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Supramolecular Assemblies in Ionic Liquid Catalysis for Aza-Michael Reaction

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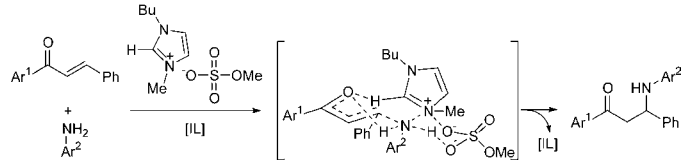
ABSTRACT



Supramolecular assemblies formed by a relay of cooperative hydrogen bonds and charge−charge interactions have been identified/characterized by (+ve) ESI and MALDI-TOF-TOF MS and MS−MS studies during the aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds in the presence of ionic liquids (ILs) digging out the role of catalysis by ILs, forming the basis of rational design/selection as organocatalysts, and offering a diagnostic model to predict/rationalize the selectivity of the aza-Michael reaction in a competitive environment.

Weak intermolecular forces, particularly hydrogen bonds (H−Bs), are harnessed by Nature to construct supramolecular structures that are essential in the life process. In utilizing weak intermolecular forces, efforts are made to visualize/generate hydrogen-bonded self-assembly as the active species in organocatalysis.[1] However, organocatalysis mediated through supramolecular assembly of small molecules formed by a network of H−Bs and charge−charge interaction remains underexplored.[2] Identification and characterization of such discrete entities that would provide a molecular level understanding of the mechanism of organocatalysis and form the basis of rational design of organocatalyst is a challenging task.

Toward this directive, we set forth to assess the organocatalytic efficiency of ionic liquids (ILs) for aza-Michael addition due to its biochemical and synthetic importance as the key step in the synthesis of bioactive natural products[3] and to assess their utility as aza-Michael adducts, which are versatile synthetic intermediates.[4] The catalytic potential of a panel of 1-butyl-3-methylimidazolium (bmim)-based room-temperature ionic liquids (RTILs) was tested for the reaction of 1,3-diphenyl-2-propenone **1a** with aniline **2a**.[5] The RTIL [bmim][$MeSO_4$] was found to be most effective and afforded the desired aza-Michael adduct 1,3-diphenyl-3-(phenylamino)propanone **3a** in high yield (Table 1). The catalytic power of the ILs is markedly influenced by the counteranion, and a drastic decrease in the catalytic efficiency was observed when the C-2 hydrogen of the bmim cation was substituted with a methyl group (compare entries 7 and 19, Table 1).

The molecular level interaction of the ILs with the substrates is envisaged through the formation of the supramolecular assembly **A** (Scheme 1) involving a relay of

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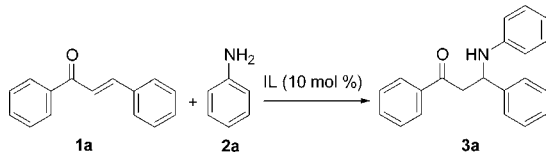
Table 1. Aza-Michael Reaction of **1a** with **2a** to form **3a** in the Presence of Various ILs[a]

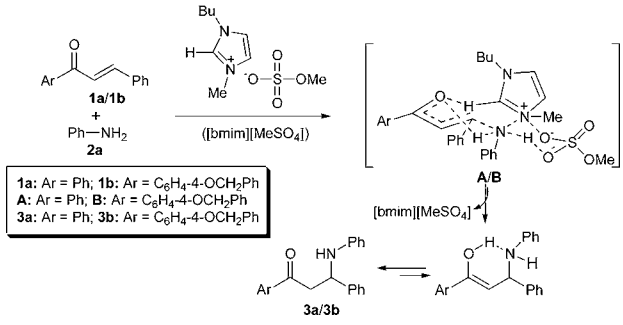


entry	IL	equiv[b]	temp (°C)	yield[c,d] (%)
1	none	1.1	80	nil[e]
2	[bmim][Br]	1.1	80	45[e]
3	[bmim][Cl]	1.1	80	64[e]
4	[bmim][BF_4]	1.1	80	40[e]
5	[bmim][ClO_4]	1.1	80	30[e]
6	[bmim][PF_6]	1.1	80	32[e]
7	[bmim][$MeSO_4$]	1.1	80	75
8	[bmim][$MeSO_4$]	1.0	80	73
9	[bmim][$MeSO_4$]	1.1	60	40[e]
10	[bmim][$MeSO_4$]	1.1	40	nil[e]
11	[bmim][$MeSO_4$]	1.2	80	77
12	[bmim][$MeSO_4$]	1.5	80	79
13	[bmim][$MeSO_3$]	1.1	80	31[e]
14	[bmim][OAc]	1.1	80	42[e]
15	[bmim][HCOO]	1.1	80	63
17	[bmim][NTf_2]	1.1	80	40[e]
18	[bmim][HSO_4]	1.1	80	65
19	[bdmim][$MeSO_4$]	1.1	80	35[e]

