

# The Interplay of Acidity and Ionic Liquid Structure on the Outcome of an Heterocyclic Rearrangement reaction

*Salvatore Marullo and Francesca D'Anna\**

Dipartimento di Scienze Biologiche, Chimiche e Farmaceutiche, Sezione di Chimica, Viale delle Scienze, Università degli Studi di Palermo, 90128 Palermo, Italy

Corresponding author: Prof. Francesca D'Anna, francesca.danna@unipa.it

## Abstract

The study of suitable probe reactions is a powerful tool to investigate the properties of non-conventional solvents such as ionic liquids (ILs). In particular, we studied the acid-catalyzed Mononuclear Rearrangement of Heterocycles (MHR) of the *Z*-phenylhydrazone of the 5-amino-3-benzoyl-1,2,4-oxadiazole into the relevant 1,2,3-triazole, in solution of ILs by means of kinetic measurements. We chose as solvents six ILs differing both in the cation and anion, in the presence of five among carboxylic and sulfonic acids as catalysts. The effect of IL anion and cation on the reactivity and on the acidic strength of the catalysts was analyzed. To this aim, we measured the acidic strength of the sulfonic acids in each ILs, estimated by the equilibrium formation constant of each acid with 4-nitroaniline. We found that the trend of reactivity as a function of the IL anion mainly reflects the larger difference in acidic strengths of the catalyst. Conversely, acidic strength spans a narrower range as a function of the IL cation. As a result, other factors come into play, such as the  $\pi$ - $\pi$  interactions involving aromatic IL cations, substrate and transition states, leading to a more articulate trend.

## Introduction

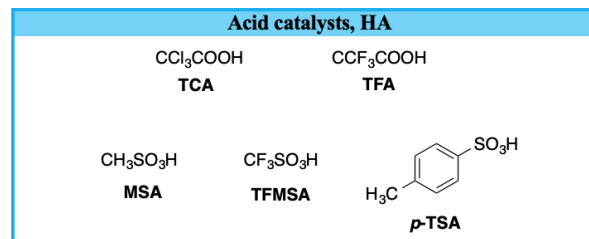
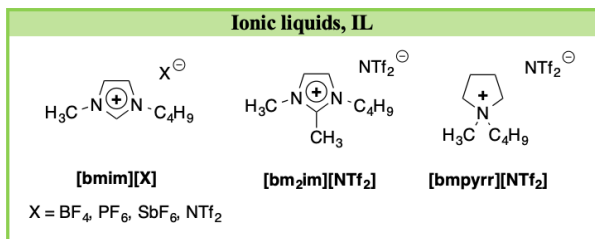
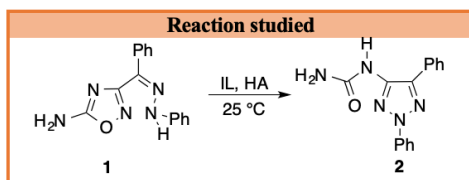
Solvents constitute an almost unavoidable component of every chemical reaction or process, and the right choice of the suitable reaction medium is of utmost importance in enabling a given transformation. On the downside, many conventional organic solvents are harmful to environment or human health and solvents make up the most abundant constituent of chemical waste. The sheer magnitude of the industrial production of solvents, estimated to approach 20 million MT (metric tons) per year,<sup>1,2</sup> gives a clear idea of the urgency to maximize the replacement of traditional solvents with safer, renewable and in general more sustainable alternatives, in agreement with the 5<sup>th</sup> principle of Green Chemistry.<sup>3</sup> For this reason, the study and application of non-conventional solvents, able to behave as suitable reaction media minimizing detrimental consequences to the environment, is a standing endeavor of present-day chemical research, which has led to the application of bio-based solvents,<sup>1,4</sup> supercritical fluids,<sup>5</sup> deep eutectic solvents<sup>6,7</sup> and ionic liquids (ILs).<sup>8</sup> ILs are low-melting organic salts, often liquid at room temperature, originally emerging in the context of sustainable solvents for their low vapour pressure and flammability. ILs provide a unique solvent environment, being composed only of ions.<sup>9</sup> Furthermore, ILs bearing aromatic ions are characterized by a distinct and persistent nanostructure,<sup>10,11</sup> which makes them full-fledged supramolecular fluids.<sup>12</sup> This greatly influences their solvent behavior and, together with their low solvating power and high solubilizing ability, results in many cases in enhanced reactivity and enables their application in a diverse array of fields, from material chemistry<sup>13</sup> to catalysis<sup>14</sup> and synthesis.

