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Can the Absence of Solvation of Neutral Reagents by Ionic Liquids Be Responsible for the High Reactivity in Base-Assisted Intramolecular Nucleophilic Substitutions in These Solvents?[†]

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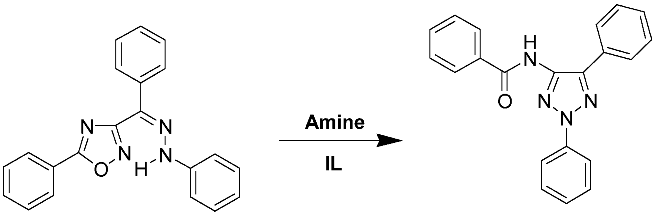

The kinetics of the rearrangement of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**2a**) induced by amines have been studied in two room-temperature ionic liquids (**IL-1**, [BMIM][BF$_4$] and **IL-2**, [BMIM][PF$_6$]). The data collected show that the reaction occurs faster in ionic liquids than in other conventional solvents previously studied (both polar or apolar, protic or aprotic). Presumably, this could depend on their peculiar ability to minimize the strong substrate−solvent, amine−solvent and amine−amine interactions occurring in conventional solvents.

Room-temperature ionic liquids (I Ls) have been proposed as environmentally benign solvents for their nondetectable vapor pressure and for their easy recyclability. I Ls promise several advantages in organic synthesis,[1] both increasing the effectiveness of the process and lowering the usage of raw materials. Several organic reactions were performed in I Ls with success but, to the best of our knowledge, quantitative aspects of reactions in I Ls have been much less investigated.[2]

To widen the applicability field of I Ls to new organic reactions, we have undertaken a kinetic study of the rearrangement (monocyclic rearrangement of heterocycles, MRH, or Boulton−Katritzky reaction, BKR)[3] of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**2a**) in two room-temperature ionic liquids: 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF$_4$] (**IL-1**) and hexafluorophosphate [BMIM][PF$_6$] (**IL-2**). **IL-1** and **IL-2** are among the ionic liquids most widely employed and could provide some information on the effect of the present anion. As a matter of fact, the presumably unlike cation−anion of different size interactions between BMIM and two anions [a larger (PF_6^-) and a smaller (BF_4^-)][4] could in turn affect the interaction between the transition state and the solvent.

We have chosen the reaction in Scheme 1 because, at least to our knowledge, no study of an intramolecular ring-to-ring rearrangement in I Ls has been so far reported in the literature. As a matter of fact, the mechanism [intramolecular (internal) nucleophilic displacement (S_{Ni}) of nitrogen onto nitrogen], transition-state structure, and kinetic details of this BKR have been deeply investigated experimentally both in several conventional solvents[3g−h,5] and in organized systems such as nonionic micelles[6] and β-cyclodextrin.[7]

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[†] Dedicated to Professor Giorgio Modena on the occasion of his 80th birthday.

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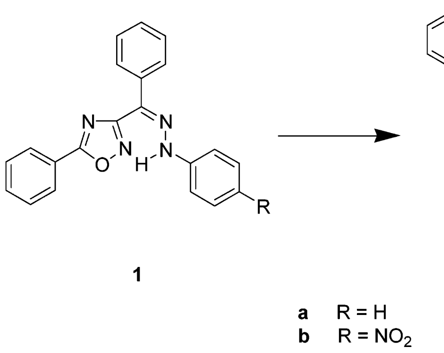
SCHEME 1



Moreover an accurate theoretical DFT study has recently furnished results convergent with experimental data strongly supporting the proposed transition-state structure for the reaction in the uncatalyzed range.[8] As a matter of fact, by measuring the rate constants for the rearrangement of **1a** into **2a** in dioxane/water at different proton concentrations it has been observed that in the 3.8−7.0 pS^+ range the reaction occurs via an uncatalyzed process (the pS^+-independent range), while at p$S^+ \geq 8.0$ a (general) base-catalyzed pathway (the pS^+-dependent range) is operating.

In other solvents (benzene, toluene, dioxane, ethyl acetate, acetonitrile and methanol) the rearrangement of **1a** has been studied in the presence of piperidine, always observing one or more piperidine-catalyzed pathways and, in some occasions (in acetonitrile as well as in methanol), a significant contribution of the uncatalyzed pathway.[5c−e]

The reactivity of some other *Z*-arylhydrazones has been also investigated. In particular, the rearrangement of the *Z*-4-nitrophenylhydrazone of 3-benzoyl-1,2,4-oxadiazole **1b** into the relevant triazole **2b** has been extensively studied in benzene (as well as in other solvents) in the presence of several primary, secondary, and tertiary amines with different basicity and steric requirements.[5e,9]

