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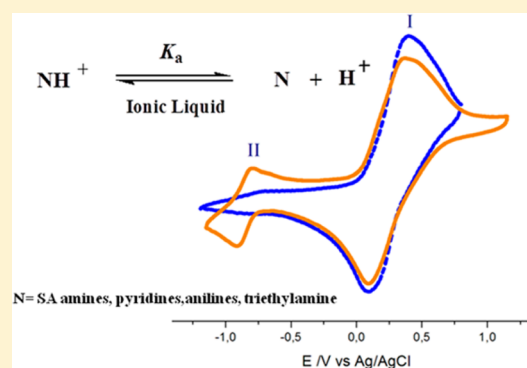
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Toward a pK_a Scale of N-base Amines in Ionic LiquidsDaniela Millán,^{*,†} Mabel Rojas,[†] José G. Santos,[†] Javiera Morales,[†] Mauricio Isaacs,[‡] Carlos Diaz,[‡] and Paulina Pavez^{*,†}[†]Departamento de Química-Física, Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 6094411, Chile[‡]Departamento de Química Inorgánica, Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 6094411, Chile

S Supporting Information

ABSTRACT: An electrochemical technique was used to investigate pK_a values of some substituted secondary alicyclic (SA) amines, pyridines (py), anilines (AN), and triethylamine (Et_3N) in different ionic liquids. The method involves cyclic voltammetry at a platinized Pt electrode. The experimental data were correlated with pK_a values reported previously in aqueous solution, and Hammett parameters were correlated with pK_a values in ionic liquids to determine ρ values in these media.



■ INTRODUCTION

The acid dissociation constant (pK_a) is one of the most important and frequently used among the physicochemical parameters. Its determination is of interest to a wide range of research fields; for example, in pharmacology the pK_a controls many aspects regarding absorption and metabolism of drugs.^{1,2} In preparative chemistry, pK_a values are used to select conditions for synthesis, and it is a helpful tool to identify reaction products by predicting the nucleofugality of leaving groups in organic reactions.^{3,4}

The influence of the solvent on the acid–base equilibrium is related to its electrostatic and solvation properties.^{5–9} In this context, several reports have been published on the pK_a determination in nonaqueous solvents and comparison of these values with those previously collected in water solution.^{5–10} In the majority of these works, spectroscopic techniques have been used to determine the pK_a of solutes, since the use of a glass electrode is often inappropriate to determine acidity or basicity of solutes in molecular solvents.

On the other hand, in the last two decades, ionic liquids (ILs) have been extensively used as alternative solvents in a wide range of catalytic and organic reactions due to their remarkable properties.^{11–15} As well as for conventional solvents, it has been demonstrated that ILs can affect rate constants, selectivity, and product distribution for some organic reactions. We have recently observed changes in both rate and selectivity on the reaction of Paraoxon with piperidine when ILs are used as solvents of the reaction.¹⁶

In IL medium the spectroscopic method has already been applied to determine the acidity of strong Brønsted acids^{17,18}

and weak carboxylic acids,¹⁹ as well as the basicity of pyridines²⁰ and some nonaromatic amines.²¹ Even though these results are useful to compare basicity or acidity strength in ILs by means of the value of their equilibrium constant for ion pair formation (amine–acid), they do not really give pK_a values. Cheng et al. described a general approach to measure absolute pK_a values of C–H type acid indicators²² and, very recently, substituted benzoic acids²³ in ILs where an indicator was titrated with a solution of acid and the change in concentration was followed by UV–vis spectrophotometry. On the other hand, Doherty et al.²⁴ have reported the first approach to measure absolute pK_a values of N-aromatic bases in ILs by electrochemical approaches, whereby potentiometric titration and cyclic voltammetry were used to determine pK_a values of some substituted pyridines in two ILs.

In a recent work we have studied the aminolysis of secondary alicyclic (SA) amines with *p*-nitrophenyl acetate in ILs. The basicity of SA amines was correlated with rate constants through a Brønsted-type plot²⁵ in order to shed light on the reaction mechanism in these ionic media. However, the most difficult task was to determine the pK_a of these amines in ILs because there is a lack of information on the pK_a determination of N-amines in ILs.

