



Michael addition kinetics of ethyl acetoacetate and 2-ethylhexyl acrylate in ionic liquids

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ABSTRACT

The Michael addition is one of the most common and versatile methods for making carbon–carbon bonds, however little is known about the potential of utilizing ionic liquids as solvents in these reactions. Initial work from our laboratory is presented, showing that model imidazolium- and phosphonium-based ionic liquid solvents can be used as effective reaction media in the Michael addition. Kinetic data are also reported and the results indicate that the use of ionic liquids as reaction media resulted in an observed rate enhancement when compared with more common organic solvents such as toluene, THF, and DMF. Observed rates were comparable to those observed in DMSO.

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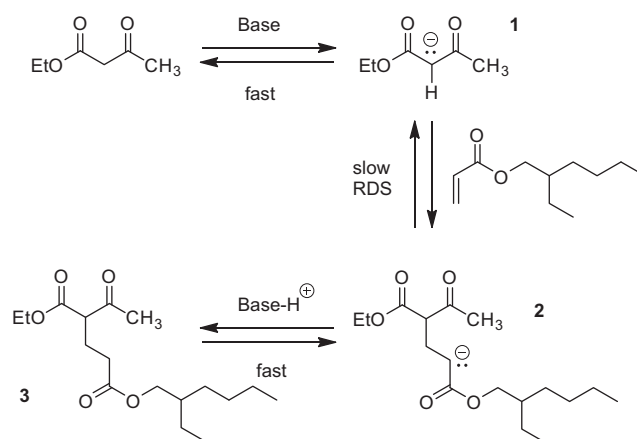
An ionic liquid is typically defined as a salt consisting completely of transient cation–anion pairs that exists in a liquid state below 100 °C. Over the past decade, it has been shown that many ionic liquids possess low vapor pressures, flammabilities, and toxicity levels.¹ For this reason ionic liquids have been viewed as possible ‘greener’ reaction media and continue to be placed at the fore-front of ongoing research as potential replacements for more common volatile organic solvents.

Current research efforts are primarily focused on ionic liquids as solvents in more ‘classical’ organic reactions. A number of such reactions have already been investigated and reported in the literature, some of which include Diels–Alder cycloadditions,² Grignard,³ Friedel–Crafts,⁴ aromatic nitration⁵ as well as more fundamental S_N1 and S_N2 reactions.^{6,7} In these reactions, various combinations of cations and anions were employed to determine their effects on reaction products, yields, and occasionally kinetics.

In this Letter, we report a series of studies which focus on the initial effects of imidazolium- and phosphonium-based ionic liquids as reaction media for the Michael addition reaction. This reaction is one of the most efficient and versatile methods of forming a carbon–carbon bond in organic chemistry, and therefore finding alternative solvents in which to perform the reaction is attractive. The Michael addition involves the 1,4-conjugate addition of an enolate anion (referred to as the Michael donor) to an activated α,β -unsaturated carbonyl containing compound (the Michael acceptor). Conjugate addition is favored over the competing 1,

2-addition of the enolate since the more stable carbon–oxygen π bond is maintained (versus the less stable carbon–carbon π bond).

The work described here is a follow-up to results previously published in part by our research group on the effects of catalyst and solvent on the rate of the reaction between ethyl acetoacetate and 2-ethylhexyl acrylate.⁸ As shown in Scheme 1, a base catalyst is employed to deprotonate ethyl acetoacetate ($pK_a = 10.7$), generating the enolate anion **1**.^{9,10} The enolate will then react with the electrophilic acrylate at the β -position, producing another enolate anion **2**. Rapid proton transfer is the last step of the reaction and



Scheme 1. Michael addition mechanism.

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serves to regenerate the base catalyst and produce the final Michael adduct **3**.

The reaction kinetics of the Michael addition have been studied extensively and are dependent upon base type and concentration as well as the concentrations of both the Michael donor (acetoacetate in this case) and the Michael acceptor (acrylate).¹⁰ We have previously shown in our group that when moderate base catalysts such as amines are employed, the concentration of the enolate anion is approximately equal to the concentration of the base when the acetoacetate is allowed to pre-equilibrate with the catalyst prior to the addition of the acrylate.^{8,9} This results in a steady-state concentration of the enolate anion and a rate law which follows pseudo-first order kinetics with respect to the concentration of the Michael acceptor (acrylate):

$$\text{Rate} = k_{\text{obs}}[\text{Acrylate}]$$

Michael addition reactions have been conducted in a number of different molecular solvents ranging from non-polar solvents such as toluene and tetrahydrofuran to polar solvents such as *N,N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO). Ionic liquids provide a unique alternative to these more common molecular solvents but have been reported sparingly in the literature. Ranu and co-workers have shown that imidazolium ionic liquids with a hydroxide counter-anion will self-catalyze the Michael addition of activated methylene compounds to conjugated ketones and esters.¹¹ Toma and co-workers investigated the kinetics of the addition of highly acidic/active methylene compounds to chalcone and have found the reaction to proceed readily in imidazolium ionic liquids; however, residual *N*-methylimidazole from the ionic liquid synthesis is thought to have compromised the rate data.¹² In the present work, the system chosen avoids this complication since ethyl acetoacetate that is not sufficiently acidic enough to be deprotonated by residual ionic liquid precursors such as *N*-methylimidazole.

