

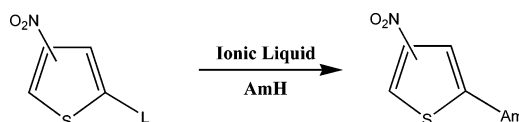
Study of Aromatic Nucleophilic Substitution with Amines on Nitrothiophenes in Room-Temperature Ionic Liquids: Are the Different Effects on the Behavior of para-Like and ortho-Like Isomers on Going from Conventional Solvents to Room-Temperature Ionic Liquids Related to Solvation Effects?

Francesca D'Anna,^{*,†} Vincenzo Frenna,[†] Renato Noto,^{*,†} Vitalba Pace,[†] and Domenico Spinelli^{*,‡}

Dipartimento di Chimica Organica "E. Paternò", Università degli Studi di Palermo, Viale delle Scienze-Parco d'Orleans II, 90128 Palermo, Italy, and Dipartimento di Chimica Organica "A. Mangini", Università degli Studi di Bologna, Via S. Giacomo 11, 40126 Bologna, Italy

fdanna@unipa.it; rnoto@unipa.it; domenico.spinelli@unibo.it

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The kinetics of the nucleophilic aromatic substitution of some 2-L-5-nitrothiophenes (para-like isomers) with three different amines (pyrrolidine, piperidine, and morpholine) were studied in three room-temperature ionic liquids ([bmim][BF₄], [bmim][PF₆], and [bm₂mim][BF₄], where bmim = 1-butyl-3-methylimidazolium and bm₂mim = 1-butyl-2,3-dimethylimidazolium). To calculate thermodynamic parameters, a useful instrument to gain information concerning reagent–solvent interactions, the reaction was carried out over the temperature range 293–313 K. The reaction occurs faster in ionic liquids than in conventional solvents (methanol, benzene), a dependence of rate constants on amine concentration similar to that observed in methanol, suggesting a parallel behavior. The above reaction also was studied with 2-bromo-3-nitrothiophene, an ortho-like derivative able to give peculiar intramolecular interactions in the transition state, which are strongly affected by the reaction medium.

Introduction

In the past few years, room-temperature ionic liquids (RTILs, usually organic onium salts) have been proposed as environmentally benign alternatives to conventional organic solvents.¹

As a result of their nonflammability and nondetectable vapor pressure, they have attracted not only academic but also industrial interest.² These organic onium salts have been used largely as solvents in organic synthesis,³ biocatalysis,⁴ electrochemistry,⁵ and separation processes,⁶ and many applications have been documented. At present, however, only a few papers have reported mechanistic studies,⁷ although, from this point of view, ionic liquids might be very interesting media, as they are formed only of ions, they provide a reaction environment

* Corresponding Authors. Phone: +39091596919 (F.D. and R.N.); +39051209-5689 (D.S.). Fax: +39091596825 (F.D. and R.N.); +390512095688 (D.S.).

[†] Università degli Studi di Palermo.

[‡] Università degli Studi di Bologna.

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that is completely different from that offered by conventional solvents, thus possibly modifying the mechanism or even changing the outcome of a reaction.

Recent studies have demonstrated that changes in the nature of the cation and/or of the counterion bring about notable variations in the properties (e.g., electrophilicity or nucleophilicity) of the reacting molecules⁸ as well as in the mechanism of reaction.⁹ Accordingly, we recently proposed a shift from the E1_{CB} (in MeOH)^{10a} to the E2 mechanism (in RTILs)^{10b} for the amine-promoted dehydrobromination of the 1,1,1-tribromo-2,2-bis(phenyl-substituted)ethanes in ionic liquids.

Despite the enormous interest in RTILs, their microscopic properties are not fully understood. Several reports have attempted to determine empirically some of their solvent parameters.¹¹ Completely different values have been obtained, however, as a result of the different natures of the molecular probes used and to the lack of a single probe able to account for different intermolecular forces and, thus, to give a reliable polarity scale.

An alternative approach, so far less investigated, is a mechanistic study in ionic liquid solution of a classic organic reaction to better understand their solvent properties by means

of the comparison with the results in a conventional solvent. For example, solvation effects of some RTILs containing the [TF₂N] anion, similar to those of acetonitrile, have been claimed studying the keto–enol tautomerism of 2-nitrocyclohexanone.¹²

According to this approach, we decided to perform a kinetic study in RTILs of the nucleophilic aromatic substitution (S_N-Ar), an organic reaction well-investigated in conventional organic solvents. Nucleophilic substitutions (aromatic as well as aliphatic) represent “one of the most important reactions” “and can lead to a wide variety of new functional groups”.¹³ For years some of us have been interested in the mechanistic aspects of this reaction in conventional organic solvents.¹⁴ Furthermore, it is well-known that the process is affected by the nature of the solvent used, and it has been used frequently as a probe to better understand the microscopic properties of solvent systems.¹⁵

Results and Discussion

Choice of Substrates and Nucleophiles. We herein report on the aromatic amination of some 2-*L*-5-nitrothiophenes (**1**), para-like derivatives, by the action of three secondary cyclic amines, namely, pyrrolidine (Pyr), piperidine (Pip), and morpholine (Mor; Chart 1). These amines show different nucleophilicities and/or structures that could cause specific interactions with organized solvents such as ionic liquids. Four different leaving groups (L = Br, OMe, OC₆H₅, and OC₆H₄-4-NO₂) were chosen to verify their leaving group ability order.

