## Basicity of Pyridine and Some Substituted Pyridines in Ionic Liquids

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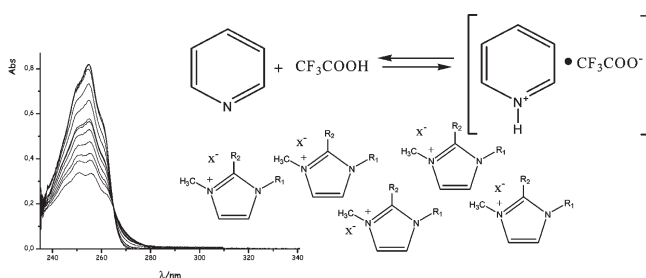
The equilibrium constants for ion pair formation of some pyridines have been evaluated by spectrophotometric titration with trifluoroacetic acid in different ionic liquids. The basicity order is the same in ionic liquids and in water. The substituent effect on the equilibrium constant has been discussed in terms of the Hammett equation. Pyridine basicity appears to be less sensitive to the substituent effect in ionic liquids than in water.

Ionic liquids (ILs) are low-temperature molten organic salts, with melting points lying often below room temperature. Due to their peculiar properties, such as low volatility, low flammability, and high stability, they have been widely used in the last two decades as alternative reaction media to conventional organic solvents for many organic reactions.[1]

Aliphatic amines[2,3] and pyridines[4] have been used as nucleophiles or bases in organic reactions performed in ILs. In some cases, rate constants are higher than those expected on the basis of the pK_a values in water, suggesting a higher nucleophilicity/basicity of amines in ILs than in conventional organic solvents.

It is well-known that the acid−base strength of amines depends on the solvent[5] and it is reasonable to expect that they can interact differently with a molecular solvent and an ionic solvent.

According to McFarlane, an uncharged nitrogen base will remain in its base form and be poorly solvated in ILs as, for example, the interaction of the nitrogen lone pair with a proton at C2, the most acidic proton of imidazolium ILs, is weaker than that with the protons of water.[6] Hence, particular caution is necessary if pK_a values determined in water are used to rationalize quantitative results obtained in ILs.[7]

Unfortunately quantitative data on the basicity of amines in ILs are quite scarce.[2,8,9] It is largely accepted that proton transfer reactions generally proceed through hydrogen-bonded complexes and ion pairs which eventually dissociate into free ions, depending on the permittivity, ε, of the solvent.[10] In water the equilibrium constant for a general proton-transfer reaction of the following charge type

$$HA + B \rightleftharpoons A^- + BH^+$$
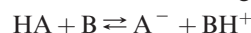
refers to the formation of free ions. In less polar media, such as the investigated ILs ($10 < \varepsilon < 29.7$),[11] due to extensive ion pairing, the measured equilibrium constants, K_{ip}, refer to ion pair rather than free ion formation.[12] Recently, D'Anna and Noto measured the equilibrium constants of ion pair formation for a number of aliphatic amines and considered these values as reliable indicators of their basic strength in ILs.[2,9]

In the present work the basicity of pyridine (Pyr) and some substituted pyridines has been estimated quantitatively from the aptitude of the base to take a proton from trifluoroacetic acid (TFA). The values of K_{ip} have been measured in the four ILs of Scheme 1 by spectrophotometric titration, adding increasing amounts of TFA to a 2×10^{-4} M solution of pyridine. A typical example is reported in Figure 1.

The absorbance at $\lambda = 255$ nm of pyridine increases upon addition of increasing amounts of TFA until a constant value is reached.

