

**Physical-Organic Aspects of Diels-Alder Reactions in  
Eutectic and other Environmental Benign Media**

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**Academy of Scientific & Innovative Research  
(AcSIR) for the degree of**

**Doctor of Philosophy  
*in*  
Chemical Sciences**



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# CERTIFICATE

This is to certify that the work incorporated in this thesis entitled, “**Physical-Organic Aspects of Diels-Alder Reactions in Eutectic and other Environmental Benign Media**” submitted by **Mr. Amit S. Nagare**, for the degree of **Doctor of Philosophy** to **AcSIR**, was carried out by the candidate under my supervision in the Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune-411008, India. Any material that has been obtained from other sources has been duly acknowledged in the thesis.

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# CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled “**Physical-Organic Aspects of Diels-Alder Reactions in Eutectic and other Environmental Benign Media**” submitted for the award of degree of **Doctor of Philosophy** in Chemical Sciences to Academy of Scientific & Innovative Research (AcSIR). This work has not been submitted by me to any other institution or university. This work was carried out by me at the CSIR-National Chemical Laboratory, Pune, India, under the supervision of Dr. Anil Kumar. Such materials as obtained from other sources have been duly acknowledged in the thesis.

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*Dedicated to*

*My*

*Family and Friends*

*Who paved my way towards light...*

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“Science urges us to occupy by our mind the immensity of the knowable world; our spiritual teacher enjoins us to comprehend by our soul the infinite spirit which is in the depth of the moving and changing facts of the world; the urging of our artistic.”

–Gurudev Rabindranath Tagore

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“When life is bitter, say thank you and grow,”  
“And when life is sweet, say thank you and celebrate.”

–Amit Nagare

## Abstract

# Physical-Organic Aspects of Diels-Alder Reactions in Eutectic and other Environmental Benign Media

In the present work, we focus on the delineation of the physical forces that are responsible for C-C bond formation reactions performed in environmental benign unconventional media. The idea of “unconventional solvents” expresses the common concern of today’s chemists to minimize the environmental impact resulting from the use of existing obnoxious solvents in chemical production. It is known that the consequence of a chemical reaction is strongly correlated to the mutual interactions between a reacting molecule and the solvent molecules surrounding it. Physico-chemical aspects of these solute-solvent interactions *i.e.* solvent effect in unusual media have been studied with reference to activation energy barrier and reactivity for usual solvents available in the literature. Throughout our research work, we have concentrated on three unusual media: i) Deep eutectic solvents (DESs), ii) Nature inspired supersaturated solvents and iii) Water. Organic reactions have been carried out in DESs, Nature inspired supersaturated solvents, water and mixed aqueous media to discern the mechanistic details from the perspective of a physico-organic chemist. To broaden the applicability of DESs in organic chemistry and biological processes, physico-organic studies have been performed to understand the efficiency and dynamics of DESs. C-C bond formation reactions have been termed as the foundation of organic synthesis since it gives a boon to the organic chemists to synthesis compounds having structures ranging from simple to complex. The Diels-Alder reactions exhibit small solvent effects due to the presence of the iso-polar activated complex. However, the rate enhancement of a Diels-Alder reaction in water opened doors for future research on solvent effect on the kinetics of a Diels-Alder reaction.

For the convenience of presentation, different features of the present research work have been discussed in six different chapters. Brief description of these chapters is given below:

**First Chapter:**

This chapter describes an introduction based on critical literature survey on green chemistry, solute-solvent interactions; carbon-carbon bond forming reactions in various green solvents, nature inspired green media, DESs and water. Particularly, the main emphasis is focused on the organic reactions to examine intricacies of organic reactions, especially kinetics and physico-chemical parameters responsible for an alteration in rate and yield of the reactions.

The Diels-Alder reaction, a  $4\pi+2\pi$  cycloaddition reaction between dienophile and diene, is synthetically imperative reaction to construct six-membered cyclic biologically active compounds with high regio- and stereo-selectivity. A quantitative picture of thermodynamic and kinetic aspects of solute-solvent interactions has been presented here to validate the essentiality of solvent to carry out chemical reactions. Efficacy of water has been described from the perspective of its use as a green solvent. Efforts have been made to briefly discuss the current understanding of the research related to organic reactions in water both in homogeneous as well as heterogeneous conditions.

Brief literature reviews comprising physico-chemical characteristics of DESs have been introduced. Organic reactions catalyzed by nature inspired solvents are briefly reviewed in this chapter. Physico-organic forces responsible for the enhancement of rate in various organic reactions have been analyzed.

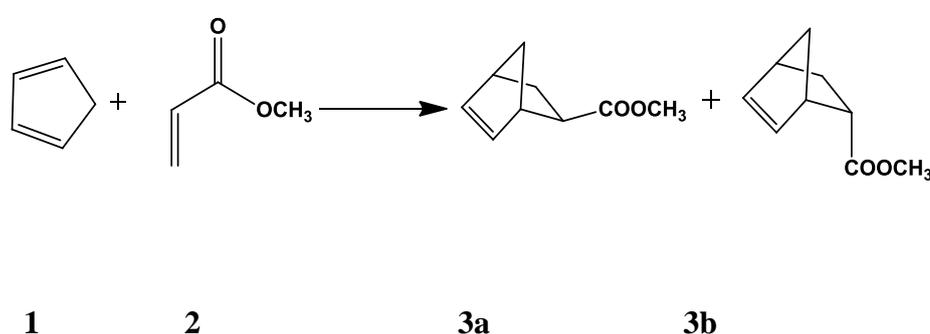
**Second Chapter:**

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. A brief note on the objectives of the designed research as well as the motivation of the present work has been penned down in the context of literature survey.

**Third Chapter:**

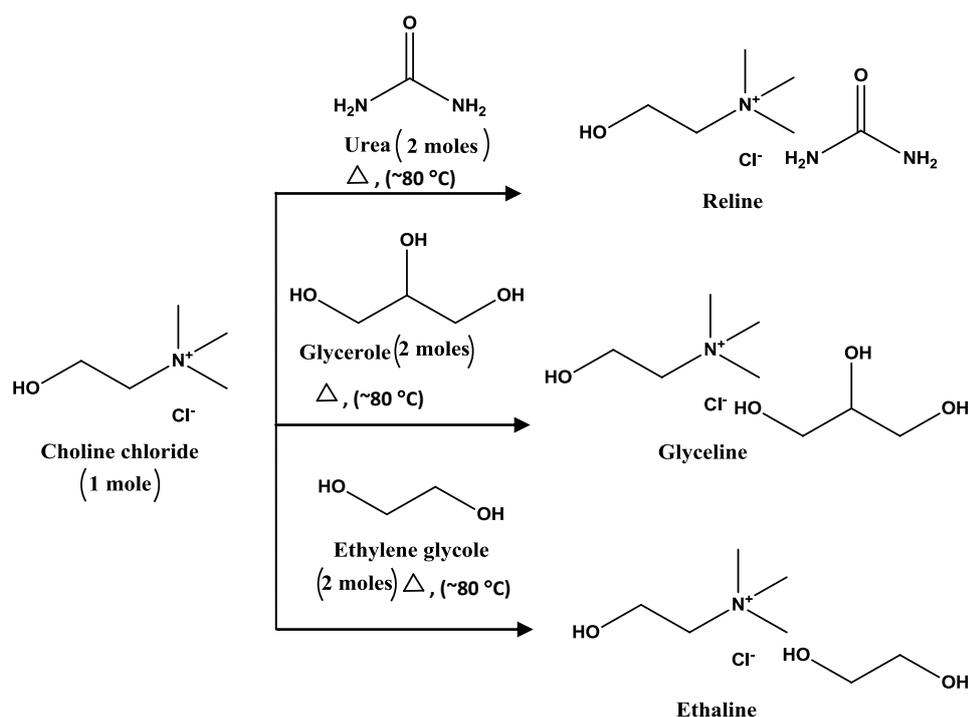
This chapter elaborates DESs examples which constitute a green hybrid of DESs-water mixtures and carbohydrate based eutectic mixtures. Based on the different solvent properties this chapter is divided into two sections,

Section I: The first part of the chapter concerned with the widening of the solvation window of water upon introduction of DESs as co-solvents to uphold its extensive application for performing organic reactions.



**Scheme 1.** The Diels-Alder reaction of cyclopentadiene (1) with methyl acrylate (2).

In the present chapter reactivity of Diels–Alder reaction has been quantified by the interactions of water DESs with the reactants and the activated complex. Hydrophobic hydration plays a pivotal role in solvation of the apolar reactants in aqueous and mixed aqueous solvent. The interactions of apolar solutes and mixed aqueous solvents are mainly guided by the extent of overlap of the hydrophobic hydration shells. The concentration of DESs in water has been increased to access nature of inter/intramolecular interactions between reactants and mixed water-DESs media. Kinetic investigations of the Diels–Alder reaction have been carried out in water-DESs solvent systems providing different individual behaviours. Different kinetic trends in the case of the water-reline mixture from water-glyceline and water-ethaline have been explained in terms of the difference in their viscosity and polarity parameters. High negative values of the pairwise interaction parameter value for aqueous glyceline and ethaline mixtures suggest that in highly aqueous region of glyceline and ethaline mixtures initial state of the reaction stabilised more than the transition state due to solvation initial state.



**Scheme 2.** Structures, compositions, and melting points of DESs.

Section II: The second part of present work is mainly focused on carbohydrate based eutectic solvents composed of glucose, fructose, maltose, *etc.* and urea/*N,N*-dimethyl urea (DMU). In this section of the chapter, efficacy of carbohydrate based eutectic solvents has been ensured through its utilization in Diels-Alder reaction. Carbohydrate-based eutectic solvent media can be regarded as highly ordered reaction media. Due to highly ordered reaction media, the viscosity of solvent tends to the higher range at low concentration of hydrogen bond donor *i.e.* urea and DMU. The Higher viscosity of the solvent media controls the key for activation energy *i.e.* for highly viscous reaction media activation energy tends to higher value and vice-versa for low viscous media. Highly viscous media holds the key behind the kinetics of bimolecular reaction because of effective formation of product it is necessary to break the order of reaction media to collect all the constituents to the reaction site. Therefore, the rate constant of bimolecular reactions in carbohydrate-based eutectic solvents are correlated with the viscosity of the solvent. In the present study carbohydrate based eutectic solvents are projected as alternative solvent media for bimolecular Diels-Alder reaction at high temperature.

Through this experimental observation, it can be concluded that though these reaction media requires higher temperature but by using these types of carbohydrate based eutectic solvents beneficial points like inexpensive, less toxic, nonvolatile, highly polar, biodegradable can be achieved. Again, simple methodological operation and environmentally benign ability will also make these designer solvent more attractive in their use.

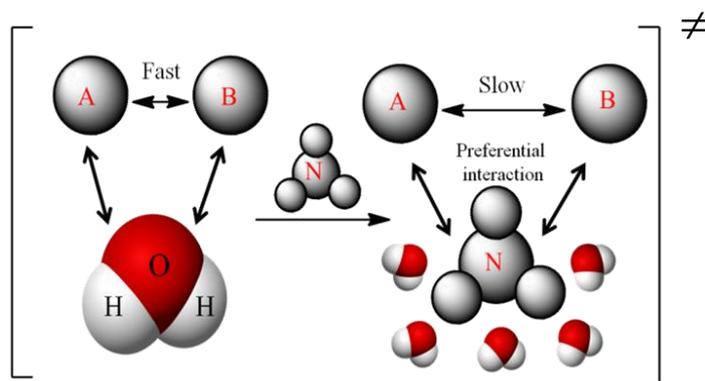
#### **Fourth Chapter:**

This chapter elaborates the delineation of physical parameters responsible for amazing augmentation in the reactivity as well as selectivity of Diels-Alder reactions in nature inspired supersaturated solvent. Thus, the significance of this organic reaction necessitates an investigation towards achieving alternative greener solvent systems in order to circumvent hazardous impact caused by the use of volatile organic solvents. In this chapter, we present nature inspired new supersaturated biodegradable medium for carrying out Diels-Alder reactions with efficacy under ambient conditions. Owing to the presence of an excess of carbohydrates and thus –OH groups, the new supersaturated solvent has been a medium of interest.

The reactivity of Diels-Alder reactions shows exceptional enhancement in a highly viscous supersaturated solvent at room temperature. Enhanced availability of hydrogen bonding of the supersaturated solvent has been determined to be responsible for the observed increment in rate. Present systematic kinetic and thermodynamic studies reveal the potential of new supersaturated solvent as an efficient environment-benign reaction medium as compared to other solvents used now.

#### **Fifth Chapter:**

This chapter deals with the kinetics and physical parameters governing Diels-Alder reaction in aqueous solution of tetraalkylammonium bromide. Depending upon the stability and solubility of proteins in aqueous salt solution envisage that LiCl, NaCl act as salting-out (S/O) and tetraalkylammonium salts, GnCl, LiClO<sub>4</sub> act as salting-in (S/I) in aqueous solution. In the identical situation, the nature of GnCl, LiClO<sub>4</sub> and LiCl show conflicting nature in polar solvents like ethylene glycol and formamide. However, it has been observed that the behaviour of tetraalkylammonium halide salts (R<sub>4</sub>NX, R = alkyl group, X = Br group) are S/I in these types of solvents.



**Figure 3:** Diagram explaining preferential interaction of reactants A and B with water and aqueous R<sub>4</sub>NX salts in TSC<sup>‡</sup>

The present work deals with the exclusivity which was shown by R<sub>4</sub>NX in aqueous solution as well as in polar solvents. Physico-organic studies of these salts expose the diverse individual behaviour of R<sub>4</sub>NX from their higher analogs in aqueous solution. The amount of S/I and S/O effect caused by aqueous R<sub>4</sub>NX has been explored by the kinetic study of Diels-Alder reaction, solubility study of hydrophobe molecule, viscosity measurements and correlation with computer simulation studies. The atypical nature of R<sub>4</sub>NX in water has also been elucidated by the Setschenov equation ( $k_s$ ) and  $\Delta G_{\text{solvation}}$  determination.

### Sixth Chapter:

Results and principle conclusions have been summarized in the present chapter. Moreover, the future prospects of research works carried out in the present thesis has been discussed in this chapter. In a nutshell, the significant contributions from investigations carried out in the present thesis are as follows:

1. Factors responsible for the rate and yield enhancement has been analyzed in the case of carbohydrate based eutectic solvents as well as green hybrid media through physico-organic investigations.
2. In addition, the possibility of use of co-solvents to delineate the contribution of polarity, hydrophobicity and mode of hydrogen bonding in C-C bond formation reaction has also been demonstrated judiciously in the present work

3. New nature inspired supersaturated solvent media to prove to be alternative media to conventional organic solvents, ionic liquids.

4. The exact role of  $R_4NX$  salts in water has been analyzed through kinetic, viscosity and solubility studies to evaluate nature of these categories of salts in ethylene glycol and formamide.

The work presented in the thesis offers a fresh outlook of the 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 Abbreviations\*

CV	Cyclic voltammogram
DES	Deep eutectic solvent
DSC	Differential scanning calorimetry
GC	Gas chromatography
IUPAC	International Union of Pure and Applied Chemistry
XRD	X-ray diffraction spectroscopy
T <sub>f</sub>	Freezing point/temperature
T <sub>g</sub>	Glass transition temperature
TLC	Thin layer chromatography
T <sub>m</sub>	Melting point/temperature
Uv	Ultraviolet
Wt %	Weight percent
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
NR	Nile red
RTIL	Room temperature ionic liquid
IR	Infrared spectroscopy
HBD	Hydrogen bond donor
<i>h</i>	Planck's constant
DMU	1, 3-dimethylurea

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Ch <sup>+</sup>	Choline
ChCl	Choline chloride
cP	centipoises
S/I	Salting-in
S/O	Salting-out
LPDE	Lithium perchlorate in diethyl ether
MPa	Mega Pascal
[EtNH <sub>3</sub> ][NO <sub>3</sub> ]	Ethyl ammonium nitrate
[Bmim][BF <sub>4</sub> ]	1- butyl-3-methylimidazolium tetrafluoroborate
[Bmim][PF <sub>6</sub> ]	1-Butyl -3- Methylimidazolium hexafluorophosphate
[EMIM]Cl	1-Ethyl-3-methylimidazolium chloride
[BMIM]Cl	1-Butyl-3-methylimidazolium Chloride
[BMIM] [FeCl <sub>4</sub> ]	1-butyl-3-methylimidazolium tetrachloroferrate
[EMIM] <sub>2</sub> [UCl <sub>6</sub> ]	1-ethyl-3-methylimidazolium hexachlorouranate
[EMIM][TaF <sub>6</sub> ]	1-ethyl-3-methylimidazolium hexafluorotantalate
[EMIM][NbF <sub>6</sub> ]	1-ethyl-3-methylimidazolium hexafluoroniobate
EXAFS	Extended X-Ray Absorption Fine Structure Spectroscopy
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
NADES	Natural deep eutectic solvent
VOCs	Volatile organic compounds
$E_T^N$	Electronic transition normalised

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$\alpha$	Hydrogen bond donor acidity
$\beta$	Hydrogen bond acceptor basicity
$\pi^*$	Polarizability
Betaine dye (30)	2, 6-Diphenyl-4-(2,4,6-triphenyl- <i>N</i> -pyridino) phenolate
Betaine dye (33)	2, 6-Dichloro-4-(2,4,6-triphenyl- <i>N</i> -pyridino) phenolate
NA	4-Nitroaniline
DENA	<i>N, N</i> -Diethyl-4-nitroaniline
ATR-IR	Attenuated Total Reflectance Infrared Spectroscopy
CESs	Carbohydrate-based eutectic solvents
R <sub>4</sub> NX	Tetraalkylammonium halide salts
DAR	Diels-Alder reaction

(Common abbreviations only)\*

# Chapter 1

## Introduction

*“Green chemistry is replacing our industrial chemistry with nature's recipe book. It's not easy, because life uses only a subset of the elements in the periodic table. And we use all of them, even the toxic ones.”*

*- Janine Benyus*



*The present chapter deals with the physico-organic and physico-chemical aspect of organic reactions in green solvent media. Significance of green solvent media in different organic transformations is followed by the introduction of various terminologies of organic reactions and solvents. In the present chapter emphasises the solvent effect which is accountable factor for unusual outcome in the case of C-C bond formation reactions.*

## 1.1 Solvents corollary in green chemistry

### 1.1.1 An overview

Functioning of our Mother Nature has been an excellent example of various complex chemical reactions which uphold this planet above other planets. Present modifications in the modernisation were largely inspired by the functioning of nature. During the 21<sup>st</sup> century, it has been observed that contemporary industrialization induce certain amount of pollution into the environment. These contemporary industrializations largely supported by the chemical transformation invented by the chemists.<sup>1</sup> Scientific evidence shows that utilisation of scientific process is also capable of solving the scientific mystery regarding the existence of human and other animals on the planet.<sup>2</sup> Emerging trends in the chemical transformations introduced unwanted hazardous pollutants in the environment. To solve this predicament, an initiative was taken to carry out scientific developments, called as Green Chemistry. These developments of chemical process include reduction of waste production, designing renewable and cost effective safer solvents and at the same time, process should not compromise with the scientific invention which leads to benefit the economy. Paul T. Anastas Director, *Center for Green Chemistry and Green Engineering* revealed that, “The utilization of a set of principles that reduces or eliminates the use or production of harmful chemical compounds in the manufacture, planning and chemical products’ application.”<sup>3</sup> During the employment of variety of disciplines in chemistry and the molecular sciences, there is a rising admiration in the promising area of green chemistry, which is a requirement in the design and attainment of sustainable development.<sup>4-6</sup>

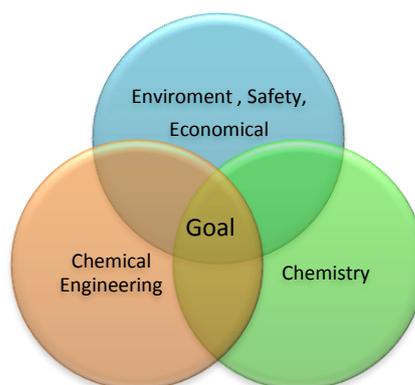
International Union of Pure and Applied Chemistry (IUPAC) embraced the definition of green chemistry as, “The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances.”<sup>3</sup> According to IUPAC standards, the development of contemporary chemical products should not be done at the expense of generation of toxic, hazardous waste. The twelve principles of green chemistry provide a constructive path for minimising toxicity, hazards and waste control.<sup>3,4</sup> According to the first principle of green chemistry which is basically related to human life and medicinal science states that, it is better to stop something bad from happening than it is to deal with it after it

has happened. The remaining 11 principles can be summarized under following headings:<sup>3</sup>

1. **Atom economy-** Synthetic methods should be planned in a way that it can make best use of the inclusion of all materials utilized in the process into the final product.
2. **Less hazardous chemical synthesis-** Synthetic methodologies should be planned and utilized in a way that it can generate extremely small or no toxicity and cause minimum hazards to surrounding environment.
3. **Designing safer chemicals-** Chemical products should be planned to conserve effectiveness of the function while minimizing toxicity.
4. **Safer solvents and auxiliaries-** The use of unnecessary solvents should be avoided through minimum solvent and low toxicity propelling methodologies; if needed use of environmental friendly solvents and auxiliaries are largely appreciated.
5. **Design for energy efficiency-** Minimum energy requirements should be encouraged for their environmental and financial impacts. Synthetic methodologies should be carried out at ambient temperature and pressure.
6. **Use of renewable feedstocks-** Use of raw material should be renewable and encouraged.
7. **Reduce derivatives-** Unnecessary modifications (use of blocking group, protection/deprotection and temporary modification of physical or chemical processes) should be restricted whenever possible.
8. **Catalysis-** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
9. **Design for degradation-** Chemical products should be designed in such a way that, at the end of their function they do not endure in the atmosphere and as an alternative break down into harmless degradation products.
10. **Real-time examination for pollution prevention-** Systematic analytical methodologies need to be further developed to allow for real-time in-process examination, prevention and control prior to the development of harmful chemical compound.
11. **Inherently safer chemistry for accident avoidance-** Chemical compounds and the form of a methodologies used in a chemical process should be chosen so as to

reduce the probable chemical accidents, fires, including chemical discharge, explosions.

Not all environmental pollution problems can be solved by simply using green chemistry methodologies, but by using these fundamental approaches we momentarily prevent environmental pollution. The constitution of Green Chemistry is made for achieving the sustainability and minimizing the hazards propelled by the conventional methods of synthesis which have potential to pollute the environment.



**Figure 1.** Graphical illustration of environment benign solvents in chemical process.<sup>7</sup>

**Figure 1** represents the utilization of solvents in chemical process in order to enhance efficiency of reactions with minimal environmental concerns.<sup>7</sup> In all the synthetic research methodologies, the use of solvent for carrying out reaction and separation purpose is essential. Sequential synthesis process requires large amount of solvents for carrying out reactions, extractions, purification of products. So among all twelve principles of green chemistry, the present thesis is mainly focused on the evolution and utilization of environment benign solvents.

## 1.2 Solvent effects in chemistry

Progress in the development of innovative solvent also propagates the development of knowledge of chemistry.<sup>8</sup> Amid all other identified solvents; water was regarded as a universal solvent. The Greek alchemists regard “*water*” as standard for all chemically active liquids. According to Greek philosophers the meaning of “*water*” is to give the whole thing liquid or dissolved. Throughout the centuries the alchemist are on the quest of exploration of universal solvent. Paracelsus (1493–1541) called water as

“*Alkahest*” or “*Menstruum universale*” due to its utilisation in dissolution and other synthetic methodology purposes, which signifies the importance of solvent in various scientific and non-scientific fields.

Between the 15<sup>th</sup> and 18<sup>th</sup> centuries, aspirant chemists had discovered numerous new solvents, new reactions, and new synthetic compounds but they fail to invent any “*Alkahest*” (the hypothetical universal solvent sought by alchemists). The practical experiments experienced in the research methodologies taught chemist “*like dissolve like*” a chemical law regarding different solvents. During this period all the concepts are conceptualised on the basis of solution and dissolution of solute in the solvent, chemists are yet to find physical or chemical intricacy behind the driving force of dissolution till that period. At that time, it was believed that the nature of substance was lost on dissolution. But Van Helmont (1577–1644) asserted that dissolved solute has not disappeared, in fact it was present in solution in aqueous form and can be recovering by some physical technique.<sup>9</sup> According to well-known Russian polymath Lomonosovs’ (1711–1765) theory about dissolution, all the solvents pierce into the aperture of the body to be dissolved and then steadily dislodge the particles. However, what kind of physico-chemical forces are behind this process of removal are unanswered at that time.<sup>3</sup>

Modern solution theory was mainly conceptualised by three scientists, amongst them first one is French researcher Raoult’s (1830–1901), who analytically studied the consequences of dissolved non-ionic compound on the alteration of freezing and boiling point of liquids. According to their observations, change in the solute/solvent ratio is directly proportional to the change in the physical properties of the solutions.<sup>10</sup>

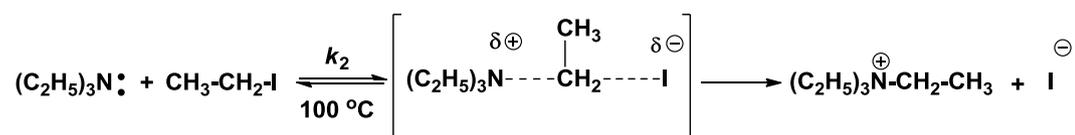
In 1884, Arrhenius theory for partial and total dissolution of ionic solutes into anions and cations in solution explains the effects of inorganic solutes on the physical properties of the solutions. According to Arrhenius, the derivation of dissociation theory can be determined by comparing the results obtained by the measurement of electro conductivity and osmotic pressure of dilute solutions.<sup>11</sup>

The Dutch physical chemist van’t Hoff made osmotic pressure measurements extremely important physico-chemical property in the study of solutions. It has been observed that by the replacement of pressure by osmotic pressure makes it as an important application for laws holding for gases to solutions.<sup>12</sup> These three

fundamental advances established the foundation in the field of modern solution theory. Therefore to their recognition, the first Nobel prizes in chemistry were awarded to van't Hoff (in 1901) and Arrhenius (in 1903). The development of solution chemistry is also associated with the revolutionary work of Ostwald (1853–1932), Nernst (1864–1941), Lewis (1875–1946), Debye (1884–1966), E. Hückel (1896–1980), and Bjerrum (1879–1958). More comprehensive reviews on the advancement of modern solution chemistry can be found in references 13–15.

### 1.2.1 Solvent effects on organic reactions

The influences of solvents on the chemical reactions are largely reflected through the alteration in the rate of reactions. Berthelot and Péan de Saint-Gilles in 1862 first noted the solvent effect on the esterification of acetic acid with ethanol.<sup>16</sup> In 1890, Russian chemist Menshutkin comprehensively studied the reaction of trialkylamines with haloalkane and come to a decision that we cannot segregate the reaction from the solvent in which it is executed.<sup>17</sup> During the preparation of acetamide, Menshutkin discovered that in the reaction of liquids, one of the reaction partner (acetic acid, aniline or vice versa) may represent an unfavourable behaviour towards the solvent. Menshutkin correlated the experimental results with solvent's chemical properties and not with physical properties.



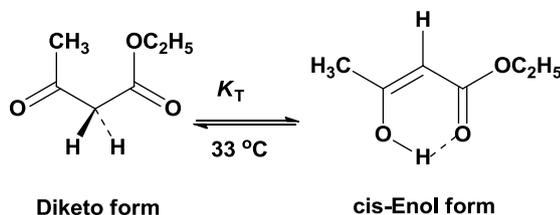
**Scheme 1.** Solvent effects on a Menshutkin reaction.<sup>17</sup>

**Table 1.** Solvent effect on Menshutkin reaction in solvents of different polarities.<sup>17</sup>

Solvent	<i>n</i> -Hexane	Benzene	Methanol	Benzyl alcohol
$k_2^{rel}$	1	36	287	742
Solvent polarity	—————→			

In 1896, the significance of solvent consequence on chemical equilibria was first explored on keto-enol tautomerism reactions.<sup>18</sup> The German chemist, Johannes Wislicenus had performed his pioneer study of the keto-enol equilibrium of ethyl formylphenylacetate in eight different solvents. However, the keto form prevailed

only in alcoholic and enol form in chloroform or benzene solvents. The final ratio in which the keto-enol forms coexist must be dependent on the nature of solvent. According to his suggested preposition, dissociation power of solvent related to dielectric constant is responsible for the coexistence of two tautomeric forms.



**Scheme 2.** Solvent effects on a tautomeric equilibrium.<sup>19,20</sup>

**Table 2.** Solvent effects on a tautomeric equilibrium.<sup>19,20</sup>

Solvent	Gas phase	<i>n</i> -Hexane	Benzene	Methanol	Acetic acid
$K_T$	0.74	0.64	0.19	0.062	0.019
% Enol	43	39	16	5.8	1.9
Solvent polarity	—————→				

Later, Stobbe was the first, who categorised and reviewed these results upon ability of solvents to isomerise tautomeric compounds. He has classified the solvents into protic and aprotic categories, which are foremost similar to contemporary solvents.<sup>21</sup>

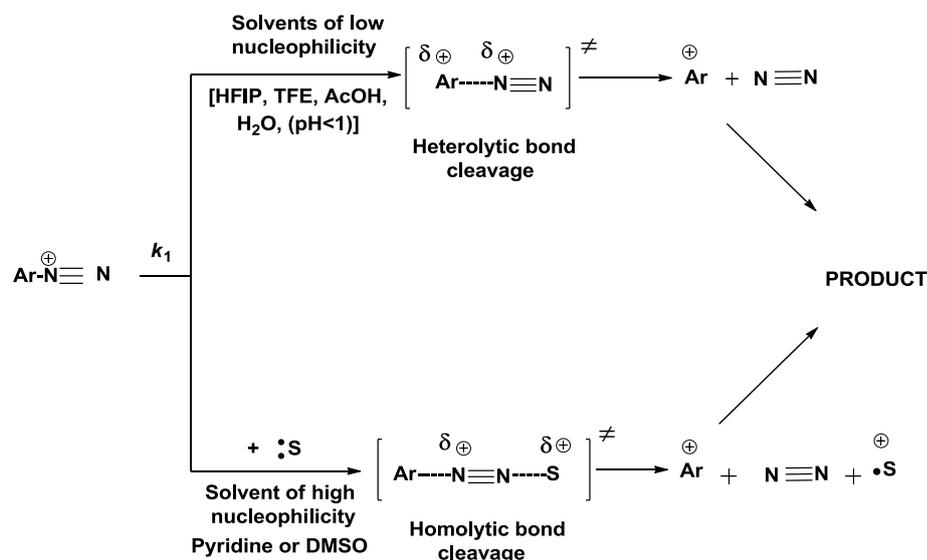
## 1.2.2 Solvent effects on chemical reactivity

In preliminary part of the introduction two reactions have been mentioned, which are mainly focused on screening the solvent effects on the reaction rate and chemical equilibria. In chemical transformation, solvent can affect the course of reaction drastically by affecting the mechanism of the reaction.

### 1.2.2.1 Solvent effect on competitive reaction mechanisms

Dediazoniating arene diazonium salts has been carried out by Zollinger *et. al.*<sup>22,23</sup> According to Zollinger *et. al.*, the mechanism of dediazoniating arene diazonium salts shows two competitive reaction mechanisms by alteration in solvents. According to the illustrated mechanism, in low nucleophilic solvents such as hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE) the rate determining step is a

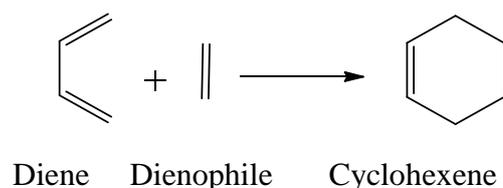
heterolytic cleavage of the diazonium ion to form aryl cation and molecular nitrogen. The heterolytic cleavage then followed by the reaction of the cation with offered nucleophile. On the other hand, a homolytic cleavage of diazonium ion is predominant to give an aryl radical and subsequent product in pyridine or dimethyl sulfoxide (DMSO), which has low redox potential and high nucleophilicity.



**Scheme 3.** Solvent effects on the competitive reaction mechanisms.<sup>22,23</sup>

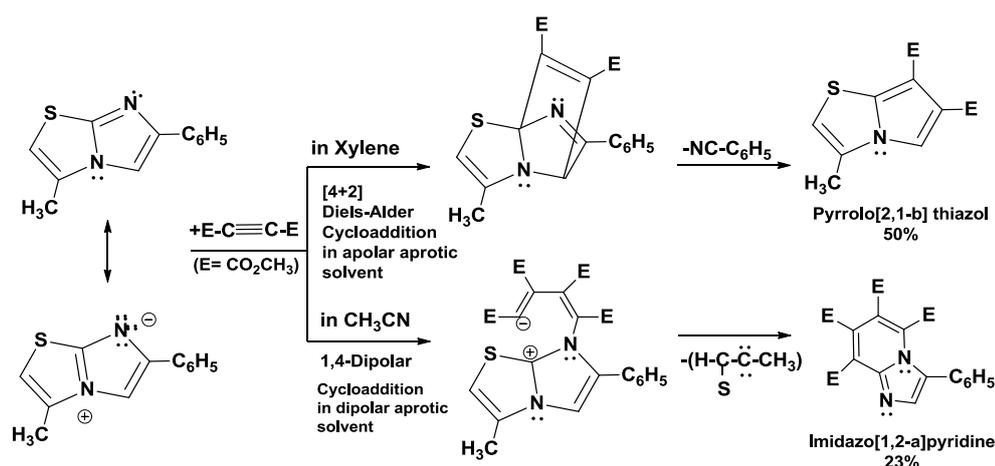
### 1.2.2.2 Solvent effect on dichotomic reaction pathway

The proficient development of carbon-carbon bonds provides the backbone of synthetic organic chemistry. Among all synthetic organic reactions, Diels-Alder reaction is one of the most important organic reactions which represent C-C bond forming reaction for the construction of cyclic structures. Diels-Alder reaction is cycloaddition reaction between a conjugated diene and alkene molecule termed as dienophile to form cyclohexene system (**Figure 4**). Otto Diels and Kurt Alder were awarded Nobel Prize in Chemistry in 1950 for their pioneer work on this reaction.<sup>24</sup>



**Scheme 4.** A typical example of Diels-Alder reaction.

Simple modification in the solvent system can lead to the different reaction mechanism and consequently different reaction product from the same reaction. Abe and co-worker has demonstrated the cycloaddition reaction of imidazo-[2,1-b]thiazole with dimethyl acetylene dicarboxylate in xylene and acetonitrile. Diels-Alder reaction of imidazo-[2,1-b]thiazole with dimethyl acetylene dicarboxylate in two different solvents (xylene and acetonitrile) gives two different products through different mechanisms.<sup>25</sup>



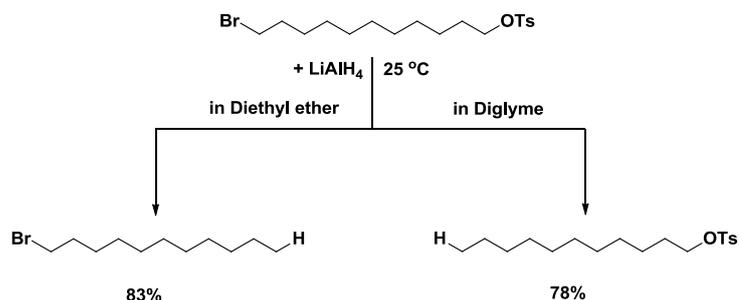
**Scheme 5.** Solvent effects in cycloaddition reaction of imidazo-[2,1-b]thiazole with dimethyl acetylene dicarboxylate.<sup>25</sup>

The mechanism of cycloaddition reaction in xylene and acetonitrile in **Figure 5** shows that in xylene, this reaction proceeds through a 4+2 $\pi$  cycloaddition pathway to give pyrrolo [2,1-b]thiazol as product; on the contrary, the same reaction propagated through a 1,4 cycloaddition pathway in a dipolar aprotic solvent like acetonitrile to give an imidazo [1,2-a] pyridine as final product. Formation of different types of reaction products clearly point out that choice of solvent determines the outcome of product.

### 1.2.2.3 Chemoselectivity in the perspective of solvent effect

IUPAC defines chemoselectivity as "the preferential reaction of a chemical reagent with one of two or more different functional groups". A reagent is said to be as high chemoselective, if reaction occurs with only a limited number of different functional groups.<sup>26</sup> The reduction of 11-bromoundecyl tosylate a bifunctional compound with lithium aluminium hydride in different solvents has been demonstrated by Krishnamurthy.<sup>27</sup> Selective reduction of tosylate group to *n*-undecyl bromide has

been carried out in diethyl ether, on the other hand in diglyme; the bromide substituent is selectively reduced to *n*-undecyl tosylate.

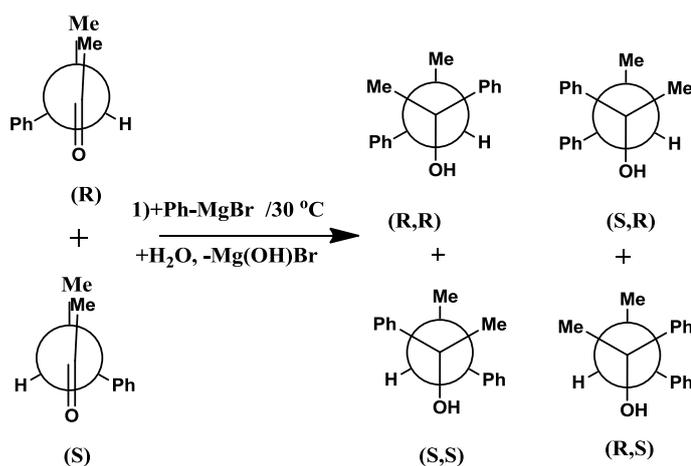


**Scheme 6.** Reduction of 11-bromoundecyl tosylate by  $\text{LiAlH}_4$  in diethyl ether and diglyme.<sup>27</sup>

Formation of different chemoselective products in these two reactions points out towards the effect of solvents on the proposition of chemoselectivity as well as reactivity of complex metal hydride.

#### 1.2.2.4 Solvent effect on stereoselectivity

Preferentially one stereoisomer formation over another in a chemical reaction is known as stereoselectivity. When the stereoisomers are enantiomers, the phenomenon is called enantioselectivity and is quantitatively expressed by the enantiomeric excess; when they are diastereoisomers, it is called diastereoselectivity and is quantitatively expressed by the diastereoisomeric excess.<sup>26</sup>



**Scheme 7.** Solvent effect on the stereoselectivity.<sup>28,29</sup>

Pérez-Ossorio and co-workers has determined solvent consequences in reaction of 3-phenylbutanone and phenylmagnesium bromide in solvents of different polarities.<sup>28,29</sup>

The reaction of 3-phenylbutanone with the Grignard reagent will give rise to the

formation of two pairs of enantiomers *i.e.*, (R,R)- and (S,S)- and (S,R)- and (R,S)-forms. The ratio of these two pairs of enantiomers shows strong solvent dependence. If the reaction is switched from apolar solvent like trimethylamine to the more polar solvent like glyme then (S,R)- and (R,S)- enantiomeric form in the product increases from 26 to 73 %. From the obtained results it can be concluded that the activated complex of the reaction is highly dipolar nature and therefore it can be strongly solvated in more polar solvent leading to formation of (S, R)- and (R, S)- products.

This thesis contributes to the understanding of different genre of solvents, as it portrays an explorative expedition in the different categories of solvents and its use as media in Diels-Alder reaction. The discussion will emphasize the organic chemistry, physico-chemical aspects of the solvents and how structural variations of different solvents provide explanation for fundamental mechanisms and its effect on the kinetic profile.