We also examined the behavior of an ortho-like derivative, namely, 2-bromo-3-nitrothiophene (**2a**), which gives peculiar intramolecular interactions in the transition state (TS), to gain information about the dependence of such interactions on the nature of the medium used.

The reaction was followed spectrophotometrically at not less than six amine concentrations (0.00869–0.0350 M) and over a significant temperature range (293–313 K), determining the thermodynamic parameters, which are a useful instrument in studying reagent–solvent interactions.

Three ionic liquids ([bmim][BF₄], [bmim][PF₆], and [bm₂-im][BF₄], where bmim = 1-butyl-3-methylimidazolium and bm₂-im = 1-butyl-2,3-dimethylimidazolium) were chosen because of the different properties of their cations and anions. In

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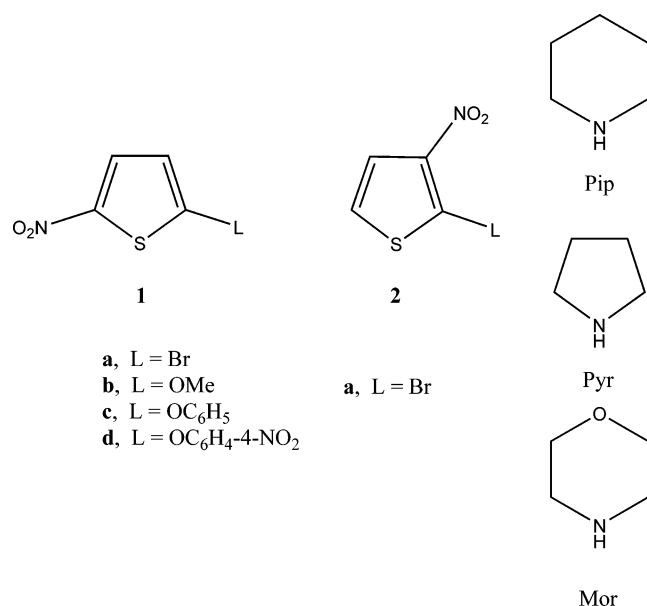
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CHART 1



particular, when going from [bmim][BF₄] to [bmim][PF₆], there is a decrease in the negative charge density of the spherical anion, whereas when going from [bmim][BF₄] to [bm₂m][BF₄] there is a decrease in the hydrogen-bond donor ability of the cations. All the above changes could significantly affect the reactivity in different ways.

The general scheme of S_NAr processes on nitrothiophenes is reported in Chart 2, whereas the observed rate constant, k_{obs} , is given by eq 1.

$$k_{\text{obs}} = (k_1 k_2 [\text{AmH}] + k_1 k_3 [\text{AmH}]^2) / (k_{-1} + k_2 + k_3 [\text{AmH}]) \quad (1)$$

Simplified kinetic expressions can be calculated as a function of the nature of the solvent, the leaving group, and the nucleophile used. In particular, if $(k_2 + k_3 [\text{AmH}]) \gg k_{-1}$, eq 2 can be derived.

$$k_{\text{obs}} = k_1 [\text{AmH}] = k_{\text{II}} [\text{AmH}] \quad (2)$$

For the substrates studied, it was reported that in benzene the amino substitution was base-catalyzed (eq 1).^{14b-j} In methanol, however, the outcome of the reaction shifted toward an uncatalyzed pathway (eq 2) because of the ability of methanol (a polar and protic solvent) to support the TS evolution.^{14c,e,f}

In the case of 2-L-3-nitrothiophenes (and generically in ortho-nitrohalogenoaromatic compounds), another factor, known as “built-in solvation,” affects the reactivity.^{14b,16} Due to intramolecular hydrogen-bond formation, which stabilizes the TS, in benzene these substrates are significantly more reactive than

the corresponding 2-L-5-nitrothiophenes, despite the possible steric hindrance that should have a negative impact on reactivity. Of course, the built-in solvation effect has little relevance in media, such as methanol, that are able by themselves to stabilize the TS and to assist its evolution.

Kinetic Data for the Amino Substitution of 1a–d in RTILs. In [bmim][X], the observed pseudo-first-order rate constants for the title reactions showed a simple linear dependence (see eq 2) on amine concentration ($k_{\text{obs}} = i + k_{\text{II}} [\text{AmH}]$), with the only exception of the morpholino-demethoxy substitution on **1b** (see later). The intercept values in most cases were negative: an outcome justified in a previous paper of ours on the basis of an acid–base equilibrium between the imidazolium cation and the amines.⁷ⁱ

The second-order rate constants (k_{II}) for substrates **1** are reported in Table 1 (complete data at different amine concentrations are available in Supporting Information: Table 4). For a useful comparison, data previously obtained in methanol are also reported.