The present study will look to investigate the effects of various solvents, including two model ionic liquids, on the Michael addition reaction of ethyl acetoacetate and 2-ethylhexyl acrylate using the base catalyst DBU (1,8-diazobicyclo[5.4.0]undec-7-ene). The molecular solvents chosen have a wide range in dielectric constants and include toluene, tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO). The two model ionic liquids that were prepared and used include *N*-pentyl-*N'*-methylimidazolium bis(trifluoromethylsulfonamide) [pnmim][NTf₂] and trihexyltetradecyl-phosphonium bis(tri-fluoromethylsulfonamide) [THTDP][NTf₂].

The syntheses of the model ionic liquids are shown in Scheme 2 and are based upon procedures previously reported in the

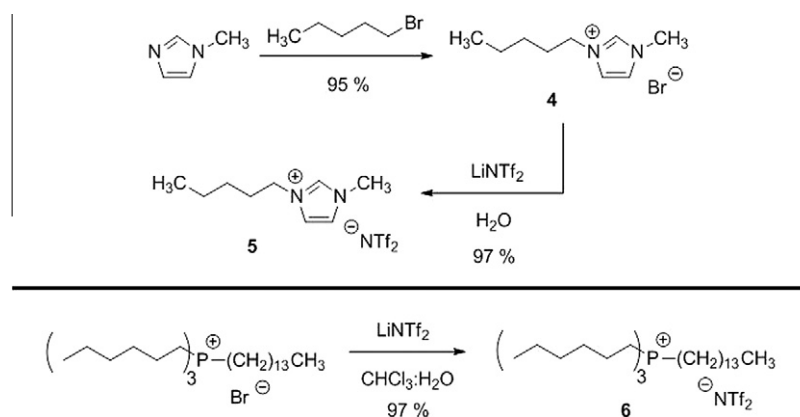
literature.¹³ The preparation of [pnmim][NTf₂] involved first the synthesis of [pnmim][Br] **4** through the reaction of *N*-methylimidazole and 1-bromopentane. Anion exchange with lithium bis(trifluoromethylsulfonimide) resulted in the desired ionic liquid **5**. The phosphonium ionic liquid **6** was prepared by anion exchange of commercially available [THTDP][Br] with lithium bis(trifluoromethylsulfonimide). Once the desired ionic liquids were isolated, they were dried in a vacuum oven at 60 °C until a constant mass was obtained to ensure that any trace solvent and/or moisture had been removed (<0.01% water).

Once the ionic liquids were isolated and structural analysis completed, a series of kinetic studies were conducted in which the pseudo-first order loss of 2-ethylhexyl acrylate was monitored by ¹H NMR over time. Concentrations of DBU were held at either 1 or 3 mol %. Rate data, half-lives, solvent choice, and catalyst levels are provided in Table 1. All kinetic runs were completed at 35 °C in duplicate with an error of ±2% and correlation coefficients of 0.998 or greater.

The data in Table 1 show that both catalyst concentration and solvent choice have a significant effect on the reaction rate of the Michael addition. Increasing the catalyst level from 1 to 3 mol % increases the steady-state concentration of enolate anion and thus results in an expected rate enhancement.

When the catalyst level was held constant, molecular solvents such as the relatively non-polar toluene and THF resulted in the lowest observed reaction rates (entries 4–7), use of the more polar DMF resulted in a moderate increase in observed reaction rates (entries 8–9) while reactions in the highly polar DMSO gave rise to the largest rate enhancements (entries 10–11). This relative rate profile for molecular solvents observed here was expected and follows work we previously reported on for the Michael addition as well as reports of other enolate addition reactions.^{8,14,15} Highly polar solvents such as DMSO are known to disrupt enolate aggregation through cation solvation,¹⁴ thus providing a stabilized transition state(s) for the reaction, leading to lower activation energies and faster kinetics.

Use of the ionic liquids [pnmim][NTf₂] and [THTDP][NTf₂] as reaction media (entries 12–13 and 15–16 respectively) resulted in observed rates that were comparable to DMSO. This large rate enhancement was unexpected since the reported studies concerning the polarities of ionic liquids place them in the same range as short chain alcohols ($\epsilon_T = 11.45$ for [pnmim][NTf₂]).¹⁶ The source of this unexpected rate enhancement cannot be fully explained given the limited data presented here, however it has been speculated that nucleophilicity may be enhanced in ionic liquids due to some reduction in the degree of ion pairing.^{7,17} Additionally, one could envision that the imidazolium and phosphonium cations



Scheme 2. Ionic liquid syntheses.

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