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Kinetic Study of Michael Addition Catalyzed by *N*-Methylimidazole in Ionic Liquids: Residual *N*-Methylimidazole in Ionic Liquids as a Strong Base

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Michael addition of malonodinitrile to chalcone was studied in classical organic solvent as well as in some common ionic liquids (ILs). Kinetic studies proved that the reaction proceeded faster in the studied ILs than in molecular solvents. *N*-methylimidazole was found to be a better basic catalyst in some ILs than in conventional solvents. Residual *N*-methylimidazole in imidazolium-based ILs can act as a basic catalyst.
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Introduction

In our previous paper,[1] we demonstrated that Michael additions of malonodinitrile as well as several other methylene-active compounds to chalcone proceeded well in some pure ionic liquids (ILs), without the addition of any catalyst. In that paper we speculated that the the acidity of methylene-active compounds could be influenced by ILs. In contrast, no product was formed in THF in the Pd-catalyzed α-allylation of 2-phenylpropanal with allyl ethyl carbonate run in IL without any additional basic catalyst.[2] Nucleophilic aromatic substitutions[3] and synthesis of quinazoline derivatives[4] are other examples of reactions that proceeded well in ILs without additional catalysts, but Michael addition reactions of carbonyl compounds to (*E*)-β-nitrostyrene catalyzed by *N*-toluensulfonyl-L-proline amide in acidic ILs did not proceed.[5]

The key step in the synthesis of most ILs is alkylation of *N*-methylimidazole with the corresponding 1-haloalkane. It was proved that unreacted *N*-methylimidazole in ILs can act as a coordinating base, which is difficult to remove from the IL.[6] Giernoth[7] described that several ILs can contain up to 1% of *N*-methylimidazole, which could explain our observation that Michael addition of C nucleophiles in ILs proceed without additional basic catalyst.[1]

N-Methylimidazole is known to be an effective catalyst for the aza-Michael reaction of N-heterocycles,[8] the enzymatic acylation of ribavirin,[9] esterification and amide formation reactions,[10] aldol reactions of silyl enol ether with aldehydes,[11] the Baylis–Hillman reaction,[12] the Claisen condensation[13] between carboxylic esters and acid chlorides or acids, and other[14] reactions. Small amounts (1–5 mol-%) of *N*-methylimidazole, as a basic impurity significantly affected H/D exchange in the synthesis of perdeuterated ILs.[15]

ILs have been described as solvent media able to increase amine basicity with respect to conventional solvents.[16] This is in accord with our observation[1] that L-proline and piperidine were much better catalysts for Michael additions of methylene-active compounds to chalcone in ILs than in dichloromethane. Imidazolium ILs have been described as polymeric hydrogen-bonded supramolecules, and mixed with other molecules they can be regarded as nanostructured materials.[17] As a consequence, generally occurring solvation processes could be drastically reduced or absent in this media,[18] and the basic strength of the amines could be much higher in ILs than in conventional organic solvents.[16]

The aim of the present paper was to examine the activity of *N*-methylimidazole both in some common ILs as well as in classical organic solvents. It has been proved that addition of molecular solvent into IL partially destroyed its polymeric structure and enhanced its solvation ability,[16] but the solvation ability of a mixture of ILs has not been described before. So, the further aim of our work was to examine if the catalytic effect of *N*-methylimidazole would changed in the mixtures of some imidazolium ILs.

Results and Discussion

We have studied Michael addition of malonodinitrile (**2**) to chalcone (**1**) in various ILs as well as conventional organic solvents (Scheme 1). The rate constants of the reactions were determined spectrophotometrically and their values are given in the Table 1.

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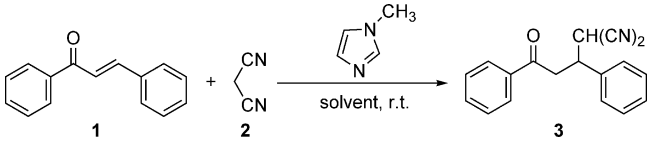

Scheme 1. Michael addition of malonodinitrile to chalcone.

Table 1. Solvent effect on the reaction rate of the Michael addition of malonodinitrile (**2**) to chalcone (**1**) catalyzed by *N*-methylimidazole.

