyst inhibition and hence unreliable measurements and statements. Performance of 6 catalysts (**1**, **5**, **8**, **9**, **10**, **13**) was monitored, using NMR to determine the conversion at room temperature (Figure 4). The catalysts were chosen so that all three groups were represented, covering the full range of measured  $pK_a$  values.



catalyst: **5**, **1**, **9**, **8**, **10**, **13** ( $pK_a$  14.0 to 5.2)

**Figure 4.** Evaluation of different acids in the Nazarov cyclization.

Based on the obtained data, the rate constants  $k_1$  for first order reaction were obtained, using two methods: linearized least squares (LLS) and nonlinear least squares (NLS) (Table 1). The  $-\log(k_1)$  values are plotted against  $pK_a$  in Figure 5.



**Figure 5.** Correlation between the acidity ( $pK_a$ ) of the catalysts and their catalytic activity (negative logarithm of the rate constant).

It is evident from Figure 5 that the catalytic activity of the investigated Brønsted acids correlates with their acidity. The higher the acidity (lower  $pK_a$ ) the higher the rate constant (lower  $-\log(k_1)$ ). This is in agreement with the findings described above. Weaker phosphoric acids have  $pK_a$  values by 6-8 units higher and rate constant values of two orders of magnitude smaller compared to their triflamide analogs. The capability of these acids to promote enantioselective transformations relies on the catalyst structure. At the same time, their ability to activate reactions, as well as influence the reaction rate, relies largely on their acidity. According to Figure 5, and in agreement with earlier experimental observations,<sup>56</sup> groups **B** and **C** show higher ability to activate and accelerate reactions compared to the group **A**.

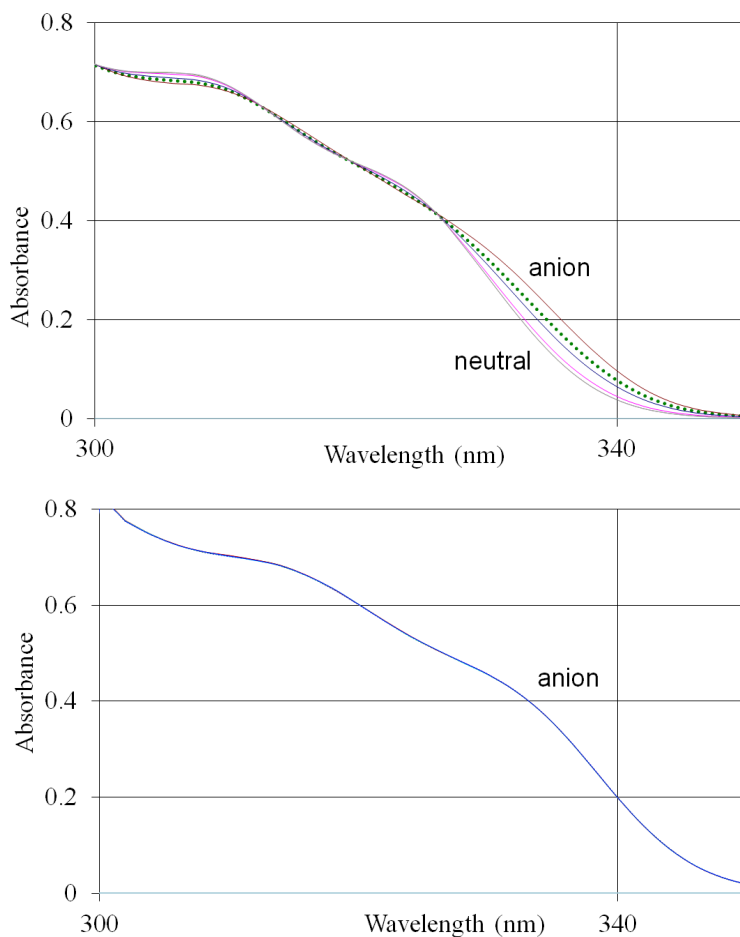
While experimental studies were in progress  $pK_a$  values of similar acids in DMSO were published by Christ *et al.*<sup>57</sup> Although all three groups (**A–C**) of acids were present in their dataset, only one acid (compound **3**) was identical. Most of the  $pK_a$  data reported – those for the weaker acids – agree well with data in MeCN, taking into account the good correlation of the  $pK_a$  values of neutral OH, NH and CH acids between MeCN and DMSO having near unity slope and an intercept in the range of 10-13  $pK_a$  units ( $pK_a$  values in DMSO are lower).<sup>6,37,40</sup>

However, three compounds **5**, **7a** and **7b** in reference 57 (**5** corresponds to a group **B** acid with  $R^1 = 4\text{-MeO-C}_6\text{H}_4$ ;  $R^2 = \text{CF}_3$ ; **7a** and **7b** to group **C** with  $R^3 = \text{H}$  and  $[\text{H}_8]$   $R^3 = \text{H}$ , respectively) belonging to the groups **B** and **C** have  $pK_a$  values very similar to the ones in group **A**. This is in contrast to findings in

MeCN. The  $pK_a$  range of the groups **A–C** in ref 57 is between 1.7 and 4.2. This is in stark disagreement with the close to 9  $pK_a$  units range of MeCN  $pK_a$  values. Christ *et al.* conclude that the acidity differences between the different catalysts are not large and that the relative acidity of the catalysts may not be the only factor explaining their catalytic performance.

In fact, when looking at general relationships between  $pK_a$  values in MeCN and DMSO,<sup>15</sup> these three acids from groups **B** and **C** should have negative or close to zero  $pK_a$  values in DMSO. At first sight it is astonishing, that groups of acids which differ by 6–7  $pK_a$  units in MeCN (which is fully rational according to their structures) have almost identical  $pK_a$  values in DMSO. However, it is known that measurements of strong acids in a given solvent can provide  $pK_a$  values of 1–3 (even though the true  $pK_a$  value can be negative), if the ionization ratio of the measured species is not monitored.<sup>58</sup>

In order to investigate this discrepancy some experiments were carried out in DMSO. First compound **3** (representative of group **A**) was dissolved in DMSO and the titration procedure was carried out (Figure 3, right). The dotted line indicates the spectrum of the initial solution of the acid when no titrants were added. It can be seen that the compounds have similar spectra in MeCN and DMSO, possessing both neutral and anionic form, indicating that the compound **3** can be successfully protonated and deprotonated in both solvents. The initial spectra indicate that moving from MeCN to DMSO the self-dissociation of the acid (*i.e.* dissociation without a base added) increases, which is logical due to the fact that DMSO is a much more basic solvent than MeCN. Secondly compound **6** was dissolved in DMSO and the spectrum of its anion (Figure 6, right) was observed because of complete ionization. A large excess of acidic titrant (TfOH) was added for protonating the anion. At the end of the titration, the concentration of triflic acid exceeded the concentration of the studied compound by 7 times. However, it was impossible to detect any neutral acid form of the acid from the spectra and most likely the solvent itself was being protonated during titration.



**Figure 6.** Spectra of compound 6 in MeCN (left) and DMSO (right).

In order to understand the differences in the results, a brief overview of the measurement method used by Christ *et al.*<sup>57</sup> is given below. Equilibrium identical to eq 4 is studied between an indicator and a studied compound (in large excess over the indicator), the ionization ratio of the indicator is monitored by UV-Vis spectroscopy. The ionization ratio of the studied compound is calculated from the amount of titrant added. Based on the ionization ratio of indicator and studied acid the  $\Delta pK_a$  is calculated. The main differences of the method of ref 57 from this work were that aqueous solution of NaOH was used as the titrant, therefore increasing water content of the solution during titration and the protonation deprotonation process of the actual compound under investigation was not directly monitored. It was reported, that the water content of the final titrated solution was below 2 vol%, this is 20000 ppm.

Christ *et al.* assumed that the studied Brønsted acids and conjugate bases either have no chromophore or undergo no spectral change upon ionization. Due to the assumption that there are no spectral changes upon ionization Christ *et al.* did not monitor the spectra of the Brønsted acids during titration, leading to the possibility that the process studied was not the desired one.

This method worked well for group **A** acids, but when the DMSO solutions of the **B** and **C** acids were prepared then the acids dissociated virtually completely. As the spectra of the studied compounds were not monitored, the self-ionization was missed. The different added amounts of aqueous hydroxide neutralized different proportions of the acid, which was already almost fully dissociated (leading to different  $H^+$  concentrations in solutions). The introduced water also modified (decreased) the  $pK_a$  values of the indicators (as well as the catalysts). The indicators actually mostly measured the extent of neutralization (the “pH” of the solution) rather than acid dissociation. The difference between the  $pK_a$  values of compounds of **B** and **C** groups in ref 57 are most probably due to the different indicators used and partial correction for self-dissociation that was done in the case of **C** group compounds, but not the **B** group compound. Probably these  $pK_a$  values cannot be measured in DMSO accurately by conventional methods, but further experiments may give more information.

Direct observation – via spectral changes – of the protonation-deprotonation process is very important for obtaining trustworthy  $pK_a$  values, especially for very strong and very weak acids (or bases). By directly observing the spectral changes of both compounds during the titration of the mixture one can reliably establish that protonation or deprotonation occurs. Based on simple observation of the spectra of a mixture of two compounds qualitative conclusions can already be made if the  $pK_a$  values of both compounds are similar or not. If the  $\Delta pK_a$  is over 0.5 units, then, if we assume that both compounds are in their neutral forms and basic titrant is added, the compound, which is more acidic, ionizes to a greater extent and the spectra of the mixture resemble combinations of the anion of the more acidic compound and neutral of the less acidic compound. If the  $\Delta pK_a$  is below 0.5 units both compounds ionize to similar degree, and the order of acidity is not distinguishable from the spectra. In case of  $\Delta pK_a$  values above 2.5 units one compound is almost fully ionized before the other starts to ionize and the large difference in acidity can be easily detected from the spectra of the mixture. This means that if the protonation-deprotonation process of both compounds is monitored, possible errors and artifacts can be avoided based on the qualitative evaluation of the spectra.

To further support the results it is instructive to look at the  $pK_a$  of picric acid, which has been measured to be 11.0 in MeCN<sup>59</sup> and is the anchor point of the acidity scale. The  $pK_a$  of picric acid in DMSO is estimated to be around 0 by Kolthoff *et al.*<sup>60</sup>, which is reasonable based on the correlations between MeCN and DMSO mentioned before. Now if one considers an acid from group **B**, determined to be 4–5 units more acidic than picric acid in MeCN, it is irrational to assume, that the order of acidity changes so drastically, that they become 2–3 units less acidic.

In a future section of this thesis the influence of water content on the relative acidities in MeCN is discussed. Although little influence is observed in the case of strong acids like the organocatalysts here, it is established that water hinders considerably the protonation of the acid anions as it acts as a competing base and it is very difficult, if not impossible, to achieve the neutral forms of studied acids. These circumstances were experienced at water level around 1%, in the case Christ *et al.* the water content rose to 2% in their experiments and it is possible that the measured  $\Delta pK_a$  values are influenced at that level of water content.

