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# Acid−Base Equilibria in Nonpolar Media. 3. Expanding the Spectrophotometric Acidity Scale in Heptane

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The UV−vis spectrophotometric ion-pair acidity scale in heptane has been significantly expanded: it includes now 21 bulky CH and NH indicator acids and spans for about 10 p$K_{ip}$ units. The phosphazene base *t*-Bu-$P_4$ was used for deprotonating. The correlations between acidities in heptane versus gas-phase acidities or acidities in DMSO or 1,2-dimethoxyethane have been made for some compounds. It was demonstrated that the substituent effects on the acidity of the studied CH acids are attenuated ca. 1.24 times when the gas phase is substituted for the nonpolar solvent, heptane. In its turn, for the series of NH acids, the latter is found to be a somewhat more differentiating solvent than DMSO.

## Introduction

In the first paper of this series,[1] we succeeded to create the first self-consistent spectrophotometric ion-pair acidity scale in the nonpolar solvent heptane. That scale contains six acids linked by nine overlapping relative acidity measurements and has a span of around 3 p$K$ units. Acidity scales, in relatively nonpolar solvents, although scarce, are not unknown. The first ion-pair acidity scales in low-polarity media were set up by Conant et al.[2] in diethyl ether ($\epsilon = 4.20$) and by McEwen[3] in benzene ($\epsilon = 2.27$). Since then, several others have been created: in cyclohexylamine[4] ($\epsilon = 4.73$), in 1,2-dimethoxyethane[5] ($\epsilon = 7.20$), and in tetrahydrofuran[6] ($\epsilon = 7.58$). However, the heptane scale[1] is to date the only acidity scale created in a medium with a dielectric constant less than 2 ($\epsilon = 1.92$). In such a nonpolar medium, ions will not dissociate but form ion pairs. The acidities measured in such a medium are called ion-pair acidities (expressed as p$K_{ip}$ values; see eqs 4 and 5 below).

Acidity data in solvents of low polarity are very valuable for several reasons, including (1) the possibility to investigate compounds in an environment that has less influence on their properties than do the polar solvents, (2) the possibility to study systems of extraordinarily high or low acidity, and (3) the possibility to mimic real processes in organic synthesis and chemical technology, many of which are carried out in nonpolar media.

The scale compiled previously contained only six compounds and had a range of less than 4 p$K$ units.[1] In this work our goal was to add numerous new compounds to the scale and to significantly expand its span. The compounds to be added are mostly CH acids that have anions with highly delocalized charge. Many of them are partially or fully fluorinated to further increase the delocalization of the charge in the anion. The criteria for selecting acids for acidity measurements in heptane are presented in ref 1.

The same method of measurement was used as previously involving the highly useful phosphazene *t*-Bu-$P_4$[7] (see Figure 1)—a very strong sterically hindered base—as the deprotonating agent. The protonated form of this base—a large cation with very delocalized positive charge—is a good counterion, because specific and electrostatic attraction effects between it and the anions are practically negligible.

When measuring acidities in polar solvents the following equilibrium is studied usually:

$$HA + S \rightleftarrows A^- + SH^+ \tag{1}$$

where S refers to the solvent. This equilibrium is also used to define the term “acidity of a compound,” which is usually expressed as p$K_a$,

$$K_a = \frac{a(SH^+)a(A^-)}{a(HA)} \tag{2}$$

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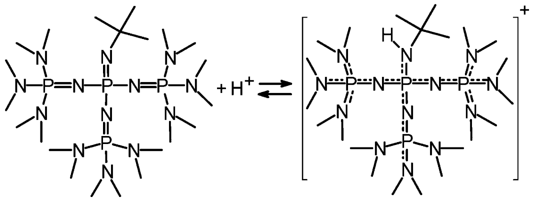

**FIGURE 1.** The structure of the base $t$-Bu-$P_4$ and its protonated form.

where $K_a$ is the equilibrium constant of the equilibrium (1) and $a$ values are activities. In nonpolar medium it is common to study the following equilibrium instead:

$$\mathrm{HA}_2 + \mathrm{A}_1^{-} \rightleftarrows \mathrm{A}_2^{-} + \mathrm{HA}_1 \qquad (3)$$