TABLE 1. Apparent First-Order Rate Constants ($k_{A,R}$)^a at 298.1 K and Calculated Second-Order Rate Constants (k_{II})^b for the Rearrangement of 1a into 2a in IL-1 and IL-2 in the Presence of Amines

Solvent: **IL-1**

	10^2 [BuA], M					
	0.217	0.435	0.869	1.30	1.52	1.74
10^3 $(k_{A,R})_{BuA}$, s^{-1}	0.0127	0.203	0.711	1.33	1.60	1.87

k_{II} (M^{-1} s^{-1}): (0.125 ± 0.004), *i* [(−3.07 ± 0.41) 10^{-4}], *n* 6, *r* 0.998

	10^2 [PIP], M					
	0.210	0.436	0.874	1.33	1.50	1.74
10^3 $(k_{A,R})_{PIP}$, s^{-1}	0.0138	0.843	3.02	5.06	6.30	8.14

k_{II} (M^{1} s^{-1}): (0.517 ± 0.028), *i* [(−1.35 ± 0.32) 10^{-3}], *n* 6, *r* 0.994

	10^2 [TEA], M					
	0.217	0.436	0.874	1.31	1.54	1.74
10^3 $(k_{A,R})_{TEA}$, s^{-1}	0.0102	0.327	1.10	1.52	2.05	2.48

k_{II} (M^{-1} s^{-1}): (0.156 ± 0.008), *i* [(−3.44 ± 0.96) 10^{-4}], *n* 6, *r* 0.994

Solvent: **IL-2**

	10^2 [PIP], M				
	0.877	1.33	1.55	1.77	2.18
10^3 $(k_{A,R})_{PIP}$, s^{-1}	0.0246	0.133	0.186	0.264	0.360

k_{II} (M^{1} s^{-1}): (0.0261 ± 0.0010), *i* [(−2.09 ± 0.15) 10^{-4}], *n* 5, *r* 0.998

[a] The rate constants were reproducible to within ±3%. [**1a**] 1.7 × 10^{-4} M (at λ 366 nm, log ϵ 4.28). [b] See text.

First we checked that **1a** does not rearrange significantly into **2a** in **IL-1** within 10 days (i.e., if a reaction occurs, $k_{A,R} \cong 10^{-8}$ s^{-1}). However, remembering the results obtained in conventional organic solvents in the presence of organic bases,[5c−e,9] we planned to measure the reactivity at 298.1 K in the presence of six different molar concentrations (0.0020−0.0174 M, see data in the Table 1) of the following bases: butylamine (BuA, a primary amine), piperidine (PIP, a secondary cyclic amine). and triethylamine (TEA, a tertiary amine), showing different structure, basicity and steric requirements.

An excellent linear dependence of $k_{A,R}$ on amine concentration has been found for each amine according to eq 1 and the following, strictly comparable k_{II} values (M^{-1} s^{-1}) have been calculated for BuA (0.125 ± 0.004, *r* 0.998), PIP (0.517 ± 0.028, *r* 0.994), and TEA (0.156 ± 0.008, *r* 0.994), respectively. Significant "negative" intercept values ($i = -3.07 \times 10^{-4}$, -1.35×10^{-3}, and -3.44×10^{-4}, for BuA, PIP and TEA, respectively) have also been calculated.[10]

$$k_{A,R} = i + (k_{II})_{amine}[\text{amine}] \qquad (1)$$

The behavior above could be related to an acid−base interaction between the acidic imidazolium ion and the amine, as confirmed by the observation that, when recording the UV−vis spectra of **IL-1** in the presence of increasing piperidine concentrations (1 × 10^{-4} to 1 × 10^{-1} M), a decrease of the absorption maximum (λ = 283 nm) and an increase of the absorption at λ = 400 nm could be evidenced. This behavior is in line with the peculiar acidic character of H-2 of **IL-1**, recently pointed out by means of ^{1}H NMR measurements in different solvents by Headley and Jackson.[11] In agreement with the hy-

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(10) This fact is not new in the literature, although it has never been discussed before. Thus, for example, by using literature data we calculated negative intercept values in the case of the reaction of methyl *p*-nitrobenzenesulfonate with halide ions.[2b]

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pothesis advanced, the calculation of the [amine] value corresponding to $k_{A,R} = 0$ in eq 1 (i.e., [amine] $= -i/k_{II}$) furnished three strictly comparable concentration values: 2.5×10^{-3}, 2.6×10^{-3}, and 2.2×10^{-3} M for BuA, PIP, and TEA, respectively. Therefore the "true" effective amine concentrations are lower than the stoichiometric ones by ca. 2.4×10^{-3} M; of course, this correction does not affect the amine-dependent slope values (k_{II}).

