HOW DO IONIC LIQUIDS AND AQUEOUS MEDIA PROMOTE ORGANIC REACTIONS?

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BY

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FEBRUARY 2009

DECLARATION

I hereby declare that the work incorporated in the thesis entitled “**How do Ionic Liquids and Aqueous Media Promote Organic Reactions?**” submitted for the degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the Physical Chemistry Division, National Chemical Laboratory, Pune from August, 2004 to February, 2009 under the supervision of Dr. Anil Kumar (Research Guide). The work is original and has not, in full or in part, formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of higher learning. I further declare that the results presented in the thesis and the considerations made therein contribute to the advancement of knowledge in the field of Chemistry, in general and to the field of solvent effects, in particular.

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**How do Ionic Liquids and Aqueous Media Promote Organic Reactions?**" submitted by Ms. Shraeddha Tiwari for the degree of Doctor of Philosophy to the University of Pune, was carried out by the candidate under my supervision in Physical Chemistry Division, National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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Dedicated to

Dada, Amma, Mummy

and

the loving memory

of Pappa

Contents

Acknowledgements

> *"Gratitude is the least articulate of the emotions, especially when it is deep." - Felix Frankfurter*

Any human accomplishment is the culmination of numerous contributions and endeavors. The present thesis is no exception. I take this opportunity to thank the special people whose kind support was the reason I could complete the task with confidence.

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I conclude in complete agreement with J. F. Kennedy when he said that 'As we express our gratitude, we must never forget that the highest appreciation is not to utter words, but to live by them.'

Abstract

HOW DO IONIC LIQUIDS AND AQUEOUS MEDIA PROMOTE ORGANIC REACTIONS?

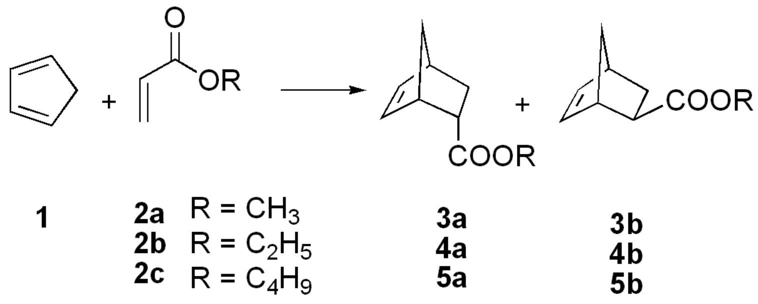
The present thesis is an attempt to understand the origin of the remarkable rate accelerations and enhanced stereoselectivities in water, aqueous salt solutions and ionic liquids. The results have been analyzed from a physical–organic perspective to delineate the contributions from the different solvent properties to the observed variations in reactivity and selectivity. The observations and the conclusions derived from such analyses have highlighted some important correlations between the physicochemical properties of the medium and the quantitative/qualitative outcome of the reactions. The thesis consists of six chapters.

A critical literature survey of the physical–organic studies on the solvent effects in carbon-carbon bond forming reactions, in particular the Diels–Alder reaction and the Wittig reaction, is described in **Chapter 1**. A brief introduction to the terminology of solvent effects is followed by the detailed discussion of the various methods used to study and quantify the solvent effects. The various aspects of hydrophobicity, including hydrogen-bonding and cohesive forces have been discussed. Particular attention has been paid to the length–scale dependence of hydrophobicity and the resulting thermodynamic signatures have been noted in brief. The history, evolution and the scope of applications of ionic liquids has been briefly reviewed. The current status of the molecular picture of ionic liquids is also discussed critically. The attempts to quantitatively study the influence of ionic liquids on the reactivity or selectivity have been discussed critically. The literature survey thus helped in identifying the potential areas of investigation which would lead to important and interesting outcomes.

The objectives of the planned research, based on the literature survey of the solvent effects, have been ennumerated in **Chapter 2**. The principal approach employed for studying the solvent effects has also been described in brief.

The role of solvent friction in determining the rate of organic reactions is the focus of the work described in **Chapter 3**. The chapter is further divided into three sections, on the basis of the reactions and the solvent media studied.

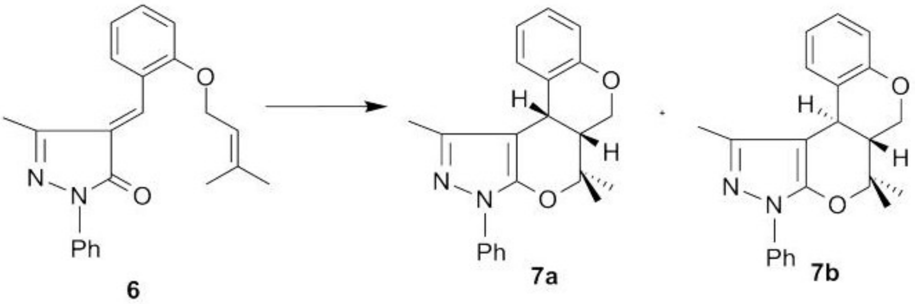
A comparative kinetic study of three simple Diels–Alder reactions involving cyclopentadiene **1** with methyl acrylate **2a**, ethyl acrylate **2b** and butyl acrylate **2c** both in water and imidazolium-based ionic liquids under identical conditions has been studied in **Section 3.1** (Scheme 1). The experimental data presented clear evidence that water can act as a more powerful solvent than the ionic liquids, as far as Diels–Alder reactions are concerned. This preliminary investigation suggested that the role of viscosity of the ionic liquids was crucial since the rate constants for all three reactions decreased with the increase in the viscosity of ionic liquids. Most importantly, the reults proved that water was definitely the solvent of choice for carrying out Diels–Alder reactions, as compared to ionic liquids.



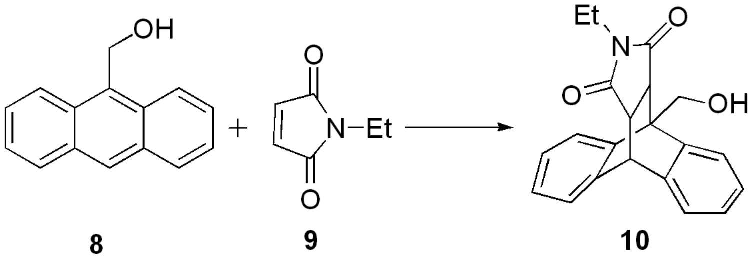
Scheme 1

The work presented in **Section 3.2** was aimed 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 (**6**) in a series of pyridinium - based ionic liquids (Scheme 2). The rates of the reaction decreased with the increasing viscosity of the ionic liquids. The lower viscosities of the bis(trifluoromethylsulfonyl)imide $[NTf_2]^-$ based ionic liquids as compared to those based on tetrafluoroborate $[BF_4]^-$ anion failed to induce a corresponding acceleration in the rates of the IMDA reaction. The results were analyzed on the basis of the current theoretical models and their failure to account for the observed trends was discussed in terms of 'effective' viscosity or microviscosity. As evident from the anionic effect, the solute–solvent specific interactions also played an important role in governing the kinetics of the reaction. These contradictory results indicated that solvent microviscosity, rather than the bulk macroscopic viscosity, should be the criteria for selecting the ionic liquids as reaction media.

The comparison of the effect of solvent friction on a bimolecular reaction with that on the intramolecular reaction was reported in **Section 3.3**. The bimolecular reaction chosen for the comparison was the Diels–Alder reaction of anthracene-9-carbinol (**8**) with *N*-ethyl maleimide (**9**) in a series of pyridinium-based ionic liquids (Scheme 3). The experimental results were compared with those predicted on the basis of the existing theoretical models.



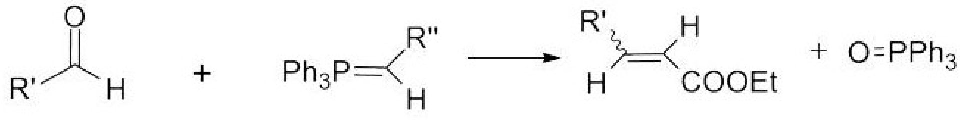
Scheme 2



Scheme 3

An unusual variation with temperature of the salt effects for "on water" Wittig reaction is discussed in **Chapter 4**, proving that hydrophobic acceleration of reactions comprising of "on water" reactants is fundamentally different from that for reactions with small non-polar solutes. The Wittig reactions of benzaldehyde (**11a**) and (carboethoxymethylene)triphenylphosphorane (**12**) were carried out in water and different aqueous salt solutions (Scheme 4). An optimum temperature of 338 K was chosen in addition to room temperature (298 K). The contrasting effect of salt additives on the rates observed in water and aqueous salt solutions could not be explained by an extension of current notion of "salting-out" and "salting-in" behaviour. The medium effects for "on water" reactions were then explained on the basis of such size-dependent hydration thermodynamics. The resultant salting effects on the kinetics of "on water" reactions differed significantly from those observed for homogeneous aqueous reactions. The temperature dependent studies were also carried out at different intermediate temperatures.

The kinetic evidence was supported by experiments with ylide samples having different surface areas and with polymer-bound ylides. The study brought out the need of modifying the conventional approach towards salting effects on hydrophobic hydration and organic reactions. The important conclusion drawn from the results was that rate acceleration by prohydrophobic additives in itself is not a sufficient evidence of the presence of a "hydrophobic effect" for a process/reaction occurring at a given length scale because the phenomenon of hydrophobic hydration itself is known to be length-scale dependent.



11a $R'=C_6H_5$
11b $R'=p\text{-}C_6H_4\text{-}NO_2$
11c $R'=p\text{-}C_6H_4\text{-}OCH_3$
11d $R'=CH_2CH_2CH_3$
11e $R'=C_4H_3O$

12a R''=COOEt
12b R''=CN

13a-e R''=COOEt
14a-e R''=CN

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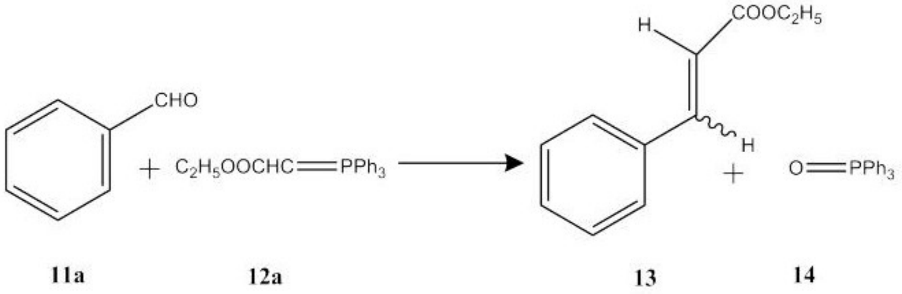
Scheme 4

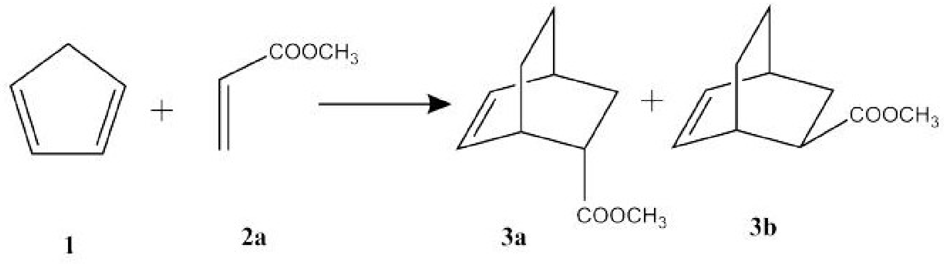
The study of how addition of increasing amounts of a cosolvent affects the reactivity and selectivity of C–C bond-forming reactions carried out in aqueous suspensions is reported in **Chapter 5**. Two important reactions were studied — the Wittig reaction of **11a** with **12** (Scheme 5) and the Diels–Alder cycloaddition of **1** with **2a** (Scheme 6). The solvent composition was varied from that of pure water to pure organic cosolvent composition. The presence of cosolvent altered the "local" solute- solvent interactions, while gradually leading to "homogenization" of the reaction medium. The systematic kinetic investigation served as a benchmark for testing the prevalent understanding of "on water" mechanism. A simple model was set up as a guiding framework to compare the experimental results. The model was then used to bridge the localized kinetic mechanism with the macroscopic picture of solvent properties and thus enabled a discussion of the experimental observations on the reactivity/selectivity with reference to changing composition of the reaction medium. The possibility of employing bulk solvent parameters to identify the dominating interactions determining interfacial reactivity and selectivity was also briefly explored.

The apparent *pseudo*-first order rate constants, k_{app}, for the Wittig reaction of **11a** with **12** plotted as a function of the solvent composition for the reaction carried out in water + 1-propanol mixtures at different temperatures showed a sharp increase when a small amount of 1-propanol was added initially. Interestingly, the rates thus reached a maximum before decreasing with further addition of the cosolvent. The sensitivity of the k_{app} to the composition of the medium increased with increasing temperature.

A similar behaviour was also observed for the Diels–Alder cycloaddition reaction of **1** with **2a** studied in water–methanol mixtures at 298 K. The rate constants increased initially with the addition of methanol. However, further increase in the amount of methanol led to a decrease in the apparent rate of the reaction.



Scheme 5



Scheme 6

The variation in the *endo*/*exo* selectivity for the reaction of **1** with **2a** was also examined in a number of water–organic cosolvent binary mixtures. The results indicated that k_{endo} (the rate of formation of the *endo* isomer) is more sensitive to the change in solvent composition as compared to the k_{exo} (the rate of formation of the *exo* isomer). The change in stereoselectivity observed results from a greater stabilization of the *endo* transition state.

The results and principal conclusions of the research work are summarized in **Chapter 6**, along with an examination of the future prospects of the studies.

Principal conclusions and significance:

The following are the significant contributions from the present work:

1. The superiority of the "universal solvent" water over ionic liquids was experimentally demonstrated for the first time. This observation was ascribed to the high viscosity of ionic liquids as compared to water.
2. The studies for the intra- and bimolecular reactions in ionic liquids have brought out the importance of microviscosity as a true indicator of the solvent friction experienced by a reactant in an ionic liquid.
3. The anomalous temperature dependence of the salting effects indicated the importance of the length-scale dependence of the hydrophobicity.
4. In addition, the possibility of employing cosolvents to enhance the reactivity and selectivity for heterogeneous reactions was also explored.

The work assumes special significance due to the emphasis on environmentally benign solvent systems. The attempt to address the shortcomings of the potential alternatives like ionic liquids for use as solvent systems is bound to lead to substantial developments in solvent designing.

List of Abbreviations*

[BMIM]	1-butyl-3-methyl imidazolium
[EMIM]	1-ethyl-3-methyl imidazolium
[OMIM]	1-octyl-3-methyl imidazolium
[BP]	1-butyl pyridinium
[HP]	1-hexyl pyridinium
[OP]	1-octyl pyridinium
[3MBP]	1-butyl-3-methyl pyridinium
[3MHP]	1-hexyl-3-methyl pyridinium
[3MOP]	1-octyl-3-methyl pyridinium
[4MBP]	1-butyl-4-methyl pyridinium
[BF_4]	tetrafluoroborate
[NTf_2]	bis(trifluoromethylsulphonyl)imide
[PF_6]	hexafluorophosphate
AAKT	Abboud-Abraham-Kamlet-Taft model
ced	cohesive energy density
DCM	dichloromethane
DMSO	dimethyl sulphoxide
IMDA	intramolecular Diels–Alder reaction
LFER	linear free energy relationship
MC	Monte Carlo simulation
MM	molecular mechanics simulation
SFG	sum frequency generation spectroscopy
THF	tetrahydrofuran
TST	transition state theory
VSFS	vibrational sum frequency spectroscopy

(*common abbreviations only)

List of Symbols[†]

α	hydrogen-bond donor acidity
β	hydrogen-bond acceptor basicity
δ	Hildebrand solubility parameter
ϵ	dielectric constant
η	viscosity of a fluid
λ	wavelength
π^*	solvent polarizability parameter
Π	interfacial pressure

A	absorbance
E_a	energy of activation of a reaction
E_η	activation energy for viscos flow
$E_{\mathrm{T}}^{\mathrm{N}}$	normalised Dimroth's E_{T} scale based on Reichardt's dye
ΔG_{solv}	free energy of solvation
$\Delta G^{\ddagger}$	free energy of activation
k	rate constant
k_2	second-order rate constant
k_{app}	apparent rate constant
k_{homo}	rate constant in a homogeneous bulk
$k_{interface}$	rate constant at an interface
$k_{intrinsic}$	intrinsic rate constant
k_{rel}	relative rate constant
k^*	reduced rate constant
k'	*pseudo*-first order rate constant
K	equilibrium constant
P_i	internal pressure of a liquid
S/S_0	relative solubility of a solute
Sp	solvophobicity parameter
t	time
T	temperature

([†]common symbols only)

1

Introduction

"...the development of our knowledge of solutions reflects to some extent the development of chemistry itself"[1]

A comprehensive literature survey of the study of solvent effects is examined in the present chapter. A discussion of the relevance of the subject area, with special emphasis on the study of the 'green' solvent systems like water, aqueous mixtures and ionic liquids is followed by the brief definitions of terminology used for describing the solvent effects. The various methods employed to study the solvent effect like modeling with empirical parameters, computational approaches, experimental studies, etc. are discussed. The potential areas for further investigations, with special reference to the Diels–Alder reaction and Wittig reaction have been emphasized.

1.1 The quest for the “ideal solvent”

The study of solvents, solutions and solvent effects has indeed been one of the oldest fascinations for mankind. The alchemists in the medieval ages were infamous for their obsession for the “menstruum universale” (the universal solvent) or the “Alkahest”. The alkahest did not materialize but the experiments led to the discovery of the earliest rule of “like dissolves like”. The science of chemistry has come a long way from the days of alchemy. The quest for the perfect solvent persists, *albeit* in a very different form. One of the prime concerns for a modern chemist is the designing of the “ideal” solvents or solvent systems as reaction media, which fulfill the desired standards of efficiency and economy. A third and equally important criterion of ‘environmental safety’ for selecting the solvents as reaction media is fast emerging and with good reasons, too.

Water and aqueous systems were the only solvents known to man for centuries. Then ancient civilizations discovered the methods of producing ethanol by fermenting grapes or sugar cane. Rapid developments in the area of organic solvents took place only in the later half of the 20th century, after the discovery of the petroleum refining process. Large-scale industrialization ensured that the organic solvents like alcohols, hydrocarbons, ketones etc. were produced in huge quantities in a cost effective manner and their application grew in both, the developed and the developing economies. Reports on toxicity soon followed in the 1920s after the introduction of chlorinated solvents. Nevertheless, the popularity of organic solvents continued to increase. According to an estimate by National Institute for Occupational Safety and Health (NIOSH), 22 million kg of organic solvents were produced in the United States in 1984.[2] Although an accurate figure is not available, estimates show that the total environmental release of five organic solvents (methanol, toluene, styrene, n-hexane and xylene) in 2007 was approximately 166,292,627 kg in the United States alone. Table 1.1 lists the estimated air emission of the 10 most commonly used volatile solvents in the United States in 2007-08, based on the toxicity release index (TRI) supplied by the industries. It also provides the estimated contribution from the chemical industry and it’s ranking as compared to the other industries.[3]

It is hardly surprising to see that the chemical and allied industries are among the leading contributors of organic pollutants among the industrial sectors. Ad-

Table 1.1: Estimated annual emissions of the volatile organic solvents in the air and the contribution from the chemical industry in USA for 2007-08.

Solvents	Estimated annual emissions(kg)		Chemical and allied industries' ranking
	Total	Chemical and allied industries	
Methanol	66,360,751	11,055,477	2
Toluene	28,823,337	4,046,006	3
Styrene	21,454,795	1,370,182	3
Hexane	20,279,180	4,127,340	2
Xylene	19,157,876	1,730,631	4
Carbondisulphide	13,492,823	9,418,850	1
Butanone	7,12,184,587	1,111,163	3
n-butyl alcohol	7,480,386	597,243	6
Acetaldehyde	58,09,320	808,398	3
Dichloromethane	5,025,624	2,323,008	1

ditionally, the E-factor rating of the fine chemicals industry is much higher than that of the bulk chemicals industry.[4] Due to the realization of the alarming hazards, the emphasis has shifted to the substitution of organic solvents by "green solvents" like water and aqueous media, ionic liquids, supercritical fluids, fluorous biphasic media, polyethylene glycol, etc. in the synthetic processes. Any such solvent substitution, however, should have to be based on thorough studies related to efficiency (in terms of effect of solvent on the yield and selectivity of the process) and economy (in terms of cost effective solvent systems and related technology). Hence, the study of solvent effects on organic reactions, particularly for the "green" solvents, has assumed great importance.

This thesis is an effort to understand the solvent effects of the "green" reaction media, namely ionic liquids and aqueous solutions from a physical-organic perspective. Knowledge of the solute–solvent interactions in these interesting and environment–friendly media will contribute in designing better solvents giving better yields and higher selectivities without compromising the interests of our environment. It is, thus, an endeavor towards the goal 'benign by design' embodied in the twelve principles of "green chemistry".[5]

The present chapter aims to define the important terms, outline the experimental and theoretical framework available for the study of solvent effects and briefly review the current literature related to physical-organic chemistry of ionic liquids and aqueous media. The chapter will conclude with a brief discussion on the solvent effects studied for the Diels–Alder and Wittig reactions — the two important C–C bond forming reactions which have been studied throughout the present work.

1.2 Definitions of solvation and solvent effect

Berthelot and Péan de Saint-Gilles made one of the earliest observations of solvent effect on the rates of esterification of acetic acid with ethanol in 1862.[6] However, the general realization of significance of the solute–solvent interactions in determining the course of a reaction came in the later half of the 20th century.[7,8] "Solvation" is the formation of a solvent shell — of tightly bound solvent molecules — around the solute molecule or ion as a result of the intermolecular forces between solute and solvent.[1]

The term "solvent effect" encompasses a broad spectrum of solute–solvent interactions and the resulting manifestations on chemical processes. Conventionally, the focus was on modeling the solvent effects in terms of dielectric constants, diffusion and cohesion parameters. It is now evident that the other properties like acidity, basicity, hydrogen bonding, polarity and specific solvation interactions cannot be ignored.[8] Not all of these factors can be subjected, at our present level of understanding and computational capacity, to a rigorous theoretical treatment. Some of these factors are subject to theoretical explanation, but even when theoretically explained or mathematically formulated, they may not be sufficiently dominant to justify the application of theory. Other effects like the polarity effects are generally discussed on the basis of empirical correlations that are widely applicable. Despite numerous breakthroughs, many aspects of solvent effects like microviscosity, microscopic dielectric constant, preferential solvation, etc. still demand further exploration.

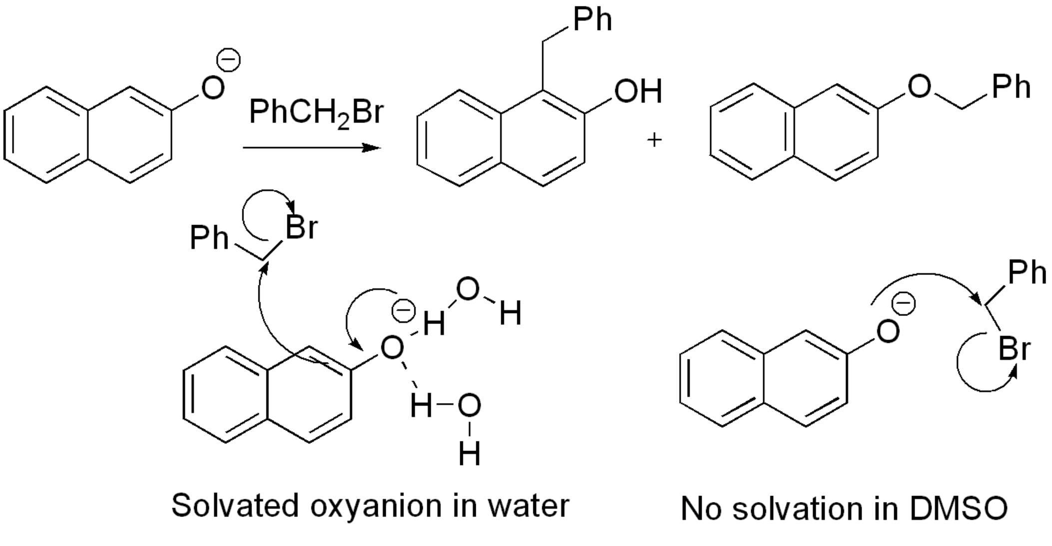
1.3 Origin of solvent effect

The key to understanding the origin of solvent effects on chemical equilibria and reactions is to separate the static and dynamic solute–solvent interactions.[9] The terms 'equilibrium' and 'nonequilibrim' interactions are often used for them, but this terminology will be avoided for the sake of clarity. The static solute–solvent interactions encompass electrostatic interactions as well as intermolecular van-der-Waals forces[10] by virtue of which the solvent can affect the energy of the solute species. The important contributions to the intermolecular solute–solvent forces arise from dipole-dipole interactions, induction forces, dispersion forces, hydrogen bonding, electron donor–electron acceptor interactions and solvophobic interaction (i.e. the aggregation of solute molecules with the expulsion of solvent molecules as a result of thermodynamically unfavorable solute–solvent energetics).[11] The term — solvophobic interaction, when applied in context of nonpolar solutes in water, is known as hydrophobic interaction.

The interactions like induction and dispersion forces are non-specific and cannot be completely saturated, while those like hydrogen bonding and electron donor–electron acceptor pair are specific and highly directional in nature. The sum of all the aforementioned interactions possible between a given solvent and the solute molecules is termed as *polarity* of the solvent. The polarity of a solvent represents its overall solvating ability. As a result of the failure of any individual physical parameter to successfully describe polarity in quantitative terms, it is often defined in terms of empirical parameters. Some examples of such empirical scales include the α-scale of hydrogen-bond donor acidity, the β-scale of hydrogen-bond acceptor basicities, the π^*-scale for polarizability, Dimroth's $E_{\mathrm{T}}^{\mathrm{N}}$ scale etc.[12]

In addition to such static solute–solvent forces, it is also important to consider the dynamical influence of the condensed phase when dynamical processes such as chemical reactions are being studied. Such dynamical influences come to the fore when the solvent molecules are capable of participating in the reaction as a reactant or a catalyst. An interesting manifestation of dynamical influences is the "solvent cage effect".[13] For very fast reactions (energy of activation, $E_a < 20$ kJ/mol), the diffusion of the reactants through the solvent (activation energy for viscos flow, $E_\eta >$20 kJ/mol, which is related to the rate of diffusion) becomes the rate determining step and such reactions are known as "diffusion-controlled" reactions. In such cases, the reactants undergo several collisions before they separate — thus appearing to be engulfed by a cage of solvent molecules. Solvent cage effects have been observed for radical reactions, electron transport reactions and ion molecules recombination reactions, etc.[14] Kochi demonstrated that the solvent cage effect was related to the viscosity of the solvent,[15] *albeit* in a complicated manner; while Martin et al. could correlate the cage effect to the internal pressure (P_i) and cohesive energy density (*ced*) of the solvent.[16]

The dynamical effect of solvent friction or viscosity is not limited to the rates of very fast reactions alone. The viscosity of the solvents also affects the kinetics of the slower reactions having a considerable activation barrier. For example, many bimolecular processes like photocyclization reaction, cycloaddition reactions, protein-ligand binding reactions and even unimolecular reactions like isomerization and conformational transitions of polymers have been studied for their viscosity dependence.[17]



Scheme 1.1:

As a result of the variety of solute–solvent interactions possible, the solvent can influence a system in numerous ways simultaneously. The choice of solvent can have a dramatic influence on the positions of chemical equilibria, on the rates and stereoselectivties of reactions and even in some rare cases, on the mechanism of the reaction. An interesting example is provided by the reaction of the oxyanion with benzyl bromide to give a substituted naphthol as the major product when water is used as the solvent (Scheme 1.1).[18] This is because solvation of the oxyanion by the water molecules through hydrogen-bonding prevents the direct attack from the O atom site. The use of dimethyl sulfoxide (DMSO) as a solvent, however, prevents the formation of the hydrogen bonds leading to the formation of ether as the major product.

Numerous examples of drastic solvent effects on chemical equilibria, rates, selectivities and mechanisms of reactions are well documented in literature.[1,7,8,19]

1.4 Thermodynamic representation of solvent effects

An appropriate and widely applicable system of notations is required to assess the solvent effects on varied chemical processes in a quantitative manner. Adopting the thermodynamic formalism involving the free energy criterion facilitated a more quantitative approach.

The effect of a solvent on the position of a chemical equilibrium can thus be expressed in terms of the change in the free energy of solvation (ΔG_{solv}). The influence of a solvent on the rate and/or selectivity of a chemical reaction is similarly represented by the thermodynamic formalism of the Transition State Theory (TST) in condensed phases.[20] The difference in rates of a reaction between a pair of solvents is quantified in terms of contribution of solvation free energy to the free energy of activation ($\Delta G^{\ddagger}$). The calculation of solvent effects on a reaction ($A + B \longrightarrow AB^{\ddagger} \longrightarrow C + D$) is essentially reduced to the calculation of the difference between the differential solvation of the activated complex ($AB^{\ddagger}$) and the initial reactants.

$$\begin{aligned} \ln k - \ln k_0 &= \frac{1}{RT}(\Delta\Delta G^{\ddagger}) && (1.1) \\ \ln k &= \ln k_0 + \frac{1}{RT}(\Delta G_{A,solv} + \Delta G_{B,solv} - \Delta G_{AB^{\ddagger},solv}) && (1.2) \end{aligned}$$

where k_0 is the rate constant of the reaction in a standard solvent or gas phase, while k is the rate constant in the solvent under consideration.

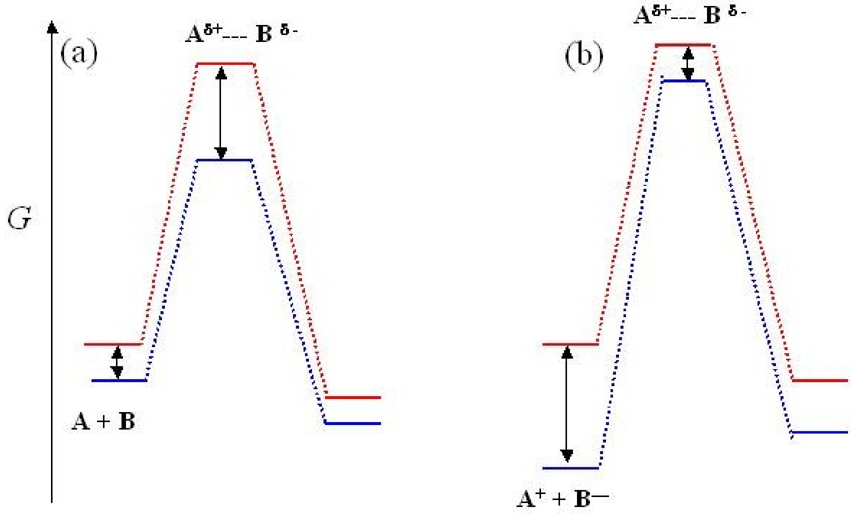


Figure 1.1: Thermodynamic formalism of the relative stabilization of the initial and transition state on going from a nonpolar solvent (red lines) to a polar solvent (blue lines) in the reactions representing (a) reaction with separation of charges in the transition state, increase in rate with increasing solvent polarity and (b) reaction with destruction of charge in transition state, decrease in rate with increasing solvent polarity.

1.5 Modeling solvent effects

A quantitative allowance for the solvent effect on the rate constants k for elementary reactions consists in establishing the following functions:

$$k = f(a, b, c, \dots m, n, o \dots)$$

where a, b and c are the parameters characterizing the properties of the reactants and m, n, and o are the parameters characterizing the properties of the medium. If all possible solute-solvent interactions are taken into account, then attempts to correlate and predict the rate constant with the medium will tend to lead to such complicated results that experimental verification is impossible. Therefore, equations correlating rate constants with medium properties are usually derived from more or less theoretically justified models. Consequently, the modeling of solvent effects has resulted from two different approaches to the problem: the empirical approach and the theoretical approach. The theoretical approach relies on the guidelines provided by broad principles from which detailed properties of matter may be computed. The method is thorough but the limited computational prowess tends to limit the general applicability of such studies at present. The empirical approach, on the other hand, relies on experimental generalizations and approximations to rationalize the solvent effects. Such methods have a wide applicability but they lack the insight offered through rigorous calculations.

1.5.1 Modeling with physical properties of solvent

The earliest attempts to devise a general model for solvent effects were made by Hughes and Ingold based on purely electrostatic interactions between the solute and the solvent molecules.[21] The model classifies the solvent effects on different reactions in terms of the charge on the reaction species and the extent of solvation expected for these reaction species. These approaches lacked the general applicability in that they could be applied to explain the solvent effects on a range of reactions. Some of the most general empirical correlations involving the influence of solvents on the rates of reactions are often based on the linear free energy relationships(LFER).[22] The LFERs are "extrathermodynamic" relationships, which lack the rigor of thermodynamics but provide information that would be inaccessible otherwise. Alternatively, LFERs can be defined as the substituent/solvent parameters obtained from the substituent/solvent dependent processes.[1] For example, Hammett proposed an equation to account for the substituent effect on the rate or equilibrium constant of a general reaction for a number of a class of aromatic compounds.[23] Hammett then expressed the reaction constant, ρ as a function of the dielectric constant, ϵ of the medium in order to reflect its solvent dependence. Hine has observed that ρ commonly increases with decrease in ion–solvating power and dielectric constant of the medium.[24] Taft's ρ^* parameter and Grunwald and Winstein's "ionizing power" Y are a few more examples where LFERs were used as a measure of solvent effects.[25]

In order to explain the role of cohesion of the solvent molecules in determining the kinetic profile of a given reaction, Richardson and Soper proposed the empirical generalization that solvents of high cohesion accelerate reactions in which the products are substances of higher cohesion than the reactants.[26] Internal pressure has been used to analyze the rate data for racemization of optically active 1,1'-binaphthyl in various organic solvents.[27] The rate constants for the racemization of 1,1'-binaphthyl were analyzed in terms of the Hildebrand solubility parameter, δ. The authors assumed that the *ced* of the solvent was equivalent to its P_i and compared the rates of racemization with *ced* of the solvent. The conformational equilibria of 4,4-dimethyl-2-silapentane and 2,3-dimethyl-2-silabutane has been investigated within the framework of internal pressure to suggest that P_i increases the population of gauche-butane conformations with respect to *trans*-butane conformations.[28]

1.5.2 Modeling with empirical properties of solvent

Since the polarity of a solvent is too complicated to be expressed in terms of a single property, chemists have resorted to the use of empirical polarity based on properly selected model processes. Most popular polarity scales are based on spectroscopic properties, chemical equilibria or kinetic measurements.[29] For example, Grunwald and Winstein[25] studied the solvolysis reactions following the SN_1 mechanism in different solvents in order to establish a correlation with the "ionizing power" of the solvent, which is one of the oldest scales of polarity.

Since the solvent polarity scale is based on a selected process, it is not universal. Satisfactory correlations can only be expected for solvent effects on processes closely related to those used to define the polarity scale. In addition, it is not always clear which of the many types of solute–solvent interactions is expressed by a certain parameter. In order to circumvent this problem, models like the Abboud - Abraham - Kamlet - Taft (AAKT) model,[30] based on multiparameter linear regression analysis were devised. However, the theoretical background and predictive capability of such approaches is difficult to justify.

1.5.3 Computational modeling

In order to calculate the static influence of the condensed phase, the free energy of solvation of a rigid solute complex is computed from model solute–solvent and solvent–solvent potentials using classical ensemble averaging and/or statistical perturbation theory, which is then added to the gas-phase potential energy profile obtained from electronic structure calculations.[31] Alternatively, the solvent can be modeled as a three dimensional continuum, where the electrostatic equations are treated by solving the Poisson equation for a dielectric medium.[32]

The continuum solvation models have been applied for the dynamic effects of the medium.[33] In some reports, the solvent molecules are treated explicitly and their motion included in the reaction coordinate.[34] Such models are appropriate for describing the caging effect or systems where the solvent itself is the reactant or the catalyst. However, it is difficult to model collective long-range dynamic effects (such as effects of solvent viscosity or long-range electric polarization of the solvent dielectric) by explicit few body methods because of the large size of the system required. The method of reduced dimensionality, based on an original contribution by Kramers,[35] is the most widely accepted tool for such problems.

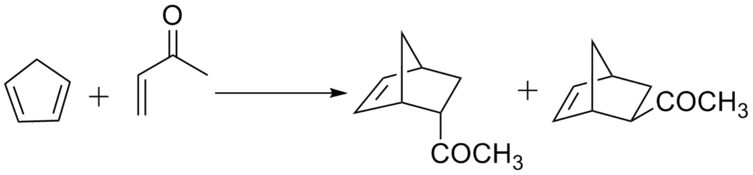
In the Kramers approach, the reaction is treated in terms of a single reaction coordinate while the rest of the system is treated as a bath. Grote–Hynes retained the one-dimensional reaction coordinate while obtaining a more general result for the transmission coefficient via a more realistic treatment of the bath using a generalized Langevin equation.[36] The approach confirms the fact that “friction/microscopic viscosity” and “nonequilibrium solvation” are equivalent in nature. The Kramers theory and its modifications have been tested for numerous systems of reactions.[37] Marcus focused on solvent reorganization as the rate limiting process in the electron transfer reactions and accordingly treated it as a reaction coordinate.[38] The experimental verification of the computational models is difficult, since it is hard to manipulate the experimental conditions so as to change only one solvent parameter.

1.6 Solvent effects in “green” solvents

1.6.1 Water and aqueous solutions

Water is rightly known as the “matrix of life”.[39] In its many different functions, water is essential to the life on earth, as we know it. It is the medium of cells and is essential for the structure of proteins, cell membranes and DNA. Apart from its central role in biological systems, water is also one of the most intriguing solvents. The deceptively simple molecular structure of water embodies a complicated and elusive three-dimensional structure and intermolecular interactions, which means that many characteristic properties of water are poorly understood.

One of the most striking and relevant examples regarding the effect of water on the rates of Diels–Alder reactions was observed by Breslow and coworkers.[40] The Diels–Alder reaction between cyclopentadiene and butenone (Scheme 1.2) showed a 700-fold increase in rate when carried out in water as compared to 2,2,4-trimethylpentane. The observation led to resurgence in the popularity of water and aqueous systems as reaction media and generated considerable interest into the physicochemical aspects of the phenomenon of "hydrophobic effect".[41]



Scheme 1.2:

An increasing number of investigations related to synthesis in aqueous media have been reported water-induced acceleration for a variety of reactions including allylation reactions, the aldol condensation, the Michael addition, the Mannich reaction, Grignard-type additions and the benzoin condensation.[42] A more detailed overview of synthetic organic chemistry in water is given in the recent review articles[43] and textbooks by Grieco[44] and Li.[45] Not only does water provide excellent chelation control, but also unique solvating properties that make it a promising reaction medium for stereoselective reactions.

The most commonly invoked explanations for the dramatic rate acceleration induced by aqueous media include the terms like "hydrophobic effect", "hydrophobic hydration" and "enforced hydrophobic hydration". The terms are often, loosely defined. Dill recommends the operational definition of hydrophobic effect, which refers to "transfers of nonpolar solutes into aqueous solution when particular characteristic temperature dependence is observed".[46] The characteristic temperature dependence of hydration of nonpolar solutes, as observed by Butler,[47] is entropy-driven at 298 K. However, the large positive change in heat capacity with temperature implies that the process becomes increasingly enthalpy dominated at higher temperatures. The behavior is typical of water and distinguishes it from other organic solvents. Since the definition is primarily an operational one, it does not reveal any information on the molecular origin of the effect. In fact, the molecular forces responsible for the hydrophobic effect have been the subject of numerous experimental and theoretical studies.[48] Hydrophobic hydration, on the other hand, refers to the "the process of cavity formation in liquid water, the insertion of an apolar solute particle, the onset of solute-solvent interactions, and the concomitant reordering of the water molecules in close proximity to the solute".