Recently Yang *et al.* studied Brønsted acid organocatalysts of the same families computationally in DMSO.<sup>61</sup> Alongside computations in DMSO they also report calculated  $pK_a$  values of some compounds on Figure 2 in MeCN solution. The comparison of the experimental and computed values is given in Table 2.

**Table 2.** Comparison of computational  $pK_a$  values in MeCN and DMSO with experimental values in MeCN.

| Compound  | Calculated $pK_a$<br>(DMSO) | Calculated $pK_a$<br>(MeCN) | Experimental $pK_a$<br>(MeCN) |
|-----------|-----------------------------|-----------------------------|-------------------------------|
| <b>1</b>  | 3.33                        | 12.86                       | 12.7                          |
| <b>2</b>  | 3.24                        | 12.81                       | 12.5                          |
| <b>6</b>  | -3.36                       | 6.04                        | 6.4                           |
| <b>7</b>  | -2.22                       | 7.13                        | 6.7                           |
| <b>10</b> | -3.08                       | 6.31                        | 6.4                           |
| <b>13</b> | -3.67                       | 5.54                        | 5.2                           |

The calculated results are from Table 1 in ref 61, the computational values are calculated by SMD/M06-2x/6-311++G(2df,2p)/B3LYP/6-31+G(d) for both solvents.

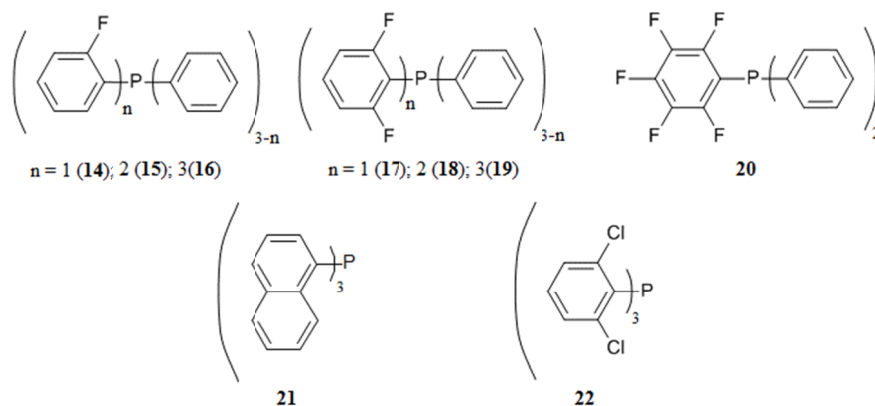
The computations predict the MeCN  $pK_a$  values with mean unsigned error of 0.3 units.<sup>61</sup> If the same computational method is used for DMSO, negative  $pK_a$  values are predicted for acids in groups **A** and **B**. The computational results agree therefore very well with the reasoning presented above, that the  $pK_a$  values in DMSO for acids in groups **B** and **C** should be negative and due to the high basicity of DMSO cannot be measured in that solvent.

### 3.2. $pK_a$ measurements of triarylphosphane catalysts

Triarylphosphanes are strong Lewis bases, that together with suitable Lewis acids, like electron deficient boranes, such as  $B(C_6F_5)_3$ , can form frustrated Lewis pairs (FLPs), if sufficient steric hindrance is involved. FLPs are used to activate molecular hydrogen in hydrogenation reactions of unsaturated organic molecules by heterolytically cleaving it.<sup>62</sup> The role of the Lewis acid is to accept the hydride and the role of the Lewis base is to capture the resulting proton,

which will be left over from the heterolytic cleavage of H<sub>2</sub>. Besides the required strong Lewis acidity of the involved Lewis acid the nucleophilicity of the Lewis base plays a crucial role in the FLP-concept for the H<sub>2</sub>-activation. The electron pair donor ability of phosphanes has been experimentally and theoretically determined by their carbocation affinity by Mayr<sup>63</sup> and Zipse.<sup>64</sup> Their results indicate a linear dependence between nucleophilicity of phosphanes and the pK<sub>a</sub> values of their conjugate acids. Accordingly, pK<sub>a</sub> value is a suitable and straight forward accessible parameter for characterization of Lewis bases in the context of FLP-mediated H<sub>2</sub>-activation. The phosphane influences the catalytic activity of FLP not only by the basicity of the phosphane, which determines the activation of H<sub>2</sub>, but also by the acidity of the corresponding phosphanes conjugated acid. The acidity is important in terms of protonating the unsaturated organic molecule, which is hydrogenated, meaning that the overall catalytic activity is a delicate balance between sufficient H<sub>2</sub> activation and capability of substrate protonation.

Altogether 10 arylphosphanes were studied, among them 8 ortho-substituted triphenylphosphanes (See Figure 7), in addition tri-1-naphthylphosphane and tris(2,6-dichlorophenyl)phosphane were studied.



**Figure 7.** The studied triarylphosphanes.

The pK<sub>a</sub> of triphenylphosphane has been measured to be 7.64 in MeCN.<sup>45</sup> The addition of each fluorine atom to the phenyl substituents is expected to decrease the basicity (and therefore the pK<sub>a</sub>) of the corresponding phosphane. Haav *et al.*<sup>45</sup> have extended the MeCN basicity scale to as low as pK<sub>a</sub> 1.3, which is very close to the experimental limit of MeCN. Initial experiments performed in this work revealed that the increasing number of halogen atoms lowers the pK<sub>a</sub> of the phosphane into the realm, where due to the solvent limit of MeCN the pK<sub>a</sub> of the least basic compounds cannot be determined in MeCN. In addition tri-1-naphthylphosphane did not dissolve in MeCN in sufficient concentration to



reliably carry out the measurements. These problems lead to the implementation of DCE as the second solvent for studies of these very weak bases. As already mentioned in previous sections, DCE has been successfully used for the measurements of very strong acids.<sup>6</sup> Although no basicity data existed for DCE, the results for strong acids assured that weak bases could also be studied in DCE. As there are no previous basicity data, a basicity scale had to be constructed from scratch (Figure 8). The span of the basicity of the studied phosphanes is determined by the basicity of tri-1-naphthylphosphane and compound **19**, which could not be measured in MeCN. These compounds are in the opposite ends of diversity of the basicity of the studied compounds.

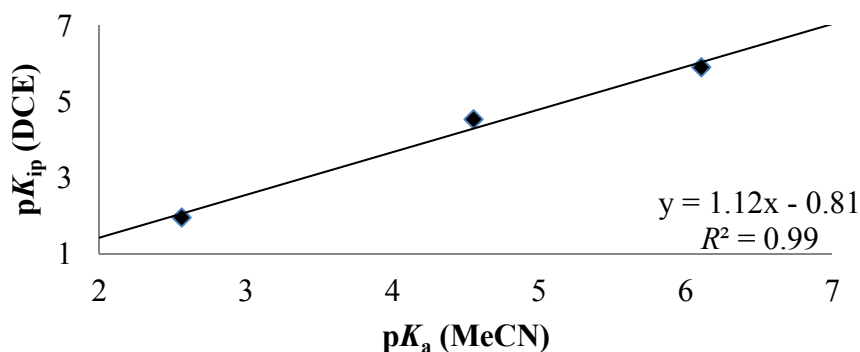
In order for the results to be comparable, the obtained  $pK_a$  data in DCE must be correlated with those obtained in MeCN. This brings the need for anchoring the  $pK_a$  values of the compounds in DCE, so that a correlation could be constructed. No absolute  $pK_a$  values have been assigned to any acids in DCE<sup>6</sup> due to the almost non-existent spontaneous ionization of acids in DCE and high influence of impurities, when the activity of proton is determined. For the same reason no absolute  $pK_a$  values are available in DCE for bases. The assigned  $pK_{ip}$  values on Figure 8 refer to the difference from compound **19** which is taken as reference with arbitrarily assigned  $pK_{ip}$  value 0.

| Compound  | $pK_a$<br>(MeCN) | $pK_{ip}$<br>(DCE) |      |      |      |
|---|------------------|--------------------|------|------|------|
| P(naph) <sub>3</sub>  | 6.8              | 6.86               |      |      |      |
| P(2-F-C <sub>6</sub> H <sub>4</sub> )Ph <sub>2</sub>              | 6.11             | 5.91               | 0.91 | 1.02 |      |
| 2,6-(OMe) <sub>2</sub> -Pyridine                                  | 7.64             | 5.88               | 0.03 | 2.01 | 2.33 |
| 4-Br-Aniline  | 9.43             | 4.83               | 0.96 | 1.38 |      |
| P(2-F-C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> Ph             | 4.55             | 4.55               | 0.22 |      |      |
| 4-CF <sub>3</sub> -Aniline  | 8.03             | 3.47               | 1.06 | 1.90 |      |
| 4-F-3-NO <sub>2</sub> -Aniline                                    | 7.67             | 2.66               | 0.82 | 1.50 |      |
| P(C <sub>6</sub> F <sub>5</sub> )Ph <sub>2</sub>                  | 2.56             | 1.96               | 0.72 |      |      |
| 2-NO <sub>2</sub> -Aniline  | 4.80             | 0.49               | 1.39 | 1.98 |      |
| P(2,6-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ) <sub>3</sub> | 0.7              | 0                  | 0.41 | 2.62 |      |
| NPh <sub>3</sub>  | 1.3              | -0.61              | 0.56 |      |      |

**Figure 8.** Constructed basicity scale in DCE together with the assigned  $pK_{ip}$  values.

For the prediction of the  $pK_a$  values of **19** and **21** in MeCN, a correlation (Figure 9) was constructed based on the measured  $pK_a$  values in MeCN and assigned  $pK_{ip}$  values in DCE for the triphenylphosphanes. Using only triphenylphosphanes enables forming a compound series with very similar properties. This is necessary to ensure that the prediction is as accurate as possible, because the differences in solvation effects between DCE and MeCN cancel out, when very similar compounds are used. Although extrapolation has to be used for both **19** and **21**, the  $pK_a$  values of both are not far from the reference acids.

The differences in solvation on different types of bases (anilines, pyridine) can be seen, when the assigned  $pK_{ip}$  values in DCE are compared to their  $pK_a$  values in MeCN. The comparison shows that the order of basicity of 2,6-(OMe)<sub>2</sub> Pyridine and 4-Br Aniline is switched, the pyridine becoming by 3  $pK_a$  units stronger base compared to the 4-Br Aniline when moving from MeCN to DCE. This is an indication that the basicity of anilines gains much more from solvation of anilinium ions by MeCN molecules. This difference is not unexpected considering the possibility of resonance stabilization of the pyridinium ion (aromaticity remains upon protonation), whereas the anilinium ion lacks the possibility to efficiently delocalize its charge to the aromatic ring upon protonation. Comparison of basicities of triphenylamine and 2-NO<sub>2</sub>-aniline shows that the former is becoming more basic compared to the latter by 2.5 units, when moving from MeCN to DCE. This is probably due to the sheer size difference of the compounds. Triphenylamine is a much larger molecule and can distribute the charge in its cation more efficiently compared to the smaller aniline, which needs the help of the solvent molecules.