An effective way to study their properties and solvent behavior, is the investigation of a suitable “probe reaction” whose mechanism is well-established in conventional molecular solvents. Ideally, such reactions should proceed through simple mechanisms. In the light of this, we successfully employed a mononuclear rearrangement of heterocycles (MHR), also known as Boulton-Katritzky

rearrangement, which allows the conversion of suitably substituted azoles through an intramolecular nucleophilic substitution. This reaction is of synthetic importance since gives access to nitrogen-containing heterocycles like triazoles, used in several fields like medicinal, pharmaceutical and materials chemistry to name only a few.<sup>15-18</sup> Furthermore, the MHR has been widely studied from a mechanistic point of view, and depending on the structure of the substrate, it can proceed through basic or acidic catalysis. Being markedly sensitive to solvent effects, it has been widely studied in conventional solvents and also in more complex systems like micelles<sup>19</sup> and cyclodextrins<sup>20</sup>.

Since the mechanism of this reaction in conventional solvents is well understood and proceeds through a concerted step, with a quasi-aromatic transition state, it has proved a suitable candidate to be used as a “probe reaction” to study the features of non-conventional solvents like ILs. In this regard, we used the MHR to investigate the properties of ILs, studying in particular the thermally activated rearrangement of related phenylhydrazone of 1,2,4-oxadiazole,<sup>21</sup> the base-catalysed MHR, which allowed us to study properties of neat ILs<sup>22-26</sup> as well as their binary mixtures<sup>27</sup> and the Lewis acid catalyzed MHR in imidazolium-based ILs.<sup>28</sup>

In general, from these studies we found, as a recurrent motive, that the reactivity is favorably influenced by a higher degree of structural order of the solvent. However other factors, arising from specific interactions among ions and substrates come into play when their structure is changed. Although the base catalyzed version of this reaction has been the object of several studies, to date there is no report in the literature on the Brønsted acid catalyzed MHR in ILs. This could allow obtaining information on the influence of Brønsted acidity in ILs as well as elucidating the influence of the structure of the ILs on reactivity. In the light of this, we studied the reactivity of the Z-phenylhydrazone of the 5-amino-3-benzoyl-1,2,4-oxadiazole (**1**, Chart 1) in into the relevant 1,2,3-triazole (**2**, Chart 1) in ILs by means of kinetic measurements. In particular, we carried out kinetic experiments in solution of six ILs differing for the coordinating ability and symmetry of the anion, as well as for the cation, aromatic or aliphatic. We employed different sulfonic and carboxylic acid as catalysts.



**Chart 1.** Reaction studied, structures of ILs and acid catalysts considered.

In particular, the rate of the rearrangement process was studied spectrophotometrically, at a temperature of 298 K at constant concentration of **1** and variable concentrations of acid.

For a comparison with conventional solvents, we also carried out kinetic experiments in 1,4-dioxan and methanol. To assess whether the reactivity trends observed mainly depend from the acidity of the medium, we estimated the acidic strength of sulfonic acids in each IL, by determining the equilibrium association constants between each acid and 4-nitroaniline.

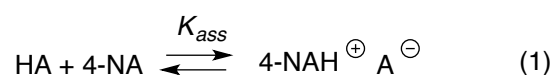
Data collected demonstrate how, in general, reactivity in IL solution cannot be explained on the grounds of a single parameter, but it is rather the interplay of different factors, among which acidic strength and structural organization of the solvent medium play a pivotal role.

## Results and discussion

### *Acidic strength measurements*

Since the reaction studied is promoted by acids, it is important to assess the acid strength of the catalyst employed in each solvent. To this aim, we determined the acidic strength of the sulfonic acids in each solvent, estimated by the equilibrium association constant with 4-NA.

The acidic strength of the acids in each solvent has been determined by following a reported procedure.<sup>29-31</sup> In particular, we recorded UV-vis spectra of solutions containing a fixed amount of 4-NA and increasing amounts of acids (HA). In each solution, when the acid protonates 4-NA, the following equilibrium is established:



where HA is the acid, 4-NA is 4-nitroaniline and 4-NAH<sup>+</sup>A<sup>-</sup> is the ion pair formed. In this kind of solvents, such species are better described as ion pairs in which the proton is shared between the ions.

The relevant equilibrium association constant can thus be expressed as:

$$K_{ass} = \frac{[4\text{-NAH}^{\oplus} \text{A}^{\ominus}]}{[\text{HA}] [4\text{-NA}]} \quad (2)$$

In all cases considered, each acid has a negligible absorbance in the wavelength range explored. Considering the mass balances on HA and NA, and assuming the validity of the Lambert-Beer law at the  $\lambda_{\text{max}}$  of 4-NA,<sup>32</sup> the spectral changes as a function of acid concentration can be related to  $K_{ass}$  by means of eq. 3,

$$\Delta A = \frac{b * \Delta \epsilon * C_{4\text{-NA}} * K_{ass} * [\text{HA}]}{1 + K_{ass} * [\text{HA}]} \quad (3)$$

where b is the optical path of the sample,  $\Delta A$  is the difference in absorbance at a suitable wavelength, between the solution under examination and the one devoid of acid,  $\Delta \epsilon$  the difference between the molar extinction coefficients of protonated and neutral 4-NA and  $C_{4\text{-NA}}$  is the analytical concentration of 4-NA.