Frank and Evans provided one of earliest molecular pictures for the hydrophobic hydration through their "iceberg model", which postulates a quasi-solid ordering of water molecules around a nonpolar solute.[49] Numerous theoretical studies have been attempted to explain all the anomalous properties of water, an exhaustive account of which would not be possible here. However the theoretical studies can be classified broadly as follows:

- Models focused on computation of the thermodynamic properties like the mixture models,[50] liquid hydrocarbon model,[51] compensation model,[52] etc.
- Models based on statistical thermodynamics - describing hydrophobic hydration in terms of radial distribution of water molecules. The virial coefficients required for the purpose were estimated using semi-empirical approaches like the Savage and Wood model[53] of pairwise additivity of functional group interactions or statistical mechanical approaches like the interaction site approach adopted by Pratt and Chandler.[54]
- Models based on scaled particle theory e.g. the model by Stillinger,[55] which incorporated the strongly directional nature of water–water interactions.
- Computational studies based on Monte Carlo (MC) or Molecular Mechanics (MM) simulations. These employ semi-empirical potential models for liquid water such as the simple point charge (SPC) model[56] and the transferable intermolecular potential functions (TIPS/TIPS2/TIP4P).[57]

The problem of the "structure of water" and its manifestation into the hydrophobic phenomena is still far from being solved. Different structural features are implicated to explain the typical physical properties of water as a solvent.

Basically, the highly structured molecular arrangement (due to the hydrogen bonding network) and the high cohesive energy are believed to be responsible for the hydrophobicity. In addition, the small size of an individual water molecule is believed to exaggerate the characteristic change in the entropy due the excluded volume effect. Recent computational studies have unearthed additional peculiarities of water that demand further investigation. The length-scale dependence of hydrophobicity, for example, was first predicted by Stillinger[55] but its plausibility was demonstrated only recently by the Lum-Chandler-Weeks(LCW) model. [58] The complete implications of the characteristic "dewetting" thermodynamics have yet to be explored.[59]

The experimental techniques required to provide crucial data substantiating the theoretical calculations are rapidly evolving. The structure of water and aqueous solutions has been probed in the bulk and at the interface using techniques like NMR studies, IR studies, Raman spectroscopy, ultrasound spectroscopy, vibrational sum frequency spectroscopy (VSFS) experiments etc.[60] For example, comparison between the hydrophobic interactions expressed in H_2O *vs.* D_2O is another experimental tool to understand the phenomenon.[61] The recent studies from Poynor and from Mezger et al. have provided irrefutable evidence for the "dewetting" behavior at mesoscopic sufaces.[62]

The complexity of the quantitative description and experimental verification of hydrophobic effects is reflected in the physical-organic studies of reactions carried out in water and aqueous systems. It is extremely difficult to delineate the different types of solvent interactions (hydrogen bonding, *ced* or dipole–dipole interactions) and the extent of their contribution to affect the rates or stereoselectivity. Nevertheless the effect of the aqueous medium is too dramatic to be ignored.[40] Hence, chemical reactivity has been used as a tool to study hydrophobic interactions.[63] In a complementary approach, the study of hydrophobic effects on a reaction is used as a mechanistic tool to determine the transition state geometries.[64] In either case, prohydrophobic and antihydrophobic additives like salts and cosolvents were utilized to modify the hydrophobic interactions.

Engberts and coworkers have studied the kinetics of a number of organic and inorganic 'probe' reactions. In one instance, the Kirkwood-Buff integrals derived from the kinetic studies of hydrolysis of 4-methoxyphenyl-2,2-dichloropropionate and for the alkaline hydrolysis of $[Fe(MeN{=}CHCH{=}NMe)p]^{2+}$, a low-spin iron(II) complex in water + 2-methyl-2-propanol (*t*-butyl alcohol) mixtures, were used to describe the preferential solvation of nonpolar solutes in the mixed aqueous systems.[65] The emerging structural model indicated that addition of a small amount of cosolvent initially leads to an increase in the strength of water–water interaction, while the composition of the solute solvation sphere becomes identical to that of the bulk solvent beyond a particular mole fraction of the cosolvent.

Breslow and coworkers used the effect phenol substituents and of antihydrophobic cosolvents (ethanol and DMSO) on the rates of the competing C- and O- alkylation processes to distinguish hydrophobic effects from other effects on these reactions, and to confirm the suggested transition states for phenoxide alkylations at oxygen and at carbon.[66] The *para* C-alkylation is slowed by the addition of cosolvents while rate of O-alkylation increases on addition of 20% DMSO. The results indicate that in water the C-alkylation involves a transition state with hydrophobic packing of the benzyl group onto the phenol ring. No *para* alkylation was observed for unsubstituted phenoxide as opposed to all of the alkyl substituted phenoxides, attributed to the packing of alkyl substituents against the aromatic ring of a benzylic electrophile. The results also indicated that O-alkylation uses the *n* electrons of the phenoxide oxygen as the nucleophile and does not have hydrophobic overlap in the transition state.

The "on water" protocol developed by Sharpless and coworkers has unlocked greater possibilities for the utilization of aqueous mixtures as reaction media.[67] (The term "reaction medium" is deemed more accurate in this context given the limited solubility of the reactants in the aqueous phase throughout the reaction.) The heterogeneity of the aqueous reaction medium was shown to be the driving force behind the reactions, rather than retarding them. The breakthrough was instrumental in disproving the major inhibition among the organic chemists regarding the insolubility of most substrates in water. Despite the fact that numerous workers have exploited the methodology with excellent results since the first report about the "on water" acceleration of organic reactions appeared in 2005,[68] very little is known about the mechanism of such rate accelerations induced by the aqueous–organic interface. Jung and Marcus proposed that the rate accelerations observed at the interface were due to the 'dangling OH group' capable of stabilizing the transition state of a reaction.[69] Such coordination was absent in completely homogeneous medium where the hydrating water molecules tried to retain their hydrogen-bonding network.

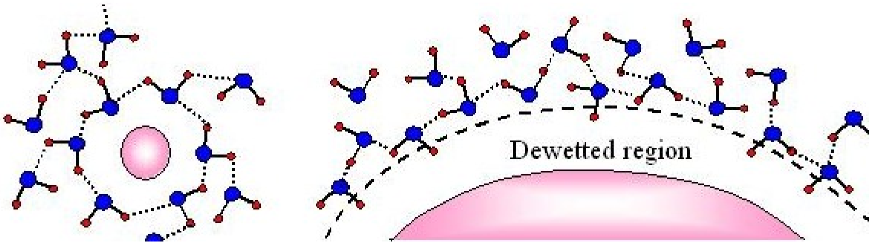
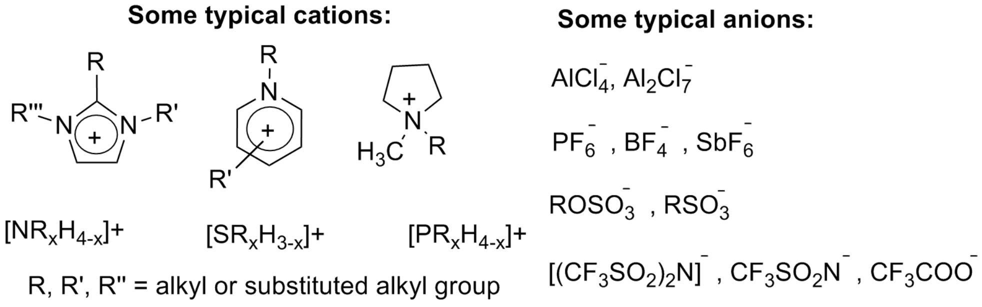


Figure 1.2: Schematic representation of the hydration of a) a small nonpolar molecule (with the retention of hydrogen bonded network around the solute), b) a mesoscopic surface with a dewetted region and dangling 'OH' bonds around the surface.

Further research related to the study of hydrophobic interactions and "on water" conditions is required for facilitating the design of substrates, catalysts and reaction conditions to fully exploit the potential of water and the aqueous mixtures as reaction media.

1.6.2 Ionic liquids

Ionic liquids are a class of "neoteric solvents" which are defined as ionic salts composed of an organic cation and an organic/inorganic anion and which exist in the liquid state below 100 °C.[70] These novel class of solvents have also been described as liquid compounds that display ionic–covalent crystalline structure. [71] Ionic liquids are thought to be promising alternatives to organic solvents due to their nonvolatlity, nonflammability, thermal and electrochemical stability and flexible miscibility. Apart from being employed as solvents for organic and bioorganic reactions,[72,73] these compounds have been used as catalysts,[74] cocatalysts, [75] ligand sources[76] and as supports for catalytic reactions.[77] The unlimited flexibility of manipulating the properties by changing the cation and anion is an added advantage not available in any other class of solvents.[78] For example, the number of possible cation–anion combinations is estimated to be as high as 10^{18}.



Scheme 1.3:

The present generation of air- and water-stable ionic liquids has come a long way from the initial haloaluminates synthesized in 1970s.[79] However, there are still some hurdles in the evolution of ionic liquids from laboratory curiosities to economically viable technology. These are non-availability of physicochemical and thermodynamic data, recyclability data, toxicity data and a lack of understanding of how can ionic liquids affect the course of a reaction.[80] The problem of lack of physicochemical information is being tackled through public databases such as ILThermo[81] managed by the US National Institute of Standards and Technology (NIST). More and more information has been collected on the physical properties and toxicity of ionic liquids in the past few years.[82,83] Since the large number of combinations available makes it tedious to measure the properties of each and every ionic liquid with sufficient accuracy, efforts have also been undertaken, with moderate success, to predict the properties of a given ionic liquid before synthesizing it.[84] A general picture of the solvent effects of ionic liquids still continues to be contentious, due to numerous reasons.

Firstly, ionic liquids represent one of the most structurally complex solvent systems. The “liquid structure” of ionic liquids at the local and mesoscopic scales in far from resolved. At the local level, neutron scattering experiments[85] and computer simulations[86] on the extent of hydrogen bonding between the cations and anions have yielded controversial results. While some workers have proposed the existence of a three-dimensional network of hydrogen bonds and their role in the mesoscopic structure,[87] others believe that the evidence is still inconclusive. [88] Experiments[89] and theoretical calculations have led to the general acceptance of structural anisotropy as an integral part of the mesoscopic structure of ionic liquids. In fact, their structural inhomogeneity at the mesoscopic levels has led to the term "mesophase".[90] The typical structural characteristics of ionic liquids affect the different properties like vaporization, liquid-liquid mixing/demixing, viscosity and non-Newtonian behavior.[91]

Secondly, ionic liquids are capable of exhibiting a large variety of solute-solvent interactions as opposed to the interactions found in conventional solvents, which are dominated by a limited number of factors. The net charges on the ions may lead to partial charge ordering and screening of dipole–dipole interactions require a fundamentally different environment of solvation as compared to molecular liquids. A number of studies have focused on the 'preferential solvation'[92] in ionic liquids in addition to conventional polarity studies.[93] Sarkar et al. have reported interesting "hyperpolarity" behavior in binary mixture of ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] with the solvent tetraethylene glycol.[94] Ionic liquids are also capable of acting as polar solvents in organic reactions containing polar molecules and as relatively nonpolar solvents in the presence of less polar molecules.[95]

Not surprising, the number of physical–organic studies attempting to correlate such complicated properties of ionic liquids to the kinetic and stereochemical outcome of the reactions have been relatively few in number. Some researchers have postulated that due to their characteristic hydrogen bonding ability, ionic liquids can act as a catalyst[96] or as an organocatalyst.[97] In a recent review, Scott et al. have compiled evidences of the non-innocent nature of ionic liquids in terms of altered reactivity of dissolved substrates, unexpected catalytic activity and unforeseen product formation.[98]

Since the interactions of the cation/anion with the solute have to compete with those between the counterions, it is important to understand the nature of bonding between the cation and the anion. The impact of mesoscopic structures on the solvation and the resulting dynamic processes should also be considered carefully. The continuum models equating the molecular properties with those observed at the macroscopic phase tend to collapse in such cases. For example, the diffusion-controlled reactions in ionic liquids are faster than those in organic solvents,[99] probably due to the channelised mesoscopic domains, which make the diffusion of small species easier. The presence of voids or channels is also used to explain the reactivity of H (hydrogen radical atoms) with aromatic solutes in ionic liquids.[100] The nucleophilicity of the I^- anion in the SN_2 reaction of methyl-4-nitrobenzenesulfonate to form 4-nitrobenzenesulfonate and iodomethane was found to be independent of the nature of the cation.[101] The Cl^- ion, on the other hand, showed a nucleophilicity sensitive to the nature of the ionic liquid cation.

The enormous promises of controlled product distribution, enhanced reactivity and recycling of reagents or catalysts by using ionic liquids, have just begun to be explored.[102] Further investigation is necessary to identify the most efficient and economical ionic liquid with minimum toxicity, maximum lifetime and increased contaminant tolerability for any given process.

1.7 Solvent effects on Diels–Alder reaction

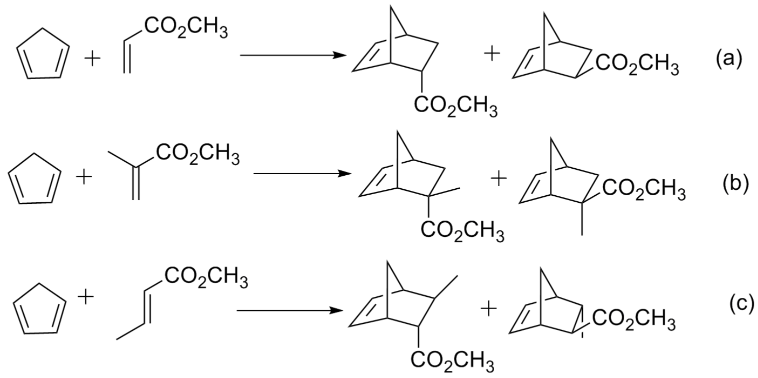
Diels–Alder reaction[103] has occupied important place in synthetic organic chemistry for constructing highly stereoselective six-membered ring systems. The remarkable efficiency of the Diels-Alder reaction in the synthesis of natural products and physiologically active molecules led to an upsurge in research activities aimed at developing newer methods to improve yields and selectivities of this reaction. A large number of original papers, reviews and monographs have been written on this subject.[104] Detailed mechanistic investigations by Woodward and Hoffmann, Fukui and Houk have contributed significantly to the mechanistic understanding of the reactivity and selectivity of these processes.[105] The most widely accepted mechanism consists of a concerted $[4\pi + 2\pi]$ pericyclic transition state, which may exhibit some degree of asynchronicity.

The rate and stereoselectivity of Diels–Alder reaction were assumed to be unaffected by the solvents, due to the isopolar transition state, until the studies by Berson et al.[106] The variation of the *endo*/*exo* ratio was explained on the basis of the polarity of the solvent. The special role of water and aqueous mixtures containing salt or cosolvent additives as a medium for Diels–Alder reactions was established by contributions from Breslow et al.,[40,107] Grieco and coworkers extended the study to micellar systems and proposed that micellar catalysis might be the reason for the acceleration of Diels–Alder reactions in aqueous media.[108] Cativella and coworkers have published a comprehensive report on how different solvent parameters (for example, polarity, Gutmann' acceptor number, solvophobicity, cohesive energy density, etc.) influence kinetics of several Diels–Alder reactions in organic solvents.[109] In the case of water, the rate enhancement has been ascribed due to solvent polarity,[1] hydrophobic packing,[40] hydrophobic hydration,[110] hydrogen bonding,[111] surface cohesive pressure,[112] etc.

Breslow interpreted the rate acceleration of Diels–Alder reactions in terms of "hydrophobic packing".[107] He supported the explanation by demonstrating that prohydrophobic salts further accelerated the reaction while antihydrophobic additives led to retardation. However, the preassociation implied by "hydrophobic packing" was found to be too shortlived to be of any practical importance. Alternatively, authors have repeatedly invoked the internal pressure of water as an explanation of the rate enhancements of Diels–Alder reactions in this solvent.[113] In a complementary approach, the *ced* has been successfully used by Gajewski in a multiparameter equation describing the solvent effect on a Diels–Alder reaction where one of the solvents was water.[114] The importance of the *ced* (along with the hydrogen-bond donating capacity) in this study underlines the importance of hydrophobic interactions in rationalising the effect of water on Diels–Alder reactions. In a remarkable development, Kumar used P_i as a non-adjustable parameter, normalized by the polarity parameter to correlate the raes and stereoselectivities of Diels–Alder reaction with the solvent properties.[115] An analysis of the relative rates of different Diels–Alder reactions in this manner yielded a good correlation (correlation with about 280 points of $\log(k_{rel})$ yielded 0954 and 0080 values for r and σ, respectively.). The results thus obtained showed that the internal pressure can explain the variations in rates and selectivites on addition of electrolytes to the reaction medium.

Engberts and coworkers introduced the "enforced hydrophobic interactions" to describe the activation of Diels–Alder reactions in water.[110] The term "enforced" is used to stress the fact that the association of the nonpolar reagents is driven by the reaction and only enhanced by water. The reduction of hydrophobic surface and hydrated volume during the activation process leads to a large gain of the entropy and a large loss of the enthalpy of water molecules.

Schneider and Sangwan correlated the rate of some Diels–Alder reactions in aqueous mixtures with the solvophobicity parameter Sp.[116] Desimoni et al. initially advocated the Acceptor Number (AN) as the dominant solvent parameter.[117] Further work based on Diels–Alder reactions in a series of organic and aqueous–organic solvents led to the development of a model based on the influence of both, solvophobicity and polarity of the medium on the stereochemical outcome of the reaction.[118] When water was not included, the rate constants could be correlated with the solvent hydrogen-bond donating ability α. Upon inclusion of water the solvophobicity parameter, Sp, contributed significantly in the LFER. The interpretation of the results was hampered by the fact that both Sp and E_T^N are intrinsically correlated parameters — the highly solvophobic solvents have higher polarity as well. The earlier work of Breslow[107] and followed by that of Kumar[119] showed that aqueous salt solutions have pronounced effect on the *endo*/*exo* ratios of simple Diels–Alder reactions. For example, higher *endo*/*exo* ratios for the reaction of cyclopentadiene with methyl acrylate (Scheme 1.4a) were obtained in LiCl, NaCl, NaBr, $CaCl_2$ and $MgCl_2$, while the lower ratios were observed in $LiClO_4$ and GnCl. The effect on selectivities increased with increase in the salt concentration. The reaction of cyclopentadiene with methyl methacrylate (Scheme 1.4b), a *exo*-selective reaction also displayed the similar salt effect, though the salt effect was weaker as compared to one noted for the previous reaction with methyl acrylate. Very recently, Sarma and Kumar noted that the salting effect on the reaction of cyclopentadiene with methyl-trans-crotonate (Scheme 1.4c) provided strong experimental evidence that hydrophobic interactions can be dominant over the secondary orbital interactions in a Diels–Alder reaction.[120]

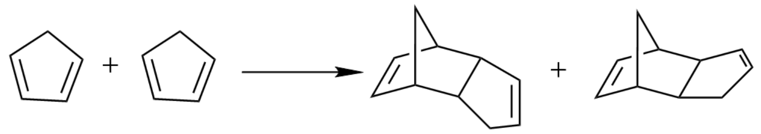


Scheme 1.4:

A combined approach of quantum and statistical mechanics was employed by Jorgensen and workers[111] to suggest the significant role of hydrogen bonding.

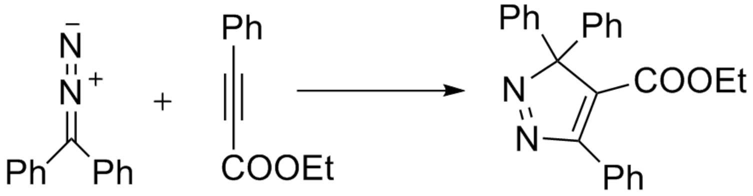
Their computations for the reactions of cyclopentadiene with butenone and with acrylonitrile (Schemes 1.2, 1.4) yielded the estimation of optimal interaction energies to be $15-2$ kcal mol^{-1} more favorable for hydrogen bonding to the oxygen or nitrogen in the transition states. The results have also been supported by experimental kinetic data.[121] In fact, a combined role of hydrogen bonding and enforced hydrophobic interactions in stabilizing transition state can be used to explain rate enhancement of Diels–Alder reactions in water.

Conventionally, both intermolecular (bimolecular) and intramolecular Diels–Alder reactions are known to show strong viscosity dependence in molecular solvents.[122,123] Interestingly, Firestone and coworkers reported an initial increase in rates with increasing viscosity, contrary to the general expectation of deceleration due to viscosity. For example, the rates of dimerisation of cyclopentadiene (Scheme 1.5) and 1,3-dipolar cycloaddition of diphenyldiazomethane with ethyl phenylpropionate (Scheme 1.6) initially rise with an increase in viscosity before falling off at higher viscosities (> 1.3 cP). The observation was explained on the basis of vibrational activation of bond-making reactions.[124] Accordingly, bond formation is favored in systems with high vibrational and low translational energy. 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, causing retardation in the rates of reactions.



Scheme 1.5:

van Eldik tried to extend the available rate data for the dimerisation reaction by measuring the monomer concentration over a wider range of conversion but came to the conclusion that there was no viscosity dependence.[125] The results by Firestone were also severely criticized by le Noble et al. who questioned the accuracy of the data and validity of the inferences.[126] le Noble states that reaction rates should necessarily be suppressed by increasing viscosity. A study by Kumar



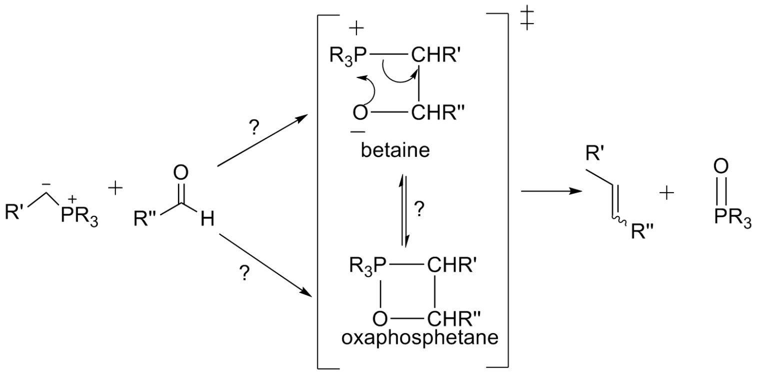
Scheme 1.6:

et al. 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.[127] The reaction rates increased with the rise in viscosity, leveled off at 1.2 - 1.3 cP before dropping with increasing viscosity beyond 1.3 cP.

In contrast, there are very few reports studying the effect of ionic liquids on the rate and *endo/exo* selectivity of ionic liquids. High *endo* selectivity in ionic liquids is explained considering the ability of the cation to act as a hydrogen bond donor.[128] Semiempirical computational analysis of the Diels–Alder reactions in protic imidazolium ionic liquids supported the view and concluded that hydrogen bonding of the protic ionic liquids to the dienophile could provide a rationale for the observed Bronsted catalysis.[129] Vidiš et al. employed the NMR based δ solvent scale to predict the stereoselectivity of Diels–Alder reactions in ionic liquids.[130]

1.8 Solvent effects on Wittig reaction

The inception of Wittig reaction by Wittig and co-workers[131] in the 1950s is considered to be one of the major breakthroughs in organic synthesis. The reaction of phosphonium ylides with aldehydes and ketones provides a route to synthesize substituted olefins with high degree of chemo- and stereoselectivity. The importance of this discovery was duly recognized when Wittig was awarded the Nobel Prize in Chemistry in 1979 for his contribution in the field. The scope, progress and application of this reaction have been well documented since, through several reviews.[132] The stereochemistry and mechanism of the reaction have also been studied extensively.[133] The mechanism of Wittig reaction was an issue of much contention until recent past (Scheme 1.7). Initially, the betaine mechanism was proposed on the basis of limited mechanistic experimental data.[134] The observed



Scheme 1.7:

solvent effects were rationalized on the basis of the betaine mechanism. For example, the increase in rates of the reactions between stabilized ylides and aldehydes with increasing solvent polarity were interpreted as an evidence in favor of the charged intermediate.[135] Subsequent experimental and theoretical studies led to the emergence of the [2+2] asynchronous oxaphosphetane mechanism as the more probable mechanism.[136] Vedejs and coworkers concluded that the insubstantial solvent effects in the reactions of non-stabilized ylides were "incompatible with the two step betaine mechanism".[137] The solvent effects thus, indicated a nonpolar transition state for the reaction. The cycloaddition leading to the oxaphosphetane intermediate followed by pseudorotation at the phosphorus and decompostion to the alkene product is now the established mechanism. The ambiguity about the mechanism of the reaction prevented extensive and quantitative studies of the solvent effects on the rates and selectivities. The use of aqueous reaction medium for accelerating the rate of the reaction was first reported recently for stabilized and semistabilized phosphonium ylides.[138,139] These were the first reports of conducting the Wittig reaction in heterogeneous aqueous medium, without the addition of any co-solvent. Wu and coworkers not only carried out the heterogeneous Wittig reaction in stabilized ylides but also demonstrated that the aqueous reactions are faster than the same reactions carried out in homogeneous organic solvent medium at comparable reaction temperature. They also carried out aqueous Wittig reaction of semistabilized phosphorus ylides generated in situ from the corresponding phosphonium salts with aromatic aldehydes.[140] They later extended the methodology to the one-pot synthesis of α, β-unsaturated carboxylic esters and nitriles through the Wittig reaction of aromatic aldehydes with stabilized ylides generated in situ.[141]

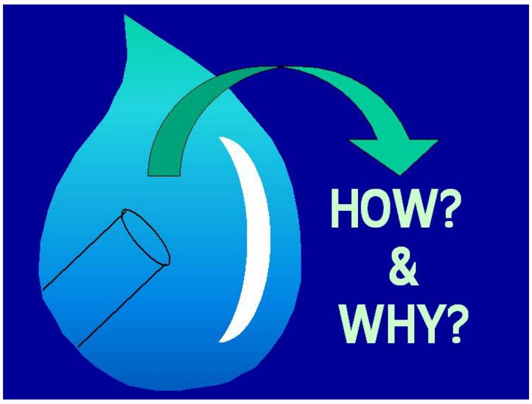
Bergdahl and coworkers, as an extension of their initial report, have used the one-pot approach to demonstrate the efficiency of water as a medium for Wittig reaction as compared to conventional organic solvents. They observed that the reactions in water were faster that all the scrutinized organic solvents except methanol. The heterogeneity of the reaction medium was a consistent feature of all the aqueous reactions conducted without addition of cosolvents. The fact that the reactants are insoluble in water implies that water is a “medium” and not a “solvent”.[141]

1.9 Conclusions

The vast literature and extensive studies dedicated to solvent effects are proofs of the importance of this area in terms of fundamental understanding and potential applications. The dynamical and complex nature of the condensed phase interactions does impose considerable demands on the theory and experiments. A detailed analysis of the solvent effects of the “green” solvents is particularly necessary for developing economically viable and chemically efficient reaction media.

2

Aims and Objectives



A brief outline of the aims and objectives of the proposed research topic as well as the methodolgies to be used for such studies is provided in the present chapter.

A thorough study of the previous literature on the solvent effects in ionic liquids and aqueous media highlighted the importance of the field. It could be safely inferred that despite the numerous attempts to understand the effect of aqueous media, the "on water" methodology was not studied from a physical–organic perspective. Detailed studies of the effect of ionic liquids as reaction media, too, were very few. The subject of research was deemed to be challenging and immensely relevant at the same time.

Physical–organic studies of the organic reactions in aqueous media had been extensively carried out to varying degrees of qualitative and quantitative details. Reactions in aqueous media thus studied were greatly influenced by the properties of the reaction medium. The numerous types of interactions possible between the solvent and solute molecules in an aqueous system had proved to be promising opportunities disguised by the challenge of our limited understanding. The physical-organic studies for reactions in ionic liquids were comparatively lesser in number. Nevertheless, the flexibility of designing ionic liquids combined with the characteristic properties (like microscopic structural inhomogeneities, non-Newtonian rheological characteristics, dual polarity etc.) had the potential to improve the yields and selectivities of chemical processes. The following were some salient features that merited further investigation:

- Very little experimental data had been reported to compare and evaluate the performance of the different classes of green solvents like water, aqueous solutions and ionic liquids as reaction media under identical conditions.

- A thorough quantitative analysis of the different molecular level interactions in aqueous media, delineating the extent of contribution to reaction acceleration hydrophobicity, hydrogen bonding and preferential solvation, had been elusive.

- The role of solvent friction or viscosity had been widely debated and hence, should have been analyzed in greater detail. The viscosity of ionic liquids had been suspected to influence the outcome of the reaction on logical grounds but was not backed by comprehensive experimental findings.

- Despite the increasing popularity of the “on water” approach, very little quantitative data was available about the reactivity and selectivity at the organic-water interface, which is required for further optimization of the reaction conditions.

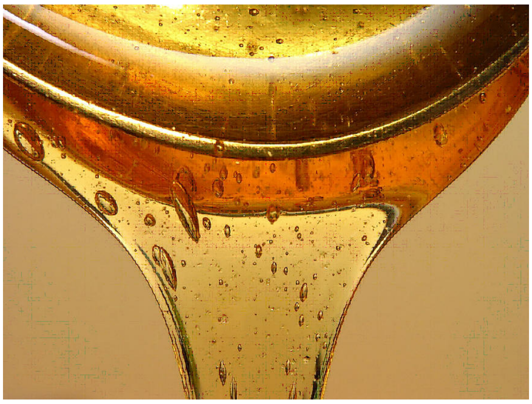
In view of the aforementioned general inferences from the literature survey, the following were the objectives for the work, aimed to provide a broad outline for the future course of research:

- To experimentally compare the efficiency of the two different classes of environmentally benign reaction media - ionic liquids and aqueous solutions. The information thus gained would be useful in identifying the thrust areas for further investigation in each of the solvent systems.
- To investigate the role of solvent viscosity in determining the course of chemical processes. The experimental observations should be further analyzed on the basis of the theoretical models to gain a molecular-level understanding.
- To discern the manifestation of the hydrophobic forces and hydrogen bonding in addition to the other interactions possible for "on water" conditions in comparison to their role in homogeneous aqueous reactions.
- To explore the possibility of modeling the reactivity and/or selectivity at the aqueous–organic interface as a function of the macroscopic properties of the reaction medium in presence of different cosolvents or salt additives.

Kinetic analysis of typical C–C bond forming organic reactions was intended to be the dominant experimental technique for achieving the aforementioned objectives. The reactions chosen for the kinetic studies were those having considerable synthetic significance and well-established mechanism. Reactions requiring ambient conditions of temperature and pressure were preferred because this ensured that further correlation with physicochemical properties of the reaction medium were not obstructed due to paucity of data.

3

Solvent Friction in Ionic Liquids as a Rate–Controlling Factor

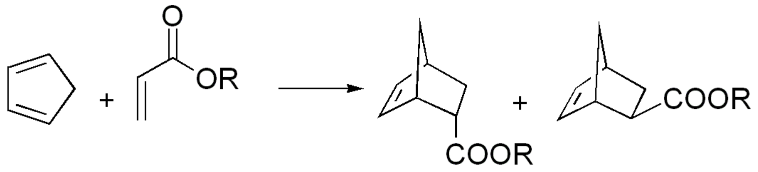


The effect of viscosity of the reaction medium on the rates of unimolecular and bimolecular Diels–Alder reactions has been studied in the present chapter. The chapter is divided into three sections. A comparison of the efficiency of ionic liquids and water as reaction media for Diels–Alder reactions is presented in Section 3.1 — the subsequent observations being the groundwork for further studies on the contribution of viscosity. The role of viscosity and microviscosity in determining the rate of an intramolecular Diels-Alder reaction carried out in ionic liquids is examined, in context of the different theoretical perspectives, in Section 3.2. An extension of the study to bimolecular Diels–Alder reaction to bring out the similarities and differences concerning the effect of the viscosity of the reaction medium is discussed in Section 3.3.

3.1 Water or ionic liquids: which is better?

3.1.1 Introduction

The dramatic rate accelerations and enhanced selectivities of Diels–Alder reactions in aqueous media have been used in many synthetic applications in the last three decades.[44,45] The increasing popularity of ionic liquids, in the meantime, led to numerous reports about their use as reaction media for Diels–Alder reactions and the scientific community arrived at a general consensus about their efficiency.[128,142] For the synthetic chemist interested in employing green solvents, it is important to know which of the two — ionic liquids or aqueous solutions — would be a better choice. The kinetics of three simple Diels–Alder reactions involving cyclopentadiene (**1**) with methyl acrylate (**2a**), ethyl acrylate (**2b**) and butyl acrylate (**2c**) were studied both in water and ionic liquids under identical conditions for the purpose of comparison (Scheme 3.1).



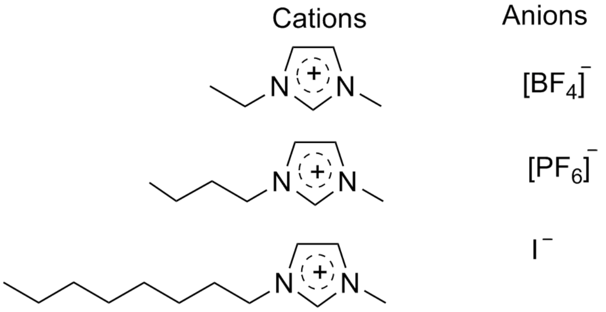
1

2a $R = CH_3$
2b $R = C_2H_5$
2c $R = C_4H_9$

3a **4a** **5a**

3b **4b** **5b**

Scheme 3.1:



Scheme 3.2:

3.1.2 Experimental section

Materials: **1** was freshly cracked from dicyclopentadiene prior to use. **2a**, **2b** (low pressure distillation) and **2c** were distilled prior to their use. 1-butyl-3-methyl imidazolium tetrafluoroborate [BMIM][BF_4], 1-butyl-3-methyl imidazolium hexafluorophosphate [BMIM][PF_6], 1-butyl-3-methyl imidazolium iodide [BMIM]I, 1-octyl-3-imidazolium hexafluorophosphate [OMIM][PF_6] and 1-ethyl-3-methyl tetrafluoroborate [EMIM][BF_4] were synthesized by the reported procedure (Scheme 3.2).[143] The ionic liquids were thoroughly dried by heating at 70 °C (343 K) under high vacuum for several hours before each kinetic run. All experimental procedures involving the ionic liquids were carried out under an atmosphere of dry nitrogen to exclude moisture (NMR spectra of the pure and dried ionic liquids listed in Appendix A).

Kinetic Analysis: For a standard kinetic run, the dienophile was added to the ionic liquid (1 mmol in 1mL of ionic liquid) and was allowed to equilibrate at the desired temperature. The temperature was controlled using a Julabo constant temperature bath with an accuracy of ±0.01 K. The reaction was initiated by addition of **1** (1 mmol in 1 mL of reaction mixture). The reaction progress was monitored at appropriate time intervals by extraction of aliquots with ether, followed by appropriate dilution and GC analysis using a Varian CP–3800 gas chromatograph (Detailed GC settings, retention times and NMR spectra for the products **3** to **5** described in Appendix B.1 and B.2). The rate constants thus determined were reproducible to within ± 6%.

3.1.3 Results and discussion

An examination of the second order rate constants, k_2 for the above referred reactions studied in water and many ionic liquids showed that the reactions were faster in water as compared to those in the ionic liquids investigated. (Table 3.1) The reaction of **1** with **2a** was 10-times faster in water as compared to [BMIM]I. Similarly, rates of the reactions of **1** with **2b** and **2c** were at least 3 to 4 times higher in water as compared to [BMIM]I.

The above experimental data presented clear evidence that water was a more powerful solvent than the ionic liquids, as far as Diels–Alder reactions were concerned. In the case of water, the rate enhancement could be better interpreted in

Table 3.1: Second order rate constants, k_2 for Diels–Alder reactions in water and ionic liquids.[a]

Reaction	k_2 (M^{-1} s^{-1})[b]		
media	**1 + 2a**	**1+2b**	**1+2c**
Water	24.07	7.89	9.71
[EMIM] [BF_4]	5.86	5.71	5.22
[BMIM] [BF_4]	4.52	3.93	3.41
[BMIM] [PF_6]	3.92	3.28	3.10
[OMIM] [PF_6]	3.11	2.46[c]	2.44
[BMIM] [I]	2.46	2.53[c]	2.05

[a] Reactions were carried out in a 1 mmol scale in 1 mL of solvent with a 1:1 equivalence of the diene and dienophile at 298 K. [b] An average of triplicate data. [c] Values equal within experimental error.

terms of enforced hydrophobic hydration and hydrogen bonding as revealed from the contributions of Engberts and Jorgensen, respectively.[110,111] The absence of hydrophobic interactions and weaker hydrogen bonding in ionic liquids might have been the important reasons for the observed difference in the rates.

Amongst the ionic liquids, the rates dropped down by a factor of two on going from [EMIM][BF_4] to [BMIM]I. The trend was consistent for all the three dienophiles studied, irrespective of the change in cation or anion. Thus the observed rate deceleration had to originate due to a property that varied in a non-specific fashion for all the ionic liquids used. An extensive examination of the different properties was undertaken. Surface tensions or densities of the ionic liquids did not show any correlation with the reaction rates. The solvophobicity, measured in terms of the ^{1}H NMR proton shift signal at the 2-position of the imidazolium ring, $\delta_H(H^2)$ also turned out to be a weak correlating property.[128] The rate constants of a Diels–Alder reaction carried out in different ionic liquids had been correlated with the H-bonding ability, expressed in terms of E_T^N parameter. The present results supported this correlation with the k_2 values of these reactions decreasing with the decrease in E_T^N values.

The literature reports[143] suggested that the viscosities of different ionic liquids used in this investigation follow the order: water < [EMIM][BF_4] < [BMIM][BF_4]

< [BMIM][PF$_6$] < [OMIM][PF$_6$] < [BMIM]I. The k_2 values for the Diels–Alder reactions decreased with the drastic increase in the viscosity of ionic liquids. (Figure 3.1) This implied that the viscosity, η of an ionic liquid could be an important parameter to correlate kinetic data of Diels–Alder reactions. The inference was in contrast to another study which showed that a Diels–Alder reaction was fastest in an ionic liquid possessing highest viscosity.[128]

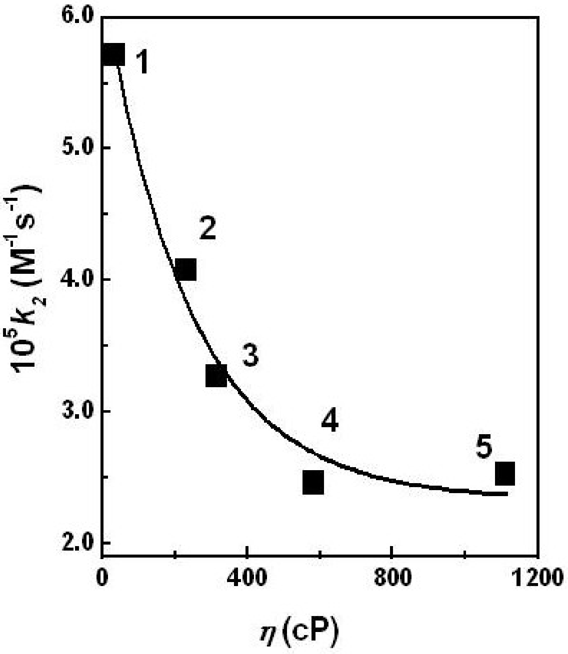


Figure 3.1: Second order rate constants, k_2 as a function of viscosity, η of the ionic liquids 1) [EMIM][BF$_4$], 2)[BMIM][BF$_4$], 3) [BMIM][PF$_6$], 4)[OMIM][PF$_6$] and 5) [BMIM]I for the Diels–Alder reaction of **1** + **2a**

In order to test the validity of the argument concerning the role of viscosity, the kinetics of the reaction of **1** with **2a** in binary ionic liquid mixtures of [EMIM][BF$_4$] and [BMIM][BF$_4$] were studied (Table 3.2). As the proportion of [EMIM][BF$_4$] increased, the magnitude of the rate constant also increased. This observation could be explained by considering the fact that the viscosity of the binary mixture decreases with an increasing fraction of the less viscous component, [EMIM][BF$_4$], thus causing a rise in the rates. This observation implied that any factor causing a reduction in η of ionic liquids would lead to a rise in the k_2 of

Table 3.2: Second order rate constants, k_2 for reaction of **1** + **2a** in a binary mixture of ionic liquids ([EMIM][BF_4] + [BMIM][BF_4])

% v/v [EMIM] [BF_4]	k_2 (M^{-1} s^{-1})[a]
0	4.52
25	5.11
50	5.32
75	5.23
100	5.85

[a] Reactions were carried out in a 1 mmol scale in 1 mL of solvent with a 1:1 ratio of **1** and **2a** at 298 K.

the reactions. The reaction of **1** with **2a** was carried out at 298 K in a mixture of [BMIM][BF_4] with dichloromethane (DCM) (45 mol % of [BMIM][BF_4] in 55 mol % of DCM) where DCM was used as a "viscosity reducer". The viscosity of the resulting mixture was 18 cP[144] as compared to $\eta = 233\,\text{cP}$ for [BMIM][BF_4]. The resulting rate constant $k_2 = 5.79 \times 10^{-5}\,M^{-1}s^{-1}$ was much higher than that in pure [BMIM][BF_4] or DCM alone.

