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III. L. Greb, S. Tussing, B. Schirmer, P. Oña-Burgos, K. Kaupmees, **M. Lõkov**, I. Leito, S. Grimme, J. Paradies, Electronic Effects of Triarylphosphines in Metal-free Hydrogen Activation: a Kinetic and Computational Study. *Chem. Sci.* **2013**, 4, 2788–2796.

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Author's contribution

Paper I. Performed all the pK_a measurements and gas-phase basicity calculations, lead author in preparing the manuscript.

Paper II. Performed all the pK_a measurements in acetonitrile, participated in preparing the manuscript.

Paper III. Performed most of the pK_a measurements in acetonitrile, participated in preparing the manuscript.

Paper IV. Performed all the pK_a measurements, participated in preparing the manuscript.

ABBREVIATIONS

A^{λ}	Absorbance at wavelength λ
a	Activity
α	Dissociation level
B	Generic abbreviation for the neutral form of a base
BH^{+}	Generic abbreviation for the protonated form of a base
DCE	1,2-dichloroethane
ε_r	Relative permittivity
FLP	Frustrated Lewis pair
GB	Gas phase basicity
GP	Gas phase
IMHB	Intramolecular hydrogen bond
K_a	Dissociation constant
MeCN	Acetonitrile
pK_a	Negative logarithm of the dissociation constant K_a
pK_{auto}	Autoprotolysis constant
z	Charge
UV-Vis	Ultraviolet-visible

INTRODUCTION

The acidity and basicity are among the most important properties of chemical compounds. Acid-base equilibria occur at least to some extent in almost all chemical processes and often decisively influence the course of these processes.

Although water is undoubtedly the most common medium for acidity or basicity studies and the behaviour of acids and bases in water is well known, molecules display acidity and basicity also in non-aqueous media and often quite differently from water. In non-aqueous media it is possible to study such compounds or compound types for which the reliable acid-base property determinations in water are difficult or impossible. Examples are very strong or weak acids and bases, compounds sensitive to water or compounds insoluble in water. Also, the determination of acidic-basic properties of compounds, which could be studied in water, is of interest in non-aqueous media because many processes where compounds behave as acids or bases take place in non-aqueous media. Another reason is that when acidity or basicity values for the same compounds are available in different media it is possible to rationalize the solvent effects to the compounds acid-base properties. Unfortunately, non-aqueous media are not perfect in terms of pK_a measurements because measurement of activity of hydrogen ion (solvated proton) is difficult and different association processes can occur. As a result, there is no such solvent that is suitable for the pK_a determinations of acids and bases of all kinds.

The aim of this thesis was to experimentally determine the basicities in acetonitrile of a number of practically and/or theoretically interesting bases belonging to different compound families – phosphanes, fulvenes, hydrazones and nitrogen heterocycles – and to rationalise their basicity in relation to the molecular structure and/or substituents. In the case of homogeneous families of phosphanes, fulvenes and hydrazones this first of all relates to different substituents or substitution patterns. In the case of the diverse set of nitrogen heterocycles the aim was to comprehensively analyse their basicity with respect to different structural effects.

1. LITERATURE OVERVIEW

1.1. Acid-base equilibrium in solutions

According the Brønsted-Lowry theory, acids are proton donors and bases are proton acceptors.[1] The following equation describes the acid-base equilibrium in solvent S:

$$HA^{z+1} + S \underset{}{\overset{K_a}{\rightleftharpoons}} A^z + SH^+ \quad (1)$$

If z = -1 in equation (1) then HA^{z+1} is a neutral acid HA and A^z is its corresponding conjugate base A^-. If z = 0 then A is a neutral base and HA^+ is the corresponding conjugate acid. SH^+ stands for the solvated hydrogen ion and the concentration of SH^+ describes the acidity of the solution. The dissociation constant K_a of the equilibrium reaction (1) is expressed as follows:

$$K_a = \frac{a(SH^+) \times a(A^z)}{a(AH^{z+1})} \quad (2)$$

In equation (2) $a(A^z)$ and $a(AH^{z+1})$ are the activities of the basic and acidic forms and activity of the solvated proton $a(SH^+)$ describes the solution acidity. Since the K_a values can differ by many orders of magnitude the negative logarithm of the dissociation constant pK_a is used more commonly than K_a:

$$pK_a = -\log(K_a) = -\log\frac{a(SH^+) \times a(A^z)}{a(AH^{z+1})} \quad (3)$$

To avoid the necessity of measuring the activity of the solvated proton $a(SH^+)$, which is difficult in non-aqueous media, the relative acidity determination approach is often used whereby the equilibrium between two bases and their conjugate acids is studied:

$$HA_1^{z+1} + A_2^z \rightleftharpoons HA_2^{z+1} + A_1^z \quad (4)$$

HA_1^{z+1} and HA_2^{z+1} are the conjugate acids of bases A_1^z and A_2^z respectively. The logarithm of the equilibrium constant of equation (4) expresses the difference of acidity between HA_1^{z+1} and HA_2^{z+1} in the given medium.

$$\Delta pK_a = pK_a\left(HA_2^{z+1}\right) - pK_a\left(HA_1^{z+1}\right) = \log\frac{a\left(HA_2^{z+1}\right) \times a\left(A_1^z\right)}{a\left(HA_1^{z+1}\right) \times a\left(A_2^z\right)} \quad (5)$$

Equation (5) shows that for relative acidity measurement there is no need to determine the activity of the solvated proton in the solution. When using bases with the same charge type then it is justified to assume that the ratio of activity coefficients $f(\mathrm{HA}^{z+1})/f(\mathrm{A}^{z})$ is the same for both studied bases[2] and because of this it is possible to replace the ratios of activities in equation (5) with ratios of equilibrium concentrations.[2] Although the pK_a value is the most used way to quantitatively express the acidities of acids in solution it also can be used for the basicities of (neutral) bases. Strictly speaking when expressing the basicity of a base B it should be said "the pK_a value of the conjugate acid of base B" but in organic chemistry usually a more simplified way of saying "the pK_a value of base B" is used. Here in this work the latter simplified way is used.

In addition to the above described dissociation process also different side processes can occur in non-aqueous media, which make pK_a measurements more difficult. If the used solvent solvates anions weakly then association processes can occur and this can also happen in acetonitrile.[3] If the association happens between the anion and its conjugate acid then this process is called homoconjugation. When the neutral form of one compound associates with the anion of another compound then it is called heteroconjugation.[3] In addition to homo- and heteroconjugation also the formation of ion pairs could happen depending on the used solvent and studied compounds.[1]

These association processes can be avoided by using suitable solvents and methods which permit the use of low concentrations. In this work these kinds of association processes were suppressed by using a polar solvent (acetonitrile) and a measurement technique that enables working with low concentrations (UV-Vis spectrophotometry).

1.2. The solvent in acid-base equilibrium

Although equation (1) is most widely used to describe the dissociation process of an acid or base (conjugate acid of the base) in a solvent, it is simplified and is valid in polar solvents and at low concentrations. According to Reichardt[1] also the ionization step should be considered in more detail when describing the dissociation process. A more comprehensive set of equilibria can be written:

$$\left(\mathrm{HA}^{z+1}\right)_S + (:\mathrm{B})_S \overset{K_1}{\rightleftharpoons} \left(\mathrm{AH}^{z+1}\cdots:\mathrm{B}\right)_S \overset{K_2}{\rightleftharpoons} (\mathrm{A}:^{z}\cdots\mathrm{HB}^{+})_S \text{ or } (\mathrm{A}:^{z}\mathrm{HB}^{+})_S \overset{K_3}{\rightleftharpoons} (\mathrm{A}:^{z}\|\mathrm{HB}^{+})_S \overset{K_4}{\rightleftharpoons} (\mathrm{A}:^{z})_S + (\mathrm{HB}^{+})_S \quad (6)$$

In equation (6) :B is a base but can also be a solvent molecule and the index S indicates that the respective species are solvated. The first step described by K_1 is the formation of the initial hydrogen bonded complex. K_2 describes the ionizing step where as a result of proton transfer a contact ion pair, or a

hydrogen bonded complex of the ionized species is formed. In the third step a solvent-separated ion pair is formed. The last step described by K_4 concludes with the dissociation of the solvent-separated ion pair and formation of free ions. The dissociation constant K_a is the product of the four equilibrium constants: $K_a = K_1 \cdot K_2 \cdot K_3 \cdot K_4$.

The most important characteristics of solvents in acid-base equilibria are the ability to separate charges, specifically solvate cations (acidity of the solvent) and specifically solvate anions (basicity of the solvent).