In solution of ILs, absorbance variations as a function of concentration of HA could not be fitted satisfactorily with Eq. 3. This is caused by interactions of acids with IL. In particular, anions like

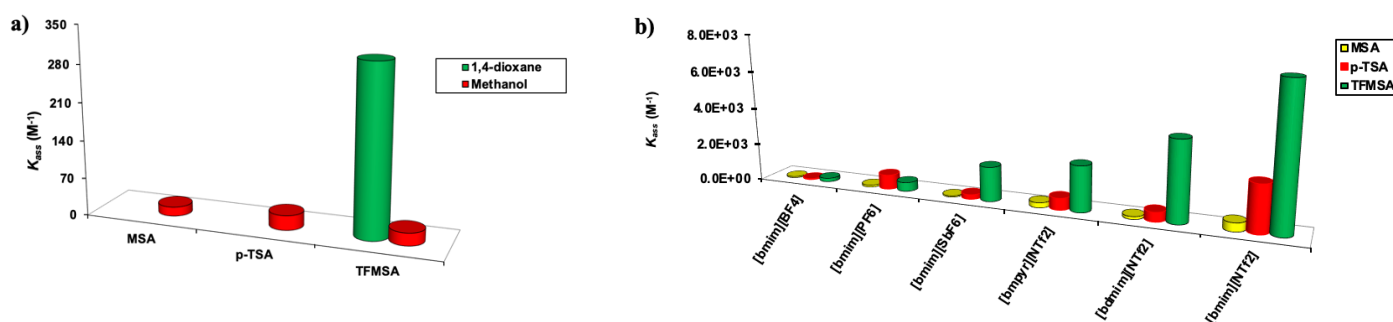
[NTf<sub>2</sub><sup>-</sup>], [BF<sub>4</sub><sup>-</sup>], [PF<sub>6</sub><sup>-</sup>] and [SbF<sub>6</sub><sup>-</sup>] can be protonated or react with HA, reducing its actual concentration.<sup>33</sup> Accordingly, in these cases,  $K_{ass}$  was determined by non-linear fitting of Eq. 4,

$$\Delta A = \frac{b * \Delta \epsilon * C_{4-NA} * K_{ass} * ([HA]-a)}{1 + K_{ass} * ([HA]-a)} \quad (4)$$

where “a” is the concentration of acid involved in the interaction with IL. Full calculation details are reported in the Supporting Information.

In all the cases considered, the trend  $\Delta A$  as a function of the concentration of acid was consistent with the formation of only 1:1 adducts, ruling out the occurrence of more complex interactions between acids and 4-NA.

It is worth noting that, irrespective of the solvents, carboxylic acids failed to induce any change in the spectrum of 4-NA, indicating that their acidic strength is not sufficient to protonate the probe. Thus, we can state that in all the solvents used, the carboxylic acids are weaker than the sulfonic acids. All the  $K_{ass}$  values calculated are reported in Figure 1 and Table S1.



**Figure 1.** Values of  $K_{ass}$  for sulfonic acids in a) conventional solvents and b) ILs.

Examination of the  $K_{ass}$  values reported in Figure 1, brings out that each acid is stronger in ILs than in conventional solvents. This is different compared with what we previously obtained when the conventional solvent was water, in which cases carboxylic acids displayed much higher strength than ILs.<sup>29,30</sup> In particular, in the case of dioxane, this can be explained considering its lower polarity and thus lower ability to stabilize the ion pair by solvation interactions.

In methanol, all the three acids practically show the same acidic strength, evidencing the occurrence of a levelling effect. This limits the magnitude of  $K_{ass}$  in this solvent.

Finally, acid being the same,  $K_{ass}$  are higher in methanol than in dioxane, in accordance with the higher solvation ability of the former, stabilizing the ion pair. The only exception is constituted by TFMSA in dioxane, where  $K_{ass}$  value is on order of magnitude higher than the one in methanol.

Moving to ILs, it is worth remembering that these solvent are generally characterized by a lower solvation power than conventional solvents, leading, in some cases, to enhanced reaction rates due to reactants being readily available to interact with each other.<sup>22</sup> Therefore, HA and 4-NA should be more available to give rise to the ion pair formation.

Looking at results reported in Figure 1b, reveals that in in each IL the acidic strength follows the same trend, MSA < *p*-TSA < TFMSA. The only exception is constituted by [bmim][PF<sub>6</sub>], in which *p*-TSA is slightly stronger than TFMSA.

To further investigate the influence of the IL components on the acidic strengths of the sulfonic acids used, we will now look at the effect exerted the nature of cation and anion, separately.