### **1.3 Solvent effect and cycloaddition reaction**

#### **1.3.1 Water promoted organic reactions in aqueous salt solutions**

Synthetic organic chemists mainly focus on two principle type of reactions: one is carbon-carbon bond formation reactions and another is transformation as well as addition of functional groups to the main organic moiety. C-C bond formation reactions have been termed as the foundation of organic synthesis since it gives a boon to the organic chemists to synthesise compounds having structures ranging from simple to complex.<sup>31-34</sup> Though the anthropologic data as well as scientific researches confirm that water has been utilized by 'Nature' as a medium to nurture the synthesis of essential proteins, peptides *etc.*, essential to germinate early sign of life in the world, still chemists usually avoid water as a solvent for common organic reactions.<sup>35,36</sup> The superiority of water as solvent to promote organic reactions has been pioneered by Breslow and his group in 1980.<sup>37</sup> In the similar line, another important contribution was made by Grieco and co-workers, who highlighted the significance of water as a solvent media in organic synthesis.<sup>38-40</sup> Since then, there have been a number of researchers interested in this field to understand the potentiality of water as solvent during organic reactions.<sup>41-49</sup>

To unravel the principle forces behind the dramatic acceleration of Diels-Alder reactions in water, researchers have come across with a number of explanations.<sup>30-52</sup> The proposed mechanism of Diels-Alder reactions follow the suprafacial interaction of a  $4\pi$ -electron system with a  $2\pi$ -electron system through cyclic transition state without any intermediate. Initially, cycloaddition reaction was considered to be insensitive to high polarity of water, but now it is an established fact that the contribution of the polarity of water could be used to elucidate the acceleration of the reaction rate.<sup>19,8,39,40</sup> In the present scenario, Breslow had invoked the idea of 'hydrophobicity' to rationalize his observations related to unprecedented acceleration of Diels-Alder reactions in water.<sup>24,25,53,54</sup> This theory suggests that non-polar molecules/reactants *i.e.* molecules insoluble in water come together to increase local concentration, followed by greater probability of collisions among reactants to avoid mutual repulsion to the solvent water.<sup>30-43</sup> A number of articles and reviews have been appeared in the literature to assess this concept of hydrophobicity and associated parameters during water promoted reactions.<sup>20-41</sup> Researchers have used prohydrophobic salts like quaternary ammonium halide ( $R_4NX$ ), guanidinium chloride (GnCl), lithium perchlorate ( $LiClO_4$ ) and anti hydrophobic salts like lithium chloride (LiCl), potassium chloride (KCl) *etc.*, to delineate the role of hydrophobic hydration in the water promoted reactions.<sup>30-43</sup> As a consequence of rigorous studies, it has been revealed that along with hydrophobic acceleration,<sup>39-43</sup> several other properties like enforced hydrophobic interactions,<sup>55-57</sup> enhanced hydrogen bonding capability of water,<sup>39-41,58,59</sup> high cohesive energy density of water,<sup>54,60-65</sup> and polarity of water<sup>8,39,40</sup> *etc.* are also responsible for promoting these organic reactions in water. Contribution of each property varies from reaction to reaction depending upon the molecular structure of the reactants.<sup>8,27-29,39,40</sup> One significant criteria of these associated with these studied is that all the reactants are taken in water in such a manner that entire reaction mixture does not exhibit any interface. This means that the reactants are completely solubilised in water. This type of reactions is termed as 'in water reaction'.<sup>26-29</sup>

The nature of prohydrophobic salts and antihydrophobic salts in all polar solvents are not similar. The behaviour of GnCl, LiCl and  $LiClO_4$  salts are contradictory in polar solvents. For example salting-in (S/I) salts like GnCl shows salting-out behavior and salting-out (S/O) salts like LiCl shows salting-in behavior in polar solvents like

ethylene glycol and formamide in contrast to water. But it has been noticed that the behavior of tetraalkylammonium halide salts is consistent to their behavior in aqueous solution. The reason behind the contradictory behaviour of S/I and S/O salts in polar solvent has been addressed in chapter 5.<sup>63</sup>

In 1990, Grieco et al. has introduced a new reaction media for Diels-Alder reaction consisting 5.0 M solution of lithium perchlorate in diethyl ether popularly known as LPDE.<sup>66</sup> Later, Kumar et al. have found that cycloaddition reactions like Diels-Alder reactions shows considerable rate acceleration in LPDE and high internal pressure of solvent media has been ascribed as the detrimental factor behind rate acceleration.<sup>67</sup> Again, in the context of the same reaction it has been suggested that, Lewis-acid catalysis of lithium cation and high polarity of solvent media assist efficient stabilisation of transition state to generate rate enhancement.<sup>68-76</sup> In order to decrease the explosive character of LPDE reaction media recently, Grieco has proposed solution of lithium trifluoromethanesulfonimide in acetone or diethyl ether as a new promising reaction media.<sup>77</sup>

In 2005, Sharpless and co-workers during their study on cycloaddition of strained cyclic systems, quadricyclane and dimethylazodicarboxylate (DMAD), in presence of excess concentration of reactants in water (heterogeneous condition) observed that rate of the reaction was nearly 400 times accelerated compared to that of homogeneous reaction condition in water.<sup>78</sup> The yield of this reaction at heterogeneous condition was also reported very high compared to the same reaction in water at homogeneous condition. It is important to be mentioned here that repetition of the same reaction in solvent free condition failed to show such pronounce rate acceleration. Later, the observations have been justified in the way that the excess concentration of the reactants (*i.e.* beyond the solubility limit of water) as well as newly created organic/ water interface play pivotal role in the rate accelerations.<sup>78,79</sup> Moreover, water appears to be the privileged medium for carrying out organic reactions, since similar reactions performed in perfluorohexane at heterogeneous condition proceeded at comparable rates to the homogeneous organic conditions.<sup>78,80</sup> These types of reaction has been categorised as ‘on water’ reactions.<sup>[78]</sup> Limited attention has been paid to the kinetics of organic reactions under heterogeneous aqueous conditions, when the reactants float on water. Here, the conditions being heterogeneous, with the reaction occurring on the surface of water *i.e.* water acts here a medium to float, and so the hydrophobic effect seemingly does not play crucial role

in these types of reactions.<sup>80-83</sup> Importantly, vigorous mixing to form a suspension or vortex formation has been proposed to be necessary condition for the reaction to proceed further.

Yung and Marcus had emphasised on the catalysing effect of 'dangling OH' present at the water/organic interface as one of the principle factor behind the enhanced reactivity of 'on water' reactions through their DFT calculations.<sup>70,84-88</sup> Vigorous stirring, pressure as well as enforced hydrophobic interactions has been envisaged as necessary conditions for higher increase of rate of 'on water' reactions by recent studies.<sup>73-75</sup> According to recent findings, the acidic surface of water acts as an accelerator of the various organic reactions.<sup>89-93</sup> Though in the literature, several example of heterogeneous water promoted reactions are available, the principle forces behind the acceleration of 'on-water' conditions are still lying in the shadow of controversy.<sup>78-82</sup> An extensive study on the on-water condition has been carried out to clarify the role of 'dangling OH' by performing C-C bond forming reactions.<sup>19-23</sup> Moreover, Diels-Alder reactions have been proved to be an essential methodology to synthesise 6-membered or higher acyclic compounds possessing higher degree of stereo- and regio- selectivity.<sup>19,78,79</sup> Efforts will be focused on the delineation of physical forces responsible for promotion of rate of organic reactions at heterogeneous condition in comparison to that of homogeneous reactions in water.

During investigation of the insights of mechanism of 'on water' reactions, researchers have emphasised on the presence of micro-interface in between organic reactants and water medium.<sup>67,70-72,76,77</sup> The presence of interface has been coined as a prime difference between 'homogeneous' or 'in water' type reactions and 'heterogeneous' or 'on water' type reactions.<sup>69-73</sup> In literature few examples are available to justify the presence of interface and its role during 'on water' reaction. The motivation behind the study of on-water reactions is to validate the role of interface during heterogeneous water promoted reaction.

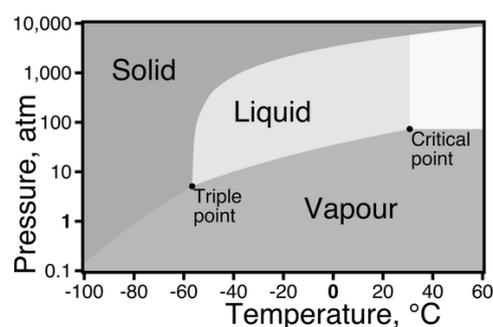
### **1.3.2 Solvent free process**

The solvent free process is one of the answers to decrease the solvent toxicity and hazards. Solvent free reactions include the reaction procedure in which one of the reactant in the reaction plays the role of solvent. In this case excess reagent serves as solvent. Mostly, the solvent-free synthesis reactions are carried out without solvent

when the reactants are liquid. Solvent free process can also be employed when reactant mixture on melting generates liquid which can be employed as solvent in same reaction. For example chlorinated natural rubber can be carried out in excess of liquid chlorine.<sup>94</sup> Mechanical extraction preferred in the case of solvent free process instead of use of organic solvent extraction. Unfortunately, it is not possible to use solvent free procedure in every reaction. Because of its limitations, less harmful solvents are utilized which can easily be recovered and are less toxic and biodegradable.

### 1.3.3 Supercritical process

Supercritical carbon dioxide (CO<sub>2</sub>) may provide good replacement to the volatile organic solvents.<sup>95-98</sup> It is non-toxic, non flammable, relatively inert, abundant and inexpensive. At temperature higher than 31 °C and pressure 7.38 MPa, CO<sub>2</sub> transform into supercritical fluid. Under these conditions the separation between gas phase and the liquid phase does not exist and therefore CO<sub>2</sub> can be described as a fluid. This can be explained by looking at the phase diagram of CO<sub>2</sub> (see **Figure 2**). The vapor and liquid region in phase diagram separates at boiling point and end at the critical point.



**Figure 2.** Phase diagram of carbon dioxide.<sup>99</sup>

At any point on the boiling line below its critical temperature and pressure, carbon dioxide exists as a liquid with vapor above it. As temperature increases, the liquid density drops due to expansion, whereas the gas density increases due to the pressure enhancement. At the critical point, the densities become identical and the distinction between liquid and gas disappears.

The CO<sub>2</sub> density can be changed by altering the temperature and pressure in the supercritical region. Supercritical CO<sub>2</sub> resembles the properties of gases and the

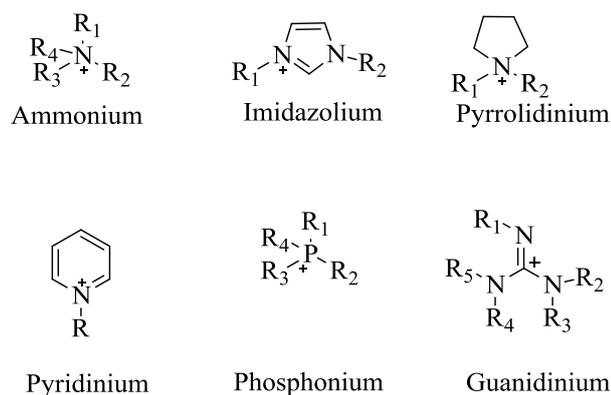
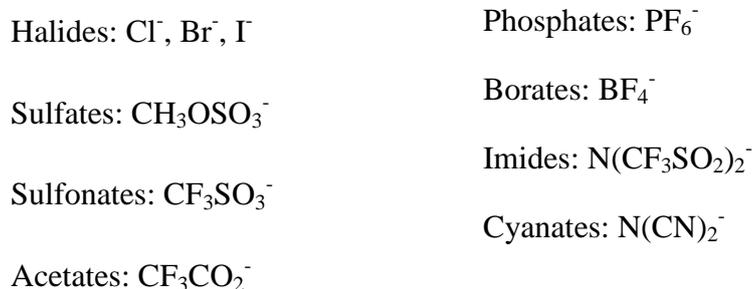
liquids. It possesses excellent properties like; it can diffuse through materials like a gas and to dissolve organic compounds like non-polar liquids. The gas and liquid like properties of supercritical carbon dioxide can be achieved by adjusting pressure, which makes supercritical CO<sub>2</sub> highly effective and promising solvent media. The reaction product separation can be performed by releasing the pressure in the system. Due to relatively simple separation procedure, supercritical processes are utilized as extraction media in food and medicine manufacturing processes, for which it eliminates the possibility of leaving toxic residues of organic solvents.<sup>84-87</sup> But all chemical substances are not soluble in the supercritical CO<sub>2</sub>, which makes the use of supercritical CO<sub>2</sub> difficult in chemical transformations. It is not a very good solvent for many (polar) substances. Moreover, it has to be used under pressure. This may lead to higher operating and equipment costs.

### 1.3.4 Room temperature ionic liquids

Room temperature ionic liquids (RTILs) were recognized as a new class of environmentally benign solvents.<sup>100-104</sup> RTILs are defined as the salts with melting points below 100 °C. RTILs can be used as alternative solvents because of their negligibly low vapour pressure and inherent low volatility. With some exceptions, there are some ionic liquids which can be distilled due to their volatility.<sup>90</sup> Notably, the first study about an ionic liquid occurred in 1914 on [EtNH<sub>3</sub>][NO<sub>3</sub>] which has melting point between 13–14 °C.

Recent advances in the development of RTILs triggered chemical research in last decade.<sup>91</sup> These RTILs are similar to high-temperature molten metallic salts, but they contain at least one organic ion that is relatively large in structure and asymmetric as compared to a metallic ion. Therefore, the attractive forces between the positively charged ions (cations) and the negatively charged ions (anions) of RTILs can be kept so spaced out that crystallization is hindered. This obstruction to crystallization give rise to a totally ionic (non-aqueous) liquid at room temperature.<sup>89,92</sup>

The most common cations and anions are shown in **Figure 3**. It is estimated that there are approximately one trillion accessible RTILs which can be used in different applications.<sup>93</sup>

**Common cations:****Common anions:****Figure 3.** Most common cations and anions.<sup>89</sup>

RTILs has tremendous ability to perform kinetic controlled organic reactions. Good thermal stability with broad electrochemical window represents the high electrochemical strength against oxidation or reduction reactions. RTILs possess these exceptional properties since these liquids are synthesized from salts which includes broad liquidus range.<sup>95</sup> On the critical front, toxicity and biodegradability of RTILs have been a growing concern over these designer solvents.<sup>91</sup> For example, in the case of some ionic liquids like [Bmim][ $\text{BF}_4$ ] and [Bmim][ $\text{PF}_6$ ], they did not show any substantial biodegradation, whereas the exchange of the anion to octyl sulfate led to 25% biodegradation under the identical conditions. Now, researchers are searching for non-hazardous, safe, degradable alternatives from which biodegradable RTILs can be designed which make them more benign in nature.<sup>103–106</sup>

**1.3.5 Deep eutectic and eutectic solvents**

In 1950, the first study was carried out on the lower melting point eutectics (ethylpyridinium chloride/ $\text{AlCl}_3$  mixtures).<sup>107</sup> Later, Osteryoung's research group has

used the *N*-butylpyridinium cation<sup>108</sup> and Hussey<sup>109</sup> explored 1-ethyl-3-methylimidazolium as cation in eutectic mixtures. About 40 years later Abbott *et al.*<sup>110,111</sup> and Sun *et al.*<sup>112,113</sup> studied the mixtures of zinc halides and quaternary ammonium halides. These preliminary developments in eutectic solvents have motivated the use of other salts and organic compounds to form eutectic mixtures with quaternary ammonium salts.

The term DES has been coined mainly to differentiate them from true ionic liquids, and also to reflect the large depression in the freezing point of the eutectic mixture. The depression of the freezing point of the eutectic mixture can be as much as several hundred degrees centigrade. Although fundamental principle of DESs which is being very similar to that of RTILs, they are not considered as true ionic liquids because they need a hydrogen bond in addition to anions and cations. The end result is similar, however; a liquid that is made up of a cation and anion is formed, but its route to the reduction of lattice energy of the system is different. This occurs mainly due to the fact that the hydrogen bond donor coordinates with the anion and withdraws the electron density of the anion from the cation. This separation leads to a weaker anion/cation interaction, which is the way DES achieve their low melting temperatures.

These eutectic solvent can be described by the general formula  $R^1R^2R^3R^4N^+X^- \cdot zY$ , where the anion  $X^-$  is generally a halide (often  $Cl^-$ ),  $R^1R^2R^3R^4N^+$  a quaternary ammonium salt and  $Y$  is a complexing agent, where  $z$  is the number of molecules required. Depending on the complexing agent  $Y$ , eutectic solvents can be divided in to four types:<sup>114,115</sup>

**Eutectic type I:** Metal salt + organic salt:  $R^1R^2R^3R^4N^+ X^- \cdot MCl_x$  with  $M = Zn, Sn, Fe, Al, Ga$ ; (e.g.  $ZnCl_2 + choline\ chloride$ <sup>110</sup>)

**Eutectic type II:** Metal salt hydrate + organic salt:  $R^1R^2R^3R^4N^+ X^- \cdot MCl_x \cdot yH_2O$  with  $M = Cr, Co, Cu, Ni, Fe$ ; (e.g.  $CoCl_2 \cdot 6H_2O + choline\ chloride$ <sup>115</sup>)

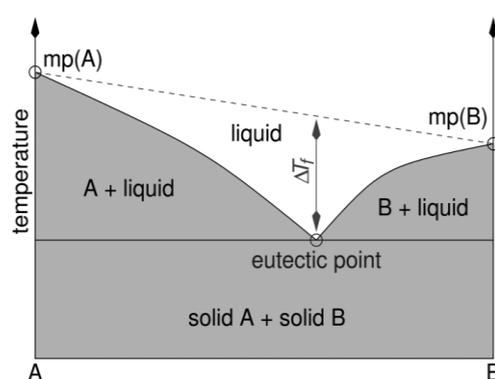
**Eutectic type III:** Hydrogen bond donor + organic salt:  $R^1R^2R^3R^4N^+ X^- \cdot R_5Z$  with  $Z = -CONH_2, -COOH, -OH$ ; (e.g.  $choline\ chloride$  and  $urea$ <sup>116</sup>)

**Eutectic type IV:** Metal chlorides + hydrogen bond donor:  $MCl_x \cdot hydrogen\ bond\ donor$  like  $urea, ethylene\ glycol, acetamide$  or  $hexanediol$ .<sup>115</sup>

Type I eutectics have relatively high viscosities, freezing points and low conductivities as compared to those with discrete anions. The advantages for these types of eutectic solvents are the ease of manufacture and their water insensitivity (with the exception of the halo aluminates), which is very important for the electrochemistry of metals. The relative proportion of anionic species depends on the eutectic solvent compositions and the anionic species have been identified in some of the eutectic such as urea.<sup>116</sup>, Al,<sup>117</sup> Sn,<sup>111</sup> Zn,<sup>111</sup> and Cr.<sup>118</sup> In some studies they have also quantified the proportion of the anionic species present.

### 1.3.5.1 Type I eutectic

In **Type I** eutectic solvents, the anhydrous metal halide *i.e.* substituted quaternary ammonium salt mixtures are used. In this area, the most investigated systems are ZnCl<sub>2</sub>, SnCl<sub>2</sub> and FeCl<sub>3</sub><sup>111</sup> which contain variety of quaternary ammonium salts. All the three metal halides, when mixed with choline chloride (ChCl) in 1: 2 ratio form metal complexes that have freezing points below 100 °C. In fact, the term deep eutectic solvents (DESs) arise from the fact that the eutectic mixtures formed by the mixing of the two components (A+B) in appropriate ratio, have melting points significantly lower than that of a theoretical ideal mixture. The eutectic point of mixture (A+B) shown in **Figure 4** having the lowest melting point.



**Figure 4.** Schematic representation of a eutectic point on a two-component phase diagram.<sup>116</sup>

The phase diagram of the metal chloride salts with ChCl clearly indicates that lewis basic eutectic solvents could not be formed with tin and zinc, probably due to the high charge density of the MCl<sub>3</sub><sup>-</sup> anion. As a result, it was found that the concentration of the Zn<sub>2</sub>Cl<sub>5</sub><sup>-</sup> species varied with the composition of the eutectic solvents.<sup>18,110,116,119–124</sup>

As the molar ratio of  $\text{ZnCl}_2$  increases to more than half percent, several lewis acidic chlorozincate clusters ( $\text{ZnCl}_3^-$ ,  $\text{Zn}_2\text{Cl}_5^-$ , and  $\text{Zn}_3\text{Cl}_7^-$ ) are formed. Similar trends were observed for eutectic solvents containing  $\text{SnCl}_2$ .<sup>111</sup>

The depression in freezing point compared to that in an ideal solution,  $\Delta T_f$  is related to the interaction between A and B. Larger the interaction larger will be the  $\Delta T_f$ . The interactions between different metal halides and the halide anion from the quaternary ammonium salt are the responsible factors for depression in freezing point. So, to get the freezing point of eutectic solvent around room temperature, the melting points of A and B are supposed to be relatively low. The same is applicable to the quaternary ammonium salts, where less symmetrical cations provide lower melting point and therefore lead to lower melting point eutectics.

During the formation of eutectic mixture it has been observed that a variety of halometallate species form eutectic mixtures. Fast Atom Bombardment, Mass spectroscopy studies suggest that most species are singly charged anionic species. However, Extended X-Ray Absorption Fine Structure spectroscopy (EXAFS) shows that,  $\text{ZnCl}_2$  and  $\text{CuCl}_2$  form  $\text{ZnCl}_4^{2-}$  and  $\text{CuCl}_4^{2-}$ , although these could be the dimers  $\text{Zn}_2\text{Cl}_6^{2-}$  and  $\text{Cu}_2\text{Cl}_6^{2-}$ .<sup>125,126</sup> The difference in structures and dimerization is explained by Hardacre and their group.<sup>100</sup> Nuclear magnetic resonance (NMR) and mass spectrometry techniques were used by Lecocq *et. al.*<sup>127</sup> to analyze the eutectics formed between zinc chloride and [BMMIM]Cl. According to their observations which was analogous to the aluminium systems,  $\text{Cl}^-$  and  $[\text{ZnCl}_3]^-$  are present in lewis basic liquids, and  $[\text{ZnCl}_3]^-$  and  $[\text{Zn}_2\text{Cl}_5]^-$  are observed in Lewis acidic liquids. Again, in IR-spectroscopy study pyridine was used as a probe to quantify the Lewis acidity. High temperature NMR spectroscopy experiments (at 110 °C) showed that the  $\text{Cl}^-$  ligand is switched between being associated with the imidazolium cation and the metal halide.

Eutectic mixture formation in  $\text{FeCl}_3$  is different from  $\text{SnCl}_2$  and  $\text{ZnCl}_2$ , in which it forms two eutectic points at 33 and 67 mol %  $\text{FeCl}_3$ , which is analogous to the  $\text{AlCl}_3$ : [EMIM]Cl system.<sup>128-130</sup> Speciation studies of  $\text{FeCl}_2$  and  $\text{FeCl}_3$  were carried out by Sitze *et al.*, who found that [BMIM]Cl form liquids with  $\text{FeCl}_2$  in the molar ratio 0.3  $\text{FeCl}_2$ : 1 [BMIM]Cl. Whereas,  $\text{FeCl}_3$  form in the molar ratio 0.53 to 1.7. Raman scattering study was used to calculate concentration of the anion in the iron system, which shows that  $\text{FeCl}_4^{2-}$ ,  $\text{FeCl}_4^-$  and  $\text{Fe}_2\text{Cl}_7^-$  were present in the mixtures. It was

also seen that Zn and Al systems were similar to Fe systems, as the relative concentrations were found to be dependent upon the Lewis acidity. The [BMIM][FeCl<sub>4</sub>] liquid was also shown to be ferromagnetic in nature.

As defined, above systems with low melting point halides should produce DESs. It is therefore not surprising that eutectic mixtures of imidazolium chloride with GaCl<sub>3</sub> and InCl<sub>3</sub> have also been reported.<sup>131,132</sup> These DESs have been used for the electrodeposition of semiconductors.<sup>133,134</sup> Other metal halides that have been studied<sup>135,136</sup> include AuCl<sub>3</sub>, NiCl<sub>2</sub> and CoCl<sub>2</sub> but their applications have been limited to synthesis. Some more exotic metals have been formulated into eutectic solvents which include [EMIM]<sub>2</sub>[UCl<sub>6</sub>]<sup>137</sup> and niobium (Nb) and tantalum (Ta) in the form of [EMIM][TaF<sub>6</sub>] and [EMIM][NbF<sub>6</sub>].<sup>138</sup> As can be seen from the systems listed above, most studies are concentrated upon halides but on the contrary, Noguera *et. al.*,<sup>139</sup> demonstrated that metal oxides in the form of CrO<sub>3</sub> and Na<sub>2</sub>MoO<sub>4</sub> could also be used to prepare ionic liquids.

### 1.3.5.2 Type II eutectic

**Type II** eutectics were developed in an attempt to include other metals into the DESs formulations. It was found that metal hydrates have a lower melting point than the corresponding anhydrous salt. Clearly, the water of hydration decreases the melting point of metal salts because it decreases the lattice energy. An experimental result for **Type II** eutectics in reference 140 shows that lower melting point of the pure metal salt  $T_f^*$ , will create a minor decline of  $\Delta T_f$ . This minor decline in  $\Delta T_f$  arises because the salts with lower lattice energy will tend to have smaller interactions with the chloride anion.<sup>140</sup>

Till date, very few studies have been carried out on **Type II** eutectics and the role of the water molecules is still largely unknown. According to one recent study on **Type II** eutectics, researchers claim that water does not act in the same way as bulk water. Metals like chromium was reduced with high current efficiency which is unaltered by the addition up to 10 weight percent of water, which suggest that the water is strongly associated with the chloride anions or the metal centre.<sup>134</sup> It is only the chromium system which has been published till date.<sup>118</sup> Metals such as Co, Cu, Ni, Al, Ca and Fe also form liquids from the metal halides particularly with the hexahydrates. The

deposition of metals such as Al and Ca is, however, not possible due to the limited potential window of these liquids.

### 1.3.5.3 Type III eutectic

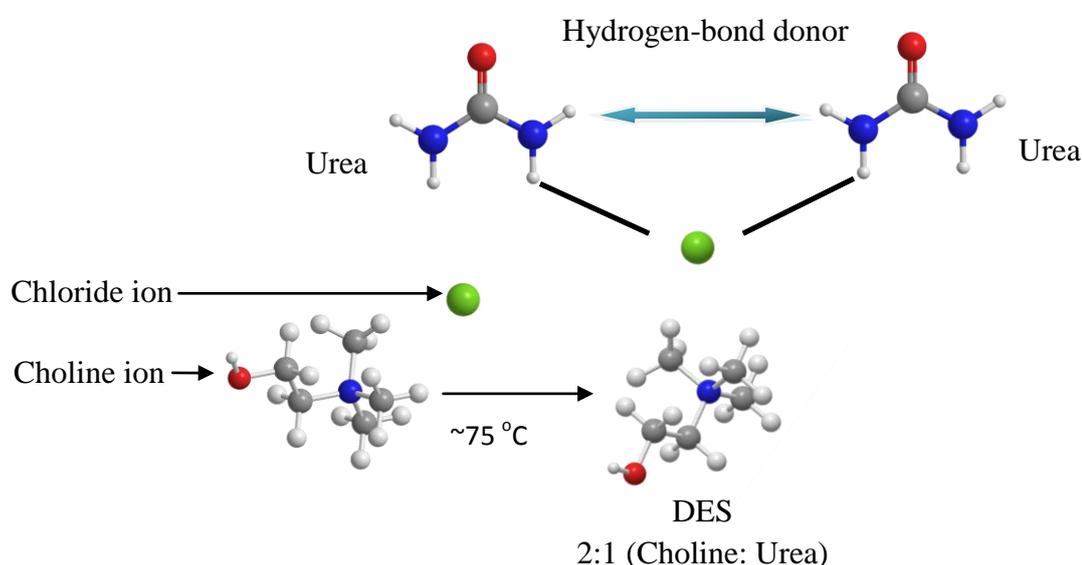
**Type III** eutectics use a simple hydrogen bond donor such as amides, carboxylic acids and alcohols to form a complex with a quaternary ammonium halide. (See **Table 3, 4, 5, 6 and 7**) As can be seen in **Figure 10**, these compounds tend to have lower freezing points than the metal halides and the depression of freezing point is accordingly lower. **Type III** eutectic fluids have interesting solvent properties and a wide variety of solutes exhibit high solubilities.<sup>18,116</sup> These eutectic systems have a large depression of freezing point. For example, the oxalic acid-choline chloride system shows a depression of freezing point of 212 °C and in the choline chloride-urea system it is 178 °C.<sup>18</sup> The freezing point depressions are not as large as the choline chloride-zinc chloride system<sup>112</sup> *i.e.* 272 °C which arises due to the covalent bonds formed in the metal chloride case. The **Type III** eutectic mixtures can be synthesised easily and are relatively inexpensive. This implies that they can be used for large scale applications such as metal finishing.

**Type III** eutectics rely on the formation of hydrogen bonds between the polar organic and the chloride anion. The existence of hydrogen bonding was shown using Heteronuclear Overhauser Effect Spectroscopy (HOESY) for the choline fluoride/urea system.<sup>116</sup> The presence of a complex between  $\text{Cl}^-$  and two urea molecules was observed using FAB-MS ( $M^- = 155$ ) additionally a signal was also identified for one  $\text{Cl}^-$  and one urea ( $M^- = 95$ ) molecule.

The freezing point of the DESs *i.e.* HBD-salt mixtures will be dependent upon the lattice energies. Interaction pattern between the salt *i.e.* anion and H-bond donor determine DESs formation. Mode of the interaction between the molecules of the salt and HBD give rise to entropy changes arising from liquid formation. The complexation reaction of chloride ions with H-bond of urea is in fact motivated by the hydrogen bonding between them, which is largely assisted by high temperature conditions. Therefore, the reduction in freezing point can also be predicted by measurement of the entropy change of DES.<sup>116</sup> These liquids have been used in

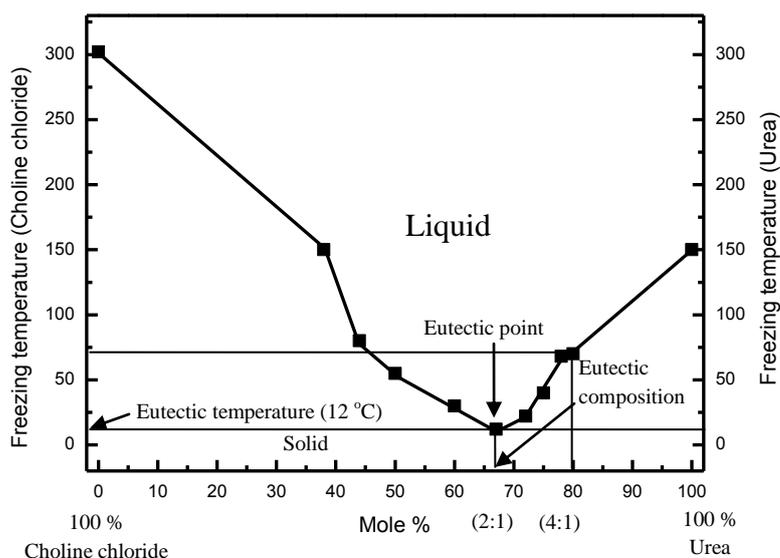
numerous studies for the electrodeposition of a variety of metals and alloys. This has been reviewed recently in many articles.<sup>141–145</sup>

Typically, DES is composed of an organic cation and an organic/inorganic anion.<sup>110,116,120,121,141,146</sup> DES is essentially a molten mixture of two or more salts that interact through hydrogen bonds. These mixtures have been termed as DES because when the two components are mixed together in the correct ratio, a eutectic point can be seen with large depression in freezing point. For example, combining quaternary ammonium halide salt *i.e.* choline chloride with urea, which are capable of forming hydrogen bonds with the halide ion of choline chloride in a 2:1 molar ratio at  $\sim 75$  °C, a DES can be formed as shown in **Figure 5**.



**Figure 5.** Schematic images of a deep eutectic solvent comprising urea and choline chloride.

The phase diagram of urea-choline chloride system is shown in **Figure 6**. The melting point of choline chloride is 302 °C and of urea is 133 °C. However, their mixture in a 2:1 molar ratio and with vigorous stirring at  $\sim 75$  °C gives deep eutectic mixture. These eutectic mixtures called as deep eutectic mixtures because they possess lowest freezing point *i.e.* upto 12 °C and beyond. DES of choline chloride and urea has simple synthetic procedure and are readily soluble in water. Choline chloride (Vitamin B<sub>4</sub>) which is one of the most popular components in the DESs synthesis makes them bio-degradable in nature.<sup>18,115,118,119,122–124</sup>



**Figure 6.** Phase diagram of urea-choline chloride deep eutectic solvent system.

In general, the freezing point of any mixture containing a quaternary ammonium salt and a hydrogen bond donor is dependent on two main things. Firstly, the individual lattice energies of both the hydrogen bond donor and the quaternary ammonium salt. Secondly, the degree to which the anion hydrogen bond donor interacts.<sup>18</sup> If the anion-hydrogen bond donor interaction is strong, the entropy of the system increases, resulting in randomness and a more disordered system, thereby offering a lower freezing point. To a certain degree, the depression in the freezing point can be a measure of the entropy change. In the present thesis, **Type III** eutectic has been explained in Chapter 3. Also, Chapter 3 will throw light on the physico-organic properties of green hybrid mixtures *i.e.* **Type III** eutectics with water.

#### 1.3.5.4 Type IV eutectic

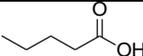
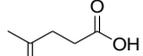
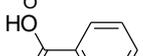
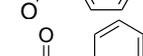
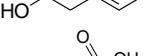
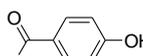
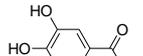
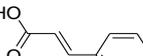
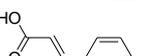
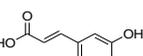
**Type IV** eutectics mainly categorise eutectic mixtures of metal chlorides like  $\text{ZnCl}_2$  and hydrogen bond donors like ethylene glycol. Experimental studies reveal that, metal chloride contains both cation and anion in which coordination between cation and hydrogen bond donor is responsible for eutectic mixture formation.<sup>115</sup>

## 1.4 Summary of the physicochemical properties

### 1.4.1 Components used and their melting points

Choline is considered as a crucial member of vitamin B family, supports a massive amount of metabolic processes, and serves as a dietary supplement of animal feeds.<sup>147</sup> It is commercially synthesized by a simple gas phase reaction between trimethylamine, ethyleneoxide, and HCl.<sup>134,147,148</sup> In the last few years, combination of different (uncharged) hydrogen bond donors of natural and synthetic origin were used in combination with choline chloride to synthesise more effective and task specific DESs.<sup>18,148–151</sup>

**Table 3.** Deep eutectic solvents based on choline chloride (ChCl) and monocarboxylic acids.

Entry	Compound	Structure	ChCl : HBD ratio		T (°C)	Ref.
1.	Valeric acid		1 : 2	$T_f$	22	152
2.	Levulinic acid		1 : 2	$T_m$	Liquid at rt	151
3.	Benzoic acid		1 : 2	$T_f$	95	18
4.	Phenylacetic acid		1 : 2	$T_f$	25	18
5.	Mandelic acid		1 : 2	$T_f$	33	159
6.	4-Hydroxybenzoic acid		2 : 1	$T_m$	87	151
			1 : 2	$T_f$	97	159
7.	Gallic acid		2 : 1	$T_m$	77	151
8.	trans-Cinnamic acid		1 : 1	$T_m$	93	151
				$T_f$	101	159
9.	p-Coumaric acid		2 : 1	$T_m$	67	151
10.	Caffeic acid		2 : 1	$T_m$	67	151

*HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).*

According to hypothesis which was proposed by Abbott, the melting point depression is caused due to the hydrogen bonding between the halide anion and the hydrogen bond donor due to charge delocalisation.<sup>116</sup> For the DESs, based on choline chloride

and hydrogen bond donor the melting point ( $T_m$ ), freezing point ( $T_f$ ), composition ratio along with the structure of hydrogen bond donors *i.e.* mono- carboxylic acids are listed in **Table 3**.

In the case of ionic liquids, the alteration in the melting point is largely dependent on the charge delocalization in the ions. Again, the melting points of ionic liquids are lowered, when the charge is greatly delocalised or when the cations and/or anions are asymmetrical.<sup>111</sup> A similar effect was observed for melts with quaternary ammonium salts: with increasing asymmetry of the cation, the melting point decreases.<sup>116</sup> Similarly, depression in freezing point also depends on the different counter (halide) negative ions present in the choline and urea mixtures.<sup>116,148,151</sup> In a subtype of DESs *i.e.* Type IV eutectics, metal-based eutectics made from metal salts like  $ZnCl_2$ ,  $FeCl_3$ ,  $SnCl_2$ ,  $AlCl_3$ , and simple organic alcohols or amides as HBDs in which donor molecule serves as a complexing agent and coordinates to the cation.<sup>115,153</sup>

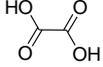
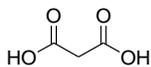
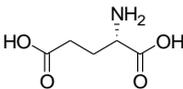
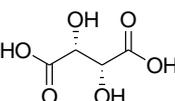
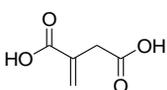
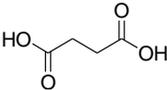
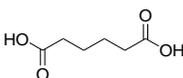
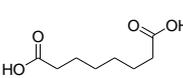
Melting point of deep eutectic solvents are unpredictable similar to their ionic liquid counterparts. The liquid nature of solid salt mixtures shows the reduction in coulomb forces. These coulomb forces get reduced with asymmetric charge distribution of the molecular ions and a large volume. The melting points ( $T_m$ ), freezing points ( $T_f$ ) or glass transition temperatures ( $T_g$ ) are summarised below (**Tables 4–11**). Surprisingly, it has been observed that RTILs and DESs shares same principle components but with different strategies *e.g.* benzoic acid (**Table 3**, entry 3) and benzoate (**Table 10**, entry 17) or tartaric acid (**Table 4**, entry 4). In many cases it has been documented that the melting points of the DESs are lower than that of RTILs. The temperature stability of the eutectic mixtures is also lower compared to the RTILs. As we know that urea decomposes at 210 °C in ChCl–urea DES;<sup>154</sup> sugars usually decompose at about 150 °C, and the most stable Bio-IL, [Ch]-[H-maleate], has a decomposition temperature of 223 °C.<sup>155</sup>

#### **1.4.2 Deep eutectic solvents based on choline chloride. See Tables 2–11**

#### **1.4.3 Ionic liquids using choline as a cation and natural products as counter ions. See Table 10**

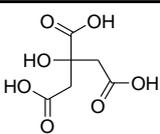
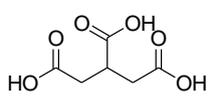
#### **1.4.4 Low melting sugar mixtures. See Tables 6-10**

**Table 4.** Deep eutectic solvents based on choline chloride and dicarboxylic acids.

Entry	Compound	Structure	ChCl : HBD ratio	T <sub>f</sub>	T (°C)	Ref.
1.	Oxalic acid		1 : 1	<i>T<sub>f</sub></i>	34	18
2.	Malonic acid		1 : 1	<i>T<sub>m</sub></i>	10	18
3.	Glutamic acid		1 : 2	<i>T<sub>f</sub></i>	13	159
4.	L-(+) Tartaric acid		2 : 1	<i>T<sub>m</sub></i>	47	151
5.	Itaconic acid		1 : 1 2 : 1	<i>T<sub>m</sub></i>	57	151
6.	Succinic acid		1 : 1	<i>T<sub>f</sub></i>	71	18
7.	Adipic acid		1 : 1	<i>T<sub>m</sub></i>	85	18
8.	Suberic acid		1 : 1	<i>T<sub>m</sub></i>	93	151

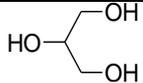
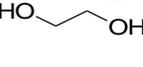
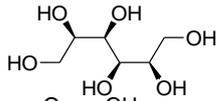
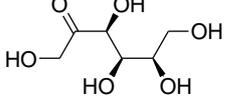
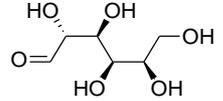
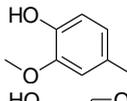
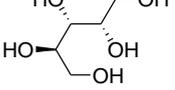
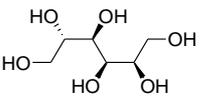
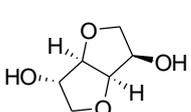
HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

**Table 5.** Deep eutectic solvents based on choline chloride and tricarboxylic acids.

Compound	Structure	ChCl : HBD ratio	T <sub>f</sub> (°C)	Ref.
Citric acid		2 : 1	69	18
Tricarballic acid		2 : 1	90	18

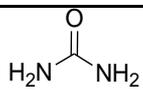
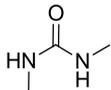
**Table 3-7** summarises **Type III** eutectics, in which hydrogen bond donor such as amides, carboxylic acids and alcohols form a complex with a quaternary ammonium halide *i.e.* choline chloride.

**Table 6.** Deep eutectic solvents based on choline chloride and alcohols.

Entry	Compound	Structure	ChCl : HBD ratio	$T_f$ (°C)	Ref.	
1.	Glycerol		1 : 2	$T_f$	-40	148
2.	Ethylene glycol		1 : 2	$T_f$	-20	159
3.	Mannitol		1 : 1	$T_f$	108	159
4.	D-Fructose		1 : 2	$T_f$	5	159
5.	D-Glucose		1 : 2	$T_f$	14	159
6.	Vanilline		1 : 2	$T_f$	17	159
7.	Xylitol		1 : 1	$T_m$	Liquid at rt	151
8.	D-Sorbitol		1 : 1	$T_m$	Liquid at rt	151
9.	D-Isosorbide		1 : 2	$T_m$	Liquid at rt	151

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

**Table 7.** Deep eutectic solvents based on choline chloride and urea derivatives

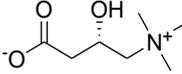
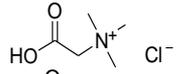
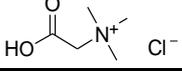
Entry	Compound	Structure	ChCl : HBD ratio	$T_f$ (°C)	Ref.
1.	Urea		1 : 2	12	116
2.	1,3-Dimethylurea		1 : 2	70	116

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

A new generation, bio-based ionic liquid which is composed of biomaterials has been reported by Fukaya *et al* in 2007.<sup>155</sup> These ionic liquids can be synthesized by two easy steps of anion exchange reaction of choline hydroxide with different carboxylates. In some cases alkanolic acids were used as counter ions.<sup>156</sup> In recent

times, room temperature ionic liquids of amino acids as anions and choline as a cation was introduced by Liu *et al.*<sup>157</sup> Choline hydroxide can also be used as starting material to prepare eighteen different aqueous amino acids. Deep eutectic mixtures of sugar, urea, and salt were synthesized by Imperato *et al.*<sup>158–160</sup> In 2011 Choi *et al.* has termed simple eutectic mixtures as “natural deep eutectic solvents” (NADES).<sup>9</sup> They had presented 30 different combinations of ChCl, organic acids, amino acids and sugars generating room temperature liquids having moderate viscosities. These solvents play important roles in various plants, *i.e.* as a water-free natural ionic liquid in cells or as solvents for biochemical reactions.

**Table 8.** Other natural ammonium salts used in eutectic mixtures.

Entry	Ammonium salt (AS)	Structure	HBD	Ratio (AS : HBD)	$T_m$ (°C)	Ref.
1.	L-Carnitine		Urea	2 : 3 (wt : wt)	74	161
2.	Betaine hydrochloride		Urea	15 : 85 (mol : mol)	27	162
3.	Betaine hydrochloride		Glycerol	$T_f$	rt	163

**Table 9.** Some eutectics based on metals and donor molecules.

Entry	HBD	Metal salt	Ratio (HBD : salt)	$T_f$ (°C)	Ref.
1.	Urea	ZnCl <sub>2</sub>	7 : 2	9	115
2.	Ethylene glycol	ZnCl <sub>2</sub>	4 : 1	-30	115
3.	ChCl	ZnBr <sub>2</sub>	1 : 2	38	119
4.	ChCl	FeCl <sub>3</sub>	1 : 2	65	119
5.	ChCl	SnCl <sub>2</sub>	1 : 2	37	119

Recently, it has been found that choline based ionic liquids can be synthesized by two steps of anion exchange reaction of choline hydroxide with different carboxylates /artificial sweeteners. Ionic liquids based on the choline cation and carboxylates and artificial sweeteners are enlisted in **Table 10**.

**Table 10.** Ionic liquids based on the cholinium cation and carboxylates (entries 1–17) and artificial sweeteners (entries 18 and 19).

Entry	Compound	Structure	$T_m$ (°C)	$T_g$ (°C)	Ref.
1.	Acetate		51	n.d. <sup>a</sup>	155
			80	n.d. <sup>a</sup>	156
2.	Propionate		n.d. <sup>a</sup>	-	153,
				74	154
3.	Butanoate		45		154
4.	Valeric acid		31		154
5.	Hexanoate		52		154
6.	Octanoate		26		154
7.	Decanoate		50		[154]
8.	Isobutyrate		35		154
9.	Pivalate		57		154
10.	Glycolate		38	-67	153
11.	Tiglate		n.d. <sup>a</sup>	-62	153
12.	H-Succinate		n.d. <sup>a</sup>	-52	153
13.	H-Maleate		25	-72	153
14.	H-Fumarate		80	n.d. <sup>a</sup>	153
15.	H-Malate		99	-40	153
16.	H-Tartrate		131	-6	153
17.	Benzoate		47	-51	153
18.	Acesulfamate		69	n.d. <sup>a</sup>	152
19.	Saccharinate		25	n.d. <sup>a</sup>	159

Expectedly, the molar ratio of anions to cations is 1 : 1<sup>a</sup> n.d. not detected.