The ability of a solvent to separate charged species can be described by using the relative permittivity (ε_r). The ε_r shows how many times is the electrostatic interaction between two charged particles weaker in the solvent than in the vacuum. A high ε_r promotes the separation of charges and the formation of ions. On the basis of the relative permittivity solvents are often arbitrarily divided into polar ($\varepsilon_r > 20$) and apolar ($\varepsilon_r < 20$). In the field of acid-base chemistry it should be emphasized that in solvents with ε_r less than 15 practically no free ions are found, in solvents with intermediate relative permittivity ($\varepsilon_r = 15 \ldots 40$) the presence of associated ions depends on the solvent as well as the solutes and their concentrations. In solvents with $\varepsilon_r > 40$ almost no ion associates exist.[1]

The "joint" property of the acidity and basicity of a solvent is the autoprotolysis constant. The autoprotolysis of a solvent is expressed by equation (7).

$$2\,\mathrm{SH} \rightleftharpoons \mathrm{SH_2^+} + \mathrm{S^-} \tag{7}$$

The products of this reaction are the lyonium ($\mathrm{SH_2^+}$) and the lyate ($\mathrm{S^-}$) ion. This equilibrium is quantitatively described by the autoprotolysis constant of the given solvent.

$$K_{\mathrm{auto}} = a(\mathrm{SH_2^+}) \times a(\mathrm{S^-}) \tag{8}$$

In a given medium the lyonium ion is the strongest possible acid and the lyate ion is the strongest possible base. Acids and bases that are stronger than these ions, respectively, are fully ionized and levelled to the level of the lyonium and lyate ion respectively. The smaller is the K_{auto} value of a solvent the wider is the range of pK_a values that can be determined in it. This means that the higher is the pK_{auto} (the negative logarithm of K_{auto}) value the better differentiating solvent it is for acid-base studies. According to the pK_{auto} solvents can be divided into amphiprotic (p$K_{\mathrm{auto}} < 20$) and aprotic (p$K_{\mathrm{auto}} > 20$) solvents.[1]

Usually the acidity and basicity of a solvent are not equally strongly pronounced and one dominates over the other. Kolthoff[4] categorized amphiprotic solvents as neutral, protogenic or protophilic according their acid-base behaviour and aprotic solvents as dipolar protophilic, dipolar protophobic and inert. Solvents that have more pronounced acidic properties than basic properties are

called protogenic solvents and if a solvent has more pronounced basic properties than acidic it is called a protophilic solvent. It can be beneficial to characterize the solvent's acidity and basicity separately. The acidity of a solvent can be expressed by using its hydrogen bond donating (HBD) and electron pair accepting (EPA) ability. The basicity of a solvent can be expressed by using its hydrogen bond accepting (HBA) and electron pair donating (EPD) ability. There are different parameters available to quantitatively describe the solvents HBD and HBA ability but the most used are the α and β parameter by Kamlet and Taft.[5]

1.3. Acetonitrile as medium for acidity or basicity determinations

The most used solvent for acid-base studies is undoubtedly water. Although water has properties that make it a suitable solvent for such studies (relatively easy to reliably measure pH[6], negligible association processes, environmentally friendly), it also has many shortcomings. Thus, non-aqueous solvents should be considered. One of the most universal non-aqueous solvents for pK_a studies is acetonitrile (MeCN).

MeCN is a weakly basic (protophobic) dipolar aprotic (ε_r = 35.94[7]) solvent with negligible acidity. MeCN has a weak HBD (α = 0.19[1]) and moderate HBA (β = 0.40[1]) ability. Because of the high relative permittivity ionic dissociation is favoured in MeCN. Due to the low autoprotolysis constant (pK_{auto} estimated to be close to 40) MeCN is a good differentiating solvent.[1] Water on the other hand is a very polar solvent (ε_r = 78.36[1]) with much stronger acidic (α = 1.17[1]) and basic (β = 0.47[1]) properties than MeCN. The high polarity means that compounds with low polarity may not dissolve in water making pK_a determination of them impossible. Unlike MeCN, water is a levelling solvent with a high autoprotolysis constant (pK_{auto} = 14.00) and therefore very strong acids and bases are fully dissociated and their strength cannot be measured easily. The low basicity of MeCN makes it a good solvent for studies of weak to moderately strong bases and strong to moderately strong acids. MeCN is not suitable for very strong bases because they decompose the solvent.[3] The negligible acidity of MeCN means that it poorly solvates anions and this could lead to association processes when studying pK_a values of acids with localized charges in the deprotonated form.[8] Some practical considerations that favour the usage of MeCN are its transparency in the UV-Vis region, availability with high purity and inertness. A large number of acids and bases with a wide pK_a range have already been studied in MeCN.[2,8,9] The pK_a scales formed from this data range over 25 orders of magnitude for acids and over 30 for bases. MeCN is the main solvent used in this work.

Although MeCN has many suitable properties for pK_a determinations it is still not perfect for all compounds. Therefore for very weak bases 1,2-dichloroethane[10,11] and for very strong bases tetrahydrofuran[12] is used. Another

widely used solvent is dimethylsulfoxide but because of its higher basicity it is mostly used for medium to weak acids and moderately strong bases.[13]

In all solvents solvent effects are more or less present and the determined acidities or basicities are actually combined properties of both the solvent and solute. As a result, the pK_a value of a compound in different solvents can differ by many orders of magnitude. The intrinsic acid-base properties of the compounds can only be studied in the gas phase (GP). Thus, GP is also a very relevant medium and should always be considered when rationalizing structural or solvent effects.[14]

1.4. Methods for pK_a determination in solution phase

There are different methods that can be used for the determinations of pK_a values. Basically a pK_a determination method can be any method which enables the quantitative measurement of a certain parameter which depends on the pH.[15]

The most used methods for pK_a determination are potentiometry and spectrophotometry. These methods can also be used in combination. To spectrophotometrically determine pK_a values it is important to calculate the relation between the activities of the protonated and deprotonated forms using the recorded spectra. It is necessary that there is a wavelength range where the absorption of the protonated and deprotonated forms are significantly different. To obtain the *absolute* pK_a value the activity of the solvated proton has to be measured. In water this can be done relatively easily and accurately using the pH scale and the potentiometric measurement method. This is, however, not the case in non-aqueous solutions. Potentiometry can also be used independently for pK_a measurement. This is based on the measurement of the activity of the hydrogen ion $a(H^+)$ in a solution with a known quantity of the acidic and basic form of the studied compound. Relatively high concentrations have to be used, which in non-aqueous solvents can lead to association processes. In potentiometry, pH standard solutions with exact pH values are used for calibration of the electrode system. In non-aqueous solvents the pH scales are usually poorly established, indicator electrode's potential is often unstable or drifts.[3] Potentiometry is more suited for pK_a determinations in water and it has been widely used there.[16,17]

As stated before, in non-aqueous media the measurement of pH is problematic and therefore a *relative* pK_a measurement method is often used, which makes it possible to find the differences of dissociation constants (ΔpK_a) of two compounds without the necessity to use pH values. When connecting these ΔpK_a values of a wide range of compounds with different pK_a values, acidity or basicity scales can be constructed.[2,8] The absolute pK_a values can be found if the scale is anchored to a compound with a previously reliably known pK_a value which in case of bases in MeCN is pyridine.[2] Using this approach comprehensive acidity or basicity scales have been constructed in MeCN[2,8], tetrahydrofuran[18] and 1,2-dichloroethane[10,11]. The advantages of spectrophoto-

metry are that low concentrations of compounds can be used, which is beneficial in non-aqueous pK_a determination and that assessment of the purity of the studied compounds and possible side processes can be made using the titration spectra. The main disadvantage is that spectrophotometry is significantly less convenient to use with molecules with no chromophores. The relative spectrophotometric method (described in detail in section 2) was used in this work.

Other methods that are used for pK_a determinations are capillary electrophoresis (CE)[19], conductometry[15], high-performance liquid chromatography (HPLC)[20] and nuclear magnetic resonance spectroscopy (NMR)[15].

1.5. Nitrogen heterocycles

Heterocycles form one of the largest and most important classes of organic compounds. This is confirmed by the fact that about 55 % of organic chemistry publications address this class.[21] The most common subclass of heterocycles are nitrogen containing heterocycles. These molecules are ubiquitous in nature, chemistry and technology. They are widely used in organic synthesis as reagents, solvents and catalysts.[22–24] Many heterocyclic compounds are bioactive and are used as medicines, narcotics or pesticides. They often serve as supramolecular building blocks, e.g. synthetic receptor molecules, molecular switches.[21,24] In analytical chemistry the chelating ability of some nitrogen heterocycles i.e. phenanthroline and 2,2′-bipyridine is used for the determination of some metal ions.[24,25] This is far from being a definitive list of the applications of nitrogen heterocycles.

Almost all nitrogen heterocycles are to some extent basic and often their basicity is essential in determining their other properties. For example in case of medicine the charge state and transport/accumulation in the human body is dependent on the basicity.[26] In water as a solvent the basicity data for hundreds of different nitrogen heterocycles can be found. To the best of the author's knowledge, there have not been any systematic studies of different nitrogen heterocycles focusing on their basicity (and to a lesser extent on their structural effects) since the 1950s and 60s done by Albert and co-workers.[16,17,27] There are no reasons to doubt in their results but they only studied 6-membered heterocycles and did not involve basicity data in non-aqueous media. There are no comprehensive studies of nitrogen heterocycles in non-aqueous media and therefore even simple heterocycles, like quinoline or isoquinoline, did not have published pK_a values in e.g. acetonitrile. More recently Hosmane et al. explored the *peri* effect in a few 6-membered heterocycles but still only pK_a values in water were used.[28] There have been some papers published about pK_a values of substituted pyridines[29,30] and imidazoles[31,32] in MeCN but the results of those studies could be somewhat questionable because for example the pK_a values of imidazole differ by over 2 pK_a units between the two articles. In order to rationalize different structural effects influencing the basicity of such heterocycles it

is beneficial to compare the previously published pK_a values in water with basicities in non-aqueous media. These media should have different properties (e.g. protic and aprotic solvents) and the gas phase should be involved for comparison. Basicity values in solvents like acetonitrile are not only usable for fundamental studies of structure effects but can also be of interest in other fields, e.g. organic synthesis, chemical power sources, etc. It can be added that MeCN is a pharmacologically relevant solvent because it has lower polarity than water and can therefore mimic the interior of cell membranes, which need to be penetrated by drug molecules to reach their targets.[33]

1.6. Phosphanes

Phosphanes are a widely used compound group in transition metal chemistry and organic synthesis. They are popular as ligands in metal complexes and nucleophilic catalysts in different reactions.[34]

A more recently developed concept for the usage of phosphanes is their use as catalysts in frustrated Lewis pair (FLP) catalysed metal-free hydrogenation reactions of alkenes originally proposed by Stephan and co-workers.[35,36] FLP-s consist of a Lewis acid and a base, which are sterically hindered from forming an acid-base adduct, allowing subsequent actions for both the Lewis base and acid on other molecules (e.g. H_2). Usually a weakly basic triarylphosphane and tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] are used for the formation of an FLP.[37] It is assumed that the pK_a value of the phosphane species plays a role in these reactions.

