

**Kinetic and Mechanistic Investigations of
1,3-Dipolar Cycloaddition and Other C-C Bond
Forming Reactions in Water and Ionic Liquids**

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BY

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DECLARATION

I hereby declare that the work incorporated in the thesis entitled “**Kinetic and Mechanistic Investigations of 1,3-Dipolar Cycloaddition and Other C-C Bond Forming Reactions in Water and Ionic Liquids**” submitted for the degree of Doctor of Philosophy to the Savitribai Phule Pune University, has been carried out by me at the Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune from January, 2010 to January, 2015 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.

Anshu Singh

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Dedicated
to my family members



Contents

Acknowledgements	iv
Abstract	vi
List of Abbreviations	xiii
1 Introduction	1
1.1 Solvent effect on chemical systems	2
1.1.1 An overview	2
1.2 Approaches for the analysis of solvent effects	5
1.2.1 Qualitative approach	5
1.2.2 Quantitative approach	5
1.3 Classification of solute-solvent interactions (specific interactions only)	8
1.3.1 Hydrogen bonds	8
1.3.2 Hydrophobic effects: definition	8
1.3.3 Possible interactions in water and mixed aqueous systems . . .	12
1.4 Solvent effect in green solvents	13
1.4.1 Specific effects of water	13
1.4.2 The effect of water on cycloaddition reactions	13
1.4.3 Water-accelerated transformations	15
1.4.4 Ionic Liquids (ILs)	16
1.5 Solvent effect on 1,3-dipolar cycloaddition reaction	21
1.6 Solvent effect on Benzoin condensation	22
1.7 Solvent effect on Baylis-Hillman reaction (BHR)	23
1.7.1 Origin and growth of BHR	24

1.7.2	Rate acceleration	25
1.7.3	Mechanism of the reaction	25
1.8	Conclusions	26
2	Aims and Objectives	36
3	Investigation of Interfacial 1,3-Dipolar Cycloaddition (1,3-DCA) Reactions	40
3.1	Salt effect at interface of 1,3-DCA reactions	41
3.1.1	Introduction	41
3.1.2	1,3-dipolar cycloaddition reactions (1,3-DCA)	42
3.1.3	Solvent effect on 1,3-DCA reactions	45
3.1.4	Present scenario: azide-alkene cycloaddition as “click reaction”	46
3.1.5	The present work	47
3.1.6	Experimental section	48
3.1.7	Results and discussion	51
3.1.8	Conclusions	59
3.2	Homogenous <i>vs.</i> heterogenous reactions at interface	60
3.2.1	Introduction	60
3.2.2	Present work	60
3.2.3	Experimental section	61
3.2.4	Results and discussion	62
3.2.5	Conclusions	69
4	A Physico-Organic Investigation of Interfacial Benzoin Condensation	74
4.1	A kinetic investigation of interfacial Benzoin Condensation	75
4.1.1	Introduction	75
4.1.2	Historical perspective of Benzoin Condensation	75
4.1.3	Motivation behind work	76
4.1.4	Experimental section	77

4.1.5	Synthesis of benzoin	77
4.1.6	Kinetic measurements	78
4.1.7	Results and discussion	79
4.1.8	Conclusions	87
5	Kinetic and Mechanistic Investigations of BHR in ILs	91
5.1	Investigation of mechanism of BHR in ILs	92
5.1.1	Introduction	92
5.1.2	Definition of problem	94
5.1.3	Experimental section	95
5.1.4	Results and discussion	97
5.1.5	Conclusions	103
5.2	Do cation of ILs affect kinetics and mechanism of BHR?	104
5.2.1	Introduction	104
5.2.2	Experimental section	104
5.2.3	Results and discussion	107
5.2.4	Conclusions	117
6	Conclusions	121
	Appendix A	125
	Appendix B	128
	Appendix C	131
	Appendix D	133
	Appendix E	134

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*“As you start and end your day, say thank you for every little things in your life.
And you will come to realize how blessed you truly are.”*

Anshu Singh

Abstract

Kinetic and Mechanistic Investigations of 1,3-Dipolar Cycloaddition and Other C-C Bond Forming Reactions in Water and Ionic Liquids

Strategies regarding construction and cleavage of C-C and C-X bonds play a central role in organic chemistry. Till date, significant information about mechanistic pathway of bond formation still has come from kinetic studies. However, interpretation of mechanistic pathway from kinetic study is not easy. It is quite obvious that charged species, formed in a reaction, can carry an envelope of solvent molecules, greatly affecting their reactivity, stability and selectivity. Interestingly, quite small changes in solvent can cause profoundest changes in reaction rates and mechanism. Although any liquid can be used as a solvent, very few are known to be used on a larger scale. For ecological and economical reasons, chemists are always confronted with the difficult task of selecting appropriate solvents for carrying out chemical processes. Generally, obnoxious volatile organic solvents are used on a larger scale due to the wide solubility window. Unfortunately, two main concerns of using organic solvents arise due to their volatility and toxicity. Nowadays, as the introduction of greener technology is high on demand in both academia and industry, the requirement of alternatives to damaging solvents has gained momentum. Currently, concepts such as atom economy and efforts towards minimization of auxiliary chemicals are the other two main concerns. Henceforth, as a promising solution to these problems, throughout our thesis we have focused on the designing and application of two main green solvents (a) water and (b) ionic liquids. Organic reactions have been performed in ionic liquids, aqueous solutions and binary mixtures of water and co-solvents in order to discern the kinetics and mechanism of organic reactions in such environment benign media. In view of this, a

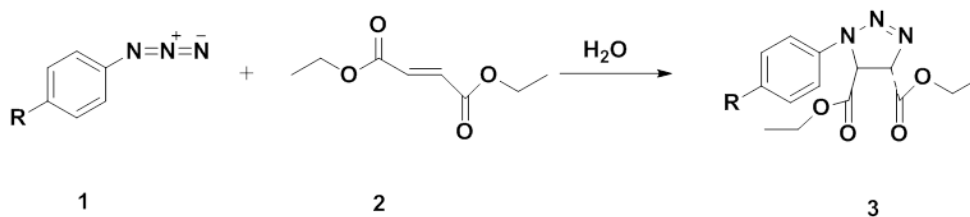
comprehensive study on the solvent effect and kinetics of certain important reaction such as Baylis-Hillman reaction, 1,3-dipolar cycloaddition and Benzoin condensation have been undertaken under the theme of the present thesis. For the convenience of presentation, different features of the present research work have been discussed in eight different chapters. Below is given brief descriptions of these chapters:

Chapter 1: This chapter introduces the experimental work described in the following chapters. The mechanistic aspects of Baylis-Hillman reaction, 1,3-dipolar cycloaddition and Benzoin condensation are discussed. This chapter presents a critical survey of literature on 1,3-dipolar cycloaddition, Baylis-Hillman and Benzoin condensation reaction. Significance of water as a medium has also been discussed in this chapter. Existence of various forces such as hydrogen bonding, hydrophobic packing and polarity has been critically examined. An attempt has been made to understand the nature and consequences of various forces existing in both homogenous and heterogenous aqueous and its binary mixtures with cosolvents. Much of the significance has been given to the current understanding of solute-solvent interactions in both homogenous and heterogenous media. A brief introduction of ionic liquids, their evolution and applications in catalyzing organic reactions has been discussed thoroughly.

Chapter 2: This chapter briefly outlines the aims and objectives of proposed research work. The work reported in this thesis emphasizes on using solvents for carrying out organic reactions. Contrary to ‘in-water’ methodology, the dramatic outcome of employing ‘on-water’ protocol for carrying out organic reactions will be the central theme of the dissertation.

Chapter 3: This chapter deals with the investigation of contribution of hydrophobic forces at the oil-water interface. It presents a brief but critical survey of the literature on the effect of water on 1,3-dipolar cycloaddition reaction, with particular emphasis on the intriguing properties of water in connection with their effect on reactivity of the reaction too. In order to investigate the origin of the molecular forces that give rise to the rate enhancement observed under heterogenous conditions, detailed kinetic studies of 1,3-dipolar cycloaddition reaction in aqueous media has been

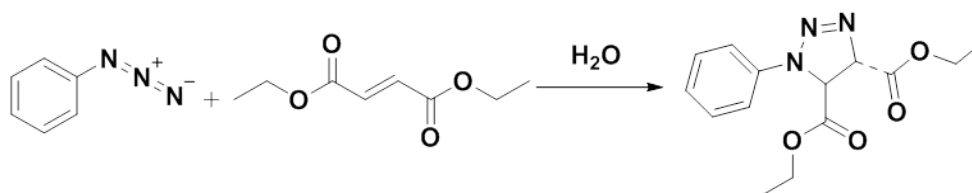
discussed in this chapter. The effect of hydrophobicity and hydrogen bonding on the interfacial reaction has been studied by assessing the reaction kinetics at different concentrations of salt solutions. The reaction kinetics in different salts such as LiCl, KCl, CaCl₂, NaCl and (C₄H₉)₄NBr has been studied. A comparative assessment of reaction in both homogenous and heterogenous aqueous reaction media has been critically analysed in this chapter. The kinetic studies divulge a conspicuous role of prohydrophobic salts under these conditions. The significance of solubility and its contribution to the ‘on-water’ reaction has been incorporated in this chapter. In order to delineate the role being played by electronic factor, a kinetic investigation of the addition of different dienes on diethyl fumarate has been endowed in this chapter. The work presented here accentuates the influence of dipole such as phenyl azide, *p*-bromophenyl azide and *p*-nitrophenyl azide on the reactivity of interfacial reaction (Scheme 1). The comparative assessment of the reaction was carried out for different reactants in identical conditions. Surprisingly, no rate enhancement was observed at higher salt concentration for all the three reactants.



Scheme 1

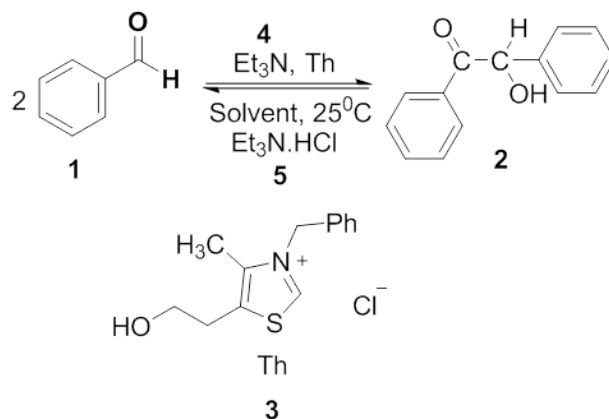
Some reports from the literature claims are critically examined and the effect of substituents on diene has been formulated in this chapter. Finally, the role of “active” interfacial area has been thoroughly discussed for the above being crucial for the desired enhancement in heterogenous reaction conditions, which have implications in determining the optimum salt concentrations and conditions required for such reactions. Further attempt has been made in the present chapter to obtain a deeper insight into the significance of heterogeneity for interfacial catalysis of reactions. Par-

ticular attention has been paid to the influence of temperature on the solubility of the participating reactants. Gradual conversion of heterogenous media to the homogeneous one and its consequence on the reactivity has been critically analysed in this section of the chapter. Serendipitous discovery of phenyl azide exhibiting decrease in solubility with increase in temperature, has been used as an investigating tool for deciphering the role of solubility in ‘on-water’ catalysis (Scheme 2). The important conclusion drawn from the results suggests that heterogeneity is very important for attaining higher interfacial reactivity.



Scheme 2

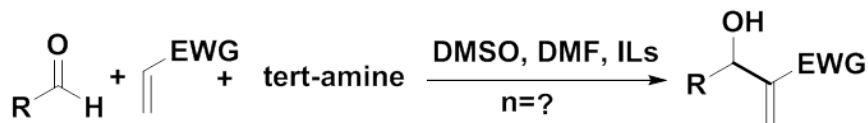
Chapter 4: This chapter elaborates our current understanding of the effect of addition of cosolvents to water. Besides increasing the solubility window, cosolvents can have profound effect on the polarity of the binary mixtures. Benzoin condensation has been thoroughly investigated in the present chapter (Scheme 3). The solvent composition was varied from pure water to 60%v/v organic cosolvents composition. The enhanced water characteristics at lower concentration of cosolvents have been given special thought in this chapter. The enhancement observed has been attributed mainly to the increase in the number density of alcohol molecules. As the length of alkyl chain of cosolvents increased, the maxima of rate constant shifted to lower concentration and become more pronounced too. An initial increase in the reactivity of reaction is observed followed by sharp fall in the reaction kinetics. An interesting interplay of hydrophobicity and polarity of the binary mixture is inevitable in the present study and has been special importance in this chapter. The reaction becomes less hydrophobically accelerated with the increase in the alkyl chain length of the



Scheme 3

monohydric alcohols. Interestingly, in the initial phase of addition of cosolvents the reaction is driven and is dominated by polarity effect. However, at higher concentration of cosolvents the reaction media become homogenous and is hydrophobically accelerated. The chapter focuses on the complex interplay in between the polarity and hydrophobic effect. The observations given in the chapter are nevertheless important reference point for future investigations of ‘on-water’ reactions.

Chapter 5: Section I: This section deals with the exhaustive investigation of the effect of ionic liquids on one of the earliest known reactions for C-C bond formation, Baylis-Hillman reaction. The kinetic and mechanistic investigations of Baylis-Hillman reaction in ionic liquids has been discussed in detail in this section. The reaction of *p*-nitrobenzaldehyde with methyl acrylate in presence of DABCO as a catalyst has been carried out in a varied range of protic and aprotic ionic liquids (Scheme 4). The section exhibits the description of the rate law study in order to delineate controversial of mechanism of this reaction. The reaction was first carried out in [EtP][NTf₂] and [OMPyr][NTf₂]. Upon plotting rate of reaction versus concentration of *p*-nitrobenzaldehyde, a straight line was obtained. This indicated the presence of one equivalent of *p*-nitrobenzaldehyde in the rate determining step of reaction. This encouraged us to further explore the reaction in other ionic liquids too. This section thoroughly describes an extensive study carried out in other ionic liquids too. Interestingly, [EtP][EtSO₄], [EtPip][EtSO₄], [EtMo][EtSO₄], [(Et)₄N][EtSO₄]



Scheme 4

and [EMIM][EtSO₄] exhibited an order of 2. The kinetic data for Baylis-Hillman reaction in certain ILs possessing ethylsulfate anion [EtSO₄]⁻, demonstrated that the rate determining step (RDS) is second order in aldehyde, while first order in acrylate and DABCO. Other ILs such as [HMPyr][NTf₂], [HP][HCOO], [BP][NTf₂] have been also scrutinized for their efficiency in catalyzing the reaction. The efficacy of viscosity of ILs is also discussed briefly in this section. The contribution of polarity towards stabilization of charged species formed during the course of reaction is also highlighted in the present section. As evident from the results, ethylsulfate based ILs need special consideration since they can change the mechanism of the reaction. Most interesting results discussed in this chapter involves change in the mechanism of the reaction with the change in the nature of ionic media. The section also includes a brief description of two types of mechanism of Baylis-Hillman reaction operating in ionic liquid. Further the detailed analysis of the role of cation of ionic liquid in the mechanism of the Baylis-Hillman reaction is reported. The reaction of *p*-nitrobenzaldehyde with methyl acrylate in presence of DABCO has been realised in different ILs. This section discusses in detail two different mechanisms operational in ILs. It also incorporates the observation that a delicate balance between these mechanisms is maintained by the ionic environment employed. The main features of the possible mechanism have been described here along with interesting kinetic consequences. The measurement of rate constants and activation energy parameters demonstrates that as the medium becomes basic, the order of the reaction changes from 1 to 2. An unexpected change in the mechanism of the reaction is observed with the change in the nature of ionic liquid. Linear Solvation Energy Relationship (LSER) has also been used as an investigating tool to delineate the respective contributions of cation and anion of the ionic liquid. The observation strongly dictates the dependency

of mechanism of Baylis-Hillman reaction on the nature of anion of ILs undertaken for study. The results and principal conclusion of the work undertaken are summarised in chapter 6.

Principal conclusions and future prospects

1. Saturation of salt effect at higher concentrations of salt for interfacial reaction has been demonstrated for the first time.
2. The study of 1,3-dipolar cycloaddition in the presence of salts has brought out the significance of presence of active interfacial area for 'on-water' catalysis.
3. Heterogeneity of the medium is an essential attribute for enhanced reactivity at the interface.
4. In addition, the possibility of use of co-solvents to delineate the contribution of polarity and hydrophobicity and in turn interfacial reactivity has also been demonstrated judiciously in the present work.
5. The mechanism of Baylis-Hillman reaction in ILs changes with the anion of ILs. This anomalous observation was ascribed to the high basicity of the anions particularly of EtSO₄ and HSO₄⁻-based ILs.

The work presented in the thesis offers a fresh outlook of physical-organic chemistry of the usage of environmental-benign media in important organic reactions. New insights into solvent effect on various organic reactions are presented herein. It will be an interesting avenue to pursue the use of such media in order to assess its other potential advantages in the kinetics and mechanistic study of other reactions of utmost importance. It is believed that the outcome of this work will provide necessary mechanistic understanding to achieve enhanced reactivity and selectivity of organic reactions.

List of Common Abbreviations*

[Pyr]	pyrrolidinium
[Opyr]	1-octylpyrrolidinium
[HMPyr]	1-hexyl-1-methyl-pyrrolidinium
[OMPyr]	1-octyl-1-methyl-pyrrolidinium
[BP]	1-butylpyridinium
[EtP]	1-ethylpyridinium
[Opy]	1-octylpyridinium
[EtPip]	1-ethylpiperidinium
[Opip]	1-octylpiperidinium
[EtMo]	1-ethylmorpholinium
[(Et) ₄ N]	tetraethylammonium
[EMIM]	1-ethyl-3-methylimidazolium
[HP]	1-hexylpyridinium
[MeMo]	1-methylmorpholinium
[Opipe]	1-octylpiperazinium
[NTf ₂]	bis(trifluoromethanesulfonyl)imide
[EtSO ₄]	ethylsulfate
[HCOO]	formate
[BF ₄]	tetrafluoroborate
[HSO ₄]	hydrogensulfate
[NO ₃]	nitrate
[CH ₃ COO]	acetate
[CF ₃ COO]	trifluoroacetate
[Br]	bromide
[MeSO ₄]	methylsulfate

(common abbreviations only)*

Chapter 1

Introduction

Preamble



The present chapter deals with the comprehensive study of the physico-chemical aspects of organic reactions carried out in environment-benign media. A discussion of the importance of the green solvent media is followed by an introduction of various terminologies used for explaining the solvent effects. The chapter concludes with special emphasis to the C-C bond formation reactions like 1,3-dipolar cycloaddition, Benzoin condensation and Baylis-Hillman reaction.

“A drop of water, if it could write out its own history, would explain the universe to us”.

-Lucy Larcom

1.1 Solvent effect on chemical systems

1.1.1 An overview

The development of the knowledge of solutions reflects to some extent the development of chemistry itself. At the bulk level, a liquid is the ideal medium to transport heat to and from exo- and endothermic reactions. Because of nonspecific and specific intermolecular forces, the rates, equilibria and selectivity of chemical reactions can be strongly influenced by the solvent. Unquestionably, reactivity of the molecules and ions in solution is largely dictated by the solvent medium.

The study of solvent effects on chemical reactivity dates back to more than a century. However, some chemists of the 19th century unravelled the interesting role played by the solvents by carrying out experiments on different solvent media, classified according to their physical properties.¹ In 1862, Berthelot and Pe'an de Saint-Gilles were the first to notice the considerable influence of the reaction medium on the rates of homogeneous chemical reactions.² In 1890, Menschutkin, in a pathbreaking study on the reaction of the trialkylamines with haloalkanes in 23 different solvents, demonstrated how the choice of one or the other could substantially affect the reaction rates.³ He performed the first detailed study of the reaction of trialkylamines with haloalkanes and stated that “*solvents are by no means inert in chemical reactions and can greatly influence the course of them*”. Since then many papers have appeared in the literature which substantiates the dramatic solvent effects on a large variety of chemical processes. Of all known substances, water was the first to be considered as a solvent. Since the time of Greek philosophers, there was a dilemma about the nature of solution and dissolution process. Initially the Greek alchemists considered all chemically active liquids under the name as “Divine water”. Henceforth, “water” was used to designate everything liquid or dissolved. The alchemist’s search for a universal solvent, the so-called “Alkahest” or “Menstruum universale”, indicates the importance given to solvents and the process of dissolution. Although the eager search of the chemists of the 15th to 18th centuries did not in fact lead to the discovery of any “Alkahest”, the numerous experiments performed led to the uncovering of new sol-

vents, new reactions, and new compounds.⁴ The theories of osmotic pressure of van't Hoff and that of electrolytic dissociation of Arrhenius were also another breakthrough in chemistry.⁵ The results of these experiments on a series of solvents propounded the first rules regarding the participation of the solvent, such as those discovered by Hughes and Ingold for the rate of the nucleophilic reactions.⁶ With the help of a simple model based on solute-solvent interactions, Hughes and Ingold concluded that when the transition state is more polar than the initial state, than an increase of the polarity of the solvent will stabilize the transition state more as compared to that of the initial state, thus leading to an increase in the reaction rates. In 1896, the first results about the role of the solvent on chemical equilibria were obtained, coinciding with the discovery of the keto-enolic tautomerism. Claisen and Wislicenus identified the medium as one of the factors which, together with the temperature and the substituents, proved to be decisive in the chemical equilibrium.⁷ Soon extensive studies began on the effect of the solvent in the tautomeric equilibria too.¹

With the increase in demand for organic solvents, it was during the industrial revolution that solvent manufacturing industries started to expand considerably and began to use chemistry as a tool to produce products that were needed by the consumers. These commercial efforts resulted in the synthesis of many new chemicals. Surprisingly, very rapidly, highly hazardous organic solvents were used in highly concentrated forms and that too in large quantities. Many reports followed that complained about the toxicity from chlorinated solvents. Although it is difficult to have exact figures but in 2007 approximately 166,292,627 kg of toxic waste in the form of volatile organic solvents were discharged in the United States alone (Figure 1.1).⁸ It is not surprising that chemical industries are leading contributors of pollutants to the environment. Until the end of the 19th century these problems were not addressed by the chemical industry and it is only recently that the industry began to respond to public criticism and political efforts. To combat the problem a new field "Green Chemistry" has been introduced. The basic principle underlying "Green Chemistry" is the design of environmentally benign products and processes which is embodied in the twelve principles of green chemistry as proposed by Anastas and Warner.⁹ Green chemistry

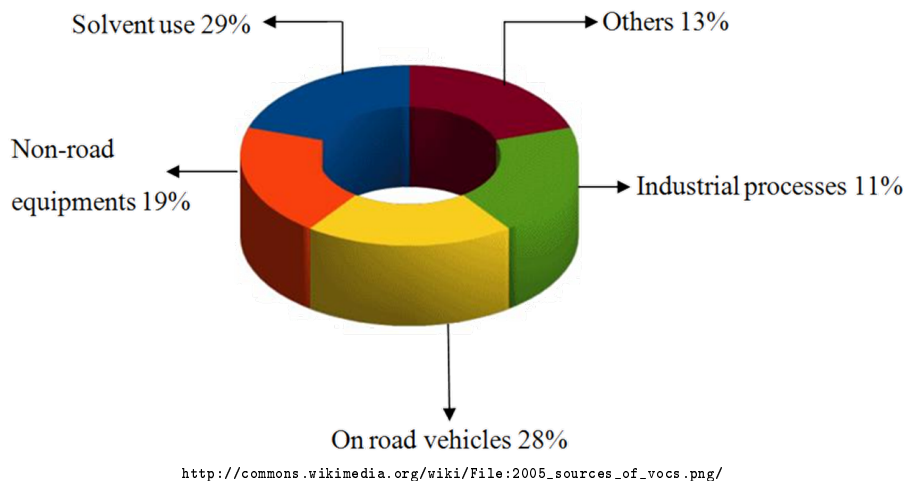


Figure 1.1: A pie chart displaying the percentage of major pollutants.

is basically pollution prevention rather than waste remediation. R. A. Sheldon has proposed a term E (environmental) factor (kg waste per kg product) as a unit for quickly assessing the environmental footprint of manufacturing processes. An assessment of the current industrial situation soon revealed that tons of kg waste per kg of the desired product was no exception in the chemical industries. The knowledge of the stoichiometric equation of the reaction can give an estimate of the waste chemicals theoretically that will be produced in the reaction. The scientists have begun to use ‘atom utilisation concept’ to quickly analyse the environmental acceptability of alternative processes to the formation of a particular product. However, any such replacement of organic solvents and processes has to be based on efficiency of the solvent in promising good selectivity, reactivity and should be cost effective too.¹⁰

This thesis is an attempt to understand the solvent effects of environment-benign media such as water and ionic liquids on the kinetics and mechanism of some simple organic reactions.

The present chapter aims to define the essential terms and various experimental framework available for understanding solvent effects and briefly review the literature survey related to physical-organic chemistry of greener media: ionic liquids and aqueous media. The chapter concludes with a brief discussion on solvent effects on reactions such as 1,3-dipolar cycloaddition, Benzoin condensation and Baylis-Hillman

reaction- the reactions investigated in the present thesis work.

1.2 Approaches for the analysis of solvent effects

Following are the two famous approaches for the analysis of solvent effects: In the past both approaches were developed simultaneously: (a) Qualitative approach (b) Quantitative approach.

1.2.1 Qualitative approach

In 1935, almost all qualitative treatments of solvent effects were based on a model developed by Hughes and Ingold for various substitution and elimination reactions.¹¹ The model considered electrical interactions between solvent and reacting species. However, the model doesnot consider the solute-solvent interactions and entropic contributions are also not incorporated in the model. Notwithstanding, the weak points, this model is still popular since it is simple and can be readily applied.

1.2.2 Quantitative approach

Most of the quantitative theory is based on transition state theory. The success of such theory depends on how accurately Gibbs energy of solvation can be determined. Other important attributes of these approaches are accurate and quantitative description of possible solute-solvent interactions, determination of the structure of the solvent, the characterization of the reacting molecules and the activated complexes. Many other semi quantitative approaches are also known which primarily can be subdivided into four major categories:

- (i) correlations with physical properties of the solvent,
- (ii) theoretical treatment of solute-solvent interactions,
- (iii) solubility and transfer parameters and
- (iv) correlations with empirical solvent parameters.

Each of these approaches are briefly discussed below:

1.2.2.1 Correlations with physical properties of the solvent

Solvents are categorized according to their physical properties. Some of the most famous correlations is with dielectric constant of the medium proposed theoretically by Eyring, Kirkwood, Laidler and Landskroener.¹² Other important correlations are with energy of evaporation of the solvent per unit volume,¹³ cohesive energy density¹⁴ and with internal pressure.¹⁵ The significance of polarisability of the solvent media is also well documented in the literature.¹⁶ In this light, correlation with polarisability of solvent is also well known.¹⁷ Generally, the result of correlations of solvent effect with these parameters is extraordinary good. However, one major drawback of this approach is the complete negligence of microscopic properties of the solvent.

1.2.2.2 Theoretical treatment of solute-solvent interactions

Although a good number of theories exist for condensed phase, an unambiguous and universal theory of the liquid state still does not exist. It was basically in late sixties when new areas of theoretical studies started emerging such as ab initio,¹⁸ molecular dynamics and quantum mechanical approaches to investigate the solvent effects on reactions.¹⁹ The development of theoretical models to explain the solvent effect is still in the growing stage and the chemical reactions investigated by such models are very often simple and elementary.

1.2.2.3 Solubility and transfer parameters

The measurements of solubilities and transfer parameters are other semiquantitative approaches to analyse the solvent effect.²⁰ The change in the initial and final transition states can sometimes be helpful in determining the solvent effects. Another interesting and fundamental approach involves study of the reactant in the gas phase. The gaseous molecules are solvated by an appropriate number of solvent molecules. The change in the reactivity of those molecules in the presence of solvent molecules can be decisive in contemplating the influence of the media on the reaction. Solubility is a thermodynamic property. Since ‘like dissolves like’, the change in the solubility

pattern of the reactant molecules can be an outcome of different physical and chemical properties of the solvent media.

1.2.2.4 Correlations with empirical solvent parameters

Empirical and semiempirical models are necessary to understand the solvent effect in a more rational way. The solvent polarity is the most significant parameter. Available list of solvent polarity scale is extensive. Most of the existing scales are based on linear solvation energy relationships.²¹ Most popular polarity scale is based on spectroscopic properties. Earliest known scale was of ‘Z value’ given by Kosower.²² Another important scale given by Dimroth and Reichardt called as $E_T(30)$ value,²³ is the most frequently used solvent polarity parameter. The probe molecule used in the spectroscopic study is pyridinium-*N*-phenoxide betaine dye which has both π - π^* and charge transfer transitions. One of the oldest polarity scale based on kinetic measurements was proposed by Winstein and Grunwald. The scale is known as ‘Y scale’ and it is based on the rate constant of solvolysis reaction of *t*-butylchloride in different solvents.²⁴ From physical-organic aspects, the use of Hansch π value,²⁵ solvophobicity parameter Sp , introduced by Abraham, are also well established.²⁶ The inherent weakness of the method is that polarity scale is not universal. Another important scale is based upon donor acceptor number.²⁷ Sometimes correlations are only satisfactory and at times it is difficult to understand which interaction is expressed by a particular parameter. To circumvent the problem of interpreting complex reactions, it is necessary to adopt a multiparameter approach. Selection of a set of independent solvent parameters that incorporates all the solute-solvent properties is difficult. This renders the discussion on the fundamental aspects and application of LSER (a multiparameter approach) quite interesting and challenging.

1.3 Classification of solute-solvent interactions (specific interactions only)

1.3.1 Hydrogen bonds

Hydrogen bonds appear in substances where there is a hydrogen atom attached to an electronegative atom, which is the case with water.²⁸ The presence of the hydrogen bonds together with this tetrahedric coordination of the molecule of water constitutes the answer to explain its unusual properties. The energy of the hydrogen bond (10-40 kJ/mol) is found to lie in between van der Waals forces (1 kJ/mol) and that of simple covalent bond (200-400 kJ/mol). Those solutes which are capable of forming hydrogen bonds have a well known affinity for solvents with similar properties, for example water. The formation of hydrogen bonds between solute molecules and those of the solvent explains, for example, the good solubility in water of ammonia and of other small alkyl chain compounds.

1.3.2 Hydrophobic effects: definition

The terminology “hydrophobic effect” includes all phenomena related to the dissolution of non-polar solutes in aqueous media. The term “hydrophobicity” is ambiguous and many different explanations are found in the literature. Preliminary factors to be accounted for hydrophobic effects are (i) breaking solute-solute interaction (ii) refilling of vacancy in the medium (iii) creation of cavity in the medium (iii) onset of solute water interactions (iv) rearrangement of water molecules. A simple way of explaining hydrophobicity can be obtained in terms of transfer of molecules from apolar solvent to water. Hydrophobic effects include two discrete processes: hydrophobic hydration and hydrophobic interaction. The terminology of hydrophobic hydration denotes the way in which nonpolar solutes affect the organisation of the water molecules in the immediate vicinity. The hydrophobic interaction explains the tendency of nonpolar molecules or parts thereof to assemble together in aqueous media.²⁹

1.3.2.1 Hydrophobic hydration

The interest in hydrophobic hydration originated mainly from the work of Butler who explained the peculiar thermodynamics connected with the transfer of nonpolar molecules from the gas phase to water.³⁰ The classical description of hydrophobic effects was given by Frank and Evans in 1945 which is still very popular. Nemethy and Scheraga later quantified the model and named it as “iceberg model”.³¹ The model explains negative entropy of solvation for hydration of apolar solutes in water. In 1959, fourteen years after Frank and Evans model, Kauzmann stressed on the importance of hydrophobic effects in protein folding.³² Although the iceberg model had profound influence on the way chemist thought about hydration phenomena, the gradual evaluation of the knowledge have raised questions on the feasibility of the iceberg model and the work is still continuing in this research area.³³

1.3.2.2 Molecular origin of hydrophobic hydration

Understanding of hydrophobic hydration is a prerequisite for understanding hydrophobic interactions. It is generally expected that upon transfer of a nonpolar molecule from the gas phase to water, the process will be entropically driven and enthalpically highly unfavourable. The accommodation of a solute molecule in the aqueous solution is thought to be energetically costly since hydrogen bonds between water molecules have to be sacrificed. So, till date one of the oldest misconception is the term “hydrophobic” itself that suggests a phobia for water experienced by the solute molecules. Moreover, recent investigations have demonstrated that interactions of the solute with the surrounding water molecules are often comparable to and sometimes even stronger than the interaction of the same solute molecule with its neighbours in the pure liquid state.³⁴ Henceforth, from the perspective of the solute, they don't have phobia for water. This leaves a choice up to the solute to decide whether to interact with a neighbouring solute molecule in aqueous solution, or stay within its own hydration shell. The solute molecules preferentially stay in the hydration shell. Henceforth, the transfer of the nonpolar solute from gas phase to water is character-

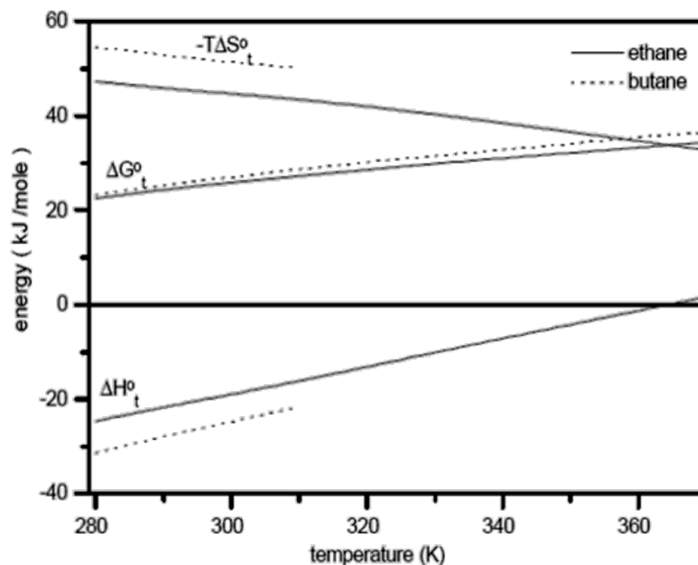


Figure 1.2: Variation of free energy of solvation with temperature. Reproduced with permission from *Faraday Discuss.* permission no. 3602920153422³⁵

ized by favourable enthalpy and reduction in entropy of the system. Evidently, water is capable of preventing the breaking of hydrogen bonds, but simultaneously it pays the price in the form of a reduction of entropy. The possible number of orientations that water molecules of first hydration shell can take is constrained by the presence of the solute. Upon increasing the temperature breaking of hydrogen bonds becomes easier whereas the construction of a relatively ordered hydrophobic hydration shell becomes increasingly difficult with increasing disorder in bulk water. The effect of temperature on free energy of solvation is given in Figure 1.2. Addition of cosolutes, such as salts and alcohols makes the formation of hydrophobic hydration shells difficult. Apparently, the structural requirements of the hydrophobic hydration shell do not tolerate the presence of significant concentrations of foreign species in the aqueous solution. Size and shape of nonpolar solute also effect the formation of hydrophobic hydration shell. Small spherical particles allow the formation of a hydrophobic hydration shell, without significant sacrifice of hydrogen bonds. Hydration of a flat surface is characterised by breaking of a large number of hydrogen bonds. Although temperature, cosolutes and curvature have striking effects on the entropy and enthalpy of hydration of nonpolar solutes, these effects largely balance each other, so

that the Gibbs energy is much less affected. As a result, the Gibbs energy of the state in which a hydrophobic hydration shell is formed is only slightly lower than that of the situation where hydrogen bonds are sacrificed instead.