Equation 3 is simplified in the sense that the anions $A_1^-$ and $A_2^-$ are generally not free in nonpolar media. They are usually ion-paired (forming contact or solvent-separated ion pairs) with cations or even aggregated into larger aggregates (ion tetramers, etc.). The extent of aggregation depends on the polarity of the medium, the nature of the anions and cations present in the solution, and the concentrations of these species. It was discussed in our previous work[1] that the conjugate anions of the studied acids are in the heptane solution bound to the large cation of protonated $t$-Bu-$P_4$ phosphazene forming “loosely bound” ion pairs similar to the “cryptate-separated” ion pairs described by Konovalov et al.[8] Hence, in our case the more correct way of expressing eq 3 is

$$\mathrm{HA}_2 + \mathrm{PH}^{+}{\cdot}\mathrm{A}_1^{-} \rightleftarrows \mathrm{PH}^{+}{\cdot}\mathrm{A}_2^{-} + \mathrm{HA}_1 \qquad (4)$$

where $PH^+$ denotes the protonated $t$-Bu-$P_4$ phosphazene. Also, it is not entirely correct to denote the ion-pair acidities obtained in heptane by p$K_a$ (which refers to ionic acidities[9]), as was done in our previous work, but rather by p$K_{ip}$ (ip stands for “ion pair”). Thus, the p$K$ of the equilibrium 4—obtained directly from the experiment—is the relative ion-pair acidity—Δp$K_{ip}$—of the acids $HA_1$ and $HA_2$:

$$\Delta \mathrm{p}K_{\mathrm{ip}} = \mathrm{p}K_{\mathrm{ip}}(\mathrm{HA}_2) - \mathrm{p}K_{\mathrm{ip}}(\mathrm{HA}_1) = \log\frac{a(\mathrm{PH}^{+}{\cdot}\mathrm{A}_1^{-})\,a(\mathrm{HA}_2)}{a(\mathrm{PH}^{+}{\cdot}\mathrm{A}_2^{-})\,a(\mathrm{HA}_1)} \qquad (5)$$

For establishing the acidity scale, we used a spectrophotometric titration method in which the ratios of concentrations of the neutral and ionic form of the studied compounds (indicator ratios) are obtained from UV−vis spectra.

## Experimental Section

**Method of p$K_{ip}$ Determination.** The relative acidities were measured using the UV−vis spectrophotometric titration technique, very similar to the one used in our previous work. It has been described in refs 1 and 10. Only the essentials will be outlined here.

A solution containing a mixture of two acids, $HA_1$ and $HA_2$, in acid form is titrated with a solution of $t$-Bu-$P_4$ until both acids are fully deprotonated by the phosphazene. The spectrum of the solution is recorded after each addition of the titrant. Both of the acids are also titrated separately to obtain the spectra of the neutral and the ionized form of both acids. From these sets of spectra the relative acidity of the two acids, $HA_1$ and $HA_2$, is calculated. The main calculation method is presented below.

To correct for the dilution caused by titrant addition, all the spectra are recalculated to constant concentration before calculations of acidity.

Because very low concentrations are used for measurements and the acids have quite similar structures and give anions with the same charge type, we assume that the activity coefficient ratios (of neutral and anion) of the two acids are equal, so that the ratios of activities in eq 5 can be replaced by the ratios of concentrations.

These ratios (indicator ratios) in eq 5 can be calculated from the absorbance spectra. The only prerequisite is that the two compounds must have different spectra in the UV−vis region and the spectrum of the acid must be different from that of the anion. These criteria are met by all the acids under study.

