

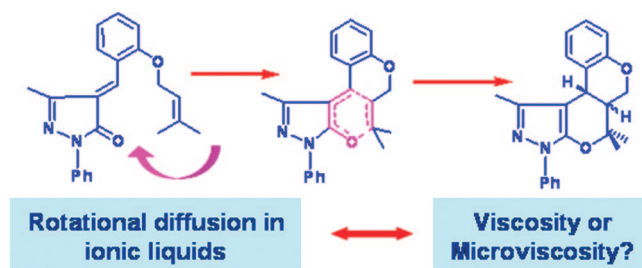
## Intramolecular Diels–Alder Reaction in Ionic Liquids: Effect of Ion-Specific Solvent Friction

Shraeddha Tiwari, Nageshwar Khupse, and Anil Kumar\*

National Chemical Laboratory, Pune 411008, India

a.kumar@ncl.res.in

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The present work aims at understanding the role of viscosity or solvent friction in ionic liquids for an intramolecular Diels–Alder (IMDA) reaction of (*E*)-1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (**1**). The results have been analyzed on the basis of the current theoretical models, and their failure to account for the observed trends is discussed in terms of “effective” viscosity or microviscosity. The rates of the reaction decrease with the increasing viscosity of the ionic liquids. As evident from the anionic effect, the solute–solvent specific interactions play a role in governing the kinetics of the reaction. The lower viscosities of the bistrifluoromethanesulfonimide [NTf<sub>2</sub>]<sup>−</sup> based ionic liquids as compared to those based on tetrafluoroborate [BF<sub>4</sub>]<sup>−</sup> anion fail to result in a corresponding acceleration in the rates of the reaction. These contradictory results indicate that solvent microviscosity, rather than the bulk macroscopic viscosity, should be the criteria for selecting the ionic liquids as reaction media.

### 1. Introduction

The growing awareness about the need to use environmentally benign solvents has led to the increasing importance of ionic liquids in carrying out various organic reactions.<sup>1</sup> The advantageous properties of ionic liquids that render them more suitable over organic solvents are summarized in many reports.<sup>2</sup> In addition, there are numerous reports highlighting the use of ionic liquids as reaction media.<sup>3</sup> However, very few attempts have been made to correlate the kinetic and stereochemical outcome

of the reactions with different physicochemical properties of ionic liquids.<sup>4</sup> In the absence of such detailed kinetic information, it is difficult to design novel ionic liquids that are capable of overcoming the limitations of the current generation of ionic liquids.<sup>5</sup> As shown in the previous work carried out in this laboratory, the highly viscous nature of a conventional ionic liquid can slow down the rate of an intermolecular Diels–Alder reaction by an order of magnitude as compared to that in water.<sup>6</sup> Hence, the synthesis of ionic liquids with low viscosity is deemed to be one of the most important challenges for the next generation of ionic liquids. To achieve this end, an extensive collection of kinetic data for a variety of organic reactions carried out in a range of ionic liquids and subsequent comparison of the results with theoretical models is essential.

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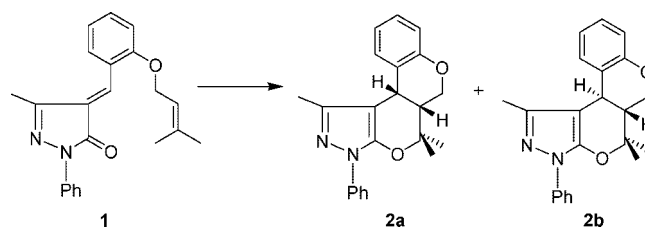
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Neta and co-workers investigated the rates of several elementary radical reactions in ionic liquids<sup>7</sup> and observed that the rates in ionic liquids were, in general, lower than those in water and organic solvents. Similar observations were made for the diffusion-controlled quenching of triplet benzophenone by naphthalene.<sup>8</sup> The *Z* to *E* isomerization of azobenzene (AB) studied in the imidazolium-based ionic liquids was not much influenced by the viscosity and the polarity of the ionic liquids, whereas the rates for isomerization of and 4-dimethylamine-4'-nitroazobenzene (DNAB) showed very large viscosity dependence.<sup>9</sup> The role of viscosity in determining the kinetic profile of bromination of alkynes in ionic liquids was also examined,<sup>10</sup> and the activation parameters showed that viscosity affected the rate of reaction by increasing the activation energy for bond breaking in the transition state. Spinelli and co-workers have investigated the mononuclear rearrangement of *Z*-phenylhydrazide of 3-benzoyl-5-phenyl-1,2,4-oxadiazole induced by amines.<sup>11</sup> The experimental data failed to show a complete correlation with either viscosity or reactivity.

In comparison, there is a paucity of data on the viscosity dependence of Diels–Alder reactions in ionic liquids. Welton had inferred, on the basis of limited results, that an increase in viscosity accelerated the Diels–Alder reactions.<sup>4</sup> Experiments from our group, on the other hand, proved that the rates decreased drastically with an increase in the viscosity of the ionic liquids used.<sup>6</sup> Conventionally, both intermolecular (bimolecular) and intramolecular Diels–Alder reactions are known to show strong viscosity dependence in molecular solvents.<sup>12,13</sup> The rate of cyclization of *N*-propargyl-9-anthramide initially rises with an increase in viscosity before falling off at higher viscosities.<sup>12</sup> Firestone and co-workers observed that the slope of the relative rates versus the relative viscosities for the above intramolecular Diels–Alder reaction was much higher than that observed for the Claisen rearrangement under similar conditions.<sup>12a</sup> The observation was explained on the basis of vibrational activation of bond-making reactions. Up to a certain limit, an increase in viscosity should lead to an increase in the rates by increasing the vibrational energy of the molecule at the cost of the translational energy. Beyond that limit, the increasing viscosity would lead to encounter control of the reaction kinetics wherein the reactants cannot “see” each other due to high viscosities.

However, van Eldik carried out kinetic studies on the dimerization of cyclopentadiene, which led them to the conclusion that “there is no obvious reason this reaction should exhibit a viscosity dependence at all”.<sup>14</sup> le Noble and co-workers have

SCHEME 1



criticized Firestone's approach in interpreting the dependence of rates on viscosities.<sup>15</sup> le Noble states that reaction rates should necessarily be suppressed by increasing viscosity. A study from this laboratory compared the rates of numerous Diels–Alder reactions with the solvent viscosity and demonstrated that the effect of viscosity was not restricted to a few substrates.<sup>16</sup> The characteristic behavior observed in all the cases was that the reaction rates increased with the rise in viscosity and leveled off at 1.2–1.3 cP before dropping with increasing viscosity beyond 1.3 cP. The report provided substantial evidence of the role of viscosity in organic solvents.