**Figure 9.** Correlation between  $pK_a$  values in acetonitrile and  $pK_{ip}$  values in DCE.

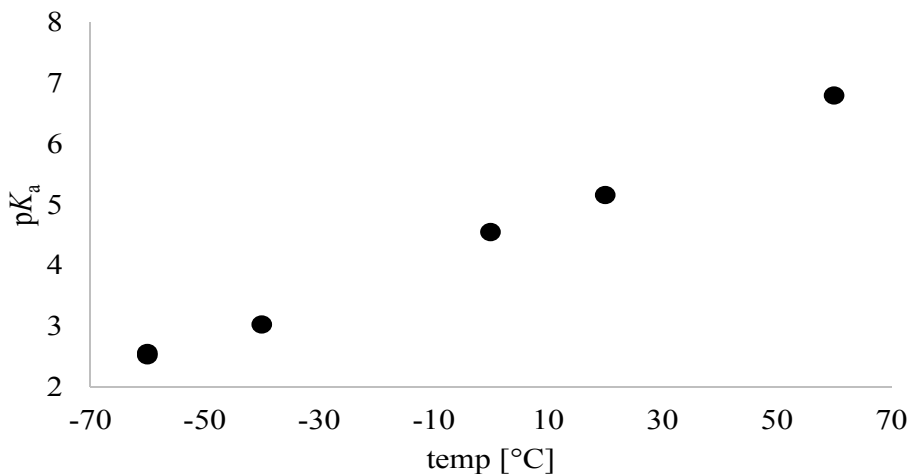
Table 3 presents the experimentally determined  $pK_a$  values of phosphanes in MeCN along with the  $pK_a$  values obtained by correlation analysis from DCE data. If the phenyl substituents are replaced by 2-fluorophenyl substituents each substitution decreases the  $pK_a$  by 1.5-1.6 units in an additive manner: from the  $pK_a$  of triphenylphosphane (7.64)<sup>45</sup> to compounds **14**, **15** and **16** with  $pK_a$  values of 6.11, 4.55 and 3.03, respectively. If the phenyl group is substituted with 2,6-difluorophenyl substituent then the  $pK_a$  decreases by about 2.5 units with the first two substitutions and only by 1.8 with the last one. This reduction can be caused by either saturation effects or by errors originating from the correlation between DCE and MeCN, as the  $pK_a$  value of compound **19** was determined from correlation. As extrapolation had to be used in order to find the  $pK_a$  value of **19**, increased error in the  $pK_a$  value can be expected. The saturation effect can be seen with **20**, where one phenyl group is fully perfluorinated. The  $pK_a$  value of compound **20** with five fluorine substituents has  $pK_a$  value of 2.56, whereas compound **18** achieves practically the same  $pK_a$  with only four fluorine substituents (in two different phenyl groups).

**Table 3.** Studied phosphanes and measured  $pK_a$  values.

| Base  | Assigned $pK_a$ (MeCN) |
|---|------------------------|
| (2-F-C <sub>6</sub> H <sub>4</sub> )(Ph) <sub>2</sub> P <b>14</b>                 | 6.11                   |
| (2-F-C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> (Ph)P <b>15</b>                 | 4.55                   |
| (2-F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> P <b>16</b>                     | 3.03                   |
| (2,6-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> )(Ph) <sub>2</sub> P <b>17</b> | 5.16                   |
| (2,6-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ) <sub>2</sub> (Ph)P <b>18</b> | 2.52                   |
| (2,6-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ) <sub>3</sub> P <b>19</b>     | 0.7 <sup>a</sup>       |
| (C <sub>6</sub> F <sub>5</sub> )(Ph) <sub>2</sub> P <b>20</b>                     | 2.56                   |
| P(naph) <sub>3</sub> <b>21</b>  | 6.8 <sup>a</sup>       |
| (2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ) <sub>3</sub> P <b>22</b>    | 1.72                   |

<sup>a</sup> Estimated from correlation with DCE data

In order to demonstrate the correlation between  $pK_a$  of the phosphane and the catalytic activity, Figure 10 illustrates the dependence between H<sub>2</sub> activation temperature and the measured  $pK_a$ . Details concerning the temperature measurement experiment as well as kinetic measurements of subsequent activation of unsaturated organic molecules can be found in in Publication II.



**Figure 10.** Correlation between the basicity ( $pK_a$  in MeCN) of the catalysts and the corresponding activation temperature of  $H_2$ .

### 3.3. The effect of water on acidity and basicity in acetonitrile

The acid-base properties of a solvent combined with its autoprotolysis have been shown to strongly influence the  $pK_a$  values of compounds in the solvent. The characteristics of the solvent are often not the only factor that has to be considered when accurate and reliable results are desired. The solvents are never absolutely pure, there are always some impurities: the manufacturing processes as well as laboratory purification procedures do not give ideally pure solvents. The most frequent impurity in solvents is water. As the moisture is all around us, gradual contamination takes place all the time. Water interacts strongly with polar solvents, so that removing all of it is practically an impossible task. Its ability to strongly interact with polar species makes water a dangerous impurity, when  $pK_a$  measurements are concerned, especially in less polar environments. As a broad generalization one can say that an acid is as strong as stable is its anion (and unstable is its neutral) and a base as strong as stable is its cation (and unstable is its neutral). When anions or cations with rather localized charge, not to mention the proton, are preferentially solvated by water molecules in non-aqueous solvents, the measured  $pK_a$  does not correspond to the value in pure solvent.

As already mentioned in previous sections some idea of the influence of impurity levels of water can be extracted from chemical intuition, but quantitative data are not found in the literature. To fill that void  $\Delta pK_a$  values of 10 pairs of acids and 13 pairs of bases were measured systematically in MeCN at four levels of water content: approximately 10, 100, 1000 and 10000 ppm. MeCN was chosen as the solvent because of its wide use in physical and

analytical chemistry as well as the previous expertise associated with MeCN in our research group. In addition to the fundamental knowledge about the influence of water, the results can be used to validate the published acidity and basicity scales, that were constructed in MeCN with water content around 40 ppm<sup>15,41</sup>.

The acid and base pairs were chosen so that the nature of the acidity/basicity center, strength of the acid or base and the amount of charge delocalization in anions/cations were different. The results are presented in Table 4. It must be noted, that no change in  $\Delta pK_a$  value can be the result of either (1) the acidity/basicity of neither of the compounds changed or (2) the acidity/basicity of both compounds changed to the same extent. Thus, the influence of water is evaluated only in relative terms – we cannot say anything about the changes in absolute  $pK_a$  values as the change of  $H^+$  activity is not known. It is very likely that the activity of proton changes very much as the water concentration is increased, because proton is definitely the most solvated species in the solution and, if possible, is preferentially or even selectively solvated by water molecules. Measuring the  $\Delta pK_a$  between two compounds avoids the need to know the changes in  $H^+$  activity, but care must be taken choosing the reference compound. CH acids were chosen as reference acids, because they should be least affected by the changes in water concentration. For the same reason phosphazenes, if possible, were chosen as references in base pairs. If feasible, the same reference compound was used for measurements in the same  $pK_a$  region. These considerations increase the comparability of the measured changes in  $\Delta pK_a$  values.

The pairs of acids **a**, **b**, **c**, **f**, **g** and **i** have also been measured in reference 15. The difference between the results in this work and results from reference 15 (with similar water content) are 0.01, 0.01, -0.01, 0.00, 0.05 and 0.20  $pK_a$  units, respectively. Base pairs **k**, **l**, **m**, **s**, **t**, **w** and **x** were also measured in reference 41, the differences being 0.04, 0.02, 0.08, 0.02, 0.00, 0.06 and 0.07, respectively. The quite large difference for pair **i** can be the result of more difficult experiment, due to the absence of spectral properties of acetic acid<sup>15</sup>. The absence of spectral properties is also the reason for increased disparity in base pairs **w** and **x**. In broad terms one can conclude that the experimental setup was kept the same in this work and references 15 and 41.