1.3.2.3 Hydrophobic interactions

Traditionally, hydrophobic interactions are assumed to be driven by the release of water molecules from the hydrophobic hydration shells of apolar solute molecules. Although, with the development of new technologies, the perception about the structure of the hydrophobic hydration shell might have changed little bit, but the basic view remains essentially unaltered. Hydrocarbons have very low solubility in water

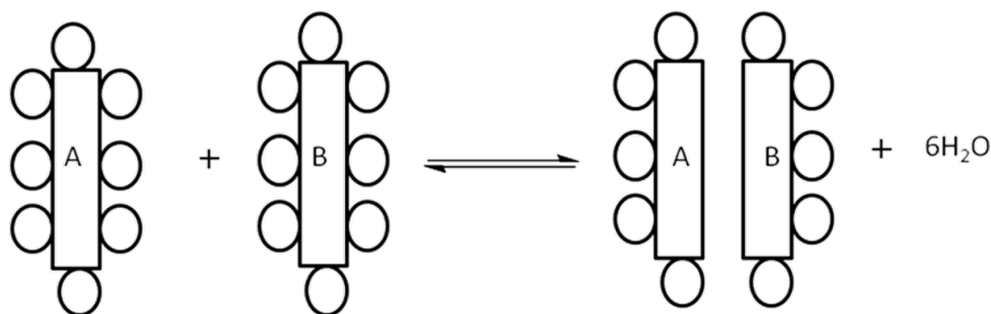


Figure 1.3: Hydrophobic interaction between two hydrocarbon molecules (circle represent water molecules).

and so the dissolution process is unfavourable with $\Delta G > 0$. Since, it is known experimentally that $\Delta H < 0$ it follows that $\Delta G = \Delta H - T\Delta S$, entropy of the system must decrease. This may be due to the consequence of highly ordered water structure in the first hydration shell. If two hydrocarbons are mixed in an aqueous solution, aggregation of hydrophobe may take place with concomitant reorganisation of water structure. With the contact between A and B, fewer water molecules are now in direct contact with the hydrocarbon molecules. It is energetically advantageous for apolar molecules to aggregate with expulsion of water molecules from their hydration shells. In order to minimise the unfavourable solute/water interactions, the apolar solute molecules (or apolar groups) will interact preferentially, thus reducing the number of

their water contacts.³⁶ This effect has been called hydrophobic interaction. The water molecules around an inert apolar solute have a higher coordination and are more ordered than in the bulk liquid. The hydrophobic interaction is shown in Figure 1.3.

1.3.3 Possible interactions in water and mixed aqueous systems

Organic reactivity in water and mixed aqueous systems are delineated by investigation of all plausible solute-solvent interactions. Hydrogen bonding in water is very important in solute-solvent interactions. Although, induced dipole-induced dipole interactions is weak in water, high dipole moment of water leads to dipole-induced dipole and dipole-dipole interactions with solutes. Among other factors, hydrophobicity and hydrophobic hydration play a significant role in the solvation of reactants and activated complex in water and in mixed aqueous solvents. Many chemical reactions are performed in solvent mixtures of water and organic co-solvents of various polarity values. The patterns of organic reactivity in mixed aqueous solutions are particularly interesting. Kinetic data for reactions in water and in mixed aqueous solvents are often intriguing and their exact interpretation is still challenging. Available reports show that water can induce high reaction rate constants and sometimes enhanced selectivity too and this makes the investigation of reactions in such media more interesting.³⁷ Addition of organic solvents can increase the solubility of organic compounds in water and hence can facilitate the study in both homogenous and heterogenous media.³⁸ Since sophisticated approaches for analyzing solvent effects are inaccessible, a thorough study of effects of solvents on a series of organic reactions in water and in mixed aqueous solvents would offer insight into the molecular basis of rate enhancements observed in such media. This study will enable organic chemists to select organic reactions, which can benefit from mixed aqueous solvents with a suitable composition with respect to solubility, reactivity and selectivity, in a judicious way.

1.4 Solvent effect in green solvents

Water and Ionic liquids (ILs): Water is the lingua franca of life on our planet and this makes it the main solvent of choice for Nature to carry out her syntheses. The deceptively simple molecular structure of water substantiates a complicated and elusive three-dimensional structure with lot of complicated, both intra and intermolecular interactions. Undoubtedly, many characteristic properties of water are still poorly understood.

1.4.1 Specific effects of water

Before 1980 the use of water as a solvent media was reported only incidentally.³⁹ In 1931, Diels and Alder performed the reaction between furan and maleic acid.⁴⁰ Change in selectivity was observed in water as compared to ether. In 1973, Eggelte, de Koning and Huisman studied the same reaction in different solvents and the beneficial effects of water were discussed for the first time.⁴¹

1.4.2 The effect of water on cycloaddition reactions

In 1980, D. Rideout and R. Breslow while investigating Diels-Alder reaction coincidentally discovered that the reaction exhibited good rate enhancements in water as compared to organic solvents even in the absence of β -Cyclodextrin.⁴² Surprisingly, the rate enhancements in water was observed to be as high as 12,800 as compared to the organic solvents. Breslow proposed hydrophobic acceleration to be responsible for the observed significant increase in the reaction rates. He supported his notion by suggesting that cycloaddition reaction can be further accelerated by adding “anti chaotropic” salts such as LiCl and KCl and can be reduced by adding “chaotropic” salts such as GnCl .³⁸ On the contrary, Grieco proposed micellar aggregation responsible for such rate enhancements.⁴³ Also Breslow, through the occasional use of terms such as “hydrophobic packing” and “aggregation” suggested that hydrophobic interactions can induce preaggregation of the reactants. The kinetic measurements of intramolecular Diels-Alder reaction, in which the diene and dienophile are already

preassociated, exhibited additional rate enhancements in water.⁴⁴ Henceforth, further investigations are necessary to understand the origin of good reactivity and selectivity in water. Alternatively, internal pressures have been also proposed to be responsible for the rate enhancements in Diels-Alder reactions. The internal pressure can be defined as the energy required to bring about an infinitesimal change in the volume of solvents at constant temperature.⁴⁵ A related, but much more applicable solvent parameter is the cohesive energy density (ced). Cohesive energy density is a measure of the energy required for evaporation of the solvent per unit volume. The ced of water is extremely high, due to the large number of hydrogen bonds per unit volume. Obviously, ced of the solvent is much more relevant than its internal pressure, since the creation of a cavity to accommodate the solute normally leads to the rupture of solvent-solvent interactions. The ced has been successfully used by Gajewski in a multiparameter equation for describing the rate of a reaction performed in water.⁴⁶ Blokzijl introduced the concept of “enforced hydrophobic interactions” to describe the activation of Diels-Alder reactions in water.⁴⁷ 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 significance of hydrophobic interactions in the aqueous acceleration was further demonstrated by a qualitative study described by Jenner demonstrating the effect of pressure on Diels-Alder reactions in water and in a number of other solvents.⁴⁸ Further study indicated that in water, a hydrogen bond donating solvent par excellence, the Diels-Alder benefits both from hydrophobic interactions and hydrogen-bonding effect. This suggestion is supported by detailed kinetic studies on a number of reactions performed in water. Computational studies also arrived at approximately the same conclusions.⁴⁹ A wealth of experimental data as well as a number of sophisticated computer simulations indicates that two important effects underlie the acceleration of cycloaddition reactions in aqueous media *i.e.* hydrogen bonding and enforced hydrophobic interactions. As per transition state theory: hydrophobic hydration raises the energy of initial state more than the transition state and hydrogen bonding interactions stabilise the more polar transition state more than the initial state. This leads to the enhancements in the rate of the

reactions in water. The influence of salts and other additives on the reactivity and selectivity of reactions in water. R. Breslow have reported the effects of chaotropic and anti-chaotropic salts on the rate of aqueous Diels-Alder reactions.³⁸ Chaotropic are salting-out agents that lower the solubility of nonpolar compounds in water mainly by affecting the formation of a cavity to accommodate the solute molecules. On the contrary anti-chaotropic salts act as salting-in agents and ensures increased solubility which results in decreased hydrophobic interactions. A more systematic investigation of the salt effects on Diels-Alder reactions showed that they correlated linearly with the size of the anion.

1.4.3 Water-accelerated transformations

Besides Diels-Alder reactions other transformations also benefit considerably from the use of water as a solvent medium. Some of the most common examples are 1,3-dipolar cycloaddition,⁵⁰ Benzoin condensation,⁵¹ Baylis-Hillman,⁵² Aldol condensation and Claisen rearrangement reactions.⁵³ All these reactions were accompanied with one common aspect- a negative volume of activation. This gave the false idea to the chemists that only hydrophobic forces are responsible for rate enhancements in water. An interesting kinetic investigation of several 1,3-dipolar cycloadditions has been performed by Steiner⁵⁴ and Wijnen.⁵⁵ The authors have demonstrated that basically hydrogen bonding and enforced hydrophobic interactions are the two factors that causes acceleration of $[3\pm 2]$ cycloadditions reactions.⁵⁶ Lot of experimental and theoretical study of claisen rearrangement has been carried out.⁵⁷ The results indicate that although, hydrophobic interactions appear tempting as an explanation, they can be sometimes overemphasized. The responsible interactions can be sometimes assisted by other factors too such as hydrogen bonding. This raises the issue pertaining to the investigations of complex interactions existing in the solvent media. In spite of the many potential advantages of water discussed so far, it is seldom used for carrying out chemical transformations on a large scale. This limitation is due to common misconception of “*corpora non agunt nisi soluta*” *i.e* substances do not react unless dissolved. Manipulations done to increase the solubility of the reactants

sometimes negate the potential advantages of water. As a result, the current burgeoning field of chemistry deal with various reactions performed in water but with the restrictions of presence of reactants at very low concentrations. In a recent discovery, Sharpless and co-workers demonstrated that organic reactions can still be realized at a faster rate under heterogenous condition as compared to those in homogenous ones.⁵⁸ The heterogenous solvent medium in this case is defined as the one in which the solutes are present above its solubility limit and the protocol is referred to as ‘on-water’. The ‘on-water’ protocol has unlocked many new possibilities of performing reactions under heterogenous reaction conditions. It was observed that heterogeneity of the medium can be sometimes helpful in accelerating the rate of reaction. The breakthrough was instrumental in removing the major elusion among organic chemist regarding the essentiality of minimum concentration of solutes for carrying out the reaction. Although, numerous workers have exploited the methodology of ‘on-water’ for excellent catalysis in many reactions, the mechanism of the reaction still remains a controversy. Many important research papers exist which discusses the mechanism but none of them are able to completely explain all the observed trend in reactivity and selectivity for ‘on-water’ reactions.⁵⁹ In 2007, Marcus and Jung proposed that the answer to the understanding of ‘on-water’ reaction is the unique chemistry that occur at the oil-water interface. At large hydrophobic surface 1 in 4 water molecules has dangling OH bond directed at the boundary. Small hydrophobic molecules can be completely hydrated by water molecules and so they lack dangling OH bonds. The penetration of these bonds provides catalytic site for the interfacial reactions (Figure 1.4).⁶⁰ Acid-base chemistry at the interface has been also cited as the force responsible for the catalysis of the reaction at the interface.^{59(a)} The challenge to completely understand the kinetic and mechanistic details of the heterogenous reactions still attracts organic and physical chemists all over the world.

1.4.4 Ionic Liquids (ILs)

Currently, a major challenge before industry and academia is to substitute more environmentally friendly technologies for traditional ones in which damaging and harmful

organic solvents are used extensively.⁶¹ ILs are considered as environmentally-benign substitute for such solvents, not only because of their low pressure but more importantly because they act as good catalyst. ILs have been drawing the attention of scientific community since early 1990s. ILs are defined as salts that are in a liquid state at or below 100 °C. This temperature limit is just for convenience as it separates ILs from high temperature molten salts.⁶² The main cause for low melting points of ILs compared with those of simple inorganic salts is basically the size difference between cations and anions of ILs. This asymmetry effects the ion-ion packing by reducing the coulombic attraction between the ions.⁶³ The cations are generally based on imidazolium, ammonium, pyridinium, pyrrolidinium, phosphonium and sulfonium derivatives. The anions may be of inorganic or organic nature. Some common examples of inorganic anions are halide, tetrachloroaluminate, tetrafluoroborate, hexafluorophosphate and bis(trifluoromethanesulfonyl)imide and common organic anions are derivatives of sulfate or sulfonate esters, trifluoroacetate, lactate, acetate or dicyanamide.⁶⁴ The structure of few of the common anions are shown in Figure 1.5. A variety of functional groups, such as fluoroalkyl, alkenyl, methoxy or hydroxyl can be also used. Functionalized ILs are often synthesized for a particular use such as for specific reactions, extractions or separations and are hence referred to as “task specific ILs” (TSILs).⁶⁵ The beginning of ILs preparation and the origin of the entire field usually date back to 1914, when ethylammonium nitrate ($[\text{EtNH}_3][\text{NO}_3]$, mp 13-14 °C) was prepared by neutralization of ethylamine with concentrated nitric acid.⁶⁶ However, the discovery failed to attract much scientific interest and ILs went largely unrecognized almost upto 1970s when organic chloroaluminates (1st generation ILs, Figure 1.6) were investigated more closely for the first time.⁶⁷ The first organic reaction successfully performed in IL reaction medium was in the 1980s.⁶⁸ However, sensitivity of ILs to air and moisture was a major obstacle in their path of generalised application. In the 1990s, Wilkes and Zaworotko reported the first preparation of new combinations of cations and anions giving air- and moisture stable ILs (2nd generation ILs, Figure 1.6).⁶⁹

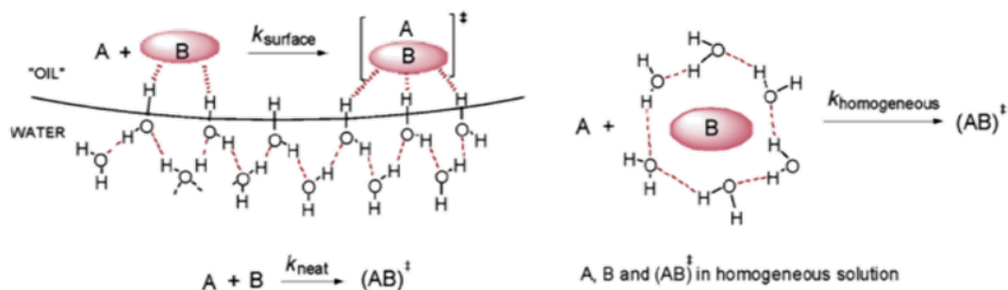


Figure 1.4: Schematic representation of the hydration of a) a small nonpolar molecule (with the retention of hydrogen bonded network around the solute), b) a mesoscopic surface and dangling “OH” bonds around the surface. Reproduced with permission from *J. Am. Chem. Soc.*⁶⁰

In 2004, Davis introduced a wide range task specific ILs, TSILs (3rd generation ILs, Figure 1.6).⁷⁰ The structures of the three generation of ILs for representation purpose is given in Figure 1.6. However, there are still complications in the evolution of ILs from laboratories to economically viable technologies. There is lack of available data on the physical and chemical properties of ILs. However, there are few database which maintains data on physical, chemical and toxic properties of ILs.⁷¹ A generalized picture of the solvent effects of ILs still continues to be litigious, due to numerous reasons. Most importantly, ILs represent one of the most complicated class of solvent media. Structural anisotropy which is an integral part of mesoscopic structure of ILs has made the study of organic reactions more difficult. Due to the structural inhomogeneity in ILs ‘mesophase’ terminology was introduced.⁷² There are few reports that discuss about three dimensional hydrogen bonding in ILs. However, one group of researchers still believe that the evidence given in favour of such bonding is inadequate. The controversy regarding the structure of ionic liquids further seeks attention and investigation. Secondly, ILs are capable of exhibiting many types of solute-solvent interactions. This can be partly attributed to the structure of ILs. Among the various families of ILs, Imidazolium salts are the most popular one. The 1-alkyl-3-methylimidazolium salts are known to exhibit unique electronic structure. The cation has a delocalized 3-centre-4-electronic configuration.

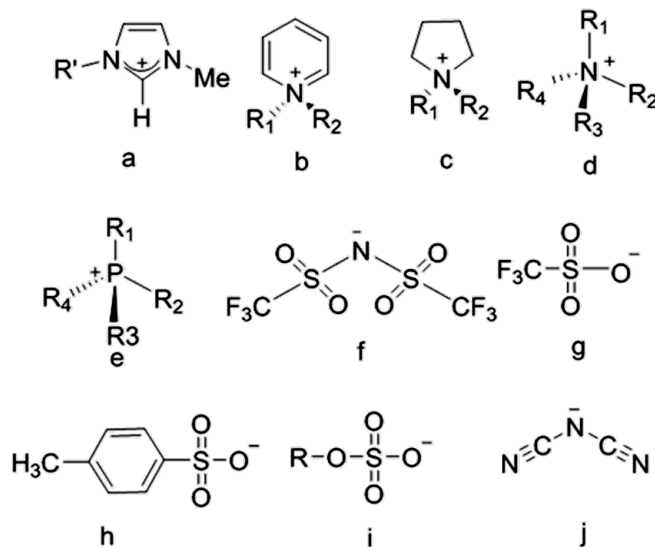


Figure 1.5: Important ions: (a) 1-alkyl-3-methylimidazolium ($[C_n\text{mim}]^+$), C_n stands for n -alkyl residues); (b) 1-alkylpyridinium ($[C_n\text{py}]^+$); (c) 1,1-dialkylpyrrolidinium ($[C_mC_n\text{pyr}]^+$); (d) tetraalkylammonium ($[N_{ijkl}]^+$); (e) tetraalkylphosphonium ($[P_{ijkl}]^+$); (f) bis(trifluoromethanesulfonyl)imide ($[\text{Tf}_2\text{N}]^-$); (g) trifluoromethanesulfonate ($[\text{TfO}]^-$); (h) tosylate ($[\text{OTos}]^-$); (i) alkylsulfates ($[C_n\text{OSO}_3]^-$); (j) dicyanamide ($[(\text{CN})_2\text{N}]^-$)

Electrons are delocalized between the three centres (two nitrogen and one central carbon atom) and a weak double bond exists between carbon atom of the aromatic cation. Although the hydrogen atoms of the ring carry the same charge, central carbon is positively charged since it is surrounded by two electronegative nitrogen atoms. This lends acidic properties to the proton attached to the central carbon of the ring.⁷³ Another interesting property is the existence of conformational equilibrium observed in ILs. Different crystalline polymorphs are sometimes observed for ILs due to the torsional motion of ILs. The butyl chain of $[\text{C}_4\text{mim}]^+$ exists in both trans-gauche and trans-trans conformations.⁷⁴ This renders nanostructure formation in the ILs. The coexistence of such conformers results in far reaching consequences on the physical and chemical properties of ILs. Due to the charged nature of ILs, a complex web of many interactions coexists in the ILs. Besides these forces other interactions such as hydrogen bonding, dipole-dipole interactions is also important. However, the presence of charged neighbours complicates the study and makes solvation pattern different

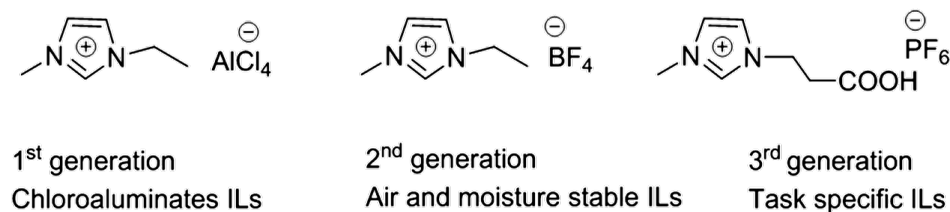


Figure 1.6: The three generation of ILs.

and difficult as compared to that of conventional media.⁷⁵ The typical structural characteristic of ILs affect different properties such as melting behaviour,⁷⁶ vapour pressure,⁷⁷ electrical conductance, ion diffusion and boiling temperature.⁷⁸

1.4.4.1 Solvent properties

Solvent properties of ILs are mainly determined by chromatographic methods. Based on hydrogen bond donation, acceptance and localisation of charge on anions, ILs are considered to be moderately polar in nature. Increasing the alkyl chain length of the cation can increase the lipophilic character of the ILs. It is possible to tune the properties of ILs by carefully choosing the cations and anions and hence it is possible to design task specific ILs for various organic reactions.

1.4.4.2 Organic reactions

ILs are proficient of exhibiting a large variety of solute-solvent interactions as opposed to the interactions found in conventional solvents. In order to substantiate the performance of ILs for future applications, it is essential to understand the origin and manifestation of such interactions, in detail. The net charges on the ions can lead to charge ordering and screening of dipole-dipole interactions. ILs can act as polar solvents in organic reactions containing polar molecules and as relatively nonpolar solvents in the presence of nonpolar molecules. The number of physical-organic studies attempting to correlate various properties of ILs to the kinetic and stereochemical outcome of the reactions has been comparatively few in number. The characteristic hydrogen bonding ability of ILs make them a promising solvent for use as a catalyst⁷⁹ and as an organocatalyst.⁸⁰ Many authors have reported the non-innocent nature of

ILs since unexpected catalytic activity and undesired product formation was observed in many cases.⁸¹ Kumar and Pawar have reported about the reversal in selectivity of Diels-Alder reaction in ILs.⁸² It was observed that Diels-Alder reaction changes its selectivity from exo (conventionally observed) to endo selectivity in chloroaluminate ILs. The lewis acid effect of AlCl_3 was held to be responsible for the observed change in selectivity of the reaction.⁸³ The dimerization reaction of cyclopentadiene was also investigated by the same group and the rate of dimerization was found to be higher in $[\text{EMIM}][\text{AlCl}_3]$ than in the $[\text{BP}][\text{AlCl}_3]$ ILs. Besides Diels-Alder reaction, the rates of Baylis-Hillman reactions in chloroaluminate ILs was also shown to be higher as compared to the reaction carried out in conventional organic solvents.⁸⁴ An interesting report was published in 2006 by Tiwari and Kumar where the constraints imposed by high viscosity of ILs on the reaction rates of Diels-Alder reaction was discussed in detail. It has been observed that the rate of reaction in water is 10 times higher as compared to highly viscous 1-butyl-3-methyl imidazolium iodide $[\text{BMIM}][\text{I}]$.⁸⁵

1.5 Solvent effect on 1,3-dipolar cycloaddition reaction

1,3-dipolar cycloaddition reaction has occupied important place in synthetic organic chemistry for the swift accretion of polyfunctionality in a fairly small skeleton and the prediction of regiochemistry for such reactions. The remarkable efficiency of such reactions in the synthesis of natural products and physiologically active molecules led to an increase in research activities aimed at developing newer methods to improve reactivities and selectivities of such reactions. The popularity of 1,3-dipolar cycloaddition reactions can be estimated from the number of reviews and articles available in the literature on the subject.⁸⁶ The mechanism of the reaction was the topic of hot debate for many decades. It was Huisgen who for the first time proposed concerted mechanism for the reaction. However, later on Huisgen have demonstrated that such reactions can also take place in a stepwise fashion with the loss in stereospecificity of

the reaction.⁸⁷ Initially like Diels-Alder reaction the rate and selectivity of the 1,3-dipolar cycloaddition reaction was assumed to be independent of the nature of the solvent medium. It was in 1991, when Y. I. K. Araki and S. Shairashi demonstrated that the rate of 1,3-dipolar cycloaddition reaction can be accelerated upto 14 times on changing the solvent media from nonpolar to ethanol water mixture.⁸⁸ Plenty of reports also came eventually which substantiated the significant role of solvents on such reactions.⁸⁹ On the contrary, there are also reports of some reactions which are incredibly slow in non polar solvents and sometimes polar solvents also fail in accelerating the reaction velocity to the desired limit.⁹⁰ The ‘on-water’ protocol proposed by Sharpless and co-workers can be an alternative choice for such reactions. In spite of available reports there are very few reports studying the role of water in the catalysis of such reactions under heterogenous conditions. The possibility of the enhancement in the rates of reactions under such conditions still remains unanswered. The contribution of various forces such as polarity, hydrophobicity and hydrogen bonding at the interface has to be delineated for proper understanding of the interfacial phenomena.

1.6 Solvent effect on Benzoin condensation

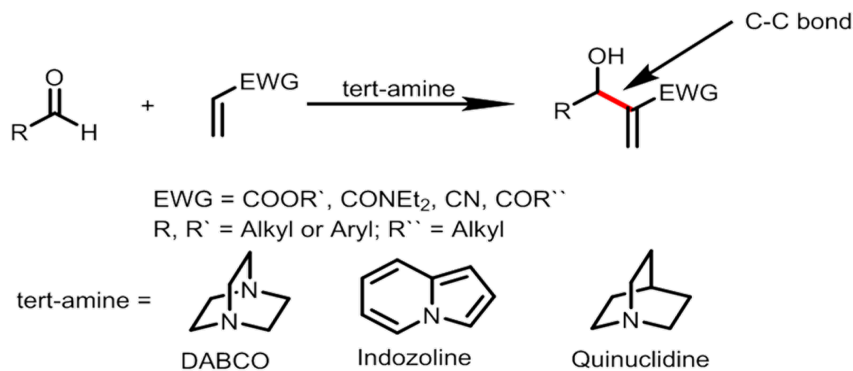
Benzoin condensation is a promising methodology to prepare a variety of α -hydroxy ketone, of utmost synthetic utility, along with the generation of a new stereocenter.⁹¹ The Benzoin condensation is of interest to chemist as a model for C-C bond formation reaction in which the catalytic group is the thiazolium moiety. The condensation reaction is known to the physico-organic chemist for decades as an excellent example of catalysis. Probably it is one of the earliest known reactions to be subjected to kinetic analysis. In 1903, Lapworth demonstrated that cyanohydrins (an intermediate) formation is faster as compared to the condensation reaction and this observation led the foundation of mechanism of the reaction.⁹² Breslow, Wiberg, Bredig and Stern also contributed a lot to the basic understanding of the mechanism of reaction.⁹³ R. Breslow, K. Groves and M. U. Mayer have demonstrated that rate of the Benzoin

condensation was much faster in water than other conventional solvents and it was increased by the addition of prohydrophobic salts and was decreased by the addition of anti hydrophobic salts. This phenomenon indicated the presence of hydrophobic effect in the reaction. The authors also compared the role of solubility of the reactants on the reaction by using various cosolvents. A reasonable correlation was observed between the solvation of the hydrophobic surface and the change in reactivity of reaction. Although the mechanistic details of the reaction have been the subject of debate since many years, very few studies deal with the overall kinetic investigations of the Benzoin condensation.⁹⁴ The ambiguity about the role of water has prevented the extensive and quantitative study of the reactivity and selectivity about the condensation reaction in water.

Water-alcohol solvents have been used extensively in the past to delineate the contribution of polarity and hydrophobic forces on various organic reactions. The nature of solute-solvent interactions and forces influencing the rate of reaction in binary mixtures are already known for homogenous solutions.⁹⁵ However, the kinetic and mechanistic study of Benzoin condensation reaction at the interface in presence of binary mixtures is still in infancy. Particularly very little is known about the contribution of hydrophobic forces at the oil-water interface. For a better understanding of the interfacial phenomena, the choice of solvents has to be made judiciously. The nature of possible solute-cosolvent and water-cosolvent interactions has to properly accounted for in the binary mixtures. Undoubtedly, the notion of measurement of kinetics of reaction with and without addition of cosolvents is a challenging and burgeoning field.

1.7 Solvent effect on Baylis-Hillman reaction (BHR)

Organic synthesis is one of the most successful fields of science with C-C and C-X bond formation and their cleavage being the most desirable and challenging field of chemistry. Selective construction of C-C and C-X bond at desired place in a reaction, where other competing sites are also available, is actually the present day



Scheme 1.1

requirement. In fact this simplifies the process of assembling a carbon framework with utmost creativity, originality and is classified as an intellectual approach of synthesis. The BHR is one such interesting reaction, which involves selective formation of C-C bond leading to densely functionalized products. Basically it is an atom economic way of synthesis of C-C bond in presence of activated alkene and an electrophile in presence of a catalyst or catalytic system (Scheme 1.1).⁹⁶ The main aspects of these reactions are (a) these are basically three component reaction (b) a chiral centre is generated thus offering opportunities for developing asymmetric molecules (c) since the products are densely functionalized so it promises synthesis of natural products of medicinal and industrial importance (d) presence of a number of parameters in the reaction, that can be altered, generate many possibilities of mechanistic variation in the reaction. This makes the investigation of mechanism of these reactions an intellectual challenge.

1.7.1 Origin and growth of BHR

The BHR came into existence in 1968 when H. Morita investigated the reaction of an aldehyde and activated alkene in presence of tricyclohexylphosphine. Subsequently, the authors filed lot of patents describing the synthetic utility of these reactions. The reaction gained its name from A. B. Baylis and M. E. D. Hillman who performed the reaction in a variety of alkenes and electrophiles.⁹⁶ Despite the potential advantages of these reactions, unfortunately the reaction remained in low ebb for almost a decade.

However, after the demonstration of synthesis of integerrinecic acid and other natural products by Drewes and Emslie in 1982⁹⁷ and by Hoffmann and Rabe in 1983,⁹⁸ the chemist became interested in the reaction. Subsequent reports from many groups have transformed these reactions into a very promising and interesting strategy for C-C bond formation.⁹⁹ This reaction is one pot combination of michael, aldol and elimination reactions. First review on BHR was published by Drewes and Roos in 1988.⁹⁷ The authors discussed possibilities of lot of variation in the reaction in terms of alkene, electrophile and catalyst. The most fascinating part of the reaction is the mechanistic aspect.

1.7.2 Rate acceleration

One of the most important concepts of BHR is the rate acceleration since the reaction is very slow and the reaction may take days to week for completion. Eventhough, systematic studies have been done to improve the rate of BHR in terms of microwave irradiation, high pressure, temperature, catalyst concentration, ILs and other additives the reaction still offers challenges for further exploration because of its simplicity and versatility.⁹⁹

1.7.3 Mechanism of the reaction

The first detailed study of the mechanism of the reaction was given by Hoffmann and Rabe in 1983.⁹⁸ Earlier in 1968, H. Morita has also proposed the mechanism of the reaction but it was exclusively for phosphine-mediated reactions. Later based on pressure dependence, rate and kinetic isotope study Hill and Isaac proposed a mechanism with one equivalent of aldehyde participating in the rate determining step of the reaction.¹⁰⁰ The mechanism was also supported by Bode and Kaye.¹⁰¹ In 2005, McQuade and co-workers proposed a new mechanism, involving hemiacetal intermediate, in aprotic polar solvents as DMSO.¹⁰² The mechanism had two equivalents of aldehyde participating in the rate determining step of reaction. Later on Robiette, Roy and Sunoj performed DFT calculations for probing the mechanism of the

reaction.¹⁰³ Many useful mechanistic details were obtained from the theoretical studies. The change in the mechanism of the reaction with the alteration in the solvent's nature and polarity is a very interesting attribute of the reaction. The ILs are novel and benign in nature, the investigation of the reaction in such a media can throw light on the mechanistic and kinetic details of the BHR in ionic media.

1.8 Conclusions

The vast literature and the extensive studies on organic reactions in environment-benign media is a proof of the growing relevance of this field of chemistry. No longer mere curiosities, the greener media are used for a number of synthetic applications. The introduction of such media will help those, who are not specialist, to use the strategy with ease for the first time. The solvent environment provided by such media is much different from those of conventional solvents. The understanding of the fundamental aspects of reactions in such solvents can make the investigation economically viable and chemically beneficial for the future studies.

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Chapter 2

Aims and Objectives

Preamble



A brief account of the aims and objectives of the work presented in the thesis is assimilated in the present chapter. The research methodologies used for carrying out the work is also discussed in the chapter. A brief study of the existing literature on the application of water and ILs as a solvent media signify the importance of implications of greener solvent media. The relevance of kinetic and mechanistic investigations of some simple organic reactions is deemed equally challenging and interesting.

The approach towards Green Chemistry can be attained by an open and interdisciplinary view of avoiding waste production once it is formed. It can be done by adopting greener ways of doing the experiments (for e.g. using water and ILs) rather than disposing off or treating the waste after the process or material has been developed. There are so many reasons to use water as a solvent for organic reactions. Firstly, water is green and inexpensive. Also the observation that some of the reactions exhibit better reactivity and selectivity in water urges the thought that even water insoluble compounds can perform better in water. However, the main reason for pursuing water as the solvent are the effect such as polarity, hydrogen bonding and hydrophobicity prevailing in water that makes the attainment of rate enhancements of reactions that is otherwise not achievable. ILs are considered as useful solvents as they possess very low vapour pressure, good thermal stability, wide liquidus range, good solubility and recyclability. Moreover, there is paucity of data on physico-organic study of reactions in ILs. Also, the flexibility in tuning the properties of ILs as per requirement makes them a potential solvent for organic reactions. These features and following observations encouraged further investigations:

- The specific point of interest is the renaissance of water as a useful solvent for many organic reactions. However, very little experimental and theoretical data are available in the literature that discuss the qualitative and quantitative comparison of ‘on-water’ and ‘in-water’ reactions.
- The role of temperature in affecting the heterogeneity and in turn the solubility of solute molecules has been widely debated. The delineation of the extent of contribution of temperature to the reaction kinetics at the oil-water interface is elusive.
- In spite of the increasing popularity of ‘on-water’ reactions, very little experimental evidences is available about the different molecular level interactions in heterogenous conditions. The contribution of hydrophobicity, polarity and hydrogen bonding at the interface is still in infancy.
- Despite the fact that numerous interactions are possible between the solvent and

solute molecules in ILs, the physical-organic studies for reactions in ILs are comparatively lesser in number. In the context of emergent field of ILs, it is very important to examine the extent up to which current knowledge can be enhanced by further optimization of reactions conditions backed by comprehensive experimental findings in ILs.

- A number of critical aspects of ILs make them an interesting medium to study chemical syntheses. The large number of possible combinations of cations and anions in ILs not only allows control over processing over the reaction but also on various possible solute-solvent interactions. However, very few studies deal with the distinct chemistry of cations and anions of ILs in influencing the kinetics and mechanism of organic reactions.

Upon examination of above mentioned features gathered from literature survey, following are the salient features of the objective of our thesis work:

- To execute the investigation on a relatively simple reacting system in both environment-benign media: water and ILs. The information thus gained will facilitate better understanding of the homogenous and ‘on-water’ reactions at the grass root level.
- To experimentally establish and compare the ‘on-water’ and ‘in-water’ reactions in presence of different salt additives.
- To discern the contribution of hydrophobicity in addition to other interactions existing at the oil-water interface. The study will be useful in future investigations in optimizing the reaction conditions by judiciously selecting salt concentrations.
- To examine the saturation limit for ‘on-water’ reactions.
- To examine the thermodynamic aspects of ‘on-water’ reactions. The results will be helpful in understanding the role of solubility of hydrophobic molecule on the kinetics of reactions at the interface.

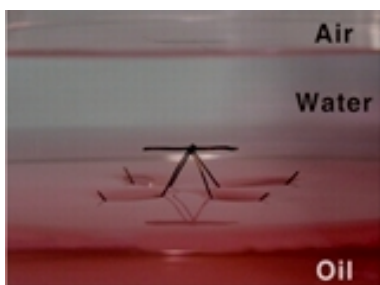
- The manifestation of the contribution of hydrophobicity, hydrogen bonding and polarity of binary mixtures of water and co-solvents for ‘on-water’ conditions is necessary to understand the complex intricacies of ‘on-water’ reactions.
- To use ILs as a reaction media to understand the mechanism of reaction with controversial reaction pathway. Of special interest will be the renaissance of ILs as a media to solve the mystery of mechanism of synthetically significant reactions.
- To have a comparative analysis of the role of cations and anions of different ILs. An attempt will be made to have both kinetic and mechanistic insight of well known organic reactions.

The main objective of the thesis is to understand the feasibility of environment-benign media to replace the volatile organic compounds for understanding the physico-organic aspects of some common and relevant organic reactions. The C-C and C-X bond formation reaction has been used as an investigating tool to achieve the above-mentioned goals. Reactions have been performed at ambient conditions for better comparisons of homogenous and heterogenous reaction conditions.

Chapter 3

Investigation of Interfacial 1,3-Dipolar Cycloaddition (1,3-DCA) Reactions

Preamble



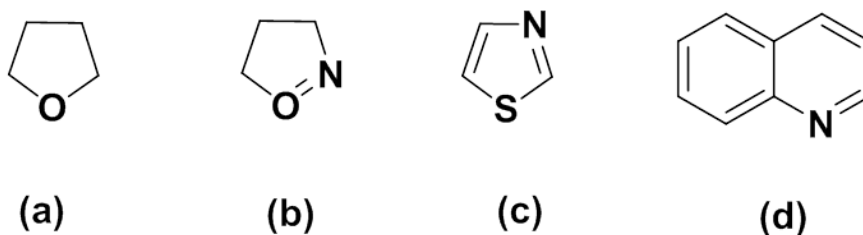
The present chapter incorporates investigation of 1,3-DCA reactions which were carefully carried out in order to inspect the contribution of hydrophobic forces towards rate enhancement at the interface. Section 3.1 deals with the investigation and analysis of the influence of different substituents on the interfacial reactivity with concomitant alteration in the electronic environment of 1,3-dipole. Prohydrophobic salt has been used as an investigating tool to delineate the conspicuous role of hydrophobic forces at the interface. A comparison of homogenous and heterogenous reactions at the interface has been thoroughly discussed in section 3.2.