A quantitative theoretical explanation for the observed viscosity dependence of intramolecular Diels–Alder reactions has not yet been reported. At present, the Kramers theory<sup>17</sup> is the most widely used stochastic model to explain the role of viscosity in determining the rates of reactions. The theory has been experimentally tested for a wide variety of reactions,<sup>18</sup> including the isomerizations.<sup>19</sup> However, to the best of our knowledge, these stochastic theories have not been applied to date to analyze the kinetics of Diels–Alder reactions, either in ionic liquids or in molecular solvents. Basilevsky et al. modeled the bimolecular Diels–Alder reaction as a pair of coordinates, one for the reaction coordinate and the other for the contraction of the solvent cavity surrounding the medium.<sup>20</sup> The corresponding kinetics covered both the equilibrium and the non-equilibrium behavior and was applied to explain the observations for high-pressure kinetics.

As part of an extensive program to investigate the physical organic chemistry of solvent effects on organic reactions,<sup>21</sup> the present work aims at understanding the role of viscosity in ionic liquids for an intramolecular Diels–Alder (IMDA) reaction of (*E*)-1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (**1**) (Scheme 1). Previous mechanistic studies on the reaction have shown that the rate of the reaction and the

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**TABLE 1.** First-Order Rate Constant,  $k$ , for the IMDA Reaction of **1** in Ionic Liquids Together with Their Viscosities,  $\eta$ , at 308 K

ionic liquid	$\eta$ (cP) <sup>a</sup>	$10^5 k$ (s <sup>-1</sup> ) <sup>b</sup>
[BP][BF <sub>4</sub> ]	66.1	4.45
[4MBP][BF <sub>4</sub> ]	95.6	3.12
[3MBP][BF <sub>4</sub> ]	86.3	3.67
[3MHP][BF <sub>4</sub> ]	129.6	2.43
[HP][BF <sub>4</sub> ]	164.2	2.23
[3MOP][BF <sub>4</sub> ]	175.4	1.68
[BP][NTf <sub>2</sub> ]	<b>35.0</b>	<b>2.17</b>
[HP][NTf <sub>2</sub> ]	<b>48.3</b>	<b>0.37</b>
[OP][NTf <sub>2</sub> ]	<b>63.0</b>	<b>0.94</b>

<sup>a</sup> Viscosity data are reproducible within  $\pm 3\%$ . <sup>b</sup> Rate constants are an average of three runs. The data agree to within  $\pm 6\%$ .

selectivity depends on the solvent and temperature.<sup>22</sup> Based on kinetic studies of **1** in different solvents, Coda and co-workers inferred that the solvent effect could be correlated with the acceptor number (AN) of the solvent.<sup>23</sup> Apart from the electrophilic character of the solvent, coordination with metal cations was also observed to accelerate the reaction.<sup>24</sup> The previous studies have provided a detailed account of the solute–solvent specific interactions, but the information on the role of viscosity is not discussed.

In section 2, we discuss the solvent-specific effect observed and analyze the activation parameters from temperature dependent studies. Section 3 consists of a discussion on the Kramers model and its applicability to our experimental data. The failure of the theory to explain the experimental trends is discussed in terms of the effective solvent viscosity or microviscosity. The effect of friction on intramolecular and intermolecular processes is discussed briefly in section 4 by comparing the results obtained for both the reactions. We conclude with a brief remark on the implications of the work for the future research in section 5. To the best of our knowledge, the present work is the first attempt to address the experimental results for the role of friction or viscosity in intramolecular Diels–Alder reactions (or any other C–C bond-forming reaction with a considerable barrier) by using quantitative stochastic approach.

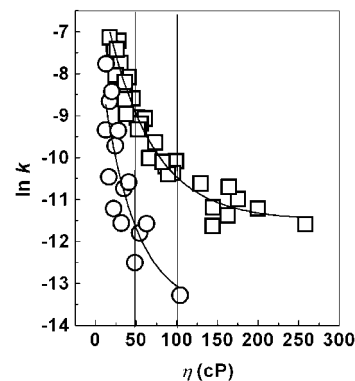
## 2. Results and Discussion

**2.1. “Solvent-Specific” Viscosity Effect.** The first order rate constants,  $k$ , for the IMDA reaction of **1** carried out in ionic liquids of varying viscosities and organic solvents are reported in Table 1. The reactions were carried out in different pyridinium based ionic liquids. The alkyl substituents on the pyridinium cation were varied to give different cations: 1-butyl pyridinium [BP]<sup>+</sup>, 1-hexyl pyridinium [HP]<sup>+</sup>, 3-methyl-1-butyl pyridinium [3MBP]<sup>+</sup>, 3-methyl-1-hexyl pyridinium [3MHP]<sup>+</sup>, 3-methyl-1-octyl pyridinium [3MOP]<sup>+</sup>, and 4-methyl-1-butyl pyridinium [4MBP]<sup>+</sup>. The anions used were tetrafluoroborate [BF<sub>4</sub>]<sup>-</sup> and bis(trifluorosulphonimide) [NTf<sub>2</sub>]<sup>-</sup>. The use of two anions resulted in a homologous series of ionic liquids differing only with respect to the alkyl substituent on the pyridinium cations. Changing the alkyl substituents, the anion, or the temperature could thus vary the viscosity of the ionic liquids.

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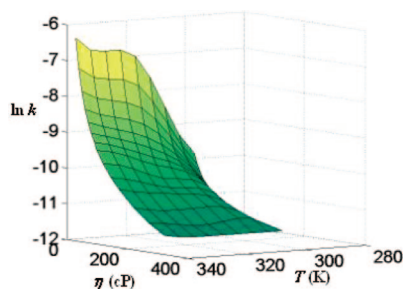
**FIGURE 1.** Plot of  $\ln k$  for the IMDA reaction of **1** against the viscosity,  $\eta$ , of pyridinium ionic liquids with [BF<sub>4</sub>]<sup>-</sup> anion (□) and [NTf<sub>2</sub>]<sup>-</sup> anion (○) at different temperatures from 298.15 to 343.15 K. The vertical lines serve as a visual guide for comparing the rates in [BF<sub>4</sub>]<sup>-</sup> and [NTf<sub>2</sub>]<sup>-</sup> ionic liquids at identical viscosities.

Table 1 also lists the viscosities,  $\eta$ , of the ionic liquids at the corresponding temperature.

