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Probing the Mechanism of Baylis-Hillman Reaction in Ionic Liquids

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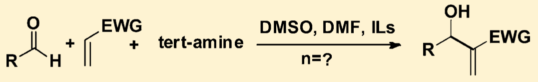
S *Supporting Information*

ABSTRACT: The kinetic data for a Baylis-Hillman reaction in certain ionic liquids possessing ethylsulfate anion $[EtSO_4]^-$ demonstrate that the rate determining step (RDS) is second order in aldehyde, but first order in acrylate and DABCO. This observation is similar to the one made by McQuade et al., who carried out this reaction in an aprotic polar solvent like DMSO. However, this is in contrast to the general observation that RDS is first order in aldehyde, acrylate, and DABCO in organic solvents.



Baylis-Hillman (B−H) reaction, a carbon−carbon bond forming reaction, offers highly functionalized products with a new stereocenter.[1] The great significance of the B−H reaction is known to organic chemists all over the world.[2−7] In spite of several investigations carried out in the past, the mechanism of B−H reaction has been an issue of debate. The standard mechanism of this reaction as proposed by Hill and Isaacs, however, could not explain the slow reaction rates, protic additive induced acceleration, dioxanone formation, and so forth. Upon the basis of the kinetic isotope effect studied by Hill and Isaacs,[8] the addition of the enolates to the aldehyde was considered the rate determining step (RDS). The mechanism proposed by Hill and Isaacs was also supported by Bode and Kaye.[9] Essential steps of the mechanism include reversible Michael addition of a tertiary amine on to the activated alkene to produce enolate, nucleophilic addition of this enolate on aldehyde to produce a zwitterionic intermediate species, followed by proton transfer and elimination of amine to give the product. The activation of aldehyde by hydrogen bonding in protic additives was considered to accelerate the reaction. If this is so, it has to compete with the enolate, which possesses higher hydrogen bond accepting ability. The reaction also shows autocatalysis in the absence of polar additives.[10,11] Several articles exist on the critical discussion of mechanism of B−H reactions.[8,12−17] The effect of temperature,[18,19] substrates,[20] Lewis acids,[21,22] Lewis bases and solvents,[23] and so forth have been investigated in depth.

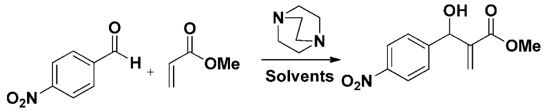
Interestingly, the reports from the research group of McQuade stated that RDS was second order in aldehyde and first order in DABCO and acrylate, when the reactions were carried out in several aprotic solvents.[24,25] Also investigated was the generality of the mechanism of B−H reaction with three aryl aldehydes in a variety of solvents.[25]

In search of environmentally benign media for carrying out chemical transformations, ionic liquids are emerging as alternative media because of their nonvolatility, nonflammability, thermal and electrochemical stability, recyclability, and flexible miscibility.[26−30] B−H reactions have also been carried out in ionic liquids, followed by critical evaluation of their mechanism in these media.[31−39]

We were intrigued with the observation that RDS is second order in aldehyde, when the reaction is carried out in aprotic polar solvent like DMSO. In view of the use of ionic liquids in a variety of organic reactions, it will be of great significance to find out whether RDS is first or second order with respect to aldehyde in ionic liquids. As a part of our research work on the physical−organic chemistry in environmentally benign media,[40−42] we now investigate the kinetics of a B−H reaction in ionic liquids.

The reaction of *p*-nitrobenzaldehyde (PNB) with methyl acrylate (Scheme 1) was performed in the presence of DABCO and different ionic liquids (Table 1). The ionic liquids selected for the study included the cations of different types, while anions varied from bis(trifluoromethanesulfonyl)imide, formate, tetrafluoroborate, and ethylsulfate.