The activation parameters of the reaction of **1** with **2a** were determined from the temperature dependence of rate constants in [BMIM][PF_4] and [EMIM][BF_4] (Figure 3.2). The activation energy, E_a thus calculated is 63.4 kJ mol^{-1} for the reaction of **1** and **2a** in [BMIM][PF_6] and 57.7 kJ mol^{-1} for the same reaction in [EMIM][BF_4]. These values were in agreement with the qualitative prediction that the reactants will have to overcome a "higher barrier" in a more viscous medium, leading to a decrease in the rate of the reaction. Nevertheless, it is important to mention that the data can provide only limited information. Any change in temperature is bound to alter both, the H-bonding ability and the viscosity of ionic liquids along with the height of the activation barrier of the reaciton. The observed temperature effect may be due to the change in either of these parameters.

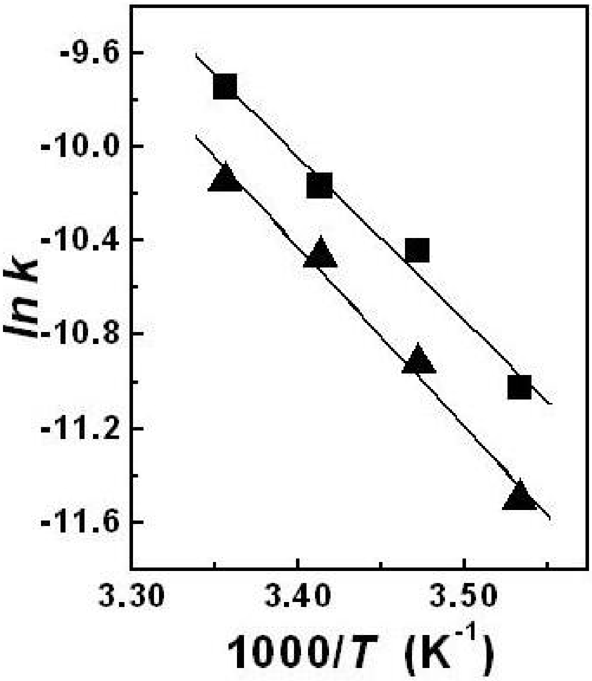


Figure 3.2: Arrhenius plots of Diels–Alder reaction of **1** + **2a** in [EMIM][BF$_4$] (■) ($r^2 = 0.99$) and [BMIM][PF$_6$] (▲) ($r^2 = 0.99$).

3.1.4 Conclusions

The results proved that water was definitely the solvent of choice for carrying out Diels–Alder reactions, as compared to ionic liquids. The high viscosity of ionic liquids was the detrimental factor, slowing down the Diels–Alder reactions. The results underlined the need for further exploration of the correlation between the rates of unimolecular and bimolecular reactions with other properties of ionic liquids. Also designing new ionic liquids or using ionic liquid mixtures with better properties was shown to give better results in terms of rates. Accordingly, further investigations were planned to throw light on the role of viscosity in the reaction kinetics.

3.2 Viscosity depedence of an intramolecular Diels–Alder reaction

3.2.1 Introduction

As concluded from the work carried out in the previous section, the highly viscous nature of a conventional ionic liquid can slow down the rate of a bimolecular Diels–Alder reaction by an order of magnitude as compared to that in water. In order to design novel ionic liquids, which are capable of overcoming the limitations of the current generation of ionic liquids,[72] it is important to understand the structure-property correlations with reference to their effects on the chemical processes. However, there have been very few attempts to correlate the physico-chemical properties of ionic liquids with the kinetic and stereochemical outcome of the reactions.[128,130,145] 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.

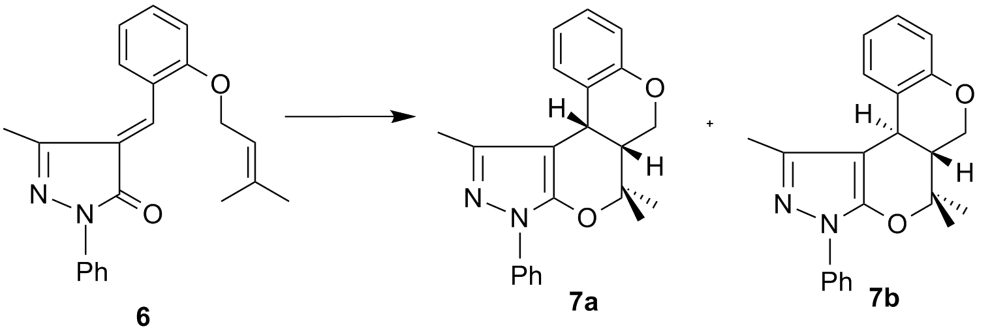
Neta and coworkers investigated the rates of several elementary radical reactions in ionic liquids[146] and observed that the rates in ionic liquids were, in general, lower that those in water and organic solvents. For diffusion-controlled reactions, the lower rate constants were attributed to the high viscosity of ionic liquids. Similar observations for the diffusion-controlled quenching of triplet benzophenone by naphthalene and reaction of solvated electrons with aromatic compounds ruled out the proposed "electron hopping" mechanism.[147] The kinetics of thermal Z to E isomerization of azobenzene (AB) and 4-Dimethylamine-4'-nitroazobenzene (DNAB) were studied in the imidazolium-based ionic liquids.[148] The isomerization of AB was not much influenced by the viscosity and the polarity of the ionic liquids while the DNAB isomerization rates showed very large viscosity dependence. The role of viscosity in determining the kinetic profile of bromination of alkynes in ionic liquids was also examined.[149] Spinelli and coworkers have investigated the mononuclear rearrangement of Z-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole induced by amines.[150] The polarity parameters like $E_{\mathrm{T}}^{\mathrm{N}}$ or π^* were insufficient to account for the observed trends in reactivity. The experimental data failed to show a complete agreement between viscosity and reactivity either.

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 data, that an increase in viscosity accelerated the Diels–Alder reactions.[128] Conventionally, both bimolecular and intramolecular Diels–Alder reactions are known to show strong viscosity dependence in molecular solvents.[122,123] For example, the rate of cyclization of *N*-propargyl-9-anthramide initially rises with an increase in viscosity before falling off at higher viscosities. Firestone and coworkers 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. The observation was explained on the basis of vibrational activation of bond-making reactions.

A quantitative theoretical explanation for the observed viscosity dependence of Diels–Alder reactions had also not been reported. At present, the Kramers theory[35] 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,[9,151] including the isomerization ones.[152] However, there was no report, which applied these stochastic theories to 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.[153] The corresponding kinetics covered both, the equilibrium and the non-equilibrium behavior and was applied to explain the observations for high-pressure kinetics. In this context, the kinetic studies of an intramolecular Diels–Alder (IMDA) reaction of (*E*)-1-phenyl-4-[2-(3-methyl-2-butenyloxy) benzylidene]-5-pyrazolone (**6**) were studied in a series of pyridinium-based ionic liquids. (Scheme 3.3).

3.2.2 Experimental section

Materials: Pyridine, 3-picolene and 4-picolene were distilled prior to use. $NaBF_4$ and $Li(NTf_2)$ ($> 99.5\%$) were used as obtained, without further purification. The ionic liquids were synthesized as per the standard procedures.[154] The ionic liquids were thoroughly dried over vacuum for 8-10 h at 70 °C (343 K). The purity of the



Scheme 3.3:

resulting sample was confirmed using NMR spectroscopy (NMR spectra of pure and dried ionic liquids listed in Appendix A).

Viscosity of ionic liquids: The viscosity was measured using a Brookfield LVDV-III cone and plate viscometer. The temperature was controlled using a constant temperature water bath with an accuracy of ± 0.01 K. The viscosities thus measured were reproducible within ± 1 %. The viscosity measurements were done with the same sample of ionic liquids as used for the kinetic runs, in order to eliminate undesirable discrepancies.

Temperature-dependent polarity measurements: All 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 evaporated under vacuum. The ionic liquid was then transferred to the cuvette under nitrogen atmosphere and sealed with a septum.[155] The λ_{max} was measured at different temperatures using Cary 50 UV-visible spectrophotometer. The temperature of the cell was controlled using the Peltier single cell accessory having accuracy of ± 0.01 K.

Kinetic analysis: The organic solvents used for the kinetic analysis were of spectroscopy grade. The substrate was synthesized with a slight modification of the procedure reported (A detailed procedure and NMR spectrum of the substrate **6** and the intermediates given in Appendix B.3). The orange crystals of the substrate were stored at sub-zero temperatures. 0.15 g (43.35 mol) of the substrate **6** was dissolved in 10 mL DCM to prepare a 4.33 mM stock solution. 20 μL of the stock solution was added to 1 mL of the ionic liquid and the DCM evaporated under vacuum to give a 0.08 mM solution of the substrate in the ionic liquid, which was equilibrated for 20 min at the desired temperature using the Peltier single cell temperature control accessory. The decay of the absorbance at $\lambda = 400$ nm due to the substrate **6** was monitored with respect to time using the UV-visible spectrophotometer to give the first order rate constant, k. The rate constants were an average of at least three kinetic runs on different samples and were reproducible within ± 6%.

3.2.3 Results and discussion

The kinetic studies of the IMDA reaction of **6** 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 $[BP]^+$, 1-hexyl pyridinium $[HP]^+$, 3-methyl-1-butyl pyridinium $[3MBP]^+$, 3-methyl-1-hexyl pyridinium $[3MHP]^+$, 3-methyl-1-octyl pyridinium $[3MOP]^+$ and 4-methyl-1-butyl pyridinium $[4MBP]^+$. The anions used were tetrafluoroborate $[BF_4]^-$ and bis(triflouromethylsulphonyl) imide $[NTf_2]^-$. The use of two different anions resulted in two homologous series of ionic liquids, differing only with respect to the alkyl substituent on the pyridinium cations. Changing the alkyl subtituents, the anion or the temperature, could thus vary the viscosity of the ionic liquids.

Table 3.3: First order rate constants, k for the IMDA reaction of **6** at 308 K in different pyridinium ionic liquids

Ionic liquids	Viscosity, η (cP)	$10^5 k$ (s^{-1})[a]
[BP] [BF$_4$]	66.1	4.45
[HP] [BF$_4$]	164.2	2.23
[3MBP] [BF$_4$]	86.3	3.67
[3MHP] [BF$_4$]	129.6	2.43
[3MOP] [BF$_4$]	175.4	1.68
[4MBP] [BF$_4$]	95.6	3.12
[BP] [NTf$_2$]	35.0	2.17
[HP] [NTf$_2$]	48.3	0.37
[OP] [NTf$_2$]	63.0	0.94

[a] The rate constants are an average of three runs. The data agrees to within ± 6%.

The rate constants, k within the $[BF_4]^-$ series of ionic liquids showed a definite correlation with the viscosity of the medium.(Table 3.3) The rate of reaction fell down from $4.45 \times 10^{-5}\,s^{-1}$ in $[BP][BF_4]$ to $1.68 \times 10^{-5}\,s^{-1}$ in $[3MOP][BF_4]$ for a corresponding change in viscosity from 175.4 cP to 66.1 cP at 308 K. The correlation between k and η was not very obvious for the $[NTf_2]^-$ series. Surprisingly, the magnitude of k in the $[NTf_2]^-$ ionic liquids was very close to that in $[BF_4]^-$ based ionic liquids. If the rate constants are indeed dependent on the viscosity of the medium, then the lower viscosity of the $[NTf_2]^-$ based ionic liquids should have led to higher rates of the IMDA reaction.

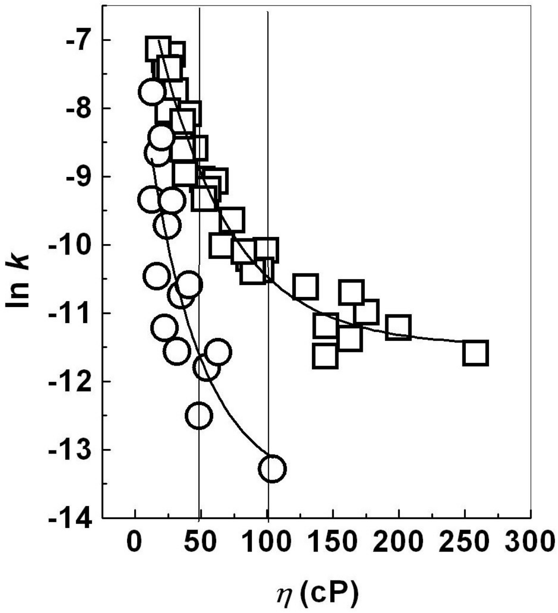


Figure 3.3: Plot of ln k for the IMDA reaction of **6** against the viscosity, η of pyridinium ionic liquids with $[BF_4]^-$ anion (□) and $[NTf_2]^-$ anion (◯) at different temperatures. (The vertical lines serve as a visual guide for comparing the rates in $[BF_4]^-$ and $[NTf_2]^-$ ionic liquids at identical viscosities).

In order to access the correlation between the rates and viscosity in greater detail, temperature dependent studies were carried out in different ionic liquids (Figure 3.3). The variation in temperature served to control the viscosity of the medium and the results plotted are a compilation of the rates in different ionic liquids at different temperatures. For the $[BF_4]^-$ series of ionic liquids, the uniform variation in the experimental data showed that the rate constants at the same viscosity were nearly equal — independent of the means by which that viscosity value was attained — changing the alkyl substituent or the temperature. The rate constants decreased uniformly with increasing viscosity, thus indicating a "universal" viscosity dependence. It was obvious however, that this "universal" trend failed to extend to the $[NTf_2]^-$ series. The $[NTf_2]^-$ based ionic liquids also showed a similar but independent trend with the changing viscosity — in fact, the decrease in rates was sharper for $[NTf_2]^-$ ionic liquids for a similar magnitude of increase in viscosity. At a given value of viscosity, the rate of the IMDA reaction of **6** in $[NTf_2]^-$ was much lower than that in the $[BF_4]^-$ ionic liquid. The projected rate constant fell from $\sim 13 \times 10^{-5}\,\mathrm{s}^{-1}$ to $\sim 3 \times 10^{-5}\,\mathrm{s}^{-1}$ when the viscosity increased from 50 cP to 100 cP for the $[BF_4]^-$ ionic liquids i.e. a decrease to nearly one-fourth of the original rate constant. For a viscosity of 100 cP for $[NTf_2]^-$ ionic liquids, the rate decreased to one-tenth of its value at 50 cP i.e. from $\sim 2.10 \times 10^{-5}\,\mathrm{s}^{-1}$ to $\sim 0.21 \times 10^{-5}\,\mathrm{s}^{-1}$.

The results indicate that in addition to viscosity, the rates are also influenced by a solvent property that varied independently of viscosity on changing from one anion series to another. Within the homologous series, this effect might still be operative but was either masked by a greater competing influence of viscosity or it changed in proportion to the viscosity. The origin of such "specific anion effects" could have been explained by one of the following possibilities:

- The change in anion from $[BF_4]^-$ to $[NTf_2]^-$ may affect the equilibrium solvation i.e. lead to static modification of the potential energy surface of the reaction. In thermodynamic formulations of the 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 is hence, reflected in the magnitude of the activation energy, E_a.

- The change in anion from $[BF_4]^-$ to $[NTf_2]^-$ may affect the strength of frictional coupling of the solvent to the reaction coordinate. It is a dynamic or non-equilibrium effect, since it implies that the solvent molecules are unable to instantaneously equilibrate with the changing configurations of the reacting molecule/s. Non-equilibrium 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 was difficult to delineate the equilibrium and the non-equilibrium solvent effects in any experimental data. For example, changing any parameter like temperature to affect the viscosity would also affect the potential energy surface of the system. The rate constants obtained by varying the reaction medium and the temperature were a function of both — temperature and viscosity i.e. $k(T, \eta)$. Thus ln k was represented as a surface on the three-dimensional plot with T and η as the independent variables (Figure 3.4).

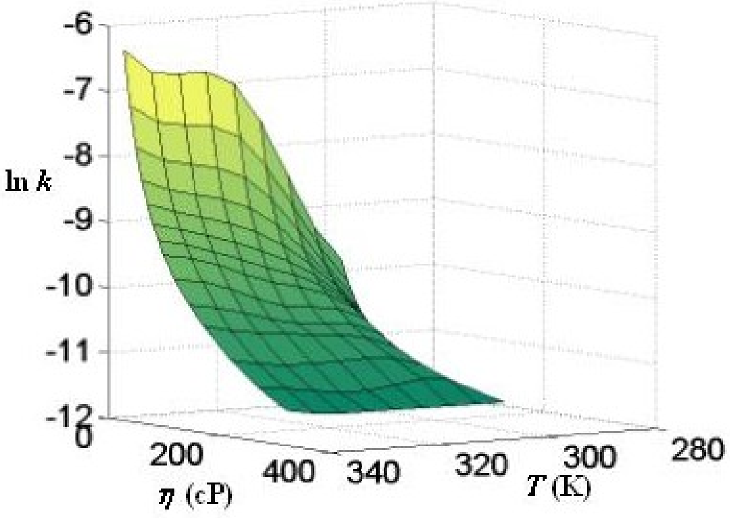


Figure 3.4: A 3-D representation of ln k for the IMDA reaction of **6** in a series of pyridinium ionic liquids as a function of viscosity, η and temperature, T.

The activation parameters were evaluated from the slope and intercept of the Arrhenius plot (representative plot in Figure 3.5) of the IMDA reaction of **6** in the ionic liquids and two other organic solvents (Table 3.4). The activation energies, E_a were higher in ionic liquids as compared to those in organic solvents. The values of E_a were almost twice the values of activation energy for viscous flow E_η of the ionic liquids. No clear trend emerged from the comparison of the E_a and the E_η values. A closer observation of the E_a values revealed some interesting details about the effect of the solvent properties on the rate of the reaction.

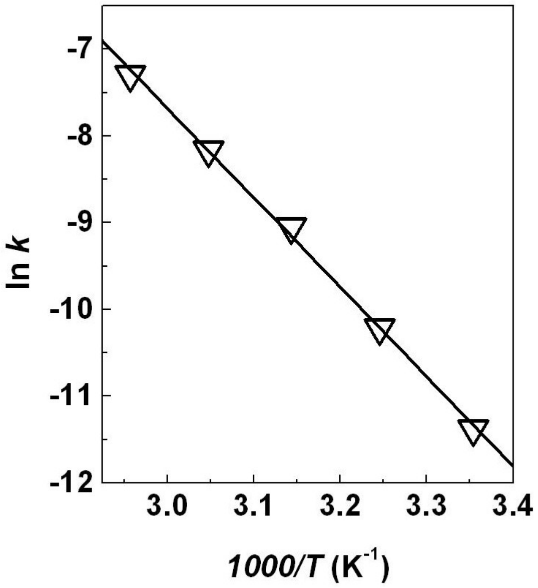


Figure 3.5: Arrhenius plot for the IMDA reaction of **6** in [3MBP][BF$_4$] (r^2 = 0.992).

Firstly, the E_a values for all the ionic liquids in the [BF$_4$]$^-$ series did not show much variation (80.99 kJ mol^{-1} to 85.75 kJ mol^{-1}) indicating that the nature of the transition state is more or less retained in all 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 was represented by the E_η values but the corresponding E_a values for the reaction did not reflect the change. For example, the E_η value increased from 31.85 kJ mol^{-1} for [BP][NTf$_2$] to 35.01 kJ mol^{-1} for [HP][NTf$_2$]. The E_a value for the IMDA reaction of **6**, on the contrary, decreased from 85.13 kJ mol^{-1} in [BP][NTf$_2$] to 66.04 kJ mol^{-1} in [HP][NTf$_2$]. The observed decrease in the rates could then be attributed to the decrease in the transmission coefficient (ln A decreased from 22.52 in [BP][NTf$_2$] to 13.23 in [HP][NTf$_2$]). The anomaly was observed for other pairs of butyl- and hexyl-substituted ionic liquids too — [BP][BF$_4$] against [HP][BF$_4$] and [3MBP][BF$_4$] against [3MHP][BF$_4$], although

Table 3.4: Activation parameters (ln A and E_a) for the IMDA reaction of **6** in different ionic liquids and organic solvents along with the activation energy for viscous flow, E_η of the ionic liquids

Solvents	ln A	E_a (kJ mol^{-1})	E_η (kJ mol^{-1})[a]
Ethylene glycol	17.81 ± 0.64	66.12 ± 1.63	-
Formamide	21.50 ± 0.29	75.64 ± 0.76	-
[BP] [BF_4]	22.97 ± 0.38	84.60 ± 1.01	40.88 ± 1.98
[HP] [BF_4]	17.89 ± 3.09	80.99 ± 8.43	51.73 ± 2.45
[3MBP] [BF_4]	23.26 ± 0.75	85.75 ± 1.99	45.78 ± 1.97
[3MHP] [BF_4]	21.23 ± 0.58	81.52 ± 1.54	46.35 ± 2.00
[3MOP] [BF_4]	22.14 ± 0.67	85.06 ± 1.83	47.22 ± 2.02
[4MBP] [BF_4]	21.53 ± 0.96	81.42 ± 2.54	48.11 ± 2.32
[BP] [NTf_2]	22.52 ± 0.32	85.13 ± 0.84	31.85 ± 1.04
[HP] [NTf_2]	13.23 ± 2.63	66.04 ± 7.16	35.01 ± 1.09
[OP] [NTf_2]	27.34 ± 1.78	100.29 ± 4.69	36.65 ± 1.04

[a] The values for E_η are approximate since they are obtained by applying the Arrhenius equation to typically non-Arrhenius ionic liquids. All the resulting plots had $r^2 > 0.90$.

the variation in activation parameters was not very drastic. Further increase in the length of the alkyl substituent led to an increase in the E_a values, as expected from the rate constants.

Another remarkable fact is that the E_a was more sensitive to the chain length of the alkyl substituent in $[NTf_2]^-$ based ionic liquids as compared to the $[BF_4]^-$ ionic liquids. The results proved that the viscosity of ionic liquids is a dominating factor but it affects the kinetic profile of the IMDA reaction of **6** in an extremely complex manner, which can either be due to static or dynamic effects or a combination of both. However, a definite conclusion in this regard needed more extensive data on the rates of different organic reactions and a thorough analysis based on a theoretical model.

3.2.4 Theoretical discussion - 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 like 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 non-equilibrium 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. It is an approximate expression for the flux of population across a barrier, given by:

$$k = \frac{\omega_0}{2\pi\omega'\tau_v}\left[(1+(2\omega'\tau_v)^2)^{1/2}-1\right]e^{-E_0/RT} \tag{3.1}$$

where ω_0 is the frequency of the potential well of the initial minimum, E_0 is the barrier height, ω' is the frequency of the barrier height and τ_v is the velocity relaxation time of the coordinate. τ_v is a function of the friction coefficient, ζ and the effective mass, m.

$$\tau_v = m/\zeta \tag{3.2}$$

For general applications, the friction coefficient ζ is replaced by the viscosity η of the medium, according to the hydrodynamic model. The rate constant is also replaced by the reduced rate consant, k^* defined as:

$$k^* = k\, e^{E_0/RT} \tag{3.3}$$

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:

$$k^* = \frac{A}{B/\eta}\left[(1+(B/\eta)^2)^{1/2}-1\right] \tag{3.4}$$

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.

$$k = F(\eta)\, e^{-E_0/RT} \tag{3.5}$$

With the above definition of k, the effect of barrier height upon the IMDA rate may be isolated from the effect of the solvent and other characteristics of the potential surface. For reactions carried out in highly viscous medium, the resultant friction ζ is very large. In such cases, τ_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 η:

$$k^* \propto 1/\eta \tag{3.6}$$

However, it is only for reactions with a small barrier of activation (0 – 5 kJ mol^{-1} approximately) that the simple inverse viscosity dependence can be observed. In practice, for majority of the isomerization reactions studied, the effect of viscosity on the rates is lower than that predicted by the theory. The experimental results for such reactions are fitted to the empirical expression:

$$k^* = (B/\eta^a) \tag{3.7}$$

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 3-dimensional space but the '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. The isoviscosity plots were evaluated for five different values of η between 25 cP to 35 cP (representative plots for $\eta = 20$ cP and 30 cP in Figure 3.6) and the resulting activation parameters were averaged (Table

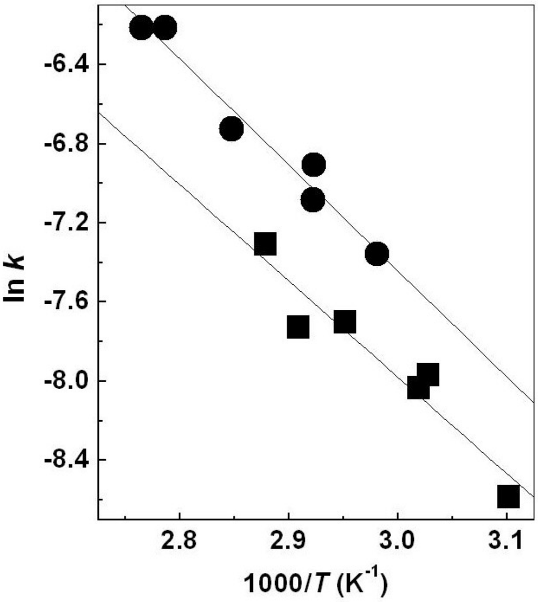


Figure 3.6: Typical isoviscosity plots for the IMDA reaction of **6** at viscosity 20 cP (●) ($r^2 = 0.983$) and 30 cP (■) ($r^2 = 0.953$)

3.5). The average E_0 value, based on the data in Table 3.5 is 39.93 kJ mol^{-1}. 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 activation energy, E_η for the viscous flow.

The isoviscosity plots were characteristically nonlinear at higher vallues of η, showing a sharper deviation in the downward direction with increasing values of η (Figure 3.7). The results indicated 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 the ln η plot (Figure 3.8). Since the isoviscosity plots for η values higher than 100 cP were non-linear, 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 η < 100 cP. The inclusion of data at higher viscosities led to a significant deviation from the linearity. The non-linearity at higher viscosities may be attributed to the fact that the E_0 determined for lower η is not “valid” for the higher

Table 3.5: Activation parameters for the IMDA reaction of **6** from the isoviscosity plots at different viscosities

η (cP)	ln A	E_a (kJ mol^{-1})
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

values of η. 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 was 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 coworkers have reported the slope of $\log k - \log \eta$ plots to be as high as -10 for the isomerization of DNAB in imidazolium ionic liquids.[148] These values were much higher than the $(0 < a < 1)$ values expected from the Kramers-Grote-Hynes model.[36] 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.

3.2.5 Effective friction or microviscosity

The failure of Kramers theory to confirm the experimental data has been explained either by using the frequency dependent friction concept[36,156] or by extending the one-dimensional model into multiple dimensions.[157] But both the theories predict a fractional power dependence of the observed rate on the viscosity $(0 < a < 1)$. It is clear that these theories cannot explain the higher sensitivity of k towards change in η. 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,[37] the bulk

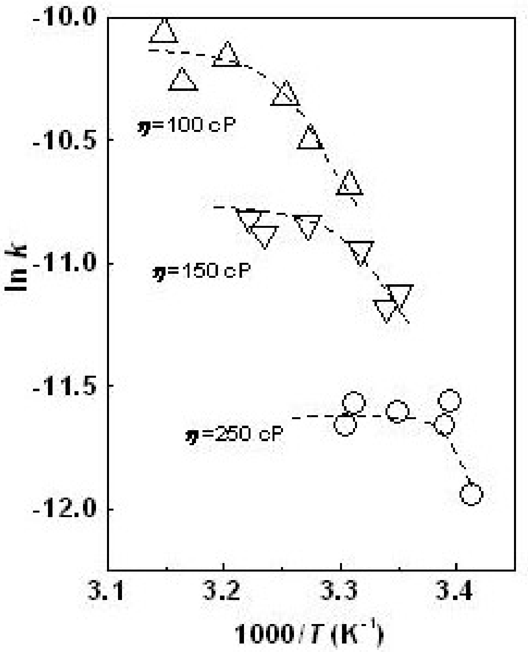


Figure 3.7: Non-linearity of the isoviscosity plots for the IMDA reaction of **6** in the $[BF_4]^-$ based ionic liquids at η = 100 cP (△), 150 cP (▽) and 250 cP (○).

viscosity is a phenomological 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 could also be influenced by the mutual interactions between the solvent and the solute molecules. The anion-specific viscosity effect on the observed rates indicates that the macroscopic or bulk viscosity is not exactly the rate-determining factor.

Firestone and Vitale had suggested that macroscopic viscosity is not an ideal quantity for correlation with rates and a measure of microscopic viscosity would be preferable.[122] The reaction pathway from the reactant **6** to the transition state involves *s*-trans to *s*-cis rotation along the O(21)–C(22) σ-bond, in order to bring the diene and the dienophile closer to the transition state geometry i.e. rotational diffusion (Figure 3.9). This is similar to the rotational diffusion of stilbene molecule discussed by Sun and Saltiel.[37] They then assumed that the friction

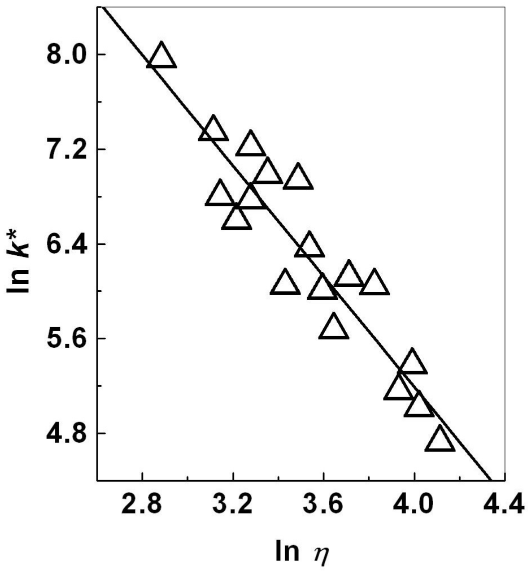


Figure 3.8: The plot of ln k^* against ln η— empirical fit to the equation ln k^* = ln B − a lnη (i.e. $k^* = (B/\eta^a)$).

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, which led to better agreement between the theoretical prediction and the experimental results. 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 **6**. The calculations would require data on the diffusion coefficients of small molecules in ionic liquids, which are currently unavailable or limited to very few ionic liquids.

Till date, there have been very few attempts to measure the microviscosity of ionic liquids.[158] Most of the studies focus on the fluorescent relaxation times of probe molecules and the effect of additives like CO_2.[143,159] Mandal and coworkers, for example, have studied the fluorescent behavior of Coumarin-153 (C-153), 4-aminophthalimide (AP) and 6-propionyl-2-dimethylaminonaphthalene (PRODAN) in pyrrolidinium ionic liquids.[160] Iwata and coworkers studied the ro-

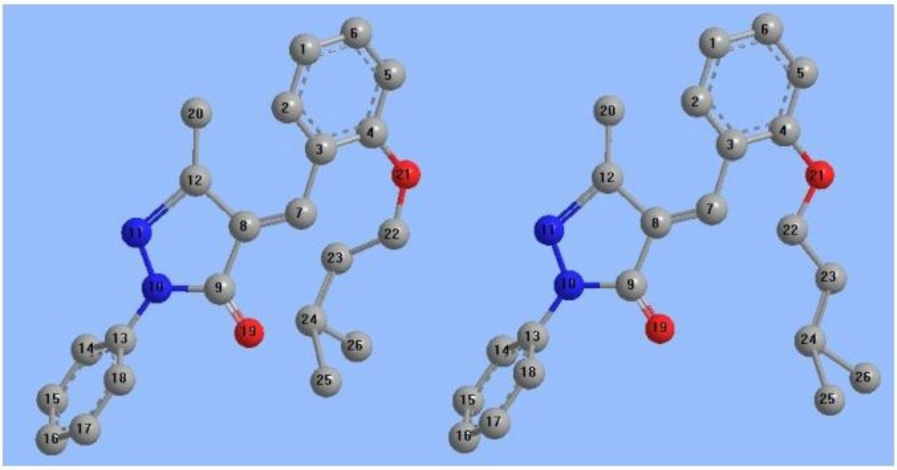


Figure 3.9: Pictorial representation of the *s*-trans to *s*-cis rotation along the O(21) – C(22) bond, required in order to bring the diene and the dienophile moieties in the proper orientation for cyclization. (Grey atoms – C, blue atoms – N and red atoms – O. Hydrogen atoms not shown)

tational diffusion of the probe 2-aminoquinoline using time-resolved fluorescence spectroscopy in a serried of aromatic and non-aromatic ionic liquids and common molecular solvents.[161] 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 $[BF_4]^-$ and the $[NTf_2]^-$ ionic liquids were nearly the same in magnitude, in spite of the difference in viscosity. However, since microviscosity depends on the structure of the solute and the solvent, the data currently available is insufficient for any further comment except that the microscopic solvent environment in ionic liquids is not well 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 **6** is an example of an inverse electron demand hetero Diels–Alder reaction. Previous studies by Desimoni and coworkers had showed that the rate of the reaction is correlated to the Acceptor Number (AN) of the solvent. [117] Thus the solvents were assumed 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. Similar reasoning was applied by Casaschi et al. to explain the Lewis acid catalysis of the IMDA reaction of **6** by inorganic perchlorates.[162] They observed that the catalytic effect was higher for cations having a higher charge to radius ratio.

The rates of the IMDA reaction of **6** in organic solvents were assessed with the multiple linear regression with the Kamlet–Taft polarity parameters. An analysis of the regression models showed dominant contributions by the α and π^* polarity parameters.

$$\begin{aligned} \ln k \;&=\; -13.069 + 1.87(\pm 0.39)\alpha + 2.61(\pm 0.52)\pi^* \\ &\quad\; (r^2 \,=\, 0.833) \end{aligned} \tag{3.8}$$

The dominance of α or hydrogen bond donating property are supported by the previous studies emphasizing the role of electrophilic nature of the solvent. The correlation between the $(\ln k)_{experimental}$ and $(\ln k)_{calculated}$ thus obtained was fairly satisfactory (Figure 3.10a).

Similar attempts to correlate the rates in ionic liquids with the solvent parameters like α, β, π^* failed — scattered plots were obtained for correlation with various combinations of the 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 ionic liquids is known to vary with temperature.[163] All the four parameters showed a small but consistent change in magnitude with changing temperature. Given the limited data available in literature, the temperature dependent polarity parameters of the ionic liquids were determined.[164] 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:

$$\ln k' \,=\, \ln B - a \ln \eta \tag{3.9}$$

The resulting ln k' values were used for multiple linear regression analysis with the polarity parameters. A reasonably good fit was obtained for a combination of the α, β and π^* parameters. (Figure 3.10b).

$$\begin{aligned} \ln k' &= -14.358 + 1.11(\pm 0.43)\alpha + 10.35(\pm 3.33)\beta \\ &\quad +10.68(\pm 4.46)\pi^* \\ &\quad (r^2 = 0.894) \end{aligned} \tag{3.10}$$

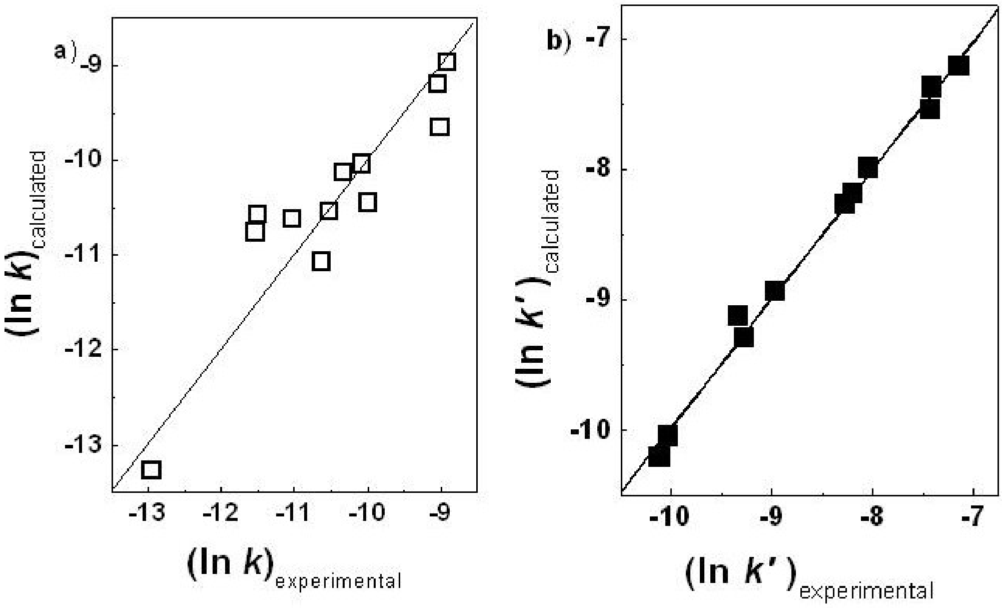


Figure 3.10: a) Plot of $(\ln k)_{calculated}$ against $(\ln k)_{experimental}$ for IMDA reaction of **6** in organic solvents, where $(\ln k)_{calculated}$ is obtained by multiple linear regression of $(\ln k)$ with α and π^*. b) Plot of $(\ln k')_{calculated}$ against $(\ln k')_{experimental}$ for IMDA reaction of **6** in ionic liquids, where $(\ln k')_{calculated}$ is obtained by multiple linear regression of $(\ln k')$ with α, β and π^*

Interestingly, the contributions by β and π^* 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, appeared to be very different. The magnitude of the coefficients also indicated 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 result explains the anion specific viscosity dependence observed. The strength of the cation–anion interaction decreases from $[BF_4]^-$ to $[NTf_2]^-$ i.e. $[NTf_2]^-$ is a weaker binding anion. The presence of $[NTf_2]^-$ as a counter-ion entails a greater charge to radius ratio as compared to that for the $[BF_4]^-$ anion. This would translate into a greater extent of bonding between the cation/anion and the substrate **6**. The substrate **6** will experience a higher friction or microviscosity. This explains the nearly identical rate constants for the reactions carried out in $[NTf_2]^-$ and $[BF_4]^-$ based ionic liquids, even though the viscosity of $[NTf_2]^-$ is much lower. In other words, changing the anion from $[BF_4]^-$ to $[NTf_2]^-$ decreases the bulk viscosity but fails to influence the microviscosity for the reactant **6**.