[a] **1a** (0.208 g, 1 mmol) was reacted with **2a** in the presence of the IL (10 mol %) for 1.5 h. [b] Molar equiv of **2a** used with respect to **1a**. [c] Isolated yield of **3a**. [d] The product was characterized by IR, NMR, and MS. [e] The unreacted starting material was recovered.

cooperative H−Bs[6] and charge−charge interactions wherein the IL exhibits an "electrophile nucleophile dual activation" role.

Scheme 1. Role of [bmim][$MeSO_4$] in the Aza-Michael Reaction



The carbonyl oxygen of **1a** forms H−B (electrophilic activation) with the C-2 hydrogen of the bmim cation due to its H−B donor ability.[7] This is followed by electrostatic interaction of the nitrogen electron lone pair of **2a** with the quaternary nitrogen atom of the bmim cation that influences the *N*-H hydrogen of **2a** for H−B formation with the oxygen atom (H−B acceptor)[8] of one of the S═O groups in $MeSO_4^-$ (nucleophilic activation) through a six-membered chairlike cyclic structure and nestles the nitrogen of **2a** in a position/orientation suitable for nucleophilic attack at the β carbon of **1a** and forms **A**. Nucleophilic attack followed by transfer of hydrogen from the NH_2 group of **2a** through the hydrogen bridge (that might provide rigidity to the noncovalently constructed supramolecular framework) in the hydrogen-bonded cluster **A** to the carbonyl oxygen of **1a** forms the enolate of the aza-Michael adduct **3a** and brings the IL back to the catalytic cycle. The decrease in the yield of **3a** in using [bdmim][$MeSO_4$] (entry 19, Table 1) that is devoid of the C-2 hydrogen at the imidazolium moiety supports electrophilic activation of **1a** through H−B formation with the C-2 hydrogen of the bmim cation. However, while the "electrophilic activation" of **1a** mediated by H−B formation with the C-2 hydrogen atom of the IL is a contributing factor in imparting the catalytic property to the IL, the counteranion also plays a crucial role (in the form of H−B acceptor of the NH_2 hydrogen) during the catalysis as the relative catalytic efficiency of the various ILs cannot be rationalized solely on the basis of H−B donor ability of the C-2 hydrogen.[9]

For a direct proof of concept, we planned to identify and characterize the supramolecular structure **A** (Scheme 1). The electrospray ionization mass spectrometry (ESI MS)[10] is the frontline analytical technique for the study of noncovalent complexes due its ability to generate efficiently the ions of noncovalent adducts in the gas phase, but its applications in identifying noncovalent cluster are restricted to large biomolecules (mass range 19000−34000 Da).[11]

We performed (+ve) ESI MS studies[12] on aliquots of samples withdrawn after 30 min from the [bmim][$MeSO_4$]-catalyzed reaction of **1a** with **2a** using variable power at the source/cone (30, 40, and 50 V) and capillary (37, 47, and 57 V). The optimum results were obtained in using the source/cone and capillary voltages of 50 and 47 V, respectively. The total ion chromatogram (TIC) revealed the presence of ions at *m*/*z* 591.59 (m_1), 551.27 (m_2), 513.11 (m_3), 495.21, 479.53 (m_4), 459.5, 446.39, 441.45 (m_5), 423.49 (m_6), 416.88, and 403.45 corresponding to [**A** + K^+], [$\mathbf{A}^+$], [**A** + K^+-Ph], [$\mathbf{A}^+$ − Bu], [$\mathbf{A}^+$ − Bu-Me], [$\mathbf{A}^+$ − Ph-Me], [$\mathbf{A}^+$ − Ph-CO], [**A** + H^+-$HMeSO_4$], [m_1 − $MeSO_4$-Bu], [$\mathbf{A}^+$ − Bu-Ph,] and [$\mathbf{A}^+$ − Ph-Me-(MeNHCHCH)], respectively (Figure 1), which are diagnostics of **A**. Further support of **A** was obtained from the tandem mass (MS−MS) studies on a few selected ions observed in the TIC.[12]