“Limitless and immortal, the waters are the beginning and end of all things on earth.” -Heinrich Zimmer

3.1 Salt effect at interface of 1,3-DCA reactions

3.1.1 Introduction

Heterocyclic compounds have a cyclic structure with at least two different kind of atoms in the ring, one is generally carbon and others are nitrogen, oxygen or sulfur atom. Presence of atleast one heterocyclic ring is an essential criteria for a compound to be referred to as heterocyclic compounds. Heterocycles are classified into two categories-aliphatic or aromatic ones (Scheme 3.1).¹



Scheme 3.1: Structure of few heterocyclic compounds (a) Tetrahydrofuran (b) 4,5-dihydroisoxazole (c) 1,3-thiazole (d) Quinoline.

Recently, heterocycles have received importance particularly because of their pharmacological as well as synthetic potential. Nature is the largest reservoir of heterocycles. In agreement with Nature's creation, chemists have artificially synthesized and customized a number of heterocyclic compounds. The justification behind Nature's preference for heterocycle is perhaps due to the fact that they are chemically tunable and are capable of fulfilling the demands of biochemical systems. Henceforth, it is of significant interest to synthesize heterocyclic compounds and their derivatives. Currently, the methods available for the synthesis of heterocyclic compounds can be grouped into the following three broad categories:-

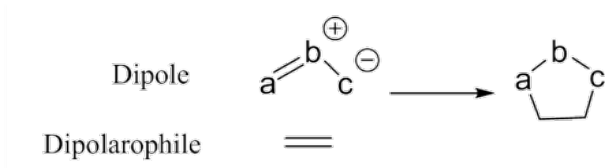
1. alteration of existing carbocyclic ring,
2. cyclisation process and
3. concerted cycloaddition reactions.

Among these three methods, cycloaddition reaction involving two simple components

appear to be a promising choice for the synthesis of heterocyclic compounds. Cycloaddition reactions are categorized as click reactions.² Such processes rapidly lead to completion of reaction in a short span of time and are highly selective for formation of a single product. Noteworthy is the fact that click reactions achieve the required characteristics by a thermodynamic force of 20 kcal mol⁻¹. Henceforth, such classes of reactions are called as “spring loaded” for a single trajectory. 1,3-DCA reactions are one such class of transformations. Mechanistically, 1,3-DCA are similar to Diels-Alder reactions and are ascribed as $[\pi^4s + \pi^2s]$ reactions.

3.1.2 1,3-dipolar cycloaddition reactions (1,3-DCA)

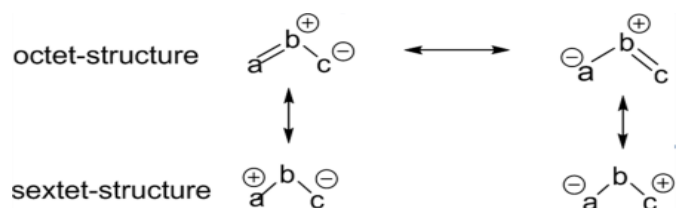
The history of 1,3-dipoles goes back to Curtius,³ who discovered diazoacetic ester in 1883. Buchner was the pioneer to describe a 1,3-DCA reaction by investigating the reaction of diazoacetic ester with α , β -unsaturated esters.⁴ In 1893, Buchner suggested that the product of the reaction of methyl diazoacetate and methyl acrylate was 1-pyrazoline and the isolated 2-pyrazole was formed after rearrangement of the 1-pyrazole. After this interesting observation, nitrones and nitrile oxides were also discovered by Beckmann, Wemer and Buss, respectively.⁵ Thus, the chemistry of 1,3-dipolar species has evolved for more than 100 years, however, the general application of 1,3-dipoles in organic chemistry was first established by the pioneering efforts of Huisgen in 1960's only.⁶ A 1,3-dipole is a dipolar structure with delocalized electrons over three atoms. The structure can be portrayed by a dipolar structure as outlined in Scheme 3.2. 1,3-dipoles can be divided into two different types: (a) allyl anion type



Scheme 3.2: A typical 1,3-DCA.

and (b) propargyl/allenyl anion type. The allyl anion type dipoles are characterized

by bent structure and have four electrons in three parallel p_z orbitals which is perpendicular to the plane of the dipole. The possibility of different resonance structures are shown below (Scheme 3.3). On the contrary, propargyl/allenyl anion type dipoles



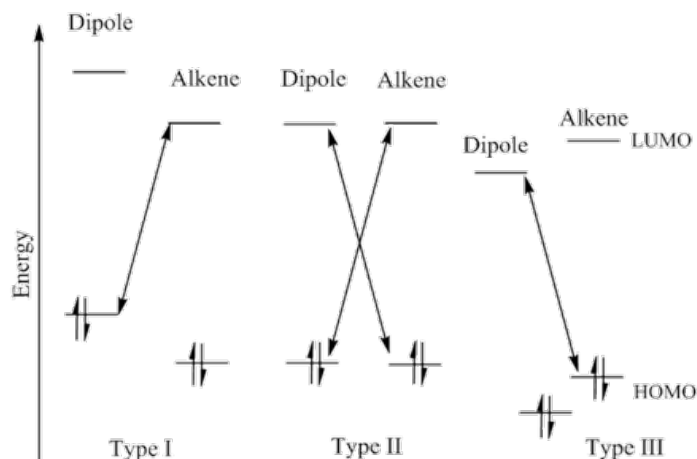
Scheme 3.3: Resonance structures in 1,3-dipole (allyl-anion type).

are linear with an extra π orbital located in the plane orthogonal to the allenyl anion type molecular orbital (MO). Generally these dipoles have nitrogen as the central atom (Scheme 3.4). 1,3-dipoles are interestingly, ambivalent molecules *i.e.* can act



Scheme 3.4: Resonance structures in 1,3-dipole (propargyl-allenyl anion).

as both nucleophiles and electrophiles. In electron rich dipoles such as nitrile ylide or diazomethane, the nucleophilic character is predominant and so these cycloadd to electron deficient multiple bonds with ease. However, electron poor species such as ozone shows electrophilic character in its reactions and thus adds to electron rich multiple bonds. The mechanism of 1,3-DCA is intriguing and controversial too. Sustmann has proposed that the transition state of the concerted reaction is controlled by the frontier molecular orbitals (FMO) of the substrates. He has classified 1,3-DCA reaction into three types on the basis of the relative FMO energies between the dipole and the alkene.⁷ In Type I, 1,3-DCA reactions, the chief FMO interaction takes place in between the HOMO_{dipole} with the LUMO_{alkene} as shown in Scheme 3.5. In Type



Scheme 3.5: FMO diagram for three types of 1,3-DCA reactions.

II, the FMO energies of the dipole and alkene are similar, so both HOMO-LUMO interactions are of equal significance. However, 1,3-DCA reactions of Type III are dominated by the interaction between the $LUMO_{dipole}$ and the $HOMO_{alkene}$. Azomethine ylides and azomethine imines are representative for Type I class of reactions. The reactions of nitrones are normally classified as Type II. 1,3-DCA reaction of nitrile oxides are classified as borderline to Type III. Azide systems belong to Type II system. Common example of Type III interactions are 1,3-DCA reactions of ozone and nitrous oxide. The introduction of electron-donating or electron-withdrawing substituents on the dipole or the alkene can change the relative FMO energies, and therefore the reaction type can change dramatically. The stereospecificity of the 1,3-DCA reaction led Huisgen to suggest a concerted mechanism for the cycloaddition reactions. However, later on R. Huisgen have demonstrated that such reactions can take place in a stepwise fashion with the loss in stereospecificity of the reaction.⁸

Dipolarophile systems: Different alkenes and alkynes can be used as dipolarophiles. Electron withdrawing groups when present as substituents can enhance the rate of the reaction. Presence of electron donating group reduces the rate of the 1,3-DCA reactions.

3.1.3 Solvent effect on 1,3-DCA reactions

Solvents can exert their influence on organic reactions through a complicated mixture of various covalent and noncovalent interactions. Chemists have tried to disentangle this intricate situation to assess the relative importance of all interactions separately. Shairashi, in 1991, reported an unusual acceleration of the 1,3-DCA reaction of 2,6-dichlorobenzonitrile *N*-oxide to 2,5-dimethyl-*p*-benzoquinone.⁸⁸ Surprisingly, an unusual acceleration of the rate constant of the reaction up to 14 times was demonstrated on changing the medium from chloroform to an ethanol-water mixture (60:40 % (v/v)). A comparison with kinetic data for conventional organic solvents demonstrated that the observed acceleration was unusually large. Except for the rate increase, the use of the aqueous solvent had another practical advantage, the precipitation of the product facilitated work-up procedures too. These kinetic data may be compared with the results of Hegarty, which revealed an increase of the second-order rate constant of the cycloaddition of *p*-nitrobenzonitrile *N*-oxide to ethyl acrylate or dimethyl maleate of less than a factor of two on changing the solvent from 1:1 water-dioxane to water. Spectacular enhancement of the rate of 1,3-dipolar cycloaddition reaction of norbornene and phenyl azide was also reported in the water rich region by J. W. Wijnen, R. A. Steiner and J. B. F. N. Engbert.⁹ However, all these reactions were performed under homogenous conditions *i.e* reactants were present within the solubility limit. Due to the limited solubility, the use of water as a solvent medium was not considered by chemical industries for many decades. Not surprisingly, water has not been a very popular solvent among organic chemists in the past. However, the development of the ‘on-water’ protocol by Sharpless and co-workers has further led to a resurgence of the scientific community’s interest in the potential applications of water and aqueous solutions as reaction media.⁵⁸ The impact of the ‘on-water’ protocol is reflected very well by the plethora of available reports employing the novel strategy of heterogenous catalysis. Recently Novartis and co-workers described a simple and elegant synthesis of cyanotriazoles from organic azides and 2-chloroacrylonitrile, under heterogenous conditions.¹⁰ Highest reaction rates were obtained in the two phase systems. The

1,3-DCA of organic azides and electron-deficient alkynes were investigated ‘on-water’ by Ju and coworkers.¹¹ Surprisingly, the reactions appeared to be facile even at room temperature and proceeded to completion in 6-12 h. Also noteworthy are the 1,3-DCA reactions of phthalazinium ylides ‘on-water’, reported by Butler and co-workers, since the reaction involved at least one solid reactant.¹² High yields were obtained in the reaction when the reaction was performed ‘on-water’. Regioisomerically pure 1,4-disubstituted 1,2,3-triazoles azido alcohol were obtained from the isomeric diepoxides and by opening the epoxides with azide anion ‘on-water’.⁵⁸ Excellent yields were obtained from cycloadditions of nitrones with allenolates performed ‘on-water’.¹³ Also reported are the quantitative yields of pyrazolines obtained by a 1,3-DCA reaction of perfluorophenyl diazomethane with unsaturated esters or nitriles.¹⁴ Another positive attribute of ‘on-water’ reactions are the easy isolation of products merely by filtration. Synthesis of benzopyrans, quinolines and fused isoxazolines was reported by Bala and Hailes in excellent yields by intermolecular 1,3-DCA reactions of nitrile oxides.¹⁵ The convenience of product isolation from the ‘on-water’ reactions was a practical advantage: no starting materials remained, and products formed precipitated from the reaction mixture.

3.1.4 Present scenario: azide-alkene cycloaddition as “click reaction”

Sharpless and co-workers working on the development of click reaction, focused on azide-alkyne cycloaddition reactions which were deprived of attention by synthetic chemists due to “azidophobia”.² They categorized this reaction as most useful among the family of 1,3-DCA reactions because azides are most convenient to be introduced and to transfer through many synthetic steps. The extreme stability of azides towards oxygen, water and the majority of synthetic and harsh conditions makes them unique for click chemistry purposes. The 1,3-DCA reaction of organic azides and olefinic bonds, leading to the formation of 1,2,3- Δ^2 -triazolines, was first reported by Wolff in 1912.¹⁶ Consequently, the work of several investigators demonstrated the generality

and limitations of the cycloaddition.¹⁷ Alder and Stein's extensive study delineated the scope of such reactions and provided information regarding the stereochemical course of the reaction.¹⁸ More recently the azide and alkene addition has received considerable attention from a number of investigators.¹⁹ However, in spite of available reports the reaction of aromatic azides and strained alkenes such as diethylfumarate is still scarce. Considering the synthetic utility of triazoles formed from cycloaddition reactions, it is necessary to focus on strategies that can eventually effect reaction rate of such slow reactions and can contribute to the better understanding of 'on-water' reactions.

3.1.5 The present work

The dramatic rate accelerations of 1,3-DCA reaction in aqueous media has been used in many applications in the last three decades. However, for a chemist, it is important to know the mechanism of any reaction or a catalytic process and the optimization of the reaction conditions is another big target to be attained. Although the available reports exhibits the exemplary rate enhancements under 'on-water' conditions, the understanding of the root cause of the 'on-water' effect and its physical-organic aspects is still in infancy. Determination of the molecular origin of 'on-water' reaction is difficult even with the combination of structural information gathered for water surface and by electronic structure calculations. Approximate kinetic models and transition state theory predictions by Y. Jung and R. A. Marcus although give an approximate idea of the interfacial orientation of water molecules but it failed to comprehend the negligible affect observed in some reactions.⁶⁰ This can be attributed to the complex nature of interfacial reactions. The accurate measurements of rate constant of interfacial reaction are not possible due to absence of precise experimental techniques and procedures and uncertainty in the exact concentrations of reactants at the interface. This limits our determination of actual interfacial rate constants. Henceforth, the kinetic and mechanistic investigation of interfacial reactions is an intimidating task. Currently, an important question is the universal nature of 'on-water' reactions which has to be further probed for taking an account of its applicability on a wider range of

already known slow reactions. It is very evident from the preceding discussion that the cycloaddition reaction of phenyl azide and alkenes such as diethylfumarate has received only limited attention. The reaction is extraordinary slow with rate constant of the order of $8.36 \times 10^{-7} \text{ M}^{-1}\text{s}^{-1}$.²⁰ The observation that such reactions involving activated reactants could constitute an effective method for the construction of highly substituted derivatives, provided additional momentum for undertaking the studies discussed in this chapter. However, the main challenge is to make the reaction faster so as to make it beneficial for the chemist. Also, the delineation of contribution of hydrophobic forces on the rates of interfacial reaction and the proper selection of appropriate dipole is another intimidating task taken up in the following section. The comparative study of effect of different substituents on the rate of 1,3-DCA reaction has been also dealt in the present work. Essentially, the present work is an exploration of the reactivity of different dipoles towards diethylfumarate, with a view to developing a better understanding of the oil-water interface. The results of the work carried out with such systems are presented in the following section. The presence of three potentially dipole functionalities viz., phenyl azide, *p*-nitrophenyl azide and *p*-bromophenyl azide renders very interesting electronic changes of dipoles from the vantage point of cycloaddition reactions.

3.1.6 Experimental section

Synthesis of phenyl azide²¹

45 ml (1.22 moles) of concentrated hydrochloric acid (98% w/v) was added to a mixture of 28 g (0.2 mol) of aniline and 80 ml of water in a 500-ml three necked flask equipped with a stirrer, a thermometer and dropping funnel. The flask was cooled in an ice-salt bath until the temperature of the mixture reached 0–5°C. After the attainment of temperature, the amine hydrochloride was diazotized by adding dropwise a solution of 14.5 g of sodium nitrite dissolved in 50 ml of water. The reaction mixture was stirred for 1 h at 0–5°C. The yellow-green solution was filtered from the traces of insoluble impurities and poured into a beaker placed in an ice

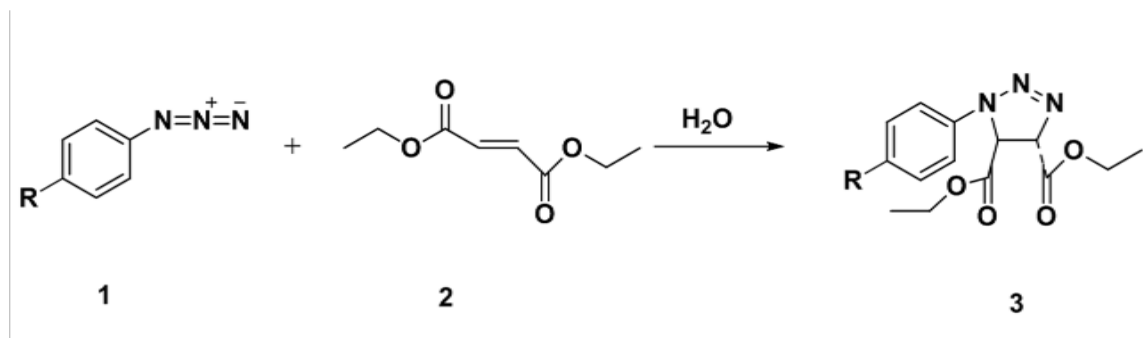
bath. To this solution, a solution of 13 g (0.2 mol of sodium azide in 50 ml of water) was added with constant stirring. The solution was extracted with diethyl ether and the ethereal fraction (containing phenyl azide) was reduced in vacuo. The total yield of phenyl azide obtained was 63–69%. The ^1H NMR spectrum of the synthesized phenyl azide agreed well with the reported data. The product was stored in dark brown bottles at very low temperatures.

Synthesis of *p*-bromophenyl azide and *p*-nitrophenyl azide

p-bromo phenyl azide was synthesized from *p*-bromoaniline and *p*-nitrophenyl azide from *p*-nitroaniline by the same procedure as followed for the synthesis of phenyl azide.

3.1.6.1 Kinetic analysis

The reaction was initiated by the addition of equimolar quantity of phenyl azide, *p*-nitrophenyl azide and *p*-bromophenyl azide to a stirred heterogenous aqueous solution of diethylfumarate (each 0.1 M), taken in a 50 ml round bottom flask, and the solution was diluted up to 2 ml with water (Scheme 3.6). The reactions were performed above the solubility limit of the reactants to ensure heterogenous conditions. The resulting solution was not clear. The temperature was controlled using a Julabo constant temperature bath with an accuracy of $\pm 0.01^\circ\text{C}$. The reaction was monitored by diluting 5 ml of aliquots in methanol, taken out from the stirred solution, at appropriate time intervals for absorbance measurements by Cary-50 UV-Visible spectrophotometer. The measurements were carried out 248, 255, and 318 nm for phenyl azide, *p*-nitrophenyl azide and *p*-bromophenyl azide respectively. All reactions were monitored for 15% conversion. The concentration of the reactant in the bulk reaction mixture was calculated at each time interval using a calibration graph. A plot between $x/a(a-x)$ vs. t yielded the values of k_2 for the reaction. For homogenous reaction condition the reactants concentrations were kept below their solubility limit. The solution was clear throughout the experiment. Diethyl fumarate (0.5×10^{-4} M) was added to a preequillibrated solution (at 25°C) of 1a (0.5×10^{-4} M taken in 1 ml



1a=phenyl azide

1b=*p*-nitrophenylazide

1c=*p*-bromophenylazide

Scheme 3.6: 1,3-dipolar cycloaddition reaction of azide **1a-c** with diethylfumarate 2.

water) and the reaction was monitored at the respective λ_{max} of azides involved in the reaction. Each experiment was carried out at least 3 times and the rate constants, k_2 , were reproducible to within $\pm 5\%$.

3.1.6.2 Salt effect

Salts examined (LiCl, KCl, CaCl₂, NaCl and (C₄H₉)₄N Br (obtained from Merck of GR grade) were dried in an oven for 5-6 h and the solutions were prepared in deionised water.

3.1.6.3 Solubility measurements

The method employed was validated by the process already reported in the literature.²² The solubility was determined by equilibrating azide in water for 3 h at the desired temperature obtained from a constant temperature bath. After 3 h of vigorous stirring followed by 1 h standing, lower phase (0.03 ml) was taken out and was diluted to 5 ml with the solvent. The concentration of azide was determined by Cary-50 UV-Visible spectrophotometer. The measurements were carried out 248, 255, and 318

nm for phenyl azide, *p*-nitrophenyl azide and *p*-bromophenyl azide respectively. Triplicate measurements were carried out and the reproducibility of the measurements were $\pm 6\%$.

3.1.7 Results and discussion

Detailed kinetic studies of 1,3-DCA reaction in aqueous media were carried out in order to delineate the origin of the molecular forces that give rise to the rate enhancement observed under heterogenous conditions. Dipole used for the study included **1a**, **1b** and **1c**. **1a** and its substituted analogs were synthesized and were used for study. In order to have a more generalised picture of the salt effect at interface, rates of the reactions were determined both in absence and presence of prohydrophobic salts such as LiCl, KCl, NaCl and CaCl₂ at 298 K in a range of concentrations varying from as low as 0.15 M to as high as 5 M.³⁸ Antihydrophobic salts such as LiClO₄ and GnCl were not used for investigations since they were observed to decrease the stability of the azides. Highest rate constants of the reaction was observed for reaction of **1a** with **2** for NaCl followed by KCl, LiCl and least was observed for CaCl₂ salt (Tables 3.1, 3.2 and 3.3). The k_2 values determined for the same reaction were minimum in the case of (C₄H₉)₄NBr. At 1.5 M salt concentration of (C₄H₉)₄NBr, the k_2 values observed was $3.25 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ which was comparatively less as compared to the k_2 values observed in presence of other salts. This can be explained by the increased solubility of the reactants in the presence of such surfactants type salts. The observation reconfirms that for substantial rate enhancement in the interfacial reaction, the insolubility of reactants in the solvent medium is a crucial criteria. Interestingly, the trend observed here partially follows the Hofmeister series²³ since observed trend can be somewhere correlated with the charge/size ratio of the cations of the salts (except NaCl which behaves abnormally). This again accentuates on the complex nature of the interfacial reactions. A comparison of the relative absorbance of homogenous and heterogenous reactions was also carried out in all the three sets of reactions. In all the cases, rates of homogenous reactions were observed to be slow as compared to that of heterogenous reactions (Figure 3.1). This was an advantage since, compara-

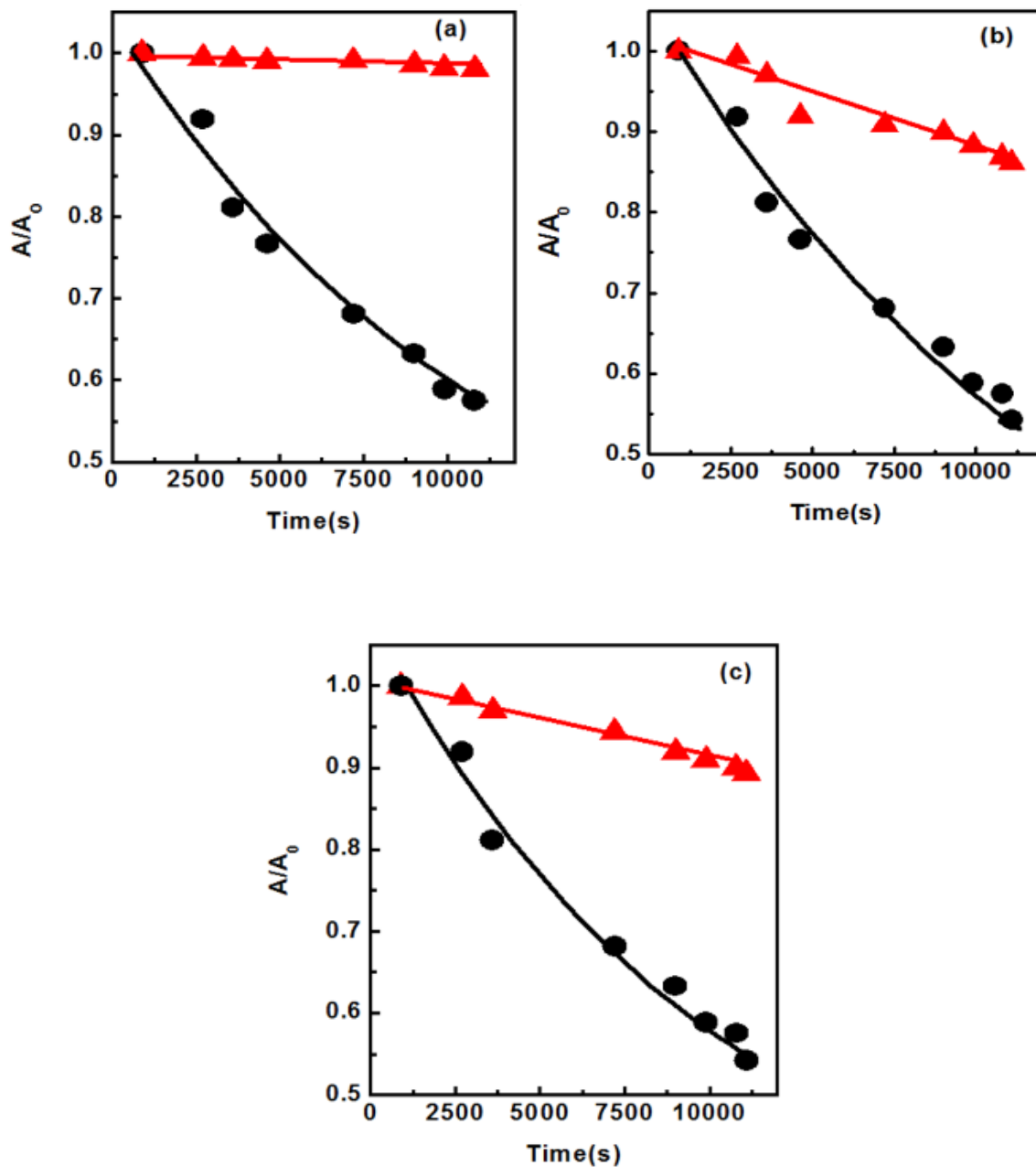


Figure 3.1: The plots of relative absorbance A/A_0 vs. time in (a) **1a** (b) **1b** and (c) **1c** at 298 K under (●) heterogenous (▲) homogenous conditions.

tively slow reaction of **1a**, **1b** and **1c** and **2** in nonpolar solvent²⁰ was observed to be significantly enhanced under aqueous heterogenous reaction conditions. The product forms a distinct oily phase, which can be isolated easily by phase separation.

3. Hydrophobic Contribution at Oil-Water Interface

Table 3.1: Relative rate constant k_{rel} (with respect to water) for aqueous salt solution of 1a with 2 at 298K; $k_{rel} = k_2$ in presence of salts/ k_2 without salt.

Entry no.	Conc.(M)	LiCl	KCl	NaCl	CaCl ₂
1	0	1	1	1	1
2	0.15	1.046	1.083	5.046	1.023
3	1	1.083	1.162	5.268	1.064
4	2	1.120	1.282	6.203	1.083
5	3.5	1.134	1.296 (3 M)	6.480	1.111
6	5	1.138	–	–	1.120

Table 3.2: Relative rate constant k_{rel} (with respect to water) for aqueous salt solution of 1b with 2 at 298K; $k_{rel} = k_2$ in presence of salts/ k_2 without salt.

Entry no.	Conc.(M)	LiCl	KCl
1	0	1	1
2	0.15	1.112	1.245
3	1	1.218	1.414
4	2	1.263	1.616
5	3.5	1.322	1.641(3 M)
6	5.0	1.331	–

3.1.7.1 Role of solubility

As explained by Engberts not only the presence of water as a media is necessary for interfacial reactions, but heterogeneity in the medium is also an elementary requirement.^{60(c)} It has been earlier reported that upon addition of methanol, beyond a certain concentration range, significant reduction in rates of reaction were observed owing to the switching of heterogenous system into homogenous state. In view of the fact that the main difference between homogenous and heterogenous condition is the insolubility of the reactants, solubility of azides were determined at each salt concentrations. KCl showed minimum salting out effect among the investigated

3. Hydrophobic Contribution at Oil-Water Interface

Table 3.3: Relative rate constant k_{rel} (with respect to water) for aqueous salt solution of **1c** with **2** at 298K; $k_{rel} = k_2$ in presence of salts/ k_2 without salt.

Entry no.	Conc.(M)	LiCl	KCl
1	0	1	1
2	0.15	1.580	2.436
3	1	1.895	4.192
4	2	2.855	4.454
5	3.5	3.647	4.628(3 M)
6	5.0	3.703	–

salts. Observed trend of solubility ratio (S/S_0) for **1a** is $KCl > LiCl > CaCl_2 > NaCl$ (Figure 3.2 (a)). These salts tend to salt out reactants from the bulk onto the interface. But this salting out was minimum in the case of KCl *i.e.* azides concentration was comparatively more in the bulk as compared to that in other salts. Consequently, minimum crowding of reactants was at the interface of the reaction when carried out in presence of KCl salt. Henceforth, due to the presence of relatively free and active interfacial area in presence of KCl salt, the observed rate constants for the reaction of **1a** and **2** were maximum in KCl followed by LiCl and then by $CaCl_2$ (Figure 3.2(b)). NaCl salt was an exception since the rate constant observed in their case was abnormally high (Figure 3.2 (c)). This is in accordance to a recent report where Na^+ ions are known to catalyse the reactions that involve ester functional group via binding to them.²⁴ Hence, it is very likely that Na^+ ion of the NaCl salt binds to the ester group of **2** and catalyses the reaction. Similar results were observed in the case of **1b** and **1c** also, where rates observed in KCl was found to be higher as compared to that of LiCl (Tables 3.1, 3.2 and 3.3). The plots of solubility *vs.* salt concentration displayed nonlinearity in the graph, which indicate the complex relation between the two parameters (Figure 3.2). Also, the trend observed in **1a** was interesting and encouraging. It was observed that at higher concentrations of salts, its effect on rate enhancement of the reaction weakend (Figure 3.3). In order to ascertain the phenom-

3. Hydrophobic Contribution at Oil-Water Interface

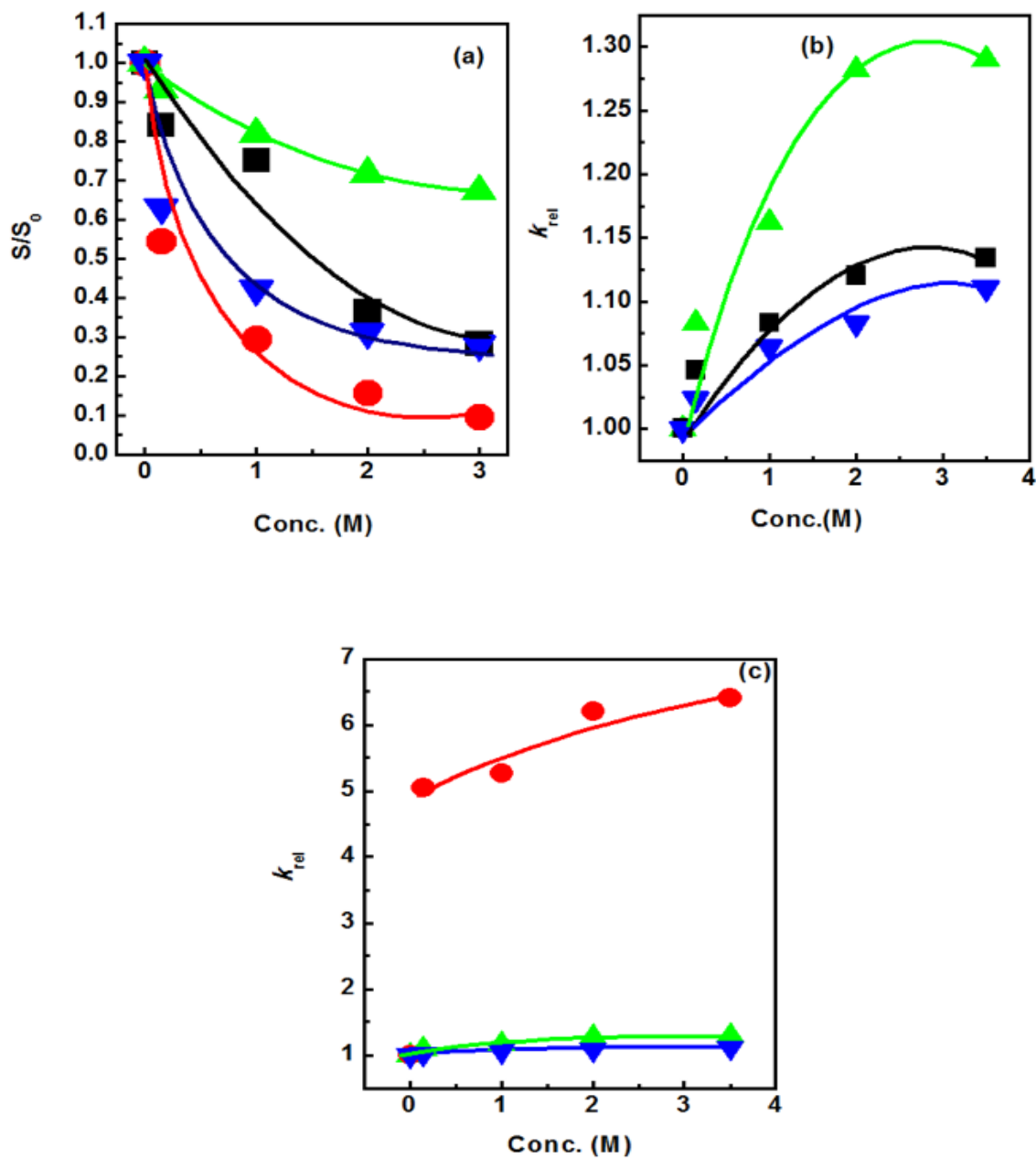


Figure 3.2: Relative plots of solubility, S/S_0 of **1a** as a function of concentration of salts in (▲) KCl (■) LiCl (▼) CaCl₂ (●) NaCl (b) plot of k_{rel} of reaction of **1a** with **2** vs. salt concentration (c) plot of relative rate constant of reaction of **1a** with **2** in the presence of different salts (including NaCl).

ena the investigations was carried out in **1b** and **1c** too. Interestingly, same trend was observed in these two moiteis too (Figure 3.4).

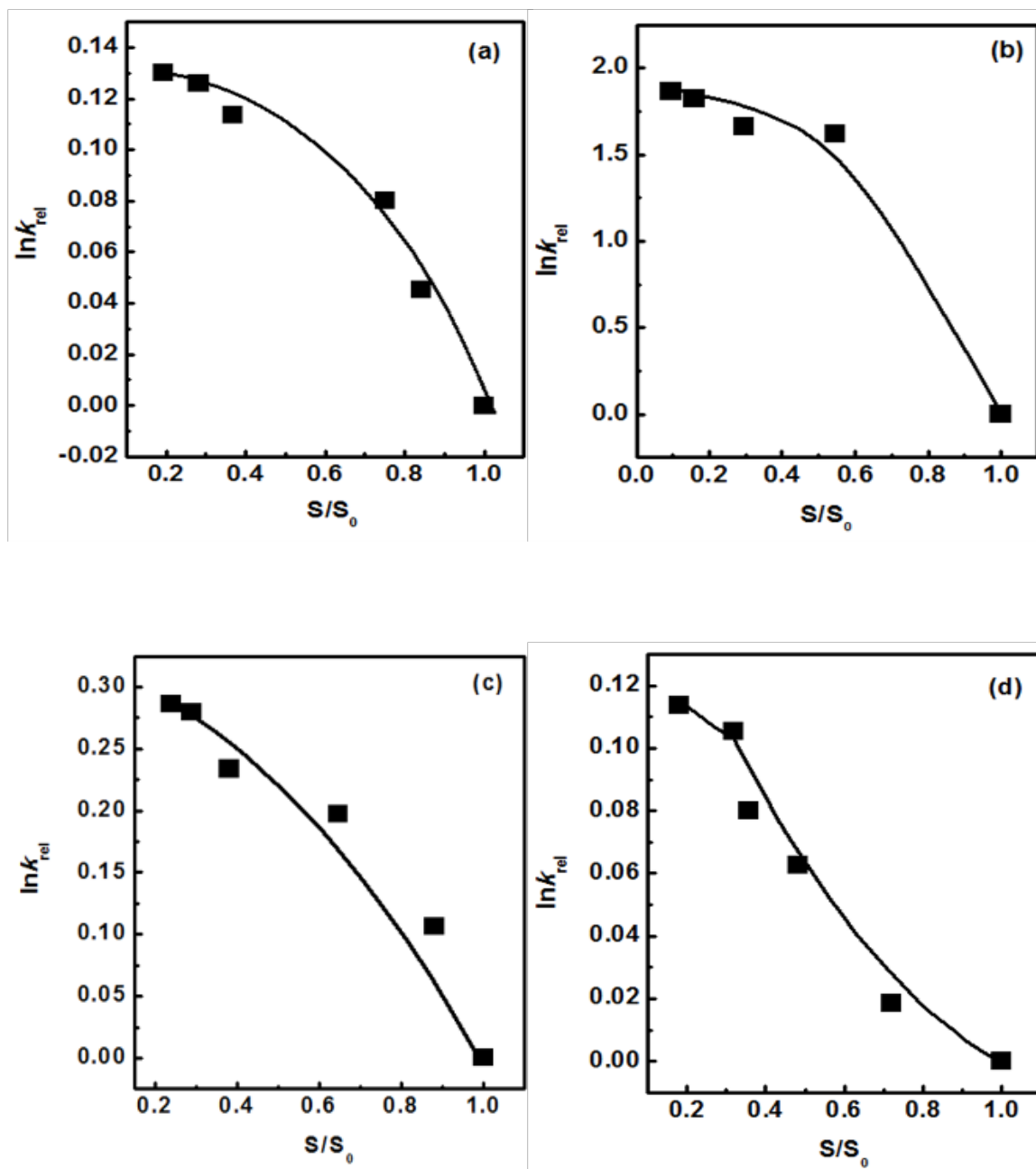


Figure 3.3: The plots of $\ln k_{rel}$ vs. S/S_0 for **1a** in (a) LiCl (b) NaCl (c) KCl and (d) CaCl_2 .

