

**RATE ENHANCEMENT OF DIELS-ALDER REACTIONS
IN SALT SOLUTIONS AND IONIC LIQUIDS**

**A THESIS SUBMITTED TO THE
UNIVERSITY OF PUNE**

**FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)**

**BY
SUVARNA S. DESHPANDE**

**PHYSICAL CHEMISTRY DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE 411008
INDIA**

**Dr. ANIL KUMAR
(RESEARCH GUIDE)**

SEPTEMBER 2006

DECLARATION

I hereby declare that the thesis entitled “**Rate Enhancement of Diels-Alder Reactions in Salt Solutions and Ionic Liquids**”, submitted for the Degree of Doctor of Philosophy to the University of Pune, has been carried out by me at the Physical Chemistry Division National Chemical Laboratory, Pune under the supervision of Dr. Anil Kumar (Research guide). The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other University.

Date:
Physical Chemistry Division
National Chemical Laboratory
Pune-411008

Suvarna S. Deshpande
(Research student)



Dr Anil Kumar
Physical Chemistry Division

Tel: +91-20-25902278
Fax: +91-20-25902636
e-mail: a.kumar@ncl.res.in

National Chemical Laboratory
Dr Homi Bhabha Road
Pune – 411 008, INDIA

CERTIFICATE

Certified that the work incorporated in the thesis, “**Rate Enhancement of Diels-Alder Reactions in Salt Solutions and Ionic Liquids**”, submitted by **Ms. Suvarna S. Deshpande**, for the degree of **Doctor of Philosophy**, was carried out by the candidate under my supervision in Physical Chemistry Division, National Chemical Laboratory, Pune, India. Materials obtained from other sources have been duly acknowledged in the thesis.

Dr. Anil Kumar
Research Guide

Date

Place

*Dedicated
To
Aai & Baba*

ACKNOWLEDGEMENTS

As I look back, I realize that I owe a lot to many people around me who have contributed directly or indirectly towards the completion of my thesis. I wish to take this opportunity to thank a few of them.

It gives me immense pleasure to express my sincere gratitude to my research guide and mentor, Dr. Anil Kumar. I cannot even begin to enumerate the different aspects of the subject that I learnt from him. He gave me a lot of opportunities for improvement in spite of my mistakes in the initial stages. I would endeavor to follow his thorough approach, emphasis on understanding and enthusiasm towards life. He has always been a constant source of support and encouragement. He taught me the importance of independent thinking and being cheerful under the most stressful conditions. His friendly nature ensured that I never felt any hesitations in approaching him for scientific discussions. All in all he will always continue to be an inspiring influence for the rest of my life.

I am extremely grateful to Mr. Sanjay Pawar who trained me in the laboratory skills in the initial stage of my research work. It would have been very difficult for me to learn all those skills on my own.

My sincere thanks are due to Dr. Usha Phalgune for her help in analyzing NMR spectra.

I take this opportunity to thank my seniors, Pramod and Rohini who helped me in improving my presentation aptitude. Pramod helped me in developing a calm and composed outlook in the face of the worst crisis of life. Rohini's constant support boosted my morale and confidence, because of which I could overcome the difficult situations of my research tenure.

I extend my thanks to my lab mates Diganta, Shraeddha and Dilip for creating friendly atmosphere in the lab and their timely help. I will always cherish the happy moments we shared together. They were always forthcoming with their suggestions regarding the problems I faced in my day-to-day lab work. Their jovial company helped me in handling the ups and downs of my research.

I had a great time with Saritha, Nagesh and Geetanjali in the lab. I thank them for their assistance in compilation of my thesis.

I will always remember the jokes and delicacies I shared with Ashwini, Nirranjan, Anita, Trupti, Mandar, Mukta, Bhalchandra, Girish and Mrudula during lunch. I thank Dhanashri, Nirmal, Mahima, Meera, Bhaskar, Kannan, Vivek, Pranjal, Shekhar, Sanjay, Raj Sankar, and Sasank for their help and for friendly support.

I also wish to thank Mr. Dipak Jori and Mr. S. F. Punekar for their prompt help in administrative matters.

I acknowledge the library staff for providing the best facilities for the literature.

I cannot forget constant faith that Mrs. Rajlakshmi Patil, my school teacher had in my abilities. I hope that I have come up to her expectations.

It was my friends, Kshitija, Preeti, Vibha and Medha who appreciated my achievements and were always there to point out my mistakes. They always took special efforts to keep my spirits high.

I express my sincere thanks to all my relatives for their blessings without which this task would not have been possible.

I have no words to express my gratitude to my parents for their unfailing love that has helped me throughout my life. I will always be indebted to them for their understanding attitude, even when I spent endless hours in the lab. The unstinted support of my younger brother, Sujeet is warmly acknowledged.

I thank Director NCL for providing the infrastructure to carry out the research work and for permitting me to submit this thesis. Finally I acknowledge CSIR, New Delhi for financial support.

Date:

Suvarna S. Deshpande

List of Abbreviations

AAKT	Abboud-Abraham-Kamle-Taft
AN	Acceptor Number
BPAC	Ba(ClO ₄) ₂ in acetone
BPC	<i>N</i> -butylpyridinium chloride
DN	Donor Numbers
EPA	Electron Pair Acceptor
EMIC	1-ethyl-3-methyl imidazolium chloride
FMO	Frontier Molecular Orbitals
HMO	Hückel Molecular Orbitals
IDA	Index of Deviation from Aromaticity
LPAC	LiClO ₄ in acetone
LPDE	LiClO ₄ in diethyl ether
MNDO	Modified Neglect of Diatomic Overlap
MO-NICS	Molecular Orbital Nucleus Independent Chemical Shifts
MPAC	Mg(ClO ₄) ₂ in acetone
NICS	Nucleus Independent Chemical Shifts
OTf	trifluoromethanesulphonate
QM/MM	quantum mechanical and molecular mechanical
SOI	Secondary Orbital Interactions
RTIL	room temperature ionic liquids
SPAC	NaClO ₄ in acetone
TLSER	Theoretical Linear Solvent free Energy Relationship
TS	Transition State
VOC	volatile organic compounds
AlCl ₃ :EMIC	1-ethyl-3-methyl imidazolium chloride
In(OTf) ₃	Indium triflate
La(OTf) ₃	Lanthanum triflate
Sc(OTf) ₃	Scandium triflate
Yb(OTf) ₃	Ytterbium triflate

[BMIM]Cl	1-butyl-3-methyl imidazolium chloride
[BMIM]I	1-butyl-3-methyl imidazolium iodide
[BMIM][BF ₄]	1-butyl-3-methyl imidazolium tetrafluoroborate
[BMIM][CF ₃ SO ₃]	1-butyl-3-methyl imidazolium trifluoromethane sulphonate
[BMIM][ClO ₄]	1-butyl-3-methyl imidazolium perchlorate
[BMIM][lactate]	1-butyl-3-methyl-imidazolium lactate
[BMIM][PF ₆]	1-butyl-3-methyl imidazolium hexafluorophosphate
[BMIM][Tf ₂ N]	1-butyl-3-methyl imidazolium sulphonimide
[EMIM][NO ₃]	1-ethyl-3-methyl imidazolium nitrate
[EMIM][PF ₆]	1-ethyl-3-methyl imidazolium hexafluorophosphate
[EMIM][Tf ₂ N]	1-ethyl-3-methyl imidazolium sulphonimide
[HMIM][BF ₄]	1-hexyl-3-methyl imidazolium tetrafluoroborate
[OMIM][BF ₄]	1-octyl-3-methyl imidazolium tetrafluoroborate

List of symbols

E_A	energy of activation
E_N	energy of activation for <i>endo</i> isomer
E_X	energy of activation for <i>exo</i> isomer
k_N	rate constant for formation of <i>endo</i> isomer
k_X	rate constant for formation of <i>exo</i> isomer
α	hydrogen bond donor ability
β	hydrogen bond acceptor ability
π^*	dipolarity-polarisability
ΔH^\ddagger	enthalpy of activation
ΔS^\ddagger	entropy of activation
ΔG^\ddagger	Gibbs free energy of activation
$\delta(\Delta G^0)_{\text{cavn}}$	Gibbs free energy of cavitation
$\delta(\Delta G^0)_{\text{soln}}$	Gibbs free energy of solution
$\delta(\Delta G^0)_{\text{solvn}}$	Gibbs free energy of solvation
ΔV^\ddagger	volume of activation

ABSTRACT

RATE ENHANCEMENT OF DIELS-ALDER REACTIONS IN SALT SOLUTIONS AND IONIC LIQUIDS

Diels-Alder reactions were believed to possess negligible solvent effects on the course of the reactions due to involvement of isopolar activated complexes. In this reaction a diene reacts with dienophile to form a cycloadduct. The usefulness of Diels-Alder reactions in organic synthesis arises from its versatility and its high regio- and stereoselectivity. The rules were developed by Woodward-Hoffmann and Fukui, independently to explain the mechanism and feasibility of these reactions.

The first report on the solvent effects on stereoselectivities of Diels-Alder reactions was appeared in 1960. The topic of the solvent effects on Diels-Alder reactions came into limelight when Breslow and his group rediscovered water as a reaction medium for these reactions. Since then, kinetic profiles and variation in stereoselectivities were started investigating by employing different solution media. Of them few important media are 1. water and its salt solutions, 2. nonaqueous salt solutions, 3. ionic liquids and 4. supercritical fluids.

These days environmental pollution caused due to volatile organic solvents has become an important issue in chemical industries. In addition to aqueous medium, ionic liquids have become popular reaction media for carrying out organic reactions. Diels-Alder reactions go faster in these media. Ionic liquids have many advantages over volatile organic solvents, so they can prove as substitutes for these organic solvents.

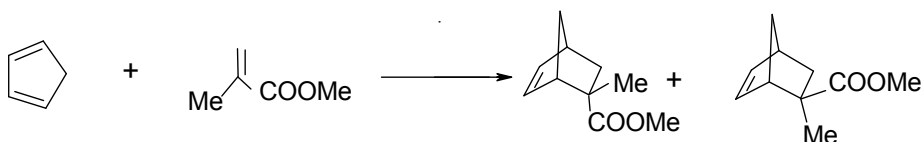
Efforts have been made to explain the enhancement in reaction rates and stereoselectivities observed in the above-discussed solvent media by various parameters. To list a few are polarity, hydrogen bonding, hydrophobic packing, internal pressure, Lewis acid catalysis. However, **no unified approach is available to explain the rate acceleration of Diels-Alder reactions in these media.**

The present thesis deals with **delineation and understanding of origins of possible forces responsible for the rate acceleration and stereoselectivities in water and its salt solutions and ionic liquids.** These have been discussed in detail in seven separate chapters.

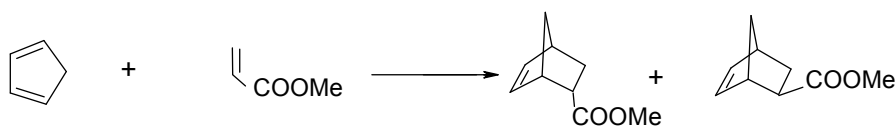
Chapter I begins with a brief introduction to Diels-Alder reactions including the types of reactions as reactions with normal electron demand and inverse electron demand. It presents a critical review on the effects of solvents on the rates and stereoselectivities of Diels-Alder reactions. The various Diels-Alder reactions carried out by employing different solvent media are discussed. Also water as a reaction medium for organic reactions other than Diels-Alder reactions has been examined. The solvent effects have been described by empirical, semi empirical and theoretical methods. On this basis, the mechanism for the Diels-Alder reaction has been discussed. The proposed possible factors for the rate variation have been summarized in the light of hydrophobic effect, polarity, Lewis acid catalysis, internal pressure etc.

Chapter II describes the objectives of the investigations carried out based on the literature survey.

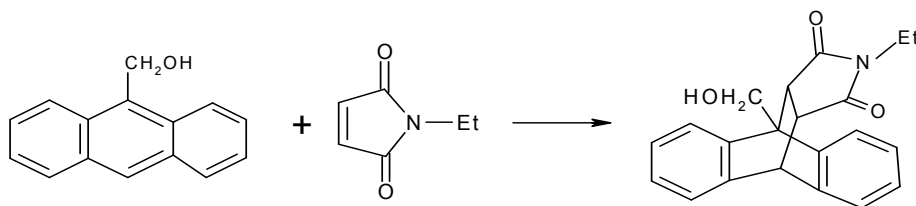
Chapter III starts with the discussion on the *exo*-selective reaction of cyclopentadiene with methyl methacrylate (Scheme 1) carried in aqueous salt solutions of CaCl_2 , Na_2SO_4 , KCl , LiCl , GnCl and LiClO_4 . The effects of salting-out agents and



SCHEME 1. The reaction of cyclopentadiene with methyl methacrylate



SCHEME 2. The reaction of cyclopentadiene with methyl acrylate



SCHEME 3. The reaction of anthracene-9-carbinol with *N*- ethylmaleimide

salting-in agents on the *endo/exo* ratios are elaborately discussed. The variation in *endo/exo* ratios in salt solutions is supported by solubility measurements. The salting-coefficients have also been calculated for this reaction.

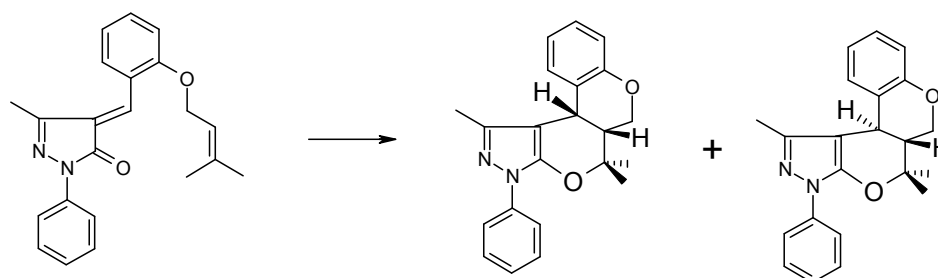
The effects of aqueous salt solutions on the reaction of cyclopentadiene with methyl acrylate (Scheme 2) have been investigated. The increase in *endo/exo* ratios in presence of salting-out agents and the decrease in *endo/exo* ratios due to salting-in agents have been discussed based on hydrophobic effect. This hydrophobic effect responsible for the rate acceleration has been quantified through measurable parameter, internal pressure of solution. Also, the effects of various sodium salts and guanidinium salts have been examined on the rates of reaction of anthracene-9-carbinol with *N*-ethylmaleimide (Scheme 3). The structure-making and -breaking abilities of these ions in aqueous medium in relation to the variation in internal pressure have been explained. The salting-zones have been defined based on the variation in internal pressure and *endo/exo* ratios. The effect of internal pressure in conjunction with negative activation volume has been studied on the rates and *endo/exo* ratios of Diels-Alder reactions.

Further in order to investigate the changing role of LiClO₄, salting-in in aqueous medium alone and salting-out in aqueous solutions of alcohols containing salts, the reaction of cyclopentadiene with methyl acrylate (Scheme 2) has been studied in aqueous mixtures of methanol, ethanol, propan-1-ol and butan-1-ol in presence of LiClO₄, LiCl, NaCl, KCl, CaCl₂ and MgCl₂. The observations made in the above mentioned reaction media have been compared with those in aqueous salt solutions and in aqueous alcohol. The role of cosolvents with increasing carbon chain length in increasing *endo/exo* ratios has been investigated. The experimentally obtained *endo/exo* ratios have been analyzed using the two parameters, 1. solvophobic power and 2. normalized polarity parameter. The equation can be used to predict the *endo/exo* ratios for the aqueous solutions of alcohols containing salts.

Diene and dienophile are sparingly soluble in aqueous medium. Taking into consideration this observation, the possibility should be checked that whether the reaction takes place at the interface. The variations in interfacial area affect the reaction rates.

Chapter IV includes discussion on ionic liquids, used as green solvents. The reasons for considering ionic liquids as green solvents are described in brief. Besides this

the advantages of employing this medium are also discussed. The rate constants obtained by conducting the intramolecular Diels-Alder reactions of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (Scheme 4) in various ionic liquids are analyzed in the light of viscosities of the media. The criteria to select the ionic liquids is discussed. The other parameters such as Lewis acid catalysis are also examined.



SCHEME 4. Intramolecular reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy) benzylidene]-5-pyrazolone

Chapter V deals with the question that whether rates of bimolecular reactions such as Diels-Alder reactions depend on viscosities of solvent media in which the reactions are performed. Experimental data have been provided in order to examine this issue. The observation that the reaction rates increase in lower viscosity range and retard in highly viscous solution has been discussed on the basis of vibrational activation theory. The effect of temperature on the viscosity dependence of reaction rates has also been studied. Based on the observations made during this study, collision control and encounter controlled region are discussed.

Chapter VI reveals the summary and conclusions of the research work.

Chapter VII deals with the experimental procedure to carry out a Diels-Alder reaction in aqueous salt solutions and ionic liquids in detail. The synthesis of various ionic liquids have been discussed are discussed briefly. The confirmation of the formation of products by NMR and the quantitative determination of the *endo/exo* ratios is described in detail. The kinetic measurements of the rate constants by GC and UV Visible spectroscopy have been described. The principle and working of GC and UV Visible spectroscopy has been discussed. Also the synthesis of substrate for intramolecular Diels-Alder reaction has been explained.

Thus, the issues discussed in the thesis presents the possible origins of forces responsible for the rate enhancement in Diels-Alder reactions in salt solutions as well as ionic liquids and hydrophobic effect in case of aqueous medium is quantified through measurable parameter, internal pressure.

CONTENTS

1. Introduction	
1.1 Introduction: Diels-Alder reaction	1
1.1.1 Background	1
1.2 Salient features	3
1.2.1 Diene and dienophile in a Diels-Alder reaction	3
1.2.2 Aromaticity of TS	5
1.3 Mechanistic aspects	5
1.4 Effects of solvents	11
1.4.1 Effect of polarity	12
1.4.2 Hydrophobic effect	13
1.4.3 Internal pressure	18
1.4.4 Lewis acid catalysis by Li ⁺ ions	24
1.4.5 Enforced hydrophobic hydration and hydrogen bonding	27
1.4.6 Solvent polarity parameters	29
1.5 Ionic liquids	32
1.5.1 Physicochemical properties of ionic liquids	34
1.5.2 Diels-Alder reactions in ionic liquids	37
2. Objectives	41
3. Reactions in salt solutions	42
3.1 <i>Endo</i> - and <i>exo</i> -selectivities of Diels-Alder reactions	42
3.2 Effects of the aqueous salt solutions on the <i>endo/exo</i> ratios of <i>exo</i> -selective reaction	44
3.3 Salting phenomena	45
3.4 Salting coefficients	50
3.5 Role of ΔV^\ddagger	55
3.6 Effects of salt solutions on a given Diels-Alder reaction	55

3.7 The quantification of hydrophobic effect through a solvent parameter	56
3.7.1 Internal pressure	57
3.8 Effects of addition of cosolvents	62
3.9 Reaction at interface	75
4. Intramolecular Diels-Alder reaction in ionic liquids	83
4.1. Intermolecular Diels-Alder reactions in ionic liquids	83
4.2. Intramolecular Diels-Alder reactions	86
4.3. Results and discussion	87
5. Role of viscosity	94
5.1. Conventional kinetic theory	94
5.2. Controversies regarding role of viscosity	94
5.3. Experimental observations	96
5.4. Discussion	103
6. Summary and conclusions	110
7. Experimental section	112
7.1 Kinetic measurements by GC	113
7.2 Intramolecular reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy) benzylidene]-5-pyrazolone	114
7.2.1 Kinetic study of UV vis spectroscopy	114
7.2.2 Synthesis of substrate	114
7.3 Synthesis of ionic liquids	116
Literature cited	132
List of publications	142

Chapter 1
INTRODUCTION

Diels-Alder reaction is often quoted as an example of a reaction that is little influenced by solvents. However for more than two decades the effects of solvents have been extensively studied on the course of these reactions. Efforts have been made to explain the kinetic profiles of the reactions carried out in various solvent media.

This chapter describes a critical literature survey on effect of solvents on Diels-Alder reactions and possible driving forces responsible for variations in their rates and stereoselectivities.

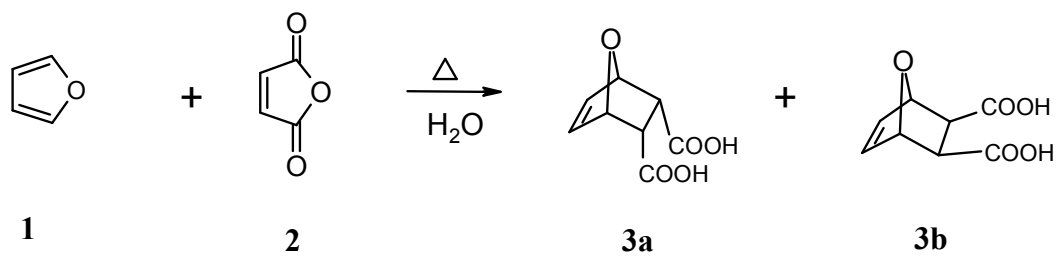
1.1 Introduction: Diels-Alder reaction

Diels-Alder reaction, a [4+2] π -cycloaddition reaction is one of the most fascinating organic reactions, both in terms of its synthetic potential and its reaction mechanism. The utility of Diels-Alder reactions in synthetic chemistry arises from the fact that the formation of six-membered rings with a double bond takes place in one step. Its synthetic utility has been reviewed by Nicolaou et al.¹

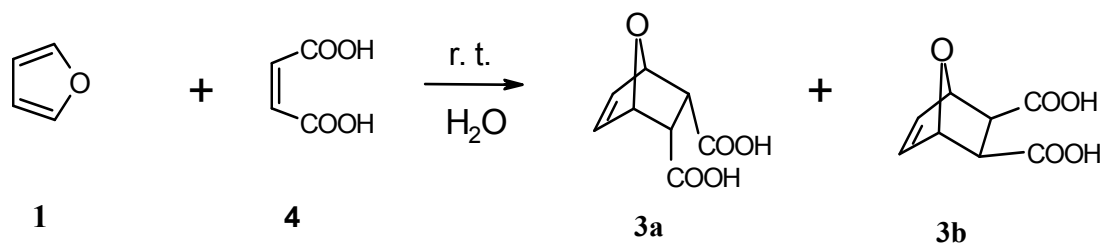
Diels-Alder reactions were believed to possess concerted mechanism due to which the rates of these reactions do not show the effect of catalyst or solvent.

1.1.1 Background

In 1928, two German scientists Otto Diels and his student Kurt Alder discovered Diels-Alder reaction for which they were awarded a Nobel Prize in 1950.² They conducted the reactions of furan (**1**) with maleic anhydride (Scheme 1.1) (**2**) and with maleic acid (**4**) (Scheme 1.2) in water at high temperature and at room temperature, respectively. The discovery of [4+2] π -cycloaddition reactions were followed by [2+2] π -, [4+4] π - [3+2] π - cycloaddition reactions.³ The concepts of the mechanism of Diels-Alder reactions are highly influenced by Woodward-Hoffmann rules.⁴ Accordingly, thermally allowed reactions occur by concerted mechanism. The mechanism of these reactions can also be explained by Fukui's FMO approach. In the case of cyclic dienes, the preferential formation of *endo*-isomer is explained by Alder rule of 'maximum accumulation of unsaturation'.⁵ The schematic diagram of the reaction of cyclopentadiene with maleic anhydride following the 'Alder rule' is shown in Figure 1.1.



SCHEME 1.1



SCHEME 1.2

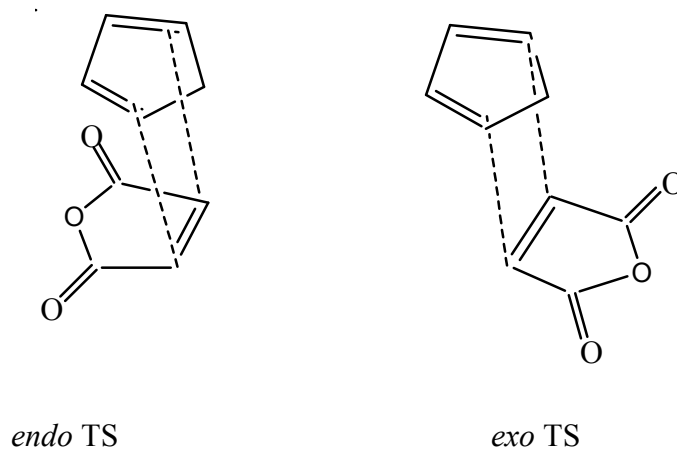


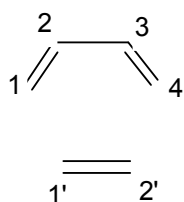
FIGURE 1.1. Cyclopentadiene with maleic anhydride following Alder rule

1.2 Salient features

Several aspects of Diels-Alder reaction have been investigated from different angles such as aromaticity of TS, stereochemistry, effect of substituents of diene and dienophile, regiochemistry, mechanism of Diels-Alder reactions etc. Few important features of these reactions are discussed here.

1.2.1 Diene and dienophile in a Diels-Alder reaction

In a Diels-Alder reaction, a double bond (dienophile) adds to a conjugated diene to form an unsaturated six-membered ring. These reactions are classified as follows: 1) reactions with normal electron demand, 2) neutral reactions and 3) reactions with inverse electron demand.^{3,6} This classification is based on an analysis of Equation 1.1, which describes mathematically the interaction of both pairs of frontier orbitals in the HMO model.⁶



$$\Delta E = \frac{(C_{1HO} \cdot C_{1'LU} \cdot \beta_{11'} + C_{4HO} \cdot C_{2'LU} \cdot \beta_{42'})^2}{E_{HO(\text{diene})} - E_{LU(\text{dienophile})}} + \frac{(C_{1LU} \cdot C_{1'HO} \cdot \beta_{11'} + C_{4LU} \cdot C_{2'HO} \cdot \beta_{42'})^2}{E_{HO(\text{dienophile})} - E_{LU(\text{diene})}} \quad (1.1)$$

The energy levels of the frontier molecular orbitals of the three types of reactions are shown in Figure 1.2.

Type 1: **Reactions with normal electron demand:** This group covers all those reactions whose $HOMO_{\text{diene}}-LUMO_{\text{dienophile}}$ separation is more important and dominates the

reactivity. Electron-donating substituents in diene raise HOMO of diene whereas electron-withdrawing substituents in the dienophile lower the LUMO of dienophile. Since interaction energy, ΔE is inversely proportional to the HOMO-LUMO energy separation, smaller is the energy gap between HOMO and LUMO greater is the interaction and ultimately the stabilization. Hence, dienes with electron-donating substituents and dienophiles with electron-withdrawing substituents favor the reaction.

Type 2: **Neutral reactions:** Here both interactions, $\text{HOMO}_{\text{diene}}\text{-LUMO}_{\text{dienophile}}$ as well as $\text{HOMO}_{\text{dienophile}}\text{-LUMO}_{\text{diene}}$ are equally important.

Type 3: **Reactions with inverse electron demand:** In this case $\text{HOMO}_{\text{dienophile}}\text{-LUMO}_{\text{diene}}$ dominates the reactivity. Electron withdrawing substituents in diene lowers the LUMO of diene and electron donating substituents in the dienophile raise the HOMO of dienophile. These reactions therefore, are accelerated by dienophiles carrying electron releasing groups and dienes carrying electron-attracting groups.

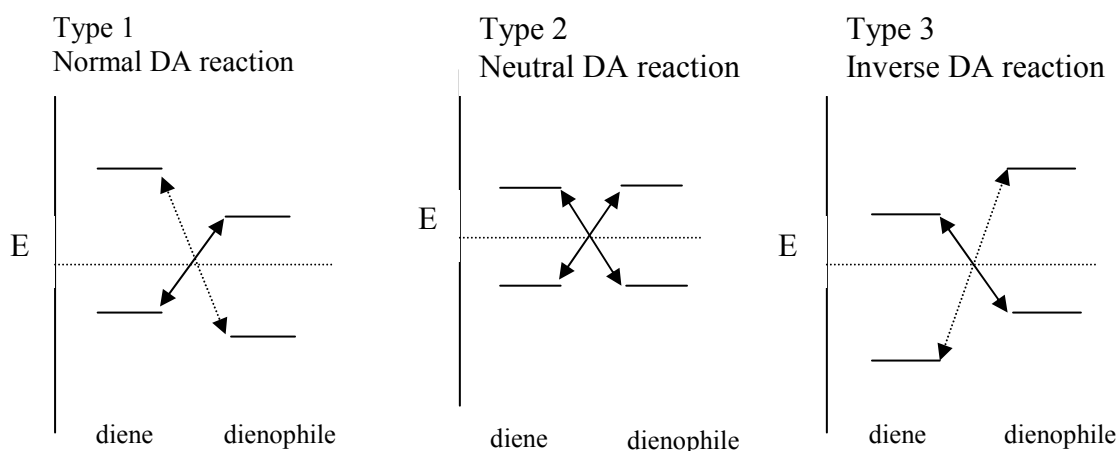


FIGURE 1.2. Types of Diels-Alder (DA) reactions showing HOMO-LUMO separation

The effects of substituents on diene and dienophile have been discussed in many articles.⁷⁻¹⁰ Another important point which has long been discussed in Diels-Alder chemistry is the aromatic nature of TS of Diels-Alder reactions.

1.2.2 Aromaticity of TS

Diene and dienophile pass through cyclic TS, which then yield a cycloadduct. Evans and Warhurst pointed out the analogy between delocalized electrons in the cyclic TS for the reaction between butadiene and ethylene and the π electrons of benzene.¹¹ In the transition state, six atomic orbitals overlap in a ring. This cyclic structure is equivalent to the overlapping of six carbon 2p atomic orbitals in benzene to form cyclic π molecular orbitals.¹² Evans stated that the resonance energies of the transition states of Diels-Alder reaction and benzene are greater than those of 1,3,5-hexatriene.¹³ Theoretical calculations allow researchers to study the aromaticity of TS of Diels-Alder reactions in greater detail. The reaction pathway of Diels-Alder reaction of quinodimethanes with ethylene was studied by density functional based ^{13}C , ^1H NMR, NICS and MO-NICS calculations, which showed that the increase of aromatic character of developing benzenoid ring was especially pronounced after the TS was reached, even though the number of π orbitals decreased.¹⁴ Further the developing ring exhibits large ring current effects during the reaction. The comparison of IDA values for the reaction of butadiene with ethylene and with that of benzene showed that TS in Diels-Alder reaction has an aromatic stabilization character.¹⁵ The aromatic character of the TS of Diels-Alder reaction has been discussed in several other articles.¹⁶⁻²⁰

1.3 Mechanistic aspects

Initially Diels-Alder reactions were believed to involve isopolar activated complex. Sauer and Sustmann examined a number of parameters in support of this conclusion.⁶ The parameters included stereospecificity, effects of solvents on kinetic profiles, influence of the structures of diene and dienophile on the reactivity, activation parameters like ΔH^\ddagger , ΔS^\ddagger , ΔG^\ddagger , ΔV^\ddagger etc.⁶ In addition to the above mentioned parameters, the aspects of Diels-Alder reactions were examined theoretically by *ab initio* calculations, FMO analysis as well as thermochemical measurements.

In due course extensive research has been carried out on different aspects of Diels-Alder chemistry. Attempts were made to elucidate the mechanism of Diels-Alder

reactions. The issue of concerted or stepwise mechanism of Diels-Alder mechanism has long been debated.

Houk and his group studied the mechanism of Diels-Alder reactions in detail. The experimental data and calculations showed that the reaction of butadiene with ethylene occurred mainly by a concerted mechanism. The stepwise process by a diradical intermediate is 2-7 kcal mol⁻¹ higher in energy than the concerted pathway.^{21,22} Since concerted and stepwise mechanisms are close in energy, the mechanism of Diels-Alder reactions still remains doubtful. The results for the forward reaction of butadiene with ethylene and the cycloreversion of cyclohexene were compared using kinetic isotope effects at several levels of theory. These results indicated the concerted reaction between butadiene and ethylene.²³

Further, in case of concerted reaction, synchronous and asynchronous nature of TS has been discussed. For the reaction of isoprene with maleic anhydride, theoretical study predicted that the methyl substituent induces a small amount of asynchronicity in *endo* as well as *exo* TS.²⁴ Evidences have been presented in support of concerted and stepwise mechanism.^{6,25-30}

Diels-Alder reactions, in general follow Arrhenius behavior. The values of E_A and ΔH^\ddagger were found to be least important since these values are generally small. However, the high values of ΔS^\ddagger (generally between -40 to -30 cal K⁻¹ mol⁻¹) indicated highly ordered TS and should be formed by simultaneous bond formation.⁶

The ΔV^\ddagger values of Diels-Alder reactions have also been used to make distinction between competing concerted and stepwise mechanism of these reactions.

ΔV^\ddagger , a TS property is the difference between the volume of TS and the sum of the volumes of diene and dienophile. Generally, Diels-Alder reactions are accompanied with negative ΔV^\ddagger in the range of -30 to -10 cm³ mol⁻¹. ΔV^\ddagger can be calculated from Equation 1.2 as shown below.

$$\left(\frac{\partial \ln k}{\partial P} \right)_T = - \frac{\Delta V^\ddagger}{RT} \quad (1.2)$$

where, k = rate constant

R = gas constant

P = pressure

T = absolute temperature

Generally, for nonpolar reactions where medium effects are small (solvation and electrostriction, a discussion on electrostriction appears in chapter 3) formation of each bond corresponds to volume shrinkage -15 to $-10 \text{ cm}^3 \text{ mol}^{-1}$ for two step process and -30 to $-20 \text{ cm}^3 \text{ mol}^{-1}$ for concerted process.³¹ The large negative ΔV^\ddagger for Diels-Alder reactions were interpreted in terms of concerted mechanism. The ΔV^\ddagger values for several Diels-Alder reactions are tabulated by van Eldik and coworkers.^{32, 33} The ΔV^\ddagger values for Diels-Alder reactions were observed to be more negative than volume of reaction (ΔV_R) (Figure 1.3). This observation indicates the more compact TS, in other words concerted mechanism is favored.

In the case of concerted reactions competing with stepwise reactions, large differences in their $\Delta\Delta V^\ddagger$ ($\Delta\Delta V^\ddagger = \Delta V^\ddagger$ (concerted) - ΔV^\ddagger (stepwise) $\approx -10 \text{ cm}^3 \text{ mol}^{-1}$) were observed.³⁴ It was further reported that since Diels-Alder reactions are promoted by increase in pressure, high pressure favors those products which are formed by

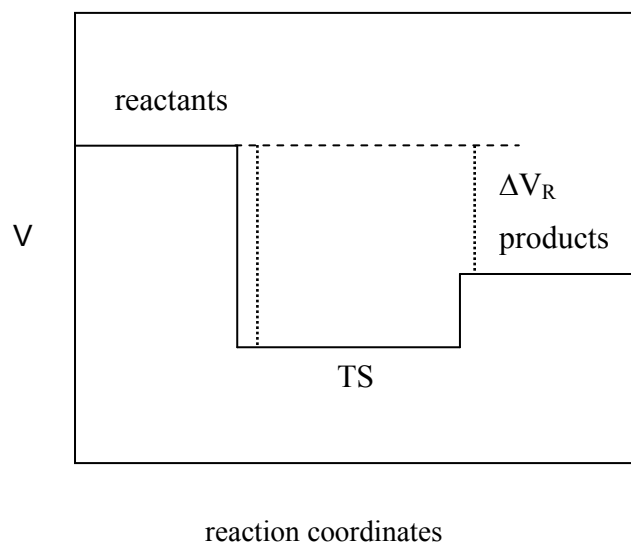
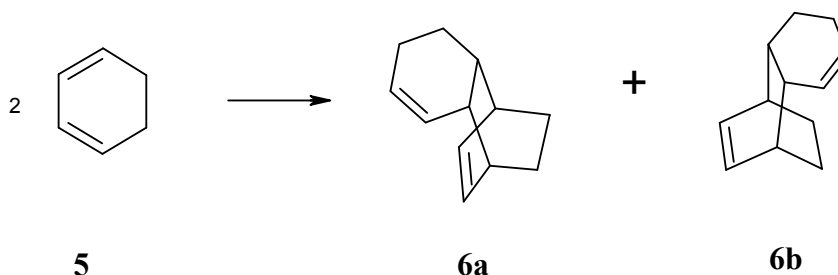


FIGURE 1.3. Change in volume in a Diels-Alder reaction

concerted mechanism. For example, in the case of dimerization of 1,3-cyclohexadiene (**5**) (Scheme 1.3), adduct **6a** formed by concerted mechanism while adduct **6b** formed by stepwise mechanism. Hence adduct **6a** was favored at high pressure. Similar observations were made for the dimerization reactions of 2-chloro-1,3-butadiene and *o*-quinodimethane, cycloaddition of 1,3-butadiene with α -acetoxyacrylonitrile.



SCHEME 1.3

Seguchi et al. calculated the difference between ΔV^\ddagger of *endo*- and *exo*-isomer of Diels-Alder reactions using Equation 1.3 as shown below.³⁵

$$\left(\frac{\partial \ln (endo/exo)}{\partial P} \right)_T = - \frac{\Delta (V^\ddagger_{endo} - V^\ddagger_{exo})}{RT} \quad (1.3)$$

As *endo/exo* ratio increased, the difference between ΔV^\ddagger of *endo*- and *exo*-isomer decreased. A large volume of contraction in the *endo* TS was attributed to secondary orbital overlap, which is also responsible for the stabilization of *endo* TS.

Further, the ΔV^\ddagger values for Diels-Alder reactions indicates late TS, in which nuclei are already at or near their final position. In contrast, low activation energies of the reaction indicated an early TS (Figure 1.4).³² Hence, it was proposed that in a Diels-Alder

reaction, the nuclei of diene and dienophile reach their final places much before the electrons move to their respective positions.

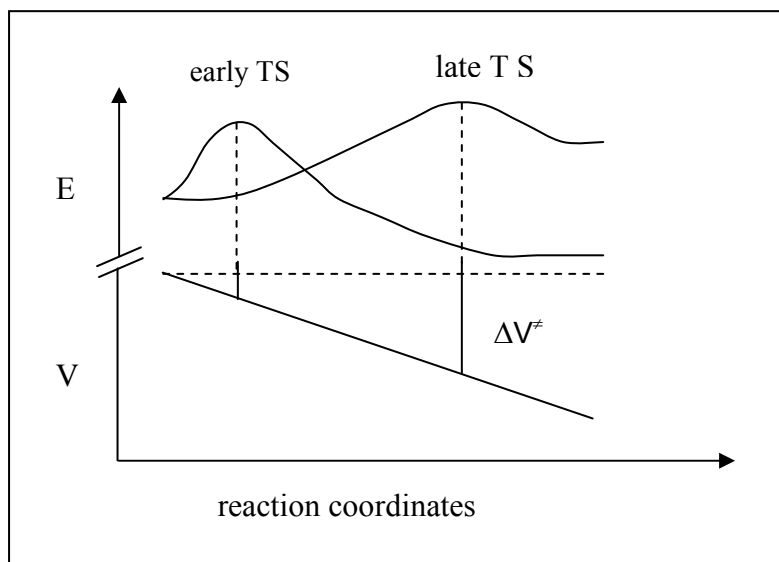


FIGURE 1.4. Energy and volume profiles to show the effect on TS

Even though the evidences are presented in favor of both the mechanisms, concerted and stepwise, synchronous and asynchronous, the mechanism of Diels-Alder reactions still remains obscure.

In the case of concerted reaction, the extra stabilization of *endo* TS has been attributed to attractive SOI.⁴ Apart from the primary orbital overlap between the actual reacting centers on diene and dienophile, overlap is also possible between nonreacting carbons of diene and unsaturated substituent on the dienophile (Figure 1.5). Such an overlap is known as SOI. Attempts were made to quantify SOI.^{36,37}

Houk and coworkers proposed that SOI were not necessary to stabilize *endo* TS relative to *exo* TS.³⁸ He examined the four TS for the reaction of butadiene with acrolein by *ab initio* calculations. The studies revealed that the distances between the carbonyl group of acrolein and butadiene atoms were similar to those present in crystal structures of various molecular complexes. The theoretical studies showed that the atoms involved in SOI were situated relatively far (2.8 Å) in the corresponding TS.^{24, 39-45}

Recently, Garcia et al. made a strong objection about the role of SOI in stabilizing *endo* TS. They stated that the conclusive evidence for the existence of SOI has never been presented.⁴⁶ They reexamined the examples given by Woodward and Hoffmann in favor of SOI. Accordingly, one of the examples is dimerization of butadiene, which was considered as a typical example to explain SOI, cannot be explained on the basis of SOI, since no significant *endo* preference is found for this reaction. Further, the preference for *endo* isomer in several Diels-Alder reactions was explained on the basis of well-known

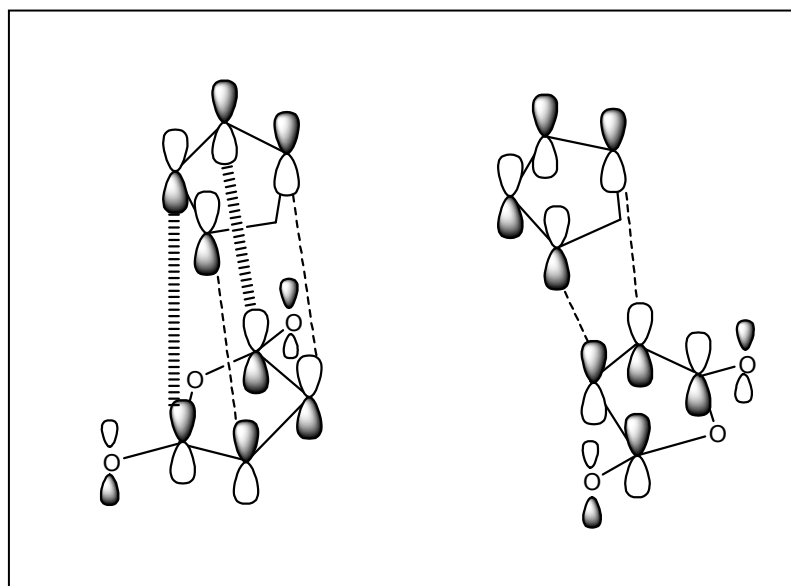
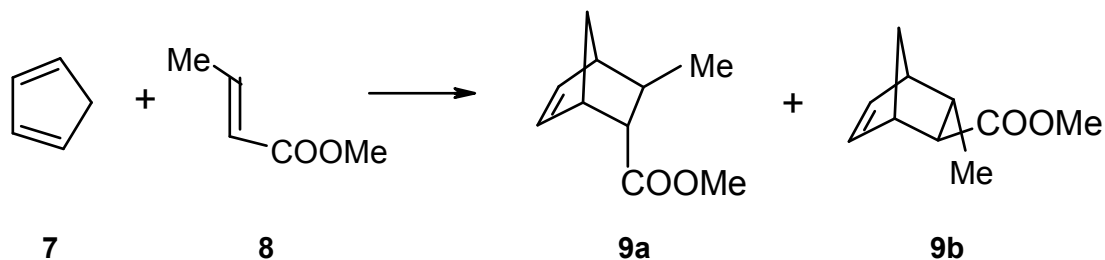


FIGURE 1.5. SOI in reaction of **7** with maleic anhydride

mechanisms such as solvent effects, steric interactions, hydrogen bonds, electrostatic forces. Further the studies of Diels-Alder reactions of cyclopentadiene with maleic anhydride, with cyclobutadiene and with norbornadiene revealed the absence of a net attractive interactions for the carbon atoms involved in SOI.⁴⁷ From these observations they concluded that the *endo* preference is not due to existence of attractive interactions between the nonreacting centers involved in SOI.