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(9) The ^{1}H NMR chemical shift values (δ in ppm in DMSO-d_6 at 40 °C) of the *C*-2 hydrogen of the ILs are as follows: [bmim][BF_4], 9.05; [bmim][ClO_4], 9.05; [bmim][PF_6], 9.06; [bmim][NTf_2], 9.08; [bmim][$MeSO_4$], 9.10; [bmim][HSO_4], 9.19; [bmim][$MeSO_3$], 9.22; [bmim][$N(CN)_2$], 9.28; [bmim][HCO_2], 9.30; [bmim][$MeCO_2$], 9.33; [bmim][Cl], 9.58.
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(12) See the Supporting Information.

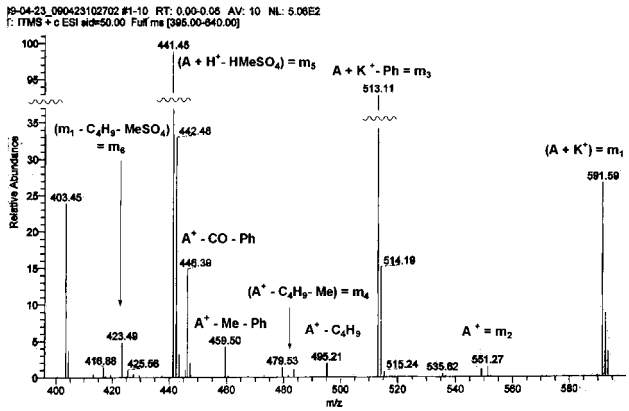


Figure 1. TIC of (+ve) ESI MS of sample withdrawn after 30 min for the reaction of **1a** with **2a** catalyzed by [bmim][$MeSO_4$].

Additional proof of **A** was obtained from (+ve) MALDI-TOF-TOF MS studies wherein the TIC exhibited the diagnostic peaks at *m*/*z* 597.34 (m_1': **A** + 2Na^+-H^+), 487.06 [**A** + H^+ + Na^+-Bu^+-OMe], 439.12 [$\mathbf{A}^+$ − H-HMeSO_4], 423.10 [**A** + K^+-Bu^+-$MeSO_4$], respectively, and the MS−MS of a few selected ions provided further structural support.[12]

The generality of the mechanistic proposal was established by demonstrating the involvement of the corresponding supramolecular structure **B** through the (+ve) ESI MS experiments on the [bmim][$MeSO_4$]-catalyzed reaction of 1-(4-benzyloxyphenyl)-3-phenylprop-2-en-1-one **1b** (1 equiv) with **2a** (1.1 equiv). The TIC (+ve) ESI MS (Figure 2) of

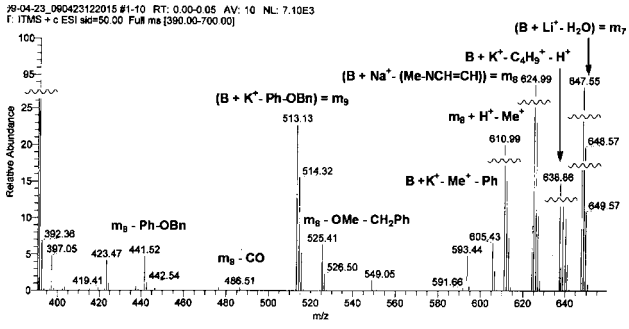


Figure 2. TIC of (+ve) ESI MS of sample withdrawn after 30 min for the reaction of **1b** with **2a** catalyzed by [bmim][$MeSO_4$].

an aliquot of sample withdrawn after 30 min exhibited ions at *m*/*z* 647.5 (m_7: **B** + Li^+-H_2O), 638.86 (**B** + K^+-H-Bu), 624.99 (m_8: **B** + Na^+-MeNCH═CH), 610.99 (m_8: H-Bu), 605.43 (**B** + K^+-Ph-CH_3), 513.13 (**B**+K^+-C_6H_4-OBn), 441.52 (m_8: C_6H_4-OBn) and proved involvement of **B** during the mechanistic course of the reaction. Further support was obtained by the MS−MS of a few selected ions observed in the TIC.[12] Additional support for **B** was derived from the (+ve) MALDI-TOF-TOF MS.[12]

When the reaction of **1a** was performed with 4-chloroaniline, 2-methylaniline, and methyl 4-aminobenzoate, the corresponding intermediate supramolecular asemblies were identified in the (+ve) ESI MS.[12] The sample of the [bdmim][$MeSO_4$]-catalyzed reaction of **1a** with **2a** did not exhibit the supramolecular structure akin to **A** in the (+ve) ESI MS and justifies that the inferior catalytic activity is due to the lack of the C-2 hydrogen.