Firstly, to evaluate the effect exerted by the nature of the cation, we consider the trend of  $K_{ass}$  detected in solution of the [NTf<sub>2</sub>]-based ILs. In particular, perusal of the results reported in Figure 1b and Table S1, reveals that for MSA and *p*-TSA  $K_{ass}$  increases along the order: [bm<sub>2</sub>im][NTf<sub>2</sub>] < [bmpyrr][NTf<sub>2</sub>] < [bmim][NTf<sub>2</sub>]. Furthermore, for each acid, the ratios of the  $K_{ass}$  values vary in a closely similar way ( $K_{ass [bm_2im][NTf_2]} : K_{ass [bmpyrr][NTf_2]} : K_{ass [bmim][NTf_2]}$  amount to 1:1.8:3.1 and 1:1.8:4.9 for MSA and *p*-TSA, respectively). The trend obtained mirrors the hydrogen bonding ability of the

IL cation, as estimated by the Kamlet-Taft parameter  $\alpha$ , which is equal to 0.381, 0.427 and 0.617 for [bm<sub>2</sub>im][NTf<sub>2</sub>], [bmpyrr][NTf<sub>2</sub>] and [bmim][NTf<sub>2</sub>], respectively.<sup>34</sup> This can be explained considering that the cation can solvate the ion pair through hydrogen bonding with the oxygen in the sulfonate ion where the negative charge builds. Consequently, the higher the hydrogen bonding donating ability of the cation, the higher the value of  $K_{ass}$ .

Moreover, [bmim][NTf<sub>2</sub>] is less bulky than [bm<sub>2</sub>im][NTf<sub>2</sub>], which implies a slightly higher charge delocalization in the latter case. Hence, [bmim][NTf<sub>2</sub>] and [bmpyrr][NTf<sub>2</sub>] have a higher charge density and this can further increase stabilization of the ion pair, and thus increase equilibrium acidity, as previously reported in the literature.<sup>35,36</sup> It is worth noting that the obtainment of not only the same trend, but also the same  $K_{ass}$  ratios, for an aliphatic and an aromatic acid, evidences how there is no particular influence on the stabilization of the ion-pair by  $\pi$ - $\pi$  interactions between the aromatic IL cations and the phenyl ring of *p*-TSA. This is in stark contrast to what we previously observed studying the acidic strength of substituted benzoic acids in the same ILs.<sup>29,30</sup>

Once again TFMSA deviates from this trend, since  $K_{ass}$  increases in the order: [bmpyrr][NTf<sub>2</sub>] < [bm<sub>2</sub>im][NTf<sub>2</sub>] < [bmim][NTf<sub>2</sub>]. We propose that with such a strong acid the further stabilization of the ion pair exerted by the IL cation, though operating, is more marginal.

Moving to the effect of the IL anion, we can observe a more articulate trend in the [bmim<sup>+</sup>]-based ILs. In particular, in all cases the lowest  $K_{ass}$  value is found in solution of [bmim][BF<sub>4</sub>], while the highest one is detected in [bmim][NTf<sub>2</sub>]. However, once again, the trend observed for TFMSA differs from the one found for MSA and *p*-TSA. For TFMSA,  $K_{ass}$  increases along the order: [bmim][BF<sub>4</sub>] < [bmim][PF<sub>6</sub>] < [bmim][SbF<sub>6</sub>] < [bmim][NTf<sub>2</sub>], while in the other cases the order observed is [bmim][BF<sub>4</sub>] ≤ [bmim][SbF<sub>6</sub>] < [bmim][PF<sub>6</sub>] < [bmim][NTf<sub>2</sub>]. From these results, we can rule out a prominent influence of the IL hydrogen bonding accepting ability, as expressed by the Kamlet-Taft  $\beta$  parameter, which in fact varies as [bmim][SbF<sub>6</sub>] < [bmim][PF<sub>6</sub>] < [bmim][NTf<sub>2</sub>] < [bmim][BF<sub>4</sub>] ( $\beta$  = 0.146, 0.207, 0.243, 0.376 for [bmim][SbF<sub>6</sub>], [bmim][PF<sub>6</sub>], [bmim][NTf<sub>2</sub>] and [bmim][BF<sub>4</sub>],



respectively).<sup>34</sup> Another factor that can affect the acidic strength is the structural organization of the IL. This is related to the extent of aggregation among ions, which, in a previous work, we estimated by Resonance Light Scattering (RLS) measurements.<sup>26</sup> Once again, a single parameter fails to account for the trend observed, since it increases following the sequence [bmim][NTf<sub>2</sub>] < [bmim][BF<sub>4</sub>] < [bmim][PF<sub>6</sub>].

Finally, it can be stated that, in general,  $K_{ass}$  appears to increase on going from ILs with anions with higher cross linking ability, such as [BF<sub>4</sub><sup>-</sup>] and [PF<sub>6</sub><sup>-</sup>], to one with a weaker cross linking anion, like [NTf<sub>2</sub><sup>-</sup>].<sup>37,38</sup>

In the light of all these considerations, we propose that the trend of  $K_{ass}$  values as a function of the IL anion is composite, and arises from the concomitant action of different factors. More specifically, results collected indicate that the stability of the ion pair with 4-NA, and hence the acidic strength of the sulfonic acids considered, is highest in the IL endowed with lower hydrogen bonding basicity and cross-linking ability.