**Table 4.** Change of relative acidities and basicities upon change of water content.

| Compound pairs <sup>a</sup>   | $C_{H2O}$<br>(ppm) <sup>b</sup> | $\Delta pK_{a\_exp}$ <sup>c</sup> | $s(\Delta pK_{a})^d$ | $\Delta\Delta pK_a^e$ | $\Delta pK_{a\_corr}$ <sup>f</sup> | $G_{solv}$ (kcal mol <sup>-1</sup> ) <sup>g</sup> |                               |                                |                               |                                |                               | $\Delta G_{solv\_corr}$<br>(kcal mol <sup>-1</sup> ) <sup>h</sup> |                               |
|---|---------------------------------|-----------------------------------|----------------------|-----------------------|------------------------------------|---|-------------------------------|--------------------------------|-------------------------------|--------------------------------|-------------------------------|---|-------------------------------|
|   |                                 |                                   |                      |                       |                                    | $G_{solv}^{neutral/cation}(A)$                    | $G_{solv}^{anion/neutral}(A)$ | $G_{solv}^{neutral/cation}(B)$ | $G_{solv}^{anion/neutral}(B)$ | $G_{solv}^{neutral/cation}(A)$ | $G_{solv}^{anion/neutral}(A)$ | $G_{solv}^{neutral/cation}(B)$                                    | $G_{solv}^{anion/neutral}(B)$ |
| Picric acid, <b>A1</b> (11.00) and<br>4-CF <sub>3</sub> -C <sub>6</sub> F <sub>4</sub> CH(CN) <sub>2</sub> , <b>A2</b><br>(10.19)   | 8                               | -0.83                             | 0.01                 | -                     | -0.83                              | -10.33  | -34.47                        | -7.76                          | -31.72                        | -                              | -                             | -   | -                             |
|   | 77                              | -0.83                             | 0.02                 | 0                     | -0.83                              | -10.33  | -34.47                        | -7.76                          | -31.72                        | -                              | -                             | 0.00  | 0.00                          |
|   | 1020                            | -0.83                             | 0.02                 | 0                     | -0.83                              | -10.33  | -34.47                        | -7.76                          | -31.72                        | -                              | -                             | 0.00  | 0.00                          |
|   | 11937                           | -0.82                             | 0.01                 | 0.01                  | -0.83                              | -10.31  | -34.48                        | -7.74                          | -31.73                        | -                              | -                             | -0.03   | -0.03                         |
| 2,4-(NO <sub>2</sub> ) <sub>2</sub> -Phenol, <b>A3</b><br>(16.66) and (4-CF <sub>3</sub> ) <sup>+</sup><br>C <sub>6</sub> F <sub>4</sub> CH(CN)COOEt, <b>A4</b><br>(16.08)  | 4                               | -0.61                             | 0.01                 | -                     | -0.61                              | -7.49   | -36.89                        | -7.59                          | -36.14                        | -                              | -                             | -   | -                             |
|   | 71                              | -0.62                             | 0.01                 | -0.01                 | -0.61                              | -7.49   | -36.89                        | -7.59                          | -36.14                        | -                              | -                             | 0.00  | 0.00                          |
|   | 997                             | -0.60                             | 0.01                 | 0.01                  | -0.61                              | -7.49   | -36.90                        | -7.59                          | -36.14                        | -                              | -                             | -0.01   | -0.01                         |
|   | 9076                            | -0.52                             | 0.01                 | 0.09                  | -0.57                              | -7.48   | -36.95                        | -7.58                          | -36.17                        | -                              | -                             | -0.08   | -0.05                         |
| 2-NO <sub>2</sub> -Phenol, <b>A5</b> (22.85)<br>and<br>(4-Me-C <sub>6</sub> F <sub>4</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN,<br><b>A6</b> (21.94)  | 6                               | -0.89                             | 0.01                 | -                     | -0.89                              | -4.27   | -47.69                        | -8.31                          | -35.46                        | -                              | -                             | -   | -                             |
|   | 87                              | -0.90                             | 0.01                 | -0.01                 | -0.89                              | -4.27   | -47.69                        | -8.31                          | -35.46                        | -                              | -                             | 0.00  | 0.00                          |
|   | 1156                            | -0.79                             | 0.01                 | 0.10                  | -0.84                              | -4.27   | -47.72                        | -8.31                          | -35.46                        | -                              | -                             | -0.04   | -0.01                         |
|   | 9516                            | -0.33                             | 0.01                 | 0.56                  | -0.57                              | -4.26   | -47.96                        | -8.29                          | -35.49                        | -                              | -                             | -0.29   | -0.05                         |
| 9-COOMe-Fluorene, <b>A7</b><br>(23.53) and<br>(4-Me-C <sub>6</sub> F <sub>4</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN,<br><b>A6</b> (21.94)   | 6                               | -1.55                             | 0.03                 | -                     | -1.55                              | -9.07   | -45.31                        | -8.31                          | -35.46                        | -                              | -                             | -   | -                             |
|   | 82                              | -1.57                             | 0.02                 | -0.02                 | -1.55                              | -9.07   | -45.31                        | -8.31                          | -35.46                        | -                              | -                             | 0.00  | 0.00                          |
|   | 906                             | -1.55                             | 0.02                 | 0                     | -1.55                              | -9.07   | -45.31                        | -8.31                          | -35.46                        | -                              | -                             | 0.00  | 0.00                          |
|   | 9676                            | -1.48                             | 0.05                 | 0.07                  | -1.55                              | -9.05   | -45.33                        | -8.29                          | -35.49                        | -                              | -                             | -0.04   | -0.05                         |
| 2,4,6-(SO <sub>2</sub> OCH <sub>2</sub> CF <sub>3</sub> ) <sub>3</sub> -<br>Aniline, <b>A8</b> (22.54) <sup>40</sup> and<br>(4-Me-C <sub>6</sub> F <sub>4</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN,<br><b>A6</b> (21.94) | 19                              | -0.56                             | 0.02                 | -                     | -0.56                              | -16.50  | -37.08                        | -8.31                          | -35.46                        | -                              | -                             | -   | -                             |
|   | 54                              | -0.56                             | 0.02                 | 0                     | -0.56                              | -16.50  | -37.08                        | -8.31                          | -35.46                        | -                              | -                             | 0.00  | 0.00                          |
|   | 1060                            | -0.55                             | 0.03                 | 0.01                  | -0.56                              | -16.49  | -37.07                        | -8.31                          | -35.46                        | -                              | -                             | 0.00  | -0.01                         |
|   | 11394                           | -0.61                             | 0.03                 | -0.05                 | -0.58                              | -16.47  | -37.05                        | -8.29                          | -35.49                        | -                              | -                             | 0.00  | -0.06                         |
| (4-NC <sub>5</sub> F <sub>4</sub> )(C <sub>6</sub> H <sub>5</sub> )NH, <b>A9</b><br>(26.34) and<br>(C <sub>6</sub> H <sub>5</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN, <b>A10</b><br>(26.14)                              | 8                               | -0.20                             | 0.01                 | -                     | -0.20                              | -7.91   | -36.48                        | -8.18                          | -37.46                        | -                              | -                             | -   | -                             |
|   | 61                              | -0.20                             | 0.01                 | 0                     | -0.20                              | -7.91   | -36.49                        | -8.18                          | -37.46                        | -                              | -                             | 0.00  | 0.00                          |
|   | 1031                            | -0.19                             | 0.01                 | 0.01                  | -0.19                              | -7.91   | -36.50                        | -8.18                          | -37.47                        | -                              | -                             | -0.01   | -0.01                         |
|   | 12167                           | 0.00                              | 0.02                 | 0.20                  | -0.13                              | -7.89   | -36.59                        | -8.16                          | -37.52                        | -                              | -                             | -0.12   | -0.07                         |
| (4-Me-C <sub>6</sub> F <sub>4</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN,<br><b>A6</b> (21.94) and<br>Benzoic acid, <b>A11</b> (21.51)   | 6                               | -0.37                             | 0.05                 | -                     | -0.37                              | -8.31   | -35.46                        | -6.52                          | -60.79                        | -                              | -                             | -   | -                             |
|   | 57                              | -0.33                             | 0.1                  | 0.04                  | -0.40                              | -8.31   | -35.46                        | -6.52                          | -60.80                        | -                              | -                             | 0.00  | -0.01                         |
|   | 1224                            | -0.56                             | 0.13                 | -0.19                 | -0.79                              | -8.31   | -35.46                        | -6.53                          | -61.07                        | -                              | -                             | -0.01   | -0.28                         |
|   | 10791                           | -1.4                              | 0.1                  | -1.03                 | -1.95                              | -8.29   | -35.49                        | -6.56                          | -62.21                        | -                              | -                             | -0.06   | -1.39                         |

| Compound pairs <sup>a</sup>   | C <sub>1H2O</sub><br>(ppm) <sup>b</sup> | ΔpK <sub>a,exp</sub> <sup>c</sup> | s(ΔpK <sub>a</sub> ) <sup>d</sup> | ΔΔpK <sub>a</sub> <sup>e</sup> | ΔpK <sub>a,corr</sub> <sup>f</sup> | G <sub>solv</sub> (kcal mol <sup>-1</sup> ) <sup>g</sup> |                                    |                                     |                                    | ΔG <sub>solv,corr</sub><br>(kcal mol <sup>-1</sup> ) <sup>f</sup> |       |
|---|---|-----------------------------------|-----------------------------------|--------------------------------|------------------------------------|--|------------------------------------|-------------------------------------|------------------------------------|---|-------|
|   |   |                                   |                                   |                                |                                    | G <sub>solv</sub> neutral/cation(A)                      | G <sub>solv</sub> anion/neutral(A) | G <sub>solv</sub> neutral/cation(B) | G <sub>solv</sub> anion/neutral(B) | A   | B     |
| HCl, <b>A12</b> (10.30) <sup>6</sup> and<br>2,3,4,5,6-<br>(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> CH(CN) <sub>2</sub> , <b>A13</b><br>(8.86) <sup>39</sup>       | 7                                       | -1.10                             | 0.02                              | -                              | -1.10                              | -0.50  | -68.56                             | -6.88                               | -31.90                             | -   | -     |
|   | 49                                      | -1.16                             | 0.05                              | -0.06                          | -1.10                              | -0.50  | -68.56                             | -6.88                               | -31.90                             | 0.00  | 0.00  |
|   | 992                                     | -0.80                             | 0.11                              | 0.30                           | -1.06                              | -0.51  | -68.60                             | -6.87                               | -31.91                             | -0.04   | 0.00  |
| <b>h</b><br>~10000  |   |                                   |                                   |                                |                                    |  |                                    |                                     |                                    |   |       |
| 9-COOMe-Fluorene, <b>A7</b><br>(23.53) and<br>Acetic acid, <b>A14</b> , (23.51)   | 10                                      | -0.21                             | 0.08                              | 0.00                           | -0.21                              | -9.07  | -45.31                             | -2.91                               | -60.84                             | -   | -     |
|   | 39                                      | -0.17                             | 0.1                               | 0.04                           | -0.24                              | -9.07  | -45.31                             | -2.91                               | -60.85                             | 0.00  | -0.01 |
|   | 1379                                    | -0.63                             | 0.03                              | -0.41                          | -0.94                              | -9.07  | -45.31                             | -2.92                               | -61.33                             | -0.01   | -0.48 |
| <b>i</b><br>~10000  |   | -1.74 <sup>4</sup>                | -                                 | -1.53                          | -2.46                              | -9.05  | -45.33                             | -2.95                               | -62.82                             | -0.04   | -1.94 |
| (4-Me-C <sub>6</sub> F <sub>3</sub> )(C <sub>6</sub> F <sub>3</sub> )CHCN,<br><b>A6</b> (21.94) and Acetic acid,<br><b>A14</b> , (23.51), <b>j</b>                      | 10584                                   | -0.26                             | 0.02                              | -                              | -                                  |  |                                    |                                     |                                    |   |       |
| Aniline, <b>B1</b> (10.62) and<br>2-methyl-8-quinolinamine,<br><b>B2</b> (11.54)  | 5                                       | 0.99                              | 0.03                              | -                              | 0.92                               | -54.71   | -3.92                              | -34.82                              | -6.62                              | -   | -     |
|   | 34                                      | 0.92                              | 0.02                              | 0.00                           | 0.92                               | -54.71   | -3.92                              | -34.82                              | -6.62                              | 0.00  | 0.00  |
|   | 936                                     | 0.91                              | 0.00                              | -0.01                          | 0.92                               | -54.73   | -3.92                              | -34.83                              | -6.61                              | 0.02  | 0.01  |
| <b>k</b><br>9247  |   | 0.82                              | 0.03                              | -0.10                          | 0.93                               | -54.85   | -3.92                              | -34.87                              | -6.61                              | 0.14  | 0.05  |
|   | 7                                       | 0.05                              | 0                                 | -                              | 0.05                               | -35.21   | -2.95                              | -34.82                              | -6.62                              | -   | -     |
|   | 34                                      | 0.05                              | 0                                 | 0.00                           | 0.05                               | -35.21   | -2.95                              | -34.82                              | -6.62                              | 0.00  | 0.00  |
| <b>l</b><br>N,N-dimethylamine, <b>B3</b><br>(11.43) and 2-methyl-8-<br>quinolinamine, <b>B2</b> (11.54)   | 943                                     | 0.06                              | 0.01                              | 0.01                           | 0.06                               | -35.21   | -2.95                              | -34.83                              | -6.61                              | 0.01  | 0.01  |
| Pyridine, <b>B4</b> (12.53) and<br>2-methyl-8-quinolinamine,<br><b>B2</b> (11.54)   | 9865                                    | 0.06                              | 0.01                              | 0.01                           | 0.06                               | -35.25   | -2.94                              | -34.87                              | -6.61                              | 0.05  | 0.06  |
|   | 5                                       | -0.93                             | 0.03                              | -                              | -0.93                              | -38.22   | -2.14                              | -34.82                              | -6.62                              | -   | -     |
|   | 34                                      | -0.91                             | 0.05                              | 0.02                           | -0.93                              | -38.22   | -2.14                              | -34.82                              | -6.62                              | 0.00  | 0.00  |
| <b>m</b><br>n-Propylamine, <b>B5</b><br>(18.43) <sup>42</sup> and<br>2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -P <sub>1</sub> (pyrr), <b>B6</b><br>(18.56)    | 1107                                    | -0.93                             | 0.02                              | 0.00                           | -0.93                              | -38.22   | -2.15                              | -34.83                              | -6.61                              | 0.00  | 0.01  |
|   | 9856                                    | -0.88                             | 0.01                              | 0.05                           | -0.93                              | -38.26   | -2.18                              | -34.87                              | -6.61                              | 0.00  | 0.06  |
|   | 5                                       | 0.18                              | 0.01                              | -                              | 0.23                               | -51.56   | 0.43                               | -25.78                              | -12.25                             | -   | -     |
| <b>n</b><br>Tr-n-propylamine, <b>B7</b><br>(18.25) <sup>42</sup> and<br>2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -P <sub>1</sub> (pyrr), <b>B6</b><br>(18.56) | 35                                      | 0.18                              | 0.01                              | 0.00                           | 0.23                               | -51.56   | 0.42                               | -25.77                              | -12.25                             | 0.00  | 0.00  |
|   | 1041                                    | 0.22                              | 0.01                              | 0.04                           | 0.20                               | -51.57   | 0.37                               | -25.77                              | -12.25                             | -0.04   | 0.00  |
|   | 9967                                    | 0.10                              | 0.01                              | -0.08                          | 0.09                               | -51.68   | 0.13                               | -25.76                              | -12.23                             | -0.18   | 0.01  |
| <b>o</b><br>Tr-n-propylamine, <b>B7</b><br>(18.25) <sup>42</sup> and<br>2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -P <sub>1</sub> (pyrr), <b>B6</b><br>(18.56) | 5                                       | 0.31                              | 0.01                              | -                              | 0.38                               | -27.71   | -0.48                              | -25.78                              | -12.25                             | -   | -     |
|   | 33                                      | 0.36                              | 0.01                              | -0.05                          | 0.38                               | -27.71   | -0.48                              | -25.77                              | -12.25                             | 0.00  | 0.00  |
|   | 1041                                    | 0.32                              | 0.01                              | -0.01                          | 0.38                               | -27.71   | -0.48                              | -25.77                              | -12.25                             | 0.00  | 0.00  |
| 9967  | 0.29                                    | 0.01                              | 0.02                              | 0.36                           | -27.72                             | -0.50  | -25.76                             | -12.23                              | -0.01                              | 0.01  |       |