Sarma and Kumar studied the reaction of cyclopentadiene (**7**) with methyl *trans*-crotonate (**8**) (Scheme 1.4) in various aqueous salt solutions.⁴⁸ They explained the observed *endo/exo* ratios in terms of hydrophobic effects. More importantly the studies

demonstrated that hydrophobic effects are dominant over SOI for this reaction in salt solutions.



SCHEME 1.4

1.4 Effects of solvents

A majority of organic reactions are carried out in solution phase. Probably one of the most critical parameters in deciding the success or failure of the reaction is the choice of solvent. The quality and suitability of reactions and chemical processes are heavily dependant upon the quality of the solvent utilized. Though solvents play several roles in the world of chemistry, it is primarily used as a reaction medium.

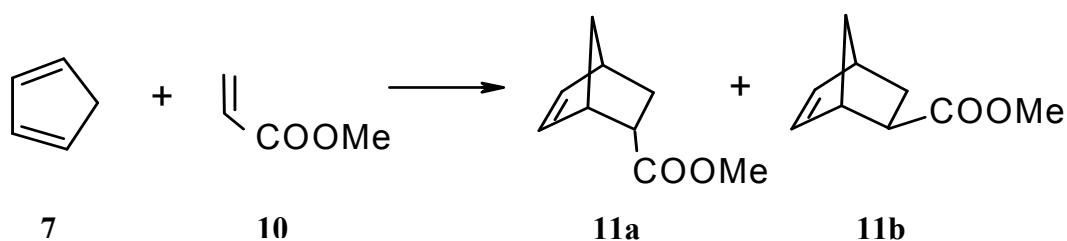
For more than two decades the effects of solvents on the rates and *endo/exo* ratios of Diels-Alder reactions have been studied. Considering the developments taking place in this area, the effects of solvents on kinetic profiles of these reactions have become a separate topic of research.

As has been discussed, Diels-Alder reactions were thought to possess negligible solvent effects on the kinetics of the reactions. This observation was based on the kinetic data of various Diels-Alder reactions in organic solvents. It was also stated that the nature of diene and dienophile made little influence on the rates of reactions. However, in 1980 Rideout and Breslow discovered that the rates of Diels-Alder reactions were dramatically accelerated when water is employed as a solvent medium.⁴⁹ Since then efforts were taken to enhance the rates and *endo/exo* ratios of Diels-Alder reactions using various solvent media. The variations in these reaction rates and *endo/exo* ratios have been ascribed to

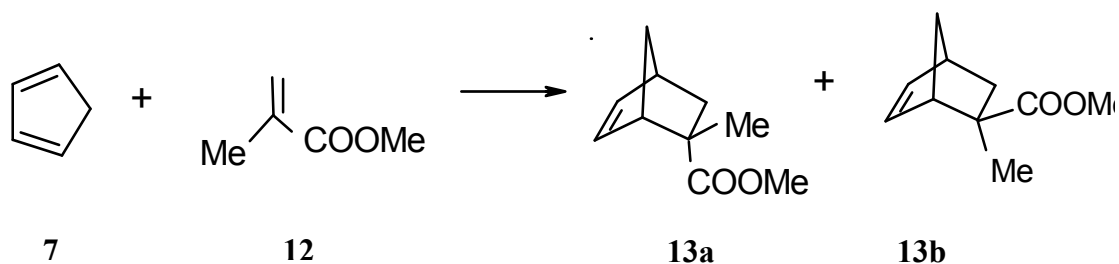
different solvent properties. The developments in this regard have been reviewed time to time.^{3, 50-57}

1.4.1 Effect of polarity

In 1962, Berson and his group investigated the effects of non-aqueous solvents on the *endo/exo* ratios of the three Diels-Alder reactions.⁵⁸ The reactions of **7** with dienophiles such as methyl acrylate (**10**) (Scheme 1.5), methyl methacrylate (**12**) (Scheme 1.6) and **8** (Scheme 1.4) were studied in organic solvents of increasing



SCHEME 1.5



SCHEME 1.6

polarity. The Alder rule was found to be of minor importance in determining the ratios of products. The reaction of **7** with **10** obeyed the rule in all solvents, whereas reaction of **7** with **12** violated it. The reaction of **7** with **8** showed borderline behavior. The reaction followed the rule in polar solvents whereas disobeyed in nonpolar solvents. Thus, the variations in *endo/exo* ratios for the three reactions in different solvents are shown in Figure 1.6.

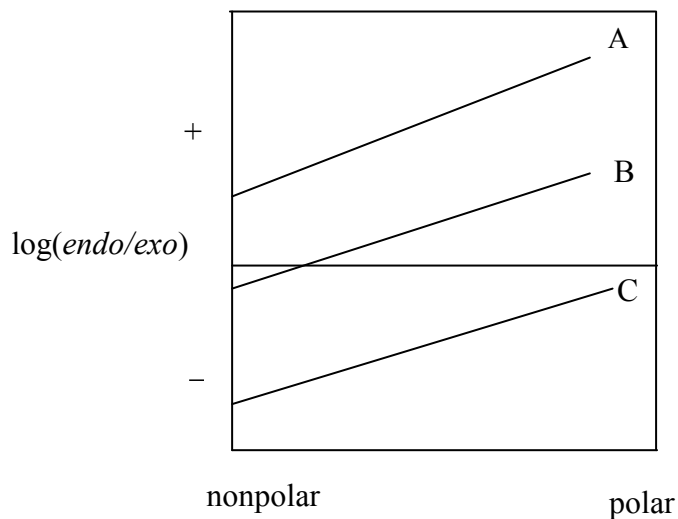


FIGURE 1.6. The *endo/exo* ratios as a function of polarities of solvents for the reactions of **7** with **10** (Scheme 1.5) (curve A), with **8** (Scheme 1.4) (curve B), with **12** (Scheme 1.6) (curve C)

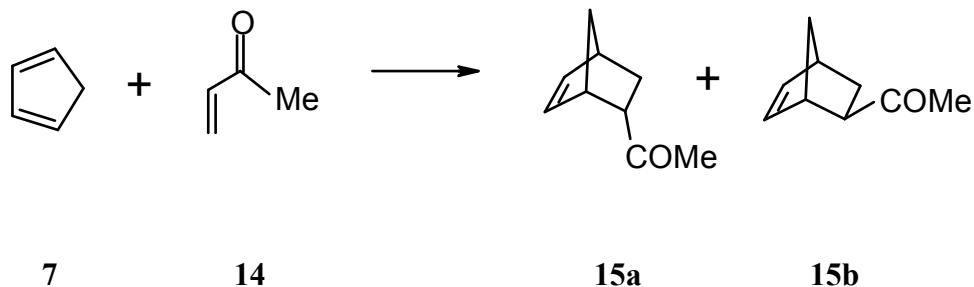
It was stated that irrespective of three reactions, the *endo/exo* ratios enhance with the increase in the polarity of the solvent. The enhancement in the *endo/exo* ratios was attributed to the polarity of solvent media.

1.4.2 Hydrophobic effect

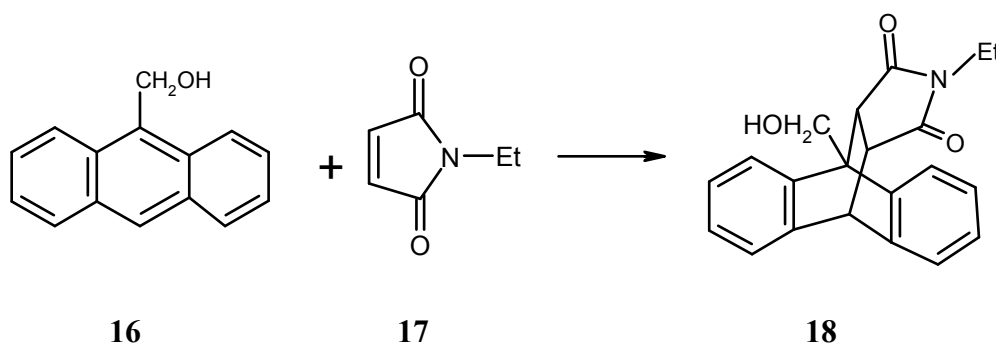
In 1980, Rideout and Breslow discovered the advantages of employing water as a reaction medium.⁴⁹ For the first time the spectacular enhancement in rates of reactions were observed, when water was chosen as a solvent medium rather than a conventional organic solvent for these reactions. The reaction of **7** with methyl vinyl ketone (**14**) (Scheme 1.7) showed about 740-fold acceleration in water as compared to that in 2,2,4-trimethylpentane, a nonpolar solvent. Also, the reaction of anthracene-9-carbinol (**16**) with *N*-ethylmaleimide (**17**) (Scheme 1.8) was observed to be 200 times faster in water than in acetonitrile.

In order to investigate whether the rate enhancement observed in water is due to hydrophobic effect or due to polarity of medium, these reactions were conducted in a polar solvent, methanol. The reaction of **7** with **14** (Scheme 1.7) was accelerated by only 12-fold when methanol was used as a solvent as compared to 2,2,4-trimethylpentane.

Further the reaction of **16** with **17** (Scheme 1.8) was actually 2 times slower in methanol than in 2,2,4-trimethylpentane whereas the same reaction was observed to be 65 times faster in water than in 2,2,4-trimethylpentane.

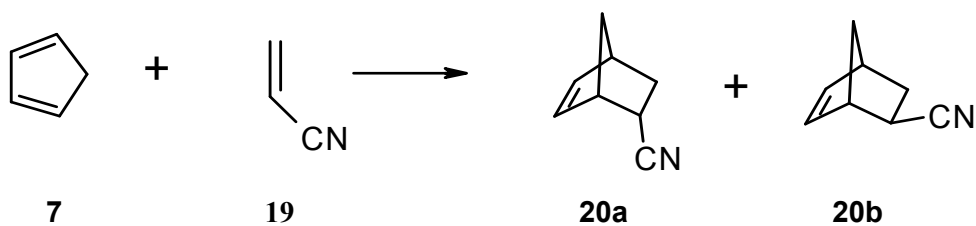


SCHEME 1.7



SCHEME 1.8

The reactions of **7** with **14** (Scheme 1.7) and with acrylonitrile (**19**) (Scheme 1.9) were conducted in the hydrophobic cavities of cyclodextrins (Figure 1.7). The reaction was accelerated by about 9-fold in 10 mmol β -cyclodextrin over water alone. However, the reaction was observed to be slowed down in the presence of smaller cavity of α -cyclodextrin as compared to water.^{49,59}



SCHEME 1.9

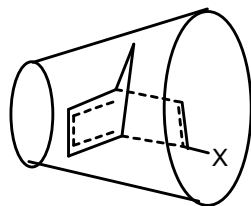


FIGURE 1.7. TS of Diels-Alder reaction in β cyclodextrin cavity

The effect of additives on kinetic profiles of the Diels-Alder reactions.^{49, 59} The rate of reaction of **16** with **17** was enhanced by about 3 times in 4.86 M aqueous LiCl. On the other hand, the same reaction was slowed down by about 3 times in 4.86 M aqueous GnClO_4 (guanidinium cation, structure is as shown in Figure 1.8).

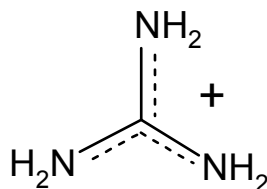


FIGURE 1.8. Structure of guanidinium cation

LiCl salts out the nonpolar molecules dissolved in water by increasing the hydrophobic effect, while guanidinium chloride salts in the nonpolar molecules as a result of decrease in hydrophobic effect.⁶⁰ The effects of various aqueous solutions of electrolytes on the rates of Diels-Alder reactions were reported by Kumar in detail.⁵⁵ The electrolytes were classified into two types: 1. salting-out agents and 2. salting-in agents. Breslow and Connors defined these salts as prohydrophobic and antihydrophobic agents.⁶¹ Electrolytes like LiCl, NaCl, NaBr, CaCl_2 act as salting-out or prohydrophobic agents in aqueous medium whereas GnCl , LiClO_4 are salting-in or antihydrophobic agents. A critical account of salting-out process and its implications in chemistry has been published by Grover and Ryall.⁶²

From these observations Rideout and Breslow attributed the dramatic rate enhancement in Diels-Alder reactions to the ‘hydrophobic effect’ of water.⁴⁹ The hydrophobic effect is the tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon-water interfacial area. The concept of the hydrophobic effect was discussed in detail by Tanford.⁶³

Since then several organic reactions including Diels-Alder reactions have been successfully conducted in water achieving higher rates and greater selectivity than before.^{5, 50-57}

Water as a solvent medium

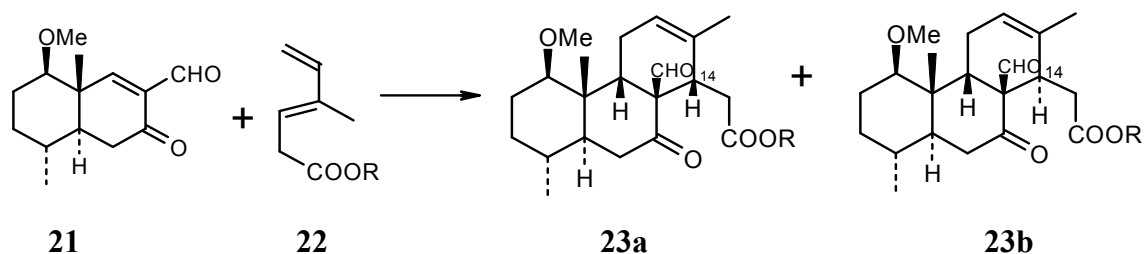
Water is the universal solvent. Numerous biological reactions within living systems inevitably occur in aqueous medium. In spite of this common observation, water was least preferred as a solvent for carrying out organic reactions. For example, Grignard reaction was strictly carried out in absence of water. The use of water as a solvent medium is advantageous in many respects. Water is the most abundant solvent available on earth. Water is inflammable and nontoxic. The process becomes more economical using water as a solvent. It is only after the discovery of water as a reaction medium by Breslow and his group; efforts have been made to carry out organic reactions in water.

Application of water in synthetic chemistry

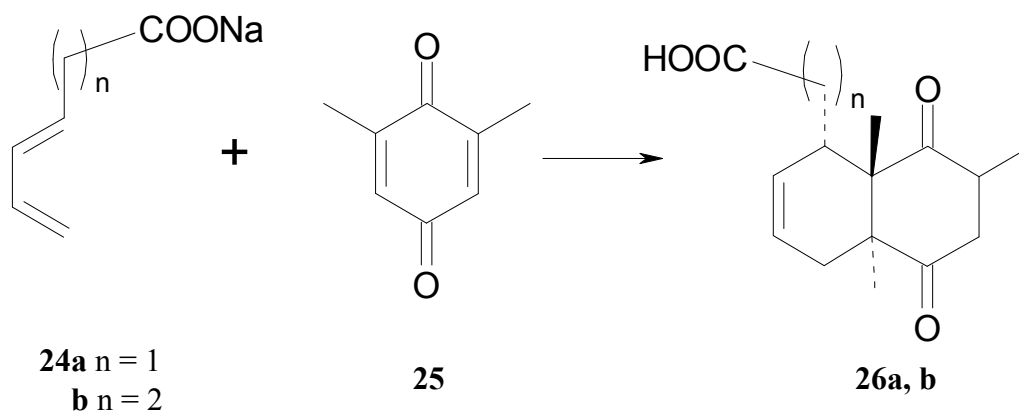
Grieco and his group established the usefulness of water in synthetic chemistry by carrying out several Diels-Alder reactions of diene carboxylates with varying dienophiles. The diene carboxylate (**21**) when reacted with dienophile (**22**) (Scheme 1.10, R = H) in aqueous medium gave Diels-Alder adducts **23a** and **23b** in 99 % yield as 3:1 stereoisomeric ratio after 4 h respectively. In sharp contrast, only a 52 % yield was obtained in benzene after 288 h.⁶⁴ The same reaction in toluene at room temperature gave 60 % yield after 168 h whereas using water as a solvent the reaction was completed in 17 h. Inspired by the observation, a large number of Diels-Alder reactions of sodium (*E*)-3,5-hexadienoate and sodium (*E*) 3,5-heptadienoate with a variety of dienophiles in aqueous medium were investigated. The reactions proceeded with excellent regiochemical control.⁶⁵ The sodium salts were generally employed since they are

conveniently generated in situ by treatment of parent dienoic acid with sodium hydroxide. However, similar results were obtained with the corresponding ammonium carboxylates. In the reaction of sodium (*E*)-3,5-hexadienoate (**24a**) and sodium (*E*) 3,5-heptadienoate (**24b**) and benzoquinone dienophile (**25**) (Scheme 1.11) the initially formed *cis*-fused adducts epimerized to the more stable *trans*-fused systems **26a** and **26b** under aqueous reaction conditions. The reactions of sodium salt of substituted heptadienoate (**27**) and methacrolein (**28**) (Scheme 1.12) were also enhanced in water.^{66,67}

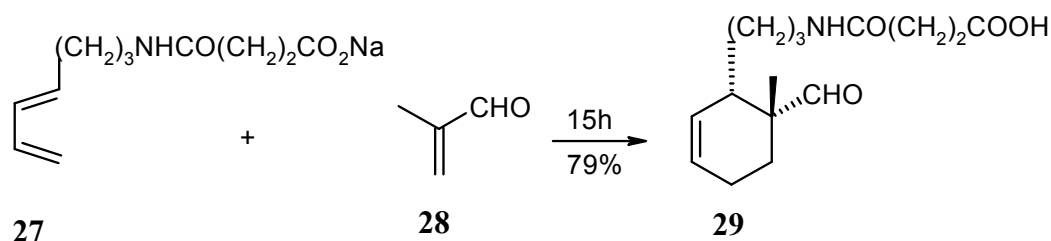
When **7** was reacted with methylmethyleammonium chloride (**30**) (Scheme 1.13) in water, 82 % yield of bicyclic amine (**31**) was obtained after 3 h.⁶⁸ The methodology developed by Larsen and Grieco on the water-mediated aza Diels-Alder reactions led Waldmann to include the use of amino acid esters as chiral auxiliaries.^{69,70}



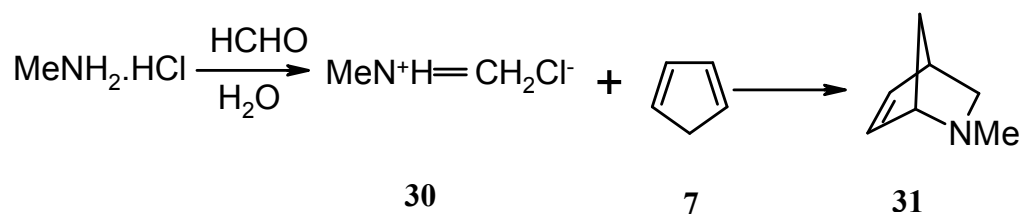
SCHEME 1.10



SCHEME 1.11



SCHEME 1.12



SCHEME 1.13

In brief, reaction rates, *endo/exo* ratios and product yields of Diels-Alder reactions can be enhanced by employing water as a solvent medium.^{66,71,72}

The reaction rates were also investigated in waterlike solvents, formamide and ethylene glycol and their salt solutions. The reaction of **7** with **14** (Scheme 7) was accelerated in formamide and ethylene glycol. However, when water was used as a solvent, the striking acceleration in reaction rate was observed. The reaction was enhanced by about 14-fold and about 10-fold in water as compared to that in formamide and in ethylene glycol, respectively. These observations indicated that ‘waterlike’ organic solvents do not share some of the peculiar properties of water.⁷³

1.4.3 Internal pressure

Grieco et al argued that the pronounced rate enhancement and the improved *endo/exo* ratios observed in aqueous medium are due to high internal solvent pressure.⁷⁴ Further the solvent media that possess internal solvent pressure equal to or greater than that of water should provide comparable rate acceleration for intermolecular cycloadditions. They employed 5 M LPDE medium for facilitating Diels-Alder reactions. Here, use of LPDE as a reaction medium deserves a special mention.

Effect of LPDE on organic reactions

The use of LPDE was first reported by Winstein, Smith and Darwish for the ionization reaction *p*-methoxyneophyl *p*-toluenesulphonate.⁷⁵ This ionization reaction was reported to be faster in acetic acid than in pure diethyl ether. However, above 0.036 M LPDE became better ionizing medium than acetic acid. The rate of the ionization reaction in 0.1 M LPDE was about 10⁵-fold higher than that in pure diethyl ether. The ionization reaction of spirodienyl *p*-nitrobenzoate was studied in LPDE and in LPAC. These results confirmed that the LiClO₄ salt effects are much larger than in diethyl ether than in acetone. The chief role of LiClO₄ in causing the very large accelerations was to provide specific electrophilic assistance to ionization.^{76,77}

Later, the exhaustive investigations have been carried out by Pocker and his school on the use of LPDE during the ionization of triphenylmethyl chloride and many other reactions in 5 M LPDE.⁷⁸ The rate of ionization reaction was faster by 7 x 10⁹ times in 5 M LPDE as compared to that in diethyl ether alone. The rearrangement of 1-phenylallyl chloride to cinnamyl chloride was also enhanced by 10⁴ times in 5 M LPDE solution.⁷⁹ The spectacular rate enhancement by LPDE-mediated organic reactions was ascribed to electrostatic catalysis by ionic aggregates.⁸⁰⁻⁸³ In order to understand the role of LiClO₄ in accelerating the reaction rates, the structural properties of LPDE should be considered.

Physico-chemical properties of LPDE

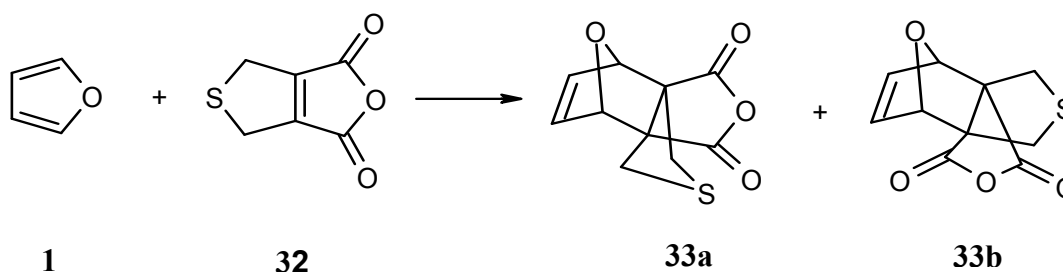
1. LiClO₄ is highly soluble in diethyl ether (6.06 M) at room temperature.⁸⁴
2. The vapor pressure data of LPDE solution shows that diethyl ether-LiClO₄ complexes are formed with a ratio of diethyl ether/LiClO₄ between 1 and 2.⁸⁵
3. The increase in dielectric constant with the concentration of LiClO₄ also indicates the formation of LiClO₄-Et₂O complexes.^{78,86}
4. The viscosity of a saturated solution of LPDE is about 800 times higher than that of pure ether at 25°C.⁸⁵

The investigations on the physico-chemical properties of LPDE solutions demonstrate that charged TS formed in the ionization reaction is stabilized by the LiClO₄-Et₂O clathrates.

Effect of LPDE on Diels-Alder reaction

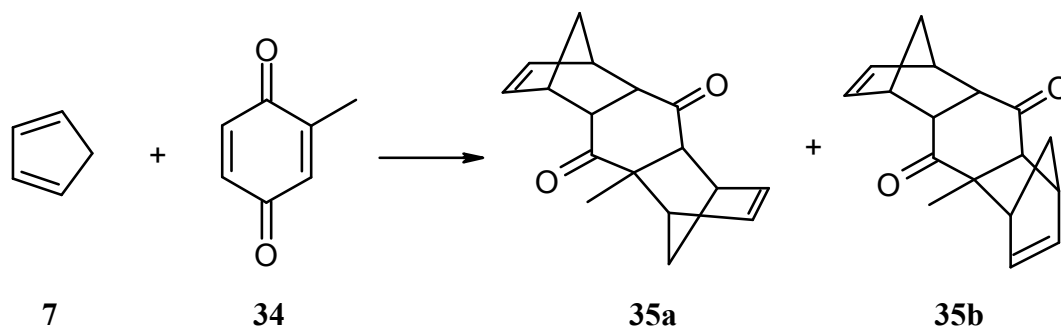
Grieco et al. successfully employed 5 M LPDE for the synthesis of cantharidin.⁷⁴ This achievement proved to be a milestone in synthetic organic chemistry. Conventionally, cantharidin was synthesized under ultrahigh pressure with lower yields for the two reasons: 1) Furan is a poor diene due to its aromatic nature and 2) The reactions involving furan cannot be carried out at elevated temperatures since the resultant cycloadducts undergo cycloreversion at high temperature.^{87,88} The reaction of **1** with 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**32**) (Scheme 1.14) in dichloromethane under an external pressure of 15 kbar (1 bar = 0.987 atm) gave the cycloadducts (**33a**, **33b**) in a ratio 85:15 in 6h. Further the exposure of methyl benzoquinone (**34**) to **7** (Scheme 1.15) in 5 M LPDE for 10 h at room temperature and atmospheric pressure afforded 74% yields as bis adducts **35a**, **35b** in a 6:1 ratio. In absence of LiClO₄, there was no evidence of formation of bis adducts **35a**, **35b** in diethyl ether.

When *trans*-piperylene (**36**) was treated with 2,6-dimethyl benzoquinone (**37**) (Scheme 1.16) in 5 M LPDE, an isolated yield of 80% was obtained in 15 min. On the contrary, a poor yield of < 20% was reported for the same reaction in water after 24 h.

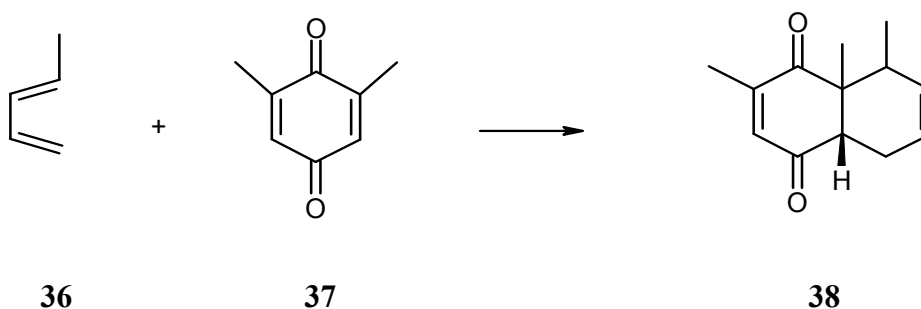


SCHEME 1.14

The above examples illustrate that the use of LPDE obviates the requirement of high pressure conditions for a Diels-Alder reaction. Since then several Diels-Alder reactions that are sluggish in organic solvents and often take days to afford adducts in low yield are made to go at a faster rate by employing 5 M LPDE. This work has been a great achievement in Diels-Alder chemistry in terms of obtaining higher yields in relatively short time at ambient conditions.

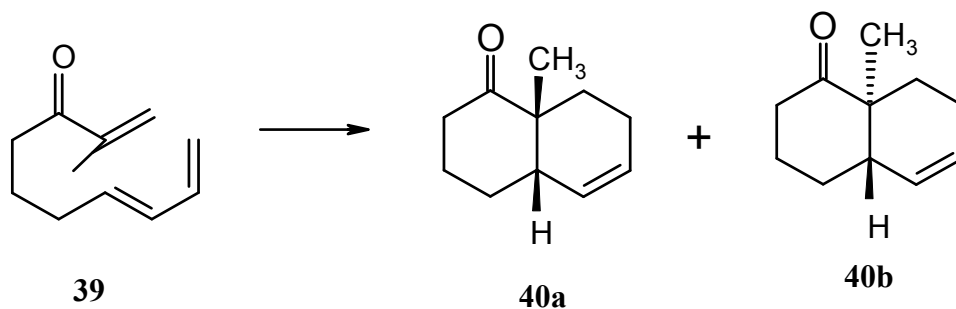


SCHEME 1.15



SCHEME 1.16

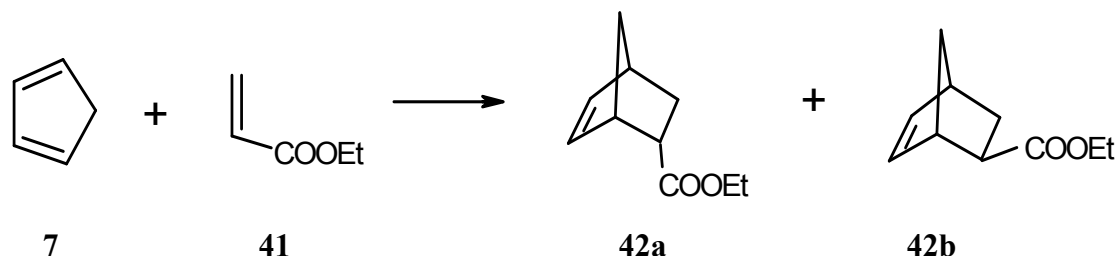
Intramolecular Diels-Alder reactions are often carried out at high temperatures in the presence of hydrocarbon solvents. The cycloadducts are obtained with modest stereoselectivity. When 5 M LPDE was employed as the medium, the reaction of alkatrienone (**39**) (Scheme 1.17) proceeded at ambient temperature in 24 h with an improved *cis:trans* distereoselectivity ratio of 3:1 (in benzene *cis:trans* ratio observed was 1.6:1).⁸⁹



SCHEME 1.17

The convenient syntheses of organic molecules in LPDE have been reviewed.^{90,91}

In order to find the limitations of 5 M LPDE in carrying out Diels-Alder reactions, Kumar and Pawar examined various Diels-Alder reactions in LPDE over concentration range up to 6.06 M.⁹² For the reaction of **36** with **37** (Scheme 1.16), a maximum rate enhancement of about 800 times than that in pure diethyl ether was noted. However, a slow decrease in the reaction rates was observed above 5 M. A substantial decrease in the yields from 83 % in 5 M to 43 % in 6.06 M LPDE was noticed. The authors also studied the reaction of **7** with ethyl acrylate (**41**) (Scheme 1.18) that gave 93 % yield with an *endo/exo* ratio of 8:1 in 5 M LPDE. The reaction was accelerated by about 26 times in 5 M LPDE than that in pure diethyl ether. However, the reaction rate began to fall above 5.5 M LPDE. This rate decrease in LPDE above 5.5 M was ascribed to very high viscosity of the medium. The viscosity of 5 M LPDE increases by about 15 times as compared to that of pure diethyl ether. Further, the viscosity of 6.07 M LPDE is

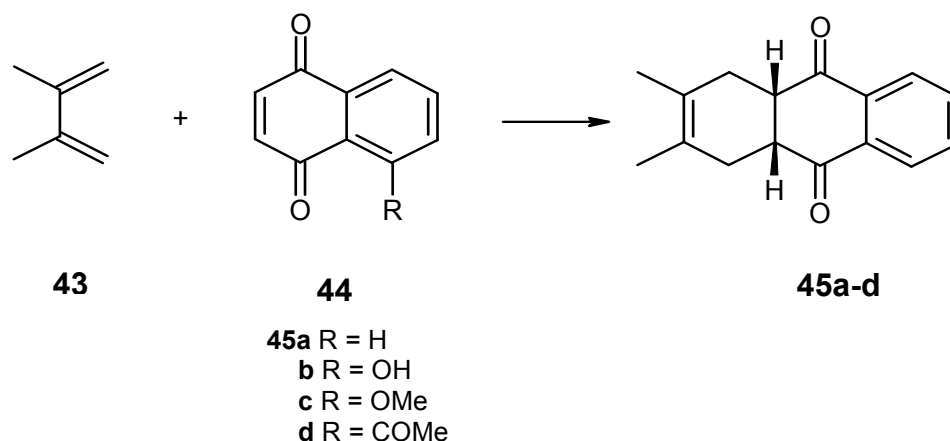


SCHEME 1.18

surprisingly enhanced by about 800 times as compared to pure diethyl ether.⁸⁵ This very high viscosity of 6.07 M LPDE retards the reaction rate above 5M LPDE. Macroviscosity (a bulk property) and microviscosity (viscosity experienced by diene and dienophile in a medium) differ depending on the size of diene and dienophile. A more detailed account on the role of viscosity in accelerating the rates of Diels-Alder reactions will be discussed in chapter 5.

Effect of other perchlorates on Diels-Alder reactions

The other perchlorate salts that have been used in synthetic organic chemistry include $\text{Mg}(\text{ClO}_4)_2$, $\text{Ba}(\text{ClO}_4)_2$, NaClO_4 in carrying out organic reactions. Casashi et al. studied the reaction between 2,3-dimethylbutadiene (**43**) and 1,4-naphthoquinone (**44a**) (Scheme 1.19) in the acetone solutions of SPAC, LPAC, BPAC and MPAC.⁹³ In spite of the limited solubility of $\text{Mg}(\text{ClO}_4)_2$ in acetone, MPAC produced maximum rate enhancement. The observed rate enhancement was in the ratio of 24:7:1.9:1 for 1 M salt concentrations of MPAC, BPAC, LPAC and SPAC, respectively. Thus the order in which these perchlorates in acetone enhanced the reaction was $\text{MPAC} > \text{BPAC} > \text{LPAC} > \text{SPAC}$.



SCHEME 1.19

Desimoni and coworkers reported asymmetric Diels-Alder reaction between **7** and 3-acryloyl-1,3-oxazolidin-2-one. They made the use of catalytic amount of Mg(II) core of catalyst derived from $\text{Mg}(\text{ClO}_4)_2$. The reaction occurred enantioselectively in the presence of $\text{Mg}(\text{ClO}_4)_2$ yielding the *endo* adduct i.e. *S*- isomer as a major product.⁹⁴

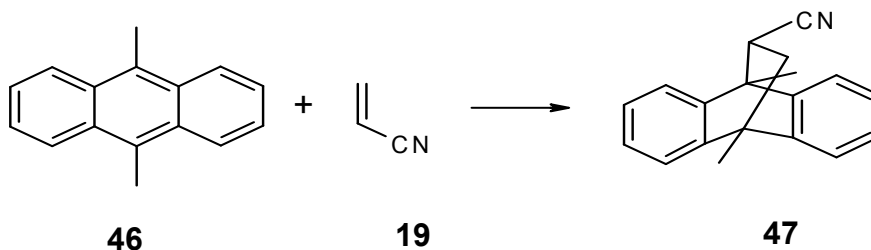
Other metal perchlorates in non-aqueous solvents have been used to speed up the Diels-Alder reactions. Out of the non-aqueous solutions the perchlorates discussed, LPDE has been most employed solvent medium.

1.4.4 Lewis acid catalysis by Li⁺ ions

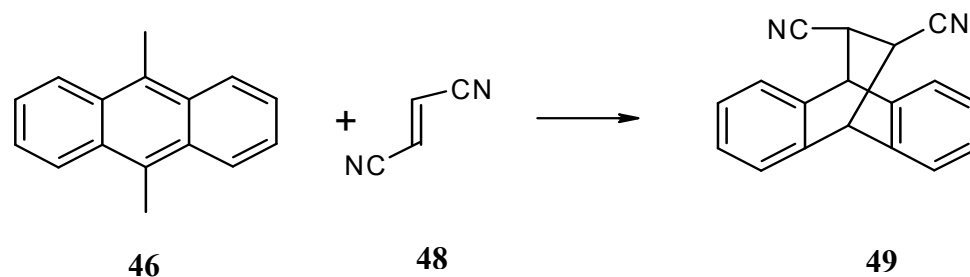
Forman and Dailey proposed an alternate explanation for the rate enhancement observed in LPDE solution.⁹⁵ They proposed that the rate enhancement in Diels-Alder reactions in LPDE was due to Lewis acid catalysis, with lithium ions functioning as the Lewis acid. As evidence they presented an example of the reaction between **19** and 9,10-dimethylantracene (**46**) (Scheme 1.20) carried out in LPDE. The rate constants of the reaction showed that the reaction was faster by 9-fold than that in pure solvent. A plot of rate constants as a function of concentration of LiClO₄ is shown as Figure 1.9.

Further the reactions of **46** with fumaronitrile (**48**) (Scheme 1.21) and isoprene with dimethyl acetylenedicarboxylate were also investigated. The rates of these two reactions in 4 M LPDE were accelerated by about 50 and 100 times, respectively than that in pure ether.

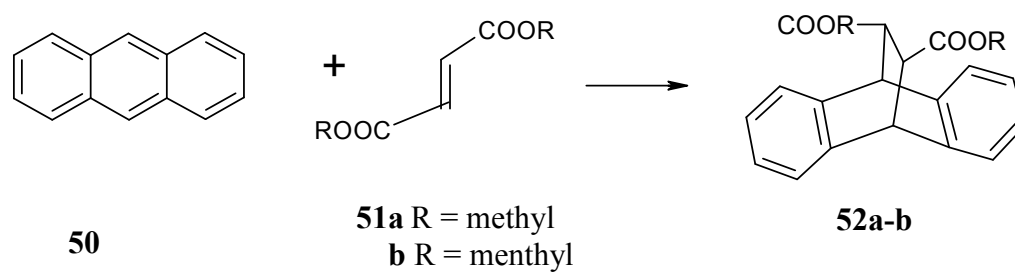
In 1960, Yates and Eaton made use of Lewis acid catalyst AlCl₃ to bring about remarkable acceleration of Diels-Alder reactions.⁹⁶ The reaction of equimolar amounts of anthracene with **2** in 0.0625 M AlCl₃ in dichloromethane was completed in 1.5 min. The time required for 95 % completion for the reaction was 4800 h in absence of AlCl₃. The reaction of anthracene (**50**) with dimethyl fumarate (**51a**) (Scheme 1.22) in presence of AlCl₃ was completed in 5 min. In dioxane, at high temperature a poor yield was obtained after 2-3 days.



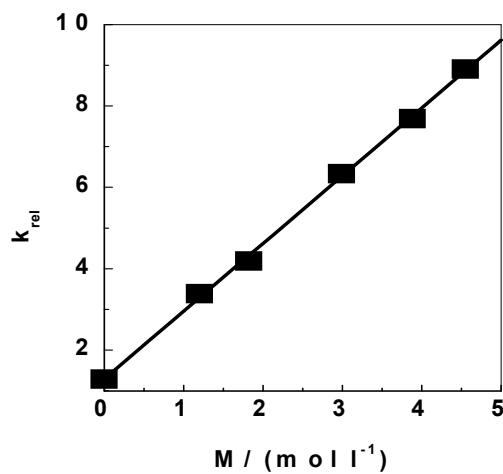
SCHEME 1.20



SCHEME 1.21



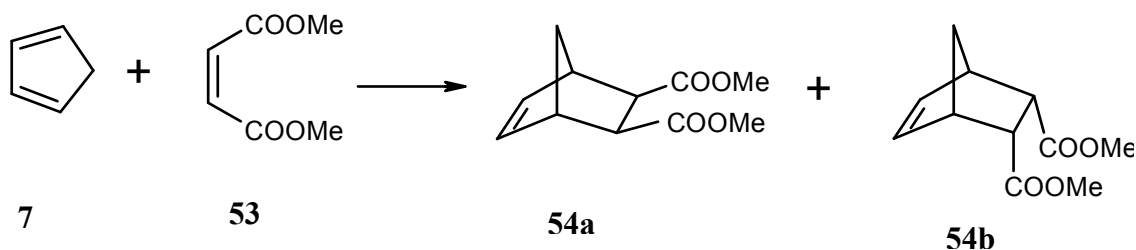
SCHEME 1.22

FIGURE 1.9. Lewis acid catalysis by Li⁺ using LPDE solution

The analysis of LPDE solution reveals the fact that below 4.25 M, LiClO₄ exists as dietherate. In this concentration range the coordination of ether molecules to the Li⁺ ions makes it a more powerful Lewis acid. The observation was consistent with the

enhancement in the rate of ionization reaction of triphenylmethyl chloride. Above 4.25 M, monoetherates exist along with dietherates. In highly concentrated solution, the clusters come together to form a lattice. This decreases the Li^+ ions available for the catalysis, which results in slowing down the reaction rate.⁹⁰

The most convincing explanation for the LiClO_4 activity based on Lewis acid catalysis was questioned by Kabalka and coworkers due to its moderate activity in liquid phase.⁹⁷ For the reaction of **7** with dimethyl maleate (**53**) (Scheme 23) they found that the modest change in *endo/exo* ratio as 3:1 in diethyl ether to 8:1 in the presence of 6 M LPDE at ambient temperature.⁹⁸



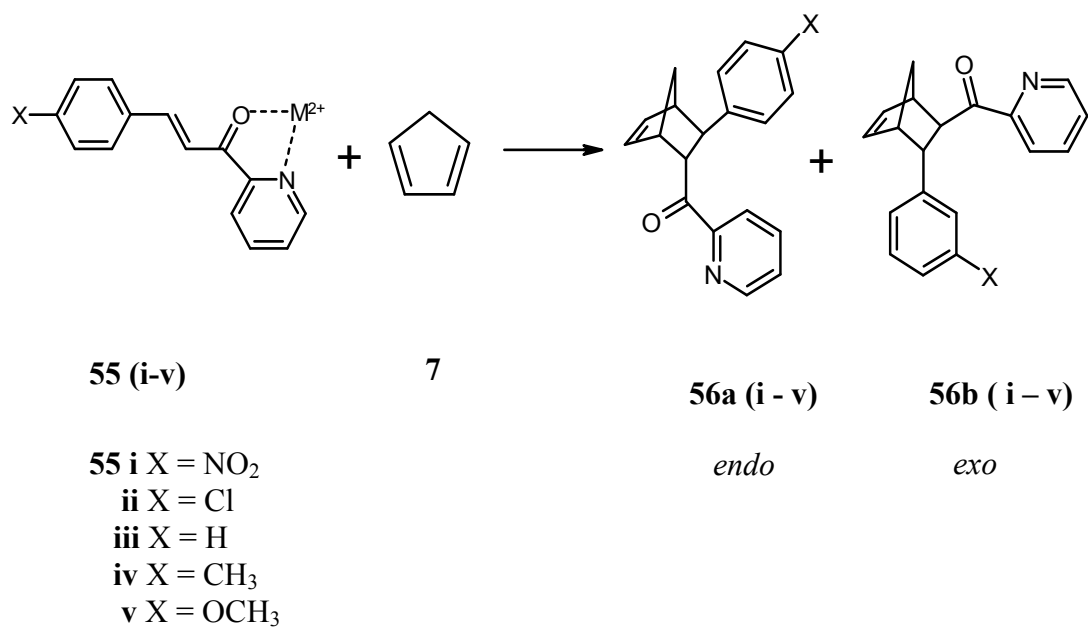
SCHEME 1.23

Another example in this regard was the reaction between **7** and (-)-dimethyl fumarate (**51b**) (Scheme 1.22) in LPDE. The percent diastereomeric excess (%DX) increased as the concentration of LiClO_4 increased, but the effect was moderate. The %DX values obtained in presence of strong Lewis acids such as AlCl_3 , Et_2AlCl were larger as compared to that in LPDE. From these results in conjunction with the NMR experiments and MNDO calculations the authors concluded that the strong intrinsic Lewis acidity of Li^+ is moderated in diethyl ether by complexation to the solvent and the counterion.