The linear dependence, similar to that observed in methanol, indicates that, at least in [bmim][X], the reaction is not catalyzed and that, accordingly, the solvent has, at least qualitatively, the same effect as methanol in supporting the course of the reaction. On quantitative grounds, the ionic liquid accelerates the reaction because of the combined action of both cations and anions. In fact, bmim acts as a hydrogen-bond donor, favoring departure of the leaving group, while BF₄[−] behaves as a hydrogen-bond acceptor versus the amine proton, thus supporting the nitrogen–hydrogen bond breaking.

Similar effects are well documented in other systems. For example, Chiappe et al. reported that, in the bromination of alkynes in ionic liquids, the breaking of the bromine–bromine bond in the 1:1 π -complex was assisted by the imidazolium cation.^{7b} In addition, Welton et al., studying aliphatic nucleophilic substitution in the presence of neutral nucleophiles such as amines, claimed that a charge separation in the TS can be stabilized by a hydrogen bond between the ionic liquid anion and the ammonium ion.^{7e}

The figures relevant to the kinetics of amino substitution of **1** in [bmim][BF₄] show that all amines react faster in RTILs than in molecular solvents (by almost 1 or 3 orders of magnitude in comparison with methanol and benzene,^{14e,i} respectively). Yadav et al. reported similar results for aromatic amination of aryl halides.¹⁷

The nucleophilicity order in [bmim][BF₄] (Pyr > Pip > Mor) is similar to that observed in methanol, but the effect of the nucleophilicity on the reaction rate is definitely more pronounced: for **1a**, Pyr/Pip/Mor = 5.8:3.7:1 in methanol and 21.8:10.9:1 in [bmim][BF₄].

The behavior observed suggests that the higher reactivity in ionic liquids could be due to a less extensive solvation of the starting amine. Lacking the solvation leveling effect, the relative

CHART 2

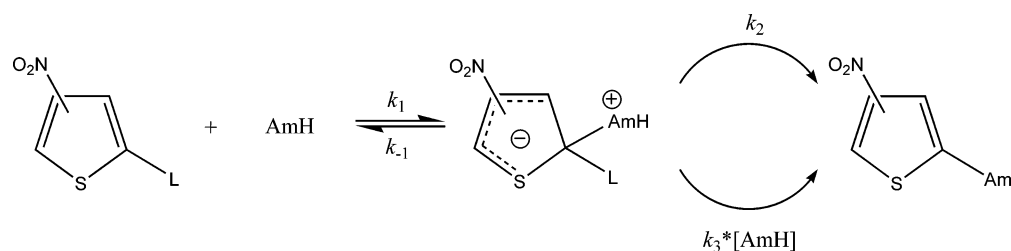


TABLE 1. Second (k_{II})^a and Third (k_{III})^b Order Rate Constants for the Aromatic Amination of **1a–d** in Ionic Liquid Solution at 298 K

substrate	amine	solvent	k_{II} (M ⁻¹ s ⁻¹)	k_{III} (M ⁻² s ⁻¹)	i
1a	Pyr	[bmim][BF ₄]	$(6.75 \pm 0.17) \times 10^{-3}$		$(-2.04 \pm 0.40) \times 10^{-5}$
	Pip	[bmim][BF ₄]	$(3.36 \pm 0.12) \times 10^{-3}$		$(-0.16 \pm 2.41) \times 10^{-6}$
	Mor	[bmim][BF ₄]	$(3.09 \pm 0.06) \times 10^{-4}$		$(-0.06 \pm 1.33) \times 10^{-7}$
	Pyr ^c	MeOH	4.02×10^{-5}		
	Pip ^d	MeOH	2.55×10^{-5}		
	Mor ^c	MeOH	6.93×10^{-6}		
	Pyr	[bmim][PF ₆]	$(2.95 \pm 0.04) \times 10^{-3}$		$(-6.51 \pm 0.75) \times 10^{-6}$
	Pyr ^e	[bm ₂ im][BF ₄]		$(3.91 \pm 1.00) \times 10^{-1}$	
1b	Pyr	[bmim][BF ₄]	$(9.39 \pm 0.33) \times 10^{-2}$		$(-2.57 \pm 0.69) \times 10^{-4}$
	Pip	[bmim][BF ₄]	$(3.92 \pm 0.12) \times 10^{-2}$		$(-2.32 \pm 0.28) \times 10^{-4}$
	Mor ^e	[bmim][BF ₄]		$(3.19 \pm 0.37) \times 10^{-2}$	
	Pip ^f	MeOH	1.57×10^{-3}		
	Mor ^{c,e}	MeOH		$(6.00 \pm 0.97) \times 10^{-2}$	
1c	Pyr	[bmim][BF ₄]	$(3.16 \pm 0.06) \times 10^{-2}$		$(7.00 \pm 1.22) \times 10^{-5}$
	Pip	[bmim][BF ₄]	$(2.03 \pm 0.09) \times 10^{-2}$		$(-5.83 \pm 1.83) \times 10^{-5}$
	Mor	[bmim][BF ₄]	$(1.58 \pm 0.07) \times 10^{-3}$		$(-1.08 \pm 0.16) \times 10^{-5}$
	Pip ^g	MeOH	$(6.77 \pm 0.39) \times 10^{-4}$		$(-2.15 \pm 0.72) \times 10^{-6}$
1d	Pyr	[bmim][BF ₄]	$(6.99 \pm 0.12) \times 10^{-2}$		$(9.79 \pm 2.41) \times 10^{-5}$
	Pip	[bmim][BF ₄]	$(4.97 \pm 0.15) \times 10^{-2}$		$(-1.09 \pm 0.32) \times 10^{-4}$
	Mor	[bmim][BF ₄]	$(3.92 \pm 0.16) \times 10^{-3}$		$(-2.90 \pm 0.33) \times 10^{-5}$
	Pip ^h	MeOH	6.14×10^{-4}		