The long chain alkyl substituent on the cation probably leads to steric hindrance for the rotational diffusion of the reactant. The effect is enhanced due to the microheterogeneous nature of the ionic liquids.[91b] This means that apart from the directional coordination with the functional groups on the cation or anion, the substrate **6** should be preferentially solvated by the non-polar alkyl chains on the pyridinium cation. This may be another factor that is 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 counterproductive 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.

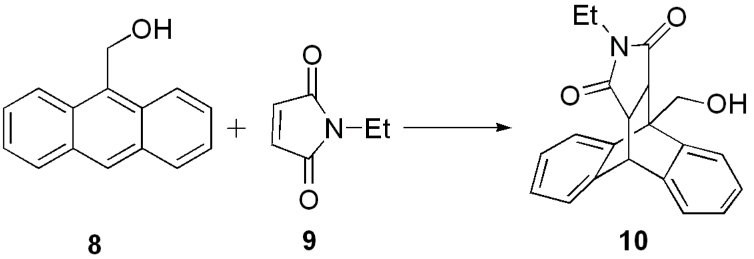
3.2.6 Conclusions

An unexpected ion-specific viscosity dependence of the rates of the IMDA reaction was observed and was attributed as a manifestation of the 'microviscosity' effect. The fact that the rate of an intramolecular reaction tends to show a strong viscosity dependence emphasizes the importance of further study along these lines. A comparison of an analogous study of a bimolecular reaction was deemed appropriate at this stage.

3.3 Viscosity dependence of bimolecular reactions

3.3.1 Introduction

The next stage in developing the correlation between the kinetics of organic reactions and the viscosity of the ionic liquids was to study the bimolecular reaction systems. The kinetics of the typical Diels–Alder reaction of anthracene-9-carbinol (**8**) with *N*-ethyl maleimide (**9**) were studied in the substituted pyridinium ionic liquids constituting the $[BF_4]^-$ and $[NTf_2]^-$ anions at diiferent temperatures (Scheme 3.4). The use of similar ionic liquids as reaction media facilitates the comparison between the results of the kinetic studies in the present work with those carried out for the unimolecular reactions in terms of the activation parameters and viscosity dependence. The section also includes a brief discussion on the physico–chemical properties of the $[BF_4]^-$ and $[NTf_2]^-$ ionic liquids responsible for the observed trends in reactivity.



Scheme 3.4:

3.3.2 Experimental section

Materials and methods: All the solvents used for the kinetic studies were of high purity (spectroscopy grade) and were used as obtained. The synthesis and purification of the ionic liquids was done according to the procedure outlined previously.[154] GR grade anthracene-9-carbinol (**8**) and *N*-ethyl maleimide (**9**) were used as obtained after ensuring their purity by recording UV-visible spectra of the pure components. NMR spectrum of the product was recorded in order to confirm its identity and to rule out the occurrence of any side reactions. All the ionic liquids employed were thoroughly dried under vacuum prior to use.

Kinetic analysis: 0.220g (1.05 mmol) of **8** was dissolved in 5 mL of DCM prior to use to give a 0.210 M stock solution. 47 μL of the stock solution was added to 1 mL of the ionic liquid, resulting in 10mM solution of the diene in the ionic liquid. 0.014g (0.112 mmol) of **9** was dissolved in 1 mL of the ionic liquid to yield a 0.112 M stock solution of the dienophile. 0.9 mL of this solution was allowed to equilibrate in a quartz cuvette at the desired temperature for 15–20 min. 0.1 mL of the 10 mM solution of **8** was then added to the cuvette. The final concentrations for a typical kinetic run were 1 mM of **8** and 100 mM of **9**. The progress of the reaction was monitored by following the time-dependent decay of the absorbance peak of **8** at $\lambda = 380$ nm. Since the concentration of the dienophile is about hundred times higher than that of the diene, the time-dependence of the decay is calculated to give the *pseudo*-first order rate constants, k'. The reported rate constants are an average of at least three kinetic runs on different samples and were reproducible within $\pm 5\%$.

3.3.3 Results and discussion

The Diels–Alder reaction of **8** + **9** is a typical reaction, which was previously employed by Breslow and Rizzo to investigate the salting effects in the hydrophobic acceleration of reactions.[165] Kumar and coworkers had employed solubility data and salting coefficients to facilitate an analysis of the salting effect in quantitative terms.[166] The reaction is, thus, fairly well-understood in terms of its mechanistic details and kinetic influences. The *pseudo*-first order rate constants, k' for the reaction **8** + **9** clearly show the viscosity–dependence of the bimolecular reaction — both in the $[BF_4]^-$ and $[NTf_2]^-$ based ionic liquids (Table 3.6). While the rate constants in the $[BF_4]^-$ based ionic liquids show a clear decrease with the increasing viscosity, the correlation between the rates and viscosity is not very apparent for the $[NTf_2]^-$ class of solvents. A similar behavior was also observed for the IMDA reaction of **6**. The lower rates in the $[NTf_2]^-$ based ionic liquids, despite their lower viscosities, observed for the intramolecular reaction of **6** was also observed for the bimolecular reaction of **8** + **9** (Figure 3.11). Although the extent of 'scattering' of data for the viscosity dependece of the Diels–Alder reaction **8** + **9** was greater than that observed for the IMDA reaction of **6**, the strong influence of the solvent viscosity was apparent from the plot.

Table 3.6: The *pseudo*-first order rate constants, k' for the Diels–Alder reaction of **8** and **9** in pyridinium ionic liquids along with their viscosities, η at 303 K.

Ionic liquids	η (cP)[a]	$10^5 k'(s^{-1})$[b]
[BP] [BF_4]	93.82	6.95
[HP] [BF_4]	212.00	6.05
[OP] [BF_4]	238.73	3.55
[3MBP] [BF_4]	117.53	5.05
[3MHP] [BF_4]	185.77	3.58
[3MOP] [BF_4]	243.61	3.02
[BP] [NTf_2]	43.42	3.97
[HP] [NTf_2]	60.95	3.43

[a] The data for viscosities are reproducible within ± 3%. [b] The rate constants are an average of three runs. The data agree to within ± 5%.

The results of the kinetic analysis of the IMDA reaction of **6** were subjected to further calculations on the basis of the Kramers theory.[35,151] The relative inefficiency of the $[NTf_2]^-$ based ionic liquids for the IMDA reaction of **6** was explained on the basis of a higher microviscosity experienced by the substrate for its rotational diffusion. This rationalization was based on a number of characteristic observations like the presence of a Smoluchowski limit as indicated by the non-linearity of the isoviscosity plots and the power dependence on viscosity (η^a, where $a > 1$). Previous modifications to the Kramers approach involved the frequency dependent friction concept[36,156] or extending the one-dimensional model into multiple dimensions.[157] Since these modifications could only be applied to fractional power dependence on solvent friction ($a < 1$), they were inadequate for the thorough computation of the observed solvent friction in ionic liquids.

In order to carry out a similar analysis for the reaction of **8** + **9**, the *pseudo*-first order rate constants were replaced by an approximate k_2 by dividing the k'

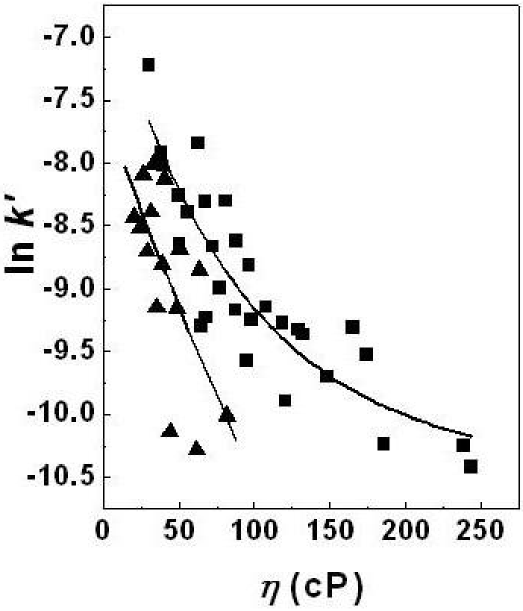


Figure 3.11: Plot of $\ln k'$ for the Diels–Alder reaction of **8** + **9** as a function of the viscosity, η of pyridinium ionic liquids with $[BF_4]^-$ anion (■) and $[NTf_2]^-$ anion (▲) at different temperatures.

with the concentration of the dienophile, which was in excess ($k' = [\mathbf{9}]_{excess}k_2$ — by definition). This was important to ensure the correct dimensionalities for the rate constant and the validity of the activation parameters thus derived. Figure 3.12 depicts a typical Arrhenius plot for the reaction in [BP][BF_4] while the activation parameters are listed in Table 3.7.

A comparative analysis of the influence of viscosity on the activation parameters of the bimolecular reaction of **8** + **9** with respect to those for the IMDA reaction of **6**, provides some interesting insights. The E_a values for the bimolecular Diels–Alder reactions in all the ionic liquids were observed to be sensitive to the variation in chain length (Table 3.7). Paradoxically, on going from butyl- to hexyl- and finally to the octyl-substituted ionic liquids, the rate constants decreased while the decreasing E_a values should have resulted in higher rate constants. This was explained by the simultaneous decrease in the $\ln A$ parameter. For example, η increased from 93.82 cP to 238.73 cP on going from [BP][BF_4] to

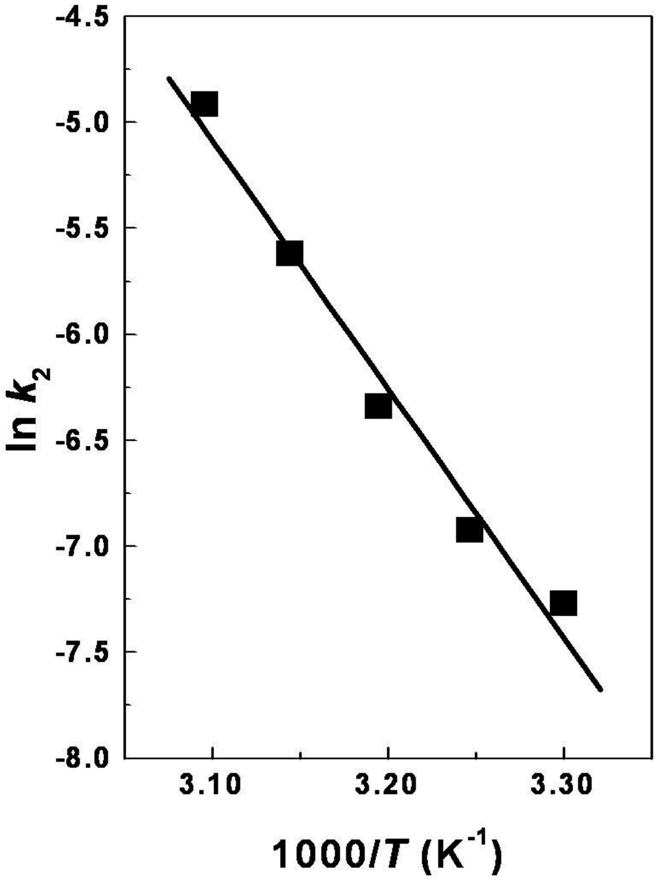


Figure 3.12: Arrhenius plot for the Diels–Alder reaction of **8** + **9** in [BP][BF$_4$] ($r^2 = 0.989$)

[OP][BF$_4$]. The E_a value for the Diels–Alder reaction, on the contrary, decreased from 97.61 kJ mol^{-1} in [BP][BF$_4$] to 74.49 kJ mol^{-1} in [OP][BF$_4$]. The observed decrease in the rates could be attributed to the decrease in the transmission coefficient ($\ln A$ falls from 31.31 in [BP][BF$_4$] to 21.80 in [OP][BF$_4$]).

A similar trend was also observed in the activation parameters of the IMDA reaction of **6**. The E_a decreased on increasing the chain length from butyl- to hexyl-, for example [BP][BF$_4$] against [HP][BF$_4$], although the variation in activation parameters is not very drastic. Further increase in the length of the alkyl substituent to octyl-, however, did not cause a further decline in the E_a parameter as observed for the bimolecular case. While the E_a for the IMDA

Table 3.7: Activation parameters, ($\ln A$ and E_a) for the reaction of **8** + **9** in different ionic liquids along with the activation energy for viscous flow, E_η.

Ionic liquids	$\ln A$	E_a ($\mathrm{kJ\,mol^{-1}}$)	E_η ($\mathrm{kJ\,mol^{-1}}$)[b]
[BP] [BF_4]	31.31 ± 3.15	97.61 ± 8.15	40.88 ± 1.98
[HP] [BF_4]	25.37 ± 5.19	83.22 ± 13.47	51.73 ± 2.45
[OP] [BF_4]	21.80 ± 4.25	74.49 ± 11.06	49.78 ± 2.66
[3MBP] [BF_4]	22.43 ± 5.53	75.57 ± 14.38	45.78 ± 1.97
[3MHP] [BF_4]	20.86 ± 4.92	71.92 ± 12.80	46.35 ± 2.00
[3MOP] [BF_4]	10.86 ± 4.27	46.89 ± 11.06	47.22 ± 2.02
[BP] [NTf_2]	18.78 ± 4.24	66.26 ± 16.21	31.85 ± 1.04
[HP] [NTf_2]	25.68 ± 5.34	84.05 ± 13.88	35.01 ± 1.09
[OP] [NTf_2]	23.34 ± 5.01	77.40 ± 15.63	36.65 ± 1.04

[a] The values for E_η are approximate since they are obtained by applying the Arrhenius equation to typically non-Arrhenius ionic liquids. All the resulting plots had $r^2 > 0.90$.

reaction of **6** was more sensitive to the chain length of the alkyl substituent in the $[NTf_2]^-$ based ionic liquids as compared to the $[BF_4]^-$ ionic liquids, no such inclination was observed in the present case. The comparison brings out the extremely complex nature in which the viscosity of ionic liquids influences the reaction profiles.

The 'intrinsic' activation parameters were determined from the isoviscosity plots (Figure 3.13). Unlike the isoviscosity plots for the intramolecular reactions, the plots for the cycloaddition of **8** to **9** were linear even at high values of viscosity. This implied that the reaction kinetics was subject to a 'non-Smoluchowski' regime. The resulting activation parameters are listed in Table 3.8 for a range of viscosities from 28 cP to 300 cP. The E_0 values remained nearly constant for different isoviscosity plots, except for the slightly increasing trend for the higher viscosities — the increase signifying an approaching Smoluchowski–like behaviour (Table 3.8). The average E_0 value, based on the data in Table 3.8 for the $[BF_4]^-$ ionic liquids is 61.78 $\mathrm{kJ\,mol^{-1}}$. Similar treatment of the $[NTf_2]^-$ ionic liquids yielded an average E_0 value of 76.03 $\mathrm{kJ\,mol^{-1}}$ and the $\ln A$ value of 22.68. It must be mentioned, however, that the average values for the $[NTf_2]^-$ ionic liquids

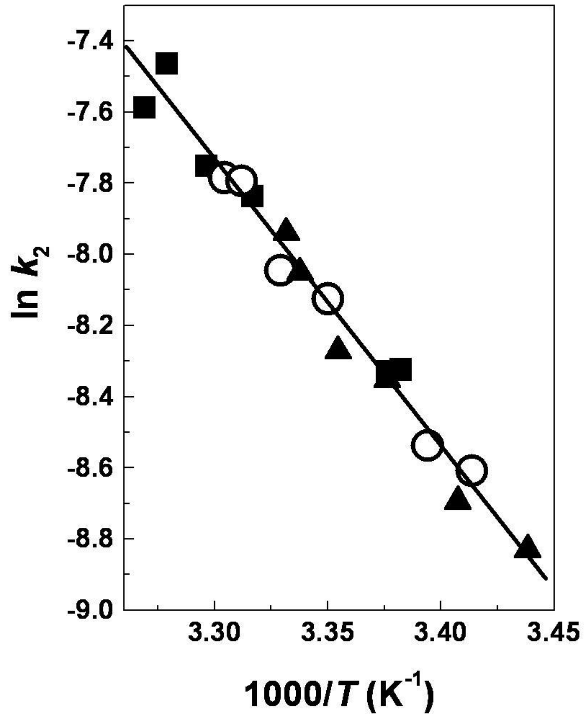


Figure 3.13: Typical isoviscosity plots for the Diels–Alder reaction of **8** + **9** in $[BF_4]^-$ ionic liquids at different viscosities - 200 cP(■), 250 cP(○) and 300 cP(▲)

are subject to greater error because the isoviscosity plots at higher viscosities exhibited a tendency towards non-linearity.

It should be noted that the overall E_0 value for the $[BF_4]^-$ based ionic liquids is lower that the E_a values listed in Table 3.7 (except for $[3MOP][BF_4]$ where the two are more or less equal within experimental error). This may imply that a fraction of E_η contributes at least partially to the activation energies, though the extent of contribution apparently decreases with increasing chain length. Due to the greater margin of error in the determination of E_0 for the $[NTf_2]^-$ ionic liquids, any quantitative comparison would be futile. However, it can be safely concluded that since E_a and E_0 are nearly equal in magnitude, the contribution of E_η to the reaction profile is limited.

As a final test for the influence of solvent frictional forces, the reduced rate constants, k_2^* for the bimolecular Diels–Alder reaction were plotted as a function

Table 3.8: Activation parameters for the Diels–Alder reaction of **8** + **9** from the isoviscosity plots at different viscosities in $[BF_4]^-$ ionic liquids.

η (cP)	$\ln A$	E_0 (kJ mol^{-1})
28	16.44 ± 2.19	59.20 ± 6.15
30	16.01 ± 2.03	58.11 ± 5.65
35	17.79 ± 3.26	63.27 ± 8.98
150	14.66 ± 3.71	56.20 ± 9.39
200	16.69 ± 2.32	61.52 ± 5.74
250	18.27 ± 1.73	65.51 ± 4.32
300	19.46 ± 2.40	68.51 ± 5.90

of viscosity (Figure 3.14), where:

$$k_2^* = k\, e^{E_0/RT} \tag{3.11}$$

such that:

$$k_2^* = (B/\eta^a) \tag{3.12}$$

The resulting value of 'a' was 0.537 for the tetrafluoroborate class of solvents, which implied an inverse, fractional power dependence on viscosity or solvent friction as opposed to the comparatively higher value observed for the IMDA reaction of **6**. The analogous plot for the $[NTf_2]^-$ based ionic liquids was highly scattered (Figure 3.15). Although a quantitative comparison between the values of 'a' is not appropriate, due to the dimensional inconsistencies between the unimolecular and the bimolecular rate constants, the results indicated that the bimolecular process was less susceptible to frictional forces in the solvent environment as compared to the intramolecular process.

The apparent paradox can be explained by considering the diffusion processes for the intramolecular and the intermolecular processes separately. While the IMDA reaction of **6** was shown to involve a primarily rotational diffusion as part of the substrate molecule, the intermolecular reaction requires translational diffusion of the reactants through the reaction medium. Since the nature of the diffusive motion and the resulting reaction coordinate, in each of these cases is

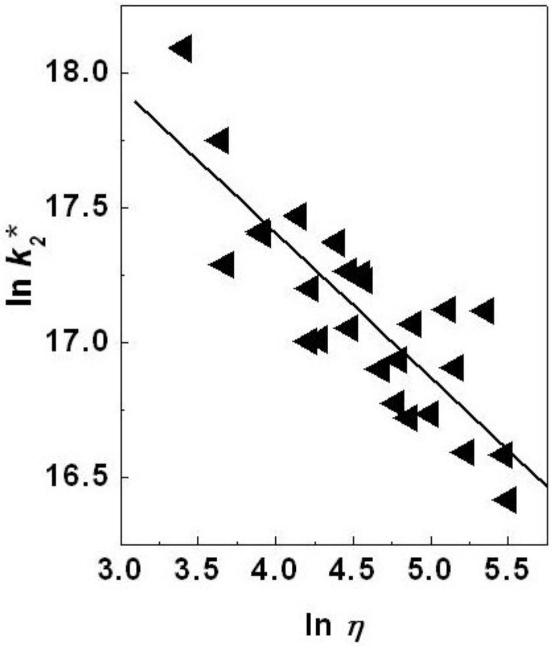


Figure 3.14: The plot of $\ln k_2^*$ against $\ln \eta$ — empirical fit to the equation $\ln k_2^* = \ln B - a \ln \eta$ i.e. $k_2^* = (B/\eta^a)$. ($r^2 = 0.836$) for the Diels–Alder reaction of **8** + **9** in $[BF_4]^-$ based ionic liquids

different, the effective friction felt by the molecules during the course of rotational and translational diffusion is also different.

Several groups have demonstrated that the translational diffusion of small molecules in ionic liquids is faster than that predicted by the Stokes-Einstein equation.[167] In a recent study of translational diffusion of molecules like benzophenone, carbon monoxide, diphenyacetylene and diphenylcyclopropenone, the diffusion coefficient was represented by a power law of the inverse of the viscosity, where the exponent is less than unity.[168] The size discrepancy between the diffusing molecules and the cations/anions of the ionic liquids translates into lesser solvent reorganization when the solute diffuses though the voids in the solvent. Thus, it is not surprising to find that in many cases, the effective friction (microviscosity) experienced by the solute for the translational motion is less than that predicted by the Stokes-Einstein equation (bulk viscosity). The ratio of the volume of the solvent molecule (V_S) to that of the probe (V_P) was also found to play

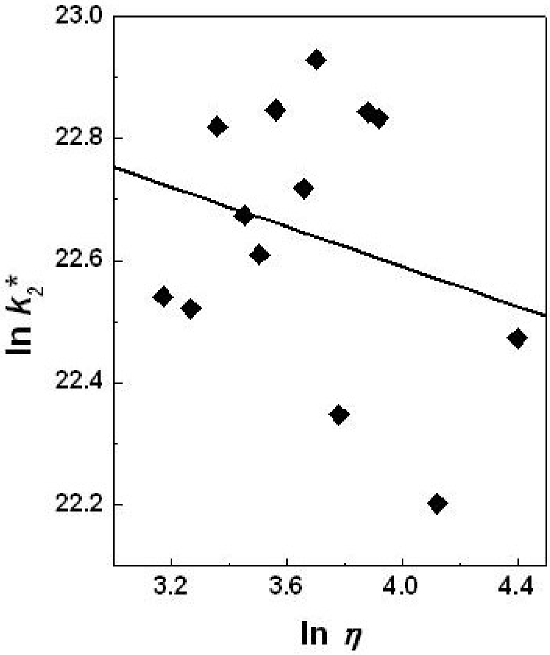


Figure 3.15: The highly scattered plot of $\ln k_2^*$ against $\ln \eta$ — empirical fit to the equation $\ln k_2^* = \ln B - a \ln \eta$ i.e. $k_2^* = (B/\eta^a)$. ($r^2 = 0.836$) for the Diels–Alder reaction of **8** + **9** in $[\mathrm{NTf_2}]^-$ based ionic liquids

a decisive role in the rotational diffusion of 9-phenylanthracene and rhodamine-110 in [BMIM][$\mathrm{PF_6}$] by applying the Gierer-Wirtz quasihydrodynamic theory.[169] More importantly, the experiments proved that in addition to mechanical friction, the solute solvent specific interactions like hydrogen-bonding interactions also affect the rotational diffusion. This explains the greater effect of viscosity on the bulkier, strongly interacting substrate for the intramolecular reaction than that on the comparatively smaller molecules diffusing translationally through the medium for the intermolecular process.

The results by Mali et al. support the present attempts to correlate the microviscosity experienced by the substrate **6** to the extent of the solute-solvent interactions, represented by the polarity parameters. The correlation between the polarity parameters and the rate constants of the reaction **8** + **9** in conventional organic solvents was also assessed in order to understand the strength of the solute-solvent specific interactions (Figure 3.16a).

$$\begin{aligned}(\ln k)_{calculated} &= -8.554(\pm 0.415) + 2.657(\pm 0.509)\alpha \\ &\quad -1.477(\pm 0.791)\beta - 1.529(\pm 0.642)\pi^* \\ &\quad (r^2 = 0.833)\end{aligned} \tag{3.13}$$

The rate constants, k for the reaction in $[\mathrm{BF_4}]^-$ ionic liquids were normalized for their viscosity dependence to give a modified rate constant, k'', as follows:

$$\ln k'' = \ln B - a \ln \eta \tag{3.14}$$

The resulting $\ln k''$ values were used for multiple linear regression analysis with the polarity parameters. Care was taken to employ the temperature-dependent polarity parameters of the ionic liquids.[164] The normalization was not carried out for the rate constants of the reaction of **8** + **9** in $[\mathrm{NTf_2}]^-$ ionic liquids, since it was assumed that the dependence of the rates on the bulk viscosity was weak. For the reaction between **8** and **9**, a reasonably good fit was obtained for a combination of the β and π^* parameters. (Figure 3.16b)

$$\begin{aligned}(\ln k'')_{calculated} &= -8.818(\pm 0.867) + 4.69(\pm 0.87)\beta \\ &\quad +4.30(\pm 0.91)\pi^* \\ &\quad (r^2 = 0.708)\end{aligned} \tag{3.15}$$

The absence of the a term in the multiple linear regression equation for the **8** + **9** reaction in ionic liquids leads to the conclusion that the hydrogen–bond donating property of the ionic liquid does not contribute to the stabilization/destabilization of the initial and the transition states. This is in contrast to the higher coefficients observed for the multiple linear regression analysis of the IMDA of **6** in ionic liquids earlier. Stronger solute–solvent interactions in the later case completely justify the higher microviscosity for that system.

3.3.4 Conclusions

The arguments yet do not explain the 'inefficiency' of the $[\mathrm{NTf_2}]^-$ ionic liquids, in terms of lower rates, despite their lower viscosity. The lack of data on the densities, dielectric constants, *ced* and other physical properties of the pyridinium class

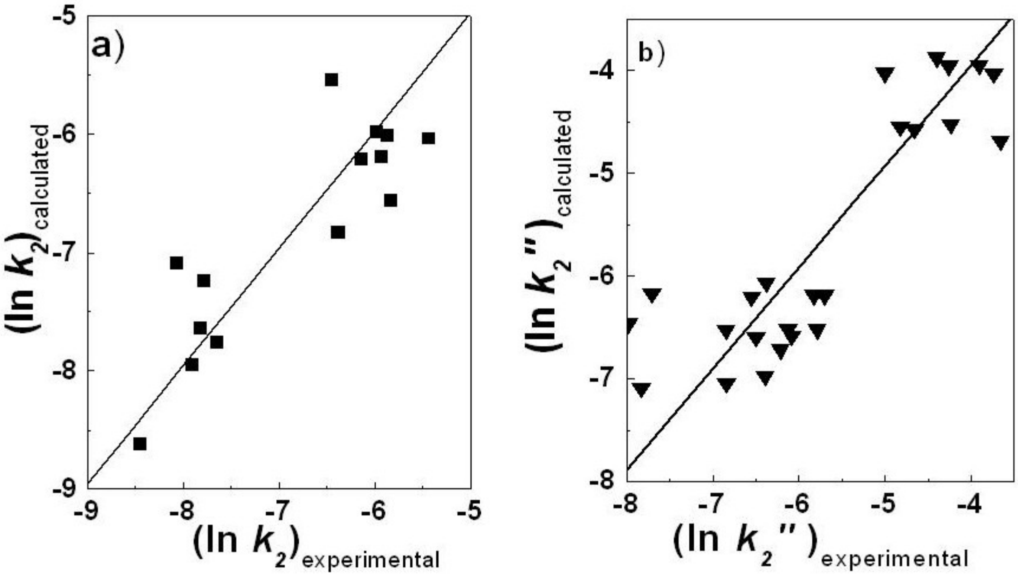


Figure 3.16: a) Plot of $(\ln k_2)_{calculated}$ against $(\ln k_2)_{experimenral}$ for the Diels–Alder reaction of **8** + **9** in organic solvents, where $(\ln k)_{calculated}$ is obtained by multiple linear regression of $(\ln k)$ with α, β and π^*. b) Plot of $(\ln k_2'')_{calculated}$ against $(\ln k_2'')_{experimental}$ for Diels–Alder reaction of **8** + **9** in ionic liquids, where $(\ln k'')_{calculated}$ is obtained by multiple linear regression of $(\ln k'')$ with β and π^*.

of ionic liquids further complicates the issue. In the absence of such quantitative information, it would be difficult to attempt any explanation for the observation. One of the few relevant studies is a model proposed by Kobrak for correlating the structure of an individual ion and the polarization character of the medium.[170] The model predicts that the strength of the solute–solvent interactions in ionic liquids is inversely proportional to the number density, ρ of the solvent ions. The correlation between the π^* parameter (a measure of the electrostatic interactions) and the number density, ρ of the ionic liquids was reportedly very high. The fact that the estimated molar volume of the $[NTf_2]^-$ ions (230 Å^3) is much greater than that for the $[BF_4]^-$ ions (73 Å^3) might be responsible for weaker solute-solvent interactions in the former.[171] The model should however, be applied with caution since it does not include structural inhomogeneities of the ionic liquids [172] nor the electrostriction about polar solutes.[173] Also, pyridinium ionic liquids were not a part of the database that was subjected to the correlational analysis.

Nevertheless, the intrinsic lack of solvating efficiency and the resultant absence of rate accelerations in $[NTf_2]^-$ based solvents is a crucial observation since the $[NTf_2]^-$ ion is one of the few discovered to date, which lower the viscosity of the ionic liquid to such a great extent. Not only does the presence of the anion impart high thermal and chemical stability, it also makes the resulting ionic liquids easier to handle due to their water-immiscibility. Although the number of the possible combinations of cations and anions forming ionic liquids is very high, only a few of them have been synthesized and still lesser number have been characterized thoroughly. Most of the novel ionic liquids synthesized in the last 5 years, including the ammonium, phosphonium and amino acid based compounds have extremely high viscosities and rely on the introduction of the $[NTf_2]^-$ anion for reducing the viscosity. Understanding the factors that can make an ionic liquid more efficient without compromising on the viscosity and handling ease is extremely important for any future work aimed at the synthesis of more efficient ionic liquids.

4

Salting Effects for the "on water" Wittig reaction: Hydrophobicity at the Interface

It looks like scientists will remain immersed in salt water for some time.[174]

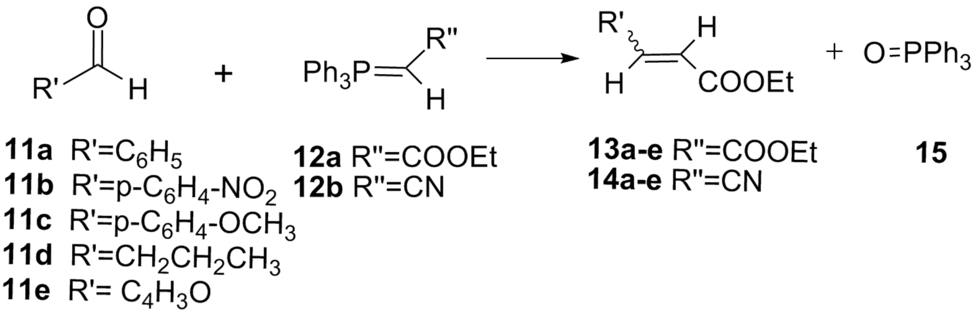
An unusual temperature-dependent effect of prohydrophobic and antihydrophobic additives on the rates of aqueous Wittig reactions is highlighted in the present chapter. Solubility studies and the kinetics of polymer-supported ylides have been pursued with an intention to understand the mechanistic features of the reaction. The observations are explained on the basis of previously reported experimental data and theoretical models about the aqueous interface. The intricacies in the complex phenomenon of length-scale dependent hydrophobicity is brought out by the interesting observations and subsequent observation.

4.1 Introduction

The development of the “on water” protocol by Sharpless and coworkers[67] has led to a revival of the scientific community’s interest in the potential applications of water and aqueous solutions as reaction media. The increasing importance of the finding is reflected in the several reports successfully employing the strategy for various purposes.[68] Future methodologies are bound to employ the “on water” technique widely, due to ease of separation of products and catalysts, recycling efficiency and controlled selectivity. However, the understanding of the physical–organic aspect of “on water” reactions is still in its infancy. The kinetic and mechanistic studies of such interfacial processes present an intimidating task, due to the difficulties in accuracy of analytical measurements, separation of individual rate determining factors and extension of the mechanism to include the complexities of a heterogeneous process and the constantly altering distribution of the reactants and products between the two phases. It becomes important to normalize the rate constants for a heterogeneous process for the reduced dimensionality. The specific rate constant for an interfacial reaction thus determined is bound to differ from that for the analogous reaction in homogeneous conditions. The localization of one of the reactants at the interface in a bimolecular reaction will invariably slow down the reaction. In order to overcome the additional energetic cost and yet lead to faster reactions, the activation energy for the interfacial process should be lower than that for the homogenous process.

Meanwhile, Wittig reactions of stabilized and semi-stabilized ylides in aqueous medium, leading to enhanced rates and yields have been recently reported.[138,139] The exact role of water in accelerating the reactions has not been explained clearly, but the involvement of “hydrophobic forces” has been indicated in almost all the reports. For example, Wu et al. have reported that the yield of the reaction of 4-anisaldehyde with (carboethoxymethylene)triphenyl phosphorane increased from 77% in 90 min in water to 94% in 30 min in 1.2 M aqueous LiCl. The increase in reactivity on addition of LiCl is assumed to be an indication of the dominance of hydrophobic forces in accelerating the reaction.

For further verification of the role of water, kinetics of the “on water” Wittig reactions were studied in various aqueous salt solutions at different temperatures (Scheme 4.1).



Scheme 4.1:

4.2 Experimental section

Materials: The aldehydes benzaldehyde (**11a**), 4-anisaldehyde (**11c**), butraldeyde (**11d**) and furfural (**11e**) were freshly distilled prior to their use. GR-grade 4-nitrobenzaldehyde (**11b**) was used as obtained. Commercially available GR grade salts - NaCl, LiCl, $LiClO_4$, guanidinium chloride (GnCl) and urea were used as obtained.

Synthesis of (carboethoxymethylene)triphenylphosphorane (12a): Ethylbromoacetate (0.751 g, 4.5 mmol) was added dropwise to the suspension of triphenylphosphine (1.049 g, 4 mmol) in 50 mL water. The resultant solution was stirred for 30 min at room temperature to give (carboethoxymethylene)triphenyl phosphonium bromide. The reaction mixture was then washed with ether to remove the unreacted starting materials. Dilute NaOH solution was added dropwise till complete precipitation of the ylide was observed. The precipitate was filtered and washed till neutral to give the ylide **12a** (NMR spectral data of the ylide presented in Appendix B.4).

Synthesis of (cyanomethylene)triphenylphosphorane (12b): The synthetic procedure was similar to that for **12a** except for the use of bromoacetonitrile in place of ethylbromoacetate (NMR spectral data given in Appendix B.4).

Kinetic Analysis: For a standard kinetic run, the 1mM aldehyde solution (10 mmol in 10 mL) was allowed to equilibrate, using a constant temperature water bath (precision 0.01 K) at the desired temperature for at least 30 min. The reaction was initiated by addition of ylide (5 mmol in 10 mL) into the above aldehyde solution. The resulting heterogeneous mixture was stirred vigorously to prevent aggregation of solid ylide particles. At regular intervals, 100 μL aliquots were withdrawn for their analysis and the reaction was quenched using 0.2 M HCl.

The amount of aldehyde in the solution was estimated by conversion to the hydrazone derivative by addition of 5×10^{-3} M methanolic solution of 2,4- dinitrophenylhydrazine.[175] On addition of 5% KOH, the hydrazone derivative gave a bright red colouration, the absorbance of which was measured spectrophotometrically. The change in absorbance due to change in concentration of the aldehyde was measured. The plot of $\ln(A_0/A)$ against time gave a straight line of gradient k', the *pseudo*-first order rate constant. The rate constant thus obtained was, in fact, an apparent rate constant, k_{app} since the reaction mixture was heterogeneous in nature. The rate constants were reproducible within ± 3% at 298 K and ± 6% at 338 K.

Homogeneous and heterogeneous kinetic analysis: For the reaction of **11a** with **12a** in homogeneous conditions, a 1.25 mM stock solution of the ylide **12a** was prepared by overnight stirring. 8 mL of the solution was equilibrated at 298 K for 30 min. The reaction was initiated by addition of 2 mL of temperature-equilibrated 5 mM solution of **11a** to result in a final concentration of 1 mM for the aldehyde and the ylide each. The progress was monitored by taking aliquots at regular intervals.

The homogeneous run was compared to the heterogeneous reaction in which 10 mL of the appropriately diluted aldehyde solution was equilibrated at the required temperature. The reaction was initiated in this case by the addition of solid ylide to result in suspension of ylide particles. The amount of aldehyde and ylide present in the reaction mixture in both the cases was identical.

4.3 Results and discussion

4.3.1 Temperature dependence of salting effect

The Wittig reaction of benzaldehyde (**11a**) and the ylide **12a** were monitored in water and different aqueous salt solutions, which included prohydrophobic salts (“salting-out” agents) like LiCl and NaCl in addition to antihydrophobic additives (“salting-in” agents) like GnCl, $LiClO_4$ and urea. An optimum temperature of 338 K was chosen, in addition to room temperature (298 K) for the kinetic analysis. Since the ylide particles were insoluble/partially soluble, the resulting reaction mixture was heterogeneous. At 338 K, the addition of 1 M LiCl and 1 M NaCl to the reaction mixture led to an observable increase in the rate of reaction of **11a** with **12a** (Table 4.1). In contrast, at 298 K, the use of prohydrophobic additives — LiCl and NaCl retarded the rate of the reaction. This observation was contradictory to all the previous reports about the rate-enhancing effect of salts like LiCl and NaCl.[48,176]

In order to confirm that the retarding effect of additives was general, the kinetic studies were repeated for different substrates — 4-nitrobenzaldehyde (**11b**), 4-anisaldehyde (**11c**), butraldeyde (**11d**) and furfural (**11e**) — under identical conditions. Retardation in rates was observed for all the three aldehyde substrates on addition of prohydrophobic salts at 298 K. The results indicated that the effect was not substrate–specific.

Table 4.1: Relative rates, k_{rel} (with respect to water) for the aqueous Wittig reactions of **11a-e** with **12a-b** in different reaction media at 298 K.[a]

Aldehyde	Ylide	T(K)	$k_{rel}^{[a],[b]}$			
			NaCl	LiCl	GnCl	$LiClO_4$
11a	**12a**	298	0.74	0.86	0.95	0.88
11a	**12a**	338[c]	1.27	1.12	0.55	1.27
11b	**12a**	298	0.83	0.99	1.10	1.06
11c	**12a**	298	0.52	0.64	0.98	0.71
11d	**12a**	298	0.61	0.70	1.62	0.81
11e	**12a**	298	0.47	0.64	1.85	0.55
11a	**12b**	298	0.57	0.56	0.96	0.59

[a] $k_{rel} = k_{app}/(k_{app})_{water}$ where k_{app} is the apparent rate constant in the given medium. All kinetic studies done with 1 M concentration of the prohydrophobic or antihydrophobic additive. Reactions carried out with 1 mmol aldehyde and 5 mmol of ylide in 10 mL of solvent. Experimental error = ± 3%. [b] The isolated yields (and E/Z ratios) at 298 K after a reaction time of 3 h are 92% (93:7) in water, 89% (91:9) in aq. LiCl, 89% (91:9) in aq. NaCl, 71% (82:18) in aq. GnCl and 84% (83:17) in aq. $LiClO_4$. [c] Experimental error = ± 6%.