Diels-Alder reactions enhanced by Lewis acid catalysis in aqueous medium have been described.^{99,100}

Engberts and coworkers reported Diels-Alder reactions that are catalyzed by Lewis acids in water.^{101,102} The reaction between **7** and bidentate dienophiles 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (**55**) (Scheme 1.24) were observed to catalyze in water in presence of Lewis acid catalysts, Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} . Relative to uncatalyzed reaction

in acetonitrile, catalysis by 0.01 M $\text{Cu}(\text{NO}_3)_2$ in water accelerated the reaction by a factor of 79300. The catalytic efficiency of the Lewis acids studied, followed the order $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} \gg \text{Zn}^{2+}$. In case of catalyzed reactions, the effect of water was less pronounced in accelerating the rates than the corresponding uncatalyzed reaction.

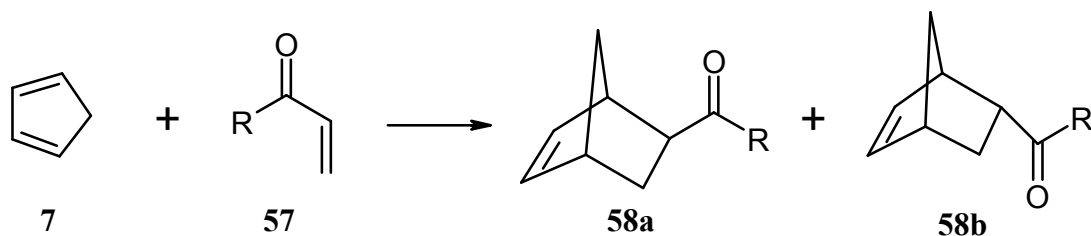


SCHEME 1.24

1.4.5 Enforced hydrophobic hydration and hydrogen bonding

Engberts and coworkers introduced the term ‘enforced pairwise hydrophobic hydration’ in order to explain the huge rate enhancements for the reaction in water and in highly aqueous binary mixtures.¹⁰³ The term ‘enforced’ distinguishes the associative process of diene and dienophile from the hydrophobic interactions between reactants that do not lead to the activated complex. They stressed the point that diene and dienophile do not aggregate in water spontaneously under the reaction conditions. In the whole process, the hydrophobicity of diene and dienophile decreases. The concept of enforced hydrophobic hydration was developed by investigating the rate constants of several Diels-Alder reactions. The reactions of **7** with alkyl vinyl ketones (**57**) (Scheme 1.25) and with 5-substituted-1,4-naphthoquinones (**44a-d**) and the intramolecular Diels-Alder

reaction of *N*-furfuryl-*N*-methylmaleamic acid were investigated in water, monohydric alcohols, aqueous solutions of monohydric alcohols. The rate constants for the reaction of **7** with **57** in water were about 200 and 5800 times larger than those in *n*-hexane. In highly aqueous solution, water become more structured by the formation of



SCHEME 1.25

hydrophobic hydration shells surrounding the apolar cosolvent molecules. The addition of structure-promoting cosolvent favored enforced hydrophobic hydration, which resulted in increasing the reaction rates. The detailed molecular picture of the enforced hydrophobic hydration is described in several articles.^{104,105}

A combined effect of both enforced hydrophobic interactions and the hydrogen bonding in stabilizing the TS was attributed as origin of rate enhancement in several Diels-Alder reactions.¹⁰⁵⁻¹⁰⁸

The contribution from hydrophobic and hydrogen bonding effects in promoting Diels-Alder reactions have been calculated using a combined QM/MM potential.

Jorgensen and coworkers combined the quantum and statistical mechanics to probe the role of water on the kinetics of Diels-Alder reactions.¹⁰⁹ The studies of the reactions of **7** with dienophiles like **19**, **14** and 2-methoxy-1,6-naphthoquinone (**44c**) showed that the rates were increased by 30, 740 and 6800 in aqueous solution than that in hydrocarbon. Thus, the substantial range of rate enhancement for different dienophiles in aqueous medium forced them to suggest that one or more additional factors are involved in rate enhancement.¹¹⁰ From the computational results, it was proposed that the aqueous acceleration for the reactions of **7** with **19** contains a significant nonhydrophobic component resulting from the enhanced polarization of the TS that leads to stronger hydrogen bonds at the carbonyl oxygen. The number of hydrogen bonds to the carbonyl

oxygen was calculated to be between 2-2.5 during the reaction. Further, the interaction of each bond was 1-2 kcal mol⁻¹ favorable for the TS than for the reactants or products. These observations reflected the sensitivity of hydrogen bonding to small charge variation. Consequently, hydrogen bonding was proposed as the key factor controlling the variation of the accelerations for Diels-Alder reactions in water.

Monte Carlo simulations predicted that the free energies of activation to be reduced on going from hydrocarbon to water by about 2.1, 3.8 and 5.0 kcal mol⁻¹ for the above-mentioned reactions.¹¹¹ These values were comparable to those obtained for transfer from gas phase to water. The studies also showed that the retro Diels-Alder reactions were accelerated in water since the cycloadducts were stabilized less effectively than the TS by water. In view of these results and the variation in solvent accessible surface area confirmed that the rate promotion in water is predominantly from enhanced hydrogen bonding between water molecules and the polarized TS and only partly due to hydrophobic association of the reactants.

Enforced hydrophobic interaction due to reduction of hydrophobic surface area during activation process was found to provide 4.6 kcal mol⁻¹ stabilization of the TS in **7** with isoprene. On the other hand, hydrophobic effects and enhanced hydrogen bonding at the TS in the reaction of **7** with **14** were found to contribute equally to the aqueous rate acceleration.¹¹²

The complex formation through hydrogen bonding in the stabilization of TS has also been suggested in enhancing Diels-Alder reactions.¹⁰⁷

1.4.6 Solvent polarity parameters

Attempts have been made to explain the rate profiles of the Diels-Alder reactions in aqueous as well as non-aqueous media in terms of the solvent polarity parameters. Polarity of a solvent is determined by its solvation capability for reactants and activated complexes as well as for molecules and excited states. It is obvious that such a definition of solvent polarity cannot be measured by an individual physical quantity such as dielectric constant. In such a situation other indices of solvent polarity are sought. The experimental results have been analyzed using the solvent properties Dimroth-Reichardt

$E_T(30)$, Mayer-Guttman acceptor number, Kosower Z, hydrogen bond donor α , hydrogen bond acceptor β , Kamlet-Taft dipolarity-polarizability π^* etc.

When $\log k$ (rate constant) values for the reaction of **43** with **44a** were plotted as a function of AN, a good hyperbolic relationship was obtained (Figure 1.10).¹¹³ Paoloni and coworkers found that the AN correlate with the energy of the LUMO of the solvent and the DN correlate with the energy of the HOMO.¹¹⁴ Acceptor solvents coordinate quinone (**44a**) at the oxygen functions lowering its LUMO as well as its HOMO. The LUMO energy of the solvent can be calculated from the Equation 1.4 given below, assuming that it is a linear function of its AN.

$$\Delta E = \frac{a - b \text{ AN}}{c - d \text{ AN}} \quad (1.4)$$

The influence of the EPA properties of the solvent on the rates of Diels-Alder reactions was first recognized in the reaction of **43** with **44a**. The rate constant of this reaction was measured in a series of 17 solvents (Scheme 1.19).¹¹⁵

The reactions of **43** with dienophiles **44a-d** also showed the hyperbolic correlation between $\log k$ and AN.¹¹⁶ The kinetic data for the intramolecular Diels-Alder reaction 1-phenyl-4-[2-(3-methylbut-2-enyloxy)phenylmethylene]pyrazol-5-one showed the same hyperbolic correlation with AN of the solvents and benzene solutions with varying amounts of acetic and haloacetic acids.¹¹⁷ From the observations it was concluded that the solvent effect and acid catalysis follow the same mechanism, increasing the reaction rate by coordination with the unsaturated heterocycle moiety whose LUMO energy is lowered.

A new solvent parameter, solvophobic power Sp developed by Abraham and coworkers was used to explain the rate variation in case of pure water and organic solvents and aqueous organic mixtures.¹¹⁸ Schneider and Sangwan presented the first quantitative description of reaction rates as a function of Sp .¹¹⁹ They found a linear correlation of $\log k$ versus Sp for the reaction of **7** with **51b** (Scheme 1.22) in aqueous organic solvents and pure solvents.

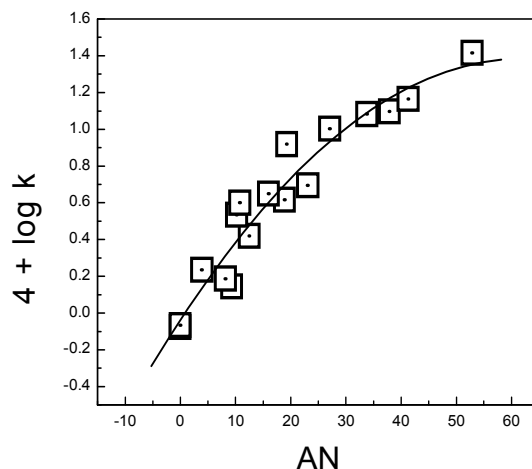


FIGURE 1.10. Correlation of rate constants with AN for the reaction of **43** with **44a** (Scheme 1.19)

Since a single parameter could not explain the rate variation in a variety of solvent, a multiparameter approach was proposed involving a combination of various solvent parameters such as Sp , α , β , various polarity scales etc. The rates of reactions of **7** with several dienophiles were correlated with the Sp and E_T , a generally accepted measure of polarity by the Equation 1.5 as shown below.¹²⁰

$$\log k = a. Sp + m E_T + \log k_0 \quad (1.5)$$

Similar approach was used to explain the rates of the reactions of **16** with methyl (*E*)-2-cyanocinnamate, methyl acrylate and (1*R*, 2*S*, 5*R*)-menthyl acrylate.^{121,122,123} The *endo/exo* product ratios of the reaction of **7** and methyl (*E*)-2-cyanocinnamate obtained in 12 water-dioxane and water-acetone media showed a fairly good correlation with Sp . The correlation curve further improved using E_T in addition to Sp .¹²⁴ The *endo/exo* ratios obtained for the reaction of **7** with **10** showed similar trend.¹²⁵

The influence of the Sp and E_T parameters on the *endo/exo* selectivity was first explored by Schneider and Sangwan.¹²⁴ The *endo* products increased in the reaction of **7** with maleic acid derivatives by the use of water in the non-aqueous solvent. A good correlation of *endo/exo* selectivity was observed with the Sp ($r = 0.9835$) parameter while with E_T , a poor correlation ($r = 0.9177$) was observed. Further, the multiparameter approach involving Sp and E_T parameters did not show an improvement in the fit ($r = 0.9850$) as compared to that of Sp alone.

The effects of solvents on the reaction between **7** and (1R, 2S, 5R)-menthyl acrylate were studied using AAKT model.¹²² The results indicated that the α parameter is the only solvent feature with a statistically significant regression coefficient.

The use of AAKT model indicated that the solvent π^* has a negative influence on the rate of reactions of *o*-quinone imine with 2,3-dimethylbutadiene and with ethyl vinyl ether.¹²⁵

Cativiela et al. described the solvent effects using the various solvent parameters on rate profiles of Diels-Alder reactions in detail.⁵³

1.5 Ionic liquids

Water is the most environment friendly solvent. In addition to aqueous reaction media, RTIL have emerged as substitutes for VOC. VOC are compounds that have a high vapor pressure and low solubility in water. Despite their widespread use, VOC are flammable and are potential health hazards. Many organic solvents are used in a number of industrial processes and due to their volatility, are emitted directly or indirectly into air during many chemical processes. These solvents go through complex chemical reactions in the atmosphere to produce VOC which have a number of indirect effects.

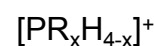
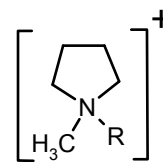
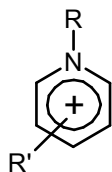
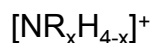
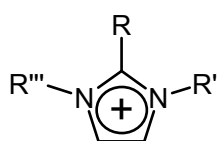
At a February 1998 meeting of the Organization for Economic Co-operation and Development (OECD) Advisory Group on Risk Management, the United States Environmental Protection Agency (US EPA) proposed four innovative activities that the OECD could undertake to promote and enhance chemical risk management. One of the activities is known as Green/ Sustainable Chemistry. Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Paul Anastas and John Warner published the 12 principles of 'Green Chemistry', in *Green Chemistry: Theory and Practice* (Oxford University Press: New York, 1998). They provide a road map for chemists to implement green chemistry. The 12 principles cover concepts such as use of safe, environment benign solvents where possible, best form of waste disposal etc.

In this regard, RTIL or ionic liquids as they are commonly known are considered as ‘green solvents’ since they reduce or eliminate environmental hazards associated with VOC.

Ionic liquids are salts that are liquids at or below room temperature. The use of ionic liquids in synthesizing organic products can be made following 12 principles of green chemistry as noted by Anastas and Warner.

Unlike molecular liquids (for example, water, ethanol, acetone etc.), ionic liquids are constituted entirely of ions, organic cations and organic or inorganic anions. Examples of some common cations and anions that are used to synthesize ionic liquids are listed in Figure 1.11.

Some typical cations:



Some typical anions:

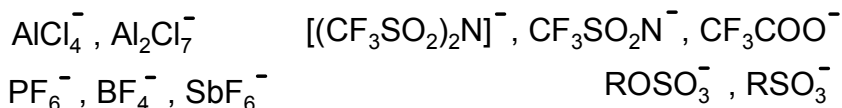


FIGURE 1.11. Typical cations and anions of ionic liquids

Important properties of ionic liquids that make them potential solvents are listed below.¹²⁶

1. They do not possess measurable vapor pressure. Also they can be used in high-vacuum system.
2. They possess high thermal stability
3. They are nonflammable.

4. They are good solvents for a wide range of both inorganic, organic materials and unusual combinations of reagents can be brought into the same phase.
5. They have the potential to be highly polar yet noncoordinating solvents.
6. Since ionic liquids can be synthesized by metathesis reaction, a range of task specific ionic liquids can be synthesized.
7. Most importantly they can be recycled for a number of times without loss of activity.

For these interesting properties, ionic liquids have been used as solvents as well as catalyst for a number of organic and inorganic reactions such as hydrogenation reactions, oxidation reactions, hydroformylation, Heck reaction olefin dimerization, electrophilic substitution etc.^{126, 127}

The first report on ionic liquid, ethylammonium nitrate (m.p. 12°C) was published in 1914.^{128, 129} A history of ionic liquids has been published by Wilkes.¹³⁰ In past few years, a very large number of papers have been published in the area of ionic liquids.^{127,128,131-134}

1.5.1 Physicochemical properties of ionic liquids

Ionic liquids offer opportunities to control the reactivity of organic compounds that is unobtainable with molecular solvents. It is noteworthy in this direction to study their properties as functions of anion, cation substitution partners.

1. Melting point

Melting points, that is solid-liquid transition temperatures of ionic liquids are below ambient temperature as low as -100°C. Melting points are influenced by structures of cations and anions. Melting point of symmetrically substituted 1,3-dialkylimidazolium cations are higher than those of unsymmetrical cations.¹³⁵ Melting points decrease with increasing alkyl substitution up to a critical point around 8-10 carbons and then increase with increasing additional substitution. Reduction in melting point can be achieved by increasing the size of the cation as well as anion. For example, the melting point of [EMIM][PF₆] is 62°C, whereas [EMIM][AlCl₄] is 7°C.¹³⁶⁻¹³⁸

The absence of strong hydrogen bonding is a major contributor to low melting point.

2. Conductivity

Since ionic liquids are composed entirely of ions, they are expected to possess very high conductivities. In practice, they possess reasonably good ionic conductivities. They are less conductive than concentrated aqueous electrolytes. The explanation for this observation was based on the reduction of available charge carriers due to ion pairing and/or ion aggregation and to the reduced ion mobility due to the large ion size. The increase in conductivity follows the order of the cation as shown below. Imidazolium \geq sulphonium > ammonium \geq pyridinium. The correlation between conductivity and anion of the ionic liquid is unclear. The conductivity and viscosity of an ionic liquid follows Walden rule. Accordingly, conductivity and viscosity of ionic liquid are inversely proportional with each other.¹³¹

3. Ionic diffusion coefficients

The diffusion coefficients of the constituent ions in ionic liquids are commonly measured either by electrochemical or by NMR method. The extensive data tabulated by Wassecheid and Welton showed that 1-ethyl-3-methyl imidazolium, a bulky cation carries major portion of the charge for all the haloaluminates studied. It was proposed that the smaller anions are more structurally constrained in the charge transport process.¹³⁹

4. Viscosity

Generally ionic liquids are more viscous than most common organic solvents. Viscosities of ionic liquids at room temperature range from 10 cP to more than 500 cP. The viscosities are affected by many factors such as temperature, presence of impurities, and size of ion as discussed below.

1) Temperature

Viscosities of ionic liquids decrease with the increase in temperature. For example, the viscosity of [BMIM][PF₆] decreases by about 27 % as the temperature changes from 293 K to 298 K.¹⁴⁰

2) Effect of impurities

Small amount of impurities can have a large effect on the viscosities of ionic liquids. Residual chloride concentrations of up to 1.5 to 6 wt. % increased the viscosity by about 30 to 600 %.¹⁴¹ In case of non-haloaluminate ionic liquid such as alkyimidazolium ionic liquid absorbs moisture from air due to which their viscosities change. Widegren et al. investigated the effect of dissolved water on the viscosities of ionic liquids such as [BMIM][Tf₂N], [EMIM][Tf₂N] and [BMIM][PF₆].¹⁴² The viscosities of these ionic liquids decrease rapidly with the increasing water content. The kinematic viscosity of [BMIM][PF₆] decreases by about 17 % with addition of only 0.19 % water. The viscosities of other two ionic liquids decrease by about 30 % with addition of 1 % water.

3) Effect of ionic structures

For ionic liquids with same anion, the larger the alkyl substituent on alkyimidazolium ring, higher is the viscosity of the ionic liquid. The general order of increasing viscosity for anion keeping the cation same is: [(CF₃SO₂)₂N]⁻ < [BF₄]⁻ < [CF₃CO₂]⁻ < [CF₃SO₃]⁻ < [(C₂H₅SO₂)₂N]⁻ < [C₃F₇CO₂]⁻ < [CH₃CO₂]⁻ < [CH₃SO₃]⁻ < [C₄F₉SO₃]⁻.¹³¹

5. Polarity

Most commonly used measure of polarity is the dielectric constant of the medium. Since measurement of dielectric constant requires a non conducting medium, it is not possible in case of ionic liquids. Therefore, the polarity scales for ionic liquids have been suggested by using various methods such as absorption spectra, fluorescence spectra, refractive index, organic reactions as probe etc. The $E_T(30)$ values for alkylammonium nitrate, thiocyanate and sulphonate salts are reported to be small as compared to those for substituted imidazolium tetrafluoroborate, hexafluorophosphate, triflate and

trifluoromethanesulphonylimide salt.¹⁴³⁻¹⁴⁵ Generally these values are dominated by the nature of cation. However the role of anion is less clear. It has also been proposed that the solvent strength and polarities of imidazolium and pyridinium based ionic liquids are between acetonitrile and methanol.¹⁴⁶ Polarities of ionic liquids have also been discussed by Chiappe and Pieraccini and Welton and coworkers.^{133,147}

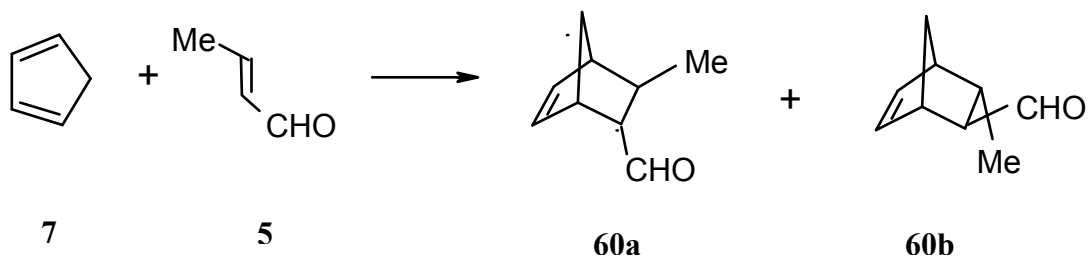
The other physicochemical properties such as melting points, densities, solubilities and solvation, electrochemical properties have been discussed in greater detail by Wassercheid and Welton.¹³¹

The various properties of ionic liquids have been reviewed many times.^{131, 134}

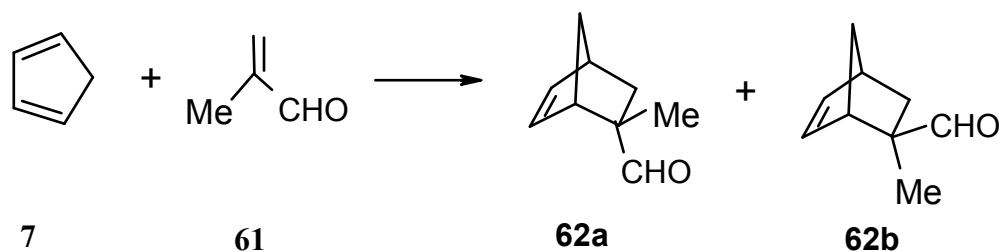
1.5.2 Diels-Alder reactions in ionic liquids

Ethylammonium nitrate was used as a reaction medium for the Diels-Alder reaction of **7** with **10** and with **14**.¹⁴⁸ The *endo* selectivity of the above mentioned reactions were enhanced by about 3 times in ethylammonium nitrate than in the nonpolar organic solvents. However the highest *endo/exo* ratio was obtained when aqueous medium was used as reaction medium.

Dialkylimidazolium salts were used as a Lewis acid catalyst for the Diels-Alder reaction of **7** with crotonaldehyde (**59**) (Scheme 1.26) and with methacrolein (**61**) (Scheme 1.27).¹⁴⁹ The *endo/exo* selectivities for the reaction of **7** with **59** were observed to be greater than 90:10. Similarly for the reaction of **7** with **60**, *endo/exo* ratio was 15:85. However the control reaction in absence of ionic liquid gave no product after 48 h.



SCHEME 1.26



SCHEME 1.27

Chloroaluminate ionic liquids can act as excellent Lewis acid catalysts since the composition of chloroaluminate ionic liquids can be easily varied from basic to acidic by changing the concentration of AlCl_3 . The two classic Diels-Alder reactions of **7** with **10** (Scheme 5) and **7** with **53** (Scheme 23) were investigated in AlCl_3 :BPC and AlCl_3 :EMIC.¹⁵⁰ In the basic (48 % AlCl_3) medium, the reaction of **7** with **53** gave only 32 % yield with *endo/exo* ratio as 4.88 after 22 h. When the reaction was allowed to continue for 72 h the yield was enhanced to 95 % with no significant change in *endo/exo* ratio. A four fold increase in *endo/exo* selectivity was observed (*endo/exo* ratio = 19), when acidic medium (51 % AlCl_3) was employed. The enhancement in *endo* selectivity in acidic medium was attributed to the increase in Lewis/ Brønsted acidity of the medium

Exo-selective reaction of **7** with **12** (Scheme 12) was converted into *endo*-selective reaction by employing chloroaluminate ionic liquids as media.¹⁵¹ In 45 % AlCl_3 :BPC 26 % *endo* products were observed. The *endo* products were enhanced by about 3 times in 60 % AlCl_3 :BPC. When 60 % AlCl_3 :EMIC was used, 4-fold increase was observed in *endo* products than that in 45 % AlCl_3 :EMIC. The applications of chloroaluminates as reaction media have been reviewed by Kumar and Sarma.¹³²

Seddon and coworkers reported that ionic liquids can be proved alternative media to LPDE solution for carrying out organic reactions.¹⁵² The reaction of **7** with **41** (Scheme 1.18) in [BMIM][lactate] was found to give 87 % yield. The yield can be increased up to 99 % by changing the concentration of the reactants. The same reaction in 5 M LPDE offered 61 % yield and in water only 30 % yield. In [BMIM][PF₆], 36 % yield was observed.

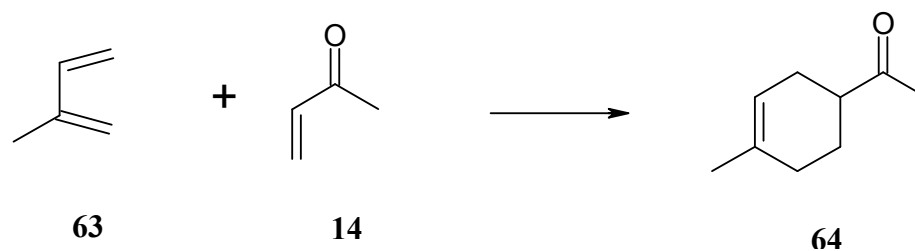
A number of air and moisture stable ionic liquids such as [BMIM][BF₄], [BMIM][ClO₄], [BMIM][CF₃SO₃], [EMIM][NO₃] and [EMIM][PF₆] have been used to carry out Diels-Alder reaction of **7** with **10** (Scheme 1.5).¹⁵³ [BMIM][BF₄] ionic liquid showed strong *endo* selectivity with the *endo* products as 86 % at room temperature. With the increase in temperature of the reaction, *endo* selectivity decreased. It was proposed that the hydrogen bond donor ability between the cation of the ionic liquid and the dienophile is responsible for the enhancement in *endo* selectivity. This was reflected in E_T values of the ionic liquids. It was further revealed that there is a competition for ability to hydrogen bond between cation of the ionic liquid with the anion and that with the dienophile in the reaction. Therefore the higher selectivities were observed in ionic liquids with strong hydrogen bond donor cation coupled with weakest hydrogen bond accepting anion.¹⁵⁴ The solvent effects on **7** with **10** reaction in ionic liquids were rationalized in terms of various factors such as hydrogen bond donor capacity of ionic liquid, steric bulk on the cation, electrostatic association between the ions of ionic liquids, HOMO and LUMO π -orbital interactions and polarities of ionic liquids.¹³³

Recently, Tiwari and Kumar have demonstrated experimentally that Diels-Alder reaction of **7** with variety of acrylates proceed faster in water than in ionic liquids.¹⁵⁵ The Diels-Alder reactions were carried out in ionic liquids such as [EMIM][BF₄], [BMIM][BF₄], [BMIM][PF₆], [OMIM][PF₆] and [BMIM]I. They clearly demonstrated that water is a more powerful solvent than ionic liquids for Diels-Alder reactions. The deceleration of the reactions was ascribed to the high viscosities as well as E_T^{30} values of ionic liquids.

It has been established that Diels-Alder reactions are accelerated by Lewis acid catalyst. In recent years, rare earth metal triflates [M(OTf)₃] have been employed as efficient Lewis acid catalysts to promote Diels-Alder reactions to offer high yields and *endo/exo* ratios.

Kobayashi and coworkers demonstrated that Diels-Alder reactions of carbonyl containing dienophiles with **7** were catalyzed by a catalytic amount of Yb(OTf)₃ to give corresponding adducts in high yields¹⁵⁶ La(OTf)₃ was shown to be stable in water.^{157,158} The reaction of **16** with 1,3-crotonyl-1,3-oxazolidin-2-one catalyzed by chiral Yb(OTf)₃ afforded 87 % yield with *endo/exo* ratio as 76:24.

The $\text{Sc}(\text{OTf})_3$ was found to be more effective catalyst than $\text{La}(\text{OTf})_3$. The reaction of **63** with **14** (Scheme 1.28) gave poor yield in presence of 10 mol % $\text{Y}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$. The reaction proceeded smoothly to give cycloadducts with 91 % yield in the presence of 10 mol % $\text{Sc}(\text{OTf})_3$.¹⁵⁹



SCHEME 1.28

$\text{Ln}(\text{OTf})_3$ with $\text{Ln} = \text{La}, \text{Pr}, \text{Yb}, \text{Nd}$ was shown to catalyze aza Diels-Alder reaction of **16** with range of aldehydes and amine hydrochlorides.¹⁶⁰

Diels-Alder reactions catalyzed by $\text{Ln}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$ have been reviewed by Kobayashi.^{161,162}

The comparison of effectiveness of triflates like $\text{Ce}(\text{OTf})_3 \cdot 5\text{H}_2\text{O}$, $\text{Y}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$ as Lewis acid catalysis was made for the reaction of **7** with **14** (Scheme 1.7). It was found that $\text{Ce}(\text{OTf})_3 \cdot 5\text{H}_2\text{O}$ is the most active catalyst in $[\text{HMIM}][\text{BF}_4]$.¹⁶³

Several papers on the use of triflates for several Diels-Alder reactions have published.^{164,165}

The literature survey shows that the Diels-Alder reaction can be accelerated by employing aqueous, nonaqueous media and ionic liquids. Several factors have been suggested to explain the kinetic profiles of Diels-Alder reactions. However, no unified approach has been put forward to explain these rate enhancements.

Chapter 2
OBJECTIVES

Since no unified approach has been suggested to explain the variation in reaction rates and stereoselectivities (*endo/exo* ratios), the aim is to investigate the factors responsible for the rate profiles of the Diels-Alder reactions. Therefore, the rate profiles of model Diels-Alder reactions carried out in different solvent media as salt solutions and ionic liquids will be the subject of investigation. Based on the literature survey discussed in chapter one, the objectives of the research work carried out are as follows:

- 1) to delineate the origin of forces responsible for the spectacular rate acceleration of Diels-Alder reaction in salt solutions,
- 2) although the dramatic rate acceleration of these reactions in aqueous media can be explained on the basis of hydrophobic effect, it remains still a qualitative explanation. The aim is to explain variations in the reaction rates and stereoselectivities (*endo/exo* ratios) through a measurable parameter,
- 3) to propose the tailor-made conditions for achieving maximum rate acceleration by solvent manipulation,
- 4) to assess the role of viscosity in determining the kinetics of Diels-Alder reactions and
- 5) to investigate the rate profiles of intramolecular Diels-Alder reaction by employing ionic liquids.

Chapter 3
REACTIONS IN SALT SOLUTIONS

In the present chapter, the effects of pure water and aqueous salt solutions on the rate constants and *endo/exo* ratios of Diels-Alder reactions of cyclopentadiene (**7**) with methyl acrylate (**10**) and with methyl methacrylate (**12**) are discussed in detail. The observations are explained on the basis of salting phenomena. The mechanistic aspects of the Diels-Alder reactions in aqueous media have also been described.

3.1 *Endo*- and *exo*-selectivities of Diels-Alder reactions

Alder's rule of 'maximum accumulation of unsaturation' is generally followed in determining the *endo* and *exo* products for Diels-Alder reactions. However, some Diels-Alder reactions violate Alder rule. Few Diels-Alder reactions are reported in the literature that show borderline behavior. The reaction of **7** with **10** (Scheme 1.5) that follows Alder rule, is *endo* selective in organic solvents as well as in water.^{58,166} The reaction of **7** with **12** (Scheme 1.6) was reported as *exo*-selective reaction in organic solvent whereas the reaction of **7** with **8** (Scheme 1.4) shows borderline behavior.⁵⁸ With all three dienophiles in the above-mentioned reactions, $\log(\textit{endo/exo})$ increases (i.e. becomes increasingly positive) as the solvent changes from nonpolar to polar. The observations can be explained if the TS is assumed involving a bimolecular aggregate in which the diene and dienophile lie in parallel planes as shown in Figure 3.1. It is clear from the

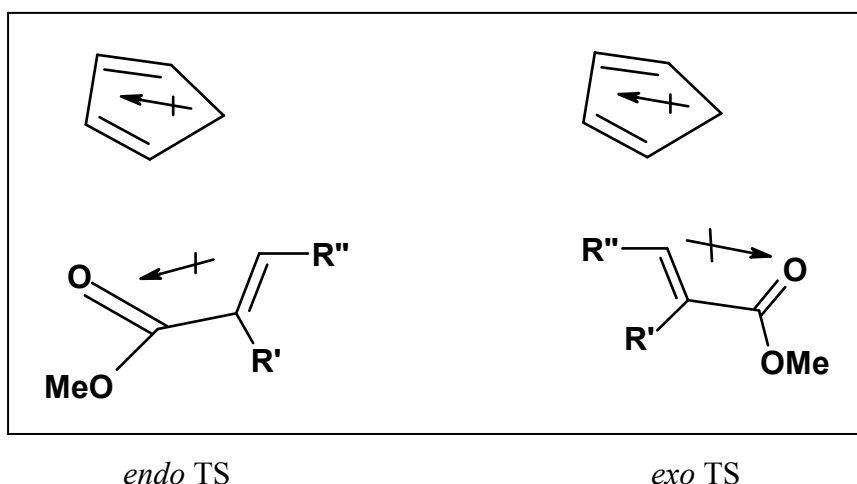


FIGURE 3.1. Orientation and dipole moments of diene and dienophile in the *endo* and *exo* TS

figure that the permanent electric dipole of the *endo* TS is greater than that of corresponding *exo* isomer since in the *endo* TS, the component dipoles point in roughly in the same direction. So the net dipole moment is greater than the *exo* TS, where the component dipoles point in roughly opposite direction.

The temperature dependence study showed that as the temperature raises, the *endo* products go on decreasing for the reactions of **7** with **10** and with **8**. For the reaction of **7** with **12**, the *endo* products increase with the increase in temperature. The temperature-dependence of the product ratio can be expressed by Arrhenius form as

$$\log (k_N / k_X) = \log (A_N / A_X) + (E_X - E_N) / 2.303 RT \quad (3.1)$$

The values for the ratios of the pre-exponential factors and for the differences in empirical activation energies can be estimated from the intercepts and slopes of plots of $\log (k_N / k_X)$ versus $1/T$. The differences in the entropies of activation are given by the equation given below

$$\Delta S_N^\ddagger - \Delta S_X^\ddagger = 2.303 R \log (A_N / A_X) \quad (3.2)$$

The differences in enthalpies of activation are identical with the differences in Arrhenius activation energies. The difference between activation enthalpies ($\Delta\Delta H^\ddagger = \Delta H_X^\ddagger - \Delta H_N^\ddagger$) and the activation entropies ($\Delta\Delta S^\ddagger = \Delta S_X^\ddagger - \Delta S_N^\ddagger$) for the *endo*- and *exo*-isomers have been reported for the reactions of **7** with **8**, with **10** and with **12**.⁵⁸ For the reaction of **7** with **10**, $\Delta\Delta H^\ddagger$ are observed to be positive in all the solvents studied indicating the *endo*-preference for the reaction. For the reaction of **7** with **12**, $\Delta\Delta H^\ddagger$ is negative in majority of the organic solvents studied. This is partially responsible for the *exo*-preference in the present reaction. Moreover, in this enthalpy-controlled reaction methyl group contributes preferentially than the various polar unsaturated groups.¹⁶⁷ The *exo*-selectivity of this reaction has been explained on the basis of the steric hindrance between the methylene hydrogens of **7** and the methyl group of **12**.¹⁶⁸

The *endo* selective reactions that follows Alder rule, for example, **7** with **10**, **7** with **14** (Scheme 1.7) are accelerated by water.⁴⁹ The dramatic rate acceleration has been attributed to the hydrophobic effect of water. Our aim is to study Diels-Alder reaction that follows anti-Alder rule.

3.2 Effects of the aqueous salt solutions on the *endo/exo* ratios of *exo*-selective reaction

As has been discussed earlier, the reaction of **7** with **12** (Scheme 1.6) is *exo*-selective in organic solvents.^{58,168-172} We carried out the reaction in water, as it serves

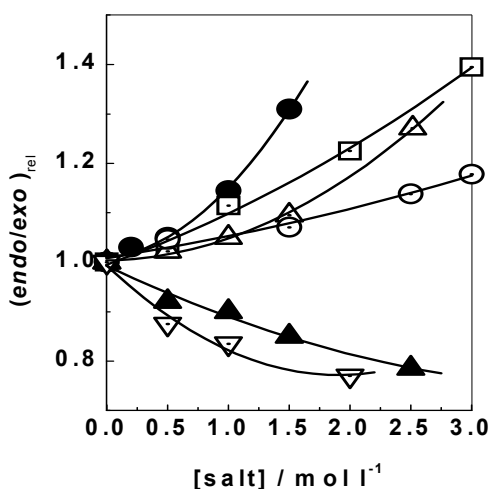


FIGURE 3.2. $(endo/exo)_{rel}$ as a function of salt concentration, $[salt]$ for the reaction of **7** with **12** (Scheme 1.6); (●) CaCl₂, (□) Na₂SO₄, (Δ) KCl, (○) LiCl, (▲) GnCl, (▽) LiClO₄.

as a reference reaction. The average value of the *endo/exo* ratio for this reaction was found to be 0.40 (*endo* as 29 %, *exo* as 71 %). This shows that water alone cannot reverse the *endo/exo* value. Further, we studied the effects of aqueous solutions of LiCl, KCl, Na₂SO₄, CaCl₂, GnCl and LiClO₄ on the *endo/exo* ratios of this reaction. Salts such as LiCl, KCl, Na₂SO₄, CaCl₂ increase the *endo/exo* ratios. This indicates that these salts enhance the amount of *endo* products. The variations in *endo/exo* ratios with increase in concentrations of salts are shown in Figure 3.2. The $(endo/exo)_{rel}$ is defined as the *endo/exo* obtained in salt solution over that in water.

In 1.5 M CaCl_2 in aqueous solution the *endo/exo* ratio enhances by 1.3 times. The same magnitude of increase i.e. about 1.3 times in the *endo/exo* ratio was observed when 3 M aqueous solution of Na_2SO_4 was used as a solvent medium for the reaction. The *endo/exo* ratio increases by about 1.3 times in 2.5 M aqueous KCl as compared to that in water. LiCl was found to be least effective in increasing the *endo* products. In aqueous solution of 3 M LiCl, the *endo/exo* enhances by only 1.1-fold over water. It is clear from the above observations that of these salts, CaCl_2 is found to be the most effective additive in enhancing the *endo/exo* ratios at 1.5 M concentration. This suggests that the *endo* product is preferred over *exo* in aqueous solution in the presence of CaCl_2 . The order in which these salts increase the *endo/exo* values is: $\text{CaCl}_2 > \text{Na}_2\text{SO}_4 > \text{KCl} > \text{LiCl}$.

On the other hand, both GnCl and LiClO_4 decrease the *endo/exo* ratios, thereby increasing the dominance of the *exo* product. In aqueous solution of 2 M LiClO_4 the *endo/exo* ratio decreases by about 0.7 times than that in water. The 2.5 M aqueous solution of GnCl shows the decrease of 0.8-fold as compared to that in water. Thus, LiClO_4 is a more effective salt than GnCl in decreasing the *endo/exo* ratios for this reaction. The increase and decrease of *endo/exo* values and rates of Diels-Alder reaction in salt solutions are attributed to the salting-out and -in phenomena.^{49,56,59,173-178}

3.3 Salting phenomena

A number of solution properties associated with ions such as salting phenomena are connected with the electrical influence of the ions on the solvent, in particular electrostriction. The understanding of such properties in detail requires the knowledge of electrostriction.

Liquid water is tetrahedrally coordinated liquid having a large structurally free volume. When ions are introduced into water, they are capable of wrenching water molecules out of the water framework so as to envelope themselves with solvent Sheaths (refer Figure 3.3). The volume change on addition of ion to water arises from the local collapse of the solvent structure. Thus in aqueous solution containing ions, the actual size of water molecules hardly changes, but the spatial arrangement of water molecules is largely modified. The water molecules are oriented in presence of ions and



FIGURE 3.3. An cation enveloped by a sheath of oriented water molecules.

are more compactly packed in the primary solvation shell as compare to water alone. Thus due to electric field of ion, water becomes more compressed. This phenomenon is molecules is largely modified. The water molecules are oriented in presence of ions and are more compactly packed in the primary solvation shell as compare to water alone. Thus due to electric field of ion, water becomes more compressed. This phenomenon is known as electrostriction. The schematic diagram is shown in Figure 3.4. The process of electrostriction depends on the charge and size of the ion.^{179,180}

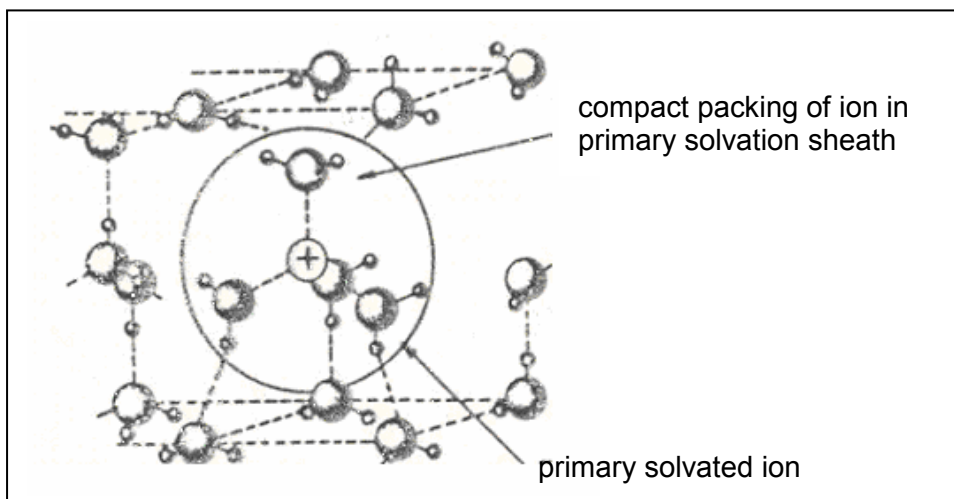


FIGURE 3.4. Schematic diagram to illustrate the principle of electrostriction, water molecules are compactly packed in primary solvation sheath

The addition of salts to water results in the decrease of volume of solution due to electrostriction. When nonelectrolytes such as diene and dienophile are added to such water solution, there are less free water molecules to dissolve diene and dienophile. Some of the nonelectrolyte molecules reassociate. Hence, they precipitate out. This is known as salting-out process.^{62,179} The salts like LiCl, NaCl, NaBr, CaCl₂, KCl act as salting-out agents in water.