The results shown in Table 1 indicate that the rate constants within the [BF<sub>4</sub>]<sup>-</sup> series of ionic liquids show a definite correlation with the viscosities of the media. The rate of reaction falls down from  $4.45 \times 10^{-5} \text{ s}^{-1}$  in [BP][BF<sub>4</sub>] to  $1.68 \times 10^{-5} \text{ s}^{-1}$  in [3MOP][BF<sub>4</sub>] for a corresponding change in viscosity from 175.4 cP to 66.1 cP at 308 K. No such correlation could however be observed between  $k$  and  $\eta$  for the [NTf<sub>2</sub>]<sup>-</sup> series. Surprisingly, the magnitude of  $k$  in the [NTf<sub>2</sub>]<sup>-</sup> ionic liquids is very close to that in [BF<sub>4</sub>]<sup>-</sup> based ionic liquids. If the rate constants are indeed dependent on the viscosity of the medium, then the lower viscosity of the [NTf<sub>2</sub>]<sup>-</sup> based ionic liquids should have led to higher rates.

In order to access the correlation between the rates and viscosity in greater detail, temperature dependence studies were carried out in different ionic liquids (Figure 1). The variation in temperature served to control the viscosity of the medium, and the results plotted in Figure 1 are a compilation of the rates in different ionic liquids at different temperatures. For the [BF<sub>4</sub>]<sup>-</sup> series of ionic liquids, the uniform variation in the experimental data show that the rate constants at the same viscosity are nearly equal, independent of the means by which that viscosity value was attained, changing the alkyl substituent or the temperature. The rate constants decrease uniformly with increasing viscosity, thus indicating a “universal” viscosity dependence. It is obvious, however, that this “universal” trend fails to extend to the [NTf<sub>2</sub>]<sup>-</sup> series. The [NTf<sub>2</sub>]<sup>-</sup> based ionic liquids also show a similar but independent trend with the changing viscosity; in fact, the decrease in rates is sharper for [NTf<sub>2</sub>]<sup>-</sup> ionic liquids for a similar magnitude of increase in viscosity. At a given value of viscosity, the rate of the IMDA reaction in an ionic liquid with [NTf<sub>2</sub>]<sup>-</sup> is much lower than that in [BF<sub>4</sub>]<sup>-</sup> anion. The projected rate constant falls from  $\sim 13 \times 10^{-5}$  to  $\sim 3 \times 10^{-5} \text{ s}^{-1}$  when the viscosity increases from 50 to 100 cP for the tetrafluoroborate ionic liquids, i.e., a decrease to 1/4 of the original rate constant. For a viscosity of 100 cP for [NTf<sub>2</sub>]<sup>-</sup> ionic liquids, the rate decreases to 1/10 of its value at 50 cP i.e., from  $\sim 2.10 \times 10^{-5}$  to  $\sim 0.21 \times 10^{-5} \text{ s}^{-1}$ .

The results indicate that in addition to viscosity, the rates are also influenced by a solvent property that varies independently of viscosity on changing from one anion series to another. Within the homologous series, this effect might still be operative but either is masked by a greater competing influence of



**FIGURE 2.** 3-D representation of  $\ln k$  for the IMDA reaction of **1** in a series of pyridinium ionic liquids as a function of viscosity,  $\eta$ , and temperature,  $T$ .

**TABLE 2.** Activation parameters ( $\ln A$  and  $E_a$ ) for the IMDA Reaction of **1** in Different Ionic Liquids and Organic Solvents along with the Activation Energy for Viscous Flow,  $E_\eta$ , of the Ionic Liquids

ionic liquid	$\ln A$	$E_a$ (kJ mol <sup>-1</sup> )	$E_\eta$ (kJ mol <sup>-1</sup> ) <sup>a</sup>
ethylene glycol	17.81 ± 0.64	66.12 ± 1.63	
formamide	21.50 ± 0.29	75.64 ± 0.76	
[BP][BF <sub>4</sub> ]	22.97 ± 0.38	84.60 ± 1.01	40.88 ± 1.98
[HP][BF <sub>4</sub> ]	17.89 ± 3.09	80.99 ± 8.43	51.73 ± 2.45
[3MBP][BF <sub>4</sub> ]	23.26 ± 0.75	85.75 ± 1.99	45.78 ± 1.97
[3MHP][BF <sub>4</sub> ]	21.23 ± 0.58	81.52 ± 1.54	46.35 ± 2.00
[3MOP][BF <sub>4</sub> ]	22.14 ± 0.67	85.06 ± 1.83	47.22 ± 2.02
[4MBP][BF <sub>4</sub> ]	21.53 ± 0.96	81.42 ± 2.54	48.11 ± 2.32
[BP][NTf <sub>2</sub> ]	22.52 ± 0.32	85.13 ± 0.84	31.85 ± 1.04
[HP][NTf <sub>2</sub> ]	13.23 ± 2.63	66.04 ± 7.16	35.01 ± 1.09
[OP][NTf <sub>2</sub> ]	27.34 ± 1.78	100.29 ± 4.69	36.65 ± 1.04

<sup>a</sup> Values for  $E_\eta$  are approximate since they are obtained by applying the Arrhenius equation to typically non-Arrhenius ionic liquids. All resulting plots had  $r^2 > 0.90$ .

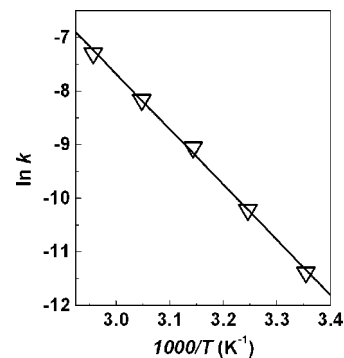
viscosity or changes in proportion to the viscosity. The origin of such “specific anion effects” can be explained by one of the following possibilities:

1. The change in anion from [BF<sub>4</sub>]<sup>-</sup> to [NTf<sub>2</sub>]<sup>-</sup> may affect the equilibrium solvation, leading to static modification of the potential energy surface of the reaction. In thermodynamic formulations of the transition state theory (TST), the effect can be quantified in terms of the difference in the free energy of solvation of the reactants and the transition state and hence is reflected in the magnitude of the activation energy,  $E_a$ .

2. The change in anion from [BF<sub>4</sub>]<sup>-</sup> to [NTf<sub>2</sub>]<sup>-</sup> may affect the strength of frictional coupling of the solvent to the reaction coordinate. It is a dynamic or nonequilibrium effect, since it implies that the solvent molecules are unable to instantaneously equilibrate with the changing configurations of the reacting molecule(s). Nonequilibrium solvation causes a breakdown of the quasi-equilibrium assumption of the TST and is manifested in terms of the friction (or viscosity) of the medium.

However, it is difficult to delineate the equilibrium and the nonequilibrium solvent effects in any experimental data. For example, changing any parameter such as temperature to affect the viscosity will also affect the potential energy surface of the system. The rate constants obtained by varying the reaction medium and the temperature are a function of both viscosity and temperature, i.e.,  $k(T, \eta)$ . Thus  $\ln k$  can be represented as a surface on a three-dimensional plot with  $T$  and  $\eta$  as the independent variables (Figure 2).