3.1.7.2 Electronic effect

Generally, cycloaddition reactions like Diels-Alder and 1,3-DCA are concerted reactions. For slow rates of the 1,3-DCA reactions, it is possible to enhance the rates via increasing the conjugation in the system or by changing the substituents on the

3. Hydrophobic Contribution at Oil-Water Interface

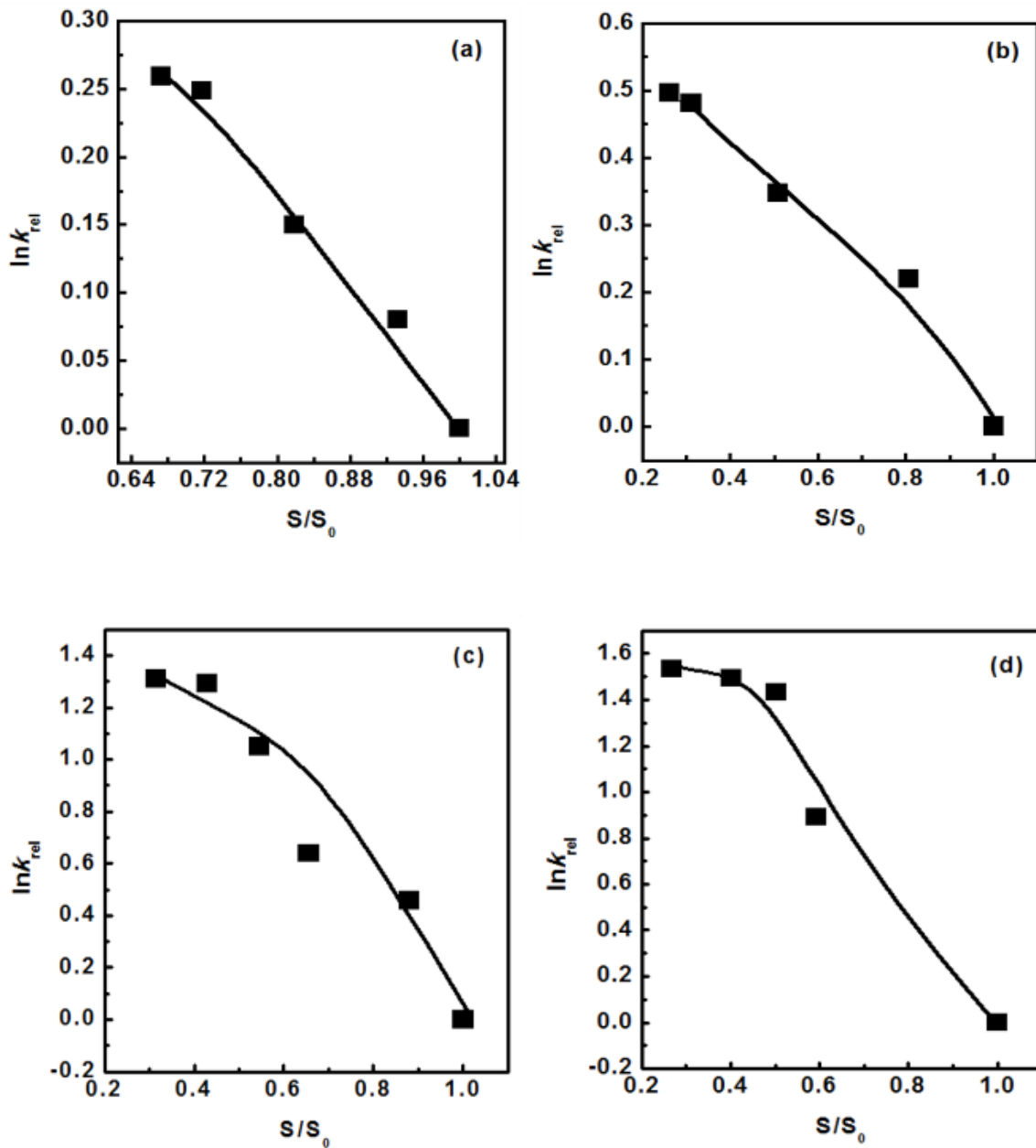


Figure 3.4: The plots of $\ln k_{rel}$ vs. S/S_0 for **1b** in (a) LiCl (b) KCl and for **1c** in (c) LiCl (d) KCl.

reactants.^{89(b)} Presence of electron donating group on the dipole or electron withdrawing group on the dipolarophile can provide maximum rate enhancements. Since reactants under investigation are charged species and medium is very polar, a study of influence of substituent at the interface is very much desirable. Upon carrying out the reaction of **1(a)**, **1(b)**, **1(c)** with **2** under identical conditions the rates observed

is the followed:

$$\mathbf{1a} > \mathbf{1b} \sim \mathbf{1c} \text{ (Figure 3.5)}$$

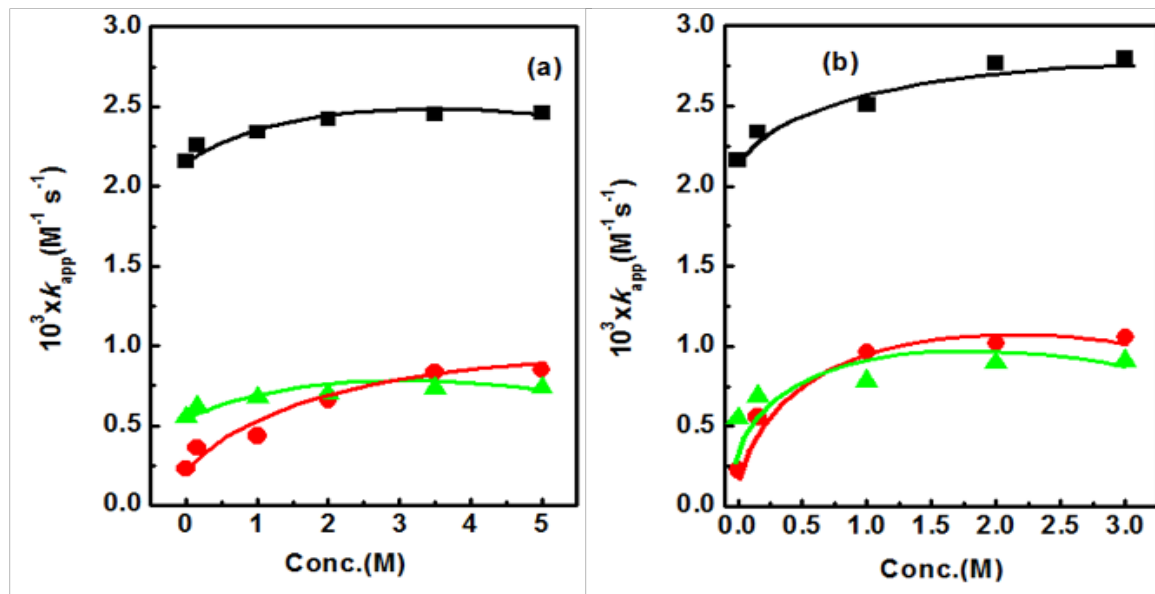


Figure 3.5: The plots of apparent rate constant, k_{rel} of (■) **1a**, (▲) **1b** and (●) **1c** in (a) LiCl and (b) KCl.

Unsubstituted azide gave maximum rate acceleration. The rate constants observed in the case of **1b** and **1c** were comparable, which could be attributed to negative inductive effect of nitro and bromo groups. These groups when present on reactants may result in electron withdrawal and hence cause reduction in nucleophilicities of the dipole. The attack on the electrophile *i.e.* **2** is therefore reduced in comparison to that of **1a**. These reactions are less favoured under the conditions in these cases.

3.1.7.3 Saturation effect

All the relative plots between rate constants and solubility data have one unusual pattern which is common in all the cases (Figure 3.3, 3.4). Surprisingly, at higher salt concentrations the enhancement observed is not pronounced. The minimal salt effect or “No Salt Effect” at higher salt concentrations can be due to the reduction in the contact area between reactants and water surface. For interfacial reactions, catalysis is only possible when reactants are hooked up or anchored at proper orientations on the

water surface. Hence, the catalysis of the reaction by stabilization of transition state with the assistance of water is hindered leading to reduced rates of reaction. At higher salt concentrations, more reactants are precipitated out onto the surface resulting in increased product formation. The products thus formed are more hydrophobic in nature than reactants and hence they prefer to stick to the interface instead of going in to the bulk water. These “pinned” products can interfere between reactant droplets formed and the water surface. This is in accordance to a recent report where it was found that beyond a concentration of reactants no rate acceleration were seen since products formed happen to accumulate at the interface.⁹⁰

3.1.8 Conclusions

Understanding of role of hydrophobicity at the interface is still a great challenge. Role of salts under heterogenous condition is entirely different to that of homogenous conditions. The reactions that occur at the interface are predominantly controlled by interfacial area of contact between the reactants and water surface. At higher salt concentrations, the accumulation of products reduces the active interfacial area and hence rates are reduced. So minimal or “No Salt Effect” at higher salt concentration can be attributed to “pinned” products. These results give an insight into the role of prohydrophobic salts at the interface.

3.2 Homogenous *vs.* heterogenous reactions at interface

3.2.1 Introduction

As concluded from the work described in the previous section, heterogeneity, presence of bare and active interface area of the medium is a crucial factor in attaining efficient rate enhancements in ‘on-water’ reactions. However, in order to overcome the limitations of the reactions, it is essential to understand the relationship between extent of heterogeneity and the rates of reaction with reference to their effects on simple organic reactions. To achieve this end, an extensive collection of kinetic data for a variety of organic reactions carried out in a heterogenous media is essential. Moreover, there have been few attempts to correlate the physico-chemical properties of interfacial reactions with kinetic outcome of reactions. Also the delineation of contribution of hydrophobic forces on reaction rates in presence of prohydrophobic salts is significant. Undoubtedly, the correlation of change in the solubility of solute molecules in presence of prohydrophobic salts and temperature is a crucial problem. Tiwari and Kumar have reported unusual temperature dependence of salt effect. The authors have proposed that the existing notion of “salting-out” and “salting-in” behaviour could not be accounted for the observed contrasting effect of salt additives on the rates in water and aqueous salt solutions at different temperatures.²⁵

3.2.2 Present work

An ‘on-water’ reaction is characterized by the insolubility of the reacting components in the medium. The solubility factor is important because heterogeneity is the common characteristic for all ‘on-water’ processes. This section deals with the investigation of effect of temperature and prohydrophobic salts on the solubility and the rate of reasonably slow 1,3-DCA of **1a** and **2**. The possibility that the salts can exert their effect at higher temperatures by controlling the solubility of the reactants could not be ignored. Henceforth, serious attempt has been made to meticulously ex-

plore the influence of effective concentration of the reactants, present at the oil-water interface, on the reaction dynamics.

3.2.3 Experimental section

Synthesis of 1a: The synthesis of **1a** was carried out as discussed in the previous section.

Kinetic analysis

The reaction was initiated by the addition of equimolar quantity of **1a** to a stirred heterogenous aqueous solution of **2** (each 0.1 M), taken in a 50 ml round bottom flask, and the solution was diluted up to 2 ml with water. The reactions were performed above the solubility limit of the reactants to ensure heterogenous condition. The resulting solution was not clear. The temperature was controlled using a Julabo constant temperature bath with an accuracy of $\pm 0.01^\circ\text{C}$. The reaction was monitored by diluting $5\mu\text{l}$ of aliquots in methanol, taken out from the stirred solution, at appropriate time intervals for absorbance measurements by Cary-50 UV-Spectrophotometer. The measurements were carried out at 248 nm. All reactions were monitored for 15% conversion. The concentration of the reactant in the bulk reaction mixture was calculated at each time interval using a calibration graph. A plot between $x/a(a-x)$ vs. t yielded the values of the k_2 for the reaction, where x denoted product formed at time t and a denotes initial concentration of the reactant.

Salt effect

Salts examined (LiCl, KCl and CaCl_2 (obtained from Merck of GR grade) were dried in an oven for 5-6 h and the solutions were prepared in deionised water.

Solubility measurements

The method employed was same as followed for the solubility measurements in the previous section.

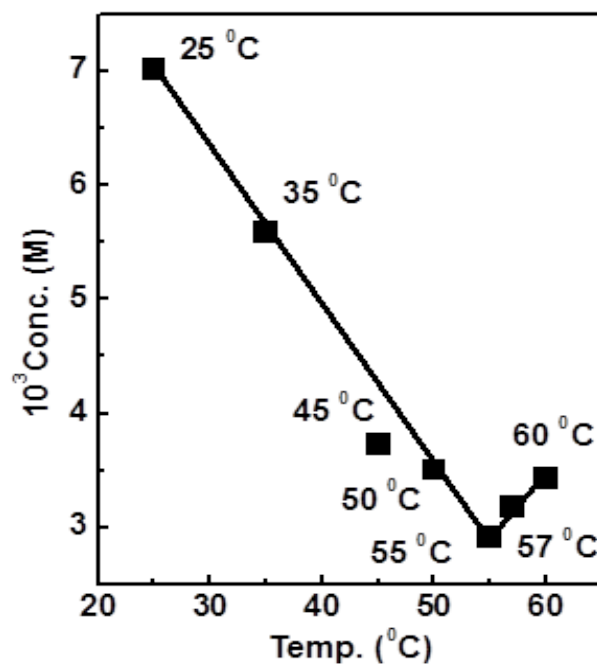
3.2.4 Results and discussion

3.2.4.1 Temperature dependent solubility measurements

Solubility is a thermodynamic quantity. When a hydrophobic solute is dissolved in water, then freezing of water takes place around the solute molecules *i.e.* the process is exothermic and the heat of solution is negative. In such a case the new interactions which are formed in between the solute and water molecules in solution phase, are stronger than the interactions broken in between the solute-solute and solvent-solvent molecules. In order to testify the behaviour of **1a** in water, herein, we have made the solubility measurements of **1a** at different temperatures ranging from 25°C to 60°C. Unexpectedly, an initial decrease in the solubility of **1a** was observed with the increase in temperature. Inverse solubility effect has been earlier observed for other aromatic moieties too like benzene, xylene, naphthalene *etc.* in water.²⁶ The decrease in solubility was consistent up to 55°C followed by an increase in the solubility of **1a** after 55°C. This unusual behaviour can be explained by the possible interactions existing in the system. The π -interactions in between the aromatic system and water molecules make the system exothermic due to the freezing of water molecules around the hydrophobe. The increase of temperature on such a system can decrease the solubility of the reactants (Le-Chatelier's principle). Upon raising temperature (up to 55°C) the solubility was observed to decrease, since the process of dissolution is exothermic hence increase of temperature drives the equilibrium in the backward direction. But once the temperature has attained 55°C then there is a balance in between heat of freezing and of heat of cavitation (endothermic process). Above 55°C the cavitation process dominates, making dissolution process feasible and hence the solubility of **1a** increases in the aqueous media. Water structure also loosens up at higher temperature, hence now the solubility of **1a** becomes favourable and it increases with temperature. This may be the responsible factor for the anomaly in the solubility behaviour of **1a**. The data are given in Table 3.4 and represented by Figure 3.6.

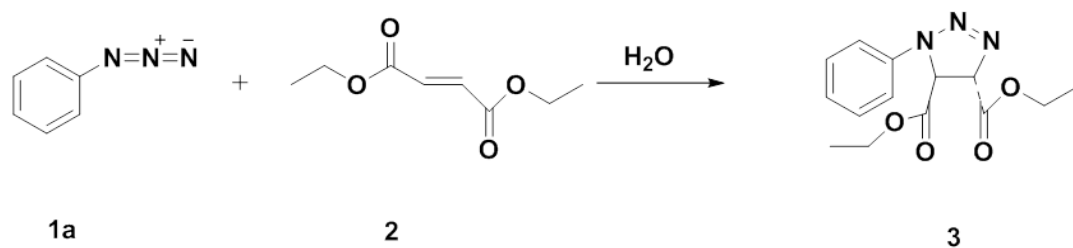
Table 3.4: Solubility data for **1a** at different temperatures.

S.no.	Temp °C	10 ³ Conc.(M)
1	25	7.02
2	35	5.55
3	45	3.73
4	50	3.50
5	55	2.91
6	57	3.18
7	60	3.43

Figure 3.6: A plot of concentration of **1a** in water as a function of temperature.

3.2.4.2 Kinetic study

The observation of the decrease in solubility with the rise in temperature motivated us to use it as an investigating tool to inspect the ‘on-water’ reaction conditions.

Scheme 3.7: 1,3-DCA reaction of **1a** with **2**.Table 3.5: Kinetic data of 1,3-DCA reaction of **1a** with **2** at different temperatures.

S. no.	Temp. °C	k_2 ($M^{-1}s^{-1}$)
1	25	0.002
2	35	0.005
3	45	0.014
4	50	0.052
5	55	0.112
6	57	0.055
7	60	0.050

Decrease in solubility of **1a** can be otherwise explained as an increase in the heterogeneity of the medium. Since, till date the role of extent of heterogeneity has not been realised in detail, henceforth herein we have made an effort to explore the consequences of the change in the heterogeneity of the media on the kinetics of the 1,3-DCA reaction. The reaction undertaken was between **1a** and **2** as dienophile to give the cycloadduct, **3**, as shown in Scheme 3.7. Interestingly, when the reaction was carried out in between **1a** and **2**, a trend reverse of the solubility was observed. The rate constant increased to maxima and then decreased. The maximum was observed at 55°C, reverse of the dip in the solubility measurements (Table 3.5 and Figure 3.7). This can be explained by the fact that the minima in solubility corresponds to maximum heterogeneity in the system. This is in accordance of earlier reports which states that heterogeneity is an important attribute for ‘on-water’ reactions. Surpris-

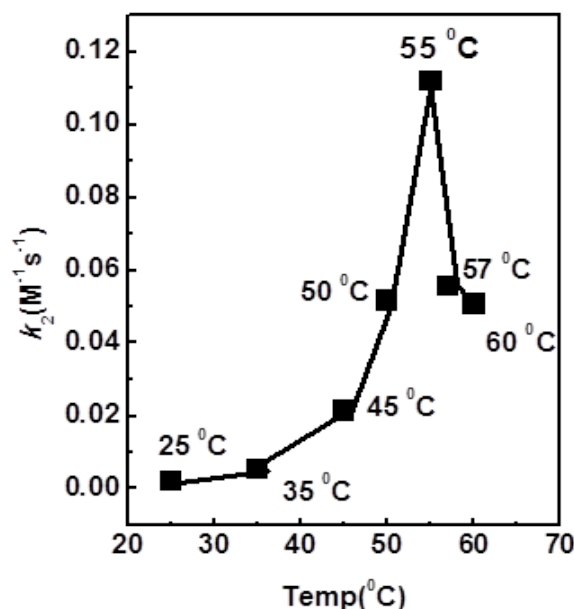


Figure 3.7: A plot of k_2 vs. temperature for 1,3-DCA of **1a** and **2**.

ingly, we observed **1a** as a moiety which exhibited inverse solubility effect and kinetic investigation on the same reconfirmed the significance of heterogeneity for effectual rate enhancements. After initial rise the fall in the rate constants of reaction can be explained by increase in the solubility of **1a** in the media. Henceforth, the system becomes homogenous and the special interfacial water characteristics are lost and as a result the reaction slows down.

3.2.4.3 Absence of hydrophobic acceleration of the reaction: crowding at the interface

The hydrophobic effect is the tendency of hydrophobic species to aggregate in water solution in order to decrease the hydrocarbon-water interfacial area. It suggests in parts the large cohesive energy of water, whose molecules would preferably bind to each other than to a hydrophobic surface. A thermodynamic criterion can sometimes be helpful in deciphering the complex nature of hydrophobic interactions. Interestingly, for homogenous reaction conditions, high endo/exo selectivity of Diels-Alder reaction has been explained by hydrophobic effects in aqueous media.^{10(b)} The special

effects of water as a solvent medium can be greatly altered by the addition of ionic solutes such as LiCl, KCl and CaCl₂. Evidence supporting the hydrophobic acceleration can be exploited by employing different salts since they can attenuate the magnitude of hydrophobicity, so such salts are useful probes. For interfacial reactions however, the definition and role of various salts is still in infancy. We have tried to investigate the combined effect of temperature and hydrophobic effect on interfacial catalysis of reaction. Herein, the kinetics of the 1,3-DCA reaction of **1a** and **2** in presence of 2M concentration of LiCl, CaCl₂ and KCl has been carried out. Interestingly, up to 55°C no hydrophobic acceleration of the reaction is observed. This is contradictory to the normal convention that salting out salts can enhance the rate of the reaction. This highlights the complex nature of oil-water interface. Addition of prohydrophobic salts decreases solubility of **1a**. Up to 55 °C **1a** depicts inverse solubility effect. Addition of salting out salts further increases the heterogeneity of the system. As per normal convention, enhancement in the heterogeneity should increase the k_2 of ‘on-water’ reactions. The results obtained are however contradictory. A better assessment of the results can be obtained by assuming that the nature of the interface is changing from a bare and active to a crowded and inactive one in a complex heterogenous media. For an effective catalysis, the presence of properly anchored reactant molecules with proper orientation at the interface is very important. Due to the anchoring of a reactant and the transition state to the surface with correct relative orientation of reactants, reactions become more facile. Without proper interfacial anchoring, two reactants simultaneously have to be reoriented to form a transition state. Henceforth, when the interface becomes crowded, due to the pumping of higher concentration of **1a**, this interfacial anchoring and catalysis of the reaction becomes difficult. The products formed are also hydrophobic so it competes with the reactants present at the interface. Due to its nature, product molecules stick at the interface and make it crowded and inactive, since less number of the water molecules are available for catalysing the reaction. The interfacial water molecules are restricted by the product molecules to effectively approach the polar and charged transition state of the reaction and thus it slows down the reaction velocity. The results indicate that although

heterogeneity is a must for effective catalysis of the reaction but presence of bare and active interface with free water molecules to catalyse the reaction is also important. On the contrary, after 55 °C there is an increase in the rate constant of the reaction. This is explainable by the solubility data for **1a**. As shown in Table 3.4 there is an increase in the solubility of **1a** after 55 °C. The increment in solubility can be correlated to a concomitant decrease in the heterogeneity or crowding at the interface. The reduction in crowding which can be designated as a steric one contributes to the availability of more bare, active interface and water molecules for the effectual catalysis of the reaction. The analysis of the reaction after 60°C was not possible since the water structure gets disturbed after such high temperature and the analysis becomes more erroneous. The results show that the presence or absence of rate acceleration on addition of prohydrophobic salts at any temperature need not be a conclusive evidence for the predominance of (or lack of) "hydrophobic effect", at least for heterogeneous aqueous reactions. The results show that unlike homogenous reaction conditions in which prohydrophobic effect can enhance the rate of the reaction, interfacial reactions are more complex. The salting effects on the kinetics of 'on-water' reactions differ significantly from those observed for homogeneous aqueous reactions. No salt effect is observed up to 55°C but it becomes visible at higher temperature. The results give an indication of the complex manner in which the presence of salting out and salting in salts are capable of influencing hydrophobicity at the interface. The k_2 values are given in Table 3.6 and relative k_2 values are given in Table 3.7. The investigation of the reaction in presence of 'salting in' salts was not possible since they decreased the stability of **1a** in water. When the reaction was carried out at a temperature above 55 °C in presence of prohydrophobic salts, it is possible that the enhancement in the solubility of **1a** overcomes the decrease in solubility of the reactant caused by the salts. As a result the interface becomes sterically less crowded and catalytically more active resulting in enhanced rates of the reaction. An interesting observation was the trend observed in the rate constant of reaction in presence of salts. The reduction in the rate constant of the reaction with the increase in temperature was maximum for CaCl₂ then for LiCl and was minimum for KCl. Hence, higher was the salting out of

3. Hydrophobic Contribution at Oil-Water Interface

Table 3.6: k_2 values for 1,3-DCA reaction of **1a** and **2** at different temperatures.

Salt(M)	$10^3 k_2 (\text{M}^{-1} \text{s}^{-1})$				
	25°C	35°C	45°C	55°C	65°C
0	2.10	5.43	21.4	112	145
LiCl	2.42	5.58	8.80	4.86	24.4
KCl	2.77	5.74	9.63	6.51	30.0
CaCl ₂	2.34	2.26	2.46	3.00	20.8

Table 3.7: Relative k_2 values for 1,3-DCA reaction of **1a** and **2** at different temperatures

S. no.	Temp. °C	LiCl (2 M)	KCl (2 M)	CaCl ₂ (2 M)
1	25	1.152	1.319	1.114
2	35	1.027	1.057	0.416
3	45	0.411	0.450	0.114
4	55	0.043	0.058	0.026
5	65	0.016	0.206	0.143

azide to the surface, more was the crowding at interface. This reduced the effective and active surface area for catalysis at the oil-water interface. Henceforth, it was CaCl₂ in which maximum salting out of the reactant was observed and upon heating maximum dissolution of excess **1a** was inevitable. The medium turned into a homogenous from a heterogenous one for CaCl₂ and this lead to reduction in the rate constant of the reaction. A similar effect was observed for LiCl and KCl too although the effect was less pronounced as compared to CaCl₂ salt. The sequence observed was in accordance of Hofmeister series with CaCl₂ having the highest charge/size ratio followed by LiCl and then by KCl. The influence of charge/size ratio of the cations on the oil-water interface is inevitable from the present study. Although due to the absence of precise experimental techniques it is difficult to reach a conclusion but the observations are undoubtedly interesting and challenging.

3.2.4.4 Critical concentration and hydrophobicity

Although heterogeneity is an essential criteria for rate enhancements of ‘on-water’ reactions, it is difficult to deny from the fact that every reactant has a critical solubility which is a characteristic of the moiety. **1a** too has a critical solubility at which interfacial rate enhancement is observed. Above critical concentration, steric crowding of reactant is observed which can be a detrimental factor in the desired rate enhancements. For a bare and active interface an optimum concentration of reactant is required in a heterogenous media. With the limitation of availability of precise experimental techniques, right now it is difficult to develop a scale for an optimum concentration required for exemplary interfacial rate enhancements. Nevertheless, present experiments and observation strengthen the concept of a ‘critical concentration’. Hydrophobic acceleration of reaction at the interface is inevitable, but the effect is guided by the optimum concentration of the reactants. Beyond a limit, when the oil-water interface is crowded, hydrophobic effect fails. This reconfirms the earlier observation that for catalysis at the interface, active free surface area of contact is very important. Upon steric crowding the interfacial area of contact is reduced and it leads to reduced rates constants of the reaction.

3.2.5 Conclusions

Phenyl azide is a very unique aromatic compound since it was observed to show inverse solubility effect up to 55°C. This can be attributed to the negative heat of solution (due to freezing of water molecules) up to 55°C. Heating of the solution drives the reaction in the backward direction *i.e.* solubility of **1a** is reduced in the system. When 1,3-DCA is carried out in between **1a** and **2**, a maximum is seen in the rate constant graph which can be correlated to the minimum in the solubility graph. This observation reconfirms that heterogeneity is an essential criteria for interfacial catalysis of reactions. By carrying out the reaction in moiety such as **1a** (showing anomalous solubility), the role of solubility in heterogenous reactions has been further emphasized upon. The temperature dependent study of hydrophobic effect on the

3. Hydrophobic Contribution at Oil-Water Interface

reaction emphasizes on the fact that the presence of bare and active interface is very important for the attainment of an effective reactive rate. The results give an insight into the fact that the presence of prohydrophobic salts can effect a reaction taking place at the interface in a complex manner.

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Chapter 4

A Physico-Organic Investigation of Interfacial Benzoin Condensation

Preamble



The present chapter deals with the investigation of overall kinetics of condensation of benzaldehyde to benzoin with the aim to develop a better understanding of the change in reactivity of the interfacial reaction in the presence of co-solvents. A key aspect of the ‘on-water’ reaction is the chemistry between solvent and reactants that occur at the oil-water interface. In particular, the orientation of water molecules at the interface plays a key role in catalyzing the reaction. An initial increase in the rate constants of reaction and later a sharp fall, with respect to the co-solvent composition, is evident in the present study.

“Water is life’s matter and matrix, mother and medium. There is no life without water.”

-Albert Szent-Gyorgyi

4.1 A kinetic investigation of interfacial Benzoin Condensation

4.1.1 Introduction

Most organic reactions for carbon-carbon bond formation are polar, involving formation of a covalent bond between an electrophile with a nucleophile. The umpolung strategy, switching the polarity of functional groups, is an interesting approach for organic synthesis. A typical example of an umpolung reaction is Benzoin condensation reaction.¹ The condensation has long provided physical-organic chemist with an excellent example of selective catalysis. Henceforth, it was one of the early known reactions subjected to kinetic study.

4.1.2 Historical perspective of Benzoin Condensation

In 1832, the cyanide-catalysed condensation of benzaldehyde was accidentally discovered by Liebig and Wohler upon treating bitter almond oil (a mixture of HCN and benzaldehyde) with KOH.² The scope of this cyanide catalysed reaction however was quite narrow since many of the substituted benzaldehyde were unreactive under these conditions. It nearly took 100 years until T. Ukai, R. Tanaka and T. Dokawa discovered that this reaction can also be catalysed by ethylthiazolium bromide in presence of a base.³ In 1903, Lapworth proposed the mechanism of the reaction involving cyanohydrin intermediate for the cyanide-catalysed Benzoin condensation reaction.⁹² One of the earliest kinetic studies was reported by Bredig and Stern who proposed that the reaction is second order in benzaldehyde and first order in cyanide ion.⁹³ In 1971, Schowen and co-workers performed an experimental investigation of the kinetics of Benzoin condensation and reconfirmed the mechanism of the reaction proposed by Lapworth through examining its components step by step.⁴ During the course of investigation, Breslow observed that thiamine was able to catalyze the Benzoin condensation.⁵ They observed that Benzoin condensation was 200 times faster in water as compared to ethanol solution. Among the plausible forces, hydrophobic

acceleration was found to be an important factor. To study the hydrophobic forces, effect of inorganic salts on the rate of aqueous cyanide catalyzed Benzoin condensation was examined by the authors. Some of the salt such as LiCl was found to accelerate the rate of reaction while some salts such as LiClO₄ were found to decelerate it.⁵¹ The divergent effects were proposed to exist from hydrophobic packing of the transition state of the reaction. Additionally, the effect of solubility of benzaldehyde on the rate of the reaction was also compared in different solvents such as *n*-propanol, ethanol, 1,4-butanediol etc. A plot of the free energy of solubility of benzaldehyde in the presence of co-solvents *vs.* free energy effect on reaction rate was linear. This confirmed that co-solvents were affecting the solvation of the hydrophobic surface of the reactant. With this observation, they interpreted that in the transition state two phenyl rings overlap each other. However, the use of cyanide for carrying out the reaction demanded extreme precautions. Later on K. B. Wilberg in their investigations using kinetic isotopic effects, observed some inconsistencies in the mechanism proposed by Lapworth and proposed a new one.⁶

4.1.3 Motivation behind work

Although several reports are available in the literature of cyanide-catalysed Benzoin condensation, the need for environmentally friendly and safer way of carrying out the reaction is still in demand. A few reports describe the preparation and usage of thiazolium based catalyst for carrying out C-C bond formation reaction. In view of the fact that, in principle, thiazolium salts return to their original state after reaction is over, makes them ideally suited for development as a novel catalyst for C-C bond formation reaction in a strategic way. Although the detailed mechanism of this reaction has been the subject of numerous investigations,⁷ very few studies deal with the overall kinetics of the Benzoin condensation.⁹⁴ Till date Benzoin condensation reaction has been reported for homogenous reaction conditions. Moreover, it will be quite interesting to investigate the interfacial catalysis of thiazolium catalysed Benzoin condensation reaction. For the understanding of how reaction occur at the interface and what are the possible driving forces, one of the fundamental approach

will be to take a reaction as simple as Benzoin condensation which is already known to exhibit the hydrophobic packing of the transition state in homogenous conditions and to observe how reaction dynamics changes at the interface. Addition of co-solvents can act as an investigating tool to analyse the hydrophobic forces. Co-solvents will affect not only the polarity of the medium but can also influence the solvation pattern of the reactant in the media. In the past water–alcohol mixtures have been employed extensively as mechanistic tools to study the origin of hydrophobic acceleration of organic reactions.⁸ These mixtures appeared to be potential solutions for the chemist’s dilemma of using water as a solvent media. Surprisingly, in all the previous studies, the concentration of the reactants in the kinetic analyses using water–alcohol systems was kept low enough to maintain complete homogeneity. The reaction of a typical ‘on-water’ system to the addition of alcoholic cosolvents and the resultant transition from heterogeneous to homogeneous reaction conditions, although of much significance, has not been systematically studied. In the present work, the effect of addition of increasing amounts of alcoholic co-solvent on the reactivity of interfacial Benzoin condensation reactions has been studied.

4.1.4 Experimental section

Materials: **1** (Scheme 4.1) with >99.5% purity obtained from M/S Sigma Aldrich was distilled prior to its use. **4**, **5** both with the purity > 99% and **3** with 99% purity were obtained from M/S Sigma Aldrich and were used as such. The solvents were obtained from Merck Germany and used as obtained. Deionised water was used for carrying out all the experiments.

4.1.5 Synthesis of benzoin

The synthesis was carried out by a standard procedure with little modifications.⁵⁰ The reaction was started by adding 5 ml of freshly obtained **1** (5g, 0.05 moles) to a 250 ml three necked round-bottomed flask containing 6.25 ml of 95% ethanol, 5 ml of deionised water, **3** (0.5 g, 2 mmol), **4** (0.5 g, 5 mmol) and **5** (0.16 g, 1 mmol). The

reaction mixture was refluxed for 2 h under inert conditions. After 2 h of stirring, the reaction mixture was cooled to room temperature. After cooling, it was washed with deionised water (3-4 times) and was filtered with a suction funnel. The crude obtained was recrystallised from 95 % ethanol. White crystals of benzoin obtained (yield = 80%) were further characterized by ^1H NMR spectra.

4.1.6 Kinetic measurements

The reaction was initiated by the addition of freshly obtained 0.39 ml of **1** (0.39 g, 0.003 mol, 0.37 M) to a vigorously stirred aqueous solution containing 0.3 ml (2 mmol, 0.2 M) of **4**, 0.04 mg (0.0003 mmol, $\mathbf{3} \times 10^{-5}$ M) of **5** and 0.001 mg (4×10^{-6} mmol, 4×10^{-7} M) of **3** in 10 ml of the solvent. The resulting solution was heterogenous. The various compositions of binary mixtures were prepared on the basis of volume fractions (% v/v). The temperature was maintained by Julabo constant temperature bath maintained at 25 °C with an accuracy of $\pm 0.01^\circ\text{C}$. The progress of the reaction was monitored by withdrawing 5 μl of reaction mixture and diluting it in 5 ml of water. The diluted sample was then injected for UV analysis by Cary 50 UV-Visible spectrophotometer. The reaction was monitored by measuring the fall in the concentration of **1** at 250 nm. The slope of $x/a(a-x)$ *vs.* time plot gave the desired k_{2app} , where x denotes product concentration at time t and a denotes initial concentration of 1. Measurement of actual rate constants is not possible due to the uncertainty in the actual concentration of 1 at the interface. So rate constants measured are apparent and not real ones. Experiments were conducted in triplicates. All the reactions were monitored before 15% conversions. The k_{2app} values were reproducible to within $\pm 3\%$.