^a $k_{II} = k_1$ (see Chart 2). ^b $k_{III} = (k_1 k_3/k_{-1})$. ^c Spinelli, D. et al., unpublished results. ^d Calculated from data reported in ref 14c. ^e This value was determined at 313 K. This temperature was chosen for decreasing the medium viscosity for [bm₂im][BF₄]; in the other two cases it was chosen for having fast enough kinetics. ^f Calculated from data reported in ref 14f. ^g Data collected in this work. ^h Calculated from data reported in ref 14e.

reactivity is amplified and truly depends on the effective nucleophilicity. In a recent paper, we proposed that the poor solvation of amines by ionic liquids increases their ability to behave as bases in a base-catalyzed ring-to-ring interconversion.⁷ⁱ

Comparison between the Reactivity of **1a–d in RTILs and in Methanol.** The order of reactivity for the piperidino substitution of **1**, with the exception of **1d** (see later), was as in methanol (with k_{II} following the trend **1b** > **1c** > **1a**), but the relative reactivities were rather different (62:27:1 for methanol and 12:6:1 for [bmim][BF₄]); this could be, in some way, a consequence of the reactivity–selectivity principle. We hypothesize specific interactions between the leaving group and the ionic liquid (both the cation and anion components), justified by the different nature of the leaving groups: bromine or oxygen are, respectively, bonded to the heteroaryl moiety. Moreover, for substrates **1b–d**, the oxygen atom of the leaving group has a different electronic density depending on the electronic requirements of methyl, phenyl, and 4-nitrophenyl groups, respectively.

The organizing ability of ionic liquids can also explain the higher reactivity of **1d**. In the ground state, this favors the conjugation, owing to π – π interactions, thus increasing the electron-withdrawing effect of the oxygen atom bonded to the heteroaryl moiety and consequently the k_1 value (see Chart 2).

The increase in reactivity of **1**, going from methanol to RTILs, could be related to an increase in medium polarity. Indeed, as the reaction implies a charge separation in the TS, every increase in the polarity of the solvent should significantly increase the reaction rate.

Several empirical parameters are useful in evaluating the polarity of a solvent. Thus, if we consider the π^* parameter as representative of a notion of “polarity,” the increase in reactivity

going from methanol ($\pi^* = 0.73$)¹⁸ to [bmim][BF₄] ($\pi^* = 1.047$)¹⁹ is well explained. However, when considering other solvent parameters (E_T^N , E_{NR}) different conclusions can be drawn. Indeed, the E_T^N (0.670 and 0.762 for [bmim][BF₄] and methanol, respectively)^{18,19} and E_{NR} (217.2 and 217.7, respectively)^{11a} values for these two solvents are quite similar.

Actually, the ionic liquid effect on the reaction studied is probably quite complex. For example, we found a reactivity for the pyrrolidino debromination of **1a** higher in [bmim][BF₄] than in [bmim][PF₆]. The observed trend agrees well with previously reported data.^{7b,i,8b} The kinetic constant values (Table 1) for the above reaction of **1a** in [bmim][BF₄] ($k_{II} = 0.00675$ M⁻¹ s⁻¹) and [bmim][PF₆] ($k_{II} = 0.00295$ M⁻¹ s⁻¹) cannot be exclusively a result of the polarity effect.

The E_T^N , E_{NR} , and π^* parameters (0.669, 216.8, 1.032 for [bmim][PF₆] and 0.670, 217.2, 1.047 for [bmim][BF₄], respectively)^{11a,19} do not explain the observed differences in reactivity. The hydrogen-bond acceptor ability, linked to the higher concentration of the negative charge in BF₄⁻ with respect to PF₆⁻, likely explains the higher efficiency of the first anion. This effect is confirmed by the higher β values reported for BF₄⁻ than for PF₆⁻ (0.376 and 0.207, respectively),¹⁸ which also are in the expected order.

