

Salt Effects on Diels–Alder Reaction Kinetics

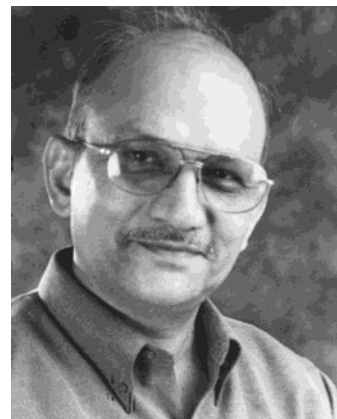
Anil Kumar*

Physical Chemistry Division, National Chemical Laboratory, Pune 411 008, India

Received February 23, 2000

Contents

I. Introduction	1
II. Scope of This Review	2
III. Reactions in Unusual Solvents	2
A. Water, A Solvent with Special Effects	2
B. Aqueous Salt Solutions	4
C. Salt Solutions in Nonaqueous Solvents	5
D. Ionic Liquids	8
IV. Origins of Forces Responsible for Variations in Rates and Stereoselectivities	9
A. Solvent Parameters	9
B. Water	9
1. Hydrophobicity	9
2. Enforced Hydrophobic Hydration and Hydrogen-Bonding Effects	10
C. Water-Like Solvents	10
D. Aqueous Ionic Solutions	11
E. Ionic Solutions in Nonaqueous Solvents	12
1. Physicochemical Properties of LPDE	12
2. Formation of Clathrates and Their Role	12
3. Polarity Effects	13
4. Lewis-Acid Catalysis	13
5. Internal Pressure Effects	15
F. Ionic Liquids	16
V. Theoretical Developments	16
VI. Miscellaneous	16
VII. Conclusion and Future Outlook	17
VIII. Acknowledgments	17
IX. References	17



Anil Kumar was born in Bijnor, Uttar Pradesh (India), in 1956. He worked at the National Chemical Laboratory, Pune (India), where he earned his Ph.D. degree in Chemistry in 1981. Later he spent two years as a postdoctoral research associate with Professor G. Atkinson, University of Oklahoma, Norman, OK, where he worked on theoretical and experimental solution chemistry involving electrolytes. In 1985, he was awarded the Alexander von Humboldt Scholarship in the laboratory of Professor Dr. E. U. Franck, University of Karlsruhe, Karlsruhe (FRG), where he was involved in the calculations of thermodynamic properties of aqueous ionic species under elevated conditions. Since 1990 he has been employed as a Scientist with the National Chemical Laboratory, Pune. His main interest is in the study of the chemistry of those systems in which ionic species play a significant role in governing their physical, chemical, or biological behavior. In recent years he has been interested in understanding the physical–organic chemistry of Diels–Alder reactions in salt solutions and biophysical chemistry of DNA molecules. Otherwise, he likes to solve crossword puzzles or read material pertaining to the origin of life on earth and ancient history. He also fathers a 13 year old daughter named Anuja.

memorable publication by Diels and Alder, the discoverers of the $[4\pi + 2\pi]$ cycloaddition, is a landmark in synthetic organic chemistry.² The $[4\pi + 2\pi]$ cycloaddition was later followed by $[2\pi + 1\pi]$, $[2\pi + 2\pi]$, $[3\pi + 2\pi]$, and other cycloadditions.¹ The remarkable importance of the Diels–Alder reaction in the synthesis of natural products and physiologically active molecules led to an upsurge in research activities aimed at developing newer methods to improve yields and selectivities of the $[4\pi + 2\pi]$

I. Introduction

Diels–Alder reaction is a powerful tool employed frequently for the synthesis of six-membered ring systems with excellent stereoselective control.¹ The

* Fax: +91 20 5893044. E-mail: akumar@ems.ncl.res.in.

cycloaddition reaction. Research work in this area has been discussed in several review articles and monographs published from time to time.¹ The concept of the mechanism of the Diels–Alder reaction was primarily governed by one of the Woodward–Hoffmann's rules,³ namely, “thermally allowed” reactions could occur by concerted mechanism. The mechanism of Diels–Alder reactions later attracted considerable debate because these reactions could not be explained in terms of a concerted mechanism alone as shown by Sauer and Sustmann⁴ and Houk and co-workers,⁵ who have discussed in detail the mechanistic aspects of these reactions.

The occurrence of isopolar activated complexes in the Diels–Alder reactions indicated that the solvent effects on the kinetics of these reactions were very small.⁴ This conclusion was based upon the analysis of the rate data for eight different cycloaddition reactions in 28 solvents with varying physicochemical properties. A poor solvent effect was also noted irrespective of the nature of dienes and dienophiles. However, as exceptions, the reactions of anthracene with 4-phenyl-1,2,4-triazolindione^{6,7a} and tetracyanoethylene^{7a,b} showed noticeable rate variations in different solvents.

In the last two decades remarkable variations in the reaction rates and stereoselectivities have been accomplished by the application of high pressure, ultrasound, solvent manipulations, catalysts, etc. Pindur, Lutz, and Otto^{1e} have discussed these developments in an exhaustive review.

II. Scope of This Review

Numerous publications on Diels–Alder reactions appear each year, and it is not an easy task to review all of them. Discussions on the use of nonaqueous organic solvents and their aqueous mixtures are also excluded, as a recent review has addressed this topic.⁸

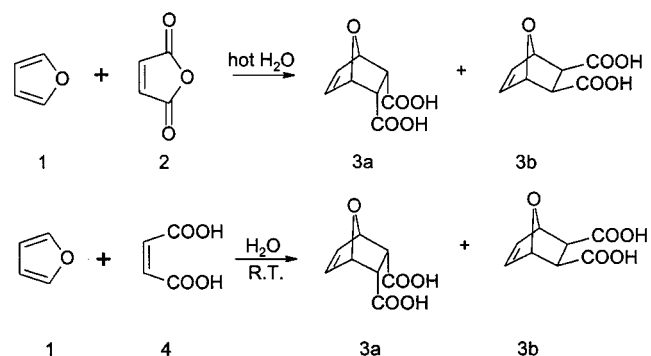
This review deals with the effect of solvent media on the reaction rates, k , and the endo/exo (or N/X) stereoselectivity ratios of Diels–Alder reactions. Solvents include salt solutions in aqueous and nonaqueous media. Salt solution signifies a solution prepared by adding inorganic salt or ionic solute in a solvent.

The main focus will be on the special roles of aqueous and nonaqueous salt solutions in altering the kinetic profiles, the how and why of salt solutions influencing reaction rates and stereoselective ratios of Diels–Alder reactions, and the physico-organic aspects of $[4\pi + 2\pi]$ cycloadditions in salt solutions. The role of ionic liquids in general organic chemistry has recently been reviewed,⁹ but their application to Diels–Alder reactions, in particular, will form part of this review. Relevant literature up to 1999 has been covered.