Room temperature ionic liquids based on amino acids as anions and choline as a cation was introduced by Liu *et al.* Array of Eutectic solvent based on amino acid and cholinium cation enlisted in **Table 11**.

**Table 11.** Eutectic solvents based on the cholinium cation and amino acids as counter ions (molar ratio 1: 1).

Entry	Counterion	$T_g(^{\circ}\text{C})$	Ref.
1.	Glycine	-61	157
2.	Alanine	-56	155
3.	Serine	-55	155
4.	Threonine	-39	155
5.	Valine	-74	155
6.	Leucine	-47	155
7.	Isoleucine	-47	155
8.	Methionine	-61	155
9.	Phenylalanine	-60	155
10.	Tryptophan	-12	155
11.	Proline	-44	155
12.	Aspartic acid	-22	155
13.	Glutamic acid	-18	155
14.	Asparagine	-14	155
15.	Glutamine	-40	155
16.	Lysine	-48	155
17.	Histidine	-40	155
18.	Arginine	-10	155

### 1.5 New supersaturated solvent as analog to natural honey

Again, to minimise environmental pollution caused by the use of volatile organic compounds (VOCs), serious efforts have been made to develop clean synthetic methodologies for preparing organic molecules having biological and industrial importance.<sup>3,164–170</sup> Amid present work in the thesis through physico-organic study we have predicted the use of natural supersaturated solvents like honey a truly green, abundantly available in nature as a powerful medium to promote C-C bond form reactions.<sup>171,172</sup> In other words, we wish to know whether honey, a natural

supersaturated medium can serve as an effective medium for carrying out organic as well as biological reactions.

Interestingly, honey has been a major source of natural proteins as well as carbohydrates and natural medicines from the inception of life in the earth.<sup>168-170</sup> According to one of the famous quotes of Einstein, the existence of human beings would be ceased to exist without pollination and honey.<sup>173</sup> In order to delineate the efficiency and 'green aspects' of nature inspired supersaturated solvent *i.e.* honey, Diels-Alder reaction has been performed in this medium. Diels-Alder reaction is a reliable method of synthesis of especially 6-membered carbon ring with stereo- as well as regio- controlled products with biological activities. Chemical composition of honey suggests that, this highly viscous medium contains carbohydrates (75%), water (18%) and organic acids (2%).<sup>174,175</sup>

In the present thesis, an attempt has been made to synthesize analog of natural honey. Analog of honey is referred to as artificial supersaturated/new supersaturated solvent. Homogeneous reaction conditions have been maintained during probe reactions. Viscosity measurement of this new supersaturated solvent suggests a very high viscosity range *i.e.*  $10^3$ . But experimental results show that, rate of bimolecular Diels-Alder reaction shows a spectacular rate increase in the new supersaturated solvent. Trends in physico-organic study reveal that the new supersaturated solvent offers a large solubility window and can play a pivotal role in hydrogen bond formation in the course of reactions *in situ* due to the presence of mono- and di-saccharides.<sup>174,175</sup> The new supersaturated solvent can be preferred over water as the reaction medium not only to achieve an enhanced rate of the reactions but also to increase the yield of the products.<sup>171-175</sup> Physical parameters responsible for enhanced rate and yield are documented in Chapter 4.

The introduction of a new supersaturated solvent as a reaction medium can certainly prove a yardstick to avoid solubility and reactivity problems arising from the use of water as a solvent. As evidenced in the present study, high viscosity of the new supersaturated solvent does not adversely affect the kinetics of these reactions as do the ionic liquids of comparable viscosities. The high viscosity of the new supersaturated solvent did not alter the kinetics possibly due to structural aspects of the new

supersaturated solvent, which is a remarkable aspect of this study and requires further investigation.

## 1.6 Conclusions

The large availability and widespread studies on organic reactions in green solvents project growing interest of contemporary chemists in green chemistry. Tailor-made environment benign solvents may replace VOCs for many industrial applications. The fundamental understanding of physico-chemical properties of these environment benign solvents can facilitate their applications in organic chemistry, material chemistry, inorganic and electrochemistry *etc.*

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## Chapter 2

### Aims and Objectives

*“Our aim as scientists is the objective truth; more truth, more interesting truth, more intelligible truth.”*

*-Karl Popper*



*A brief outline of the aims and objectives of the proposed research works described in the present thesis has been provided in the current chapter.*

The principles of Green Chemistry are based upon the interdisciplinary approach towards the reduction of harmful compounds produced during the course of the reaction. The production of waste material can be avoided by the adaptation of greener conduct of performing experiments rather than tedious disposal processing after waste generation. The principle objective of the present thesis is to understand efficacy and superiority of environment benign media over volatile organic compounds (VOCs) from the perspective of a physico-organic chemist. The main aim of this thesis is to project alternatives of VOCs in the form of green solvents like water, deep eutectic solvents (DESs) and nature-inspired supersaturated solvent.

Water is regarded as the universal source of reaction media due to its vast availability and greenness. In some cases, it has also been found that water insoluble reactants show unexpectedly better results in water promoted reactions. Meanwhile, the major motive behind the selection of water as reaction media is the utilisation of its special properties like polarity, hydrogen bonding and hydrophobicity. These properties are regarded as the responsible factors behind enhancement in reaction rates. Again, the special effect shown by water can be greatly altered with the help of ionic solutes such as LiCl, NaCl, LiClO<sub>4</sub> and tetraalkylammonium halide salts.

DESs can be also considered as extremely important solvents as they show significant properties like non-toxicity, ready biodegradability, good thermal stability, wide liquidus range, good solubility and recyclability. But still, there is some scarcity regarding physico-organic properties database on the organic reaction in DESs.

Medicinal theories believe that nature uses one of the extraordinary solvents *i.e.* natural honey to kill the bacteria found in the environment. Natural honey is equipped with unique properties to tackle bacteria, largely important in medicinal science. Present thesis delineates the physico-chemical forces responsible for rate acceleration of C-C bond formation reaction in nature inspired supersaturated solvent. Enhanced rate acceleration in this kind of nature inspired supersaturated solvent can put forward the answer for the medicinal use of natural honey. Diels-Alder reaction has been used as the probe reaction throughout the thesis and emphasis has been given to the delineation of physico-organic forces accountable for the enhancement/decrement of rate, yield and selectivity of Diels-Alder reaction.

In view of aforementioned general features gathered from the literature survey, following are the salient objectives of the thesis aimed to provide a broad outline of the research work carried out:

- to investigate cosolvent effect in DESs, Diels-Alder reaction has been carried out in three water-DESs mixtures. The addition of water to DESs modifies the structural properties of DESs. In the present study physico-chemical properties of three DESs and their 'green hybrid' (*i.e.* water-DESs mixtures) has been investigated,
- to delineate ready water miscibility property of water-DESs mixtures spectroscopic techniques like Kamlet-Taft polarity parameters, NOSEY and FTIR studies has been employed,
- to examine the effect of hydrogen bond donor in a eutectic solvent of carbohydrate based eutectic solvents kinetic and viscosity studies have been employed,
- to determine the role of nature inspired carbohydrate based supersaturated biodegradable medium biologically important C-C bond formation reactions has been carried out under ambient conditions,
- to elucidate the effect of excess –OH groups and high viscosity of nature inspired carbohydrate based supersaturated solvent physico-chemical properties of nature inspired carbohydrate based supersaturated solvent has been determined,
- to find out the motivation behind the S/I behaviour of  $R_4NX$  in all polar solvents, physico-organic studies has been carried out in aqueous  $R_4NX$  and
- to delineate cause behind the different individual behaviour of  $(CH_3)_4NBr$  salts from rest of the  $R_4NX$  aqueous solution.

The main purpose of the thesis is to recognize the viability of green media to replace VOCs using the understanding of physico-organic aspects through some common organic reactions. Reactions have been performed at ambient conditions for understanding reactions under homogenous and heterogeneous conditions.

## Chapter 3

### Physico-Organic Insights of Deep Eutectic Solvents

*“Neither sugar nor salt tastes particularly good by itself. Each is at its best when used to season other things.”*

*-Unknown*



*Deep eutectic mixtures (DESs) are regarded as a new genre of environment benign, biodegradable green and cost effective option to VOCs and ionic liquids. Recently discovered water miscible nature of DESs meets its applications in chemical and industrial process. The addition of water to DESs modifies the specific properties of DESs which tune them for specific applications. In the present chapter physico-organic properties of three DESs and their choline based ‘green hybrid’ of water-DESs.*

*In the search for environmentally benign solvent media, a new class of solvents composed of mixtures of carbohydrates with urea or methylated urea has been noted to be effective in enhancing the reaction rates of a bimolecular organic reaction. In the present study, Diels-Alder reaction is used as probe reaction and the solvent effect on reaction has been analysed through kinetic study.*

### 3.1 Cosolvent mediated kinetic investigations of Diels-Alder reaction in deep eutectic solvents

#### 3.1.1 Introduction

In last three decade, deep eutectic solvents (DESs) have been used in synthetic organic chemistry for various purposes *i.e.*, as a catalyst, solvent and reagent. DESs have now been established as potential replacements for volatile organic compounds (VOCs) due to their attractive physico-chemical properties in many chemical transformations.<sup>1-7</sup> DESs show special properties like low vapour pressure, nonflammability, large solubility window, recyclability, etc., which facilitate synthetic and chemical transformations. These physical properties of DESs can be simply altered by tuning of ionic counterparts in respective DESs. DESs are considered as new generation room temperature ionic liquids (RTILs) because of their extraordinary physico-chemical properties over conventional RTILs. Properties like low-cost and simple methods of preparation, high boiling point, trouble-free handling, recyclability, low toxicity and comparable solubility window make DESs as a superior option over RTILs and VOCs.<sup>8-17</sup> The synthesis of DESs is relatively simple; for example, gentle heating of salts like choline chloride (vitamin B<sub>4</sub>) and urea (a hydrogen bond donor) in definite ratio below 100 °C produce this new generation substitute of RTILs.<sup>8,9</sup> DESs are considered as a viable option in organic synthesis, catalysis, biochemistry, electrochemistry and in a variety of different fields.<sup>10-15</sup>

Physico-chemical properties of DESs are largely dependent upon the composition of parent counterparts e.g. H-bond acceptor salt and H-bond donor urea. The interactive forces between H-bond acceptor salt and H-bond donor principally determine the physico-chemical properties of individual DESs. Physical parameters like temperature, pressure and addition of a cosolvent can also significantly alter the physical properties of DESs as well as the solvent system. These significant changes in the physical properties of DESs and solvent systems arise due to different inter and intramolecular interactions in the system.

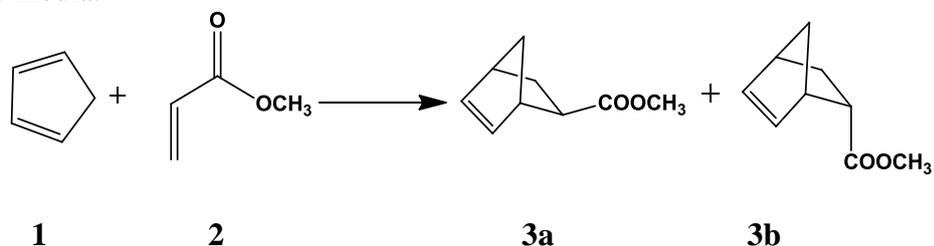
In view of these changed physico-chemical properties of DESs, addition of DESs as cosolvent has been employed. In the present work, water has been taken as core solvent of water-DESs mixture and DESs has been taken as the choice of cosolvent. Selection of water-DESs systems has been done in order to determine the typical

water miscibility properties of DESs. The combination of water-DESs system forms “green fusion” due to their individual green properties. DESs are not actually hygroscopic in nature but they are readily miscible in water. Systematic experimental investigation of the water-DESs system could provide imperative information to understand the effect of inter and intramolecular interaction on the structural properties of water-DESs mixtures. Additionally, deployment of water as co-solvent in the DESs can also help to understand solute-solvent and solute-co-solvent interactions in the system.<sup>18–26</sup> The present study of the water-DESs system has been designed to quantify the effect of structural properties of water on the overall dynamics of DESs.

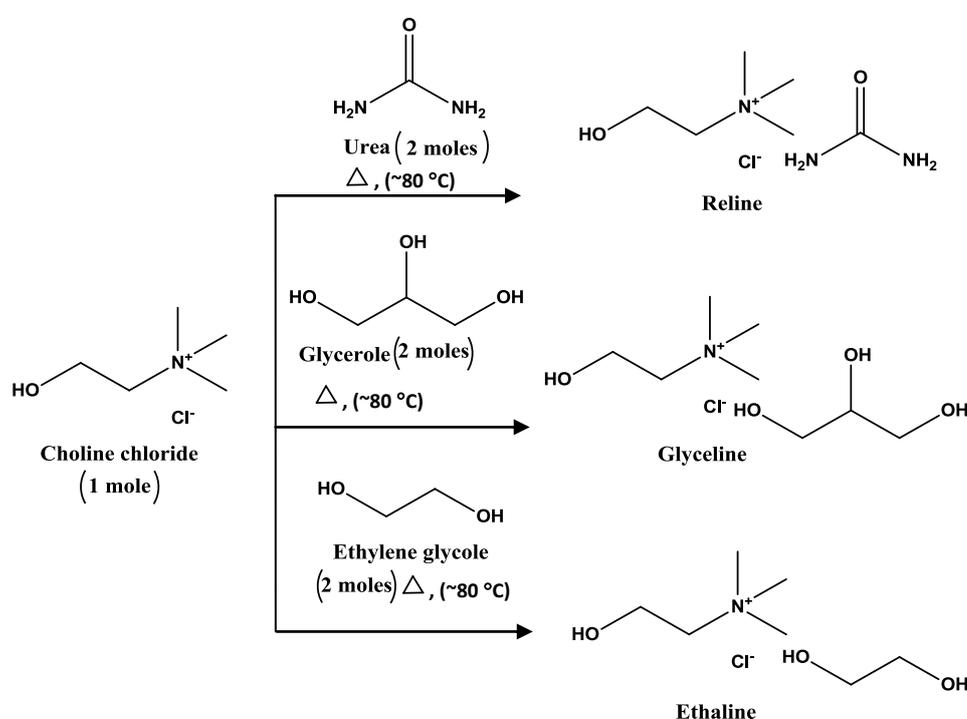
Out of numerous organic reactions, Diels-Alder reaction is regarded as one of the most important C-C bonds forming reaction because of its ability to form six-membered ring structure with excellent control over stereoselectivities of the products.<sup>27–32</sup> It has been documented in the literature that Diels-Alder reaction display very little solvent effect in organic solvents due to the presence of isopolar transition state.<sup>33</sup> However, spectacular rate enhancement in water promoted Diels-Alder reaction shows the definite impact of solvent in rate enhancement of reaction. A point is to be noted here that the rate enhancement in water is relatively much higher than those of other volatile organic solvents.<sup>34</sup> On the account of established experimental analysis available in the literature, the present study involves the use of Diels-Alder reaction as a model reaction to analyse the effects of DESs on the water.

On the environment benign and economical perspective, water can serve as a superior option to volatile organic solvents.<sup>33–44</sup> In the context of an organic reaction, a systematic study of the relationship between reaction rate and empirical properties like solute-solvent and solvent-cosolvent interactions can be of importance to get better yields, rate enhancements and stereoselectivities.<sup>42,45–47</sup> Recent studies on DESs show better yields as well as rates of numerous organic reactions in highly polar media.<sup>48–61</sup> According to previous reports on ionic liquids, the rate of Diels-Alder reaction of cyclopentadiene and methyl acrylate and its higher analogs have been found to be sluggish in ionic liquids. In these cases, the viscosity of solvent media (RTILs) plays a crucial factor in determining reaction rate.<sup>62</sup> In the case of DESs, it has been observed that viscosity of water-DESs media continuously increases upon increasing DESs in water. The viscosity of solvent mixtures varies linearly as a

function of the amount of cosolvent in the mixture. It thus can probably be estimated that the tailor made water-DESs mixture composition can replace volatile organic solvents in organic reactions. In organic reactions, where the water sensitive reactants result in very less yield and selectivity, the water-DESs mixtures can serve as an effective media.



**Scheme 1.** The reaction of cyclopentadiene (1) with methyl acrylate (2)



**Scheme 2.** Structures, compositions, and melting point of DESs.

In the context of almost all organic reactions, the polarity of solvent media affects both the kinetics of reaction as well as selectivity of products. Polarity parameters *i.e.*, electronic transition normalised ( $E_T^N$ ), hydrogen bond donor acidity ( $\alpha$ ), hydrogen bond acceptor basicity ( $\beta$ ), polarizability ( $\pi^*$ ), of pure DESs and water-DESs mixture can provide a better insight of solute-solvent interactions on the reaction rate profile.

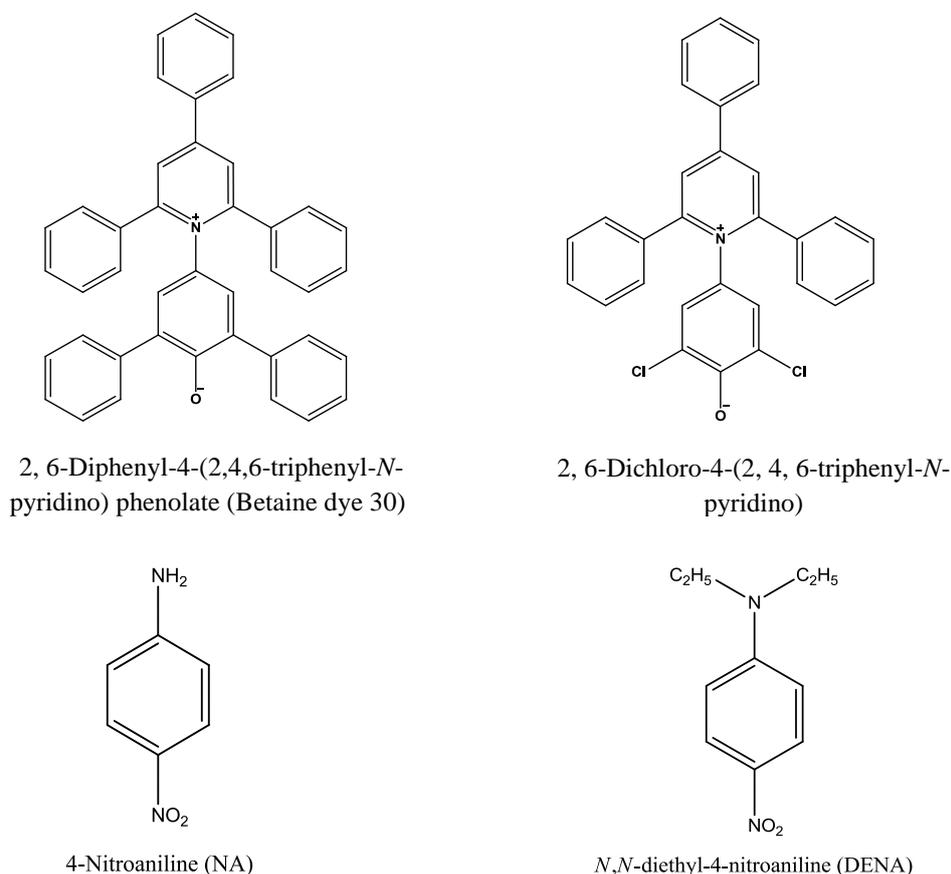
The particular mode of behaviour (ideal/non-ideal) of polarity parameters can provide the impact of solute-solvent and solvent-co-solvent interaction on the kinetics of Diels-Alder reaction. In the present study, we have investigated the kinetics of Diels-Alder reaction in water mixtures of three choline based 'green hybrids' of DESs *i.e.* reline, glyceline and ethaline. The three DESs were prepared by mixing 1 mole of choline chloride with 2 moles of urea, glycerol, 1, 2-ethanediol, respectively. (**Scheme 2**). Trends in the kinetic profile have been explained on the basis of viscosity, polarity, IR, NMR, activation parameter and pairwise interaction theory.

### 3.1.2 Experimental section

**3.1.2.1 Materials and synthesis of DESs:** Dicyclopentadiene (**1**) and Methyl acrylate (**2**) were procured from M/s. Merck Co. Ltd. The diene (**1**) was freshly cracked from its dimer (Dicyclopentadiene) and stored in a deep freeze. Betaine dyes (**30**) and (**33**), 4-nitroaniline, and *N,N*-diethyl-4-nitroaniline (**Scheme 3**) were purchased in the highest available purity from Fluka ( $\geq 99\%$ , HPLC), Spectrochem. Co. Ltd., and Frinton Laboratories, respectively. Solvents used in the present study *i.e.*, ethaline, glyceline, and reline were prepared by mixing choline chloride ( $\geq 99\%$  from Sigma-Aldrich) with 1,2-ethanediol (99.8%, anhydrous from Sigma-Aldrich), glycerol ( $\geq 99.5\%$ , spectrophotometric grade from Sigma-Aldrich), and urea ( $\geq 99\%$  from Sigma-Aldrich), respectively, in a mole ratio of 1:2 followed by stirring under heating ( $\sim 80^\circ\text{C}$ ) until a homogeneous, colorless liquid has been formed. The spectroscopic measurements have been performed by NMR and FTIR spectroscopy. Absolute ethanol was used to prepare probe stock solutions. Doubly distilled deionized water with  $\geq 18.0\text{ M}\Omega\text{-cm}$  resistivity was obtained from a Millipore Milli-Q Academic water purification system.

The stock solution of the required dye was freshly prepared in dichloromethane prior to use. The stock solution was added dropwise to the DESs, and the solvent was evaporated under vacuum. The DES was then transferred to the cuvette under nitrogen atmosphere and sealed with a septum. The  $\lambda_{\text{max}}$  was measured at different temperatures using a Cary 50 UV-visible spectrophotometer.<sup>63-65</sup> All the polarity values are within reproducibility of  $\pm 0.4\%$ . The temperature of the cell was controlled using the single cell accessory having an accuracy of  $\pm 0.1^\circ\text{C}$ .

A precalculated amount of the DES or the (water-DES) mixture is directly added to the cuvette, and the solution is thoroughly mixed. The solubility of a probe within a DES or (water-DES) mixture is checked using the linearity of the absorbance versus the concentration plots.



**Scheme 3.** The molecular structure of solvatochromic probes.

NMR spectra were recorded with the help of Bruker's India NMR spectrometer at 200, 400, and 500 MHz. Chemical shifts are reported in ppm. Coupling constants ( $J$ -values) are reported in Hertz. Attenuated and reflectance-Fourier-transform infrared (ATR-FTIR) absorbance data were acquired with the help of Agilent Technologies Cary 660 ATR double-beam spectrophotometer from 4000 to 400  $\text{cm}^{-1}$ . The liquid samples were evenly spread on KBr pellets to record the FTIR spectra. All spectroscopic measurements were performed at least in triplicate starting from sample preparation, and the results were averaged. All spectra were duly corrected by measuring the spectral responses from suitable blanks, prior to data analysis and statistical treatment.

**3.1.2.2 Kinetic analysis:** First, 0.6 ml (7.0 mmol) of methyl acrylate was dissolved in 10 ml of DESs by vigorous stirring at 25 °C. Then, 0.4 ml (7.0 mmol) of freshly cracked cyclopentadiene was added through a syringe in the above solution under vigorous stirring. During the kinetic study, 1 ml of the reaction mixture was abstracted at a certain time interval and the product was extracted with an ethereal solution. Thereafter, it was injected for gas chromatographic analysis. Second order rate constants,  $k_2$  obtained from GC were within the accuracy limit of  $\pm 6\%$ .

Viscosity was measured with Brookfield programmable viscometer after calibrating it against water and aqueous  $MgCl_2$  solutions with an accuracy of  $\pm 2\%$  at 25 °C.<sup>66</sup>

At the completion of the reaction product was separated by extraction with an ethereal solvent. The crude product was obtained by simple evaporation of solvent on rotary vapor which was then run through the column of silica of mesh 80-90 size with elute of 3 % of ethyl acetate and petroleum ether to obtain the pure product.

**3.1.2.3 Determination of the second order rate constant:** From the gas chromatographic analysis, the extent of the reaction ( $x$ ) can be estimated by plotting the amount of product as a function of time. Since for the reaction (**Scheme 1**), products have been formed due to reactions between the two reactants in 1:1 ratio; the concentration of the remaining reactants would be equal with respect to time. It implies that if 'a' is initial concentration of both the reactants. Now  $(a-x)$  will give the remaining reactants in the solvent at time 't' after commencing the reaction at  $t=0$ . The plot between  $x/a(a-x)$  vs. 't' gives the value of  $k_2$  in each case.<sup>67</sup> Temperature dependent  $k_2$  values have been obtained by performing the reactions in reaction jacket attached with Julabo constant temperature water bath with an accuracy of  $\pm 0.1^\circ C$ .

### 3.1.3 Results and discussion

In recent reports, it has been noted that the Diels-Alder reaction was accelerated by many folds in water condition in contrast to in conventional organic solvents.<sup>34</sup> It should be noted here that under 'in water' condition principle forces behind the rate enhancement are solvent polarity,<sup>33,68</sup> hydrogen bonding,<sup>69-72</sup> hydrophobic packing,<sup>73-78</sup> enforced hydrophobic interaction,<sup>79,80</sup> and Lewis acid catalysis<sup>81-85</sup> of the solvent. It has been also confirmed that hydrophobic interaction plays a crucial role in rate enhancement in both in water and on water *i.e.* heterogeneous reaction condition.<sup>86-89</sup>

The Diels-Alder reaction of **1** and **2** (**Scheme 1**) was carried out in the binary mixtures of water with different DESs such as reline (composed of choline chloride and urea), glyceline (composed of choline chloride and glycerol) and ethaline (composed of choline chloride and ethylene glycol). Nature of the cosolvent affects the solute-solvent and solvent-cosolvent interactions through various physical parameters. It is very well known fact that the Diels-Alder reaction of **1** and **2** (**Scheme 1**) is faster in water in comparison to than that of ionic liquids and molecular solvents. The spectacular rate enhancements of Diels-Alder reaction were first documented by Rideout and Breslow.<sup>34</sup> Similarly, Tiwari and Kumar have reported the faster rates of reaction for Diels-Alder reaction in water as compared to ionic liquids, who determined that the high viscosities of solvents cause decreased number of effective collisions between reactant molecules.<sup>61</sup> The analogous condition was observed in the current context, in which the Diels-Alder reaction was 2-4 times faster in the water as compare to in DESs. The consequences of viscosity on the kinetic profile of the reaction were observed by Firestone and Vitale.<sup>90-94</sup> According to these authors, the value of slope observed for relative rate versus relative viscosity for Diels-Alder reaction was much greater as compared to similar type of comparison observed for the Claisen rearrangement in same solvents. Correlation between kinetic profile and viscosity in two different type of organic reaction is possible because these reactions share same common features like very low dependence of reaction on solvent polarity, Effect of viscosity was also found to be important in the dimerization reaction of cyclopentadiene where the rate of reaction decreases linearly with increasing viscosity.<sup>95,96</sup> An another very interesting observation regarding the effects of solvent viscosity on the rate of reaction was observed by Kumar *et. al.*, where the rate of reaction increases up to ~1.2 cP with increasing viscosity then drop sharply with increasing viscosity.<sup>97</sup> Additionally, it has been found that the rate of 1, 3 dipolar cycloaddition reaction of diphenyldiazomethane with ethyl phenylpropiolate rises till ~1 cP and thereafter decreases continuously.<sup>94</sup> From these examples, it is clear that viscosity of solvents definitely contributes toward the alteration of the rate of reaction but the reason behind the abnormal reaction rate increase and then sudden decrease has not been investigated on molecular level till date. These abnormal results, however, cannot be explained by kinetic theory as the bond making of reactant in the reaction is independent of viscosity. Firestone and co-worker have explained this unusual nature in terms of vibrational activation theory, in which high vibrational and

low translational energies promote the bond-making in reaction.<sup>93,94,98</sup> At a high viscosity of the solvent, the translational mode of the molecule slows down, which ultimately convert translational mode into the vibrational mode of molecules. At exceedingly high viscosities encounter controlled regime took over control. In this region, virtual freedom of movement amongst reactant molecules in this microenvironment is restricted. This reduction in the degree of freedom of reactant molecules results in the reduction of the rate of reaction.

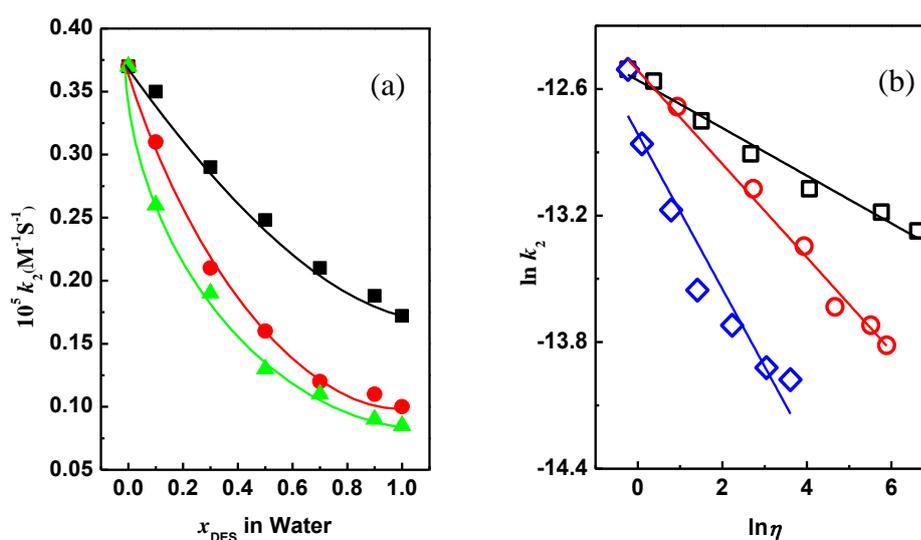
### 3.1.3.1 Effect of the concentration of DESs and viscosity of water-DESs mixtures on reaction profile

The reaction between **1** and **2** had been carried out in the binary mixtures of reline, glyceline, ethaline in water as a function of the mole fraction of the second component in the binary mixture, *i.e.*,  $x_{\text{DES}}$  at 25 °C. **Figure 1(a)** shows concentration dependence of second-order rate constant ( $k_2$ ) for the Diels-Alder reaction of **1** with **2** in the binary mixtures of DESs *i.e.* reline, glyceline, ethaline in water. The rate constant  $k_2$  decreases with an increase in the concentration of DESs in the binary mixture. Around five-fold decrease in the  $k_2$  value has been observed in the binary mixture of ethaline in water. The extent of decrease in the value of  $k_2$  was maximum in the case of ethaline in water as compare to reline and glyceline in water. On the other hand, reline and glyceline in water show slow decrease about three-folds and four-fold in rate constant values. It is interesting to observe here that the extent of decrease in the value of  $k_2$  in reline in water is minimum as compared to other DESs for the same DESs concentration in water.

In the highly aqueous region of the water-DESs mixtures, the rate constants decrease from the  $0.37 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  for pure water to  $0.29 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  for  $x_{\text{DES}} = 0.3$  of reline in water and viscosity increases from 0.89 to 4.5 cP. In a similar manner, the rate constant values for a binary mixtures of glyceline and ethaline in water decrease from the  $0.37 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  for pure water to  $0.21 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  and  $0.19 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  for  $x_{\text{DES}} = 0.3$ , respectively.

The consequent viscosity increase for water-glyceline mixture ranges from 0.89 to 15.35 cP and for water-ethaline mixture ranges from 0.89 to 2.2 cP. Beyond this point although the comparative viscosity increase in the case of the water-reline mixture is extremely high *i.e.* 4.5 to 750 cP, however, for the same composition rate constant

decrease in water-reline mixture is relatively low *i.e.*  $0.29 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  to  $0.17 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$ . A viscosity value for corresponding compositions ranges from 15.35 to 359.87 cP and 2.2 to 37 cP for water-glyceline and water-ethaline mixtures. Since the viscosity change in water-glyceline and water-ethaline mixtures beyond,  $x_{\text{DES}} = 0.3$  is comparatively less than that of the water-reline mixture, therefore, it is required to investigate the role of viscosity behind abnormal results in the case of three water-DESs mixtures.



**Figure 1.** (a) The plots of  $k_2$  against mole fraction of binary mixtures of reline (■), glyceline (●), ethaline (▲) in water; (b) The plots of  $\ln k_2$  against  $\ln \eta$  in binary mixtures of reline (□), glyceline (○), ethaline (◇) in water at 25 °C.

In order to assess the role of viscosity, the rate constants were also plotted as a function of viscosity. **Figure 1(b)** represents the plots of  $\ln k_2$  against  $\ln \eta$  in binary mixtures of reline, glyceline, ethaline in water in 25 °C. Linear correlation in the plots of  $\ln k_2$  against  $\ln \eta$  in binary mixtures of binary mixtures reline, glyceline, ethaline suggest that viscosity of solvent media controls kinetic profile of the reaction. The equivalence in the trends of all the three water-DESs binary mixtures projects the minimum possibility of any specific interaction between the component of the binary mixture and the reactants. Results obtained for the reaction suggest that rate constant values are a linear function of the composition of DESs in water for entire viscosity range.

From the plots of rate constants  $k_2$  versus different concentrations of DESs in water, **Figure 1(a)**, it is observed that the rate constants decrease with increase in the concentration of DESs in water. Concentration-dependent studies suggest that viscosity of all water-DESs mixture increase with an increase in the concentration of DESs. But the extent of decrease in the rate constants in each case is different. In the first case, though the viscosity of the water-reline mixture is highest but still the extent of rate decrease in rate constants is comparable with its other two water-DESs mixtures. It seems that high viscosity of water-reline mixture facilitates the rate of reaction by lowering the energy of transition state of a reaction in the highly viscous region. From the experimental data presented in **Figure 1(b)**, it can be asserted that variation of the rate with respect to solvent viscosity in the present case shows an unusual trend, the rate constant value of the reaction decreases in all cases of the water-DESs mixture. This unusual behaviour of the rate of reaction in highly viscous media is exactly opposite to our common understandings on the basis of conventional kinetic theory.<sup>33,99-101</sup> This unusual behavior of water-reline mixture in term of viscosity and comparative high rate constants leads us to comprehend the observations on the basis of a kinetic theory which is beyond our conventional kinetic theory.

The plausible reason for the enhanced rate of a bimolecular reaction in the viscous region lies in fast and successful encounters of the reactants with proper orientation of reactants.<sup>33,97-99</sup> The reactions pursued here are C-C bond formation reactions and we know from the vibration-activation kinetic theory that since the process of bond-making takes longer time as compared to single vibration, bond formation takes place competently between slow-moving reactants.<sup>89,94,102,103</sup> The present observation can be discussed on the basis of collision-controlled reactions between two reactants and due to the presence of a large number of encounters among reactants in the collision regime, the rate of the reaction is independent of the effect of the solvent viscosity.<sup>89,94</sup> In highly viscous region of water-reline mixture *i.e.* from  $x_{\text{reline}} = 0.4$  to 0.9, comparatively high rate constants of the Diels-Alder reactions has been observed. This abnormal behavior is almost analogous to the situation of enzyme catalyzed bimolecular reactions where dynamic sites of the enzyme always offer a pool of high viscous region.<sup>89,94,104,105</sup> In the enzyme catalyzed reaction, the presence of the dynamic site provides a cohesive environment to catalyzed the reaction.<sup>94,106</sup>

Present experimental results can also be explained if we consider comparative differences in the size of reactants and solvent molecules. The structural difference between reactants and solvent molecules shows that size of both cyclopentadiene as well as methyl acrylate is significantly smaller as compared to that of the size of choline chloride-urea eutectic mixture present in the reline.<sup>102</sup> It implies that the reactants *i.e.* cyclopentadiene and methyl acrylate come in contact with a small segment of the choline chloride-urea eutectic mixture and its composition with water. Thus, micro-viscosity experienced by the reactants is of moderate value as compared to that of macro-viscosity which is the reflection of the entire water-reline mixture.<sup>89,94,100,101</sup> However, the absence of such unusual rate enhancement in ionic liquids specifies that only high viscosity of water-reline mixture (in high reline concentration in water) is not the lone factor to promote the rate of reactions.

It is a known fact that diastereofacial selectivity of Diels-Alder reaction can be affected by the solvent effect. The hydrogen donor capability and solvent polarity are the common effects favouring endo adduct in the case of Diels-Alder reaction.<sup>107</sup> Induced hydrophobic interaction along with hydrogen bond donor capability and polarity of water govern the endo selectivity in the case of Diels-Alder reaction in water. In water hydrophobic effect stabilizes the compact endo transition state than extended exo transition state. The modified arrangement of the water-DESs favours the endo stereoisomer (endo: exo ~ 3.7) over exo-stereoisomer of the product in all water-DESs mixtures.

The Linear correlation between rate constant and solvent viscosity indicates that the effect of other factors on the rate constants of Diels-Alder reaction is relatively small. Other contributing factors, however, can be listed as: (1) on addition of DESs to water, prominent decrease of the polarity of transition state can occur, (2) in water-DESs mixture different class of DESs (reline, glyceline and ethaline) project antihydrophobic nature to solvate organic reactant independently, and (3) rate constant differences in the three categories of water-DESs mixtures shows that extent of hydrogen bonding in the transition state plays diminutive role.<sup>108</sup> The difference in the trends of rate constant decrease in the water-DESs mixtures points out towards polarity difference of water and DESs along with hydrogen bonding capacity of water and DESs molecules. Previous reports on the dramatic rate enhancement of Diels-

Alder reaction in water condition suggest that hydrophobic effect plays a prominent role in rate enhancement over other effects in the highly aqueous region.<sup>105</sup> The addition of DESs to water will continuously decrease the hydrophobic effect, which ultimately reflect the decrease of rate constants of the reaction. This decrease in the hydrophobic effect can also help reactant molecules to solvate separately, which retards the diffusion process of the reaction rate.

In the present case, the concept of pairwise interactions can be used to understand the rate difference in three different classes of water-DESs mixtures in the highly aqueous region. A pioneer work of Engberts and coworkers on hydrophobic hydration enable the correlation of reaction rates with pairwise interactions in the highly aqueous region.<sup>79</sup> According to this concept, the rate of reaction has been discussed in the terms of pairwise Gibbs function interaction parameters recognized by corresponding interactions of the cosolvent molecules with the initial state and the activated complex. The thermodynamic parameters responsible for the solute-solute interactions in aqueous media can be determined by this additive principle.<sup>79</sup>

The presence of pairwise interaction and quantitative analysis of kinetic medium effects for highly dilute solutions can be explained by the linear relationship between  $\ln(k_2/k_2^0)$  versus molality of cosolvent (DESs), given by equation 1.

$$\ln\left(\frac{k_2}{k_2^0}\right) = \frac{2}{RT}G(C)m - n\Phi M_1 m \quad \mathbf{1}$$

where  $k_2^0$  is the second order rate constant in pure water and  $k_2$  is the a second order rate constant in the water-DESs mixtures for Diels-Alder reaction,  $m$  is the molality of reline,  $\Phi$  is the practical osmotic coefficient of water ( $\Phi = 1$  for highly aqueous solution),  $n$  is the number of water molecules present in the activated complex,  $M_1$  is the molar mass of water and  $G(C)$  is the difference in Gibbs energy of interaction between the DESs and the initial state and the DESs and the transition state, respectively. The  $G(C)$  values determine the effect of DESs on the Gibbs energy of activation for Diels-Alder reaction in the water-DESs mixture. Effect of cosolvent on the Gibbs energy of activation can be represented by  $G(C)$  which is obtained from the slope of linear plot between  $\ln(k_2/k_2^0)$  vs molality  $m$  of the cosolvent.

Above documented  $G(C)$  values have been determined for aqueous solutions of reline, glyceline, ethaline. The high negative value of  $G(C)$  parameter for Diels-Alder reaction in **Table 1** suggest that initial state of the reaction is highly stabilised by the DESs.

**Table 1.** The  $G(C)$  values for the Diels-Alder reaction in the aqueous solutions of DESs at 25 °C.

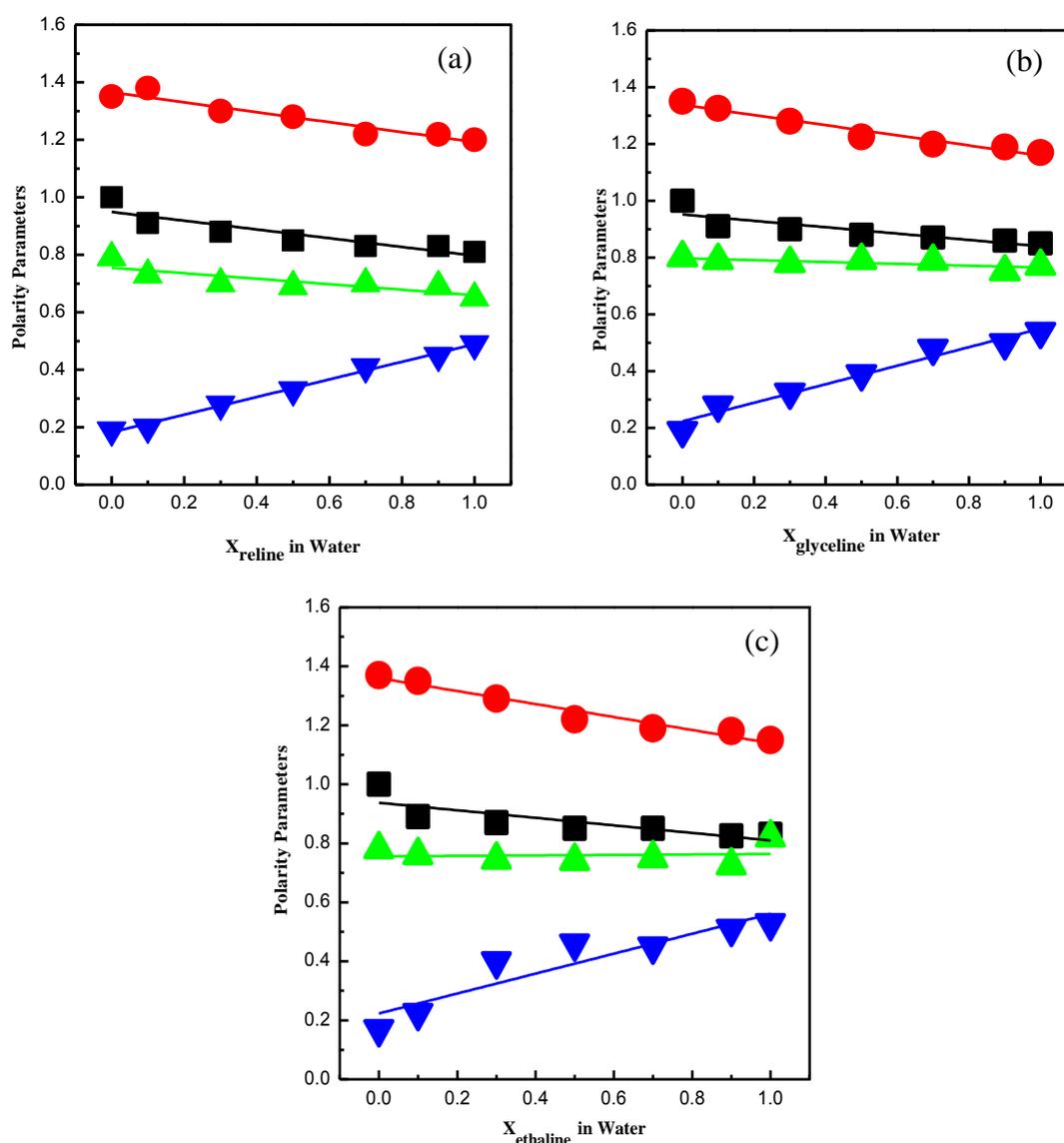
Sr. no.	DES	$G(C), J\ kg\ M^{-2}$
1.	Reline	-29.42
2.	Glyceline	-175.15
3.	Ethaline	-184.11

This initial state stabilisation does not allow effective collation of reactants **1** and **2** at the highly aqueous condition of the water-DESs mixture. High negative values for glyceline and ethaline also indicate that for these cosolvents, the extent of stabilisation of initial state is more as compare to the transition state, which ultimately reflects in the decreased reaction rates. Point to be noted here that behaviour of the water-reline mixture is different in the highly aqueous region from its other two counterparts, which points out towards a different pattern of solvation behaviour, dominant in different water-DESs mixtures.