On the contrary, in salting-in process the ions loosely bound water molecules in their aqueous solutions. This results in increase of the solubility of nonelectrolytes. The examples of salting-in agents are GnCl and LiClO₄. The pictorial presentations of salting-out and salting-in processes are shown in Figure 3.5.

Accordingly, the salting-out agents lower the solubilities of diene and dienophile as compared to the solubilities in water. The reverse effect takes place in presence of salting-in agents. The salting-out agents like NaCl, NaBr, CaCl₂, Na₂SO₄, KCl, LiCl are also known as structure-makers whereas the salting-in agents GnCl and LiClO₄ are called as structure-breakers.

In the electrostrictive region (primary solvation sheath), the ionic charge on the ion completely orients the surrounding water molecules. The water molecules in this region although rapidly exchanging, are immobilized to a greater extent compared to bulk water. Since the water molecules are more firmly packed in around an electrostrictive ion than in bulk water, the net volume of the system is decreased in the electrostrictive region. When this region is dominant, the ion is called as structure-making ion.¹⁸¹ The regions in water are shown in Figure 3.6.

Water in the second solvation sheath are less immobilized or tightly packed. In the intermediate region between the electrostricted region and the bulk water, the orientation of water molecules is diminished. The orientation of water molecules is large enough to interfere with the formation of the normal water structure. If this region of less structure is dominant, the ion is classified as structure-breaker ion.¹⁸¹

In case of salting-out agents, the structure-making ability of cation outweighs the structure-breaking ability of anion. The salts such as CaCl₂, KCl, Na₂SO₄ and LiCl act as salting-out agents for the reaction of **7** with **12**. The salting-out agents increase the

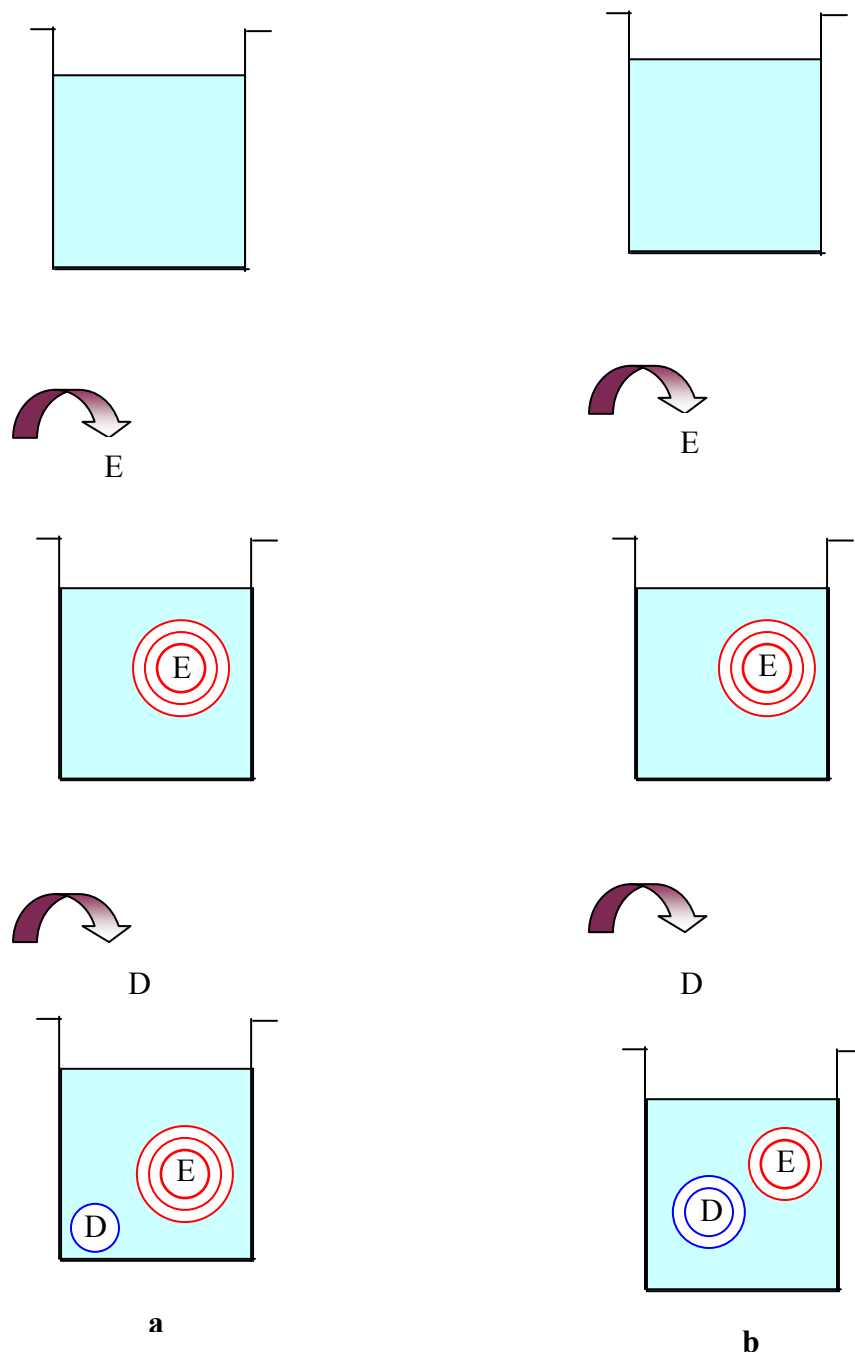


FIGURE 3.5. Salting-out (a) and salting-in (b) processes. The shaded portion denotes water, involving electrolyte, E, diene or dienophile, D

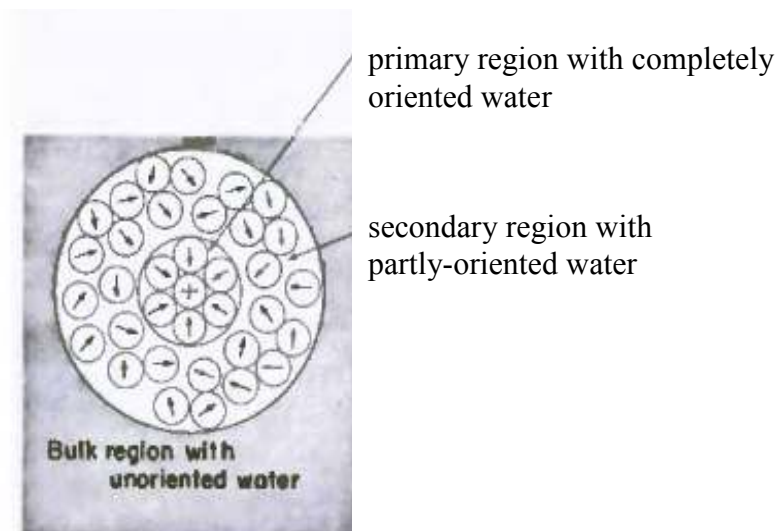


FIGURE 3.6. The neighborhood of an ion consists of three regions with differing solvent structures: 1) the primary or structure-forming region, 2) the secondary or structure-breaking region and 3) the bulk region.

hydrophobic effect operating in the solvent medium. This results in decrease of the solubilities of diene and dienophile, which consequently accelerates the *endo/exo* ratios. The salts like GnCl and LiClO_4 decrease the hydrophobic effect and so the *endo/exo* ratios.

The variations in *endo/exo* ratios obtained in aqueous salt solutions are supported by the solubility data of **12** in aqueous solutions of CaCl_2 , Na_2SO_4 , KCl , LiCl , GnCl and LiClO_4 . Figure 3.7 shows the relative solubilities of **12** in aqueous solutions of salting-out and salting-in agents. The salts, CaCl_2 , Na_2SO_4 , KCl and LiCl lower the solubility of **12** as compare to in water and thus **12** salts out. On the other hand, GnCl and LiClO_4 increase the solubility of **12** through the salting-in effect. The quantity $(S/S^0)_{\text{MMA}}$ shows the relative solubility of **12** and is defined as the solubility of **12** in salt solution over that in water.

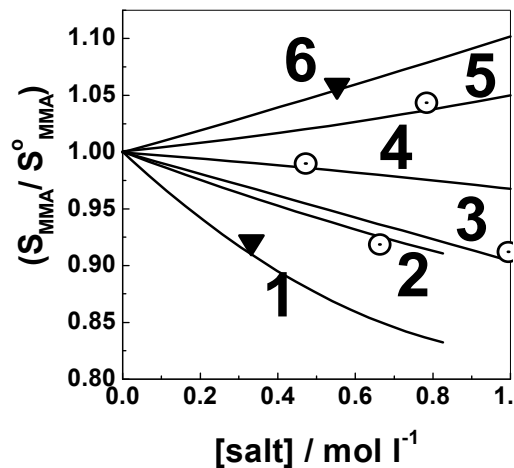


FIGURE 3.7. Relative solubilities of methyl methacrylate, ($S_{\text{MMA}}/S_{\text{MMA}}^0$) in (1) CaCl_2 , (2) Na_2SO_4 (3) KCl (4) LiCl (5) GnCl (6) LiClO_4 ; lines are calculated, points experimental.

3.4 Salting coefficients

The solubility of a nonelectrolyte in an aqueous salt solution is given by the Setschenow equation as shown in Equation 3.3.

$$\log (S_o/S) = k_s c \quad (3.3)$$

where, S_o is solubility of nonelectrolyte in pure water

S is solubility of nonelectrolyte in salt solution

c is the concentration of salt in mol l^{-1}

k_s is the salting coefficient

The k_s is a characteristic value of a given salt- nonelectrolyte (diene or dienophile in case of Diels-Alder reaction) pair. The McDevit-Long theory of the salt effect attributes the sign of k_s to the influence of salt on the structure of water.¹⁷⁸ In salting-out phenomenon the water structure is compressed and it becomes more difficult to introduce nonelectrolyte in solution. This predicts a positive value of k_s as a result of decrease in

solubility ($S_o > S$) of nonelectrolyte. On the other hand, water structure is loosened on addition of salt in salting-in phenomenon. This results in increasing solubility of nonelectrolyte ($S_o < S$) in salt solution. This gives a negative value of k_s . In practice, the Setschenow equation is found to be valid only at low salt concentration. So the k_s value is obtained by differentiating with respect to c as

$$k_s = \left(- \frac{d(\log S)}{d c} \right)_{c \geq 0} \quad (3.4)$$

In order to rationalize the salting effects in this reaction, the salting-out and -in coefficients are computed using scaled particle theory.¹⁸² It has been successfully applied to variety of properties, including solubilities.^{166,183,184} The salting coefficients, κ_s are obtained from the computational methodology developed by Shoor and Gubbins,¹⁸⁵ and by Pierotti¹⁸⁶ on the basis of scaled particle theory.

The phenomenon of dissolution of a nonelectrolyte in any solution can be assumed as a combination of two processes, first is the formation of a cavity large enough to accommodate a nonelectrolyte and second is solvation of non-electrolyte.

$$k_s = \left(\frac{d(g_1^h / 2.3 kT)}{d c} \right)_{c \geq 0} + \left(\frac{d(g_1^s / 2.3 kT)}{d c} \right)_{c \geq 0} + \left(\frac{d \log \sum \rho_j}{d c} \right)_{c \geq 0} \quad (3.5)$$

where g_1^h is the free energy when a cavity large enough to hold the nonelectrolyte molecule is formed in the solution, g_1^s is the free energy when nonelectrolyte is introduced into the cavity and ρ_j is the number density of a solution species.

The methodology has been extended to obtain a general expression for κ_s applicable to any salt-nonelectrolyte pair.¹⁸⁷ The κ_s is a combination of three terms: κ_a accounting for the work required to create a cavity large enough to accommodate a nonelectrolyte molecule, either diene or dienophile, κ_b for introducing the diene or dienophile in the cavity and κ_c giving the number density of solution species. The general expressions obtained for κ_s , κ_a , κ_b and κ_c are as follows:

$$\kappa_s = \kappa_a + \kappa_b + \kappa_c \quad (3.6)$$

$$\begin{aligned} \kappa_a = & 2.15 \times 10^{20} (\sigma_3^3 + \sigma_4^3) - 2.47 \times 10^{-4} \phi_0 + \sigma_1 [6.45 \times 10^{20} (\sigma_3^2 + \sigma_4^2) + \\ & 1.34 \times 10^{28} (\sigma_3^3 + \sigma_4^3) - 4.23 \times 10^4 \phi_0] + \sigma_1^2 [6.45 \times 10^{20} (\sigma_3 + \sigma_4) + \\ & 4.01 \times 10^{28} (\sigma_3^2 + \sigma_4^2) + 1.32 \times 10^{36} (\sigma_3^3 + \sigma_4^3) - 4.17 \times 10^{12} \phi_0] \end{aligned} \quad (3.7)$$

where, ϕ_0 = apparent molal volume of the salt at infinite dilution

σ_1 = diameter of diene or dienophile

σ_3 = diameter of cation

σ_4 = diameter of anion

$$\begin{aligned} \kappa_b = & -1.85 \times 10^{14} (\epsilon_1/k)^{1/2} \{ \alpha_3^{3/4} Z_3^{1/4} [(\sigma_1 + \sigma_3)^3 / \sigma_3^3] + \alpha_4^{3/4} Z_4^{1/4} [(\sigma_1 + \sigma_4)^3 / \sigma_4^3] \} \\ & 6.26 \times 10^{17} \phi_0 (\epsilon_1/k)^{1/2} (\sigma_1 + \sigma_2)^3 + 4.00 \times 10^{-2} \phi_0 \alpha_1 / (\sigma_1 + \sigma_2)^3 \end{aligned} \quad (3.8)$$

where, α_1 = polarizability of diene or dienophile

α_3 = polarizability of cation

α_4 = polarizability of anion

Z_3 = total number of electrons in cation

Z_4 = total number of electrons in anion

σ_2 = diameter of water molecule

$$= 2.75 \times 10^{-8} \text{ cm}$$

ϵ_j/k = energy parameter, evaluated from the Mavroyannis-Stephen theory¹⁸⁸

$$\epsilon_j/k = 2.28 \times 10^{-8} \alpha_j^{3/2} Z_j^{1/2} / \sigma_j^6 \quad (3.9)$$

$$\kappa_c = 0.016 - 4.34 \times 10^{-4} \phi_o \quad (3.10)$$

The values obtained by using Equations 3.7, 3.8 and 3.10 are listed in Table 3.1. As seen from Table 3.1. It is worth interesting to compare the relative contributions of the three terms κ_a , κ_b and κ_c to the total salting coefficient κ_s . It is clear from the Table 3.1 that κ_c is a small quantity. Further, κ_a is a positive quantity in case of all the salts. For all the *endo/exo* ratio-enhancing salts, the κ_a values are high and positive suggesting that cavitation is not easier in the presence of these salts. The free energy for cavity formation becomes more positive as the concentration of salt increases. In this way, it is more difficult to form a cavity in an aqueous solution of salting-out agents than in pure water.

The κ_b values are negative. It indicates that the diene or dienophile experiences a net attractive force. This can be interpreted as once a cavity is formed in a salt solution, it is easier to introduce a non-electrolyte molecule i.e. diene or dienophile than it is in pure water. However, the small magnitudes of κ_b in these salts suggest that solvation of diene and dienophile is not possible. On the other hand, highly negative κ_b values in GnCl and LiClO_4 indicate strong solute-solvent interactions leading to the salting-in effect. For small molecules the value of κ_b is small. As the size of the diene or dienophile increases, both κ_a and κ_b increase. The sign of κ_s depends on the relative magnitudes of κ_a and κ_b .

The resultant κ_s is a product of competition between κ_a and κ_b . The positive κ_s (salting-out) values are observed for CaCl_2 , Na_2SO_4 , KCl and LiCl , while negative (salting-in) for GnCl and LiClO_4 . The κ_s values follow the order, in which the salts affect the *endo/exo* values. Thus, the effect of these salts stems from the salting-out.

TABLE 3.1. Contributions of κ_a , κ_b and κ_c , and total salting coefficients, κ_s for the reaction of **7** with **12** (Scheme 1.6) in salt solutions

salt	κ_a	κ_b	κ_c	κ_s
CaCl ₂	0.568	-0.051	0.016	0.533
Na ₂ SO ₄	0.461	-0.041	0.008	0.428
KCl	0.313	-0.029	0.004	0.288
LiCl	0.239	-0.017	0.003	0.225
GnCl	0.078	-0.373	-0.029	-0.324
LiClO ₄	0.048	-0.483	-0.055	-0.490

The cavity formation and solvation phenomena in relation to *endo/exo* ratios can also be independently supported by the Gibbs free energy computations. The relative change in the Gibbs free energy on addition of a salt in a reaction $\delta(\Delta G^\circ)_{\text{soln}}$ can be given as that in Equation 3.11.

$$\delta(\Delta G^\circ)_{\text{soln}} = \delta(\Delta G^\circ)_{\text{cavn}} + \delta(\Delta G^\circ)_{\text{solvn}} \quad (3.11)$$

The computed $\delta(\Delta G^\circ)_{\text{cavn}}$ and $\delta(\Delta G^\circ)_{\text{solvn}}$ values from scaled particle theory are plotted in Figure 3.8. For GnCl and LiClO₄, the $\delta(\Delta G^\circ)_{\text{solvn}}$ is larger than $\delta(\Delta G^\circ)_{\text{cavn}}$ confirming that the salting-in effect by these salts originates from solvation effects. On the other hand, due to the electrostriction effect in CaCl₂, Na₂SO₄, KCl and LiCl, less empty space is available for accommodating the diene and dienophile leading to salting-out. This is consistent with the trend of κ_a values shown in Table 3.1 for these salts.

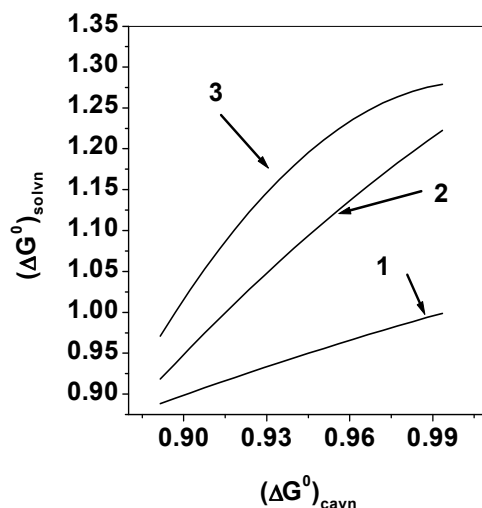


FIGURE 3.8. Plots of $\delta(\Delta G^\ddagger)_{\text{solvn}}$ against $\delta(\Delta G^\ddagger)_{\text{cavn}}$ for the reaction of **7** with **12** (Scheme 1.6) in CaCl_2 (1), GnCl (2), LiClO_4 (3)

3.5 Role of ΔV^\ddagger

The role of ΔV^\ddagger in understanding the kinetics of Diels-Alder reactions carried out in solvents is well established.¹⁸⁹ Diels-Alder reactions are accompanied by negative ΔV^\ddagger suggesting compact TS. The ΔV^\ddagger for Diels-Alder reactions have been tabulated.^{32,33} In the Diels-Alder reaction, where *endo* product is preferable over *exo*, for example, the reaction of **7** and **10**, the ΔV^\ddagger of the *endo* TS is lower (more negative) than that of the *exo* (less negative). The ratio of $\Delta V^\ddagger_{\text{endo}} / \Delta V^\ddagger_{\text{exo}}$ is 1.17.¹⁶⁶ In the *exo*-selective reaction such as the present reaction of **7** with **12** carried out in organic solvents, the ratio of ΔV^\ddagger of *endo* over that of *exo*, $\Delta V^\ddagger_{\text{endo}} / \Delta V^\ddagger_{\text{exo}}$ is less than unity (0.78).³⁵ This suggests preference of the *exo* TS over the *endo*.

3.6 Effects of salt solutions on a given Diels-Alder reaction

Several Diels-Alder reactions have been successfully accelerated by employing water as a reaction medium.⁵⁰⁻⁵⁷ The rates of the reactions can further be altered by addition of additives. The reaction of **16** with **17** is about 2.5 times faster as compared to

that in water when 4.86 M LiCl is added, but about 3 times slower on addition of 4.86 M GnCl.^{49,59} Further the reaction of **7** with **14** is faster when LiCl is added to water, but slightly slower when aqueous GnCl is used. LiCl increases hydrophobic effect and GnCl decreases it. The salts such as LiCl are known to increase hydrophobic effect and they, therefore decrease the solubility of hydrocarbons in water. These salts are known as prohydrophobic agents or salting-out agents. On the contrary, the salts like GnCl and LiClO₄ decrease the hydrophobic effect thus, increase the solubility of hydrocarbon. These are antihydrophobic agents or salting-in agents.

Kumar and coworkers have investigated the variations in the *endo/exo* ratios for the reaction of **7** with **10** (Scheme 1.5) in salt solutions at different concentrations of salts.¹⁶⁶ The salts included were LiCl, NaCl, NaBr, CaCl₂, GnCl and LiClO₄. Salts such as LiCl, NaCl, NaBr and CaCl₂ enhance the *endo/exo* ratios whereas GnCl and LiClO₄ decrease them. The results were analyzed in light of the salting-out and -in coefficients.

As has been discussed earlier, the arrangement of water molecules due to the presence of ions is greatly influenced. This is reflected in the physico-chemical properties of the salt solutions, for example surface tension of salt solution. It is observed that the surface tension, σ of water increases sharply when a salt such as LiCl, NaCl, NaBr and CaCl₂ is added to pure water. In the cases of aqueous GnCl and LiClO₄, this increase in surface tension is relatively weak. At 1 M salt concentration the values of derivatives, $\partial (\log (endo /exo)) / \partial \Delta\sigma$ were calculated as 0.113, 0.076, 0.060, 0.014, -0.037 and -0.173 for LiCl, NaCl, NaBr, CaCl₂, GnCl and LiClO₄ respectively. These derivatives showed the remarkable effect of the surface tension of salt solution on the *endo/exo* ratios.

3.7 The quantification of hydrophobic effect through a solvent parameter

In the past Diels-Alder reactions were carried out in organic solvents under high external pressure. It has been proposed that the rate enhancements observed in aqueous media and that when high external pressure is applied, are directly related. Therefore, the solvents that possess high internal pressure promote Diels-Alder reactions.

3.7.1 Internal pressure

Intermolecular forces give a liquid its cohesion. The attractive forces mainly comprise hydrogen bonding, dipole-dipole, multipolar and dispersion interactions. Repulsive forces, acting over very small intermolecular distances, play a minor role in the cohesion process under normal circumstances. Cohesion creates a pressure within a liquid of between 10^3 to 10^4 atmospheres. Dissolved solutes experience some of this pressure. The amount of pressure on the solutes increases when they interact with solvent hydrogen bonding, charge-transfer, coulombic or van der Waals interactions. Thus a solution always exists under pressure. This is known as internal pressure.¹⁹⁰

On this background, we attempt to quantify the hydrophobic effect that affects the *endo/exo* ratios observed in aqueous salt solutions through internal pressure, a solvent property.

It is noted that prohydrophobic salts increase the internal pressure of water (1654 atm) due to the electrostriction process occurring between an ion and water. These salts also enhance hydrophobic interactions. On the contrary, antihydrophobic salts decrease internal pressure of water due to antielectrostriction effect and also the hydrophobic interactions. Essentially the internal pressure of water increases or decreases due to the phenomenon of electrostriction, where an ion, owing to its strong electric field, orients water molecules thus causing a reduction in volume.^{180,191} This in turn raises the internal pressure of water. These effects are a function of salt concentration and depend on the nature of salt.

The effects of aqueous solutions of series of sodium and guanidinium salts on the rates of the reaction of **16** with **17** have been studied.¹⁹² The rates of the reaction decrease as the radii of the anion increase. The rates of the present reaction obtained in 2 M aqueous salt solutions of NaCl, NaBr, NaBF₄, NaClO₄, NaPF₆, NaAsF₆, GnCl, GnBr, GnBF₄, GnClO₄ are studied as a function of the internal pressures of the respective salt solutions.

The internal pressure, P_i of the salt solution can be estimated from the knowledge of isothermal compressibility, β_T , thermal expansion coefficient, α and absolute temperature, T from the Equation 3.12 as shown below.

$$P_i = \frac{\alpha T}{\beta} \quad (3.12)$$

Thermal expansion coefficient can be calculated as shown in Equation 3.13

$$\alpha = - \frac{1}{\rho} \frac{d\rho}{dT} \quad (3.13)$$

The isothermal compressibility, in turn can be calculated from Newton-Laplace's equation as given in Equation 3.14.

$$\beta = \frac{1}{u^2 \rho} \quad (3.14)$$

where, u = speed of sound

ρ = density of the solution

Thermal expansion coefficient and isothermal compressibility are calculated from the solvent properties.^{192,193}

Thus the estimated values of internal pressures of the salt solutions are given below¹⁹⁴

TABLE 3.2. Values of internal pressure (P_i) caused by 2 M salt

sodium salts		guanidinium salts	
salt	P_i/bar	salt	P_i/bar
Cl ⁻	3805	Cl ⁻	1445
Br ⁻	3740	Br ⁻	1420
BF ₄ ⁻	2260	BF ₄ ⁻	1246
ClO ₄ ⁻	1550	ClO ₄ ⁻	1161
PF ₆ ⁻	1460		
AsF ₆ ⁻	1391		

The rate constants plotted against the internal pressure of the aqueous salt solutions is as shown in Figure 3.9. The relative rate constants k_{rel} are defined as mentioned for the reaction of **7** with **10**. The relative internal pressure $P_{int,rel} = P_{int,s} / P_{int,w}$, where $P_{int,s}$ is the internal pressure of the salt solution. As k_{rel} indicates the change in rate constant in salt solution over that in pure water, $P_{int,rel}$ means the change in hydrophobicity in salt solution over that in pure water in terms of internal pressure. There is a strong linear correlation of k_{rel} with $P_{int,rel}$ for both the salt solution, as shown by the following relationship:

for sodium salts,

$$k_2 = 0.5168 + 0.3559 P_i \quad (3.15)$$

for guanidinium salts,

$$k_2 = -0.3660 + 1.0466 P_i \quad (3.16)$$

It is clear from the Figure 3.9 and the above correlation that if $P_{int,rel} = 0$, then $k_{rel} = 1$ indicating water is a reference solvent for the reaction. Sodium salts like NaBF₄, NaClO₄, NaPF₆ and NaAsF₆ decrease the internal pressure of water owing to the structure-breaking abilities of these anions, as the large ions have a low charge density. This is opposite to what is observed for the Li⁺, Na⁺ etc. where cations are the structure-

makers. The stronger structure-breaking powers of BF_4^- , ClO_4^- , PF_6^- and AsF_6^- outweigh the structure-making ability of Na^+ ion, resulting the dominance of the structure-breaking environment. This results in lowering of the internal pressure of water in a variety of salts solutions. On the other hand, anions such as Cl^- and Br^- in conjunction with a small cation Na^+ act in a same direction. Cation and anion due to their small sizes increase the internal pressure of water. In case of guanidinium salts, guanidinium cation outweighs the structure-making abilities of smaller anions. As a result, guanidinium salts decrease the internal pressure of water. In short, the internal pressure of aqueous solutions is strongly affected by the structure-making and -breaking abilities of the ions. A strong

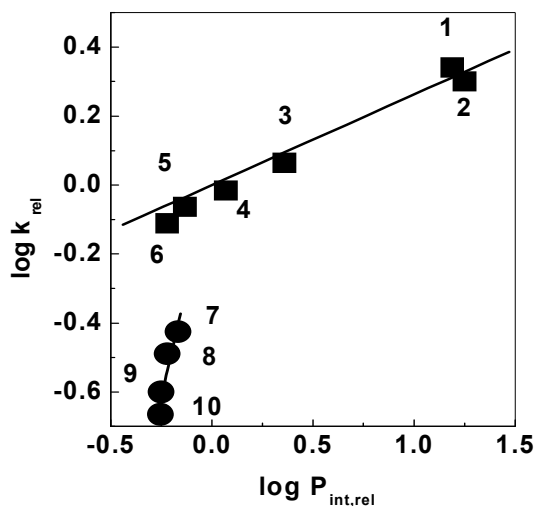


FIGURE 3.9. Rate constant k_2 for the reaction of 16 with 17 (Scheme 1.8) in sodium (■) salts: (1) NaCl, (2) NaBr, (3) NaBF₄, (4) NaClO₄, (5) NaPF₆, (6) NaAsF₆ and in guanidinium (●) salts: (7) GnCl, (8) GnBr, (9) GnBF₄, (10) GnClO₄ as a function of internal pressure, P_i caused by aqueous salt solution

linear correlation observed suggests hydrophobic packing or unpacking of diene and dienophile in the sodium and guanidinium salts, respectively. As Diels-Alder reactions are accompanied with $-\Delta V^\ddagger$, the increased internal pressure leads to enhancement of reaction rates. In other words, the packing of diene and dienophile is enhanced by $-\Delta V^\ddagger$ and higher internal pressure. On the contrary, the decreased internal pressure in guanidinium salt solutions (and in some sodium salt solutions) coupled with $-\Delta V^\ddagger$ further inhibits the reaction rates, as evident from Figure 3.9.

The same concept can be applied to delineate the *endo/exo* ratios obtained from the reaction of **7** with **10** in concentrated aqueous LiCl, NaCl, NaBr, CaCl₂, LiClO₄, and GnCl solutions.¹⁶⁶ As the TS for *endo* isomer is more compact than *exo*, the increase in the *endo/exo* ratios with increase in the concentrations of prohydrophobic salts can be explained on the basis of $-\Delta V^\ddagger$ and high internal pressure. The reduced *endo/exo* ratios obtained in GnCl and LiClO₄ type of salts explain the inhibition of these ratios due to weakening of hydrophobic effects as expressed in terms of internal pressure. The $\log(\textit{endo/exo})_{\text{rel}}$ values are plotted against corresponding $P_{\text{int,rel}}$ in various salt solutions of different concentrations, as shown in Figure 3.10. At higher $P_{\text{int,rel}}$ values, the log

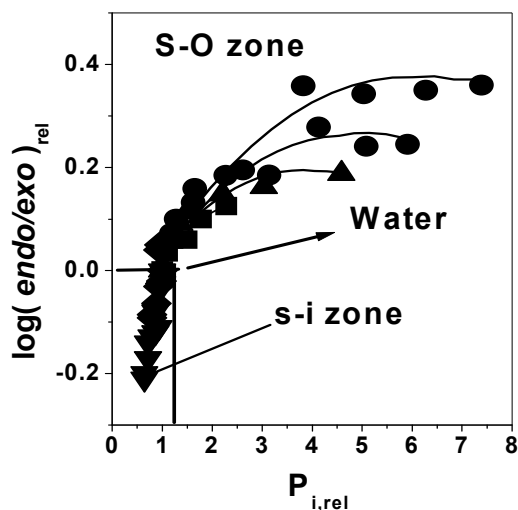


FIGURE 3.10. Variation of $\log(\textit{endo/exo})_{\text{rel}}$ with $P_{\text{int,rel}}$ for the reaction of **7** with **10** (Scheme 1.5) in aqueous salt solutions of LiCl, NaCl, NaBr, CaCl₂, GnCl, LiClO₄

endo/exo values taper off suggesting the maximum in hydrophobic effects. Based on $P_{\text{int,w}}$ and $P_{\text{int,s}}$ three zones are suggested characterizing the variations in reaction rates in salt solutions.¹⁶⁶ These zones are: $P_{\text{int,s}} > P_{\text{int,w}}$ = salting-out (enhanced relative hydrophobicity with respect to water), $P_{\text{int,s}} < P_{\text{int,w}}$ = salting-in (reduced relative hydrophobicity with respect to water) and $P_{\text{int,s}} = P_{\text{int,w}}$ = no salt effect (hydrophobic effect due to water alone). As internal pressure has been correlated with hydrophobicity, it is possible to correlate these zones in terms of hydrophobicity and so the reaction rates.

The linear relationship in the case of Rizzo's data plotted in Figure 3.9 was possible as rate data were collected only at a single salt concentration. These observations are also valid for the reaction of **7** with **10** in GnBr , CH_3COOGn , GnClO_4 and Gn_2SO_4 .¹⁹⁵ The *endo/exo* ratios are suppressed in the guanidinium salts except in Gn_2SO_4 . Both the enhancement and inhibition in *endo/exo* values can be easily explained in terms of the enhanced or reduced hydrophobic effects as expressed by internal pressure.

In short, it has been demonstrated the immediate use of the new interpretation of hydrophobicity in delineating the effects of water and their salt solutions on the kinetics of Diels-Alder reactions. From the above, it seems that the relative hydrophobicity can be judged from the relative internal pressure of water and solutions, which is useful in understanding the salt effect on Diels-Alder reactions. It should be possible to apply the above development to other Diels-Alder reactions in salt solutions in nonaqueous solvents.

3.8 Effects of addition of cosolvents

The literature survey and the above observations show that LiClO_4 acts as a salting-in agent in aqueous medium decelerating the rates and the *endo/exo* ratios. Contrary to this, several Diels-Alder reactions have been promoted in presence of LiClO_4 in diethyl ether.⁷⁴ The enhancement in kinetic profiles of Diels-Alder reactions have been attributed to several factors like Lewis acid catalysis, internal pressure, clathrate formation.^{74,78-83,95} Thus, LiClO_4 in water acts as a salting-in agent, while it is salting-out agent in diethyl ether

We aim to investigate whether LiClO_4 , which is a salting-in agent in aqueous medium, can be forced to change its role from rate inhibitor to rate accelerator just by solvent manipulation. Further it also allows to explore if the solvent properties can be attuned by adjusting the amounts of solvents and the salts.

Engberts and coworkers studied the reactions of **7** with **14** (Scheme 1.7) and with **44** as well as the intramolecular Diels-Alder reaction of *N*-furfuryl-*N*-methylmaleamic acid in water, monohydric alcohols, and highly aqueous solutions containing monohydric alcohols and other organic cosolvents.¹⁰³ The activation parameters were determined for these reactions. The *endo/exo* ratios were found to be more in the highly aqueous

solutions of alcohols as compared to that in hydrocarbon. At critical mole fractions of water, which were about 0.6, 0.7, and 0.8 in mixtures of water with alcohol, the *endo/exo* ratio decreased rapidly. In alcohol rich aqueous solutions, the *endo/exo* ratios were found to be the lowest, similar to that found in hydrocarbon.

Cativiela et al. have examined the *endo/exo* ratios of Diels-Alder reactions of isoprene and **7** with **10** and with **14** in pure solvents and aqueous mixtures.¹⁹⁶ As the concentration of organic solvents in water increases, the *endo/exo* ratios increase. The *endo/exo* ratios for Diels-Alder reaction of **7** with **51b** (Scheme 5.3) and with methyl (*E*)- α -cyanocinnamate (**78**) (Scheme 5.4) have also been reported.¹²²⁻¹²³

However, no report has been available that describes the variation of *endo/exo* ratios in presence of salt solutions of aqueous alcohols. The effects of various salt solutions of aqueous and organic mixtures on the rates and *endo/exo* ratios have been studied in detail. The reaction of **7** with **10** was investigated in pure alcohols such as methanol, ethanol, propan-1-ol and butan-1-ol. On going from lower homologous, methanol to higher homologous butan-1-ol, the *endo/exo* ratio goes on decreasing.

LiClO₄ offers 73 % *endo* products in 1 M aqueous medium with a reduction of 7% products as compared to that in water alone. On the other hand, *endo* products are observed as 82 % in aqueous LiCl. This change in *endo* products i.e. *endo/exo* ratio is related to the solubilities of diene and dienophile in aqueous medium. The studies suggest that the interactions of LiClO₄ with water are dramatically altered as compare to aqueous methanol. Thus the salt-solvent interactions are of paramount importance in governing the kinetic profiles of Diels-Alder reactions. Salting-in agents like GnCl and LiClO₄ increase the solubilities of the reactants in water, in turn decreasing the *endo/exo* ratios. In contrast, salting-out agents such as LiCl, NaCl, KCl etc. in aqueous medium increase *endo/exo* ratio by decreasing the solubilities of the reactants.

In order to understand how these salts in aqueous alcohols influence the *endo/exo* ratios, the reaction was then carried out in aqueous alcohol solutions of LiClO₄, a salting-in agent in water and in the LiCl, NaCl, KCl the salting-out agents in aqueous medium. The aqueous solution of 40 % methanol containing 1 M LiClO₄ offers about 89 % *endo* isomer, which reduces to 83 % in 40 % butan-1-ol. Similarly in aqueous solution of 40 % methanol containing 1 M NaCl 85 % *endo* product is obtained whereas aqueous NaCl

solution of 40 % butan-1-ol offers 83 % *endo* isomer. It seems that as the hydrophobic nature of alcohol goes on increasing with the carbon chain length, the *endo/exo* ratio decreases.

It is surprising that another potential salting-in agent GnCl , in methanol-water mixtures does not offer noticeable change in the *endo*-products. This resulted in aborting further experiments in other solvents. It therefore appears that the interaction of ClO_4^- with aqueous methanol plays significant role in converting a salting-in agent to a salting-out. In case of LiClO_4 , complex formation with some organic solvents takes place to form clathrates. The presence of these clathrates can enhance the *endo*-products. The water-rich methanol solutions do not favor the clathrate formation and thereby decreasing *endo* product formation. GnCl , on the other hand does not form clathrates with methanol.

Further, the reactions were conducted in aqueous LiClO_4 , LiCl , NaCl , KCl , CaCl_2 and MgCl_2 using alcohol as a cosolvent with composition ranging from 10 to 40 %. The effects of the cosolvents such as methanol, ethanol, propan-1-ol and butan-1-ol were studied for the above mentioned aqueous salt solutions.

The reaction of **7** with **10** (Scheme 1.5) was carried out in 1 M aqueous LiClO_4 with 10 to 40 % methanol as cosolvent. The *endo* isomer in 10 % methanol is observed to be 86 %, a sharp rise of about 13 % over the *endo* product can be observed in aqueous LiClO_4 alone, as shown in Figure 3.11. On increasing the composition of methanol from 10 to 40 %, the yield of *endo* product is enhanced to 89 %, a gain of 30 % as compared to that in aqueous LiClO_4 . When these results are compared with the *endo* isomer corresponding to 40 % aqueous methanol, it is observed that the increase is about 1.6 fold. Furthermore, the increase in concentration of methanol to aqueous LiClO_4 decreases the *endo* product.

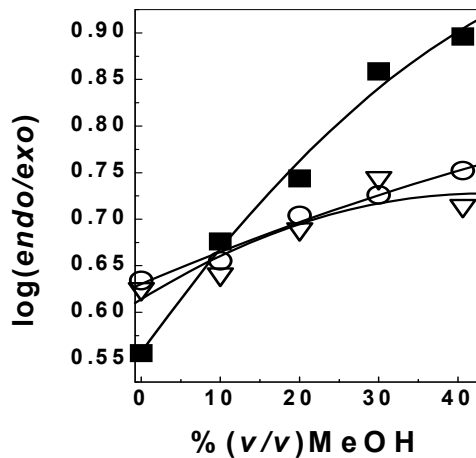


FIGURE 3.11. Variations of $\log(\text{endo/exo})$ with increasing concentration of methanol containing salts LiClO_4 (■), LiCl (○), NaCl (▽)

Thus, the role of LiClO_4 as a salting-in agent in aqueous medium is forced to change to a salting-out agent just by addition of a small amount of alcohol as a cosolvent. It seems that a type of complex (clathrate) is formed involving LiClO_4 , methanol and water that enhances the hydrogen bonded water structure, in other words the structuredness of water. The interaction of ClO_4^- with methanol-water plays an important role in the formation of the complex. This gives rise to a solvophobic effect. The increase in methanol composition increases the solvophobicity which, in turn results in acceleration of *endo* product. This effect is maximum at 40% alcohol-water containing salt, in this case LiClO_4 in which the *endo/exo* ratio is also highest over the whole concentration range.

Unlike salting-in agent, salting-out agents in aqueous medium retain their characteristic of increasing the *endo/exo* stereoselectivity ratio even on addition of cosolvent to aqueous salt solution. However, the magnitude of increase in *endo* product is lower in salts like LiCl , KCl etc. than in LiClO_4 in aqueous mixture of alcohol. In the case of an aqueous solution of LiCl , the addition of cosolvent to the solution causes little difference in the *endo/exo* ratio. The *endo* product, which is about 82 % in 1M aqueous LiCl , increases to 86 % on addition of 40 % methanol. The increase in *endo* products which is about 2.2 fold in 40 % aqueous methanol containing LiClO_4 as compared to

aqueous LiClO_4 now reduces to 1.3 times in the same composition of aqueous alcohol containing LiCl over that in its aqueous solution. The *endo* product obtained corresponding to 40 % methanol is only 1.1 times greater than that obtained in aqueous methanol. These results highlight the central role played by the ClO_4^- ion in clathrate formation. In LiCl , no complex formation is possible due to absence of the counterion effect.

Similar results have been noted when a mixture of alcohol and water containing salts NaCl and KCl are employed as media. An 1 M aqueous NaCl solution with 40 % methanol offers 84 % *endo* product, an increase of about 1.2 fold over aqueous salt solution. 1 M KCl in 40 % aqueous methanol offered about 85 % *endo* product, which is 1.4 times more than that in its aqueous solution. When CaCl_2 and MgCl_2 in 40 % aqueous methanol are employed, the 84% *endo* product is observed. From these results, KCl emerges as an effective salt for increasing the *endo/exo* ratio out of salting-out agents in aqueous medium. However, LiClO_4 shows the maximum increase in *endo/exo* ratio.