However, some different explanations about the reactivity in [bmim][BF₄] have been advanced. It was attributed to a low solubility of the nucleophile^{8b} or to a change in its absolute nucleophilicity.⁷ⁱ Moreover, the different negative charge distributions on BF₄⁻ and PF₆⁻ can affect the distance between the imidazolium rings of the solvent, which would lead to a different catalytic effect owing to more or less pronounced π – π interactions.⁷ⁱ

The structure of the cation of a RTIL plays in turn an important role, as also the hydrogen-bond donor ability of the

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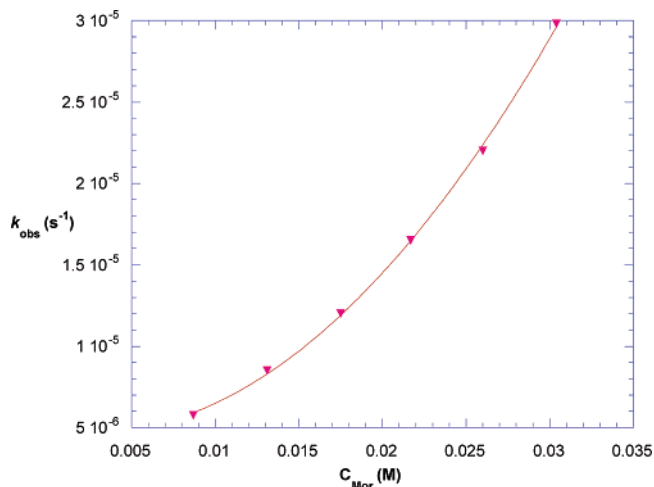


FIGURE 1. Plot of k_{obs} (s^{-1}) vs [Mor] for **1b** at 313 K.

solvent appears to be very important. In fact, a change in the cation component of an ionic liquid, going from bmim to bm_2im , can cause a different reactivity and mechanism.^{7d,10} Herein, for the pyrrolidino debromination of **1a** in $[\text{bm}_2\text{im}][\text{BF}_4]$, a different dependence of k_{obs} on amine concentration was observed ($k_{\text{obs}} = (k_1 k_3 / k_{-1}) [\text{AmH}]^2 = k_{\text{II}} [\text{AmH}]^2$). This could be explained by the fact that bm_2im , a cation less able to form a hydrogen bond, needs a second amine molecule to assist the leaving group departure. The different effect of the imidazolium cation in bmim and bm_2im , related to its different hydrogen-bond donor ability, is well documented. In particular, the nucleophilicity of the chloride anion,²⁰ the endo-selectivity for a Diels–Alder reaction,²¹ and the conversion and reaction rates of a Tsuji–Trost allylic substitution²² were explained by the different natures of the cations involved.

The morpholino substitution of **1b** in $[\text{bmim}][\text{BF}_4]$ showed a nonlinear dependence on amine concentration (Figure 1).

The same dependence was found in methanol. This result shows that this behavior could be unique to the considered leaving group/nucleophile couple. Furthermore, in contrast to all other cases, the reaction was faster in methanol than in ionic liquid. The higher reactivity in methanol could be due to the high crowding of the activated complex as a result of the presence of a second amine molecule. Methanol molecules reorganize themselves more easily than those of ionic liquids around the TS, thus providing a more effective stabilization in this particular case.

Kinetic Data for the Amino Substitution of 2a. For comparison, we also gathered kinetic data relevant to the amino substitution of **2a** with Pyr, Pip, and Mor in $[\text{bmim}][\text{BF}_4]$. The observed pseudo-first-order rate constants showed a simple linear dependence on amine concentration, and the second-order rate constants (k_{II}) are reported in Table 2 (rate data at different amine concentrations are available in Supporting Information: Table 5). Data previously collected in methanol and in benzene are also reported.

In line with the kinetic data for **1a**, also **2a** is more reactive in $[\text{bmim}][\text{BF}_4]$ than in methanol. The reactivity ratio, (k_{II})_b,

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TABLE 2. Second (k_{II}) Order Rate Constants for the Aromatic Amination of **2a** in Ionic Liquid Solution at 298 K

amine	solvent	k_{II} ($\text{M}^{-1} \text{s}^{-1}$)	i
Pyr	$[\text{bmim}][\text{BF}_4]$	$(3.44 \pm 0.11) \times 10^{-2}$	$(-3.08 \pm 2.39) \times 10^{-5}$
Pip	$[\text{bmim}][\text{BF}_4]$	$(9.20 \pm 0.09) \times 10^{-3}$	$(-8.80 \pm 1.98) \times 10^{-6}$
Mor	$[\text{bmim}][\text{BF}_4]$	$(1.09 \pm 0.03) \times 10^{-3}$	$(1.16 \pm 0.59) \times 10^{-6}$
Pyr ^a	MeOH	4.59×10^{-4}	
Pip ^b	MeOH	1.76×10^{-4}	
Pyr ^a	benzene	1.68×10^{-3}	
Pip ^c	benzene	4.25×10^{-4}	

^a This value was determined at 293 K. Spinelli, D. et al., unpublished results. ^b Data collected from ref 14d. ^c Data collected from ref 14b.