The magnitude of the relative rates was found to depend on the concentration of the salt added. The effect was exactly opposite at the two temperatures: 298 K and 338 K (Figure 4.1). An extension of current notion of “salting-out” and “salting-in” behaviour could not have accounted for this contrasting effect of salt additives on the rates in water and aqueous salt solutions.[177]

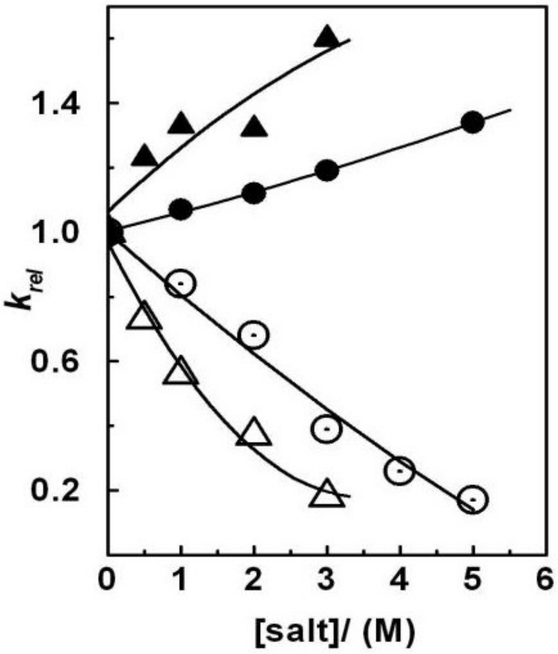


Figure 4.1: Relative rates for the Wittig reaction of **11a** with **12a** in aq. NaCl at 338 K (▲), aq. LiCl at 338 K (●), aq. LiCl at 298 K (⊙) and aq. NaCl at 298 K(△)

The results for the antihydrophobic additives were equally remarkable. Firstly, the rates did not show a clear trend in the presence of $LiClO_4$. At 298 K, the rate of reaction between **11a** and **12a** decreased in a solution of 1 M $LiClO_4$ as compared to that in water only. At 338 K, however, the reaction proceeded faster in presence of 1 M $LiClO_4$. Further kinetic analysis at 338 K using higher concentrations of $LiClO_4$ was not possible due to experimental limitations. This observation showed that the effect of 1 M $LiClO_4$ solution (a salting-in additive) was similar to that observed for the salting-out salts like LiCl and NaCl. The addition of urea, on the other hand, led to rate-enhancement at both the temperatures — 298 K and 338 K. The reaction of **11a** with **12a** in 1 M aqueous urea as reaction medium at 298 K was 38% faster than that in water only, while at 338 K, the increase in rate was 78% in urea solution as compared to that in water at the same temperature. The behaviour of all the three antihydrophobic additives was sufficiently inconsistent with each other to prevent generalization on the basis of salting-in and salting-out property. While GnCl had a negligible effect on the rate of the reaction at 298 K, the presence of $LiClO_4$ at the same temperature caused retardation in the rates. Both the salt additives decrease the rates at 338 K. Urea is the only additive of those studied, which accelerated the Wittig reaction at both the temperatures.

The salting effects of slower reacting aldehyde substrates like **11c** were difficult to study due to the non-linearity in the the plots of $\ln(A_0/A)$ against time, t (the slopes of which were used to determine the apparent rate constants, k_{app}) at 338 K. The plots showed a characteristic break in all the reaction media studied (Figure 4.2). The break was sharper for the salting-in or antihydrophobic salts like GnCl and $LiClO_4$. For GnCl, in particular, the slope was close to zero after some initial increase. The discontinuity or break was more prominent for the slower-reacting substrates. The more reactive aldehydes probably underwent complete or nearly complete conversion into products before the occurrence of a similar change in the rate determining interactions. Such discontinuity is generally a characteristic feature of reactions, which involve a change in the rate determining step or the dominant molecular interactions. Since the nature of the break was highly sensitive to the changes in the composition of the reaction medium, it was thought to be caused by changes in the reactant–solvent interaction.

The temperature dependent kinetics were studied to gain further information about the intriguing aspects. The temperature dependence of the rate of the reaction **11a** + **12a** in water and in 3 M LiCl was studied from 298 K to 338 K (Figure 4.3). However, extending the kinetic studies to lower temperatures revealed a discontinuity or non-linearity in the Arrhenius plots for the “on water” reaction mixture. The Arrhenius plot of the reaction of **11a** with **12a** in water (Figure 4.4a) was non-linear, with a break in linearity at a point corresponding to approximately $T = 318$ K. (An attempt to fit a least-squares line gave an error of 8.25% in the slope and 16.55% in the intercept.) Such a break in linearity is generally associated with a change in mechanism or the rate-determining step. It

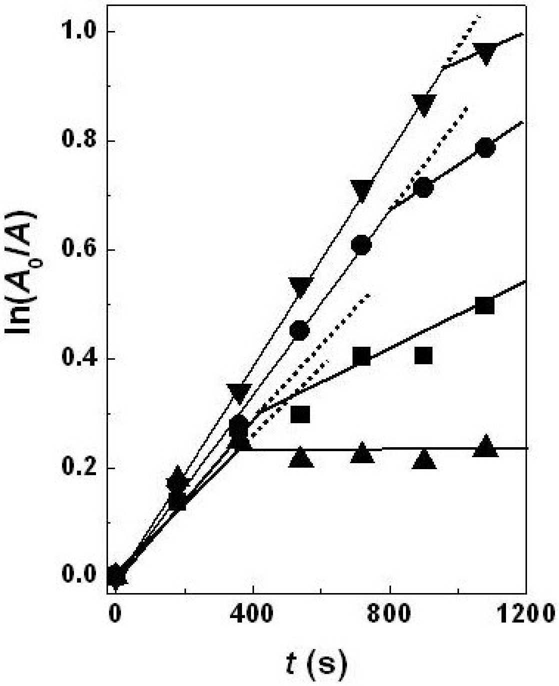


Figure 4.2: Non-linearity in the plot of $\ln(A_0/A)$ against time, t for the Wittig reaction of **11c** with **12a** at 338 K in 1M NaCl(▼), 1M LiCl(⊙), water (■) and 1M GnCl (▲).

is highly improbable that the mechanism of the reaction should undergo a change within a temperature interval of 40 K. The non-linearity may thus arise due to a change in the rate determining step or increasing dominance of some competitive step in the mechanism. The Arrhenius plot of the same reaction in 1-propanol was linear, thus effectively ruling out the possibility of a change in the mechanism at a given temperature and implicating the role of the reaction medium (Figure 4.4b).

Thus, the salient features emerging from the kinetic studies of the salting effects for “on water” Wittig reaction can be summarized as follows:

- The addition of any salt to the reaction medium at 298 K, except urea, was observed to lead to a decrease in the apparent rate of the reaction. The effect was independent of the aldehyde substrate employed and was, in fact observed for numerous salt additives conventionally known for their

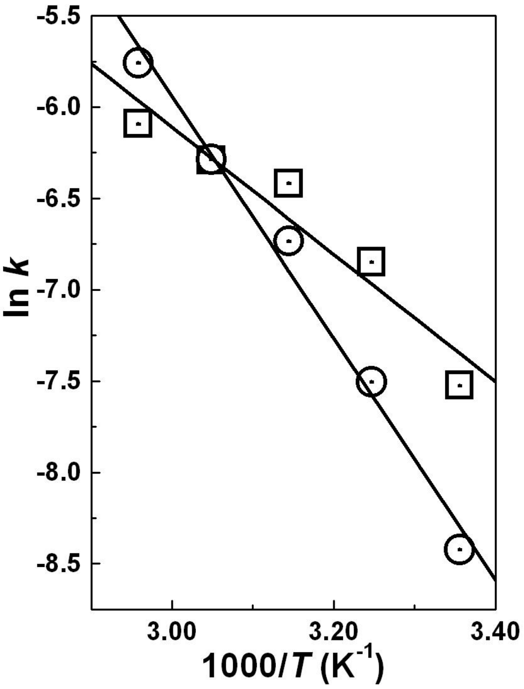


Figure 4.3: Arrhenius plots for the Wittig reaction of **11a** with **12a** in water (⊡) and 3 M LiCl (⊙).

prohydrophobic or salting-out behaviour (Table 4.1).

- At higher temperature, i.e. 338 K, the presence of salts like LiCl and NaCl accelerated the reaction, while the salts like GnCl lowered the rate of the reaction.
- $LiClO_4$, known to be an antihydrophobic additive, caused an increase in the rate at 338 K.
- Urea was the only additive among those studied which could accelerate the reaction at the lower as well as the higher temperature.
- The rate profiles for the slower reacting substrates and the Arrhenius plot for the "on water" showed a non-linear behaviour.

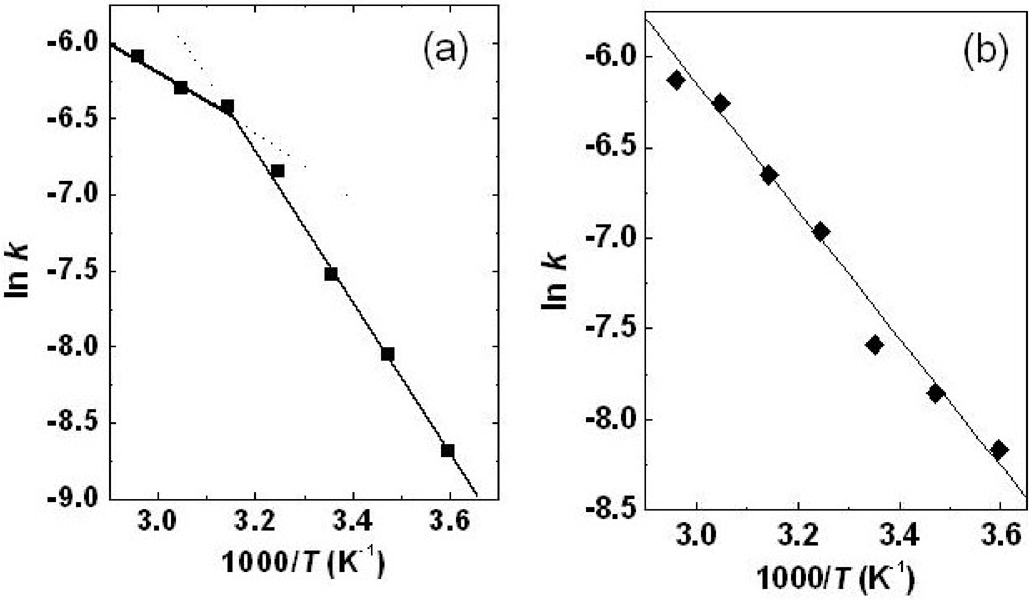


Figure 4.4: a) Non-linearity in the Arrhenius plot for the "on water" Wittig reaction of **11a** with **12a**. b) Arrhenius plot for the Wittig reaction of **11a** with **12a** in 1-propanol.

An "on water" reaction is characterized by the insolubility of the reacting components in the medium and the typical "dewetting" thermodynamics at the mesoscopic to macroscopic water-organic interface.[58] The solubility factor is important because heterogeneity is the common characteristic for all "on water" processes. If the reaction takes place predominantly by the "on water" pathway, then the surface of the solid ylide particles will be the "site" of the interfacial Wittig reaction. The spatial arrangement of water molecules around a macroscopic surface such as the ylide particle will differ significantly from that around a hydrophobically hydrated solute molecule.[59] In order to understand the cause of the anomalous behaviour in the presence of additives, it was important to ascertain whether the reaction was indeed accelerated due to the prevalent "on water" conditions and if it did, to determine the magnitude of the resulting rate acceleration by comparing with the rates observed in conventional solvents. Then, each of the two factors could be analyzed independently for their role in the distinctive reactivity patterns.

4.3.2 Reaction in homogeneous bulk or “on water”

For a heterogeneous reaction mixture, the reaction can take place either at the surface of the ylide particle (interfacial reaction) or in the bulk water (homogeneous reaction). Two identical sets of reactions — one consisting of completely homogeneous reaction mixture and another of a heterogeneous nature — were carried out. The concentration of **11a** did not change much after 40 min for the homogeneous reaction at 298 K (Figure 4.5). Under identical conditions, more than 25% of the **11a** had undergone conversion to the product in heterogeneous conditions within 35 - 40 min. This provided substantial evidence that the reaction pathway was predominantly interfacial in nature.

Table 4.2: Apparent rate constants (k_{app}) for Wittig reaction of **11a** with **12a** samples having varied particle sizes at 298 K.

Particle diameter,(μm)[a]	$10^4 k(\mathrm{s}^{-1})$[b]
162.7	3.47
131.7	5.28
70.5	5.37
64.8	5.51
39.4	5.95

[a] Samples of different particle sizes prepared by using a rolling ball mill and their diameter determined using a particle size analyzer. [b] Reactions carried out with 1 mmol of **11a** and 5 mmol of **12a** in 10 mL of water. Experimental error = ± 4%.

The rates were determined for ylide samples having different particle sizes (Table 4.2). A smaller particle size leads to a greater surface area exposed to the reaction medium, and this is reflected in the higher apparent rate constants. The observations provided additional evidence for the predominantly “on water” or interfacial mechanism of the reaction.[67] In such cases, the heterogeneous conditions are actually found to “catalyze” the reactions by a notable magnitude.[69]

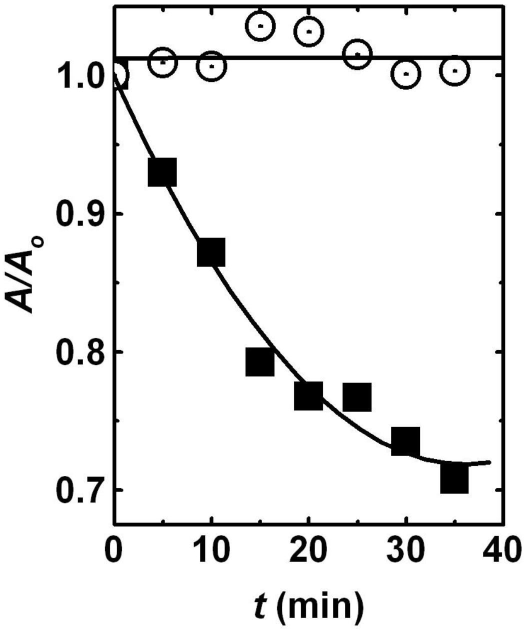


Figure 4.5: Relative absorbance A/A_0(an indicator for the extent of conversion) against time, t plotted for the reaction of **11a** with **12a** at 298 K under (⊙) homogeneous conditions and (■) heterogeneous conditions.

A better assessment of the magnitude of the hydrophobic effect could be obtained by comparison of the rate of the reaction in water to that in conventional organic solvents (Table 4.3). The apparent rate constant in water was higher than the *pseudo*-first order rate constants, k' in all other organic solvents used, except methanol and ethylene glycol (“water-like” solvents). However, the reaction was heterogeneous in water and had been shown to occur primarily at the interface. For proper comparison with homogeneous reactions in organic solvents, the rate constants must be converted appropriately and reduced to the same units. Extending the kinetic model proposed by Jung and Marcus to reduce the rate constants for the homogeneous and the interfacial Wittig reactions to similar units,[69] the rate constants in organic solvents were converted to k_{homo}

and those in water and aqueous solutions to $k_{interface}$, both referred commonly as $k_{intrinsic}$.

Homogeneous reaction:

$$k_{intrinsic} = k_{homo} = \frac{M_0}{Z_H}\frac{k}{[\mathrm{B}]_0} \tag{4.1}$$

where M_0 is the molar concentration of the solvent, $[\mathrm{B}]_0$ is initial concentration of the reactant taken in excess and Z_H is the coordination number for homogeneous reaction (≈ 6).

Heterogeneous or interfacial reaction:

A few assumptions should me made about the reaction system in order to extend the model by Jung and Marcus to the “on water” Wittig reaction system. Jung and Marcus had specified that the organic phase should not contain any water for the model to be valid. Since the organic phase in this case was a solid particle (the ylide particles), this assumption is valid for the “on water” Wittig reaction system. The ylide particles were bound to exclude any water in the interior. The rest of the assumptions are stated as follows:

1. The ylide particles were spherical with a radius r (the statistical average obtained from the results of particle size distribution analysis taken).
2. The reaction products were removed from the surface of the particles as soon as they are formed, thus implying a reduction in the size of the particles.
3. The surface coordination number Z_S was taken as 4.
4. The water-ylide interaction and solvent reorganization around the ylide particles was much faster than the interfacial chemical reaction.

The fact that the “neat” reaction did not occur (physical barrier for the permeation of aldehyde molecules inside the solid ylide particles) further simplified the situation. For the “on water” Wittig reaction, if [A] is the instantaneous concentration of aldehyde at time t and $n_{BS}(t)$ is the “mole fraction” of the ylide molecules on the surface of the solid ylide particles, then:

$$-\frac{d[\mathrm{A}]}{dt} = k_{interface}[\mathrm{A}]Z_S n_{BS}(t) \tag{4.2}$$

where Z_S is the surface coordination number, 4. For a sample with an average particle radius r, the quantity $n_{BS}(t)$ can be correlated with the surface-to-volume ratio as follows:

$$\frac{n_{BS}(t)}{n_B(t)} = \frac{4\pi r^2(t)dr}{(4/3)\pi r^3(t)} \tag{4.3}$$

where $n_B(t)$ is the total mole fraction of ylide at time t, dr is the molecular radius of ylide molecule and $r(t)$ is the radius of the "spherical" ylide particle at time t.

$$\begin{aligned}
n_{BS}(t) &= \frac{3\,dr}{r(t)} n_B(t) &(4.4)\\
-\frac{d[\mathrm{A}]}{dt} &= k_{interface}[\mathrm{A}]Z_S\frac{3\,dr}{r(t)} n_B(t) &(4.5)\\
-\int \frac{d[\mathrm{A}]}{[\mathrm{A}]} &= 3k_{interface}Z_S\frac{n_B(t)\,dr}{r(t)}\int dt &(4.6)\\
k_{interface} &= \frac{r(t)}{3Z_S n_B(t)dr} \times (-1/t)\ln([\mathrm{A}]/[\mathrm{A}]_0) &(4.7)\\
k_{interface} &= \frac{r(t)}{3Z_S n_B(t)dr}\, k_{app} &(4.8)
\end{aligned}$$

Taking $r(t) \approx 0.8r$, which corresponds to the radius of a particle when 50% of the reaction is complete simplifies the evaluation of the equation. Since B is taken in excess, the "mole fraction" of B is taken to be constant.

$$n_B(t) = n_B(0) = \frac{[\mathrm{B}]_0}{[\mathrm{A}]_0 + [\mathrm{B}]_0} \tag{4.9}$$

Given the initial "concentration" of A and B are in a 1:5 ratio, the quantity $n_B(0) = 0.83$.

$$k_{interface} = \frac{r}{2.49 Z_S dr}\, k_{app} \tag{4.10}$$

The "intrinsic" rate constants, $k_{intrinsic}$ thus derived have the same units and are compared in Table 4.3.

For the reaction in water, the particle size was taken to be 19.72 μm as determined by particle size analysis and the molecular radius of the ylide, dr was considered as 5 Å. The recalculated intrinsic rate constants, $k_{intrinsic}$ brought out the drastic difference in the rates of the Wittig reaction "on water" or aqueous media as compared to those in organic solvents (Table 4.3). The $k_{intrinsic}$ for the Wittig reaction between **11a** + **12a** in *n*-heptane as compared to that in water at 298 K differed by three orders of magnitude. Although the apparent rates

Table 4.3: Comparison of the *pseudo*-first order rate constants, k' and the intrinsic rate constants, $k_{intrinsic}$ for the reaction of **11a** with **12a** in different solvents.

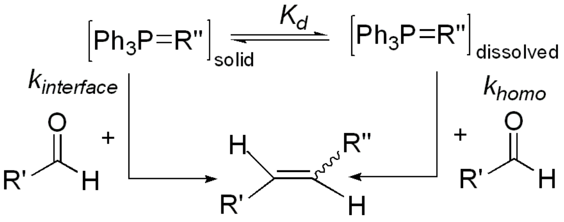
Solvents	$10^4 k(\mathrm{s}^{-1})$[a]	$10^3 k_{intrinsic}(\mathrm{s}^{-1})$[b]
Chloroform	0.13	5.42
Dimethylsulphoxide	0.14	6.57
Acetonitrile	0.23	14.68
Ethyl acetate	0.32	10.92
n- Heptane	0.55	12.51
Water	5.28[c]	2090.79
Methanol	8.34	686.32
Ethylene glycol	12.02	717.25

[a] Samples of different particle sizes prepared by using a rolling ball mill and their diameter determined using a particle size analyzer. [b] Reactions carried out with 1 mmol of **11a** and 5 mmol of **12a** in 10 mL of water. Experimental error = ± 4%. [c] For water, rate constant $k' = k_{app}$.

were higher in methanol and ethylene glycol than in water, a comparison of the intrinsic rate constants indicated that the “on water” reaction was the fastest. This contradiction can be explained if it is noted that only a limited number of ylide molecules (the molecules at the interface) are available for the aqueous interfacial reaction i.e. the actual amount of the ylide available for the reaction at any given point of time is negligible when compared to that calculated on the basis of the formal concentration. The results suggest that the apparent 14% decrease in rate in 1 M aqueous LiCl at 298 K relative to that in water reflects a much drastic change in the intrinsic rates of the reaction ($k_{intrinsic}$ for 1 M LiCl $= 5.91\ \mathrm{s}^{-1}$). The actual magnitude of the salting effects for “on water” reactions is, thus, very high.

4.4 Role of solubility

As previously mentioned, the main difference between reactions carried out “on water” and in organic solvents is the insolubility of the reactants. In addition, numerous physicochemical processes can possibly dominate the effect of additives on the rates. The possibility that the salts exert their effect at higher temperatures by controlling the solubility equilibrium of the ylide could not be ruled out (pictorial representation of the solubility equilibrium model shown in Scheme 4.2). The addition of LiCl or NaCl should ‘salt-out’ the ylide, thus increasing the proportion of the undissolved ylide and favouring the faster “on water” reaction as compared to the sluggish homogeneous reaction of the dissolved ylide. Similarly, if the presence of an additive like GnCl promotes the dissolution of the ylide, then the decrease in rate is expected, since $k_{homo} \ll k_{interface}$. Complete dissolution of ylide implies that negligible amount of the ylide would be available for the interfacial pathway, and hence, the abrupt “plateau” observed for the slower reacting aldehydes as seen in Figure 4.2. Before proposing any further hypothesis, a detailed study of the solubility trends was necessary.



Scheme 4.2:

The solubility of the phosphorus ylide **12a** was measured in the aqueous salt solutions at different concentrations of the salts to explain the apparent anomaly in salting effects. The phosphorus ylide was chosen for the solubility studies because of the fact that it is the reactant which remains partially/completely undissolved in the given reaction conditions. The relative rates $\ln(k_{rel})$ plotted against relative solubilities $\ln(S/S_0)$ failed to show any correlation at 298 K (Figure 4.6a) while a linear correlation was observed for the data at 338 K (Figure 4.6b).

The results showed that the solubility of the substrates is capable of explaining the trends in reactivity on the basis of the salting-out/salting-in mechanism at higher temperatures but fails to show correlation with the results at room temperature. Assuming that the solubility changes play a decisive role in the reaction kinetics, the rate-accelerating effect of $LiClO_4$ at 338 K could be explained by the

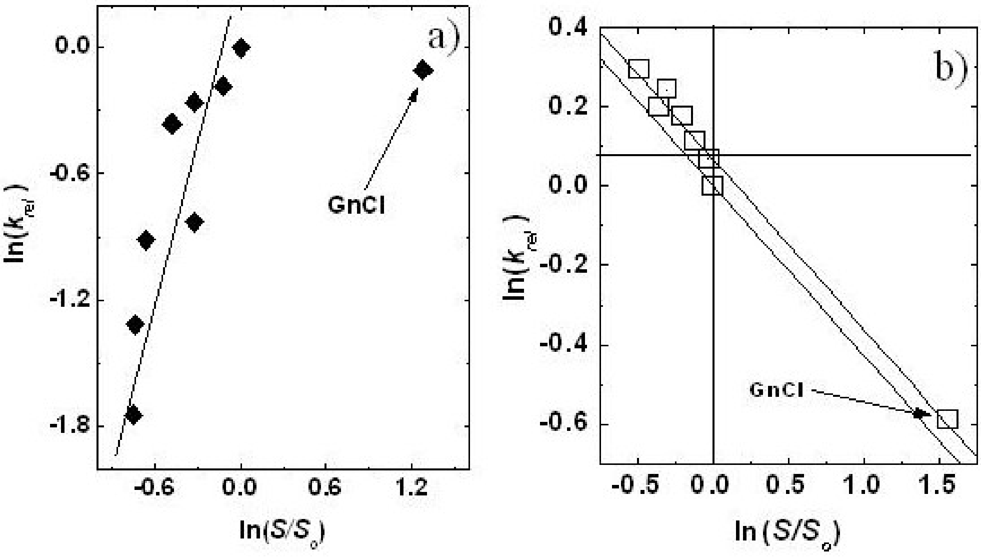


Figure 4.6: Plot of $\ln(k_{rel})$ against $\ln(S/S_0)$ for aqueous salt solutions at a) 298 K and b) 338 K.

fact that it acts as a “salting-out” agent at that temperature for lower concentrations (1 M $LiClO_4$) as shown in Figure 4.7. This behaviour of $LiClO_4$ has also been mentioned in one of the previous reports regarding the salting effects on the selectivity of Diels–Alder reactions.[119] But it is important to ascertain that the observed correlation is not misleading or coincidental.

In order to explore whether the solubility of the ylide is limited only to being an “indicator” property or it is the driving force in determining the reaction rates, experiments were carried out with polymer-supported ylides, which excluded the contribution of solubility completely by virtue of the ylide being covalently bound to the polymer bead. It would be then possible to delineate the contributions due to the changes in dewetting phenomenon and those due to variations in solubility of the substrates. It was observed that the anomalous temperature–dependent salting effects persist for the reactions with the polymer-bound ylide as well (Table 4.4). The presence of salt additives at 298 K slowed down the progress of the reaction while the same additives accelerated the rates at 338 K — the acceleration being proportional to the concentration of the salt additives. Although these observations cannot completely discount the role of the substrate

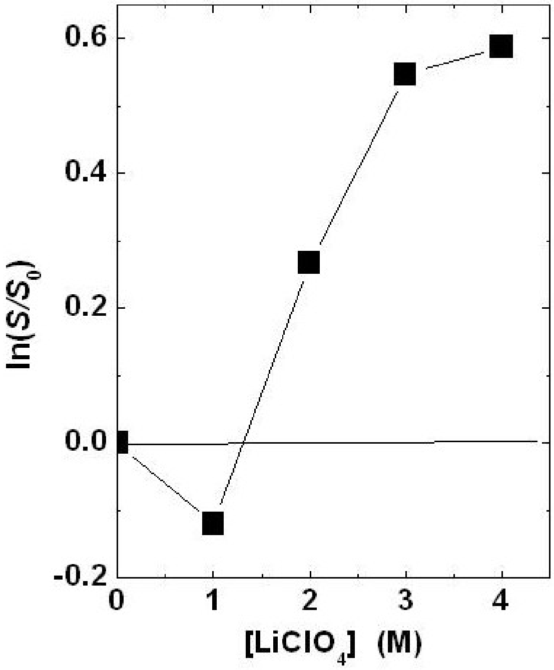


Figure 4.7: Relative solubity $\ln(S/S_0)$ of ylide **12a** in aqueous $LiClO_4$ solutions as a function of concentration of salt at 298 K.

solubility, its dominance in explaining the odd temperature-related salting effects of the “on water” Wittig reactions is definitely limited and it cannot be the sole factor determining the temperature dependence of the salting effect.

Alternatively, the ‘dewetting’ phenomenon caused by the length-scale dependence of hydrophobic hydration to explain the drastic variations in the rates for interfacial reactions in aqueous media with temperatures could be invoked. The characteristic spatial arrangement of water molecules around an extended macroscopic interface and its effect on the interfacial processes is a crucial aspect of the model. Only limited experimental data and theoretical guidelines are available since it is extremely difficult to design experiments, which can give any conclusive evidence about the salting effects on dewetting of suspended ylide particles.

Table 4.4: Relative rates, k_{rel} for the reaction of **11a** with polymer supported form of the ylide **12a** in aqueous solutions.

Reaction medium	T (K)	$k_{rel}^{[a],[b]}$
0.5 M NaCl	338	1.52
1.0 M NaCl	338	1.73
1.5 M NaCl	338	2.02
2.0 M NaCl	338	2.53
0.5 M LiCl	338	1.41
1.0 M LiCl	338	1.54
1.5 M LiCl	338	1.75
2.0 M LiCl	338	1.88
1.0 M GnCl	338	0.46
1.0 M $LiClO_4$	338	0.22
1.0 M NaCl	298	0.72
1.0 M LiCl	298	0.86
1.0 M GnCl	298	0.33

[a] $k_{rel} = k_{app}/(k_{app})_{water}$ where k_{app} is the apparent rate constant in the given medium. [b] Experimental error 4% at 298 K and 6% at 338 K.

4.4.1 Ion effects at the interface

In order to comprehend the temperature dependence of the salting effects, it is important to know the structure of water at the water–ylide interface with reference to its effect on the reaction energetics at ambient temperature i.e. 298 K. Then the effect of the ions from the added salts on the structural features at the interface and the consequent outcome of the reaction rates at 298 K should be correlated. It is possible that addition of salts like NaCl may lead to a greater “dewetting” of the ylide i.e. a lesser number of water molecules at the interface available with free –OH bonds. The resultant change in the extent of interaction (wider “dewetted” region or lesser water molecules at the interface) may lead to a weaker “on water” effect. But this reasoning does not provide any clue for the relative effects of different salts or the inverse effect due to change in temperature. The inverse effect of additives at higher temperature suggests a change in the nature of the interfacial interactions with temperature. Hence, understanding the change in the structure of water and the interfacial interactions as a function of temperature so as to elucidate the interplay of forces at 338 K would be the next stage of reasoning. The effect of salt additives on the altered interfacial interactions at the higher temperature should explain the atypical observations satisfactorily.

The interface between the ylide and aqueous medium, which is the site for the Wittig reaction, is a macroscopic interface. The “dewetting” at the interface induced by the lengthscale dependence of hydrophobicity implies that it may then be treated as an extended air-water interface (Figure 4.8).[59] As a result, the salting effects for the Wittig reaction at the ylide-water interface can be analyzed in terms of the experimental and computational information readily available for the air-water surface. *Ab initio* molecular dynamics simulations have shown that the air-water interface is typified by the presence of free or ‘dangling’ –OH bonds, which are estimated to constitute 36% of the interface. [178] In comparison, the sum frequency generation (SFG) spectra for the air-water interface showing a sharp feature at 3700 cm^{-1} for the free –OH bonds indicate that these bonds occupy approximately 20% of the interface.[179] The simulations also showed that the lowering of the HOMO for each water molecule near the interface results in increase in the number of ‘reactive sites’ as compared to the bulk. This observation supports the ‘dangling’ –OH catalyzed “on water” reaction mechanism, proposed by Jung and Marcus.[69]

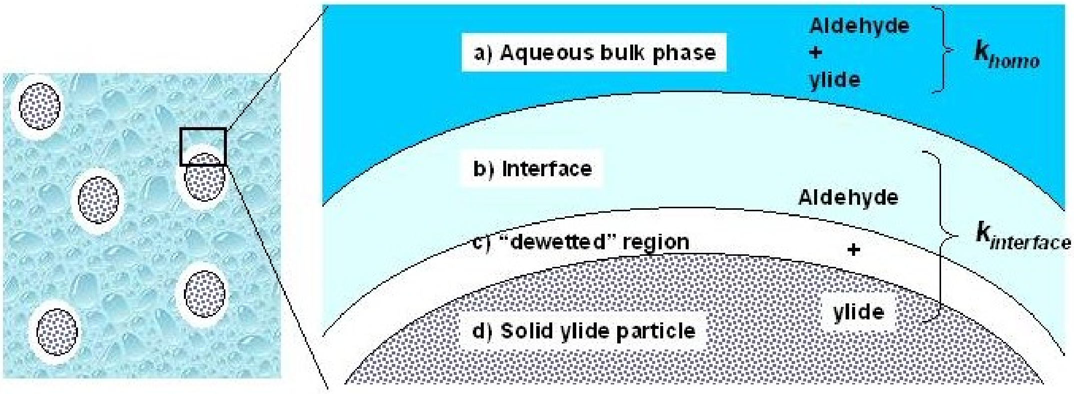


Figure 4.8: Schematic representation of the “on water” Wittig reaction.

The introduction of ionic components in the system has interesting consequences on the distribution of the ‘dangling’ –OH groups through displacement perturbation.[180] Most importantly, the discernible effect of the salt additives on the interfacial properties may thus be independent of the kosmotropic and chaotropic convention[174] and may even follow inverse Hofmeister series (SO_4^{2-} < NO_3^- < I^-) as shown by spectroscopic measurements.[181] Recent modeling studies have shown that large, polarizable anions tend to be polarized by the surface anisotropy and are stabilized by the attractive ion-water polarization interactions, leading to an overall excess anion adsorption for the interface.[182] Inorganic cations are excluded from the surface but are present below the surface so as to form associated ion pairs with the anions. The ion pair disrupts the hydrogen-bonded network at the interface due to the anionic interactions with the free –OH bonds. The effective perturbation, also known as the specific ion effect at the interface, depends on the anion charge density, polarizability, ionic association and ionic strength. The disruption of the free –OH bonds in the presence of ionic components was also by SFG experiments in which the free –OH peak disappears at high concentration of the additives.[183]

The specific ion effect thus explains the observation of a reduced rate constant at 298 K due to the addition of any salt to the medium. The disturbed free –OH network in the presence of the chloride ions in NaCl and LiCl is less effective in catalyzing the “on water” pathway. Since the polarizability of the anion depends on the extent of its ionic association with the cation, which in turn determines the resultant perturbation of the free –OH bonds at the interface, the Li^+ salts are bound to show a weaker effect as compared to the Na^+ salts. Unlike the halide salts of sodium and other metal cations, similar data for interfacial behaviour of GnCl salts is unavailable at this stage, making it difficult to comment about the effect of the GnCl salts. The fact that addition of GnCl lowers the surface tension while the other salts are known to increase it, indicates that the interfacial behaviour of GnCl is bound to be different from the other salts additives. The relatively higher polarizability of the Gn^+ cation and its ability to participate in the hydrogen bonding network in a manner not possible for the Na^+ or the Li^+ ions, may cause minimal perturbation of the interfacial arrangement of water molecules. The results in Table 4.5 for different salts, are thus, in good agreement with the polarizability model. More importantly, the rate reducing tendency of the highly polarizable ClO_4^- salts at 298 K can also be clarified by the ion-specific perturbation effect along the same lines, without invoking the kosmotropic/chaotropic convention.

Table 4.5: Relative rate constants, k_{rel} for the “on water” Wittig reaction of **11a** + **12a** in aqueous solutions at 298 K.

Reaction medium	$k_{rel}^{[a]}$
1.0 M KBr	0.66
1.0 M KCl	0.65
1.0 M NaBr	0.81
1.0 M $NaNO_3$	0.71
1.0 M $NaClO_4$	0.59

[a] $k_{rel} = k_{app}/(k_{app})_{water}$ where k_{app} is the apparent rate constant in the given medium. Experimental error 3% at 298 K.

The extension of the aforementioned reasoning to the results obtained at higher temperature should be based on the effect of temperature on the free –OH network. The free –OH bonds at the interface are known to persist up to temperatures as high as 353 K.[179] Computational studies have also indicated that the orientational order at the interface, up to a depth of $\sim$ 7 Å, is identical at $T = 275$ K and $T = 360$ K.[184] However, thermodynamic study of the hydrophobic association at mesoscopic to macroscopic length scales points toward a minimum in ΔG of hydrophobic association at $T \approx 340$ K, the minimum shifting to lower temperatures and becoming more pronounced with increasing solute size.[185] The minimum is associated with a sharp decrease in the entropical contribution, such that the value of ΔS at $T = T_S = 360$ K is zero. It is noteworthy that for temperatures at which ΔS is zero, the ordering of the interfacial water molecules does not disappear. The paradox is resolved by considering the fact that an increase in temperature will cause a decrease in the density of water molecules, leading to a proportional increase in the translational entropy at the interface relative to the bulk.

It is difficult to speculate on how the addition of salts can affect the interfacial interactions at higher temperatures due to the fact that no information is available for aqueous interfaces in the presence of salts at higher temperatures.

Nevertheless, it is interesting to note that the hydrophobic association at the interface undergoes a transition from entropy dominance at lower temperatures to enthalpy dominance at higher temperature ($\Delta S = 0$). It is then possible that the enthalpic contribution to the interfacial interactions due to the addition of salt additives becomes dominant at a higher temperature (338 K), whereas it might be less at a lower temperature (298 K), resulting in an inverse effect of the salt additives on the rates of the Wittig reaction. The non-linearity of the Arrhenius plot is an additional evidence for such a transition. This approach provides only a tentative guideline for further relevant work in the area.

4.4.2 Urea at the interface

The specific ion interactions at the air-vapour interface cannot be extended to account for the special effect of urea on the rates of the reaction. Remarkably, urea is the only additive which increases the rate of the “on water” Wittig reaction at 298 K. The effect of urea on the structure of water has been the subject of much controversy — with evidences supporting a chaotropic effect,[186] kosmotropic effect[187] and negligible change in water structure.[188] Recent simulation studies have demonstrated conclusively that urea can participate in the hydrogen-bonding network of water within the tetrahedral geometric constraints and with minimum disruption of the overall structure.[189] The similarity in the resulting urea–water hydrogen bonding with water–water hydrogen bonding is shown by the fact that the local oxygen distribution pattern for urea is similar to that for the oxygens in bulk water.

Unlike the ionic salt additives, no experimental information is available for the spatial arrangement of urea at the air–water interface and its consequences for the free –OH network. But given the fact that urea molecules tend to assimilate themselves into the hydrogen-bonding network in the bulk, it is possible that the urea molecules at the interface do not disrupt the free –OH bonds of water. The hydrogen atoms in urea can act as additional sites for accelerating the reaction, provided the orientation of the urea molecule is appropriate. These speculations can be verified only after substantial information, experimental and computational, is available.

4.5 Conclusions

The present work brings out the fundamental difference between the salting effects for “on water” reactions as opposed to those observed for homogeneous aqueous reactions. The temperature dependence of the salting effects provides evidence of the fact that the interfacial interactions are governed by specific ion effects rather than the conventional chaotropic/kosmotropic interactions. An explanation for the effects of salt additives on aqueous processes should, thus, take into account the relevant lengthscale of interactions. Understanding the physical-organic aspects for such processes is bound to greatly enhance the potential applications of the “on water” methodology.

5

Interfacial Reactivity and Stereoselectivity of "on water" Reactions in the Presence of Alcoholic Cosolvents

The world will be a better place when scientists — and nations — solve their respective boundary problems.[190]

A detailed study of the variation in the interfacial reactivity and selectivity of "on water" reactions in the presence of increasing amounts of alcoholic cosolvents is discussed in the present chapter. The initial increase in the rates of "on water" on the addition of alcoholic cosolvents is contrary to the sharp decrease in rates observed for the homogenous aqueous reactions. The existing theoretical framework is presented in terms of a typical "on water" process to enable a discussion of the experimental observations with reference to changing composition of the reaction medium. On the basis of the interesting observations of reactivity and selectivity variation with composition of the reaction medium, a simple 'signature' characteristic is proposed for "on water" reactions.