### 3.1.3.2 Effect of overall polarity of the water-DESs mixture on reaction profile

Previously documented study on DESs shows that choline chloride based DESs shows a hygroscopic tendency.<sup>109</sup> A number of common ionic liquids like imidazolium-based ionic liquids are hygroscopic in nature but surprisingly they show limited water miscibility.<sup>110-112</sup> However, choline chloride-based DESs such as reline, glyceline and ethaline which are explored in this study are absolutely water miscible in nature. Therefore, on the beneficial front (keeping in mind the water's and DESs environmental benign properties) in the present study DESs and water combinations has been used to evaluate how water can modify the physico-organic properties of DESs in an efficient manner.<sup>106</sup> The addition of DESs to the water provides vital information regarding solvation behaviour of DESs. Polarity determination study with the help of thermosolvatochromic Kamlet-Taft parameters can provide extremely important information regarding molecular solvation within DESs.

In order to determine the effect of polarity on the kinetic profile of Diels-Alder reaction between **1** and **2**, thermosolvatochromic Kamlet-Taft parameters of water-DESs mixtures at different mole fraction has been determined. **Figure 2** represents the variation of (polarity parameters with  $x_{DES}$  in water at 25 °C. Careful examination of all three plots suggests, linear decrease of  $E_T^N$  value with increase of DESs in water-DESs mixture. Again trends observed for all three plots of  $E_T^N$  values show negligible preferential solvation.



**Figure 2.** Variation of  $E_T^N$  (■),  $\pi^*$  (●),  $\alpha$  (▲), and  $\beta$  (▼) with mole fraction of (a) Reline ( $x_{reline}$ ), (b) Glyceline ( $x_{glyceline}$ ), (c) Ethaline ( $x_{ethaline}$ ) in water at 25 °C.

Comparison between rate constant values for Diels-Alder reaction and polarity parameters propose that rate constant values decreases with the decreasing polarity *i.e.*  $E_T^N$  value of solvent system. From **Figure 1** for each of the combination *i.e.* water-reline, water-glyceline, water-ethaline; it has been observed that as water-DES mixture concentration moves from highly aqueous region to low aqueous region, rate of reaction decreases with decrease in the  $E_T^N$  value. Previous physico-organic studies on cycloaddition reactions advocate that Diels-Alder cycloaddition reaction occurs through isopolar transition state.<sup>113</sup> Therefore, present observations recommend that the rate constant values of Diels-Alder reaction are highest in pure water where the  $E_T^N$  value of water is also highest. However, as the overall polarity of the water-DESs solvent system decreases, the rate constant values also decreases. These correlations of reaction rate with solvent polarity as well as viscosity indicate that solvent polarity and viscosity play detrimental role in governing the rate of the reaction at different concentration phases in tandem.

In **Figure 2(a)** it can be clearly observed that the hydrogen bond donating ability *i.e.*  $\alpha$  value of water-reline mixture decreases with increasing concentration of reline. Decrease in the  $\alpha$  value with increasing reline concentration shows that hydrogen bond donating ability of the solvent mixture decreases with the addition of reline. According to previous observations on the kinetic study of Diels-Alder reaction, transition state of the reaction can also be stabilised by the hydrogen bonding donating ability of solvents, which causes the enhanced rate of reaction.<sup>63,66</sup> Similarly, in the present case, the deficiency of hydrogen bonding affect kinetic course by slowing down the reaction rate with increased reline concentration in the solvent system.

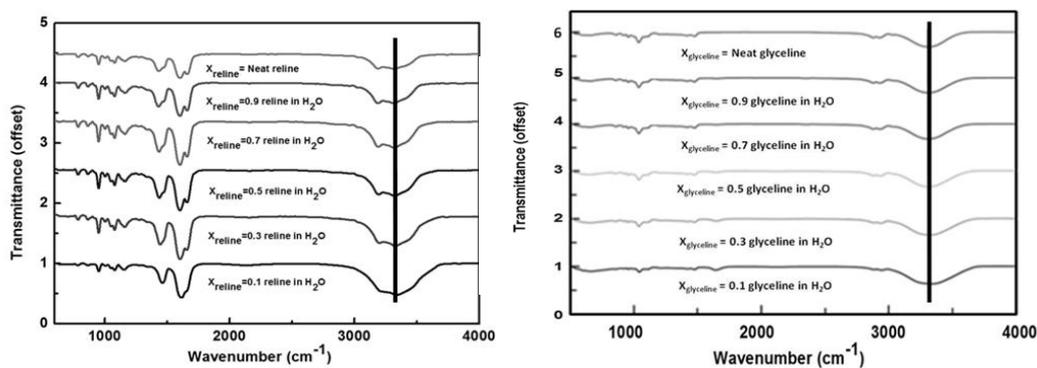
Comparison of rate constant and  $\alpha$  values of Diels-Alder reaction in three water-DESs mixtures gives the impression that  $\alpha$  value governs the pattern of decrease of rate constant. Careful observation of  $\alpha$  values in **Figure 2** for water-reline, water-glyceline and water-ethaline shows that, in water-reline mixtures hydrogen bond donating tendency decreases which results in the decreased rate of reaction. But for the same reaction extent of rate decline differs in water-glyceline and water-ethaline mixtures. Rate constant values in water-reline mixtures are high as compare to water-glyceline and water-ethaline mixtures. A possible reason for this difference in rate can be

explained by the  $\alpha$  value. The decrease in the hydrogen bond donating ability with an increase in the concentration of reline in water may increase interstitial accommodation of water molecules up to certain mixture concentration. These interstitial accommodations of water molecule within water-reline mixture assist reaction rate. It can be noted here that the interstitial accommodation of water in case of the water-reline mixture and interspecies hydrogen bonding seen in **Figure 2(b)** and **2(c)** by a slight increase in  $\alpha$  value could be the responsible factors behind the difference in the rate of reaction in water-DESs mixtures. The  $\alpha$  values for water-glyceline and water-ethaline mixtures in **Figure 2 (b)** and **Figure 2 (c)** indicate that with an increase in the concentration of glyceline and ethaline in mixture provide a slight increase in the  $\alpha$  value of water-glyceline and water-ethaline mixtures. On the other hand, prominent rate decrease in case of water-glyceline and water-ethaline mixtures was observed as compare to the water-reline mixture. These observations in the case of water-glyceline and water-ethaline mixtures point out toward the strong role of interspecies hydrogen bonding within water-DESs mixtures. In **Figure 1** all three water-DESs mixture shows similar trends in terms of hydrogen bond accepting ability *i.e.* basicity  $\beta$ , polarizability *i.e.*  $\pi^*$ . The  $\beta$  values of all three water-DESs mixture increase with an increase in the concentration of DESs in the water on the other hand polarizability *i.e.*  $\pi^*$  value decrease with increase in the concentration of DESs in water. These trend of  $\beta$ ,  $\pi^*$  values suggest that these polarity parameters do not have the prominent influence on the rate constant values of Diels-Alder reaction.

### 3.1.3.3 Analysis of water-DESs mixtures through FTIR and NMR spectroscopy

To determine the interaction patterns between different species and analysis of structures in the water-DESs mixtures Fourier transform infrared spectroscopy (FTIR) analysis has been carried out at 25 °C. **Figure 3** represents the FTIR spectra of water-reline mixtures and water-glyceline mixtures respectively.<sup>114,115</sup> The FTIR absorption spectrum of pure reline has been represented at the top in **Figure 3(a)**, it contains characteristic peaks at, 3317  $\text{cm}^{-1}$  for  $\nu_s \text{NH}_2$ , 3189  $\text{cm}^{-1}$  for  $\delta_s \text{NH}_2$ , 1606  $\text{cm}^{-1}$  for  $\delta_{as} \text{NH}_2$ , 1165  $\text{cm}^{-1}$  for  $\nu_{as} \text{CN}$  and 953  $\text{cm}^{-1}$  for  $\nu_{as} \text{CCO}$ . The presence of a peak at 953  $\text{cm}^{-1}$  for  $\nu_{as} \text{CCO}$  also confirms the presence of  $\text{Ch}^+$  in all the samples. This observation also suggests that structure of  $\text{Ch}^+$  is not destroyed in any sample by dilution. As we move from dilute region to concentrated region in the water-reline

mixture in **Figure 3 (a)**, no significant shift has been observed for  $\nu_{\text{as}} \text{CN}$  and  $\nu_{\text{as}} \text{CCO}$  peaks. On the other hand, absorption peaks for  $\nu_{\text{s}} \text{NH}_2$  show red shifts  $3353 \text{ cm}^{-1}$  to  $3317 \text{ cm}^{-1}$  and for  $\delta_{\text{as}} \text{NH}_2$   $1626 \text{ cm}^{-1}$  to  $1606 \text{ cm}^{-1}$ . **Figure 3(a)** imply that low aqueous region of water-reline mixtures ( $x_{\text{reline}} = 0.9$  reline in water) has less broad peaks as compared to that of highly aqueous water-reline mixtures ( $x_{\text{reline}} = 0.1$  reline in water).



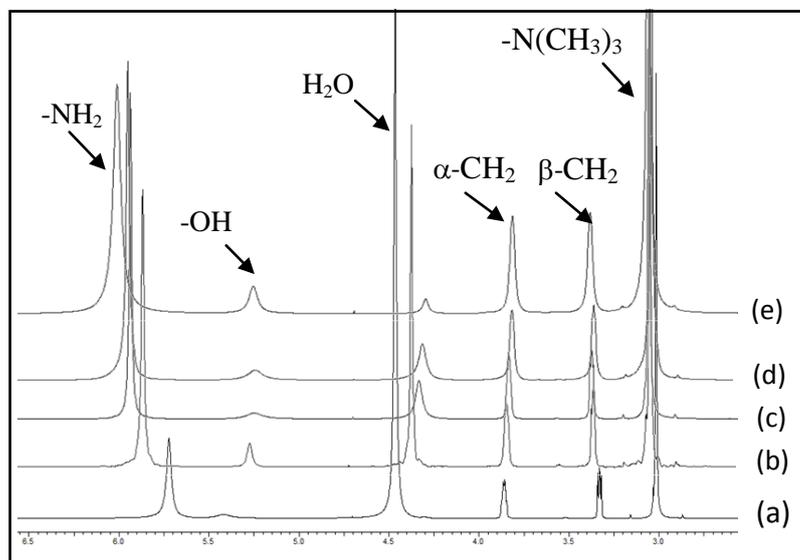
**Figure 5.** FTIR absorbance spectra of the water-reline mixture (A) and water-glyceline mixture (B) at 25 °C.

It is already known that hydrogen bonding plays an essential role in the formation of DESs but surprisingly in the case of water-reline mixture hydrogen bond donating ability of mixture decreases with increasing reline concentration.

From above observations, we can conclude that urea–chloride and urea–urea H-bonding intensifies within water-reline mixture upon addition of reline in the water-reline mixture. The FTIR absorbance spectra’s for water-reline mixtures provide similar results which have good concurrence with hydrogen bond donating acidity  $\alpha$  values of mixtures. These results also support rate constants trends obtained in the case of Diels-Alder reaction in water-reline mixtures. Significant experimental studies on the reline solvent confirm that during formation of reline solvent, hydrogen bonding between the urea and chloride anion increase enormously.<sup>106,116,117</sup> Results obtained in the case of water-reline mixture hint towards the interstitial accommodation of water within the water-reline mixture, which is principle interaction present within the system.

In FTIR absorbance spectra of water-glyceline mixtures in **Figure 3 (b)** shows similar –OH stretch as that of the water. Another point should be noted here that as we move

from highly diluted regime of glyceline in water to highly concentrated regime broadness of absorption peaks increase, which clearly points towards H-bonding present within the system. Present results are also supported by the density and viscosity data for aqueous glyceline mixtures.<sup>25</sup>

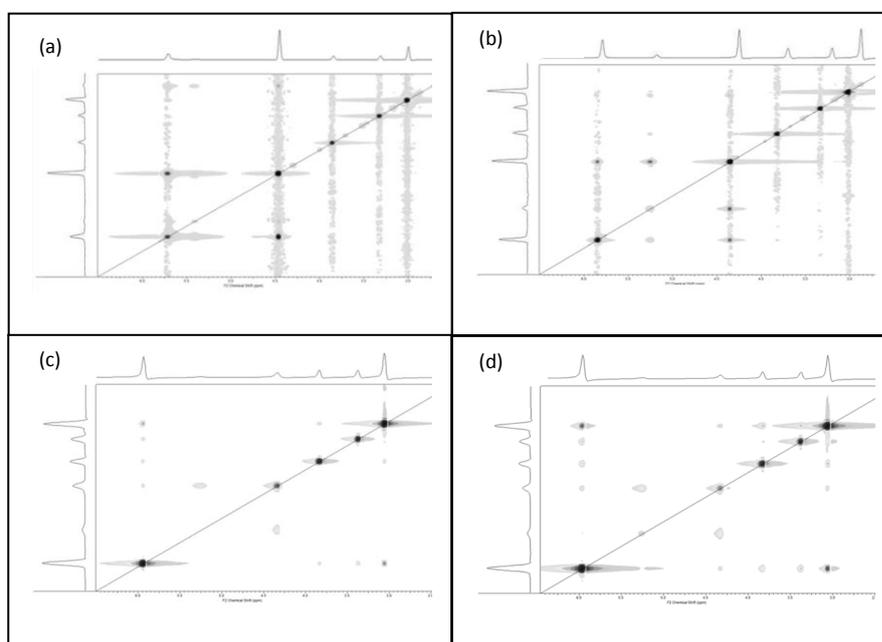


**Figure 4:** Stacking of  $^1\text{H}$  NMR spectra showing different mole fraction of reline present in water: (a) 0.1 mole fraction, (b) 0.3 mole fraction, (c) 0.5 mole fraction, (d) 0.7 mole fraction, (e) 0.9 mole fraction.

In the case of water-reline mixtures, a different trend of kinetic results has been observed. Therefore, the mode of interaction in water-reline mixture has been analysed by  $^1\text{H}$  NMR spectroscopy and Nuclear Overhauser effect spectroscopy (NOESY) at 25 °C. Chemical shift for the 0.1 - 0.9 mole fraction of reline in water has been shown in **Figure 4**. It implies that, as we move from 0.1 - 0.9 mole fraction, the chemical shift trends for  $-\text{OH}$ , water,  $\alpha\text{-CH}_2$ ,  $\beta\text{-CH}_2$  and  $-\text{N}(\text{CH}_3)_3$  shifted towards the downfield shift. It clearly indicates that addition of reline to water breaks organise structure of water and after certain limit *i.e.* 0.1 mole fraction, reline structure is intact in the mixture and interact with itself only. Upfield shift in the chemical shift of  $-\text{NH}_2$  in water-reline mixture indicates the presence of H-bonding interaction in the mixture, between proton of  $-\text{NH}_2$  and  $\text{Cl}^-$ . As the mixture concentration shifts from dilute to the concentrated region of reline, the H-bonding

interaction within reline intensifies. The hydrogen bonding interaction between chloride anion and a proton from the urea are responsible for the upfield shift.

NOESY study for reline and water mixture shows intermolecular interaction up to certain concentrations (**Figure 5**). This observation signifies that the molecules of reline *i.e.* choline chloride and urea in the liquid state are aggregated into larger structures. **Figure 5(a)** for 0.1 mole fraction reline illustrate the intermolecular interaction between  $-\text{NH}_2$  of urea and water. A cursory look at **Figure 5(b)** for 0.3 mole fraction shows a slight increase in intermolecular interaction between  $-\text{OH}$  group of Choline cation and water.



**Figure 5.**  $^1\text{H}$ - $^1\text{H}$ - NOESY study correlation between reline (choline chloride-urea) and water;(a) 0.1 mole fraction of reline in water, (b) 0.3 mole fraction of reline in water, (c) 0.5 mole fraction of reline in water, (d) 0.7 mole fraction of reline in water.

**Figure 5(c)** and **Figure 5(d)** evidently prove that high concentration of reline in water will form aggregates with reline molecules through intermolecular H-bonding interaction *i.e.*,  $-\text{NH}_2$  group of urea interacts with  $-\text{N}(\text{CH}_3)_3$  group of choline cation rather than interacting with water molecules. From the results obtain through FTIR and NMR spectroscopy that interstitial accommodation of water is evident in the water-reline mixture. On the other hand, interspecies H-bonding is present in the water-glyceline mixtures.<sup>118</sup>

### 3.1.3.4 Temperature dependent study

The activation parameters for the Diels-Alder reaction in water and three water-DESs mixtures are shown in **Table 2**. A careful investigation of the activation parameters reveals that the activation energy of Diels-Alder reaction is minimum in case of water (homogeneous condition) *i.e.* 90 k J mol<sup>-1</sup> and maximum in the case of Water-ethaline *i.e.* 99 k J mol<sup>-1</sup>. A Smaller value of activation energy in the case of water implies that the energy of the transition state is relatively lower for Diels-Alder reaction in water compared to that in water-DESs mixtures.

**Table 2.** Activation parameters derived from the reaction between **1** with **2** (Scheme 1)

Sr. No.	Solvents	$\Delta^{\#}S$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$\Delta^{\#}H$ (k J mol <sup>-1</sup> )	$E_a$ (k J mol <sup>-1</sup> )
1.	Water	-75.65	88.32	90.23
2.	Water-reline	-45.07	90.47	93.00
3.	Water-glyceline	-30.76	95.14	97.68
4.	Water-ethaline	-26.18	96.85	99.39

The values of rate constants obtained for the Diels-Alder reaction in water and water-DESs mixtures are in accord with the activation energy parameters. We have also calculated the free energy change ( $\Delta^{\#}G$ ) for the reaction in different solvents. The values of  $\Delta^{\#}G$  parameter in different solvents also suggest that the rate should be maximum in the case of water whereas minimum for water-ethaline mixture. The negative values of  $\Delta^{\#}S$  imply the retardation of the reaction. As we move from pure water to water-reline, water-glyceline and water-ethaline mixtures, the value of  $\Delta^{\#}S$  parameter decreases. On the other hand, trends observed for  $\Delta^{\#}H$  advocate that reaction carried out in water condition requires minimum energy to cross activation energy barrier. In water-DESs mixtures, water-reline mixture requires minimum energy and water-ethaline requires the highest energy. Kinetic study of Diels-Alder reaction suggests that the rate of reaction is highest in water condition as compares to water-DESs mixtures. From this observation, we can predict that Diels-Alder reaction carried out in water and water-DESs mixtures are enthalpically driven.

In the present case, the hydrophobic effect of water plays an important role in rate enhancement of reaction carried out in pure water. Hydrophobic effect of water promotes the rate of reaction which is in accord with the decreased value of  $\Delta^\ddagger H$ .

Conversely, in the case of water-reline mixtures, the hydrophobic effect decreases due to the increased interstitial accommodation of water. Comparatively higher values of rate constants obtain for water-reline mixture than other two water-DESs mixtures indicate that interstitial accommodation of water provides cohesive support to the effective collision of reactant at transition state in water-DESs mixtures.

The negative values of entropy in water-glyceline and water-ethaline mixtures suggest that the interspecies hydrogen bonding in these mixtures provide less assistance in the collision of reactants at the transition state. In the case of the entropy of the solvent system, in water condition of the reaction has endothermic nature of enthalpy is highest but as we move from water-reline, water-glyceline and water-ethaline mixtures the endothermic nature of enthalpy decreases. The decrease in the rate of the reaction in the water-DESs system also supports the outcome of the activation parameters of the study.

### 3.1.4 Conclusions

Kinetic investigations of the Diels–Alder reaction have been carried out in water-DESs solvent systems providing different individual behaviours. Different kinetic trends in the case of the water-reline mixture from water-glyceline and water-ethaline have been explained in terms of the difference in their viscosity and polarity parameters. High negative values of  $G(C)$  parameter for aqueous glyceline and ethaline mixtures suggest that pairwise interaction values for highly aqueous region stabilise of initial state by solvation.

The experimental outcome suggests that stabilization of initial state proves to be a decisive factor behind of decrease in the rate of the Diels-Alder reaction. Again, FTIR and NMR spectroscopy study provide evidence regarding the unusual kinetic behaviour of water-reline mixtures. Experimental results show that, interstitial accommodation provided by the interaction of urea and halide in mixture responsible for the comparatively different behaviour of reline than glyceline and ethaline in water. Structural similarities between aqueous glyceline and ethaline mixtures suggest

that interspecies hydrogen bonding interaction proves to be the detrimental factor in deciding the fate of kinetic profile of reaction.

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## 3.2 Carbohydrate-based deep eutectic solvent media for Diels-Alder reaction

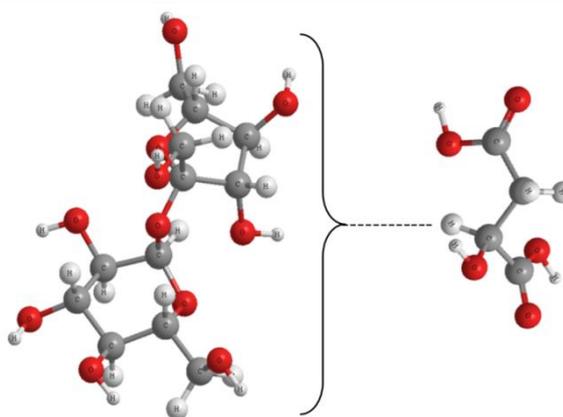
### 3.2.1 Introduction

According to the twelve principles of green chemistry, adapted methodologies should consider environmentally benign solvents. Taking these green chemistry principles into consideration the solvents used in the synthetic chemistry should be safe to the human as well as environment also the procedure of synthesizing of these solvents should be sustainable to the environment.<sup>1,2</sup> In the quest of green solvents, room temperature ionic liquids (RTILs) are regarded as an extensively explored group of unconventional reaction media. RTILs are defined as the salts which contain asymmetric organic cations and symmetric organic/inorganic anions having a melting point below 100 °C.<sup>3</sup> The exceptional properties like low water content, stability against air/ moisture, high chemical and thermal stability, low flammability, excellent solvation potential, high heat capacity, density and conductivity, negligible low vapor pressure make them a potential replacement for volatile organic compounds (VOCs).<sup>4,5</sup> On contrast, one major question in this regard is the impact of RTILs on the environment.<sup>4,5</sup> According to the principles of green chemistry discussed in the preceding chapter, the ideal green solvent should show low acute toxicity and rapid degradability in the environment to minimize the pollution. In this respect, we can't generalize RTILs as either green or toxic but their impact on the environment is basically judged by their constituents structural properties.<sup>5b</sup> By taking these environmental supporting aspects into account for achieving greener process, reaction media can be design by consuming biomaterials which exhibit unique physico-chemical properties like RTILs with excellent advantages over biodegradability and non-toxic starting materials. The recent development of biomaterials based solvents has gained momentum since it is easy to synthesize these solvents by low-cost starting materials.

The solvent based on the renewable and environmental benign resources known as “deep eutectic solvents” (DESs) was coined by Abbott *et al.* in 2003.<sup>6</sup> DESs contains definite mixture of hydrogen bond donor and simple halide containing salts which produce liquid solvent.<sup>7</sup> Till date different molecules has been used as hydrogen bond donors (synthetic and natural) with definite composition of biodegradable salt such as choline chloride (vitamin B<sub>4</sub>).<sup>7-11</sup> The melting point of the DESs mixtures can be

predictable, even though some general trends can be obtained by comparing the physico-chemical properties of a couple of mixtures. According to the hypothesis proposed by Abbott and coworker, the depression in the melting point of DESs is caused due to the presence of hydrogen bonding between the hydrogen bond donor and the halide anion as well as upon increasing the asymmetry of the cations of the molecule.<sup>6</sup> Furthermore, the hydrogen bond strength of the different negatively charged counter ions of the choline salts are responsible for influencing the freezing points in choline chloride-urea (DES) mixtures. Synthesis procedure of DESs are relatively simple as compared to the RTILs, mixing of H-bond donor (*e.g.* urea) and neutral compound (*e.g.* carbohydrate or choline chloride) under continuous stirring with heating up to ~80 °C produce eutectic solvent. A homogeneous, transparent liquid was which has lower freezing point than individual component regarded as carbohydrate-based eutectic solvent (CES).<sup>7-11</sup>

In 2011, “Natural deep eutectic solvents” (NADESs) composed of simple eutectic mixtures of sugars, amino acids, organic acids and choline chloride has been proposed by Choi *et al.* Thirty different blends of NADESs from sugars, amino acids, organic acids and choline chloride were reported along with their physical properties.<sup>12</sup> **Figure 1** depicts one of the examples of NADESs, in which sucrose and malic acid form eutectic solvent due to the presence of H-bond interaction between proton of malic acid and –OH group of sucrose.



**Figure 1.** Possible H-bond interactions in NADESs composed of sucrose and malic acid.<sup>12</sup>

These NADESs, which basically comprises of compounds having high molecular weight gives highly viscous liquid at room temperature. It has been reported that NADESs can be used by plants as a water-free solvent for biochemical reactions in plant cells. The stability of NADESs has been established by  $^1\text{H}$ - $^1\text{H}$  Nuclear Overhauser enhancement spectroscopy correlation between sucrose and malic acid. Intermolecular hydrogen bonding between sucrose and malic acid plays a significant role in the stability of NADESs for their consumption in plant cells.<sup>12</sup>

Recent established kinetic study on Diels-Alder reaction signifies the proficiency of utilization of water as a solvent over the RTILs and VOCs. The kinetic study obtained for Diels-Alder reaction in water reveal the remarkable enhancement in the rate and selectivity. Use of water also felicitates organic synthesis due to some peculiar properties such as low price, negligible toxicity, easy accessibility and high reaction rate.<sup>13-15</sup> The enhancement in the rate of bimolecular C-C bond formation reactions has been also witness by the use of water and it's salt solutions. Pronounced increase in the rate of reaction in aqueous and aqueous salt solutions has been explained in terms of polarity,<sup>16-22</sup> hydrophobic packing,<sup>23,24</sup> hydrogen bonding, hydrophobic hydration<sup>25,26</sup> and Lewis acid catalysis.<sup>27,28</sup> Out of all these special effects shown by the aqueous environment, hydrophobic packing of substrate molecules provide enhancement in reaction rates, yields and stereoselectivity of the products. Again Breslow and Guo has been proposed a plausible alternative to the water by suggesting a combination of salt solutions in “water-like solvents” *i.e.*, ethylene glycol, formamide etc.<sup>29,30</sup> However, we cannot generalize the use of water and water-like solvents for all organic reactions since most of the reactants show solubility restriction in aqueous media and most of the reagents used in organic synthesis are sometimes water sensitive in nature.<sup>31</sup> Additionally, most of the reaction require a catalyst to enhance yield and selectivity of the product. All these problems regarding reactivity of reagents and the requirement of additional catalyst in the aqueous media can be resolved by the appropriate selection of sugar-urea-salt mixtures as a solvent.

CES can serve the reaction as solvent and also can act as media to catalyze the reaction.<sup>32-34</sup> By providing high yield of the reaction with selectivity in a short time, sugar-urea-salt solvents playing a triple role *i.e.*, solvent, reagent, and catalyst.<sup>32</sup> A new age sugar-urea-salt eutectic mixture has been discovered by Imperato *et. al.*

These eutectic mixtures generally exhibit melting point above 60 °C.<sup>35-37</sup> To evaluate the significance of CESs as a proficient media in the synthetic and biological systems, C-C bond formation reactions has been carried out as model reaction.<sup>38</sup> In recent times, low-melting mixtures of CESs has been used for C-C bond formation reactions *e.g.* Biginelli, Heck, and Sonogashira cross-coupling, *etc.*<sup>39, 40</sup>

This chapter mainly emphasizes on the application of biomaterial inspired renewable resources (mixtures of urea or its derivatives with carbohydrates) as a solvent in organic synthesis. Carbohydrate-urea-salt eutectic solvents provide a unique alternative to VOCs which can help in the reaction methodologies as ecologically and economically.<sup>27</sup>

### 3.2.2 Experimental section

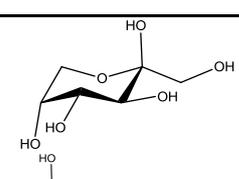
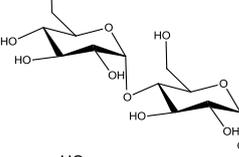
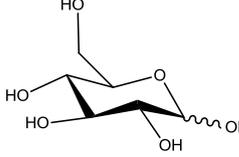
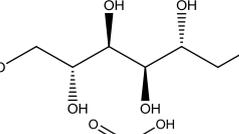
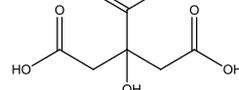
**3.2.2.1 Chemicals and materials:** Mannitol, Maltose, Fructose and Citric acid of AR grade were purchased from Thomas Backer. Dextrose (anhydrous), Urea, Calcium chloride, and Cyclopentadiene of GR grade were used as acquired from Merck. Ammonium chloride was purchased from Loba Chemie. Methyl acrylate and *N, N*-dimethylurea (DMU) were obtained from Spectrochem. The characterization and their purities were determined by NMR spectroscopy. Absolute ethanol was used to prepare probe stock solutions. Doubly distilled deionized water with  $\geq 18.0$  M $\Omega$ ·cm resistivity was obtained from a Millipore Milli-Q Academic water purification system.

The stock solution of the required dye was freshly prepared in dichloromethane prior to use. The stock solution was added dropwise to the CESs, and the solvent was evaporated under vacuum. The DES was then transferred to the cuvette under nitrogen atmosphere and sealed with a septum. The  $\lambda_{\text{max}}$  was measured at different temperatures using a Cary 50 UV-visible spectrophotometer. All the polarity values are within reproducibility of  $\pm 0.4$  %. The temperature of the cell was controlled by the single cell accessory having an accuracy of  $\pm 0.1$  °C.

**3.2.2.2 Preparation of CESs:** The stable melt of low-melting mixtures of bulk carbohydrates, urea and inorganic salts can be obtained by using these components in defined composition. **Table 1** summarizes structures, components and melting temperature of CESs. The thermal stability of CESs has been analyzed by differential scanning calorimetry (DSC), through three heating-cooling cycles. The thermal

analysis demonstrates that no thermal decay has been seen at observed temperatures. The stability of CESs as a reaction medium were checked by heating the mixtures at 95 °C for 4 h. DSC studies reveal that these mixtures are thermally stable.<sup>2</sup>

**Table 1:** List of carbohydrates, urea/DMU, inorganic salts structures and melting point ( $T_m$ ) as constituents of CESs.

Carbohydrates	Structure	$T_m / ^\circ\text{C}$	Urea	Salt
Fructose		80	DMU	-
Maltose		90	DMU	NH <sub>4</sub> Cl
Dextrose		90	Urea	-
Mannitol		85	DMU	NH <sub>4</sub> Cl
Citric acid		75	DMU	-

**3.2.2.3 Viscosity determination:** Viscosity measurements have been done by using Brookfield Ultra-Rheometer (LVIII). The viscosity data were obtained by using the following equation,

$$\eta = (100/\text{RPM}) \times \text{TK} \times \text{Torque} \times \text{SMC}$$

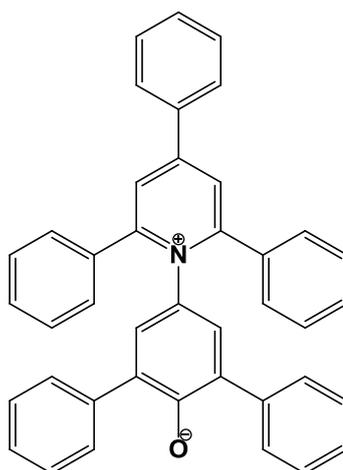
where, RPM is the rotation per minute, TK (0.09373) is the viscometer torque constant and SMC (0.327) is the spindle multiplier constant, respectively. Calibration of Brookfield Ultra-Rheometer (LVIII) has been done against the viscosity data of water and aqueous CaCl<sub>2</sub> solution.<sup>41</sup> The temperature of the all experimental solution was maintained at respective melting temperatures by using a Julabo thermostat bath. The viscosity measurements have been done with an accuracy of  $\pm 1$  %. All the

measurements have been done in this work are repeated three times and the average of the triplicate reading has been reported with the precision of  $\pm 0.3$  %.

**3.2.2.4 Kinetic analysis:** In a typical run, 0.4 ml (7.0 mmol) of the freshly cracked cyclopentadiene was dissolved in 2 ml of the CES (Citric acid-DMU) solution, and then 0.6 ml (7.0 mmol) of methyl acrylate was dissolved in 8 ml of the CES solution. The solution containing cyclopentadiene was added to the solution of methyl acrylate. The reaction mixture was magnetically stirred at 75 °C for about 5 h. The *endo* and *exo* stereoselectivities were determined using  $^1\text{H}$  NMR spectroscopy with an accuracy of  $\pm 5$  % which is good agreement with the literature value<sup>42</sup> as well as our earlier work.<sup>43</sup> Each reaction was carried out three times and the *endo/exo* ratios were reproducible to within  $\pm 5$  %.

The reaction was monitored by extraction of aliquots with ether followed by the appropriate dilution at appropriate time intervals through Gas Chromatography analysis. The GC configuration consists of CPSIL 5 CB column of length 15 m and diameter 0.25 mm with a flow rate of 0.8 mL/min of nitrogen. The injector and the detector temperature were maintained at 200 °C and 250 °C respectively. The total run time was 20.56 min with chlorobenzene as the internal standard. The GC method was calibrated with respect to the product concentration and the amount of product formed as a function of time gave the extent of the reaction. A plot of  $x/a(a-x)$  versus time 't', where 'a' is the concentration of the reactant, for the reaction CES (Citric acid-DMU) solution at 75 °C gives the rate constant  $k_2$ , which is determined from the slope of the graph. The precision of the rate constants as from an average of triplicate measurements under identical conditions was better than 3 %. The rate constants thus determined were reproducible to within 6 %.

**3.2.2.5 Measurement of polarity parameters ( $E_T^N$ ):** The  $E_T^N$  values for CESs were measured via the standard solvatochromic methods.<sup>44</sup> The measurement of  $E_N^T$  parameter of CESs has been carried out by using Reichardt's dye no. 30 (**Figure 2**) as a probe molecule. The minute amount of Reichardt's dye no. 30 was added to the CESs at 65 °C with vigorous stirring. Samples containing probe molecules was then transferred to the cuvette for the measurement of  $\lambda_{\text{max}}$  (in nm).



**Figure 2.** Structures of Reichardt's dye no. 30.

Temperature of the sample was kept constant at 65 °C using the Peltier setup with an accuracy of  $\pm 0.01$  °C. The  $E_T(30)$  value for the CESs were calculated from the molar transition energy (in  $\text{kcal mol}^{-1}$ ) of Reichardt's dye using equation (1).

$$E_T(30) = hc \nu_{\max}(30) N_A = 28591 / \lambda_{\max} \quad (1)$$

The  $E_T^N$  values of CESs was calculated via the normalization of  $E_T(30)$  parameter, using water ( $E_T^N=1$ ) and TMS ( $E_T^N=0$ ) as reference solvents.

$$E_T^N = [E_T(30)_{\text{solvent}} - E_T(30)_{\text{TMS}}] / [E_T(30)_{\text{water}} - E_T(30)_{\text{TMS}}]$$

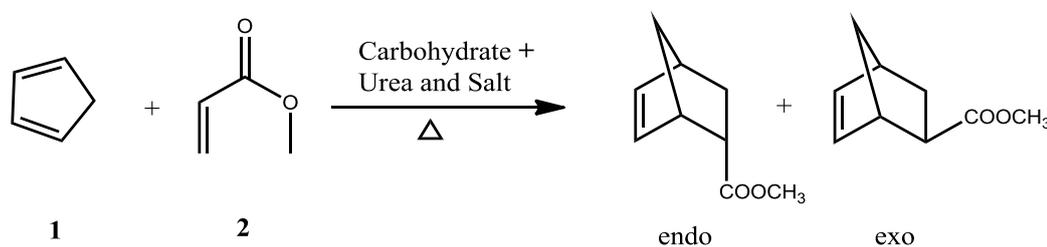
$$E_T^N = [E_T(\text{solvent}) - 30.7] / 32.4 \quad (2)$$

### 3.2.3 Results and discussion

After careful observation of **Table 1** we can say that, in spite of high individual melting temperature of carbohydrates, urea/DMU and  $\text{NH}_4\text{Cl}$  they provide CESs with a relatively lower melting temperature than 100 °C. The recent reports on the synthesis of DESs, has been shown that the depression in the melting temperature of eutectic mixture is due to the H-bonding interaction between the hydroxyl groups of carbohydrate, urea and  $\text{NH}_4\text{Cl}$  salts.<sup>2,12,35,36,39</sup> In CESs, the use of inorganic salt is implemented for the further reduction in the melting point. The individual melting points of Fructose and DMU are 103 °C and 180 °C respectively, but they form a clear, colourless and viscous melt at  $\sim 80$  °C. Similarly, the melting point of Maltose, DMU and Ammonium chloride are 102 °C, 180 °C and 334 °C, respectively, but

definite ratio of these components gives stable, viscous melt at 90 °C. Similarly, melting point of Dextrose is 146 °C and Urea is 133 °C but it forms clear and highly viscous melt at 90 °C with definite ratio of these two compounds. Similarly, Melting point of Mannitol is 168 °C but still it form a stable viscous melt at 85 °C with DMU and NH<sub>4</sub>Cl in an appropriate composition. Again, melting point of Citric acid is 153 °C and it form clear viscous CES with DMU at 75 °C. For example, for Fructose-DMU (40:60) melt, a composition of 0.12 mol of DMU and 0.03 mol of Fructose provides a stable melt at 80 °C. These CESs are employed as a solvent media as well as catalyst in many biotransformations and organic reactions for enhancement of yield and selectivity of the product.<sup>45-48</sup>

In order to understand the role of H-bond donor in CESs, a kinetic study of Diels-Alder reaction of cyclopentadiene (**1**) and methyl acrylate (**2**) (**Scheme 1**) was carried out in an array of CESs, which is composed of a different ratio of carbohydrates, urea and salt. The rate constant, percentage yields, viscosity, reaction temperature and  $E_T^N$  values for Diels-Alder reaction of cyclopentadiene and methyl acrylate has been given in the **Table 2**.



**Scheme 1.** Diels-Alder reaction of cyclopentadiene (**1**) and methyl acrylate (**2**) was carried out in CESs.

The  $E_T^N$  values for the given composition for CESs have been shown in **Table 2**. From **Table 2** it is clear that, all the CESs possesses high polarity values. Amongst all the CESs, Fructose-DMU contains highest  $E_T^N$  value i.e., 1.19 and lowest one for Dextrose-urea i.e., 1.06. It has been well known that the Diels-Alder reactions proceed *via* isopolar transition state.<sup>49</sup> Therefore, high polarity along with viscosity of CESs plays a pivotal role in deciding the rate, yield and selectivity of the product.

**Table 2.** Kinetic analysis, reaction conditions, percentage yields, viscosities and  $E_T^N$  data for Diels-Alder reaction of **1** and **2** in CESs.

Composition of melt	Reaction T/ °C	$10^5 k_2 / \text{M}^{-1} \text{s}^{-1}$	% Yield <sup>a</sup>	$\eta / \text{cP}$	$E_T^N$
Fructose-DMU (40:60)	80	23.59	65	35.3	1.19
Maltose-DMU-NH <sub>4</sub> Cl (20:70:10)	90	2.62	79	80.9	1.14
Dextrose-urea (50:50)	90	4.04	65	24.9	1.06
Mannitol-DMU-NH <sub>4</sub> Cl (40:60:10)	85	3.06	74	-	1.08
Citric acid-DMU (40:60)	75	3.17	-	289.6	1.22

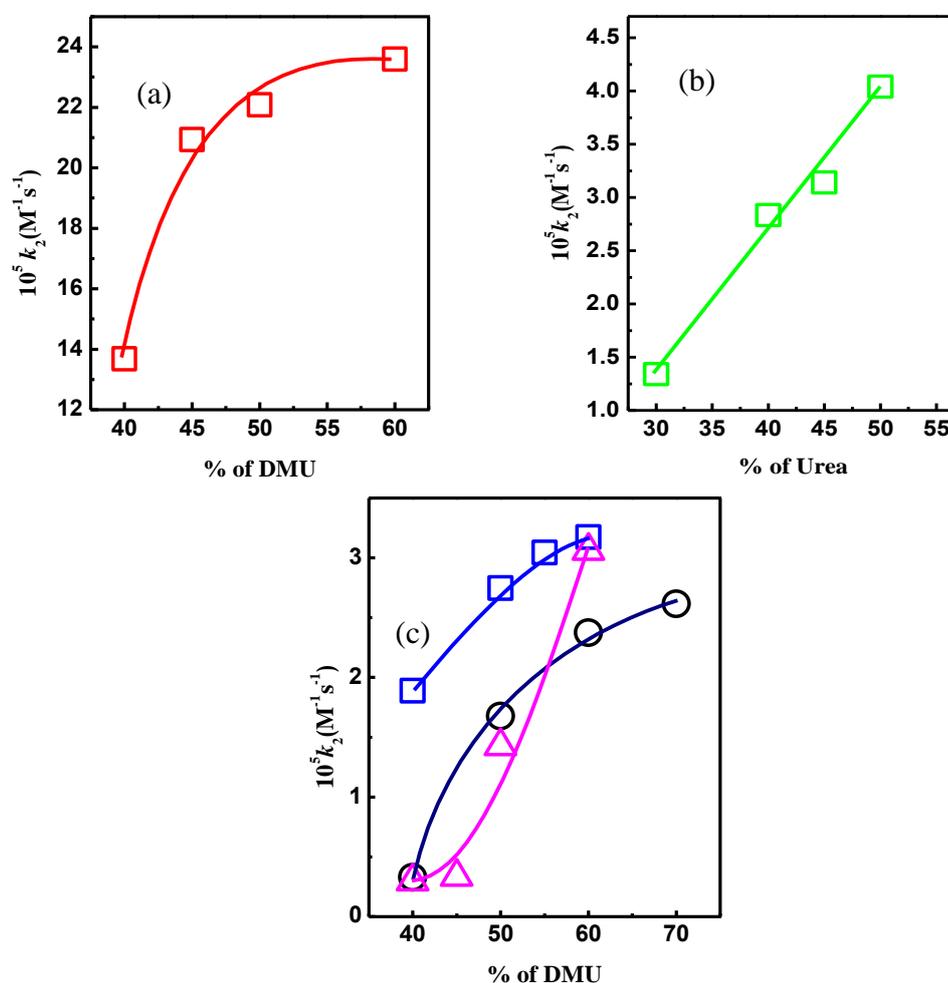
<sup>a</sup> Isolated yields after extraction, <sup>b</sup> Determined by GC.