The simple (first-order) dependence of the reactivity on the amine concentration (whichever the amine) evidences in **IL-1** a behavior largely different from the more complex one observed in conventional organic solvents where, in the presence of piperidine, the rearrangement of **1a**[5c−f] occurred with different kinetic laws depending on the solvent polarity. In highly polar solvents (such as acetonitrile and methanol, where also a significant contribution of the uncatalyzed pathway could be evidenced) and, in contrast, in low polarity solvents (such as benzene, toluene, dioxane and ethyl acetate) a first- and a second-order dependence on the amine concentration were observed, respectively.[5c−g] Moreover in the instance of **1b**,[5e,9] the substrate most deeply investigated in benzene, it was observed that in the presence of amines of different basicities and steric requirements the rearrangement follows a first-order dependence with tertiary amines (or with highly hindered secondary amines), but a second- and a third-order dependence with secondary and primary amines, respectively.

To gain information about the base and solvent effects a comparison with data in conventional solvents is appropriate. For this we chose benzene (PhH) and acetonitrile (ACN) as good examples of solvents with completely different properties. In PhH and in ACN different kinetic laws were observed depending on the amine used; thus, to compare data in ionic liquid with those for **1a** and **1b** in the two abovementioned solvents, we calculated rate constant values at 0.01 M amine concentration.

As far as base effects are concerned, for the rearrangement of **1a** in **IL-1** (see data in Table 1) only a small reactivity variation [at 298.1 K, $(k_{II})_{BuA}:(k_{II})_{TEA}:(k_{II})_{PIP} = 1:1.2:4.1$] has been observed. In contrast, a much larger and a similar reactivity range were observed for **1b** in PhH (at 313.1 K, 1:66:188)[9b] and in ACN (at 283.1 K, 1:1.1:8.1),[5f] respectively. The effect of the reactivity-selectivity principle could, at least in part, account for the different behavior observed in the three solvents (PhH, ACN, and **IL-1**), but it must be remembered that in benzene, as well as in other conventional solvents, amine−solvent and amine−amine interactions could strongly differentiate the amines on the basis of their nature and of their steric requirements (both intrinsic, that is, structure-dependent and external, that is, dependent on amine−solvent interactions) unlike what probably occurs in **IL-1** and ACN (see following).

Looking now at the solvent effect on the reactivity of **1a** in the presence of piperidine, always comparing data at amine concentration 0.01 M, we observed a very large increase of the reactivity on going from PhH to ACN or **IL-1**: $(k_{A,R})_{PhH}:(k_{A,R})_{ACN}:(k_{A,R})_{\mathbf{IL-1}}$[12] $= 1:1.2 \times 10^5:3.5 \times 10^5$. Certainly the polar nature of **IL-1** plays a role in making it a very effective solvent for the rearrangement herein. As a matter of fact, the PIP-catalyzed reaction rate of the rearrangement of **1a** in **IL-1** is higher than those measured in any of the solvents previously tested, also including ACN, which together with DMSO has been so far considered the favorite solvent for S_N2[13] and then for S_Ni reactions.[5d−f,13] The peculiar behavior of ACN was related[5d−f] not only to its HBD acidity and solvatochromic constants (α 0.19, E_T^N 0.460) but also to its HBA basicity (β 0.40) which in the whole makes it able to provide assistance to the reaction.[13]

However, in the case of **IL-1** we think that its efficiency as a solvent able to promote MRH cannot be ascribed only to its high polarity. Probably, acting as an organizing medium because of $\pi-\pi$ interactions, it could help the *Z*-phenylhydrazone **1a** to assume the suitable geometry for the occurrence of the intramolecular reaction, according to the hypothesis that the high solubility of aromatic compounds in I Ls could be related to some kind of clathrate formation.[14]

As the properties of I Ls are largely controlled by the nature of both the cation and the anion,[4] in order to gain further information concerning the anion influence we have studied the rearrangement at 298.1 K of **1a** in another room-temperature ionic liquid, namely, 1-butyl-3-methylimidazolium hexafluorophosphate (**IL-2**), in the presence of PIP at five concentrations of amine (0.009−0.022 M). Once more an excellent linear dependence of $k_{A,R}$ versus [PIP] with a negative intercept value ($i = -2.09 \times 10^{-4}$) was found and a k_{II} (M^{-1} s^{-1}) of 0.0261 (±0.0010, r 0.998) was calculated. In this case an amine concentration value corresponding to $k_{A,R} = 0$ was calculated (8×10^{-3} M), well in agreement with the observation[11] that **IL-2** is more acidic than **IL-1**.

The reactivity of **1a** in **IL-2** is lower than in **IL-1** by a factor of ~20. A similar reactivity trend in tetrafluoroborate and in hexafluorophosphate salts was recently observed in the nucleophilic substitution of 2-(3-bromopropyl)naphthalene with potassium acetate[2e] and the outcome was attributed to a low solubility of the nucleophilic reagent. Also in the triplet energy transfer from benzophenone to naphthalene a large reactivity variation was observed by changing the solvent anion from hexafluorophosphate to bis(trifluoromethanesulfonyl)imide,[2c] attributed to different charge distributions in the anions.