Bearing in mind that N-amines (aromatic and nonaromatic) have been extensively used as nucleophiles or bases in organic reactions performed in ILs,^{25–27} in this study we report the pK_a


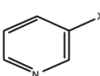
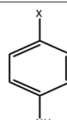
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of some substituted pyridines, SA amines, anilines, and triethyl amine (shown in Scheme 1) in four ILs by means of cyclic

Scheme 1. Structure of Amines Used in This Study

	X		X		X
Piperidine	CH ₂	Pyridine (py)	H	Aniline	H
1-(2-Hydroxyethyl piperazine)	NHCH ₂ CH ₂ OH	3-Chloro py	Cl	3-Chloroaniline	Cl
Morpholine	O	3-Methyl py	Me	3-Methylaniline	Me
1-Formylpiperazine	NCHO			3-Methoxyaniline	MeO
				N,N-Dimethylaniline	

voltammetry. The chosen ILs share the common anion bis(trifluoromethane)sulfonimide [NTf₂⁻], which is a weakly basic anion, and its use would provide the absence of any external interference in the acidity scale determination.¹⁹ The cations were chosen due to their structure and their ability to donate a H-bond and possess π - π interactions: 1-butyl-3-methylimidazolium [Bmim], 1-butyl-2,3-dimethylimidazolium [Bm₂im], 1-butyl-3-methylpyrrolidinium [Bmpyrr], and ethyl-dimethylpropyl ammonium [EtmpAm]. These are shown in Scheme 2. The voltammograms were obtained at room temperature and in the presence of a strong acid (HOTf = trifluoromethanesulfonic acid). The results will be correlated with the pK_a values of amines reported in water, and the substituent effect on the pK_a will be discussed through the Hammett equation.

EXPERIMENTAL SECTION

Materials. All ionic liquids were purchased and dried before use on a vacuum oven at 70 °C for at least 2 h and stored in a dryer under nitrogen and over calcium chloride. Water contents determined by Karl Fischer titration were <200 ppm.

Electrochemical Measurements. These were carried out using a CH Instrument 760c potentiostat, in a three-electrode cell. The working electrode was a platinized Platinum (P-Pt) disk from CH instrument ($r = 1.5$ mm), Pt wire (4 cm²) was used as a counter electrode and Ag/AgCl (3 M KCl) as the

reference electrode. For measurements in ILs media the compartment of the reference electrode was sealed, separated from solution and connected by a Pt bridge to the working solution. This bridge was used as a Luggin capillary to avoid moisture contamination, during the time scale of the experiments.²⁸ All measurements were performed at 298 K under a dry nitrogen atmosphere. In several cases the Internal Resistance (IR) compensation control program was used,²⁹ in order to compensate the uncompensated resistance (R_u) of the solution. The estimated IR compensation were: 593 Ω , 638 Ω , 749 Ω and 992 Ω for [Bmim]NTf₂, [Bm₂im]NTf₂, [Bmpyrr]NTf₂ and [EtmpAm]NTf₂, respectively. The potential drift in these media was calibrated with the ferrocene/ferrocinium redox couple (see Figures S1–S4 in Supporting Information). The drift was about 10 mV, 42 mV, 60 mV and 83 mV from the value obtained without IR compensation for [Bmim]NTf₂, [Bm₂im]NTf₂, [Bmpyrr]NTf₂ and [EtmpAm]NTf₂, respectively. The reproducibility of the Cyclic voltammetry measure was calculated using ferrocene/ferrocinium redox couple in [Bmim]NTf₂, for $N = 14$ experiments $\Delta E_p = 90 \text{ mV} \pm 15 \text{ mV}$.

Electrode Preparation. The Pt disk electrode was covered with a fresh electrochemical coating of platinized platinum, which allows obtaining an electrochemically quasireversible H⁺/H₂ redox couple. The electrodeposition of platinum on the electrode surface was carried out under electrolysis at controlled potential (2 V) during 30 s, in a solution of chloroplatinic acid (3 g) and lead acetate (0.02 g) dissolved in 100 mL of distilled water. A Pt wire was the anode during electrodeposition. The determination of potential differences was performed with the software of the instrument.