$\text{mimBF}_4 / (k_{\text{II}})_{\text{MeOH}}$, goes from 52 for Pip up to 75 for Pyr. The relative reactivity for the different amines (Pyr/Pip/Mor = 31:8.4:1) is quite similar to that for **1a** reported above.

A comparison among the reactivities of **1a** and **2a** in benzene, methanol, and $[\text{bmim}][\text{BF}_4]$ shows that, under similar conditions, **2a** is always more reactive than **1a**. The reactivity ratio $[(k_{\text{II}})_{2a} / (k_{\text{II}})_{1a}]$ for the pyrrolidino substitution significantly decreases from 747 in benzene to 11 in methanol and 5 in $[\text{bmim}][\text{BF}_4]$. A similar trend was also found for the piperidino substitution.

As noted previously, the high reactivity ratios observed in benzene show that built-in solvation is operative and very effective in this solvent,^{14b,16} strongly increasing the reactivity of ortho-like isomers.²³ This effect, occurring only in the ortho-like isomer, strongly lowers the differences in reactivity on going from benzene to $[\text{bmim}][\text{BF}_4]$. Despite the fact that $[\text{bmim}][\text{BF}_4]$ seems to have a scarce solvating effect, it affects reactivity ratios like methanol. This could be a consequence of different balancing of their behaviors; as a matter of fact, methanol heavily solvates both **1a** and **2a**, in contrast, $[\text{bmim}][\text{BF}_4]$ does not.

Activation Parameters for $\text{S}_{\text{N}}\text{Ar}$ in RTILs. Kinetic constants measured in RTILs sometimes show significant curvature in Arrhenius or Eyring plots, which has been related to temperature-dependent changes in the solvent structure.²⁴ Thus, for a careful analysis of the temperature effect, the substitution reaction was carried out at five temperatures in a relatively narrow range (from 293 to 313 K). The activation parameter values are collected in Table 3, with the values in methanol reported for comparison (data at different temperatures are available in Supporting Information: Table 6).

In the conditions employed, a nonlinear plot of $\log(k_{\text{obs}}/T)$ versus $1/T$ was observed only for the base-catalyzed morpholino demethoxylation of **1b**. In this case, however, where k_{obs} is expressed by eq 1 (see above), the nonlinear trend could be related to the complexity of the reaction mechanism (which would cause different temperature effects on the various steps of the reaction) rather than to structural changes in the solvent. For all the other cases, a good linear correlation guarantees that the calculated activation parameters only depend on the substitution process considered.

With respect to methanol, in every case, the aromatic amination in RTILs is enthalpy favored but entropy disfavored (with the exception of the pyrrolidino debromination of **1a** in both $[\text{bmim}][\text{BF}_4]$ and $[\text{bmim}][\text{PF}_6]$). The differential enthalpic

(23) In five-membered derivatives, such as **2a**, the hyperortho relationship occurring between C-2 and C-3 atoms of the thiophene ring further increases the k_{2a}/k_{1a} ratios, especially in nonpolar solvents.

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TABLE 3. Activation Parameters for the Aromatic Amination of **1a–d** and **2a** in Ionic Liquid

substrate	amine	solvent	ΔH^\ddagger (kJ/mol)	ΔS^\ddagger (J/K mol)	ΔG^\ddagger_{298K} (kJ/mol)
1a	Pyr	[bmim][BF ₄]	55.6 ± 3.9	−133 ± 13	95.2
	Pip	[bmim][BF ₄]	49.0 ± 2.2	−159 ± 7	96.4
	Mor	[bmim][BF ₄]	52.4 ± 1.9	−168 ± 6	102.6
	Pyr ^a	MeOH	62.1	−153	107.5
	Pip ^b	MeOH	64.1	−150	108.7
	Mor ^a	MeOH	64.0	−161	111.9
	Pyr	[bmim][PF ₆]	55.0 ± 1.0	−141 ± 3	97.1
	Pyr	[bm ₂ im][BF ₄]	49.0 ± 1.4	−161 ± 5	96.9
	1b	Pyr	[bmim][BF ₄]	32.3 ± 1.1	−189 ± 4
Pip		[bmim][BF ₄]	26.9 ± 1.2	−216 ± 4	91.3
Mor		[bmim][BF ₄]			
Pip ^c		MeOH	46.2	−176	98.7
1c	Pyr	[bmim][BF ₄]	42.9 ± 0.9	−162 ± 3	91.3
	Pip	[bmim][BF ₄]	33.8 ± 1.7	−197 ± 5	92.5
	Mor	[bmim][BF ₄]	19.4 ± 0.8	−269 ± 3	99.5
1d	Pyr	[bmim][BF ₄]	39.9 ± 3.1	−165 ± 10	89.3
	Pip	[bmim][BF ₄]	31.5 ± 1.0	−196 ± 3	90.1
	Mor	[bmim][BF ₄]	28.8 ± 1.0	−230 ± 3	97.3
	Pip ^d	MeOH	53.5	−159	100.9
2a	Pyr	[bmim][BF ₄]	42.1 ± 3.3	−164 ± 3	90.9
	Pip	[bmim][BF ₄]	44.7 ± 1.1	−166 ± 3	94.2
	Mor	[bmim][BF ₄]	46.3 ± 0.8	−178 ± 3	99.2
	Pyr ^a	MeOH	55.2	−156	101.5
	Pip ^e	MeOH	60.4	−146	103.9