4.1.6.1 Solubility measurements

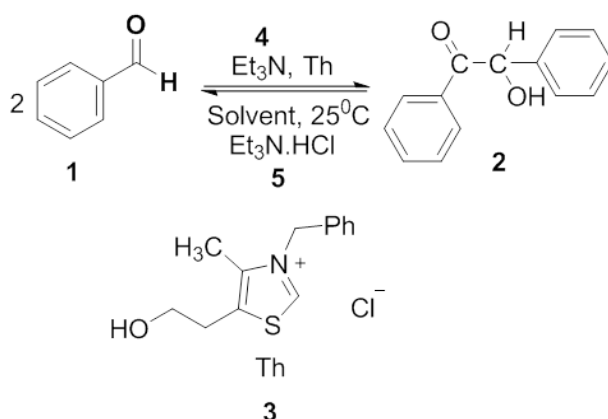
The solubility was determined by equilibrating **1** in the desired binary mixture at 25°C for 3 h. The temperature was maintained by a Julabo constant temperature bath. After 3 h of vigorous stirring followed by 1 h standing, lower phase (0.03 ml) was

taken out and was diluted in 5 ml of water. The concentration of **1** was determined by Cary-UV 50 spectrophotometer at 250 nm in water, 248 nm in methanol, 246 nm in ethanol, 255 nm in formamide, 242 nm in 1-propanol and 240 nm in *n*-butanol (the λ_{max} may change slightly with the change in the solvent composition of the binary mixture). The concentration of **1** in pure water was found to be 0.08 M. The concentration was measured relative to a prepared standard in the same solvent. For example the standard solution for the solubility measurements of water-methanol-**1** was water-**1** solution with identical conditions. Triplicate measurements were carried out and the reproducibility of the solubility measurements was $\pm 6\%$.

4.1.7 Results and discussion

The condensation of benzaldehyde (**1**) to benzoin (**2**) (Scheme 4.1), with triethylamine (**4**) as a base and 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride (**3**) as a catalyst has been carried out in varying composition of co-solvents in water. Et₃N.HCl (**5**) acts as a buffer. Our attempts of carrying out the reaction in other aldehydes like *p*-nitrobenzaldehyde, *p*-methoxybenzaldehyde and *p*-chlorobenzaldehyde were thwarted due to the very slow kinetics of the reaction.⁹

The co-solvents used for the analysis were dimethyl sulfoxide, formamide, methanol,



Scheme 4.1: The investigated Benzoin condensation reaction

ethanol, 1-propanol and *n*-butanol. Not surprisingly, very few studies for interface

have been reported so far.¹⁰ The apparent second order rate constants, k_{2app} , are plotted against the composition of co-solvents as shown in Figure 4.1. Interestingly, the k_{2app} showed an initial increase at low composition, followed by a fall at higher composition of co-solvents. The changes of the k_{2app} of Benzoin condensation in binary mixtures of water and co-solvents are characterized by critical compositions of water, which separates two distinct ranges of solvent composition.

4.1.7.1 The water-rich media

In this range (90% to 100% composition) there is an initial rise at 90% composition followed by fall in the k_{2app} of the reaction for methanol, ethanol and formamide. With addition of co-solvents, the microenvironment around reactants changes as compared to the bulk solution. Also, compared to the surface of pure liquids, the surfaces of binary mixtures are far more complicated. Vibrational Sum Frequency Generation technique (VSFG) has been extensively used to explain the effect of various co-solvents on the orientation of molecules at the interface¹¹ The VSFG study has shown that there is an initial increase in the most probable angle between H₂O dipole and surface normal (up to mole fraction=0.059) and at higher concentrations (mole fraction = 0.11) the angle declines.¹² This indicates enhancement in surface characteristics of water at lower concentration of co-solvents and the decline in the orientations of interfacial water molecules at higher concentrations. SFG signals obtained from binary mixture are much larger than pure solvents too. As alkyl chain length increases, the maxima shifts to lower composition and become more pronounced too. At low composition, maintaining the strong H₂O-H₂O hydrogen bonding network is the deciding force in determining the interfacial structure and reactivity. Benzoin condensation involves charged intermediates, henceforth more structured and hydrogen bonded water surface can stabilize the charged species more effectively, leading to higher k_{2app} of the reaction. Formamide can also stabilize the charged intermediates by hydrogen bonding. Moreover, at higher composition there is a decrease in the number of properly oriented interfacial water molecules leading to reduction in the extent of stabilization of the charged species. This can be the reason for observation of a fall in the k_{2app}

of the reaction.(Table 4.1) Second very prominent zone that was visible encompasses range from 70% to 100% composition of water. This region also exhibits an initial increase and then a decrease in the k_{2app} of the reaction. For both 1-propanol, DMSO the maxima are at 70% and for *n*-butanol it is at 80% composition. The initial rise in the k_{2app} can be due to the enhanced water characteristics at lower composition of such solvents. The shift in the maxima to higher composition of co-solvents for 1-propanol, DMSO and *n*-butanol as compared to that of methanol, ethanol and formamide can be attributed to hydrophobic acceleration imparted by former solvents. Lower maxima of the k_{2app} for *n*-butanol may be attributed to different solubility of **1** in the solvent. *n*-butanol, a relatively less polar among the investigated solvents, can dissolve a higher concentration of hydrophobic **1**. Henceforth, with the addition of relatively small amount of *n*-butanol the reaction could reach the maximum k_{2app} followed by homogenisation. Increasing the concentration of co-solvents results in reaction becoming less hydrophobically accelerated, so the fall is observed. Another interesting observation is the trend in the k_{2app} of the reaction for different solvents (for 70% to 100% composition):

formamide > methanol > ethanol > 1-propanol > DMSO > *n*-butanol

Minimum k_{2app} was observed for *n*-butanol. Surprisingly, the trend correlated precisely with the $E_T(30)$ value of the solvents. Clearly, formamide is the most polar one followed by methanol, ethanol, 1-propanol than DMSO and *n*-butanol. More polar solvent stabilizes the charged intermediates effectively and yield higher k_{2app} of the reaction.

4.1.7.2 The alcohol-rich media

This region comprises composition range between 40 to 70% of co-solvents in water. At higher composition, the interface vanishes at a particular composition (characteristic of a particular solvent), and the medium behaves as a homogenous one. In such a situation, the medium loses its aqueous character and the intermediates of the reaction are actually preferentially solvated by co-solvent molecules. At higher composition,

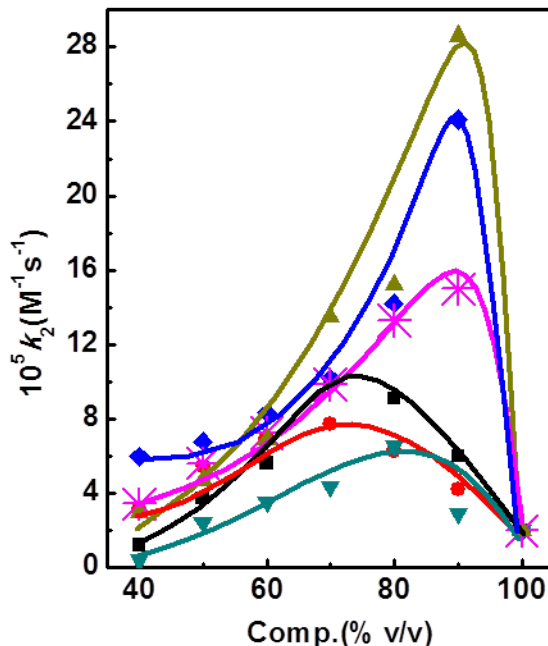


Figure 4.1: The plots of k_{2app} *vs.* composition of co-solvents in water for (\blacktriangle) formamide, (\blacklozenge) methanol, ($*$) ethanol, (\blacksquare) 1-propanol, (\bullet) DMSO and (\blacktriangledown) *n*-butanol. k_{2app} (in pure methanol) = $6.44 \times 10^{-7} \text{ M}^{-1}\text{s}^{-1}$ and k_{2app} (in pure water, heterogenous condition) = $2 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$.

formation of dynamic clusters of the solvents is observed which can preferentially solvate the reactant and the intermediates. However, the extent of stabilization rendered by co-solvents is always less as compared to that of water. Hence, beyond a particular limit the medium starts behaving as a normal homogenous media. The ‘on-water’ reaction disappears and consequently reduction in k_{2app} is observed. The observed maxima can be described as a characteristic composition for the departure of the complex heterogenous reaction media to a homogenous one. On an average after 70% composition, the reaction kinetics is driven by presence of co-solvents as these are the predominant species present in the medium. In addition to the observed decrease in the k_{2app} of the reaction in alcohol-rich zone, the trend observed is also quite intriguing. (Table 4.1)

Unlike water-rich zone where the reaction dynamics is being controlled by polarity of the binary mixture, the alcohol-rich mixtures show a completely different trend to be explained. The k_{2app} values observed follow the trend as:

Table 4.1: Relative rate constant k_{rel} (with respect to water) for aqueous salt solution of **1a** with **2** at 298K; $k_{rel} = k_2$ in presence of salts/ k_2 without salt.

% v/v	$10^5 k_2 (\text{M}^{-1}\text{s}^{-1})$					
	1-propanol	DMSO	methanol	<i>n</i> -butanol	ethanol	formamide
100	2.0	2.0	2.0	2.0	2.0	2.0
90	6.0	4.2	24	2.9	15.0	28.6
80	9.1	6.5	14	6.2	13.3	15.2
70	9.0	7.7	10	4.3	9.8	13.5
60	5.6	7.1	8.3	3.5	7.5	6.9
50	3.7	5.4	6.8	2.4	5.6	4.7
40	1.2	3.2	6.0	0.4	3.4	3.0

Table 4.2: Relative solubility, S/S_0 (solubility in presence of co-solvents/solubility in absence of any co-solvents) of benzaldehyde, 1.

% v/v	S/S_0					
	DMSO	formamide	<i>n</i> -butanol	ethanol	methanol	1-propanol
100	1.0	1.0	1.0	1.0	1.0	1.0
90	2.68	2.76	4.96	1.38	1.07	3.31
80	3.43	4.23	7.50	3.0	1.28	4.96
70	5.07	6.28	8.48	4.31	1.53	7.30
60	6.68	7.83	10.13	4.83	2.10	9.14
50	7.82	9.38	11.36	6.21	2.39	10.40
40	8.20	10.04	11.78	7.03	2.45	11.31

methanol > ethanol > DMSO > formamide > 1-propanol > *n*-butanol

Unexpectedly, the trend cannot be correlated to the one observed for the water-rich zone. It was observed that the binary mixture in which the reaction was more hydrophobically accelerated was the one which had maximum k_{2app} . In simpler terms, the media in which the reactants showed maximum solubility was the one with minimum k_2 of the reaction. This interpretation is in accordance of Engberts statement

that heterogeneity is an important criteria for ‘on-water’ reaction.¹³ Linear Solvation Energy Relationship, which is an important scales for understanding and interpreting solvent behaviour, was also tried as an investigating tool.¹⁴ However, our attempt failed due to the complex intricacies of the oil-water interface.

4.1.7.3 Solvent polarity and hydrophobicity

Co-solvents not only enhance the solubility of reactants but can also decrease the polarity of medium. For the delineation of hydrophobic forces in a heterogenous media, the study of solubility is very important. At low composition of co-solvents, S/S_0 of **1** was found to be comparatively less. As already discussed, observed k_{2app} (water-rich zone) is satisfactorily explained by the $E_T(30)$ of the binary mixture. We then attempted to correlate k_{2app} with the hydrophobic contribution of co-solvents. Accordingly, S/S_0 of **1** in mixtures were measured and found to follow the trend as (Table 4.2 and Figure 4.2):

n-butanol > 1-propanol > formamide > DMSO > ethanol > methanol

However, in water-rich zone the observed sequence of k_{2app} is:

formamide > methanol > ethanol > 1-propanol > DMSO > *n*-butanol

There was no correlation between the S/S_0 of **1** and k_{2app} in the water-rich zone. Moreover, for alcohol-rich zone, a good correlation of k_{2app} with S/S_0 of **1** was observed. The k_{2app} obtained after 70% composition were as follows:

methanol > ethanol > DMSO > formamide > 1-propanol > *n*-butanol

The above trend observed was opposite to that of S/S_0 . Quite strikingly and vice versa to the water-rich zone, an increased solubilization led to the diminished ‘on-water’ effect in alcohol-rich zone. The reaction becomes less hydrophobically accelerated with the increase in the alkyl chain length of the monohydric alcohols. So, unlike previous examples¹⁵ available in the literature for homogenous system, the analysis seems to be complicated. Moreover, there are reports that hydrophobic

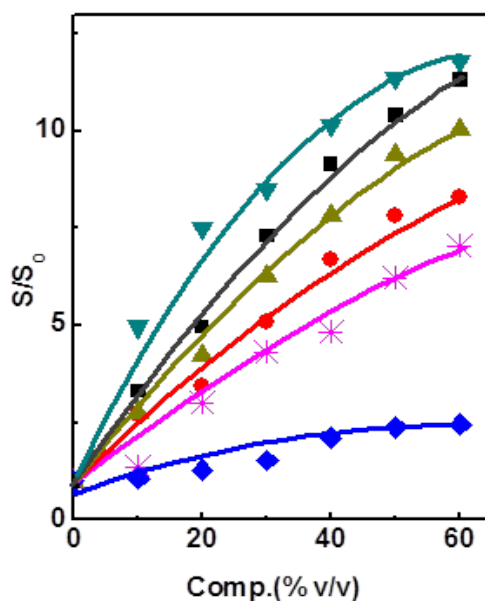


Figure 4.2: The plots of S/S_0 *vs.* composition of co-solvents in water for (▲) formamide, (◆) methanol, (*) ethanol, (■) 1-propanol, (●) DMSO and (▼) *n*-butanol.

acceleration of reactions comprising ‘on-water’ reactants is fundamentally different from that of reactions with small non polar solutes in a homogenous media.²⁵ In the initial phase of addition of co-solvents, the reaction is driven and dominated by the polarity effect. However, at higher composition of co-solvents the reaction media becomes homogenous and is hydrophobically accelerated. Dependency of the k_{2app} and S/S_0 values on composition is shown in Figure 4.3 and 4.4. This demonstrates the combined participation of the three important characteristics of solvent media, the area divided in between the effective force by a critical composition of the binary mixture.

Although, performing organic reactions in water of water-insoluble compounds, as benzaldehyde, appear counterintuitive but this investigation has proved that examining such heterogenous reaction is a worthwhile endeavor. ‘On-water’ Benzoin condensation is observed to be faster as compared to in-water reactions. The controversy regarding the responsible forces for enhancement in the rate of ‘on-water’ reaction has been although partly but judiciously resolved in the present work. The forces existing

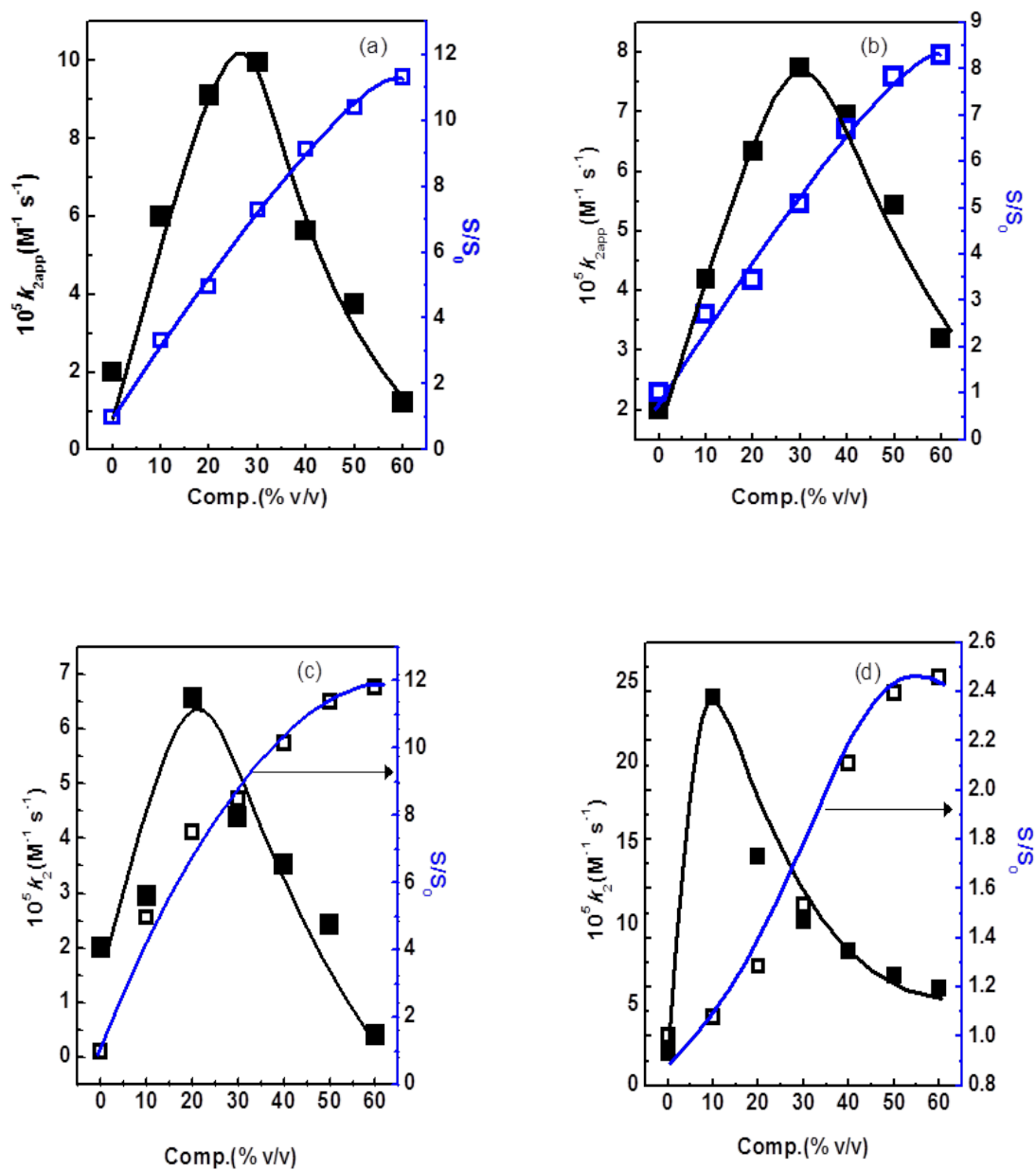


Figure 4.3: The plots of k_{2app} (■) and S/S_0 (□) *vs.* increasing composition (% v/v) of co-solvents for (a) 1-propanol (b) DMSO (c) ethanol (d) formamide.

at the interface has been found to be a function of % v/v of co-solvents composition. The interfacial forces can be tuned by controlling the percentage composition of the binary mixture employed for carrying out the experiment. The present work brings out the fundamental difference between contribution of polarity, hydrogen bonding and hydrophobicity on interfacial Benzoin condensation reaction. Henceforth, the ques-

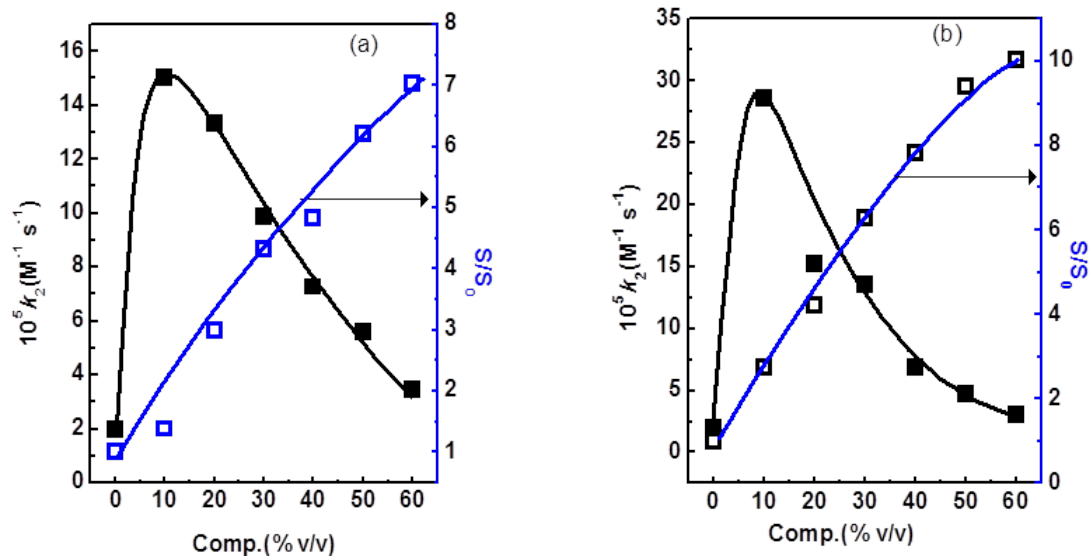


Figure 4.4: The plots of k_{2app} (■) and S/S_0 (□) *vs.* composition (% v/v) of co-solvents for (a) *n*-butanol (b) methanol.

tion raised in the beginning (a) the comparative analysis of ‘in-water’ and ‘on-water’ reactions (b) delineation of the plausible forces responsible for the ‘on-water’ effects has been appropriately addressed by careful selection of experimental conditions. The reaction was much faster in water as compared to other conventional organic solvents. Thus the question raised in the beginning has been appropriately addressed by the selection and investigation of interfacial Benzoin condensation reaction.

4.1.8 Conclusions

In conclusion, our report suggests that there are more than one factor that contributes to the ‘on-water’ Benzoin condensation reaction in a complex manner. At lower concentrations of co-solvents, the reaction is dominated by polarity and hydrogen bonding effects. Initial rate accelerations are correlated with increasing solvent polarity. Such rate accelerations in the present case of the ‘on-water’ Benzoin condensation are derived from the potential of interfacial water to stabilize the polar transition state and intermediates. However, at higher concentrations the reaction is mainly governed by the hydrophobic effects, as these effects are pronounced only at higher concentrations of co-solvents. Existence of a ‘critical composition’ for each of

the investigated aqueous binary mixture has been proven at which there is a transition of reaction site from interface to the bulk solution. Nevertheless, with this understanding the future designing of reactions for carrying ‘on-water’ reactions can be obtained in a more rational way.

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Chapter 5

Kinetic and Mechanistic

Investigations of BHR in ILs

Preamble



The present chapter includes an extensive and quantitative study of the kinetics and mechanism of BHR in ILs used as a solvent media. Section 5.1 deals with the kinetic study in a range of ILs where it has been observed that the rate determining step of the reaction is second order in aldehyde while first order in methyl acrylate and DABCO. Section 5.2 deals with an extensive investigation of the reaction which stresses that apparently, a simple BHR can occur by two different exclusive mechanisms in ILs. The delicate balance among these mechanisms is maintained by the ionic environment employed.

“How can something so necessary to life so completely elude the mass consciousness?”

-Judy Beebe

5.1 Investigation of mechanism of BHR in ILs

5.1.1 Introduction

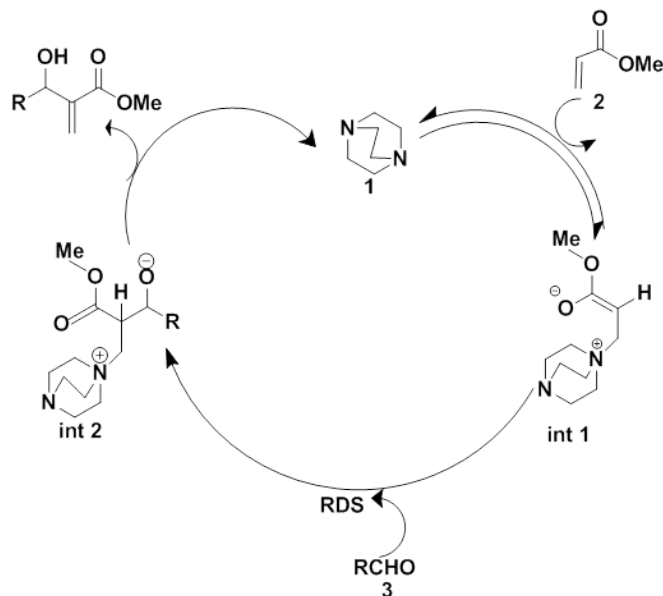
Organic synthesis is one of the most successful and useful disciplines of science. The strategies regarding construction of C-C bond forms a central theme in organic synthesis. Therefore, the development of such strategies still represents the forefront in science. The present day synthetic organic chemistry mainly requires atom economy, operationally useful and simple C-C bond forming reactions. The most significant ones are Aldol reaction,¹ Wittig reaction,² Reformatsky reaction,³ Claisen rearrangement,⁴ Friedal-Crafts reaction,⁵ Diels-Alder reaction,⁶ BHR etc⁹⁶. Out of these chemical transformations, BHR simplifies the process of assembling a carbon framework, which involves creativity, originality, intellectual input and hence is a very promising reaction.

5.1.1.1 Origin and growth

The origin of BHR dates back to 1972 to a German patent filed by A. B. Baylis and M. E. D Hillman.⁹⁶ It is basically a three component reaction involving the coupling of α -position of activated alkene and carbon electrophiles in presence of tertiary amines giving rise to multifunctionalized product. Although this reaction is promising and fascinating, the reaction has missed the attention of chemists for centuries. It was only in 1980's that chemists started looking at this reaction from a new perspective. After the demonstration of synthesis of many important natural products by Drewes and Emslie in 1982⁹⁷ and by Hoffmann and Rabe in 1983,⁹⁸ the chemist became interested in the reaction. The exponential growth and importance of the reaction is evident from the plethora of reports available in the literature.⁷

5.1.1.2 Mechanism

Undoubtedly, BHR is one of the most powerful and versatile C-C bond forming reactions in organic synthesis. Despite the fact that BHR was first described some 40 years ago, the debate still continues in the scientific community regarding the exact



Scheme 5.1: Mechanism of BHR as proposed by Hill and Isaacs.

reaction mechanism and the kinetics of this important reaction.⁸ In 1983, Hoffmann was the first to propose a mechanism for the BHR.⁹⁸ In 1990, Hill and Isaacs have proposed a mechanism based on pressure dependence, rate and kinetic isotope effect.¹⁰⁰ They proposed that α -proton cleavage was not taking place in the rate determining step of the reaction. A kinetic study of the reaction between acetaldehyde and acrylonitrile was followed and the rates observed depended linearly on the first power of each concentration, confirming the empirical rate expression as:

$$\text{rate} = k_3[\text{MeCHO}][\text{ACN}][\text{DABCO}]$$

Based upon these studies they proposed the mechanism of the BHR to be proceeding in three important steps as (a) Michael addition, involving attack of a base on an activated alkene, forming an enolate (b) nucleophilic attack of the enolate on an aldehyde (c) proton transfer and the elimination of base resulting into product formation (Scheme 5.1). Although, global mechanistic pathway of the reaction proposed by Hill and Isaacs is widely accepted today, the controversy regarding the rate determining step of the reaction is still the focus of many discussions on fundamental understanding of the reaction. Later, Bode and Kaye, using acrylates also supported

Hill and Isaacs mechanism.¹⁰¹ A significant contribution was due to McQuade and co-workers who discovered a new pathway of the reaction.¹⁰² Surprisingly, they observed that when the reaction was carried out in polar aprotic solvent as DMSO, a new mechanism was operating based on hemiacetal intermediate. The reaction showed second order dependence on aldehyde concentration. Although the report was quite intriguing, the mechanistic investigation of the reaction in a varied range of solvents is still less studied. Henceforth, the inquisitiveness regarding the reaction still persists and attracts further investigations into the physico-organic and mechanistic aspects of the reaction in different solvent media.

5.1.2 Definition of problem

It is evident from the literature analysis that there are different views on the mechanism of BHR. The lack of extensive experimental proof is the basis for disagreement in the mechanism of reaction. Together with these issues and our continued interest in the use of environment-benign media prompted us to explore the kinetics as well as mechanistic aspect of the BHR. Recently, ILs have been employed as a solvent media for catalyzing many important organic reactions.⁹ ILs possess many interesting properties such as wide temperature window, negligible vapour pressure, recyclability etc. which make them different from other conventional solvents and facilitate attributes which are of fundamental interests to chemists. An ionic liquid consists of cation and anion, either of which or both may interact with the reactants and affect the course and outcome of the reaction. BHR has also been carried out in ILs. There are reports describing acceleration of DABCO catalysed BHR in imidazolium based ILs.¹⁰ However, undesirable side reactions were observed in imidazolium salts, with a hydrogen substituent at C-2 position, which were deprotonated under mildly basic conditions.⁸¹ This undesired reaction were partly overcome by the application of C-2 substituted imidazolium salts for carrying out BHR.¹¹ Efficient catalysis with good yield and reduced reaction times were reported for pyridinium based ILs too.¹² However, the need of application of efficient ILs for carrying out BHR still stimulates a continuous research effort.

5.1.3 Experimental section

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

5.1.3.1 Synthesis of ILs

All ILs were synthesized by the reported methods.

Synthesis of ethylsulfate-based ILs¹³

To an ice cold solution of pyridine (6 mmol) in 10 ml of toluene, the drop-wise addition of diethyl sulphate (6 mmol) was carried out in an inert atmosphere. Temperature was never allowed to rise above 40°C. After 4h of stirring, upper organic layer was removed by decantation, the remaining solvent was removed in vacuo and was further dried under reduced pressure for 12h. Similar procedure was followed for synthesis of other ethylsulfate-based ILs.

Synthesis of NTf₂-based ILs¹⁴

The synthesis involved two steps: a) quaternization: to a stirred solution of slightly excess (10%) of haloalkane (17.5 mmol), 1-methylpyrrolidine (14.6 mmol) was added. The reaction mixture was then refluxed for 12h and the temperature was not allowed to rise above 70°C. The unreacted starting material was removed by washing with ethyl acetate 3-4 times and the excess solvent was removed by rotary evaporator. The compound was further dried under reduced pressure, and b) metathesis: To a stirred solution of Lithium bis(trifluoromethane)sulfonimide (10 mmol) in deionised water, halogenated product (10 mmol) of step 1 was added under inert atmosphere. The mixture was stirred for 12 h. The desired product was obtained by repeated extraction

of the reaction mixture in DCM. The collected fraction in DCM was subjected to heating in a rotary evaporator followed by drying under reduced pressure. Similar procedure was followed for synthesis of other NTf₂-based ILs.

Synthesis of [HP][HCOO]¹⁵

This ionic liquid was synthesized by mixing equimolar amount of acid and base. The synthesis was carried out by drop-wise addition of pyridine (25.2 mmol) as a base to a stirred solution of formic acid (25.2 mmol) under ice cold condition. After 8h of stirring, the excess water was removed in vacuo. The ionic liquid synthesized was further dried under reduced pressure for 10h. All the synthesized ILs were subjected to Karl-fisher titrator to estimate the water content to be less than 30 ppm. The halides estimated by Vollhard titration were within the recommended range.¹⁶

Synthesis of BF₄-based ILs¹⁵

The synthesis was carried out by a procedure same as for NTf₂-based ILs. The synthesis involved two steps (a) quaternization: To a stirred solution of 1-bromoethane (17.5 mmol), pyridine was added. The mixture was refluxed for 12h and was then washed with ethylacetate (3-4 times). The product was then properly dried under vacuum. To this halogenated product in DCM, NaBF₄ (10 mmol) was added and the reaction mixture was stirred for 12h. The crude ionic liquid in DCM was filtered and was dried by rotary evaporator. All the ILs synthesized were stored in inert conditions and were characterized by ¹H NMR spectra. The moisture content of the ILs were measured by Karl Fisher titration and was found to be less than 50 ppm. Wherever required, the halide content was also measured by Volhard titration.¹⁶

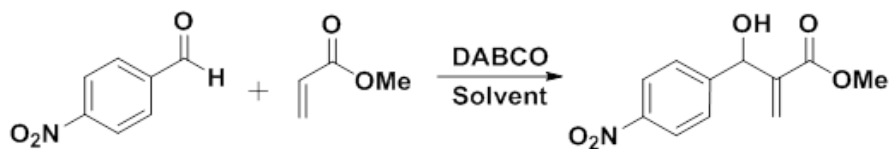
5.1.3.2 Kinetic measurements

The reaction was initiated by adding 0.9028 ml (1M) of methyl acrylate to a stirred solution containing 1 ml of DABCO (1M) and PNB in 1 ml of the solvent. The reaction was monitored with the help of a UV-Visible spectrophotometer and by measuring the disappearance of PNB at wavelength of $\lambda_{max} = 270$ nm. A plot of absorbance

versus concentration gave slope as the rate of reaction. The concentration of PNB was varied from 0.01 M to 0.08 M, keeping the concentrations of DABCO and methyl acrylate as constant. The rates were determined for each concentration of PNB. Order plots were made by plotting the rate *vs.* concentration of PNB. Rate constant were determined from the rate law equation. In order to calculate the rate constants, the concentrations of DABCO and methyl acrylate were constant throughout. Each reaction was carried out thrice. The rate constants were reproducible to $\pm 3\%$. Entire kinetic course was followed before 15% conversion. No byproducts were noted during the reaction.

5.1.4 Results and discussion

We were fascinated with the observation that RDS is second order in aldehyde, when the reaction is carried out in aprotic polar solvent like DMSO. As clear from the previous work, the solvent selected for the reaction has an important role to play in kinetics of organic reactions. To achieve this end, an extensive collection of kinetic data on BHR is essential. The present investigation aims at achieving the same in environment-benign media.¹⁷ The reaction of PNB with methyl acrylate (Scheme



Scheme 5.2: The investigated BHR.

5.2) was carried out in different ILs in the presence of DABCO. The ILs selected for the study included the pyridinium, pyrrolidinium, piperidinium, morpholinium and ammonium-based organic cations, while anions varied as bis(trifluoromethanesulfonyl) imide, formate, tetrafluoroborate and ethylsulfate. The kinetic results are summarized in these ILs are shown in Table 5.1. The reaction was first carried in [EtP][NTf₂] and [OMPyr][NTf₂] for which the rates *vs.* concentration of PNB, [PNB], are plot-

ted in Fig. 5.1 (a) and (b), respectively. A straight line was obtained indicating the order of the reaction, n , to be unity. Similar plots yielding $n=1$ were obtained, when the reaction was carried out in other ILs like [HMPyr][NTf₂], [HP][HCOO] and [BP][NTf₂]. Very interestingly, as shown in Table 5.1, the reaction showed order of the reaction, $n=2$ in [EtP][EtSO₄], [EtPip][EtSO₄], [EtMo][EtSO₄], [(Et)₄N][EtSO₄] and [EMIM][EtSO₄]. The plots of the rates are given in Fig. 5.2. We tried to investigate the reaction in 1-ethyl-pyridinium tetrafluoroborate, [EtP][BF₄] too to check the effect of anion while keeping the cation common. The linear relationship between rate and the concentration of aldehyde showed that anion played role in deciding the order of reaction. As seen from the data listed in Table 5.1, no influence of cation of ionic liquid was observed on the order of the reaction. Our efforts to measure the kinetics of this reaction in many ILs containing [BF₄]⁻ and [PF₆]⁻ species were not successful due to their high viscous behaviour. We then investigated the variation in rates of reaction in the ionic liquid solutions. For this purpose, we carried out the reaction in four different concentrations of [EtP][EtSO₄] prepared in DMF and CHCl₃ with high and low dielectric constants, respectively. The plots (Fig. 5.3) based upon the data obtained show a linear dependence of the rates on the concentrations of the ionic liquid indicating a first-order dependence of the reaction. The rate versus the ionic liquid concentration data for both the solvents were linearly fitted with an average correlation coefficient as high as 0.995 and root mean squares deviation as low as $0.005 \times 10^{-4} \text{ M s}^{-1}$ (Figure 5.3). In addition, to ascertain the role of other two reactants, the rate plots were also drawn against the concentration of methyl acrylate and DABCO. Interestingly, they also demonstrated a straight line with $n=1$ confirming that the reaction in ILs was first in order with respect to both methyl acrylate and DABCO. In order to gain confidence in our methodology, we also repeated the experiments carried out by the group of McQuade¹⁰² in which DMSO was taken as a solvent and obtained excellent agreement between the kinetic data from both the sources. The values of the rate constants, k_2 is higher by about 7-times in [HMPyr][NTf₂] as compared to that in [BP][NTf₂]. Except the imidazolium-based ionic liquid [EMIM][EtSO₄], the maximum k_2 value was obtained in [(Et)₄N][EtSO₄].

Table 5.1: The Names and Acronyms of ILs and the Kinetic Data.