**2.2. Activation Parameters.** The activation parameters evaluated from the temperature-dependent kinetics of the ionic liquids and two other organic solvents are listed in Table 2, and Figure 3 represents a typical Arrhenius plot. The activation



**FIGURE 3.** Arrhenius plot for the IMDA reaction of **1** in [3MBP][BF<sub>4</sub>] ( $r^2 = 0.992$ ).

energies,  $E_a$ , are higher in ionic liquids as compared to those in organic solvents. The values of  $E_a$  are almost twice the values of activation energy for viscous flow,  $E_\eta$ , of the ionic liquids. No clear trend emerges from the comparison of the  $E_a$  and the  $E_\eta$  values. A closer observation of the  $E_a$  values reveals some interesting details about the effect of the solvent properties on the rate of the reaction.

First, the  $E_a$  values for all of the ionic liquids in the [BF<sub>4</sub>]<sup>-</sup> series do not show much variation (80.99–85.75 kJ/mol), indicating that the nature of the transition state is more or less retained in all of these ionic liquids. The viscosity increases on going from butyl-substituted ionic liquids to hexyl-substituted ionic liquids, leading to a decrease in the rates of reactions. The increase in the viscosity is represented by the  $E_\eta$  values, but the corresponding  $E_a$  values for the reaction do not reflect the change. For example, the  $E_\eta$  value increases from 31.85 kJ/mol for [BP][NTf<sub>2</sub>] to 35.01 kJ/mol for [HP][NTf<sub>2</sub>]. The  $E_a$  value for the IMDA reaction, on the contrary, decreases from 85.13 kJ/mol in [BP][NTf<sub>2</sub>] to 66.04 kJ/mol in [HP][NTf<sub>2</sub>]. The observed decrease in the rates can then be attributed to the decrease in the transmission coefficient ( $\ln A$  falls from 22.52 in [BP][NTf<sub>2</sub>] to 13.23 in [HP][NTf<sub>2</sub>]). The anomaly is observed for other pairs of butyl- and hexyl-substituted ionic liquids too: [BP][BF<sub>4</sub>] against [HP][BF<sub>4</sub>] and [3MBP][BF<sub>4</sub>] against [3MHP][BF<sub>4</sub>], although the variation in activation parameters is not very drastic. Further increase in the length of the alkyl substituent leads to an increase in the  $E_a$  values, as expected from the rate constants.

Another remarkable fact is that the  $E_a$  is more sensitive to the chain length of the alkyl substituent in the [NTf<sub>2</sub>]<sup>-</sup> based ionic liquids as compared to the [BF<sub>4</sub>]<sup>-</sup> ionic liquids. The results clearly prove that the viscosity of ionic liquids is a dominating factor, but it affects the kinetic profile of the IMDA reaction in an extremely complex manner, which can be due to either static or dynamic effects or a combination of both.

### 3. Theoretical Discussion

**3.1. Kramers Theory.** Numerous reports have established the role of viscosity for diffusion-controlled processes extensively in the form of an inverse relationship between the diffusion coefficient and the viscosity. In contrast, there is no in-depth theoretical model for the effects of viscosity on “activation-controlled” reactions such as the Diels–Alder reaction. Rate constants of such activation-controlled reactions may be analyzed using the Kramers approach. The Kramers theory studies the effect of nonequilibrium forces or “friction” on the rate of the reaction by modeling the reaction progress as the

passage of a single reaction coordinate over a frictional potential barrier. The rest of the system is treated as a bath in terms of a Langevin equation of motion.<sup>17</sup> It is an approximate expression for the flux of population across a barrier given by

$$k \frac{\omega_0}{2\pi\omega'\tau_v} [(1 + (2\omega'\tau_v)^2)^{1/2} - 1] e^{-E_0/RT} \quad (1)$$

where  $\omega_0$  is the frequency of the potential well of the initial minimum,  $E_0$  is the barrier height,  $\omega'$  is the frequency of the barrier height, and  $\tau_v$  is the velocity relaxation time of the coordinate.  $\tau_v$  is a function of the friction coefficient,  $\zeta$ , and the effective mass,  $m$ .

$$\tau_v = \frac{m}{\zeta} \quad (2)$$

For general applications, in accordance with the hydrodynamic model, the friction coefficient  $\zeta$  is replaced by the viscosity  $\eta$  of the medium. The rate constant is also replaced by the reduced rate constant,  $k^*$ , defined as

$$k^* = k e^{(E_0/RT)} \quad (3)$$

where  $E_0$  is the intrinsic activation energy. The parameter  $E_0$  can be determined from the isoviscosity plots. This would entail the delineation of the effects of temperature and viscosity from  $k(T, \eta)$ . The hydrodynamic Kramers expression is then

$$k^* = \frac{A}{B/\eta} [(1 + (B/\eta)^2)^{1/2} - 1] \quad (4)$$

where  $A = \omega_0/2\pi$  and  $B/\eta = 2\omega'\tau_v$ . For any practical application, the expression can be simplified so as to express the observed rate constant as a function of temperature and viscosity.

$$k = F(\eta) e^{(-E_0/RT)} \quad (5)$$

With the above definition of  $k^*$ , we may try to isolate the effect of barrier height upon the IMDA rate from the effect of the solvent and other characteristics of the potential surface. For reactions carried out in highly viscous medium, the resultant friction  $\zeta$  is very large. In such cases,  $\tau_v$  exceeds the characteristic time scale for solvent relaxation. This is known as the high friction limit or the Smoluchowski limit, wherein the Kramers theory predicts an inverse relation between the reduced rate constant,  $k^*$  and  $\eta$ :

$$k^* \propto \frac{1}{\eta} \quad (6)$$

However, it is only for reactions with a small barrier of activation ( $\sim 0-5$  kJ/mol) that the simple inverse viscosity dependence can be observed. In practice, for the majority of the isomerization reactions studied, the reaction rate falls off more slowly with viscosity than predicted from theory.<sup>19</sup> The experimental results for such reactions are fitted to the empirical expression

$$k^* = \frac{B}{\eta^a} \quad (7)$$

The value of  $a$  is taken as a measure of the deviation of the experimental data from the Smoluchowski limit behavior. Typically, the value of  $a$  falls between zero and unity. The Smoluchowski limit is also known as the diffusion-controlled limit. However, the term “diffusion” does not refer to the spatial diffusion of the molecules in three-dimensional space but the

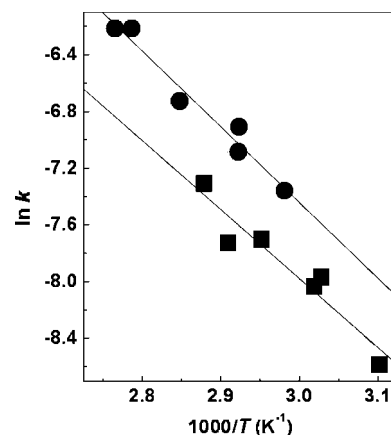


FIGURE 4. Typical isoviscosity plots for the IMDA reaction of **1** at viscosity 20 cP (●) ( $r^2 = 0.983$ ) and 30 cP (■) ( $r^2 = 0.953$ ).