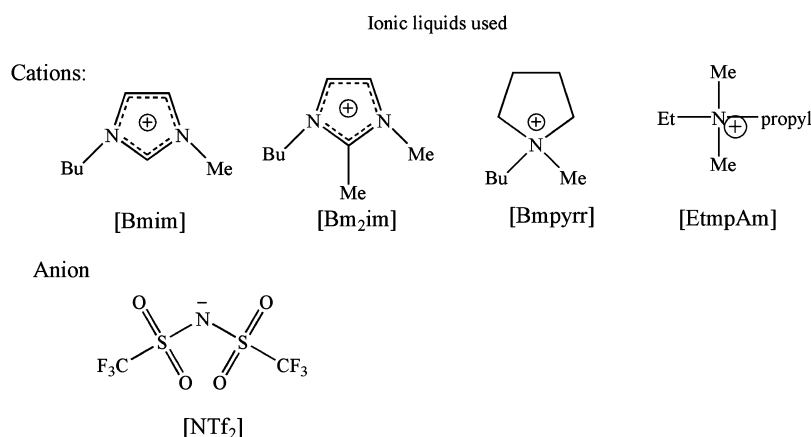
RESULTS AND DISCUSSION

Data collection about basicity or acidity of solutes in nonaqueous solvents has been a recurrent topic, since several kinds of reactions are governed by the pK_a of a molecule. As mentioned above, this parameter is useful to predict reaction products and also to help in determining reaction mechanism. Our purpose is to determine the pK_a values of amines of different nature (aromatic, alicyclic, and aliphatic), which are potential nucleophiles or bases to be used in organic chemistry.

Previous studies have reported that electrochemical methods performed on a P-Pt electrode seem to be a good approach to determine pK_a values of N-based amines in ionic liquids.²⁴

It is considered that during the neutralization reaction of a strong acid (HTOf in this work) with the base Am, the species

Scheme 2. Structure of the Ionic Liquids Used in This Study



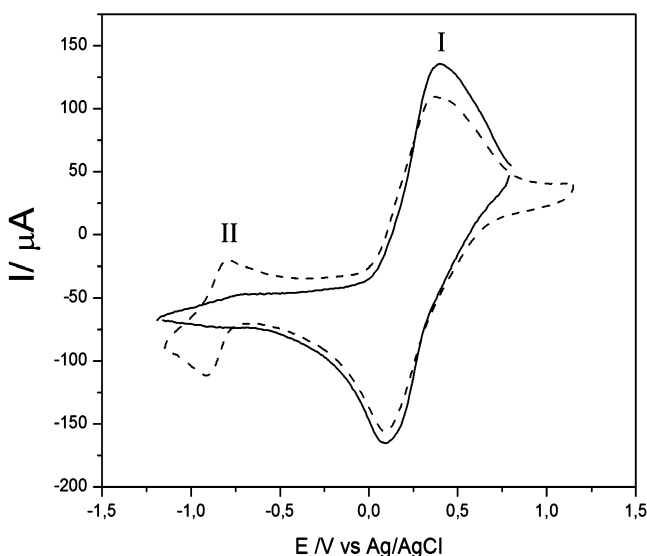
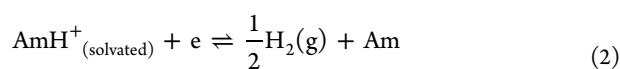
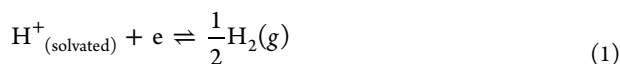


Figure 1. Cyclic voltammogram (CV) of HOTf (0.56 M) (solid line) and CV of triethyl amine (0.15 M) + HOTf (0.56 M) (dashed line) in [Bm₂im]NTf₂.

H⁺, H₂, Am, and AmH⁺ are in equilibrium, in the ionic liquid solution. If these species are in contact with a conducting surface, *i.e.* an electrode, a redox system is established as denoted in eqs 1 and 2.



These redox processes allow us to express the equilibrium formed by the Nernst equation, describing the system through eq 3.

$$E = E_1 = E_2 = E_1^\circ + \frac{R}{T} \ln \frac{[\text{H}^+]}{P_{\text{H}_2}^{1/2}} = E_2^\circ + \frac{R}{T} \ln \frac{[\text{AmH}^+]}{[\text{Am}]P_{\text{H}_2}^{1/2}} \quad (3)$$

where E_1 , E_2 , and E_1° , E_2° are the measured and standard potentials, respectively (in the medium being examined) of

redox systems 1 and 2, R is the gas constant, T is the absolute temperature, F is Faraday's constant, and $P_{\text{H}_2}^{1/2}$ is the H₂ gas pressure.

