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On Catalysis by Ionic Liquids

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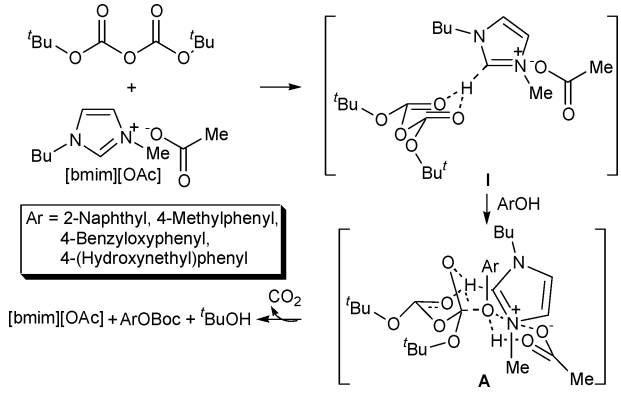
The concept of green solvent has emerged due to the adverse effect of volatile organic solvents on the environment, and an expectation has been built up on the use of ionic liquids (ILs) as the solvent of the future.[1] However, the environment friendly image of ILs is under scrutiny[2] due to combustibility[3] and cytotoxicity[4] of some ILs that raise concerns over their use as solvents. Thus, to utilize the unique ability of ILs to modulate reactivity and selectivity of organic reactions, it requires redefining their use and organocatalysis[5] offers a new direction. However, it is unclear how ILs catalyze organic reactions! Often the course of the organic reaction under the influence of ILs takes a completely different route with the change of the cation or the anion for which no rationale has been derived so far leaving the choice of the ILs at random. The present work is aimed toward acquiring a molecular level understanding of the mechanism of catalysis by ILs.

The *O*-*tert*-butoxycarbonylation of 2-naphthol **1** with Boc_2O was carried out at rt (~40 °C) for 2 h under neat conditions using catalytic amounts (10 mol %) of [bmim][BF_4], [bmim][OAc], and [bmim][HSO_4] as a panel of neutral, basic, and acidic ILs,[6] respectively. The *tert*-butyl naphthalene-2-yl carbonate **2** was formed in 97% yield in the presence of [bmim][OAc], but [bmim][BF_4] and [bmim][HSO_4] afforded 10 and 20% yields, respectively.[7]

The C-2 hydrogen of the bmim cation is expected to induce electrophilic activation of Boc_2O. The chemical shifts of the C-2 hydrogen of [bmim][BF_4], [bmim][OAc], and [bmim][HSO_4] are δ 9.38, 10.2, and 10.27 ppm, respectively,[7] and imply that the hydrogen bond (HB) formation ability of the C-2 hydrogen should follow the order [bmim][HSO_4] > [bmim][OAc] > [bmim][BF_4]. Thus, the catalytic efficiency of the ILs is not solely due to the bmim cation, and the counteranion also plays an important role in the molecular level interaction during the catalysis. Herein we propose an "electrophile nucleophile dual activation" role of the IL through a "relay of cooperative hydrogen bond and charge−charge interactions" (Scheme 1).

Scheme 1. Role of [bmim][OAc] in Catalyzing *O*-*t*-Boc Formation



The importance of HB involving the C-2 hydrogen was justified by a drastic decrease in the yield of **2** (30%) when 1-butyl-2,3-dimethylimidazolium acetate [bdmim][OAc], devoid of the C-2 hydrogen, was used as the catalyst (10 mol %).[7] The lack of appreciable catalytic activity of [bmim][BF_4] is due to the inability of its C-2 hydrogen to form HB with Boc_2O, as the bmim cation of [bmim][BF_4] is an inferior HB donor.[8] However, [bmim][HSO_4] was found to be less active than [bmim][OAc], although the C-2 hydrogen in [bmim][HSO_4] is expected to be a better HB donor than that of [bmim][OAc]. This supports the proposal of the involvement of the counteranion in the catalytic process. The better HB acceptor[9] ability of AcO^- in [bmim][OAc] leads to formation of the six-membered hydrogen-bonded cluster **A** and makes [bmim][OAc] more effective compared to [bmim][HSO_4]. To prove the importance of HB formation of AcO^- with the OH hydrogen, a selectivity study was performed for the reaction of 4-hydroxymethyl phenol **3** with Boc_2O catalyzed by [bmim][OAc] that resulted in chemoselective *O*-*t*-Boc formation of the phenolic OH.[7] The better HB donor ability of the phenolic OH compared to that of the alcoholic OH permits the formation of the hydrogen-bonded structure **A** involving the phenolic OH and the AcO^- and provides rationale for the observed chemoselectivity.

The reactivity/selectivity is not controlled by pK_a, as phenols/thiols with lower pK_a values reacted slowly during *O*/*S*-*t*-Boc formation.[7] During competition between phenol (pK_a 10.02) and 4-nitrophenol (pK_a 7.15), a 78:22 selectivity is observed for *O*-*t*-Boc formation in favor of phenol.[7] A general base path is also not operative due to the lack of effect of the pK_a on reactivity and is further ruled out due to inferior results with NH_4OAc and [bdmim][OAc].[7] These highlight the importance of HB in the mechanistic course of the reaction. Further evidence to this effect are derived from IR, ^{1}H NMR, and MALDI-MS.