Scheme 1. Investigated Baylis-Hillman Reaction



The reaction was first carried in $[EtP][NTf_2]$ and $[OMPyr][NTf_2]$ for which the rates v concentration of PNB are plotted in Figure 1a and b, respectively. We obtained a straight line indicating the order of the reaction, *n*, to be unity. Similar plots yielding $n = 1$ were obtained in other ionic liquids like $[HMPyr][NTf_2]$, [HP][HCOO], $[BP][NTf_2]$, and $[EtP][BF_4]$. Very interestingly, as shown in Table 1, the reaction showed order of the reaction $n = 2$ in $[EtP][EtSO_4]$, $[EtPip][EtSO_4]$, $[EtMo][EtSO_4]$, $[(Et)_4N][EtSO_4]$, and $[EMIM][EtSO_4]$. The plots of the rates are given in Figure 1c−e for the reaction in $[EtMo][EtSO_4]$, $[EtP][EtSO_4]$, and $[EtPip][EtSO_4]$, respectively. An effort was made to carry out the reaction in $[EtP][BF_4]$ to check the effect of anion while keeping the cation common. The linear relationship between the rate and the concentration of aldehyde showed that the

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Table 1. Names and Acronyms of Ionic Liquids and Kinetic Data Obtained in the Present Work

names of ionic liquids	acronyms	aldehyde order[a], *n*	k_2/ (M^{-1} s^{-1})
1-octyl-1-methyl-pyrrolidinium bis (trifluoromethanesulfonyl)imide	[OMPyr] [NTf_2]	1	0.034
1-hexyl-1-methyl-pyrrolidinium bis(trifluoromethanesulfonyl)imide	[HMPyr] [NTf_2]	1	0.054
Pyridinium formate	[HP] [HCOO]	1	0.037
1-butyl-pyridinium bis(trifluoromethanesulfonyl)imide	[BP] [NTf_2]	1	0.008
1-ethyl-pyridinium bis(trifluoromethanesulfonyl)imide	[EtP] [NTf_2]	1	0.060
1-ethyl-pyridinium ethylsulfate	[EtP] [$EtSO_4$]	2	0.246
1-ethyl-pyridinium tetrafluoroborate	[EtP][BF_4]	1	0.007
1-ethyl-piperidinium ethylsulfate	[EtPip] [$EtSO_4$]	2	0.250
1-ethyl-morpholinium ethylsulfate	[EtMo] [$EtSO_4$]	2	0.057
Tetra-ethyl-ammonium ethylsulfate	[$(Et)_4N$] [$EtSO_4$][b]	2	2.81
1-ethyl-3-methylimidazolium ethylsulfate	[EMIM] [$EtSO_4$]	2	7.45

[a] Value rounded off. [b] At 60 °C.

anion played a role in deciding the order of the reaction. As seen from the data listed in Table 1, no influence of cation of ionic liquid was observed on the order of the reaction. Our efforts to measure the kinetics of this reaction in many ionic liquids containing $[BF_4]^-$ and $[PF_6]^-$ species were not successful due to their highly viscous behavior.

We then investigated the variation in the rates with the concentrations of ionic liquid solutions. We carried out the reaction in four different concentrations of [EtP][$EtSO_4$] prepared in DMF and $CHCl_3$ with high and low dielectric constants, respectively. The plots (Figure 2) show a linear dependence of the rates on the concentrations of the ionic liquid indicating a first-order dependence of the reaction. The rate versus ionic liquid concentration data for both solvents were linearly fitted with an average correlation coefficient as high as 0.995 and root mean square deviations as low as 0.005 × 10^{-4} M s^{-1}.

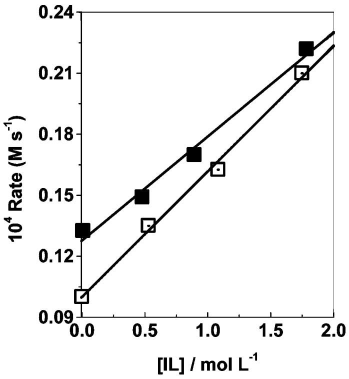


Figure 2. Rates as a function of the concentration of [EtP][$EtSO_4$] in (□) $CHCl_3$ and (■) DMF.

In addition, the rate plots against the concentration of methyl acrylate and of DABCO also demonstrated a straight line confirming that the reaction in ionic liquids was first order with respect to methyl acrylate and also of DABCO.