When two partially ionized acids, $HA_1$ and $HA_2$, are in the same solution, the Beer’s law for net absorbance at wavelength $\lambda$ can be written [the optical path length, 1 cm, is equal for all substances and is included in $A^{\lambda}$; also, normalized concentrations for the acids ($[\mathrm{HA}_1] = 1 - [\mathrm{A}_1^-]$ and $[\mathrm{HA}_2] = 1 - [\mathrm{A}_2^-]$) are used, absorbance caused by solvent is compensated, and $t$-Bu-$P_4$ is transparent]:

$$A^{\lambda} = [\mathrm{HA}_1]\epsilon_{\mathrm{HA}_1}{}^{\lambda} + [\mathrm{A}_1^{-}]\epsilon_{\mathrm{A}^{-}_{1}}{}^{\lambda} + [\mathrm{HA}_2]\epsilon_{\mathrm{HA}_2}{}^{\lambda} + [\mathrm{A}_2^{-}]\epsilon_{\mathrm{A}^{-}_{2}}{}^{\lambda} \qquad (6)$$

The $\epsilon_X{}^{\lambda}$ values are normalized concentration absorptivities (extinction coefficients) of respective species. Rearrangement gives

$$A^{\lambda} = \epsilon_{\mathrm{HA}_1}{}^{\lambda} + \epsilon_{\mathrm{HA}_2}{}^{\lambda} + [\mathrm{A}_1^{-}](\epsilon_{\mathrm{A}^{-}_{1}}{}^{\lambda} - \epsilon_{\mathrm{HA}_1}{}^{\lambda}) + [\mathrm{A}_2^{-}](\epsilon_{\mathrm{A}^{-}_{2}}{}^{\lambda} - \epsilon_{\mathrm{HA}_2}{}^{\lambda}) \qquad (7)$$

And finally:

$$\frac{A^{\lambda} - \epsilon_{\mathrm{HA}_1}{}^{\lambda} - \epsilon_{\mathrm{HA}_2}{}^{\lambda}}{(\epsilon_{\mathrm{A}^{-}_{2}}{}^{\lambda} - \epsilon_{\mathrm{HA}_2}{}^{\lambda})} = [\mathrm{A}_1^{-}]\frac{(\epsilon_{\mathrm{A}^{-}_{1}}{}^{\lambda} - \epsilon_{\mathrm{HA1}}{}^{\lambda})}{(\epsilon_{\mathrm{A}^{-}_{2}}{}^{\lambda} - \epsilon_{\mathrm{HA}_2}{}^{\lambda})} + [\mathrm{A}_2^{-}] \qquad (8)$$

The equation has evolved into a linear equation with slope $[A_1^-]$ and intercept $[A_2^-]$. All the $\epsilon_X{}^{\lambda}$ values are constants at a fixed wavelength and they can be determined from spectra containing only one acid in entirely ionized or neutral form. If we take a spectrum of a solution containing both acids in partially ionized form and vary the $\lambda$, then the terms containing absorbance and the absorptivities are variables and the $[A_1^-]$ and $[A_2^-]$ are constants, which can be determined from regression analysis, and the relative ion-pair acidity can be calculated as follows:

$$\Delta \mathrm{p}K_{\mathrm{ip}} = \log\frac{[\mathrm{A}_1^{-}](1 - [\mathrm{A}_2^{-}])}{[\mathrm{A}_2^{-}](1 - [\mathrm{A}_1^{-}])} \qquad (9)$$

This general calculation method is universal; the only prerequisite is that the ratio of the concentration of a particular acid in the mixture solution and in pure solution must be accurately known. Even small errors in the concentration ratios tend to

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introduce large errors in $\Delta pK_{ip}$ values. The larger the errors, the bigger the $\Delta pK_{ip}$. To minimize these errors, the solutions of an acids were made from dilute stock solution. The amount of the stock solution could be accurately weighed.

In simpler cases different simplified calculation methods were used[11] (see also ref 1 for details).

**The Solvent.** The requirements for the solvent suitable for this work have been described before.[1] We used commercial heptane (Super Purity Solvent, assay 99.9%). It was additionally dried before use by letting it stand on molecular sieves (4 Å, 4–8 mesh) for at least 3 days. The molecular sieves were dried before use by keeping them in vacuo (<1 Torr) and then heating to 300 °C in vacuo until the pressure remained constant.