In ^{1}H NMR, the C-2 hydrogen of [bmim][OAc] shifted from δ 10.20 to 10.09 in the presence of Boc_2O indicating its coordination with Boc_2O. Immediately after the addition of 4-methylphenol **4** to the mixture of Boc_2O and [bmim][OAc], it shifted to δ 9.75 and progressively to δ 9.92, 9.98, and 10.22 after 15, 30, and, 45 min, respectively (Figure 1). These corroborate the involvement of the C-2 hydrogen to form **A** in which the anionic oxygen of Boc_2O, resulting from nucleophilic attack by the phenolic OH, causes shielding of the C-2 hydrogen by HB.

In IR, the $\nu_{C=O}$ of AcO^- of [bmim][OAc] appeared at 1630 cm^{-1} and did not change significantly (1635 cm^{-1}) in the presence of Boc_2O. It shifted to 1618 cm^{-1} immediately after the addition of **4** to the mixture of Boc_2O and [bmim][OAc] and reappeared at 1635 cm^{-1} after the completion of the reaction.[7] The decrease in the $\nu_{C=O}$ suggests HB formation between the phenolic OH and the AcO^-.

For direct evidence for **A**, mass spectrometric "ion fishing"[10] was performed. The MALDI-TOF-TOF MS of an aliquot of sample withdrawn after 45 min during the [bmim][OAc] catalyzed reaction

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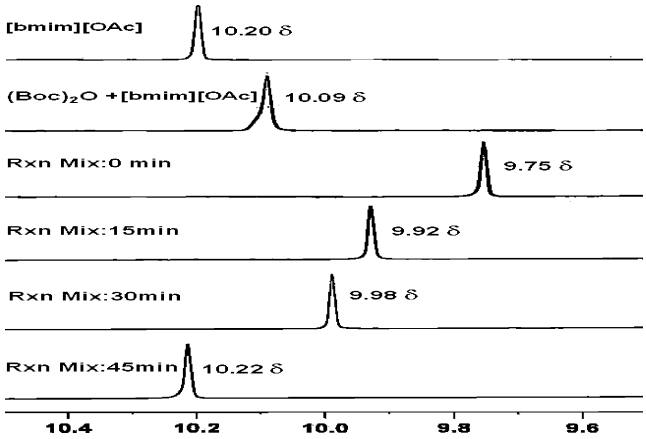


Figure 1. Shift in the ^{1}H NMR of the C-2 hydrogen of [bmim][OAc].

of 4-benzyloxyphenol **5** with Boc_2O showed ions at *m/z* 664.57 (m_1), 648.55 (m_2), 618.22, 600.42, 577.12, and 573.07 corresponding to the [A + K^+ + Na^+ − Me^+], [A + K^+ + Li^+ − Me^+], [AH^+], [A^+ − H − Me], [m_1 − Me − OBu^t], and [m_1 − CH_2Ph], respectively (Figure 2). However, the MALDI-TOF-TOF MS of

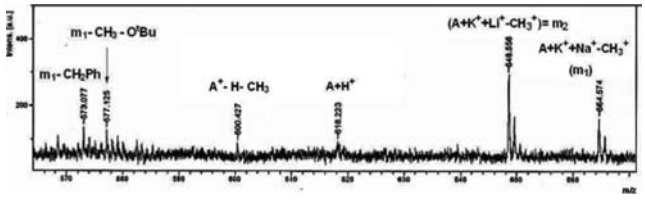


Figure 2. MALDI-TOF-TOF MS.

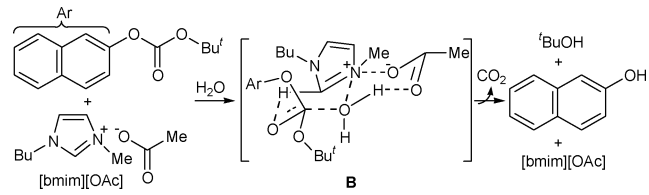
samples from the reaction of **5** with Boc_2O carried out separately in the presence of [bmim][BF_4] and [bmim][HSO_4] did not exhibit any ion peak of the corresponding hydrogen-bonded clusters. Further structural information was derived from the tandem MS (MS^2) studies on m_1 and m_2.[7] The ion peaks at *m/z* 608.03 (m_1 + H^+ − $C_4H_9^+$), 559.88 (A^+ − C_4H_9), and 551.84 (m_1 + H^+ − $^tBu^+$ − C_4H_9) in the MS^2 of m_1 support the presence of the bmim moiety in **A**. The characteristic ion peak at *m/z* 511.90 (m_2 − HCO_2 − CH_2Ph) in the MS^2 of m_2 indicated that the AcO^- anion of the IL is involved in the formation of **A** and the ion peaks at *m/z* 357.52 ($bmim^+$ + Boc_2O) and 139.26 ($bmim^+$) provided further support for involvement of the bmim cation to form **A**.