As the cosolvent changes from methanol to ethanol, the increase in *endo* product decreases for the Diels-Alder reaction. In 1M aqueous LiClO_4 using ethanol as a cosolvent, 87% *endo* product is observed, while it is 90 % corresponding to methanol as a cosolvent (Figure 3.12). In other words, increasing the carbon chain length of the

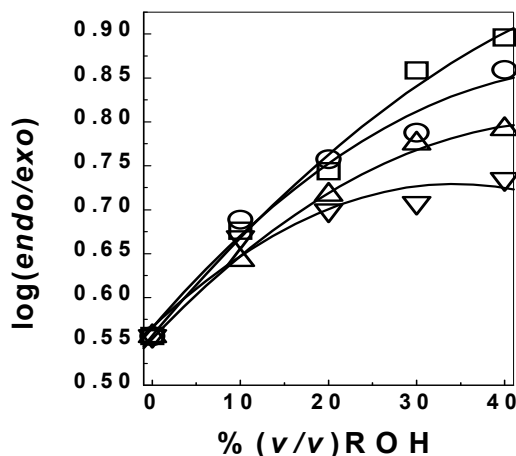


FIGURE 3.12. $\log(\text{endo/exo})$ as a function of various aqueous alcohols methanol (□), ethanol (○), propan-1-ol (Δ), butan-1-ol(▽), containing LiClO_4

cosolvent reduces the *endo* products. It is reported that the increase in carbon chain length of the cosolvent weakens the structuredness of water which was gained because of the addition of the methanol. This tendency becomes more prominent in case of propan-1-ol and butan-1-ol as a cosolvent. In the mixture of water and propan-1-ol containing LiClO₄ the *endo* product reduces to 85 % which is about 1.4 times reduction as compared to that in 40% methanol as a cosolvent. Employing higher homologous of alcohol as cosolvent, reduces the *endo* products more. Thus, on going from methanol to butan-1-ol, a decrease of 10 % in *endo* product is observed. It is clear that the effect of cosolvent on *endo/exo* ratio reduces with increase in carbon chain length.

LiCl, as we have seen, increases the *endo* product in presence of cosolvent. When ethanol is used as a cosolvent instead of methanol, the *endo* product increases to 87 % (Figure 3.13). Further increase in carbon chain length of the cosolvent reduces the increase in *endo* isomer. In aqueous LiCl solution of 40 % propan-1-ol as well as butan-1-ol, the *endo* product is 84 %. In 1 M aqueous LiCl solution of butan-1-ol the increase in

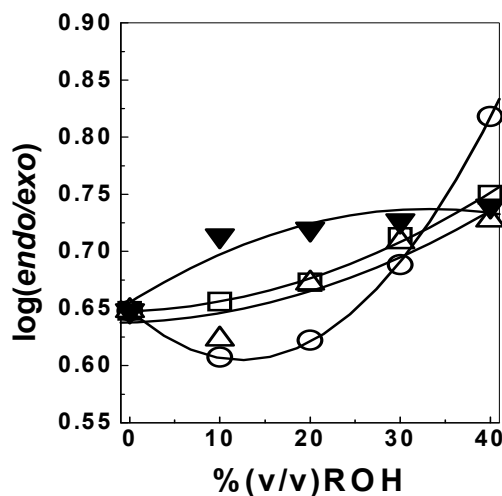


FIGURE 3.13. The plot of $\log(\text{endo/exo})$ in aqueous methanol (□), ethanol (O), propan-1-ol (Δ) and butan-1-ol (▼) containing 1M LiCl

endo/exo ratio is not significant even on increasing the composition of butan-1-ol as compare to that in 40 % ethanol. The rate increase from 10 to 40 % methanol is 1.7 times,

which reduces to only 1.1 times on going from 10 to 40 % butan-1-ol for aqueous LiCl. The enhancement in rate vanishes with the increase in carbon chain length of the cosolvent. The results suggest that when aqueous LiCl is employed, ethanol is the most effective cosolvent in order to increase the *endo/exo* ratio. Similar results can be noted for 1 M aqueous NaCl using cosolvent. The *endo* product obtained is about 84 % in 40 % methanol with an increase in *endo* product of about 1.2-fold as compared to *endo* isomer obtained only in 1 M aqueous NaCl. When 40 % ethanol was added to 1 M aqueous NaCl instead of methanol, the *endo* product observed is 86 %, an increase of about 1.4 fold over that in its aqueous solution only. Using higher homologues such as butan-1-ol, the *endo* isomer observed is only 83 %. For NaCl, 40 % ethanol offered maximum *endo/exo* ratio.

In the case of KCl, the alcohols such as methanol, ethanol and butan-1-ol offers about the same amount of *endo* isomer (84 %) at 40 % composition of alcohol (Figure 3.14). In 40 % methanol, the *endo* isomer increases by about 1.3 times as compare to its aqueous solution only. Further increase in carbon chain length does not alter the *endo* product significantly.

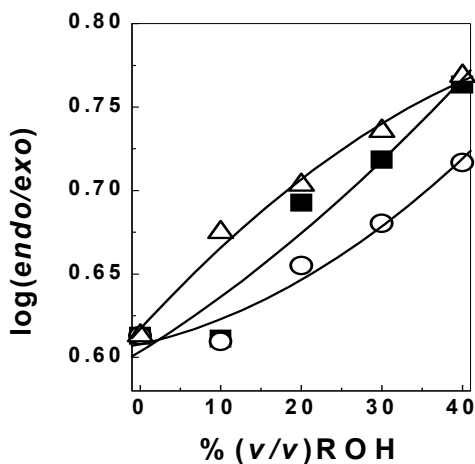


FIGURE 3.14. $\log(\text{endo/exo})$ as a function of aqueous alcohol composition for methanol (□), ethanol (O), and butanol (Δ) containing KCl

For CaCl_2 , methanol and butan-1-ol enhances the *endo/exo* ratio by about 1.2 times as compared its aqueous solution. The same is the case with MgCl_2 . An increase in the carbon chain length does not alter the *endo* product significantly.

To support the experimental *endo/exo* data, the solubility of methyl acrylate in 40% aqueous solutions of methanol and butan-1-ol containing LiCl and LiClO_4 has been measured. It is observed that the solubility of methyl acrylate in LiClO_4 -methanol-water (0.046 M) is higher than that in LiCl-methanol-water (0.04 M). Also methyl acrylate is more soluble in LiClO_4 -butanol-water than in aqueous butanol solution containing LiCl. These studies have shown that the solubility of methyl acrylate is maximum in 40 % aqueous methanol solution containing LiClO_4 . This system offers the highest *endo/exo* ratio.

Attempts have been made to analyze the experimental results by multiparameter equations using a linear combination of existing empirical solvent parameters. A literature survey shows that several empirical parameters are employed to understand the correlation between kinetic parameters and solvent properties like Kamlet-Taft dipolarity-polarizability π^* , hydrogen bond donor α , hydrogen bond acceptor β as well as Kosower Z , Mayer-Gutmann AN, Dimroth-Reichardt $E_T(30)$ etc.^{50,197-201}

The influence of the electron pair acceptor properties of the solvents was investigated on the rates of the reaction of 2,3-dimethylbutadiene with 1,4-naphthoquinone measured in solvents of increasing polarity.¹¹⁵ The rates of the reaction between **7** and diethyl fumarate (**51c**) carried out in binary water-methanol and water-1,4-dioxane mixtures were correlated with the S_p parameter.¹¹⁹

It is important to note that E_T is a blend of π^* and α properties of solvent. Also, S_p and E_T parameters show an intrinsic correlation, as the most solvophobic media are the most polar media. Hence, the good correlation of rates with one parameter does not mean that the rates of reaction depend on only that particular parameter. In view of this, multiparameter approaches were considered.

The AAKT model has been used to analyze the results of the reaction of **7** with methyl acrylate. Both the parameters, π^* and α were found to be important in explaining the solvent effects observed. It has been observed that the *endolexo* ratios of

the reaction of **7** and isoprene with **10** and with **14** mainly depends on the Sp and α properties of the solvent.¹⁹⁶

We attempted to analyze the data to explain the rates and stereoselectivities taking into account the parameters π^* , α and β abilities of the solvents.²⁰² However the unavailability of these parameters for the aqueous alcohol solutions restricted its further use. The influence of Sp and solvent polarity (represented by E_T) on the *endo/exo* stereoselectivity was investigated.^{122,124,118,203} We analyzed the *endo/exo* ratios obtained in various salt solutions of aqueous alcohol using these two parameters Sp and E_T^N as given below in Equation 3.15.

$$\log(\textit{endo/exo}) = a + b Sp + c E_T^N \quad (3.15)$$

The multiple regression analysis of the data reveals that LiClO_4 in all aqueous alcohols shows significant regression coefficients (correlation coefficient, $r > 0.9885$, standard deviation, $s.d. < 0.01$, F statistics = 1462.53). LiCl shows a good correlation coefficient in aqueous solutions of methanol, ethanol and propan-1-ol ($r > 0.9000$, $s.d. < 0.0500$, F statistics > 5). For the other salts such as NaCl , CaCl_2 , KCl and MgCl_2 significant regression coefficients are noted. In general, in aqueous butan-1-ol solution, poor r values are noted as compare to other aqueous alcohol solutions. For CaCl_2 in butan-1-ol-water mixture a poor correlation coefficient has been observed ($r = 0.4913$, $s.d. = 0.0295$, F statistics = 0.4831). The regression coefficients are noted as compare to other aqueous alcohol solutions. For CaCl_2 in butan-1-ol-water mixture a poor correlation coefficient has been observed ($r = 0.4913$, $s.d. = 0.0295$, F statistics = 0.4831). The regression coefficients are listed in Table 3.3.

TABLE 3.3. The values of parameters a, b and c of equation 1 and regression coefficients such as correlation coefficient as r, standard deviation as s. d. and F statistics for the reaction of 7 with 10 (Scheme 1.5) are listed.

aqueous mixtures of	a	b	c	r	s.d.	F statistics
LiClO₄						
methanol	-15.8122	1.7385	19.1852	0.9997	0.0033	1462.53
ethanol	3.7246	-0.9119	-3.3082	0.9979	0.0057	233.43
propan-1-ol	-6.3663	1.9127	8.5101	0.9972	0.0062	175.81
butan-1-ol	1.0598	-0.1454	-0.3566	0.9886	0.0051	43.43
LiCl						
methanol	1.4124	-0.5036	-0.3697	0.9887	0.0077	43.65
ethanol	-0.8434	-0.3001	2.5650	0.9099	0.0499	5.05
propan-1-ol	-2.6944	0.8196	4.1558	0.9961	0.0049	127.19
butan-1-ol	0.1537	-0.3088	1.1798	0.9494	0.0062	9.38
NaCl						
methanol	-6.0636	0.7767	7.7475	0.9154	0.0181	5.41
ethanol	-0.2671	-0.1857	1.6266	0.9822	0.0134	27.60
butan-1-ol	1.5936	0.1544	-1.4766	0.9321	0.0134	6.86
KCl						
methanol	-5.8858	0.3744	7.9293	0.8846	0.046	3.83
ethanol	2.3156	-0.5439	-1.8119	0.9985	0.0029	339.21
butan-1-ol	1.3307	-0.2574	-0.6071	0.9442	0.0181	25.36
CaCl₂						
methanol	-35.5819	5.3885	40.2253	0.9661	0.0211	14.23
butan-1-ol	1.3950	0.2836	-1.3232	0.4913	0.0295	0.48

	MgCl₂					
methanol	-14.6180	1.9073	17.3376	0.9306	0.0296	6.70
ethanol	4.1673	-1.0089	-3.9516	0.9767	0.0195	20.93
butan-1-ol	1.1099	0.1011	-0.7372	0.9133	0.0121	10.53

The experimental *endo/exo* ratios *versus* the *endo/exo* ratios calculated using the equation mentioned above are plotted as shown in Figure 3.15. For aqueous methanol solution containing LiClO₄ a good regression coefficient is obtained. Fairly good regression coefficients are obtained for the other systems and are given below. KCl in aqueous butan-1-ol shows the highest standard deviation.

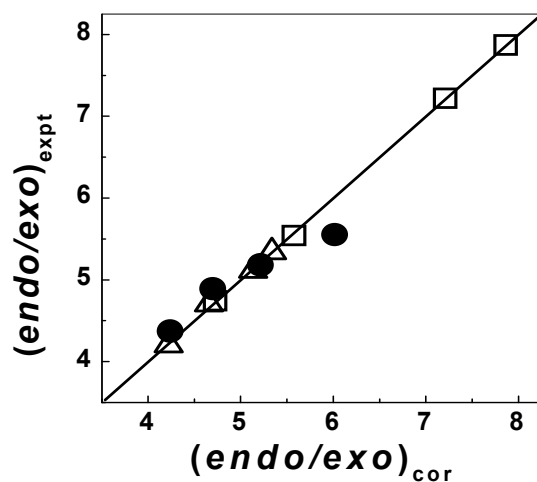


FIGURE 3.15.a

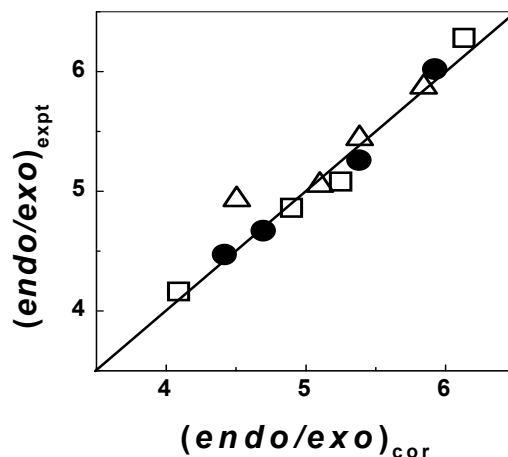


FIGURE 3.15.b

FIGURE 3.15. The plots of $(endo/exo)_{expt}$ versus $(endo/exo)_{cor}$ by the model used for aqueous solutions of (a) 1 M $LiClO_4$ methanol (\square), 1 M $CaCl_2$ in methanol (\bullet), 1 M $LiCl$ in propan-1-ol (Δ) (b) 1 M $MgCl_2$ in ethanol (\bullet), 1 M $NaCl$ in ethanol (\square), 1 M KCl in butan-1-ol (Δ). Solid line shows the best fit.

If any solvent that lowers the dielectric constant of water is added to aqueous medium, a separate phase is formed. If any salt is added to this solution, it distributes itself in the two phases, aqueous and the nonaqueous medium. When butan-1-ol is added to water, it lowers the dielectric medium of water and forms a separate phase. If a salt like, $LiCl$, $NaCl$, $CaCl_2$, KCl , $MgCl_2$ is added to water, it distributes itself in water and butan-1-ol depending upon dielectric constants of solvents. The effective concentration of salt in aqueous phase is determined and listed below in Table 3.4.

TABLE 3.4. The effective concentration of salt in aqueous phase

LiCl-butan-1-ol-water		
aqueous solutions of (v/v)	[LiCl] before reaction, M	[LiCl] after reaction, M
10 % butan-1-ol	1.114	1.031
20 % butan-1-ol	1.250	1.148
30 % butan-1-ol	1.429	1.352

40 % butan-1-ol	1.667	1.626
-----------------	-------	-------

CaCl₂·2H₂O-butanol-water

aqueous solutions of	[CaCl₂·2H₂O] before reaction, M	[CaCl₂·2H₂O] before reaction, M
10 % butan-1-ol	1.112	0.953
20 % butan-1-ol	1.252	1.033
30 % butan-1-ol	1.412	1.199
40 % butan-1-ol	1.662	1.460

NaCl-butanol-water

aqueous solutions of	[NaCl] before reaction, M	[NaCl] after reaction, M
10 % butan-1-ol	1.112	1.058
20 % butan-1-ol	1.251	1.146
30 % butan-1-ol	1.425	1.391
40 % butan-1-ol	1.671	1.685

KCl-butanol-water

aqueous solutions of	[KCl] before reaction, M	[KCl] after reaction, M
5 % butan-1-ol	1.056	1.038
10 % butan-1-ol	1.115	1.023
15 % butan-1-ol	1.180	1.156
20 % butan-1-ol	1.254	1.173
30 % butan-1-ol	1.433	1.355
40 % butan-1-ol	1.671	1.655

MgCl₂.6H₂O -butan-1-ol-water

aqueous solutions of	[MgCl ₂ .6H ₂ O] before reaction, M	[MgCl ₂ .6H ₂ O] after reaction, M
5 % butan-1-ol	1.053	1.029
10 % butan-1-ol	1.111	1.058
15 % butan-1-ol	1.176	1.100
20 % butan-1-ol	1.250	1.210
30 % butan-1-ol	1.429	1.362
40 % butan-1-ol	1.667	1.539

3.9 Reaction at interface

A careful study on the effects of solvents on Diels-Alder reactions illustrates involvement of hydrophobic effect, polarity, Lewis acid catalysis, internal pressure, hydrophobic hydration, etc. However, it is of importance to realize that either one or both diene or dienophile participating in Diels-Alder reactions, are completely or partially miscible in solvent medium, for example, cyclopentadiene is partially soluble in water, dienophiles like methyl acrylate, methyl methacrylate, methyl *trans*-crotonate have similar characteristics. As both diene and dienophile are not miscible in water, one may speculate the role of interfacial phenomena in altering the kinetic profiles of these reactions. On the other hand, if a Diels-Alder reaction is carried out in organic solvents, both miscibility and solubility of substrates may render the reaction medium very near to homogeneous nature. One therefore, may preclude the role of interfacial phenomena in Diels-Alder reactions carried out in organic solvents and their salt solutions, for example, LPDE. During several experiments performed in the laboratory it was clearly evident that the reaction mixture was not homogeneous and there existed immiscible layers.

Before we discuss the results obtained in this investigation, it is useful to define certain terms used herein:

Molecules in a liquid attract one another. A molecule entirely inside a liquid is attracted equally from all sides. So the net pull on the molecule is zero. The molecule at

the surface experiences only attractive force by other molecules below it. So the surface of the liquid is always under the state of tension. Hence, the surface tension of a liquid is defined as the energy required to expand the surface of a liquid by unit area. Surface energy quantifies the disruption of chemical bond that occurs when a surface is created. The region where the two phases meet is commonly called as interface. Few types of interfaces are liquid-liquid, solid-liquid. The liquid-liquid interface is shown in Figure 3.16. Interfacial energy can be defined as the work done to increase the surface by one unit of area.

With a view to exploring the role of interfacial phenomena in Diels-Alder reactions we designed the following experiments. The experiments were designed on the basis of available reaction surface for diene and dienophile. This means that if test tubes of different known diameters are selected for carrying out reactions, it will be possible to acquire different interfacial area for reaction.

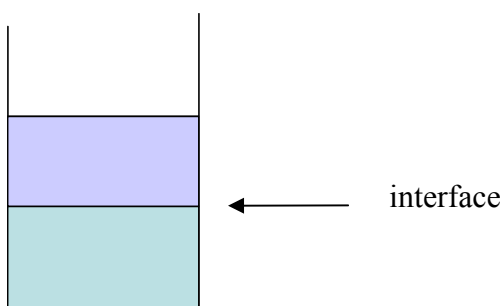


FIGURE 3.16. Schematic representation of the liquid-liquid interface

The reaction of **7** with **10** (Scheme 1.5) was carried out in reaction vessels (test tubes) of different diameters. The diameters of the test tubes ranged from 10.5 mm to 22 mm i. e. 10.5 mm, 13.5 mm, 16 mm, 22 mm. The results are summarized in Table 3.5. The reactions were first carried out in pure water. As the interfacial area of the test tube increases the rates of the reaction, k_2 increases. When the interfacial area increases by 1.3 times, the k_2 value also raised by 1.6 times in pure water as compared to the lowest interfacial area considered. Further an increase in interfacial area by about 2.1 times

accelerates the reaction by 2.1 times. When the interfacial area changes from $3.46 \times 10^{-4} \text{ m}^2$ to $15.21 \times 10^{-4} \text{ m}^2$ (increase in interfacial area by about 4.4 times), the k_2 value increases by 3.2-fold, as evident from the Table 3.5. The dependence of k_2 on interfacial area of reaction is demonstrated in Figure 3.17.

We have also investigated the variations in rate profiles of the reaction of **7** with **10** (Scheme 1.5) in the presence of salting-out and –in agents in aqueous medium from an angle of interfacial area. The rates were determined in the aqueous salt solutions of 5 M LiCl, 2 M Na₂SO₄, 1 M CaCl₂ and 5 M GnCl. The salting-out agents, LiCl, Na₂SO₄ and CaCl₂ speed up the reaction with the increase in the interfacial area. The k_2 value was observed to be raised by about 3.1-fold in the test tube of largest interfacial area ($15.21 \times 10^{-4} \text{ m}^2$) as compared to that of lowest interfacial area ($3.46 \times 10^{-4} \text{ m}^2$). For a given interfacial area, for example, $15.21 \times 10^{-4} \text{ m}^2$, the k_2 value enhances by about 1.6 times in aqueous solution 5 M LiCl over pure water.

TABLE 3.5. Variations in second-order rate constants, k_2 in various solution media for the reaction of **7** with **10** (Scheme 1.5) with the change in interfacial area

Solvent media	$k_2 \times 10^6 \text{ (M}^{-1} \text{ s}^{-1}\text{)}$			
	TT1	TT2	TT3	TT4
H ₂ O	0.32	0.51	0.67	1.03
5 M aqueous LiCl	0.52	0.76	0.99	1.66
1 M aqueous CaCl ₂	0.35	0.60	0.77	1.31
2 M aqueous Na ₂ SO ₄	0.41	0.71	0.82	1.31
5 M aqueous GnCl	0.26	0.41	0.62	0.75

Rate constants are average of triplicate runs. Test Tube, TT of different interfacial areas are given as follows: TT1 corresponds to an interfacial area $3.46 \times 10^{-4} \text{ m}^2$, TT2 corresponds to an interfacial area $5.73 \times 10^{-4} \text{ m}^2$, TT3 corresponds to an interfacial area $8.04 \times 10^{-4} \text{ m}^2$, and TT4 corresponds to an interfacial area $15.21 \times 10^{-4} \text{ m}^2$

Similar observations were made when aqueous solution of 2 M Na₂SO₄ was used as a solvent medium. The k_2 values are observed to be higher by about 3.2-fold in the test tube of $15.21 \times 10^{-4} \text{ m}^2$ interfacial area as compared to that of $3.46 \times 10^{-4} \text{ m}^2$ interfacial area. Since Na₂SO₄ is acting as a salting-out agent in aqueous medium, it enhances the reaction rate by about 1.4 times over water alone for the interfacial area of $5.73 \times 10^{-4} \text{ m}^2$.

CaCl₂ being a salting-out agent in water, accelerates the reaction of **7** with **10**. In 1 M aqueous CaCl₂ solution the reaction rate was enhanced by 1.3-fold for the given interfacial area ($15.21 \times 10^{-4} \text{ m}^2$). Further as the interfacial area increases from $3.46 \times 10^{-4} \text{ m}^2$ to $15.21 \times 10^{-4} \text{ m}^2$, the k_2 value increases by about 3.7 times.

Here it is noteworthy to state that although GnCl acts as a salting-in agent in aqueous medium, the reaction is accelerated as the interfacial area increases at a specific GnCl concentration. The rate of reaction decelerates by about 0.7 times in 5 M aqueous GnCl over pure water. It is clear from the Figure 3.17 that though the k_2 values are lower in aqueous GnCl than in pure water, these values increase with the increase in the interfacial area. The k_2 value in test tube of the largest interfacial area was found to be 2.8-fold higher than that in test tube of the smallest interfacial area.

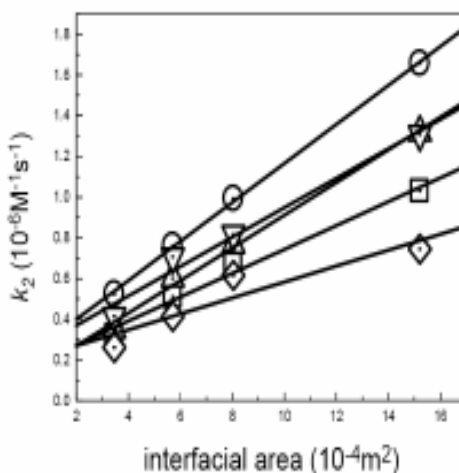


FIGURE 3.17. Variations of second-order rate constants of the reaction of **7** with **10** (Scheme 1.5) in pure water (□), aqueous solutions of LiCl (○), CaCl₂ (Δ), Na₂SO₄ (∇) and GnCl (◇) as a function of interfacial area

Our data collected from all the test tubes in water and its salt solutions are consistent with the general influence of salts on kinetics of Diels-Alder reactions.

It is clear from the graph that the k_2 values for the reaction in water are less than that in salting-out agents for the respective interfacial area whereas the values are more than that in salting-in agent.

From the results listed in Table 3.5 and depicted in Figure 3.18, it is clear that a remarkable rate enhancement can be achieved just by increasing the interfacial area or the diameter of the test tube, provided reaction conditions are maintained throughout identical. It is interesting to note that an increase in interfacial area by 100 %, the rate constant of reaction **7** with **10** increases by similar value. This is also true for other test tubes.

Below, a tentative mechanism is proposed to account for the role of interface in controlling rates of a simple Diels-Alder reaction.

As cyclopentadiene, a nonpolar molecule is sparingly soluble in water, it therefore is projected above the water layer in the reaction mixture containing water as a solvent medium. On the other hand, methyl acrylate the dienophile is partially soluble in water. It therefore remains partly in the water phase and partly above water under reaction condition. This arrangement is shown in Figure 3.19. The *carboxylate* group of the dienophile is polar and solvated in aqueous environment affecting the surface tension of water. The alkene part of the compound is slightly hydrophobic in nature and thus tends to partially project outside towards air pointing to cyclopentadiene. Now that if the reaction is taking place at the interface, the rate constant should increase with the diameter of the test tubes. It is understood here that the diameter of the test tube does not correctly indicate the interfacial area of the reaction mixture in the test tube. This is due to the reason that on mechanically shaking and stirring of the reaction, the interface is broken into tiny droplets thereby enhancing the interfacial area as established. Though it is possible to compute interfacial area of a test tube by simple formulae,²⁰⁴ the task becomes very stringent when the solution contains two reactants and solvent molecules. In the case of the reaction taking place in aqueous LiCl or Na₂SO₄, the number of free water molecules decrease with increasing concentration of cation as a result of hydration.

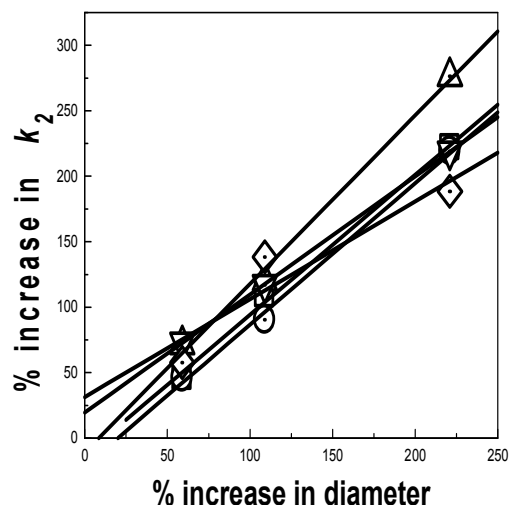


FIGURE 3.18. The % increase in second-order rate constant k_2 over that in the test tube of lowest diameter as a function of the % increase in the diameter of test tube over the test tube of lowest diameter in pure water (\square), aqueous solutions of LiCl (\circ), CaCl₂ (Δ), Na₂SO₄ (∇) and GdCl₃ (\diamond)

The less number of water molecules in aqueous LiCl solution as compared to in pure water, more methyl acrylate becomes available to cyclopentadiene present towards air, thus facilitating the reaction and thus rate constants increase. It may be noted that the rate enhancement of Diels-Alder reaction in aqueous LiCl involves two mutually dependent components: (1) contribution due to salting or hydration-behaviour and (2) pushing of methyl acrylate to the surface at which the reaction is taking place. On the contrary, aqueous GdCl₃ salt will induce more dissolution of methyl acrylate thereby pushing the methyl acrylate molecules away from the surface. In this case too, such effects are present with only difference that water molecules will participate in hydration of non-electrolytes. This will lead to decrease in the rate constant. Such methods under reaction conditions need to be developed in future. It is also important to check how surface tension of water, for example, is altered upon addition of cyclopentadiene or methyl acrylate. This information once available at different temperatures will be helpful in calculating entropy changes associated at interface at which the reaction

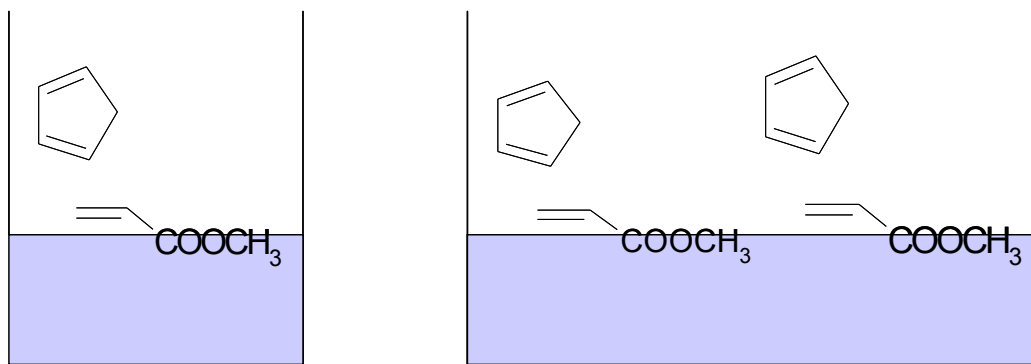


FIGURE 3.19. The proposed orientation of diene and dienophile at interface. The shaded portion denotes water phase.

is taking place. This should also merit investigation in aqueous salt solution to obtain a complete picture. This aspect is beyond the scope of this dissertation and hence not included here.

The enhanced rate constants with the increased interface areas are consistent with this interpretation. Contrary to this, if the reaction is completely homogeneous in nature, the measured rate constants will be independent of interfacial area. Since there is a dependence between the two, the significance of interface for Diels-Alder reaction comes to fore. Now that if temperature of the reaction is enhanced, the rate constant increases. This experimental fact is explained on the basis of the fact the interface is further broken into very small droplets thereby further promoting the reactions. Needless to state the enhanced thermal energy will work in the opposite direction, but it appears that the rate enhancement due to interface is dominant than the destabilizing power of the increased thermal energy.

These studies confirm the following:

- 1) If either diene or dienophile create heterogeneity in water, the enhanced interfacial area by selecting size of test tubes may serve to be an important tool for promoting such Diels-Alder reactions
- 2) If the above condition is met by most of Diels-Alder reactions this tool could be successfully employed to make tailor made recommendations for optimizing the reaction conditions.

In nutshell, the Diels-Alder reactions of **7** with **10** and with **12** can be explained in terms of hydrophobic effect salting effects and internal pressure. The internal pressure of the solvent media can be one of the possible parameters to quantify hydrophobic effect of aqueous media. The tentative mechanism for Diels-Alder reaction carried out in water and aqueous salt solutions have been proposed. The role of LiClO₄ can be changed from salting-in in aqueous medium to salting-out by solvent manipulation.

Chapter 4
INTRAMOLECULAR DIELS-ALDER
REACTION IN IONIC LIQUIDS

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

The present chapter describes the effects of various ionic liquids on the rate profile of intramolecular Diels-Alder reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone. To date rates and stereoselectivities of intermolecular Diels-Alder reactions have been studied in various ionic liquids. However, a very few reports are available in the literature on the study of intramolecular Diels-Alder reactions carried out in ionic liquids. In this chapter, an attempt is made to investigate the kinetics of Diels-Alder reactions in ionic liquids used as solvent media.

4.1. Intermolecular Diels-Alder reactions in ionic liquids

Intermolecular Diels-Alder reactions (in which diene and dienophile are present as two separate moieties) have been extensively studied using ionic liquids as solvent media. Rates and stereoselectivities of these intermolecular reactions have been correlated with various solvent parameters of ionic liquids.^{131, 133, 154, 205}

In late 1980s an attempt was made to assess rates and *endo/exo* ratios of intermolecular Diels-Alder reaction of **7** with **10** (Scheme 1.5) and with **14** (Scheme 1.7) in ethylammonium nitrate.¹⁴⁸ The *endo* product and rate enhancement for these reactions in this ionic liquid has been compared with that obtained in water and in other organic solvents. It has also been explored if ethylammonium nitrate shares some common solvent properties with aqueous medium that speed up these reactions. Ethylammonium nitrate resembles water in many respects. Like water, ethylammonium nitrate possesses a high cohesive energy density. Also, the standard free energies, enthalpies and entropies of solution for several nonpolar gases in ethylammonium nitrate parallel to those in water. However, the use of ethylammonium nitrate could not be further argued in view of its explosive nature.

A very large number of reports have been published discussing the physico-chemical properties of ionic liquids.^{131, 133, 134, 205} These properties include polarity, melting point, thermal stability, viscosity, density, ionic diffusion coefficient, conductivity, refractive index, surface tension, etc. Since 1990s, rates and *endo/exo* ratios of intermolecular Diels-Alder reactions carried out in ionic liquids have become available. Rates and *endo/exo* ratios of Diels-Alder reactions have been correlated with solvent parameters.^{133, 135, 154, 155, 205} The *endo/exo* ratios for the reaction of **7** with **10**

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

(Scheme 1.5) have been studied in ionic liquids containing $[\text{BMIM}]^+$, $[\text{BM}_2\text{IM}]^+$ and in organic solvents.¹⁵⁴ The fastest rate of reaction has been observed in the most viscous ionic liquids. The reaction slows down as the viscosity of the ionic liquid is reduced. When the *endo/exo* ratios for the above reaction, carried out in $[\text{BMIM}][\text{BF}_4]$ and $[\text{BM}_2\text{IM}][\text{BF}_4]$ are compared, it is observed that higher *endo/exo* ratios can be obtained in $[\text{BMIM}][\text{BF}_4]$ than in $[\text{BM}_2\text{IM}][\text{BF}_4]$. This is attributed to the hydrogen bond-donating ability through the proton on C2 of the imidazolium ring as shown in Figure 1. The formation of a H-bond from the cation of the ionic liquid to the dienophile is a Lewis acid-base interaction.²⁰⁶ The selectivity of the reaction is still enhanced when ionic

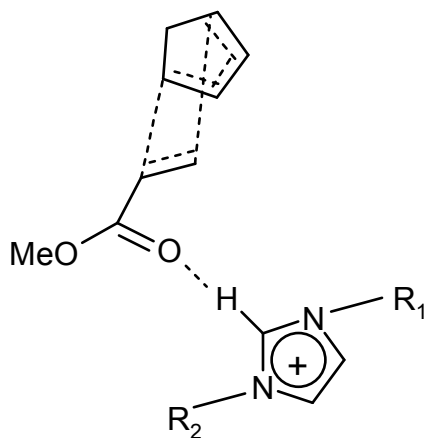


FIGURE 4.1. The hydrogen bond interaction of imidazolium cation in the TS of the reaction of **7** with **10** (Scheme 1.5)

liquids such as $[\text{HO}(\text{CH}_2)_2\text{MIM}][\text{N}(\text{Tf})_2]$ and $[\text{EtNH}_3][\text{NO}_3]$ with strong hydrogen bond abilities are used. Since E_T^N values are dominated by ability of a solvent to hydrogen bond with the solute, the *endo/exo* ratios can be correlated with the E_T^N values of the ionic liquids.

Vidis and coworkers have examined the *endo/exo* ratios of the reaction of **7** with **10** (Scheme 1.5) in the ionic liquids of different anions as well as of cations.²⁰⁵ In general, selectivities of intermolecular Diels-Alder reaction decrease as the length of alkyl chain attached to the cation increases. The functional groups such as *hydroxy*, *carbonyl*, *nitrile* and *benzyl*-groups increase the selectivity as compared to that by alkyl

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

chain on the cation. Further, higher *endo/exo* selectivities are observed in 1-alkyl-2,3-dimethylimidazolium ionic liquids than in their 1-alkyl-3-methylimidazolium analogues. These observations indicate that the hydrogen bond-donor properties of the cation do not satisfactorily account for the observed *endo/exo* ratios. The *endo/exo* ratios of this reaction have been correlated with the NMR spectroscopy based-empirical solvent parameter scale, namely Δ scale. A semi-empirical solvent scale, TLSER has also been used to correlate with the *endo/exo* ratios. In short, the *endo/exo* ratio of Diels-Alder reactions in ionic liquids is noted to depend on the following factors:

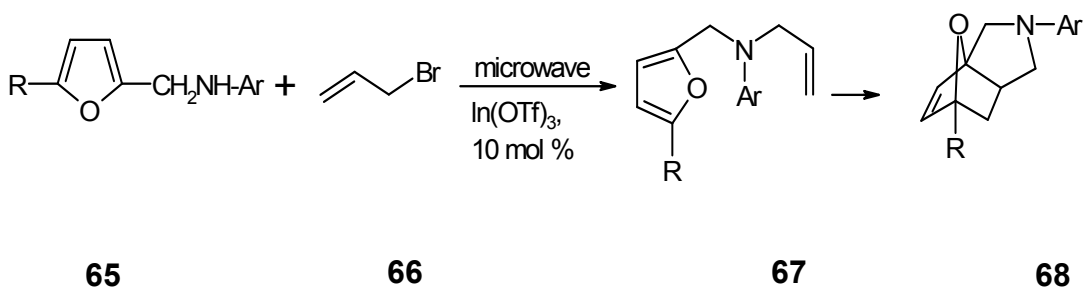
- 1) hydrogen bond donor capacity of the ionic liquid that can stabilize the TS,
 - 2) long substituents on the cations lower selectivities presumably due to steric interactions between TS and the cation,
 - 3) hardness of ions in ionic liquids: The strong interaction between ions of ionic liquids results in less interaction between the ionic liquid and the TS. This leads to decrease in selectivity,
 - 4) HOMO and LUMO π -orbital interaction: Lower energy separation between HOMO and LUMO of reactants increase the selectivity of products, and
 - 5) polarity of ionic liquid: all types of interactions contribute to yield higher selectivities.
- Hence, the selectivity can be explained by the solvent polarity scale that takes into account maximum number of interactions.

Recently, Tiwari and Kumar have attempted to correlate the rates of Diels-Alder reactions of **7** with acrylates carried out in various ionic liquids with several solvent properties such as surface tensions, solvophobicities, $\delta_H(H^2)$, $E_T(30)$ and viscosities of solvent media.¹⁵⁵ The authors suggested that the rate constants of these reactions decrease with decrease in E_T^{30} values of ionic liquids. They have also proposed that the rate constants for these reactions decrease with increase in viscosities of ionic liquids possibly due to diffusion problems encountered by the reactants.

The investigations of the literature data show that the effects of the different ionic liquids on rates and *endo/exo* selectivities of the intermolecular Diels-Alder reactions have been studied extensively. However, very few studies concerning the effects of ionic liquids on intramolecular (diene and dienophile are present in the same molecule) Diels-Alder reactions are available.^{207, 208}

4.2. Intramolecular Diels-Alder reactions

Several physical methods have been used to accelerate intramolecular Diels-Alder reactions. Prajapati and coworkers have conducted the intramolecular Diels-Alder reaction of acyclic amine by microwave irradiation in presence of $\text{In}(\text{OTf})_3$.²⁰⁷ When the mixture of (2-furfuryl)aniline (65) and allyl bromide (66) (Scheme 4.1) was irradiated under microwaves for 8 min in presence of a catalytic amount of $\text{In}(\text{OTf})_3$, 85 % product was obtained. When the reaction mixture was irradiated under microwaves for 20 min in absence of $\text{In}(\text{OTf})_3$, only 6-8 % yield was observed. The advantages of $\text{In}(\text{OTf})_3$ as a Lewis acid catalyst is that it is soluble in both aqueous and organic media and is easily recovered from the aqueous layer after the completion of the reaction and the reaction is completed within few minutes.



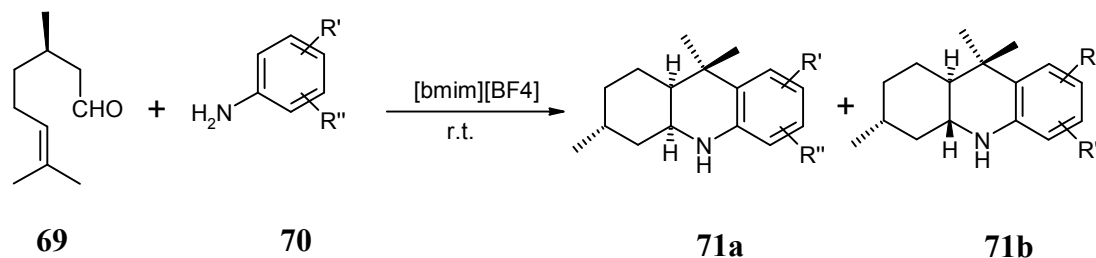
SCHEME 4.1

Yadav et al. have used various ionic liquids to promote the intramolecular aza-Diels-Alder reaction of arylimines derived from arylamines and (*R*)-(-)-citronellal or 3-methylcitronellal (69) (Scheme 4.2) to afford octahydroacridine derivatives in excellent yield under mild and neutral conditions.²⁰⁸

Most of the imines are hygroscopic, unstable at high temperatures and are difficult to purify either by distillation or by column chromatography. To circumvent these difficulties, the authors have developed the methodology in which the isolation of the unstable imines prior to reaction is not required. The 2-azadienes are reported to

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

undergo intramolecular hetero-Diels-Alder reaction in the air and moisture stable ionic liquid [BMIM][BF₄] in absence of any acid catalyst to afford 1,2,3,4,4a,9,9a,10-octahydroacridine derivatives in high yield. As an example, the treatment of (*R*)-(+)-citronellal with aniline in [BMIM][BF₄] at room temperature over a period of 1 h resulted in the formation of 3,9,9-trimethyl-1,2,3,4,4a,9,9a,10-octahydroacridine in 95 % yield.