**The Acids.** The acids were prepared at the Institute of Organic Chemistry in Novosibirsk and their preparation has been previously described: **1**, **4**, **7**, **20**;[12] **2**, **15**;[13] **3**;[14] **5**;[15] **6**;[16] **9**, **11**, **13**, **14**, **17**;[17] **10**, **12**;[18] **18**, **19**, **21**.[19] Compounds **8** and **16** were kind donations from the laboratory of the late Prof. R. W. Taft at the University of California–Irvine.

**Phosphazene *t*-BuP$_4$.** *t*-BuP$_4$ was of the same origin as used in previous work.[1]

**Experimental Setup.** All procedures –drying of the heptane, preparing of solutions (with the exception of the sonication of stock solutions; see below), weighing of substances, and carrying out the spectrophotometric measurements–were carried out in a commercial glovebox under an atmosphere of argon. The atmosphere in the glovebox was constantly circulated through a purification system containing activated carbon, molecular sieves, and activated copper for removal of residues of volatile organics, water vapor, and oxygen, respectively. The residual concentrations of water and oxygen in the atmosphere of the glovebox during the measurements were constantly monitored and were at or below 1 ppm.

For spectrophotometric titration, a commercial spectrometer equipped with an external sample compartment positioned in the glovebox was used. The external sample compartment was connected to the spectrometer via quartz fiber-optic cables.

The temperature in the external sample compartment was constantly monitored. The temperature was always between 25.0 and 28.5° C.

Usually all solutions were used within 3 days, but in a few cases solutions as old as 5 days were used. In these particular cases, no deviations of the spectra of the titration experiment from the usual behavior was observed. Because of slow dissolution of the substances in heptane, the vials of stock solutions were tightly closed, removed from the glovebox, and sonicated in an ultrasonic bath for around 30 min. The concentrations of the acids in the stock solutions were between 0.02 and 2 mM. Working solutions were prepared gravimetrically by dilution of the stock solution. The concentrations of the working solutions were between ca. $1 \times 10^{-6}$ and $1 \times 10^{-4}$ M, in most cases between $0.9 \times 10^{-5}$ and $2 \times 10^{-5}$ M. The concentrations of the titrant solution were between 0.1 and 1 mM.

Vials and pipets used in our work were washed with ethanol before heating in an oven at 150 °C for at least 5 h and were then immediately transferred to the glovebox. Before use the vials were washed with dry acetonitrile in the glovebox, dried in vacuo, then washed with heptane and then dried again in vacuo. Cleaning of the spectrophotometric cell was carried out the same way, except that the heating step was skipped.

## Results and Discussion

The results of the measurements are presented in Figure 2. The compounds as well as their salts with *t*-Bu-P$_4$ were found to be sufficiently soluble in heptane. The Beer's law was found to hold for the acids and their anions at low concentrations [$(1 \times 10^{-6})$–$(1 \times 10^{-4})$ mol/L] used. When a new compound was under investigation for the first time, the time required to reach the acid–base equilibrium was assessed. In cases where the equilibrating time was long, care was taken during titration to ensure that the equilibrium was reached after each addition of the titrant solution.

Each arrow in Figure 2 represents the relative acidity of an acid pair calculated from one titration experiment. To make the results more reliable and to be able to estimate the consistency of the results, we carried out multiple overlapping measurements. The entire range from **1** to **21** involves two independent pathways of measurements, and the relative acidity of any two acids can be obtained by combining at least two independent sets of measurements.[20] The presumable uncertainties of the results are best estimated from Figure 2 by observing how good the agreement is between different pathways of measurements.

The $pK_{ip}$ values of the individual compounds were obtained using the least squares minimization procedure described in ref 21. The scale is anchored to arbitrarily chosen reference compound **3**, for which $pK_{ip}$ was arbitrarily taken as 0. For our results, the standard deviation of minimization $(s) = 0.06$ p$K$ units.[21] This is a low enough value for the scale to be considered self-consistent. This value was also taken as the basis for giving the absolute $pK_{ip}$ values with two decimal places.