Taking into account that there is no information available about the activity of the solutes in these media, the equation was written assuming the activity is equivalent to the molar concentration of the solutes. Equation 3 permits us to write the dissociation constant K_a for the equilibrium of the conjugate acid AmH⁺ and the pK_a as a function of the relevant standard reduction potentials of each process, E_1 and E_2 , as shown in eq 4. This relationship is useful to calculate the pK_a value through potentiometric methods.²⁴

$$\begin{aligned} E_2^\circ - E_1^\circ &= \frac{RT}{F} \ln \frac{[\text{H}^+][\text{Am}]}{[\text{AmH}^+]} \\ &= \frac{2.003RT}{F} \log K_a = -0.059pK_a \end{aligned} \quad (4)$$

However, when these systems are studied by cyclic voltammetry, the process described by eq 1 can be observed in the cyclic voltammogram of Figure 1 (solid line, peak 1) and it has been described as a H⁺/H₂ redox couple.³⁰ When an amine is added to a solution of strong acid, an acid–base equilibrium is established (see eq 2) and the appearance of a second reversible or quasi-reversible redox process is observed at more negative potentials. This has been described as a AmH⁺/Am process (as seen in Figure 1, dashed line peak II); thus, the reduction peak for H⁺ decreases with the addition of amine, while the corresponding reduction peak for AmH⁺ increases.²⁴

Based on the Nernst equation, the difference between the potential values of the voltammetric peaks, either anodic, cathodic, or half-wave, $E_{1/2}$ ($E_{1/2} = (E_{\text{pc}} + E_{\text{pa}})/2$, this criterion was used in this work), must be the same as the difference between their respective standard potentials. To determine a cyclic voltammetric value of pK_a , eq 4 was applied considering $T = 298 \text{ K}$.²⁴

In this manner the voltammograms of a series of secondary alicyclic (SA) amines, pyridines, anilines, and triethyl amine were obtained in different ionic liquids, and the calculated pK_a values are reported in Table 1. As an example, CVs for SA amines in [Bm₂pyrr]NTf₂ can be seen in Figure 2. The CVs for all other amines are included in the Supporting Information (see Figures S5–S11), and they exhibit an analogous voltammetric behavior to that in Figure 2. However, the

Table 1. pK_a Values of Some Primary, Secondary, and Tertiary Amines Determined in Ionic Liquids by Cyclic Voltammetry

	water	[Bmim]BF ₄	[Bmim]NTf ₂	[Bm ₂ im]NTf ₂	[Bm ₂ pyrr]NTf ₂	[EttmpAm]NTf ₂
piperidine	11.2 ^a	15.6 ^e	18.4	20.0	19.2	19.4
1-(2-hydroxyethyl) piperazine	9.4 ^a	14.3 ^e	17.5	18.8	17.9	17.9
morpholine	8.4 ^a	13.9 ^e	16.6	16.1	16.9	16.5
1-formylpiperazine	7.8 ^a	13.2 ^e	13.4	14.6	15.7	15.6
Et ₃ N	10.7 ^b		18.9	18.5	18.8	19.2
pyridine (py)	5.2 ^c	8.6 ^f	10.5 ^f	11.2	12.8	13.7
3-picoline	5.7 ^c		11.2 ^f	11.7	12.3	13.7
3-chloropyridine	4.1 ^c		9.3	9.4	9.1	8.9
4-chloroaniline	4.0 ^d		7.8			
aniline (An)	4.6 ^d		8.1			
4-methylaniline	5.1 ^d		8.7			
<i>N,N</i> -dimethylaniline	5.1 ^d		9.1			
4-methoxyaniline	5.3 ^d		8.6			

^aSee refs 33–34. ^bSee ref 35. ^cSee ref 36. ^dSee ref 37. ^eSee ref 25. ^fSee ref 24.