In general, it is apparent that the strength of each acid is much more influenced by the nature of the IL anion, with respect to the cation. This can be evidenced by comparing the ratios between the highest and lowest  $K_{ass}$  values, for each acid, as a function of the nature of the IL anion or cation.

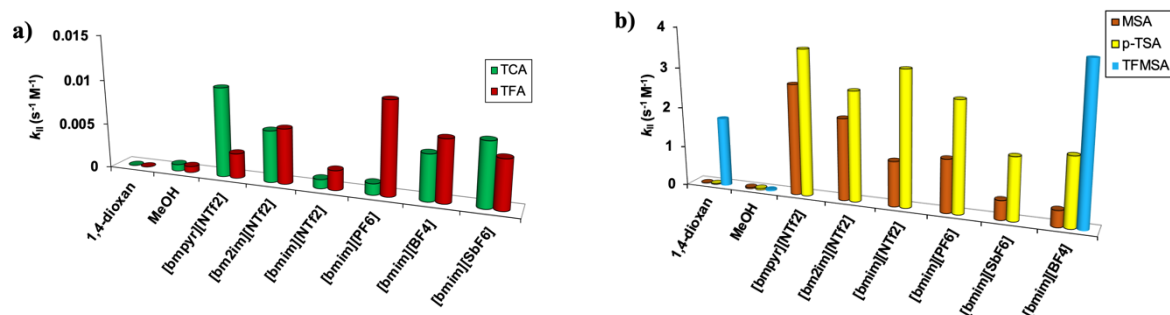
In particular, these amount to 3.2, 4.6 and 2.1 for MSA, *p*-TSA, TFMSA when the cation is changed, whereas the ratios raise to 7.5, 38 and 39 for the same acids in the [bmim<sup>+</sup>]-based ILs, differing for the anion. These findings agree with previously reported observations about the acidity levels in ILs solutions of strong acids.<sup>39</sup> However, the rather complex influence of several concomitant factors on the observed acidity in ILs, including interactions between the conjugated base and the IL cation, as well as the affinity between acidic proton and IL anion has been previously reported.<sup>40</sup>

### Kinetic measurements

All kinetic experiments were conducted at 298.1 K, observing, in all cases, pseudo-first order kinetic traces. Plotting the observed kinetic constants as a function of acid concentration, we obtained linear trends. Fit of the experimental trends as a function of the acid catalyst according to Eq. 5,

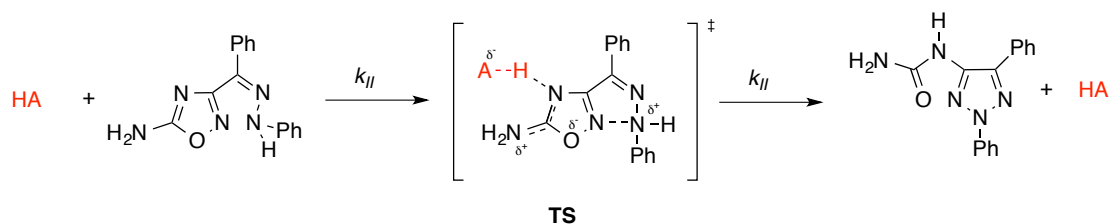
$$k_{\text{obs}} = i + k_{\text{II}} [\text{HA}] \quad (5)$$

allowed us to calculate the second-order rate constants  $k_{\text{II}}$  reported in Figure 2 and Table S2.



**Figure 2.** Second-order kinetic constants for the rearrangement of 1 into 2 at 298.1 K, in solution of ILs and conventional solvents, in the presence of a) carboxylic- and b) sulfonic acids.

In every case, we obtained statistically meaningless intercept values, in agreement with the absence of the uncatalyzed pathway under the present experimental conditions. These first observations show that, regardless of the solvent used, the reaction proceeds through the same mechanism, involving one molecule of acid in the rate determining step. In agreement with findings previously reported in the literature,<sup>41-43</sup> we hypothesize a concerted mechanism involving the protonation of the N-4 of the oxadiazole ring, the basic center of substrate, which facilitates the concomitant nucleophilic attack of the N-H group in the side chain on the N-2 of the oxadiazole ring. A schematic representation of the proposed course of reaction is depicted in Scheme 1.



**Scheme 1.** Proposed course of reaction and transition state (TS) for the acid-catalyzed rearrangement of **1** into **2** in solution of ILs.

A similar kinetic behavior was found when same reaction was studied in toluene, in the presence of 2,2-dichloroalkanoic acids as catalysts,<sup>42</sup> whereas, a multi-pathway mechanism was found, involving one and two molecules of acid, respectively, in the presence of other halogenoacetic acids.<sup>42,43</sup> Furthermore, the rearrangement follows a specific-acid catalyzed pathway in a water/1,4-dioxan solvent mixtures, in the presence of citrate buffers, in which case the rate tends to a limiting value.<sup>41</sup>

From the plots reported in Figure 2 it is possible to observe that the rearrangement of **1** occurs much faster in ILs compared with conventional solvents. This agrees with similar findings obtained for the same kind of reaction promoted by bases<sup>22,24</sup> or Lewis acids,<sup>28</sup> and can be explained on the grounds of either the weaker solvation interactions operating in ILs, compared with conventional solvents, or the higher acidic strength, in the case of the sulfonic acids.