Entry	Solvent	Catalyst [mol-%]	k ($\times 10^{-4}$) [s^{-1}]	$t_{1/2}$ [s]
1	CH_2Cl_2	10	–[a]	–
2	CH_2Cl_2	1[b]	–[a]	–
3	CH_3CN	5	0.30	23105
4	CH_3CN	10	0.43	16120
5	CH_3CN	1[b]	6.72	1031
6	THF	0	1.00	6931
7	THF	5	1.26	5501
8	THF	10	1.52	4560
9	[emim]SO_4Et	0	0.16	43475
10	[emim]SO_4Et	5	1.80	3851
11	[emim]SO_4Et	10	2.12	3270
12	[bmim]PF_6	0	0.17	40066
13	[bmim]PF_6[c]	0	–[a]	–
14	[bmim]PF_6	5	1.70	4077
15	[bmim]PF_6	10	2.70	2567
16	[bmim]PF_6	1[b]	18.90	366
17	[bmmim]PF_6	0	4.78	1450
18	[bmmim]PF_6	5	5.50	1260
19	[empyr]SO_4Et	0	0.17	41259
20	[empyr]SO_4Et	5	0.61	11438
21	[empyr]SO_4Et	5[d]	0.26	27182

[a] No reaction was observed during 4 h. [b] Piperidine was used as a catalyst. [c] IL was extracted with aqueous HCl before reaction. [d] Pyridine was used as a catalyst.

No reaction was observed in CH_2Cl_2 neither with the addition of *N*-methylimidazole (10 mol-%) nor with the addition of piperidine (1 mol-%). The rate constant of the reaction in CH_3CN was $k = 0.30 \times 10^{-4}$ s^{-1}, when 5 mol-% of *N*-methylimidazole was used, and it increased ($k = 0.43 \times 10^{-4}$ s^{-1}) when 10 mol-% of the catalyst was used. The most common solvent for Michael addition of malonodinitrile to chalcone is THF. The reaction proceeded in THF without any catalyst with a rate constant of 1.00×10^{-4} s^{-1}. Reactions with 5 and 10 mol-% of *N*-methylimidazole proceeded more quickly with $k = 1.26 \times 10^{-4}$ s^{-1} and $k = 1.52 \times 10^{-4}$ s^{-1}, respectively.

The test reaction of **1** with **2** proceeded in [emim]SO_4Et (1-ethyl-3-methylimidazolium ethylsulfate) and [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate) without any additional catalyst with rate constants of 0.16×10^{-4} s^{-1} and 0.17×10^{-4} s^{-1}, respectively. We assumed that some residual *N*-methylimidazole catalyzed these reactions. In contrast, the influence of a basic catalyst was more impressive in ILs than in THF. Addition of *N*-methylimidazole to the reactions mixtures in ILs increased the reaction rate to 1.80×10^{-4} s^{-1} (5 mol-%) and 2.12×10^{-4} s^{-1} (10 mol-%) for [emim]SO_4Et and to 1.70×10^{-4} s^{-1} (5 mol-%) and 2.70×10^{-4} s^{-1} (10 mol-%) for [bmim]PF_6 (Table 1, Entries 9–11, 14, 15). To confirm the hypothesis about residual *N*-methylimidazole in imidazolium-based ILs, we performed the addition of **2** to **1** in [bmim]PF_6, which was extracted several times with HCl (10 vol.-% in water) before the reaction. No reaction ($k = 0$ s^{-1}) was observed during 4 h at room temperature in such a solvent (Table 1, Entry 13), thus confirming our assumption.

The Michael addition proceeded very well in [bmmim]-PF_6 (1-butyl-2,3-dimethylimidazolium hexafluorophosphate), which is an IL with a methyl group instead of a hydrogen atom at C(2). Reaction without any additional catalyst proceeded with $k = 4.78 \times 10^{-4}$ s^{-1} and with 5 mol-% of *N*-methylimidazole with $k = 5.50 \times 10^{-4}$ s^{-1} (Table 1, Entries 17 and 18). It is well known that the C(2) proton of the 1,3-dialkylimidazolium cation is acidic; the p*K*a of the simple imidazolium cation in DMSO and H_2O was found to be in the range of 21–24.[17] The acidic C(2) proton in [emim]SO_4Et and [bmim]PF_6 is probably able to interact with a basic catalyst through hydrogen bonding and decreases its activity.