In the recent years there have been intense developments in the FLP based catalysis and additionally to simple alkenes the metal free hydrogenation has been studied for alkynes, arenes, heteroarenes, polyaromatics, carbonyl compounds etc.[38] Although FLP catalysts are significantly slower than the known Rh, Ir, Pd, Pt or Ru catalysts, do not tolerate impurities and are not universally effective for all kind of compounds they are generally cheaper and environmentally friendlier than the mentioned metal catalysts.[39]

1.7. Arylhydrazone molecular switches

Molecular switches are molecules which can reversibly interconvert between two distinct forms by the application of an external stimulus which can be chemical, electrochemical or photochemical.[40] One versatile framework for molecular switches is the hydrazone functional group. Due to their modularity, straightforward synthesis, functional diversity and stability towards hydrolysis hydrazones are not only a popular choice for molecular switches but also in other fields of chemistry.[41,42]

After inducing small structural changes into different parts of the initial configurational arylhydrazone switch other types of molecular switches have

been obtained. This has led to the preparation of switches which can coordinate metal ions, fluorescent after exposure to cyanide ion, deprotonate after co-ordinating a metal ion, liquid crystal molecular switches and research is still continuing to find new possibilities.[43] Even an easy-to-fabricate gel pad tester based on an arylhydrazone molecular switch has been developed which could be used to determine e.g. spoiled fish.[44]

Although much research has been carried out in the field of configurational molecular switches (mainly photoswitches[40]) arylhydrazone switches are one of first families of chemically (pH) activated configurational molecular switches.[45] For the usage of pH-controlled molecular switches their basicity is an important parameter, because it determines at which pH the switching happens and also influences the strength of intramolecular hydrogen bond (see Table 3 for structure of such molecular switches).

1.8. Fulvenes

Fulvenes are cyclic polyenes with unsaturated exocyclic substituents.[46] The cycle has an odd number of carbon atoms up to 9. The most studied fulvenes are pentafulvenes.[47] Pentafulvene has been an interesting research object because it is a cyclic isomer of benzene with nonbenzenoid aromaticy which extent is dependent on the exocyclic substituent.[47] An interesting feature of these compounds is their appreciable basicity – uncommon for hydrocarbons.[48] Pentafulvenes are mainly used in organic synthesis of polycycles, natural products and also various organometallic complexes where the fulvene molecule is a ligand.[47,49,50]

2. EXPERIMENTAL SECTION

2.1. General aspects

In this work the previously developed spectrophotometric method for relative pK_a determination was used. A brief description of the method will be given here. In this work only the pK_a values of bases were determined so for clarity the methodology and calculations are described in terms of bases from here on.

The determination of pK_a values is based on the determination of the differences of the pK_a values (ΔpK_a values) of two bases. The first base is a compound of interest with an unknown pK_a value and the second one is a reference base with a previously known pK_a value. Firstly, both compounds are individually titrated in MeCN. It is important for the calculations to register the correct spectra for the neutral and fully protonated forms. It is also beneficial to register at least 3 spectra in between in order to confirm the purity and absence of side processes. The spectra of the neutral and ionic form have to be different for both bases and the absorption maxima of both compounds should have a different wavelength. After individual titrations the mixture of both bases is also titrated. In case of the mixture the spectra of at least 15 titration points including the neutral and fully protonated was registered. From the spectrophotometric data the dissociation levels of both bases for each titration point can be calculated which in turn can be used to calculate the ΔpK_a of the bases (the calculation method is described in more detail in chapter 2.2).

All spectrophotometric titrations were carried out inside an MBraun Unilab glovebox which was filled with 99.999 % pure argon constantly circulating through a gas purification system. The moisture and oxygen levels were monitored in real time and they were always under 10 ppm. The Perkin-Elmer Lambda 40 (or 45) UV-Vis spectrophotometer used was connected to an external cell compartment inside the glovebox with optical fibre cables.

The solution concentrations for titrations were $2 \cdot 10^{-5}$ – $1.2 \cdot 10^{-4}$ mol l^{-1} and the titrant solutions had a concentration of $3 \cdot 10^{-3}$ – $6 \cdot 10^{-3}$ mol l^{-1}. Because of the low concentrations only small amounts of the studied compounds were needed.

Trifluoromethanesulfonic acid (TfOH, Aldrich, 99+ %) and tert-butyliminotris(pyrrolidino)phosphorane [t-Bu-P1(pyrr), Aldrich, ≥97 %] were used to prepare acidic and basic titrant solutions. Commercial acetonitrile (Romil SpS far-UV/gradient quality) was used as the solvent after drying on molecular sieves (3 Å) which resulted in a water content below 5 ppm. The water content was determined by Karl Fischer titration using a Mettler Toledo DL32 coulometer. The origin of the reference bases and the compounds studied is described in previous papers[2,9] and publications I–IV.

2.2. Calculation method

The basis for the calculation of results of the used UV-Vis spectrophotometric method is the Lambert-Beer law.

$$A_{\mathrm{X}}^{\lambda} = \varepsilon_{\mathrm{X}}^{\lambda}[X]l \tag{9}$$

In equation (9) A_{X}^{λ} is absorption of species X on wavelength λ, $\varepsilon_{\mathrm{X}}^{\lambda}$ is the molar absorption coefficient of compound X at wavelength λ and [X] is the equilibrium concentration of X. The absorption path length l can be removed from the following equations because it is equal to 1 when using a 1 cm cuvette like it was the case in this work. If there are two neutral bases B_1 and B_2 in a solution at equilibrium with their protonated forms B_1H^+ and B_2H^+ then equation (9) for the solution can be written as follows:

$$A^{\lambda} = \varepsilon_{\mathrm{B_1}}^{\lambda}[\mathrm{B_1}]l + \varepsilon_{\mathrm{B_1H^+}}^{\lambda}[\mathrm{B_1H^+}]l + \varepsilon_{\mathrm{B_2}}^{\lambda}[\mathrm{B_2}]l + \varepsilon_{\mathrm{B_2H^+}}^{\lambda}[\mathrm{B_2H^+}]l \tag{10}$$

The concentrations of the two bases B_1 and B_2 can be expressed the following way:

$$C_1 = [\mathrm{B_1}] + [\mathrm{B_1H^+}] \text{ and } C_2 = [\mathrm{B_2}] + [\mathrm{B_2H^+}] \tag{11}$$

When replacing the concentrations from equation (11) into equation (10) then the absorption can be expressed as follows:

$$A^{\lambda} = \varepsilon_{\mathrm{B_1H^+}}^{\lambda}C_1 l + \varepsilon_{\mathrm{B_2H^+}}^{\lambda}C_2 l + [\mathrm{B_1}]\left(\varepsilon_{\mathrm{B_1}}^{\lambda} - \varepsilon_{\mathrm{B_1H^+}}^{\lambda}\right)l + [\mathrm{B_2}]\left(\varepsilon_{\mathrm{B_2}}^{\lambda} - \varepsilon_{\mathrm{B_2H^+}}^{\lambda}\right)l \tag{12}$$

In order to implement equation (12) it is necessary to use the molar absorption coefficients of the neutral bases B_1 and B_2 and their protonated forms B_1H^+ and B_2H^+ calculated from the experimentally registered titration spectra of pure bases B_1 and B_2.

$$\varepsilon_{\mathrm{B_1H^+}}^{\lambda} = \frac{A_{\mathrm{B_1H^+}}^{\lambda}}{C_1^{\circ}} \text{ and } \varepsilon_{\mathrm{B_1}}^{\lambda} = \frac{A_{\mathrm{B_1}}^{\lambda}}{C_1^{\circ}} \tag{13}$$

$$\varepsilon_{\mathrm{B_2H^+}}^{\lambda} = \frac{A_{\mathrm{B_2H^+}}^{\lambda}}{C_2^{\circ}} \text{ and } \varepsilon_{\mathrm{B_2}}^{\lambda} = \frac{A_{\mathrm{B_2}}^{\lambda}}{C_2^{\circ}} \tag{14}$$

After combining equations (13) and (14) with equation (12) and regrouping its members the following equation is obtained:

$$\underbrace{A^{\lambda} - A_{\mathrm{B_1H^+}}^{\lambda}\frac{C_1}{C_1^{\circ}} - A_{\mathrm{B_2H^+}}^{\lambda}\frac{C_2}{C_2^{\circ}}}_{y} = \underbrace{\frac{[\mathrm{B_1}]}{C_1^{\circ}}}_{b_1}\underbrace{\left(A_{\mathrm{B_1}}^{\lambda} - A_{\mathrm{B_1H^+}}^{\lambda}\right)}_{x_1} + \underbrace{\frac{[\mathrm{B_2}]}{C_2^{\circ}}}_{b_2}\underbrace{\left(A_{\mathrm{B_2}}^{\lambda} - A_{\mathrm{B_2H^+}}^{\lambda}\right)}_{x_2} \tag{15}$$