Some of the measurements were also performed with the compounds studied in our previous work[1] (see Figure 2). Therefore, as a result of the minimization, some of the earlier published values changed slightly. The changes never exceeded 0.06 $pK_{ip}$ units, and one may conclude that the current measurements are consistent with the earlier ones.

Many of the compounds investigated in this work have also been studied in DMSO[17,22–24] or 1,2-dimethoxyethane[16,25] (DME) solutions and in the gas phase[23,24,26,27]

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[11] There are often isosbestic points in the spectra, which means that, at some wavelength, absorbance of an acid does not depend on its degree of ionization. Often one of the acids absorbs at longer wavelength than the other one and its indicator ratio can be determined from the spectrum of the mixture in the presence of that other acid. In these cases, the indicator ratio of one of the acids can be calculated separately and then used to calculate the ratio of the second one.

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[20] For example, the relative acidity of compounds **10** and **6** can be found as follows: direct measurement 1.47; 1.13 + 0.04 + 0.24 = 1.41; 1.13 + 0.28 + 0.02 = 1.43; 1.13 + 0.4 = 1.43.

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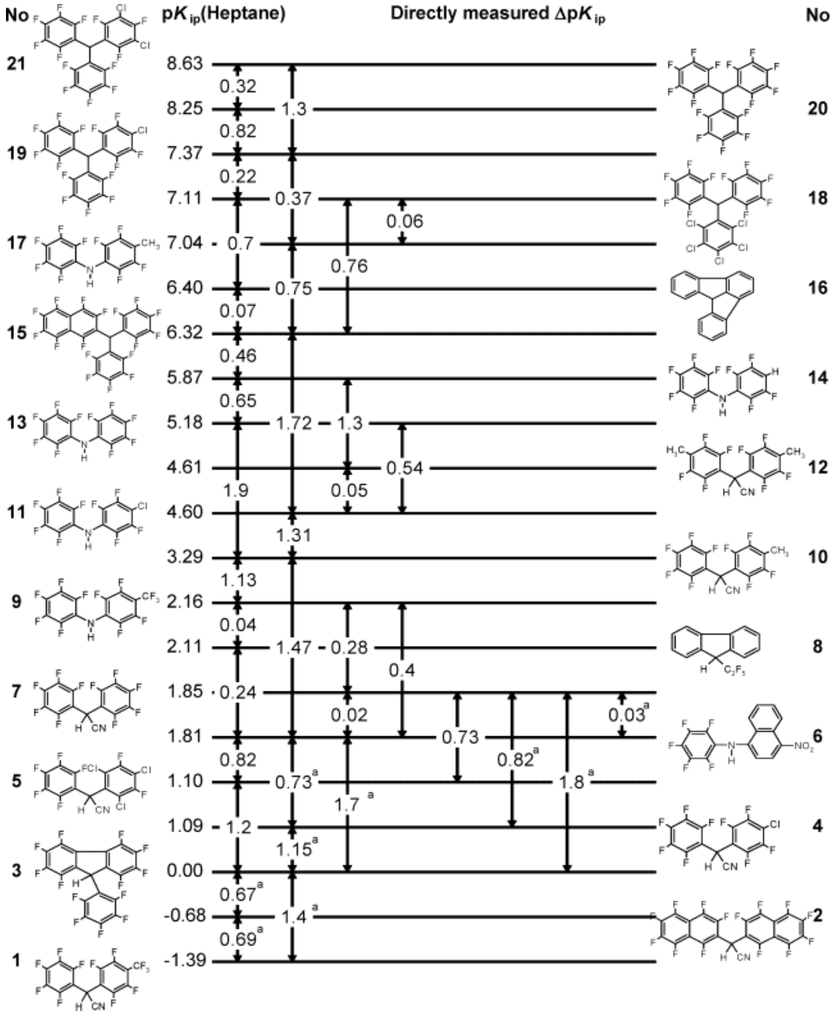

**FIGURE 2.** Spectrophotometric acidity scale in heptane. The scale is anchored to arbitrarily chosen reference compound **3**.