III. Reactions in Unusual Solvents

On the basis of a careful survey of the literature, solvent effects can be classified into four categories: (i) water, conventional organic solvents, and their aqueous mixtures, (ii) aqueous salt solutions, (iii)

Scheme 1



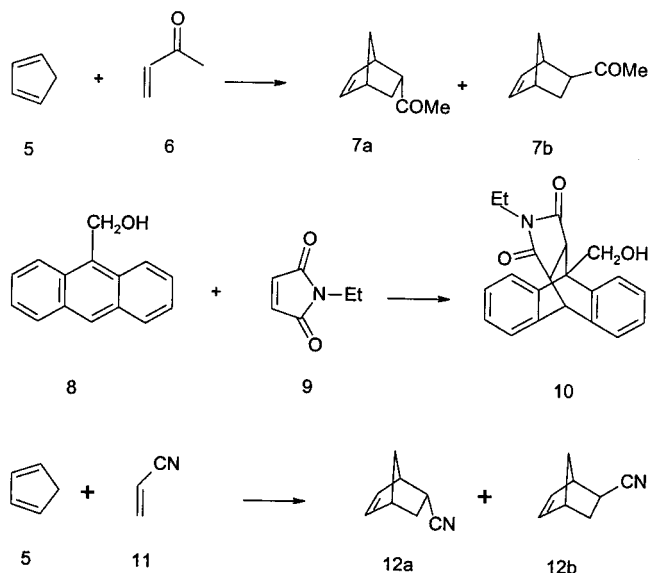
nonaqueous solvents and their salt solutions, and (iv) ionic liquids that are in molten state at low or ambient temperatures.

Before examining the role of salt solutions on the rates and stereoselectivities of Diels–Alder reactions, it is important to mention the startling discovery of the special role of water in these reactions.

A. Water, A Solvent with Special Effects

Water plays a key role in biochemical, geochemical, and other natural processes. In 1931, Diels and Alder themselves performed the cycloaddition of furan (1) with maleic anhydride (2) in hot water in order to give diacid 3 (Scheme 1).^{10a} Later, the reaction of 1 with maleic acid (4) was carried out in water^{10b,c} at room temperature to yield 3 (Scheme 1). Two decades ago Breslow and co-workers¹¹ discovered the special effect of water on Diels–Alder reaction. Spectacular enhancement in the reaction rates was reported for the first time when water was chosen as a solvent medium rather than a conventional organic solvent in carrying out Diels–Alder reactions. For example, the reaction of cyclopentadiene (5) with methyl vinyl ketone (6) was reported to be 730-fold faster in water than in 2,2,4-trimethylpentane (Scheme 2). A 12-fold

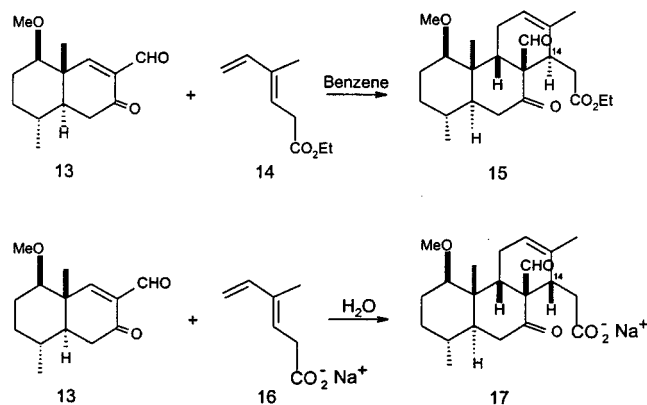
Scheme 2



increase in the reaction rate was, however, noted in methanol. Further, this effect was tested in the case

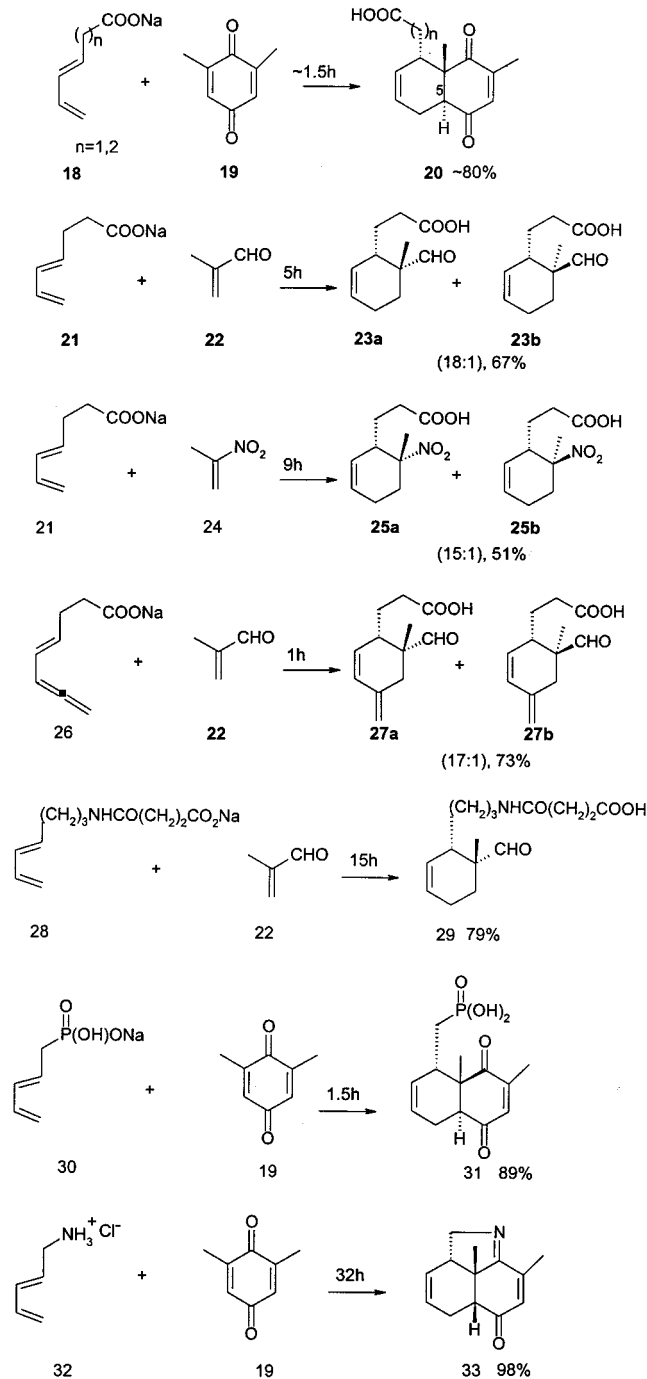
Table 1. Some Examples of Water-Mediated Diels–Alder Reactions

reactions	comments
5 + 6 ¹¹	730-fold faster in water than in 2,2,4-trimethylpentane
8 + 9 ¹¹	200-times faster in water than in 2,2,4-trimethylpentane
5 + 11 ¹¹	30 times faster than in water than in 2,2,4-trimethylpentane
diene carboxylates (sodium salts) (18, 21, 26, 28) + dienophile (19, 22, 24) ^{13,14a}	excellent yields; accelerated reaction under ambient conditions
30 + 19 ¹⁴	as effective as diene carboxylate
32 + 19 ¹⁵	pentadienylammonium less reactive than hexadienyl homologue

Scheme 3

of the reaction of anthracene-9-carbinol (**8**) with *N*-ethylmaleimide (**9**) (Scheme 2). This reaction was observed to be 65-fold faster in water than in methanol and 200 times faster in water than in acetonitrile. The reaction rate was witnessed to be minimum in 2,2,4-trimethylpentane. The reaction of **5** with acrylonitrile (**11**) (Scheme 2), while exhibiting no appreciable difference in reaction rates in both 2,2,4-trimethylpentane and methanol, was about 30 times faster in water than in 2,2,4-trimethylpentane. These examples of Diels–Alder reactions clearly show the enormous rate enhancements that can be achieved by the use of water as a solvent medium.^{11a}