With the only exception of TFMSA, among conventional solvents and acid being the same, reactions in methanol are faster than the ones conducted in 1,4-dioxane. This can be easily explained on the grounds of the different polarity of the two solvents, as expressed by the dielectric constants ( $\epsilon = 2.25$  and 32.5 for 1,4-dioxane and methanol, respectively).<sup>44</sup> It is indeed reported in the literature that in conventional organic solvents, the reaction is favored by an increase in solvent polarity.<sup>45</sup>

The seemingly contradictory result observed in the presence of TFMSA is related to its higher acidic strength in this solvent with respect to methanol, as expressed by the  $K_{ass}$  values reported in the previous section.

Further examination of the results reported in Figure 2 reveals that reactivity in ILs is, in general, much more sensitive to the nature of the solvents, compared with molecular solvents.

To gain deeper insight on the reactivity in solution of ILs, we will now examine the effect exerted by IL anion and cation separately, for carboxylic and sulfonic acids.

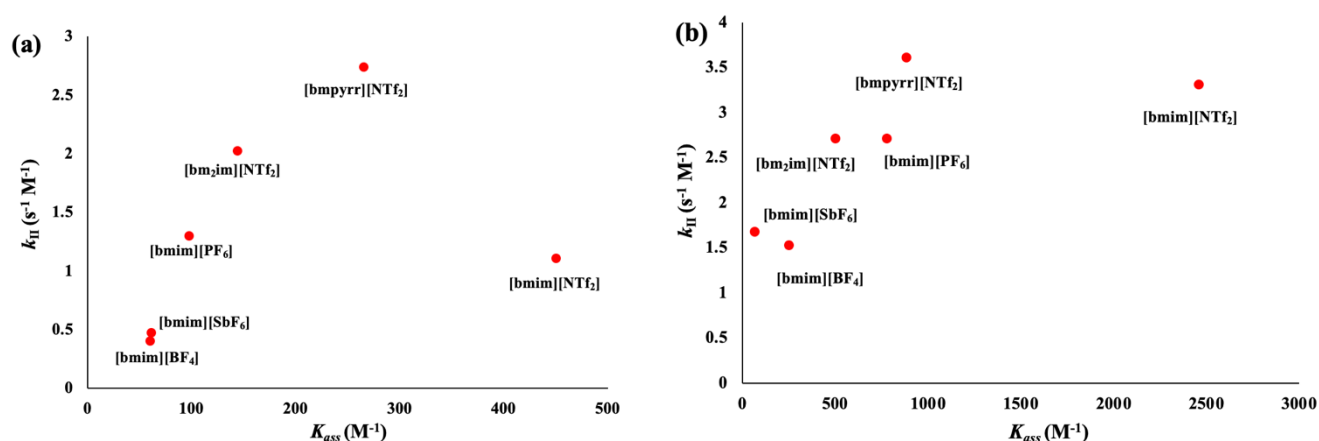
Looking at the plot reported in Figure 2a, highlights that rates measured in the presence of TCA and TFA follow very different trends as a function of the solvent. In particular, focusing on the IL cation effect, in the presence of TCA,  $k_{II}$  is highest in solution of the aliphatic [bmpyrr][NTf<sub>2</sub>] and increases along the series [bmim][NTf<sub>2</sub>] < [bm<sub>2</sub>im][NTf<sub>2</sub>] < [bmpyrr][NTf<sub>2</sub>]. This suggests that the rearrangement is slowed down in solution of aromatic ILs; we propose that in these more organized ILs, the catalyst may be forced to a less optimal conformation to approach the substrate, leading to a higher activation energy. Conversely, in solution of [bmpyrr][NTf<sub>2</sub>], lacking intermolecular  $\pi$ - $\pi$  interactions among cations, the acid “enjoys” a higher conformational freedom, resulting in a faster rearrangement.

A markedly different picture is detected in the presence of TFA, in which case  $k_{II}$  increases following the order [bmim][NTf<sub>2</sub>] < [bmpyrr][NTf<sub>2</sub>] < [bm<sub>2</sub>im][NTf<sub>2</sub>]. Unlike what happens in the presence of TCA, in this case the reactivity order inversely parallels the cation hydrogen bonding ability, as expressed by the Kamlet-Taft parameter  $\alpha$ , which amounts to 0.381, 0.427 and 0.631 for [bm<sub>2</sub>im][NTf<sub>2</sub>], [bmpyrr][NTf<sub>2</sub>] and [bmim][NTf<sub>2</sub>], respectively.<sup>34</sup>

Moving to the reactivity detected in the presence of sulfonic acids in solution of ILs, the results reported in Figure 2b, clearly show that the rearrangement occurs more than two orders of magnitude faster, compared to carboxylic acids. This is expected on the grounds of the much higher acidic strength of sulfonic acids. It is worth noting that we could measure  $k_{II}$  in the presence of TFMSA only in solution of [bmim][BF<sub>4</sub>]. In the other cases, the reaction was too fast to measure kinetic constants with an acceptable degree of accuracy.