### 3.2.3.1 Effect of hydrogen bond donor on the rate constant of the Diels-Alder reaction

Alteration in the hydrogen bond donor ratio in CESs composition can provide important information regarding factor influencing the rate profile of the reaction. The effect of percentage composition of urea/DMU in the CESs melts has been demonstrated by plotting percentage composition of urea/DMU against the value of  $k_2$  in **Figure 3**.

The reaction was carried out in the solutions of fructose and DMU to yield a value of  $k_2$  as  $23.6 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ . As seen from the results in **Table 2** that mixture of citric acid with DMU is not an effective solvent medium to carry out this reaction as the reaction becomes very slow with poor yield. While the mixture of dextrose with urea offered 65 % yield, indicating that high viscosity of solvent media overcome solvent polarity in dextrose based CES. The reaction was noted to be nearly twice as fast in the mixture of 60 % DMU with fructose as compared to its 40 % mixture with fructose. A similar increase in the rate constants has been observed while moving from urea/DMU-poor mixtures to its rich mixtures in CESs. High rate constants values in H-bond donor rich media for Diels-Alder reaction implies that along with polarity, hydrogen bonding interaction plays a pivotal role in stabilization of transition state. In **Figure 3**, the second order rate constant  $k_2$  are plotted against the percentage of urea or DMU in the of CESs.

In all CESs composition, the second order rate constant values increase with increasing the extent of H-bond donor in the mixture. These data demonstrated that the values of  $k_2$  are strongly dependent on the percentage composition of urea in the solvent media.



**Figure 3.** The plot of  $k_2$  versus composition of mixtures of CESs for Diels-Alder reaction; (a) Fructose-DMU ( $\square$ ); (b) Dextrose-urea ( $\square$ ); (c) Maltose-DMU-NH<sub>4</sub>Cl ( $\circ$ ), Mannitol-DMU-NH<sub>4</sub>Cl ( $\triangle$ ), Citric acid-DMU ( $\square$ ).

Further, the reaction was also carried out in ternary mixtures of DMU-NH<sub>4</sub>Cl with maltose and mannitol. The reaction was again noted to be slow but products yield was comparatively high in amount. The CESs of mannitol/DMU/NH<sub>4</sub>Cl (40:60:10) shows the yield 74 % of the product at 85 °C with  $k_2$  value as  $3.06 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ , while solvent mixture like dextrose/urea (50:50) at 90 °C gives 65 % of the product yield. On the other hand, citric acid/DMU (40:60) gives the melt at 75 °C with the product in traces with  $k_2 = 3.17 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ .

### 3.2.3.2 Effect of the viscosity of reaction media on rate profile of the reaction

The CESs media are mixtures of two or more compounds, can provide colorless melt for the reaction at high temperature. The third component in the mixture is utilized for the further reduction in melting temperature of the melt. Due to the high molecular weight and large size of carbohydrate molecules, they produce highly viscous media when mixed with the urea/DMU. Further addition of salts like  $\text{NH}_4\text{Cl}$  facilitates the CESs by decreasing melting temperature but fails to decrease the viscosity of media.

**Table 3** illustrates the viscosity data of the CESs and in all the cases the viscosities of CESs are high enough to affect the rate of the reaction. The melting points of the different solvent mixtures are different for the formation of a stable melt. As the percentage composition of DMU in fructose/DMU melt increases, the  $k_2$  value also increases from  $13.68 \times 10^{-5}$  to  $23.59 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$ . The value of  $k_2$  increases from  $1.89 \times 10^{-5}$  to  $3.17 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  in the case of the citric acid-DMU mixture also. The glucose/urea melt offers a range of second-order rate constant values from  $k_2 = 1.34 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  to  $4.04 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  ranging for urea poor to urea rich region in CESs. As we move from lower percentage to higher percentage of DMU in CESs about 8-fold increase in rate constants has been observed in the maltose/DMU/ $\text{NH}_4\text{Cl}$ , while about 11-times observed in the case of mannitol/DMU/ $\text{NH}_4\text{Cl}$ .

Since these solvent media are composed of two or more solutes and are clearly forms stable melts, the rates of the reaction are expected to depend upon the viscosities of the media. While the role of viscosity on the kinetics of organic reactions has been a subject of controversy till date, studies from this laboratory have confirmed that the viscosity of organic solvents has a profound influence on the rates of Diels-Alder reactions.<sup>50,51</sup>

In a typical example of a kinetic study of Diels-Alder reaction in different solvents, it has been found that initially, the  $k_2$  values increase with an increase in viscosity up to 1 cP and then decrease with viscosity above 1 cP. The increase in rate up to the 1 cP range is ascribed to the vibrational activation theory, according to which an increase in viscosity facilitates the bond making phenomenon.<sup>50</sup>

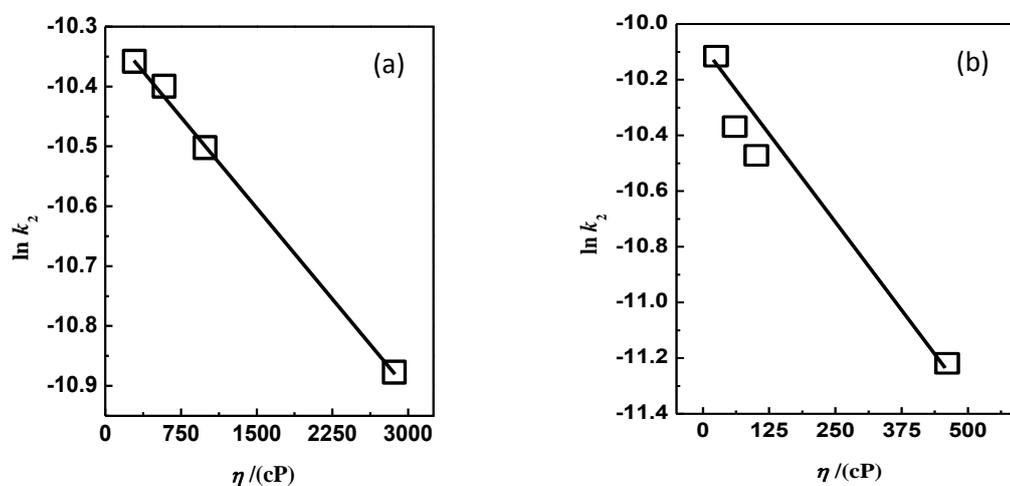
**Table 3.** Viscosity and rate constant data of different carbohydrate-based CESs at their respective individual melting temperatures.

Fructose-DMU at 80 °C		
% of DMU	$10^5 k_2 / \text{M}^{-1} \text{s}^{-1}$	$\eta / \text{cP}$
40	13.68	318.4
45	20.94	195.3
50	22.09	134.5
60	23.59	35.3
Citric Acid-DMU at 75 °C		
% of DMU	$10^5 k_2 / \text{M}^{-1} \text{s}^{-1}$	$\eta / \text{cP}$
40	1.89	2863
50	2.75	990
55	3.04	584
60	3.17	289.6
Dextrose-Urea at 90 °C		
% of Urea	$10^5 k_2 / \text{M}^{-1} \text{s}^{-1}$	$\eta / \text{cP}$
30	1.34	461.3
40	2.83	101.2
45	3.14	60.5
50	4.04	24.9
Maltose-DMU-NH <sub>4</sub> Cl at 90 °C		
% of DMU	$10^5 k_2 / \text{M}^{-1} \text{s}^{-1}$	$\eta / \text{cP}$
40	0.33	1732.7
50	1.68	313.4
60	2.38	187.4
70	2.62	80.9
Mannitol-DMU-NH <sub>4</sub> Cl at 85 °C		
% of DMU	$10^5 k_2 / \text{M}^{-1} \text{s}^{-1}$	$\eta / \text{cP}$
40	0.29	-
45	0.33	-
50	1.43	-
60	3.06	-

In this region, the vibrational modes are enhanced at the expense of the translational modes. However, the rates are lowered in solvents possessing high viscosities. Since the reactants cannot "see each other" in such a highly dense and viscous environment, the rates decrease in such a region.

From the viscosity data given in **Table 3**, it is observed that the viscosity of the respective melt decreases with a decrease in the percentage of urea/DMU. These results show that viscosity plays a significant role in determining the rate of the reaction. Similar observations were shown in **Figure 4**, in which the  $\ln k_2$  values are

plotted against  $\eta$  for the citric acid-DMU and glucose-urea mixtures, showing a strong linear correlation between  $\ln k_2$  and  $\eta$ .



**Figure 4.** Representative plots for  $\ln k_2$  vs.  $\eta$  for Diels-Alder reaction in (a) Citric acid based CES and (b) Dextrose based CES.

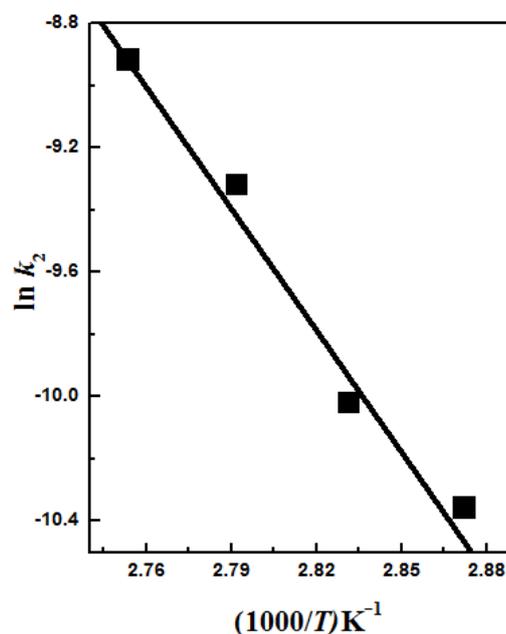
The temperature dependent kinetics of Diels-Alder reaction was also investigated. An Arrhenius plot for the reaction in citric acid-DMU for the ratio (40:60) at varying temperatures (**Figure 5**) gives a value of activation energy as  $108.28 \text{ kJ mol}^{-1}$ . In some cases, the role of the polarity of these highly viscous solvents has been suppressed by the viscosity of the solvent. The  $E_T^N$  value for Fructose-DMU mixture is highest and in the same solvent the highest rate constant has been also obtained which implies that high polarity and viscosity plays significant role in rate acceleration.

In the perspective of the reaction studied herein, the carbohydrate-urea melts used as media possess extremely high viscosity when compared with that of water, which will decrease with increasing percentage of urea in the melt. In the present study, the rate of reaction increases with the extent of decrease in viscosity of solvent media. In other words, we can say that the order of magnitude of the diffusion coefficients contrasts with the viscosity of the solvent melt.

The relationship between the self-diffusion coefficient and viscosity was analyzed by the Stokes-Einstein equation,

$$D = kT / 6\pi r \eta$$

where  $k$  = Boltzmann constant ( $1.38 \times 10^{-23} \text{ J K}^{-1}$ ),  $\eta$ =solvent viscosity (cP),  $T$  = temperature in °C,  $r$  = radius of solute molecule related to molecular weight.



**Figure 5.** The plot of  $\ln k_2$  versus  $1000/T$  for the Citric acid based CES in 40:60 composition.

From the data given in **Table 3**, we observe that the experimental rate constants for the carbohydrate melt used for Diels-Alder reaction are low when the percentage of urea in the melt is low. This suggests that the carbohydrate-urea melts employed in the present study do not behave as high polar solvents. Therefore, on the basis of the above results, we suggest that polarity is not the sole parameter that determines the solvent effect on rate constant in Diels-Alder reaction since the reaction requires separation and reassembly of solvent molecules.

Carbohydrate-urea melts are highly ordered reaction media and the activation energies for reactions carried out in these melts can be high because it is necessary to break the order of the medium to bring together all the components to the reaction site. Therefore, the rate constants are better correlated with solvent viscosity. In summary, the present study is an attempt to demonstrate the potential of CESs as an effective solvent media to accelerate a bimolecular organic reaction at high temperature.

### 3.2.4 Conclusions

In the present study, CESs media can be regarded as highly ordered reaction media. Due to highly ordered reaction media, the viscosity of solvent tends to be in the higher range at low concentration of hydrogen bond donor *i.e.*, urea/DMU. Higher viscosity of the solvent media controls the key for activation energy *i.e.*, for highly viscous reaction media activation energy should be high and vice-versa for low viscous media. Highly viscous media holds the key behind the kinetics of bimolecular reaction because for effective formation of product it is necessary to break the order of reaction media to collect all the constituents to the reaction site. Therefore, it can be concluded that rate constant of bimolecular reactions in these CESs are correlated with the viscosity of the solvent.

In the present study carbohydrate based CESs are projected as alternative solvent media for bimolecular Diels-Alder reaction at high temperature. Through this experimental observation it can be concluded that these reaction media requires a higher temperature, but by using these types of CESs search for inexpensive, less toxic, non-volatile, highly polar, biodegradable, simple methodology operation and environmentally benign ability will be achieved.

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## Chapter 4

# Nature Inspired New Supersaturated Solvent to Promote C-C Bond Formation Reaction at Room Temperature

*“The life of man would be made extremely difficult if the bee disappeared.”*

- Charles Darwin



*The Diels-Alder reaction, a  $4\pi+2\pi$  cycloaddition reaction between dienophile and diene, is synthetically imperative reaction to construct six-membered cyclic biologically active compounds with high regio- and stereo-selectivity. Thus, the significance of this organic reaction necessitates an investigation towards achieving alternative greener solvent systems in order to circumvent hazardous impact caused by the use of volatile organic solvents. In this chapter, we present a nature inspired new supersaturated biodegradable medium for carrying out Diels-Alder reactions with efficacy under ambient conditions. Owing to the presence of excess of carbohydrates and thus  $-OH$  groups, new supersaturated solvent has been a medium of interest.*

*The reactivity of Diels-Alder reactions shows exceptional enhancement in highly viscous supersaturated solvent at room temperature. Encounter controlled reaction kinetic theory has been applied to describe this unusual trend. Metastable structure and enhanced availability of hydrogen bonding of the supersaturated solvent have been responsible for the observed increment in rate. Present systematic kinetic and thermodynamic studies reveal the potential of new supersaturated solvent as an efficient environment-benign reaction medium as compared to other solvents used now.*

## 4.1 Evolution of nature inspired solvent

### 4.1.1 An overview

In last three decades, the concept “green” has emerged as a new importance ideology in the chemistry. The concept of green chemistry and sustainable development of chemical processes altered the mode of opinions in organic synthesis and chemical engineering process.<sup>1</sup> In perspective of twelve principles of green chemistry, reduction of the hazardous environmental impacts caused due to the use of solvents in chemical synthesis process and production became a preceding objective. In contemporary synthetic chemical methodology, the most important challenge is to find bio-inspired environment benign solvents as an alternative for volatile organic solvents (VOCs).<sup>2</sup> Innovative approaches have been taken for finding of safe substitutes with more environment benign properties.

In order to synthesize an organic compound, judicious selection of a solvent that is environmental benign and recyclable for a wide range of reactants is appealing in the realm of modern drive to minimise cost as well as environmental pollution.<sup>3-6</sup> In view of environmental pollution caused by the use of volatile organic compounds (VOCs), serious efforts have been made to develop clean synthetic methodologies for preparation of organic molecules having biological and industrial importance.<sup>7-15</sup>

The ecological impact of chemical methodologies stresses upon their economical viability and environmental affability.<sup>1</sup> One of the endeavours in the area of organic synthesis is to find out potential replacement for VOCs to develop inherently clean synthetic methodologies.<sup>1</sup> In this context, it is vital to discover the efficacy of a natural or nature inspired bio-degradable solvent as an alternative reaction media for chemical synthesis. A truly green nature solvent, abundantly available, and the low costs of itself promotes natural supersaturated solvent which mimic natural honey can be consider as a predominantly attractive new supersaturated solvent.<sup>12-14,55</sup>

Interestingly, natural supersaturated solvents like honey has been a major source of natural proteins as well as carbohydrates and natural medicines approximately from the inception of life in the earth.<sup>12-15</sup> In the recent developments, Dutch scientist Dr. Tineke Creemers from the *Centre for Plant Breeding and Reproduction Research in Wageningen* has modified the plants genetically so that honey produced from

respective nectar contains medicinally improved proteins. Creemers and their research group principally work on the invention of gene promoter which is very particular for nectar generating organ of the plant. By articulating genes conditioning under these promoters, particular and very specific proteins are generated in the nectar, which was then bring together by bees and concentrated them into honey. The high concentration of carbohydrates in the honey composition then stabilizes the protein structure which further increase the medicinal value of the honey.<sup>14,16</sup>

In these chapter, unique properties of nature inspired supersaturated solvent have been investigated in the view of natural honeys' contribution in evolution of life. Physico-organic study carried out in present chapter helps to understand the role of natural honey's in biologically important reactions carried out in nature (antibacterial and antifungal properties).<sup>17-19</sup> Secondly, whether nature inspired new supersaturated solvent can serve a powerful medium to promote C-C bond forming reactions. In other words, the present work describes whether this new supersaturated solvent media serve as an effective medium for carrying out such reactions. Judicious selection of a solvent medium that is environmental benign and recyclable for a wide range of reactions for carrying out organic synthesis is of great priority.<sup>3-6,20,21</sup>

In the context of modern chemistry, environmental benign protocols have been innovatively developed to avoid the contagious VOCs that are purely based on the accessibility of 'thermodynamic push up' forces through the performance of important organic reactions.<sup>22-24</sup> As a result, water, hydrofluorocarbons, ionic liquids, supercritical fluids etc. have emerged as important alternative solvents or techniques to VOCs for carrying out organic synthesis.<sup>23-28</sup> Pioneering research by Breslow and Grieco and their groups have resuscitated the potency of water as reaction medium by performing Diels-Alder reactions.<sup>25,26</sup> Careful investigations have linked the enhanced reactivity and selectivity for the water-promoted reactions with the intricacies of structure of water. High cohesive energy density, hydrophobic interactions, hydrogen bonding stabilization, high polarity of water etc. have been cited as the reasons for water accelerated reactions.<sup>25,26,29-35</sup> However, a large number of organic reactions have been carried out 'in water' in the presence of co-solvents to increase the solubility of the reactants and enhance the yield of product.<sup>36-42</sup>

In view of small amount of reaction product recovered from water during homogeneous condition, efficient protocols have been developed to use minimal amount of water to achieve improved yield of organic reactions *i.e.* organic reactions have been carried out under heterogeneous condition or ‘on water’ condition.<sup>43–45</sup> The water-mediated organic reactions are faster at interface than in homogeneous condition. In ‘on-water’ methodology, along with hydrophobic interactions, easy availability of trans hydrogen bonding at reactant/water interface further stabilize the transition state to lower activation energy compared to that required for homogeneous condition.<sup>46–48</sup> Although this method has been explored further as an highly efficient way to obtain organic reaction products with improved reactivity as well as better yield in comparison to the similar reactions in VOCs, the narrow profile of chemoselectivity as well as regioselectivity of water towards the vast organic reactants impart restrictions to wide applicability of ‘on water’ protocols.<sup>43–48</sup> Further, the reaction rates have been noted to be adversely affected by high viscosity of ionic liquids, though several merits to use ionic liquids for carrying the reactions have been noted.<sup>49</sup> Viscosity of the solvent medium, including that of ionic liquid has been shown to a significant property to influence the reaction rates. There are several instances of enhancing reactivity as well as selectivity of water promoted organic reactions by co-solvents like mono-ols, poly-ols, THF *etc.*<sup>36–39</sup> However, this improvement in reactivity either levels off or falls down after certain concentrations of the cosolvents.<sup>50</sup>

**Table 1.** The chemical composition used to prepare artificial new supersaturated solvent:<sup>a</sup>

Entry no.	<sup>a</sup> Component	Composition (%)
1.	Water	18.10
2.	Fructose	38.90
3.	Glucose	31.82
4.	Sucrose	1.44
5.	Maltose	8.10
6.	Gluconic acid	1.27
7.	Gluconolactone	0.37

<sup>a</sup>The modified data given in table on the basis of ref. 55, the composition (%) of a component is an average of 490 natural honey samples.

As a part of experimental investigations, efforts had been carrying out for designing of innovative environment benign solvents for synthesizing organic compounds. In this work, an interesting solvent termed as ‘new supersaturated solvent’ has been introduced and the use of which accelerates the simple Diels-Alder reaction, useful in synthesizing 6-membered carbon rings with excellent control on stereo- and regioselectivity-controlled products.<sup>51-54</sup> The synthesis of the new supersaturated solvent was inspired by the naturally available supersaturated product ‘honey’ which has been a major source of natural proteins as well as carbohydrates and natural medicines approximately from the inception of life in the earth.<sup>12-15,55</sup>

However, in present work the use of other minute constituent *i.e.* mineral ash, vitamins, proteins *etc.* had been avoided since, these minor components are only present in natural honey. During preparation of present new supersaturated solvent of carbohydrates addition of minute constituent *i.e.* mineral ash, vitamins, proteins *etc.* had been avoided since these minor components mostly contribute towards the medicinal beneficiaries of honey.<sup>12</sup>

Additionally, we have also desisted ourselves from using harmful chemicals like phenol and thymol, the presence of which in honey has recently been quantitatively sensed by Ag-based carbon nano-composites.<sup>56,57</sup> We have emphasized on the preparation of the artificial supersaturated solvent for its further application in reaction analysis instead of using naturally available honey; since honey has been considered as one of the major source of food product in some countries.

In this solvent, water is supersaturated with carbohydrates, organic acid and organic ketone, *etc.* The components and corresponding percentages of the new supersaturated solvent have been tabulated in **Table 1**.<sup>55</sup> The newly proposed supersaturated solvent possesses very high viscosity (2161 cP). It has been earlier documented that the reaction rates of Diels-Alder reaction increases with an initial increase in the viscosity (1.2 cP) of organic solvents and then decrease in the solvents of higher viscosity than 1.2 cP.<sup>54</sup> The rate enhancement can be explained in terms of vibration-activation theory while the rate decrease by encounter controlled theory.<sup>58-60</sup> In view of very high viscosity, the reaction should have been very slow. On the contrary, it can be noted in the present study that the reaction proceeded at very high rates.

## 4.2 Experimental procedure

**4.2.1 Chemicals:** Dicyclopentadiene (**1**) and methyl acrylate (**2**) were procured from M/s. Merck Co. Ltd. Anthracene-9-carbinol (**4**), *N*-ethyl maleimide (**5**), glucose, fructose, galactose, maltose, gluconic acid were used as bought from M/s. Sigma Aldrich Co. Other monosaccharides and disaccharides were obtained from a commercial firm and volatile impurities if any were removed from the commercially procured chemicals prior to their use by drying them for 6 hr under vacuum.

**4.2.2 Preparation of new supersaturated solvent:** **A.** New supersaturated solvent (with gluconic acid) has been prepared by using percentage composition described in **Table 1**. For the preparation of 10 g of artificial honey, we have taken 1.81 g of water, 3.89 g of fructose, 3.182 g of glucose, 0.144 g of sucrose, 0.81g of maltose, 0.127 g of gluconic acid, and 0.037 g of gluconolactone in sealed tube (M/s. Sigma Aldrich Co.). It was already made sure that all carbohydrate added to sealed tube are dried under vacuum for ~ 6 hr prior to their use. Then the mixture of carbohydrate is heated at temperature 120 °C under vigorous stirring for 4 hr.

**B.** New supersaturated solvent (without gluconic acid) has been prepared by using percentage composition described in **Table 1**. For the preparation of 10 g of artificial honey, we have taken 1.81 g of water, 3.89 g of fructose, 3.309 g of glucose, 0.144 g of sucrose, 0.81g of maltose, and 0.037 g of gluconolactone in sealed tube (M/s. Sigma Aldrich Co.). It was already made sure that all carbohydrate added to sealed tube are dried under vacuum for ~ 6 hr prior to their use. Then the mixture of carbohydrate is heated at temperature 120 °C under vigorous stirring for 4 hr.

**C.** For the preparation of saturated solution of glucose first 6.9 g of glucose was added to 10 g of water in a sealed tube and then the mixture was heated at 120 °C under vigorous stirring for ~4 hr. Supersaturated solution of glucose was prepared by the addition of 7.5 g of glucose in to 10 g of water and consequent heating at 130 °C under vigorous stirring for ~4 hr. Similarly, saturated solution of fructose has been prepared by addition of 38 g of fructose in to 10 g of water in sealed tube followed by heating at 120 °C under vigorous stirring for ~4 hr. Supersaturated solution of fructose was made by addition of 40 g of fructose to 10 g of water in sealed tube followed by heating at 130 °C under vigorous stirring for ~4 hr.

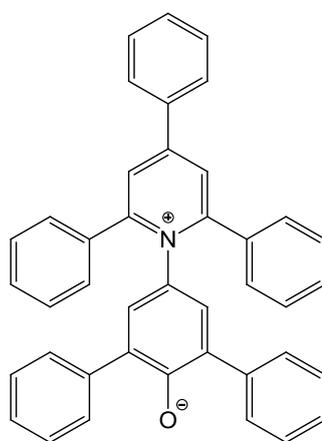
**4.2.3 Kinetic analysis:** The reaction described at **Scheme 1** was initiated by adding 5 ml of 1 M homogeneous solution cyclopentadiene (**1**) in supersaturated solvent to a 5 ml of 1 M homogeneous solution of methyl acrylate (**2**) kept under vigorous stirring at 25 °C. The reaction illustrated at **Scheme 2** was also performed the following same procedure as shown for **Scheme 1**, only the reactants are at per **Scheme 2**. During the kinetic study, 1 ml of the reaction mixture was taken out by micropipette at certain time interval and the product was extracted with water at first and thereafter, followed by further extraction with ethereal solvent. Thereafter, it was injected for gas chromatographic (GC) analysis. Following the temperature programme set for the experiment (**Scheme 1**) which is 18.51 min, we have abstracted reaction mixture after minimum 20 min interval. The similar procedure has been followed for at least five times to determine corresponding second order rate constants,  $k_2$  for each experiment. The reliability of the calculated rate constants  $k_2$  was checked by calibrating GC method against the kinetic data reported for the reaction of cyclopentadiene and (-) menthyl acrylate in methanol.<sup>61</sup> Hence the reported  $k_2$  values obtained from GC method are accurate to  $\pm 6\%$ . The precision of  $k_2$  values as determined by triplicate measurements under identical conditions was  $\pm 3\%$ . The reported  $k_2$  value is an average of triplicate measurements. Viscosity has been measured with Brookfield programmable viscometer, calibrated against water and aqueous  $MgCl_2$  solutions with an accuracy of  $\pm 1\%$  at 25 °C.<sup>62</sup>

**4.2.4 Determination of second order rate constant:** From the gas chromatographic analysis the extent of the reaction ( $x$ ) can be monitored by plotting the amount of product as a function of time. Since for both the reactions (**Scheme 1** and **Scheme 2**), the products have been formed due to reactions between the two reactants in 1:1 ratio; the concentration of the remaining reactants would be equal with respect to time. It implies that if 'a' is initial concentration of both the reactants (1 M of each of **1** and **2** have been used in case of **Scheme 1** and 1 M of each of **4** and **5** have been used in the case of **Scheme 2**).

Herein, the  $(a-x)$  values give the remaining reactants in the solvent at time 't' after commencing the reaction at  $t = 0$ . The plot between  $x/a$  ( $a-x$ ) vs.  $t$  gives the value of  $k_2$  in each case. Temperature dependent  $k_2$  values were obtained by performing the

reactions in a reaction jacket attached to Julabo constant temperature water bath with accuracy  $\pm 0.1$  °C.

**4.2.5 Measurement of  $E_N^T$  polarity parameter:** The  $E_N^T$  values of Honey were measured via the standard solvatochromic methods.<sup>63</sup> For the measurement of  $E_N^T$  parameter of natural honey (Litchi honey), Reichardt's dye no. 30 (**Figure 1**), is used as a probe molecule. The minute amount of Reichardt's dye no. 30 was added to the honey at 40 °C with vigorous stirring. Samples containing probe molecules was then transferred to the cuvette for the measurement of  $\lambda_{\max}$  (in nm).



**Figure 1.** Structures of Reichardt's dye no. 30.

Temperature of the sample was kept constant at 25 °C using the Peltier setup with an accuracy of  $\pm 0.01$  °C.  $E_T(30)$  value for the honey were calculated from the molar transition energy (in kcal mol<sup>-1</sup>) of Reichardt's dye using equation (1).

$$E_T(30) = hc \nu_{\max}(30) N_A = 28591/\lambda_{\max} \quad (1)$$

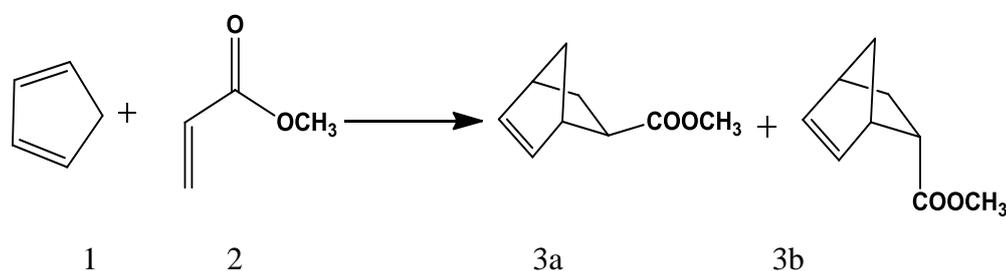
The  $E_N^T$  values of honey was calculated via the normalization of  $E_T(30)$  parameter, using water ( $E_N^T = 1$ ) and TMS ( $E_N^T = 0$ ) as reference solvents.

$$\begin{aligned} E_N^T &= [E_T(30)_{\text{solvent}} - E_T(30)_{\text{TMS}}] / [E_T(30)_{\text{water}} - E_T(30)_{\text{TMS}}] \\ &= [E_T(\text{solvent}) - 30.7] / 32.4 \end{aligned} \quad (2)$$

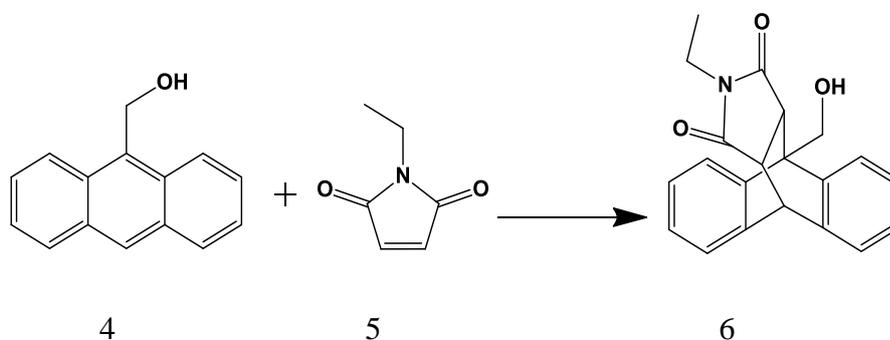
### 4.3 Results and discussion

A simple Diels-Alder reaction between cyclopentadiene (**1**) with methyl acrylate (**2**) (**Scheme 1**) has been carried out at 25 °C in different solvents including newly synthesized supersaturated solvent, water/supersaturated solvent, supersaturated solution of fructose and glucose, honey, water *etc.* Except water, the reaction condition has been maintained to be homogeneous for all other solvent.

The experimentally determined second order rate constant ( $k_2$ ) value of the reaction performed in new supersaturated solvent is  $7.92 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  with 92 % yield in case of **Scheme 1**. While the reaction of **4** and **5** (**Scheme 2**) proceeded with the  $k_2$  value as  $4.88 \times 10^{-1} \text{ M}^{-1}\text{s}^{-1}$  with 95 % isolated yield. For **Scheme 1** the result shows that these reactions are accelerated by at least 8-times in supersaturated solvent as compare to heterogeneous or ‘on water’ condition. The reaction of **1** and **2** (**Scheme 1**) in new supersaturated solvent resulted in about 20 times increment in the second order rate constant ( $k_2$ ) in comparison to ‘in water’ reactions *i.e.*,  $3.05 \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ .



**Scheme 1.** The reaction of cyclopentadiene (**1**) with methyl acrylate (**2**)

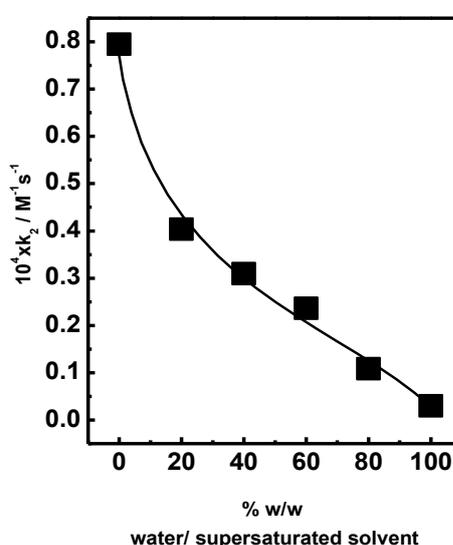


**Scheme 2.** The reaction of anthracene-9-carbinol (**4**) with *N*-ethyl maleimide (**5**)

### 4.3.1 Effect of the principle components of new supersaturated solvent during performance of the reactions

#### 4.3.1.1 The role of water in supersaturated solvent

To delineate the effect of water to new supersaturated solvent, we have added water at % w/w to the supersaturated solvent to understand the role of water. In this process we have indirectly lowered the degree of supersaturation of the solvent upon gradual addition of water to it. We have performed the reaction according to **Scheme 1** in each of these compositions *i.e.* water and supersaturated solvent (% w/w).

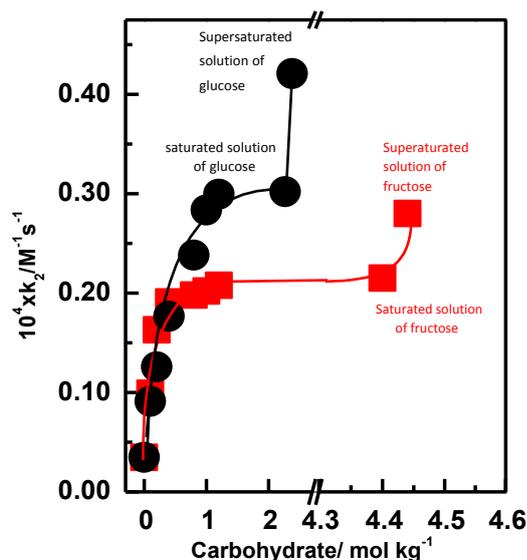


**Figure 2.** Change in the second order rate constants ( $k_2$ ) upon addition of (% w/w) of water to new supersaturated solvent during the reaction of **1** with **2** (**Scheme 1**). Line has been drawn to guide the readers' eyes.

From the trend of the data shown in **Figure 2**, it is obvious that the reaction shows highest value of  $k_2$  *i.e.*  $7.92 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$  in the new supersaturated solvent (all component including gluconic acid) and the rates of the reaction decrease gradually upon increasing percentage of water in supersaturated solvent. An examination of **Figure 2** reveals that the  $k_2$  values are higher as compared to that observed in the case of pure water (at homogeneous condition) *i.e.*  $3.05 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ . It indicates that presence of hydrogen bond donating components along with water contribute additionally over the factor *i.e.* enhanced hydrophobic interactions which have been observed to play pivotal role in unusual enhancement of rates of organic reactions

realized in pure water.<sup>25,26,40-45</sup> The enhanced  $k_2$  values compared to pure water entail additional catalysing factors along with hydrophobic interactions among reactants. At this juncture, we can safely presume on the basis of the composition of ‘new supersaturated solvent’ that greater availability of hydrogen bonding sites due to the presence of multiple hydroxyl groups might have contributed to catalyse the reaction.<sup>40</sup>

#### 4.3.1.2 Significance of carbohydrates to supersaturated solution



**Figure 3.** Rate constants ( $k_2$ ) of reactions of **1** with **2** in aqueous solution of fructose (■) and glucose (●) as a function of carbohydrate content in molality.

To comprehend the role of carbohydrates, we have performed the reaction (**Scheme 1**) both in aqueous solution of glucose and fructose separately, since both of these carbohydrates constitute the principle fraction (~71 % w/w see **Table 1**) of the ‘new supersaturated solvent’. We have determined the  $k_2$  values in the presence of increasing molal concentration of glucose and fructose in water (**Figure 3**). In both the aqueous solution of carbohydrates, the rate of reaction enhances up to a certain concentration (~1.5 mol kg<sup>-1</sup>) of the carbohydrates before achieving near equilibrium situation depending on the respective structural properties of the carbohydrates.<sup>64-67</sup> Present observations imply that the ability of the carbohydrates to offer multiple hydrogen bonding sites seems to be one of the major decisive factor behind the increment in the rate of the reactions with increase molality of carbohydrates.<sup>36-42</sup> The variation in the rate constants (**Scheme 1**) from new supersaturated solvent provokes us to investigate the role of hydrogen bonding with concern.

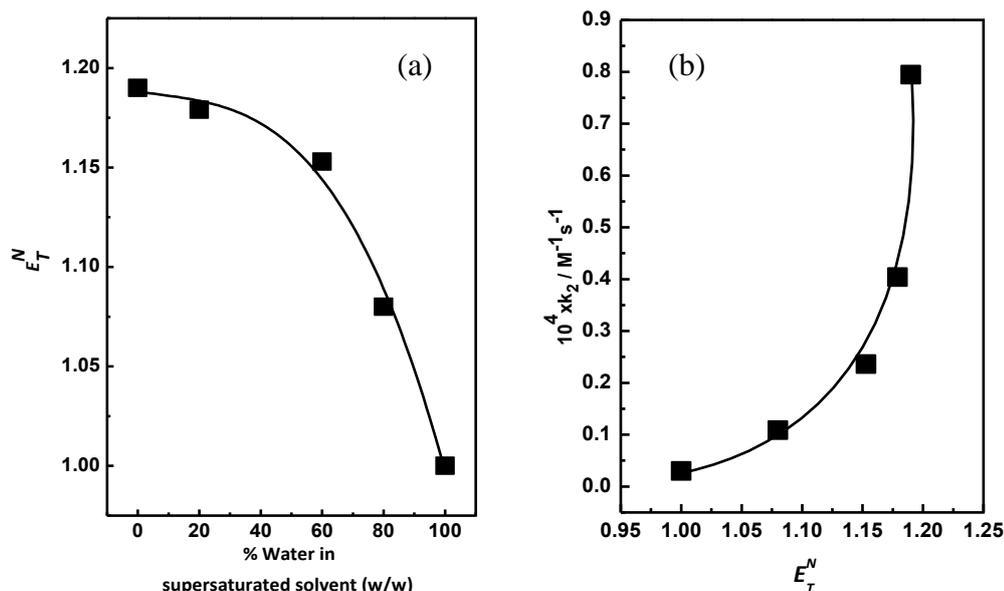
Observation of at least 10 times enhancements in the  $k_2$  values (**Figure 3**) compared to those of observed in saturated aqueous solution of glucose and fructose implies that additional accelerating factors arise in supersaturated state which were absent in saturated solution. Till date, as per literature survey, no bimolecular organic reactions have been carried out beyond saturation *i.e.* solubility limit of co-solutes in water<sup>36-39</sup> because in most of the cases, it has been observed that the presence of co-solutes in solvent it has been observed in solvent either accelerate or decelerate the reactions at the at the initial concentrations followed by equilibrium values of  $k_2$  *i.e.* no significant change in the value of  $k_2$  is further observed. This levelling off phenomena in  $k_2$  values leads researchers not to proceed beyond saturation limit of the co-solutes. From **Figure 2**, the loss of degree of supersaturation by the addition of water is reflected through the sharp decrease in  $k_2$  values on going from pure supersaturated solvent to 80:20 (% w/w) supersaturated solvent and water mixture.

#### 4.3.1.3 Effect of organic acid induced polarity in the supersaturated solvent

It should be noted that the transition state of the Diels-Alder reaction is semi-polar rather than iso-polar.<sup>23-24</sup> It signifies that reactivity of this type of reaction will be affected by the variation in the polarity of the solvent where the reaction is being carried out. In order to understand the polarity issues of the ‘new supersaturated solvent’, we have carried out the reaction (**Scheme 1**) in a supersaturated solvent comprised of only carbohydrates and lactone as described in **Table 1**, *i.e.* gluconic acid has not been used in this supersaturated solvent (now composition has been adjusted keeping in the mind that gluconic acid [1.27 %] is absent in this mixture).

**Table 2.** Effect of organic acid on the rate of organic reaction.

Entry no.	Composition	Polarity ( $E_T^N$ )	$k_2 / \text{M}^{-1}\text{s}^{-1}$
1.	Supersaturated solvent without gluconic acid	1.03	$0.71 \times 10^{-5}$
2.	Supersaturated solvent with gluconic acid	1.19	$7.92 \times 10^{-5}$
3.	Honey	1.17	$5.61 \times 10^{-5}$



**Figure 4.** (a) Variation in  $E_T^N$  as a function of % (w/w) of water in supersaturated solvent and (b) Variation in  $k_2$  as a function of  $E_T^N$  for the reaction of **1** with **2** in aqueous supersaturated solvent.