TABLE 3. Activation Parameters for the IMDA Reaction of **1** from the Isoviscosity Plots at Different Viscosities

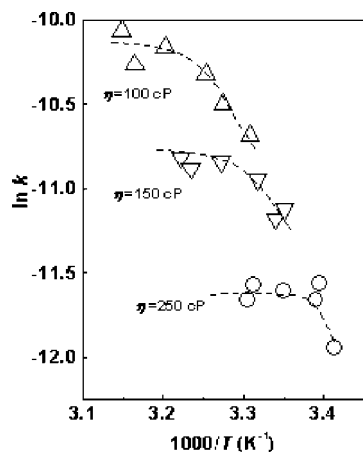
$\eta$ (cP)	$\ln A$	$E_a$ (kJ mol <sup>-1</sup> )
25	6.46 ± 1.62	39.35 ± 4.60
28	6.91 ± 2.09	41.03 ± 5.87
30	6.62 ± 2.29	40.46 ± 6.40
32	6.32 ± 2.43	39.88 ± 4.16
35	5.87 ± 1.86	38.97 ± 7.61

diffusion of the reacting system over the energy barrier in a one-dimensional motion. Hence, the diffusion control in the Smoluchowski limit implies that the friction with the solvent molecules causes dissipation of energy to such an extent that it becomes the rate-determining factor. This is essentially distinct from the diffusion control in the conventional sense, which implies that the “encounter” of the reacting species is hindered by the solvent friction and thus becomes the rate-determining entity. This justifies the application of the Kramers model to unimolecular processes where the reacting functional groups are present in close spatial proximity.

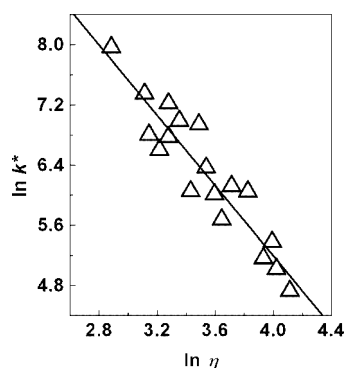
If the effect of viscosity is indeed dominant, then the  $E_0$  thus determined from the isoviscosity plots should be independent of the ionic liquid or the viscosity value taken as fixed for the plot. Figure 4 shows the typical isoviscosity plot evaluated at  $\eta = 20$  and 30 cP. Similar plots were evaluated for five different values of  $\eta$  between 25 and 35 cP, and the resulting activation parameters are listed in Table 3. The average  $E_0$  value based on the data in Table 3 is 39.93 kJ/mol. The  $E_0$  value is lower than the observed  $E_a$  values for the different ionic liquids. This may indicate that the observed activation energies are comprised, at least partially, of the viscosity activation energy,  $E_\eta$ .

Another important fact is the nature of the isoviscosity plots at higher values of  $\eta$  (Figure 5). The plots are characteristically nonlinear, showing a sharper deviation in the downward direction at higher values of  $\eta$ . The results indicate a breakdown of the TST regime, as is expected for the reactions in the high friction or Smoluchowski limit.

In order to evaluate the confirmation or deviation of the results from the theory, the value of  $a$  was determined from the  $\ln k^*$  versus  $\ln \eta$  plot (Figure 6). Since the isoviscosity plots for  $\eta$  values higher than 100 cP were nonlinear and the  $E_0$  parameter was evaluated for the data in the lower range of viscosities, the empirical fit was limited to rate constants for reactions in which  $\eta < 100$  cP. The inclusion of data at higher viscosities led to a significant deviation from linearity. The nonlinearity at higher



**FIGURE 5.** Nonlinearity of the isoviscosity plots for the IMDA reaction of **1** in the  $[\text{BF}_4]^-$  based ionic liquids at  $\eta = 100$  cP ( $\Delta$ ), 150 cP ( $\nabla$ ) and 250 cP ( $\circ$ ).



**FIGURE 6.** Plot of  $\ln k^*$  versus  $\ln \eta$ ; empirical fit to the equation  $\ln k^* = \ln B - a \ln \eta$  (i.e.,  $k^* = (B/\eta^a)$ ).

viscosities may be attributed to the fact that  $E_0$  determined for lower  $\eta$  is not “valid” for the higher values of  $\eta$ . The absolute value of the resulting slope, 2.33, was greater than unity and hence cannot be explained on the basis of any existing version of the Kramers theory. The slope is observed to decrease for reduced rate constants at higher viscosities. Such a scale of deviation has not been observed for any of the friction-dependent reactions studied in molecular solvents. Asano and co-workers have reported the slope of  $\log k$  versus  $\log \eta$  plots to be as high as  $-10$  for the isomerization of DNAB in imidazolium ionic liquids.<sup>9</sup> These values are much higher than the  $0 < a < 1$  values expected from the Kramers–Grote–Hynes model. The authors rationalized the observation on the basis of the electrostatic interactions of the highly polar transition state for the isomerization of DNAB involving extensive reorganization of the solvating cations and anions.

**3.2. Effective Friction or Microviscosity.** The failure of the Kramers theory to explain the experimental data has been explained either by using the frequency dependent friction concept<sup>25</sup> or by extending the one-dimensional model into multiple dimensions.<sup>26</sup> However, both of the theories predict a fractional power dependence of the observed rate on the viscosity ( $0 < a < 1$ ). It is clear that these theories cannot be applied to explain the results presented in this work. The

deficiency may be traced to the use of hydrodynamic limit, which assumes that the friction experienced by the reactant is identical to the viscosity of the medium. While the term “friction” is known to include forces opposing mechanical, internal, and dielectric diffusion,<sup>27</sup> the bulk viscosity is a phenomenological entity that mainly reflects resistance to translational diffusion. A more reasonable explanation would be based on the concept of microviscosity or the actual microscopic friction experienced by the reacting solute molecules. The microviscosity, thus defined, would be proportional to the bulk viscosity but can also be influenced by the mutual interactions between the solvent and the solute molecules. In addition, the effect of anion on the observed viscosity dependence indicates that the macroscopic or bulk viscosity is not exactly the rate-determining factor.