5.1 Introduction

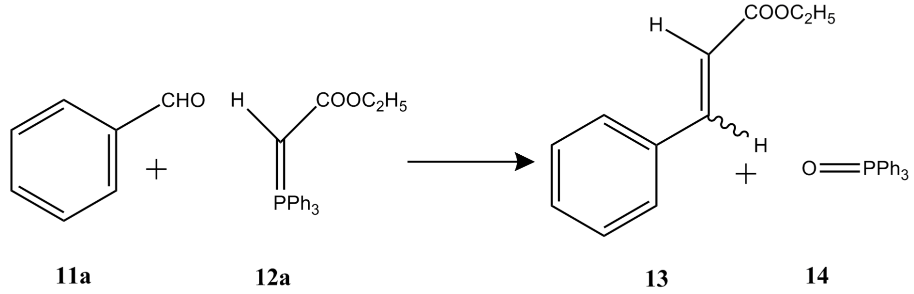
The spectacular rate–enhancing effect of water as a solvent medium is widely reported for numerous organic reactions.[43] However, the marginal solubility of organic substrates in water and aqueous media was thought to be a major deterrent in the scaling up of aqueous reactions for practical applications. In order to overcome this limitation, considerable efforts were directed towards the functionalization of substrates or reagents[191] or towards the design of biphasic processes using phase transfer catalysts.[192] The “on water” protocol promoted by Sharpless and coworkers established that the low solubility of organic substrates in aqueous systems need not necessarily be a deterrent to the progress of the reaction.[67] Contrary to conventional views, the interfacial mechanism was observed to be the dominating pathway for most of the transformations. The “on water” pathway is also known to have an influence on the regio- and stereochemical outcome of the reaction.[193]

Despite these encouraging developments, the industrial-scale applications of the “on water” methodology may still face numerous obstacles, including the lack of in-depth understanding of the mechanistic processes at the water-organic interface. Very little is known quantitatively about the reactivity or selectivity of the substrates at the interface. This is not surprising, given the numerous practical and analytical difficulties present in studying the interface. Even when a satisfactory analytical procedure has been established for studying the interface, the interpretation of the results is not straightforward. Any interfacial reaction is affected by numerous processes like diffusion of the reactants to the interface, the orientation of the reactants at the interface and the solubility effects. It is only recently that significant progress has been achieved in this direction through detailed modeling approaches and sophisticated analytical techniques.[194] The application of these techniques has resulted in the emergence of a comprehensive picture in terms of solvation and reactivity at the interface.[195] Nevertheless, the use of such sophisticated analytical techniques is limited. The introduction of simpler methods of analysis and a general ‘rule-of-thumb’ for characterizing and differentiating the “on water” reactions from their homogeneous counterparts would be preferred.

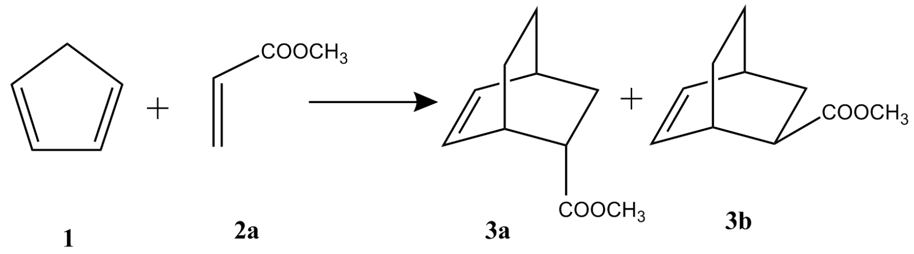
For example, almost all the studies on the hydrophobic effects on selectivities of Diels–Alder reactions employ dienes and dienophiles in concentrations well within the solubility limits.[63,107, 110,176] Given the low solubility of most of the reactants, this means that the concentrations are extremely low to be of any practical relevance. Thus, while the predictions and models were valid for the typically homogeneous reaction systems, the inferences could not be extended to suspensions or heterogeneous reaction systems. Most of the hypotheses put forth in the studies may not be relevant for the actual scaled-up processes. In view of the interesting temperature dependence of the salting-in and salting-out additives for “on water” Wittig reactions observed in the previous chapter, further study was deemed necessary and instrumental in unraveling the fundamental processes that govern the “on water” catalysis.

Another impediment for scale-up of “on water” reactions is the fact that the stirring power per unit volume required to produce a given value of interfacial area per unit volume increases with the volume of the reaction vessel/container. In scaled-up reaction systems, where the extension of the interface is small compared to the volume of bulk phases, the increase in the absolute rate caused by the interface may be more than compensated by the very much larger amounts of reactants present in the bulk phases. In order to ensure a smooth transition of the “on water” protocol from a chemist’s flask to the reactor vessel, it is important to address these issues.

Water–alcohol mixtures have been employed extensively in the past as mechanistic tools to study the origin of hydrophobic acceleration of organic reactions.[66,196] These mixtures appeared to be promising solutions for the “synthetic chemists’ dilemma” of choosing between the enhanced absolute reactivity at the aqueous interface against the very much larger amounts of reactants and the resultant greater conversion accessible in the bulk phases. Ironically, in all the previous studies, the concentration of the reactants in the kinetic analyses using water–alcohol systems was kept low enough to ensure complete homogeneity, even in pure water. The response of a typical “on water” system to the addition of alcoholic cosolvents and the resultant transition form heterogeneous to homogeneous reaction conditions, although of much practical significance, has not been studied.



Scheme 5.1:



Scheme 5.2:

In the present work, the effect of addition of increasing amounts of an alcoholic cosolvent on the reactivity and selectivity of C–C bond forming reactions carried out in aqueous suspensions was studied. The focus was on two important class of C–C bond forming reactions — the Wittig reaction of benzaldehyde (**11a**) with (carboethoxymethylene)triphenylphosphorane (**12a**) (Scheme 5.1) and the Diels–Alder cycloaddition of cyclopentadiene (**1**) with methyl acrylate (**2a**) (Scheme 5.2). The solvent composition was varied from that of pure water to pure alcohol composition. The presence of the cosolvent could alter the “local” solute- solvent interactions, while gradually leading to “homogenization” of the reaction medium. The possibility of employing bulk solvent parameters to identify the dominating interactions determining interfacial reactivity and selectivity was explored.

5.2 Experimental section

Materials: The aldehyde **11a** and the dienophile **2a** were distilled prior to their use. the diene **1** was freshly cracked from its dimer and stored in deep freeze. GR grade solvents and deionized water were used for the experiments. The ylide **12a**

and the polymer-supported ylide were synthesized as described in Section 4.2 on page 70.

Kinetic analysis: The standard kinetic procedures were as mentioned in Section 3.3.3 on page 56 and Section 4.2 on page 70. Rates determined by using GC analysis with chlorobenzene as the internal standard. For the estimation of rate of formation of the *endo* isomer, k_{endo} and the rate of formation of the *exo* isomer, k_{exo} independently, the GC was calibrated seperately for each isomer. **1** was condensed with acrylic acid and the resultant *endo* and *exo* bicyclic acids were separated by iodolactonization method as reported earlier by Evans et al. [197] The iodolactone was cleaved reductively with zinc and acetic acid to get pure *endo* acid in high yield.[198] The bicyclic acids were then individually treated with methanol and concentrated H_2SO_4 under reflux for 18 h to get the corresponding esters — methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (**3a**, **3b**). Identical GC response factors observed for both the isomers. The reactions carried out with 2.5 mmol of **1** and 12.5 mmol of **2a** (a 1:5 ratio of the diene and the dienophile) at 298 K to determine the independent rate constants, k_{endo} and k_{exo} (NMR spectrum of iodolactone intermediates described in Appendix B.5).

5.3 Results and discussion

5.3.1 Theoretical framework

The study of an “on water” process, in accordance with the convention adopted for any interfacial process, can be represented at three different levels — the kinetic or molecular level, the local or microscopic level and the macrokinetic or macroscopic level — each employing a seperate model. The information from a lower scale model is used as an input for the model at the next scale. The kinetic model is built in accordance with the principles of formal kinetics and describes chemical interaction between the components of the system at the molecular level in terms of mechanism, energies of activation, and rate and equilibrium constants of chemical reactions.

The local model builds on the information derived from the kinetic model, taking into account the inhomogeneous distribution energy and reactants in the bulk phases and the interface. The local model is characterized by mass transfer rate, conversion of the transferred reactant, topology of the reaction zone, concentrations and distribution of reaction groups, etc. In order to understand the solvent effects of “on water” reactions, the pseudophase formalism which treats the aqueous suspension as a three–layer bulk system and ignores the temporal variation in shape and size of the suspended droplets/solid particles is modified (Figure 5.1). The reaction mixture is assumed to consist of three distinct pseudophases: an aqueous phase (w), an organic phase (o) and the interface (i). For “on water” reactions, the organic phase consists of the water insoluble reactants suspended in aqueous environment. The reactants are partitioned between the three pseudophases based on relative affinities and diffusion processes — denoted by the respective partition functions. A complete quantitative analysis of the kinetic or stereoselectivity data would involve estimation of the partition coefficients (K) and the rate constants (k). Care must be taken to rule out the other possible scenario experimentally, wherein one of the reactants is transferred through the interface into the bulk and the reaction takes place in the bulk, near the interface but not “on” the interface.

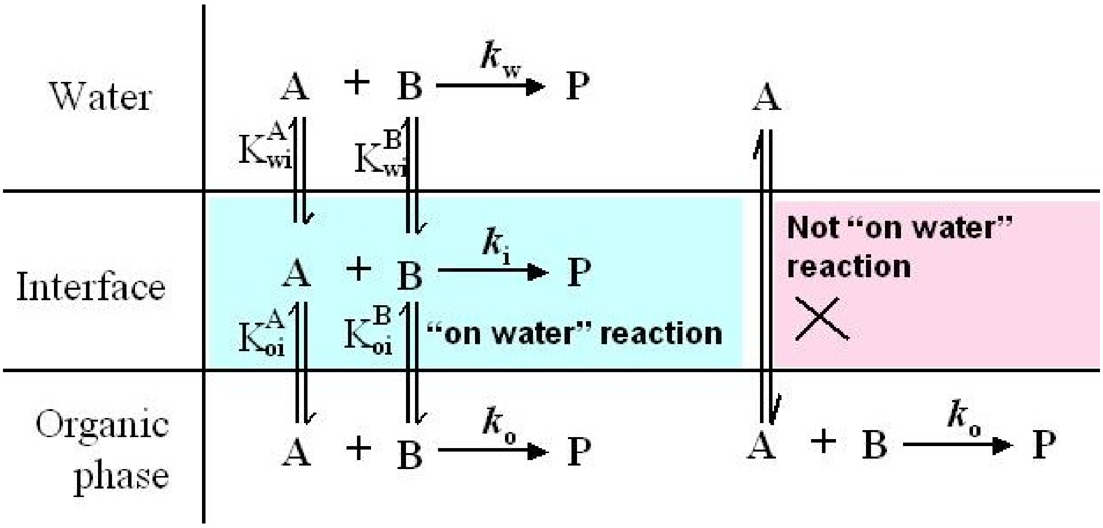


Figure 5.1: Local kinetic model for a general “on water” reaction

The observed rate of the reaction is in effect, the total of the rates at all the pseudophases and the rates of diffusion and adsorption of the reactants. Some important assumptions will be made for simplifying the application of the model to experimental kinetic data of common C–C bond forming reactions:

1. The diffusion of the reactants to the reaction site in the bulk or the interface in a typiccal “on water” reaction is much faster than the rate of the reaction. This implies that the distribution of the reactants between the pseudophases is an equilibrium property and the process is not diffusion limited. (Exceptions include electron transfer reactions, free radical reactions, proton transfer reactions etc.)

2. The reaction does not undergo a change in the mechanism from one pseudophase to another. The basic rate law describing the order of the reaction remains the same in all the pseudophases.

3. The rates of the reaction in the three pseudophases are largely independent, affecting each other only by changing the net amount of the reactants available for the process.

In order to reduce the rates in the neat, aqueous and interfacial pseudophases to the same units, the approach suggested by Jung and Marcus was followed. [69] Accordingly, the rates were described in terms of the number mole fraction of reactant B, n_B. Taking Z_x to be the coordination number between the two reactants in a given pseudophase, the product $Z_x n_B(t)$ represented the probability that the two reactants were within the “reacting distance” at a given time instant t. The resulting rate expression was given by equation 5.1, subject to the conditions stated in equations 5.3 and 5.4.

$$\frac{d[\mathrm{P}]}{dt} = k_o[\mathrm{A}]_o[\mathrm{B}]_o + k_w[\mathrm{A}]_w[\mathrm{B}]_w + k_i[\mathrm{A}]_i[\mathrm{B}]_i \tag{5.1}$$

$$\begin{aligned}\frac{d[\mathrm{P}]}{dt} &= k_o[\mathrm{A}]_o Z_o n_{\mathrm{B}o} + k_w[\mathrm{A}]_w Z_w n_{\mathrm{B}w} + k_i[\mathrm{A}]_i Z_i n_{\mathrm{B}i} \\ &= k_o[\mathrm{A}]_o Z_o n_{\mathrm{B}o} + k_w[\mathrm{A}]_w Z_w n_{\mathrm{B}w} + k_i N_d \bar{\mathrm{A}}_i Z_i n_{\mathrm{B}i} \end{aligned} \tag{5.2}$$

$$[\mathrm{A}]_o + [\mathrm{A}]_w + [\mathrm{A}]_i = [\mathrm{A}]_\mathrm{T} \tag{5.3}$$

$$n_{\mathrm{B}o} + n_{\mathrm{B}w} + n_{\mathrm{B}i} = (n_\mathrm{B})_\mathrm{total} \tag{5.4}$$

where N_d is the total number of suspended droplets or particles in the reaction mixture and $\bar{\mathrm{A}}_i$ is the average number of molecules of species A on the surface of one droplet or particle at time t. The model was general enough to accommodate multi-component or multistep reactions, although only the case of an irreversible single-step bimolecular reaction is pictorially represented (Figure 5.1). Since the model did not contain any a priori dependence on the shape of the interface, it could be applied to highly agitated systems as well.

The results thus obtained led to the macroscopic or macrokinetic model, which could predict the evolution of the characteristics of the reaction system as a whole in terms of the bulk properties of the solvent systems and measurable properties of the interface. In case of systems with intensive stirring, the macroscopic model is often the only tool for establishing the relation between the experimentally observed characteristics and the processes occurring at the interface. For macrokinetic modeling of the interface, the two intrinsic properties of interfaces — the interfacial pressure and the interfacial potential are generally known to influence the reaction rate. In the case interfacial pressure, Π:

$$[\partial(\ln k)/\partial\Pi] = \Delta A^{*}/RT \tag{5.5}$$

where ΔA^{*} is the difference in area between the transition complex and the reactant molecules i.e. area of activation. It can be seen that the effect of interfacial pressure on reaction velocity depends on the sign as well as the magnitude of ΔA^{*}. When the intensity factor is electrical potential, V:

$$[\partial(\ln k)/\partial V] = \Delta q^{*}/RT \tag{5.6}$$

where Δq^{*} is the difference in the electric charge between transition complex and the reactant molecules. Provided that q and V are of the same sign, the rate of the reaction will increase or decrease as V is increased or decreased.

Understanding the macrokinetic behavior of the system can also help to increase efficiency of laboratory and industrial synthetic processes. Hence, an attempt was made to develop a macroscopic scenario relating the change in stereoselectivity at the interface as a function of solvent composition to the bulk solvent properties.

5.3.2 Interfacial reactivity of "on water" reactions

The reactivity of substrates at the interface may be intrinsically different from that of an analogous reaction in the homogeneous phase due to energetic and geometric factors. The reduction of dimensionality of diffusion is known to induce rate acceleration under specific conditions.[199] The interface can influence the progress of a reaction by affecting the rate of adsorption/diffusion of the reactant and availability of reactive sites, changing the concentration and orientation of the reactants with respect to the bulk, etc.[200] This makes quantitative discussion of the processes difficult.

Not surprisingly, very few kinetic studies at interfaces have been reported [195,190] since the first study by Bell studied regarding the kinetics of oxidation of benzoyl-*o*-toluidine with aqueous potassium permanganate at a flat liquid-liquid interface.[201] Systematic studies of solvent effects on the products of interfacial polycondensation reactions was carried out by Morgan and coworkers[202] when they demonstrated that the molecular weight of the polymer product was a dependent on the solvent used.

5.3.2.1 Solid-liquid interface: Wittig reaction

The rates of the Wittig reaction between the aldehyde **11a** and ylide **12a** were estimated in a series of water–1-propanol mixtures at four different temperatures. The apparent *pseudo*-first order rate constants, k_{app} plotted as a function of the solvent composition, showed a sharp increase when a small amount of 1-propanol was added initially, reaching a maximum before decreasing with further addition of the cosolvent (Figure 5.2). The sensitivity of the k_{app} to the composition of the medium increased with increasing temperature. For example, the apparent rate was observed to increase from a value of $1.7 \times 10^{-4}\,\mathrm{s}^{-1}$ in pure water to $15.9 \times 10^{-4}\,\mathrm{s}^{-1}$ in 40% v/v aqueous propanol at 278 K, which corresponds to a 9-times rise in rate. At 308 K, the magnitude of k_{app} increased from $7.6 \times 10^{-4}\,\mathrm{s}^{-1}$ in pure water to $83.1 \times 10^{-4}\,\mathrm{s}^{-1}$ at just 20% aqueous 1-propanol, which corresponds to rise in rates by a factor of 11 times. The position of the maximum in rate constants also shifted to lower values of the cosolvent volume fraction with increasing temperature.

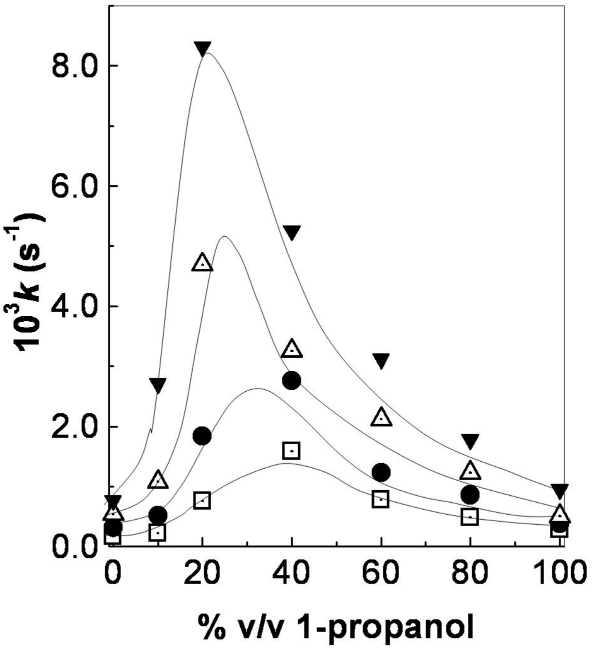


Figure 5.2: Apparent rate constants, k_{app} for the Wittig reaction of **11a** + **12a** against composition of the reaction medium in terms of the volume fraction of 1-propanol at 278 K (□), 288 K (•), 298 K (△) and 308 K (▼).

In order to explain the results, the different ways in which the addition of a cosolvent can affect the “on water” process must be taken into account. For aqueous reactions in purely homogeneous conditions, the addition of cosolvents is known to give rise to a number of additional interactions. The initial addition of cosolvents like alcohol enhances the local structure of water and thus makes the hydrophobic interactions entropically more favourable.[203] At the same time, the favourable interactions of the cosolvent with the reactant will effectively stabilize the initial state. At higher mole fractions of the cosolvent, highly dynamic clusters of the cosolvent molecules are formed.[203] The composition of the microenvironment around the reactants is different from the bulk composition and “preferential solvation” of the reactants by either of the solvent components may be observed.

Beyond a particular solvent composition, the binary mixtures start to behave like conventional organic solvent, exhibiting smooth variation in the rates and stereoselectivity trends. The analysis of the effect of cosolvent addition is further complicated if the aqueous reaction is initially carried out in a heterogeneous environment. Small amounts of the added cosolvent should affect the composition of the bulk phases as well as the interface. It may also affect the orientation and mutual interaction of the water and reactant molecules at the interface. Increasing mole fraction of the cosolvent induces a heterogeneous to homogeneous phase change. Thus, the observed enhancement of the reactivity is the combined outcome of a number of physico-chemical factors. The cosolvent is expected to influence to overall process by affecting the partition of the reactants and by influencing the rate constants (Figure 5.1).

The “on water” Wittig reaction involved a solid–liquid interface and hence, could be treated as the simplest possible variant of the model in Figure 5.1, since $k_o = 0$. The insoluble ylide suspended in the aqueous phase is a solid, and hence the absence of the other reactant in the organic phase precludes any reaction in the organic phase. Initially, under “on water” conditions, the reaction is plausible only at the interface (k_i) or in the bulk water phase (k_w). Kinetic studies in Section 4.3.2 on page 78 have provided evidence that in pure water, $k_i \gg k_w$. Hence the reaction could be modeled as a system where both the reactants were confined to the interface. For all practical purposes:

$$\frac{d[\mathrm{P}]}{dt} = k_i N_d \bar{\mathrm{A}}_i Z_i n_{\mathrm{B}i} \tag{5.7}$$

It is reasonable to assume that the addition of cosolvent will affect the process in one or all of the following ways:

1. It will lead to increased solubility of the ylide, thus shrinking the ylide particles. Since the factor ($N_d\bar{\mathrm{A}}_i/[\mathrm{A}]$) is inversely proportional to r, the radius of the ylide particle,[69] the initial decrease in the radius of the solid particle — provided all other factors including N_d are constant — should be manifested as an increase in the rate of the interfacial process. The dissolved ylide increases the contribution of the reaction in the bulk water. As more and more cosolvent is added, increasing amounts of ylide should be dissolved, making the homogeneous process in bulk water more and more feasible. The overall process in aqueous mixture has to be described as the sum of the second and third terms in equation 5.1.

2. Alternatively, the increase in the rates observed may also partially result from enhanced local structure of the reaction medium at the reaction site induced by the cosolvent i.e. apart from the effect on the partition or distribution of the reactants between the pseudophases, a direct effect of solvent composition on the magnitude of k_i and k_w will also play a role.

3. At a particular composition, the interface vanishes (the ylide completely dissolves) and then the kinetic trend is similar to that observed for the homogenous water–organic cosolvent systems. The overall rate is now a function of the rate in the bulk aqueous–organic phase, k_{w+o}.

   $$\frac{d[\mathrm{P}]}{dt}_{water+cosolvent} = k_{w+o}\mathrm{A}_{w+o}Z_{w+o}n_{\mathrm{B}w+o} \tag{5.8}$$

   (note: k_{w+o} stands for the rate in aqueous–organic phase)

4. Increasing the concentration of cosolvent further results in the reaction becoming less hydrophobically accelerated. The reaction medium loses its typically aqueous character while the reactants and transition state are being preferentially solvated by the 1-propanol molecules. Finally, the binary mixture starts resembling a conventional organic solvent as reflected in the conventional decrease in rates observed for such solvent environments. In terms of the model in Figure 5.1,

   $$k_{w+o}\mathrm{A}_{w+o}Z_{w+o}n_{\mathrm{B}w+o} \Rightarrow k_o\mathrm{A}_oZ_on_{\mathrm{B}o} \tag{5.9}$$

The maximum in the rate – composition curve could then be interpreted as the point where the system departs from complex interfacial behaviour to the conventional homogeneous kinetics. The shift in the position of the maximum with temperature also implicated the role of phase transitions in the observed kinetic trends. The initial increase in rates might be the result of increased solubility or a change in the solvation at the interface upon the addition of 1-propanol or a combination of both the factors. In order to elucidate the role of solubility, the kinetic experiments were repeated with polymer-supported form of ylide **12a** under identical conditions at 298 K. The estimated k_{app} are plotted in Figure 5.3 as a function of the composition of the reaction medium. The maximum in the rate was still observed when the possibility of solubility effect is completely excluded, thus indicating that the initial increase in rates originated predominantly due to the change in the structure of the reaction medium upon addition of alcohol.

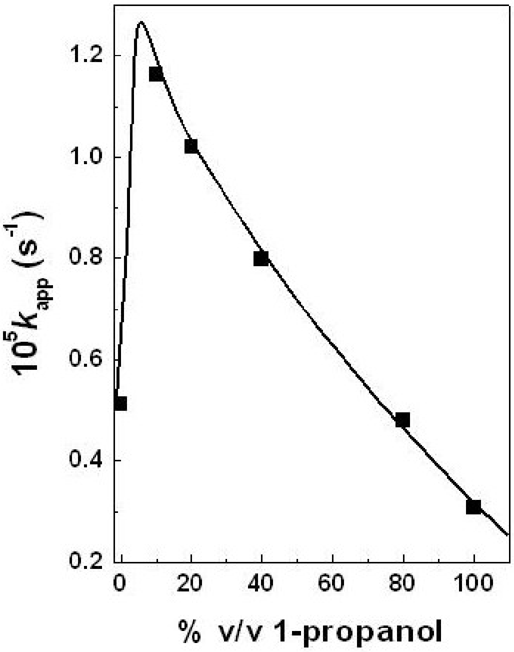


Figure 5.3: Apparent rate constant, k_{app} for the Wittig reaction of **11a** + polymer-supported form of ylide **12a** in water–1-propanol mixtures at 298 K. (The line is drawn to guide the reader’s eye.)

The characteristic orientations of alcohol and water molecules at the water-vapour interface and their effect on the surface characteristics have been studied by SFG spectroscopy[204] and molecular modeling studies.[205] The linear increase of the number of ethanol – ethanol hydrogen bonds and linear decrease of water – water hydrogen bonds at the interface indicates that the addition of ethanol enhances the self-clustering of ethanol and breaking of the hydrogen-bonded network of water in the solution.[205b] The most probable angle between the H_2O dipole at the liquid/vapour interface and the surface normal is 67.5 ° at 0.059 mole fraction of ethanol as compared to 74 ° for pure water, signifying enhanced orientation ordering on addition of ethanol. After the initial increase, the orientation of the surface H_2O molecules starts decreasing from 0.11 mole fraction of ethanol until it is sharply peaked at about 141.5 ° for 0.40 mol fraction of ethanol with no predominate orientation existing 3 Å below the interface.[205a] These observations suggest that the addition of alcohols initially tends to enhance the surface characteristics of water, before further addition depletes those features. This typical behaviour may hold the explanation for the anomalous increase in the rates observed. However, further evidence in form of experiments and theoretical calclulations would be required to explain the phenomenon satisfactorily.

5.3.2.2 Liquid-liquid interface: Diels–Alder reaction

The Diels–Alder reaction was the one of the first organic reactions, which was observed to be hydrophobically accelerated.[40] One of the earliest reports on Diels–Alder reactions carried out in aqueous suspensions coincided with the initial reports on hydrophobic acceleration of Diels–Alder reaction.[107a] Breslow and coworkers demonstrated that the hydrophobic effect on the *endo*/*exo* selectivity persists even in water–insoluble systems — i.e. when the relatively high concentration of the diene or dienophile, beyond its solubility limit, led to the formation of a distinct organic phase. The origin of the high selectivity ratios was proposed to be related to the known effects of polar media and the need to minimize the transition state surface area at the organic – water interface.

The only reports on interfacial Diels–Alder reactions are either based on the microemulsions[206] or supported dienophile.[207] Gawalt et al. used subtituent effects to study the mechanism of an Diels–Alder reaction between the diene and chemisorbed mercaptobenzoquinone as the dienophile.[207] Kinetic studies of the Diels–Alder cycloaddition reaction of **1** with **2a** in water–methanol mixtures at 298 K showed a trend similar to that observed for the Wittig reaction. The rate constants apparently increase initially with the addition of methanol. However, further increase in the amount of methanol led to a decrease in the apparent rate of the reaction. These observations are unlike the reported trend of reactivity in homogeneous aqueous mixtures. Engberts and coworkers determined the kinetic parameters for intra- and intermolecular Diels–Alder reactions in highly aqueous solutions of monohydric alcohols.[110,208] Based on the quantitative analysis, a model was developed in terms of enforced pairwise hydrophobic interactions between the diene and the dienophile. Previous studies of the kinetics of the

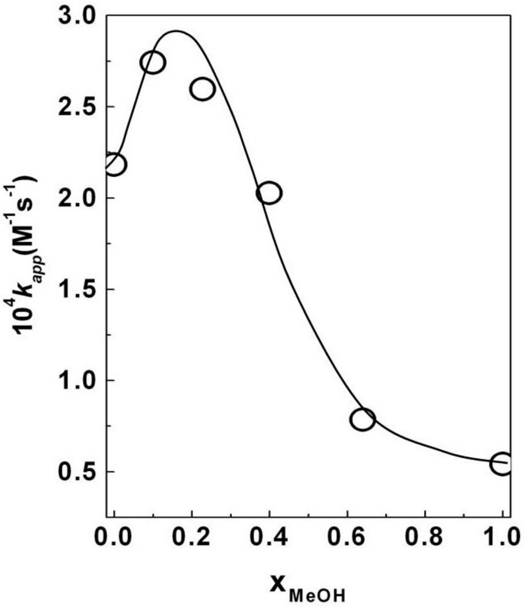


Figure 5.4: Apparent rate constant, k_{app} for the Diels–Alder reaction of **1** + **2a** in water–methanol mixtures as a function of the mole fraction of methanol, x_{MeOH} at 298 K.

Diels–Alder reaction in aqueous alcohol mixtures reported an initial sharp decrease followed by a gradual decrease in the rates on addition of alcohols as cosolvents. Marginal increase in the rate was observed for the reaction of **1** with naphthaquinone at 298 K when a small amount of cosolvent (ethanol, 1-propanol, 2-methyl-2-propanol) was added.[208] It is notable that while the rates in pure water were observed to be entirely entropic in origin, the rates observed in 10 mol% of 1-propanol were entirely of enthalpic origin, the enthalpy overcoming the unfavourable entropy. Engberts attributed the initial rise in reactivity to the enhanced structure of water upon addition of small amount of cosolvent. This feature was lost as the proportion of cosolvent was increased till the rate effects in the medium reflected those for a predominantly organic environment.

The approach required for the interpretation of results would be similar to that adopted for the Wittig reaction, except for the fact that the system is a more complex liquid-liquid interface, wherein $k_o \neq 0$. The initial reaction in purely “on water” conditions, is no longer dependent on exclusively one term — the process in the organic and aqueous phase have also to be taken into account. Also, the vigorous agitation in the reaction medium entails that the system is phase–dispersed rather than phase separated. In such cases, not only is the interfacial area unknown, but it may also vary from experiment to experiment, depending on the variations in hydrodynamic conditions and/or physical properties of the system unlike the solid-liquid interface.

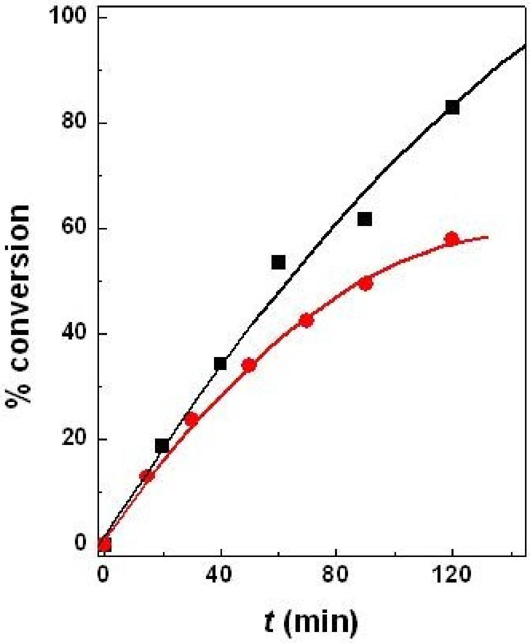


Figure 5.5: % conversion to product against time, t for the Diels–Alder reaction of **1** + **2a** in neat medium (■) and “on water” conditions (●) at 298 K. The formal concentration of the diene and the dienophile was taken to be 1.0 M each for the “on water” kinetic experiment.

As stated previously, it is important to determine the relative magnitude of k_i, k_o and k_w. Since the solubility of **1** is less than 10 mM in pure water, the initial contribution from k_w should be very small. The organic pseudophase in this case would be analogous to the “neat” medium. A comparison of the % conversion observed for the neat (no water) and “on water” reactions, is shown in Figure 5.5. Despite the fact that the effective concentration of the diene and the dienophile at the liquid–liquid interface and hence available for the interfacial reaction pathway is very less as compared to that available for the neat reaction, the conversion is comparable. This indicates that $k_o < k_i$. The higher *endo/exo* ratios obtained for the “on water” reaction (4.83 for 0.1 M of **1** and 0.5 M of **2a**) as compared to that in the neat medium (2.67) is an additional evidence for the higher magnitude of the interfacial rate constant. Thus, the reaction is predominantly interfacial when carried out in pure water only.

The addition of methanol is bound to change the composition of the aqueous and the organic phase simultaneously, along with the effects on the interfacial structure and homogeneity as listed previously for the Wittig reaction. Since, the role of the interfacial pathway is less significant as compared to that for the Wittig reaction, the observed sensitivity of the rates to the solvent composition in this reaction system is also lower.

Thus, the results have demonstrated that the “on water” reaction systems show an initial increase in the rates when small amounts of alcohols are added as cosolvent. This observation might be considered the signature of “on water” reaction kinetics.

5.3.3 Selectivity at the interface

The *endo/exo* ratio for the reaction **1** + **2a** were examined in a series of aqueous mixtures of methanol and 1-propanol at 298 K. The concentration of the alcoholic component was kept low enough to ensure that the heterogeneity and hence, the “on water” characteristic of the system is least perturbed. The *endo* selectivity of the reaction increases when small amounts of alcoholic cosolvents are added to the system.(Figure 5.6) This observation is contrary to that made by Engberts for the reaction of **1** with methyl vinyl ketone in aqueous solutions of a series of monohydric alcohols.[110b] However, the concentration of the diene and the dienophile employed were very low (in the millimolar range) and hence, were homogenous in nature. It was observed that in case of such homogenous aqueous reactions, the *endo/exo* ratio decreased sharply on addition of small quantities of alcohol.

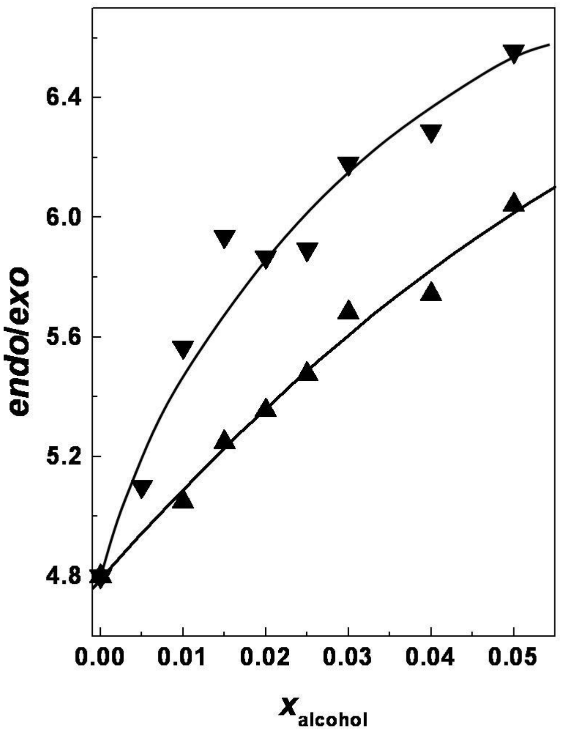


Figure 5.6: Variation in *endo*/*exo* ratio of the Diels–Alder reaction between **1** and **2a** against mole fraction of methanol (▲) and 1-propanol (▼) at 298 K in water–alcohol binary mixtures.

The kinetic control *endo* selectivity of the Diels–Alder reaction over the transition from the "on water" to the homogeneous phase was confirmed by the fact that the *endo*/*exo* ratio reflects the trend in reactivity — increasing initially before decreasing to the value of the organic cosolvent. Figure 5.7 shows the variation in *endo*/*exo* ratios with composition of the solvent medium. The choice of cosolvents was based on the nature of the plausible solute -cosolvent and water-cosolvent interactions as per the structural features of the cosolvent. The selectivity was thus studied in mixtures of a polar protic solvent — methanol, a polar aprotic solvent — dimethylsulphoxide (DMSO), a weakly polar solvent — tetrahydrofuran (THF) and a nonpolar solvent — dioxane. The composition of the reaction medium spanned the range from pure water to pure cosolvent. The change in stereoselectivity was, in effect, monitored from that in the heterogeneous or "on water” conditions at one extreme to that in entirely homogeneous medium at the other extreme.

It is interesting to observe that higher selectivities are obtained in aqueous binary mixtures than in water or cosolvent alone — except for water–THF mixtures where a smooth decrease in selectivity is seen. For example, the *endo*/*exo* ratio increases by 65% on the addition of 40% v/v methanol. This observation is drastically different from the previous studies of the effects of cosolvents on the ratio of the *endo* and *exo* products. Engberts and coworkers reported a dramatic decrease in the *endo*/*exo* product ratio for the aqueous reaction of **1** with methyl vinyl ketone on addition of simple aliphatic alcohols.[208a]

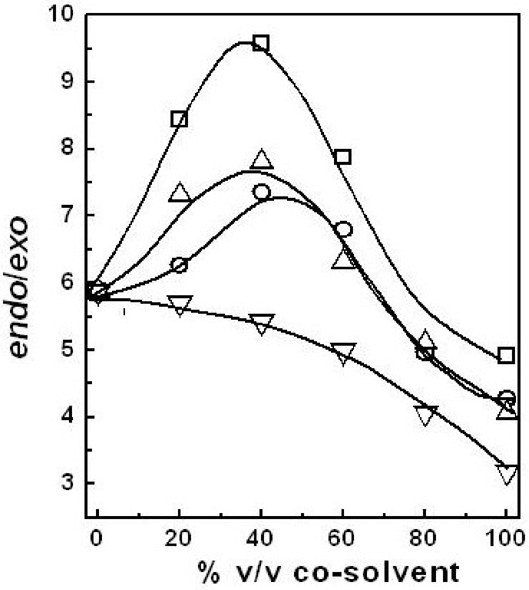


Figure 5.7: Plots of *endo*/*exo* ratios against solvent composition (% v/v) of water + cosolvent methanol (□), DMSO (△), dioxane (○) and THF (▽) for the Diels–Alder reaction **1** + **2a** at 298 K.

A thorough kinetic analysis was necessary to understand the molecular basis of solvent interactions leading to higher stereoselectivity. In the kinetic analysis, the second order rate constants of formation of the *endo* isomer (k_{endo}) and the *exo* isomer (k_{exo}) were determined independently for each solvent composition.

The *endo* and the *exo* isomers were separated by the iodolactonization procedure and the gas chromatograph was calibrated independently for both the isomers. The variation in the relative rates with solvent composition is shown in Figure 5.8. While k_{exo} does not change on addition of 20% v/v methanol, k_{endo} increases by 36% of its value in pure water in the presence of 20% v/v methanol. The results indicate that k_{endo} is more sensitive to the change in solvent composition as compared to the k_{exo}. It would be reasonable to assume that the change in stereoselectivity observed results from a greater stabilization of the *endo* transition state at the interface.

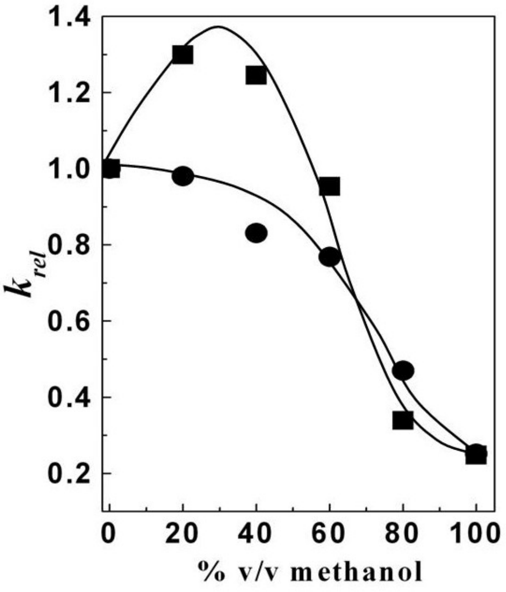


Figure 5.8: Plots of relative rates, $k_{rel}(= k/k_{water})$ for the formation of the *endo* (■) and the *exo* (●) isomers against % v/v of methanol in water at 298 K.