From **Table 2**, we can say that  $k_2$  values are very high for the supersaturated solvents containing gluconic acid *i.e.*  $7.92 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$  as compared to that of in the supersaturated solvent without gluconic acid which is  $0.71 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ . From the data, it can be concluded that the presence of acidic component which contributes to the higher polarity of the new supersaturated solvent causes at least 11 times enhancements in the  $k_2$  values.<sup>68,69</sup> Moreover, resemblance of the polarity value as well as the  $k_2$  values of this ‘new supersaturated solvent’ having gluconic acid with the natural supersaturated solvent *i.e.* ‘honey’ signifies that new supersaturated solvent (with gluconic acid) resemblance in physico-chemical property of natural analogue.

The polarity effect ( $E_T^N$ ) on  $k_2$  values of reaction (**Scheme 1**) is also evident during present experiments related to the gradual addition of water to the new supersaturated solvent. As we increase the percentage (w/w) of water in new supersaturated solution polarity ( $E_T^N$ ) decreases from ( $E_T^N$ ) = 1.19 to ( $E_T^N$ ) = 1.00 (**Figure 4a**) and the corresponding rate constant also diminishes proportionally (**Figure 4b**). From the observations, it can be concluded that high polarity of the supersaturated solvent stabilizes the semi-polar transition state of the reaction (**Scheme 1**) and thus decreases

the activation energy required for the reaction and contributes towards enhancement of spectacular rate enhancements of the organic reactions.

#### 4.3.1.4 A comparative study with natural honey

To validate the proposal of the new supersaturated solvent as a mimic of natural honey, we have performed similar reactions in litchi honey which is a unifloral honey. In the introduction we have already stated that we have prepared this supersaturated solvent comprising of all the mono-sacharides and di-sacharides keeping in mind the constituents of litchi honey.<sup>70</sup> The rate constant for the reaction between **1** with **2** in natural litchi honey ( $k_2$ ) was  $5.61 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$ . However, the same reaction (**Scheme 1**) shows the  $k_2$  is  $7.92 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  in new supersaturated solvent. Upon comparing these two  $k_2$  values, it is obvious that new supersaturated solvent possesses similar or superior efficacy when compared to even naturally available supersaturated solvent honey. The preference of introduction of new supersaturated solvent during performance of organic reactions lies in its composition which is the judicious blend of hydrophobic and hydrophilic components as inspired from ‘Natures unique supersaturated solvent’ viz. ‘honey’.<sup>12,15,36-39</sup> The presence of long carbon skeleton of the carbohydrates will induce more hydrophobic effect which is inherent to pure water. Moreover, since the reaction activation energy is also minimised by the hydrogen bonding stabilisation due to the presence of hydrogen bond donating or accepting components, the new supersaturated solvent will be the right choice as a plenty of -OH groups (hydrogen bond donating groups) present in the solvent. The superiority of the new supersaturated solvent also lies in the fact that it offers large solubility window since it is a blend of both polar components *i.e.* water, gluconic acid, gluconolactone and comparatively less polar components like fructose, glucose, Maltose, *etc.*<sup>38-39, 43-45</sup>

#### 4.3.1.5 Reaction in the eutectic melts of carbohydrate

Since hydrophobic interactions which play crucial role in promoting organic reactions in water under homogeneous condition by forcing the apolar reactants to integrate together and subsequently stabilizing the transition state as well as destabilizing the hydrophobically hydrated reactants,<sup>29-35</sup> we have expected the rate enhancement in ‘new supersaturated solvent’ to be the consequence of hydrophobic interactions force

due to the presence of water (~18-19 % w/w) in new supersaturated solvent. However, modest involvement of water (**Figure 2**) during the performance of the reactions leads us to examine the issue with utmost concern. The question was whether carbohydrates present in the ‘new supersaturated solvent’ can themselves act as the substitution to new supersaturated solvent. Therefore, we performed the same reaction (**Scheme 1**) in eutectic solvents of glucose and *N, N*-dimethyl urea (DMU) (rate constants in all the eutectic solvents have been measured at 85 °C). In the present case we have not used water during formation of the eutectic mixture.<sup>72</sup> To obtain the liquid melt, the temperature of the eutectic mixture has been raised to 85 °C. The composition of the mixture of glucose and DMU in the melt has been set as 50:50; 60:40; 70:30 (w/w) in present case *i.e.* the amount of glucose has been increased systematically in the melts.<sup>73</sup> To compare the results obtained in different solvents,  $k_2$  values along with yield (%) and temperature (°C) have been enlisted in the **Table 3**.

**Table 3.** A tabular representation of the second order rate constant ( $k_2$ ), yield %, temperature and reaction time (Min) for reaction of **1** with **2** (**Scheme 1**).

Entry no.	Solvent composition	Temp./ °C	$10^4 k_2$ / $M^{-1}s^{-1}$	Yield %	Reaction Time (Min)
1.	Water	25	0.03	82	90
2.	Litchi Honey	25	0.56	~92	75
3.	Supersaturated carbohydrate solvent without gluconic acid	25	0.071	89	< 90
4.	Supersaturated carbohydrate with gluconic acid	25	0.79	92	~70
5.	Glucose + DMU(W/W)				
	50:50	85	0.33	76	
	60:40	85	0.27	62	~70
	70:30	85	0.21	60	

It has been found that rate constant for **Scheme 1** in eutectic solvents are about 10 times higher (though at higher temperatures) as compared to supersaturated

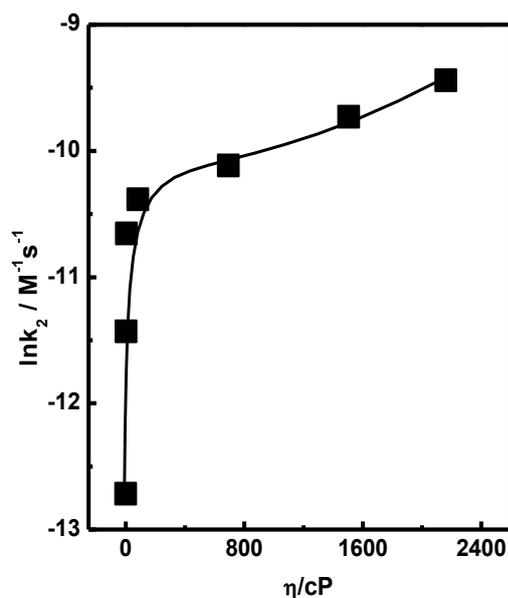
carbohydrate solvent (supersaturated solvent of carbohydrates without gluconic acid) (c/f. **Table 3**). On the other hand, rate constant ( $k_2$ ) value for supersaturated carbohydrate solvent with gluconic acid is 2 times higher than that of eutectic solvents at room temperature. The comparable trend of  $k_2$  value between new supersaturated solvent and eutectic solvent establishes information about the capability of hydrogen bonding of the carbohydrates, which is one of the principle reasons behind the rate enhancement in new supersaturated solvent.

It appears that eutectic solvents may replace new supersaturated solvent. A careful examination reveals that the temperature of performance for the reaction in these eutectic solvents is 85 °C, which is quite higher compared to room temperature *i.e.* 25 °C. We cannot use these eutectic mixtures as solvents for performing the reaction at 25 °C, since 85 °C is the lowest possible complete melting point of mixtures at their specified compositions. To use these eutectic mixture as a solvent (liquid state), we must have to carry out the reaction at the temperature  $\geq 85$  °C.<sup>[71–73]</sup>

The temperature dependent studies reveal that the activation energy required for the reaction (**Scheme 1**) in new supersaturated solvent is 64.18 kJ mol<sup>-1</sup> as compared to 108.28 kJ mol<sup>-1</sup> in the presence of carbohydrate-urea eutectic solvent mixture. Elevation of the temperature of the carbohydrate-urea eutectic solvent mixture is unavoidable in any condition, since at room temperature (25 °C) physical state of carbohydrate mixture is solid.<sup>71,73</sup> The results establish the fact that presence of minimal amount of water is essential along with the carbohydrates which is source of hydrogen bonding and a modest amount of solvophobicity to perform the Diels-Alder reaction at room temperature with elevated reactivity and selectivity. Additionally it should be noted that during the estimation of the efficacy of eutectic solvents, many organic compounds are charred at these higher temperatures of the carbohydrate melts.

#### 4.3.1.6 Thermodynamic activation parameters and viscosity of new supersaturated solvent

The most striking observations can be obtained upon comparing the values of  $k_2$  (**Scheme 1**) in water (viscosity 0.89 cP at 25 °C) and new supersaturated solvent (viscosity 2161 cP at 25 °C).



**Figure 5.** Variation of rate constants ( $\ln k_2$ ) of the reaction of **1** with **2** with respect to  $\eta$  in aqueous supersaturated solvent

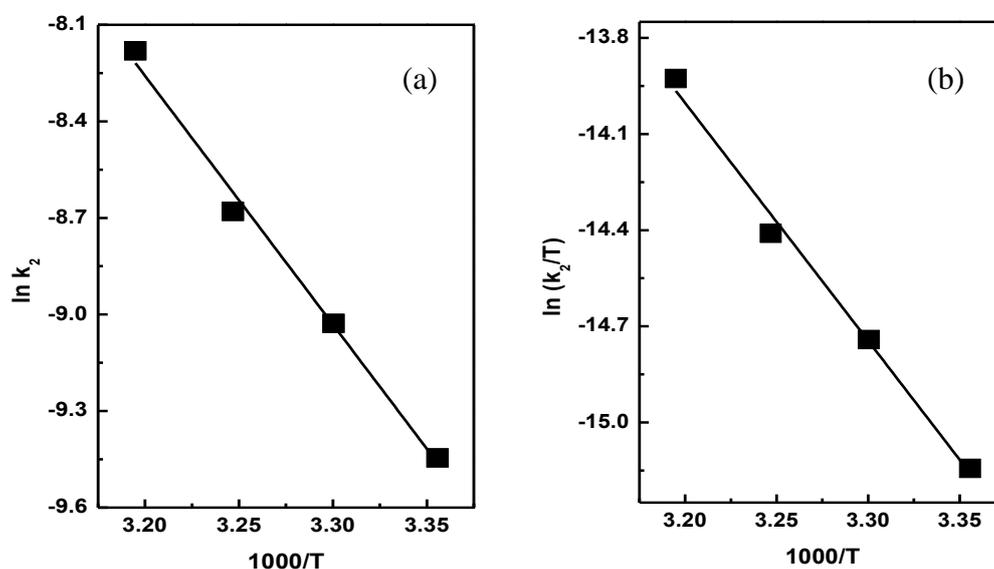
It can be emphasized that high viscosity of new supersaturated solvent does not show any detrimental effect in the reaction. To support experimental observations we have measured viscosities of water: supersaturated solvent mixture (composition is same as described in **Table 1**) and plotted  $\ln k_2$  as a function of  $\eta$  (**Figure 5**). From this trend shown in **Figure 5**, it can be equivocally asserted that high viscosity of ‘new supersaturated solvent’ had been continuously reduced upon increasing the concentration of water (*i.e.* addition of water will lead the super-saturation towards saturation and later to unsaturation of the system). However, rate of the reaction decreases upon addition of water (**Figure 2**), which is opposite to common understandings on the basis of conventional kinetic theory. The present observation can be discussed on the basis of collision-controlled reactions between two reactants.<sup>74–77</sup>

According to collision controlled reaction theory, it can be proposed that the presence of large number of encounters among reactants inside the collision regime is the responsible factor for high rates of reaction. The resultant anomaly between viscosity and rate of the reactions can be explained in the light of vibration-activation kinetic theory. In accordance to this theory, effective bond formation occurs among slow moving reactants since bond formation proceeds at slower rate as compared to single

vibration.<sup>58-60,74-77</sup> Observed high rate constant of the reaction at higher viscous supersaturated solvent can be compared with the rate acceleration intermolecular reactions like Diels-Alder reactions, 1,3-dipolar cycloadditions under high pressure, which indirectly increases the viscosity without significant contribution towards decrease in phantom volume ( $\Delta V^\ddagger$ ).<sup>58</sup> Moreover, even during intramolecular reactions like Claisen rearrangement of phenyl allyl ether, where diffusion is not necessary is catalysed in the presence of high viscous solvents.<sup>59</sup>

It is also known to us that formation of high viscous cleft region by unreactive amino acids present in enzyme is also one of the principle factors behind the promotion of enzyme-catalysed organic reactions.<sup>59</sup> Though argument can be raised regarding the validity of collision controlled vibrational-activation theory to understand the observed higher value of rate constants in a solution having viscosity of in the order of 103 cP, since till date this theory has been applied for moderately viscous solvents. This perceptible restriction can easily be done away with if micro-viscosity which actually controls the local phenomena is being considered instead of macro-viscosity of the solvent.<sup>58</sup> Due to the presence of large mismatch in size of the solvent (reaction medium) and solutes (reactants); the bulk viscosity applied by the solvent cannot be fully experienced by the solutes. In present reaction system, a large mismatch prevails among reactants (cyclopentadiene and methyl acrylate) and the constituent carbohydrates of the supersaturated solvent. In this context microviscosity should be more feasible parameter compared to that of macro-viscosity.<sup>58,78,79</sup> It implies that the extent of viscosity experienced by the reactants and corresponding transition state will be within the moderate range which is feasible for the application of vibrational activation theory.<sup>78,79</sup> From the above results we can say that extremely high viscosity of the supersaturated solvent cannot be considered as a barrier for its use as solvent, which is also be supported through the results obtained during performance of the reaction (**Scheme 1**) upon the addition of water to supersaturated solvent (**Figure 5**). To understand the role of activation parameter on reaction kinetics in the new supersaturated solvent, temperature dependent studies have been performed for **Scheme 1**, the activation energy of the reaction in new supersaturated solvent is 64.18 kJ mol<sup>-1</sup> (**Figure 6a**) compared to that of 90.63 kJ mol<sup>-1</sup> 'in water'.<sup>80</sup> We have also compared the values of activation parameters of the reactions obtained through Eyring

plot with the same parameters associated to same reaction (**Scheme 1**) while performed in water both at ‘homogeneous’ and ‘heterogeneous’ conditions.



**Figure 6.** The plots of the temperature dependent study for the calculation of activation parameters (a) Arrhenius plot ( $\ln k_2$  v/s  $1000/T$ ) and (b) Eyring plot ( $\ln k_2/T$  v/s  $1000/T$ ), for **Scheme 1** in new supersaturated solvent.

From comparison of the  $\Delta^\ddagger S$  values (**Table 4**), it is obvious that in the case of new supersaturated solvent the reaction is entropically more similar to that of ‘on water’ condition. Since higher hydrogen bonding imparts lesser values to  $\Delta^\ddagger H$ ,<sup>62,80,81</sup> it can be inferred that rate of the reaction is controlled by the hydrogen bonding in new supersaturated solvent and not by the hydrophobic forces, similar to ‘on water’ reaction.<sup>46-48,62,80,81</sup> On the other hand activation parameters for ‘in water’ reaction indicates the lesser effect of hydrogen bonding for this type of reactions compared to the reaction in new supersaturated solvent and ‘on water’ reaction. Moreover hydrogen bonding will impart new bonding with reactants and the transition state of the reaction *i.e.* both the reactants and the transition state will be more stabilized energetically through hydrogen bonding with the reaction medium both in case of ‘on water’ as well as in ‘new supersaturated solvent’.<sup>62,80,81</sup>

High viscosity of the supersaturated solvent promotes the Diels-Alder reactions, which is almost similar to the situation of enzyme catalyzed bimolecular reactions where active sites of the enzyme always offer a pool of high viscous region.<sup>82,83</sup>

**Table 4.** Activation parameters for reaction (**Scheme 1**) in different solvents.

Entry no.	Solvent	$\Delta^{\#}H$ (kJmol <sup>-1</sup> )	$\Delta^{\#}S$ (J mol <sup>-1</sup> K <sup>-1</sup> )
1.	Supersaturated solvent	61.68	-116.56
2.	In water <sup>78</sup>	88.32	-75.65
3.	On water <sup>78</sup>	57.18	-147.24

However, we should keep in mind that the vibration-activation theory has been applied for moderately viscous solvents only till date.<sup>58-60</sup> This restriction should not allow us to explain present experimental condition where the viscosity is in the order of 103 cP in the light of collision controlled vibrational-activation theory. However, this apparent limitation can easily be avoided if we stress on the definition of ‘active site’ which form high viscous cleft. The ‘active site’ of an enzyme is a three-dimensional cleft formed by a group that originates from unlike parts of the amino acid sequence—in fact, residues far-off in the sequence interconnects more effectively than neighboring residues in the amino acid sequence.<sup>84</sup> This implies that the ‘active site’ *i.e.* the catalytic part of enzyme possesses different structure as well as viscosity compared to that of the whole enzyme. This phenomenon leads us to concentrate over micro-viscosity which actually controls the local effects instead of macroviscosity of the supersaturated solvent.<sup>58-60</sup>

In present experiments, size of both cyclopentadiene as well as methyl acrylate is significantly smaller as compared to that of the size of long chain carbohydrates present in the supersaturated solvent.<sup>82,83</sup> It implies that the reactants *i.e.* cyclopentadiene and methyl acrylate come in contact with small segment of the full long carbohydrate chains. Thus, micro-viscosity experienced by the reactants is of moderate value as compared to that of macro-viscosity which is the reflection of entire long carbohydrate chain.<sup>58-60,78,79</sup> In this perspective, there should be no constraint over justifying the unusual enhancement of the rate of Diels-Alder reaction on the basis of collision controlled vibrational activation theory. However, the absence of such unusual rate enhancement in ionic liquids specifies that only high viscosity of supersaturated solvent is not the lone factor to promote the rate of reactions.

#### 4.3.1.7 A comparative view of saturated, unsaturated and supersaturated solution

Performance of the reaction (**Scheme 1**) in unsaturated, saturated and supersaturated aqueous solution of fructose (**Table 5**) shows that stereoselectivity of the product *i.e.* endo/exo ratio is 3.5, 3.0 and 3.6 for unsaturated, saturated and supersaturated aqueous solutions of fructose, respectively.

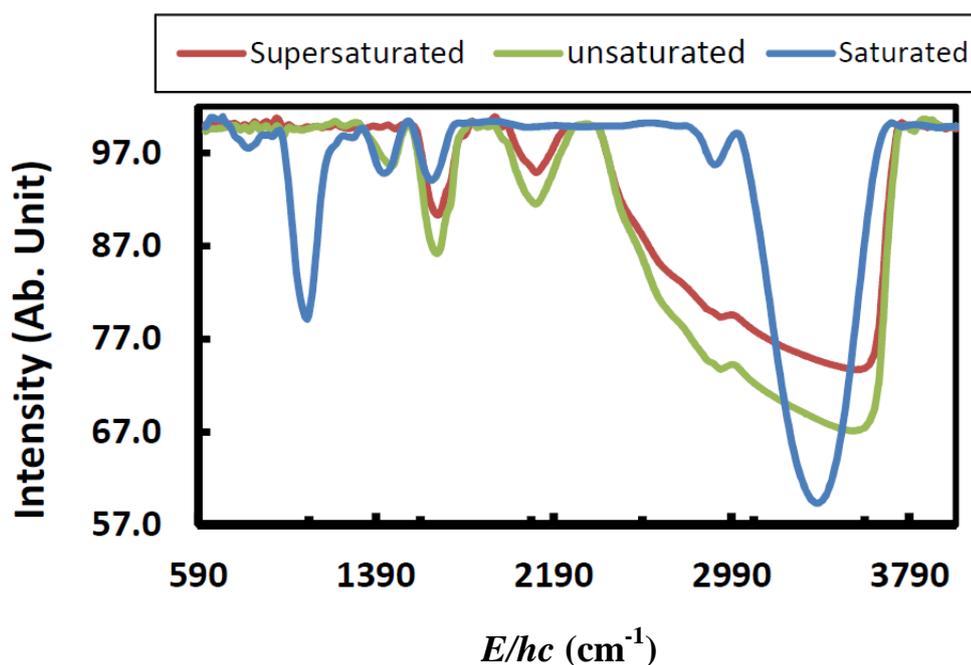
**Table 5.** The values of Endo/Exo, Yield (%), Temperature (°C) and Reaction Time for aqueous solution of fructose in unsaturated, saturated and supersaturated condition, reaction of **1** and **2** (**Scheme 1**)

Entry no.	Aqueous solution of fructose	endo : exo	Yield (%)	Temp./ °C	Reaction time (min)
1.	Unsaturated condition	3.5	94	25	~85
2.	Saturated condition	3.0	91	25	~90
3.	Supersaturated condition	3.6	92	25	~80

The values of stereoselectivity of the reaction (**Scheme 1**) also suggest the proposed resemblance of the new supersaturated aqueous fructose solution with that of that of supersaturated solution of urea in water where urea has been found to be more hydrated at its supersaturation state in water through neutron scattering method.<sup>82,83</sup> The modified arrangement of the new supersaturated carbohydrates favours the endo stereoisomer (endo: exo ~ 3.8) over exo-stereoisomer of the product. It implies that along with reactivity new supersaturated solvent can also offer stereoselectivity which is comparable with standard green solvents like water.<sup>43-45,62,80,81</sup>

However the stereoselectivity for aqueous supersaturated solution of fructose (3.6) is similar to that of the aqueous unsaturated fructose solution (3.5). Infra-red spectroscopy data observed for aqueous fructose solution shows that the structure of aqueous unsaturated solution of fructose mimics the structure of aqueous supersaturated solution. It has been also supported by proposition advocated by Burton *et. al.*, new supersaturated solvent mimics more to the unsaturated solvent structurally more than saturated solvent, this observation can be applied to understand

the unusual acceleration of rate of the reaction through hydrogen bonding in new supersaturated solvent.<sup>82,83</sup>

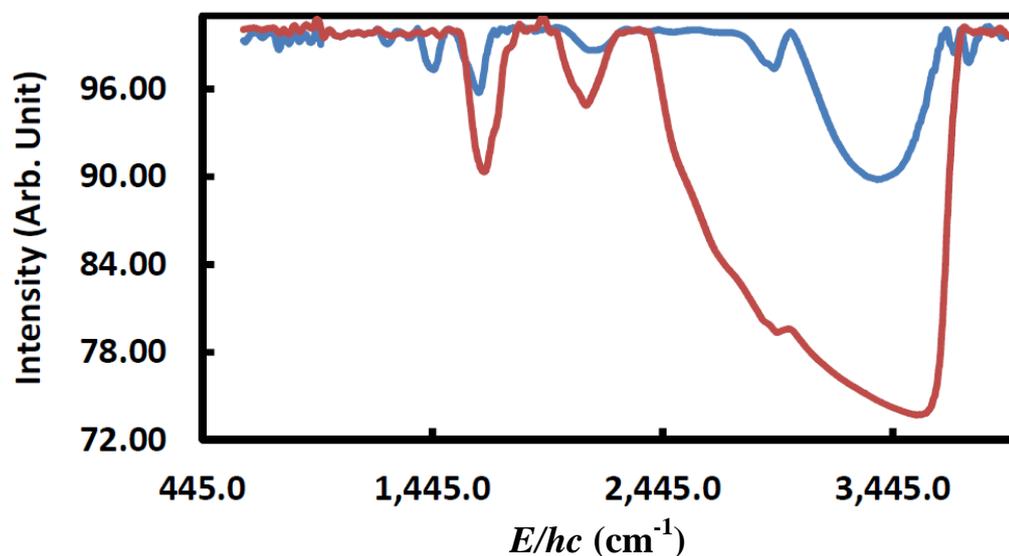


**Figure 7.** Superimposed FTIR spectra *i.e.* Transmittance vs.  $E/hc$  ( $\text{cm}^{-1}$ ) plots of the aqueous solution of fructose.

To cultivate the additional factors possessed by the supersaturated solvent, we have compared the FTIR spectra of aqueous fructose solution at three conditions *i.e.* unsaturated, saturated and supersaturated condition. We have chosen to concentrate only on aqueous solution of fructose since fructose constitutes highest percentage in supersaturated solvent (*c/f.* **Table 1**). However, the individual effect of other constituents cannot be ruled out. We have avoided the inclusion of other constituents just to keep the discussion away from massive complications, since a conglomerate of FTIR spectra of all the constituents might lead to ineffective conclusion. A careful examination of **Figure 7** establishes the fact that the nature of hydrogen bonding in both the unsaturated and supersaturated solvents is almost similar, while distribution of hydrogen bonding in saturated aqueous solution of fructose differs from both of them.

This spectroscopic comparison (**Figure 7**) justify that at supersaturated condition the metastable solute in aqueous solution of fructose acquires a structure where it can stabilize the reactant as well as transition state upon providing enthalpic stabilization

through hydrogen bonding which is comparable to that of unsaturated solution. Present observations can also be substantiated by the recent neutron scattering study of aqueous urea solution where at supersaturated condition urea water interactions increases at the expense of urea-urea interaction.<sup>82, 83</sup>

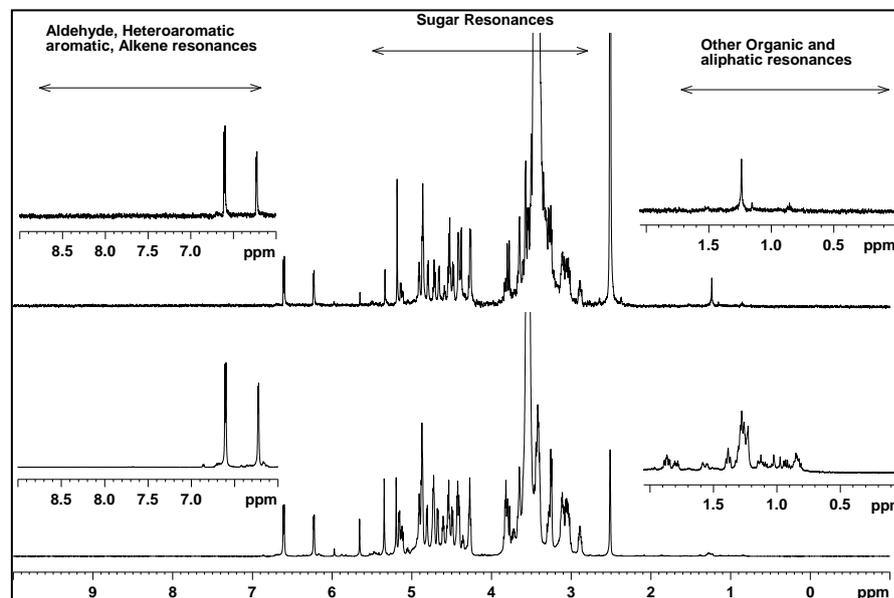


**Figure 8.** Superimposed FTIR spectra describing comparative plots of transmittance (Arb. Unit) with respect to  $E/hc$  ( $\text{cm}^{-1}$ ) of supersaturated fructose (red line) and artificial new supersaturated solvent (blue line).

Moreover to justify experimental proposition we can say that, the orientation of catalyzing functional group *i.e.* ‘-OH group’ of the carbohydrate (in artificial new supersaturated solvent) acquire almost similar structure that has been observed in case of supersaturated fructose solution. We have obtained FTIR spectra of artificial new supersaturated solvent and compared it with that of obtained with fructose supersaturated solution (**Figure 8**). **Figure 8** implies that there is change in the intensity of the transmission peaks, from moving to supersaturated fructose to artificial new supersaturated solvent but very modest changes have been observed in the shape and position the peaks in. This concurrence establishes our choice of studying three different type of solution of fructose only. Other constituents of the supersaturated solvent render their effects on deciding the mechanism of the reaction, however the structural orientation of functional groups especially ‘-OH groups’ remain almost similar to that achieved by fructose at supersaturated condition. This

situation can be comparable with ‘formation of viscous cleft’ by active sites of enzymes during catalysis of biological reactions.

#### 4.3.1.7 Recyclability of new supersaturated solvent



**Figure 9.** A comparative  $^1\text{H}$ -NMR study to show the recyclability of the new supersaturated solvent

It is known to us that along with greenness, the solvent should meet the criteria of its uses for multiple times from the economic perspective.<sup>3-6,20,21</sup> Recyclability of supersaturated solvent after performance of reactions (**Scheme 1**) has been asserted upon comparing  $^1\text{H}$  NMR of new supersaturated solvent before and after its utilization as a solvent. Recyclability of new supersaturated solvent ensures that the criteria *i.e.* economic viability is also feasible of this new solvent along with its environmental affability. We have carried out both the reactions in the recovered solvent after its first use. The yields of the reactions are 89 % for **Scheme 1** which are almost similar to previously obtained yields.

Additionally,  $k_2$  values are  $7.58 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  for **Scheme 1**. It implies that the efficacy of recycled solvent remains almost same as compared to that freshly prepared solvent. Rigorous experiments entail that factors like the stabilization of transition states of these reactions through hydrogen bonding, enhanced internal pressure due to metastable solutes at supersaturated condition in new supersaturated solvent are the

deciding factors to decrease the activation energy in new supersaturated solvent.<sup>27-35</sup> The introduction of new supersaturated solvent as reaction medium will certainly prove a yardstick to avoid solubility and reactivity problem arises during use of water as solvent. As substantiated above, high viscosity of new supersaturated solvent does not adversely affect the kinetics of Diels-Alder reactions as do the ionic liquids of comparable viscosities. It can be safely concluded that the sufficient availability of hydrogen bonding in new supersaturated solvent due to presence of carbohydrates as well as the structural assistance offered by the supersaturated solution makes new supersaturated solvent a unique green solvent. At the end, it is important to realize that the significantly important Diels-Alder reactions can take place with better reactivity and selectivity under ambient conditions.

We have noted extremely small changes (in peaks) in the recycled <sup>1</sup>H NMR spectra of supersaturated solvent, on comparison if we evaluate their intensity with the major carbohydrate peaks it seems to be almost negligible in their respective intensities. We have repeated the reaction between **1** and **2** in recovered supersaturated solvent which yields  $k_2$  value as  $7.55 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  with yield 94.2 %. This observation proves the sustainability of supersaturated solvent as a recyclable alternative.

#### 4.4 Conclusions

Though we have carried out two Diels–Alder reaction in the present work, the present systematic delineations univocally justifies ‘new supersaturated solvent’ as a potential bio-degradable and economically viable solvent to carry out organic reactions particularly the cycloaddition reactions under ambient conditions. For the Diels-Alder reactions carried out in the highly viscous (2161 cP) new supersaturated solvent, the increase of the  $k_2$  values about 26 times compared to that of water (0.89 cP at 25 °C) has been presented in the context the vibrational-activation theory. New supersaturated solvent not only enjoys superiority over all the present available solvents in terms of enhanced solubility, effortless methodology for synthesis but also possess amicable molecular arrangements necessary to promote organic reactions. Moreover, present observations suggest that honey could have been participated in various biological transformations during evolution of life since the structure and property relationship of ‘new supersaturated medium’, a mimic of natural honey afford the favorable condition for chemical reactions to occur efficiently.<sup>55</sup> Again, the

present investigations can act as an yardstick to evaluate the medicinal benefits of honey *i.e.* how honey prevents the growth of micro-organisms in the affected part of the body.<sup>55</sup> However, further investigations are required to comprehend origin of the effectiveness of the ‘new supersaturated solvent’ and the detailed intricacies of structure of new supersaturated carbohydrate in the ‘new supersaturated solvent’ for its wider applications in future.

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## Chapter 5

# Unusual Salt Effect of Aqueous Tetraalkylammonium Salts in Water Promoted Diels-Alder Reaction

*“Water is at the centre of every chemical reaction, and therefore should be the earth's most precious gift”.*

*-Janine Benyus*

Distribution of Earth's Water



Depending upon the stability and solubility of proteins in aqueous salt solution envisage that LiCl, NaCl act as salting-out (S/O) and tetraalkylammonium salts, GnCl, LiClO<sub>4</sub> act as salting-in (S/I) in aqueous solution. In the identical situation, the nature of GnCl, LiClO<sub>4</sub> and LiCl show conflicting nature in polar solvents like ethylene glycol and formamide. However, it has been observed that the behaviour of tetraalkylammonium halide salts (R<sub>4</sub>NX, R = alkyl group, X = Br group) are S/I in these types of solvents.

The present work deals with the exclusivity which was shown by R<sub>4</sub>NX in aqueous solution as well as in polar solvents. Physico-organic studies of these salts expose the diverse individual behaviour of R<sub>4</sub>NX from their higher analogs in aqueous solution. The amount of S/I and S/O effect caused by aqueous R<sub>4</sub>NX has been explored by the kinetic study of Diels-Alder reaction, solubility study of hydrophobe molecule, viscosity measurements and correlation with computer simulation studies. The atypical nature of R<sub>4</sub>NX in water has been also elucidated by the Setschenov equation ( $k_s$ ) and  $\Delta G_{\text{solvation}}$  determination.

## 5.1 Introduction

In ‘solution chemistry’, liquid water draws interests due to its mystifying physico-chemical properties. Evaluation of physical intricacies of water is already an important fact and therefore, the addition of solutes significantly expands the range of observed phenomena. Liquid water is a ubiquitous solvent.<sup>1</sup> From the discussion of the preceding chapter, it is understandable that liquid water supports chemical reactions connecting an enormous variety of mechanisms and processes in their reaction pathway.<sup>1</sup> There are reports stating that liquid water can serve as a solvent medium for achieving chemical transformation by decreasing the activation energy barrier during the course of a reaction. In this case, low solubility of reactants/solutes in liquid water project water as a reaction media, not solvent.<sup>2</sup> However, for the promotion of this type of reactions, the criteria is that the reactants must have the capability of formation of hydrogen bonding with the media.<sup>3</sup> Because of the formation of hydrogen bonding with media the transition state of the reaction is being more stabilised than that of the condition of the absence of hydrogen bonding.<sup>4</sup> But there are several synthetic organic reactions which have mechanistic and synthetic complications in which liquid water cannot serve as media.<sup>5</sup>

In 1888, Franz Hofmeister has reported an effect called as Hofmeister series, which has been recognised as one of the most revolutionary phenomenon.<sup>6</sup> Ions which stabilize the structure of surrounding water molecule are termed as the structure-making (kosmotropes) consequently; ions which destabilize the structure of surrounding water molecule are termed as the structure-breaking (chaotropes). Different genre of salts has different capabilities of salting-out proteins. Based on the efficiency of salts to separate out protein from its solution, the anions and cations appear to follow a specific order. The specific ordering of ions is evident for various macroscopic properties like chromatographic selectivity, surface tension and protein protein-denaturation temperatures.<sup>7</sup>

### Most Stabilizing

#### Strongly hydrated anions



#### Weakly hydrated cations

### Most destabilizing

#### Weakly hydrated anions

#### Strongly hydrated actions

The effect caused by the ions in the specific order can be understood by careful examination of solvation pattern around the ion.<sup>7(f)</sup> Hofmeister series has been instrumental in determining the directing influence of the ions, more specifically the influence of anions of the dissolved salts on the surrounding water molecules. The stabilization and destabilization effect reflected by the ions on the water molecules in solvation shell can be understood by the equilibrium between the water–water and ion–water interactions, which differ significantly with the variation of charge density on the solute surface. Hofmeister effect has explained only the basis of direct ion interactions and effect of salt is only restricted to their vicinal water molecule and not beyond that.<sup>8</sup>

In this study, a range of aqueous solution of tetraalkylammonium halide salts has been utilized as solvent media for water-promoted Diels-Alder reaction.<sup>9</sup> Diels-Alder reaction is an example of  $(4+2)\pi$  cycloaddition concerted reaction, which follows photochemically or thermodynamically guided mechanism pathway for carrying out reaction between diene and dienophile.<sup>10</sup> Diels-Alder reaction serves as the remarkable step in synthesizing higher reactivity and stereoselectivity cyclic organic compounds. Established theoretical studies concluded that the transition state of the Diels-Alder reaction was semi-polar nature.<sup>11</sup> Among all natural and artificial solvents, water has been largely investigated due to its ubiquities and environment benign in nature. The supremacy of the water in exploring enhanced reactivity and selectivity has been pointed out by Breslow and by Grieco group.<sup>12</sup> Their experimental findings are also supported by several theoretical and experimental studies of various research group later.<sup>13,14</sup> The principle factor accountable for the rate enhancement in water is enforced hydrophobic interaction. This enforced hydrophobic interactions can also be explained in terms of the interactions between apolar reactants in the transition state, which is responsible for minimum exposure of reactants to the water molecules environment.<sup>13</sup> The water promoted reactions are also felicitated in terms of reactivity and selectivity by some additional factors like hydrogen bonding, cohesive energy density (ced), polarity *etc.*<sup>13</sup> Structure of water provides exceptional structural modifications and high cohesive energy density to the reactants which drive the course of reaction towards high rate.<sup>13(f-j), 14</sup>

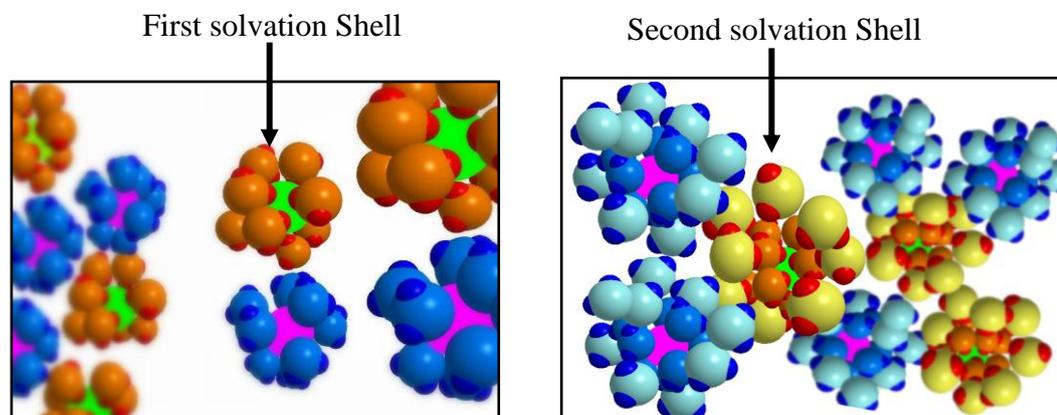
In order to understand the action of hydrophobic forces qualitatively and quantitatively, chemical reactions have been carried out in aqueous inorganic salt

solutions. These inorganic salts in water modify the extent of hydrophobic forces experienced by the reactants and transition state due to varying interactions in water molecules.<sup>13-15</sup>

Depending upon enhancement or the diminishing ability of inorganic salts, the hydrophobicity of water due to inorganic salts are categorised in into two parts *viz.* pro-hydrophobic or salting-out (S/O) and anti-hydrophobic or salting-in (S/I) salts.<sup>15</sup> In an aqueous solution of inorganic salts, the rate enhancement and diminishing effects of the reaction are caused by the S/I and S/O agents. This alteration in rate can be explained in terms of the capability of inorganic salts to modify the structure of water molecules surrounding reactants and activation complex of the reaction.<sup>15 (d-f)</sup> Inorganic salts like NaCl, LiCl act as a S/O agent in water because it is responsible for volume contraction for the solute. This volume contraction around the solute molecule caused due to the modification water molecule structures around the ions.

To understand the structural modification of water molecules around inorganic salts in solvation shells several spectroscopic and computer simulation studies have been studied rigorously in recent times. Microscopic experimental evidence show that different ions influence the water structure surrounding the ions.<sup>16</sup> According to the recent reports presented by Tielrooij *et. al.*, the femtosecond time-resolved infrared (fs-IR) spectroscopy and terahertz dielectric relaxation (DS) spectroscopy along with computer simulations offer a new perspective regarding the rotational and translational movement of water molecules in solution.<sup>17</sup> Through the terahertz dielectric relaxation (DS) spectroscopy experiments, they have found that charge density of ions is a principle responsible factor for directing the orientation dynamics of water molecules in ion surrounding. In the same respect tiny and multivalent ions will provide additional hydration numbers to the respective ions. Hydration pattern of ions is understandable from the example of aqueous NaCl is depicted in **Figure 1**. In this drawing, water molecules orient with structural modification in the (left) first hydration shells of cations ( $Na^+$ , pink) and anions ( $Cl^-$ , green) in an aqueous sodium chloride solution; (right) water molecules beyond first hydration shells of cations ( $Na^+$ , pink) and anions ( $Cl^-$ , green) in an aqueous sodium chloride solution (**Figure 1**). On the basis of their observations, they concluded that the effects caused by the ions on water dynamics cannot be additive. So for specific combinations of cations and

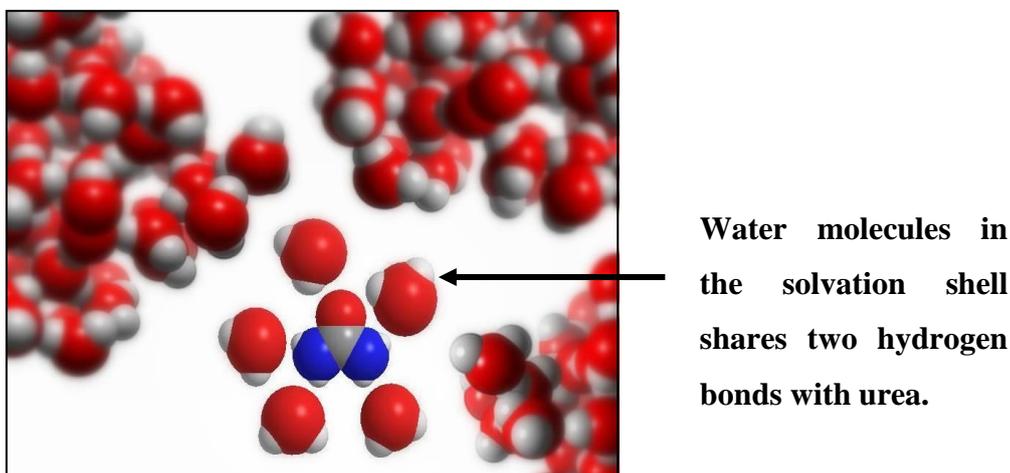
anions, dynamics of water is affected well beyond the first hydration shell. This finding is also consistent with our experimental findings of aqueous tetraalkylammonium salts.



**Figure 1.** Water molecules in the first (left) first hydration shells of cations ( $\text{Na}^+$ , pink) and anions ( $\text{Cl}^-$ , green) in an aqueous sodium chloride solution; (right) water molecules beyond first hydration shells of cations ( $\text{Na}^+$ , pink) and anions ( $\text{Cl}^-$ , green) in an aqueous sodium chloride solution. Both the diagrams inspired by the structure and dynamics of these water molecules are ion specific and different from bulk water.