The terms $\frac{[B_1]}{C_1^\circ}$ and $\frac{[B_2]}{C_2^\circ}$ in equation (15) are the dissociation levels α_1 and α_2 of bases B_1 and B_2. The "°" in the superscript refers to pure compound. $\frac{C_1}{C_1^\circ}$ and $\frac{C_2}{C_2^\circ}$ are the ratios of concentrations of bases B_1 and B_2 in the mixture solution and pure solution also termed as the relative concentrations. The dissociation levels $\alpha_1 = \frac{[B_1]}{C_1^\circ}$ and $\alpha_2 = \frac{[B_2]}{C_2^\circ}$ for each titration point can be determined by the two-parameter linear regression analysis from equation (15). The dissociation levels obtained from these calculations are used to determine the ΔpK_a value using equation (16).

$$\Delta pK_a = \log\frac{\alpha_1(1-\alpha_2)}{\alpha_2(1-\alpha_1)} \tag{16}$$

Depending on the spectral characteristic of the investigated compounds it can be possible to calculate the dissociation levels α_1 and α_2 by only using the titration spectra of the mixture of bases B_1 and B_2. In order to use this alternative calculation method an analytical wavelength has to be present where the molar absorption coefficients of the neutral (B_1) and protonated (B_1H^+) forms are equal ($\varepsilon^\lambda_{B_1} = \varepsilon^\lambda_{B_1H^+}$). This means that neither of the forms absorbs at this wavelength or it corresponds to an isosbestic point. It is important that the neutral (B_2) and protonated form (B_2H^+) of the second base have different molar absorption coefficient ($\varepsilon^\lambda_{B_1} \neq \varepsilon^\lambda_{B_1H^+}$) at this particular wavelength. If these conditions are fulfilled, then the dissociation level α_1 can be calculated using equation (17) where A^λ is the absorption on the analytical wavelength λ, $A^\lambda_{B_1+B_2}$ is the absorption of the neutral forms and $A^\lambda_{B_1H^+ + B_2H^+}$ is the absorption of the protonated forms in the mixture solution.

$$\alpha_1 = \frac{[B_1]}{[B_1H^+]} = \frac{A^\lambda - A^\lambda_{B_1H^+ + B_2H^+}}{A^\lambda_{B_1+B_2} + A^\lambda_{B_1H^+ + B_2H^+}} \tag{17}$$

The dissociation level α_2 is calculated the same way the except that the conditions described above must be *vice versa*. If the dissociation levels are known, then the ΔpK_a is calculated by using equation (16).

If a studied compound does not absorb in the UV-Vis region (i.e. is "invisible") or the spectral change during titration is very small its ΔpK_a can still be determined. The mixture of known amounts of this invisible base and a visible reference base is then titrated with the titrant of known concentration. In this case the dissociation level of the reference base is calculated according to equation (17). If the amount of the reference base in the solution, the titrant added and the reference base's dissociation level are known then the dissociation level of the invisible compound can be calculated. For this calculation method the exact amount of the added titrant before each

registration of the spectrum has to be known. This means that the concentrations of both titrants, the studied base and the reference base also have to be known. For achieving this higher amounts of compounds are used for weighing to minimize errors originating from the weighing of small amounts. Nevertheless, this approach is still not as accurate as the approach that uses the spectra of both compounds.

2.3. Gas-phase computations

Basicities in the solvent phase are a combined property of the studied molecules and the solvent. Intrinsic basicities of molecules can only be studied in the gas phase, where no solvent effects occur. The gas-phase basicity is defined by the Gibbs free energy change of the protonation reaction of base B in the gas phase as shown on equations (18) and (19).

$$\mathrm{B} + \mathrm{H}^+ \xleftrightarrow{\Delta G_\mathrm{b}} \mathrm{BH}^+ \tag{18}$$

$$\mathrm{GB} = -\Delta G_\mathrm{b} = RT \ln K \tag{19}$$

In the largest gas-phase basicity database – the NIST Chemistry Webbook[51] – experimental GB values were available for only approximately half of the heterocyclic compounds studied in this thesis. Therefore, basicities in the gas phase had to be calculated in order to obtain GB values for all the studied heterocycles.

The GB values and energies of isodesmic reactions were calculated with the G4MP2 methodology[52] by using the Gaussian 09[53] suite. G4MP2 uses geometries, vibrational frequencies and thermal corrections obtained at the B3LYP/6-31G(2df,p) level. When possible, varying starting geometries of bases (both neutral and protonated) were used for finding the most stable conformer of each species. If several possible protonation sites were present within a molecule the most stable protonated form was found. The conformers of B and BH^+ with the lowest energies were used for calculating GB values. All geometries corresponded to true energy minima. This was judged by the absence of imaginary frequencies in the vibrational spectra of the calculated species.

Quantum chemical calculations were also used for calculating free energy changes of isodesmic reactions. Isodesmic reactions are chemical reactions (usually hypothetical) in which both the number and the type of chemical bonds does not change in the course of the reaction. Isodesmic reactions are useful for elucidating the effects of molecular structure on properties.[54,55] In the case of basicity, the same isodesmic reactions are calculated for both neutral molecules and their protonated forms. This enables estimating the energetic contributions of different structural effects to basicity – both in the neutral as well as in the protonated form.[56] Usually reaction enthalpies are preferred for the

calculations of isodesmic reactions.[54,57] However, if the number of molecules does not change and no intramolecular cyclization takes place then Gibbs free energies can also be utilized and have the advantage to being linked directly with basicities.[56] In this thesis Gibbs free energies are used for isodesmic reaction calculations. The calculated isodesmic reactions can be found in Table 2 of Paper I.

3. RESULTS AND DISCUSSION

In this chapter the results of all pK_a determinations in MeCN are presented. The absolute pK_a values in MeCN were determined similarly as previously reported[58] by minimizing the sum of squares of differences of the experimentally measured ΔpK_a values and the assigned pK_a values according to equation (20)

$$SS = \sum_{i=1}^{n_m} \{\Delta \mathrm{p}K_\mathrm{a}^i - [\mathrm{p}K_\mathrm{a}(\mathrm{HB}_2^+) - \mathrm{p}K_\mathrm{a}(\mathrm{HB}_1^+)]\}^2 \quad (20)$$

in which $\Delta \mathrm{p}K_\mathrm{a}^i$ is the measured difference between the pK_a values of the conjugate B_2 and B_1, $\mathrm{p}K_\mathrm{a}(\mathrm{HB}_2^+)$ and $\mathrm{p}K_\mathrm{a}(\mathrm{HB}_1^+)$ are the absolute pK_a values of the conjugate acids of bases B_2 and B_1 found by the least-squares procedure, n_m is the number of pK_a measurements carried out and n_c is the number of compounds which pK_a was determined. Each pK_a value is reported as a result of at least two and usually three ΔpK_a measurements against different reference bases.

The reliability and consistency of the results can be evaluated by using the consistency standard deviation, which is defined by equation (21).

$$s = \sqrt{\frac{SS}{n_\mathrm{m} - n_\mathrm{c}}} \quad (21)$$

3.1. Conjugated nitrogen heterocycles

3.1.1. Overview of the results

The pK_a values of 30 conjugated nitrogen heterocyclic bases have been determined in MeCN. The structures of all studied heterocycles are presented on Figure 1. A total of 86 ΔpK_a measurements were carried out yielding a consistency standard deviation of 0.04, which indicates good consistency of the data. The experimental pK_a values, as well as calculated GB values, experimental GB values and pK_a values in water found in literature, are presented in Table 1.

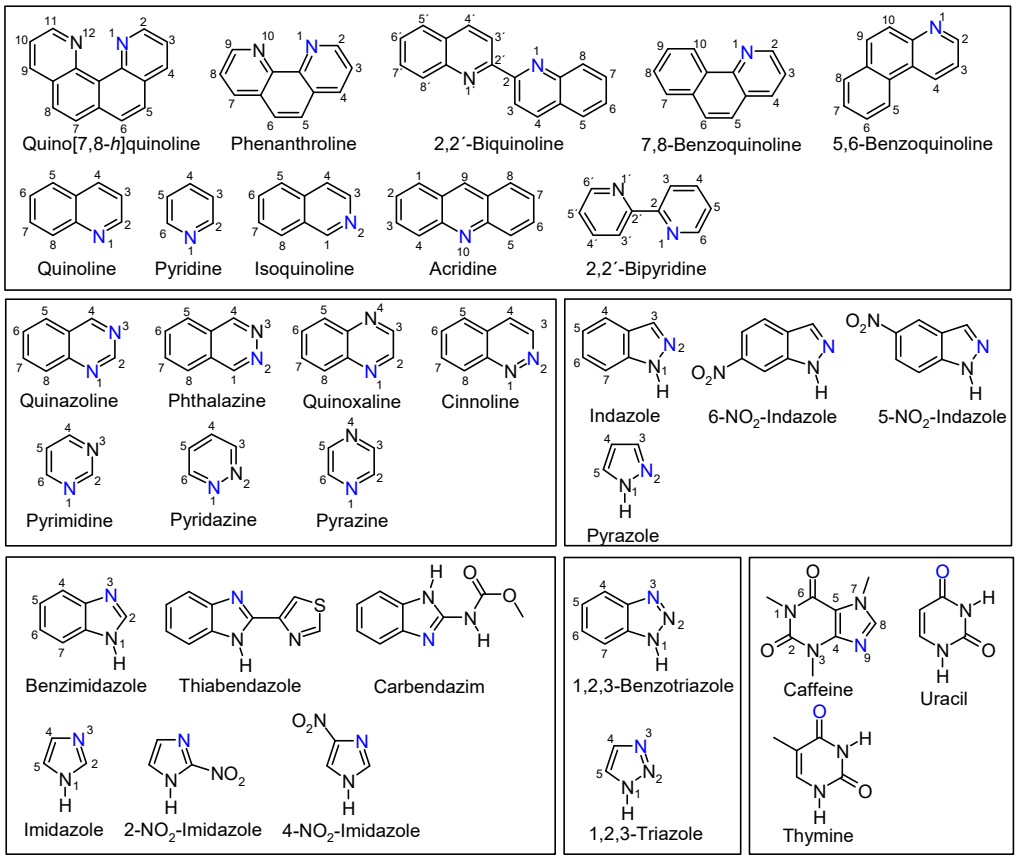


Figure 1. Structures of the heterocyclic compounds for which pK_a values were determined. The favoured protonation sites according to G4MP2 gas-phase calculations are highlighted in blue. The pK_a of cinnoline and pyridine was not determined in this work but was used in discussions.