| Compound pairs <sup>a</sup>  | C <sub>H2O</sub><br>(ppm) <sup>b</sup> | ΔpK <sub>a,exp</sub> <sup>c</sup> | s(ΔpK <sub>a</sub> ) <sup>d</sup> | ΔΔpK <sub>a</sub> <sup>e</sup> | ΔpK <sub>a,corr</sub> <sup>f</sup> | G <sub>solv</sub> (kcal mol <sup>-1</sup> ) <sup>g</sup> |                                    |                                     |                                    | ΔG <sub>solv,corr</sub><br>(kcal mol <sup>-1</sup> ) <sup>h</sup> |       |
|--|--|-----------------------------------|-----------------------------------|--------------------------------|------------------------------------|--|------------------------------------|-------------------------------------|------------------------------------|---|-------|
|  |  |                                   |                                   |                                |                                    | G <sub>solv neutral/cation(A)</sub>                      | G <sub>solv anion/neutral(A)</sub> | G <sub>solv neutral/cation(B)</sub> | G <sub>solv anion/neutral(B)</sub> | A   | B     |
| Ph <sub>3</sub> P, <b>B8</b> (7.61) and 4-thiocyanato-N,N-dimethylamine, <b>B9</b> (8.77) <sup>45</sup>  | 4                                      | 1.20                              | 0.01                              | –                              | 1.20                               | -28.80   | -10.17                             | -49.67                              | -8.05                              | –   | –     |
|  | 38                                     | 1.20                              | 0.01                              | -0.01                          | 1.20                               | -28.80   | -10.17                             | -49.67                              | -8.05                              | 0.00  | 0.00  |
|  | 1042                                   | 1.22                              | 0.00                              | 0.01                           | 1.20                               | -28.80   | -10.16                             | -49.67                              | -8.05                              | 0.00  | 0.01  |
|  | 9439                                   | 1.24                              | 0.01                              | 0.03                           | 1.18                               | -28.79   | -10.14                             | -49.71                              | -8.04                              | 0.02  | 0.05  |
| MePh <sub>2</sub> P, <b>B10</b> (9.96) and 4-thiocyanato-N,N-dimethylamine, <b>B9</b> (8.77) <sup>45</sup>   | 4                                      | -1.19                             | 0.01                              | –                              | -1.13                              | -30.05   | -6.82                              | -49.67                              | -8.05                              | –   | –     |
|  | 38                                     | -1.22                             | 0.01                              | -0.03                          | -1.13                              | -30.05   | -6.82                              | -49.67                              | -8.05                              | 0.00  | 0.00  |
|  | 1042                                   | -1.21                             | 0.01                              | -0.02                          | -1.14                              | -30.05   | -6.82                              | -49.67                              | -8.05                              | 0.00  | 0.01  |
|  | 9713                                   | -1.03                             | 0.04                              | 0.16                           | -1.16                              | -30.05   | -6.80                              | -49.71                              | -8.04                              | 0.02  | 0.05  |
| 2-Cl-C <sub>6</sub> H <sub>4</sub> -P <sub>1</sub> (pyrr), <b>B11</b> (20.17) and 4-Br-C <sub>6</sub> H <sub>4</sub> -P <sub>1</sub> (pyrr), <b>B12</b> (21.19) <sup>46</sup>  | 6                                      | 1.02                              | 0.02                              | –                              | 1.02                               | -26.18   | -14.85                             | -30.82                              | -14.85                             | –   | –     |
|  | 37                                     | 1.04                              | 0.03                              | 0.02                           | 1.02                               | -26.18   | -14.85                             | -30.82                              | -14.85                             | 0.00  | 0.00  |
|  | 1017                                   | 1.03                              | 0.01                              | 0.01                           | 1.02                               | -26.18   | -14.85                             | -30.82                              | -14.86                             | 0.00  | -0.01 |
|  | 9868                                   | 0.99                              | 0.02                              | -0.04                          | 1.05                               | -26.16   | -14.85                             | -30.81                              | -14.90                             | -0.02   | -0.06 |
| Ph <sub>3</sub> P(pyrr), <b>B13</b> (22.34) and 4-Br-C <sub>6</sub> H <sub>4</sub> -P <sub>1</sub> (pyrr), <b>B12</b> , (21.19)  | 6                                      | -1.11                             | 0.03                              | –                              | -1.11                              | -26.63   | -13.11                             | -30.82                              | -14.85                             | –   | –     |
|  | 37                                     | -1.07                             | 0.05                              | 0.04                           | -1.11                              | -26.63   | -13.11                             | -30.82                              | -14.85                             | 0.00  | 0.00  |
|  | 1017                                   | -1.08                             | 0.02                              | 0.03                           | -1.11                              | -26.63   | -13.11                             | -30.82                              | -14.86                             | -0.01   | -0.01 |
|  | 9868                                   | -1.07                             | 0.04                              | 0.04                           | -1.10                              | -26.62   | -13.15                             | -30.81                              | -14.90                             | -0.05   | -0.06 |
| Ph <sub>3</sub> P(dma), <b>B14</b> (21.25) and 4-Br-C <sub>6</sub> H <sub>4</sub> -P <sub>1</sub> (pyrr), <b>B12</b> , (21.19)   | 6                                      | -0.06                             | 0.01                              | –                              | -0.06                              | -25.23   | -8.28                              | -30.82                              | -14.85                             | –   | –     |
|  | 37                                     | -0.05                             | 0.01                              | 0.00                           | -0.06                              | -25.23   | -8.28                              | -30.82                              | -14.85                             | 0.00  | 0.00  |
|  | 1017                                   | -0.06                             | 0.00                              | 0.00                           | -0.05                              | -25.23   | -8.28                              | -30.82                              | -14.86                             | 0.00  | -0.01 |
|  | 9868                                   | -0.07                             | 0.00                              | -0.01                          | -0.01                              | -25.22   | -8.27                              | -30.81                              | -14.90                             | 0.00  | -0.06 |
| Ph <sub>3</sub> P(dma), <b>B14</b> (21.25) and PhTMG <b>B15</b> , (20.84)  | 5                                      | -0.42                             | 0.01                              | –                              | -0.42                              | -25.23   | -8.28                              | -27.76                              | -6.83                              | –   | –     |
|  | 39                                     | -0.41                             | 0.00                              | 0.01                           | -0.42                              | -25.23   | -8.28                              | -27.76                              | -6.83                              | 0.00  | 0.00  |
|  | 1128                                   | -0.41                             | 0.00                              | 0.01                           | -0.41                              | -25.23   | -8.28                              | -27.76                              | -6.83                              | 0.00  | -0.01 |
|  | 10185                                  | -0.40                             | 0.01                              | 0.02                           | -0.38                              | -25.22   | -8.27                              | -27.75                              | -6.87                              | 0.00  | -0.04 |
| HP <sub>1</sub> (dma), <b>B16</b> (25.85) and PhP <sub>2</sub> (dma), <b>B17</b> , (26.46), <b>w</b> <i>t</i> -BuP <sub>1</sub> (dma), <b>B18</b> (26.98) and PhP <sub>2</sub> (dma), <b>B17</b> , (26.46), <b>x</b> | 5                                      | 0.62                              | 0.05                              | –                              | 0.35                               | -23.72   | -4.40                              | -22.84                              | -13.87                             | –   | –     |
|  | 35                                     | 0.55                              | 0.03                              | -0.07                          | 0.35                               | -23.72   | -4.40                              | -22.84                              | -13.87                             | 0.00  | 0.00  |
|  | 5                                      | -0.51                             | 0.03                              | 0.00                           | -0.57                              | -20.47   | -2.30                              | -22.84                              | -13.87                             | –   | –     |
|  | 35                                     | -0.48                             | 0.03                              | 0.03                           | -0.57                              | -20.47   | -2.30                              | -22.84                              | -13.87                             | 0.00  | 0.00  |