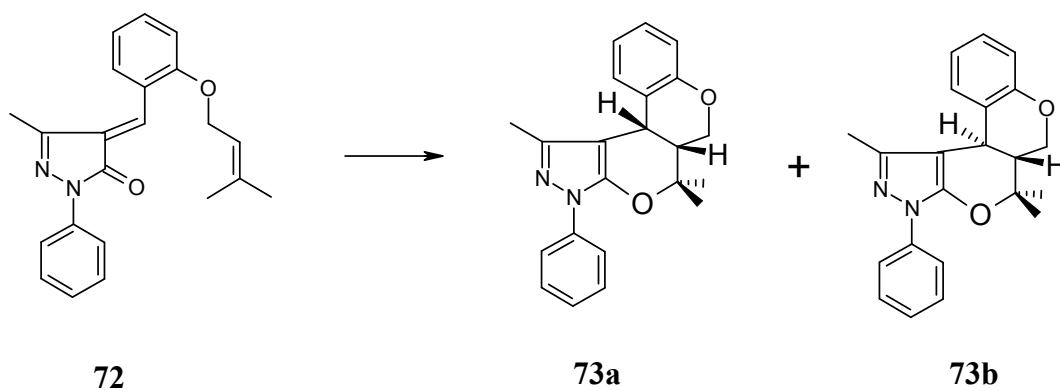


SCHEME 4.2

In view of a very limited data available in the literature, we aim to study the variation in the kinetics of intramolecular Diels-Alder reactions in ionic liquids.

4.3. Results and discussion

The kinetic profile of intramolecular hetero-Diels-Alder reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (Scheme 4.3) has been investigated in various ionic liquids since this reaction is reported to give good yields.



SCHEME 4.3

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

The ionic liquids used are of varying chain length on the imidazolium cation such as [EMIM][BF₄], [BMIM][BF₄] and [OMIM][BF₄] and also of different anions like [BMIM][PF₆] and [BMIM]I. The reaction has also been carried out using ionic liquids in the presence of triflates.

The rate constants of the reaction of 1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone conducted in several organic solvents have been correlated with the AN of solvents. As the AN of solvents increase, the rates of reactions also increase. In this case, the solvents are acting as electrophiles.

The interaction between FMOs of solvents and heterodienes in hetero-Diels-Alder reactions with inverse electron demand, gives a stabilization of the LUMO of heterodiene, a lower energy separation between this and HOMO of dienophile and the rate of reaction again increases with increase in the AN of the solvent.

The intramolecular reaction of **72** in various organic solvents of increasing polarity is reported to give *de* diastereomers in 90 % yield.²⁰⁶ The plot of selectivity of the *de* diastereomers against the polarity (E_T^N) of the solvents gives a very approximately linear correlation.

The reaction has also been conducted in 1.4 M MPAC, 2 M BPAC, 4 M LPAC, 2.6 M SPAC.⁹³ Among these salt solutions, LPAC is found to be most effective in enhancing the rates of intramolecular hetero-Diels-Alder reactions. The reaction of **72** has shown about 217 times increase in 4 M LPAC than in pure acetone solution. In this case, the solvated metal cation, acting as a Lewis acid, coordinates the diene moiety. Since the cation behaves as an electrophile, its LUMO interacts with the HOMO of heterodiene and the LUMO of this latter is stabilized by electrostatic interaction. This results in a lower energy separation between the FMOs of diene and dienophile and ultimately the rate of reaction is increased. As the charge density on the cation increases, the Lewis acid ability to catalyze the reaction increases.

The activation parameters for this reaction in the presence and absence of inorganic perchlorates show no dramatic changes from uncatalyzed to cation-catalyzed reaction.

In order to examine the kinetic profiles of intramolecular hetero-Diels-Alder of **72** in ionic liquids, we first studied the rate of the reaction in organic solvent,

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

dichloromethane. It has been observed that the rate constant, k of this reaction in dichloromethane is 10 times higher than that in acetone as reported in the literature.⁹³ The rate constants obtained in this study are listed in Table 4.1.

As evident from the data listed in Table 4.1, the rate is observed to be about 56 times higher in [EMIM][BF₄] than in dichloromethane.

The increase in carbon chain on C-1 of imidazolium cation results in a slow drop in rates of reactions. When [BMIM][BF₄] is used as a solvent medium, the rate of reaction increases by about 50 times as compared to that in dichloromethane. Further when ionic liquid changes from [BMIM][BF₄] to [OMIM][BF₄], the rate of reaction decelerates by 4.4 times. However, the reaction shows 11-fold increase over dichloromethane.

TABLE 4.1. The rate constants, k of the reaction **1** (Scheme 4.3) in various solvent media.

Solvent medium	Rate constant, $k \times 10^6 \text{ (s}^{-1}\text{)}^a$
dichloromethane	6.30
acetone ^b	0.63
4 M LPAC	137.0
[EMIM][BF ₄]	353.7
[BMIM][BF ₄]	318.5
[BMIM][PF ₆]	72.3
[OMIM][BF ₄]	72.2
[BMIM]I	could not be determined
0.2 mol % La(OTf) ₃ + [BMIM][BF ₄]	Slow
0.5 mol % La(OTf) ₃ + [BMIM][BF ₄]	675.9
1 mol % La(OTf) ₃ + [BMIM][BF ₄]	too fast to follow by UV Vis spectroscopy
water	no product detected

a. rate constants are average of triplicate runs and accurate to 5 %, **b.** see reference 93.

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

A significant decrease in rate of reaction has been observed when the anion changes from BF_4^- to PF_6^- keeping the cation same i.e. by changing the ionic liquid from $[\text{BMIM}][\text{BF}_4]$ to $[\text{BMIM}][\text{PF}_6]$. When $[\text{BMIM}]\text{I}$ is used as a solvent, the reaction becomes very sluggish. This restricts the measurement of k in this ionic liquid.

The rare earth metal triflates in conjunction with ionic liquids have been found as an effective Lewis acid catalyst to accelerate Diels-Alder reactions, Michael reactions, aldol-type reactions. The $\text{Ln}(\text{OTf})_3$ as well as $\text{Sc}(\text{OTf})_3$ have been widely used in Diels-Alder reactions to enhance the reactions.

We have carried out intramolecular hetero-Diels-Alder reaction of **72** in $[\text{BMIM}][\text{BF}_4]$ in presence of $\text{La}(\text{OTf})_3$ of varying concentration. The reaction is observed to be too slow to measure the k in 0.2 mol % $\text{La}(\text{OTf})_3$. When the concentration of $\text{La}(\text{OTf})_3$ increases to 0.5 mol %, the k increases by 2.1 times over that in pure $[\text{BMIM}][\text{BF}_4]$. The reaction becomes very fast when concentration of $\text{La}(\text{OTf})_3$ increases to 1 mol %.

It has been observed that water is more effective solvent medium than ionic liquids for the reaction of **7** with acrylates in order to gain the maximum rate enhancement.¹⁵⁵ Several organic reactions including intermolecular Diels-Alder cycloadditions have been promoted in water. Lewis acid catalysis, hydrophobic hydration, polarity, internal pressure of solution media, hydrophobic effect have been assigned as possible reasons.⁵⁶ In fact, hydrophobic packing of diene and dienophile in intermolecular Diels-alder reaction in aqueous medium promotes the formation of cycloadduct. However, when intramolecular Diels-Alder reaction of **72** is carried out in water, no such effects are observed. It is clear that two different molecules are not available in water facilitating hydrophobic packing. It is therefore, imperative that aqueous salt solutions may not have pronounced effect on the progress of intramolecular Diels-alder reaction of **72**. This is also seen when water was used as a solvent. As described above, formation of products from **72** in LPAC is accelerated due to Lewis acid catalysis or electrostatic catalysis or internal pressure effects.

The results have been analyzed on the basis of different solvent parameters of ionic liquids such as viscosity, solvophobicity, α , β etc.

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

The rate of reaction is observed to be highest in the ionic liquid of very low viscosity, [EMIM][BF₄]. As the viscosity of the ionic liquid, [BMIM][BF₄] increases, the reaction slows down. In case of [BMIM][PF₆], the viscosity is lower than that of [BMIM][BF₄], but the *k* is found to be higher than that in [BMIM][BF₄].

TABLE 4.2. Reported viscosities of various ionic liquids

Ionic Liquid	viscosity (cP)	reference
[EMIM][BF ₄]	32	209
[BMIM][BF ₄]	233	147
[BMIM][PF ₆]	207	210
[BMIM]I	1110	211
[OMIM][BF ₄]	-	

Firestone studied the intramolecular Diels-Alder cyclization of *N*-propargyl-9-anthramide (**75**) (Scheme 5.1) in a series of glymes.²⁰⁹ A significant correlation between the relative rate and relative viscosity was found. The rates of the reaction were explained on the basis of vibrational activation theory. According to this theory, bond-making reactions are promoted by vibrational energy in the reactants and high translational energy is detrimental to the reaction. (A detailed discussion on vibrational activation theory appears in chapter 5).

It should be noted that in the literature there is wide discrepancy between the values of viscosity of ionic liquids like [EMIM][BF₄], [BMIM][PF₆] for example. This may be due to the viscosities are sensitive to the water content and other impurities. Therefore, at this stage it is not possible to comment on the dependency of the *k* values on the viscosities of ionic liquids. Since in the intramolecular Diels-Alder reaction, diene and dienophile are part of a single molecule, there should not be any diffusion problem for reactants. Therefore variations in viscosities of solvent media are not expected to show any effects on the rates of reaction and it is true in the current investigation.

The rate constants have been tried to correlate with the polarity parameter, E_T^N . The E_T^N values have been reported for the ionic liquids [BMIM][BF₄] and [BMIM][PF₆]

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

as 0.670 and 0.669.¹⁴⁷ In view of the almost similar values of both the ionic liquids, it is not possible to state anything about the dependency of k . The E_T^N values for other ionic liquids should be made available in due course to show a correlation between the two.

The values of β and α parameters have also been available for the above mentioned ionic liquids.¹⁴⁷ The values of β are 0.73 and 0.77 whereas of α are 0.72 and 0.41 for [BMIM][BF₄] and [BMIM][PF₆], respectively. However, considering the observed rate constants, it has not been possible to explain the rate constant on the basis of α and β parameters. The k values increase with the decrease in the α values. The k values for the reaction are inversely correlated to the β values of ionic liquids.

The π^* values are available in the literature.¹⁴⁷ For [BMIM][BF₄] and [BMIM][PF₆], the π^* values are 1.09 and 0.91, respectively. For acetone and dichloromethane the π^* values are 0.71 and 0.82, respectively. The rate constants observed in these solvent media show dependency on the π^* parameter. The rate constants obtained in ionic liquids and in organic solvents, acetone and dichloromethane are plotted as a function of π^* values as shown in Figure 4.2.

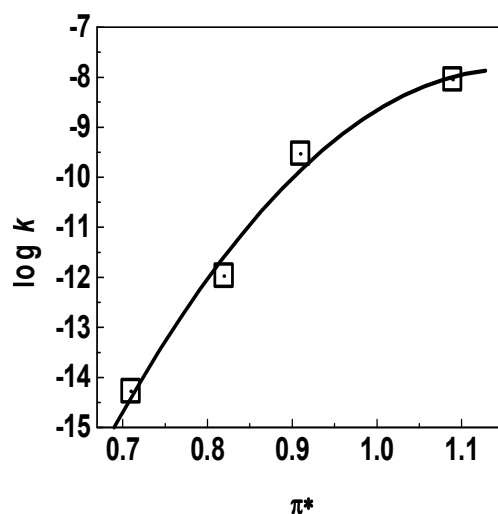


FIGURE 4.2. Variation in rate constants as a function of π^* for the intramolecular hetero-Diels-Alder reaction of **1** (Scheme 4.1)

4. Intramolecular Diels-Alder Reaction in Ionic Liquids

The rate of reaction in [BMIM][BF₄] in the presence of La(OTf)₃ offers optimum rate enhancement. The rate acceleration can be explained on the basis of Lewis acid catalysis by La(OTf)₃. In this intramolecular hetero-Diels-Alder reaction with inverse electron demand, LUMO of electrophilic cation interacts with the HOMO of diene. The LUMO of diene is stabilized by electrostatic interactions. This results in a lower energy separation between the FMOs of the diene and dienophile. This ultimately reflects in the enhancement of the reaction rates.

The reaction of 1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone was studied in nonaqueous solvents at various temperatures.¹¹⁷ From the Arrhenius plots, activation parameters ΔH^\ddagger and ΔS^\ddagger were calculated. The $-\Delta S^\ddagger$ values remained nearly constant. The values (21.5 e.u.) were about half the $-\Delta S^\ddagger$ values for the intermolecular hetero-Diels-Alder reaction of 4-*o*-methoxy-benzylidene-1-phenyl-5-pyrazolone and isobutylvinyl ether (39-40 e.u.).

The ΔH^\ddagger values were larger in intramolecular hetero-Diels-Alder (18.7, 19.3 and 18.0 kcal mol⁻¹ in benzene, 1,4-dioxane and methanol respectively) than in intermolecular hetero-Diels-Alder (12.1, 12.5 and 9.9 kcal mol⁻¹ for the same solvents respectively). This significant difference (about 7 kcal mol⁻¹) was not due to the orbitalic term (ΔE , given by Equation 1.4) but due to the strain energy required for its cyclic system to reach the transition state.

The extensive literature survey shows that the solvent parameters for the commonly used ionic liquids have not been studied in detail. Due to lack of the data on the solvent parameters of the ionic liquids, it has not been possible to satisfactorily explain the rate constants of intramolecular hetero-Diels-Alder reaction of **1** on the basis of parameters reported. However, the above investigation firmly establishes the rate dependence of intramolecular Diels-Alder reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone on the dipolarity/ polarizability parameter π^* of ionic liquids, a noteworthy point here.

Chapter 5
ROLE OF VISCOSITY

This chapter describes the role of viscosity in determining the kinetics of the organic reactions. It has been a debatable issue whether rates of Diels-Alder reactions depend on the viscosity of solvent media in which reactions are performed. On the basis of the investigations related to the rates of Diels-Alder reactions, it has been possible to examine the rates and endo/exo ratios of Diels-Alder reactions in terms of viscosities of solvent media.

5.1. Conventional kinetic theory

According to conventional kinetic theory, the rates of the collision-controlled reactions are independent of viscosity and that of encounter-controlled reactions are inversely proportional to viscosity of medium. Thus, a bond making reaction, bimolecular or intramolecular, should proceed independent of viscosity. However, reactions slow down at very high viscosity. On parallel lines, bimolecular reactions such as Diels-Alder reactions are expected to be independent of viscosity of the medium.

5.2. Controversies regarding role of viscosity

Firestone and coworkers investigated the role of viscosity on the kinetics of Diels-Alder reactions.²¹² It has been shown that the intramolecular Diels-Alder cyclization of *N*-propargyl-9-anthramide (**74**) (Scheme 5.1) increases with viscosity of several glymes. Another example is the dimerization of **7** (Scheme 5.2), reported by Wasserman et al.²¹³ The rate of dimerization reaction in paraffin oil is about twice than that in carbon tetrachloride. In dicyclopentadiene as a solvent, the dimerization reaction is about 3.3 times faster than that in monomeric cyclopentadiene. The group investigated the role of viscosity in promoting the rates of Diels-Alder reactions. The above examples demonstrate that the rates of Diels-Alder reaction and viscosity are correlated with each other. The authors have further demonstrated that high pressure accelerates some bond-making reactions through elevation of solvent viscosity, which is a nonvolume related way to speed up reaction. Since rates of Diels-Alder reactions are enhanced by increasing viscosities, the acceleration due to change in pressure does not come solely due to change in volume. Therefore, it has been commented that the reported ΔV^\ddagger contains some nonvolume related part. The ΔV^\ddagger have been obtained by measuring the effect of pressure

on the reaction rates as shown in Equation 1.2. While calculating ΔV^\ddagger , it is assumed that the entire acceleration in the reaction rates due to high pressure is the result of shrinkage in volume. Therefore, the ΔV^\ddagger calculated from the change in rate as a function of change in pressure is termed as phantom activation volume. The phantom activation volume has been estimated for the dimerization of **7**. With the rise in viscosities of solvent media, reaction rate first rises and then falls. The phantom activation volume is calculated over the viscosity range where reaction rate rises since the rate increase is entirely due to increase in viscosity. The phantom activation volume for the dimerization reaction has been reported as $-13.72 \text{ cm}^3 \text{ mol}^{-1}$ (61% of the ΔV^\ddagger reported). Following this procedure, phantom activation volumes have been calculated for a large number of Diels-Alder reactions.²¹⁴

However, recently questions have been raised whether viscosity really contributes to the rate acceleration of Diels-Alder reaction.^{215, 216} Consequently, the existence of phantom activation volume has also been argued. le Noble and Asano have stated that the rate acceleration in a nonvolume related way is fundamentally wrong. The study of the rate constant as a function of molecular weight of solvent (due to which viscosity of solvent also varies) should be examined from various angles in order to find out which property of solvent affects the rates of reactions.²¹⁵ Hamann and le Noble have calculated the second-order rate constant for the reaction of diphenyldiazomethane and ethyl phenylpropiolate.²¹⁷ The plot of reaction rates as a function of viscosities of solvent media has been found with low precision and less accurate. Further when the calculations are done correctly, the authors do not find any dependency of reaction rates on viscosities of solvent media, also negligible corrections (less than uncertainty) in the ΔV^\ddagger values have been estimated.

The dimerization reaction of **7** has been repeated by Weber and van Eldik using solvents mentioned in the literature.²¹⁶ Since this reaction is reported to give low yields, kinetic measurements have been done over reaction periods of at least one half-life of the reaction. Moreover, cloudy solutions of **7** in *n*-alkane have been observed. The results reported by the authors show no dependency of reaction rates on the viscosities of the media. Eventually they have concluded that phantom activation volumes are real activation volumes.

Firestone and Swiss have clarified the objections raised by presenting numerous organic reactions including radical-radical combination reaction, isomerization reaction where the reaction rates increase with viscosities of solvent media. Therefore they have proposed the ΔV^\ddagger is not a physically accurate value.²¹⁸⁻²²⁰

5.3. Experimental observations

Here an attempt is made to explore whether the rates of Diels-Alder reactions are altered by the variation in viscosities of the solvent media. Even though this issue has been supported and criticized earlier, it would be more appropriate to assess this point by the experimental data. In this connection, we set to explore our experimental data and the existing data as a step to resolve the issue of the role of viscosity on rates of Diels-Alder reactions.

The strength of the whole study lies in the fact that both the reaction rates or *endo/exo* ratios and the viscosities of solvents used to carry out the reactions have been measured at the same temperature. This eliminates any discrepancy in the correlation. We started the study by investigating the simple Diels-Alder reaction of **7** with **10** (Scheme 1.5) has been investigated in different solvents. The *endo/exo* ratios of this reaction are studied as a function of polarity of solvent media under the reaction conditions described in the literature.⁵⁸ The *endo/exo* ratios are obtained at 30°C in the solvents given in Set 3 for Reaction 3 (Scheme 1.5) (given at the end of this chapter) and are compared with the values obtained by Berson and coworkers.⁵⁸ The *endo/exo* ratios are plotted as a function of viscosities of the media as shown in Figure 5.1. The *endo/exo* ratios of this reaction are observed to be dependent on the viscosities of the solvent media. The *endo/exo* values increase up to ~ 1 cP. Above 1 cP *endo/exo* values go on decreasing with viscosities of media.

This reaction has also been studied in solvents mentioned in alcohols and their aqueous solutions (Set 3 for Reaction 3) at 25°C.^{122, 197} The *endo/exo* values in these solutions follow the same trend. When the temperature is raised to 30°C the maximum of the *endo/exo* ratios for this reaction is shifted to 0.8 cP.

Nakagawa has made contrasting observation for the reactions of **7** with **10** (Scheme 1.5) and with **19** (Scheme 1.9) at 22°C in the solvents mentioned in Set 2 for

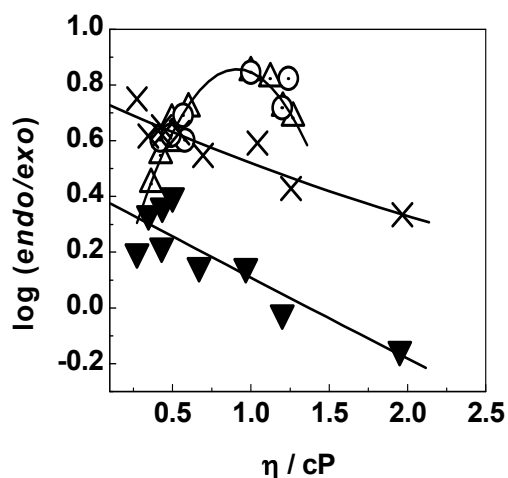


FIGURE 5.1. Plots of $\log(\text{endo/exo})$ for the reactions of (1) **7** with **10** (Scheme 1.5) (Δ) at 30 °C, (\blacktriangledown) at 22 °C and (O) at 30 °C and (2) **7** with **19** (Scheme 1.9) (\times) at 22 °C

Reaction 3.²²¹ The *endo/exo* ratios for the reaction of **7** with **10** decrease monotonically with the increase in viscosities of the solvent media. Similarly, the reaction of **7** with **19** at 22°C show a noticeable decrease in *endo/exo* values with respect to viscosities of the solvents at 22°C. When we carried out this reaction under the same conditions (Reaction 3) reported by Nakagawa et al., a complete different trend is observed.²²² The $\log(\text{endo/exo})$ values thus obtained are plotted as a function of viscosities of the solvent media as shown in Figure 5.2. The $\log(\text{endo/exo})$ -viscosity, η plot for the reaction of **7** with **10** is steeper than the one obtained from Nakagawa et al. (Figure 5.2). The $\log(\text{endo/exo})$ values increase with viscosity. The maximum in $\log(\text{endo/exo})$ value obtained is observed at viscosity 0.5-0.6 cP. Further, a clear decrease in $\log(\text{endo/exo})$ values are observed from 1 to 2 cP.

The *endo/exo* ratios for the reaction of **7** with **14** (Scheme 1.7) have been investigated in the solvents as given in Set **1** for Reactions **4**. The *endo/exo* values first increase with viscosity up to 1 cP followed by a sharp decline between viscosity of 1 and 2 cP.

In another study, several Diels-Alder reactions have been studied in LPDE of concentration up to 6 M. It is noted that the rate decrease above 5 M LPDE has been related to very high viscosity of LPDE solution. No dramatic increase in the viscosity of

LPDE is observed up to a concentration of 5 M. However, the viscosity of nearly saturated (6.06 M) LPDE increases by about 800% as compare to that of pure diethyl ether.⁹² A highly viscous environment is, therefore considered to play an inhibitive role due to diffusional problems causing the reaction rates to fall.

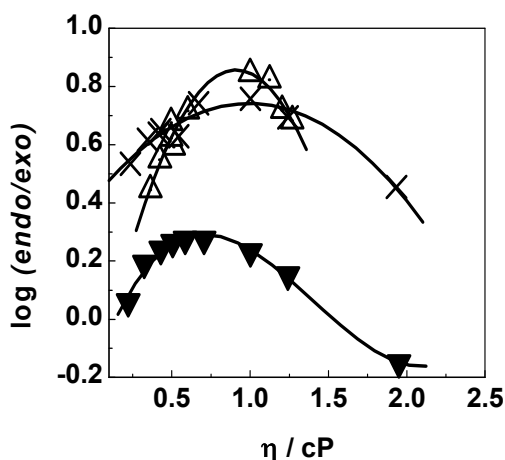


FIGURE 5.2. Log(*endo/exo*) - η plots for the reaction of **7** with **10** (Scheme 1.5) (Δ), (\times) and with **19** (Scheme 1.9) (\blacktriangledown)

To get a clear picture, the $\log k$, where k is rate constant is plotted as a function of solvent viscosity for the reactions of **7** with **10** (Scheme 1.5), with (-) menthyl acrylate (**51b**) (Scheme 1.3) and with methyl (*E*)- α -cyanocinnamate (**78**) (Scheme 1.4).^{123, 222} The solvents used for these reactions are given in Set **3** for Reaction **3**, for Reaction **5** and for Reaction **6**. The rates of the reaction of **7** with **10** increase with viscosity up to 0.75 cP. The rates decline in the viscosity range of 0.75-1.25 cP. The rates of the reaction of **7** with **51b** in several solvents show a slow increase from 0.25 to 1 cP before declining the viscosity up to 1.5 cP. The reaction of **7** with **78** has been reported in several aqueous mixtures of acetone and dioxane. If $\log k$ for this reaction is plotted against the viscosities of these aqueous mixtures (as shown in Figure 5.3), the rates increase up to \sim 0.75 cP and then show a fall in the viscosity range of 0.75-1.5 cP. The $\log k - \eta$ plots for both the reactions of **7** with **10** and with **51b** are quite steep. However, the $\log k - \eta$ plot for **7** with **78** (Scheme 5.4) show a slow increase.

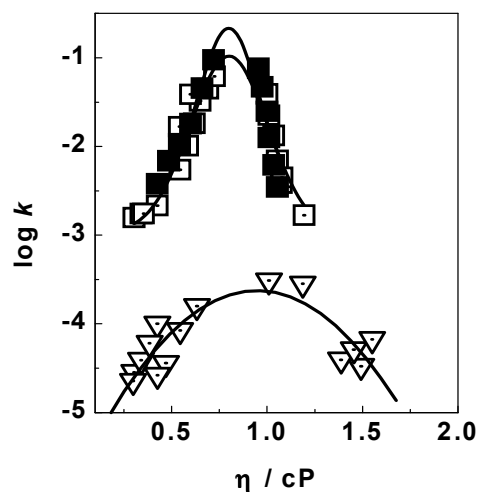


FIGURE 5.3. Plots of $\log k$ vs η for the reactions of **7** with **10** (Scheme 1.5) (\square), with **51b** (Scheme 5.3) (\blacksquare) and with **78** (Scheme 5.4) (∇) in different solvents

The reaction of **7** with **12** (Scheme 1.6) offers higher proportion of *exo*-products (follow anti-Alder rule) as compared to that with methyl acrylate (follow Alder rule) which yield higher proportion of *endo*-products.⁵⁸ Similarly, the reaction of **7** with **8** (Scheme 1.4) gives slightly higher proportions of *endo*-products in polar products and slightly higher proportions of *exo*-products in nonpolar solvents (borderline behavior).⁵⁸ The $\log(\textit{endo/exo}) - \eta$ plots for these two reactions at 30°C are shown in Figure 5.4. It is clear from the graph that the *endo/exo* ratios show a very small positive rise in the viscosity range of 0.37-1.1 cP. These reactions were not carried out in the solvents having viscosity above 1.2 cP. Hence it has not been possible to observe the decline in the reaction rates. The $\log(\textit{endo/exo})$ values for these reactions do not include the data in methanol due to the points falling beyond the trend shown.

We then examined the viscosity dependence of the rate constants for the reaction of **43** with **44a** (Scheme 1.19) in the solvents given for reaction **7** at 80°C.¹¹⁵ These data shown in Figure 5.5 indicate that the rates show a steep increase in the solvents possessing viscosity in the range of 0.4-0.9 cP. A decrease in rates can be witnessed in the viscosity range of 1.4-2 cP.

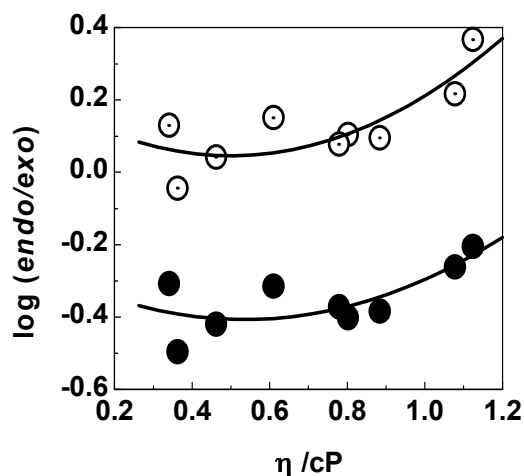


FIGURE 5.4. Plots of $\log(\text{endo/exo}) - \eta$ for the reactions of **7** with **8** (Scheme 1.5) (O) and with **12** (Scheme 1.6) (●) at 30 °C

Further, the rates of the reactions of *N*-(2'-4'-dichloro-6'-oxo-2',4'-cyclohexadien-1-ylidene)-4-nitrobenzamide (**80**) with **43** (Scheme 5.5) and with ethyl

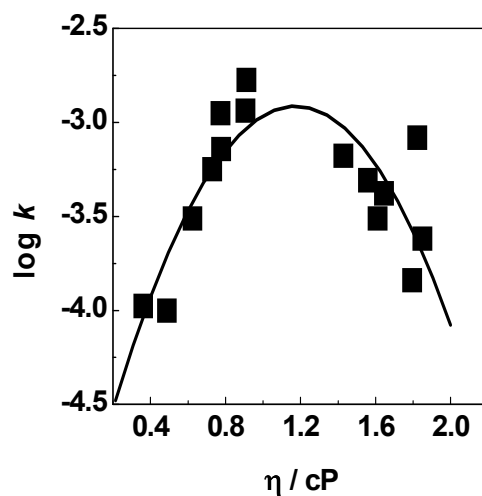


FIGURE 5.5. Plots of $\log k$ for the reactions of **43** with **45a** (Scheme 1.19) at 80 °C

vinyl ether (**82**)¹²⁵ (Scheme 5.6) show prominent maxima at ~ 1.2 cP before declining sharply in the viscosity range up to 2 cP (Figure 5.6). Also, the $\log k - \eta$ plots for the reactions of **43** with **44b-d** (Scheme 1.19) in a variety of solvents¹¹⁶ (as mentioned for Reaction **10**) are shown in Figure 5.6, where a modest increase in rates can be noted with

the solvent viscosity reaching a maximum at ~ 1.2 cP followed by a leveling of the curves and then a mild decrease in the rate of the reactions.

From the above, it is clear that both the *endo/exo* ratios and the rates of Diels-Alder reactions show dependence on viscosities of solvents. Another important observation is that although the viscosity increases by about 3 times, the rates can vary by as much as 100 times. This is contradictory to the general observation that for a diffusion-controlled bimolecular reaction, the ratio of rate change should be comparable with that of the viscosity. No explanation is available to describe this observation, which is entirely based on the examination of the experimental rate data (Figures 5.3 and 5.6), and no theoretical assumptions are involved in this observation.

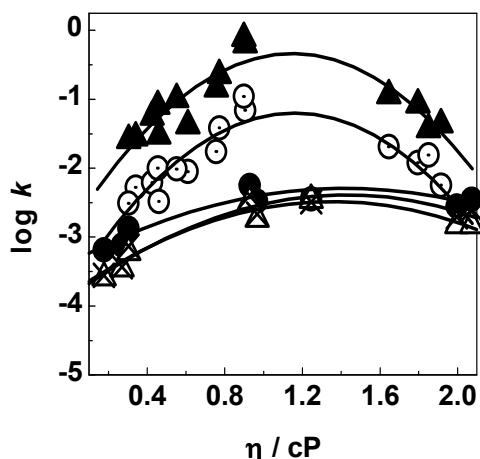


FIGURE 5.6. Dependence of $\log k$ on the solvent viscosity **43** + **44b** (\bullet), + **44c** (Δ), + **44d** (\times) (Scheme 1.19); **6M** + **8M** (Scheme 5.7) (\blacktriangle), and + **43** (Scheme 5.6) (O)

Though Berson et al.⁵⁸ have carried out temperature dependent studies of the reactions of **7** with different dienophiles at three or four temperatures, their data cannot be deemed the best data set in the present context, as temperatures selected for each solvent are not common. In view of this, the reaction of **7** with **10** (Scheme 1.5) has been carried out in five solvents (acetone, methanol, acetic acid, 2-methoxyethanol, and 1-propanol) of graded viscosities at three different temperatures, i.e., 2, 25, and 33°C (Figure 5.7). It is interesting to note that $\log(\textit{endo/exo})$ increases sharply in the viscosity range of ~ 0.3 to ~ 1 cP before showing a sharp decline in these solvents with viscosities

varying between ~ 1.5 and ~ 2 cP. The aim of conducting temperature dependent studies is to examine whether changes in temperature in the reaction brought any changes in the plot shown in the foregoing studies. It is clear from the plot that as the temperature increases and the solvent viscosity decreases, a drop in the $\log(\text{endo/exo})$ value is witnessed. With the rise in temperature, the solvent viscosity decreases (in this temperature range) and the maximum $\log(\text{endo/exo})$ value shifts to the left: $\log(\text{endo/exo})$ - 0.9 at η 1.3 cP at 2°C; $\log(\text{endo/exo})$ - 0.83 at η 1.2 cP at 25°C; and $\log(\text{endo/exo})$ - 0.82 at η 0.91 cP at 33°C.

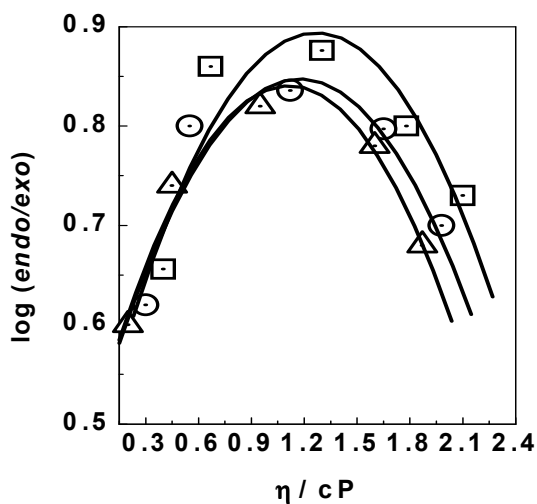


FIGURE 5.7. Plots of $\log(\text{endo/exo})$ against the solvent viscosity for the reaction of **7** with **10** (Scheme 1.5), 2 °C (\square), 25 °C (\circ), 33 °C (Δ)

From the examples examined above, it is clear that rates of different Diels-Alder reactions vary with the viscosities of solvents. The contents described in this work clearly dispel the confusion over the relationship between rates of Diels-Alder reactions and solvent viscosities. In the above text, it has not been our main objective to put forward any theory in support of data but to demonstrate by plotting the rate-viscosity data in a consistent manner whether a correlation between rates of Diels-Alder reactions and the solvent viscosity exists at all. This work shows that there is such a correlation. The rate enhancement in the low viscosity range cannot be accounted for in terms of current

kinetic theory, as the bond-forming reactions are independent of viscosity in this collision controlled regime.

5.4. Discussion

Firestone and coworkers have interpreted this behavior in terms of vibrational activation theory.^{212, 222} They proposed two requirements for the Diels-Alder reactions to take place based on vibrational activation theory. 1) Reactions of complex molecules requiring significant activation energy take place only through vibrational, not translational activation. Thus the reactants must possess enough vibrational energy to overcome the barrier. 2) The formation of a new bond must be vibrationally coupled to the breaking of the bond. This coupling requires sufficient time for several vibrations. It has been further proposed that if the translational energy is present in excess, it inhibits the reaction. This is because the reactants undergo hard collisions, in which they rebound in less time than it takes for vibrational coupling. However when soft collisions take place the reactants get sufficient time to couple vibrationally with each other. Thus, soft collisions are most effective in accelerating the Diels-Alder reactions.

On this basis, vibrational activation theory predicts that typical bond-making reactions should go faster at high viscosities. This is because bond-making processes are promoted by high vibrational but low translational energy. Both the modes are favored at high viscosity of medium. This regime is known as collision-controlled regime. The schematic representation of the different regions is shown as Figure 5.8. Hence the energy content of the molecule is shifted from translational to vibrational mode.

On parallel lines, as an example, the acceleration of organic reactions by enzymes has been explained. Enzymes immobilize the reactants by providing a microenvironment of high viscosity wherein the reaction takes place rapidly. However, the bulk medium is of low viscosity. This allows the reactants and products to come together and separate without hindrance.

At very high viscosities, the relative freedom of movement of reactants in the microenvironment of the encounter pair becomes limited. In such highly viscous environment, reactants cannot see each other and the reaction is consequently slowed down. This region is known as encounter-controlled or diffusion-controlled regime.

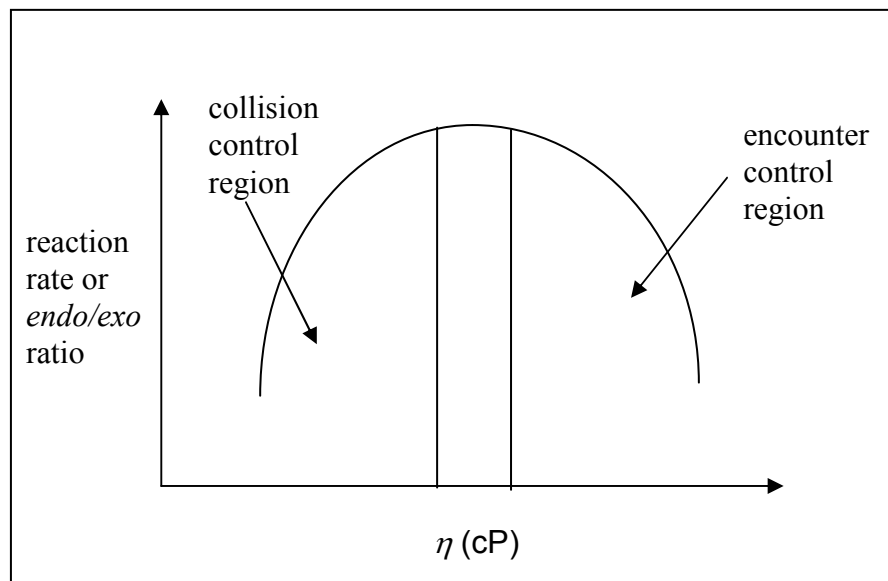
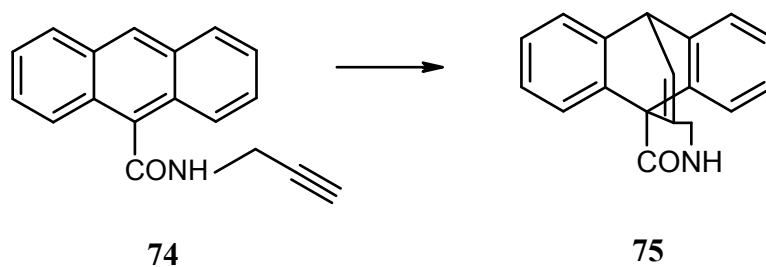


FIGURE 5.8. The different regions shown for the variations in reaction rates or *endo/exo* ratios as a function of viscosities of the media

In nutshell, on the basis of vast number of Diels-Alder reactions investigated, it is concluded that the rates and *endo/exo* ratios of different Diels-Alder reactions vary with the viscosities of the solvent media in which reactions are carried out.

Conditions for the reactions investigated to study the dependence of reaction rates on the viscosities of the media are given below.

1) Diels-Alder cyclization of *N*-propargyl-9-anthramide

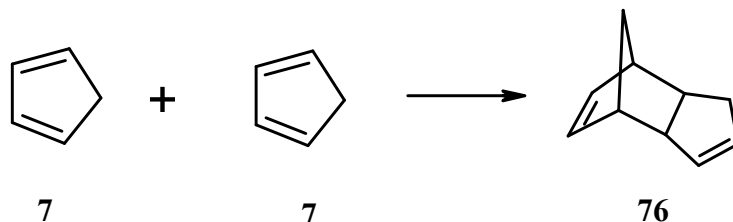


SCHEME 5.1

Solvents: Glyme, diglyme, triglyme and tetraglyme

Reaction temperature, t: 100°C

2) Dimerization of cyclopentadiene



SCHEME 5.2

Solvents: Set (1): *n*-octane, *n*-decane, *n*-undecane, *n*-dodecane, *n*-tridecane, *n*-tetradecane and *n*-heptadecane

Reaction temperature, t: 25°C

Set (2): *n*-butanol, *t*-butanol, chlorobenzene, *n*-propanol, ethanol, toluene, acetone, diethyl ether, dichloromethane, dioxane, methanol, chloroform and carbon tetrachloride

Reaction temperature, t: 40°C

3) Reaction of 7 with 10 (Scheme 1.5)

Solvents: Set (1) methanol, acetic acid, ethanol, 1,2-dichloroethane, acetone, acetonitrile, nitromethane, pyridine, dimethylformamide, 1,2-dimethoxyethane, decalin and triethylamine

Reaction temperature, t: 30°C

Set (2) methanol, ethanol, acetone, *n*-propanol, ethyl acetate, diethyl ether, cyclohexane, toluene, *n*-hexane, heptane and decalin

Reaction temperature, t: 22°C

Set (3) methanol, aqueous solutions of 50, 60, 70, 80, 90 % methanol, acetone, aqueous solutions of 50, 60, 80 % acetone, dioxane, aqueous solutions of 50, 60, 70, 80, 90 % dioxane, acetonitrile, ethanol and formamide

Reaction temperature, t: 25°C

Set (4) *n*-hexane, dichloromethane, acetone, aqueous solutions of 40, 80 % acetone, acetonitrile, nitrobenzene, dioxane, aqueous solutions of 30, 50, 60 % dioxane, aqueous solutions of 30, 60, 70 % methanol, trifluoroethanol and hexafluoroisopropanol

Reaction temperature, *t*: 30°C

Set (5) acetone, methanol, acetic acid, 2-methoxyethanol and 1-propanol

Reaction temperature, *t*: 2°C, 25°C and 33°C

3) Reaction of 7 with 19 (Scheme 1.9)

Solvents: methanol, ethanol, acetone, *n*-propanol, ethyl acetate, diethyl ether, cyclohexane, toluene, *n*-hexane, heptane and decalin

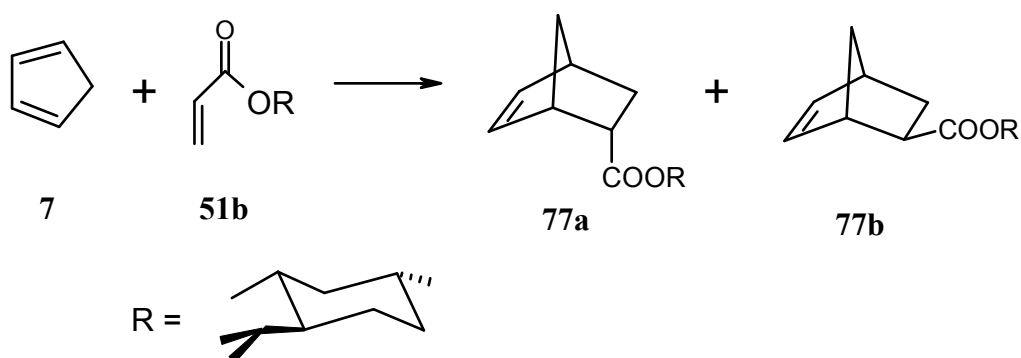
Reaction temperature, *t*: 22°C

4) Reaction of 7 with 14 (Scheme 1.7)

Solvents: *n*-hexane, dichloromethane, acetone, aqueous acetone mixtures, methyl acetate, acetonitrile, nitrobenzene, dioxane, aqueous dioxane mixtures, aqueous methanol mixtures, trifluoroethanol and hexafluoroisopropanol

Reaction temperature, *t*: 30°C

5) Reaction of 7 with 51b

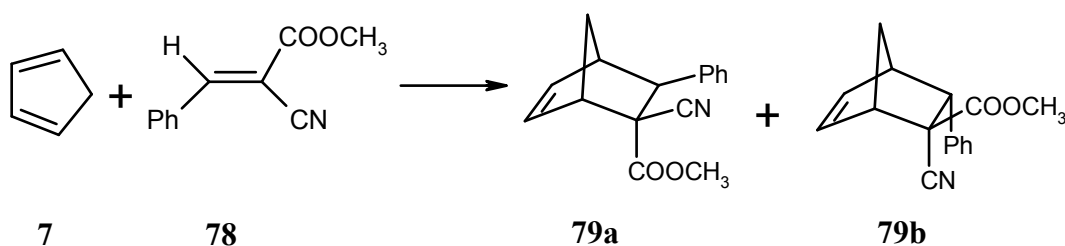


SCHEME 5.3

Solvents: chlorobenzene, benzonitrile, isopropanol, *n*-hexane, dichloromethane, acetone, aqueous solution of 80 % acetone, acetonitrile, nitrobenzene, ethyl acetate, dioxane, aqueous solutions of 50, 60 % dioxane, isopropanol, methanol, aqueous solutions of 60, 70 % methanol, trifluoroethanol and hexafluoroisopropanol.