The superior role of water over other conventional solvents on [4+2] cycloadditions was established by Grieco and co-workers during the synthesis of quassinoids.¹² The reaction of a dienophile (**13**) with ester of 4-methyl (*E*)-3,5-hexadienoic acid (**14**) (Scheme 3) in benzene for 72 h gave the major product with undesired stereochemistry. However, use of the sodium salt of 4-methyl (*E*)-3,5-hexadienoic acid (**16**) (Scheme 3) as diene in water resulted in a dramatic rate acceleration with desired reversal in stereoselectivity.¹³ By carrying out several Diels–Alder reactions of diene carboxylates with varying dienophiles, the general usefulness of water in synthetic chemistry was established by Grieco and his group.^{13,14} For all the reactions studied by them, a sharp increase in the reaction rates, *N*/*X* ratios, and product yields was observed in aqueous Diels–Alder reactions. Other modified dienes, like ammonium diene carboxylates, monosodium diene phosphonate, and dienylammonium chloride, also reduced the reaction time and enhanced the yield of cycloadducts.^{14,15} A few examples of these reactions are shown in Scheme 4. An important point to note in this regard is the potential advantage of monosodium phosphonate headgroup as it can buffer the reaction medium if sensitive functionalities are involved in the Diels–

Scheme 4

Alder reactions. The methodology developed by Larsen and Grieco^{15c} on the water-mediated aza Diels–Alder reactions led Waldmann to include the use of amino acid esters as chiral auxiliaries.¹⁶ Advantages achieved by the use of water as solvent for some Diels–Alder reactions in water are noted in Table 1.

Table 2. Effect of Salt Solutions on the Reactions of 8 with 9 (Scheme 2)¹⁹

solvent	$k_{\text{rel}} (= k/k_{\text{water}})^a$
water	1
methanol	0.015
2,2,4-trimethylpentane	0.035
aqueous 4 M LiCl	2.2
aqueous 4.86 M	2.5
aqueous 2 M GnCl	0.56
aqueous 4.86 M GnCl	0.32
aqueous 4 M LiClO ₄	0.68
aqueous 2 M GnClO ₄	0.37

^a Value of the second-order rate constant, k_2 in water = $226 \pm 7 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

In short, it can be concluded that the use of water in the synthesis of natural products was effectively proven by designing new strategies of Diels–Alder reactions. These strategies in water have been discussed in detail elsewhere.^{1j,k} An article by Garner¹⁸ on Diels–Alder reaction in aqueous media is another valuable addition to our knowledge on the subject. Garner¹⁸ tabulated the water-mediated reactions carried out by Grieco and his group.

B. Aqueous Salt Solutions

The special effects of water as a solvent medium for Diels–Alder reactions can be greatly altered by the addition of ionic solutes such as LiCl, NaCl, LiClO₄, etc. The kinetic measurements on the reaction of 5 with 6 (Scheme 2) have shown that a solution of 4.86 M LiCl increased the reaction rate by 2.5 times, while a marginal decrease was noted in the presence of guanidinium chloride (GnCl).^{11a} The reaction of 8 with 9 (Scheme 2) in 4.86 M GnClO₄ slowed the reaction rate by 3 times,¹⁹ whereas a 4.8 M LiCl solution increased the reaction rate by 2.5 times.^{11,b} In 4.7 M GnCl solution, the reaction rate declined by about one-third of its value observed in water. Further, with rate enhancing salts, like LiCl, the reaction rates increased with the increasing ionic concentration. Similarly, the increase in the ionic concentrations of the rate-retarding salts, like GnCl, GnClO₄, etc., decreased the reaction rates.¹⁹ A summary of the ionic effects on the reaction of 8 with 9 (Scheme 2) is presented in Table 2. Breslow's study on this topic dealt with how these salt solutions influenced the reaction rates and the N/X ratios of Diels–Alder reactions.²⁰ The N/X ratio of 25 for the reaction of 5 with 6 in water increases to 28 in LiCl and declines to 22 in GnCl.^{11a,d,20} In an attempt to analyze the role of anions on the reaction rates, the reaction of 8 with 9 was carried out in 2 M aqueous solutions of NaCl, NaBr, NaBF₄, NaClO₄, NaPF₆, and NaAsF₆. All these sodium salts accelerated the reaction rates. The rate enhancement in these sodium salt solutions decreases with the increase in the size of anions.²¹ A decrease in the reaction rates, however, was observed in 2 M solutions of GnCl, GnBr, GnBF₄, GnSCN, and GnClO₄. These effects are illustrated in Figure 1, where the rate constants, k , are plotted against anionic radii, r , for both sodium and guanidinium salts. The linear variation of k with r indicates that the rate variations for aqueous Diels–Alder reaction follow the Hofmeister series.²²

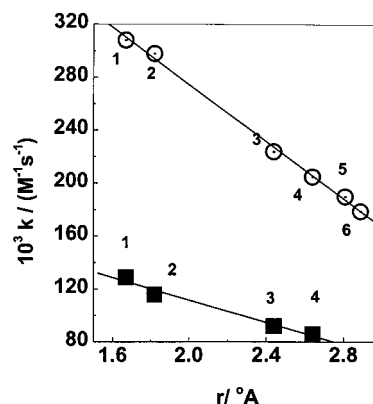


Figure 1. Rate constants, k , versus anionic radii, r , of sodium (○) and guanidinium (■) salts used for the reaction of 8 with 9: (1) Cl⁻, (2) Br⁻, (3) BF₄⁻, (4) ClO₄⁻, (5) PF₆⁻, (6) AsF₆⁻. Data from ref 21.

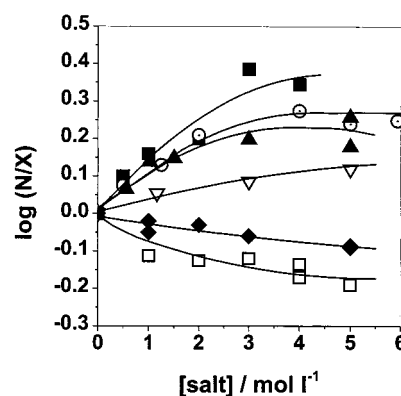
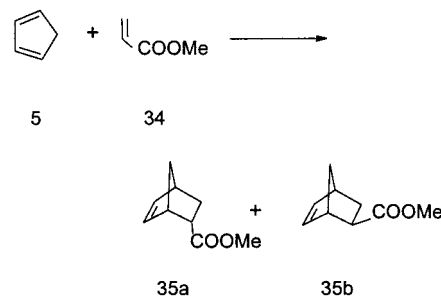


Figure 2. Plots of $\log(N/X)$ and the salt concentrations of aqueous LiCl (■), NaCl (○), NaBr (△), CaCl₂ (▽), GnCl (◆), and LiClO₄ (□) for the reaction of 5 and 34. Data from ref 23.

Recently published experimental data also confirm the concentration dependence of salt solutions in altering the rate data and N/X ratios of Diels–Alder reaction. With regard to stereoselectivity ratios, the N/X values for the reaction of 5 with 34 (Scheme 5)

Scheme 5



in different aqueous salt solutions have recently been published.²³ The reactions were conducted in LiCl, NaCl, NaBr, CaCl₂, GnCl, and LiClO₄ with the salt concentration ranging up to 6 M. The results obtained are plotted in Figure 2 in the form of $\log(N/X)$ as a function of the salt concentration. Examination of this figure shows two clearly opposite trends in the variations of $\log(N/X)$ values concerning the salt concentration. One group of salts, such as LiCl, NaCl, NaBr, and CaCl₂, enhances the N/X ratios, while

another group comprising LiClO_4 and GnCl decreases the ratios. The $\log(N/X)$ values varying with the salt concentrations begin to level off at high salt concentrations. These reactions were carried out with fixed amounts of **5**, **34**, and salt solution. The parameter that varied during the investigation was the concentration of salt solutions. The N/X values in these rate-increasing salt solutions follow the order $\text{LiCl} > \text{NaCl} > \text{NaBr} > \text{CaCl}_2$. Out of the rate-decreasing salts, LiClO_4 is more effective than GnCl in reducing the N/X ratios for this reaction. A recent study has shown that the endo products for the reaction of **5** with **34** are a function of available water content in salt solutions.²⁴ The interactions in aqueous salt solutions have been discussed by Breslow.²⁵ The monograph in general is a useful compilation of important articles in this area.