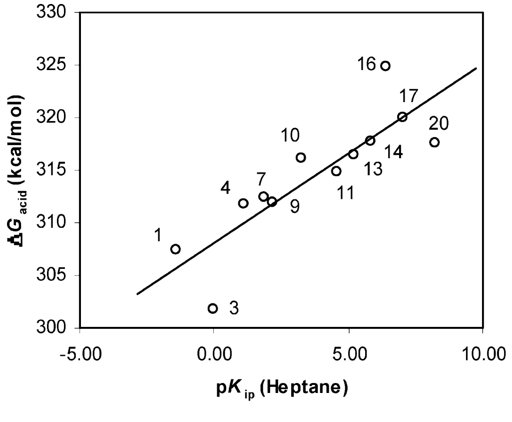

**FIGURE 3.** Correlation between the p$K_{ip}$ values in heptane and acidities in the gas phase of the compounds **1**, **3**, **7**, **14**, **20**;[27] **4**, **10**, **16**;[26] **9**;[24] and **11**, **13**, and **17**.[23]

The overall correlation between the acidities in heptane and in the gas phase is presented in Figure 3 (compounds **1**, **3**, **4**, **7**, **9**, **10**, **11**, **13**, **14**, **16**, **17**, and **20** are included). The compound that deviates the most from the correlation line is **3** (also **16** and **20** to a lesser extent). The correlation equation[28] is as follows: $\Delta G_{acid} = (308.2 \pm 1.6) + (1.69 \pm 0.33)pK_{ip}(\text{heptane})$, $r^2 = 0.72$, $s = 3.3$ kcal mol$^{-1}$, $n = 12$. The attenuation factor,[29] which reflects the sensitivity of reaction series toward the substituent effects while going from the gas phase into heptane, is $(1000 \times 1.69/2.30RT) = 1.24$. Therefore, in general, the intrinsic acidities in the gas phase are 1.24 times more sensitive toward substituent effects than in heptane. The same correlation of only diarylacetonitriles used in this work (**1**, **4**, **7**, **10**) gives the equation $\Delta G_{acid} = (309.8 \pm 0.37) + (1.78 \pm 0.18)pK_{ip}(\text{heptane})$, $r^2 = 0.98$, $s = 0.60$ kcal mol$^{-1}$, $n = 4$, and the solvent attenuation factor is $(1000 \times 1.78/2.30RT) = 1.31$. For NH acids (**9**, **11**, **13**, **14** and **17**) the following equation was found: $\Delta G_{acid} = (307.9 \pm 0.72) + (1.66 \pm 0.14)pK_{ip}(\text{heptane})$, $r^2 = 0.98$, $s = 0.50$, $n = 5$. The attenuation factor is then $(1000 \times 1.66/ 2.30RT) = 1.21$.

The overall correlation between the NH and CH acidities in heptane and DMSO is presented in Figure 4

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[28] In all the correlation equations, the standard deviations of the regression coefficients are given as their uncertainties.

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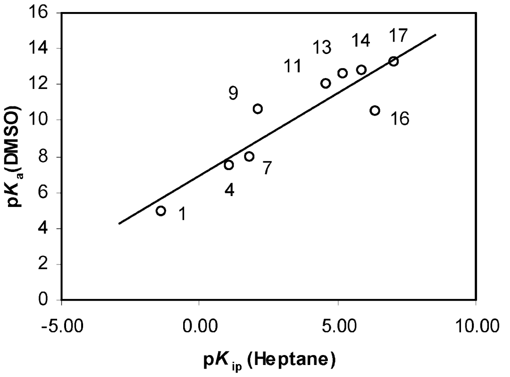

**FIGURE 4.** Correlation between the p$K_{ip}$ values in heptane and DMSO of the compounds **1**, **4**;[23] **7**, **16**;[22] and **9**, **11**, **13**, **14**, and **17**.[17]