A literature survey of an aqueous solution of urea fails to represent a vivid picture on the S/I and S/O nature of urea while dissolved in water.<sup>15e</sup> However recently, Rezus *et. al.* have reported contradictory results in the case of solvation dynamics of the urea molecule.<sup>18</sup> To study the structure and dynamics of water molecules around urea molecules, they have used polarization-resolved mid-infrared pump-probe spectroscopy. According to their experimental findings, at 8 M concentration of urea shows approximately similar orientation dynamics of water molecules around the urea molecules to that of pure water. These results indicate the unusual nature of urea, even at higher concentrations; urea has a negligible or an extremely small effect on the hydrogen bonding dynamics of urea and water molecules. An experimental observation inspired representation of solvation structure of the urea molecule is proposed in **Figure 2**.<sup>18</sup> Rezus *et. al.* reported in their study that only one water molecule per urea is stationed by urea molecule, which shows approximately six times sluggish orientational dynamics in bulk water. The water molecules which

associated with the urea molecules are tightly bound and form water–urea complexes through hydrogen bonding. In this intermolecular complex formation between water–urea molecules; urea is being projected as extremely weak salting out (S/O) agent in water.



**Figure 2.** Solvation structure of the urea molecule inspired by the experimental findings in reference.<sup>18</sup> In this complex, one of the water molecules in the solvation shell shares two hydrogen bonds with urea.

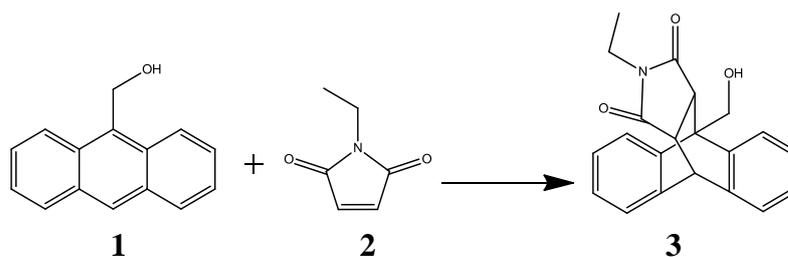
In the same context, aqueous solution of  $GnCl$ ,  $LiClO_4$ ,  $R_4NX$  break the well organized structure of water hence known as the S/I agents.<sup>15(e)</sup> The influence of  $R_4NX$  type salts concentration on solubility of apolar compounds in water can be given by Setschenov equation, *i.e.*,

$$\ln [c_i/c_i(0)] = -k_s c_s \quad (1)$$

where,  $c_i$  and  $c_i(0)$  are the molar solubilities of the hydrophobic solute in the aqueous solution of  $R_4NX$  and in pure water, respectively;  $c_s$  is molar concentration of the  $R_4NX$  and  $k_s$  is the Setschenov S/O coefficient of salt.<sup>19</sup> The characteristics of salts as well as the nature of the non-electrolytes are crucial factors in the determination of  $k_s$ .<sup>20</sup> In this equation, a positive value of  $k_s$  (salting constant) specifies that the salt is acting as S/I agent by increasing the solubility of an apolar moiety in water and, on the other hand, a negative value of  $k_s$  implies S/O agent by decreasing the solubility of the apolar compound in aqueous solution.

With the advent of molecular interpretations of rearrangements of water structure, classical ideas *viz.* the decrease of molar volume, variation of surface tension, cavity formation etc. behind the activities of introduced salt in aqueous solution has been overturned.<sup>21,22</sup> Direct interactions among electrolyte ions and apolar moiety have been proposed to interpret the salting phenomena. In recent work by Falabella and Teja,<sup>23</sup> it has been found that the size of the hydrophobe governs the S/I and S/O character of salts in water. During the determination of Henry's constant value for 2-ketones in aqueous  $R_4NX$ , the authors had observed that all the 2-ketones show S/I behaviour in salt solutions except 2-propanone. The parameters guiding salt effect increase with the size of the hydrophobe in the case of inorganic salts and decrease with the size in the case of  $(CH_3)_4NBr$ . These observations were also supported by the solubility determination study of methane, ethane, propane and butane in aqueous  $R_4NX$ .<sup>24</sup>  $R_4NX$  type of salts shows S/I nature except  $NH_4Cl$ . The opposite nature of  $NH_4Cl$  has been justified because the dependence on the size of hydrophobe and tetraalkylammonium cation is directed by hydrophobic interactions between the ion and the hydrophobic molecule.

The reaction between anthracene-9-carbinol (**1**) and *N*-ethyl maleimide (**2**) (**Scheme 1**) has been carried out to investigate salt effect in the hydrophobic acceleration of reaction.<sup>25,26</sup>

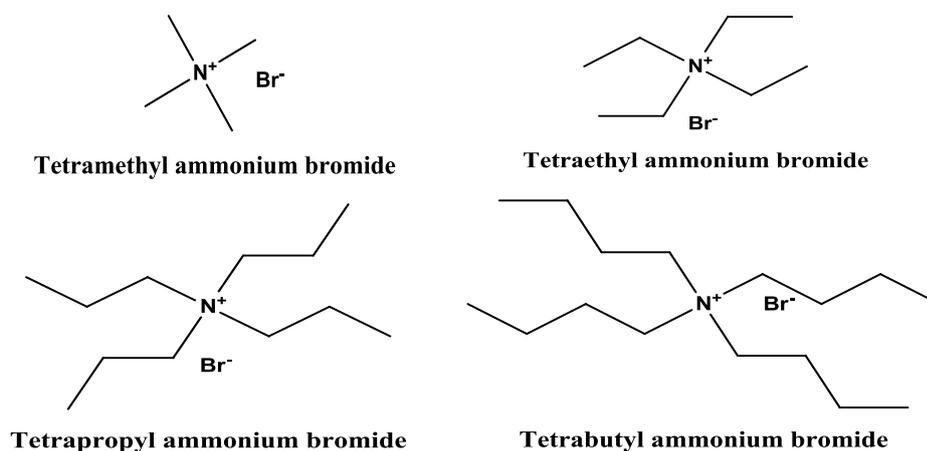


**Scheme 1:** The reaction of anthracene-9-carbinol (**1**) and *N*-ethyl maleimide (**2**) at aqueous solution of tetra alkyl ammonium based salts at ambient condition.

Salt effects, solvent effects and interfacial effects have been proven to be useful in influencing the mechanism of Diels–Alder reaction as well as other organic reactions till date.<sup>5(d),27,28</sup> There are several theories available to explicate the physico-chemical behaviour of the aqueous saline solution, because it is associated with the protein aggregation and precipitation.<sup>14</sup> In the present context, it is of importance to

understand the environmentally significant phenomena in terms of model study. Diels–Alder reactions in water have chosen as a model system to study because it has been proved to be an effective way to synthesize biologically important molecules with superior selectivity and reactivity.

In order to understand the molecular origin of salt effects caused by  $R_4NX$  on Diels–Alder reactions, relative rate constants ( $k_{rel}$ ) obtained for **Scheme 1** in different salt concentrations of aqueous  $(CH_3)_4NBr$ ,  $(C_2H_5)_4NBr$ ,  $(C_3H_7)_4NBr$  and  $(C_4H_9)_4NBr$  have been determined. For determination of relative rate constants, the rate constant in pure water has been assigned the reference value, *i.e.*  $k_2 = 0.283 \text{ M}^{-1}\text{s}^{-1}$  to calculate  $k_{rel} = k_2$  in salt solution/ $k_2$  in pure water. In each case, the steric hindrance as well as the size of the  $R_4NX$  has been increased by invoking larger alkyl groups.



**Scheme 2.** The schematic representations of the molecular structures of  $R_4NX$ .

## 5.2 Experimental procedure

**5.2.1 Materials and methods:** Tetraalkylammonium halide salts were purchased from M/s. Spectrochem Co. and were recrystallized from water and dried under vacuum for 12 h. For preparing aqueous solutions of salts of different concentrations; deionized water was used. Anthracene-9-carbinol (GR grade) and *N*-ethyl maleimide (99.5% pure) were used as purchased from M/s. Sigma-Aldrich. The product formation was followed by TLC and purity has been ensured by obtaining and matching  $^1\text{H-NMR}$  spectra as discussed in the literature.<sup>31(b)</sup> All the measurements

were carried out at  $25 \pm 0.1^\circ\text{C}$  using a constant temperature water bath supplied by Julabo.

**5.2.2 Kinetic analysis:** For the kinetic analysis at higher concentrations of both **1** and **2** (above the solubility limits) were taken so as to obtain the maximum solubility limit of the reactants. Reactants **1** and **2** are sparingly soluble in water and salt solutions, henceforth, in order to ensure the maximum solubility limit of **1** and **2**, and to achieve the equal concentrations of both the solvents in reaction mixtures, separate equilibration of the reactants was carried out. Here the procedure for water as an example has been given. The reactants were separately suspended in water **1** (0.12 g) and **2** (0.199 g) in 10 ml of water each. The temperature of the solution was maintained by Julabo constant temperature bath with an accuracy of  $\pm 0.01^\circ\text{C}$ . The solution of **1** and **2** was stirred vigorously for 6 h followed by 2 h standing. The solubility value finally obtained for **1** was  $7.9 \times 10^{-4}$  M and for **2** was  $8.0 \times 10^{-3}$  M. For a standard kinetic run, the reaction was initiated by adding 9.09 ml of solution **1** and 0.91 ml of solution **2** in a jacketed flask connected to the constant temperature bath. A similar procedure has been followed for other salt solutions as well. The reaction progress was monitored at the appropriate time intervals by extraction of aliquots with ethyl acetate followed by appropriate dilution and further analysis in GC (Varian CP-3800 Gas Chromatography instrument). The GC method was calibrated with respect to the reactant concentration and the amount of reactant decrease as a function of time to obtain the extent of the reaction with respect to time. A plot of  $x/a(a-x)$  against inverse of time 't', where 'a' stands for the initial concentration of the reactant for the reaction **1** with **2** and 'x' represents the concentration of the reactant at time 't'. The reaction is carried out at  $25 \pm 0.1^\circ\text{C}$ . The rate constants thus determined were reproducible to within  $\pm 6\%$ .

**5.2.3 Solubility measurements:** Solubility of **1** has been determined by measuring the optical densities of a solution saturated with **1** in both pure water and salt solutions following absorption spectra with a Carry 50 UV/vis spectrophotometer (Varian make) at  $\lambda_{\text{max}}=364$  nm. The changes in the ionic concentrations produce variation in the absorptivity of solute **1**. An average of three readings has been noted as the final value of solubility. All the measurements were carried out at  $25 \pm 0.1^\circ\text{C}$  using a Peltier supplied with the spectrophotometer.

**5.2.4 Viscosity determination:** Viscosity measurements were carried out with a Brookfield Ultra-Rheometer (LVIII). The viscosities were obtained using the equation,

$$\eta = (100/\text{RPM}) \times \text{TK} \times \text{Torque} \times \text{SMC}$$

where, RPM; TK (0.09373) and SMC (0.327) are the rotation per minute, viscometer torque constant and spindle multiplier constant, respectively.

The calibration of the instrument was carried out against the viscosity data of water and aqueous  $\text{CaCl}_2$  solutions.<sup>54</sup> The temperature of the solution was maintained to within  $25 \pm 0.1$  °C using a Julabo constant temperature thermostat bath. The viscosities were measured with an accuracy of  $\pm 1\%$ . Each measurement reported here is an average of triplicate reading with a precision of  $\pm 0.3\%$ .

## 5.3 Results and discussion

### 5.3.1 Effect of concentrations of aqueous $R_4NX$ salt on kinetic profiles of the Diels–Alder reaction

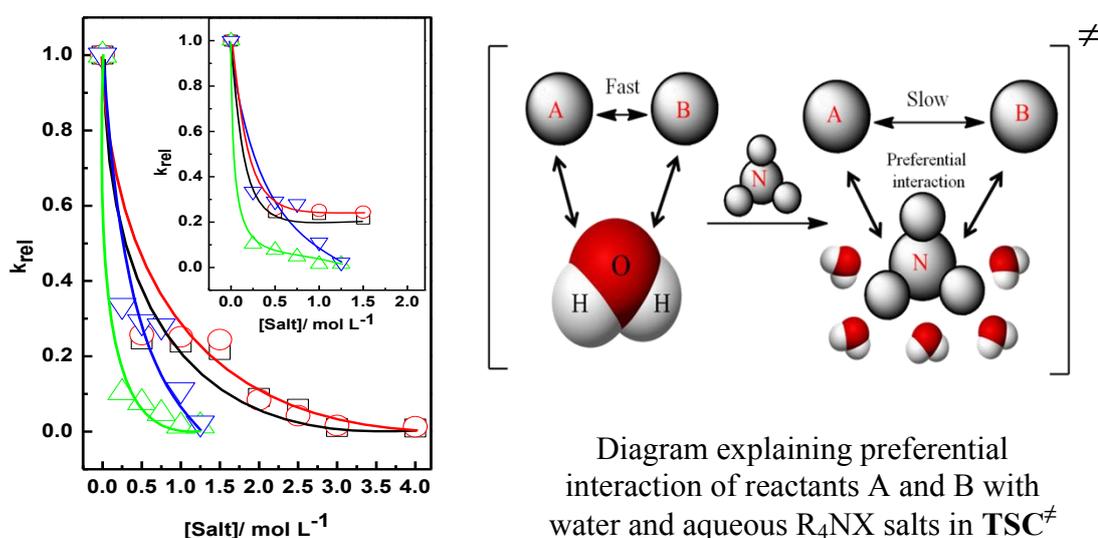
The reaction between **1** and **2** had been carried out in aqueous solutions of  $(\text{CH}_3)_4\text{NBr}$ ,  $(\text{C}_2\text{H}_5)_4\text{NBr}$ ,  $(\text{C}_3\text{H}_7)_4\text{NBr}$  and  $(\text{C}_4\text{H}_9)_4\text{NBr}$  at different concentrations at room temperature (25 °C). Concentration dependence of relative rate ( $k_{\text{rel}}$ ) for the reaction has been enlisted in **Table 1**. The influence of variation in concentration of the salts on  $k_{\text{rel}}$  values has been shown in **Figure 1**. Around four-fold decrease in  $k_{\text{rel}}$  values has been observed in 1 M aqueous solution of  $(\text{CH}_3)_4\text{NBr}$  and  $(\text{C}_2\text{H}_5)_4\text{NBr}$ . However, in 4 M aqueous solution of  $(\text{CH}_3)_4\text{NBr}$  and  $(\text{C}_2\text{H}_5)_4\text{NBr}$ , the extent of decrease in the value of  $k_{\text{rel}}$  were extreme around 108-folds and 78-fold, respectively. On the other hand,  $(\text{C}_3\text{H}_7)_4\text{NBr}$  and  $(\text{C}_4\text{H}_9)_4\text{NBr}$  show decrease about 66-folds and 45-folds relative rate constants decrease for 1.25 M. It is interesting to observe that the change in the value of relative rate ( $k_{\text{rel}}$ ) caused by  $(\text{CH}_3)_4\text{NBr}$  and  $(\text{C}_2\text{H}_5)_4\text{NBr}$  is minimum as compared to that of  $(\text{C}_4\text{H}_9)_4\text{NBr}$  for the same salt concentrations.



Here, R<sub>A</sub> and R<sub>B</sub> represent the reactants **1** and **2**, respectively; [TSC]<sup>‡</sup> represents transition state of the reaction.

**Table 1.** Concentration dependence of relative rate constants ( $k_{\text{rel}}$ ) for the reaction of **1** and **2** in aqueous R<sub>4</sub>NX.

[(CH <sub>3</sub> ) <sub>4</sub> NBr]		[(C <sub>2</sub> H <sub>5</sub> ) <sub>4</sub> NBr]		[(C <sub>3</sub> H <sub>7</sub> ) <sub>4</sub> NBr]		[(C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> NBr]	
[Salt] (mol L <sup>-1</sup> )	$k_{\text{rel}}$	[Salt] (mol L <sup>-1</sup> )	$k_{\text{rel}}$	[Salt] (mol L <sup>-1</sup> )	$k_{\text{rel}}$	[Salt] (mol L <sup>-1</sup> )	$k_{\text{rel}}$
0.0	1.0	0.0	1.0	0.0	1.0	0.0	1.0
0.5	0.2435	0.5	0.2574	0.25	0.1037	0.25	0.3348
1.0	0.2348	1.0	0.2515	0.50	0.0770	0.50	0.2919
1.5	0.2153	1.5	0.2441	0.75	0.0482	0.75	0.2806
2.0	0.0910	2.0	0.0844	1.00	0.0148	1.00	0.1108
2.5	0.0619	2.5	0.0419	1.25	0.0152	1.25	0.0225
3.0	0.0109	3.0	0.0160				
4.0	0.0094	4.0	0.0128				



**Figure 1.** The plots of  $k_{\text{rel}}$  against molar concentration of [R<sub>4</sub>NX] in aqueous (CH<sub>3</sub>)<sub>4</sub>NBr(□), (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr(○), (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr(△) and (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr(▽). The inset picture shows the variation of earlier concentration up to 2 M.

From the plot of  $k_{\text{rel}}$  versus concentration of R<sub>4</sub>NX (**Figure 1**, LHS), it has been observed that the reaction proceeds slowly upon a continuous increment of the concentration of salts. The situation can safely be depicted by the representative diagram at the right-hand side of **Figure 1**. It signifies that the effect of hydrophobic

interaction which has been discussed as one of the principle reasons to bring the reactants closer is being increasingly hindered upon rise in the concentration of salt in the reaction media. Moreover, it can be safely concluded that in the presence of  $R_4NX$  the reactant molecules preferentially interact more with salt cation individually rather than each other. From the inset plot in **Figure 1** (right-hand corner), individual behaviour of  $R_4NX$  up to their 2 M concentration in aqueous solution can be observed clearly. Upon careful evaluation of the diagram displayed at inset of **Figure 1**, it can state that all the salts promote salting-in (S/I) behaviour. However, the extent of decrease in  $k_{rel}$  values in the case of  $(CH_3)_4NBr$  is smaller as compared to that of  $(C_2H_5)_4NBr$ ,  $(C_3H_7)_4NBr$  and  $(C_4H_9)_4NBr$ . The possible explanation of this unusual behaviour in the presence of  $(CH_3)_4NBr$  can be obtained by correlating with surface tension behaviour of these categories of salts in aqueous solutions. It is known to us that the addition of all the salts irrespective of S/I and S/O salts increases the surface tension of water, but in our cases it has been observed that all the  $R_4NX$  salts decrease the surface tension of water except for  $(CH_3)_4NBr$ , which slightly raises the surface tension of water.<sup>21</sup> The behaviour of amphiphilic organic ions in water generally discussed in terms of the balance between hydrophobic hydration of non-polar groups and electrostrictive hydration of the ionic groups.<sup>21,22,29</sup> According to Tamaki *et al.*,<sup>22</sup>  $(CH_3)_4NBr$  in its aqueous solution behaves like a simple inorganic salt. In  $(CH_3)_4NBr$ , because of the presence of small alkyl group the electrostrictive hydration which is mainly caused by the ionic part of the molecule wins over the hydrophobic hydration caused because of the presence of methyl group in their respective structures and consequently the surface tension of aqueous  $(CH_3)_4NBr$  solution raises slightly.

On the contrary, in the case of  $(C_2H_5)_4NBr$ ,  $(C_3H_7)_4NBr$  and  $(C_4H_9)_4NBr$ , the hydrophobic hydration effect exceeds the electrostrictive hydration caused by the central ionic part because of the presence of long alkyl groups in a cationic part of the salts. Therefore, the surface tension of aqueous salt solution decreases and the transfer of these salts from bulk to the surface of the water is a spontaneous process.<sup>22</sup> Thus,  $(C_2H_5)_4NBr$  and its higher homologue salts can be classified as hydrophobic structure maker.<sup>30</sup> Salts like guanidinium salts show similar behaviour on the rate of the reaction. Following the concentration-dependent kinetic study for the **Scheme 1** in 2 M of  $GnCl$ ,  $GnSCN$  and  $GnClO_4$ , it has been reported that all the salts decelerate the rate of the reaction.<sup>30</sup> In simple sense, S/O salts felicitate as well as stabilize the

transition state of the reactions with the hydrophobic packing of diene and dienophile. However, on the contrary, S/I agents fail to do the same.<sup>29</sup>

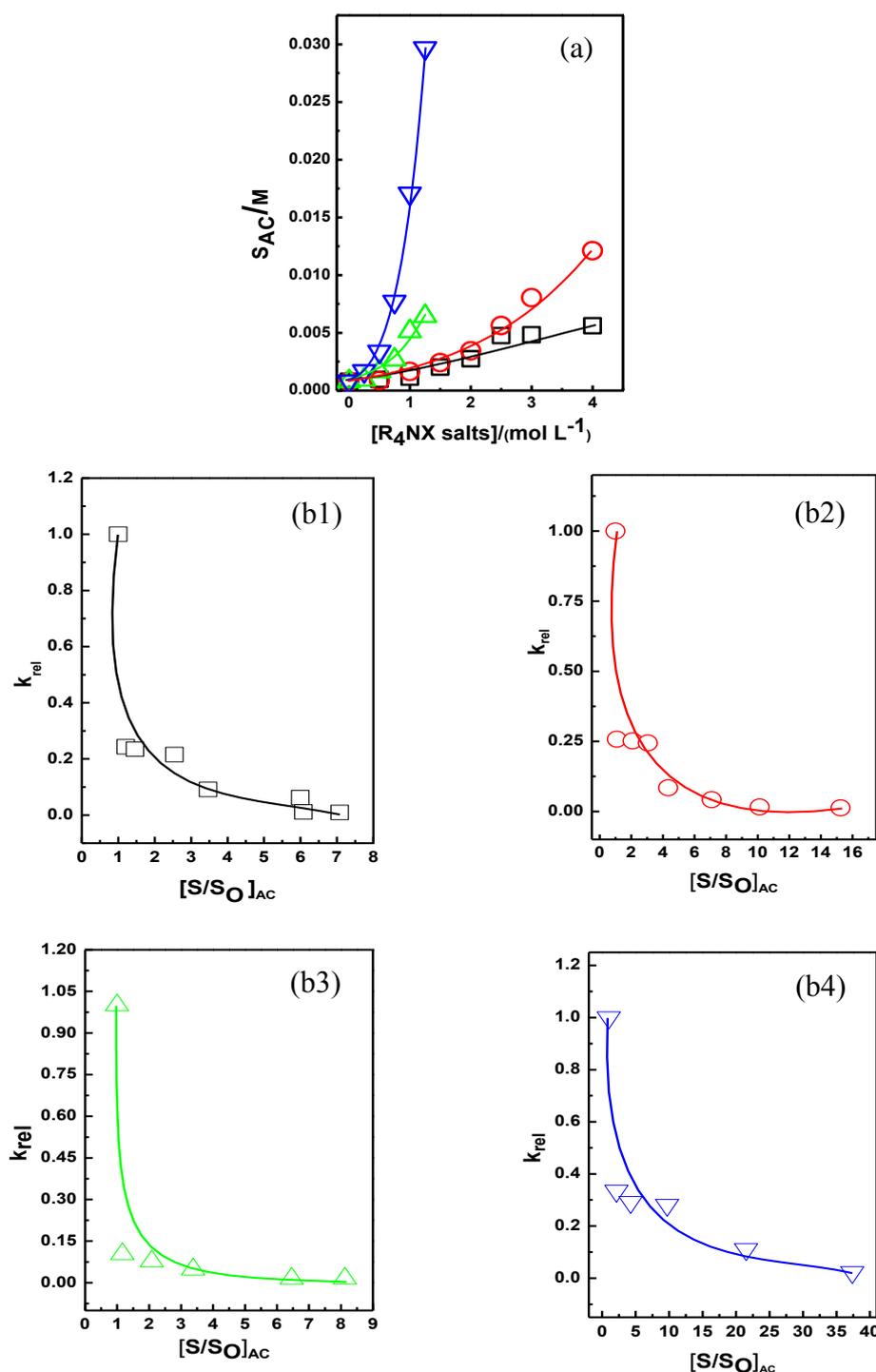
### 5.3.2 A correlation between aqueous R<sub>4</sub>NX concentrations and relative rate constants with solubility of reactant

To justify our proposition regarding the qualitative study of the extent of S/I nature of R<sub>4</sub>NX, solubility experiments of **1**, *i.e.* solubility of anthracene-9-carbinol (S<sub>AC</sub>) in different concentrations of R<sub>4</sub>NX in aqueous condition has been carried out and correlated with  $k_{rel}$  value of reaction.

Solubility experiments of **1** at different concentrations of R<sub>4</sub>NX in aqueous solution have been carried out to examine the role of S/I behaviour on the kinetics of reactions. **Figure 2(a)** indicates the solubility as the function of concentration of tetraalkylammonium salts, in which it has been observed that (CH<sub>3</sub>)<sub>4</sub>NBr and (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr show little increase in the solubility with increasing concentration of salt, *i.e.* the solubility of **1** increases up to 0.005 M in 4 M concentration of (CH<sub>3</sub>)<sub>4</sub>NBr, whereas the solubility of **1** in the case of (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr salt is 0.0121 M in 4 M concentration of salt. On the other hand, the solubility enhances sharply for (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr and (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr, *viz.*, up to 0.006 M and 0.03 M, respectively, for 1.25 M concentration of R<sub>4</sub>NX. A comparison of the solubility trends in (CH<sub>3</sub>)<sub>4</sub>NBr and (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr indicates that the value of solubility of anthracene-9-carbinol, *i.e.* S<sub>AC</sub> shows extremely modest change up to 4 M for (CH<sub>3</sub>)<sub>4</sub>NBr salt. This study indicates the borderline S/I effect of (CH<sub>3</sub>)<sub>4</sub>NBr salt, which was also consistent with its previously reported surface tension behaviour.<sup>21</sup> On the other hand, (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr and (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr show a sharp increase in the solubility up to 0.006 M and 0.03 M, respectively, for a small range of concentration, and this indicates that the solubility of **1** is directly proportional to the concentration of R<sub>4</sub>NX in water. For the prediction of the consequence of solubility on rate,  $k_{rel}$  have been plotted against (S/S<sub>o</sub>)<sub>AC</sub> in aqueous solution. From the plot of  $k_{rel}$  against (S/S<sub>o</sub>)<sub>AC</sub> in **Figure 2(b)**, it can be stated that the value of  $k_{rel}$  for (CH<sub>3</sub>)<sub>4</sub>NBr drops sharply to 7.07 value of (S/S<sub>o</sub>)<sub>AC</sub>; on the other hand, the values of (S/S<sub>o</sub>)<sub>AC</sub> increase sharply up to 15.25 for (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr which was approximately twice as compared to that of (CH<sub>3</sub>)<sub>4</sub>NBr. The value of  $k_{rel}$  for (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr drops sharply to 0.334 and then decrease slowly throughout the measured

region of  $(S/S_o)_{AC}$ . The sudden decrease in values of  $k_{rel}$  is directly proportional to the substantial increment in the solubility of molecule **1**. The  $k_{rel}$  value reaches at 0.0093 for  $(CH_3)_4NBr$ , and this signifies that the solubility determination of **1** in aqueous  $R_4NX$  solution provides imperative evidence about the individual nature of  $R_4NX$  in water. Comparative plots of  $k_{rel}$  versus  $(S/S_o)_{AC}$  in aqueous solution of  $(C_3H_7)_4NBr$  and  $(C_4H_9)_4NBr$  shows that, the extent of increase in solubility is large in the case of  $(C_4H_9)_4NBr$ , *i.e.* 37.37 value of  $(S/S_o)_{AC}$  as compared to  $(C_3H_7)_4NBr$ . This points out that the solubility of **1** plays an important role in understanding the individual S/I behaviour of  $R_4NX$ , which can be determined by comparing the extent of decrease in the  $k_{rel}$  value with respect to  $(S/S_o)_{AC}$ . The correlation between the extents of a decrease in the  $k_{rel}$  values separates the nature of  $(CH_3)_4NBr$  from rest of the salts. From the above observation it is clear that solubility contributes directly to the rate of the reaction and consequently to the S/I nature of the  $R_4NX$ . Our experimental investigations are consistent with the previous observations, in which the  $R_4NX$  salts like  $(CH_3)_4NBr$  and  $(C_2H_5)_4NBr$  show almost no effect on the rates or the solubility of benzene, while  $(C_4H_9)_4NBr$  increases the solubility of benzene and subsequently decreases the rate in water and water-like solvents.<sup>31</sup>

The solubility results obtained in this study are also consistent with previous solubility study of benzene in aqueous solution of  $R_4NX$ . The  $R_4NX$  increase the solubility of benzene in water as well as in ethylene glycol and formamide. This unusual nature was exactly opposite behaviour to all other S/I salts which act as S/O salts in ethylene glycol and formamide.<sup>15(e)</sup>  $R_4NX$  display S/I nature in polar solvents because the sizes of both hydrocarbon and the salt ion are extremely important. The size of the hydrophobe in relation to the size of void will determine the extent of solubility of hydrophobe in the salt solution. More precisely, the explanation of S/I behaviour can be explained by two factors, (i) the structural change in the medium caused by indirect interactions between the hydrophobe and salt and (ii) direct interactions caused by the hydrophobic contacts between ion and hydrophobe. The S/O effect seems to be caused by enhanced cage structure of water in presence of salts, which solvate hydrocarbon chain of the salt cation inside and consequently the solubility of the hydrophobe decreases in the aqueous salt solution.<sup>32</sup> The possibility of the hydrophobe to enter into the cage structure of water is reduced which has been indicated by a decrease in the solubility.



**Figure 2.** (a) The plots of solubility of anthracene-9-carbinol ( $S_{AC}$ ) against the concentration of aqueous solution of  $[R_4NX]$  in  $\text{mol L}^{-1}$ . In this figure, the symbols for individual  $[R_4NX]$  are as follows:  $(CH_3)_4NBr$  ( $\square$ ),  $(C_2H_5)_4NBr$  ( $\circ$ ),  $(C_3H_7)_4NBr$  ( $\triangle$ ) and  $(C_4H_9)_4NBr$  ( $\nabla$ ); (b) The plots of  $k_{rel}$  against  $(S/S_0)_{AC}$  in aqueous solution of (b1)  $(CH_3)_4NBr$  ( $\square$ ), (b2)  $(C_2H_5)_4NBr$  ( $\circ$ ), (b3)  $(C_3H_7)_4NBr$  ( $\triangle$ ) and (b4)  $(C_4H_9)_4NBr$  ( $\nabla$ ).

The interactions between ion and hydrophobic molecule will determine the S/I effect, higher the hydrophobic interactions higher will be the S/I effect.<sup>33</sup>

The Setschenov S/O coefficients ( $k_s$ ) of salts (c/f. **Equation (1)**) play a predominant role in the determination of the contribution of solubility in S/I nature of aqueous R<sub>4</sub>NX. Denaturation of nucleic acid and proteins can be correlated with the extent of solubility of hydrocarbon in aqueous solution of urea, GnCl *etc.*<sup>33</sup> The alteration in the solubility of hydrophobic nonpolar solute **1** in water was determined in the presence of R<sub>4</sub>NX.<sup>6</sup>

The transfer of chemical potential between water and salt solution can be expressed as:

$$\Delta\mu_{solvation} = 2.3 k_s \times RT \quad (2)$$

where,  $k_s$  is the salt's Setschenov S/O coefficient, R is the universal gas constant and T is temperature expressed in °C. Setschenov coefficients having values  $k_s < 0$  for molecules that tends to show S/I behaviour in which it generally dissolved the nonpolar solute.<sup>20,34</sup> The tetraalkylammonium cation shows S/O behaviour for smaller the size and shape of the hydrophobe which can be expressed in terms of their molecular volume.<sup>34</sup> In some cases, the same salt will S/O small hydrophobes (*i.e.* positive  $k_s$ ) but will S/I large hydrophobe. **Table 2** represents the value of  $k_s$  for **1** in aqueous solution of R<sub>4</sub>NX. The  $k_s$  value increases with the increment in molar volume of the salts. The negative trends of  $k_s$  value suggest that all the salts are of S/I in nature. The substantial differences in the  $k_s$  values specify the variation in nature of R<sub>4</sub>NX based upon size of salts (e.g. (CH<sub>3</sub>)<sub>4</sub>NBr shows borderline behaviour in  $k_s$  because of its smaller size and molecular weight). The increase in S/I behaviour might be caused by the two factors, van der Waals dispersive forces<sup>33</sup> and hydrophobic interactions. Because of the presence of aromatic character in **1**, the van der Waals interactions are higher in all the salts in listed in **Table 2**. This S/I nature is also enhanced by the presence of hydroxyl group in the hydrophobe structure of **1**.<sup>35</sup>

The number of ions per unit volume termed as ion density or ion concentration. The typical S/I and S/O nature of salts depend on the ion density of water and salts in the vicinity of the hard sphere of solute.<sup>32</sup> The similar trend of data is evident in our

experimental observations. In our case, the value of solvation free energy, *i.e.*  $\Delta\mu_{\text{solvation}}$  decreases from (CH<sub>3</sub>)<sub>4</sub>NBr to (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr giving the brief indication of increasing S/I effect ranges from (CH<sub>3</sub>)<sub>4</sub>NBr to (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr. Unusual behaviour of (CH<sub>3</sub>)<sub>4</sub>NBr is being highlighted through the trends in the  $k_s$  values and  $\Delta\mu_{\text{solvation}}$  from their higher analogues salt in aqueous solutions.

**Table 2.** Setschenov S/O coefficient  $k_s$  (kg mol<sup>-1</sup>) (molal scale) for anthracene-9-carbinol (**1**) and  $\Delta\mu_{\text{solvation}}$  at 25 °C

Entry no.	Salts	$k_s$	$\Delta\mu_{\text{solvation}}$ (J mol <sup>-1</sup> )
1.	(CH <sub>3</sub> ) <sub>4</sub> NBr	-0.592	-3373
2.	(C <sub>2</sub> H <sub>5</sub> ) <sub>4</sub> NBr	-0.747	-4256
3.	(C <sub>3</sub> H <sub>7</sub> ) <sub>4</sub> NBr	-1.688	-9618
4.	(C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> NBr	-2.971	-16929

According to some authors, S/I nature emerges out of large ion or non ionic molecules (*viz.* urea) break up the ordered structure of water, and thus formation of cavitation become easier.<sup>15</sup> Another opinion regarding the matter, S/I salt can improve the solvation of hydrocarbon which can be seen as the increase in solubility of hydrocarbon in water on addition of R<sub>4</sub>NX which decreases the hydrophobic effect.<sup>34,35</sup> This can be explained by **Equation (3)**, which accounts for the effect on the energy cost of cavitation and energy cost of solvation on S/I effect.

$$\delta (\Delta G^\circ)_{\text{solution}} = \delta (\Delta G^\circ)_{\text{cavitation}} + \delta (\Delta G^\circ)_{\text{solute solvation}} \quad (3)$$

An inquisitive follow up of **Equation (3)** can supply the validation akin to S/I nature of R<sub>4</sub>NX in aqueous media. In the line of Breslow and Guo, it can be stated that because the polarity of Gn<sup>+</sup>, Li<sup>+</sup> and ClO<sub>4</sub><sup>-</sup> is higher than R<sub>4</sub>N<sup>+</sup> cation, Gn<sup>+</sup>, Li<sup>+</sup> and ClO<sub>4</sub><sup>-</sup> decrease the  $(\Delta G^\circ)_{\text{cavitation}}$  when they are dissolved in water.<sup>15(e),21,22</sup> If any S/I agent attempts to make cavity formation easier, it needs to break the structure of water, which ultimately results in lowering the surface tension of the solution. However, the observed surface tension effect was exactly opposite in all the salts except R<sub>4</sub>NX category of salts. The addition of S/I salt like GnCl, LiClO<sub>4</sub> increases the surface tension similar to their S/O counterpart, but the extent of increment is not at per that of S/O salt. Following this observation, it can be justified that when S/I salt

is added to aqueous solution, cavitation in water is not an easier phenomenon. The surface tension of R<sub>4</sub>NX shows contradictory nature with respect to (CH<sub>3</sub>)<sub>4</sub>NBr as well as its higher analogues. The mean slope of the variation of surface tension with respect to concentration of the R<sub>4</sub>NX, *i.e.*  $(\partial\Delta\sigma/\partial c)_T$ , where,  $\Delta\sigma$  represents the difference in surface tension of water with and without salt at concentration (c) is 0.5 for [(CH<sub>3</sub>)<sub>4</sub>NBr] (TMAB), -6.3 for [(C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr] (TEAB), -27 for [(C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr] (TPAB) and -137 for [(C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr] (TBAB), respectively.<sup>21</sup> In the present case, it can be suggested that R<sub>4</sub>NX make water molecules better solvator in which they collaborate in direct manner with hydrocarbon **1**. After addition of R<sub>4</sub>NX to aqueous solution, reactant **1** prefers to bind directly with the salt in comparison with that of water. The substantial rate decrease in the Diels–Alder reaction provides an evidence of the S/I behaviour of R<sub>4</sub>NX. In the context of the present reaction, it can infer that R<sub>4</sub>NX behave like detergent in which they decrease the surface tension of water by solubilizing the **1**. From the above observations, it can be predicted that the solvation factor in **Equation (3)** may be the responsible factor for the S/I behaviour of the R<sub>4</sub>NX in aqueous solution.<sup>31</sup> Because of smaller size of (CH<sub>3</sub>)<sub>4</sub>NBr, it provides less amount of assistance to the incoming **1** molecule in the solvation shell. This behaviour is also supported by the trends observed in  $\Delta\mu_{solvation}$  and  $k_s$  values, which shows that (CH<sub>3</sub>)<sub>4</sub>NBr provides less cohesive environment to the solvation of **1** as compared to that in aqueous solution of (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr, (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr and (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr.

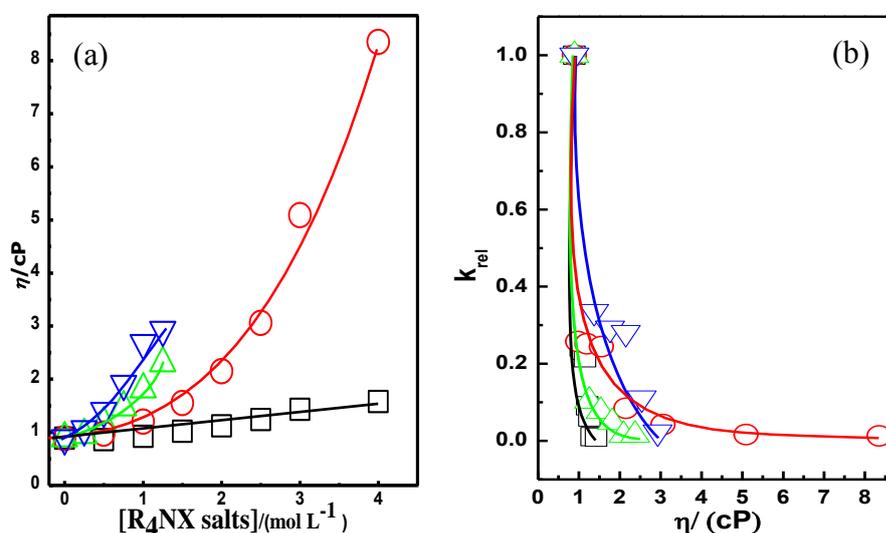
### 5.3.3 Consequences of viscosity of aqueous R<sub>4</sub>NX on relative rates of Diels–Alder reaction

The viscosity of R<sub>4</sub>NX in aqueous media influences the individual S/I nature. The viscosity of reaction medium restricts the movement of reactants directly and influences the solubility of the hydrophobe in aqueous media as well as the kinetics of the reaction.<sup>35</sup> The determination of viscosity of aqueous solutions of R<sub>4</sub>NX can impart quantitative picture of S/I nature of these salts.

To study the impact of viscosity on S/I effect, the viscosities at different concentrations of R<sub>4</sub>NX have been determined and correlated with relative rate constants,  $k_{rel}$  of Diels–Alder reaction in aqueous solutions. From the plot of  $\eta$  against the concentrations of R<sub>4</sub>NX [**Figure 3(a)**], while comparing the behaviour of two

salts, *i.e.* (CH<sub>3</sub>)<sub>4</sub>NBr and (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr, the viscosity values remain almost constant up to 4 M for (CH<sub>3</sub>)<sub>4</sub>NBr; however it raises sharply to 8.5 cP at 4 M concentration of (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr. A similar rise in the viscosity of (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr and (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr salts has been observed upto 1.25 M concentration of salt in water. To estimate the effect of viscosity on the rate profile and S/I nature of salts,  $k_{rel}$  values and viscosities ( $\eta$ /cP) of R<sub>4</sub>NX at their different concentrations has been correlated. This study leaves an impression of two different behaviours of these salts at same concentrations. From the plots of  $k_{rel}$  as a function of viscosity  $\eta$  in aqueous solutions, it is interesting to note here that the  $k_{rel}$  value in each case of R<sub>4</sub>NX salt falls with an increase in viscosity. In the first case, the  $k_{rel}$  values decrease very sharply from 1 to 0.0093 in aqueous solution of (CH<sub>3</sub>)<sub>4</sub>NBr followed by a variation in the viscosity from 0.89 to 1.42 cP [see **Figure 3(b)**]. Observed decrease in  $\eta$  values for small region of rate constant indicates that Diels–Alder reaction between **1** and **2** is comparably faster in (CH<sub>3</sub>)<sub>4</sub>NBr, *i.e.* effect of viscosity is very modest in this salt solution. On the other hand the increase in viscosity was large in aqueous (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr which ranges from 0.89 to 8.35 cP. For this salt, this sharp increase in viscosity and subsequent effect on  $k_{rel}$  values which decreases from 1 to 0.0128 are being observed. For aqueous (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr the viscosity increases sharply from 0.83 to 2.3 cP for very small variation in the concentrations of the salts, *i.e.* from pure water to 1.25 M; consequently  $k_{rel}$  values decrease from **1** to 0.0152, which signifies sluggish reaction in high viscous reaction media. Among all the above three salts, the rate was slowest in (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr, and it ranges from **1** to 0.0225, in which variation in viscosity ranges from 0.89 to 2.9 cP only upto presence of 1.25 M (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr in water. The fall in the  $k_{rel}$  values specifies that the rates of reaction have been highly influenced by most pronounced S/I behaviour of (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr. This viscosity and rate correlation of bimolecular reaction gives a comparative thought of both the parameters influencing the course of the reaction through transition state. The complete microscopic behaviour of the R<sub>4</sub>NX in water can be analysed by using Jones–Dole equation. Rate of the reaction can also be correlated with the Jones–Dole viscosity  $B$  coefficient.<sup>7(a),36-39</sup> The values of  $B$  coefficient for (CH<sub>3</sub>)<sub>4</sub>NBr, (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr, (C<sub>3</sub>H<sub>7</sub>)<sub>4</sub>NBr and (C<sub>4</sub>H<sub>9</sub>)<sub>4</sub>NBr are +0.101 dm<sup>3</sup>mol<sup>-1</sup>, +0.343 dm<sup>3</sup>mol<sup>-1</sup>, +1.085 dm<sup>3</sup>mol<sup>-1</sup> and +1.354 dm<sup>3</sup>mol<sup>-1</sup>, respectively.<sup>36</sup> The magnitude of  $B$  coefficient for the bromide ion and tetraalkylammonium ions as -0.042, +0.1434, +0.385, +1.092 and +1.396 dm<sup>3</sup>mol<sup>-1</sup> has been also determined at 25 ± 0.1°C.<sup>40</sup>

According to the theory, the absolute reaction rate is largely influenced by the viscosity of the reaction media which was mainly useful for determining activation energy and entropy of viscous flow.<sup>41</sup> From the available data in the literature,<sup>39,42</sup> energy and entropies of activation for viscous flow for tetraalkylammonium cation can be calculated. The positive trend in the activation energy value suggests that tetraalkylammonium cation except  $(CH_3)_4N^+$  cation increase the viscosity because of the presence of large structure ion. This enhancement in the viscosity of aqueous solution of higher analogues of  $R_4NX$  is because of ice-like structure formation which was referred as *apo-surface*. Ions for which the force field is not sufficient enough to organize water molecules at or around the ionic surface are said to be *hydrated apo-surface*. In the case of  $(CH_3)_4N^+$  cation, negative activation energy indicates weak *peri-surface hydration*.<sup>43</sup> Ions for which the force field is of sufficient to organize water molecules at the ionic surface are said to be *hydrated peri-surface*. The weak structure making ability of  $(CH_3)_4N^+$  cation is evident from the weak orientation of water about the large ion which participates more readily in the fluctuation of the water structure.<sup>36,39</sup> The  $B$  coefficients were interrelated to the ion size and their respective consequence on the structure of solvent.<sup>39,44,45</sup>



**Figure 3** (a) The plots of  $\eta$  against concentration of  $R_4NX$ ; (b) The plots of  $k_{rel}$  as a function of viscosity  $\eta$  in aqueous solutions of  $(CH_3)_4NBr$  ( $\square$ ),  $(C_2H_5)_4NBr$  ( $\circ$ ),  $(C_3H_7)_4NBr$  ( $\triangle$ ) and  $(C_4H_9)_4NBr$  ( $\nabla$ ).