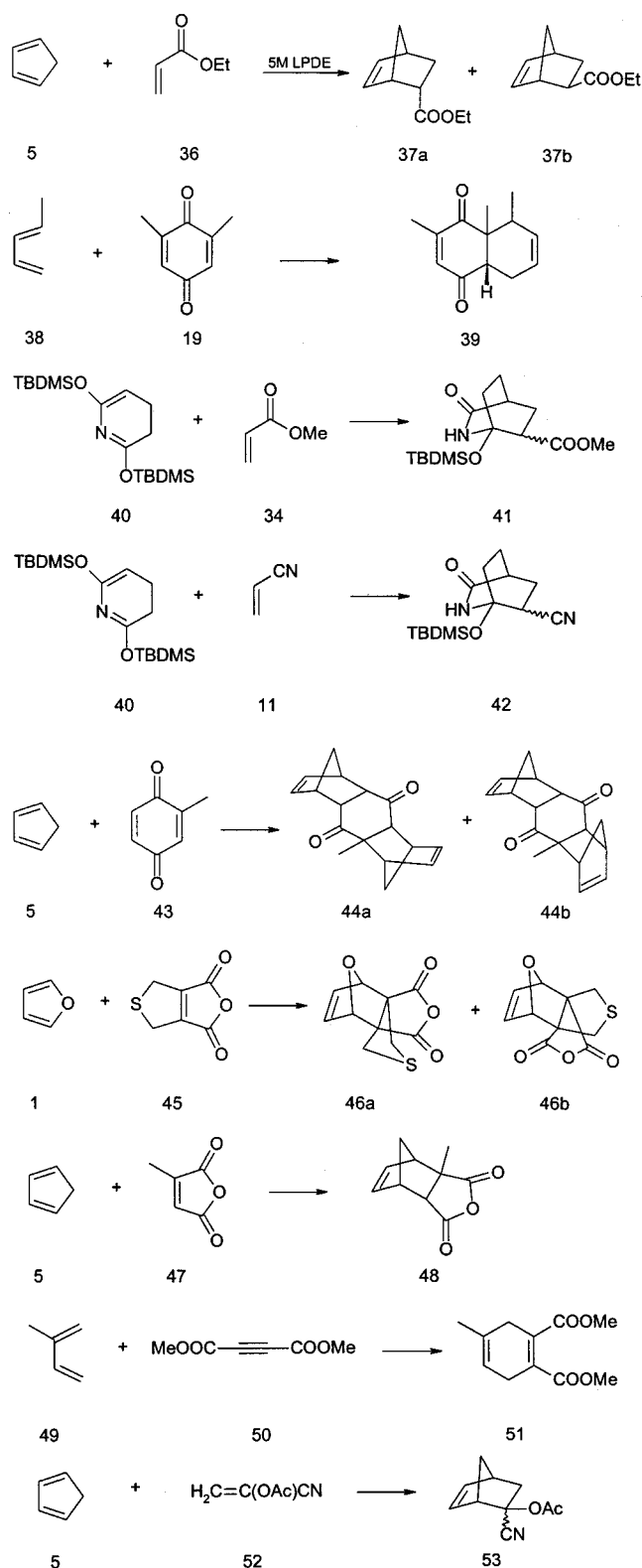
C. Salt Solutions in Nonaqueous Solvents

Solutions of LiClO_4 in diethyl ether (LPDE) have been found to be the most effective solvent medium with a highly positive impact on the kinetic progress of Diels–Alder reactions. As a matter of fact, the use of LPDE was first explored for the ionization reaction of *p*-methoxyneophyl-*p*-toluenesulfonate and that of spirodienyl-*p*-nitrobenzoate.²⁶ On the basis of rate accelerations of these reactions in LPDE as compared to those in acetic acid, it was suggested that such solvent media might be useful in carrying out ionization reactions. Several years later, the allylic rearrangement of 1-phenylallyl chloride to cinnamyl chloride was accelerated in LPDE showing an overall increase of about 85 600-fold over organic solvents.²⁷ The rate acceleration in this and other reactions was attributed to the electrostatic catalysis by the clathrates of LiClO_4 in diethyl ether.²⁸ Later, during a study of the steric course of Diels–Alder reactions in LPDE types of solutions, it was suggested that these polar solutions could be used for kinetic control for organic chemical reactions.²⁹

In 1990, Grieco, Nunes, and Gaul made a startling discovery by employing a 5 M LPDE solution in Diels–Alder reactions that were sluggish otherwise.³⁰ These authors reported impressive rate accelerations for several Diels–Alder reactions in LPDE. The initial effect of a 5 M LPDE was seen on the reaction of **5** with ethyl acrylate (**36**) (Scheme 6), giving 93% yield with the N/X ratio as 8:1, when compared to those achieved (73% and 4:1) in water alone. The encouraging results for this reaction led them to explore the potential of LPDE on other Diels–Alder reactions. In their novel work, they conducted several reactions involving different dienes and dienophiles in 5 M LPDE solutions. A summary of these and other reactions studied by Grieco and co-workers is given in Table 3 with comments on the yields and reaction conditions with regard to the advantages over conventional solvents.

The reaction of *trans*-piperylene (**38**) with 2,6-dimethylbenzoquinone (**19**) is extremely sluggish in water with less than 20% yield after 24 h (Scheme 6). The same reaction is completed within 15 min in 5 M LPDE, giving 80% yield. The reaction of aza diene (**40**) with **34** in benzene was reported to give

Scheme 6



cycloadduct (**41**) (Scheme 6) with a 74% yield in 72 h at 60 °C.³¹ The same reaction when carried out in 5 M LPDE results in 80% yield in 5 h. The reaction of **40** with **11** in LPDE was carried out in 3 h with 78% yield as compared to 48 h with 73% yield in benzene.

The cycloaddition of **5** with methylbenzoquinone (**43**) is another exciting outcome of Grieco's efforts to offer simple methods in synthetic organic chemistry (Scheme 6). This reaction has been reported to

Table 3. Important Diels–Alder Reactions (Scheme 5) Accelerated in LPDE³⁰

reactions	reaction conditions in conventional media	outcome of the use of LPDE
5 + 36	water; 5 h; ambient temp.; yield = 73%; N/X = 4:1	5 h; ambient temp.; yield = 93%; N/X = 8:1
38 + 19	water; 24 h; ambient temp.; yield = 20%	<15 min.; ambient temp.; yield = 80%
40 + 34	benzene; 72 h; 60 °C; yield = 74%	5 h; ambient temp.; yield = 80%
40 + 11	benzene; 48 h; 60 °C; yield = 73%; (N/X) = 1: 9	3h; ambient temp.; yield = 78%; (N/X) = 1:3.7
5 + 43 1 + 45 (cantharidin synthesis)	reaction temp. = 75 °C medium = methylene chloride; reaction time = 6 h; pressure = 15 kbar; (N/X) = 85:15	reaction time = 10 h reaction time = 9.5 h; ambient temp. and pressure; yield = 70%; (N/X) = 85:15
5 + 2-methyl maleic anhydride (47)	neat; reaction time = 24 h; reaction temp. 60 °C; reaction yield = 94%	reaction time = 3 h; ambient conditions; yield= 90%
2-methyl butadiene (49) + acetylenedicarboxylic acid dimethyl ester (50)	reaction time = 12 h; yield = 50%	reaction time 12 h; yield = 94%
5 + 1-cyanovinyl acetate (52)	reaction time >24 h; yield= 24%	reaction time = 4 h; yield= 79%

take place at 75 °C under a high pressure of 7895 atm (1 atm \approx 10⁵ Pa) in 60% yield.³² Employing 5 M LPDE, the above cycloaddition was realized at room temperature and ambient pressure in 10 h with 74% yield and N/X ratio of 6:1.