The values of the rate constants, k_2, are higher by about 7 times in [HMPyr][NTf_2] as compared to that in [BP][NTf_2].

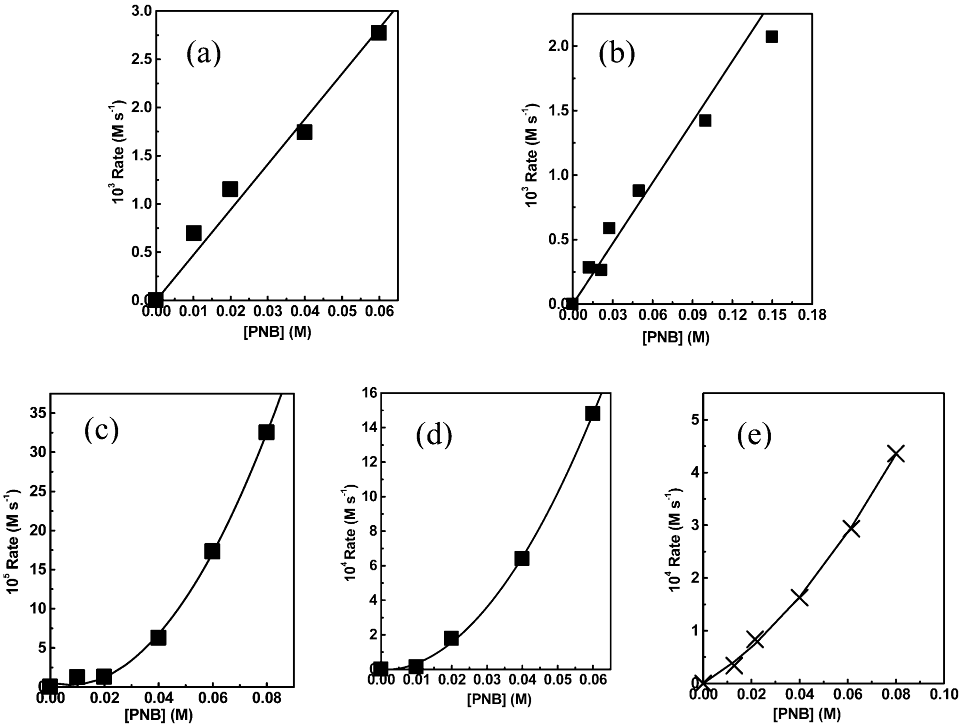


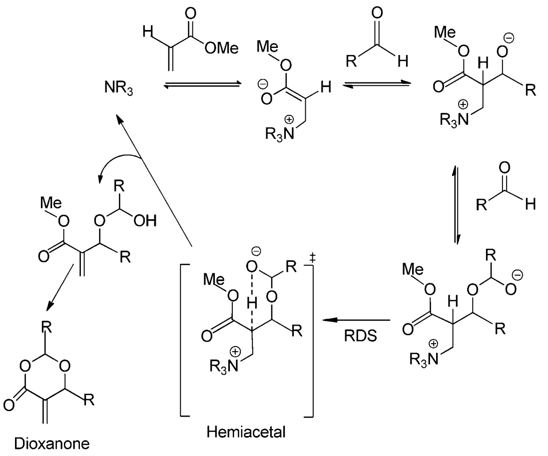
Figure 1. Plots of the rate v PNB concentration for B−H reaction in (a) [EtP][NTf_2] root-mean-square deviation, σ = 0.09 × 10^{-3} M s^{-1}, correlation coefficient, r = 0.977, (b) [OMPyr][NTf_2] σ = 8.2 × 10^{-5} M s^{-1}, r = 0.989, (c) [EtMo][$EtSO_4$] σ = 0.39 × 10^{-6} M s^{-1}, r = 0.988, (d) [EtP][$EtSO_4$] σ = 0.57 × 10^{-4} M s^{-1}, r = 0.989, and (e) [EtPip][$EtSO_4$] σ = 0.085 × 10^{-4} M s^{-1}, r = 0.988.