Firestone and Vitale suggested that macroscopic viscosity was not an ideal quantity for correlation with rates and a measure of microscopic viscosity would be preferable.<sup>12a</sup> The reaction pathway from the reactant **1** to the transition state involves *s-trans* to *s-cis* rotation along the O(21)–C(22)  $\sigma$ -bond, in order to bring the diene and dienophile closer to the transition state geometry, i.e., rotational diffusion (Figure 7). This is similar to the rotational diffusion of the stilbene molecule discussed by Sun and Saltiel.<sup>28</sup> They assumed that the friction experienced by the rotating molecule was equivalent to that experienced in translational diffusion of the toluene molecule and employed the diffusion coefficients of toluene to compute the microviscosity. Excellent fits of the Kramers expression were obtained when the microviscosity was employed. The friction experienced by the substrate in the present work is also due to a similar rotational diffusion. The results presented in this work could also be modeled as translational diffusion of a moiety bearing structural resemblance to the dimethylbutenyloxy moiety in the substrate **1**. The calculations would require data on the diffusion coefficients of small molecules in ionic liquids, which are currently unavailable.

To date, there have been very few attempts to measure the microviscosity of ionic liquids.<sup>29</sup> Most of the studies focus on the fluorescent relaxation times of probe molecules and the effect of additives such as  $\text{CO}_2$ .<sup>30</sup> For example, the fluorescent behavior of coumarin-153 (C-153), 4-aminophthalimide (AP), and 6-propionyl-2-dimethylaminonaphthalene (PRODAN) in pyrrolidinium ionic liquids has been investigated.<sup>31</sup> Iwata and co-workers studied the rotational diffusion of the probe 2-aminoquinoline using time-resolved fluorescence spectroscopy in a series of aromatic and nonaromatic ionic liquids and common molecular solvents.<sup>32</sup> It was observed that the rotational correlation times were proportional to the macroscopic solvent viscosity for molecular solvents. The correlation was lost for the rotational diffusion time in ionic liquids, especially the aromatic ionic liquids. Notably, the rotational diffusion times in the  $[\text{BF}_4]^-$  and the  $[\text{NTf}_2]^-$  ionic liquids were nearly the same in magnitude, despite the difference in their viscosities. However, since microviscosity depends on the structure of the solute

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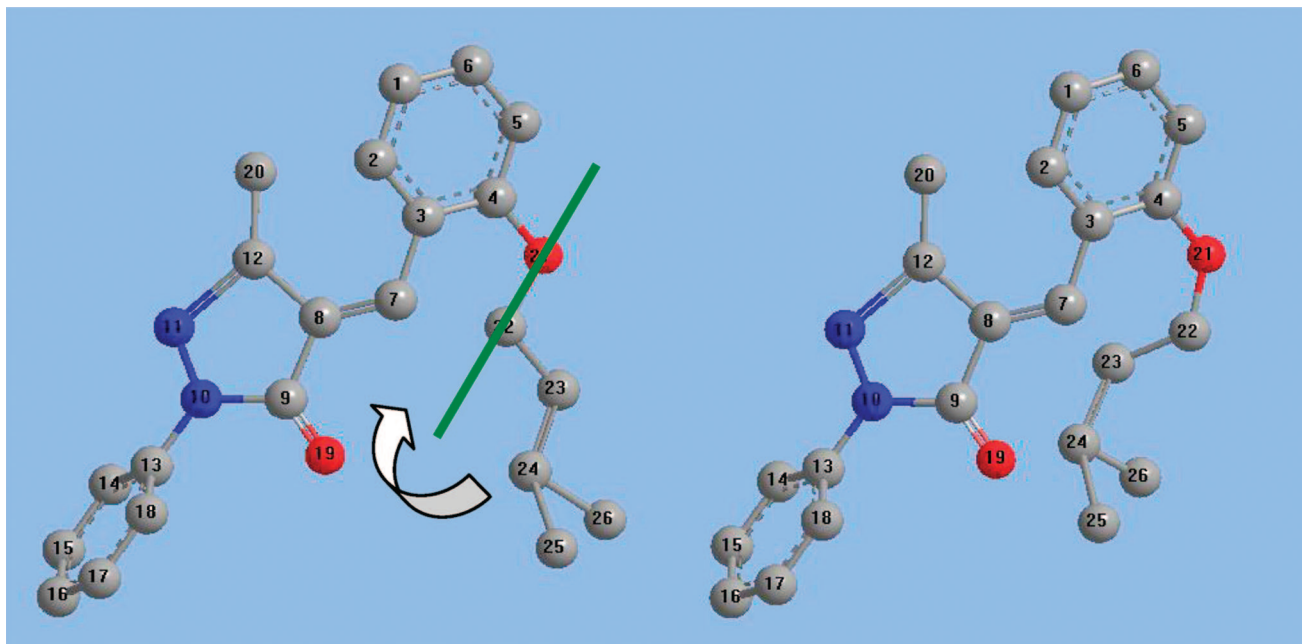
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**FIGURE 7.** Pictorial representation of the *s-trans* to *s-cis* rotation along the O(21)–C(22) bond, required in order to bring the diene and the dienophile in the proper orientation for cyclization. (Grey atoms, C; blue atoms, N; and red atoms, O. Hydrogen atoms not shown.)

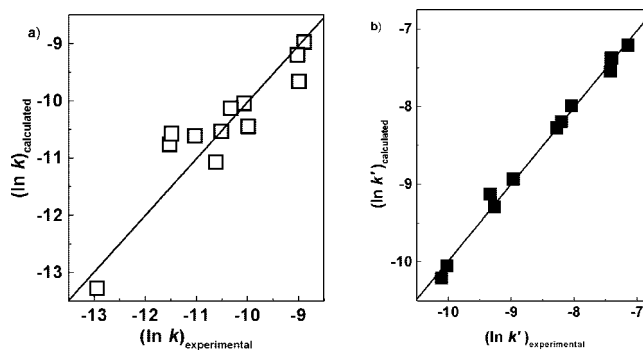
and the solvent, the data currently available are insufficient for any further comment except that the microscopic solvent environment in ionic liquids is not adequately represented by the macroscopic solvent properties such as viscosity.

The kinetic data obtained can thus be explained only after a detailed investigation of the solute–solvent specific interactions at a mechanistic level. The IMDA reaction of **1** is an example of an inverse electron demand hetero Diels–Alder reaction. Previous studies assumed the solvents to behave as electrophiles, which coordinate with the carbonyl of the pyrazolone, lowering the energy separation between the HOMO of the dienophile and the LUMO of the heterodiene, thus increasing the rate of the reaction.<sup>23</sup> Similar reasoning was applied by Casaschi et al. to explain the Lewis acid catalysis of the IMDA reaction of **1** by inorganic perchlorates.<sup>24</sup> They observed that the catalytic effect was higher for cations having a higher charge:radius ratio.