These reactions serve as examples of the powerful application of LPDE in accelerating sluggish reactions.³³ One of the most fascinating discoveries by Grieco and co-workers in this connection is the formal synthesis of cantharidin in 5 M LPDE under ambient temperature and pressure.³⁰ Conventionally cantharidin was synthesized by applying an external ultrahigh pressure of \sim 15 k bar on the reaction mixture containing **1** and 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**45**) (Scheme 6) in methylene chloride. This classic synthesis by Dauben, Kessel, and Takemura³⁴ required 6 h to undergo completion under high pressure, yielding an 85:15 mixture of cycloaddition products. Since **1** is known to be a poor diene due to its aromatic nature, application of ultrahigh pressure is required to effect the cycloaddition.³⁵ When Grieco and co-workers attempted the above reaction in 5 M LPDE, quite surprising results were obtained. The reaction in LPDE proceeded at ambient temperature and pressure in 9.5 h with higher yield (70%) and a mixture of cycloadducts in an 85:15 ratio. The reaction illustrates the use of LPDE in obviating the requirement of ultrahigh-pressure conditions in a Diels–Alder reaction. This work, a milestone in terms of achieving the facile reaction conditions and higher yields in a relatively short duration, later inspired researchers all over the world to employ 5 M LPDE in carrying out slow and difficult Diels–Alder reactions.

Extensive efforts of Grieco and co-workers further demonstrated the utility of LPDE in enhancing the N/X ratios of intramolecular Diels–Alder reactions and catalyzing the formation of cycloadducts useful as building blocks for the preparation of amino sugar antibiotics.³⁶ A dramatic enhancement of stereoselectivity ratios has been reported for intramolecular Diels–Alder reactions in 5 M LPDE in the presence

of 1–10 mol % camphorsulfonic acid.³⁷ The use of Li⁺ ion catalyst in concentrated LPDE to promote chelation-controlled addition of trialkylallylstannanes to aldehydes has offered a new and useful synthetic method to diastereoselective carbon–carbon bond formation.³⁸ In an effort to expand the scope of such solvent media to Diels–Alder reactions, Grieco and Ghosez employed concentrated solutions of lithium trifluoromethanesulfonimide in either diethyl ether or acetone. This solvent medium was noted to offer an unexpected influence of the counterion on both the yields and N/X selectivity as compared to LPDE.³⁹

Though LPDE is the most popular solvent medium used for rate acceleration, the role of some other perchlorates has also been examined in altering the reaction rates. The effects of perchlorate salts of sodium, lithium, barium, and magnesium in acetone on the rates of several Diels–Alder reactions were kinetically investigated.⁴⁰ ¹³C NMR spectroscopy was employed as a tool to investigate the mechanism of coordination of solvated metal cations acting as catalysts. The use of ¹³C NMR spectroscopy was guided by ¹H NMR studies of the solvation of LiClO₄ in acetone, as the chemical shift of acetone methyl protons increased with respect to the salt concentration.⁴¹

First, the reaction between 2,3-dimethylbutadiene (**54**) and 1,4-naphthoquinone (**55**) with direct electron demand was studied in acetone solutions of NaClO₄ (SPAC), LiClO₄ (LPAC), Ba(ClO₄)₂ (BPAC), and Mg(ClO₄)₂ (MPAC) (Scheme 7). The experimental log *k*_{rel} (*k*_{rel} = *k*_{salt soln}/*k*_{acetone}) data as a function of the salt concentration for the above reaction are plotted in Figure 3. It can be seen in Figure 3 that MPAC produces maximum rate enhancement despite the limited solubility of Mg(ClO₄)₂ in acetone. The order in which these perchlorates in acetone enhance the reaction is MPAC > BPAC > LPAC > SPAC. For instance, at 1 M salt concentration, the observed rate enhancement is in the ratio of 24:7:1.9:1 for MPAC:BPAC:LPAC:SPAC. Note the tapering of the log *k*_{rel} vs salt concentration plots at high salt concentrations

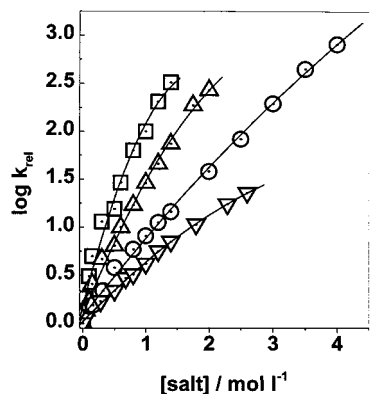


Figure 3. Plots of $\log k_{\text{rel}}$ ($k_{\text{rel}} = k_{\text{salt soln}}/k_{\text{acetone}}$) against concentration of perchlorate salts in acetone solutions for the reaction of **54** and **55**: (□) MPAC; (△) BPAC; (○) LPAC; (▽) SPAC. Data from ref 40.

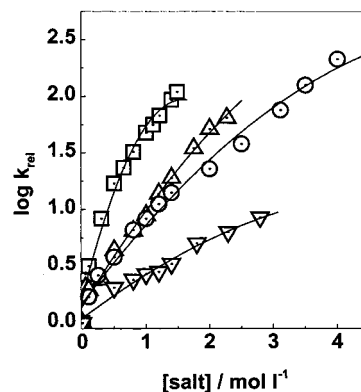
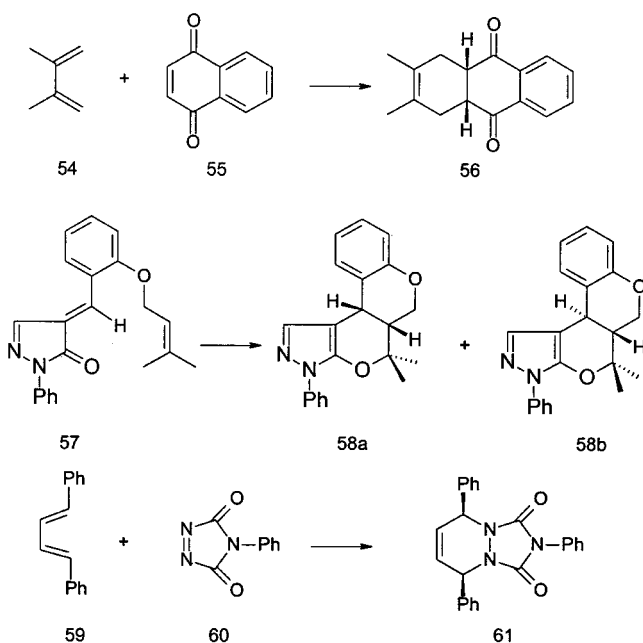


Figure 4. Plots of $\log k_{\text{rel}}$ against concentration of perchlorate salts in acetone solutions for intramolecular reaction of **57**; symbols are the same as in Figure 3. data from ref 40.