Leaving the imidazolium-based ionic liquid [EMIM][EtSO$_4$], the maximum k_2 value was obtained in [(Et)$_4$N][EtSO$_4$]. Low k_2 value of the reaction in [EtMo][EtSO$_4$] is possibly the result of very high viscosity (2124 cP at 298 K) of this ionic liquid. The retarding effect of high viscosity of ionic liquids has been discussed elsewhere.[40] The k_2 value noted in [EMIM][EtSO$_4$], though the highest, bears no significance. It may be noted that 60% yield was obtained in [HP][HCOO] in which the reaction was first order in PNB. On the contrary, the use of [EtPip][EtSO$_4$], in which the rates were reported to be second order with respect to PNB, resulted in 66% product. Rosa, Afonso, and Santos reported acceleration of B−H reactions in these ionic liquids.[31] Later, Aggarwal et al.[43] demonstrated that the use of these ionic liquids led to low yields resulting from direct addition of the deprotonated butylmethylimidazolium to the aldehyde. Accordingly, the imidazolium-based type of ionic liquids under basic condition are deprotonated to offer species that can be reactive with electrophile.

The relative permittivity and polarity data for all the ionic liquids used in this work are not yet available. However, the increasing $E_T(30)$ values[44,45] of [BP][NTf$_2$] (50.23 kcal mol^{-1}), [OMPyr][NTf$_2$] (51.7 kcal mol^{-1}), and [HMPyr][NTf$_2$] (51.9 kcal mol^{-1}) can be correlated with the rate enhancement as shown in the form of the k_2 values listed in Table 1. The rate increase is favored by an increase in polarity of the media.

McQuade et al.[24,25] have discussed the RDS to be second order in aldehyde in DMSO. On the basis of the competition experiments carried out between methyl acrylate and α-^{2}H acrylate, it has been very well established that cleavage of the α-^{2}H bond takes place in the RDS of the reaction.[24,25] The second order dependence on the aldehyde concentration has also been confirmed with the help of kinetic investigation and the rate law equations. Accordingly, 2 equiv of aldehyde should be participating in RDS rather than 1 as originally proposed by Hill and Isaacs.[8] Upon the basis of the experimental observations reported here, we also state and agree that, in certain ionic liquids, a similar mechanism (Scheme 2) takes place involving 2 equiv of aldehyde. The mechanism includes (a) the reversible Michael addition, involving the attack of DABCO on activated alkene to form an enolate (zwitterionic species), (b) the attack of enolate on the first equivalent of aldehyde in order to give a second zwitterionic species, (c) formation of a hemiacetal intermediate as a result of the attack of second zwitterionic species on another equivalent of aldehyde, (d) transfer of a proton from the α-position C−H bond to alkoxide (RDS), and last (e) elimination of base and the formation of product.

Scheme 2. Mechanism of Baylis-Hillman Reaction Proposed by McQuade et al.



The product formed by both the mechanisms, i.e., as proposed by Hill and Isaacs and McQuade, are the same (see Supporting Information for ^{1}HNMR spectra). It is noted that B−H reaction is first order in PNB in ionic liquids like [HP][HCOO] as proposed by Hill and Isaacs and second order in PNB in ionic liquids like [EtMo][EtSO$_4$]. From the above data, it is clear that, if the reaction is carried out in the ionic liquid possessing [EtSO$_4$]$^-$ anion, the RDS is second order with respect to aldehyde. Both DMSO and [EtSO$_4$]$^-$ possess high electron density as evident from the hydrogen bond acceptor ability or basicity denoted by a solvent parameter called β. The β values for DMSO and the [EtSO$_4$]$^-$ containing ionic liquids are 0.743 and 0.788.[44−46] DMSO can solvate the cation, and therefore, the solvation of the cation allows the anion to attack 1 equiv of aldehyde resulting in the formation of an alkoxide. The developed negative charge can be satisfied by proton transfer from the α-carbon leading to an unstable 4-membered transition state. Such proton transfer is, however, not favorable in view of geometrical constraints. The electron-rich solvents like DMSO or the ionic liquid containing [EtSO$_4$]$^-$ activate the negative charge on oxygen atom of alkoxide in order to attack on the second equivalent of aldehyde leading to the formation of a hemiacetal intermediate. The proton transfer can now take place from the α-position to the alkoxide oxygen via a six-membered transition state. The remaining mechanism is the same involving the elimination of base and the formation of product.