<sup>a</sup> members of the acid (Ax) and base (Bx) pairs, literature pK<sub>a</sub> values (from ref 15 in case of acids and from ref 41 in case of bases unless specified otherwise) in brackets following compound name and number. <sup>b</sup> the approximate uncertainty of water content determination is ca ± 5 ppm in the middle range and ca ± 2 ppm in the low range; <sup>c</sup>ΔpK<sub>a,exp</sub> denotes experimentally determined relative acidity ΔpK<sub>a,exp</sub> = pK<sub>a</sub>(HA<sub>2</sub>) - pK<sub>a</sub>(HA<sub>1</sub>). <sup>d</sup> experimental standard deviation of ΔpK<sub>a</sub> allows evaluating the within-series agreement of ΔpK<sub>a</sub> values. <sup>e</sup> change in pK<sub>a</sub> units compared to the driest solvent for that acid pair. <sup>f</sup> Corrected computational ΔpK<sub>a</sub> values (ΔpK<sub>a,corr</sub> = ΔpK<sub>a,calc</sub> - ΔpK<sub>a,calc</sub><sup>0</sup> + ΔpK<sub>a,exp</sub> - 0 indicates the driest solvent used). <sup>g</sup> calculated Gibbs free energies of solvation with COSMOtherm using the default procedure; <sup>h</sup> ΔG<sub>solv,corr</sub> = (G<sub>solv anion/neutral</sub> - G<sub>solv neutral/cation</sub>) - (G<sub>solv neutral/cation</sub><sup>0</sup> - G<sub>solv neutral/cation</sub><sup>0</sup>), calculated using results from pair j

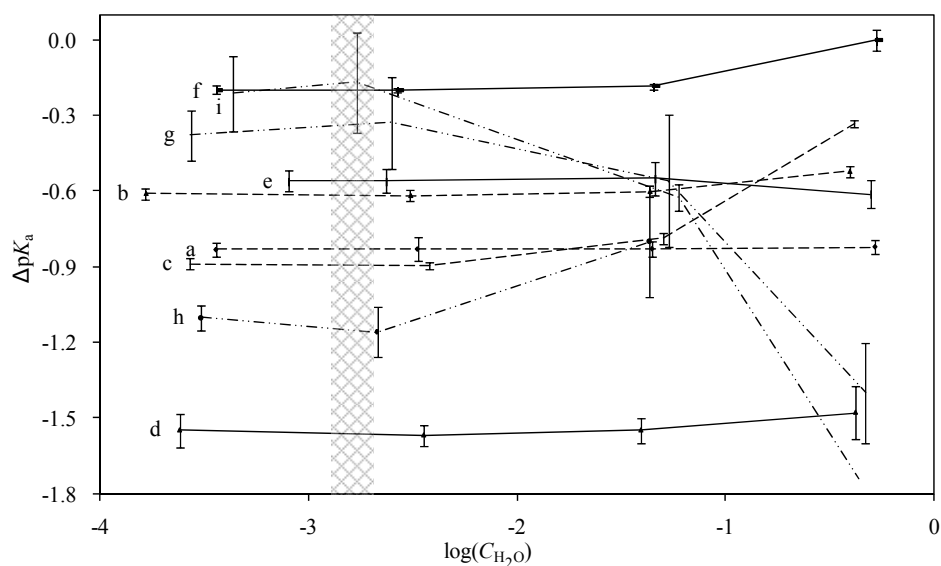


**Table 5.** Charge delocalization in anions and cations expressed by the *WAPS* and *WANS* parameters, respectively

| Acid   | <i>WAPS</i> | Base   | <i>WANS</i> |
|--|-------------|--|-------------|
| Picric acid; <b>A1</b>   | 4.3         | Aniline; <b>B1</b>   | 8.2         |
| 4-CF <sub>3</sub> -C <sub>6</sub> F <sub>4</sub> CH(CN) <sub>2</sub> ; <b>A2</b>           | 2.4         | 2-methyl-8-quinolinamine; <b>B2</b>  | 3.8         |
| 2,4-(NO <sub>2</sub> ) <sub>2</sub> -Phenol; <b>A3</b>                                     | 4.9         | <i>N,N</i> -dimethylaniline <b>B3</b>  | 4.7         |
| (4-CF <sub>3</sub> -C <sub>6</sub> F <sub>4</sub> )CH(CN)COOEt; <b>A4</b>                  | 2.1         | Pyridine; <b>B4</b>  | 7.2         |
| 2-NO <sub>2</sub> -Phenol <b>A5</b>  | 6.2         | <i>n</i> -Propylamine; <b>B5</b>   | 8.9         |
| (4-Me-C <sub>6</sub> F <sub>4</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN; <b>A6</b>       | 1.7         | 2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -P <sub>1</sub> (pyrr); <b>B6</b> | 1.3         |
| 9-COOMe-Fluorene; <b>A7</b>  | 3.1         | Tri- <i>n</i> -propylamine; <b>B7</b>  | 2.6         |
| 2,4,6-(SO <sub>2</sub> OCH <sub>2</sub> CF <sub>3</sub> ) <sub>3</sub> -Aniline; <b>A8</b> | 1.3         | Ph <sub>3</sub> P; <b>B8</b>   | 2.1         |
| (4-NC <sub>3</sub> F <sub>4</sub> )(C <sub>6</sub> H <sub>5</sub> )NH; <b>A9</b>           | 2.8         | 4-SCN- <i>N,N</i> -dimethylaniline <b>B9</b>   | 3.5         |
| (C <sub>6</sub> H <sub>5</sub> )(C <sub>6</sub> F <sub>5</sub> )CHCN; <b>A10</b>           | 2.4         | MePh <sub>2</sub> P; <b>B10</b>  | 2.8         |
| Benzoic acid; <b>A11</b>   | 7.1         | 2-Cl-C <sub>6</sub> H <sub>4</sub> -P <sub>1</sub> (pyrr); <b>B11</b>                | 1.2         |
| HCl; <b>A12</b>  | 35.9        | and 4-Br-C <sub>6</sub> H <sub>4</sub> -P <sub>1</sub> (pyrr); <b>B12</b>            | 1.3         |
| 2,3,4,5,6-(CF <sub>3</sub> ) <sub>5</sub> C <sub>6</sub> CH(CN) <sub>2</sub> ; <b>A13</b>  | 1.5         | Ph-P <sub>1</sub> (pyrr); <b>B13</b>   | 1.3         |
| Acetic acid; <b>A14</b>  | 16.2        | Ph-P <sub>1</sub> (dma); <b>B14</b>  | 1.8         |
|  |             | PhTMG; <b>B15</b>  | 2.5         |
|  |             | HP <sub>1</sub> (dma); <b>B16</b>  | 2.4         |
|  |             | PhP <sub>2</sub> (dma); <b>B17</b>   | 1.1         |
|  |             | <i>t</i> -BuP <sub>1</sub> (dma); <b>B18</b>   | 1.7         |

*WAPS* and *WANS* values are given in ( $e/\text{\AA}^4$ ), where  $e$  is electron charge; for better readability here and in subsequent discussion *WAPS* and *WANS* values are multiplied by  $10^5$ .

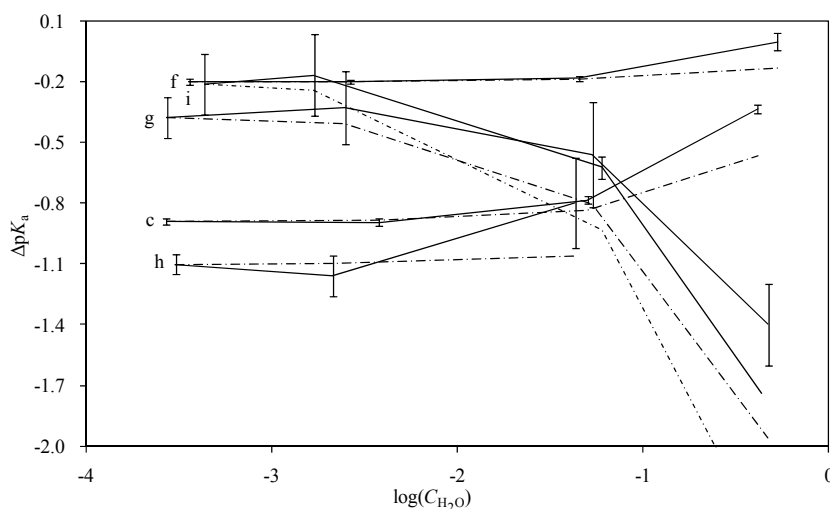
Pairs **a**, **b** and **c** form a group, in which the number of nitro substituents and consequently the strength of the phenol is varied. Picric acid and **A2** are strong acids and both have delocalized charge in their anions with *WAPS* values 4.3 and 2.4, respectively. Data in Table 4 reveal that water does not influence the  $\Delta pK_a$  values at up to 11000 ppm concentrations. Only marginal changes are evident in solvation energies of the anions, meaning that water has little influence on both anions. The relative acidity in the pair **b**, 2,4-dinitrophenol (**A3**) and **A4**, where both acids are weaker than in pair **a** by five orders of magnitude, behaves differently. At water concentrations over 9000 ppm contraction of the  $\Delta pK_a$  value by 0.1  $pK_a$  units is observed. This can be interpreted as the strength of the OH acid increases more due to the specific solvation of its anions by the water molecules when increasing water content. For the acid pair **c** composed of acids **A5** and **A6**, which are yet by another five orders of magnitude weaker, this effect is even more expressed: the relative strengthening of 2-nitrophenol at water content 9500 ppm is already 0.56 units. The 2-nitrophenolate ion is solvated better at water content of 1% by 0.27 kcal mol<sup>-1</sup>.



**Figure 11.** Influence of water content (expressed as logarithm of molar concentration) on the relative acidities ( $\Delta pK_a$ ) of acid pairs. Each pair is designated with a letter from Table 4. The crosshatched area on the graph represents the water content during experiments in ref 15. Vertical error bars represent the double value of standard deviation.

Based on the results of pairs **b** and **c** the influence of traces of water on the  $\Delta pK_a$  can be considered small if the  $WAPS$  value is 4.5 or lower. The comparison of acid pairs **b** and **c** is informative from the aspect that the steric hindrance of the anionic center is identical for anions of **A3** and **A5**, at the same time the influence of water is quite different. This demonstrates that although the accessibility of the anionic center is important, the degree of charge localization on the anionic center, which is higher in 2-nitrophenolate, is at least as important.

There is no single family of bases, whose strength could be varied in a wide range. Table 4 contains bases ranging from phosphanes with  $pK_a$  around 8 to phosphazenes with  $pK_a$  around 27. The overall changes in  $\Delta pK_a$  values of cationic acids upon addition of water are much smaller, rarely exceeding the experimental uncertainties. In the case of bases and the changes occurring with increase of water content in the solvent cannot interpreted as being the consequence of changing the base strength.