(compounds **1**, **4**, **7**, **9**, **11**, **13**, **14**, **16**, and **17** are included). p$K_a$(DMSO) = (6.89 ± 0.71) + (0.92 ± 0.16) p$K_{ip}$(heptane), $r^2 = 0.83$, $s = 1.26$, $n = 9$. The slope 0.92 ± 0.16 does not permit one to make any conclusions for the relative differentiating power[30] (which reflects the change of the sensitivity of reaction series toward the substituent effects while going from the DMSO into heptane) of heptane and DMSO. However, if only NH acids (**9**, **11**, **13**, **14**, and **17**) are included, then the following equation is found: p$K_a$(DMSO) = (9.44 ± 0.23) + (0.57 ± 0.04)-p$K_{ip}$(heptane), $r^2 = 0.98$, $s = 0.16$, $n = 5$. It appears that heptane differentiates these NH acids 1/0.57 = 1.76 times better than DMSO.

In ref 26, correlations between acidities in the gas phase and DMSO have been carried out for different groups of compounds. For the group of diarylacetonitriles (series 6 in Table 3 of ref 26), which can be directly compared with the results of this work, the attenuation factor 1.61 was found. The same correlation with compounds **1**, **4**, and **7** between DMSO and heptane gives p$K_a$(DMSO) = (6.29 ± 0.11) + (0.98 ± 0.07)p$K_{ip}$(heptane), $r^2 = 0.99(4)$, $s = 0.18$, $n = 3$.

The correlation between the acidities in heptane and 1,2-dimethoxyethane (DME) is presented in Figure 5 (compounds **1**, **4**, **5**, **7**, **10**, **15**, **18**, and **20** are included). p$K_{ip}$(DME) = (4.63 ± 0.24) + (0.98 ± 0.05)p$K_{ip}$(heptane), $r^2 = 0.98$, $s = 0.45$, $n = 8$.

One can see that for the studied group of CH acids the differentiating power of heptane does not differ significantly from that of DMSO or DME. This does not hold for the studied group of NH acids: heptane appears to be 1.76 times better a differentiator for these acids than DMSO.

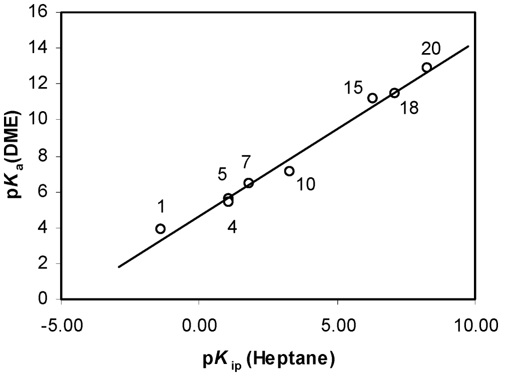

**FIGURE 5.** Correlation between the p$K_{ip}$ values in heptane and 1,2-dimethoxyethane (DME) of the compounds **1**, **4**, **7**, **10**, **15**, **18**, **20**,[25] and **5**.[16]

It was demonstrated earlier[22,23,26] that the solvent attenuation factors depend significantly on the nature of the deprotonation center of the acids (CH, NH, OH, etc.) as well as on the given collection of included substituents. Therefore, a significantly more extensive data bank of p$K_{ip}$ values in heptane is needed to further study of the relative differentiating power of the gas phase, apolar and dipolar aprotic solvents of Brønsted acids of different classes. Work along these lines is in progress in our laboratories.

## Conclusion

Our results demonstrate that experimental studies of acid−base equilibria can be readily carried out, even in solvents of polarity as low as heptane. The success of the experiments is, however, critically dependent on the base used for deprotonation of acids (the protonated form of the base must be bulky and have very extensively delocalized charge) as well as on the choice of acids themselves (their anions must have as delocalized charge as possible).

The UV−vis spectrophotometric ion-pair acidity scale in heptane has been significantly expanded: it includes now 21 bulky CH and NH indicator acids and spans for about 10 p$K_{ip}$ units. It was demonstrated that the substituent effects on the acidity of the studied CH acids are attenuated ca. 1.24 times when the gas phase is substituted for the nonpolar solvent heptane. In its turn, for the series of NH acids, the latter is found to be a somewhat more differentiating solvent than DMSO.

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