^a Spinelli, D. et al., unpublished results. ^b Calculated from data reported in ref 14b. ^c Calculated from data reported in ref 14e. ^d Data collected in this work. ^e Calculated from data reported in ref 14d.

contribution could be due to the extensive solvation of the starting materials in methanol. On the other hand, the unfavorable entropic contribution in ionic liquids agrees with the bimolecular mechanism of the reaction and with the fact that on going from the initial to the TS there is no release of solvating molecules. Moreover, the zwitterionic TS should interact with the RTILs much more than the starting reagents.

The enthalpy values range from 19.4 to 55.6 kJ/mol, whereas the entropy values range from −269 to −133 J/K mol. Narrower ranges (≈ 18 kJ/mol for ΔH^\ddagger and 26 J/K mol for ΔS^\ddagger) were observed in methanol. The medium effect seems more important in RTILs than in methanol, where the strong interactions in both initial states and TSs provide a leveling effect. In contrast, RTILs could cause a wider spectrum in interaction intensity.

According to previous reports on going from conventional solvents to RTILs, the activation parameters in some cases are not very sensitive to the solvent used, while in other cases, significant changes have been detected.^{7d–f} The activation parameters have been analyzed as a function of the following: (i) the possible interactions between TS and RTILs; (ii) the nature of the leaving group; and (iii) the nucleophile used. We acknowledge, however, that the experimental values could depend on the balance of some different factors that act in opposite directions.

Activation Parameters of the Pyrrolidino Debromination of **1a in Different RTILs.** The values for the title reaction in [bmim][BF₄] and [bmim][PF₆] can be explained on the grounds of different cation (ammonium part of TS)–anion (BF₄[−] or PF₆[−]) interactions and of the hydrogen-bond acceptor and hydrogen-bond donor ability of ionic liquids. In particular, less-negative entropy values are expected due to an alteration of the ionic liquid structure rising by formation of a charge-separated TS from neutral starting materials.^{7e} The observed

entropy trend cannot be explained only on the basis of the β solvent parameter; the [bmim][BF₄], with the higher β value (0.376),¹⁸ would show a less-negative ΔS^\ddagger value.

This can only be a partial explanation, however, as [bm₂im][BF₄], with a similar β value (0.363),¹⁸ shows a more negative entropy value. Furthermore, [bmim][PF₆], with the lowest β value (0.207),¹⁸ shows an intermediate entropy value. Also, the other solvent parameters do not allow a unique explanation of the variation in activation parameters as a function of the nature of ionic liquids. This could be due to the fact that the solvent parameters for ionic liquids are probably inadequate. Indeed, it is questionable whether the empirically derived measurements of solvent properties can be exclusively attributed to RTILs or whether they are also affected by the nature of the compounds and the occurring reaction.²⁵

Effect of the Leaving Group in **1 on the Activation Parameters.** With the exception of the reaction with morpholine, the enthalpy values increase, that is, become less favorable, in the order OMe < OC₆H₄–4–NO₂ < OPh < Br. As was previously pointed out, the lowest activation enthalpy observed for **1b** could be related to the large resonance interaction between methoxy and nitro groups (via heteroaryl), which lowers the electronic reorganization occurring for the TS formation of the S_NAr. The trend observed parallels that of k_1 values (see Chart 2) and could also be due to the different electronegativities of atoms bonded to the heteroaryl moiety (oxygen and bromine) and, among the oxygenated groups, to the different oxygen electron densities and steric demands. Indeed, the higher electronegativity of the oxygen atom could induce a higher positive charge density, then favoring the nucleophilic attack. The entropy variation follows the order OMe < OC₆H₄–4–NO₂ \approx OPh < Br. The enthalpy and entropy variations balance between themselves thereby determining no large differences in k_1 values. The entropy trend seems to indicate that the breaking down of the ionic liquid structure is more extensive for the “late” TS of **1a** and less extensive for the “early” TS of **1b–d**. It is interesting to note that anions with a highly symmetrical distribution of negative charge, such as BF₄[−], permit interaction with several of the surrounding cations. So the later rather than the bulkier TS (**1a** having the lowest k_1 value) should induce a more extensive breaking down of the cross-linking of the ionic liquid structure.

The rather similar entropy values of **1c** and **1d** indicate similar steric hindrance for the two phenoxy groups. Furthermore, the entropy values for **1b** could reflect the higher order around the TS as a consequence of the low steric hindrance of the methoxy group.