The values of  $k_{II}$  reported in Figure 2b also shows that, in a given IL, the order of reactivity is always the same, increasing along the series  $MSA < p\text{-TSA} < TFMSA$  which agrees with the order of acidic strength detected in each IL, with the notable exception of  $[bmim][PF_6]$ ; in this case, although  $p\text{-TSA}$  is slightly stronger than  $TFMSA$ , this latter is still the most efficient catalyst.

To verify the existence of a correlation between reactivity and acidic strength, we plotted the values of  $k_{II}$  as a function of  $K_{ass}$ , for each acid, obtaining the plots reported in Figure 3.



**Figure 3.** Plots of second-order kinetic constant  $k_{II}$  as a function of the  $K_{ass}$  values determined in each IL for a) MSA and b) *p*-TSA.

A first glance at Figure 3 reveals that in neither case we found a linear correlation between rate constant and acidic strength. The same plots show that for each acid, in most cases, the rate increases with the acidic strength, indicating that this is certainly a factor favoring the reactivity, although a complete correlation could not be found.

To gain further insight on how rate changes as a function of the IL used, we dissected the effects exerted by the nature of the IL cation and anion.

Looking at the effect exerted by the IL anion, we can observe that, sulfonic acid being the same, the trend of  $k_{II}$  is dictated by the acidic strength in that IL. In particular, in the presence of MSA,  $k_{II}$  increases following the order  $[bmim][BF_4] \approx [bmim][SbF_6] < [bmim][PF_6] \approx [bmim][NTf_2]$ , which

parallels the trend of the  $K_{ass}$  values reported in Table S1 for the same acid. In the same way, for *p*-TSA, the second-order kinetic constants  $k_{II}$  follow the trend  $[bmim][BF_4] \approx [bmim][SbF_6] < [bmim][PF_6] < [bmim][NTf_2]$ , closely resembling the variation of  $K_{ass}$ , which increases along the order  $[bmim][BF_4] < [bmim][SbF_6] < [bmim][PF_6] < [bmim][NTf_2]$ .

When we consider how reactivity varies as a function of the IL cation, a different picture emerges, and no obvious correlation between the second-order kinetic constants and acidity strength is detected. More specifically, considering the  $[NTf_2^-]$ -based ILs, in the presence of MSA  $k_{II}$  increases following the trend  $[bmim][NTf_2] < [bm_2im][NTf_2] < [bmpyrr][NTf_2]$ , whereas  $K_{ass}$  increases along the sequence  $[bm_2im][NTf_2] < [bmpyrr][NTf_2] < [bmim][NTf_2]$ .

Similarly, in the presence of *p*-TSA,  $k_{II}$  increases in the order  $[bm_2im][NTf_2] < [bmim][NTf_2] < [bmpyrr][NTf_2]$ , while  $K_{ass}$  once again follows a different trend,  $[bm_2im][NTf_2] < [bmpyrr][NTf_2] < [bmim][NTf_2]$ . It is therefore clear that, in this case, the trend observed arises from the interplay of different factors, besides the acidic strength of the catalyst.

Recalling what we discussed in the previous section, the reactivity trend allows us to rule out a significant influence of the hydrogen bonding ability of the IL cation, estimated by the Kamlet-Taft parameter  $\alpha$ . Conversely, the drop of rate detected in solution of ILs bearing aromatic cations, could be explained considering the possible  $\pi$ - $\pi$  interactions involving aromatic IL cations, substrate and the transition state. In particular, the aromatic IL cations could stabilize the initial state more than the transition state, which is less aromatic than the former. As a result, an increase in the activation energy of the process occurs, leads to a reduction in reaction rate. In solution of  $[bmpyrr][NTf_2]$ , this effect is not operating, therefore, in both cases, we found the highest reaction rate.

To sum up, for the reactions conducted in the presence of MSA and *p*-TSA, the trends of rates as a function of the nature of the IL anion are mainly dictated by differences in acidic strength, whereas a more complex influence of acidity and solvent-solute interactions explains the trends observed as a function of the IL cation. It is important to note that changing the IL anion gives rise to the largest differences in acidic strength, whereas, for both MSA and *p*-TSA, acidic strength values span a

narrower range as a function of the nature of the IL cation. Hence, for ILs with different anions, the larger differences in acidity appear to outweigh other parameters, deriving from interactions with the reactants or transition state, in influencing the rate.

Conversely, when the IL cation is changed, the lower difference in acidic strengths allow other factors to become manifest in influencing the rate, giving rise to a less predictable trend.