**Figure 12.** Comparison of corrected calculated ( $\Delta pK_a$ ) values of acid pairs most influenced by changing water content to experiment at different water contents (expressed as logarithm of molar concentration). Solid line indicates experiments, fragmental line calculated values.

For acid pairs **d** and **e** slight changes of  $\Delta pK_a$  is observed at water content of around 10000 ppm, by 0.07 and 0.05  $pK_a$  units, respectively, but the impact of water is not nearly as large as for 2-nitrophenol (an OH acid). The  $pK_a$  values of CH and NH acids with large molecules can be considered to have similar sensitivity to water. Both the experimental and calculated data suggest that in pair **e** the compound **A6** was influenced more by addition of water relative to compound **A8**. This can be explained by the slightly smaller *WAPS* value and the bulky oxygen rich  $-\text{SO}_2\text{OCH}_2\text{CF}_3$  substituent groups in **A8**, which shield the acidity center on nitrogen atom and are good hydrogen-bond acceptors. According to the solvation energies all four acids are little influenced by water. The changes are so small and similar that only slight changes in  $\Delta pK_a$  can be observed experimentally.

In order to further investigate the effect of water on NH acids another pair, **f**, consisting of 4  $pK_a$  units weaker (relative to pair **e**) NH and CH acids (**A9** and **A10**, respectively) was studied. The anion of the NH acid in this case becomes more stabilized at water content over 12000 ppm and this results in a 0.2  $pK_a$  unit contraction of the  $\Delta pK_a$  value. The *WAPS* values are 2.8 for **A9** and 2.4 for **A10**. This suggests that the charge delocalization is in both anions similarly extensive. The observed change in  $\Delta pK_a$  could be explained by the pyridyl group in **A9**. The negative charge concentration is high on the exposed nitrogen atom of the pyridyl group which leads to higher sensitivity towards water. The changes are also observable in solvation energies. Although the *WAPS* values of compounds **A2** and **A10** are similar the differences in  $G_{\text{solv}}$  of compound **A10**

are highest among the CH-acids used in this study. This additionally confirms that the influence of water is related to the acid strength.

For bases, notable changes are occurring in pairs **k**, **m**, **n** and **q**. The latter in combination with pair **p** compares two phosphanes Ph<sub>3</sub>P (**B8**) and MePh<sub>2</sub>P (**B10**) against 4-thiocyanato-*N,N*-dimethylaniline (**B9**). An impact on the  $\Delta pK_a$  value of pair **q** with MePh<sub>2</sub>P was seen, up to 0.16  $pK_a$  units in the wettest solvent. This was not seen with Ph<sub>3</sub>P. As opposed to the other base pairs, where changes in  $\Delta pK_a$  are observed, in pair **q** MePh<sub>2</sub>P seems to lose its basic strength relative to **B9** upon addition of water. No clear interpretation of the observed effect can be given.

In base pairs **k**, **m** and **n** the changes are caused by the nature of the basicity center along with the charge delocalization in the corresponding cation. The base pairs **k**, **l** and **m** form a group in which the steric crowding of the basicity center and the position of the basicity center in relation to the aromatic ring varies. Aniline, pyridine and *N,N*-dimethylaniline were measured against the same reference base. Observable, yet moderate changes in  $\Delta pK_a$  value were only seen in the pair **k** containing aniline, the  $\Delta pK_a$  shifted by 0.1  $pK_a$  units in the MeCN with water content of 9247 ppm, indicating that if the  $pK_a$  of the reference base is considered unchanged, then aniline becomes a stronger base upon addition of water. This is presumably caused by more efficient preferential solvation by water molecules (as opposed to acetonitrile molecules) of the anilinium cation, where charge delocalization is inefficient. This effect is not observed with the pyridinium ion, where charge delocalization is slightly more efficient. In the anilinium ion the charge cannot be efficiently delocalized over the aromatic ring via resonance as compared to the pyridinium ion in which the charge can be delocalized over the aromatic ring by resonance. This difference is manifested also by the solvation energies of the cations, that of the anilinium ion being by almost 20 kcal mol<sup>-1</sup> more negative according to the COSMO-RS calculations or by 10 kcal mol<sup>-1</sup> more negative according to the Minnesota solvation database.<sup>65</sup> In the case of *N,N*-dimethylaniline, the shielding of the basicity center by the two methyl groups minimizes the solvent effect. The calculated Gibbs free energies of solvation (Table 6) also suggest that pyridine is least influenced by the addition of water to its MeCN solution out of the three bases.

Base pairs **n** and **o** consist of two alkylamines – *n*-propylamine **B5** and tri-*n*-propylamine **B7** – measured against a bulky phosphazene base **B6**. This group was chosen because contrary to MeCN, in water tri-*n*-propylamine is a stronger base than *n*-propylamine: the  $pK_a$  values of **B5** and **B7** in water<sup>66</sup> are 10.53 and 10.65, respectively as compared to 18.43 and 18.25 in MeCN<sup>41</sup>. Both COSMO-RS calculations and experiments suggest that *n*-propylamine is affected by the increasing water content ( $\Delta pK_a$  decreased by 0.08 units), whereas tri-*n*-propylamine is not. Table 4 reveals that the computed  $\Delta pK_a$  data are in the case of *n*-propylamine at variance with the computed solvation free energy data: with increasing water content, the solvation free energies of both neutral and cation become more negative, but the neutral is more affected. This should lead to a

decrease of basicity, but the opposite is observed. The *WANS* value of 2.59 for tri-*n*-propylammonium cation indicates a far better charge delocalization compared to *n*-propylammonium ion (*WANS* 8.89).

The influence of charge delocalization is dramatically more noticeable in the case of acids. The series with nitrophenols can be considered as the first indication of that, but in phenolate ions resonance stabilization considerably facilitates charge delocalization. Resonance stabilization is absent if the carboxyl group is deprotonated, *i.e.* in benzoic acid, which is investigated in pair **g**. To further look into the dependence of charge delocalization, acetic acid along with hydrochloric acid were included into the study.

For benzoic acid (**A11**), which was measured against compound **A6**, the impact of water was severe. Its relative strength increased by 0.19 units at water content of 1000 ppm and by 1.03 units at 10000 ppm. This is easily interpreted: negative charge in benzoate anion is only weakly delocalized into the aromatic ring, because only the field-inductive effect is operational. This leads to quite high *WAPS* value of 7.1. The charge is concentrated on the two exposed oxygen atoms of the carboxylate group, which are good hydrogen bond acceptors. Water molecules form easily hydrogen bonds with the COO<sup>-</sup> group providing significant stabilization that acetonitrile molecules are unable to provide. In the anion of 2-nitrophenol (**A5**) the charge is delocalized more to the aromatic ring and to the nitro group. The hydrogen bonds formed are therefore weaker. This is supported by the difference in energetic effects of solvation of benzoic acid and 2-nitrophenol. The  $\Delta G_{\text{solv}}$  values -1.36 and -0.29, respectively.

For the pair **h** the  $\Delta pK_a$  value at water content around 1000 ppm in Table 4 is not fully accurate (the  $\Delta pK_a$  value should actually be larger). This is because the neutral form of the acid **A13** could not be observed in the solution with high water content. The spectral data suggest that a large fraction of the acidic titrant was consumed for protonating water. It was impossible to take this effect into account due to the fact that HCl is an acid transparent in the UV region. The experiment at water content around 10000 ppm was also carried out but the protonation of water was so extensive that getting even near the protonated forms of the acids was impossible and the attempts to calculate the  $\Delta pK_a$  were unsuccessful. Spectra of neutral form from drier solvents can be used to calculate  $\Delta pK_a$  if both of the studied compounds have spectra in UV-Vis region. The gathered data for pair **h** suggest that the behavior of HCl is similar to weaker OH-acids: the low water content (<100 ppm) does not influence the determination of  $\Delta pK_a$  values, but the impact is clearly visible at higher concentrations of water. Here the impact is large due to the lack of charge distribution in the single-atom chloride anion. According to the *WAPS* value (and not unexpectedly from the viewpoint of chemical intuition) Cl<sup>-</sup> is the most charge-localized anion in this study. The effect of water on HCl is nevertheless not as large as on acetic acid (see below) according to the experiments, also, the computations do not seem to predict the effect. Two possible reasons are: (1) the atomic radius of chlorine is higher than oxygen and (2) COSMO-RS is known to display below-average accuracy in describing monoatomic ions<sup>67</sup>.

Acetic acid of the pair **i** is a weak acid with highly localized charge. In Table 4 the data for experiment in solvent with the highest content of water is estimated because the acid-strengthening effect of water on acetic acid was so severe that the  $\Delta pK_a$  became too large to be measured. Significant changes in  $\Delta pK_a$  were observed at water content of 1000 ppm. Both the calculated  $\Delta pK_a$  values and energetic effect of solvation are in agreement with experimentally measured and with the evaluated values.

The pair **j** containing only one experiment at water content of 1% was measured to elucidate the behavior of acetic acid. Acetic acid being 1.57  $pK_a$  units weaker acid than compound **A6** in pure MeCN became 0.26 units stronger acid at water content of ca 10000 ppm. The  $\Delta pK_a$  of pair **d** is contracted when going from few ppm water level to ca 10000 ppm level by 0.07  $pK_a$  units. Thus we can estimate the difference of pair **i** to be ca -1.74  $pK_a$  units at ca 10000 ppm level. This correlates to the estimation from the spectral data of the original experiment for pair **i** which suggested that the  $\Delta pK_a$  is more negative than -1.5  $pK_a$  units.

Base pairs **r**, **s**, **t**, **u**, **w** and **x** consist of different imino-phenyl phosphazenes, varying in the substitution of the phenyl group, the nature of the amine (dma, pyr) substitution as well as in the number of phosphorous atoms. Phenyl tetramethylguanidine is also in one of the pairs (**u**). The experiments show no changes in  $\Delta pK_a$  values in any of these pairs upon addition of water, this is also predicted by the calculations. In experiments with stronger phosphazenes it was noticed that in solvents with higher water content, larger than usual amounts of basic titrant were needed to completely deprotonate the protonated bases. This suggests that the acidic properties of water molecules were coming into play and a part of the titrant was consumed for deprotonation of water. In the case of base pairs **w** and **x**, the measurements even at a water content of 1000 ppm were impossible, due to the spectral properties of  $HP_1(\text{dma})$  (**B16**) and  $t\text{-BuP}_1(\text{dma})$  (**B18**). These base pairs require a calculation method which exploits the titrant moles used in the titration. With the part of the titrant used for protonation of water the results are not reliable anymore.