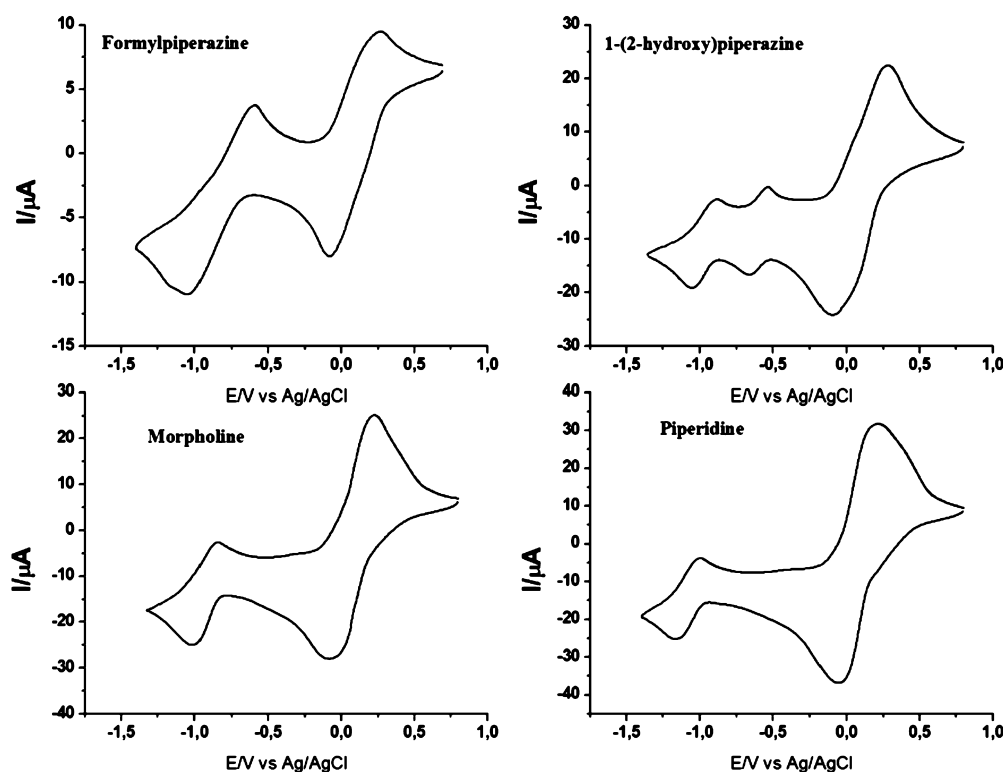


Figure 2. CVs obtained in [Bmpyrr]NTf₂ (scan rate 50 mV s⁻¹) of HOTf (0.56 M) + Amine (0.15 M).

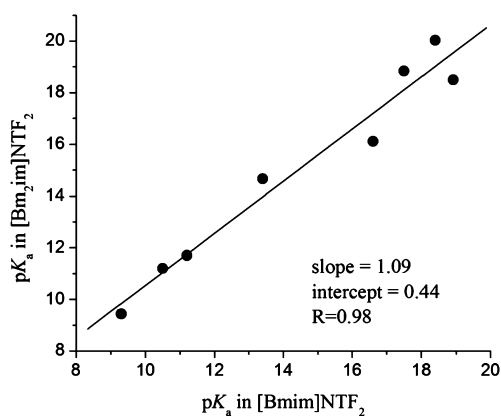


Figure 3. Double pK_a plot between pK_a values in [Bmim]NTf₂ and [Bm₂im]NTf₂.

potential values of the corresponding redox processes are different depending on the amine structure and ionic liquid.

In Figure 2, the peak corresponding to the reduction of the strong acid HOTf corresponds to that close at 0 V (for example, $E_{1/2}$ for morpholine is 0.07 V). The observed peaks are rather broad; it has been established that this feature is related to a sluggish kinetics of the reagents on the P–Pt electrode.³¹ Furthermore, this behavior can be expected due to the viscosity of the ionic liquid media. According to this, the second peak observable at negative potentials is due to the presence of AmH⁺ (for example, $E_{1/2}$ for morpholine is −0.93 V). Voltammograms for 1-(2-hydroxyethyl)piperazine in all ionic liquids studied show a new peak, which can be attributed to reduction of the EtO[−] group ($E_{1/2}$ = −0.56 V, in Figure 2). The assignment of this redox process was carried out by comparison with the related piperazines used through this work.

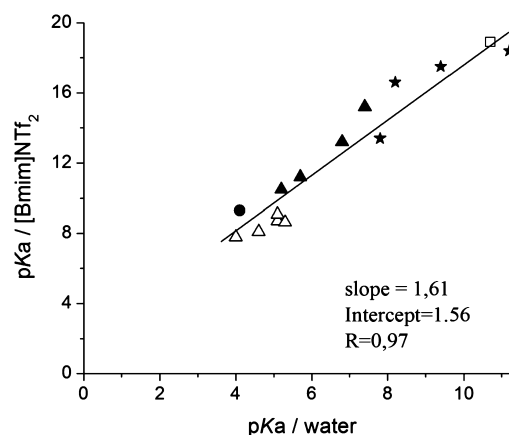


Figure 4. Double pK_a plot, water vs [Bmim]NTf₂. (Δ) anilines, (●) pyridines (this work), (□) Et₃N, (▲) pyridines (ref 24), (★) SA amines.