Reaction temperature, *t*: 30°C

6) Reaction of **7** with methyl (*E*)- α -cyanocinnamate (**78**)



SCHEME 5.4

Solvents: aqueous solutions of 20, 30, 40, 50, 60, 70 % acetone and aqueous solutions of 20, 30, 40, 50, 60, 70 % 1,4-dioxane

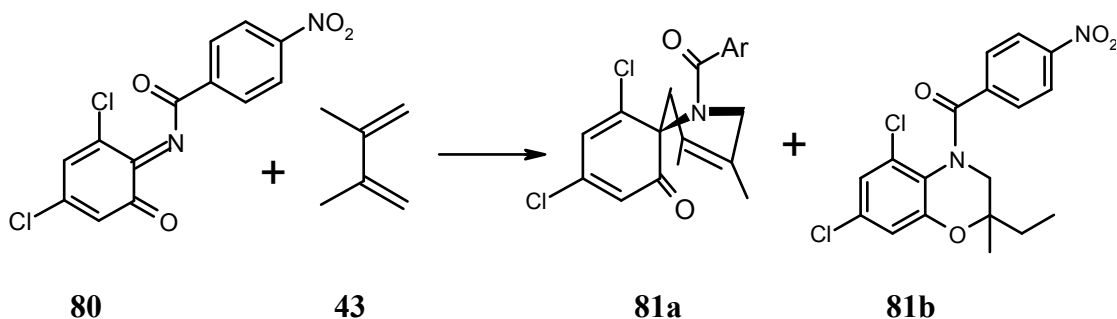
Reaction temperature, *t*: 25°C

7) Reaction of **43** with **44a** (Scheme 1.19)

Solvents: cyclohexane, *n*-hexane, ethyl acetate, benzene, diethyl ether, acetone, dioxane, acetonitrile, dimethylformamide, chloroform, dimethyl sulphoxide, *t*-butanol, isopropanol, ethanol, methanol and acetic acid.

Reaction temperature, *t*: 80°C

8) Reaction of **43** with *N*-(2'-4'-dichloro-6'-oxo-2',4'-cyclohexadien-1-ylidene)-4-nitrobenzamide (**80**)

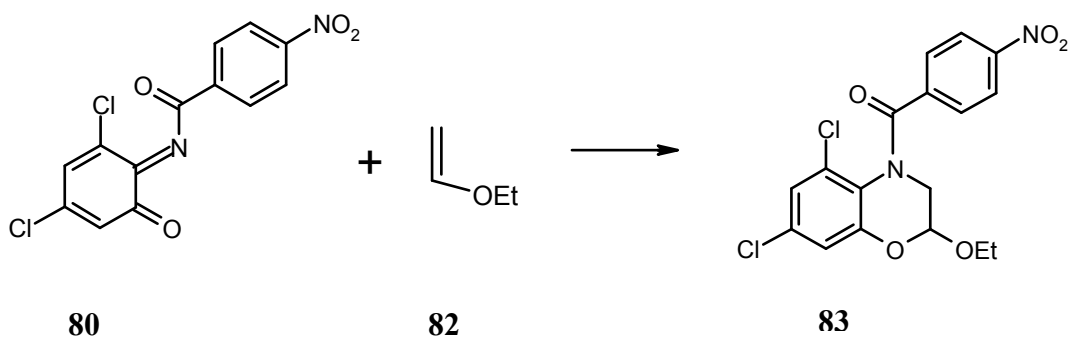


SCHEME 5.5

Solvents: cyclohexane, butanone, acetone, ethyl acetate, 1,4-dioxane, nitrobenzene, acetonitrile, nitromethane, chloroform, carbon tetrachloride, tetrahydrofuran, toluene, dimethoxymethane, chlorobenzene and 1,2-dichloroethane

Reaction temperature, t: 20°C

9) Reaction of **80** with **82**



SCHEME 5.6

Solvents: cyclohexane, butanone, acetone, ethyl acetate, 1,4-dioxane, nitrobenzene, acetonitrile, nitromethane, chloroform, carbon tetrachloride, tetrahydrofuran, toluene, dimethoxymethane, chlorobenzene and 1,2-dichloroethane

Reaction temperature, t: 20°C

10) Reaction of 43 with 44(b-d) (Scheme 1.19)

Solvents: cyclohexane, ethyl acetate, benzene, dimethyl sulphoxide, isopropanol, ethanol, methanol and acetic acid

Reaction temperature, t: 80°C

11) Reaction of 7 with 12 (Scheme 1.6)

Solvents: acetic acid, ethanol, 1,2-dichloroethane, acetonitrile, nitromethane, pyridine, dimethylformamide, 1,2-dimethoxyethane and triethylamine.

Reaction temperature, t: 30°C

12) Reaction of 7 with 8 (Scheme 1.4)

Solvents: acetic acid, ethanol, 1,2-dichloroethane, acetonitrile, nitromethane, pyridine, dimethylformamide, 1,2-dimethoxyethane and triethylamine.

Reaction temperature, t: 30°C

Chapter 6
SUMMARY AND CONCLUSIONS

In this Ph. D. dissertation an attempt has been made to investigate the origin of forces responsible for the dramatic rate acceleration and the stereoselectivity (*endo/exo*) ratios for Diels-Alder reactions in various solvent media. The kinetic profiles of Diels-Alder reactions have been examined in solvent media such as water, organic solvents, aqueous salt solutions, aqueous solutions of alcohols containing salts and in ionic liquids. The observations have been explained on the basis of hydrophobic effect, salting effects, internal pressures as well as viscosities of solvent media. The salting-out agents promote the *endo/exo* ratios of the *endo*- and *exo*-selective reactions, whereas the salting-in agents decelerate them. The salting-coefficients have been calculated for the reaction of cyclopentadiene with methyl methacrylate. The salting-out agents increase the internal pressure of aqueous medium, which in turn accelerates the reactions rates and the *endo/exo* ratios. Contrary to this, the salting-in agents decrease the internal pressure of aqueous medium. This results in the decrease of the reaction rates and the *endo/exo* ratios. The salting-zones for the reaction of cyclopentadiene with methyl acrylate have been defined on the basis of internal pressure of solvent media. The reactants in this reaction form a heterogeneous mixture in aqueous salt solutions. Hence, the rates of this reaction have been studied as a function of interfacial area. A tentative mechanism for the reaction taking place in aqueous medium has been proposed. Further LiClO₄ which is a salting-in agent in aqueous medium is forced to change its role from salting-in to salting-out by solvent manipulation.

The intramolecular hetero-Diels-Alder reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone has been carried out in ionic liquids, with and without metal triflates. The dependency of the rates of the reaction has been explored with solvent parameters of ionic liquid.

The role of viscosity of solvent medium in enhancing rates of reaction has been a debatable issue for a long time. The experimental observations on rate constants of various Diels-Alder reactions have been discussed in the light of viscosities of solvent media.

The research work carried out in the thesis can be concluded in the form of the following statements:

- 1) Enhancement in Diels-Alder reactions can be explained on the basis of hydrophobic effect, internal pressure, salting effects as well as viscosity.

- 2) Internal pressure can be one of the possible parameters to quantify the hydrophobic effect.

- 3) The solvent conditions have been proposed to promote rates and *endo/exo* ratios. Further work may be helpful to recommend tailor-made condition for optimizing the yields and other parameters.

- 4) The rate dependence of intramolecular hetero-Diels-Alder reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone on the dipolarity/polarizability parameter π^* of ionic liquids.

- 5) The role of viscosity in enhancing the kinetic profiles of Diels-Alder reactions have been investigated by examining experimental observations.

This thesis in nutshell addresses several physical-organic aspects of Diels-Alder reactions and does not center around the development of synthetic methodology. The studies presented herein are purely physical-organic in nature.

Chapter 7
EXPERIMENTAL SECTION

This chapter describes the procedure of the experiments carried out during the investigations.

The rates of simple model Diels-Alder reactions such as reaction of cyclopentadiene (**7**) with methyl acrylate (**10**) (Scheme 1.5), **7** with methyl methacrylate (**12**) (Scheme 1.6) and anthracene 9-carbinol (**16**) with *N*-ethylmaleimide (**17**) (Scheme 1.8) were investigated. The reactions were carried out in solvent media like pure water, organic solvents, their salt solutions and ionic liquids. The salts chosen were LiCl, NaCl, NaBr, CaCl₂, KCl, LiClO₄ and guanidinium chloride.

A typical procedure to carry out a Diels-Alder reaction of **7** with **10** (Scheme 1.5) is given below.

All commercially available (Merck) salts were recrystallized from alcohol or aqueous alcohol, then dried under vacuum for 6 h. These recrystallized salts were used throughout the investigations. AR grade alcohols (Merck) were used without further purification. Deionized water was used for the reactions carried out in aqueous media. Non-aqueous solvents were dried on molecular sieves overnight. **7** was freshly cracked from its dimer (Merck, b.p. 46°C). **10** (Merck, b.p. 78°C) obtained from Merck was used immediately after its distillation. The salt solutions were prepared by dissolving them in minimum amount of solvent and then diluted up to the appropriate mark as per the required concentration. In a typical run, 0.6 ml (6.67 mmol) of **10** was dissolved in 10 ml of the desired salt solution. Then 0.6 ml (7.21 mmol) of freshly cracked **7** was added to the salt solution containing dienophile. The reaction mixture was magnetically stirred at 30°C for about 5 h.

The reaction was worked up with ethyl acetate and excess of water to ascertain that the reaction mixture is free of salt solution. Further the products were purified by column chromatography as usual.

The *endo*- and *exo*- products were characterized using NMR as described in the literature.²²¹ The *endo/exo* ratios were determined by gas chromatography. Nitrogen as carrier gas, injector temperature 250°C detector temperature 280°C, retention times: *exo* cycloadduct 8.559 min., *endo* cycloadduct 8.969 min. Each reaction was carried out 3 times and the *endo/exo* ratios were reproducible to within 5 %. GC and NMR were used to check the dimerization of **7**, which was found to be negligible.

In case of the reaction of **7** with **12** (Scheme 1.6), 1 mL **7** (18.00 mmol) and 1 mL **12** (15.00 mmol) were used. The reaction mixture was allowed to stir magnetically for about 9 h at 30°C. The remaining reaction conditions were kept same as discussed above.

In order to carry out the reaction of **7** with **10** in salt solutions of aqueous alcohols, aqueous alcohol solutions (v/v) were prepared using de-ionized water. The salts were dissolved to these aqueous alcohol solutions to make the salt solutions.

The effect of change in surface area on the reaction of **7** with **10** was studied by carrying out the reactions in the test tubes of varying diameters. The rate constants of these reactions were calculated as described below.

7.1 Kinetic measurements by GC

The reaction of **16** with **19** (Scheme 1.8) was followed by gas chromatography. Kinetic measurements were done by monitoring the disappearance of the peak for dienophile, **12**. The reaction of **7** with **12** was started as mentioned above. The reactions were quenched after a time interval of 20 min with diethyl ether. Diethyl ether was allowed to evaporate at low temperature taking care that the reaction mixture would not evaporate. Then 0.5 mL of the reaction mixture was diluted with acetone in order to analyze the concentration of **12** by gas chromatography. Gas chromatograph used was Varian CP 3800. The conditions used for the analysis by gas chromatography were as follows: Nitrogen as carrier gas, injector temperature 150°C detector temperature 250°C. The sample was analyzed by using isothermal method keeping the constant temperature of the column oven at 40°C for 20 min. The retention time for methyl acrylate was 2.1 min. The reactions were monitored for 3h following the above mentioned procedure.

The concentration of cyclopentadiene was calculated from the concentrations of **12**, since the reaction took place as 1:1 mole of diene and dienophile. The graph for this second order reaction was plotted as $\ln [(Ab)/ (Ba)]$ as a function of time t , where A , B were initial concentrations of diene and dienophile, respectively; a , b were the concentrations of diene and dienophile left at time t . The second order rate constant, k_2 is related to the slope of the graph as shown below:

$$\text{slope} = \frac{-1}{k_2 (A - B)}$$

7.2 Intramolecular reaction of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone

The substrate 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (**72**) (0.017 g, 0.05 mmol) was added to 3 mL of the desired ionic liquid. The reaction was carried out under nitrogen atmosphere. The 0.3 mL sample was quenched with dichloromethane every after 10 min. and was analyzed by UV vis spectroscopy as discussed below.

7.2.1 Kinetic study of UV vis spectroscopy

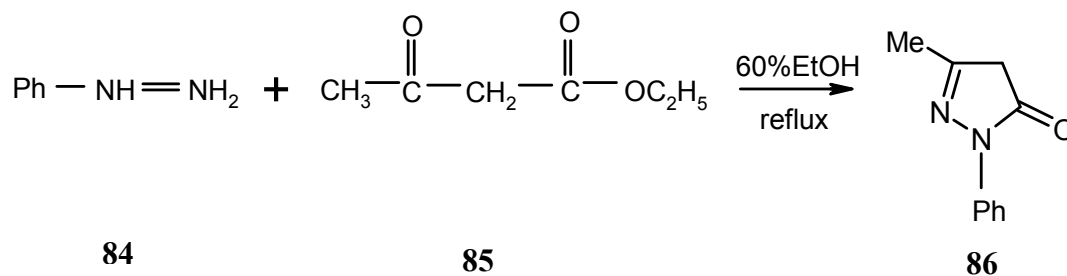
The rates of the reaction **72** in different ionic liquids were followed by monitoring the disappearance of the chromophore (**72**) on Varian UV vis spectrophotometer. The solutions were measured in 1 cm cuvette of 3 mL capacity. Measurements were taken at the wavelengths of 390-410 nm depending on the solvent media. The reaction follows first order kinetics. The concentration of the **72** was determined from the calibration curve. The slope of the graph of concentration as a function of time gave the first order rate constant for the reaction.

7.2.2 Synthesis of substrate

The reactant **72** for the intramolecular Diels-Alder reaction was synthesized in three steps as described below.

Step 1: Synthesis of 3-methyl-1-phenyl-5-pyrazolone (**86**)

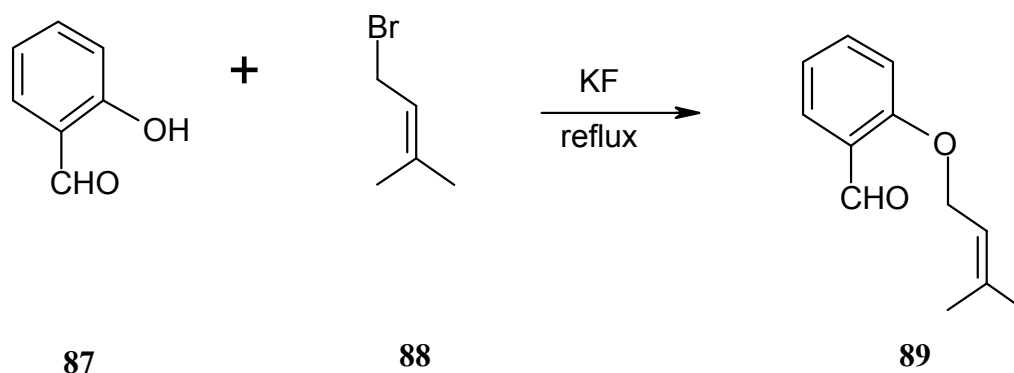
To a well-stirred solution of ethylacetoacetate (**85**) (7.44 g, 57.05 mmol,) in 60% ethanol (12 mL) was added dropwise phenylhydrazine (**84**) (6.02 g, 55.56 mmol) at such a rate that the temperature was kept below 50°C (approximately 30 min). The yellow reaction mixture was stirred at room temperature for 2 h, then refluxed for 4 h, and finally allowed to cool to room temperature. To this reaction mixture, diethyl ether was added. The yellow crystals obtained were recrystallized from 50 % ethanol water to obtain white crystals. ¹H NMR (200 MHz, CDCl₃): δ 7.88 (d, *J*) 7.7 Hz, 2H), 7.4- 7.1 (m, 8H), 3.82 (s, 2H), 3.45 (s, 2H), 2.5 (s, 3H)



SCHEME 7.1

Step 2: Preparation of 3-methyl-2-butenyloxybenzaldehyde (89**)**

A mixture of salicylaldehyde (**87**) (50.98 mmol, 6.05 g), 1-substituted 3-bromo-1-propenes (**88**) (9.49 g, 63.73 mmol), and potassium fluoride (11.859 g, 203.92 mmol) in



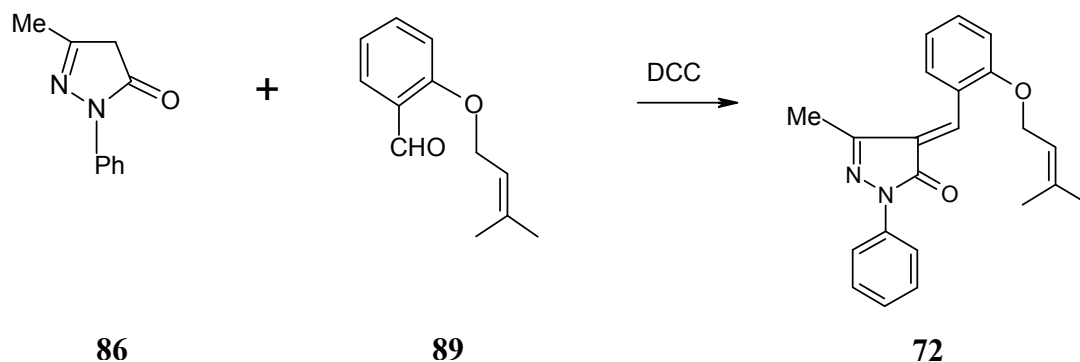
SCHEME 7.2

acetone (300 mL) was refluxed for 72 h. After filtration of inorganic salts, evaporation of filtrate gave a solid. Recrystallization of ethanol gave colorless needles in the yields. ¹H NMR (200 MHz, CDCl₃): δ 10.2 (s, 1H), 7.8-7.1 (m, 4H), 6.95 (m, 2H), 5.45 (t, 1H), 4.50 (d, 2H), 1.65 (d, 6H).

Step 3: Synthesis of 1-phenyl-3-methyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (72**)**

To a stirred solution of 1-phenyl-3-methyl-5-pyrazolone (**86**) (1.03 g, 5.91 mmol) and 2-alkenyloxybenzaldehyde (**89**) (1.02 g, 5.53 mmol) in dichloromethane (30 ml), about 3 g of *N,N'*-dicyclohexylcarbodiimide were added. The solution began to become

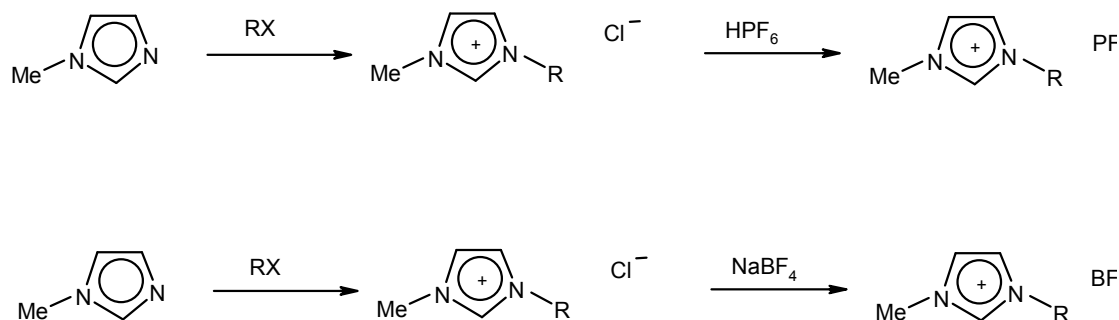
orange and stirring was continued at room temperature until thinlayer chromatography showed the starting products disappeared (about 8 h). The solution was evaporated to dryness at room temperature and the residue was chromatographed on silica gel Merck (70-230 mesh) (eluant petroleum ether-ethyl acetate 9:1). The orange fraction was collected, the solvent was evaporated at room temperature and the residue crystallized from the cooled solution as deep orange crystals. m.p. 78-79⁰C (35% yield). ¹³C NMR (CDCl₃): δ 153.67, 147.62, 147.28, 138.57, 131.89, 128.42, 125.31, 120.98, 120.35, 119.39, 116.44, 96.30, 80.65, 62.99, 38.18, 30.29, 26.03, 25.39, 15.29.



SCHEME 7.3

7.3 Synthesis of ionic liquids

The ionic liquids were synthesized according to the procedure given in the literature.^{223, 224} The generalized schemes to synthesize ionic liquids are as shown below.



SCHEME 7.4. Synthesis of typical ionic liquids

Synthesis of 1-butyl-3-methyl imidazolium chloride [BMIM]Cl

The 1-methyl imidazole obtained from Merck (7.05 g, 85.26 mmol) was taken in three neck round bottom flask fitted with a water condenser and a gas inlet. 1-Chlorobutane (10.26 g, 110.84 mmol) (Merck) was added to the reaction vessel with continuous magnetic stirring under nitrogen. The reaction mixture was heated until two phases were formed. The top phase, containing the unreacted starting material, was decanted and ethyl acetate (A. R. grade 300 mL) was added to the vessel. The reaction mixture was washed with ethyl acetate thrice. The product was slightly yellow. The product was recrystallized from acetonitrile and dried under vacuum at 80°C for 6h to yield pure crystalline [BMIM]Cl.

Synthesis of 1-butyl-3-methyl imidazolium tetrafluoroborate [BMIM][BF₄]

A solution of [BMIM]Cl (5.72g, 32.87 mmol) in acetone (500 mL) at room temperature was added to sodium tetrafluoroborate (3.607 g, 32.87 mmol). After 24 h stirring, the resulting NaCl precipitate was then filtered through a plug of celite and volatiles were removed by rotary evaporation to a yellowish clear liquid. The product was dried for 6h under high vacuum. ¹H NMR (200 MHz, CDCl₃): 8.89 (s, 1H), 7.41 (d, 2H), 4.13 (t, 2H), 3.89 (s, 3H), 1.79 (m, 2H), 1.27 (m, 2H), 0.88 (t, 3H).

Synthesis of 1-ethyl-3-methyl imidazolium bromide [EMIM]Br

The same procedure as discussed for [BMIM]Cl was used with the change that 1-bromoethane (12.07 g, 110.84 mmol) was employed instead of 1-chlorobutane.

Synthesis of 1-ethyl-3-methyl imidazolium tetrafluoroborate [EMIM][BF₄]

The same procedure was used as discussed for [BMIM][BF₄] with the change that [EMIM]Br (6.15 g, 32.37 mmol) was employed instead of [BMIM]Cl. ¹H NMR (200 MHz, CDCl₃): 9.22 (s, 1H), 7.82 (m, 2H), 4.56 (m, 2H), 4.26 (s, 3H), 1.85 (t, 3H).

Synthesis of 1-butyl-3-methyl imidazolium hexafluorophosphate [BMIM][PF₆]

The same procedure was used as discussed for [BMIM][BF₄] with the change that phosphoric acid (6.60 g, 34.77 mmol) were added dropwise to the vigorously stirred solution of [BMIM]Cl in acetone was employed instead of [BMIM]Cl. ¹H NMR (200 MHz, CDCl₃): 8.67 (s, 1H), 7.29 (d, 2H), 4.04 (t, 2H), 3.80 (s, 3H), 1.72 (m, 2H), 1.20 (m, 2H), 0.81 (t, 3H).

Synthesis of 1-octyl-3-methyl imidazolium chloride [OMIM]Cl

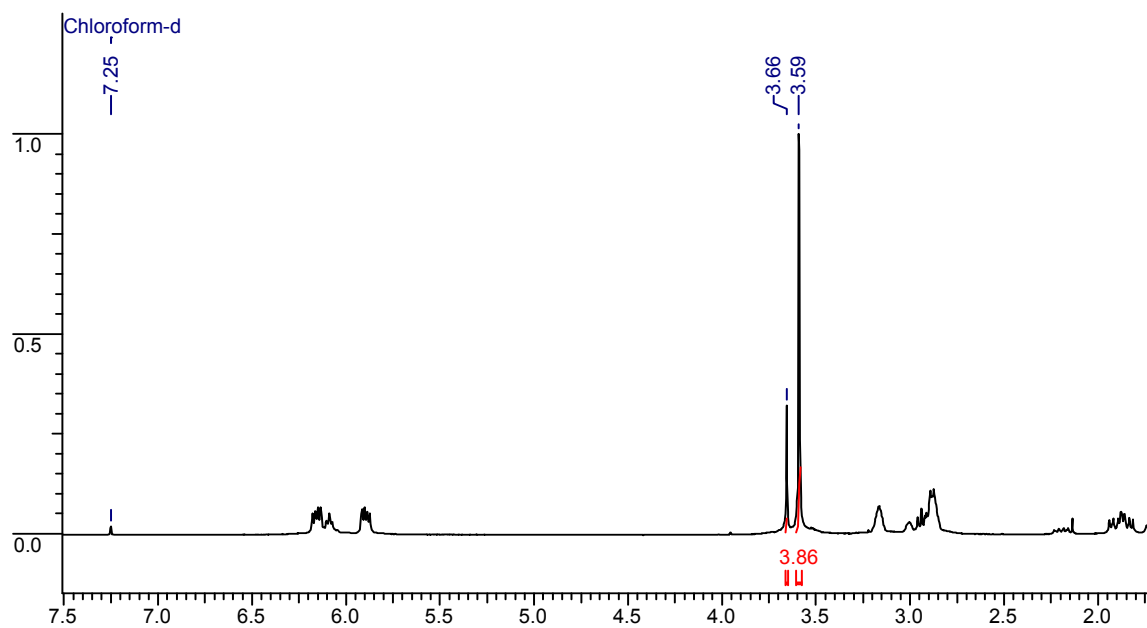
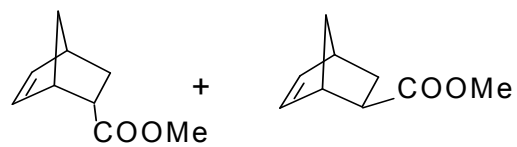
The same procedure was used as discussed for [BMIM]Cl. However, 1-chlorooctane (16.47g, 110.84 mmol) was employed instead of 1-chlorobutane.

Synthesis of 1-octyl-3-methyl imidazolium tetrafluoroborate [OMIM][BF₄]

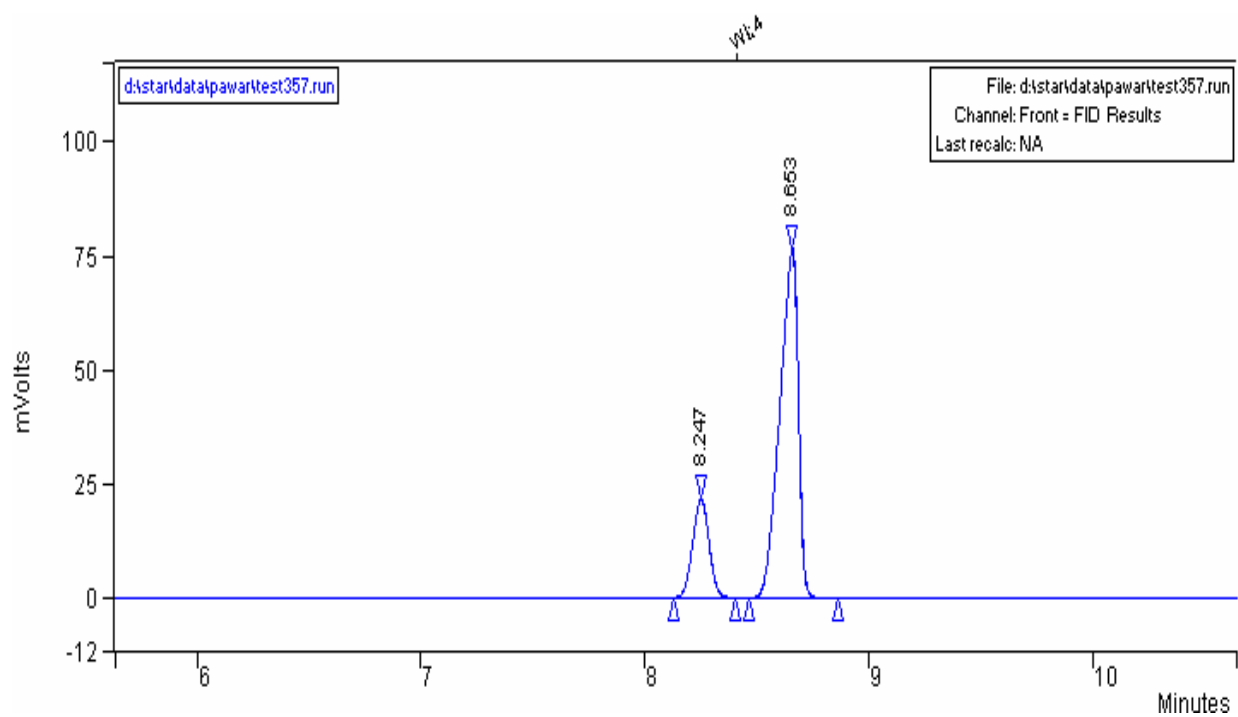
The same procedure was used as discussed for [BMIM][BF₄] with the change that [OMIM]Cl (5.50g, 23.91 mmol) was employed instead of [BMIM]Cl. ¹H NMR (200 MHz, CDCl₃): 8.68 (s, 1H), 7.34 (d, 2H), 4.17 (t, 2H), 3.95 (s, 3H), 1.88 (t, 2H), 1.28 (m, 12H), 0.89 (t, 3H)

Synthesis of 1-butyl-3-methyl imidazolium iodide [BMIM]I

The same procedure was used as discussed for [BMIM]Cl with the change that 1-iodobutane (20.39 g, 110.84 mmol) was employed instead of 1-chlorobutane. ¹H NMR (200 MHz, CDCl₃): 9.71 (s, 1H), 7.48 (d, 2H), 4.19 (t, 2H), 3.96 (s, 3H), 1.76 (m, 2H), 1.21 (m, 2H), 0.79 (t, 3H)



7. Experimental section



2 channels

Channel 1 FID in Volts
 Channel 2 FID in Volts
 Base rate 10.0000 Hz Bunch 4 Effective rate 10.00000 Hz. T = 0.001667 min.
 6848 points from 0.000 to 11.413 minutes
 Sampling every 4 point(s)
 Printing points from 0.000 to 11.413 min, point 0 to 6847
 Channels 1 to 2
 Results for Channel Front = FID
 Title: Report Title
 Run File: d:\star\data\pawar\test357.run

 Injection Info

Method: C:\star\isothermal.mth
 Sample: 1std
 Injection Date: Mon Jul 14 15:26:33 2003
 Vial: 1 Injection Number: 1 Volume: 1.0 uL Position: 1
 Operator: suvarna
 Instrument: Varian GC3800

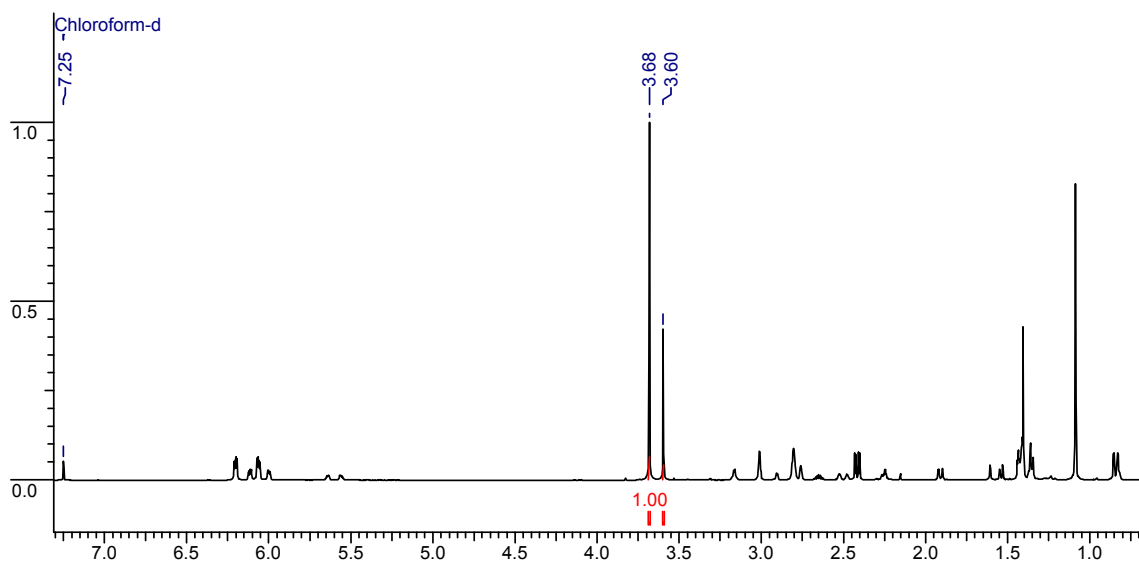
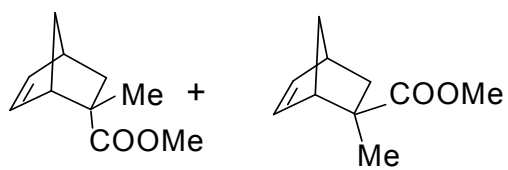
 Recalc Info

Recalc Method: C:\star\isothermal.mth
 Recalc Date: Mon Jul 14 15:37:53 2003
 Operator: suvarna
 Instrument: Varian GC3800
 Sample Rate: 10.000 Hz.
 Measurement Type: 1 = Area
 Calculation Type: 1 = %
 Normalize Results: No

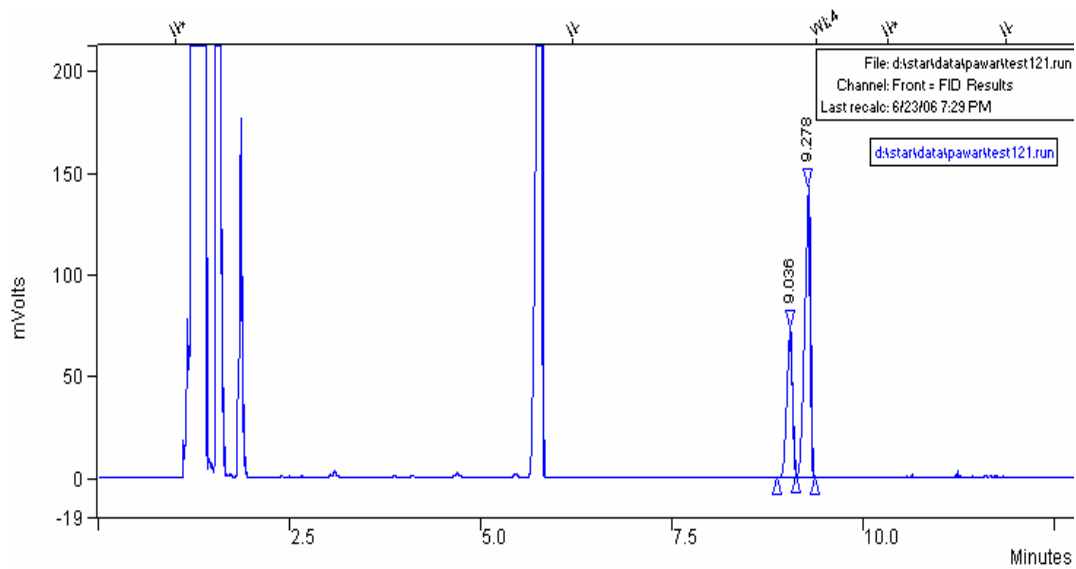
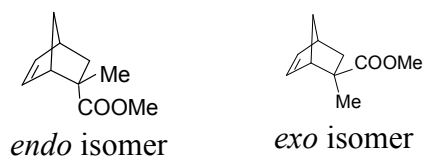
 Peak Info for Channel Front

Peak No.	Result	Retention time (min)	Time offset (min)	Area (counts)	Seperation code	Width (1/2) sec
1	66.254730	1.258	0.0000	2435854	VV	0.81
2	18.584621	1.280	0.0000	683263	VB	1.04
3	0.046105	1.387	0.0000	1695	TF	0.00
4	0.187874	2.230	0.0000	6907	BB	1.05
5	3.005504	8.247	0.0000	110497	BB	4.80
6	11.921169	8.653	0.0000	438282	BB	5.44

7. Experimental section



7. Experimental section



7. Experimental section

Title :
Run File : D:\star\data\pawar\test121.run
Method File : c:\windows\temp\~test357-front.tmp
Sample ID : CPMMA

Injection Date: 1/4/03 4:10 PM Calculation Date: 6/23/06 7:29 PM

Operator : suvarna Detector Type: 3800 (10 Volts)
Workstation: COMPAQ_SBM Bus Address : 44
Instrument : Varian GC3800 Sample Rate : 10.00 Hz
Channel : Front = FID Run Time : 12.818 min

Star Chromatography Workstation Version 6.00 ** 02640-21d0-c65-00b0 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak Status No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Width Sep. Code	1/2 (sec)
1		34.0216	9.036	0.000	374545	BV	4.8
2		65.9784	9.278	0.000	726359	VB	4.8
Totals:		100.0000		0.000	1100904		

Total Unidentified Counts : 1100904 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

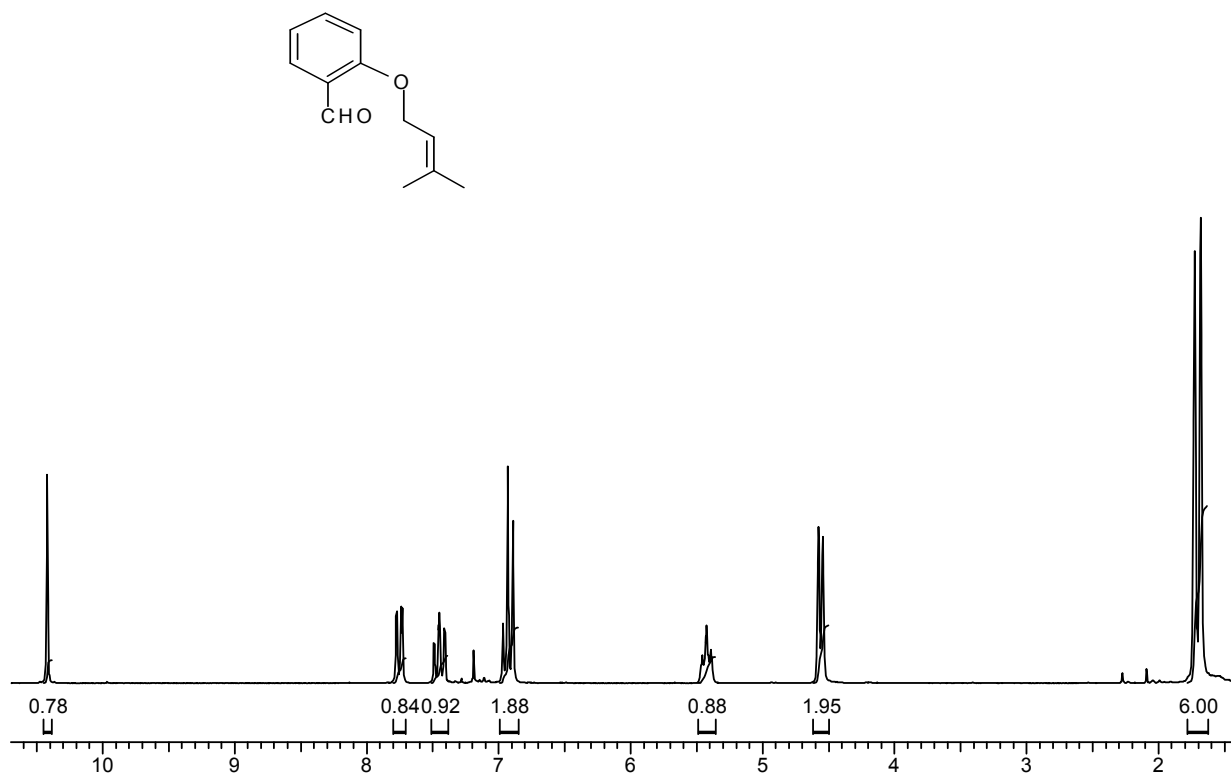
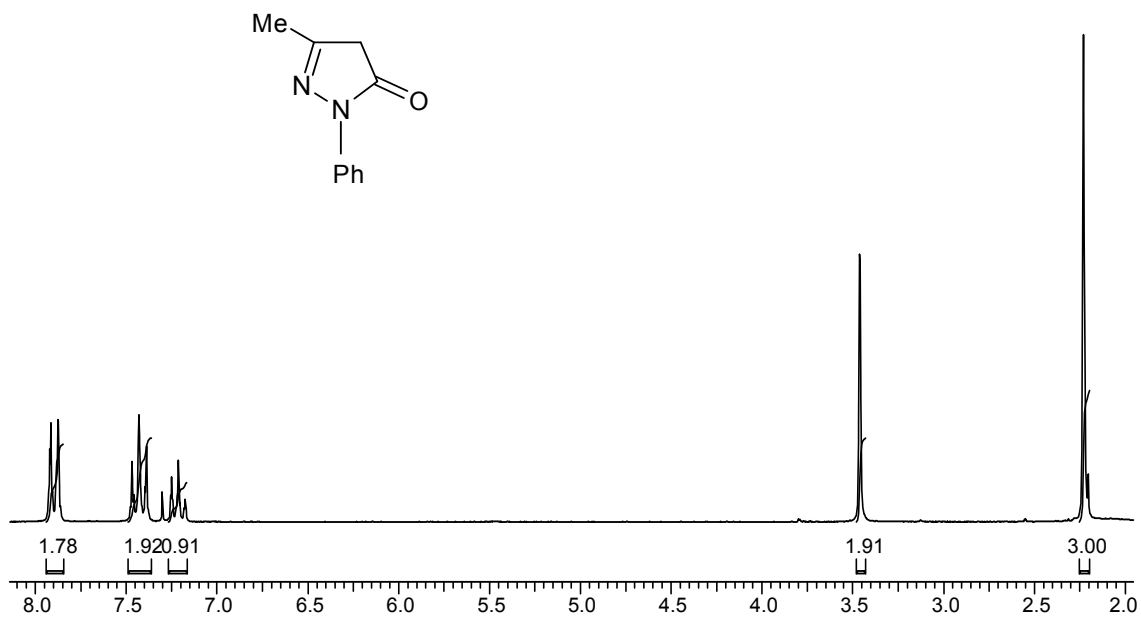
Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