Acronyms	Aldehyde order,n	$k_2(\text{M}^{-1}\text{s}^{-1})$
[OMPyr][NTf ₂]	1	0.034
[HMPyr][NTf ₂]	1	0.054
[HP][HCOO]	1	0.037
[BP][NTf ₂]	1	0.008
[EtP][NTf ₂]	1	0.060
[EtP][EtSO ₄]	2	0.346
[EtP][BF ₄]	1	0.007
[EtPip][EtSO ₄]	2	0.250
[EtMo][EtSO ₄]	2	0.006
[(Et) ₄ N][EtSO ₄]	2	2.81
[EMIM][EtSO ₄]	2	7.45

The k_2 value noted in [EMIM][EtSO₄], though the highest, bears no relevance. It is important to recall the work of Rosa, Afonso and Santos,¹⁰ who reported acceleration of BHR in these ILs. Repetition of the kinetic data in [EMIM][EtSO₄] did not alter the results.

The relative permittivity and polarity data for all the ILs used in this work are not yet available. However, the increasing $E_T(30)$ values of [BP][NTf₂] (50.23 kcal mol⁻¹), [HMPyr][NTf₂] (52.07 kcal mol⁻¹) and [OMPyr][NTf₂] (57.0 kcal mol⁻¹) can be correlated with the rate enhancement as shown in the form of the k_2 values listed in Table 5.1.¹⁸ Since the reaction involves formation of charged intermediates, it is possible that the observed rate increase is supported by an increase in polarity of the media. A clear picture will emerge when the polarity data for different ILs become available in due course. The mechanism of the reaction that RDS is second order in aldehyde in DMSO has been discussed by McQuade and co-workers¹⁰² On the basis of the competition experiments carried out between methyl acrylate and α -2H acrylate, it has been very well established by McQuade and co-workers that cleavage of α -2H bond takes place in the RDS of the reaction. The second order

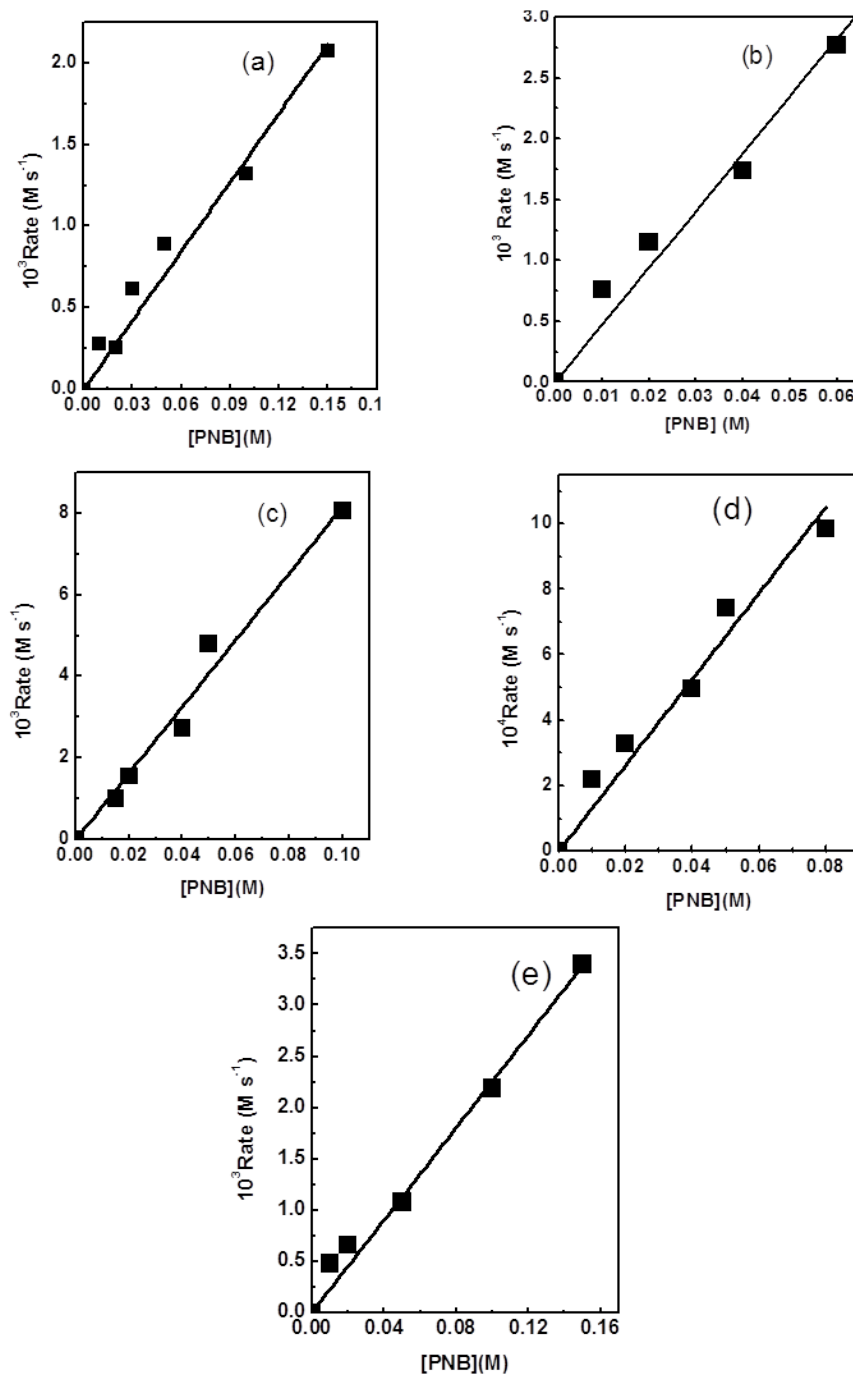


Figure 5.1: The plots of the rate *vs.* the PNB concentration for BHR in (a) $[\text{OMPyr}][\text{NTf}_2]$ (b) $[\text{EtP}][\text{NTf}_2]$ (c) $[\text{HMPyrr}][\text{NTf}_2]$ (d) $[\text{BP}][\text{NTf}_2]$ (e) $[\text{HP}][\text{HCOO}]$.

dependence on the aldehyde concentration has also been confirmed with the help of kinetic investigation and the rate law equations. Accordingly, two equiv. of aldehyde should be participating in RDS rather than one as originally proposed by Hill and

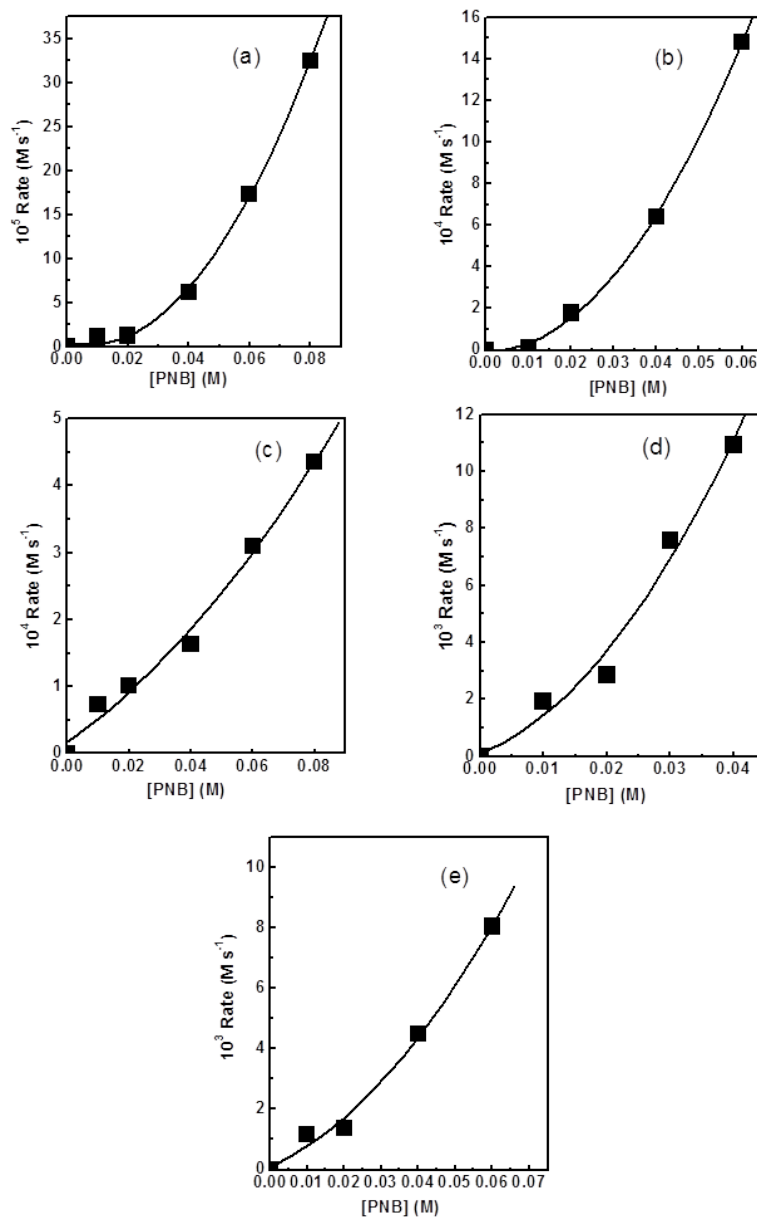


Figure 5.2: The rates as a function of PNB concentration in (a) [EtMo][EtSO₄], (b) [EtP][EtSO₄] (c) [EtPip][EtSO₄], (d) [Emim][EtSO₄], and (e) [(Et)₄N][EtSO₄].

Isaacs.¹⁰⁰ Based upon the experimental observations reported here, we also state and agree that in certain ILs, the similar mechanism (Scheme 5.3) takes place involving two equiv. of aldehyde. The mechanism includes a) the reversible Michael addition, involving the attack of DABCO on activated alkene to form an enolate (zwitterionic species), b) the attack of enolate on the first equiv. of aldehyde in order to give second zwitterionic species, c) formation of a hemiacetal intermediate as a result of the attack

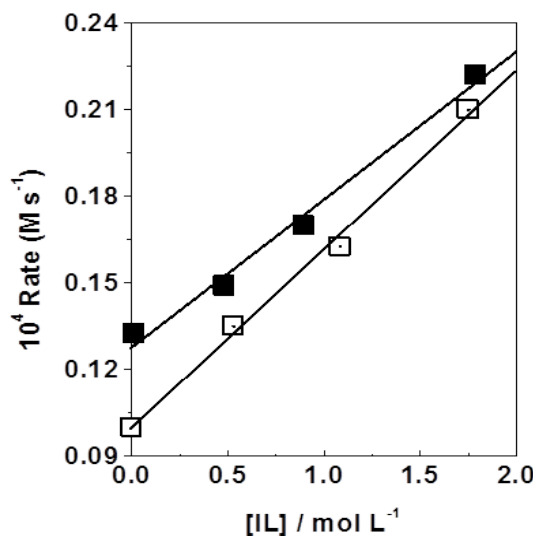
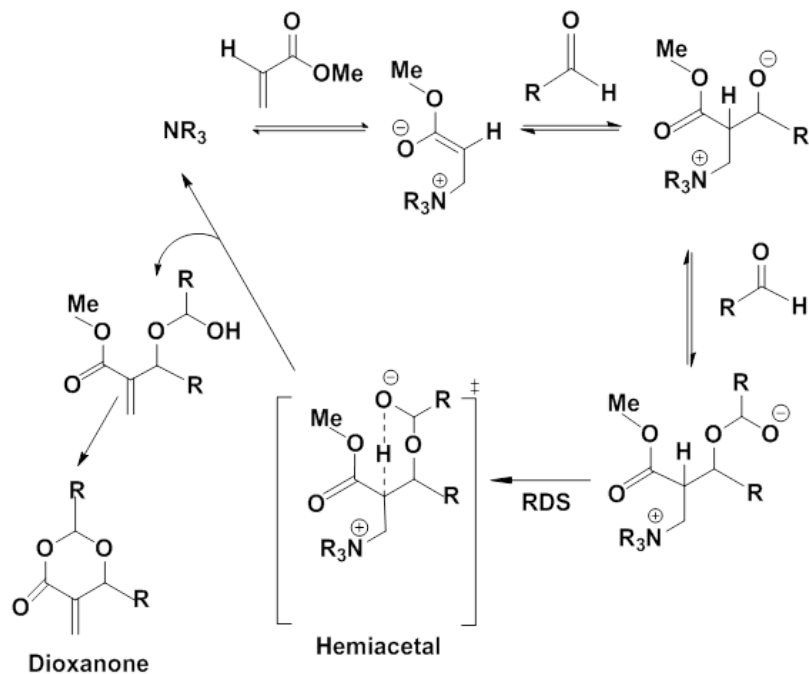


Figure 5.3: The rates as a function of the concentration of $[\text{EtP}][\text{EtSO}_4]$ in (\square) CHCl_3 and (\blacksquare) DMF.

of enolate on the second equiv. of aldehyde, d) transfer of a proton from α -position of alkene to alkoxide (RDS) in this mechanism and lastly e) elimination of the base and the formation of the product. From the above data, it is clear that if the reaction is carried out in the ionic liquid possessing $[\text{EtSO}_4]^-$ anion, the RDS is second order with respect to aldehyde. Both DMSO and $[\text{EtSO}_4]^-$ possess high electron density as evident from the hydrogen bond acceptor ability or basicity denoted by a solvent parameter called β . The β values for DMSO and the $[\text{EtSO}_4]^-$ containing ILs are 0.743 and 0.707.¹⁸ DMSO can solvate or stabilize the cation in general when the reaction is carried out in the presence of DMSO. This preferential solvation of the cation allows the anion to attack equiv. of aldehyde resulting in the formation of an alkoxide anion as discussed above. The developed negative charge can be satisfied by proton transfer from α -carbon leading to an unstable 4-membered transition state. Such a proton transfer is however not favorable in view of geometrical constraints. The electron-rich solvents like DMSO or the ionic liquid containing $[\text{EtSO}_4]^-$ anion, activate the negative charge on oxygen atom on alkoxide in order to attack on second equiv. of aldehyde leading to the formation of hemiacetal intermediate. The proton transfer can now take place from α -position to the alkoxide oxygen *via* a six-membered

Scheme 5.3: Mechanism of BHR as proposed by McQuade *et al.*

transition state. The remaining mechanism is the same involving the elimination of the base and the formation of the product.

5.1.5 Conclusions

Interestingly, the mechanism of BHR in ILs is dependent upon the anion of the ILs used for realizing the reaction. The RDS is second order with respect to aldehyde and follows the similar mechanism as proposed by the group of McQuade.

5.2 Do cation of ILs affect kinetics and mechanism of BHR?

5.2.1 Introduction

BHR offers a promising strategy to construct highly functionalized product with a new stereocentre⁷. The mechanism of BHR is still a debatable issue. It is well known that microenvironment generated by a solvent can profoundly affect a reaction outcome. ILs are made up of cations and anions either or both of which can interact with the reactive species. As concluded from the previous section, anions of ILs can affect the kinetics and mechanism of BHR. In comparison to anion effect, there is paucity of data on the affect of cation of ILs on organic reactions. Tom Welton and co-workers investigated the nucleophilicities of Cl⁻, Br⁻ and I⁻ ion in [bmim][NTf₂], [bm₂im][NTf₂], [bmpy][NTf₂] and observed that changing the cation of ILs was affecting the relative nucleophilicities of halide ions.¹⁹ To thoroughly investigate the role of cations and anions, herein this section, Linear solvation energy relationship (LSER) have been employed as a part of our investigating tool. As per our knowledge, the influence of various ILs on the reactivity of BHR by LSER has not been systematically reported earlier. Herein, we have also investigated the BHR in a variety of solvents with differing cations and anions. In this context the BHR of PNB with methyl acrylate has been carried out in different ILs in presence of DABCO (Scheme 5.1).

5.2.2 Experimental section

1,4-Diazabicyclo [2.2.2]octane [DABCO] with (> 99% purity) and PNB, (> 98% purity) were obtained from M/S Sigma Aldrich company and were used without further purification. Methanol, DCM, toluene, dimethylsulfate, ethyl acetate were used as obtained from Merck Germany. Methyl acrylate was distilled prior to use. 1-morpholine, 1-bromobutane, pyrrolidine, piperidine, 1-methylimidazole, pyridine, Lithium bis(trifluoro -methane)sulfonimide (>99% purity) was used as obtained from

M/S Sigma Aldrich company.

5.2.2.1 Synthesis of ILs

Synthesis of NTf₂-based ILs ¹⁴

The synthesis is reported in the previous section.

Synthesis of [Pyr][HCOO]-based ILs ²⁰

[Pyr][HCOO] was synthesized by mixing equimolar amounts of acid and base. The synthesis was carried out by equimolar and drop-wise addition of pyrrolidine to a stirred solution of 95% (v/v) formic acid solution under ice cold conditions. The excess water was removed in vacuo after stirring for 8h. The synthesized ionic liquid was further dried under reduced pressure for 10h. Other protic ILs based on CH₃COO⁻ and CF₃COO⁻ anions were synthesized by adding the equimolar amounts of pyrrolidine and acetic acid (99.7% v/v) for [Pyr][CH₃COO], pyrrolidine and trifluoroacetic acid (99% v/v) for [Pyr][CF₃COO]. The nitrate-based ionic liquid was prepared by adding equimolar amounts of 70% (v/v) nitric acid to a stirred solution of pyrrolidine in a dropwise manner for 2 h. The temperature was kept below 20°C. Final traces of water were removed under high pressure. Purity of the ILs synthesized was further confirmed by ¹H NMR spectra and agreed well with the literature reports.

Synthesis of HSO₄-based ILs ²¹

Dropwise addition of 1 equiv. of conc. H₂SO₄ to an ice cold solution of 1-octylpyrrolidinium bromide (6mmol, 1 equiv.) was carried out in a 250 ml two necked round bottom flask. The mixture was refluxed for 48 h and HBr formed as a byproduct was distilled out of the condenser. The excess solvent was removed by rotary evaporator followed by drying under reduced pressure. Similar procedure was followed for synthesis of other-HSO₄-based ILs. Purity of the ILs synthesized was further confirmed by a good agreement of ¹H NMR spectra with the reported values.⁵

Synthesis of MeSO₄-based ILs¹³

To an ice cold solution of 1-morpholine in 10 ml of toluene, 6 mmol of dimethylsulfate was added in a dropwise manner. The synthesis was carried out in an inert atmosphere. Temperature was kept below 40°C throughout the experiment. After 4h of vigorous stirring, upper organic layer was removed by decantation, the remaining solvent was removed in vacuo and was further dried under reduced pressure for 12h. The purity of the ionic liquid synthesized was further confirmed by ¹H NMR spectra.

5.2.2.2 Kinetic measurements

The reaction was initiated by the addition of methyl acrylate 0.9028 ml (1 M) to the stirred solution of PNB and 1 ml of DABCO (1M) in a given solvent (Scheme 5.2). The temperature was maintained by Julabo constant temperature bath maintained at 25 °C with an accuracy of $\pm 0.01^\circ\text{C}$. The progress of the reaction was tracked by extracting 1 ml of reaction mixture in ether at appropriate time intervals. Chlorobenzene was used as an internal standard. The extracted sample was injected for GC analysis using a Varian CP-3800 gas chromatogram. All reactions were monitored before 15% conversion. No byproducts were observed during entire reaction. Relative peak area was at prior calibrated with respect to the pure product of BHR. The k_2 values were obtained from the integration of the peak area of the product with respect to internal standard at different intervals of time. The plot of $x/a(a-x)$ versus time and of $\ln(a/a-x)$ versus time gave the value of pseudo second order and of first order rate constant respectively. Order plots were made by plotting rate versus concentration of PNB. Linear dependence of the rate of reaction on aldehyde concentration exhibited reaction to be of first order and nonlinear dependence was an indication of second order. The rate constants measured were reproducible to $\pm 3\%$.

5.2.2.3 Determination of activation parameters

Activation parameters were determined by measuring rate constants, k_2 , in different ILs at 5 different temperatures. Required temperature was maintained by Julabo

constant temperature bath with an accuracy of $\pm 0.01\text{K}$. The reaction was initiated by the addition of methyl acrylate, 0.9028 ml (1 M) to a stirred solution of PNB (0.04 M) and DABCO (1M) in 1 ml of solvent. The progress of the reaction was followed by GC. 1 ml of aliquot was taken out from the reaction mixture at appropriate time intervals and was further diluted and extracted in ether. The extracted sample was then injected for GC analysis. Chlorobenzene was used as an internal standard. Calculation of k_2 has already been explained in the kinetic measurement section. Already established in the literature, Arrhenius and Eyring equations were used for the calculation of activation parameters. Each experiment was carried out in triplicate and the standard error in measurement was $\pm 6\%$ [Pyr][HSO₄], $\pm 8\%$ [Opy][HSO₄] and $\pm 10\%$ for [Opyr][HSO₄].

5.2.3 Results and discussion

The physico-chemical properties of the solvent are an important determinant of the solute-solvent interactions and resultant kinetic parameters. It is evident that the solvent environment can dramatically alter the outcome of a reaction. As ILs have the ability to act as a potent reaction media, different from that offered by any other solvent, it is expected that ILs may influence the kinetics and mechanism of the BHR. In order to concentrate on the role of cations of ILs on BHR, an extensive study with different cations of ILs was carried out. The ILs synthesized and used in the reaction were based on different cations as pyridinium, pyrrolidinium, piperidinium, morpholinium and anions were based on acetate, formate, methylsulfate, hydrogen sulphate, bis(trifluoromethanesulfonyl)imide and nitrate. Amino acids and imidazolium based ILs cannot be used for investigation due to the involvement of side reactions (Table 5.2).⁸¹

[Pyr][NO₃], [Pyr][CH₃COO], [Pyr][HCOO], [Mbpyr][NTf₂], [Pyr][CF₃COO] showed linear dependence on PNB concentration (Figure 5.4). On the contrary the plot of rate ($\partial c/\partial t$) versus concentration for [Pyr][HSO₄], [Opyr][HSO₄], [Opip][HSO₄], [Pyr][HSO₄] and [MeMo][MeSO₄] based ILs shows second order dependence on *p*-nitrobenzaldehyde concentration (Table 5.2, Figure 5.5). An order of two indicated

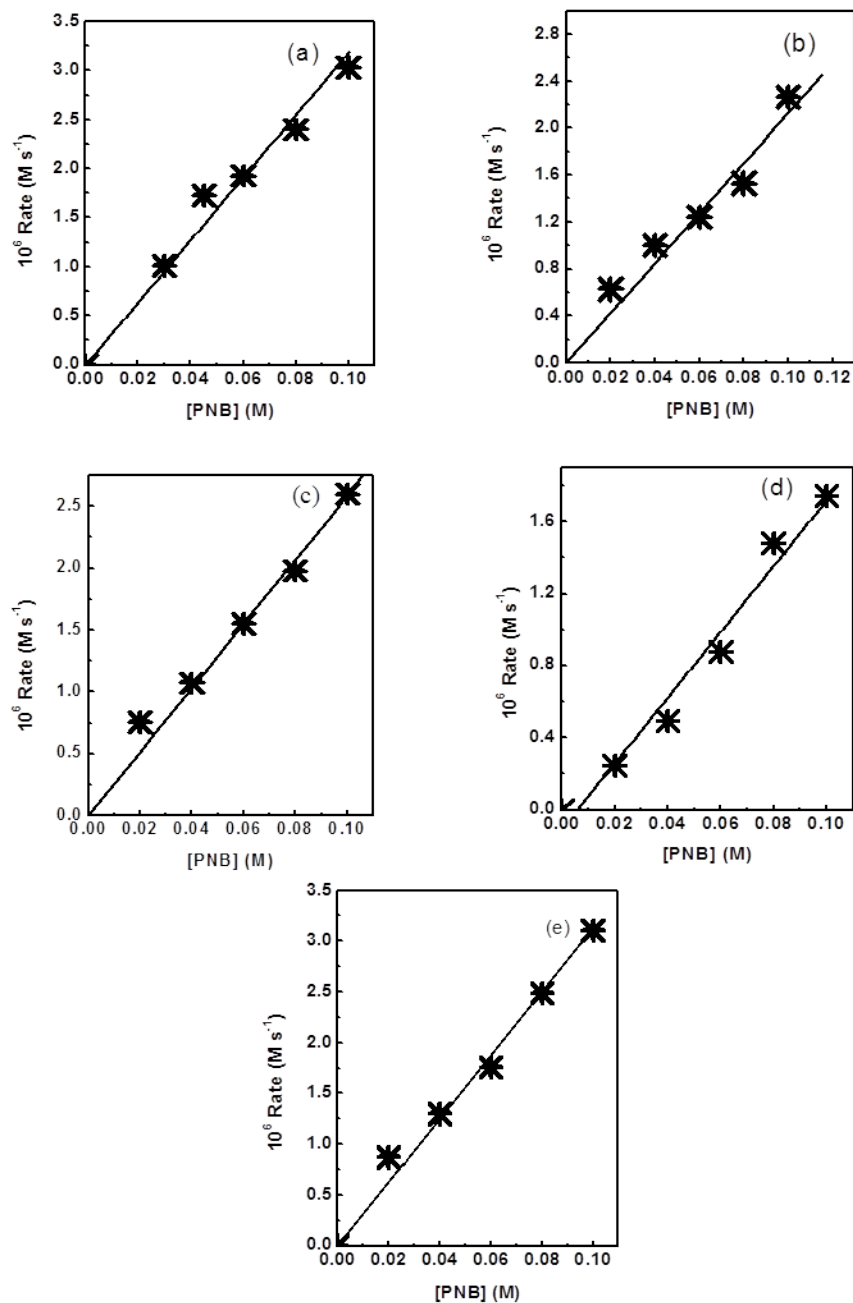


Figure 5.4: The plots of the rate, $(\partial c/\partial t)$ vs. concentration of 1 for BHR in (a) $[\text{Mbpyr}][\text{NTf}_2]$, correlation coefficient, $r=0.982$, (b) $[\text{Pyr}][\text{CH}_3\text{COO}]$, $r=0.958$, (c) $[\text{Pyr}][\text{NO}_3]$, $r=0.994$, (d) $[\text{Pyr}][\text{CF}_3\text{COO}]$, $r=0.980$, (e) $[\text{Pyr}][\text{HCOO}]$, $r=0.987$

involvement of two equivalents of PNB in the rate determining step of the reaction. On the contrary, an order of one proved the existence of one equivalent of aldehyde in the rate determining step of the reaction. This observation suggested that probably

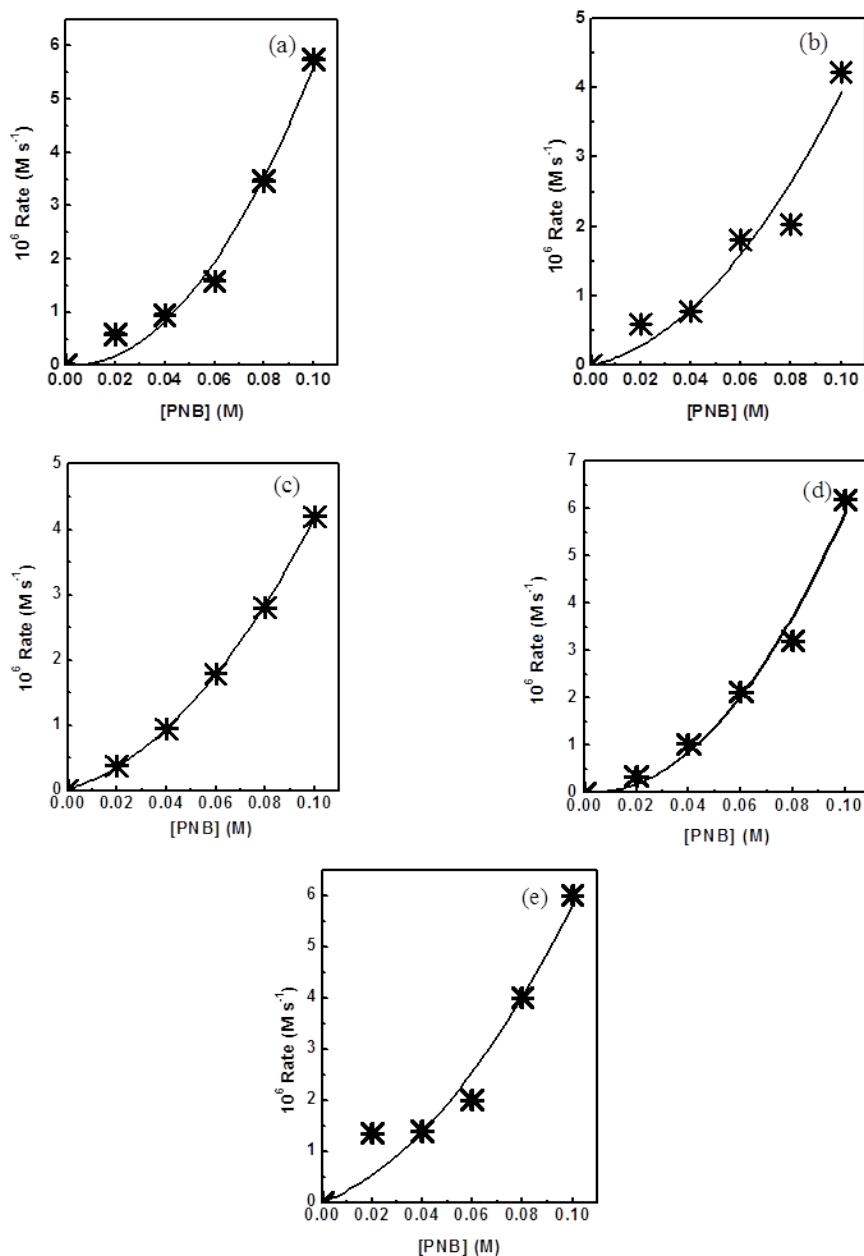


Figure 5.5: The plots of the rate, $(\partial c/\partial t)$ vs. concentration of 1 for the reaction of 1 with 2 in presence of DABCO in (a) [Opip][HSO₄], correlation coefficient, $r=0.997$, (b) [Opy][HSO₄], $r=0.952$, (c) [MeMo][MeSO₄], $r=0.999$, (d) [Pyr][HSO₄], $r=0.985$ (e) [Opyr][HSO₄], $r=0.961$.

there was a change in the mechanism of the reaction with the change in the structure of ionic liquid. The yield obtained in case of [Pyr][HSO₄] and [Pyr][HCOO] ILs were 70% and 68% respectively. Further, to investigate the role of cations in the kinetic and mechanistic aspect of reaction, a number of ILs with same anion and different

Table 5.2: The Names and Acronyms of ILs and the Kinetic Data.

Acronyms	Aldehyde order, n	k_2 (<i>pseudo rate constants</i>)
[Opyr][HSO ₄]	2	$1.18 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$
[Opy][HSO ₄]	2	$7.35 \times 10^{-4} \text{ M}^{-1}\text{s}^{-1}$
[Opip][HSO ₄]	2	$1.22 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$
[Pyr][HSO ₄]	2	$1.35 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$
[MeMo][MeSO ₄]	2	$1.13 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$
[Pyr][NO ₃]	1	$3.46 \times 10^{-5} \text{ s}^{-1}$
[Pyr][CH ₃ COO]	1	$3.33 \times 10^{-5} \text{ s}^{-1}$
[Pyr][HCOO]	1	$4.15 \times 10^{-5} \text{ s}^{-1}$
[Mbpypyr][NTf ₂]	1	$4.00 \times 10^{-5} \text{ s}^{-1}$
[Pyr][CF ₃ COO]	1	$1.94 \times 10^{-5} \text{ s}^{-1}$
[Bmim][Br]	Too fast	–
[Opipe][HSO ₄]	solid < 90°C	–

cations were synthesized. Surprisingly, no change was observed in the order of the reaction upon changing the cation of ILs. This was quiet intriguing as it indicated the ostensible role played by the cations of ILs in influencing the mechanism of the reaction. [Opyr][HSO₄] ionic liquid was solid at room temperature and the kinetic study was performed at higher temperatures (55 °C). Higher rate constants observed in [Opyr][HSO₄] can be explained by the influence of higher temperature employed for carrying out the experiments. [Pyr][HSO₄], [MeMo][MeSO₄] and [Opip][HSO₄] exhibited higher k_2 values due to high value of solvatochromic parameter, β , 0.966. β parameter is a measure of basicity or electron accepting tendency of the anions of ILs. Higher value of β indicates presence of higher electron density on the anions of ILs, which can probably greatly affect the kinetics of the reaction by interacting strongly with the zwitterionic species formed during the course of the reaction. The reaction was comparatively slow in other anion based ILs such as HCOO⁻, NTf₂⁻, CF₃COO⁻, CH₃COO⁻ and NO₃⁻ due to the lower β values. ¹⁸

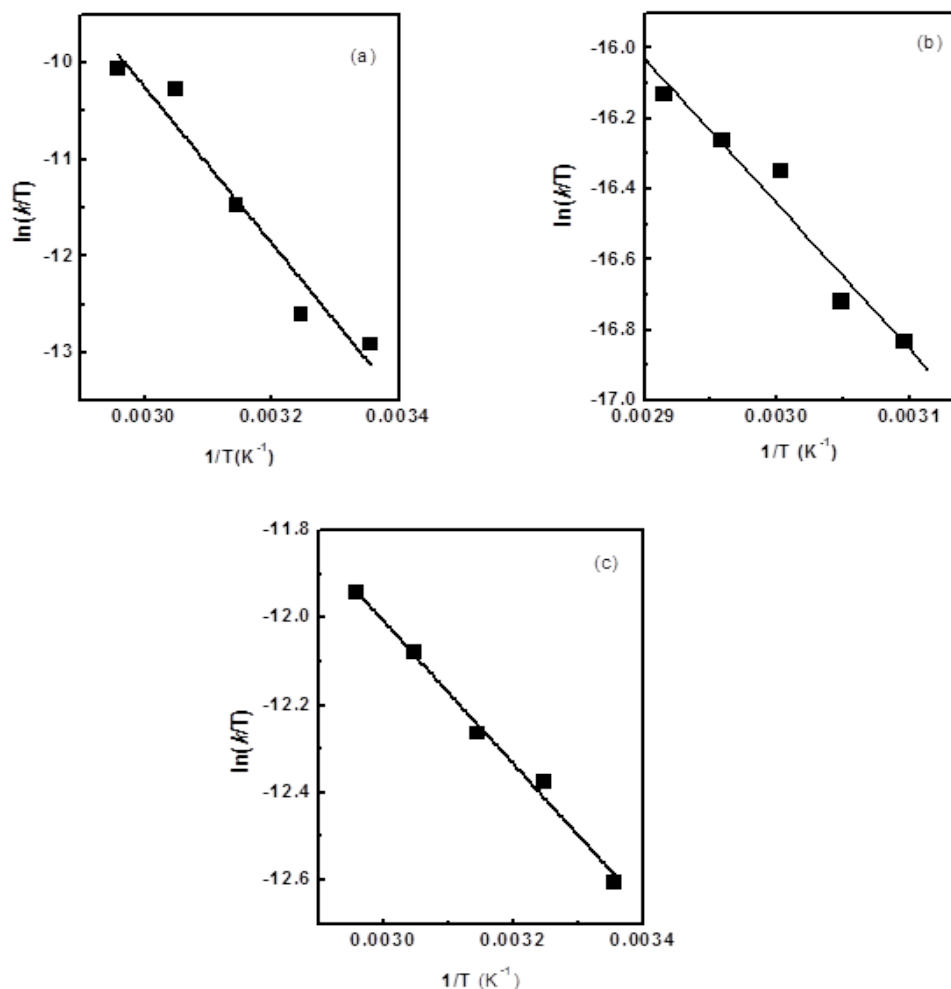


Figure 5.6: Eyring plot ($\ln(k/T)$ vs. $1/T$) for PNB in (a) $[\text{OPy}][\text{HSO}_4]$ (b) $[\text{OPyr}][\text{HSO}_4]$ and (c) $[\text{Pyr}][\text{HSO}_4]$

5.2.3.1 Eyring activation parameters

With the purpose of obtaining greater insight into the mechanism of the reaction activation parameters, $\Delta^\ddagger H$ and $\Delta^\ddagger S$ were both determined using Eyring equation (Figure 5.6). E_a^\ddagger was calculated from Arrhenius equation (Figure 5.7). The reaction in $[\text{Pyr}][\text{HSO}_4]$ and $[\text{Opy}][\text{HSO}_4]$ was carried out at 25, 35, 45, 55 and 65 °C.