In short, we have demonstrated that the mechanism of the Baylis-Hillman reaction in ionic liquids is dependent upon the anion of the ionic liquids used for realizing the reaction. The RDS is second order with respect to aldehyde and follows the similar mechanism proposed by McQuade's group.

■ EXPERIMENTAL SECTION

Materials. 1,4-Diazabicyclo [2.2.2]octane [DABCO] with >99% purity) and *p*-nitrobenzaldehyde, PNB (>98% purity), were used without further purification. DMSO, methanol, DMF, dichloromethane, toluene, diethylsulfate, and ethyl acetate were used as obtained. 1-Methylimidazole, pyridine, 1-methylpyrrolidine, morpholine, triethylamine, and lithium bis(trifluoromethane)sulfonimide (>99.9 purity) were used as such. Methyl acrylate was distilled prior to its use.

Synthesis of Ionic Liquids. All ionic liquids were synthesized by the reported methods.

Synthesis of Ethylsulfate-Based Ionic Liquids.[47] To an ice cold solution of pyridine (6 mmol) in 10 mL of toluene, the dropwise addition of diethyl sulfate (6 mmol) was carried out in an inert atmosphere. The temperature was never allowed to rise above 40 °C. After 4 h of stirring, the upper organic layer was removed by decantation, and the remaining solvent was removed in vacuo and further dried under reduced pressure for 12 h. A similar procedure was followed for synthesis of other ethylsulfate-based ionic liquid.

Synthesis of NTf$_2$-Based Ionic Liquids.[48] The synthesis involved two steps: (a) Quaternization: To a stirred solution of slight excess (10%) of haloalkane (17.5 mmol), 1-methylpyrrolidine (14.6 mmol) was added. The reaction mixture was then refluxed for 12 h and the temperature was not allowed to rise above 70 °C. The unreacted starting material was removed by washing with ethyl acetate 3−4 times and the excess solvent was removed by rotary evaporator. The compound was further dried under reduced pressure. (b) Metathesis: To a stirred solution of lithium bis(trifluoromethane)sulfonimide (10 mmol) in deionized water, the halogenated product (10 mmol) of step 1 was added under inert atmosphere. The mixture was stirred for 12 h. The desired product was obtained by repeated extraction of the reaction mixture in DCM. The collected fraction in DCM was subjected to heating in a rotary evaporator followed by drying under reduced pressure. A similar procedure was followed for synthesis of other NTf_2^--based ionic liquids.

Synthesis of [HP][HCOO].[49] This ionic liquid was synthesized by mixing equimolar amounts of acid and base. The synthesis was carried out by dropwise addition of pyridine (25.2 mmol) as a base to a stirred solution of formic acid (25.2 mmol) under ice cold condition. After 8 h of stirring, excess water was removed in vacuo. The ionic liquid synthesized was further dried under reduced pressure for 10 h.

All the synthesized ionic liquids were subjected to Karl Fisher titrator to estimate the water content to be less than 30 ppm. The halides estimated by Volhard titration[50] were within the recommended range.

Kinetic Measurements. The reaction was initiated by adding 0.9028 mL (1 M) of methyl acrylate to a stirred solution containing 1 mL of DABCO (1 M) and PNB in 1 mL of the solvent. The reaction was monitored with the help of a UV−visible spectrophotometer and by measuring the disappearance of PNB at wavelength of λ_{max} = 270 nm. A plot of absorbance versus concentration gave slope as the rate of reaction. The concentration of PNB was varied from 0.01 to 0.15 M keeping the concentration of others constant. The rates were determined for each concentration of PNB. Order plots were made by plotting the rate versus concentration of PNB. Rate constants were determined from the rate law equation. In order to calculate the rate constants, the concentrations of DABCO and methyl acrylate were kept constant throughout. Each reaction was carried out thrice. The rate constants were accurate to ±3%. Entire kinetic course was followed before 15% conversion. No byproducts were noted during the reaction.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra for the product, standard B−H reaction mechanism as scheme and additional kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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