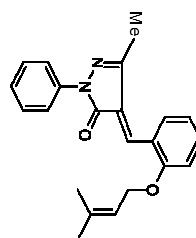
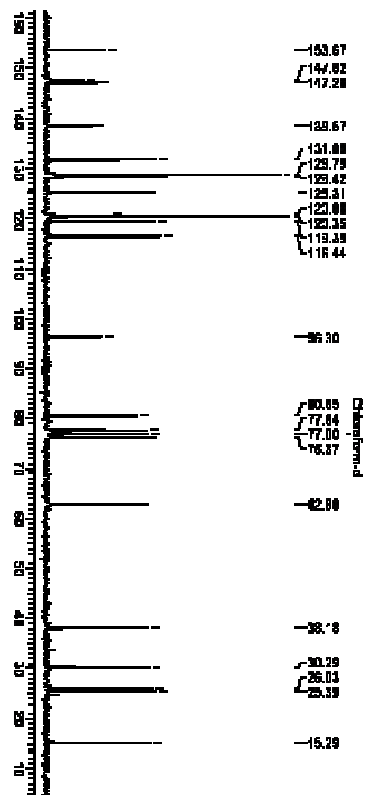
Baseline Offset: -20 microVolts LSB: 1 microVolts

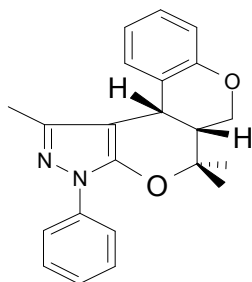
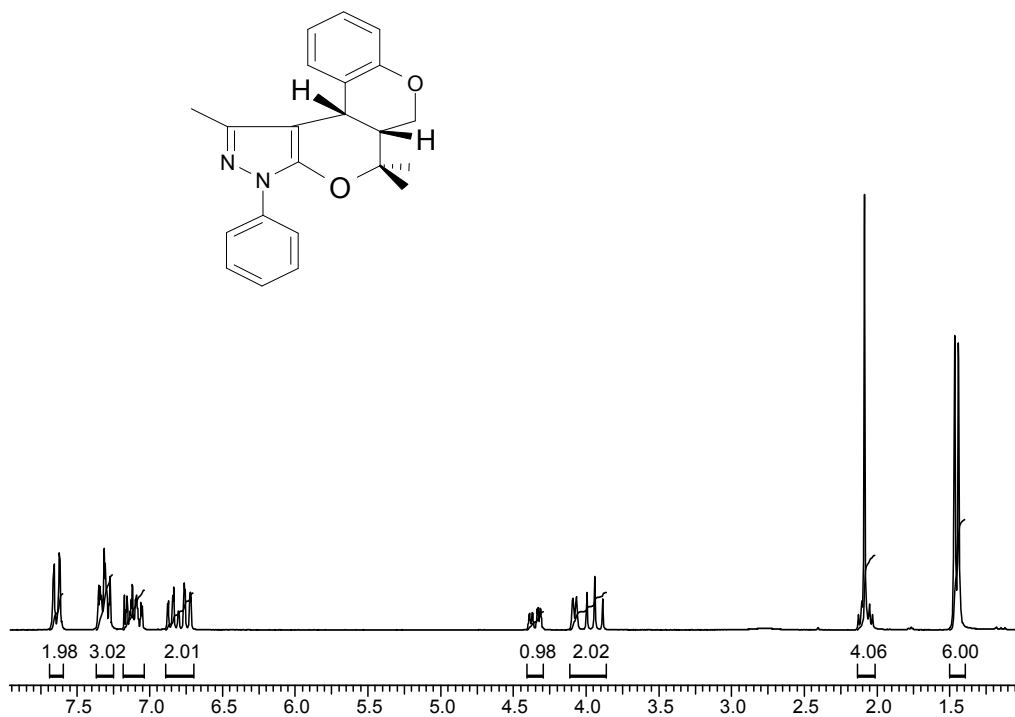
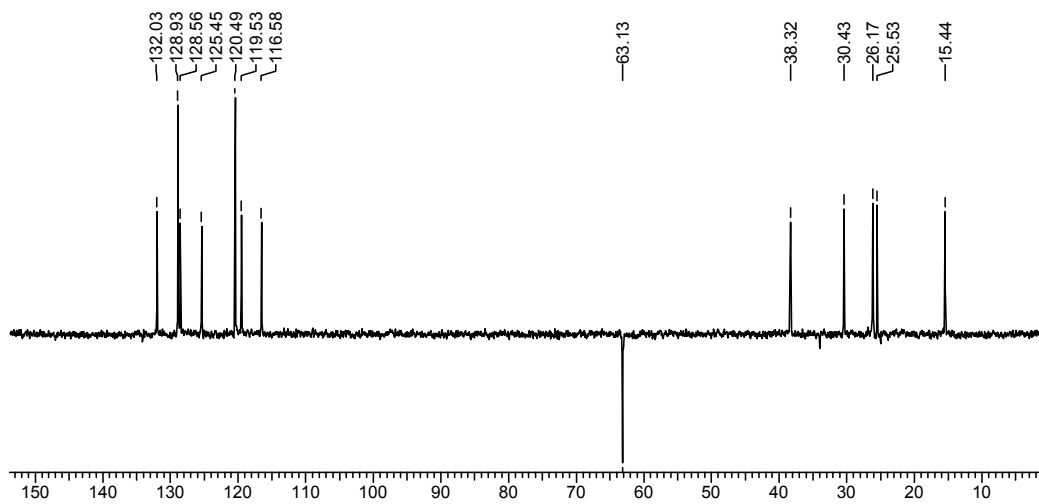
Noise (used): 25 microVolts - monitored before this run

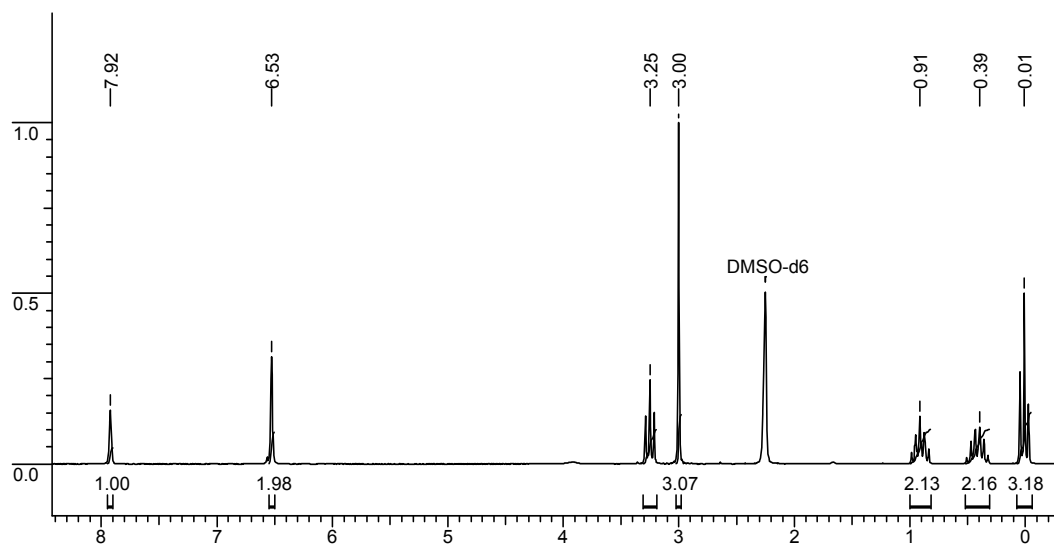
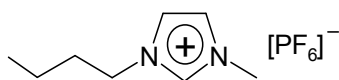
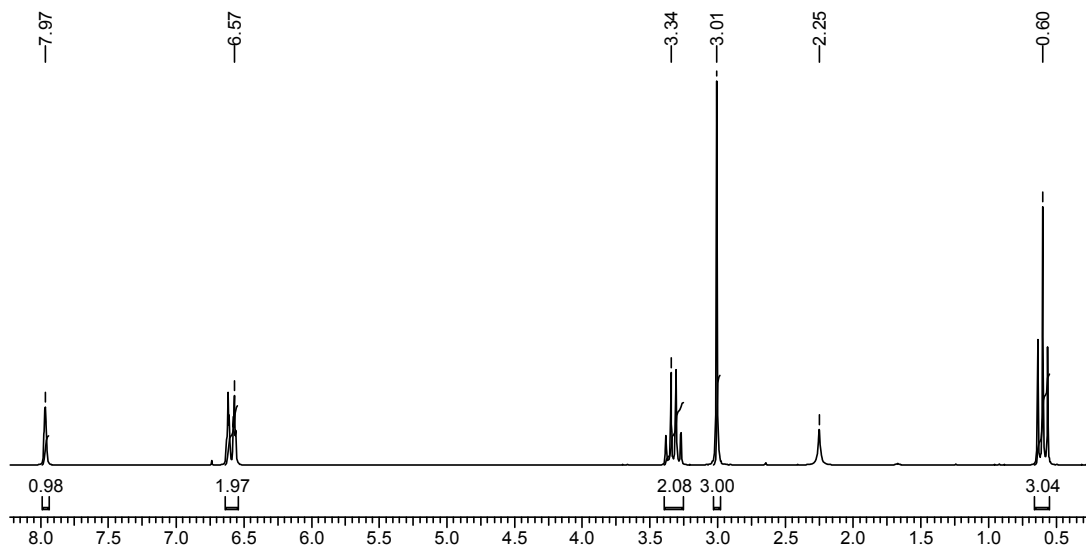
Vial: 1 Injection Number: 1 Volume: 1.0 uL Position: 1

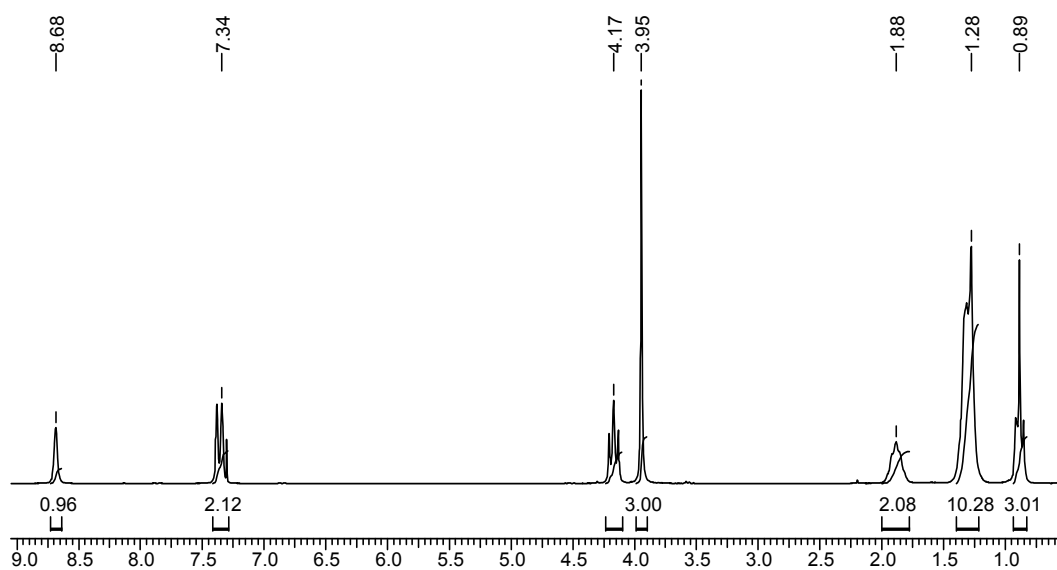
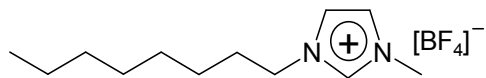
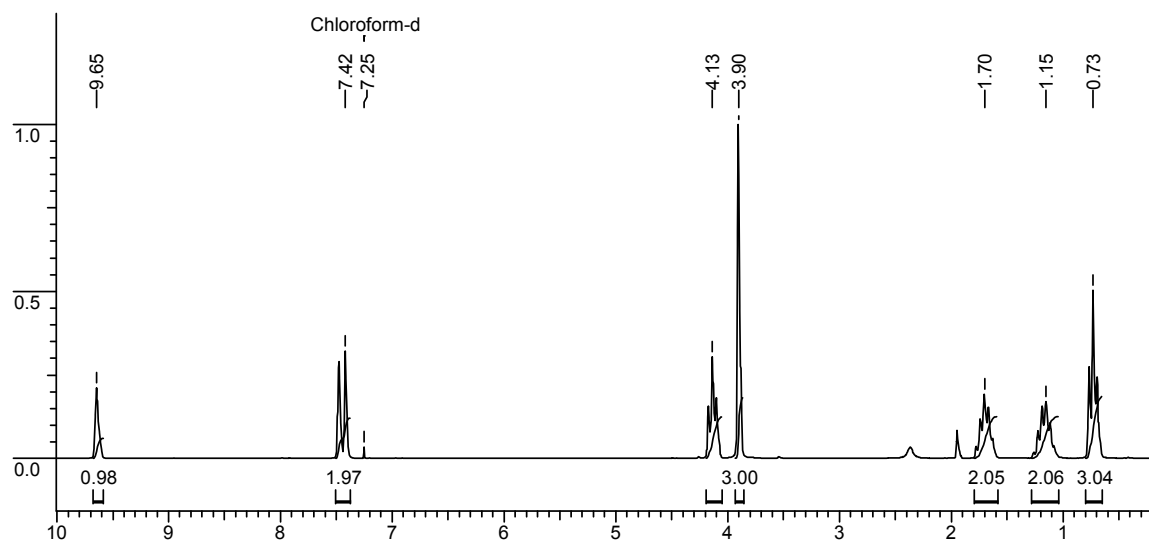
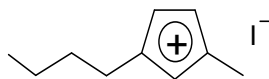
7. Experimental section

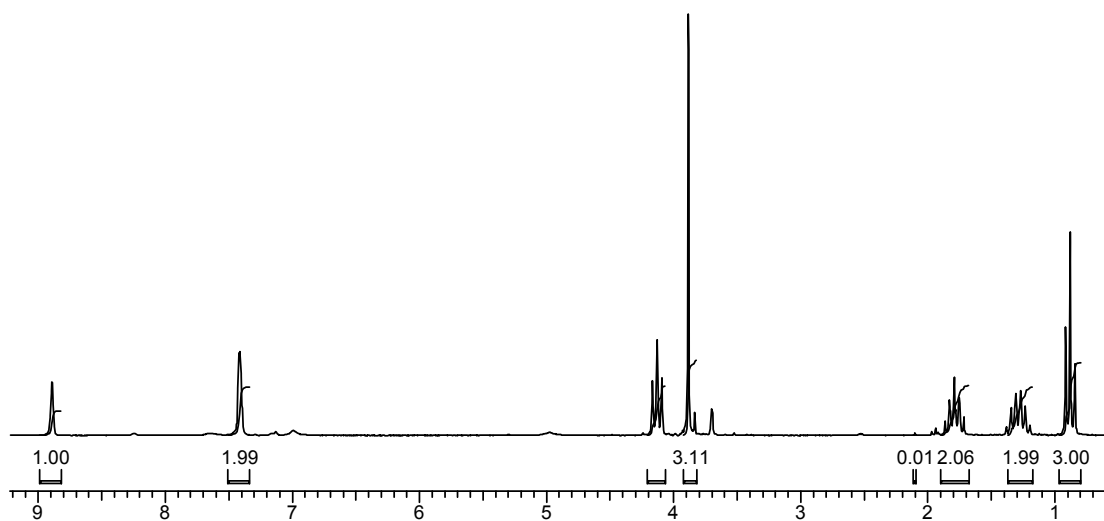


¹³C NMR

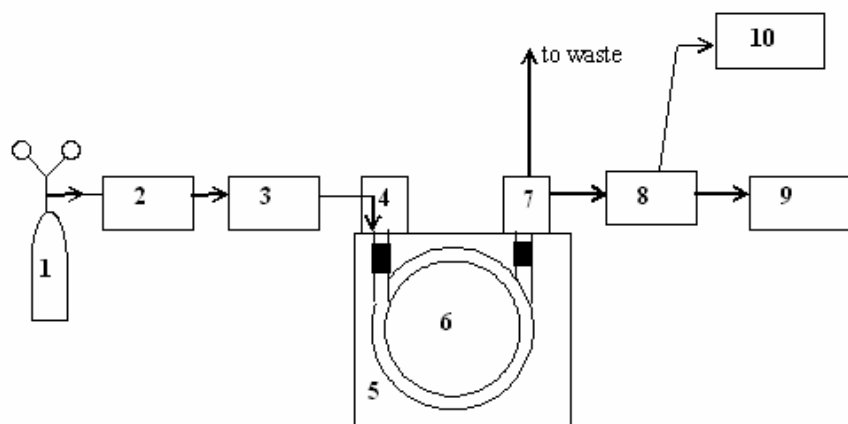
^{13}C DEPT







Schematic diagram of gas chromatograph



1. Gas supply
2. Flow controller
3. Flowmeter
4. Injection system
5. Column oven
6. Capillary Column
7. Detector
8. Amplifier
9. Recorder
10. Integrator

Literature cited

- (1) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, 41, 1668.
- (2) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, 460, 98.
- (3) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford **1990** and references cited therein.
- (4) Woodward, R. B.; Hoffmann, R. *Angew Chem. Int. Ed., Engl.* **1969**, 8, 781.
- (5) Alder, K.; Stein, G. *Angew. Chem.* **1937**, 50, 514.
- (6) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed., Engl.* **1980**, 19, 779.
- (7) Houk, K. N. *J. Am. Chem. Soc.* **1973**, 95, 4092.
- (8) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, 101, 8378.
- (9) Robiette, R.; Marchard-Brynaert, J.; Peters, D. *J. Org. Chem.* **2002**, 67, 6823.
- (10) Khuong, K. S.; Beaudry, C. M.; Trauner, D.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, 127, 3688.
- (11) Evans, M. G.; Warhurst, E. *Trans. Faraday. Soc.* **1938**, 34, 614.
- (12) Dewar M. J. S. *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 761.
- (13) Evans, M. G. *Trans. Faraday. Soc.* **1939**, 35, 824.
- (14) Corminboeuf, C.; Heine, T.; Weber, J. *Org. Lett.* **2003**, 5, 1127.
- (15) Sakai, S. *J. Phys. Chem. A* **2006**, 110, 6339.
- (16) Jiao, H.; Schleyer, P. J. *J. Phys. Org. Chem.* **1998**, 11, 655.
- (17) Sakai, S. *J. Phys. Chem. A* **2000**, 104, 922.
- (18) Manoharan, M.; De Proft, F.; Geerling, P. *J. Org. Chem.* **2000**, 65, 7971.
- (19) Kraka, E.; Wu, A.; Cremer, D. *J. Phys. Chem. A* **2003**, 107, 9008.
- (20) Cheng, M. -F.; Li, W. -K. *Chem. Phys. Lett.* **2003**, 368, 630.
- (21) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, 39, 213.
- (22) Houk, K. N.; Lin, Y. -L.; Brown F. K. *J. Am. Chem. Soc.* **1986**, 108, 554.
- (23) Storer, J. W.; Raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, 116, 9675.
- (24) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, 118, 9984.
- (25) Goldstein, E.; Beno, B. R.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, 118, 6036.

- (26) Roberson, M.; Jepsen, A. S.; Jorgensen, K. A. *Tetrahedron* **2001**, 57, 907.
- (27) Mayr, H.; Ofial, A. R. Sauer, J.; Schmied, B. *Eur. J. Org. Chem.* **2000**, 2013.
- (28) Singleton, D. A.; Schumeier, B. E.; Hang, C. Thomas, A. A.; Leung, S. –W, Merrigan, S. R. *Tetrahedron* **2001**, 57, 5149.
- (29) Isobe, H.; Takano, Y.; Kitagawa, Y.; Kawakami, T.; Yamanaka, S.; Yamaguchi, K.; Houk, K. N. *J. Phys. Chem. A* **2003**, 107, 682.
- (30) Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, 43, 9633.
- (31) McCabe, J. R.; Eckert, C. A. *Acc. Chem. Res.* **1974**, 7, 251.
- (32) Asano, T.; Le Noble, W. J. *Chem. Rev.* **1978**, 78, 407.
- (33) van Eldik, R.; Asano, T.; Le Noble, W. J. *Chem. Rev.* **1989**, 89, 549.
- (34) Klarner, F.; Krawczyk, B.; Ruster, V.; Deiters, U. K. *J. Am. Chem. Soc.* **1994**, 116, 7646.
- (35) Seguchi, K.; Sera, A.; Maruyama, K. *Tetrahedron Lett.* **1973**, 17, 1585.
- (36) Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1999**, 64, 6697.
- (37) Arrieta, A.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **2001**, 66, 6178.
- (38) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, 54, 1129.
- (39) Birney, D. M.; Houk, K.N.; *J. Am. Chem. Soc.* **1990**, 112, 4127.
- (40) Jorgensen, W. L.; Lim, D.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, 115, 2936.
- (41) Ruiz-Lopez, M. F.; Assfeld, X.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, 115, 8780.
- (42) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Tetrahedron* **1997**, 53, 6057.
- (43) Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, 120, 2415.
- (44) Calvo-Losada, S.; Suarez, D. *J. Am. Chem. Soc.* **2000**, 122, 390.
- (45) Singleton, D. A. *J. Am. Chem. Soc.* **1992**, 114, 6563.
- (46) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, 33, 658.
- (47) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Eur. J. Org. Chem.* **2005**, 85.
- (48) Sarma, D.; Kumar, A. *Org. Lett.* **2006**, 8, 2199.
- (49) Rideout D. C.; Breslow R. *J. Am. Chem. Soc.* **1980**, 102, 7816.
- (50) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, Verlag Chemie, Weinheim, **2003**.

- (51) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, 93, 741.
- (52) Li, C-J. *Chem. Rev.* **1993**, 93, 2023.
- (53) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 94, 741.
- (54) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, 209.
- (55) Grieco, P.A. Blackie *Organic Synthesis in Water*; First Ed., Glassgow **1998**.
- (56) Kumar, A. *Chem. Rev.* **2001**, 101, 1.
- (57) Li, C-J.; Chan, T-H. *Chem. Soc. Rev.* **2006**, 35, 68.
- (58) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, 84, 297.
- (59) Breslow, R. *Acc. Chem. Res.* **1991**, 24, 159 and references cited therein.
- (60) von Hippel, P. H.; Schleich, T. *Acc. Chem. Res.* **1969**, 2, 257.
- (61) Breslow, R.; Connors, R. V. *J. Am. Chem. Soc.* **1995**, 117, 6601.
- (62) Grover, P. K.; Ryall, R. L. *Chem. Rev.* **2005**, 105, 1.
- (63) Tanford C. *The Hydrophobic Effect*; Wiley: New York, **1980**.
- (64) Grieco, P. A.; Garner, P.; He, Z. **1983** *Tetrahedron Lett.* 24, 1897.
- (65) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, 48, 3137.
- (66) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, 42, 2847.
- (67) Yoshida, K.; Grieco, P. A. *Chem. Lett.* **1985**, 155.
- (68) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, 51, 3553.
- (69) Waldmann, H. *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 274.
- (70) Waldmann, H. *Liebigs Ann. Chem.* **1989**, 231.
- (71) Grieco, P. A.; Yoshida, K.; He, Z. *Tetrahedron Lett.* **1984**, 25, 5715.
- (72) Grieco, P. A.; Garner, P.; Yoshida, K.; Huffman, J. C. *Tetrahedron Lett.* **1983**, 24, 3807.
- (73) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, 110, 5613.
- (74) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, 112, 4595.
- (75) Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, 81, 5511.
- (76) Winstein, S.; Friedrich, E. C.; Smith, S. *J. Am. Chem. Soc.* **1964**, 86, 305.
- (77) Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1956**, 78, 2763.
- (78) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, 92, 2075.
- (79) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, 92, 4033.

- (80) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1971**, 93, 2905.
- (81) Pocker, Y.; Ellsworth, D. L. *J. Am. Chem. Soc.* **1977**, 99, 2284.
- (82) Pocker, Y.; Ciula, J. C. *J. Am. Chem. Soc.* **1988**, 110, 2904.
- (83) Pocker, Y.; Ciula, J. C. *J. Am. Chem. Soc.* **1989**, 111, 4728.
- (84) Willard, H. H.; Smith, G. F. *J. Am. Chem. Soc.* **1923**, 45, 286.
- (85) Ekelin, K.; Sillen, L. G. *Acta Chem. Scand.* **1953**, 7, 987.
- (86) Kraus, C. A.; Strong, L. E., *J. Am. Chem. Soc.* **1950**, 72, 166.
- (87) Dauben, W. G.; Kessel, C. R.; Takemura, K. H., *J. Am. Chem. Soc.* **1980**, 102, 6893.
- (88) Dauben, W. G.; Krabenhof, H. O. *J. Am. Chem. Soc.* **1976**, 98, 1992.
- (89) Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994** 35, 2663.
- (90) Sankararaman, S.; Edward Nesakumar, J.; *Eur. J. Org. Chem.* **2000**, 2003.
- (91) Heydari, A. *Tetrahedron* **2002**, 58, 6777.
- (92) Kumar, A.; Pawar, S. S.; *J. Org. Chem.* **2001**, 66, 7646.
- (93) Casashi, A.; Desimoni, G.; Faita, G.; Ivernizzi, A. G.; Lanati, S.; Righetti, P. P.; *J. Am. Chem. Soc.* **1993**, 115, 8002.
- (94) Desimoni, G.; Faita, G.; Ivernizzi, G.; Righetti, P. P.; *Tetrahedron* **1997**, 53, 7671.
- (95) Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1991**, 113, 2761.
- (96) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, 82, 4436.
- (97) Bains, S.; Pagni, R. M.; Kabalka, G. W.; Pala, C.; *Tetrahedron Asymmetry* **1994**, 5, 821.
- (98) Pagni, R. M.; Kabalka, G. W.; Bains, S.; Plesco, M.; Wilson, J.; Bartmess, J.; *J. Org. Chem.* **1993**, 58, 3130.
- (99) Kagan, H. B.; Riant, O. *Chem. Rev.* **1997**, 92, 1007.
- (100) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439.
- (101) Otto, S.; Bertocin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, 118, 7702.
- (102) Otto, S.; Engberts, J. B. F. N. *Tetrahedron Lett.* **1995**, 36, 2645.
- (103) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, 113, 4241.
- (104) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem. Int. Ed. Eng.* **1993**, 32, 1545.

- (105) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, 67, 823.
- (106) Mersbergen, D.; van Wijnen, J. W., Engberts, J. B. F. N. *J. Org. Chem.* **1998**, 63, 8801.
- (107) Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, 63, 8989.
- (108) Otto, S.; Blokzijl, W.; Engberts, J. B. F. N. *J. Org. Chem.* **1994**, 59, 5372.
- (109) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, 113, 7430.
- (110) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, 59, 803.
- (111) Chandrasekhar, J.; Shariffskul, S.; Jorgensen, W. L. *J. Phys. Chem. B* **2002**, 106, 8078.
- (112) Furlani, T. R.; Gao, J. *J. Org. Chem.* **1996**, 61, 5492.
- (113) Mayer, U.; Gutmann, V.; Gerger, W. *Monatsh. Chem.* **1975**, 106, 1235.
- (114) Sabatino, A.; La Manna, G.; Paoloni, L. *J. Phys. Chem.* **1980**, 84, 264.
- (115) Corsico Coda, A.; Desimoni, G.; Ferrari, E.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1984**, 40, 1611.
- (116) Desimoni, G.; Faita, G.; Righetti, P. P.; Tornaletti, N.; Visigalli, M. . *Chem. Soc. Perkin Trans. 2* **1989**, 437.
- (117) Corsico Coda, A.; Desimoni, G.; Faita, G.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1989**, 45, 775.
- (118) Abraham, M. H.; Grellier, P. L.; Andrew McGill, R. *J. Chem. Soc. Perkin Trans. 2* **1988**, 3391.
- (119) Schneider, H-J.; Sangwan, N. K. *J. Chem. Soc. Chem. Commun.* **1986**, 1787.
- (120) Sangwan, N. K.; Schneider, H-J. *J. Chem. Soc. Chem. Commun.* **1989**, 1223.
- (121) Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1990**, 3, 414.
- (122) Cativiela C, Garcia J. I.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A.; *J. Phys. Org. Chem.* **1991**, 4, 48.
- (123) Cativiela, C.; Garcia, I.; Mayoral, J. A.; Royo, A. J.; Salvatella, L.; Assfeld, X.; Ruiz-Lopez, M. F. *J. Phys. Org. Chem.* **1992**, 5, 230.
- (124) Schneider, H-J.; Sangwan, N. K. *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 896.
- (125) Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1991**, 47, 5857.
- (126) Welton, T. *Chem. Rev.* **1999**, 99, 2071.

- (127) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, 39, 3772.
- (128) Walden, P. *Bull. Acad. Imper. Sci. (St. Petersburg)* **1914**, 1800.
- (129) Sugden, S.; Wilkins, H. J. *J. Chem. Soc.* **1929**, 1291.
- (130) Wilkes, J. S. *Green Chem.* **2002**, 4, 73.
- (131) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis* Wiley-VCH and references cited therein.
- (132) Kumar, A.; Sarma, D. *Ionic Liquids IIIB: Progress, Challenges and Opportunities* ACS symposium series 902, Eds. Rogers, R. D.; Seddon, K. R., **2005**.
- (133) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, 18, 275.
- (134) Hu, Y. F.; Xu, C. M. *Chem. Rev.* **2006** (available on web, DOI: 10.1021/cr0502044)
- (135) Ngo, H. L.; LeCompte, K.; Hargens, L.; Mc Ewan A. B.; *Thermochim. Acta.* **2000**, 97, 357.
- (136) Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D.; *Chem. Commun.* **1994**, 299.
- (137) Wiles, J.S.; Levisky, J. A.; Wilson, R. A.; Hussey, C. L. *Inorg. Chem.* **1982**, 21, 1263.
- (138) Fannin, A. A.; Floreani, D. A.; King, L. A.; Landers, J. S.; Piersma, B. J.; Stech, D. J.; Vaughri, R. L.; Wilkes, J. S.; Williams, J. L. *J. Phys. Chem.* **1984**, 88, 2614.
- (139) Hussey, C. L.; Sanders, J. R.; Oye, H. A. *J. Electrochem. Soc.* **1985**, 132, 2156.
- (140) Baker, S. N.; Baker, G. A.; Kane, M. A.; Bright, F. V. *J. Phys. Chem. B* **2001**, 105, 9663.
- (141) Seddon, K. R.; Stark, A.; Torres, M. –J.; *Pure Appl. Chem.* **2000**, 72, 2275.
- (142) Widegren, J. A.; Laesecke, A.; Magee, J. W. *Chem. Commun.* **2005**, 1610.
- (143) Poole, S. K.; Shetty, P. H.; Poole, C. F. *Anal. Chim. Acta.* **1989**, 218, 241.
- (144) Herfort, L. M. Schneider, H. *Liebigs Ann. Chem.* **1991**, 27.
- (145) Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *J. Chem. Soc. Perkin Trans. 2* **2001**, 433.
- (146) Aki, S. N. V. K.; Brennecke, J. F.; Samanta, A. *Chem. Commun.* **2001**, 413.
- (147) Crowhurst, L.; Mawdsley, P. R.; Perez-Arlandis, J. M.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2003**, 5, 2790.
- (148) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, 30, 1785.

- (149) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, 38, 3097.
- (150) Lee, C. W. *Tetrahedron Lett.* **1999**, 40, 2461.
- (151) Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2004**, 69, 1419.
- (152) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, 23.
- (153) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, 40, 793.
- (154) Aggarwal, A.; Lancaster, L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, 4, 517.
- (155) Tiwari, S.; Kumar, A. *Angew. Chem. Int. Ed. Engl.* **2006**, 118, 4942.
- (156) Kobayashi, S.; Hachiya, I.; Takahari, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, 33, 6815.
- (157) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, 59, 3590.
- (158) Kobayashi, S. *Syn. Lett.* **1994**, 64.
- (159) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, 34, 3755.
- (160) Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, 37, 2169.
- (161) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.
- (162) Kobayashi, S. *Eur. J. Org. Chem.* **1995**, 15.
- (163) Silvero, G.; Arevalo, M. J.; Bravo, J. C.; Avalos, M.; Jimenez, J. L.; Lopez, I. *Tetrahedron* **2005**, 61, 7105.
- (164) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S. -g.; Choi, J. H. *Chem. Commun.* **2001**, 1122.
- (165) Yadav, J. S.; Reddy, B. V. S.; Uma Gayathri, K.; Prasad, A. R. *Synthesis* **2002**, 2537.
- (166) Pawar, S.S.; Phalgune, U.; Kumar, A. *J. Org. Chem.* **1999**, 64, 7055.
- (167) Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, 92, 6548.
- (168) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, 31, 2032.
- (169) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin 2* **1974**, 15.
- (170) Gonzalez, A.; Holt, S. L. *J. Org. Chem.* **1982**, 47, 3186.
- (171) Houk, K. N. *Tetrahedron Lett.* **1970**, 11, 2621.
- (172) Houk, K. N.; Luskus, L. J. *J. Am. Chem. Soc.* **1971**, 93, 4606.
- (173) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, 24, 1901

- (174) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1995**, 117, 6601.
- (175) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, 113, 4340
- (176) Rizzo, C. J. *J. Org. Chem.* **1992**, 57, 6382.
- (177) Long, F. A.; McDevitt, F. W. *Chem. Rev.* **1952**, 51, 119.
- (178) McDevitt, F. W.; Long, F. A. *J. Am. Chem. Soc.* **1952**, 74, 1773.
- (179) Bockris, J. O'M.; Reddy, A. K. N. *Modern Electrochemistry* Plenum Press, New York, **1970**.
- (180) Marcus, Y. *J. Phys. Chem. B* **2005**, 109, 1854.
- (181) Horne, R. A. *Water and Aqueous Solutions* Wiley-Interscience, Massachusetts, **1976**.
- (182) Reiss, H.; Frisch, H.L.; Lebowitz, J. L. *J. Chem. Phys.* **1959**, 31, 369
- (183) Reiss, H. *J. Phys. Chem.* **1992**, 96, 4736.
- (184) Kumar, A. *J. Am. Chem. Soc.* **1993**, 115, 9243
- (185) Shoor, S. K.; Gubbins, K. E. *J. Phys. Chem.* **1969**, 73, 498.
- (186) Pierotti, R. A. *Chem. Rev.* **1976**, 76, 717 and references cited therein.
- (187) Masterton, W. L.; Lee, T. P. *J. Phys. Chem.* **1970**, 74, 1776.
- (188) Mavroyannis, C.; Stephen, M. *J. Mol. Phys.* **1962**, 5, 629
- (189) Drljaca, A.; Hubbard, C. D.; van Eldik, R.; Asono, T.; Basilevsk, M. V.; Le Noble, W. J. *Chem. Rev.* **1998**, 98, 2167 and references cited therein.
- (190) Dack M. R. *J. Chem. Soc. Rev.* **1975**, 4, 211.
- (191) Desnoyers, J. E.; Verall, R. E.; Conway, B. E. *J. Chem. Phys.* **1965**, 43, 243
- (192) *International Critical Tables*; McGraw Hill: New York **1928**; Vol. 3.
- (193) Sohonel, O.; Novothy, P. *Densities of Aqueous Solution in Inorganic Substances* Elsevier, Amsterdam, **1985**; pp 335.
- (194) Kumar, A. *J. Org. Chem.* **1994**, 59, 230.
- (195) Kumar, A.; Phalgune, U.; Pawar, S. S. *J. Phys. Org. Chem.* **2001**, 14, 577.
- (196) Cativiela, C.; Garcia, J. I.; Mayoral, J. A. Salvatella, L. *J. Chem. Soc. Perkin Trans. 2* **1994**, 847.
- (197) Taft, R. W.; Kamlet, M. J. *J. Am. Chem. Soc.* **1976**, 98, 2886.
- (198) Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, 98, 377.
- (199) Kosower, E. M. *J. Am. Chem. Soc.* **1958**, 80, 3253.

- (200) Mayer, U.; Gutmann, V.; Gerger, W. *Monatsh, Chem.* **1975**, 106, 1235.
- (201) Dimroth, K.; Reichardt, C.; Siepmann, Bohlmann, F. *Liebigs Ann. Chem.* **1963**, 661, 1.
- (202) Kamlet, M. J.; Abboud, J. M.; Abraham, M. J.; Taft, R. W. *J. Org. Chem.* **1983**, 48, 2877.
- (203) For normalized E_T parameter see: Marcus, Y.; *J. Chem. Soc., Perkin Trans. 2* **1994**, 1751.
- (204) MacRitchie, F. *Chemistry at Interfaces*, Academic Press, Inc California **1990**
- (205) Vidis, A.; Ohlin, A.; Laurency, G.; Küsters, E.; Sedelmeier, G.; Dyson, P. *Adv. Synth. Catal.* **2005**, 347, 266.
- (206) Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. *J. Org. Chem.* **1988**, 53, 810.
- (207) Prajapati, D.; Laskar, D. D.; Sandhu, J. S.; *Tetrahedron Lett.* **2000**, 41, 8639.
- (208) Yadav, J. S.; Reddy, B. V. S.; Chetia, L.; Srinivasulu, G.; Kunwar A. C. *Tetrahedron Lett.* **2005**, 46, 1039.
- (209) Fuller, J.; Carlin, R. T.; Osteryoung, R. A. *J. Electrochem. Soc.* **1997**, 144, 3881.
- (210) Baker, S. N.; Baker, G. A.; Kane, M.A.; Bright, F. V. *J. Phys. Chem. B* **2001**, 105, 9663.
- (211) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, 3, 156.
- (212) Firestone, R. A.; Vitale, M. A. *J. Org. Chem.* **1981**, 46, 2160.
- (213) Benford, G. A.; Kaufmann, H.; Khambata, B. S.; Wasserman, A. *J. Chem. Soc.* **1939**, 870.
- (214) Swiss, K. A.; Firestone, R. A. *J. Phys. Chem. A* **2000**, 104, 3057.
- (215) le Noble, W. J.; Asano, W. *J. Phys. Chem. A* **2001**, 105, 3428.
- (216) Weber, C. F.; van Eldik, R. *J. Phys. Chem. A* **2002**, 106, 6904.
- (217) Hamann, S. D.; le Noble, W. J. *J. Phys. Chem. A* **2004**, 108, 7121.
- (218) Firestone, R. A.; Swiss, K. A. *J. Phys. Chem. A* **2001**, 105, 3430.
- (219) Firestone, R. A.; Swiss, K. A. *J. Phys. Chem. A* **2002**, 106, 6909.
- (220) Firestone, R. A.; Swiss, K. A. *J. Phys. Chem. A* **2004**, 108, 7124.
- (221) Nakagawa, K.; Ishii, Y.; Ogawa, M. *Tetrahedron* **1976**, 32, 1427
- (222) Firestone, R. A.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 14, 389

- (223) Kim, K. S.; Shin, B. K.; Lee, H. *Korean J. Chem. Eng.* **2004**, 21, 1010.
- (224) Bonhote, P.; Dias, A-P.; Papageorgiou, N.; Kalyanasundaram, K.; Gratzel, M.
Inorg. Chem. **1996**, 35, 1168.

List of publications

1. **Suvarna S. Deshpande**, Usha D. Phalgune and Anil Kumar, Salt effect on the *endo/exo* ratio of the reaction of cyclopentadiene with methyl methacrylate, *Tetrahedron* **2002**, *58*, 8759-8762.
2. Anil Kumar and **Suvarna S. Deshpande**, Exploring the re-evaluated interpretation of hydrophobicity to explain rates of Diels-Alder reactions in aqueous salt solutions, *J. Phys. Org. Chem.* **2002**, *15*, 242-245
3. Anil Kumar and **Suvarna S. Deshpande**, Experimental evidence to support viscosity dependence of rates of Diels-Alder reactions in solvent media, *J. Org. Chem.* **2003**, *68*, 5411-5414.
4. **Suvarna S. Deshpande**, Sanjay S. Pawar, Usha Phalgune and Anil Kumar, Converting the role of LiClO₄ from salting-in to salting-out in Diels-Alder reactions by solvent manipulation, *J. Phys. Org. Chem.* **2003**, *16*, 633-635.
5. **Suvarna S. Deshpande** and Anil Kumar, Stereoselectivity ratios in a simple Diels-Alder reaction in aqueous salt solutions of alcohols, *Tetrahedron* **2005**, *61*, 8025-8030.
6. Diganta Sarma, Sanjay Pawar, **Suvarna S. Deshpande** and Anil Kumar, Hydrophobic effects in a simple Diels-Alder reaction in water, *Tetrahedron Lett.* **2006**, *47*, 3957-3958.

Chapter in the book

1. **Suvarna S. Deshpande** and Anil Kumar, Activation of Organic Reactions by Perchlorates, Bentham Science publishers, **2005**, v. 1, 215-232 Editor: Atta-ur-Rehman, Guest editor: G. Jenner

To be communicated

1. **Suvarna S. Deshpande** and Anil Kumar, Interfacial area in Diels-Alder reactions (manuscript under preparation)
2. **Suvarna S. Deshpande** and Anil Kumar, Kinetics of Intramolecular Diels-Alder reactions in ionic liquids (manuscript under preparation)

Conferences attended

1. Rate profiles of Diels-Alder reactions in green solvents: poster presented at IUPAC sponsored Second International symposium in Green/ Sustainable Chemistry, University of Delhi, 10 -13 Jan, 2006
2. Importance of interface in Diels-Alder reactions: poster presented at 7th CRSI National Symposium in Chemistry, IACS, Kolkata, 4 - 6 Feb, 2005
3. Salt effects on Diels-Alder reactions: poster presented at 5th National Symposium in Chemistry, Chennai, 7 - 9 Feb, 2003