It should be mentioned that we also tried to determine pK_a values of amines in [Bmim]DCA. However, in this IL it was not possible to obtain a good CV because both the redox processes, H⁺/H₂ and AmH⁺/Am, were not observed. This behavior could be explained in terms of the basicity reported for this anion, which has been considered as a base able to accept a proton, according to the Brønsted definition.³² Therefore, after strong acid addition, the equilibrium $DCA_{anion} + H \rightleftharpoons DCA$ is fully displaced to DCA. Therefore, when the amine is added, it is not able to compete for the proton with the DCA anion.

Table 1 shows that in all cases the pK_a values obtained in ionic liquids are greater than those reported in aqueous solution and they change as the cation structure of the ionic liquid changes. In fact, these ILs were chosen due to their structures and H-bond ability; nevertheless, there is not a good trend

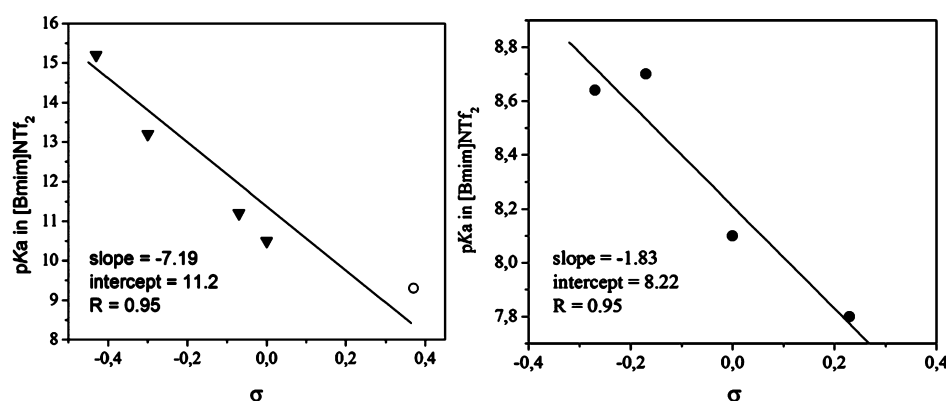


Figure 5. Hammett-Taft plots for pyridines (▲) (ref 24), 3-chloropyridine (○), and anilines (●) in [Bmim]NTf₂.

between the pK_a values found and H-bond ability for the cation of IL.

Inspection of the data reveals that all pK_a values in [Bmim]BF₄ are about 2–3 pK units lower (i.e., more acidic) than those in ILs sharing a common anion NTf₂[−]. This is not difficult to explain because the negative charge in BF₄[−] is more localized and its size is smaller than that of NTf₂[−], causing a stronger solvation effect than its counterpart. This major solvation effect increases the acidity of the amines. Therefore, it would be reasonable to expect that an amine were more acidic in an ionic liquid with anions of smaller size and higher proton affinity.²² Thus, as seen in Table 1, it is evident that the anion plays an important role in the acidity of the IL. With respect to the cation effect on the pK_a values, a comparison of the ILs sharing an NTf₂[−] anion is worthy. Contrasting the pK_a values in [Bmpyr]⁺ and [EtmpAm]⁺ cations, it can be seen that they are quite similar, which means that the change from alicyclic to an aliphatic cation does not much affect the pK_a . In addition, slight differences were obtained when changing from an aromatic to a nonaromatic cation, for example SA amines in [Bm₂im]NTf₂ and [Bmpyr]NTf₂. It is noteworthy that for Et₃N, pyridine, and 3-methylpyridine the values reported in ref 24 are 2–3 units lower than those in Table 1, probably due to the different methodology.