The variation in the S/I nature of  $R_4NX$  can be predicted by calculating the size of hydrophobe which inserted in the salt solution. Recent molecular dynamics and

simulation studies for aqueous  $R_4NX$  signify the results according to the hydrophobe size.<sup>30</sup> The small ions cause S/O effect because of the exclusion of hydrophobes from the first hydration shell of ion; on the other hand bigger ions fail to do so.<sup>46,47</sup> Zhang and Cremer found that the Hofmeister effect was caused by the presence of the salt which produced change in the hydration of water structure.<sup>47</sup> The  $R_4NX$  show this unusual behaviour when hydrophobic solute was added to its solution. Hydrophobic effects and ion solubility in water have been previously explained by NPT Monte Carlo simulations of the Mercedes-Benz (MB) + dipole model of water.<sup>32,46</sup> In this study they proposed that  $(CH_3)_4N^+$  cation provides enhanced access by a first shell of water where the dipole of water electrostatically interacts with  $(CH_3)_4N^+$  cation. Herein first water shell will help in setting up a second solvation shell which designed itself to act as receptacle to bind with the nonpolar solute. By doing this nonpolar solute actually interacts more with  $(CH_3)_4N^+$  cation rather than other hydrophobe which leads to increase in the solubility and the S/I effect of the salt.

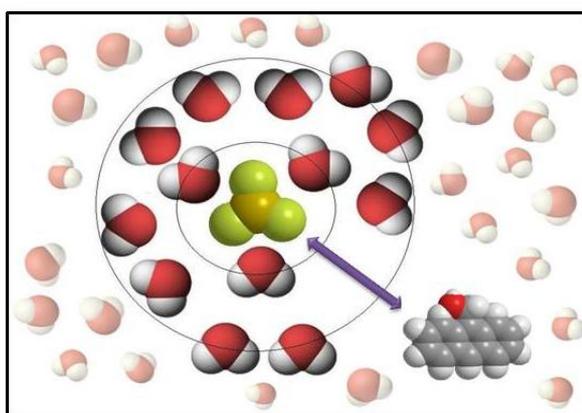
The correlation of our experimental observations with the conclusions obtained through receptacle model study provides the information regarding microscopic and structural interpretation of  $(CH_3)_4N^+$  cation and **1** interaction in water.<sup>34(b),45</sup> It has to be pointed out here that S/I behaviour can be correlated with the hydrophobic hydration in electrolyte solutions versus the hydration in pure water. According to this proposition, the ions having low charge density are loosely hydrated to form first solvation shell of water dipolar molecule. Additionally, it would also help to create second solvation shell through which the hydrophobic molecules can directly come across the ion to solvate the hydrophobic molecules.<sup>30,48</sup>

These interactions require an opening of a solute-size cavity in the first solvation shell of  $(CH_3)_4N^+$  cation which is opposed because of high entropic cost in the case of kosmotropes. However, the process is entropy driven in the chaotropes, because S/I process is reinforced by favourable solute–solvent energy change. NPT Monte Carlo simulations of Mercedes-Benz along with dipole model of water appropriately predicts the S/I behaviour of  $(CH_3)_4N^+$  cation. According to this model, the free energy transfer of hydrophobic solutes having different size can be calculated by Widom method.<sup>46,48</sup> The value of  $\Delta\Delta G$  (the difference in free energy transfer into solution vs. pure water) is reduced with the size of hydrophobe and the value of

Setschenov S/O coefficient  $k_s$ , therefore provides the correlation of  $k_s$  with the size of nonpolar solute for S/I and S/O salts.<sup>23,24,34</sup> The size of reactant **1** is larger than that of benzene molecule; therefore, by simple correlation with molecular size of reactant **1** the S/I nature of  $R_4NX$  can be estimated.

**Figure 4** shows that there is maximum probability of water molecule near the central  $(CH_3)_4N^+$  cation and the density of water molecule between the wedges of the  $(CH_3)_4N^+$  cation is highest. The above observation is also consistent with the findings obtained by molecular dynamic study of practical models as well as experimental data.<sup>21(b),49,50</sup> The special arrangement of water molecules around the  $(CH_3)_4N^+$  cation shows that these water molecules preferentially occupy the space between  $(CH_3)_4N^+$  cation and conventional hydrophobic cage like water. The angular distribution of the water molecule around the ion is caused by the electrostatic effect of water molecule.

The water molecules in the structure arrange respective positive end of their dipole away from the ion. It is known to us that  $(CH_3)_4N^+$  cation has large size and low charge density on the external side; so for accommodating this effect, water molecules in the first solvation shell arrange themselves in wedges so that the possibility of approach to the central nitrogen ion should be maximum. This will also encourage the water–water inter hydrogen bonding around  $(CH_3)_4N^+$  cation which organizes the water molecules in its first and second solvation shells.<sup>49-52</sup>



**Figure 4.** A diagram showing solvation of nonpolar solute *i.e.* anthracene-9-carbinol (**1**) supported by cavitation (inspired from the obtained results).

Here,  $(CH_3)_4N^+$  cation acts as high charge density ion for first shell water molecule which can act as strongly ordered ion like lithium ion  $+ 0.48 k_B T$ .<sup>46</sup> These observations were also supported by the  $B$  values obtained from Jones–Dole equation. For  $Li^+$ ,  $B$ -coefficient is  $+ 0.146 \text{ dm}^3 \text{ mol}^{-1}$ , and  $(CH_3)_4N^+$  cation the value is  $+ 0.123 \text{ dm}^3 \text{ mol}^{-1}$ .<sup>53</sup> Positive value of the  $B$ -coefficient is indicative of typical kosmotrope ion.<sup>46</sup> For second solvation shell, the arrangement of water molecule was typical cage like which is mainly because of two factors: (i) influence of first solvation shell of water and (ii) hydrophobic effect arises from methyl group on the  $(CH_3)_4N^+$  cation.

The S/I behaviour of  $(CH_3)_4N^+$  cation can be investigated by the extent of potential force between ion and the molecule **1** which is similar to the observations obtained in NPT Monte Carlo simulations of the Mercedes-Benz (MB) + dipole model of water. The increase in the opening in second solvation shell cavity indicates highest probability of appearance of **1**. The main utility of  $(CH_3)_4N^+$  cation was to facilitate water molecules to arrange them in cage like structure in second solvation shell, which was responsible for creating opening for the insertion of hydrophobic molecule like **1**. Because of strong electrostatic ordering of first solvation shell of water around  $(CH_3)_4N^+$  ion, first solvation shell arranges second solvation shell water in prestructured water arrangement and this arrangement now can act as receptacle that can bind tightly to hydrophobe, *i.e.* **1**. Hydrophobic molecule demonstrate S/I effect only when it loses hydration to the ion and due this effect the hydrophobe like **1** will prefer to be near in the shell near nitrogen molecule of ion.<sup>31(b),45</sup> These theoretical observations consistent with our experimental findings were solubility of **1** increases with the concentration of  $R_4NX$  [**Figure 2 (a)**].

Our data can be correlated with the recent observations that the rate of the reaction between cyclopentadiene and methyl acrylate decreases upon addition of ammonium-water.<sup>5(d)</sup> Though the reason of decrease in this case has not been described as S/I effect, the plausible explanation is that the addition of ammonium ion with increasing concentration progressively replaces water from the oil/water interface, and consequently the influence of water in terms of hydrophobic interactions and hydrogen bonding decreases has been presented.

The  $k_s$  values of salt's Setschenov S/O coefficient and  $\Delta\mu_{solvation}$  values along with kinetic study indicate S/I behaviour of all quaternary ammonium halide salts, but their individual behaviour was separated by  $B$  coefficient values with respect to the concentrations of salts. The solubility behaviour and viscosity study clearly reveal the borderline behaviour of  $(CH_3)_4NBr$  salt.

The activation parameters for  $(CH_3)_4NBr$  and  $(C_2H_5)_4NBr$  have been calculated by Arrhenius equation. The activation energy  $E_a^\ddagger$  for  $(CH_3)_4NBr$  was  $22.20 \text{ kJ mol}^{-1}$ , while on the other hand the activation energy for  $(C_2H_5)_4NBr$  was  $58.35 \text{ kJ mol}^{-1}$ . This clearly indicates the sensitivity of the activation parameters over the size of the molecule. The results associated with the activation parameter separate the individual behaviour  $(CH_3)_4NBr$  and  $(C_2H_5)_4NBr$  from each other. Addition of only four extra methyl group (because four ethyl groups replace four methyl groups in  $(C_2H_5)_4NBr$ ) causes the retardation of the rate of the reaction increasing the activation energy barrier by  $36.15 \text{ kJ mol}^{-1}$ . Moreover in the introduction the function of a S/I salt has been already elaborately discussed, *i.e.* it breaks the co-operative hydrogen bonding among water molecules and the process intensifies with the presence of higher hydrophobic groups, *i.e.* in our case alkyl groups in the salt. The same process is obvious from the activation parameter data described in **Table 3**.

**Table 3:** Activation parameters of the reaction (**Scheme 1**) for the presence of aqueous  $(CH_3)_4NBr$  and  $(C_2H_5)_4NBr$ .

Entry no.	Salts	$E_a^\ddagger / \text{kJ mol}^{-1}$	$\Delta^\ddagger H / \text{kJ mol}^{-1}$	$\Delta^\ddagger S \text{ J mol}^{-1} \text{ K}^{-1}$
1.	$(CH_3)_4NBr$	22.19	19.63	-226.99
2.	$(C_2H_5)_4NBr$	58.35	55.81	-106.34

Comparison of activation enthalpy values of  $(CH_3)_4NBr$  and  $(C_2H_5)_4NBr$  justifies that upon increasing the alkyl chain length, the endo-thermic nature of salt increases and it implies that the tendency of bond breaking by the  $R_4NX$  increases on moving from  $(CH_3)_4NBr$  to  $(C_2H_5)_4NBr$ . Upon addition of the ethyl substituted tetraalkyl salts,

higher number of hydrogen bonds among water molecules is ruptured and favours more dissolution of the apolar reactants, which in turn diminishes the hydrophobic interactions. This phenomenon of bond breaking which increases more free water molecules can also be substantiated by increase in activation entropy by almost 120 J mol<sup>-1</sup> K<sup>-1</sup>. Any change in temperature will alter both the H-bonding ability and the viscosity of all R<sub>4</sub>NX in aqueous condition.

The study illustrates the interrelation among thermodynamic as well as kinetic parameters with molecular nature of solvation of R<sub>4</sub>NX in water while performing Diels–Alder reaction *in situ*.

## 5.4 Conclusions

The rate studies for R<sub>4</sub>NX provide the information about the unusual S/I behaviour of (CH<sub>3</sub>)<sub>4</sub>NBr which shows slightly different behaviour from rest of the salts. This unusual behaviour has been explained by experimentally estimated Setschenov S/O coefficient ( $k_s$ ) values, viscosity  $B$  coefficient and finally by comparing the activation energy values for (CH<sub>3</sub>)<sub>4</sub>NBr and (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr. An unambiguous difference in the  $E_a^\ddagger$  values obtained during the presence of (CH<sub>3</sub>)<sub>4</sub>NBr and (C<sub>2</sub>H<sub>5</sub>)<sub>4</sub>NBr in reaction medium, *i.e.* water indicates the difference in the S/I behaviour of these two salts in aqueous media. The S/I and S/O nature of the salt can be correlated with the physico-organic parameters which show the correlation with size of the salts.

The viscosity correlation with the rate of reaction and solubility of **1** at different salt concentrations provides support to the rate profiles.  $\Delta\mu_{solvation}$  and solubility determination offer structural perspective of reactant molecule and salts. The extreme viscosity decrease in smaller section of relative rate constant indicates that Diels–Alder reaction of **1** with **2** is comparably faster in (CH<sub>3</sub>)<sub>4</sub>NBr, *i.e.* effect of viscosity and solubility was modest in this salt solution. The individual characteristics of all R<sub>4</sub>NX in aqueous solution have been investigated in this study.

The solvation of the reactants at molecular level in the presence of R<sub>4</sub>NX in water plays a vital role in directing the nature as well as the extent of salting effect. On the basis of our experimental data, it can be emphatically conclude that the presence of long alkyl groups in R<sub>4</sub>NX felicitates the higher dissolution of the non-polar reactants

by rearranging water molecules upto second solvation shell around the dissolved salts. The present study will encourage the future researchers to investigate the molecular insight of 'salting-in' effect of large salts from the new perspective.

## 5.5 References

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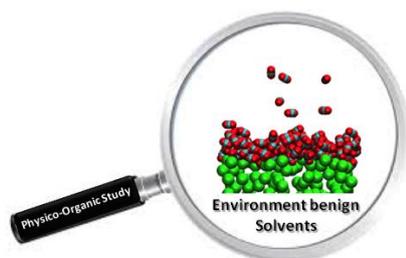
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# Chapter 6

## Conclusions



*In the last chapter of the thesis, the experimental work described in the previous chapters has been briefly evaluated. The chapter principally includes significant observations incorporated by the kinetic studies on C-C bond formation reactions. Furthermore, one of the most significant themes of the thesis is the evolution of different environment benign media through kinetic and physico-organic investigations in Diels-Alder reactions.*

In summary, the solvent effects of DESs, aqueous binary mixtures of DESs, nature-inspired supersaturated, aqueous tetraalkylammonium halide salts on simple organic reactions have been investigated in the present work. The selection of the above mentioned solvent systems was made on the basis of their economic and environmental viability. The salient features of these investigations are:

1. detailed kinetic and spectroscopic analysis of C-C bond formation reaction has been carried out in different DESs mixtures as 'green hybrid solvents' using reline-water, ethylene-water and glyceline-water mixtures. The formation of DESs from different salts and hydrogen bond donors has been described in greater details. Kinetic and viscosity study of green hybrid solvents reveal the different individual behaviour of reline-water mixture from rest of the DESs water mixtures. Kamlet-Taft polarity parameter studies suggest that high concentration of DESs in water decreases the polarity of overall mixture. Therefore, the rate constant values decrease linearly with the polarity of solvent mixtures. Substantial decrease in the  $\alpha$  values with increasing reline concentration in water provides clue about the interstitial hydrogen bonding in water-reline mixture. A high negative  $G(C)$  parameter, indicating pairwise interactions of water-ethaline and water-glyceline mixtures indicate the greater stabilization of the reactant state in comparison to transition state through solvation process in highly aqueous region. Again, the polarity and FTIR spectroscopy studies specify that the interspecies hydrogen bonding is a dominant factor in water-ethaline and water-glyceline mixtures. Temperature dependent and NOSEY study for water-reline mixtures also confirms the above findings,

2. effect of an H-bonding counterpart in CESs composition through kinetic study has been investigated. Experimental findings suggest that high viscosity and polarity of CESs emerges as a detrimental factor behind the alteration of rate of the Diels-Alder reaction,

3. Nature-inspired supersaturated solvent has been investigated through physico-organic study. Rate constants observed for Diels-Alder reaction in this Nature inspired supersaturated solvent obtained to be much higher as compared to other molecular solvents. According to experimental observations, the viscosity of this nature-inspired supersaturated solvent has the amplitudes of  $10^3$  cP. Kinetic results for Diels-Alder reaction suggest that high viscosity of nature inspired supersaturated solvent facilitate

the reaction profile through the stabilisation of transition state of reaction. Again, polarity and temperature dependent studies show that enhanced availability of –OH group and structural advancement in supersaturated condition prove to be responsible factors behind the enhanced rate of reactions and,

4. the kinetic studies of water promoted C-C bond formation reactions are based on the concept of hydrophobicity. In order to study the salt effect in water and water like solvents, prohydrophobic salts ( $R_4NX$ ,  $LiClO_4$  *etc.*) and antihydrophobic salts ( $LiCl$ ,  $KCl$  *etc.*) are used to delineate the role of hydrophobic hydration in the water promoted reactions. In the present study, the ideal behaviour of  $R_4NX$  salts in water has been examined, which will aid to comprehend the reason behind S/I nature of  $R_4NX$  salts in water and water like solvents. Kinetic study of Diels-Alder reaction in aqueous  $R_4NX$  solution reveals that  $(CH_3)_4NBr$  salt shows less S/I effect as compared to the rest of  $R_4NX$  salts. Viscosity and solubility studies confirm the diverse individual S/I effect of  $R_4NX$  salts. The viscosity correlation with the rate constants and solubility of reactants at different salt concentrations provides support to the rate profiles. Experimental results suggest that the solvation of the reactants in the bimolecular reaction at the molecular level in the presence of  $R_4NX$  in water plays a key role in directing the S/I nature of the salts.

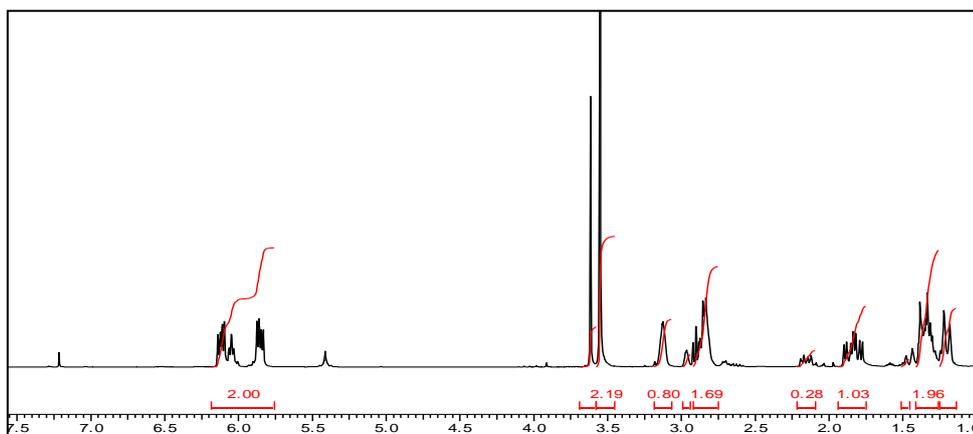
The methodical investigations of solvent effects offer twin advantages of expansion of the fundamental understanding of the subject and assuring better ‘solution’ for practical applications in near future.

## Appendix

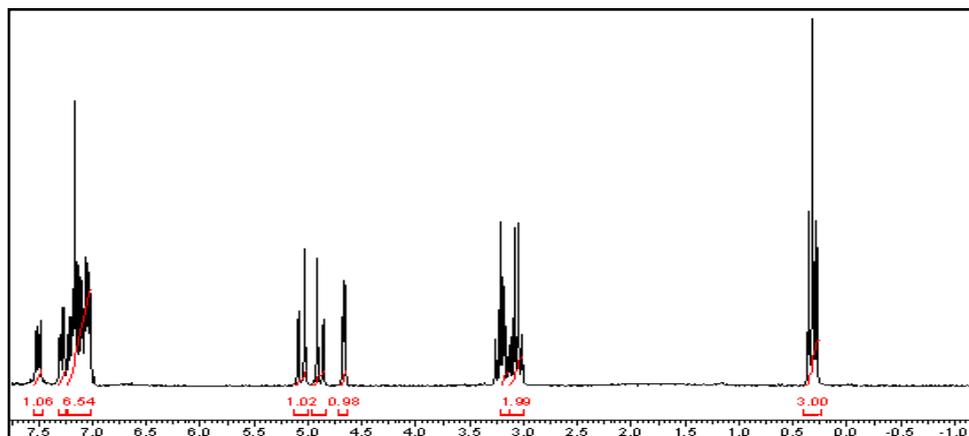
### A. NMR spectra and GC data

#### 1. NMR Spectra.

1.1 The NMR spectra of the product of the reaction of cyclopentadiene with methyl acrylate: Methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 1.22 (d, 1H), 1.39 (m, 2H), 1.67 (m, 1H), 2.78 (m, 2H), 3.14 (s, 1H), 3.57 (s, 3H), 5.97 (bs, 2H).

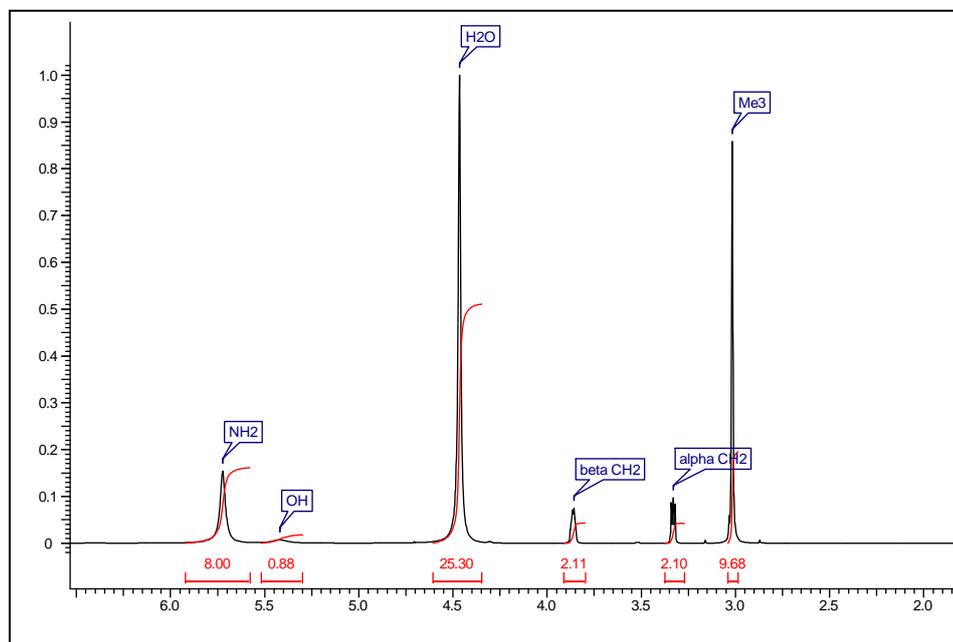


1.2 The NMR spectra of the product of Anthracene-9-carbinol (**4**) with *N*-ethyl maleimide (**5**): adduct (**6**)  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.61 (d, 1H), 7.39 (d, 1H), 7.11–7.33 (m, 6H), 5.16 (d, 1H), 4.98 (d, 1H), 4.77 (d, 1H), 3.34 (m, 1H), 3.17 (q, 2H), 0.41 (t, 3H).

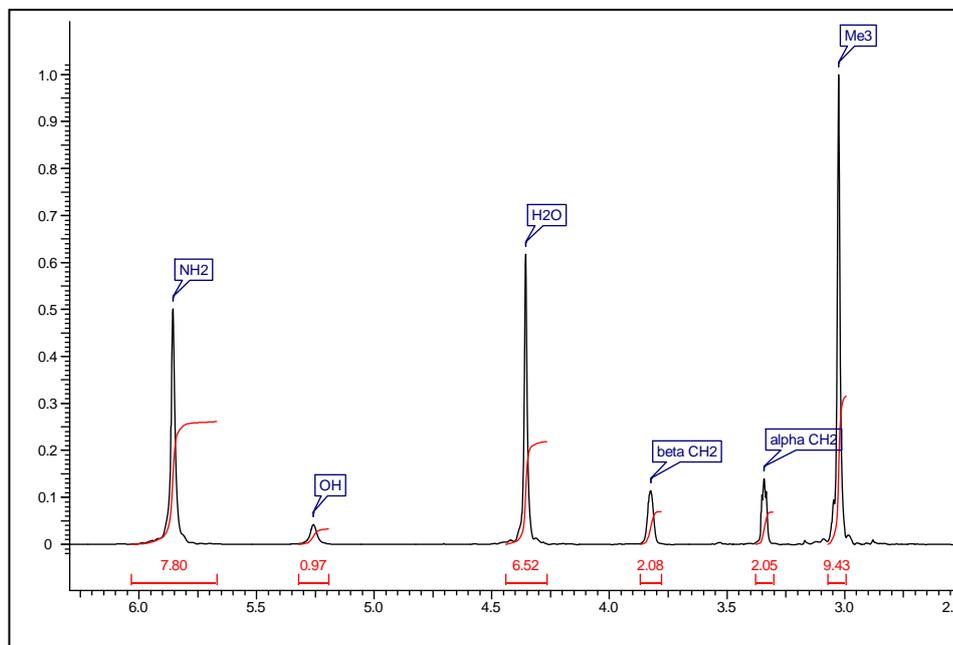


### 1.3 Spectroscopic Information of Reline (1:2).

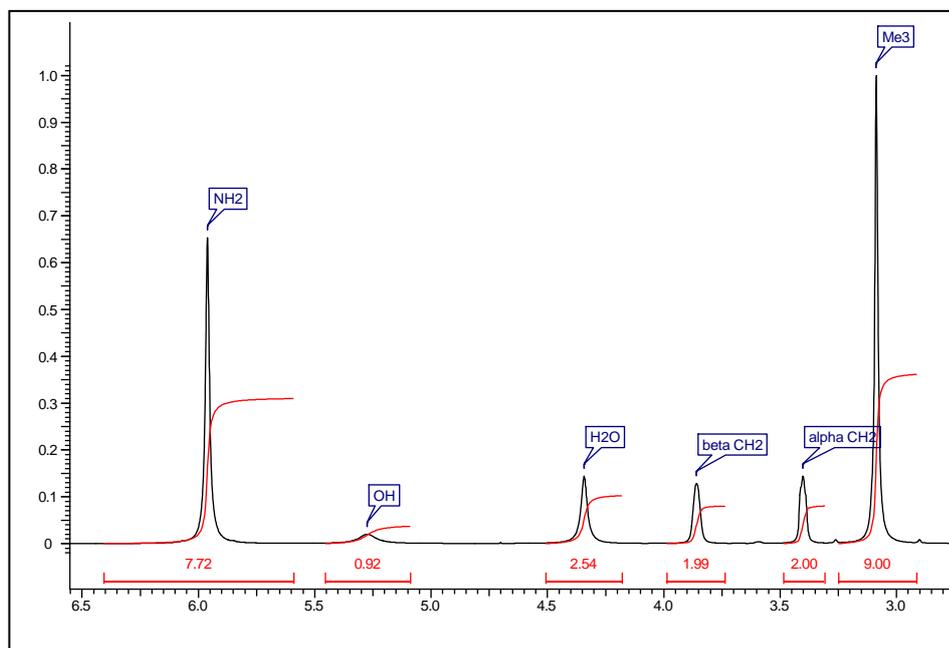
1.3.1 0.1 Mole fraction DES in H<sub>2</sub>O NMR D<sub>2</sub>O Capillary, 500 MHz, 25 °C temperature.



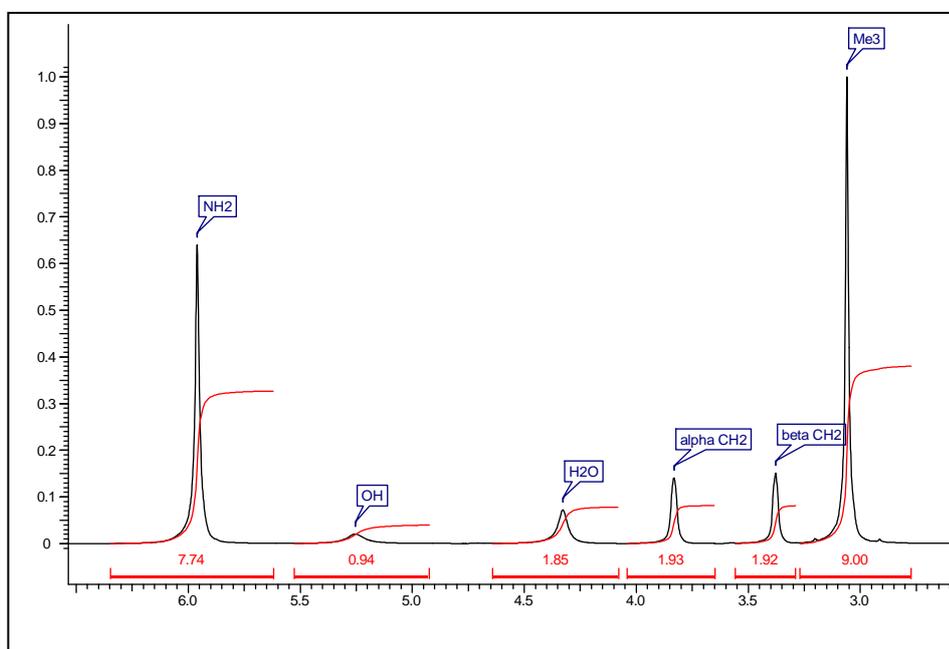
1.3.2 0.3 Mole fraction DES in H<sub>2</sub>O NMR D<sub>2</sub>O Capillary, 500 MHz, 25 °C temperature.



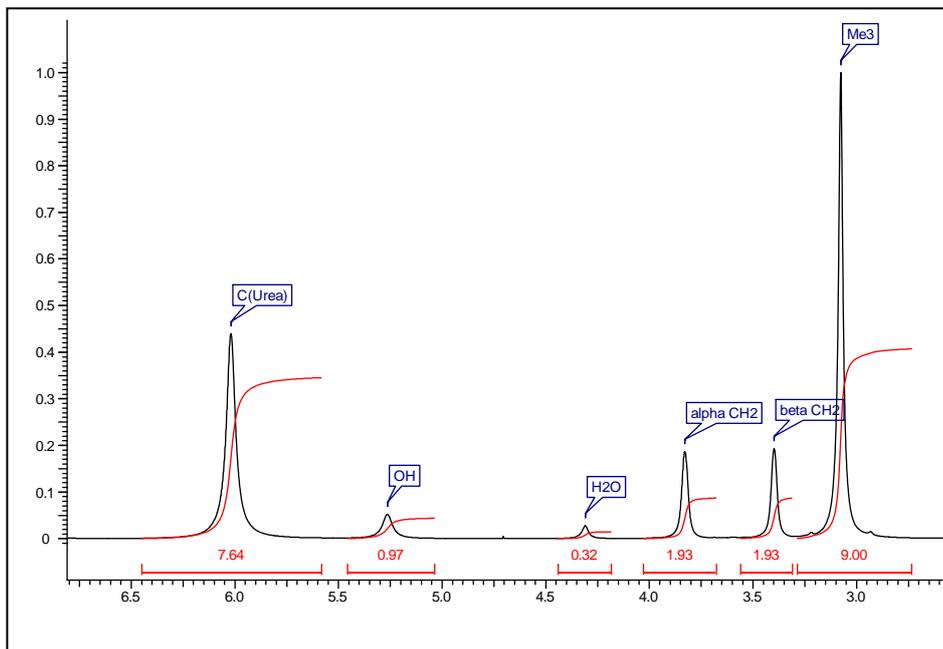
1.3.3 0.5 Mole fraction DES in H<sub>2</sub>O NMR D<sub>2</sub>O Capillary, 500 MHz, 25 °C temperature.



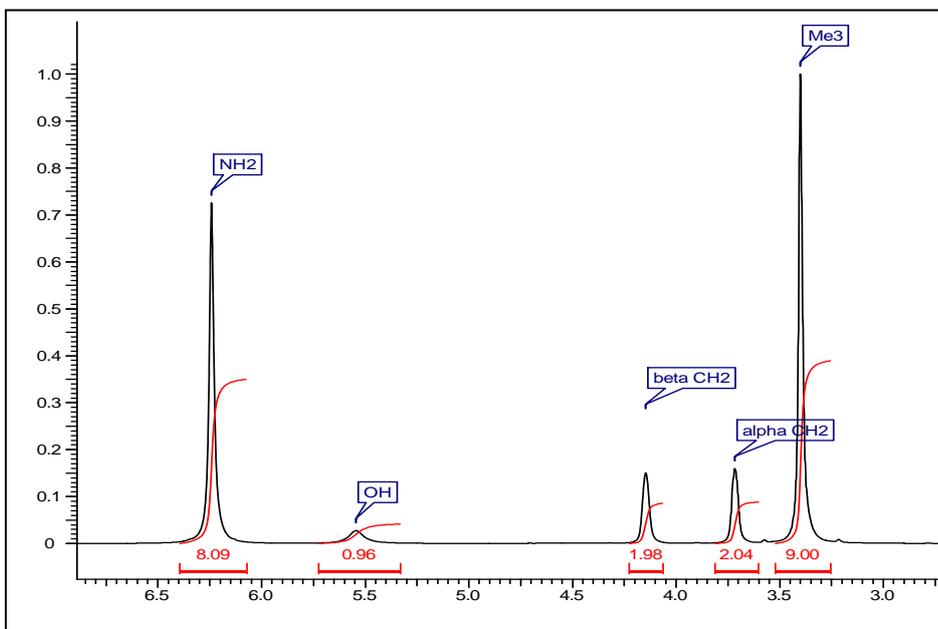
1.3.4 0.7 Mole fraction DES in H<sub>2</sub>O NMR D<sub>2</sub>O Capillary, 500 MHz, 25 °C temperature.



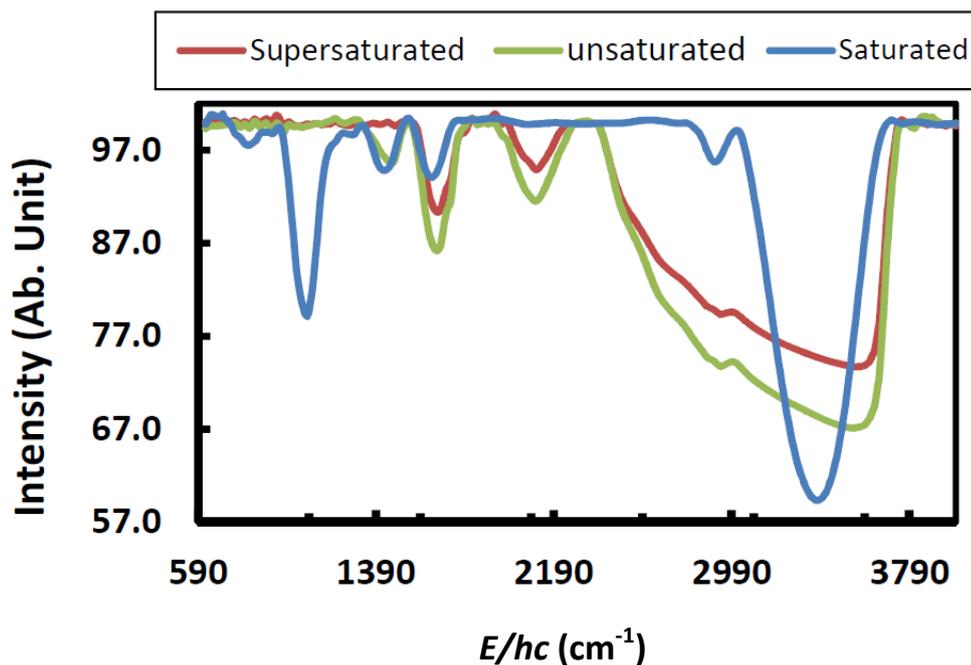
1.3.5 0.9 Mole fraction DES in H<sub>2</sub>O NMR D<sub>2</sub>O Capillary, 500 MHz, 25 °C temperature.



1.3.6 Reline <sup>1</sup>H NMR D<sub>2</sub>O Capillary, 500 MHz, 25 °C temperature : Me<sub>3</sub>, 9H, s, 3.42; α-CH<sub>2</sub>, 2H, m, 3.73; β-CH<sub>2</sub>, 2H, m, 4.18; OH, 1H, v. broad, 5.50; NH<sub>2</sub>, 8H, broad, 6.24.



## 1.4 Superimposed FTIR spectra.



**Figure 1.** Transmittance vs.  $E/hc$  ( $\text{cm}^{-1}$ ) plots of the aqueous solution of fructose.

### 2. The detail GC method:

i) The following parameters were set for a typical kinetic analysis for the product: Methyl bicycle [2.2.1] hept-5-ene-2-carboxylate (**3**) formation during the kinetic analysis of Diels-Alder reaction between cyclopentadiene (**1**) with methyl acrylate (**2**).

Column make: CP SIL 5CB

Column length: 15m

Internal diameter: 0.25 mm

Film thickness: 0.25-micron

Flow rate: 0.8 ml/min of nitrogen

Injector temperature: 200 °C

Detector temperature: 250 °C.

Total run time 18.51 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 °C for 5 min.)

Internal Standard (IS): Chlorobenzene

Typical Retention Times of the compounds analyzed:

Compound Retention time (min)

Compound	Time (min)
IS	3.48
3(a)	15.95
3(b)	16.02

ii) The following parameters were set for a typical kinetic analysis for the product of adduct (**6**) formation during the kinetic analysis of Diels-Alder reaction between Anthracene-9-carbinol (**4**) with *N*-ethyl maleimide (**5**).

Column make: CP SIL 5CB

Column length: 15m

Internal diameter: 0.25 mm

Film thickness: 0.25-micron

Flow rate: 0.8 ml/min of nitrogen

Injector temperature: 200 °C

Detector temperature: 280 °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 55 °C and then maintain at 180 °C for 5 min.)

Compound	Time (min)
IS	2.56
4	14.73

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

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## Appendix

### B. List of publications:

1. “Eutectic mixture-directed kinetics of Diels-Alder reaction” Amit S. Nagare, Anil Kumar, *Indian J. Chem.*, **2011**, 50A, 788-792.
2. “The water-promoted Diels-Alder reaction in quaternary ammonium salts” Amit S. Nagare, Arpan Manna, Pramod D. Sonawane, Anil Kumar, *J. Phys.Org.Chem.*, **2015**, 28, 665–673.
3. “Spectacular Rate Enhancement of Diels-Alder Reactions in High Viscous Supersaturated Solvent: An Unusual Observation”, Amit Nagare, Arpan Manna, Anil Kumar, *J. Phys.Org.Chem.*, *Manuscript under review*.
4. “Can a Diels-Alder Reaction Accelerate in a Supersaturated Solvent at Room Temperature ?” Amit Nagare, Arpan Manna, Anil Kumar, *New J. Chem.*, *Manuscript under preparation*.
5. “Physico-Organic Insights of Deep Eutectic Solvents” Amit Nagare, Arpan Manna, Anil Kumar, *Manuscript under preparation*.

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## Appendix

### C. Posters Presentations:

1. Participated in a conference on “Green Chemistry” organized by Society of Chemical Industry (SCI) and Pesticides Manufacturers and Formulators Association of India (PMFAI) at Mumbai on 15<sup>th</sup> April 2009.
2. Participated in a conference on “Catalysis for Sustainable Energy and Chemicals” organized by CSIR-National Chemical Laboratory, Pune from 18<sup>th</sup>-21<sup>th</sup> January 2009.
3. Poster presented at a conference on “Discussion Meeting on Chemical Reactions in Unusual Media” organized by CSIR-National Chemical Laboratory, Pune from 8<sup>th</sup>-9<sup>th</sup> January 2009 as a part of NCL Diamond Jubilee celebrations.
4. Participated in “11<sup>th</sup> CRSI National Symposium in Chemistry” organized by CSIR-National Chemical Laboratory, Pune from 6<sup>th</sup>-8<sup>th</sup> February 2009.
5. Poster presented at “12<sup>th</sup> CRSI National Symposium in Chemistry and 4<sup>th</sup> CRSI-RSC Symposium in Chemistry” organized by IICT and NIPER Hyderabad from 4<sup>th</sup>-7<sup>th</sup> February 2010.

6. Poster presented at “13<sup>th</sup> CRSI National Symposium in Chemistry” organized by NISER and KIIT University, Bhubaneswar, from 4<sup>th</sup>-6<sup>th</sup> February 2011.
7. Won best poster award for poster presented at “Annual Divisional Symposium-Physical and Materials Chemistry” Division organized by CSIR-National Chemical Laboratory, Pune from 13<sup>th</sup> December 2011.
8. Poster presented at “National Science Day and IYC-2011” organized by CSIR-National Chemical Laboratory, Pune from 24<sup>th</sup>-25<sup>th</sup> February 2011.
9. Poster presented at “National Science Day” celebration event organized by CSIR-National Chemical Laboratory, Pune from 27<sup>th</sup>-28<sup>th</sup> February 2012.
10. Poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 26<sup>th</sup>-27<sup>th</sup> February 2013.
11. Poster presented at “16<sup>th</sup> CRSI National Symposium in Chemistry” organized by IIT Mumbai, from 7<sup>th</sup>-9<sup>th</sup> February 2014.
12. Poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 25<sup>th</sup>-26<sup>th</sup> February 2014.
13. Poster presented at “17<sup>th</sup> CRSI National Symposium in Chemistry” organized by CSIR-National Chemical Laboratory, Pune from 6<sup>th</sup>-8<sup>th</sup> February 2015.

14. Won “NCL RF-Agnimitra Memorial poster award 2015” for poster presented at “National Science Day” organized by CSIR-National Chemical Laboratory, Pune from 25<sup>th</sup>-26<sup>th</sup> February 2015.

# Errata