Reaction in the IL [empyr]SO_4Et (1-ethyl-3-methylpyridinium ethylsulfate) without any catalyst proceeded similarly to those in [emim]SO_4Et and [bmim]PF_6, $k = 0.17 \times 10^{-4}$ s^{-1} (Table 1, Entry 19). Addition of *N*-methylimidazole (5 mol-%) had a smaller influence on the reaction rate ($k = 0.61 \times 10^{-4}$ s^{-1}) than addition of the same amount of this catalyst to [emim]SO_4Et or [bmim]PF_6. It is probably due to a less organized structure of pyridinium ILs in comparison to imidazolium ILs.[16,17] Michael addition of **2** to **1** in [empyr]SO_4Et with 5 mol-% of pyridine as catalyst proceeded with a rate constant of 0.26×10^{-4} s^{-1} (Table 1, Entry 21).

Comparison of the reaction rate for the Michael addition of malonodinitrile (**2**) to chalcone (**1**) in various solvents catalyzed by 5 mol-% of *N*-methylimidazole is depicted in the Figure 1.

It was of interest also to check the basicity of piperidine in ILs. In accordance with previous studies[1,19] the basic strength of piperidine was found to be much higher in some

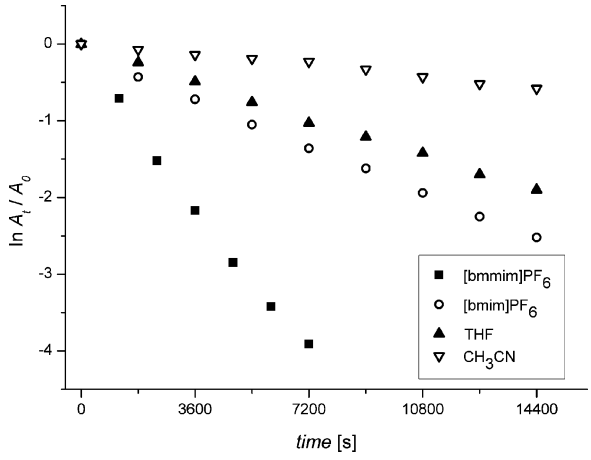

Figure 1. Comparison of the reaction rate for the Michael addition of malonodinitrile (**2**) to chalcone (**1**) in various solvents catalyzed by 5 mol-% of *N*-methylimidazole.

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common ILs than in conventional organic solvent. No reaction of **1** with **2** under piperidine (1 mol-%) catalysis was observed during 4 h in CH_2Cl_2. The rate constant of the reaction with 1 mol-% piperidine in CH_3CN was $k = 6.72 \times 10^{-4}$ s^{-1}, whereas the reaction (with the same amount of catalyst) proceeded in [bmim]PF_6 with the rate constant $k = 18.90 \times 10^{-4}$ s^{-1} (Table 1, Entries 2, 5, and 16).