To prove that **A** or **B** is not simply the most stable noncovalent adduct generated by aggregation of the mixture components in the dissolved state, the mixtures of [bmim]-[$MeSO_4$] and the aza-Michael adducts **3a** and **3b** were separately subjected to (+ve) ESI MS and MALDI-TOF-TOF MS, and no ion peak characteristics of the corresponding noncovalent adduct were observed.

The implication of the mechanistic model is that the catalytic power of the IL should be governed by its ability to form supramolecular structures akin to **A**/**B** and a measure of the catalytic efficiency of an IL may be obtained by identification and estimation of the abundance/concentration of the supramolecular assemblies corresponding to **A**/**B** during the course of the reaction using mass spectrometric techniques.[13]

To substantiate this, the reaction of **1a** with **2a** was separately carried out in the presence of mixtures (10 mol % each) of [bmim][$MeSO_4$] and [bmim][Cl], [bmim][$MeSO_4$] and [bmim][OAc], [bmim][$MeSO_4$] and [bmim][Br], [bmim][$MeSO_4$] and [bmim][BF_4], and [bmim][$MeSO_4$] and [bmim][$MeSO_3$]. The aliquots of sample withdrawn after 30 min from each of these reaction mixtures were subjected to (+ve) ESI MS, and the ion currents of the ions at *m*/*z* 551.71 and 475.24, 551.71 and 499.28, 551.71 and 519.19, 551.71 and 527.27, and 551.71 and 535.25 were measured.[12] In all of these cases, the area of the ion at *m*/*z* 551.71 corresponding to the hydrogen-bonded cluster of [bmim][$MeSO_4$] was found to have a higher value than those derived from the other ILs and justified the superior catalytic activity of [bmim]-[$MeSO_4$].[12] A good correlation was observed for the ion current ratio of the cluster corresponding to **A** derived from a set/pair of ILs and the ratio of the product (aza-Michael adduct **3a**) yields obtained from the reaction catalyzed separately by the individual IL (Table 2).

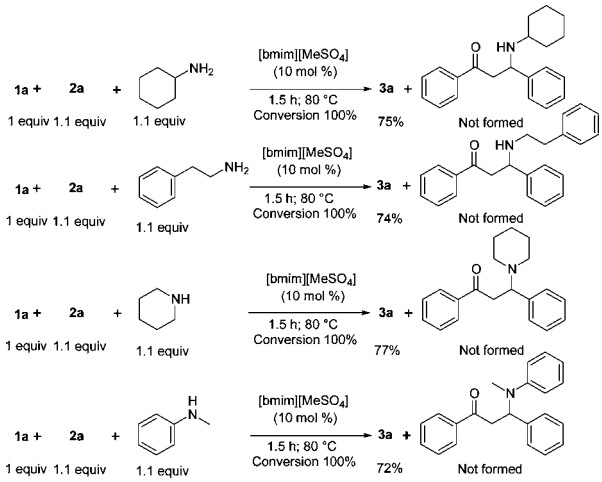
Table 2. Assessment of Relative Catalytic Power of a Pair of ILs

entry	IL	*m*/*z* (A^+)	ion current	ratio (*x*:*y*)	yield[a] (%) (IL_1:IL_2)
1	[bmim][$MeSO_4$](IL_1)	551.71	53415 (*x*)		
	[bmim][$MeSO_3$](IL_2)	535.25	26964 (*y*)	1.98	2.41
2	[bmim][$MeSO_4$](IL_1)	551.71	125423 (*x*)		
	[bmim][BF_4] (IL_2)	527.27	80816 (*y*)	1.55	1.88
3	[bmim][$MeSO_4$](IL_1)	551.71	404000 (*x*)		
	[bmim][OAc] (IL_2)	499.28	285977 (*y*)	1.41	1.7
4	[bmim][$MeSO_4$](IL_1)	551.71	236027 (*x*)		
	[bmim][Br] (IL_2)	519.19	177276 (*y*)	1.33	1.67
5	[bmim][$MeSO_4$](IL_1)	551.71	179230 (*x*)		
	[bmim][Cl] (IL_2)	475.24	155851 (*y*)	1.15	1.17

[a] The ratio of the yield (Table 1) of **3a** obtained by the reaction of **1a** with **2a** catalyzed separately by the individual IL_1/IL_2.