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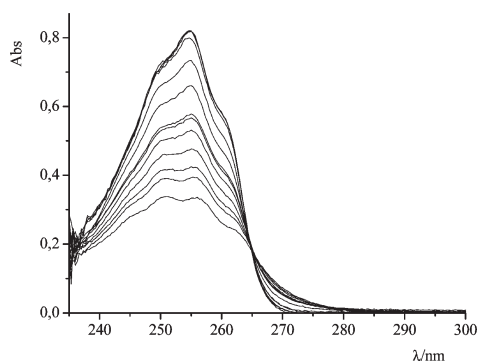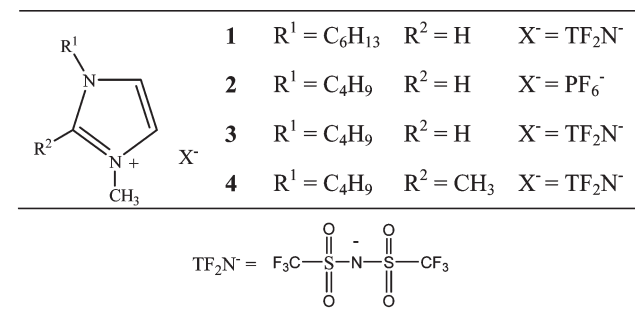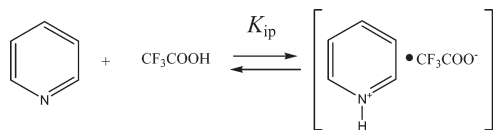
FIGURE 1. Spectrophotometric titration of a 2×10^{-4} M solution of pyridine with increasing amounts of trifluoroacetic acid in IL **1**.

SCHEME 1. **Structures of the Investigated ILs**

1	$R^1 = C_6H_{13}$	$R^2 = H$	$X^- = TF_2N^-$
2	$R^1 = C_4H_9$	$R^2 = H$	$X^- = PF_6^-$
3	$R^1 = C_4H_9$	$R^2 = H$	$X^- = TF_2N^-$
4	$R^1 = C_4H_9$	$R^2 = CH_3$	$X^- = TF_2N^-$

SCHEME 2

The presence of one isosbestic point (Figure 1) indicates that the single equilibrium of Scheme 2 is operating in the considered ILs.

The total absorbance, Abs, of the solution is given by eq 1:

$$\text{Abs} = \varepsilon_{Pyr}[Pyr] + \varepsilon_{ip}[PyrH^+ \cdot TFA^-] \qquad (1)$$

where ε_{Pyr} and ε_{ip} are the molar absorptivity of free pyridine and the ion pair $PyrH^+ \cdot TFA^-$, respectively. [Pyr] and $[PyrH^+ \cdot TFA^-]$ are related to each other by eq 2:

$$K_{ip} = [PyrH^+ \cdot TFA^-]/[Pyr][TFA] \qquad (2)$$

Proper mathematical treatment of the data gave the equilibrium constant values for ion pair formation, K_{ip}, reported in Table 1. A typical titration curve is reported in Figure 2.

In all cases the pyridine stoichiometric concentration fits well the experimental absorbances (solid line in Figure 2), so that there is no evidence of interaction between pyridine and the IL cation.

It is noteworthy that the measured K_{ip} values parallel the ability of the IL cations to act as hydrogen bond donors, as expressed by their α values[13] (Table 1). The hydrogen bond interaction between the ion paired TFA anion and the IL cation probably occurs as depicted in Scheme 3.

TABLE 1. K_{ip} **Values for the Protonation of Pyr with TFA at 25.0 °C in Some ILs**

solvent	α	$K_{ip}/10^5$	pK_{ip}	$k^{Pyr}/10^{-2}$ $(s^{-1} mol^{-1} dm^{-1})^c$
IL **1**	0.650^a	3.49(±0.49)	−5.54	29.1
IL **2**	0.634^b	1.01(±0.15)	−5.00	13.5
IL **3**	0.617^b	0.542(±0.049)	−4.73	10.1
IL **4**	0.381^b	0.282(±0.023)	−4.45	8.40