Effect of the Nucleophile on the Activation Parameters. Concerning the dependence of activation parameters on the nucleophile (Table 3), there are significant differences between methanol and RTILs. In addition, Mor seems to have a peculiar behavior. Indeed, as observed previously, the kinetic constant of **1b** showed a nonlinear dependence on temperature. In this case, the resulting reaction was base-catalyzed (see eq 1), so the activation parameters for Mor are composite and then not comparable to those for Pyr and Pip. Furthermore, the low enthalpy values for Mor could be due to the stabilization of TS by an intramolecular electrostatic interaction between the ammonium group and the partially negatively charged oxygen atom of Mor. In addition, we assume that there is a more

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organized TS because of the hydrogen-bond between bmim and the oxygen atom.

The significant difference in the activation parameters between Pyr and Pip can be ascribed to the different positions (earlier or later) of the TS along the reaction coordinates. For example, a more significant interaction TS/anion of RTIL will be more operative for a late TS than for an early one. Moreover, a RTIL/substrate/nucleophile system with a higher order degree should be more affected by a disordering effect. However, if strong electrostatic or hydrogen-bond interactions are operative, perturbative effects could become less important.

Activation Parameters for S_NAr of **2a.** The activation parameters for **2a** in [bmim][BF₄] show that the substitution is enthalpy favored but entropy disfavored with respect to **1a**. All this agrees well with the occurrence of the built-in solvation effect, which induces a higher stabilization and organization of the TS. However, if we consider the differences in activation parameters for piperidino substitution of **1a** and **2a** in benzene (9.2 kJ/mol for ΔH^\ddagger and 20.9 J/K mol for ΔS^\ddagger), the above effect is, of course, more important in benzene than in ionic liquids.

Conclusions

Ionic liquids represent intriguing solvent systems, which cannot be described only by means of the usual solvent parameters. Indeed, most of our results seem to be justifiable on the grounds of the order and of the organizing ability of these systems. Furthermore, the reaction rate is influenced by the dimensions and charge distributions of anions as well as by the hydrogen-bond ability of cations in the RTIL used. Compared to methanol, the RTIL components have less strong interactions with reagents. However, as opposed to methanol, RTILs seem to be able to exalt the difference in the interactions among the zwitterionic TS and the ionic liquid components, resulting in the large spectrum of activation parameters observed. On going from conventional solvents to RTILs, we noted an interesting difference in the effect of a RTIL on the reactivity of para-like and ortho-like isomers.

Experimental Section

Materials. Commercial compound **1a** and 1,4-dioxane were used without any other purification. Commercial [bmim][BF₄], [bm₂im][BF₄], and [bmim][PF₆] were dried on a vacuum line at 60 °C at least for 2 h and stored in a dryer under argon and over calcium chloride. Amines were freshly distilled before use. Compounds **1b**,²⁶

1d,²⁷ and **2a**²⁸ were prepared according to the methods reported.

5-Nitro-2-phenoxythiophene (1c). A mixture of 1 mM of 2-bromo-5-nitrothiophene (**1a**) and 1 mM of potassium phenoxide in 10 mL of dioxane was refluxed for 2 h, following the disappearance of **1a** by means of TLC. The dioxane was eliminated at reduced pressure, and the resulting yellow solid was washed with water and extracted with toluene. After elimination of the toluene, the residue was crystallized from methanol to give 0.160 g of the product. Mp: 86 °C.

IR (Nujol; cm⁻¹): ν 3112; 1533; 1359. NMR (CDCl₃, 300 MHz): δ_H 6.27 (d, 1H, $J = 4.5$), 5.85 (m, 5H), 4.90 (d, 1H, $J = 4.5$); δ_C 171.4, 158.2, 132.3, 130.7, 128.3, 121.2, 111.6. Anal. Calcd for C₁₀H₇NO₃S: C, 54.3; H, 3.2; N, 6.3; S, 14.5. Found: C, 54.6; H, 3.0; N, 5.9; S, 14.7.

Kinetic Measurements and Calculations. UV-vis spectra and kinetic measurements were carried out by using a spectrophotometer equipped with a Peltier temperature controller, which is able to keep the temperature within 0.1 K.

Kinetic runs were carried out over the temperature range 293–313 K. The sample for a typical kinetic run was prepared by injecting into a quartz cuvette (optical path 0.2 cm) 500 μ L of IL, 50 μ L of a solution of substrate in 1,4-dioxane, and then 25 μ L of a concentrated solution of amine in 1,4-dioxane, previously thermostated. The concentration of substrate was constant and equal to 0.00019 M, and the amine concentration ranged from 0.00869 up to 0.0350 M. The reactions were all studied over six half-lives or more. In all cases, the correlation coefficient was higher than 0.9998.

To evaluate the possibility of reusing ILs, we tried a fast and simple treatment of the solvent used. Thus, 5 mL of the used [bmim][BF₄] was extracted four times with 3 mL of Et₂O. The IL layer was kept under vacuum at 60 °C for 2 h and reused. The apparent first-order rate constants then obtained were reproducible within $\pm 15\%$, with respect to values determined in fresh IL. All kinetic data were analyzed by means of the Kaleidagraph 3.0.1 software.

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Supporting Information Available: Rate constants collected at different amine concentrations and at different temperature values. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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