The MALDI-TOF-TOF-MS of an aliquot of sample of the [bmim][OAc] catalyzed reaction of **1** with Boc_2O exihibited ions at *m/z* 584.23 (A + Na^+), 539.90 (A + K^+ − MeCOOH), 501.91 (A^+ − H − C_4H_9) in conformity with the formation of **A**.[7] The ion peak at *m/z* 539.90 provides evidence of the involvement of the AcO^- in HB formation in the intermediate cluster. These generalized the mechanistic model (Scheme 1).

The catalytic efficiency of the IL was next tried for de-*O*-*tert*-butoxycarbonylation. The *O*-*t*-Boc deprotection was achieved in 98% yield by treatment of **2** in water at 100 °C (bath temp) for 3 h in the presence of [bmim][OAc] (10 mol %).[7] The role of [bmim][OAc] is depicted as a relay of HBs and charge−charge interactions to form the cluster **B** (Scheme 2). The poor result (∼30% yield) obtained in the presence of [bdmim][OAc] is due to the inability to form the intermediate corresponding to cluster **B** as [bdmim][OAc] is devoid of the C-2 hydrogen.

For direct evidence of **B**, aliquot portions of the reaction mixture of the [bmim][OAc] catalyzed reaction of **2** drawn after 90 min

Scheme 2. Role of [bmim][OAc] in *O*-*t*-Boc Deprotection



was subjected to MALDI-TOF-TOF MS studies that exhibited ions with *m/z* 426.80 (m_3: B + Na^+), 359.86 (B^+ − CO_2), 346.67 (B^+ − C_4H_9), 318.63 (B^+ − C_4H_9 − CO), 302.63 (m_4: B^+ − C_4H_9 − CO_2), 284.60 (m_4 − H_2O), 270.60 (m_4 − Me^+ + H^+), 245.76 (**2** + H^+) (Figure 3). The MS^2 of m_3 formed ions with *m/z* 426.81 (B +

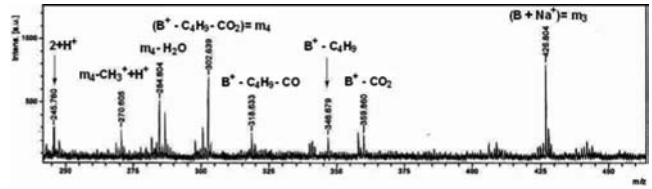


Figure 3. MALDI-TOF-TOF MS.

Na^+), 285.63 (B^+ − CO_2 − ^tBuOH) and provided further structural support to the intermediate **B**.[7]

The role of the imidazolinium based ILs has been envisaged as an "electrophile nucleophile dual activation by a relay of cooperative hydrogen bond and charge−charge interactions" in catalyzing *O*-*t*-Boc formation and deprotection. The mechanism of catalysis highlights the importance of not only the imidazolinium based cationic moiety for "electrophilic activation" of the substrate through HB formation with the C-2 hydrogen but also "nucleophilic activation" of the other reactant by HB interaction with the counteranion of the IL. Further implication of this study is that with prior knowledge/assessment of the HB donor ability of the C-2 hydrogen of the imidazolinium cation, HB acceptor/donor properties of the substrate/reactant and the HB acceptor property of the anion of the ILs should provide a predictive power for rational use of ILs in catalyzing various organic reactions.

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Supporting Information Available: Experimental procedure, spectroscopic data, and scanned spectra. This information is available free of charge via the Internet at http://pubs.acs.org/.

References

(1) Earle, M. J.; Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1391.
(2) Ranke, J.; Stolte, S.; Störmann, R.; Atning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183.
(3) Smiglak, M.; Reichert, W. M.; Holbrey, J. D.; Wilkes, J. S.; Sun, L. J.; Thrasher, S.; Kirichenko, K.; Singh, S.; Katrizky, A. R.; Rogers, R. D. *Chem. Commun* **2006**, 2554.
(4) Garcia-Lorenzo, A.; Tozo, E.; Tojo, J.; Teijeira, M.; Rodriguez-Berrocal, F. J.; Gonzalez, M. P.; Martinez-Zorzano, V. S. *Green Chem.* **2008**, *10*, 508.
(5) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(6) MacFarlane, D. R.; Pringle, J. M.; Johansson, K. M.; Forsyth, S. A.; Forsyth, M. *Chem. Commun.* **2006**, 1905.
(7) See Supporting Information.
(8) Lungwitz, R.; Friedrich, M.; Linert, W.; Spange, S. *New J. Chem.* **2008**, *32*, 1493.
(9) Lungwitz, R.; Spange, S. *New J. Chem.* **2008**, *32*, 392.
(10) Santos, L. S. *Eur. J. Org. Chem.* **2008**, 235.

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