Scheme 7



indicating the possibility of the maximum acceleration of reaction rates. If the experimental $\log k_{\text{rel}}$ data are plotted as a function of $\log x$, x being the molar fraction of salt, the resultant plots are linear up to 1.4, 1.4, 2, and 1.6 M for MPAC, BPAC, LPAC, and SPAC, respectively. The divergence from linearity in the high-concentration region, particularly evident for LPAC, may indicate the presence of other catalytic species in the solutions. As discussed earlier, these species might be similar to clathrates formed by LiClO_4 and diethyl ether.^{27,28} Another reaction with inverse electron demand, i.e., intramolecular hetero-Diels–Alder reaction of (*E*)-1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone (**57**) carried out in the above perchlorate solutions, merits a brief discussion (Scheme 7). The $\log k_{\text{rel}}$ vs salt concentration data for this reaction plotted in Figure 4 indicate a lower enhancement in the reaction compared to the reaction of **54** with **55** (Scheme 7). For example, the reaction rates **57** in 1 M MPAC, BPAC, LPAC, and SPAC are increased by 48, 9, 8.4, and 2.7 times while those of **54** with **55** by 102, 28.7, 8.1, and 7.1 times, respectively. It appears that the

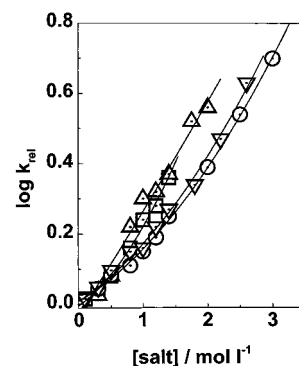


Figure 5. Plots of $\log k_{\text{rel}}$ against concentration of perchlorate salts in acetone solutions for the reaction of **59** with **60**; symbols are the same as in Figure 3. Data from ref 40.

solutions of perchlorates in acetone are more effective for the above-mentioned Diels–Alder reaction with direct electron demand than that with inverse electron demand. The order of reactivity for both the reactions obeys the charge radius ratios as $\text{Mg}^{2+} > \text{Ba}^{2+} \approx \text{Li}^+ > \text{Na}^+$.⁴⁰

The kinetic profiles of the reaction of *trans,trans*-1,4-diphenylbutadiene (**59**) with 4-phenyl-1,2,4-triazoline-3,5-dione (**60**) (Scheme 7), the rate constants for this reaction in the form of $\log k_{\text{rel}}$, and the salt concentration are depicted in Figure 5. An examination of this figure shows that the rate constants for this reaction are not strongly influenced by the perchlorate salts. At 1 M salt concentration of MPAC, BPAC, LPAC, and SPAC, the rate enhancement in the above reaction is in a ratio of 1.2:1.4:1:1, respectively.

The use of MPAC has also been explored in some hetero-Diels–Alder reactions with good success in terms of enhanced stereoselectivities and yields.⁴² Considerable rate enhancement of the reaction of anthracene with *p*-benzoquinone derivatives has been noted in the presence of $\text{Mg}(\text{ClO}_4)_2$ in acetonitrile.⁴³ A 4 M solution of LiClO_4 in nitromethane has also been found to accelerate those Diels–Alder reactions in which nitroalkenes act as dienophiles.⁴⁴ The cycloaddition reactions of several *p*- and *o*-quinones with dienes have also been noted to give high yields in LiClO_4 –nitromethane solution.⁴⁵ The effect of

solvent medium consisting of LiClO_4 and dichloromethane on endo product has also been studied.⁴⁶ The use of LPDE and other similar solvent media has also been discussed in Russian chemical literature indicating wide applications of these media in accelerating several sluggish Diels–Alder reactions.⁴⁷ Subsequently, use of LPDE was explored in Claisen rearrangement, benzoin condensation, and other organic reactions.^{1k,17a}

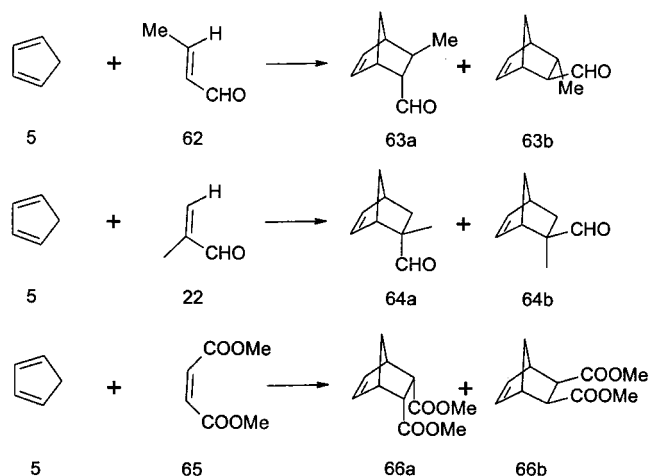
D. Ionic Liquids

Though the primary objective of this part of the review is to emphasize the special effects of ionic solutions on kinetic profiles of the Diels–Alder reactions, it would be apposite to discuss the upcoming application of ionic melts also in this context. The ionic melts that are liquid at ambient temperature are being referred to as a new class of solvent media for conducting several organic reactions.⁴⁸ Very recently an excellent review has appeared on the room-temperature ionic liquids where the preparation, properties, and applications of ionic liquids have been discussed.⁹ The author has, however, devoted a brief paragraph to the use of ionic liquids in Diels–Alder reaction. $[\text{EtNH}_3]\text{NO}_3$, an ionic liquid at 285 K known in the chemical literature for more than 80 years,⁴⁹ was chosen as a solvent medium for the reaction of **5** with **34** (Scheme 5) and with **6** (Scheme 2).⁵⁰ The enhancement in both the reaction rates and stereoselectivities in $[\text{EtNH}_3]\text{NO}_3$ was not remarkably different from those in water.^{11b,c,51} As the reaction conditions in different solvent media were not identical, no quantitative comparison of the results could be meaningful. The above reaction in water takes place in a heterogeneous medium owing to the very low solubility of **5** in water. However, **5** is about 100 times more soluble in $[\text{EtNH}_3]\text{NO}_3$ than in water, thus allowing the reaction to take place under homogeneous conditions. The idea behind the use of $[\text{EtNH}_3]\text{NO}_3$ in the above synthesis was based on the striking similarities in the physical properties of this melt with water.^{52a,b} An important property of this liquid is its high cohesive energy density which is associated with the hydrophobic effect. On the basis of the micelle-forming tendency of hydrocarbons in formamide and ethylene glycol (these solvents exhibit some of the properties of water), the authors argued that large solvophobic effects in $[\text{EtNH}_3]\text{NO}_3$ might be responsible for the rate enhancement.^{52c,d}

An attempt was made to use moisture-stable ionic liquid dialkylimidazolium salts ($\text{R}_2\text{I}_m^+ \text{X}^-$) in carrying out the reaction of **5** with crotonaldehyde (**62**) and **22** (Scheme 8).⁵³ The yields and N/X ratios for the reaction of **5** with **62** and **22** in the presence of dialkylimidazolium bromide and trifluoroacetate were almost identical. The yields (~37%) and N/X ratios (95:5) for the reaction of **5** with **62** were the same in both dialkylimidazolium bromide and trifluoroacetate. For the reaction of **5** with **22**, a yield of about 40% and a N/X value of 15:85 were noted to be similar in both salts.