## Conclusions

We studied the kinetics of the acid catalyzed MHR of the *Z*-phenylhydrazone of the 5-amino-3-benzoyl-1,2,4-oxadiazole into the relevant 1,2,3-triazole in solution of ILs bearing different anions and cations, in the presence of two carboxylic and three sulfonic acids. In this latter case, we measured the acidic strength in each IL and, for comparison, in two molecular solvents, methanol and 1,4-dioxane. We found that all the sulfonic acids considered showed higher strength in solution of IL compared with the conventional solvents. IL being the same, the trend found for acidic strength was always MSA < *p*-TSA < TFMSA. Furthermore, the strength of each acid was differently affected by the nature of the IL ions. In particular, the effect of the nature of the cation was mainly ascribed to its hydrogen bonding donating ability, whereas a composite effect of the anion was found, related to its cross-linking ability and hydrogen bond basicity. In general, however, variation of the IL anion induced larger differences of acidic strength than the IL cation.

Regarding the kinetic investigation, in all cases the rearrangement occurred through the same mechanism, involving one molecule of acid in the rated determining step, and we observed faster reactions in solution of ILs compared with conventional solvents. Once again different trends were observed as a function of the nature of IL ions. In particular, for sulfonic acids, the trend of second-order kinetic constants as a function of the IL anion was largely dependent on the different acidic strength of each acid in the IL considered. Conversely, the trend of reactivity as a function of the IL

cation was more articulate, and explained as a balance of acidic strength and the stabilizing effect on substrate and transition states of  $\pi$ - $\pi$  interactions with aromatic IL cations.

## Experimental section

### *Materials*

Commercial methanol and 1,4-dioxane were distilled before use. Trichloroacetic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid monohydrate and 4-nitroaniline were purchased and used without further purification. Commercially available 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF<sub>4</sub>] and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF<sub>6</sub>] were dried on a vacuum line at, 70 °C, for at least for 2 h and kept in a desiccator under argon and over calcium chloride. 1-butyl-3-methylimidazolium hexafluoroantimonate [bmim][SbF<sub>6</sub>], 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [bmim][NTf<sub>2</sub>], 1-butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide [bm<sub>2</sub>m][NTf<sub>2</sub>] and N-butyl-N-methylpyrrolydinium bis(trifluoromethylsulfonyl)imide [bmpyrr][NTf<sub>2</sub>], were prepared by anion metathesis with NaSbF<sub>6</sub> or LiNTf<sub>2</sub> from the corresponding chlorides, according to reported procedures.<sup>46</sup>

Z-phenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole and the relevant 1,2,3-triazole were prepared according to a reported procedure.<sup>47</sup>

### *Determination of association equilibrium constant between acids and 4-nitroaniline*

The association equilibrium constants between 4-nitroaniline and sulfonic acids were determined according to previously reported procedures.<sup>29,30</sup>

The sample for a typical measurement was prepared by mixing in a quartz cuvette (optical path 0.2 cm) 500  $\mu$ L of ionic liquid or conventional solvent, 50  $\mu$ L of 4-nitroaniline solution and 25  $\mu$ L of acid solution. Both 4-nitroaniline and acid were added as concentrated solutions in 1,4-dioxane; in



the instance of measurements carried out in methanol, they were added as concentrated solutions in anhydrous methanol. The concentration of 4-nitroaniline was kept constant ( $2.5 \cdot 10^{-4}$  M), while acid concentration typically ranged from 0 to 0.15 M. Each sample was thermostated at 298 K before measurement. The working wavelength was chosen by difference of the spectra of 4-nitroaniline solution and the mixture containing the highest amount of acid. In all cases, acids did not absorb significantly at this wavelength. Ion pair formation constants were calculated by fitting experimental data as described in the Supporting Material.

### *Kinetic measurements*

All kinetic and spectrophotometric measurements were carried out by using a UV-vis spectrophotometer equipped with a Peltier controller, able to keep temperature constant within 0.1 °C. The sample for a typical kinetic run was prepared by mixing in a quartz cuvette (optical path 0.2 cm), 500  $\mu$ L of ionic liquid or conventional solvent, 50  $\mu$ L of a substrate solution in dioxane and 25  $\mu$ L of a concentrated solution of the acid in dioxane, previously thermostated at 298 K. In the instance of kinetic measurements in methanol, both substrate and acid were added as concentrated solutions in methanol. Substrate concentration was kept constant at  $1.5 \cdot 10^{-4}$  M. Acid concentrations typically ranged from 0.0025 M to 0.02 M.

Reactions were followed over at least three half-lives. Apparent first order kinetic constants were reproducible within  $\pm 5\%$ . Kinetic data were analyzed by means of KALEIDAGRAPH 4.0 software package.

### **Supporting information**

Tables of  $K_{\text{ass}}$  and  $k_{\text{II}}$  values. Tables of observed kinetic constants. Plots of spectrophotometric titrations for acidic strength determination, and plots of observed kinetic constants as a function of acid catalyst concentration.

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