Table 1. Experimental basicities in MeCN, H_2O and the gas-phase and calculated GB values. The bases measured in this work are in bold, the rest of the data is taken from the literature.

	Base	ΔpK_a	pK_a(MeCN)[a]	pK_a(H_2O)	GB(exp)[b]	GB(calc)[c]
1	2-Cl-$C_6H_4P_1$(pyrr)		20.17			
2	**Quino[7,8-*h*]quinoline**		**19.61**	12.0[c]	-	244.1
3	2,5-Cl_2-$C_6H_3P_1$(pyrr)		18.52			
4	4-NO_2-$C_6H_4P_1$(pyrr)		18.51			
5	2,3-$(NH_2)_2$-Pyridine		15.24			
6	**Imidazole**		**15.05**	6.95[d]	217.3	218.1
7	2,4-$(NO_2)_2$-$C_6H_3P_1$(pyrr)		14.88			
8	2,6-$(NH_2)_2$-Pyridine		14.77			
9	2,6-Cl_2-4-NO_2-$C_6H_2P_1$(pyrr)		14.43			
10	2,6-$(CH_3)_2$-Pyridine		14.13			
11	2,6-NO_2-$C_6H_3P_1$(pyrr)		14.12			
12	**Phenanthroline**		**13.68**	5.12[p]	>217	230.9
13	**Benzimidazole**		**13.52**	5.56[e]	220.0	219.8
14	2-CH_3-Pyridine		13.32			
15	**Isoquinoline**		**12.69**	5.46[f]	219.9	220.4
16	**Acridine**		**12.67**	5.62[f]	224.8	225.8
17	Pyridine		12.53	5.23[f]	214.7	214.7
18	**Thiabendazole**		**12.42**	4.64[g]	-	223.8
19	**2,2´-Bipyridine**		**12.26**	4.54[h]	223.1	225.0
20	**Carbendazim**		**12.24**	4.53[i]	-	221.9
21	**Quinoline**		**11.96**	4.93[f]	220.2	219.8
22	**5,6-Benzoquinoline**		**11.96**	5.15[h]	-	222.6
23	4-CH_3O-Aniline		11.86			
24	2-CH_3-Quinoline-8-amine		11.54			
25	**Phthalazine**		**11.55**	3.47[f]	-	219.5
26	N,N-Me_2-Aniline		11.43			
27	**2,2´-Biquinoline**		**11.28**	3.66[n]	-	230.0
28	**7,8-Benzoquinoline**		**10.84**	4.25[h]	-	221.3
29	Aniline		10.62			
30	Cinnoline		10.5[c]	2.29[f]	216.2	217.4
31	2-CH_3-Aniline		10.50			
32	**Pyridazine**		**10.07**	2.33[f]	209.6	210.5
33	2-CH_3O-Pyridine		9.93			
34	1-Naphtylamine		9.77			
35	3-Cl-Pyridine		9.55			
36	4-Br-Aniline		9.43			
37	**Quinazoline**		**9.19**	1.95[i]	-	212.3
38	**Pyrazole**		**9.1**	2.48[q]	205.7	206.0
39	**Pyrimidine**		**8.72**	1.3[f]	204.5	204.6
40	2,4-F_2-Aniline		8.39			
41	4-CF_3-Aniline		8.03			
42	**1,2,3-Triazole**		**7.9**	1.17[q]	202.5	202.4
43	2-Cl-Aniline		7.86			
44	**Pyrazine**		**7.74**	0.6[f]	202.4	202.0
45	4-F-3-NO_2-Aniline		7.67			
46	2,6-$(CH_3O)_2$-Pyridine		7.64			
47	**Indazole**		**7.61**	1.25[j]	207.7	208.3
48	**Caffeine**		**7.51**	0.60[k]	-	210.0
49	**Quinoxaline**		**7.40**	0.56[f]	208.8	208.9
50	**Benzotriazole**		**6.88**	0.42[l]	-	210.2
51	2-Cl-Pyridine		6.79			
52	N,N-Ph_2-N-CH_3-Amine		6.52			
53	**4-NO_2-Imidazole**		**6.34**	-0.16[m]	-	201.6
54	4-NO_2-Aniline		6.22			
55	2,5-Cl_2-Aniline		6.21			
56	**2-NO_2-Imidazole**		**5.54**	-0.81[d]	-	200.4
57	2,6-Cl_2-Aniline		5.06			
58	**5-NO_2-Indazole**		**4.91**	-0.96[e]	-	197.8
59	**6-NO_2-Indazole**		**4.88**	-0.97[e]	-	197.7
60	2-NO_2-Aniline		4.80			
61	4-Cl-2-NO_2-Aniline		3.80			
62	2-Cl-4-NO_2-Aniline		3.66			
63	**Uracil**		**3.38**	~0.5[o]	201.2	200.2
64	**Thymine**		**2.70**	~0[o]	203.2	203.1
65	2,3,4,5,6-Cl_5-Aniline		2.35			

[a] pK_a values measured in this work are given in bold, the rest are reference bases from literature[2,9]. [b] Ref.[51] [c] Calculated GB or pK_a values from Paper I. [d] Ref.**[59]** [e] Ref.**[60]** [f] Ref.[17] [g] Ref.**[61]** [h] Ref.[16] [i] Ref.**[62]** [j] Ref.**[63]** [k] Ref.**[64]** [l] Ref.**[65]** [m] Ref.**[66]** [n] Ref.**[67]** [o] Ref.**[68]** [p] Ref.**[69]** [q] Ref.**[70]**

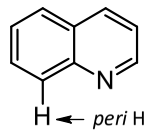
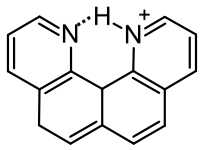
Out of the studied nitrogen heterocycles 16 had experimental GB values in literature. This situation made it possible to compare the calculated GB values from this thesis and the experimental literature values. Doing so, a root-mean-square error of 0.71 kcal mol^{-1} was obtained with the largest deviation being 1.9 kcal mol^{-1} belonging to 2,2′-bipyridine while most of the other calculated values did not deviate from the experimental values by more than 1 kcal mol^{-1}. This shows that the calculated GB values are of good quality, the used G4MP2 calculation method is suitable for the calculation of GB values of nitrogen heterocycles and it was reasonable to use these values for the discussion and calculation of isodesmic reactions.

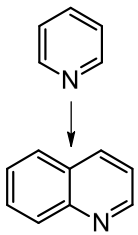
The compounds in Figure 1 can be further classified on the basis of their structures. The six-membered heterocycles embrace the families of pyridines, diazines, and compounds containing several pyridine rings. The five-membered heterocycles can be divided into derivatives of imidazole, pyrazole and 1,2,3-triazole. The within-family trends of basicities of the heterocycles can be followed in different media. Both structural and solvent effects on basicity are discussed below. Additionally to the experimentally determined pK_a values in MeCN and calculated GB values during this work also aqueous pK_a values found from literature are used in the discussion. The used isodesmic reactions can be found in Paper I (in Table 2 and in the discussion section).

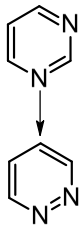
3.1.2. Relations between structure and basicity

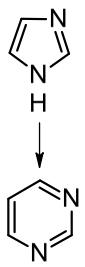
The main findings are presented in Table 2. A more detailed discussion is found in Paper I.

Table 2. Effect of a number of structural features on the basicity of the conjugated nitrogen heterocycles.

Structural feature, example	Mechanism of influencing basicity	Effect in the gas phase, examples	Effect in solution, examples
Hydrogen in the *peri* position (*peri*-H) 	(1) Stabilizes the neutral base (B) via interaction with the lone pair and (2) hinders solvation of the protonated base (BH^+). However, the effect is small and can be overshadowed by other structural changes (e.g. increasing the size of the aromatic system).	• The effect is essentially absent in the pair **isoquinoline** and **quinoline**. They have similar GB: **isoquinoline** has only by 0.6 kcal mol^{-1} higher GB value. • According to isodesmic reaction quinoline → isoquinoline (Paper I, Table 2) the lower GB of **quinoline** is caused, first of all, by the stronger stabilization of B. See Table 2 in Paper I for actual values.	• Intermediate effect: **Isoquinoline** is by 0.7 (MeCN) or 0.5 (water) pK_a units more basic than **quinoline**.
Intramolecular hydrogen bond (IMHB) in protonated form 	(1) Offers strong stabilization to BH^+ relative to the neutral; (2) in rigid systems (e.g. phenanthroline, quino[7,8-*h*]quinoline) lone pair repulsion may simultaneously markedly destabilize the neutral. Both effects increase the intrinsic basicity. (3) In solution IMHB reduces solvation of BH^+, thereby slightly decreasing basicity.	• The effect is very pronounced in the GP. • **2,2'-bipyridine** is by 6.7 kcal mol^{-1} more basic than its hypothetical analogue not forming IMHB in BH^+. • The estimated basicity-increasing effect of lone-pair repulsion in B and the IMHB in BH^+ on the GB value of **phenanthroline** and **quino[7,8-*h*]quinoline** is 11–12 and 20-24 kcal mol^{-1}, respectively. These estimates are obtained on the basis of isodesmic reactions (11) – (13) from Paper I. • On the basis of direct comparison of basicities **phenanthroline** (IMHB in BH^+) is by 8 kcal mol^{-1} more basic than **5,6-benzoquinoline** (no IMHB).	• The effect is less pronounced in solution and depends on solvation ability of the solvent. • On the basis of available experimental data it can be quantitatively estimated by comparing **phenanthroline** with **5,6-benzoquinoline**. Phenanthroline is by 1.7 pK_a units more basic in MeCN and has very similar basicity in water.