The rates of the IMDA reaction in organic solvents were assessed with the multiple linear regression with the Kamlet–Taft polarity parameters. An analysis of the regression models shows dominant contributions by the  $\alpha$  and  $\pi^*$  polarity parameters. The results showing the dominance of  $\alpha$  or hydrogen bond donating property are supported by the previous studies emphasizing the role of electrophilic nature of the solvent.<sup>23</sup> Figure 8a shows the correlation between the  $(\ln k)_{\text{exp}}$  and  $(\ln k)_{\text{calcd}}$ , which were obtained by using the following equation:

$$(\ln k)_{\text{calcd}} = -13.069 + 1.87(\pm 0.39)\alpha + 2.61(\pm 0.52)\pi^* \quad (r^2 = 0.833) \quad (8)$$

Similar attempts to correlate the rates in ionic liquids with the solvent parameters such  $\alpha$ ,  $\beta$ ,  $\pi^*$ , and  $E_{\text{T}}^{\text{N}}$  failed; scattered plots were obtained for correlation with  $E_{\text{T}}^{\text{N}}$  or various combinations of the other parameters. One of the possible reasons for the failure could be the effect of temperature on the polarity of ionic liquids. Unlike the commonly used organic solvents, the polarity of a very few ionic liquids is known to vary with



**FIGURE 8.** (a) Plot of  $(\ln k)_{\text{calcd}}$  against  $(\ln k)_{\text{exp}}$  for IMDA reaction of **1** in organic solvents, where  $(\ln k)_{\text{calcd}}$  is obtained by multiple linear regression of  $(\ln k)_{\text{exp}}$  with  $\alpha$  and  $\pi^*$ . (b) Plot of  $(\ln k')_{\text{calcd}}$  against  $(\ln k')_{\text{exp}}$  for IMDA reaction of **1** in ionic liquids, where  $(\ln k')_{\text{calcd}}$  is obtained by multiple linear regression of  $(\ln k')_{\text{exp}}$  with  $\alpha$ ,  $\beta$ , and  $\pi^*$ .

temperature.<sup>33</sup> All four parameters showed a small but consistent change in magnitude with changing temperature. Given the limited data available in literature, we measured the temperature-dependent polarity parameters of the ionic liquids in our laboratory for this purpose.<sup>34</sup> The rate constants failed to show a correlation even after the temperature effect was accounted for. Considering the fact that the rates were observed to be viscosity-dependent, this lack of correlation was not very surprising. When a process is dominated by one of the solvent parameters governing the reaction, the effect of other variables, though present, tends to get “masked”. In order to overcome this difficulty, the rate constant,  $k$ , for the reaction in ionic liquids was corrected for its viscosity dependence to give a modified rate constant,  $k'$ , as follows:

$$\ln k' = \ln B - a \ln \eta \quad (9)$$

The resulting  $\ln k'$  values were used for multiple linear regression analysis with the polarity parameters. A reasonably

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good fit was obtained for a combination of the  $\alpha$ ,  $\beta$ , and  $\pi^*$  parameters (Figure 8b).

$$\ln k'_{\text{calcd}} = 14.3584 + 1.11(\pm 0.43)\alpha + 10.35(\pm 3.33)\beta + 10.68(\pm 4.46)\pi^* \quad (r^2 = 0.894) \quad (10)$$

Interestingly, the contribution by  $\beta$  and  $\pi^*$  are dominant in affecting the rate of the reaction in ionic liquids, unlike the correlation in common organic solvents. The solvation of the substrate in organic solvents and ionic liquids, thus, appears to be very different. The magnitude of the coefficients also indicates a high degree of association between the substrate and the cations and/or anions of the ionic liquid. Although it is difficult to comment on the exact nature of the interactions, the results do provide a guide for further reasoning.

The most important consequence of the strong interaction between the ions of the ionic liquid and the reacting molecule is manifested in the form of the high microviscosity experienced by the molecule. This concept of microviscosity explains why the value of  $a$  is greater than unity. This is possible only when the actual friction experienced by the molecules is higher than the macroscopic observable viscosity. On the basis of the assumption of a strong interaction between the ions in the solvent medium and the reacting molecules, we can attempt to further elucidate the molecular level explanation for the experimental observations.

These results explain the anion specific viscosity dependence observed. The strength of the cation–anion interaction decreases from  $[\text{BF}_4]^-$  to  $[\text{NTf}_2]^-$ , i.e.,  $[\text{NTf}_2]^-$  is a weaker binding anion. The presence of  $[\text{NTf}_2]^-$  as a counterion entails a greater charge: radius ratio as compared to that for the  $[\text{BF}_4]^-$  anion. This would translate into a greater extent of bonding between the cation/anion and the substrate **1**. The substrate will experience a higher friction or microviscosity. This explains the nearly identical rate constants for the reactions carried out in  $[\text{NTf}_2]^-$  and  $[\text{BF}_4]^-$  based ionic liquids, even though the viscosity of  $[\text{NTf}_2]^-$  is much lower. In other words, changing the anion from  $[\text{BF}_4]^-$  to  $[\text{NTf}_2]^-$  decreases the bulk viscosity but fails to influence the microviscosity for the reactant.

The long chain alkyl substituent on the cation probably leads to steric hindrance for the rotational diffusion of the reactant. The effect is enhanced as a result of the microheterogeneous nature of the ionic liquids.<sup>35</sup> This means that apart from the directional coordination with the functional groups on the cation or anion, the substrate should be preferentially solvated by the nonpolar alkyl chains on the pyridinium cation. This may be another factor responsible for the greater friction experienced by the substrate. When the length of the alkyl substituent is increased from butyl to hexyl, the strength of coordination of the reactant with the cation should decrease, leading to lesser effective “electrostatic” friction felt by the molecule. Further increase in the chain length may be counter-productive since the crowded hydrocarbon environment in the solvation sphere causes an increase in the “mechanical” friction. The crowding of hydrocarbon entities decreases the probability of the crossover of the barrier by the transition state.

#### 4. Comparison with bimolecular Diels–Alder reactions

The analysis of the present results in terms of a theoretical model for the role of solvent viscosity is crucial, not only to understand the intramolecular processes but also because of its

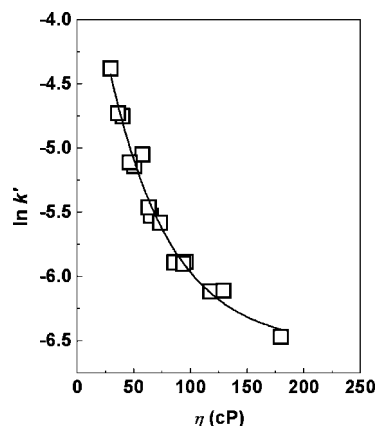
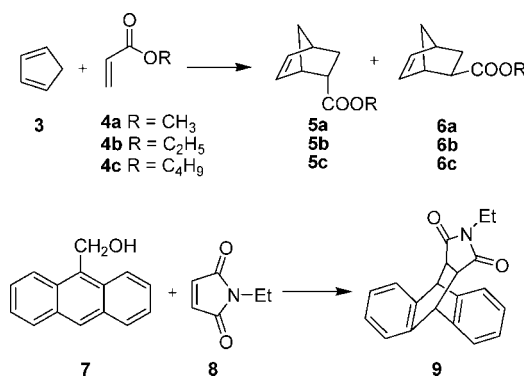


FIGURE 9. Plot of  $\ln k'$  (where  $k'$  is the pseudo-first-order rate constant for the Diels–Alder reaction of **7** with **8**) as a function of viscosity,  $\eta$ .