A comparison between the reactivity in the two I Ls is surely of interest, considering that we have pointed out that the **1** to **2** rearrangement is largely affected by the very nature of the solvent: thus we think that differences in solvent properties of the two I Ls could cause significant reactivity differences.

Unfortunately, measurements of dielectric constants of I Ls appear at present not available, and thus other parameters useful to determine their "polarities" must be used. E_T^N, α, and β parameters appear particularly promising for discussing solvent effects in our case. As matter of fact E_T^N and α, as expected, are quite similar for **IL-1** and **IL-2** (E_T^N 0.673 and 0.667; α 0.73 and 0.77,

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[12] This value was referred at 313.1 K.

[13] Reichardt, C. *Solvents and Solvent Effect in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2003.

[14] Atwood, J. L. *Liquid Clathrates, Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 1.

respectively) while β are significantly different (β 0.72 and 0.41, respectively)[13] and could be related to the higher negative charge concentration and then to a higher basic efficiency for **IL-1** with respect to **IL-2**. Considering the role exerted by the solvent in MRH because of its ability to assist proton abstraction in the transition state the large decrease of HBA basicity (i.e., the decrease of β, see above) on going from tetrafluoroborate to hexafluorophosphate well accounts for the decrease observed in the reactivity $(k_{\mathrm{II}})_{\mathbf{IL-1}}/(k_{\mathrm{II}})_{\mathbf{IL-2}} \cong 20$. Anyway, the differences in the β values cannot completely explain the observed "solvent" effect: indeed, ACN and **IL-2** have very similar β values (0.40[13] and 0.41,[13] respectively) but significantly different effects on the reactivity of **1a** $[(k_{\mathrm{II}})_{\mathrm{ACN}}/(k_{\mathrm{II}})_{\mathbf{IL-2}} = 6.5$, with $E_{\mathrm{T}}^{\mathrm{N}}$ values moreover disfavoring ACN]. On the other hand it is well-known that it is questionable whether the empirically derived measurements of solvent properties could be exclusively referred to room-temperature ionic liquids or whether the different polarity of ionic liquids is also affected by the nature of the tested compounds.[15] For the reasons above, we believe that the difference in reactivity could be a consequence of the fact that, as reported, "there is no single ionic liquid behavior; rather there are a range of properties possible across the ever growing range of ionic liquids discovered and yet to be discovered".[16]

In conclusion, the data collected seem to indicate that I Ls, besides the properties that make them very promising green solvents, can be useful for mechanistic studies. Indeed, with the exception of an acid−base equilibrium between imidazolium ion and amine, other interactions (such as substrate−**IL**, amine−**IL**, and amine−amine) seem to be absent or to have scarce relevance; thus, solvent effects that often make difficult the mechanistic interpretations for a reaction can be avoided. Therefore the use of room-temperature ionic liquids as reaction solvents appears a very useful tool both from a synthetic and a mechanistic point of view. As a matter of fact they show an effect on the reactivity similar to that exerted by dipolar aprotic solvents such as ACN, DMSO, or DMF (e.g., potassium 2-naphtholate reacts with 1-bromobutane in **IL-2** at a similar rate as observed in DMSO or DMF but with the large advantage of an easy separation of the reaction products).[17] Moreover, ionic liquids do not solvate the reagents but can largely affect the formation of polar transition states, a fact that can be particularly interesting for mechanistic studies.

Experimental Section

Materials. The *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole and the relevant triazole were prepared according to a procedure reported.[18] All other products were commercial. BMIMBF$_4$ and BMIMPF$_6$ 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. 1,4-Dioxane (for fluorescence) was used without further purification. Amines were freshly distilled before use.

UV−vis spectra and kinetic measurements were carried out by using a spectrophotometer equipped with a peltier temperature controller, able to keep the temperature within ±0.1 K.

Kinetic Measurements and Calculations. Kinetic runs were carried out at 298.1 K. The sample for a typical kinetic run was prepared by injecting into a quartz cuvette (optical path 0.2 cm) 500 μL of **IL**, 50 μL of a solution of **1a** in 1,4-dioxane, and then 25 μL of a concentrated solution of amine in 1,4-dioxane, previously thermostated. The concentration of **1a** was constant and equal to 0.00017 M, and the amine concentration ranging from 0.0021 up to 0.0218 M. The absorbance at $\lambda = 360$ nm was plotted versus time and showed a simple exponential dependence. 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 I Ls, we tried a fast and simple treatment of the solvent used. Thus, 5 mL of used **IL-1** was extracted four times with 3 mL of Et$_2$O. 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 ±15% with respect to values determined in fresh **IL-1**.

All kinetic data were analyzed by means of the KALEIDAGRAPH 3.0.1 software.

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