Structural feature, example	Mechanism of influencing basicity	Effect in the gas phase, examples	Effect in solution, examples
Fusion of an additional benzene ring to single ring heterocycles 	(1) Increases the volume for the distribution of the positive charge in BH^+; (2) fused benzene ring may act as an electron-withdrawing or donating group depending on the relative overall electronegativity of the initial heterocycle; (3) *peri* effect is possible.	• Fusion of an additional ring universally increases the basicity. • According to isodesmic reactions the stabilizing effect in BH^+ amounts to 6.0 kcal mol^{-1} in the case of **pyridine → quinoline**, 5.6 kcal mol^{-1} in the case of **pyridine → isoquinoline**, 4.2 kcal mol^{-1} in the case of **imidazole → benzimidazole**. • Comparison between **pyridine** and **quinoline/isoquinoline** shows that the latter have a 5.1 and 5.7 kcal mol^{-1} GB value. • Benzodiazines have 7 – 9 kcal mol^{-1} higher GB values than their corresponding diazines (e.g. **quinazoline** has 7.7 kcal mol^{-1} higher GB value than **pyrimidine**). • For 5-membered heterocycles with two nitrogen atoms the effect is smaller but in three nitrogen 5-membered heterocycles the effect is comparable to 6-membered heterocycles. **Benzimidazole** is only 1.7 kcal mol^{-1} more basic than **imidazole**. • Comparison of **1,2,3-triazole** to **1,2,3-benzotriazole** shows that the latter has a 7.8 kcal mol^{-1} higher GB.	• In solution the effect is mixed. • In MeCN **pyridine** is by 0.57 pK_a units more basic than **quinoline** and 0.16 pK_a units less basic than **isoquinoline**. In water the corresponding values are 0.30 and 0.23. • **Phthalazine** and **quinazoline** are more basic than **pyridazine** and **pyrimidine** by 1.48 and 0.47 pK_a units in MeCN and by 1.14 and 0.65 pK_a units in water. • **Imidazole** has a 1.53 unit higher pK_a value than **benzimidazole** in MeCN and 1.39 in water. • In case of **1,2,3-benzotriazole** and **1,2,3-triazole** the former is by 1.02 pK_a units more basic in MeCN and by 0.75 pK_a units in water.

Structural feature, example	Mechanism of influencing basicity	Effect in the gas phase, examples	Effect in solution, examples
Relative position of nitrogen atoms in the 5- or 6-member ring 	(1) Presence of two neighboring nitrogen atoms destabilizes the B due to lone pair repulsion. (2) A nitrogen atom in the *meta* or *para* position acts as an electron withdrawing group in 6-member heterocycles. (3) Due to the resonance effect the additional nitrogen in the *para* position has a larger effect.	• The effect is very strong. • The order of basicity of diazines is the same in all three media: **pyridazine** > **pyrimidine** > **pyrazine**. • **Pyridazine** has a 5.9 kcal mol^{-1} and 8.5 kcal mol^{-1} higher GB value than **pyrimidine** and **pyrazine** respectively and is mainly caused by the relatively less stable B of pyridazine. According to isodesmic reactions (pyridazine + benzene → 2 pyridine and analogous reactions with pyrimidine and pyrazine from Table 2 of Paper I) the B of **pyridazine** is 21.9 kcal mol^{-1} and 17.7 kcal mol^{-1} less stable than **pyrimidine** and **pyrazine** respectively. • **Imidazole** has a 12.1 kcal mol^{-1} higher GB value than **pyrazole**. According to isodesmic reactions (reaction (19) from Paper I) this large difference is caused first of all by the 23.0 kcal mol^{-1} more stable BH^+ of **imidazole** compared to **pyrazole**.	• The effect is strong to very strong depending on situation. • **Pyridazine** is by 1.36 pK_a units more basic than **pyrimidine** in MeCN and by 1 unit more basic in water. • **Pyrimidine** is by 0.98 pK_a units more basic than **pyrazine** in MeCN and by 0.7 units in water. • **Imidazole** is by 5.95 pK_a units more basic than **pyrazole** in MeCN and by 4.47 units in water.

Structural feature, example	Mechanism of influencing basicity	Effect in the gas phase, examples	Effect in solution, examples
Effect of ring size 	(1) Five-membered aromatic heterocycles have a higher overall electron density than six-membered aromatic heterocycles. This effect can in some compounds be outweighed by the steric hindrance of two N-H fragments in close vicinity. (2) In 6-membered heterocycles the second nitrogen acts as an electron withdrawing group.	• The effect is very strong. • Comparison of the GB values show that **imidazole** is a stronger base than **pyrimidine** in the gas phase by 13.5 kcal mol^{-1}. • **Pyrazole** on the other hand is a weaker base than **pyridazine** by 4.5 kcal mol^{-1}. • The same trends can be observed when comparing the benzo annulated analogues of the above-mentioned heterocycles.	• The effect is very strong. • **Imidazole** is a stronger base than **pyrimidine** also in MeCN and water by 6.33 and 5.65 pK_a units respectively. • **Pyrazole** is a weaker base than **pyridazine** in MeCN by 0.97 pK_a units but in water its pK_a is 0.15 units higher.

As can be seen from the table above and the discussion in Paper I the basicity data gives a good opportunity to rationalize the relations between the basicity of the heterocycles and their structure.

3.1.3. Correlation of basicity values of nitrogen heterocycles in different media

Using the experimentally determined pK_a values, calculated GB values and the collected basicity values from literature different correlations could be made (Figure 2). Uracil and thymine are not included to the correlations because gas phase calculations suggest protonation to oxygen instead of nitrogen, differently from all the other compounds.

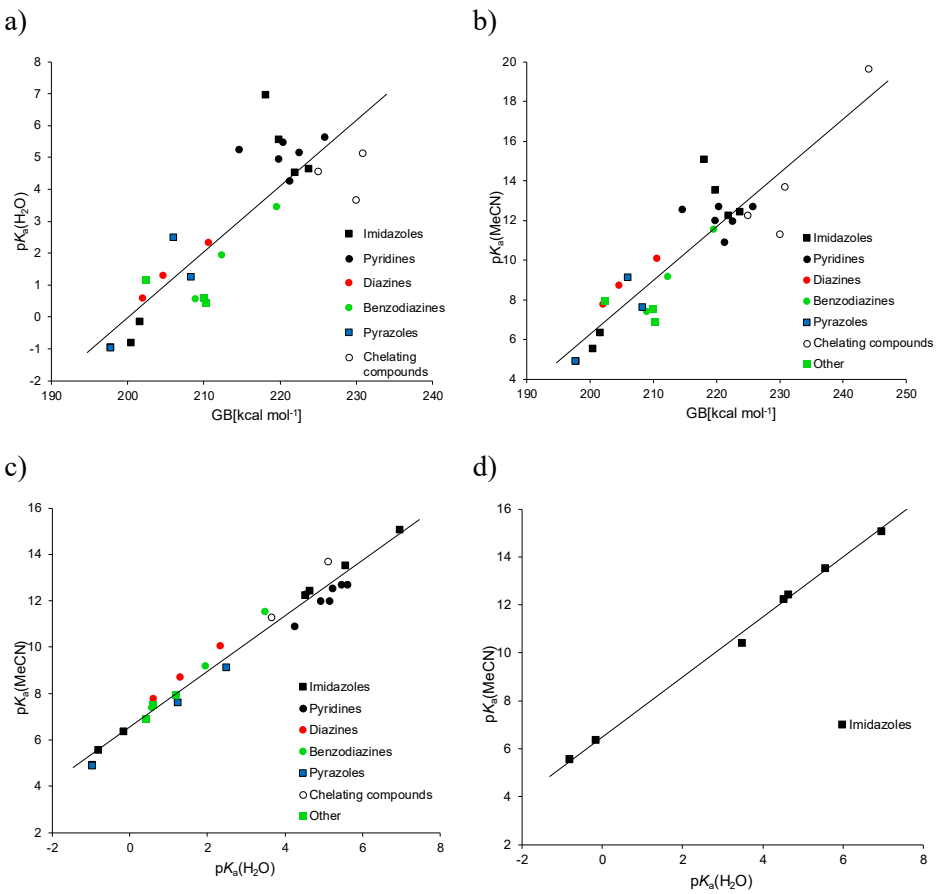


Figure 2. Correlation of basicity values in: a) GP and H_2O; b) GP and MeCN; c) H_2O and MeCN; d) H_2O and MeCN (only imidazoles).