The reaction for $[\text{OPyr}][\text{HSO}_4]$ was carried out at 50 to 70 °C at an interval of 5 °C. These values are reported in Table 5.3. The higher magnitude of entropy for the reaction can credibly be associated with a process in which two successive bond formations occurred in conjunction with development of full charges. The E_a^\ddagger values

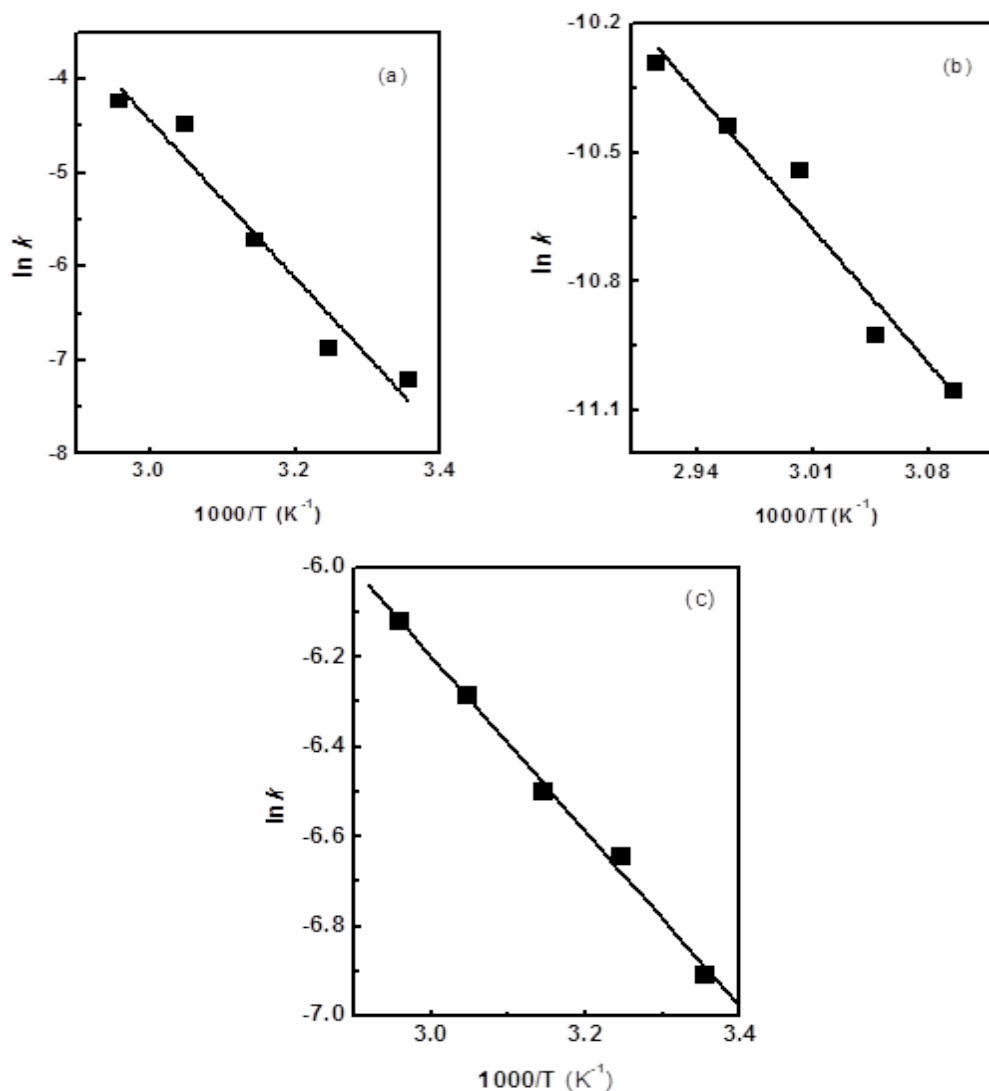


Figure 5.7: Arrhenius plots ($\ln k$ vs. $1000/T$) for the reaction of *p*-nitrobenzaldehyde, 1 and methyl acrylate, 2 with DABCO in ILs in (a) [OPy][HSO₄] (b) [OPyr][HSO₄] and (c) [Py][HSO₄].

Table 5.3: Activation Parameters for the Reaction of PNB and methyl acrylate with DABCO in ILs.

ILs	E_a^\ddagger (kJ mol ⁻¹)	$\Delta^\ddagger H$ (kJ mol ⁻¹)	$\Delta^\ddagger S$ (J mol ⁻¹ K ⁻¹)
[Pyr][HSO ₄]	16.30	13.70	-256.20
[OPyr][HSO ₄]	129.51	126.74	92.11
[Opy][HSO ₄]	69.95	67.31	-80.76

for [Pyr][HSO₄] is minimum which is in accordance of observation of higher rate constants of the reaction. The E_a^{\neq} values observed for [Opy][HSO₄] was comparatively higher. This can be a determinant factor in the observed slow pace of the reaction as reported in Table 5.2. Higher enthalpy of activation observed for [Opyr][HSO₄] can be explained by a noticeable change of the reaction from being exergonic to endergonic. This can provide a rationalization of the fact that the reaction cannot be performed at elevated temperatures. Higher entropy for reaction in [Opyr][HSO₄] suggests that bond formation becomes comparatively difficult at elevated temperatures.²² In spite of unfavourable $\Delta^{\neq}S$ the reaction carried out in [Opyr][HSO₄] possesses k_2 of the order of $1.18 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$. This can be explained by very high β value of the sulfate based ionic liquid. Henceforth, it is possible that presence of sulfate based anions makes thermodynamically unfavorable reaction, kinetically favorable. In order to delineate the effect of longer alkyl chain length on the kinetics and mechanism of the reaction, [Opyr][HSO₄] and [Opy][HSO₄] ILs were also deeply scrutinized. Results indicate that there is an increase in the E_a^{\neq} energy from [Pyr][HSO₄] to [Opyr][HSO₄] suggesting that increase in the alkyl chain length of the cation can decrease the rate of the BHR. Irrespective of increased activation energy barrier, the observed order of the reaction in [Pyr][HSO₄], [Opyr][HSO₄] and [Opy][HSO₄] remains 2. This is an exciting observation that the mechanism of the reaction is independent of the alkyl chain length of the cation. The reaction follows the same pathway in the investigated ILs. Long alkyl chain length of cation is acting as a surfactant to slow down the reaction velocity as shown in Table 5.2. The interaction of the cation of ionic liquid with the reactants is comparatively weaker as compared to that of the anions. This may be due to the higher charge density on the anions as compared to that of the cations. Electron rich anion can influence the reaction mechanism, containing charged species, in a more rational way as compared to that of cation.

5.2.3.2 Solvent-reactivity relationship

At present one of the most comprehensive and widely used solvent scales for understanding and interpreting solvent behaviour in reaction dynamics is linear solvation

energy relationship (LSER). The characterization of molecular environment of reactants by the use of solvatochromic probes by LSER is well documented in the literature. The interaction of solvatochromic dyes with pure solvents or mixtures are a combination of many effects. The basic principle of LSER is that attractive solute-solvent interaction can be represented as a linear combination of nonspecific dipolarity/polarizability (π^*) and specific hydrogen bond formation effect. Latter is a combination of many interactions and have been separated into various solute-solvent interactions for simplification. The main factors which have been taken into considerations hydrogen bond accepting tendency (β) and hydrogen bond donar tendency (α). A range of interactions varying from intermolecular specific and non specific solute-solvent interactions can be accounted by LSER which is expressed as:

$$(XYZ) = (XYZ)_0 + aA + bB + cC$$

Where $(XYZ)_0$ designates property in a nonpolar medium, a, b, and c are coefficients which shows the dependence of physical and chemical properties (XYZ) in a particular solvent on various properties of the solvent. The foundation of the equation is from Kamlet-Taft equation which has been verified many times in the literature. It is one of the most successful quantitative methods for describing solvent effect with a multiparameter equation. The most established multivariate of LSER is that of Kamlet and Taft given by:²³

$$(XYZ) = (XYZ)_0 + a\alpha + b\beta + c\pi^*$$

Where α is hydrogen bond donation, β is hydrogen bond accepting tendency (basicity) and π^* is the dipolarity/polarizability tendency. In case of reactions the equation can be written as:

$$\log k_{obs} = \log k_0 + a\alpha + b\beta + c\pi^* + \text{other parameters}$$

We then tried to find a correlation between reaction rate constants and solvatochromic parameters. At first linear regression was carried out followed by multiple regressions. The rate constants were also separately fitted with the individual α , β and π^* parameters. The correlation coefficient very clearly demonstrated the dependency of k_2 on

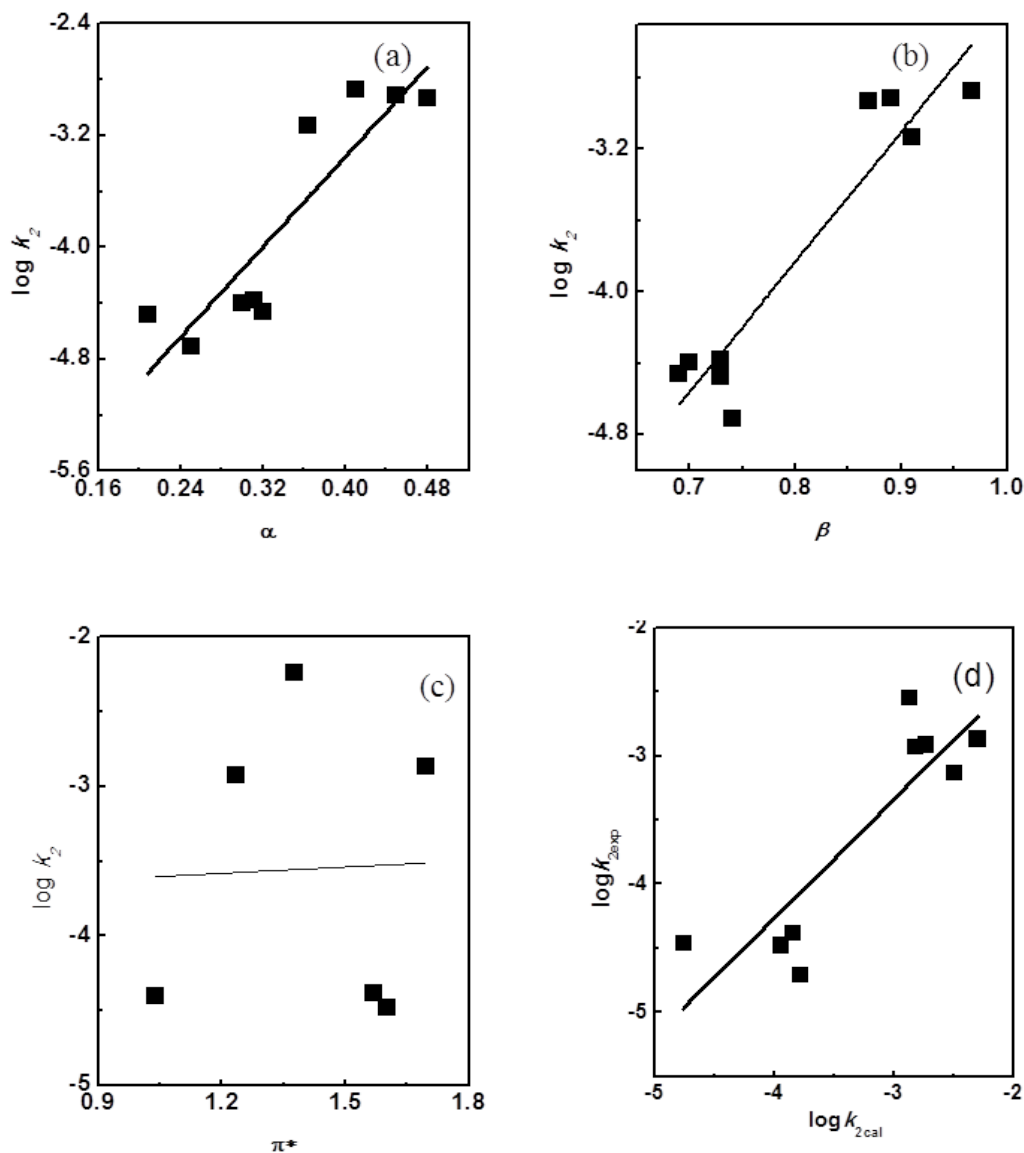


Figure 5.8: The plots of $\log k_2$ versus (a) α , correlation coefficient = 0.774 (b) β , coefficient = 0.876 and (c) π^* , correlation coefficient = -0.248) (d) correlation between \log of k_{2cal} and k_{2exp}

β value (Figure 5.8(b)). Monoparametric equation do not give satisfactory results. The resulting correlation, obtained by multiple regression, is significant although with some scatter gave the coefficient values as follows:

$$\log k_{2cal} = -8.581 + 1.069\alpha + 6.022\beta - 0.325\pi^* \quad (r_2 = 0.997)$$

Undoubtedly, all the parameters appear to be important here. Contribution of α and π^* is comparatively negligible as shown by regression values. However, the contribution of β is dominant in affecting the rate of the reaction. The magnitude of coefficient of β indicates a good degree of interaction between the anions of ILs and the intermediates. Upon plotting the values, correlation pattern as shown in Figure 5.8(d) is obtained. The correlation thus obtained between $\log k_{2exp}$ and $\log k_{2cal}$ is fairly satisfactory.

5.2.3.3 Mechanism of the reaction

The above results proves the predominance of the role of the anion of ILs in catalysing the BHR. A minor role is played by α whereas π^* plays insignificant role. Biparametric equation contributes significantly to the rate constants with β factor playing an important role. Increase in the alkyl chain length only increases the activation energy of the reaction. It has no significant effect on the order of the reaction. However, the presence of HSO_4^- as anion does affect the mechanism of the reaction. As HSO_4^- ion has a high β value, it can considerably affect the mechanism and kinetics of the BHR. In 2005, K. E. Price, S. J. Broadwater, B. J. Walker and D. T. McQuade have reported second order dependence of rate of BHR on aldehyde concentration. Polar aprotic solvent like DMSO which has a high β value (0.743) was very effectual in driving the reaction to a new pathway which was different to the one proposed by Hill and Isaacs. Based upon our experimental observations, we also propose a similar mechanism in ILs which is exclusively 'anion dependent'. The steps involved are (a) the reversible Michael addition, b) the attack of enolate on the first equivalent of PNB in order to give second zwitterionic species, c) attack of second zwitterionic species on another equivalent of aldehyde leading to formation of a hemiacetal intermediate d) proton transfer from the α -position C-H bond to alkoxide (RDS) and e) product formation and elimination of base. The electron rich species such as DMSO and HSO_4^- ion when present in the reaction medium, can decrease the stability of the negative charge present on the alkoxide oxygen. These species solvate only cation making negative charge highly reactive. The unstable negative charge tries to satisfy

itself by proton transfer from α -carbon. This transfer leads to a strained 4-membered transition state. Such proton transfer is geometrically unfavourable too. The species then attacks another equivalent of aldehyde to form a highly stable 6-membered transition state. The proton transfer from α -carbon to alkoxide ion is now energetically favourable. The attack generates a hemiacetal intermediate. Last step of the mechanism involves elimination of base and product formation. The results give a insight into the mechanistic pathway of the reaction and quite interestingly suggests that HSO_4 , MeSO_4 based anion follows McQuade pathway with two equivalents of aldehyde present in the rate determining step of the reaction (Scheme 5.3) and other anion based ILs follows Hill and Isaacs pathway with only one equivalents of aldehyde present in the rate determining step of the reaction (Scheme 5.1).

5.2.4 Conclusions

This section deals with kinetic experiments to demonstrate that the mechanism of the BHR is not general for all ILs. The nature of the anion of ILs and its basicity can be a very important deciding factor in deciding the pathway of the reaction. Sulfate based ILs are very unusual in their behaviour since they are the only anions which have two equivalents of PNB participating in the rate determining step of the reaction. Other anions have only one equivalent of PNB participating in the rate determining step of the reaction. The valid mechanism in ILs can be a function of the β value of the anion of ionic liquid. The role of the solvent in the kinetics and the rate of reaction has been further confirmed by the Kamlet-Taft based LSER approach. The choice of the best parameter for every type of interaction is very critical because of the complexity of the reaction medium and also because of their susceptibility towards more than one aspects of the undergoing reaction. Kamlet-Taft based LSER approach also show that BHR exhibits anion dependency. The good correlations can be explained by the high basicity of the anions of ILs involved. It has been shown that both rate constant and mechanism of BHR shows dependency on more basic anions. The work presented in this section demonstrates that the ILs with more basic anions follow McQuade mechanism while ILs with less basic ones follow Hill and Isaacs mechanism.

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Chapter 6

Conclusions

Preamble



In the last chapter of the thesis the experimental work described in the previous chapters have been briefly evaluated. Furthermore, two pivotal themes of the thesis, kinetic and mechanistic study of organic reactions in environment-benign media, have been reviewed. The chapter basically includes important observations assimilated by the kinetic studies on C-C and C-X bond formation reactions. Finally, the prospects of 'on-water' reactions for future studies have been discussed.

In summary, the solvent effects of ILs and aqueous binary mixtures on simple organic reactions have been investigated in the present work. The solvent systems—ILs and aqueous systems—were selected on the basis of their economic and environmental viability. The salient features of these investigations are:

(1) The immiscibility of solute molecules in water encouraged the investigation of ‘on-water’ reactions. The initial comparisons of the rates of the 1,3-DCA reaction in homogenous and heterogenous reaction medium demonstrated that water is a better reaction medium under ‘on-water’ conditions. Not only the reaction occurred predominantly at the interface but the rate of heterogenous reaction was found to be higher than homogenous reactions too. Additionally, enhancement of the rates of reaction was observed in presence of prohydrophobic salts, which confirmed the existence of hydrophobic forces at the interface. Further, kinetic studies of the reaction have revealed a retardation of the rate constants after a limiting concentration of the prohydrophobic salts has reached. It was proposed that properties that represent the bulk phenomena were evident at the interface too, although with some limitations. Steric crowding of reactants, after critical concentration of salts is reached, may be the reason for observed saturation effect. The reactions that occur at the interface are predominantly controlled by interfacial area of contact between the reactants and water surface. At higher salt concentrations, the accumulation of products reduces the active interfacial area and hence reaction slows down. “No Salt Effect” at higher salt concentration can be an important characteristic of interfacial reactions. In addition, electronic factors also play pivotal role in deciding the kinetic outcome of the interfacial reactions.

(2) Many experiments were carried out to probe the hydrophobic effect in detail, including temperature dependent kinetic studies in presence of prohydrophobic salts. The investigation of solubility measurements of phenyl azide revealed an interesting pattern. The solubility first decreased with an increase in temperature, however it increased at higher temperatures. The solubility results were advantageously used for the kinetic study of 1,3-DCA reaction. The rate constant of reaction exhibited a pattern that was exactly reverse of the trend observed for solubility results. Further,

addition of 2M salt concentration of LiCl, KCl and CaCl₂ exhibited some intriguing results. The rate constants first decreased and then increased but the maximum change was evident for CaCl₂ followed by LiCl and KCl. The trend partially followed the Hofmeister series. The results indicated that beyond a limit, when the oil-water interface is crowded, hydrophobic effect fails. No hydrophobic effect is evident at the room temperature, however it is evident at higher temperatures. The need for maintaining an optimum concentration of hydrophobic molecule for rate enhancements of interfacial reactions was stressed. The limited experimental and theoretical data available in the literature, regarding the water-organic interface, prevented a thorough and complete analysis of the interface.

(3) The use of alcohols as co-solvent has enhanced and encouraged the approach of chemist for using water as a solvent medium for carrying out organic reactions. The investigation of the use of C-C bond formation reactions as a function of addition of co-solvent led to some surprising results. An initial increase in the rate constants of the reaction followed by a fall in the rate constants was evident in the present study. The changes of the k_{2app} of benzoin condensation in binary mixtures of water and co-solvents are characterized by critical compositions of water, which separates two distinct ranges of solvent composition: water rich and alcohol rich zone. At lower concentrations of co-solvents, the reaction is dominated by polarity and hydrogen bonding effects. However, at higher concentrations the reaction is mainly governed by the hydrophobic effects, as these effects are pronounced only at higher concentrations of co-solvents. Existence of a 'critical composition' for each of the investigated aqueous binary mixture has been proven at which there is a transition of reaction site from interface to the bulk solution. It is possible to investigate the water-organic interface in greater detail in the near future employing sophisticated SFG spectroscopic techniques. The correlation between bulk measurable solvent properties and the interfacial reactions (as in 'on-water' reactions) would help in designing the reaction conditions to achieve optimum reactivity.

(4) The future studies of organic reactions in ILs may greatly benefit from the efforts to delineate the kinetic and mechanistic details of the reactions in the media.

Existence of dual mechanism in ILs was evident with the change in the basicity of anion in ILs. The results can be helpful for physico-organic chemists who desire to investigate the mechanism of reactions. The anions of ILs are more effective than the cations in terms of interactions with the charged species. Also, the selection of the optimum parameter to describe various interaction is very critical because of the complexity of the reaction medium and their susceptibility towards multiple aspects of the reaction. The valid mechanism in ILs can be a function of the β value of the anion of ILs. Kamlet-Taft based LSER approach also establishes that mechanism of BHR exhibits anion dependency. The work presented in the thesis demonstrates that the ILs with more basic anions follow McQuade mechanism while ILs with less basic ones follow Hill and Isaacs mechanism.

The systematic study of the solvent effect on the reactions can assist in better understanding of the kinetic and mechanistic aspects of reactions in environment-benign media. Also a comprehensive database of the physicochemical properties of all the ILs synthesized till date is very important. The efforts to lower the cost of the ILs would provide a motivation for large-scale applications in industries. The methodical investigations of the solvent effect in the present study may be helpful in future studies for enhancing the practical applications of aqueous media and ILs.

Appendix A

NMR Spectra of Ionic Liquids

The NMR spectra of synthesized and properly dried ionic liquids are reported below (^1H NMR, 200 MHz, CDCl_3):

1-octyl-1-methyl-pyrrolidinium bis

(trifluoromethanesulfonyl)imide [OMPyr][NTf₂]: δ 0.85 (t, $J = 7.0$ Hz, 3H), δ 1.28 (m, 10 H), δ 1.82 (m, 2H), δ 2.31 (m, 4H), δ 3.29 (s, 3H), δ 3.29 (m, 2H), δ 3.45 (b, 4H).

1-hexyl-1-methyl-pyrrolidinium

bis(trifluoromethanesulfonyl)imide [HMPyr][NTf₂]: δ 0.85 (t, $J = 7.0$ Hz, 3H), δ 1.34 (m, 6H), δ 1.70 (m, 2H), δ 2.25 (m, 4H), δ 3.03 (s, 3H), δ 3.29 (m, 2H), δ 3.51 (m, 4H).

pyridinium formate [HP][HCOO]:

δ 7.65 (m, 1H), δ 8.09 (m, 1H), δ 8.22 (m, 2H), δ 8.73 (m, 1H), δ 13.78 (s, 1H)

1-butyl-pyridinium bis(trifluoromethanesulfonyl)imide

[BP][NTf₂]: δ 0.98 (t, 3H), δ 1.38 (m, 2H), δ 1.96 (m, 2H), δ 4.58 (m, 2H), δ 8.02 (m, 2H), δ 8.5 (m, 1H), δ 8.81(m, 2H)

1-ethyl-pyridinium bis(trifluoromethanesulfonyl)imide

[EtP][NTf₂]: δ 1.56 (t, 3H), δ 4.57 (m, 2H), δ 7.94 (m, 2H), δ 8.41 (m, 1H), δ 8.72 (m, 2H).

1-ethyl-pyridinium ethylsulfate [EtP][EtSO₄]: δ 1.24 (t, 3H), δ 1.68 (t, 3H), δ 4.01 (q, 2H), δ 4.83 (m, 2H), δ 8.16 (m, 2H), δ 8.60 (m, 1H), δ 9.21(m, 2H).

1-ethyl-pyridinium tetrafluoroborate [EtP][BF₄]: δ 1.24 (t, 3H), δ 4.01 (q, 2H), δ 8.12 (m, 2H), δ 8.50 (m, 1H), δ 9.0(m, 2H).

1-ethyl-piperidinium ethylsulfate [EtPip][EtSO₄]: δ 1.34 (t, 6H), δ 1.6 (q, 2H), δ 1.92 (m, 4H), δ 2.92 (m, 2H), δ 3.19 (m, 2H), δ 3.49(m, 2H), δ 4.11 (m, 2H), δ 8.25 (b, 1H).

1-ethyl-morpholinium ethylsulfate [EtMo][EtSO₄]: δ 1.34 (t, 6H), δ 2.96(m, 2H), δ 3.27 (m, 2H), δ 3.57 (m, 2H), δ 4.01 (m, 6H), δ 8.6 (b, 1H).

1-octylpiperidinium hydrogensulfate [Opip][HSO₄]: δ 0.85 (t, J = 7.0 Hz, 3H), δ 1.24 (m, 10 H), δ 2 (m, 8H), δ 2.98 (m, 2H), δ 3.31 (m, 2H), δ 3.76 (m, 2H), δ 9.42 (b, 1H), δ 11.11 (b, 1 H).

Pyrrolidinium hydrogensulfate [Pyr][HSO₄]: δ 1.92 (m, 4H), δ 3.27 (m, 4H), δ 7.80 (s, 1H), δ 8.76 (s, 1H).

1-methylmorpholinium methylsulfate [MeMo][MeSO₄]: δ 2.95 (m, 2H), 3.29 (m, 2H), δ 3.49 (s, 3H), δ 3.79 (s, 3H), δ 4.01 (m, 4H), δ 8.8 (s, 1H).

Pyrrolidinium nitrate [Pyr][NO₃]: δ 1.97 (m, 4H), δ 3.31 (m, 4H), δ 8.88 (b, 2H).

Pyrrolidinium acetate [Pyr][CH₃COO]: δ 1.93 (m, 7H), δ 3.16 (m, 4H), δ 8.31 (s, 2H).

Pyrrolidinium formate [Pyr][HCOO]: δ 1.90 (m, 4H), δ 3.26 (m, 4H), δ 7.88 (s, 1H), δ 8.40 (s, 1H).

1-butyl-1-methylpyrrolidinium

bis(trifluoromethanesulfonyl)imide [Mbpvr][NTf₂]: δ 0.99 (t, J = 7.2 Hz, 3H), δ 1.43 (m, 2H), δ 1.71 (m, 4H), δ 2.29 (m, 4H), δ 3.30 (s, 3H), δ 3.71 (m, 2H), δ 3.83 (m, 2H).

Pyrrolidinium trifluoroacetate [Pyr][CF₃COO]: δ 1.91 (m, 4H), δ 3.14 (m, 4H), δ 7.86 (s, 2H).

1-butyl-3-methylimidazolium bromide [Bmim][Br]: δ 0.94 (t, J = 7.32 Hz, 3H), δ 1.35 (m, 2H), δ 1.86 (m, 2H), δ 4.11 (s, 3H), δ 4.31 (t, J = 7.4 Hz, 2H), δ 7.33 (s, 1H), 7.42 (s, 1H), δ 10.47 (s, 1H).

Appendix B

NMR and GC Data

GC parameters for kinetic analysis of BHR in ILs

The following parameters were kept for the kinetic analysis:

Column make	CP SIL 5CB
Internal diameter	0.25 mm
Column length	15m
Film thickness	0.25-micron
Injector temperature	200 °C
Flow rate	1 ml/min of nitrogen
Detector temperature	250 °C
Total run time	18.95 min (hold at 70°C for 5 min ramp at 4°C, then maintain at 100°C for 0 min, ramp at 79°C and then maintain at 180° for 5 min)
Internal Standard (IS)	Chlorobenzene

Typical Retention Times of the compounds analyzed:

(a) IS = 4.806 min

(b) Product = 14.657 min

The GC method was already calibrated with respect to the product concentrations using pure samples of the Baylis-Hillman products. The amount of product formed as a function of time gave the extent of the reaction (x).

**NMR spectra of the synthesized reactants and products of
1,3-Dipolar cycloaddition reaction:**

Phenyl azide (1a): ^1H NMR (200 MHz, CDCl_3): δ 7.03 (m, 2H), δ 7.15 (t, $J = 7.5$ Hz, 1H), δ 7.36 (m, 2H).

***p*-nitrophenylazide (1b):** ^1H NMR (200 MHz, CDCl_3): δ 7.15 (m, 2H), δ 8.26 (m, 2H).

***p*-bromophenylazide (1c):** ^1H NMR (200 MHz, CDCl_3): δ 6.91 (m, 2H), δ 7.46 (m, 2H).

**NMR spectra of products of 1,3-dipolar cycloaddition
reaction:**

diethyl (4S)-1-phenyl-4,5-dihydro-1H-1,2,3-triazole

-4,5-dicarboxylate (3a): ^1H NMR (200 MHz, CDCl_3): δ 1.24 (m, 6H), δ 4.22 (m, 4H), δ 4.66 (d, $J=6.44$ Hz, 1H), δ 4.94 (d, $J=6.44$ Hz, 1H), δ 6.62 (m, 2H), δ 6.73 (t, $J=7.33$ Hz, 1H), δ 7.13 (m, 2H).

diethyl (4S)-1-(4-nitrophenyl)-4,5-dihydro-1H-1,2,3-triazole-

4,5-dicarboxylate (3b): ^1H NMR (200 MHz, CDCl_3): δ 1.33 (m, 6H), δ 4.25 (m, 4H), δ 5.04 (d, $J=7.02$ Hz, 2H), δ 5.04 (d, $J=7.02$ Hz, 1H), δ 7.18 (m, 2H), δ 8.24 (m, 2H).

diethyl(4S)-1-(4-bromo)-4,5-dihydro-1H-1,2,3-triazole-4,5-

dicarboxylate (3c): ^1H NMR (200 MHz, CDCl_3): δ 1.23 (m, 6H), δ 4.18 (m, 4H), δ 4.72 (d, $J=6.52$ Hz, 1H), δ 4.86 (d, $J=6.52$ Hz, 1H), δ

6.49 (m, 2H), δ 7.20 (m, 2H).

NMR spectra of product of Benzoin Condensation:

2-hydroxy-1,2-diphenylethan-1-one (Benzoin): ^1H NMR (200 MHz, CDCl_3): δ 4.45 (d, $J=6.07$ Hz, 1H), δ 5.95 (d, $J=6.07$ Hz, 1H), δ 7.3 (m, 7H), δ 7.5 (t, $J=7.20$ Hz, 1H), δ 7.90 (d, $J=7.08$ Hz, 2H).

NMR spectra of product of BHR:

2-[Hydroxy(4-nitrophenyl)methyl]acrylic Acid Methyl Ester: ^1H NMR (200 MHz, CDCl_3): δ 8.18 (d, $J = 8.84$ Hz, 2H), δ 7.52 (d, $J=8.8$ Hz, 2H), δ 6.37 (s, 1H), δ 5.89 (s, 1H), δ 5.61 (s, 1H), δ 3.70 (s, 3H).

Appendix C

List of Publications

- Singh, A.; Kumar, A.

“Probing the Mechanism of Baylis-Hillman Reaction in Ionic Liquids.”

J. Org. Chem. **2012**, *77*, 4775-4779.

- Singh, A.; Kumar, A.

“Kinetic and Mechanistic Investigations of Baylis-Hillman Reaction in Ionic Liquids.”

RSC Adv. **2015**, *5*, 2994-3004.

- Singh, A.; Kumar, A.

“Investigation of Interfacial Benzoin Condensation Reaction” *Org.*

Biomol. Chem. (to be communicated).

- Singh, A.; Kumar, A.

“Salt Effect at Oil-Water Interface of 1,3-Dipolar Cycloaddition Reaction.”

(manuscript under preparation).

- Singh, A.; Kumar, A.

“Flip-Flop Nature of “On water” reactions: Phenyl azide and Temperature Do the Trick”

(manuscript under preparation).

- Singh, A.; Kumar, A.

“Heterogenous versus Homogenous Reactions at Oil-Water Interface”.

(*Chem. Rev.* under preparation).