5.3.4 Macrokinetic analysis of interfacial selectivity

Due to the difficulties involved in studying the liquid–liquid interfacial reaction systems, an empirical approach based on multiple linear regression was adopted. Such analysis has been previously reported for studying the *endo*/*exo* selectivity of Diels–Alder reaction. Schneider and Sangwan correlated the log (*endo*/*exo*) for the Diels–Alder reaction between **1** and various dienophiles with the solvophobicity parameter, *Sp* while demonstrating that the role of the E_T^N parameter was marginally important.[116] This was in contrast to the observations by Cativiela et. al. regarding the selectivity of the reaction between **1** and α-cyanocinnamate who concluded that apart from solvophobicity, the polarity of the medium also played a significant role.[118a] Further work based on Diels–Alder reactions of **1** with **2a** in a series of organic and aqueous–organic solvents led to the development of a model based on the influence of both, solvophobicity and polarity of the medium on the stereochemical outcome of the reaction.[118b] The interpretation of the results was hampered by the fact that both *Sp* and E_T^N are intrinsically correlated parameters — the highly solvophobic solvents have higher polarity as well. A comprehensive report on how different solvent parameters (for example, polarity, Gutmann’ acceptor number, solvophobicity, cohesive energy density, etc.) of organic solvents influence kinetics of several Diels–Alder reactions is published by Cativiela and coworkers.[109]

Apart from the use of empirical polarity scales to explain the stereoselectivity of Diels–Alder reactions, the internal pressure of the reaction medium has also been considered to be a dominating factor.[113] Kumar was able to successfully predict the reactivity and selectivity of a number of reactions in aqueous and organic salt solutions using equations based on non-adjustable parameters.[115]

In the present case, it would be difficult to extend the previous models to explain the selectivity since the study includes “on water” as well as homogeneous data points. Nevertheless, a preliminary multiple regression analysis for the purely “on water” *endo*/*exo* values in aqueous alcohols (shown in Figure 5.6) was attempted with the internal pressure, P_i and the dielectric constant, ϵ of the medium. The choice of the two properties is based on the correlation of the rates of interfacial reactions with Π and V. The interfacial pressure is a function of the interfacial tension (by definition, Π = difference in the surface tension of the two phases), which in turn, can be deduced from the internal pressure.[209] The dielectric constant is included to account for the influence of the electric potential (References for the P_i and ϵ values or the thermodynamic data used for computing the P_i values of the water–cosolvent binary mixtures given in Appendix C). Both the quantities are not empirical and can be determined by simple models, which enhances their usefulness as fitting procedure. The results (Figure 5.9)

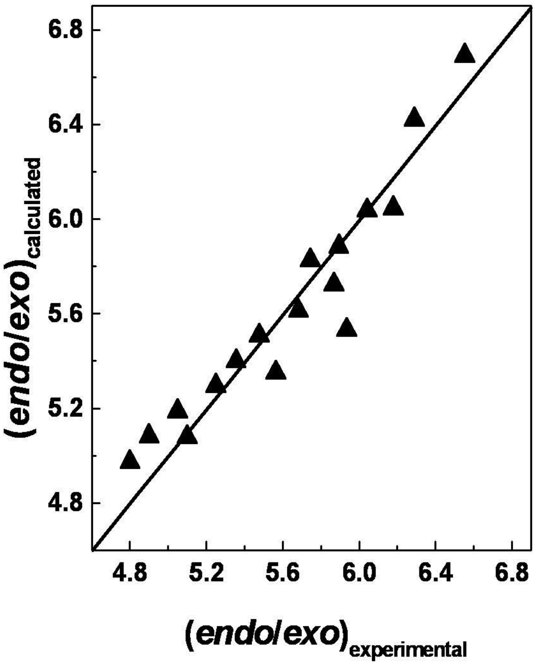


Figure 5.9: Plot of $(endo/exo)_{\text{calculated}}$ against $(endo/exo)_{\text{experimental}}$ for the Diels–Alder reaction of **1** + **2a**. $(endo/exo)_{\text{calculated}}$ obtained from multiple linear regression analysis with P_i and ϵ.

show that the regression yields good results, at least for the homologous series of water + alcohols in the strictly heterogeneous limits. The regression equation employed for determining $(endo/exo)$calculated was:

$$\begin{aligned}(endo/exo)_{\text{calculated}} &= 35.88(\pm 7.61) - 0.0076(\pm 0.0025)P_i \\ &\quad -0.37(\pm 0.09)\epsilon \\ &\quad (r^2 = 0.986)\end{aligned} \tag{5.10}$$

The approach failed when extended to explain the rate effects due to addition of cosolvents like DMSO, dioxane and THF as well as methanol. It was observed that the k_{endo} and k_{exo} can be expressed in terms of the two properties for one water–cosolvent system at a time but not for all the systems together. The correlation gave good agreement when data from one system only were used (Table 5.1), but failed when all the data from all the cosolvents are used for the multiple regression analysis simultaneously.

Table 5.1: Results of the multiple regression analysis of k_{endo} and k_{exo} involving P_i and ϵ for the Diels–Alder reaction of **1** + **2a** ($\ln k = \ln k_0 + a_1 P_i + a_2 \epsilon$)

Cosolvents	$\ln k_0$	$10^3 a_1$	$10^2 a_2$	r^2
		$\ln k_{endo}$		
Methanol	-12.83 ± 0.70	3.90 ± 1.33	4.65 ± 0.65	0.942
DMSO	-23.59 ± 0.73	4.62 ± 0.54	17.92 ± 0.81	0.992
Dioxane	-12.73 ± 0.22	7.73 ± 0.57	3.58 ± 0.20	0.992
THF	-12.43 ± 0.43	3.17 ± 0.88	4.16 ± 0.35	0.981
		$\ln k_{exo}$		
Methanol	-13.67 ± 0.24	2.37 ± 0.46	3.55 ± 0.23	0.988
DMSO	-23.96 ± 1.07	4.34 ± 0.79	16.04 ± 0.12	0.984
Dioxane	-13.78 ± 0.25	6.29 ± 0.62	2.79 ± 0.22	0.985
THF	-13.27 ± 0.34	2.49 ± 0.69	3.06 ± 0.27	0.978

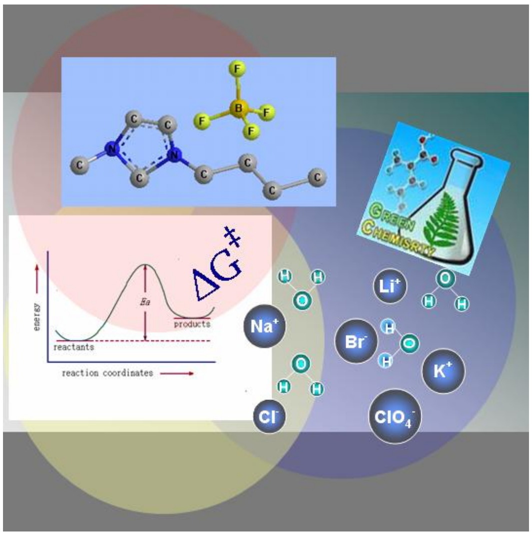
This is not surprising since the number of contributions from different factors in a complex manner and the change in the “site” of the reaction from the interface to the bulk with gradual increase in the cosolvent proportion make a simplistic analysis difficult. The observations, nevertheless, are valuable reference points for any future investigations towards the multiparameter analysis.

5.4 Conclusions

The characteristic response of the reactivity and selectivity of “on water” reactions to the addition of alcohols as cosolvents have been presented. The unconventional increase in rates in the presence of small amounts of alcohol can serve as a preliminary “signature” test for the “on water” reaction systems, where the interfacial pathway dominates. The results also underline the fundamental differences between the solvent effects in homogeneous and the interfacial pathways, which have not been completely explained. Further studies to unravel the mysteries of the “on water” reactions are planned with the dual aims of enhancing the fundamental understanding and translating the information into viable “green” technology.

6

Conclusions



The important observations and conclusions of the thesis have been summarized in the present chapter. The relevance of the results for the environmentally benign solvent systems is duly emphasized from the theoretical and practical perspectives. The future outlook has also been briefly discussed.

The present thesis culminates with the realization that the characteristically complex nature of solvent effects can be harnessed for ensuring faster, more selective organic reactions employing environment–friendly reaction media.

The work presented in this thesis focused on the study of solvent effects in ionic liquids and aqueous media on organic reactions. The solvent systems — ionic liquids and aqueous systems — were chosen on the basis of their environmentally benign nature. The method of investigation pursued was mostly kinetic studies, which facilitated the estimation of crucial thermodynamic parameters.

The initial comparison of the rates of Diels–Alder reactions in ionic liquids and water demonstrated that water is a better reaction medium in terms of the rates of the reactions. The retardation of the rates in ionic liquids was attributed to their high viscosity. Further kinetic studies on the intramolecular and bimolecular Diels–Alder reactions in pyridinium-based ionic liquids showed that the manifestation of the high viscosity of ionic liquids was a complex phenomenon. It was proposed that microviscosity, which is a function of the bulk viscosity but may also be influenced by other solvent properties, should be considered as a crucial parameter. In addition, the microviscosity was process-specific entity, varying greatly for different processes carried out in the identical sets of ionic liquids. The need for designing ionic liquids with lower viscosity and microviscosity was stressed.

While water emerged as a better reaction medium, the immiscibility of most of the organic reactants in water prompted the study of "on water" Wittig reactions. The addition of salt additives to the reaction medium was found to have remarkably opposite effects at two different temperatures. Numerous experiments were carried out to probe the effect in detail, including temperature dependent kinetics and use of polymer-supported ylide. Not only was the reaction observed to occur predominantly at the inteface, but the rate of the interfacial reaction was observed to be much faster than those in conventional organic solvents. The results indicated that the adsorption of the ions at the water-ylide interface was responsible for the contrasting observations. The limited experimental and theoretical data available in the literature regarding the water–organic interface prevented a thorough and complete analysis.

The use of alcohols as cosolvents was a logical approach to overcome the limited solubility of substrates when water was being employed as a reaction medium for synthesis. The studies on the rate and selectivity of C–C bond forming reactions "on water" as a function of the amount of cosolvent additions led to few surprising observations in terms of the initial increase in the rates and stereoselectivities on addition of small amounts of cosolvents. The observations provide another evidence that the chemistry at the water–organic interface is fundamentally different from that in the bulk.

The future studies on viscosity effects in ionic liquids could benefit greatly from efforts to estimate the process-specific microviscosity values. The comparison between the experimental results and the values theoretically predicted on the basis of the microviscosity would be required to assess the validity of the current theories of solvent friction. The water–organic interface could be investigated in greater detail in the near future employing sophisticated SFG spectroscopic techniques and molecular modeling studies. Binary ionic liquid–water mixtures have been reported in the literature but not investigated as reaction media from a physical–organic perspective. The correlation between bulk measurable solvent properties and the interfacial reactions (as in “on water” reactions) would help in tailoring the reaction conditions to achieve optimum reactivity and selectivity. For encouraging the use of ionic liquids, a comprehensive database of the physicochemical properties of all the ionic liquids synthesized till date is very important. Also, efforts to lower the cost of the ionic liquids would provide an incentive for lage-scale applications in industries. The development of comprehensive theoretical models to explain the solvent effects in ionic liquids and water–organic interface would be helpful in choosing the appropriate reaction medium.

The systematic study of solvent effects provides the dual advantage of improving the fundamental understanding of the subject and promising better ‘solutions’ for practical applications.

Appendix A

NMR Spectra of Ionic Liquids

The NMR of the pure and dried ionic liquids recorded before using them as reactionb media are as follows:

1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.78 (t, 3H), 1.26 (m, 2H), 1.60 (m, 2H), 3.78 (s, 3H), 4.15 (t, 2H), 7.46 (s, 2H), 8.97 (s, 1H).

1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF$_6$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.82 (t, 3H), 1.35 (m, 2H), 1.65 (m, 2H), 3.78 (s, 3H), 4.15 (t, 2H), 7.46 (s, 2H), 8.68 (s, 1H).

1-butyl-3-methylimidazolium iodide [BMIM]I: ^{1}H NMR (200 MHz, DMSO-d_6) 0.98 (t, 3H), 1.45 (m, 2H), 1.98 (m, 2H), 4.16 (s, 3H), 4.45 (t, 2H), 7.50 (s, 2H), 9.65 (s, 1H).

1-ethyl-3-methylimidazolium tetrafluoroborate [EMIM][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.98 (t, 3H), 3.61 (s, 3H), 3.98 (q, 2H), 7.15 (d, 2H), 8.71 (s, 1H).

1-octyl-3-methylimidazolium hexafluorophosphate [OMIM][PF$_6$]: ^{1}H NMR

(200 MHz, DMSO-d_6) 0.61 (t, 3H), 0.97 (bm, 10H), 1.65 (m, 2H), 3.75 (s, 3H), 3.99 (t, 2H), 7.20 (s, 2H), 8.49 (s, 1H).

1-butylpyridinium tetrafluoroborate [BP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.85 (t, 3H), 1.08 (m, 2H), 1.84 (m, 2H), 4.30 (t, 2H), 7.48 (t, 2H), 7.62 (t, 1H), 8.30 (d, 2H).

1-hexylpyridinium tetrafluoroborate [HP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.91 (t, 3H), 1.12 (m, 6H), 1.90 (m, 2H), 4.50 (t, 2H), 7.94 (t, 2H), 8.32 (t, 1H), 8.64 (d, 2H).

1-octylpyridinium tetrafluoroborate [OP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.98 (t, 3H), 1.24 (m, 10H), 1.82 (m, 2H), 4.75 (t, 2H), 7.94 (t, 2H), 8.32 (t, 1H), 8.64 (d, 2H).

1-butyl-3-methylpyridinium tetrafluoroborate [3MBP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.74 (t, 3H), 0.95 (m, 2H), 1.48 (m, 2H), 4.30 (t, 2H), 7.51 (dd, 1H), 7.98 (d, 1H), 8.31 (d, 1H), 8.38 (s, 1H).

1-hexyl-3-methylpyridinium tetrafluoroborate [3MHP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.83 (t, 3H), 1.12 (m, 6H), 1.52 (m, 2H), 2.32 (s, 3H), 4.32 (t, 2H), 7.51 (dd, 1H), 7.98 (d, 1H), 8.31 (d, 1H), 8.38 (s, 1H).

1-octyl-3-methylpyridinium tetrafluoroborate [3MOP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.98 (t, 3H), 1.24 (m, 10H), 1.95 (m, 2H), 2.51 (s, 3H), 4.53 (t, 2H), 7.84 (dd, 1H), 8.25 (d, 1H), 8.65 (d, 1H), 8.73 (s, 1H).

1-butyl-4-methylpyridinium tetrafluoroborate [4MBP][BF$_4$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.82 (t, 3H), 1.16 (m, 2H), 1.56 (m, 2H), 2.33 (s, 3H), 4.20 (t, 2H), 7.55 (d, 2H), 8.47 (d, 2H).

1-butylpyridinium bis(trifluoromethylsulphonyl)imide [BP][NTf$_2$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.85 (t, 3H), 1.30 (m, 2H), 1.88 (m, 2H), 4.48 (t, 2H), 7.95 (t, 2H), 8.42 (t, 1H), 8.71 (dd, 2H).

1-hexylpyridinium bis(trifluoromethylsulphonyl)imide [HP][NTf$_2$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.83 (t, 3H), 1.26 (m, 6H), 1.91 (m, 2H), 4.50 (t, 2H), 7.99 (t, 2H), 8.42 (t, 1H), 8.74 (d, 2H).

1-octylpyridinium bis(trifluoromethylsulphonyl)imide [OP][NTf$_2$]: ^{1}H NMR (200 MHz, DMSO-d_6) 0.81 (t, 3H), 1.24 (m, 10H), 1.95 (m, 2H), 4.54 (t, 2H), 8.01 (t, 2H), 8.45 (t, 1H), 8.75 (d, 2H).

Appendix B

NMR and GC data

B.1] GC Parameters for Kinetic Analysis of Diels–Alder reactions:

The following parameters were set for a typical kinetic analysis:

Column make	CP SIL 5CB
Column length	15 m
Internal diameter	0.25 mm
Film thickness	0.25-microns
Flow rate	0.7 mL/min of nitrogen
Injector temperature	280 °C
Detector temperature	250 °C
Total run time	15.56 min (Hold at 50°C for 7 min, ramp at +80 °C and then maintain at 175 °C for 6 min)
Internal Standard (IS)	Chlorobenzene

Typical Retention Times of the compounds analysed:

Compound	Retention time (min)
Chlorobenzene (IS)	6.28
3a	8.92
3b	8.96
4a	9.26
4b	9.43
5a	10.05
5b	10.10

NOTE: The GC method was calibrated with respect to the product concentrations using pure samples of the products. The amount of product formed as a function of time gave the extent of the reaction.

B.2] NMR spectra of the products 3 to 5 of Diels–Alder reactions:

methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (3a, b): ^{1}H NMR (200 MHz, $CDCl_3$) 1.22 (d, 1H), 1.39 (m, 2H), 1.67 (m, 1H), 2.78 (m, 2H), 3.14 (s, 1H), 3.57 (s, 3H), 5.97 (bs, 2H).

ethyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (4a, b): ^{1}H NMR (200 MHz, $CDCl_3$) 1.12 (d, 1H), 1.43 (m, 2H), 1.49 (t, 3H), 2.65 (m, 2H), 3.14 (bs, 1H), 4.02 (m, 2H), 6.01 (bs, 2H).

butyl bicyclo[2.2.1]hept-5-ene-2-carboxylate (5a, b): ^{1}H NMR (200 MHz, $CDCl_3$) 1.22 (d, 1H), 1.43 (m, 6H), 1.67 (m, 1H), 2.77 (m, 2H), 3.14 (bs, 1H), 4.10 (m, 2H), 6.13 (bs, 2H).

B.3] Synthesis of IMDA substrate 6:

a] Synthesis of 3-methyl-1-phenyl-5-pyrazolone:

Phenylhydrazine (0.602 g, 5.56 mmol) was added dropwise to a well-stirred suspension of ethylacetoacetate (0.744 g, 5.70 mmol) in water so as keep the temperature of the reaction mixture below 50 °C. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 2 h and finally allowed to cool to room temperature. A few drops of dilute sulfuric acid were added. The yellow crystals obtained were recrystallized from 50% aqueous ethanol to result in white crystals of 3-methyl-1-phenyl-5-pyrazolone. ^{1}H NMR (200 MHz, $CDCl_3$): 2.18 (s, 3H), 3.42 (s, 2H), 7.16 (m, 1H), 7.38 (m, 2H), 7.84 (m, 2H).

b] Synthesis of 3-methyl-2-butenyloxybenzaldehyde:

Salicylaldehyde (0.605 g, 5.098 mmol) was added to a biphasic system comprising of dichloromethane and 20% aqueous NaOH with tetrabutylammonium bromide as the phase transfer catalyst. 1.3 equivalent of dimethyl allyl bromide (0.987 g, 6.63 mmol) was then added. The reaction mixture was stirred at room temperature for 6 h. The product was isolated by column chromatography of the extraction to give a colourless oily liquid. ^{1}H NMR (200 MHz, $CDCl_3$): 1.65 (d, 6H), 4.50 (d, 2H), 5.37 (t, 1H), 6.86 (m, 2H), 7.38 (m, 1H), 7.70 (m, 1H), 10.38 (s, 1H).

c] Synthesis of (E)-1-phenyl-4-[2-(3-methyl-2-butenyloxy) benzylidene] -5-pyrazolone:

3-methyl-2-butenyloxybenzaldehyde (0.56 g, 2.76 mmol) was added to a solution of 3-methyl-1-phenyl-5-pyrazolone (0.52 g, 2.85 mmol) and 1.5 g of *N*,*N*'-dicyclohexylcarbodiimide (DCC) in dichloromethane. The solution started turning orange and was stirred at room temperature for ∼8 h. The solution was evaporated to dryness and the residue was subjected to column chromatography to isolate orange crystals of the purified product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.70 (d, 6H), 2.27 (s, 3H), 4.56 (d, 2H), 5.42 (t, 1H), 6.89 - 8.20 (m, 9H).

B.4] NMR spectra of phosphorus ylides:

(carboethoxymethylene)triphenylphosphorane (12a): ^{1}H NMR (200 MHz, $CDCl_3$) 0.89 (t, 3H), 3.87 (q, 2H), 7.20 (s, 1H), 7.55 (m, 15H).

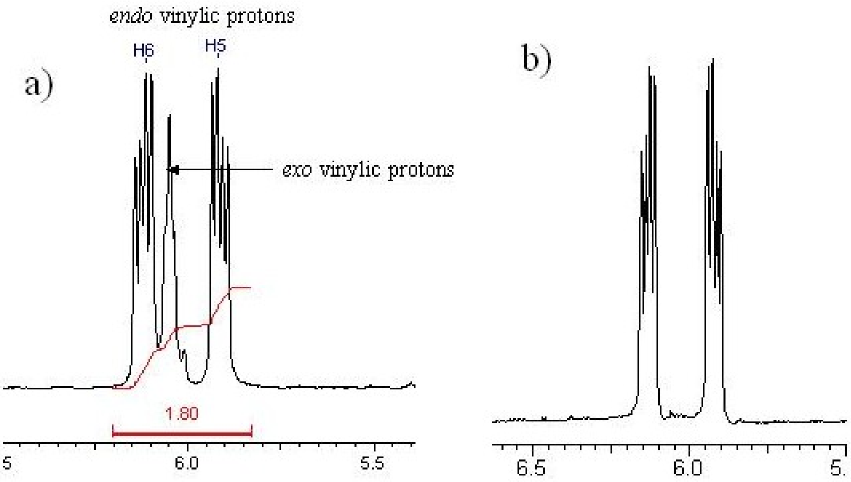
(cyanomethylene)triphenylphosphorane (12b): ^{1}H NMR (200 MHz, $CDCl_3$) 7.15 (s, 1H), 7.65 (m, 15H).

B.5] NMR spectra of *endo* and *exo* acids and esters for the iodolactone procedure:

bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, *endo* and *exo* mixture: ^{1}H NMR (200 MHz, $CDCl_3$) 1.31 (m, 2H), 1.65 (m, 1H), 3.01 (m, 2H), 3.20 (s, 1H), 5.97 (bs, 2H), 11.5 (bs, 1H).

iodolactone derivative of *endo* acid: ^{1}H NMR (200 MHz, CDCl$_3$) 1.76 (m, 2H), 2.01(m, 1H), 2.31 (dd, 1H), 2.52 (dd, 1H), 2.67 (s, 1H), 3.20 (bs, 1H), 3.78 (d, 1H), 5.20 (d, 1H).

The separation of the two stereoisomers was confirmed by the absence of the signal due to the exo vinylic peak (seen in a) in the NMR spectrum of *endo* adduct, **3a** (seen in b).



Appendix C

Literature for physicochemical properties of binary mixtures

References for the P_i and ϵ values or the thermodynamic data used for computing the P_i values of the water–cosolvent binary mixtures

- Thermal expansivity and isothermal compressibility data for water–methanol mixtures:
  Easteal, A. J.; Woolf, L. A. *J. Chem. Thermodynamics* **1985**, *17*, 49.

- Thermal expansivity data for water–1-propanol mixtures:
  Kiyohara, O.; Benson, G. C. *J. Soln. Chem.* **1980**, *9*, 791.

- Thermal expansivity data for water–DMSO and water–dioxane mixtures:
  Tôrres, R. B.; Marchiore, A. C. M.; Volpe, P. L. O. *J. Chem. Thermodynamics* **2006**, *38*, 526.

- Thermal expansivity data for water–tetrahydrofuran mixtures:
  Kiyohara, O.; D'Arcy, P.; Benson, G. C. *Can. J. Chem.* **1978**, *56*, 2803.

- Compressibility and heat capacity data for water–1-propanol mixtures:
  Kiyohara, O.; Benson, G. C. *J. Soln. Chem.* **1981**, *10*, 281.

- Speed of sound and refractive index data for water–DMSO, water–dioxane and water–terahydrofuran mixtures:
  Aminabhavi, T. M.; Gopalkrishna, B. *J. Chem. Eng. Data* **1995**, *40*, 856.

- Heat capacity data for water–DMSO mixtures:
  Visser, C. D.; Heuvelsland, W. J. M.; Dunn, L. A.; Somsen, G. J. *J. Chem. Soc., Faraday Trans. I* **1978**, *74*, 1159.

- Heat capacity data for water–dioxane mixtures:
  Stallard, R. D.; Amis, E. S. *J. Phys. Chem.* **1952**, *74*, 1781.

- Speed of sound and heat capacity data for water–tetrahydrofuran mixtures:
  Kiyohara, O.; Benson, G. C. *Can. J. Chem.* **1979**, *57*, 1006.

- Refractive index data for water–methanol mixtures:
  Arce, A.; Blanco, A.; Soto, A.; Vidal, I. *J. Chem. Eng. Data* **1993**, *38*, 336.

- Dielectric constants for water–methanol mixtures:
  Albright, P. A.; Gosting, L. J. *J. Am. Chem. Soc.* **1946**, *68*, 1061.

- Dielectric constants for water–1-propanol mixtures:
  Sato, T.; Chiba, A.; Nozaki, R. *J. Chem. Phys.* **2000**, *113*, 9748.

- Dielectric constants for water–DMSO mixtures:
  Kaatze, U.; Pottel, R.; Schäfer, M. *J. Phys. Chem.* **1989**, *93*, 5623.

- Dielectric constants for water–dioxane mixtures:
  Critchfield, F. E.; Gibson, J. A. Jr.; Hall, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 1991.

- Dielectric constants for water–tetrahydrofuran mixtures:
  Critchfield, F. E.; Gibson, J. A. Jr.; Hall, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 6044.

Appendix D

List of Publications

- Tiwari, S.; Kumar, A.
  "Diels-Alder Reactions Are Faster in Water than in Ionic Liquids at Room Temperature "
  Angew. Chem. Int. Ed. **2006**, *45*, 4824.

- Tiwari, S.; Kumar, A.
  "Unusual Temperature Dependence of Salt Effects for "on water" Wittig Reaction: Hydrophobicity at the Interface"
  Chem. Commun. **2008**, 4445.

- Tiwari, S.; Khupse, N. D.; Kumar, A.
  "Intramolecular Diels-Alder Reaction in Ionic Liquids: Effect of Ion-specific Solvent Friction"
  J. Org. Chem. **2008**, *73*, 9075.

- Tiwari, S.; Kumar, A.
  "Electrostriction: Fundamentals and its Application in Understanding Kinetics of Diels-Alder Reactions with Supporting and Opposing Views"
  Chem. Rev. (under revision).

- Tiwari, S.; Kumar, A.
  "Viscosity Effects in Bimolecular vs. Intramolecular DielsAlder Reactions in Pyridinium Ionic Liquids: Translational vs. Rotational Diffusion"
  (communicated)

- Tiwari, S.; Kumar, A.
  "Physical Chemistry of Organic Reactions in Aqueous Media"
  Chem. Soc. Rev. (to be communicated)
- Tiwari, S.; Kumar, A.
  "Reactivity and Stereoselectivity at the Aqueous-Organic Interface"
  (manuscript under preparation)
- Tiwari, S.; Kumar, A.
  "Salting Effects for Heterogeneous Wittig Reactions"
  (manuscript under preparation)

Appendix E

Posters and Oral Presentations

- Poster presented at IUPAC sponsored "Second International symposium in Green/Sustainable Chemistry", 10th-13th January, 2006, University of Delhi.
- Oral presentation at 2nd JNOST Symposium, 11th-14th October, 2006, Jaipur.
- Poster presented at "8th Tetrahedron Symposium - Challenges in Organic Chemistry", 27th -29th June, 2007, Berlin, Germany.
- Poster presented at "10th CRSI National Symposium on Chemistry", 1st - 3rd February, 2008, IISc, Bangalore.
- Oral presentation at "One-day Physical and CMC Joint Divisional Symposium", 22nd October, 2008, NCL, Pune.

References

[1] Reichardt, C. *Solvent Effects in Organic Chemistry;* Verlag Chemie: Weinheim, 1979.

[2] For further details, see: www.emedicine.com/neuro/TOPIC285.HTM.

[3] Based on Toxicity Release Inventory (TRI) data compiled at Scorecard: The Pollution Information Site - www.scorecard.org.

[4] a) Sheldon, R. A. *Pure Appl. Chem.* **2000,** *72,* 1233. b) Sheldon, R. A. *Chem. Commun.* **2008,** 3352.

[5] a) Anastas, P. T.; Warner, J. C., Eds.; *Green Chemistry: Theory and Practice;* Oxford University Press: Oxford, 1998. b) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002,** *35,* 686.

[6] a) Berthelot, M.; de Saint-Gilles, P. *L. Ann. Phys. et Phys., 3 Ser.* **1862,** *65,* 385. b) Berthelot, M.; de Saint-Gilles, P. *L. Ann. Phys. et Phys., 3 Ser.* **1862,** *66,* 5. c) Berthelot, M.; de Saint-Gilles, P. *L. Ann. Phys. et Phys., 3 Ser.* **1863,** *68,* 225.

[7] Coetzee, J. F.; Ritchie, C. D. *Solute Solvent Interactions;* volume 1 and 2 Marcel Dekker Inc.: New York, 1976.

[8] Amis, E. S. *Solvent Effects on Reaction Rates and Mechanism;* Academic Press: New York, 1966.

[9] a) Truhlar, D. G.; Hase, W. L.; Hynes, J. T. *J. Phys. Chem.* **1983,** *87,* 2664. b) Truhlar, D. G.; Garrett, B. C.; Klippenstein, S. J. *J. Phys. Chem.* **1996,** *100,* 12771.

[10] a) Hirschfelder, J. O. *Intermolecular Forces;* Interscience: New York, 1967. b) Buckingham, A. D. *Pure Appl. Chem.* **1970,** *24,* 123.

[11] See pages 9 to 26 in [1] for detailed discussion and references of each of these solute–solvent intermolecular forces.

[12] a) Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlmann, F. *Leibigs Ann. Chem.* **1963,** *661,* 1. b) Reichardt, C. *Leibigs Ann. Chem.* **1971,** *752,* 64. c) Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976,** *98,* 377, 2886. d) Yokoyama, T.; Taft, R. W.; Kamlet, M. J. *J. Am. Chem. Soc.* **1976,** *98,* 3233. e) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977,** *99,* 6027, 8325 and references cited therein.

[13] a) Franck, J.; Rabinowitsch, E. *Trans. Faraday Soc.* **1934,** *30,* 120. b) Rabinowitsch, E.; Wood, W. C. *Trans. Faraday Soc.* **1936,** *32,* 1381.

[14] a) Hammond, G. S.; Sen, J. N.; Boozer, C. E. *J. Am. Chem. Soc.* **1955,** *77,* 3244. b) Rebbert, R. E.; Ausloos, P. *J. Phys. Chem.* **1962,** *66,* 2253. c) Lyon, R. K.; Levy, D. H. *J. Am. Chem. Soc.* **1961,** *83,* 4290. d) Lyon, R. K. *J. Am. Chem. Soc.* **1964,** *86,* 1907. e) Loan, L. D.; Murray, R. W.; Story, P. R. *J. Am. Chem. Soc.* **1965,** *87,* 737. f) Lorenz, O.; Parks, C. R. *J. Org. Chem.* **1965,** *30,* 1976.

[15] Sheldon, R. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1970,** *92,* 4395.

[16] Nodelman, N.; Martin, J. C. *J. Am. Chem. Soc.* **1976,** *98,* 6597.

[17] a) Kitazawa, M.; Yabe, T.; Hirata, Y.; Okada, T. *J. Mol. Liq.* **1995,** *65,* 321. b) Bullock, A. T.; Cameron, G. G.; Smith, P. M. *J. Chem. Soc. Faraday Trans. II* **1974,** *70,* 1202. c) Mashimo, S. *Macromolecules* **1976,** *9,* 91. d) Beece, D.; Eisenstein, L.; Frauenfelder, H.; Good, D.; Marden, M. C.; Reinisch, L.; Reynolds, A. H.; Sorensen, L. B.; Yue, K. T. *Biochemistry* **1980,** *19,* 5147.

[18] Clayden, J. P.; Greeves, N.; Warren, S.; Wothers, P. D. *Organic Chemistry;* Oxford University Press: New York, 2001.

[19] a) Cook, M. J.; El-Abbady, S.; Katritzky, A. R.; Guimon, C.; Pfister-Guillouzo, G. *J. Chem. Soc. Perkin. Trans. II* **1977,** 1652. b) Gordon, A.; Katritzky, A. *Tetrahedron Lett.* **1968,** *9*, 2767. c) Frank, J.; Katritzky, A. R. *J. Chem. Soc. Perkin. Trans. II* **1976,** 1428.

[20] a) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions;* Wiley: New York, 1963. b) Wiberg, K. B. *Physical Organic Chemistry;* Wiley: New York, 1964. c) Laidler, K. J. *Chemical Kinetics;* McGraw Hill: New York, Second ed.; 1965. d) Lin, S. H.; Li, K. P.; Eyring, H. . In *Physical Chemistry - An Advanced Treatise*, Vol. VII; Eyring, H.; Henderson, D.; Jost, W., Eds.; Academic Press: New York, 1975.

[21] a) Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1935,** 244. b) Hughes, E. D. *Trans. Faraday Soc.* **1941,** *37,* 603. c) Hughes, E. D.; Ingold, C. K. *Trans. Faraday Soc.* **1941,** *37,* 657. d) Cooper, K. A.; Dhar, M. L.; Hughes, E. D.; Ingold, C. K.; MacNulty, B. J.; Woolf, L. I. *J. Chem. Soc.* **1948,** 2043. e) Ingold, C. K. *Structure and Mechamism in Organic Chemistry;* Cornell University: Ithaca, New York, Second ed.; 1969.

[22] a) Wells, P. R. *Linear Free Energy Relationships;* Academic Press: London, 1968. b) Chapman, N. B.; Shorter, J., Eds.; *Advances in Linear Free Energy Relationships;* Plenum Press: New York, 1972. c) Shorter, J. *Correlation Analysis in Organic Chemistry - An Introduction to Linear Free Energy Relationships;* Clarendon Press: Oxford, 1973. d) Johnson, C. D. *Chem. Rev.* **1975,** *75,* 755.

[23] Hammett, L. P. *J. Am. Chem. Soc.* **1937,** *59,* 96.

[24] Hine, J. *Physical Organic Chemistry;* Mc-Graw-Hill: New York, 1964.

[25] a) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948,** *70,* 846. b) Taft, R. W. *J. Am. Chem. Soc.* **1952,** *74,* 3120. c) Taft, R. W. . In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956.

[26] Richardson, M.; Soper, F. G. *J. Chem. Soc.* **1929,** 1873.

[27] Cotler, A. K.; Clemens, L. M. *J. Phys. Chem.* **1964,** *68,* 651.

[28] Ouellette, R. J.; Williams, S. H. *J. Am. Chem. Soc.* **1971,** *93,* 466.

[29] a) Reichardt, C. *Angew. Chem. Int. Ed.* **1965,** *4,* 29. b) Kosower, E. M. *An Introduction to Physical Organic Chemistry;* Wiley: New York, London, Sydney, 1968. c) Reichardt, C. *Angew. Chem. Int. Ed.* **1979,** *18,* 98. d) Isaacs, N. S. *Physical Organic Chemistry;* Longman House: Essex, England, Second ed.; 1995.

[30] Abraham, M. H.; Grellier, P. L.; Abboud, J. L. M.; Doherty, R. M.; Taft, R. W. *Can. J. Chem.* **1988,** *66,* 2673.

[31] a) Jorgensen, W. L. *Adv. Chem. Phys. Part 2* **1988,** *70,* 469. b) Bash, P. A.; Field, M. J.; Karplus, M. *J. Am. Chem. Soc.* **1987,** *109,* 8092. c) Beveridge, D. L.; DiCapua, F. M. *Annu. Rev. Biophys. Biophys. Chem.* **1989,** *18,* 431. d) Jorgensen, W. L. *Acc. Chem. Res.* **1989,** *22,* 184. e) Kollman, P. A.; Merz, K. M., J. *Acc. Chem. Res.* **1990,** *23,* 246. f) Gao, J. *J. Am. Chem. Soc.* **1991,** *113,* 7796. g) Gao, J.; Xia, X. *J. Am. Chem. Soc.* **1993,** *115,* 9667.

[32] a) Rivail, J. L. . In *New Theoretical Concepts for Understanding Organic Reactions*; Bertrán, J.; Csizmadia, I., Ed.; Kluwer: Dordrecht, 1989. b) Tomasi, J.; Persico, M. *Chem. Rev.* **1994,** *94,* 2027. c) Cramer, C. J.; Truhlar, D. G. . In *Solvent Effects and Chemical Reactivity*; Tapia, O.; Bertrn, J., Eds.; Kluwer: Dordrecht, 1996.

[33] a) Andrés, J. L.; Lledós, A.; Bertrán, J. *Chem. Phys. Lett.* **1994,** *223,* 23. b) Assfeld, X.; Ruiz-Lopez, M. F.; González, J.; Lopez, R.; Sordo, J. A.; Sordo, T. L. *J.Comput. Chem.* **1994,** *15,* 479. c) Suárez, D.; Assfeld, X.; González, J.; Ruiz-Lopez, M. F.; Sordo, T. L.; Sordo, J. A. *J. Chem. Soc., Chem. Commun.* **1994,** 1683.

[34] a) Tuñón, I.; Silla, E.; Bertrán, J. *J. Chem. Soc., Faraday Trans.* **1994,** *90,* 1757. b) Coitiño, E. L.; Tomasi, J.; Ventura, O. N. *J. Chem. Soc., Faraday Trans.* **1994,** *90,* 1745.

[35] a) Kramers, H. A. *Physica (Utrecht)* **1940,** *7,* 284. b) Chandrasekhar, S. *Rev. Mod. Phys.* **1943,** *15,* 1.

[36] Grote, R. T.; Hynes, J. T. *J. Chem. Phys.* **1980,** *73,* 2715.

[37] a) Saltiel, J.; Sun, Y.-P. *J. Phys. Chem.* **1989,** *93,* 6246. b) Sun, Y.-P.; Saltiel, J.; Park, N. S.; Hoburg, E. A.; Waldeck, D. H. *J. Phys. Chem.* **1991,** *95,* 10336. c) Cho, M.; Hu, Y.; Rosenthal, S. J.; Todd, D. C.; Du, M.; Fleming, G. R. . In *Activated Barrier Crossing*; Fleming, G. R.; Hanggi, P., Eds.; World Scientific: River Edge, NJ, 1993. d) Sumi, H.; Asano, T. *Chem. Phys. Lett.* **1995,** *240,* 125. e) Sumi, H.; Asano, T. *J. Chem. Phys.* **1995,** *102,* 9565. f) Anderton, R. M.; Kauffman, J. F. *J. Phys. Chem.* **1994,** *98,* 12125.

[38] a) Marcus, R. A. *J. Chem. Phys.* **1956,** *24,* 966, 979. b) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964,** *15,* 155.

[39] "Water is life's matter and matrix, mother and medium" - Quote by Albert Szent-Gyorgyi, 1937 Nobel Laureate for Medicine.

[40] Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980,** *102,* 7816.

[41] a) Ben-Naim, A. *Hydrophobic Interactions;* Plenum Press: New York, 1980. b) Tanford, C. *The Hydrophobic Effect;* Wiley: New York, Second ed.; 1980.