After a gap of about 10 years, the dialkylimidazolium bromides and trifluoroacetate ionic liquids have very recently been employed to study their effect on

Scheme 8



the N/X ratios of the above-mentioned reaction.⁵⁴ The ionic liquids used in the investigation were $[\text{bmim}][\text{BF}_4]$, $[\text{bmim}][\text{ClO}_4]$, $[\text{emim}][\text{CF}_3\text{SO}_3]$, $[\text{emim}][\text{NO}_3]$, and $[\text{emim}][\text{PF}_6]$, where $[\text{bmim}]^+$ and $[\text{emim}]^+$ are 1-butyl-3-methylimidazolium and 1-ethyl-3-methylimidazolium species. In $[\text{emim}][\text{BF}_4]$, the increase in reaction time from 2 to 72 h at a constant temperature of 293 K led to an increase in yield by about 46% but with a decrease in the N/X ratios by about 25%. Under similar reaction conditions, i.e., 72 h and 298 K, a maximum yield of 91% was observed in $[\text{bmim}][\text{BF}_4]$ with the lowest N/X ratio of 4.3:1. On the other hand, $[\text{bmim}][\text{ClO}_4]$ under the above reaction conditions gave an N/X ratio of 5.3:1. No relationship between the yield and the N/X ratios could, however, be established in identical reaction conditions.

Though chloroaluminate ionic melts have been earlier employed in Friedel–Craft reactions and other related organometallic reactions, its application in Diels–Alder reaction has been explored very recently. The chloroaluminates comprised $\text{AlCl}_3:\text{MCl}$, with MCl being *N*-1-butylpyridinium chloride (BPC) or 1-ethyl-3-methyl-1*H*-imidazolium chloride (EMIC). EMIC can impart a Lewis acidity that can have profound effect on the rates and stereoselectivity of Diels–Alder reactions. Another important feature of chloroaluminates is their ability to create acidic or basic composition by altering the amount of either AlCl_3 or BPC/EMIC as required. The chloroaluminates have been employed as solvent media for the reaction of **5** with **34**.⁵⁵ Like $[\text{emim}][\text{BF}_4]$, the yield of this reaction in the presence of chloroaluminate was observed to increase with reaction time. The N/X ratios, however, did not vary with respect to the reaction time. A notable observation in this regard is the critical role of the composition of chloroaluminates on both the N/X ratios and reaction rates. A marginal increase in AlCl_3 from 48% to 51% in the composition of chloroaluminates caused a 4-fold increase in the stereoselectivity ratios and a dramatic 24 times enhancement in the second-order reaction rates. A comparative study of the above reaction in chloroaluminates, $[\text{EtNH}_3]\text{NO}_3$, and water shows that the reaction rate in the acidic chloroaluminate is several times higher than that observed in the other

Table 4. Ionic Liquid-Mediated Diels–Alder Reactions

ionic liquid	reactions	conditions	remarks
[EtNH ₃] ₃ NO ₃ ⁵⁰	5 + 34	reaction at room temperature	yields comparable; reaction rates 1 order less than in water
dialkylimidazolium bromide and trifluoroacetate ⁵³	5 + 62	reaction time 72 h reaction temperature up to 70 °C; reaction time from 2 to 72 h	yield = 36%; (N/X) = 95:5
several other salts of dialkylimidazolium ⁵⁴	+ 22 5 + 62	reaction temperature up to 70 °C; reaction time from 2 to 72 h	yield = 40%; (N/X) = 15:85 comparable yields and rates
chloroaluminates ⁵⁵	+ 22 5 + 34	room temperature	(N/X) higher than [EtNH ₃] ₃ NO ₃ and water and depend on the acidity of the liquid;
	+ 65	reaction time from 22 to 72 h	as above, but no data in support of claim are given
1-butyl-3-methylimidazolium trifluoroborate and similar ionic liquids ⁵⁶	5 + 36 ; + 65 ; + 49 ; + 36 ; + 6	temp. range = -15 to 80 °C; reaction time up to 72 h	reduced yields; comparable rates

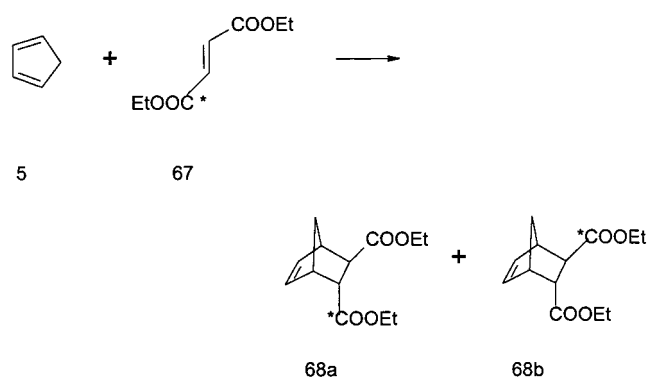
two solvents. Though the author has not discussed the quantitative results for the reaction of **5** with dimethyl maleate (**65**) (Scheme 8), it is claimed that chloroaluminates offer results similar to those obtained for the reaction of **5** with **34** in water.

In another recent work, the comparative performance of ionic melts and LPDE has been studied with respect to their effectiveness on the progress of Diels–Alder reaction.⁵⁶ The ionic melts selected for the study were 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([bmin][Otf]), hexafluorophosphate ([bmin][PF₆]), tetrafluoroborate ([bmin][BF₄], and lactate. The use of [bmin][Otf] for the reaction of **5** with **65** (Scheme 8), **36** (Scheme 6), and **11** (Scheme 2) offers comparable yields with those obtained from the use of LPDE and water. However, the reaction time is longer in ionic melts for several reactions as compared to those in LPDE and water. Another major difference between [bmin][PF₆] and LPDE for the reaction of **5** and **36** is the reduced yield (36%) of the product in [bmin][PF₆] as compared to that in LPDE (61%). The Diels–Alder reactions carried out in the ionic liquids are listed in Table 4.

IV. Origins of Forces Responsible for Variations in Rates and Stereoselectivities

A. Solvent Parameters

In the case of water and its mixtures with other usual organic solvents, several solvent properties have been considered for explaining the rate variations in Diels–Alder reactions. A recent review by Cativiela and co-workers summarizes these developments.^{1f} The parameters representing different solvent properties are as follows: Brownstein's solvent polarity parameter, *S*, Reichardt's polarity parameter, *E_T*, Kosowers polarity parameter, *Z*, and Gutmann's acceptor number, AN. The reaction rates of a few Diels–Alder reactions can be easily fitted with Gutmann's parameter, AN, using a hyperbolic equation.⁵⁷ An important parameter in this regard is the solvophobic power, *S_p*, of the solvent media. The reaction of **5** with diethyl fumarate (**67**) (Scheme 9) in aqueous methanol and aqueous 1,4-dioxane in 13 solvents was used to establish the importance of

Scheme 9

solvophobic power in describing the reaction rates and stereoselectivities.⁵⁸ An examination of all these solvent parameters shows that no unique parameter is applicable to a majority of Diels–Alder reactions studied. In view of this result, a multiparameter approach was proposed consisting of a combination of different solvent properties, such as polarity, solvophobicity, hydrogen-bond-donor capability, and other modified polarity scales such as *E_T* values with good accuracy.⁵⁹

B. Water

The origins of forces responsible for dramatic rate accelerations of Diels–Alder reactions in water could be studied with respect to hydrophobic packing, enforced hydrophobic hydration, and hydrogen-bonding effects.