We next hypothesized that the importance of H−B formation involving the NH_2 hydrogen of the amine in the mechanistic course of the reaction should direct a selective aza-Michael reaction of a common Michael acceptor during competition involving amines with varying H−B formation ability. Thus, **1a** was separately treated with mixtures of **2a** and cyclohexylamine, **2a** and 2-phenethylamine, **2a** and piperidine, and **2a** and *N*-methylaniline in the presence of 10 mol % of [bmim][$MeSO_4$] that resulted in the formation of **3a** as the only product in 75, 74, 77, and 72% yields, respectively (Scheme 2).[12]

Scheme 2. Reverse Selectivity for Aza-Michael Reaction Catalyzed by [bmim][$MeSO_4$] in Intermolecular Competition



The reverse selectivity compared to the reported aza-Michael addition wherein aliphatic amines are observed to react in preference to aromatic amines provides the attractive feature of the IL-catalyzed reaction. The selective aza-Michael reaction with the aromatic amine (weak nucleophile) in preference to the aliphatic amine (stronger nucleophile) suggests that the nucleophilicity is not the only decisive factor. The outcome of selectivity can be rationalized by the mechanistic model (Scheme 1) that takes into account the H−B and charge−charge interactions in addition to amine nucleophilicity. Hence, the selectivity/reactivity of different amines should be governed by the ease of formation of the relevant noncovalent adducts.

When the reaction of **1a** was carried out individually with cyclohexylamine, 2-phenethylamine, piperidine, and *N*-methylaniline in the presence of [bmim][$MeSO_4$] (10 mol %) and an aliquot of these reaction mixtures, withdrawn after 30 min, was subjected to (+ve) ESI MS, no ions of the supramolecular assembly analogous to **A** was observed as the poor H−B donor ability of the aliphatic/alicyclic amines was not conducive to the formation of the cluster akin to **A**. In case of *N*-methylaniline, the absence of the supramolecular structure similar to **A** could be due to the lack of involvement of the hydrogen bridge that is expected to provide rigidity/stability to the noncovalent cluster. Thus, no aza-Michael adduct formation takes place for the reaction of **1a** with *N*-methylaniline although the latter is more nucleophilic than **2a**. When aliquots of samples withdrawn after 30 min from each of the reaction mixtures of the [bmim][$MeSO_4$] catalyzed reaction of **2a** and cyclohexylamine, **2a** and 2-phenethylamine, **2a** and piperidine, and **2a** and *N*-methylaniline were subjected to (+ve) ESI MS experiments, only the ion at *m*/*z* 551.71 corresponding to the cluster **A** derived from **1a**, **2a**, and [bmim][$MeSO_4$] was detected and provides rationale for the selectivity. Although the nitrogen atom in cyclohexylamine, 2-phenethylamine, and piperidine is more nucleophilic compared to that in **2a**, no significant amount of formation of the aza-Michael adduct of these amines was observed due to the poor H−B donor ability of these amines because of which these amines could not effectively form the supramolecular assembly akin to **A**.

The supramolecular assemblies of small molecules formed by a relay of cooperative H−Bs and charge−charge interactions have been identified and characterized by (+ve) ESI and MALDI-TOF-TOF MS and MS−MS to reveal the molecular level role of ILs in promoting an aza-Michael reaction. The mechanistic model provides a conceptual advancement for a qualitative and quantitative assessment of catalytic power of ILs for an aza-Michael reaction through mass spectrometric identification of the supramolecular assemblies and is diagnostic for predicting the selectivity through determination of the concentration (ion current) of the relevant supramolecular assemblies and should promote rational development of sustainable chemistries using ILs. The supramolecular structures **A**/**B** reveal a new type of cooperative H−Bs herein classified under "charge−charge-cooperativity" and designated as "charge−charge-assisted hydrogen bond" (CCAHB), relinking the fields of crystal engineering and ionic liquids.[14]

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Supporting Information Available: Typical procedure, spectral data, and scanned spectra of unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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