^{a}Determined according to the procedure described in ref 13. ^{b}From ref 13. ^{c}Second order rate constant values for the Pyr-catalyzed enolization reaction of 2-NCH from ref 4.
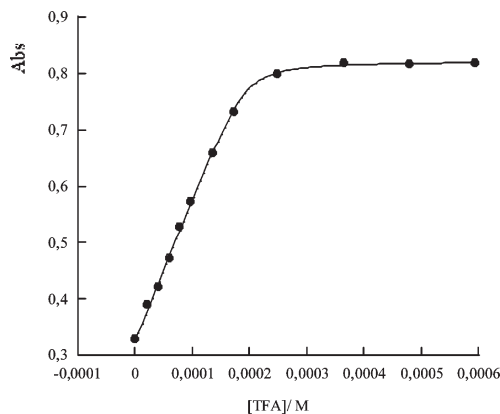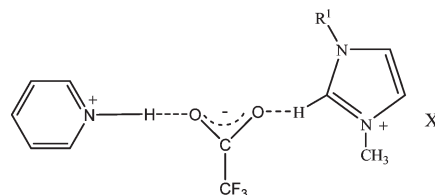

FIGURE 2. Plot of absorbance of pyridine as a function of TFA concentration in IL **1** fitted into eq 1 (solid line).

SCHEME 3

It is surprising that IL **4** follows the trend even if it lacks the C2 proton. However, it has been shown that the other ring protons also play an important role in hydrogen bonding.[14]

The difference in K_{ip} values for IL **2** and IL **3** is probably due to the different hydrogen-accepting abilities of their anions: PF_6^- ($\beta = 0.207$)[13] and TF_2N^- ($\beta = 0.243$)[13] and the related capabilities of interfering in the H-bond network of Scheme 3.

The basicities of differently substituted pyridines were analogously evaluated in IL **2** following the same titration procedure. The K_{ip} values obtained are listed in Table 2.

As expected, the introduction of a ring substituent significantly affects the basicity of pyridine and the basicity order in ILs and in water appears to be the same.

To compare more rigorously the basicities of pyridines in ILs and in water, the experimental K_{ip} values in ILs have been treated according to an equation (eq 3) originally

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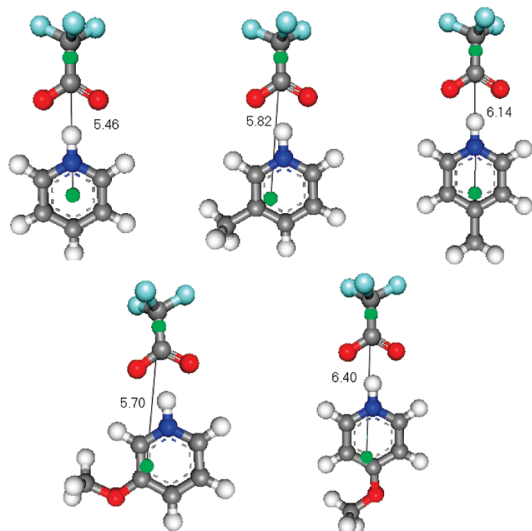
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TABLE 2. Experimental K_{ip} Values for Pyridine and Some Substituted Pyridines in IL **2**, K_d Values for Ion Pair Dissociation Estimated by the Fuoss Equation, and Calculated K_{eq}^{IL} in IL **2** and K_{eq}^{W} in H_2O for the Protonation of Pyridines

base	$K_{ip}/10^5$	$K_d/10^{-5}$	K_{eq}^{IL}	$K_{eq}^{W}/10^5$
3-methoxyPyr	0.818(±0.03)	11.5	9.43	0.023[a]
Pyr	1.01(±0.15)	8.46	8.52	0.045[a]
3-methylPyr	1.26(±0.09)	13.2	16.6	0.145[a]
4-methylPyr	1.84(±0.60)	18.5	34.1	0.316[a]
4-methoxyPyr	2.74(±0.40)	23.7	64.9	1.26[a]

[a]Value calculated as the ratio between the K_a, in water, of TFA and the K_a, in water, of the protonated base.

SCHEME 4. Inter-Ion Distances Obtained by PM3 Calculations

FIGURE 3. Hammett plot for the equilibrium of the reaction between X-substituted pyridines and TFA in IL **2** ($\rho = -2.17$ solid line) and in H_2O ($\rho = -4.53$ dotted line).