The correlations of GB values and pK_a values in H_2O (equation (22)) or MeCN (equation (23)) are poor. This makes sense because the GP is a markedly different medium compared to H_2O and MeCN.

$$\mathrm{p}K_\mathrm{a}(\mathrm{H_2O}) = 0.21\mathrm{GB_{calc}} - 41.42 \quad (22)$$
$$r^2 = 0.741;\ s(\text{slope}) = 0.02;\ s(\text{intercept}) = 5.14;\ S = 1.23;\ n = 28$$

$$\mathrm{p}K_\mathrm{a}(\mathrm{MeCN}) = 0.27\mathrm{GB_{calc}} - 47.98 \quad (23)$$
$$r^2 = 0.820;\ s(\text{slope}) = 0.02;\ s(\text{intercept}) = 5.07;\ S = 1.46;\ n = 29$$

The correlation between pK_a values in MeCN and water is much better.

$$\mathrm{p}K_\mathrm{a}(\mathrm{MeCN}) = 1.20\mathrm{p}K_\mathrm{a}(\mathrm{H_2O}) + 6.57 \quad (24)$$
$$r^2 = 0.972;\ s(\text{slope}) = 0.04;\ s(\text{intercept}) = 0.15;\ S = 0.50;\ n = 28$$

An even better correlation (equation (25)) can be obtained when only using one type of heterocycles. The following correlation includes all the imidazole compounds (also benzimidazole) and also the pK_a values of 5-NO_2-benzimidazole and 2-NH_2-imidazole previously reported by Kaljurand et al.[2]

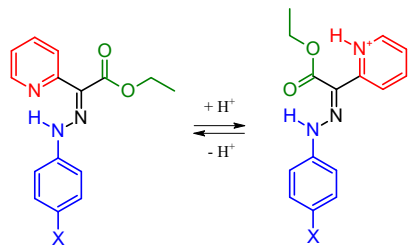
$$\mathrm{p}K_\mathrm{a}(\mathrm{MeCN}) = 1.26\mathrm{p}K_\mathrm{a}(\mathrm{H_2O}) + 6.47 \quad (25)$$
$$r^2 = 0.997;\ s(\text{slope}) = 0.03;\ s(\text{intercept}) = 0.13;\ S = 0.22; n = 8$$

Similar slope and intercept values for correlations in MeCN and water have been previously reported for substituted pyridines (pK_a(MeCN) = 1.27pK_a(H_2O) + 6.04; *s*(slope) = 0.05; *s*(intercept) = 0.30)[2] and (pK_a(MeCN) = 1.25pK_a(H_2O) + 6.34; *s*(slope) = 0.02; *s*(intercept) = 0.11)[71]. There is no statistically significant difference between the slopes and intercepts of these correlations and correlation (24).

3.2. Arylhydrazone molecular switches

The pK_a values of 11 arylhydrazone-based pH-sensitive molecular switches were determined in MeCN.[IV] The results are presented in Table 3.

Table 3. The pK_a values and protonation reaction of arylhydrazone based molecular switches in MeCN**.**



Compound	–X	pK_a(MeCN)
M1	$-N(CH_3)_2$	13.39
M2	–OH	12.92
M3	$-O(CH_2)_5CH_3$	12.86
M4	$-OCH_3$	12.82
M5	–H	12.26
M6	–F	12.26
M7	–Br	12.08
M8	–Cl	12.08
M9	$-COOCH_3$	11.6
M10	–CN	11.4
M11	$-NO_2$	10.2

As shown in Table 3, after protonation the initial IMHB between the pyridyl nitrogen and the hydrazone hydrogen atom breaks, configurational change occurs and a new IMHB forms between the hydrazone hydrogen and oxygen atom of the carbonyl group. These configurational changes on protonation-deprotonation in the studied compounds cause slowness of establishing of the equilibrium shown in Table 3. This also made the pK_a determinations more complicated and time consuming because it was necessary to wait for establishing of the equilibrium after each titrant addition. It was found that the equilibrium established in 10–15 minutes for compounds **M1** – **M4**, in 15–20 minutes for **M5** – **M8** and in 40–50 minutes for **M9** – **M11**. These are qualitative estimations. The protonation of these compounds is still a very fast process but the rate limiting step is the configurational change.[72] Although it may seem that rotation happens around the C=N double bond this is actually not the case. Landge et al. have reported that because of hydrazone-azo tautomerization the rotation happens actually around the C-N single bond.[72]

Because the only difference between the studied compounds is the substituent X, a correlation with the pK_a values and the resonance (σ_R) and inductive (σ_F) substituent constants[73] could be made using the linear free energy relationship equation ($pK_a = pK_a^0 + \rho_R\sigma_R + \rho_F\sigma_F$) developed by Taft[74]. This yielded the following equation:

$$pK_a = 12.33 - 2.03\sigma_R - 1.13\sigma_F \quad (26)$$
$$s(pK_a^0) = 0.10;\ s(\rho_R) = 0.18;\ s(\rho_F) = 0.22;\ r^2 = 0.974; S = 0.11$$

M11 was not included in this correlation because of the not so reliable pK_a value (see Paper IV). From equation (26) it can be seen that the basicities of the studied arylhydrazones are almost twice as sensitive to the resonance effect as to the inductive effect.

3.3. Triarylphosphanes

In this work the basicity of 9 different triarylphosphanes was studied (see Figure 3 for the structures).[III] The consistency standard deviation from 19 ΔpK_a measurements in MeCN is 0.04 indicating good consistency of the results. The results are presented in Table 4. The pK_a value of **P6** in MeCN was determined by using a correlation with DCE pK_a data measured by Karl Kaupmees.

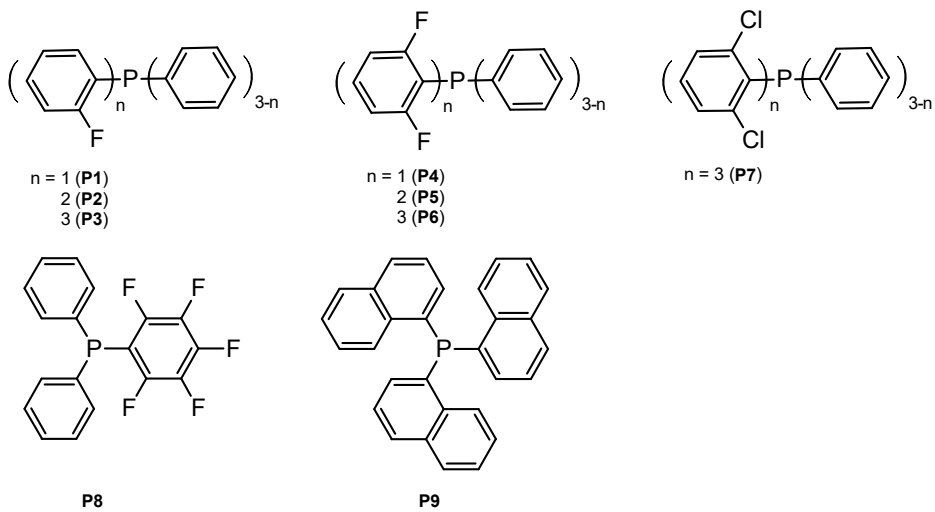


Figure 3. Structures of the studied triarylphosphanes.

Because the compounds **P1**, **P2**, **P3** only differ from each by the number of 2-F-substituted aromatic rings it is reasonable to compare their pK_a values with the unsubstituted triphenylphosphane (pK_a(MeCN) = 7.64[9]). It appears that the pK_a values trend well with the number of substituted aromatic rings, as displayed in Figure 4. Each additional 2-F- substituted ring lowers the pK_a value of triphenylphosphine by 1.52–1.55 pK_a units. Compounds **P4**, **P5** and **P6** have a different number of benzene rings with two fluoro substituents in *ortho* positions. Expectedly, the 2,6-F_2- disubstitution in the aromatic ring has a larger effect than 2-F- substitution on the pK_a value of triphenylphosphane. The interesting observation is that each additional benzene ring with fluoro substituents in both *ortho* positions has a different pK_a lowering effect. The

basicity-decreasing effect of the first difluoro substituted ring is 2.48, the second 2.64 and the third 1.82 pK_a units. The value 1.82 in case of the third aromatic ring is possibly of lower accuracy because the pK_a value of **P6** was not directly determined in MeCN as stated above.

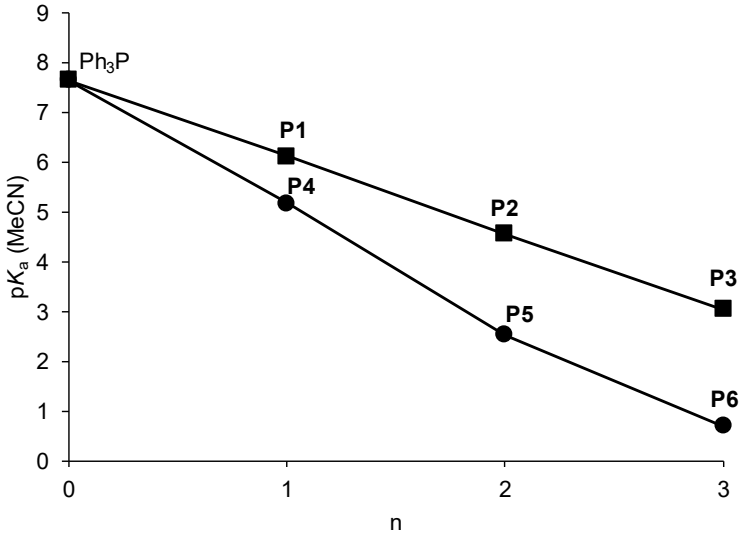
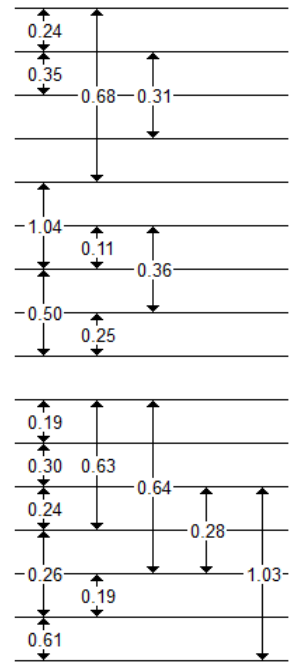


Figure 4. The relation between the pK_a and the number (n) of 2-F- and 2,6-F_2-substituted triphenylphosphanes.