#### SCHEME 2



possible extension to the study of intermolecular processes. It would be interesting to extend the observations and the resulting theoretical models to the bimolecular Diels–Alder reactions.

A fundamental difference between the intramolecular and intermolecular processes is the form in which the solvent friction is manifested. The intramolecular Diels–Alder reaction of **1**, for example, experiences friction with the solvent molecules in the course of the rotational diffusion of the reacting moieties. The bimolecular process, on the other hand, can be visualized as a translational diffusion of the reactants to form an “encounter complex” and subsequent collisions of the molecules leading to the formation of the product. The frictional forces experienced in the course of translational diffusion need not be the same as those for rotational diffusion, particularly for microheterogeneous reaction media like ionic liquids.

Nevertheless, the bimolecular Diels–Alder reactions are also known to show similar trends in rates with variation in viscosity of ionic liquids. Kinetic studies for the reaction of cyclopentadiene (**3**) with different acrylates (**4a–c**) (Scheme 2) in a series of imidazolium-based ionic liquids showed a steep decrease in rates with increasing viscosity.<sup>6</sup> The decrease in rates was uniform despite the fact that different anions and alkyl-chain substituents were used for the study. Strikingly similar results were also obtained for the kinetic studies of the Diels–Alder reaction of anthracene-9-carbinol (**7**) with *N*-ethyl maleimide (**8**) carried out in a series of pyridinium ionic liquids (Figure 9). The viscosity dependence of the bimolecular Diels–Alder reaction of **3** with **4a** was previously reported.<sup>16</sup> However, the viscosity dependence of the intramolecular reaction of **1** in molecular solvents was not studied previously. The results from

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the kinetic investigations in the present work show that there is no correlation between the rates of cyclization of **1** in organic solvents with the viscosity of the solvents. This indicates that the low viscosity of these media is insufficient to translate into a frictional hindrance to the rotational diffusion motion. The frictional forces become effective only at higher viscosities, as seen in the ionic liquids. In contrast, the bimolecular Diels–Alder reactions show viscosity dependence at  $\eta$  values as low as 0.5 cP. It is worth mentioning that although the results prove that diffusion is a crucial factor in determining the magnitude of the observed rates in Diels–Alder reactions, these reactions cannot be termed as “diffusion-controlled” processes, since the rate of chemical conversion ( $k_{\text{intrinsic}}$ ) is comparable in magnitude to the rate of diffusion ( $k_{\text{diffusion}}$ ). The term “partial diffusion control” would be more appropriate for such processes. Further studies on the role of frictional forces for bimolecular processes are under investigation in our laboratory and will be reported in near future.

## 5. Conclusions

The present results provide conclusive evidence that the effect of friction, manifested as the microviscosity experienced by the reactants, is an important factor in controlling the rates for simple “activation-controlled” organic reactions. The data have been analyzed for the applicability of the Kramers model or its modifications. The failure of the current models emphasizes that microviscosity is the important factor in determining the kinetic profile of a reaction. The molecular level discussion on the origin of microviscosity effects on the rates of reactions in ionic liquids should be useful in guiding the course of future experiments.

An estimation of the microviscosity of the ionic liquids is crucial for further improvements in the experimental and theoretical studies. Apart from the viscosity, the microviscosity experienced by the molecules may vary with other characteristics of the solute–solvent interactions. The results underline the need to synthesize novel ionic liquids with lower viscosity as well as lower microviscosity. In our opinion, solvent friction and polarity parameters of ionic liquids may not be the only factors determining the kinetics of Diels–Alder reactions in ionic liquids. We are now aiming to study the possible contribution of other solvent properties of ionic liquids to the kinetic variations of organic reactions carried out in these media.

## 6. Experimental Section

**Synthesis of Ionic Liquids.** Pyridine, 3-picolene, and 4-picolene were distilled prior to their use.  $\text{NaBF}_4$  and  $\text{Li}(\text{NTf}_2)$  (>99.5%) were used as obtained, without further purification. The ionic liquids were synthesized according to the standard procedures<sup>36</sup> and

thoroughly dried over vacuum for 8–10 h at 70 °C. The purity of the resulting sample was confirmed using  $^1\text{H}$  NMR spectroscopy.

**Viscosity of Ionic Liquids.** The viscosity was measured using a cone and plate viscometer. The temperature was controlled using a constant temperature water bath with an accuracy of  $\pm 0.01$  °C. The viscosities thus measured were reproducible within  $\pm 3\%$ . The viscosity measurements were carried out with the same sample of ionic liquids as used for the kinetic runs and at the same temperatures, in order to eliminate undesirable discrepancies.

**Temperature-Dependent Polarity Measurements.** All of the dyes used for the measurements were of ultrahigh purity. The stock solution of the required dye was freshly prepared in dichloromethane prior to use. The stock solution was added dropwise to the ionic liquid, and the solvent was evaporated under vacuum. The ionic liquid was then transferred to the cuvette under nitrogen atmosphere and sealed with a septum.<sup>37</sup> The  $\lambda_{\text{max}}$  was measured at different temperatures using UV–visible spectrophotometer. The temperature of the cell was controlled using the single cell accessory having an accuracy of  $\pm 0.1$  °C.

**Kinetic Analysis.** The organic solvents used for the kinetic analysis were spectroscopy grade. The substrate was synthesized with a slight modification of the procedure reported (see Supporting Information for a detailed procedure and NMR spectrum of the substrate **1**). The purity of the substrate was confirmed using  $^1\text{H}$  NMR spectroscopy. The orange crystals of the substrate were stored at  $-20$  °C.

Next, 0.15 g (43.35  $\mu\text{mol}$ ) of the substrate **1** was dissolved in 10 mL of dichloromethane to prepare a 4.33 mM stock solution. Twenty microliters of the stock solution was added to 1 mL of the ionic liquid, and the dichloromethane was evaporated with vacuum to give a 0.08 mM solution of the substrate in the ionic liquid. The kinetic measurements were made using a UV–visible spectrophotometer. The decay of the absorbance at  $\lambda = 400$  nm due to the substrate **1** was monitored with respect to time in order to give the first order rate constant,  $k$ . The reported rate constants are an average of at least three kinetic runs on different samples and were reproducible within  $\pm 6\%$ .

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**Supporting Information Available:** Synthesis of the substrate **1**, spectroscopic data and a representative kinetic plot. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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