**Table 6.** Comparison of experimental<sup>65</sup> and calculated (COSMO-RS) values of Gibbs free energy of solvation in acetonitrile.

| Compound                          | $G_{\text{solv}}$ (kcal mol <sup>-1</sup> ) |            |
|-----------------------------------|---|------------|
|                                   | Experimental                                | Calculated |
| Benzoate                          | -55.4                                       | -60.8      |
| Acetate                           | -58.8                                       | -60.8      |
| 2,4-dinitro Phenolate             | -36.0                                       | -36.9      |
| Anilinium ion                     | -76.8                                       | -54.7      |
| Pyridinium ion                    | -66.7                                       | -38.2      |
| Tri- <i>n</i> -propylammonium ion | -57.9                                       | -27.7      |
| Toluene                           | -4.7  | -0.8       |
| Ethanol                           | -4.4  | -0.7       |

The last six columns of Table 4 present the COSMO-RS computational estimates of Gibbs free energies of solvation of the different species of acid and base pairs. In order to put these calculated values into a perspective compared to experimental values, a comparison is presented in Table 6 for species, for which experimental solvation free energies in acetonitrile are available. It can be seen that the trends are more or less reproduced, but the absolute values differ very strongly between experiments and computations.

The influence of water on the solvation of acid anions is very strong, for acetate ion the solvation free energy becomes more negative by 2.0 kcal mol<sup>-1</sup> according to calculations. The influence of water on the solvation of neutral acids is, on the other hand, almost negligible. For protonated bases the influence of water on solvation energies does not exceed 0.14 kcal mol<sup>-1</sup>. On the other hand, the influence of water on the solvation energies of free bases is often almost the same and in some cases even exceeds that of the cations (*n*-propylamine, phenyl tetramethylguanidine, Ph<sub>3</sub>P, MePh<sub>2</sub>P, 4-Br-C<sub>6</sub>H<sub>4</sub>-P<sub>1</sub>(pyrr), Ph-P<sub>1</sub>(pyrr), tripropylamine). In the base pair **n**, the calculations of the Gibbs free energies of solvation suggest that the changes in p*K*<sub>a</sub> of *n*-propylammonium ion are caused by the increase of the solvation free energy of the neutral species. In the pair **k**, the changes of the solvation of the cation are responsible for the shift in the Δp*K*<sub>a</sub> value.

The absolute values of solvation free energies of cations are, as expected, significantly higher than those of the neutral bases. It can be seen that the *G*<sub>solv</sub> values of the phosphazenium cations with efficiently delocalized charge (protonated forms of **B6**, **B11**, **B12**, **B13**, **B14**, **B16**, **B17**, **B18**, **B19**, **B20**) are mostly in the range of -20 to -30 kcal mol<sup>-1</sup>. In all these cations stabilization by hydrogen bonding is virtually impossible because of steric reasons. Also protonated tri-*n*-propylamine and protonated phosphanes fall into this group. The solvation energies of cations with a single sterically unshielded N-H bond, capable of donating one hydrogen bond, are around -35 to -38 kcal mol<sup>-1</sup> (pyridinium and *N,N*-dimethylanilinium). The solvation energies of cations able to donate (at least in theory) up to three hydrogen bonds are in the region of -52 to -55 kcal mol<sup>-1</sup>. A notable deviation from this picture is displayed by 4-thiocyanato-*N,N*-dimethylanilinium with *G*<sub>solv</sub> = -50 kcal mol<sup>-1</sup>. It is unclear whether this deviation is caused by the high polarizability of the SCN substituent or by limitations of the COSMO-RS procedure.

### 3.4. Guidelines for experiments

Based on the obtained knowledge of the influence of water content, recommendations can be given, which should be valid also in other non-aqueous solvents. The water content below 100 ppm is acceptable in a polar solvent, such as MeCN, for acids and bases in the medium p*K*<sub>a</sub> range (11–20 in acetonitrile) water content slightly higher, but not exceeding 1000 ppm is still tolerable. In apolar media (*e.g.* 1,2-dichloroethane) small polar, especially ionic,

solutes are expected to be strongly preferentially solvated by the available water molecules and therefore the water content should be kept as low as possible (below 10 ppm for relative  $pK_a$  measurements). Operating at the edges of acidity/basicity scales, where acid-base properties of water come into play, the water content should be also as low as possible, because water strongly hinders the full deprotonation/protonation of the studied compounds, as was the case for acid pair **h** and base pairs **w** and **x**.

Our experience is that if all the manipulations with compounds and solvent (including solution preparation) are made in an inert-gas glovebox (less than 1 ppm water level in the argon gas atmosphere) and the glassware is dried in drying oven for 12 hours at 150 °C then the residual water content of ultra-dry (specified water content by manufacturer is less than 50 ppm) UV-grade acetonitrile is taken down below 10 ppm by keeping the solvent on 3 Å granulated molecular sieves for at least 20 hours. Storage of this solvent on molecular sieves for at least 20 hours will not change its spectral properties in the UV range. One should consider that for removing water from the solvent having a higher initial water content, a different solvent treatment approach (changing the molecular sieves several times, combining with other water removal techniques, *etc*) may be needed and this may alter the spectral properties in the UV-Vis range (*i.e.* possible increase of absorbance) or introducing impurities involved in the acidic-basic equilibrium into the solvent.

In the case of  $pK_a$  measurements, experimental techniques, that allow the direct observation of studied compound(s), are recommended. In this way the protonation/deprotonation process is monitored and possible competing equilibria can be detected and taken into account if needed.



## SUMMARY

This thesis is focused on solvent characteristics, that influence the  $pK_a$  measurements in non-aqueous media and is divided into two major sections. First  $pK_a$  measurements for two sets of compounds are carried out revealing the importance of knowledge of solvent properties in order to achieve accurate and reliable results. In the second section the influence of the most frequent impurity, water, in non-aqueous solvents is systematically investigated at impurity levels for both acids and bases on the example of acetonitrile.

$pK_a$  values of 13 chiral acid catalysts, based on phosphonic acid and its esters are measured in acetonitrile. The results confirm the previous empirical assumption, that the catalytic activity is correlated to the acidity of the compounds. Furthermore the results reveal, that  $pK_a$  values of similar compounds reported by another research group in DMSO may contain errors. This discrepancy is investigated and discussed in detail and evidence is presented in favor of the results of this work .

Another set of compounds, triarylphosphanes, a part of a Frustrated Lewis Pair catalyst system, have been investigated.  $pK_a$  values of 10 such compounds have been measured in acetonitrile. The very low basicity (exceeding the scope on MeCN) of one of the compounds, as well as insolubility of another in MeCN, meant that in order to get comparable values in MeCN, these two compounds had to be measured in 1,2-dichloroethane. In order to predict the  $pK_a$  values in MeCN using correlations, a basicity scale, spanning 7 orders of magnitude, was constructed in DCE. Once again the results of the  $pK_a$  measurements help to rationalize the observed catalytic activity of the corresponding catalytic system.

In the second part of the thesis, the influence of water, at low concentration, below 1% (w/w), is systematically studied on the relative acidities and basicities. It is quantitatively shown, that acids are much more influenced by the increase of water content in solvent, compared to bases. Higher impacts are observed in case of acids and bases with localized charges in corresponding ions. In order to quantify the charge delocalization in ions, two computational parameters *WAPS* (for anions) and *WANS* (for cations) are proposed. The strength of the acids as well as the nature of acidity center is shown to affect the changes in relative acidity upon increase of water content.

The results of this thesis help to improve and fine-tune catalytic systems, as the  $pK_a$  values of the involved compounds have been reliably measured. The quantification of influence of impurity levels of water allows evaluation of the already published acidity and basicity data as well as plan future experiments. The results are also helpful for those chemists who rely on the acidity or basicity data of their reactants or catalysts but now, in some cases, can avoid the costly and time-consuming solvent purification step.

## SUMMARY IN ESTONIAN

### Happelisus ja aluselisus mittevesikeskkondades: solvendi omaduste ja puhtuse mõju

Väitekiri keskendub solventide parameetritele, mis mõjutavad  $pK_a$  mõõtmisi mitte-vesikeskkondades. Väitekiri on jagatud kahte ossa, kus esimeses käsitletakse kahe komplekti ainete  $pK_a$  mõõtmisi, mis ilmestavad vajadust teada solvendi parameetreid, et jõuda täpsete ja usaldusväärsete tulemusteni. Teises osas uuritakse süstemaatiliselt mitte-vesikeskkondades kõige levinuma lisandi, vee, mõju nii hapete kui ka aluste suhtelisele tugevusele atsetonitriili keskkonna näitel.

Mõõdeti 13 fosfoonhapetel ja nende estritel põhineva kiraalse happelise katalüsaatori  $pK_a$  väärtused atsetonitriilis. Tulemused kinnitavad eelnenud kogemuslikke arvamusi, et nende katalüsaatorite katalüütiline aktiivsus sõltub nende happelisusest. Lisaks leiti, et uuringu käigus teise uurimisgrupi poolt avaldatud  $pK_a$  väärtused sarnastele ühenditele DMSO keskkonnas võivad olla märgatava veaga. Leitud lahkevusi uuriti põhjalikult ja näidati võimalikud vea allikad ning esitati tõendusmaterjal käesolevas töös saadud  $pK_a$  väärtuste kasuks.

Teiseks ainete komplektiks olid triarüülfosfaanid, mida kasutakse osana frustreeritud Lewise paari katalüsaatori süsteemis. Mõõdeti kümne sellise ühendi  $pK_a$  väärtused atsetonitriilis. Ühe ühendi väga madal aluselisus, ja teise mittelahustumine atsetonitriilis, tingis vajaduse neid aineid mõõta 1,2-dikloroetaanis (DCE). Selleks, et DCE andmetest oleks võimalik ennustada MeCN andmeid konstrueeriti esmakordselt DCE-s 7 suurusjärku hõlmav aluselisuse skaala. Saadud tulemused aitavad selgitada uuritud katalüütilise süsteemi aktiivsust.

Väitekirja teises osas uuriti väga madalate veesisalduste (alla 1%) mõju hapete ja aluste suhtelisele tugevusele. Kvantitatiivselt näidati, et happed on tõusva veesisalduse suhtes tundlikumad kui alused. Suurimad muutused mõõdetud suhteliste happelisuste ja aluseliste juures ilmsid ainetel, mille ioonides on laeng lokaliseeritud. Laengu delokalisatsiooni hindamiseks pakuti välja kaks arvutuslikku parameetrit: *WAPS* (anioonidele) ja *WANS* (katioonidele). Hapete puhul sõltub veesisalduse mõju ka hapete tugevusest ja happelise tsentri iseloomust.

Käesolevas väitekirjas avaldatud tulemused aitavad parendada uuritud katalüsaatoreid, sest nende happelis-aluselised omadused on nüüd usaldusväärsetel mõõdetud. Madalate veesisalduste mõju kvantifitseerimine annab võimaluse hinnata juba avaldatud andmete usaldusväärsust ja planeerida tulevasi eksperimente. Samuti on nüüd võimalik keemikutel, kes oma uuringutes  $pK_a$  väärtustele tuginevad vältida kalleid ja ajamahukaid solvendi puhastamise etappe, kui on teada, et mõnel juhul kasutatavate ainete happelis-aluselised omadused solvendi lisandite mõjul oluliselt ei muutu.

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