The phosphane **P7** is an analogue of **P6** having chloro substituents instead of fluoro. The pK_a value of **P7** is approximately 1 unit higher than **P6** meaning that chloro substituents have a smaller basicity-decreasing effect on triarylphosphanes. Phosphane **P9** has a 1.09 units lower pK_a value than triphenylphosphane. The lower pK_a value of **P9** is caused by the more extensive conjugation of the lone pair the phosphorus atom with the naphthyl groups than the phenyl groups.

Table 4. The experimentally determined pK_a values of triarylphosphanes in MeCN.

	Base	pK_a	ΔpK_a
1	2-Cl-pyridine	6.79	
P9	**$(C_{10}H_7)_3P$**	**6.55**	
2	4-NO_2-aniline	6.22	
3	2,5-Cl_2-aniline	6.21	
P1	**(2-F-C_6H_4)$(Ph)_2P$**	**6.10**	
P4	**(2,6-F_2-C_6H_3)$(Ph)_2P$**	**5.16**	
4	2,6-Cl_2-aniline	5.06	
5	2-NO_2-aniline	4.80	
P2	**(2-F-C_6H_4)$_2$(Ph)P**	**4.55**	
6	5-Cl-2-NO_2-aniline	3.22	
P3	**(2-F-C_6H_4)$_3$P**	**3.03**	
7	2,3,5,6-Cl_4-aniline	2.73	
P8	**(C_6F_5)$(Ph)_2P$**	**2.56**	
P5	**(2,6-F_2-C_6H_3)$_2$(Ph)P**	**2.52**	
8	2,3,4,5,6-Cl_5-aniline	2.35	
P7	**(2,6-Cl_2-C_6H_3)$_3$P**	**1.72**	

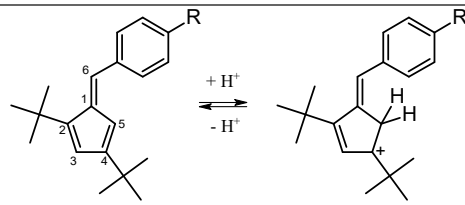


The Jan Paradies research group used the pK_a values determined in MeCN to show the dependency of the temperature needed to activate H_2 molecules during the hydrogenation reaction of alkenes and the basicity of the used fluoro substituted triarylphosphane catalyst. It was found that the higher the pK_a the higher the temperatures that are needed for the reaction (more details in Paper III).

3.4. Pentafulvenes

The basicities of 7 substituted 6-phenylpentafulvenes were determined in MeCN (Table 5).[II] For compounds **F1** – **F5** it was possible to carry out pK_a measurements in MeCN and a consistency standard deviation of 0.04 was obtained. **F6** and **F7** were too weak bases to be reliably measured in MeCN. Therefore, the pK_a for **F6** and **F7** was found from correlation of DCE basicity values measured by Robert Järviste.

Table 5. pK_a determination results and protonation reaction of the studied 6-phenylpentafulvenes.

	Compound	–R	pK_a(MeCN)
	F1	–$N(CH_3)_2$	10.29
	F2	–OCH_3	4.57
	F3	–CH_3	3.52
	F4	–H	2.93
	F5	–Cl	2.58
	F6	–CN	1.18[a]
	F7	–NO_2	0.87[a]

[a] pK_a values obtained from correlation.

The studied pentafulvenes protonate to the carbon atom at position C5 giving a stable carbocation. No decomposition was observed during the pK_a measurements according to the UV-Vis spectrum. Its stability comes from the extensive delocalization of the positive charge over the whole molecule. The much higher pK_a value of **F1** indicates protonation to the dimethylamino group instead of C5 carbon.

After correlation of the pK_a values with the resonance (σ_R) and inductive (σ_F) substituent constants the following equation was obtained:[II]

$$\mathrm{p}K_a = 2.92 - 4.80\sigma_R - 1.93\sigma_F \quad (27)$$
$$s(\mathrm{p}K_a^0) = 0.16;\ s(\rho_R) = 0.45;\ s(\rho_F) = 0.38;\ r^2 = 0.986;\ S = 0.21$$

When comparing the correlations (26) and (27) it seems that the basicity of pentafulvenes is more sensitive towards substituent effects than the basicity of arylhydrazones.

SUMMARY

In this thesis the basicities of the members of 4 different compound families were investigated. These compounds were triaylphosphanes, pentafulvenes, arylhydrazones and a wide variety of nitrogen heterocycles. Altogether 57 new pK_a values in acetonitrile were experimentally measured using the UV-Vis spectrophotometric method. Additionally, the GB values for all 30 investigated nitrogen heterocycles were determined computationally.

Using the experimentally determined pK_a values in acetonitrile as well as basicity values from literature and computed GB values, the main factors coming from structural features determining the basic strength of nitrogen heterocycles were rationalized. These structural features were: presence of the *peri* hydrogen, intramolecular hydrogen bond, fusion of additional benzene ring, relative position of nitrogen atoms in the ring and ring size. It was found that these effects are present in all studied media but to a different extent. The *peri* effect causes decrease in basicity in all media although in the gas phase the decrease is very small. The presence of an intramolecular hydrogen bond in the protonated species of a heterocycle is a basicity increasing effect and it was found to be very pronounced in gas phase but in solvents its scope depends on the solvents solvation ability. Similarly, the fusion of an additional benzene ring is a basicity increasing effect in the gas phase but generally not in solution. A second nitrogen in a 6-member heterocycle acts as an electron withdrawing group thus decreasing the basicity with respect to the analogous one nitrogen heterocycle. The scope of such decreasing effects depends on the position of the second nitrogen in all studied media. Five membered heterocycles have higher electron densities than their six membered counterparts thus making them somewhat more basic. Nevertheless, other effects could outweigh that.

The calculated gas phase basicities for nitrogen heterocycles were shown to be of good quality and it justified to use these in the rationalization of structural effects.

It was shown that the pK_a values of nitrogen heterocycles correlate well in water and acetonitrile. The pK_a values of substituted pentafulvenes and arylhydrazones correlate well with the Hammett substituent parameters.

The obtained correlations, as well as rationalization of structure-basicity relationships can be used for pK_a estimations of similar compounds.

The pK_a values of arylhydrazones and triarylphosphanes determined for this thesis have been used by our collaborators to show relations between the basicity and behaviour of these compounds in their fields of application.

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SUMMARY IN ESTONIAN

Mõnede lämmastiku, fosfori ja süsiniku aluste aluselisus atsetonitriili keskkonnas

Käesoleva doktoritöö raames uuriti nelja aineperekonda kuuluvate ühendite aluselisusi. Need ühendid olid triarüülfosfaanid, pentafulveenid, arüülhüdrasoonid ja lai valik lämmastikheterotsükleid. Kokku määrati eksperimentaalselt 57 uut pK_a väärtust atsetonitriili keskkonnas kasutades UV-Vis spektrofotomeetrilist meetodit. Lisaks sellele määrati arvutuslikult gaasifaasi aluselisuse (GB) väärtused kõigile 30 uuritud heterotsüklilisele ühendile.

Kasutades eksperimentaalselt määratud pK_a väärtusi atsetonitriilis, arvutuslikke GB väärtusi ja varasemalt kirjanduses avaldatud pK_a väärtusi vesikeskkonnas uuriti struktuuri iseärasuste poolt põhjustatud mõjutusi erinevate heterotsüklite aluselisusele. Nendeks struktuurseteks iseärasusteks osutusid *peri* vesiniku olemasolu, sisemolekulaarne vesinikside protoneeritud vormis, täiendavalt liidetud aromaatne tuum, lämmastiku aatomite suhteline asukoht tsüklis ja tsükli suurus. Leiti, et need mõjutused on olemas kõigis uuritud keskkondades, aga nad mõjutavad aluselisust erineval määral. *Peri* efektil on heterotsüklitel aluselisust alandav toime kõigis keskkondades, kuigi gaasifaasis on see väga väike. Sisemolekulaarse vesiniksideme olemasolu aluse protoneerunud vormis põhjustab aluselisuse suurenemist, mis on märkimisväärne gaasifaasis. Solvendis oleneb selle efekti ulatus solvendi solvateerivast mõjust. Täiendava aromaatse tuuma liitmine heterotsüklile omab aluselisust tõstvat mõju gaasifaasis, aga mitte solvendi keskkonnas. Teine lämmastikuaatom kuuelülilises tsüklis käitub kui elektronaktseptoorne asendusrühm ja seega põhjustab madalamat aluselisust võrreldes analoogse heterotsükliga, milles on üks lämmastikuaatom. Selle efekti suurus sõltub kõigis keskkondades teise lämmastiku suhtelisest asukohast. Viielülilistel heterotsüklitel on kõrgem elektrontihedus kui nende kuuelülilistel analoogidel, mistõttu on nemad üldiselt ka kõrgema aluselisusega, kuigi teised efektid võivad sellest suurema mõjuga olla.

Näidati, et heterotsüklite pK_a väärtused korreleeruvad hästi atsetonitriili ja vesikeskkonna vahel. Uuritud pentafulveenide ja arüülhüdrasoonide aluselisused korreleeruvad hästi Hammett'i substituendikonstantidega.

Käesolevas töös esitatud korrelatsioone ja struktuuri-aluselisuse sõltuvuste uuringut saab edaspidi kasutada sarnaste ühendite pK_a väärtuste hindamisel.

Käesolevas töös määratud arüülhüdrasoonide ja triarüülfosfaanide pK_a väärtusi kasutati koostööpartnerite poolt näitamaks sõltuvusi aluselisuse ja uuritud ühendite käitumise vahel nende rakendusvaldkonnas.

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PUBLICATIONS

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