[42] a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971,** *10,* 496. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974,** *39,* 1612. c) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985,** *50,* 910. d) Lubineau, A. *J. Org. Chem.* **1986,** *51,* 2142. e) Tychopoulos, V.; Tyman, J. H. P. *Synth. Commun.* **1986,** *16,* 1401. f) Lubineau, A.; Meyer, E. *Tetrahedron* **1988,** *44,* 6065. g) Kool, E. T.; Breslow, R. *J. Am. Chem. Soc.* **1988,** *110,* 1596. h) Denmark, S. E.; Lee, W. *Tetrahedron Lett.* **1992,** *33,* 7729. i) Lubineau, A.; Augé, J. *Tetrahedron Lett.* **1992,** *33,* 8073. j) Loh, T.-P.; Li, X.-R. *Chem. Commun.* **1996,** 1929. k) Li, C.-J.; Chen, D.-L.; Lu, Y.-Q.; Haberman, J. X.; Mague, J. T. *J. Am. Chem. Soc.* **1996,** *118,* 4216.

[43] a) Li, C.-J. *Chem. Rev.* **1993,** *93,* 2023. b) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994,** 741. c) Lindström, U. M. *Chem. Rev.* **2002,** *102,* 2751. d) Li, C.-J. *Chem. Rev.* **2005,** *105,* 3095. e) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006,** *35,* 68. f) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C. J. *Chem. Rev.* **2007,** *107,* 2546.

[44] Grieco, P. A. *Organic Synthesis in Water;* Blackie Academic and Professional: London, 1998.

[45] Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media;* Wiley: New York, 1997.

[46] Dill, K. A. *Science* **1990,** *250,* 297.

[47] Butler, J. A. V. *Trans. Faraday Soc.* **1937,** *33,* 229.

[48] Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem. Int. Ed.* **1993,** *32,* 1545 and references cited therein.

[49] Frank, H. S.; Evans, M. W. *J. Chem. Phys.* **1945,** *13,* 507.

[50] a) Nemethy, G.; Scheraga, H. A. *J. Chem. Phys.* **1962,** *36,* 3382, 3401. b) Nemethy, G. *Angew. Chem. Int. Ed.* **1967,** *6,* 195.

[51] a) Baldwin, R. L. *Proc. Natl. Acad. Sci.* **1986,** *83,* 8069. b) Murphy, K. P.; Privalov, P. L.; Gill, S. J. *Science* **1990,** *247,* 559.

[52] a) Lumry, R.; Battistel, E.; Jolicoeur, C. *Faraday Symp. Chem. Soc.* **1982,** *17,* 93. b) Huot, J.-Y.; Battistel, E.; Lumry, R.; Villeneuve, G.; Lavallel, J.-F.; Anusiem, A.; Jolicoeur, C. *J. Solution Chem.* **1988,** *17,* 601.

[53] a) Savage, J. J.; Wood, R. H. *J. Solution Chem.* **1976,** *5,* 733. b) Okamoto, B. Y.; Wood, R. H.; Thompson, P. T. *J. Chem. Soc. Faraday Trans. I* **1978,** *74,* 1990.

[54] a) Pratt, L. R. *Annu. Rev. Phys. Chem.* **1985,** *36,* 433. b) Pratt, L. R.; Chandler, D. *J. Chem. Phys.* **1977,** *67,* 3683.

[55] Stillinger, F. H. *J. Solution Chem.* **1973,** *2,* 141.

[56] Berendsen, H. J. C.; Postma, J. P. M.; vanGunsteren, W. F.; Hermans, H. J. . In *Intermolecular Forces*; Pullman, B., Ed.; Reidel: Dordrecht, 1981.

[57] Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983,** *79,* 926.

[58] a) Lum, K.; Chandler, D.; Weeks, J. D. *J. Phys. Chem. B* **1999,** *103,* 4570. b) Huang, D. M.; Chandler, D. *Proc. Natl. Acad. Sci.* **2000,** *97,* 8324. c) Chandler, D. *Nature* **2005,** *437,* 640.

[59] a) Rajamani, S.; Truskett, T. M.; Garde, S. *Proc. Natl. Acad. Sci.* **2005,** *102,* 9475. b) Graziano, G. *J. Phys. Chem. B* **2006,** *110,* 11421. c) Chandler, D. *Nature* **2007,** *445,* 831.

[60] a) Hertz, H. G.; Leiter, H. *Z. Phys. Chem. (Munich)* **1982,** *133,* 45. b) Walrafen, G. E.; Hokmabadi, M. S.; Yang, W.-H.; Chu, Y. C.; Monosmith, B. *J. Phys. Chem.* **1989,** *93,* 2909. c) Tominaga, Y.; Fujiwara, A.; Amo, Y. *Fluid Phase Equilibria* **1998,** *144,* 323. d) Modig, K.; Pfrommer, B. G.; Halle, B. *Phys. Rev. Lett.* **2003,** *90,* 075502. e) Nickolov, Z. S.; Miller, J. D. *J. Colloid Interface Sci.* **2005,** *287,* 572. f) Shen, Y. R.; Ostroverkhov, V. *Chem. Rev.* **2006,** *106,* 1140. g) Jungwirth, P.; Tobias, D. J. *Chem. Rev.* **2006,** *106,* 1259. h) Bakker, H. J. *Chem. Rev.* **2008,** *108,* 1456. i) Saito, S.; Ohmine, I. *J. Chem. Phys.* **2006,** *125,* 084506.

[61] a) Ben-Naim, A.; Wilf, J.; Yaacobi, M. *J. Phys. Chem.* **1973,** *77,* 95. b) Luan, C. H.; Urry, D. W. *J. Phys. Chem.* **1991,** *95,* 7896. c) Graziano, G. *J. Phys. Chem. B* **2000,** *104,* 9249. d) Graziano, G. *J. Chem. Phys.* **2004,** *121,* 1878.

[62] a) Poynor, A.; Hong, L.; Robinson, I. K.; Granick, S.; Zhang, Z.; Fenter, P. A. *Phys. Rev. Lett.* **2006,** *97,* 266101. b) Mezger, M.; Reichert, H.; Schröder, S.; Okasinski, J.; Schröder, H.; Dosch, H.; Palms, D.; Ralston, J.; Honkimäki, V. *Proc. Natl. Acad. Sci.* **2006,** *103,* 18401.

[63] Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003,** *1,* 2809.

[64] Breslow, R. *Acc. Chem. Res.* **2004,** *37,* 471.

[65] Blandamer, M. J.; Blundell, N. J.; Burgess, J.; Cowles, H. J.; Engberts, J. B. F. N.; Horn, I. M.; Warrick, P. *J. Am. Chem. Soc.* **1990,** *112,* 6854.

[66] Breslow, R.; Groves, K.; Mayer, M. U. *J. Am. Chem. Soc.* **2002,** *124,* 3622.

[67] a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005,** *44,* 3275. b) Klijn, J. E.; Engberts, J. B. F. N. *Nature* **2005,** *435,* 746.

[68] a) Wu, X.; Liu, J.; Li, X.; Zanotti-Gerosa, A.; Hancock, F.; Vinci, D.; Ruan, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2006,** *45,* 6718. b) González-Cruz, D.; Tejedor, D.; de Armas, P.; Morales, E. Q.; Garcia-Tellado, F. *Chem. Commun.* **2006,** 2798. c) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem. Int. Ed.* **2007,** *46,* 9073. d) González-Cruz, D.; Tejedor, D.; de Armas, P.; Garcia-Tellado, F. *Chem. Eur. J.* **2007,** *13,* 4823. e) Chakraborti, A. K.; Rudrawar, S.; Jadhav, K. B.; Kaur, G.; Chankeshwara, S. V. *Green Chem.* **2007,** *9,* 1335. f) Cozzi, P. G.; Zoli, L. *Green Chem.* **2007,** *9,* 1292. g) Cozzi, P. G.; Zoli, L. *Angew. Chem. Int. Ed.* **2008,** *47,* 4162. h) Shapiro, N.; Vigalok, A. *Angew. Chem. Int. Ed.* **2008,** *47,* 2849.

[69] Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007,** *129,* 5492.

[70] a) Welton, T. *Chem. Rev.* **1999,** *99,* 2071. b) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000,** *72,* 1391. c) Sheldon, R. *Chem. Commun.* **2001,** 2399. d) Wasserscheid, P.; T., W. *Ionic Liquids in Synthesis;* Wiley-VCH Verlag: Stuttgart, Germany, 2002. e) Dupont, J.; Suarez, P. A. Z. *Phys. Chem. Chem. Phys.* **2006,** *8,* 2441. f) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007,** *107,* 2615. g) Weingärtner, H. *Angew. Chem. Int. Ed.* **2008,** *47,* 654.

[71] Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000,** *39,* 3772.

[72] a) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005,** *18,* 275 and references cited therein. b) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002,** *182,* 419. c) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005,** *61,* 1015.

[73] Marcos, A. P. M.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. *Chem. Rev.* **2008,** *108,* 2015.

[74] a) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999,** *40,* 793. b) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999,** *1,* 23, 517. c) Ludley, P.; Karodia, N. *Tetrahedron Lett.* **2001,** *42,* 2011. d) Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002,** *43,* 4657. e) Conner, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L. *J. Am.Chem. Soc.* **2002,** *124,* 914. f) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002,** *4,* 3583. g) Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003,** *68,* 2812.

[75] a) Chauvin, Y.; Gilbert, B.; Guibard, I. *J. Chem. Soc., Chem. Commun.* **1990,** *23,* 1715. b) Chauvin, Y.; Einloft, S.; Olivier, H. *Ind. Eng. Chem. Res.* **1995,** *34,* 1149.

[76] a) Parshall, G. W. *J. Am. Chem. Soc.* **1972,** *94,* 8716. b) Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* **1999,** 1247.

[77] a) Mehnert, C. P.; Cook, R. A.; Dispenziere, N. C.; Afeworki, M. *J. Am. Chem. Soc.* **2002,** *124,* 12932. b) Riisager, A.; Eriksen, K. M.; Wasserscheid, P.; Fehrmann, R. *Catal. Lett.* **2003,** *90,* 149. c) Yang, Y.; Lin, H.; Deng, C.; She, J.; Yuan, Y. *Chem. Lett.* **2005,** *34,* 220. d) Yang, Y.; Deng, C.; Yuan, Y. *J. Catal.* **2005,** *232,* 108. e) Hamza, K.; Blum, J. *Eur. J. Org. Chem.* **2007,** 4706.

[78] Brennecke, J. F.; Maginn, E. J. *AIChE J.* **2001,** *47,* 2384.

[79] a) Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc. Chem. Commun.* **1992,** 965. b) Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem. Int. Ed.* **1996,** *34,* 2698. c) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996,** *15,* 1217. d) Bonhôte, P.; Dias, A.-P.; Papageorgiou, N.; Kalyanasundaram, K.; Grátzel, M. *Inorg. Chem.* **1996,** *35,* 1168.

[80] Joglekar, H. G.; Rahman, I.; Kulkarni, B. D. *Chem. Eng. Technol.* **2000,** *30,* 819.

[81] a) NIST Ionic Liquids Database, ILThermo. NIST Standard Reference Database 147. National Institute of Standards and Technology,

Standard Reference Data Program: Gaithersburg, MD, 2006. http://ILThermo.boulder.nist.gov/ILThermo/. b) Dong, Q.; Muzny, C. D.; Kazakov, A.; Diky, V.; Magee, J. W.; Widegren, J. A.; Chirico, R. D.; Marsh, K. N.; Frenkel, M. *J. Chem. Eng. Data* **2007,** *52,* 1151.

[82] Zhang, S.; Sun, N.; He, X.; Lu, X.; Zhang, X. *J. Phys. Chem. Ref. Data* **2006,** *35,* 1475.

[83] Zhao, D.; Liao, Y.; Zhang, Z. *Clean* **2007,** *35,* 42.

[84] a) Abbott, A. P. *ChemPhysChem* **2004,** *5,* 1242. b) Abbott, A. P. *ChemPhysChem* **2005,** *6,* 2502. c) Gardas, R. L.; Coutinho, J. A. P. *Fluid Phase Equilibria* **2008,** *266,* 195. d) Pensado, A. S.; Pádua, A. A. H.; Comuñas, M. J. P.; Fernández, J. *J. Phys. Chem. B* **2008,** *112,* 5563. e) Larriba, C.; Yoshida, Y.; de la Mora, J. F. *J. Phys. Chem. B* **2008,** *112,* 12401.

[85] a) Hardacre, C.; Holbrey, J. D.; McMath, S. E. J.; Bowron, D. T.; Soper, A. K. *J. Chem. Phys.* **2003,** *118,* 273. b) Hardacre, C.; McMath, S. E. J.; Nieuwenhuyzen, M.; Bowron, D. T.; Soper, A. K. *J. Phys. Condens. Matter* **2003,** *15,* S159.

[86] a) Hanke, C. G.; Price, S. L.; Lynden-Bell, R. M. *Mol. Phys.* **2001,** *99,* 801. b) Del Pópolo, M. G.; Lynden-Bell, R. M.; Kohanoff, J. *J. Phys. Chem. B* **2005,** *109,* 5895. c) Bühl, M.; Chaumont, A.; Schurhammer, R.; Wipff, G. *J. Phys. Chem. B* **2005,** *109,* 18591. d) Bhargava, B. L.; Balasubramanian, B.; Klein, M. L. *Chem. Commun.* **2008,** 3339 and references cited therein.

[87] Dupont, J. J. *Braz. Chem. Soc.* **2004,** *15,* 341.

[88] Schröder, C.; Rudas, T.; Steinhauser, O. *J. Chem. Phys.* **2006,** *125,* 244506.

[89] a) Schröder, U.; Wadhawan, J. D.; Compton, R. G.; Marken, F.; Suarez, P. A. Z.; Consorti, C. S.; de Souza, R. F.; Dupont, J. *New J. Chem.* **2000,** *24,* 1009. b) Santos, L. M. N. F.; Lopes, J. N. C.; Coutinho, J. A. P.; Esperanca, J. M. S. S.; Gomes, L. R.; Marrucho, I. M.; Rebelo, L. P. N.

J. Am. Chem. Soc. **2007,** *129,* 284. c) Shigeto, S.; Hamaguchi, H. *Chem. Phys. Lett.* **2006,** *427,* 329.

[90] Hamaguchi, H.-O.; Ozawa, R. *Adv. Chem. Phys.* **2005,** *131,* 85.

[91] a) Rebelo, L. P. N.; Lopes, J. N. C.; Esperana, J. M. S. S.; Guedes, H. J. R.; Lachwa, J.; Najdanovic-Visak, V.; Visak, Z. P. *Acc. Chem. Res.* **2007,** *40,* 1114. b) Hu, Z.; Margulis, C. J. *Acc. Chem. Res.* **2007,** *40,* 1097 and references cited therein. c) Hunt, P. A. *J. Phys. Chem. B* **2007,** *111,* 4844.

[92] a) Fletcher, K. A.; Pandey, S. *J. Phys. Chem. B* **2003,** *107,* 13532. b) Sarkar, A.; Pandey, S. *J. Chem. Eng. Data* **2006,** *51,* 2051.

[93] a) Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *J. Chem. Soc., Perkin Trans 2* **2001,** *4,* 433. b) Crowhurst, L.; Mawdsley, P. R.; Perez-Arlandis, J. M.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2003,** *5,* 2790. c) Reichardt, C. *Green Chem.* **2005,** *7,* 339. d) Lee, J. M.; Ruckes, S.; Prausnitz, J. M. *J. Phys. Chem. B* **2008,** *112,* 1473.

[94] Sarkar, A.; Trivedi, S.; Baker, G. A.; Pandey, S. *J. Phys. Chem. B* **2008,** *112,* 14927.

[95] Anderson, J. L.; Ding, J.; Welton, T.; Armstrong, D. W. *J. Am. Chem. Soc.* **2002,** *124,* 14247.

[96] Welton, T. *Coord. Chem. Rev.* **2004,** *248,* 2459.

[97] a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001,** *40,* 3726. b) Schreiner, P. R. *Chem Soc. Rev.* **2003,** *32,* 289.

[98] Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007,** *63,* 2363 and references cited therein.

[99] a) Grodkowski, J.; Neta, P.; Wishart, J. F. *J. Phys. Chem. A* **2003,** *107,* 9794. b) Buzzeo, M. C.; Klymenko, O. V.; Wadhawan, J. D.; Hardacre, C.; Seddon, K. R.; Compton, R. G. *J. Phys. Chem. B* **2004,** *108,* 3947.

[100] a) Bresme, F.; Alejandre, J. *J. Chem. Phys.* **2003,** *118,* 4134. b) Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.; Sheppard, O.; Hardacre, C.; Rogers, R. D. *Chem. Commun.* **2003,** 476.

[101] a) Saito, K.; Kambe, S.; Sakurai, A.; Midorikawa, H. *Synthesis* **1982,** 1056. b) Kojima, H.; Nakamura, K.; Yamamoto, K.; Inoue, H. *Synthesis* **1996,** 1193. c) Zhang, H.; Yang, G.; Chen, J.; Chen, Z. *Synthesis* **2004,** 3055.

[102] a) Lancaster, N. L.; Welton, T.; Young, G. B. *J. Chem. Soc. Perkin Trans. 2* **2001,** 2267. b) Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003,** *68,* 6710. c) Crowhurst, L.; Lancaster, N. L.; Arlandis, J. M. P.; Welton, T. *J. Am. Chem. Soc.* **2004,** *126,* 11549. d) Chiappe, C.; Pieraccini, D. *J. Org. Chem.* **2004,** *69,* 6059. e) D' Anna, F.; Frenna, V.; Pace, V.; Noto, R. *Tetrahedron* **2006,** *62,* 1690.

[103] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928,** *460,* 98.

[104] a) Desimoni, G.; Tacconi, G.; Barco, A.; Polloni, G. P. *Natural Product Synthesis through Pericyclic Reactions, ACS Monograph 180;* American Chemical Society: Washington, D.C., 1983. b) Oppolzer, W. *Angew. Chem., Int. Ed.* **1984,** *23,* 876. c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis;* Pergamon: Oxford, 1990. d) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reactions;* Wiley: New York, 1990. e) Ressig, H.-U. Organic Synthesis Highlights. In ; VCH: Weinheim, 1991. f) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992,** *92,* 1007. g) Stipanovic, R. D. *Environ. Sci. Res.* **1992,** *44,* 319. h) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993,** *93,* 741. i) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed.* **1994,** *33,* 497. j) Laschat, S. *Angew. Chem., Int. Ed.* **1996,** *35,* 289. k) Kumar, A. *Chem. Rev.* **2001,** *101,* 1.

[105] a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry;* Verlag Chemie: Weinheim, 1970. b) Fukui, K. *Acc. Chem. Res.* **1971,** *4,* 57. c) Houk, K. N. *Acc. Chem. Res.* **1975,** *8,* 361.

[106] Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962,** *84,* 297.

[107] a) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983,** *24,* 1901. b) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984,** *25,* 1239. c) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988,** *110,* 5613. d) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991,** *113,* 4340. e) Breslow, R. *Acc. Chem. Res.* **1991,** *24,* 159 and references cited therein.

[108] a) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983,** *24,* 1897. b) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983,** *48,* 3137. c) Grieco, P. A.; Garner, P.; Zhen-min, H. *Tetrahedron Lett.* **1984,** *25,* 5715. d) Yoshida, K.; Grieco, P. A. *Chem. Lett.* **1985,** 155.

[109] Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996,** *25,* 209.

[110] a) Blokzijl, W.; Engberts, J. B. F. N.; Blandamer, M. J. *J. Am. Chem. Soc.* **1990,** *112,* 1197. b) Blokzijl, W.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1992,** *114,* 5440. c) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem. Int. Ed.* **1993,** *32,* 1545. d) Rispens, T.; Engberts, J. B. F. N. *J. Org. Chem.* **2002,** *67,* 7369.

[111] a) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991,** *113,* 7430. b) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992,** *114,* 10966. c) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994,** *59,* 803. d) Jorgensen, W. L.; Blake, J. F.; Lim, D.; Severance, D. L. *J. Chem. Soc. Faraday Trans.* **1994,** *90,* 1727.

[112] a) Dack, M. R. J. *Chem. Soc. Rev.* **1975,** *4,* 211. b) Pirrung, M. C. *Chem. Eur. J.* **2006,** *12,* 1312.

[113] a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990,** *112,* 4595. b) Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987,** *52,* 1001. c) Kumar, A. *J. Org. Chem.* **1994,** *59,* 230.

[114] Gajewski, J. J. *J. Org. Chem.* **1992,** *57,* 5500.

[115] Kumar, A. *J. Phys. Org. Chem.* **1996,** *9,* 287.

[116] a) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986,** 1787. b) Sangwan, N. K.; Schneider, H.-J. *J. Chem. Soc., Perkin Trans. 2* **1989,** 1223.

[117] a) Desimoni, G.; Faita, G.; Righetti, P.; Tornaletti, N.; Visigalli, M. *J. Chem. Soc., Perkin Trans. 2* **1989,** 437. b) Burdisso, M.; Desimoni, G.; Faita, G.; Righetti, P.; Tacconi, G. *J. Chem. Soc., Perkin Trans. 2* **1989,** 845. c) Corsico Coda, A.; Desimoni, G.; Faita, G.; Righetti, P.; Tacconi, G. *Tetrahedron* **1989,** *45,* 775. d) Desimoni, G.; Faita, G.; Pasini, D.; Righetti, P. *Tetrahedron* **1992,** *48,* 1667.

[118] a) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1990,** *3,* 414. b) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1991,** *4,* 48. c) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Royo, A. J.; Salvatella, L.; Assfeld, X.; Ruiz-Lopez, M. F. *J. Phys. Org. Chem.* **1992,** *5,* 230. d) Ruiz-Lopez, M. F.; Assfeld, X.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993,** *115,* 8780.

[119] a) Pawar, S. S.; Phalgune, U.; Kumar, A. *J. Org. Chem.* **1999,** *64,* 7055. b) Deshpande, S. S.; Phalgune, U.; Kumar, A. *Tetrahedron* **2002,** *58,* 8759.

[120] Sarma, D.; Kumar, A. *Org. Lett.* **2006,** *8,* 2199.

[121] Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990,** *31,* 3381.

[122] a) Firestone, R. A.; Vitale, M. A. *J. Org. Chem.* **1981,** *46,* 2160. b) Swiss, K. A.; Firestone, R. A. *J. Org. Chem.* **1999,** *64,* 2158. c) Swiss, K. A.; Firestone, R. A. *J. Phys. Chem. A* **1999,** *103,* 5369.

[123] a) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982,** *23,* 303. b) Dolbier, W. R.; Seabury, M. J. *J. Am. Chem. Soc.* **1987,** *109,* 4393. c) Dunams, T.; Hoekstra, M.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988,** *29,* 3745. d) Valgimigli, L.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996,** *61,* 7947.

[124] Jaffe, S. B.; Anderson, J. B. *J. Chem. Phys.* **1969,** *51,* 1057.

[125] Weber, C. F.; van Eldik, R. *J. Phys. Chem. A* **2002,** *106,* 6904.

[126] Hamann, S. D.; le Noble, W. J. *J. Phys. Chem. A* **2004,** *108,* 7121.

[127] Kumar, A.; Deshpande, S. S. *J. Org. Chem.* **2003,** *68,* 5411.

[128] Aggarwal, A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002,** *4,* 517.

[129] Janus, E.; Goc-Maciejewska, I.; Ł ożyński, M.; Pernak, J. *Tetrahedron Lett.* **2006,** *47,* 4079.

[130] Vidiš, A.; Ohlin, C. A.; Laurenczy, G.; Küsters, E.; Sedelmeier, G.; Dyson, P. J. *Adv. Synth. Catal.* **2005,** *347,* 266.

[131] a) Wittig, G.; Giessler, G. *Liebigs Ann. Chem.* **1953,** *580,* 44. b) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954,** *87,* 1318. c) Wittig, G. *Science* **1980,** *210,* 600 and references cited therein.

[132] a) Maerckar, A. *Org. React.* **1965,** *14,* 270. b) Gosney, I.; Rowley, A. G. . In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979. c) Bestmann, H. J.; Vostrowsky, O. . In *Topics in Current Chemistry, Wittig Chemistry*, Vol. 109; Boschke, F., Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1983. d) Johnson, W. A. *Ylides and Imines of Phosphorus;* John Wiley and Sons: New York, 1993. e) Kolodiazhnyi, O. I. *Phosphorus Ylides: Chemistry and Application in Organic Synthesis;* Wiley-VCH: New York, 1999.

[133] a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989,** *89,* 863. b) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994,** *21,* 1.

[134] a) Tripett, S. *Q. Rev., Chem. Soc.* **1963,** *17,* 406. b) Johnson, A. W. *Ylide Chemistry;* Academic Press: New York, 1966.

[135] a) Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963,** *85,* 1888, 3878. b) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964,** *29,* 3327.

[136] a) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2005,** *127,* 13468. b) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2006,** *128,* 2394.

[137] a) Froyen, P. *Acta Chem. Scand.* **1972,** *26,* 2163. b) Aksnes, G.; Khalil, F. Y. *Phosphrous Relat. Group V Elem.* **1972,** *2,* 105.

[138] a) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005,** *46,* 4473. b) Wu, J.; Zhang, D.; Wei, S. *Synth. Commun.* **2005,** *35,* 1213.

[139] Wu, J.; Zhang, D. *Synth. Commun.* **2005,** *35,* 2543.

[140] Wu, J.; Yue, C. *Synth. Commun.* **2006,** *36,* 2939.

[141] El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.* **2007,** *72,* 5244.

[142] a) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989,** *30,* 1785. b) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999,** *1,* 23. c) Fischer, T.; Sethi, A. R.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999,** *40,* 793. d) Lee, C. W. *Tetrahedron Lett.* **1999,** *40,* 2461. e) Song, C. E.; Roh, E. J.; Shim, W. H.; Choi, J. H. *Chem. Commun.* **2000,** 1695. f) Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2004,** *69,* 1419.

[143] a) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, R.; Haag, R. *Angew. Chem. Int. Ed.* **2002,** *41,* 3964. b) Bonhôte, P.; Dias, A. P.; Papageorgiou, N.; Kalyansundaram, K.; Gratzel, M. *Inorg. Chem.* **1996,** *35,* 1168. c) Seddon, K. R.; Stark, A.; Torres, A.-J. *Pure Appl. Chem.* **2000,** *72,* 2275. d) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Brokers, G. A.; Rogers, R. D. *Green Chem.* **2001,** *3,* 156. e) Noda, A.; Hayamizu, K.; Watanabe, M. *J. Phys. Chem. B* **2001,** *105,* 4603. f) Baker, S. N.; Baker, G. A.; Kane, M. A.; Bright, F. V. *J. Phys. Chem. B* **2001,** *105,* 9663. g) Branco, L. C.; Rosa, J. N.; Ramos, J. J. M.; Afonso, C. A. M. *Chem. Eur. J.* **2002,** *8,* 3671.

[144] Wang, J.; Tian, Y.; Zhao, Y.; Zhuo, K. *Green Chem.* **2003,** *5,* 618.

[145] a) D'Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. *J. Org. Chem.* **2006,** *71,* 5144. b) Wells, T. P.; Hallett, J. P.; Williams, C. K.; Welton, T. *J. Org. Chem. ASAP article* **2008,** *73,* 5585.

[146] a) Behar, D.; Gonzalez, C.; Neta, P. *J. Phys. Chem. A* **2001,** *105,* 7607. b) Behar, D.; Neta, P.; Schultheisz, C. *J. Phys. Chem. A* **2002,** *106,* 3139. c) Grodkowski, J.; Neta, P. *J. Phys. Chem. A* **2002,** *106,* 5468, 9030, 11130. d) Skrzypczak, A.; Neta, P. *J. Phys. Chem. A* **2003,** *107,* 7800.

[147] McLean, A. J.; Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *Chem. Commun.* **2002,** 1880.

[148] Baba, K.; Hajime, O.; Itoh, E.; Itoh, S.; Noda, K.; Usui, T.; Ishihara, K.; Inamo, M.; Takagi, H. D.; Asano, T. *Chem. Eur. J.* **2006,** *12,* 5328.

[149] Chiappe, C.; Conte, V.; Pieracinni, D. *Eur. J. Org. Chem.* **2002,** 2831.

[150] D'Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. *J. Org. Chem.* **2006,** *71,* 9637.

[151] a) Hynes, J. T. *Ann. Rev. Phys. Chem.* **1985,** *36,* 573. b) Hänggi, P.; Talkner, P.; Borkovec, M. *Rev. Mod. Phys.* **1990,** *62,* 251.

[152] a) Velsko, S. P.; Fleming, G. R. *Chem. Phys.* **1982,** *65,* 59. b) Keery, K. M.; Fleming, G. R. *Chem. Phys. Lett.* **1982,** *93,* 322. c) Velsko, S. P.; Fleming, G. R. *J. Chem. Phys.* **1982,** *76,* 3553. d) Velsko, S. P.; Waldeck, D. H.; Fleming, G. R. *J. Chem. Phys.* **1983,** *78,* 249. e) Courtney, S. H.; Fleming, G. R. *Chem. Phys. Lett.* **1984,** *103,* 443.

[153] Basilevskii, M. V.; Ryaboi, V. M.; Weinberg, N. N. *J. Phys. Chem.* **1991,** *95,* 5533.

[154] a) Crosthwaite, J. M.; Muldoon, M. J.; Dixon, J. N. K.; Anderson, J. L.; Brennecke, J. F. *J. Chem. Thermodynamics* **2005,** *37,* 559. b) Papaiconomou, N.; Salminen, J.; Lee, J.-M.; Prausnitz, J. M. *J. Chem. Engg. Data* **2007,** *52,* 833.

[155] Mellein, B. R.; Aki, S. N. V. K.; Ladewski, R. L.; Brennecke, J. F. *J. Phys. Chem. B* **2007,** *111,* 131.

[156] Grote, R. F.; Hynes, J. T. *J. Chem. Phys.* **1982,** *77,* 3736.

[157] a) Sumi, H.; Marcus, R. A. *J. Chem. Phys.* **1986,** *84,* 4894. b) Sumi, H. *J. Phys. Chem.* **1991,** *95,* 3334. c) Sumi, H. *J. Chem. Phys.* **1994,** *100,* 8825.

[158] Funston, A. M.; Fadeeva, T. A.; Wishart, J. F.; Castner, E. W. *J. Phys. Chem. B* **2007,** *111,* 4963.

[159] Lu, J.; Liotta, C. L.; Eckert, C. A. *J. Phys. Chem. A* **2003,** *107,* 3995.

[160] Mandal, P. K.; Samanta, A. *J. Phys. Chem. B* **2005,** *109,* 15172.

[161] Iwata, K.; Kakita, M.; Hamaguchi, H. *J. Phys. Chem. B* **2007,** *111,* 4914.

[162] Casaschi, A.; Desimoni, G.; Faita, G.; Invernizzi, A. G.; Lanati, S.; Righetti, P. *J. Am. Chem. Soc.* **1993,** *115,* 8002.

[163] Lee, J.-M.; Ruckes, S.; Prausnitz, J. M. *J. Phys. Chem. B* **2008,** *112,* 1473.

[164] Khupse, N. D.; Kumar, A. unpublished results.

[165] a) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991,** *113,* 4340. b) Rizzo, C. J. *J.Org. Chem.* **1992,** *57,* 6382.

[166] Kumar, A.; Pawar, S. S. *Tetrahedron* **2002,** *58,* 1745.

[167] a) Muldoon, M. J.; McLean, A. J.; Gordon, C. M.; Dunkin, I. R. *Chem. Commun.* **2001,** 2364. b) Wishart, J. F.; Neta, P. *J. Phys. Chem. B* **2003,** *107,* 7261.

[168] Nishiyama, Y.; Fukuda, M.; Terazima, M.; Kimura, Y. *J. Chem. Phys.* **2008,** *128,* 164514.

[169] Mali, K. S.; Dutt, G. B.; Mukherjee, T. *J. Chem. Phys.* **2008,** *128,* 054504.

[170] Kobrak, M. N. *J. Phys. Chem. B* **2007,** *111,* 4755.

[171] Kobrak, M. N. *Green Chem.* **2008,** *10,* 80.

[172] a) Canongia-Lopes, J. N. A.; Pádua, A. A. H. *J. Phys. Chem. B* **2006,** *110,* 3330. b) Wang, Y.; Voth, G. A. *J. Phys. Chem. B* **2006,** *110,* 18601.

[173] Shim, Y.; Choi, M. Y.; Kim, H. J. *J. Chem. Phys.* **2005,** *122,* 044510.

[174] Tobias, D. J.; Hemminger, J. C. *Science* **2008,** *319,* 1197.

[175] Vogel, A. I. . In *Vogel's Textbook of Quantitative Chemical Analysis*, 5th ed.; Jeffrey, G. H.; Bassett, J.; Mendham, J.; Denney, R. C., Eds.; ELBS-Longman: UK, 1989.

[176] Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1997,** *62,* 2039.

[177] a) McDevit, W. F.; Long, F. A. *J. Am. Chem. Soc.* **1952,** *74,* 1773. b) Breslow, R.; Guo, T. *Proc. Natl. Acad. Sci.* **1990,** *87,* 167.

[178] Kuo, I.-F. W.; Mundy, C. J. *Science* **2004,** *303,* 658.

[179] Du, Q.; Superfine, R.; Freysz, E.; Shen, Y. R. *Phys. Rev. Lett.* **1993,** *70,* 2313.

[180] Schnitzer, C.; Baldelli, S.; Shultz, M. J. *J. Phys. Chem. B* **2000,** *104,* 585.

[181] Gopalakrishnan, S.; Jungwirth, P.; Tobias, D. J.; Allen, H. C. *J. Phys. Chem. B* **2005,** *109,* 8861.

[182] a) Jungwirth, P.; Tobias, D. J. *J. Phys. Chem. B* **2002,** *106,* 6361. b) Dang, L. X. *J. Phys. Chem. B* **2002,** *106,* 10388.

[183] a) Peterson, P. B.; Saykally, R. J. *Annu. Rev. Phys. Chem.* **2006,** *57,* 333. b) Shultz, M. J.; Baldelli, S.; Schnitzer, C.; Simonelli, D. *J. Phys. Chem. B* **2002,** *106,* 5313. c) Richmond, G. L. *Chem. Rev.* **2002,** *102,* 2693.

[184] Foster, K.; Raghavan, K.; Berkowitz, M. *Chem. Phys. Lett.* **1989,** *162,* 32.

[185] Zangi, R.; Berne, B. J. *J. Phys. Chem. B* **2008,** *112,* 8634.

[186] a) Finer, E. G.; Franks, F.; Tait, M. J. *J. Am. Chem. Soc.* **1972,** *94,* 4424. b) Hoccart, X.; Turrell, G. *J. Chem. Phys.* **1993,** *99,* 8498.

[187] a) Vanzi, F.; Madan, B.; Sharp, K. *J. Am. Chem. Soc.* **1998,** *120,* 10748. b) Chitra, R.; Smith, P. E. *J. Phys. Chem. B* **2000,** *104,* 5854.

[188] a) Mountain, R. D.; Thirumalai, D. *J. Am. Chem. Soc.* **2003,** *125,* 1950. b) Klimov, D. K.; Straub, J. E.; Thirumalai, D. *Proc. Natl. Acad. Sci.* **2004,** *101,* 14760. c) Astrand, P.-O.; Wallqvist, A.; Karlstroem, G. *J. Phys. Chem.* **1994,** *98,* 8224.

[189] Wallqvist, A.; Covell, D. G.; Thirumalai, D. *J. Am. Chem. Soc.* **1998,** *120,* 427.

[190] Menger, F. M. *Chem. Soc. Rev.* **1972,** *1,* 229.

[191] a) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986,** *108,* 3512. b) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986,** *27,* 1975. c) Russell, M. G.; Warren, S. *Tetrahedron Lett.* **1998,** *39,* 7995. d) Sieber, F.; Wentworth, P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999,** *64,* 5188. e) Russell, M. G.; Warren, S. *J. Chem. Soc. Perkin Trans. I* **2000,** 505.

[192] a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis;* VCH: Weinheim, 3rd ed.; 1993. b) Starks, C. M.; Liotta, C. L.; Halpern, M. E. *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives;* Chapman and Hall: New York, 1994. c) Sasson, Y.; Neumann, R., Eds.; *Handbook of Phase-Transfer Catalysis;* Blackie Academic and Professional: London, 1997. d) Halpern, M. E., Ed.; *Phase-Transfer Catalysis (ACS Symposium Series 659);* American Chemical Society: Washington, DC, 1997. e) Orsini, F.; Sello. G.; Fumagalli, T. *Synlett* **2006,** 1717.

[193] a) Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2006,** *47,* 4707. b) Price, B. K.; Tour, J. M. *J. Am. Chem. Soc.* **2006,** *128,* 12899.

[194] a) Hanna, G. J.; Noble, R. D. *Chem. Rev.* **1985,** *85,* 583. b) Tsukahara, S. *Analytica Chim. Acta* **2006,** *556,* 16. c) Slevin, C. J.; Unwin, P. R. *Langmuir* **1997,** *13,* 4799.

[195] Benjamin, I. *Chem. Rev.* **1996,** *96,* 1449 and references cited therein.

[196] a) Arnett, E. M. . In *Physico-Chemical Processes in Mixed Aqueous Solvents*; Franks, F., Ed.; Heinemann Educational Books Ltd.: London, 1967. b) Haak, J. R.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1986,** *108,* 1705.

[197] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988,** *110,* 1238.

[198] Rondestvedt, C. S.; Nooy, C. D. V. *J. Am. Chem. Soc.* **1955,** *77,* 4878.

[199] Astumian, R. D.; Schelly, Z. A. *J. Am. Chem. Soc.* **1984,** *106,* 304.

[200] MacRitchie, F. . In *Interfacial Synthesis - Fundamentals*; Millich, F.; Carraher, C. E., Eds.; Marcel Dekker: New York, 1977.

[201] Bell, R. P. *J. Phys. Chem.* **1928,** *32,* 882.

[202] Morgan, P. W. *Condensation Polymers by Interfacial and Solution Methods;* Interscience: New York, 1965.

[203] a) Matteoli, E.; Lepori, L. *J. Chem. Phys.* **1984,** *80,* 2856. b) Nishikawa, K.; Hayashi, H.; Iijima, T. *J. Phys. Chem.* **1989,** *93,* 6559.

[204] a) Stanners, C. D.; Du, Q.; Chin, R. P.; Cremer, P.; Somorjai, G. A.; Shen, Y.-R. *Chem. Phys. Lett.* **1995,** *232,* 407. b) Braun, R.; Casson, B. D.; Bain, C. D. *Chem. Phys. Lett.* **1995,** *245,* 326. c) Casson, B. D.; Braun, R.; Bain, C. D. *Faraday Discuss.* **1996,** *104,* 209. d) Sung, J.; Park, K.; Kim, D. *J. Phys. Chem. B* **2005,** *109,* 18507.

[205] a) Stewart, E.; Shields, R. L.; Taylor, R. S. *J. Phys. Chem. B* **2003,** *107,* 2333. b) Andoh, Y.; Yasuoka, K. *J. Phys. Chem. B* **2006,** *110,* 23264. c) Pártay, L. B.; Jedlovszky, P.; Vincze, A.; Horvai, G. *J. Phys. Chem. B* **2008,** *112,* 5428.

[206] Engberts, J. B. F. N.; Fernándes, E.; García-Río, L.; Leis, J. R. *J. Org. Chem.* **2006,** *71,* 4111.

[207] Gawalt, E. S.; Mrksich, M. *J. Am. Chem. Soc.* **2004,** *126,* 15613.

[208] a) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991,** *113,* 4241. b) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000,** *72,* 1365.

[209] a) Davis, H. T.; Scriven, L. E. *J. Phys. Chem.* **1976,** *80,* 2805. b) Rosseinsky, D. R. *J. Phys. Chem.* **1977,** *81,* 1578.

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