FIGURE 4. Plot of the second-order rate constant for the Pyr-catalyzed enolization reaction of 2-NCH against K_{ip} values in the studied ILs.

proposed by Fuoss[15] for the equilibrium between ion pairs and free ions from classical electrolytes.

$$K_{ass} = 1/K_d = (2.524 \times 10^{-3})a^3 \mathrm{e}(e^2/(a\varepsilon kT)) \quad (3)$$

In eq 3, K_{ass} is the ion association constant, a is the interion distance, e is the electronic charge, ε is the permittivity of the solvent, k is the Boltzmann constant, T is the temperature in Kelvin, and K_d is the 1:1 ion pair dissociation constant.

The interion distances used in eq 3 were estimated by optimizing the structures at a semiempirical level, using the PM3 Hamiltonian as implemented in the computer program SPARTAN 04 (Wave function Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612). The centers of mass of the ions were determined by using the computer program WebLab ViewerPro 3.20. The obtained values are reported in Scheme 4.

The equilibrium constants for free ion formation in ILs, K_{eq}^{IL}, can be obtained from the experimental K_{ip} values according to eq 4:

$$K_{eq}^{IL} = [PyrH^+][TFA^-]/[Pyr][TFA] = K_{ip}K_d \quad (4)$$

The corresponding acid−base equilibrium constants for the different pyridines and TFA in water, K_{eq}^{W}, have been calculated as the ratio of the acid dissociation constants, K_a, of TFA and pyridinium ions. These values are also reported in Table 2.

We are aware of the fact that the use of the Fuoss equation could not be fully adequate as it was derived for spherical
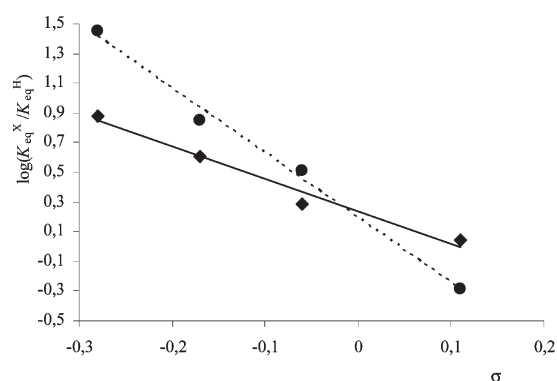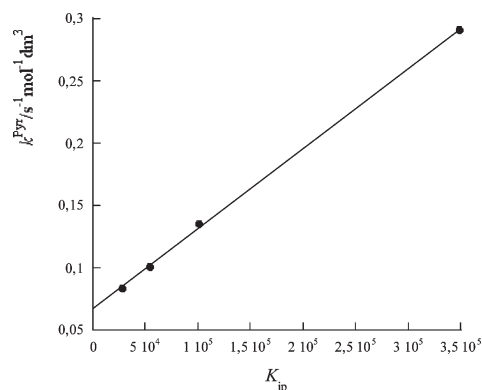
ions, so its application to nonsymmetrical ions is somewhat uncertain. Moreover, the Fuoss equation takes into account only the permittivity of the solvent and does not take into account specific solute−solvent interactions.[15] However, the Hammett plots of Figure 3 show that a linear correlation between $\log(K_{eq}^{X}/K_{eq}^{H})$ and the substituent parameter σ exists both in IL **2** (Figure 3, solid line) and in water (Figure 3, dotted line). As our primary aim was estimating the relative basicities of pyridines in the two different solvent systems, the linearity of these plots is encouraging in spite of the above-mentioned limitations of the present Fuoss-type treatment.

It clearly appears that the sensitivity to the substituent effect on the pyridine basicity strongly decreases on passing from water ($\rho = -4.53$) to IL **2** (-2.17, respectively) and this is somewhat surprising in view of the well-known[16] high "levelling off" effect of water.