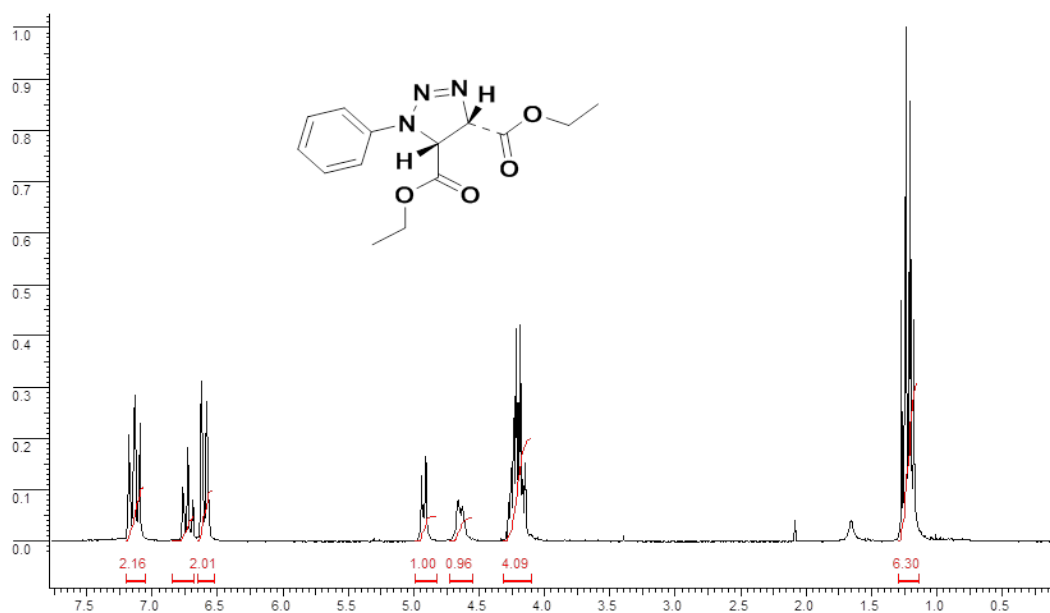
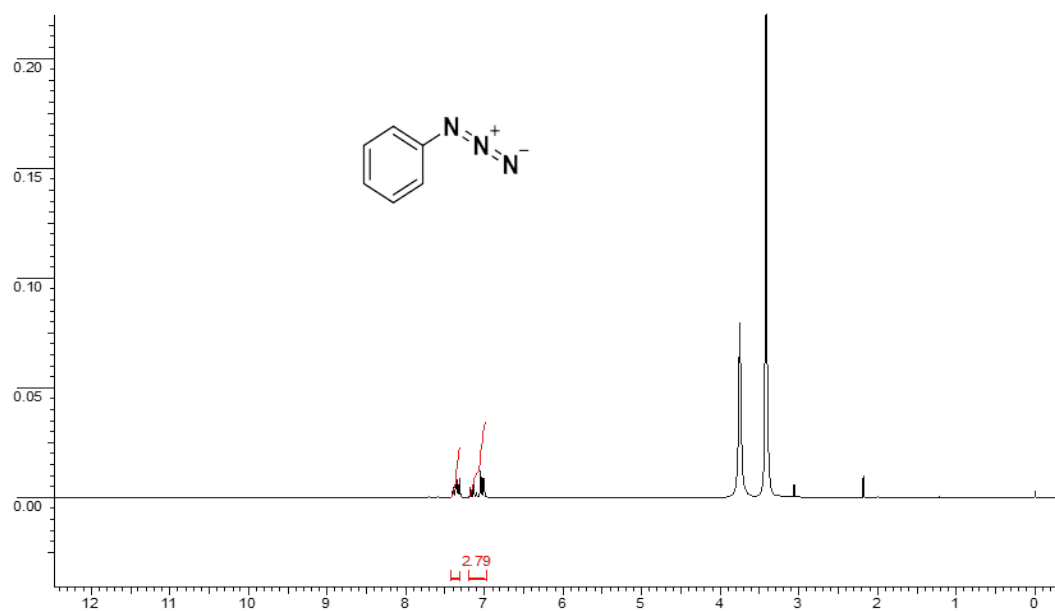
Appendix D

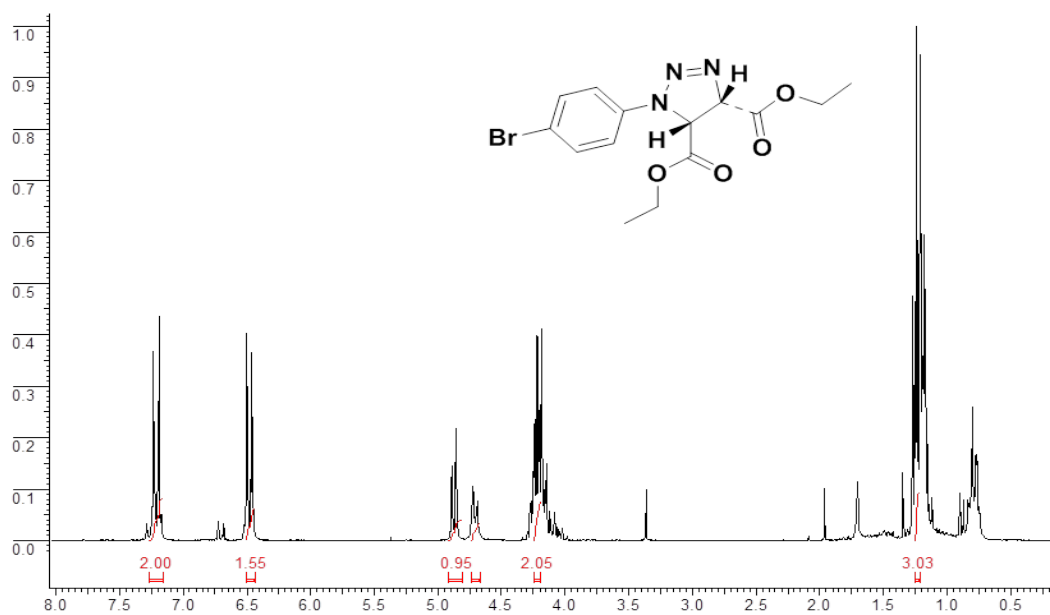
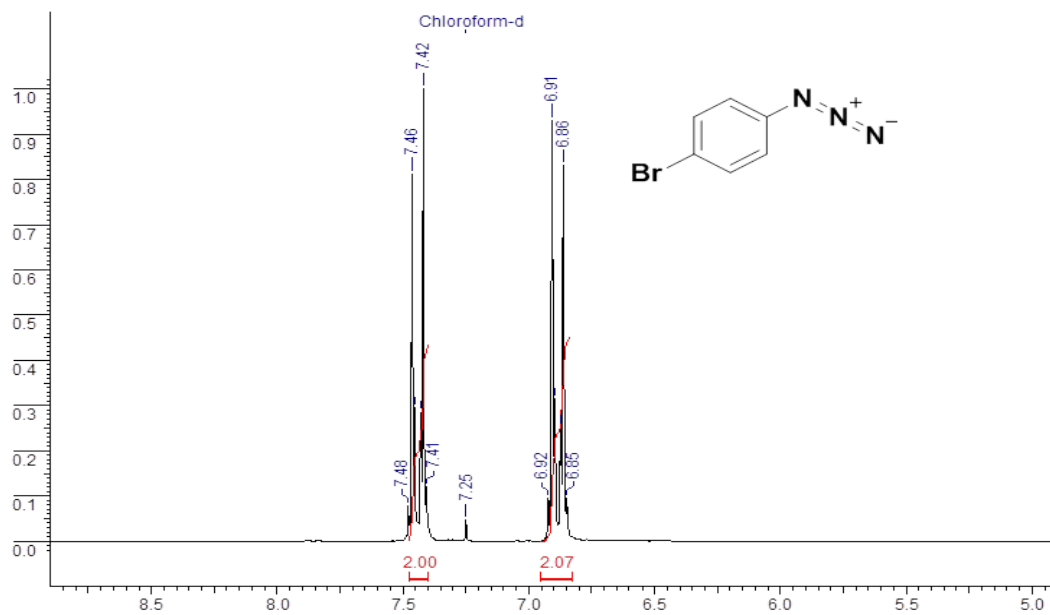
Posters and Oral presentations

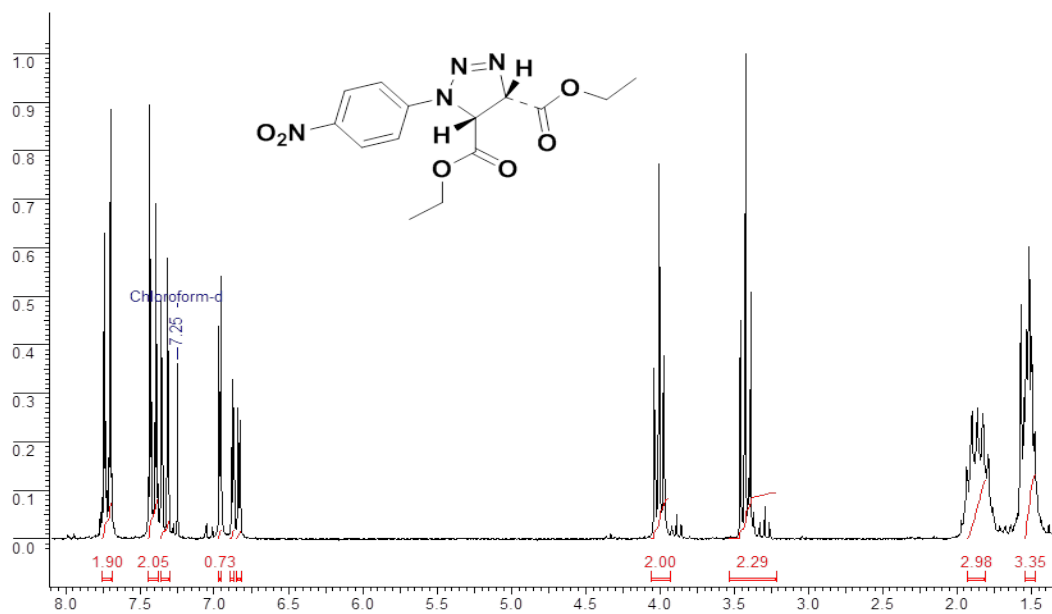
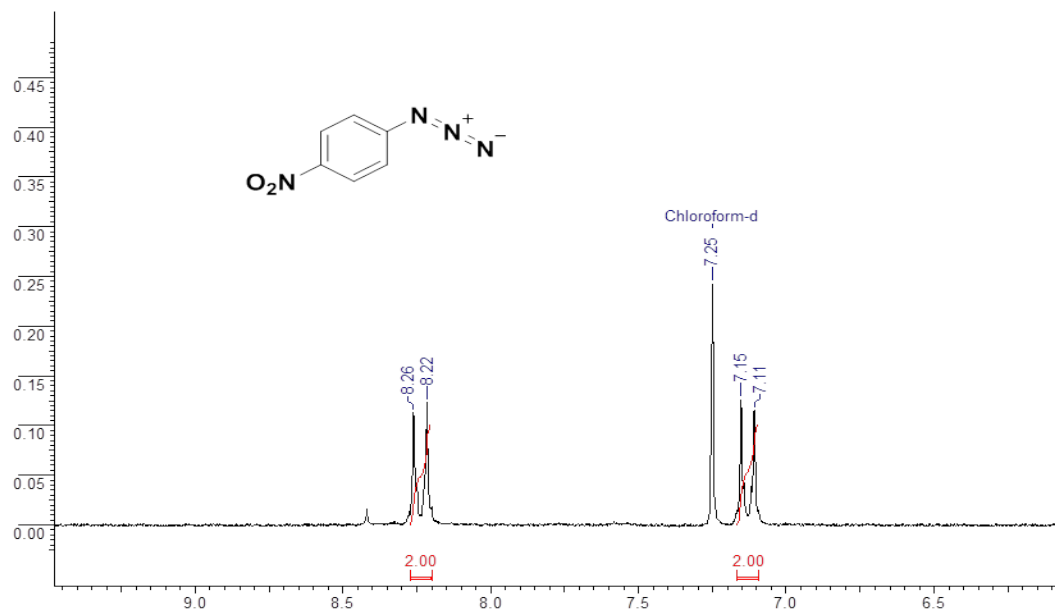
- Won best poster award for poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 27th-28th February 2011.
- Poster presented at “CRSI Zonal meeting” organized by CSIR-National Chemical Laboratory, Pune from 13th-14th May 2011.
- Poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 27th-28th February 2012.
- Poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 27th-28th February 2013.
- Poster presented at “16th CRSI National Symposium in Chemistry (NSC-16)” organized by IIT Mumbai from February 7th-9th 2014.
- Poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 27th-28th February 2014.

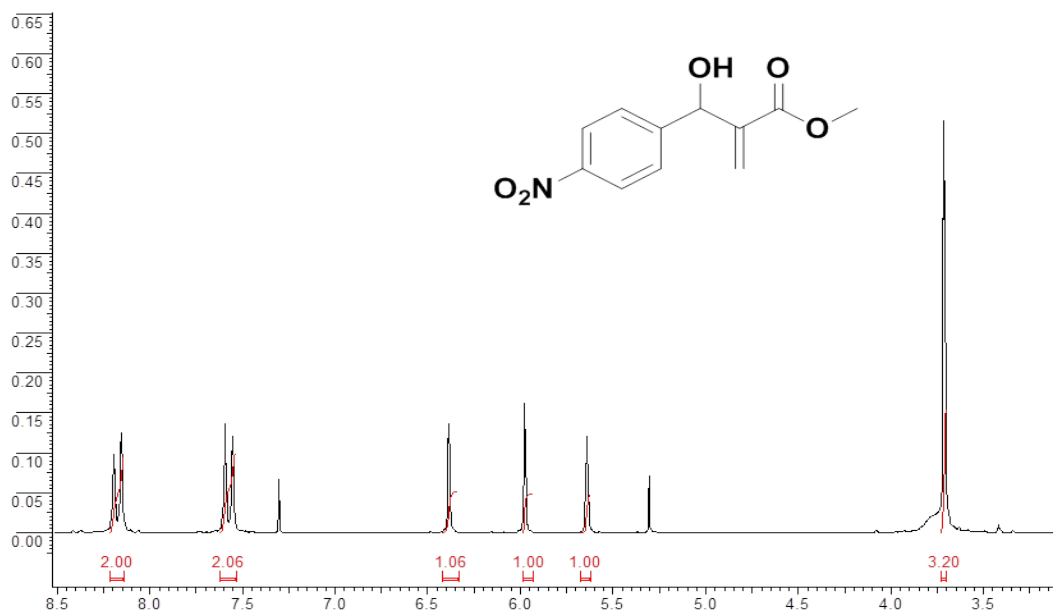
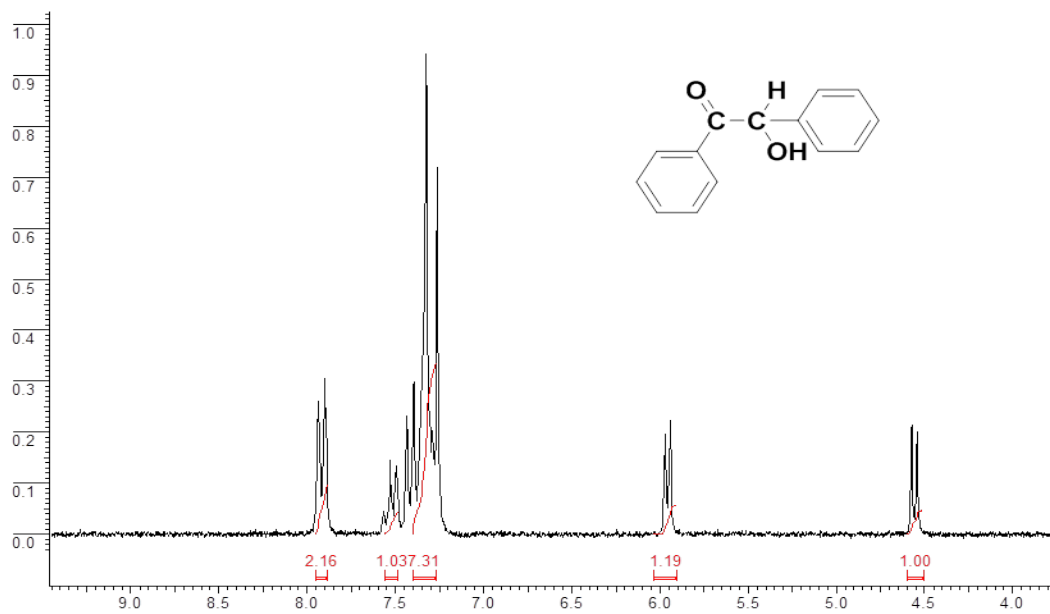
Appendix E

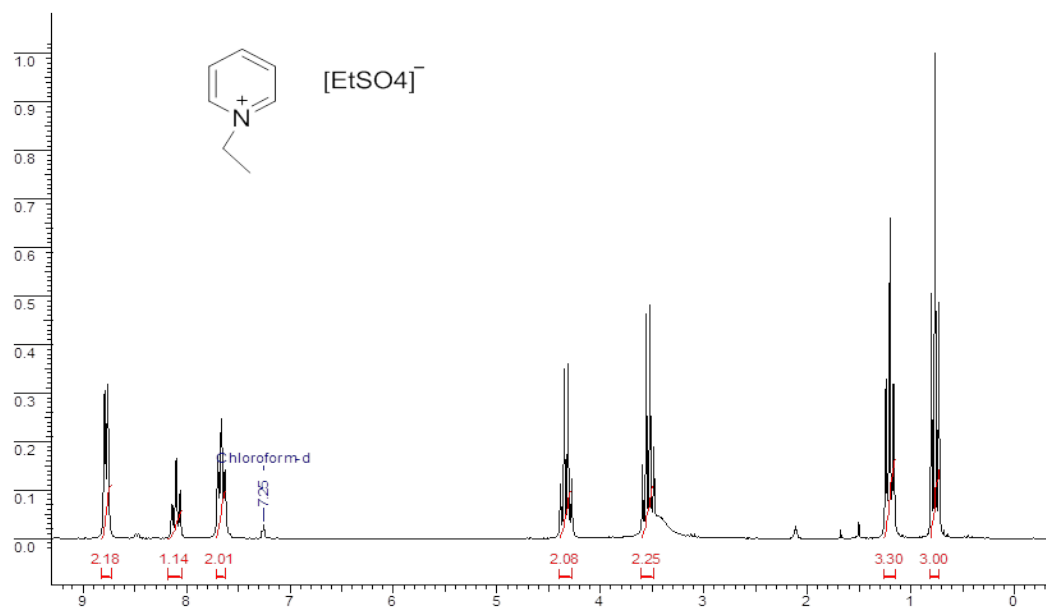
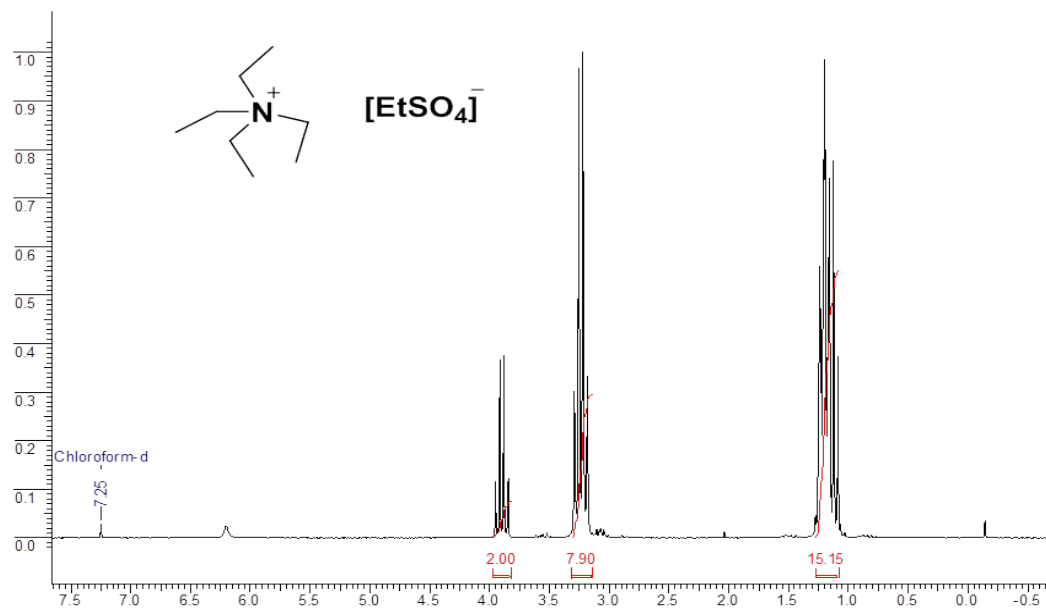
NMR Spectra:

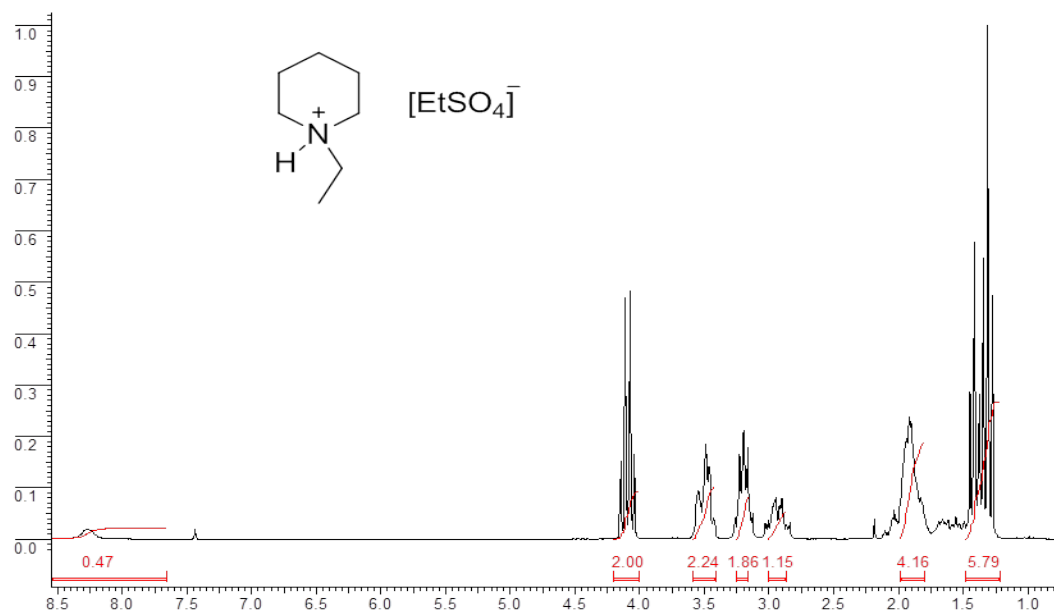
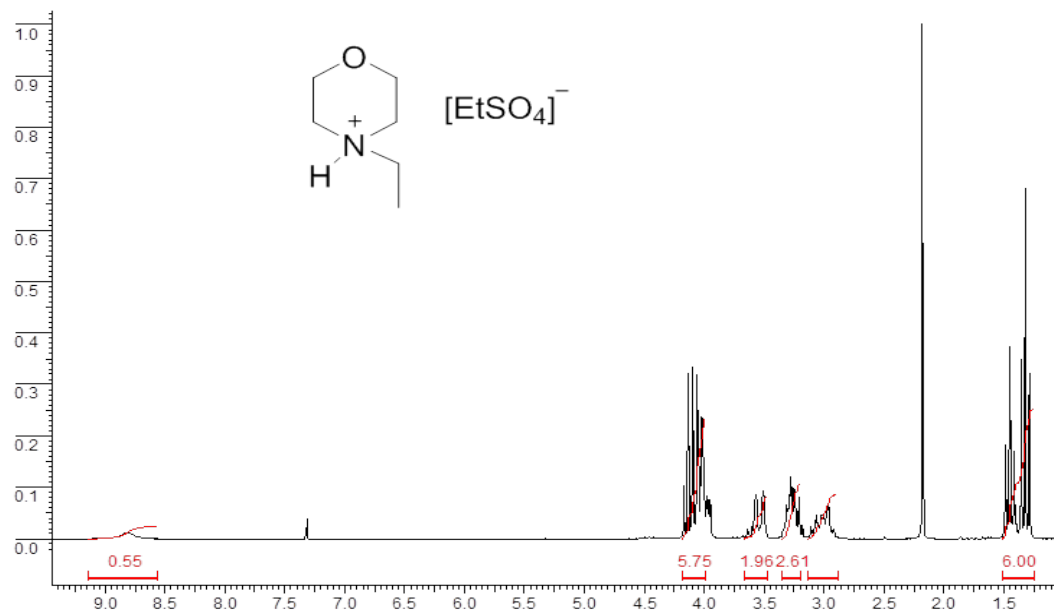


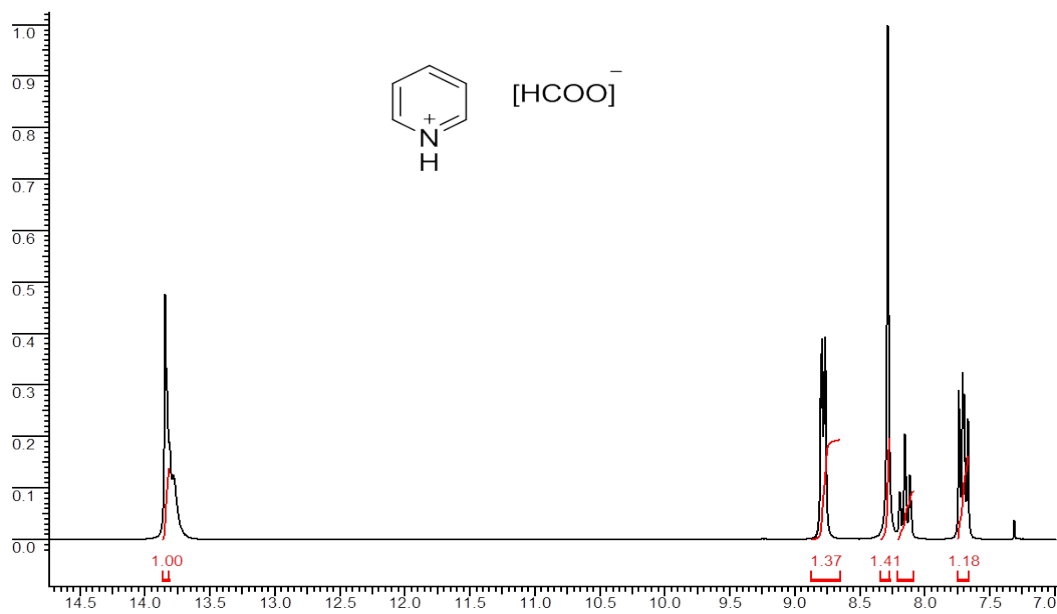
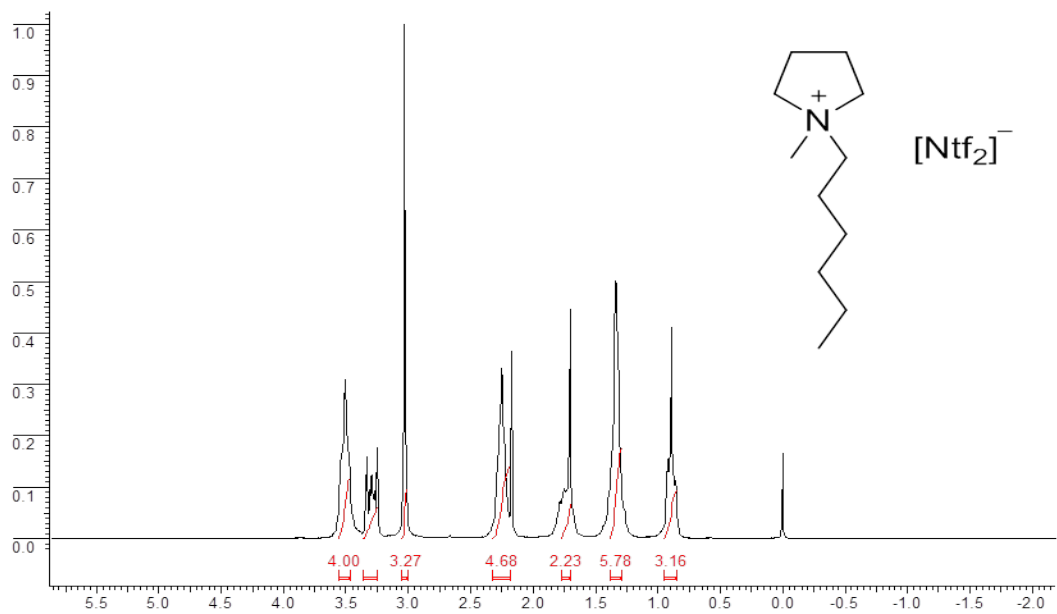


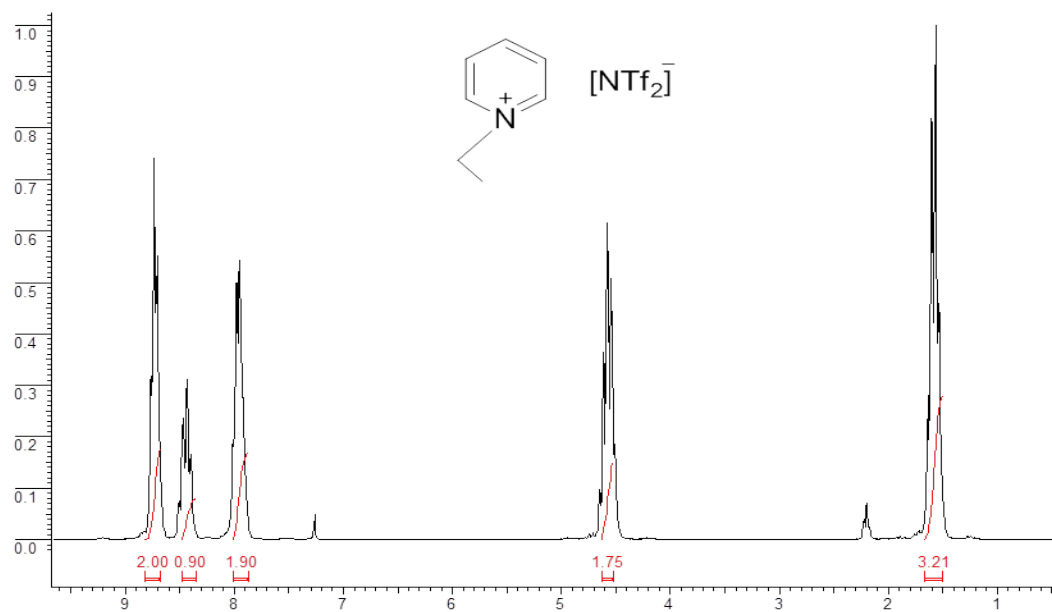
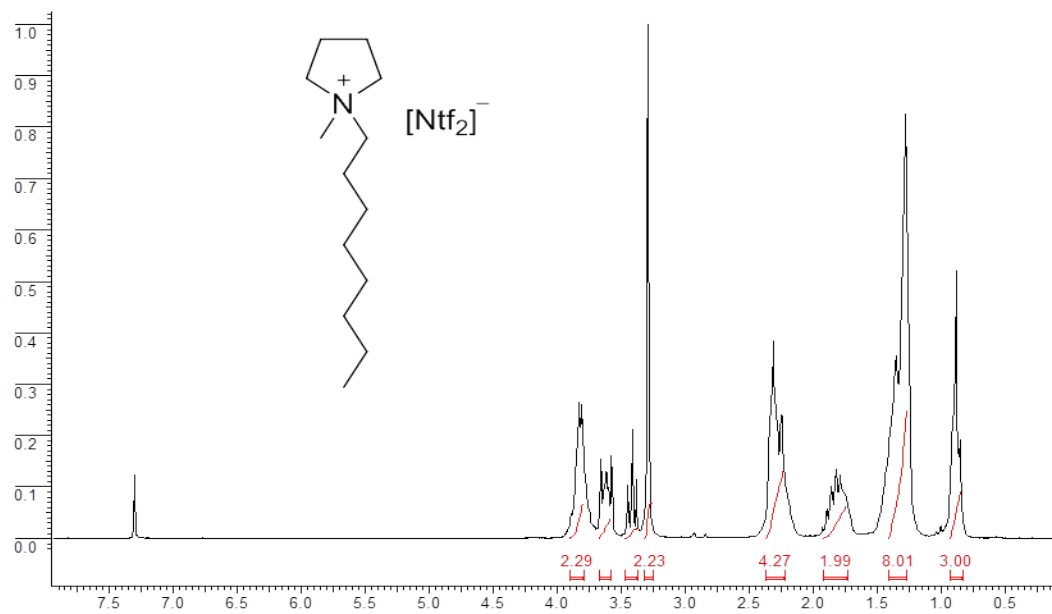


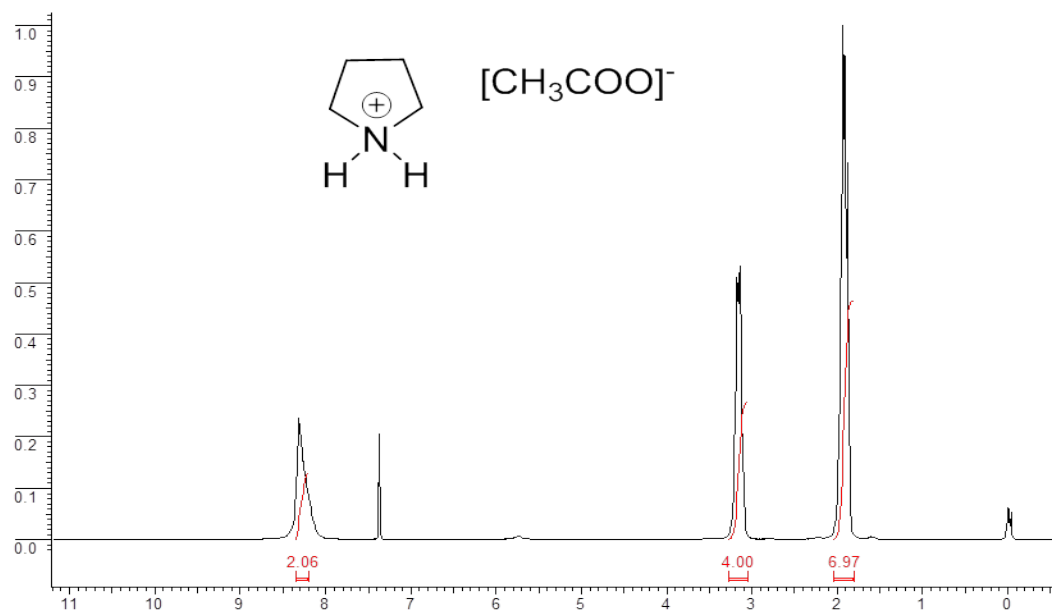
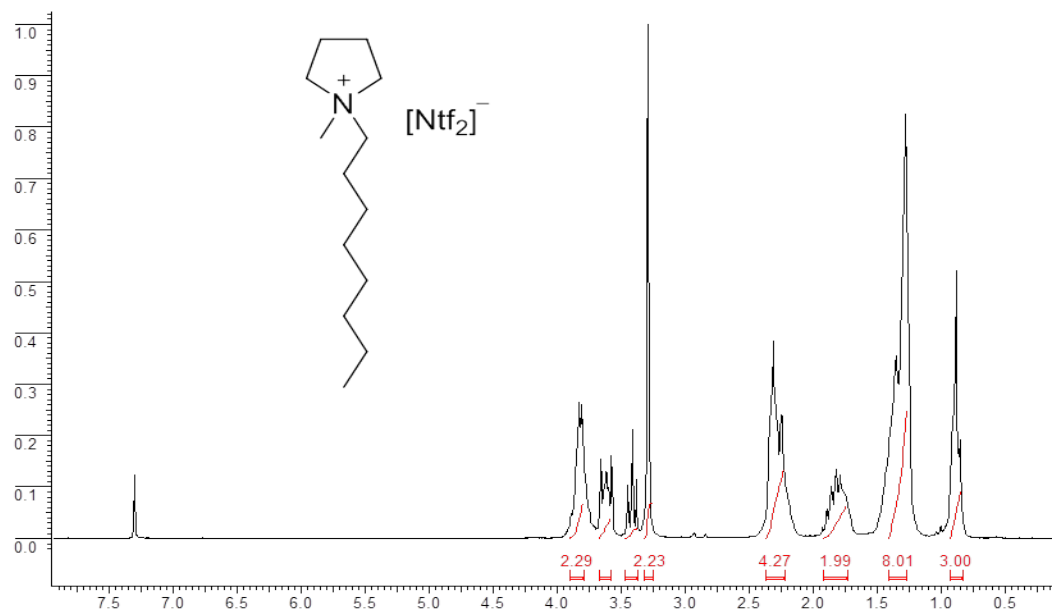


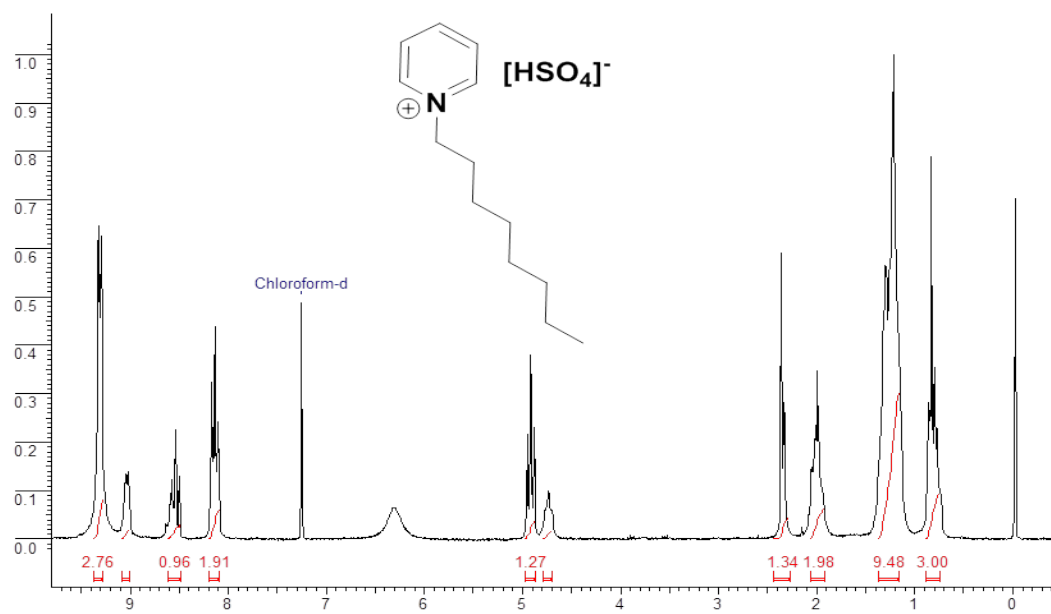
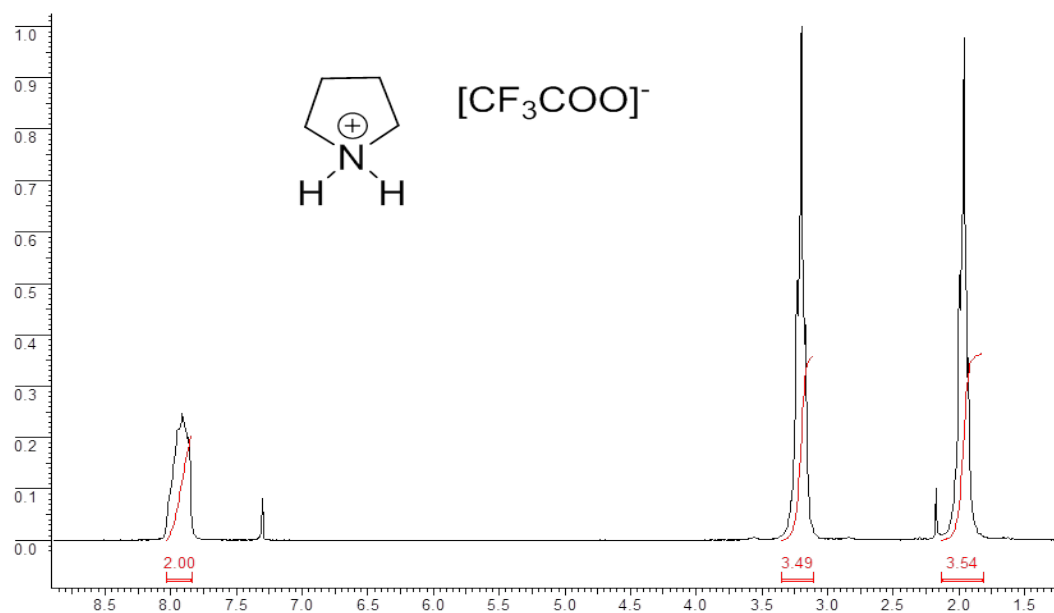












(for rest spectra pl. refer *RSC Adv.* **2015**, *5*, 2994-3004.)

Erratum