Recently, it was described that ILs are nanostructurally organized with ionic networks and nonpolar regions. There are "blocks" along the network of the mixture that are ordered in the same way as in the neat liquids, with clustering of the alkyl groups into nonpolar domains.[20,21] D'Anna[16] described that the addition of dioxane into [bmim]BF_4 partially destroys its polymeric structure and enhance its solvation ability. A decrease in amine basicity in [bmim]BF_4/dioxane binary mixture was detected. Therefore, we wondered what would be the reaction rate for the addition of **2** to **1** in some binary mixtures of imidazolium-based ILs. The results are collected in Table 2. Rate constants of the reaction with 5 mol-% of *N*-methylimidazole in [bmim]PF_6 and [emim]SO_4Et were $k = 1.70 \times 10^{-4}$ s^{-1} and $k = 1.80 \times 10^{-4}$ s^{-1}, respectively, but the reaction rate significantly dropped ($k = 1.03 \times 10^{-4}$ s^{-1}) in a mixture of these solvents (Table 2, Entries 1, 2, and 5). Similar results were obtained when the reaction was performed in a mixture of [emim]SO_4Et and [bmim]$N(CN)_2$. The rate constant was $k = 1.11 \times 10^{-4}$ s^{-1}, whereas for neat ILs it was $k = 1.80 \times 10^{-4}$ s^{-1} ([emim]SO_4Et) or $k = 3.69 \times 10^{-4}$ s^{-1} {[bmim]$N(CN)_2$}. In contrast, the reaction rate in the mixture of [bmim]$N(CN)_2$ and [bmim]PF_6 decreased just slightly ($k = 3.39 \times 10^{-4}$ s^{-1}) in comparison with neat [bmim]$N(CN)_2$ ($k = 3.69 \times 10^{-4}$ s^{-1}). Similarly, the reaction rate in a mixture of [bmim]PF_6 and [bmmim]PF_6 dropped to 5.31×10^{-4} s^{-1}, whereas in neat [bmmim]PF_6 it was 5.50×10^{-4} s^{-1}. These results can be explained either by distortion of solvent structure of individual ILs or by the fact that ILs with the SO_4Et anion can, in the presence of traces amount of water, hydrolyze to the HSO_4 anion, which can protonate the residual *N*-methylimidazole. Our observations are in accordance with the results of D'Anna[22] that the effect of binary mixtures [bmim]X/cosolvent on the reaction course cannot be ascribable to simple polarity, viscosity, or conductivity effects, but a whole set of parameters has to be considered.

Table 2. Study of the reaction rate for the Michael addition of malonodinitrile (**2**) to chalcone (**1**) in various IL and their mixtures catalyzed by 5 mol-% of *N*-methylimidazole.

Entry	Solvent	k ($\times 10^{-4}$) [s^{-1}]	$t_{1/2}$ [s]
1	[emim]SO_4Et	1.80	3851
2	[bmim]PF_6	1.70	4077
3	[bmim]$N(CN)_2$	3.69	1879
4	[bmmim]PF_6	5.50	1786
5	[emim]SO_4Et + [bmim]PF_6[a]	1.03	6730
6	[emim]SO_4Et + [bmim]$N(CN)_2$[a]	1.11	6245
7	[bmim]$N(CN)_2$ + [bmim]PF_6[a]	3.39	2045
8	[bmim]PF_6 + [bmmim]PF_6[a]	5.31	1305

[a] Mixture 1:1 (vol./vol.).

Conclusions

We proved that residual *N*-methylimidazole in several ILs can act as a basic catalyst. Its basicity, as well as the basicity of piperidine is higher in ILs than in conventional solvents. For reactions studied in ILs, residual amounts of *N*-methylimidazole or the acidity of the IL itself can have a profound effect on the outcome of the reaction.

Experimental Section

General: The ILs [bmim]PF_6, [bmmim]PF_6, and [bmim]$N(CN)_2$ were purchased from Merck (high purity), [emim]SO_4Et was purchased from Io-li-tec (99+%), and [empyr]SO_4Et was purchased from Solvent Innovation (99%). ILs were used without any purification.

General Procedure: Chalcone (**1**; 0.208 g, 1.0 mmol) was added to the IL (2 mL), and the mixture was irradiated in an ultrasonic cleaning bath for 15 min to dissolve chalcone. Malonodinitrile (**2**) (0.660 g, 10.0 mmol) and the catalyst (0, 5, and 10 mol-%, respectively) were then added, and the reaction mixture was stirred for 2 or 4 h at room temperature. Aliquots (0.1 mL) of the reaction mixture were removed at 20 min intervals and diluted with CH_2Cl_2 to 100 mL.

The kinetic measurements were performed in a quartz spectrophotometric cell ($l = 0.1$ cm) by using an Agilent 8453 UV/Vis spectrophotometer. The rate constants k were determined by monitoring the decrease of chalcone in dilute reaction mixture (0.5×10^{-3} mmol/mL) by detecting the decrease in its absorption band at 308 nm (wavelength where chalcone has its maximum absorption in CH_2Cl_2). At very low concentration of chalcone, on the basis of the Beer rule and its linear relation between the concentration of chalcone and its absorbance, a first-order disappearance of chalcone is observed. The slope of the plot is the pseudo-first order constant k and $t_{1/2}$ is the half-life time of the Michael addition.

Acknowledgments

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