A major difference in pK_a values should be expected when going from [Bmim]⁺ to [Bm₂im]⁺, since the acidity of the hydrogen atom at position 2 of the imidazolium ring confers a stronger hydrogen-bond donor ability than that of [Bm₂im]⁺, where position 2 is blocked by a methyl group. Instead, only small variations were found. Thus, it is clear that the above shows that ignoring ion-pair interactions in these organic salts and treating anions and cations as separate entities in these solvents is not capable of uncovering all the subtle factors involved in such complex systems. The greater effect of anion on acidity as compared to cation should be due to its stronger solvation toward the proton compared with the solvation of the cation toward the ammonium.

On the other hand, with the aim to compare the results obtained in the different ILs we performed linear correlations between the pK_a 's obtained in the four ILs. As shown in Figure 3, a plot between pK_a values obtained in [Bmim]NTf₂ and [Bm₂im]NTf₂ gives an excellent correlation ($R = 0.99$), which validates our methodology. Similar correlations were found by plotting [Bmim]NTf₂ against the other ILs (see figures S12 and S13, in Supporting Information).

In addition, taking as a reference the pK_a values reported for the series of amines under study we performed regression

analyses to examine the relationships between the scales obtained in different ILs and aqueous solution. Figure 4 shows the correlation between pK_a of amines reported in water and those in [Bmim]NTf₂ determined in this work. In this plot we have included four pK_a values of substituted pyridines reported in ref 24 (marked as ▲ in the plot). As seen these values of pK_a agree with the good correlation found for our data set. In the other ILs used in this study the same trend was found when plotting pK_a in ionic liquids vs pK_a in water (see figures S14–S16, in Supporting Information).

As mentioned before, the pK_a values of these series of amines are always greater than those published in water. This difference is reflected by the ΔpK_a (pK_a IL – pK_a water), which varies depending on the IL and the amine family. For example as seen in Figure 4, ΔpK_a for anilines (Δ) is *ca.* 4 while ΔpK_a for Et₃N (□) is *ca.* 7. Therefore, this method could be used as a useful tool to predict pK_a values of N-base amines in ionic liquids by interpolation of the linear plots (see Supporting Information, figures S14–S16).

Since the determination of pK_a in ionic liquids is a challenging task we have considered applying the Hammett and Taft equation^{38,39} as another method to predict pK_a of pyridines and anilines in these media. The Hammett–Taft model has been widely used to predict the acidity constant values of organic compounds in aqueous solution. The expression of the model is given in eq 5, where pK_a represents the dissociation constant of a substituted organic compound, pK_0 is the pK_a of the unsubstituted parent compound, ρ is the reaction constant and σ is a substituent constant.

$$pK_a = pK_0 - \rho\sigma \quad (5)$$

From the slope of the plot of eq 5, the value of ρ was obtained for pyridines and anilines in [Bmim]NTf₂, as shown in Figure 5. Analysis of these plots reveals an interesting change of the absolute value of the slope from pyridines (7.19) to anilines (1.83). This result is surprising since, although the ρ value in aqueous solution is also greater for pyridines [the ratio ρ_{py}/ρ_{An} is *ca.* 1.2 ($\rho_{py} = 5.25$; $\rho_{An} = 4.58$)],⁴⁰ our results show that this ratio is $\rho_{py}/\rho_{An} \approx 3.9$, in contrast with the results in water.

The difference in ρ values found in Figure 5 can be attributed mainly to the amine structure and thereby to the larger solvation ability of [Bmim]NTf₂ toward anilines compared with pyridines. Therefore, the effect of the substituent on the dissociation constant would be lower for anilines.

■ CONCLUSIONS

The absolute pK_a values of a series of N-based amines were determined in four ionic liquids. The results show a dependence of the pK_a value on the nature of the IL used. In all cases, pK_a values found in ILs follow the same trend and they are greater than those reported in aqueous solution.

The electrochemical approach used (cyclic voltammetry) in this work is an accurate method to determine pK_a values of organic compounds in ionic liquids. Regression analyses were performed between the pK_a values determined in ionic liquid, and excellent linear correlations were found. This result validates our procedure.

Two different methods were used to predict pK_a values in ionic liquids. The first one is an interpolation of data from the linear plot of pK_a in ionic liquids and pK_a in water. The second one is the Hammett–Taft approach. Both of these methods are good tools to predict pK_a values of organic compounds in ionic liquids.

■ ASSOCIATED CONTENT

■ Supporting Information

The double pK_a plot for ILs used, CVs of SA amines, anilines, pyridines, and Et_3N , and CVs obtained from ferrocene solution in the ILs used. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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