We have recently studied[4] the kinetics of the tautomerization reaction of 2-nitrocyclohexanone (2-NCH) using pyridine and some substituted pyridines as the catalysts in different ILs. It turned out that the reaction in ILs is much faster than that in conventional organic solvents. Linear Brønsted correlations were obtained for the enolization reaction and the derived β values ($\beta > 0.9$) suggest that the transition state is shifted toward the enolate intermediate in ILs. In the Brønsted correlations pK_a values in water of the corresponding pyridinium cations were used as indicators of

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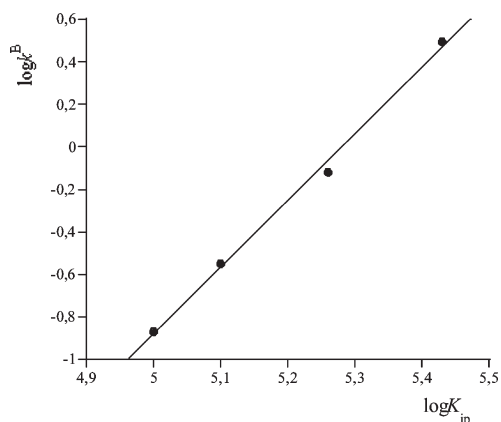
FIGURE 5. Brønsted-type plot for the base-catalyzed enolization reaction of 2-NCH in IL **2**.

basicity, despite the fact that these values, as mentioned above, may not adequately describe the acid−base strength of the catalysts in ILs. The unexpectedly high rate of tautomeric interconversion of 2-NCH in the studied ILs is possibly due to the ability of ILs not only to stabilize the enolate-like transition state, but also to enhance the relative basicity of the pyridine catalysts. A plot of the second-order rate constants,[4] k_1^{Pyr}, for the pyridine-catalyzed enolization reaction of 2-NCH in the four investigated ILs against K_{ip} is strictly linear (R^2 = 0.999, Figure 4). Apparently the IL-solvent effect on the basicity of pyridine is an important factor in determining the rate of the enolization process.

A linear Brønsted-type correlation (R = 0.998) has been obtained by plotting the second order rate constants[4] for the base-catalyzed enolization of 2-NCH in IL **2**, log k^B, against the log K_{ip} values of the different pyridines, B (Figure 5). The measured β value is considerably higher than unity (β = 3.1 ± 0.1) showing that the kinetic substituent effect on the enolate formation is larger than that on the equilibrium of ion pair formation. This is in agreement with previous evidence[4] that the transition state of the rate-determining proton transfer step of the base-catalyzed enolization reaction

of 2-NCH in ILs has a structure that closely resembles that of the enolate intermediate.

In conclusion, the basicities of pyridine and some substituted pyridines have been estimated in different ILs. It turns out that the experimental basicity (K_{ip}) order of pyridines in ILs **2** and in water (K_a) is the same. Pyridine basicities seem to be less sensitive to the substituent effect in IL **2** than in water. Finally the most likely explanation of the previously observed Brønsted β values > 0.9[4] for the enolization reaction of 2-NCH in ILs is that the reaction occurs via a solvent-stabilized enolate-like transition state.

Experimental Section

Materials. Trifluoroacetic acid was a commercial sample of AnalaR grade and was used without further purification. Commercial pyridine, 3-methylpyridine, 4-methylpiridine, 3-methoxy-pyridine, and 4-methoxypyridine have been distilled in the presence of NaOH before each experiment. ILs of Scheme 1 were prepared from the corresponding halides, following reported procedures.[1c,17,18] The purity of imidazolium salts was checked by ESI-MS and UV spectrophotometry (purified [bmim]$^+$ salts containing [Cl]$^-$ or [Br]$^-$ < 0.1 ppm have no absorption band in the 250−300 nm region).[19] After drying (2 h at 80 °C under vacuum) the water amount in ILs was determined by the Karl Fisher technique by using an apparatus composed of a stand titrator and a coulometer. A water content within 120−150 ± 20 ppm was found for ILs **1**, **3**, and **4**, whereas a water content of 348 ± 25 ppm was found for IL **2**.

Spectrophotometric Titrations. A small aliquot of a stock solution of 0.1 mol dm^{-3} of TFA in CH$_2$Cl$_2$ was added to the cuvette containing pyridine or the substituted pyridines dissolved in the appropriate IL. The concentration of the base was kept constant at 2×10^{-4} mol dm^{-3} in all experiments. The spectra were registered after equilibrium had been established at each added TFA concentration.

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