1. Hydrophobicity

As seen earlier,¹¹ the reactions of **5** with **6** and with **11** proceeded significantly faster in water than in 2,2,4-trimethylpentane, a nonpolar organic solvent (Scheme 2). Since a moderate increase in the reaction rates of the above reactions was observed in methanol, the polarity of the medium could not be ascribed to a major rate-influencing parameter. Further, the reaction of **8** with **9** was slower in methanol than in 2,2,4-trimethylpentane, as the hydrogen-bonded association of both these species was disrupted (Scheme 2). These observations led Breslow to suggest that

hydrophobic effects⁶⁰ are the principal forces operating in water, which enhance the reaction rates by several orders.²⁰ The hydrophobic effect is the tendency of nonpolar molecules and molecular segments in water solution to avoid contact with water. This can be achieved if such molecules either escape to a separate phase or cluster in order to decrease the hydrocarbon–water interfacial area. The hydrophobic clustering or aggregation is driven by either entropy or enthalpy, i.e., “an improved enthalpy of solvation of a substrate can come at the expense of solvent restriction and entropy loss”.²⁰ Thus, to decrease the contact with water, the diene and dienophile tend to aggregate in an aqueous system. This process of aggregation of diene and dienophile in water is known as hydrophobic packing, which has been shown to give rise to large rate accelerations in water. The support to the hydrophobic packing was also provided by carrying out the reactions of **5** with **6** and with **11** in β -cyclodextrin.^{11a} According to these experiments and the concept of hydrophobicity, **5** and dienophile should fit into the cavity of β -cyclodextrin resulting in rate enhancement. However, as the cavity of β -cyclodextrin is smaller than the size of anthracene-9-carbinol, the enhancement of reaction rates of **8** with **9** (Scheme 2) in β -cyclodextrin cannot be explained.^{11a} It is shown that antihydrophobic cosolvents can slow the reactions in water of species with hydrophobic surfaces. This rate retardation or acceleration will depend on whether the transition states are more or less hydrophobic than the reactants. These findings, supported by quantum mechanical calculations, render the hydrophobic effect as a mechanistic tool for understanding the reaction profiles of different reactions, including cycloadditions.⁶¹

2. Enforced Hydrophobic Hydration and Hydrogen-Bonding Effects

The ‘enforced hydrophobic hydration’ is another explanation proposed to describe the rate acceleration in water and its mixtures with different alcohols.⁶² In aqueous medium the destabilization of the initial state is considered as a rate-promoting parameter. The decrease of hydrophobic surface area with the progress of reaction leads to the stabilization of the transition state relative to the initial state. The term ‘enforced’ is employed to stress that the hydrophobic interactions are operative as they are an integral part of the activation process. Engberts and co-workers⁶² introduced the concept of enforced hydrophobic hydration. In this process the hydrophobicity of diene and dienophile is decreased during the process of activation. Diene and dienophile do not aggregate spontaneously under the reaction conditions. This observation is expressed by the term ‘enforced’. To account for the large effect of water on Diels–Alder reactions, the enforced hydrophobic binding process is more favorable in water than in conventional organic solvents. On the basis of the Gibbs energy associated with the direct diene–dienophile pair potential and the rearrangement of water molecules accompanying the enforced hydrophobic hydration, it is possible to state that the reduction of the hydrophobic surface and hydrated volume during the

activation process leads to a large gain of the entropy and a large loss of the enthalpy of water molecules.¹⁸ The studies have shown that both an unfavorable enthalpy contribution and a larger favorable entropy contribution lead to the reduction of free energy of the activation process. The detailed molecular picture of the enforced hydrophobic hydration is described in several articles.^{18,60c,62a} Several papers have appeared to explain the rate enhancement of Diels–Alder reactions in aqueous solutions of alcohols by quantifying the components of the enforced hydrophobic hydration.⁶² Though a recent work by Breslow on the influence of cosolvents on the aqueous Diels–Alder reactions supports⁶³ the enforced hydrophobic hydration, its extension to salt solutions seems cumbersome. On the other hand, the concept of hydrophobic packing of diene and dienophile can be easily understood in the ionic solutions. This is due to the fact that the ion–ion, ion–dipole, dipole–dipole, and ion–hydrated water interactions cannot be easily accounted for in terms of the enforced hydrophobic hydration. Theoretical developments in this regard are awaited.

Jorgensen and co-workers combined the quantum and statistical mechanics to probe the role of water on the kinetics of Diels–Alder reactions.⁶⁴ They proposed that if enforced hydrophobic interactions were the only cause of acceleration, then the plots of Gibbs energies of transfer for both the activated complex and product should bear a resemblance. In view of the dissimilarity in these plots, it was suggested that one or more additional factors could be involved in enhancing the reaction rates in water. For the reactions of **5** with **6** and with **11** (Scheme 2), the use of a sophisticated computational technique estimated the optimal interaction energies to be 1.5–2 kcal mol⁻¹ more favorable for hydrogen bonding to the oxygen or nitrogen in the transition states. The computational results suggested that hydrogen-bonding effects are very significant in addition to the hydrophobic component. This work on the role of hydrogen bonding on the reaction rates has also been confirmed by experimental kinetic data.⁶⁵ For the reaction of **5** with **6** in water and trifluoroethanol, a comparison between the Gibbs free energies of the initial states and the activated complex has shown that hydrogen bonding stabilizes the activated complex more than the initial state.

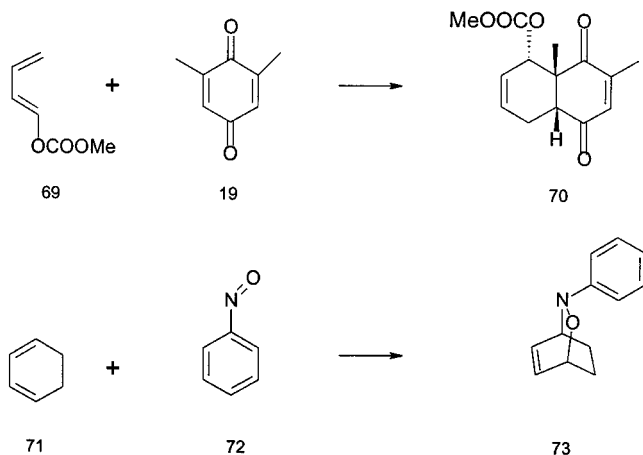
A combined effect of both enforced hydrophobic interactions and the hydrogen-bonding in stabilizing the transition state was attributed as origin of rate enhancement in several Diels–Alder reactions.⁶⁶

The hydrophobic and hydrogen-bonding effects have also been investigated using Monte Carlo simulations.⁶⁷ The results reveal that the hydrophobic effects play a profound role in the rate enhancement of aqueous reaction of **5** with **6**.

C. Water-Like Solvents

It is important to briefly mention the effect of ‘water-like’ solvents on the Diels–Alder reaction. The use of formamide in place of water for carrying out the reaction of **5** with **34** (Scheme 5) has offered comparable yields and N/X ratios.⁶⁸ Since formamide

Scheme 10



has a very high relative permittivity, the enhanced kinetic profiles may be due to solvophobic interactions. Similarly, the reaction of 1-acetoxy-1,3-butadiene (**69**) with **19** (Scheme 10) is accelerated in the presence of ethylene glycol.⁶⁹ Breslow and Guo^{11d} also investigated the kinetic progress of Diels–Alder reactions in the above solvents but with different results. The reaction of 1,3-cyclohexadiene (**71**) with nitrosobenzene (**72**) (Scheme 10), for example, is faster in formamide and ethylene glycol but still slower in water. Furthermore, salts such as GnCl and urea that decrease reaction rates and stereoselectivities in water do not show any influence in formamide and ethylene glycol solutions.^{11d} It seems that the solubilities of diene and dienophile are not altered by the salts in these solvents.

D. Aqueous Ionic Solutions

The rate enhancement and decrease of Diels–Alder reactions by aqueous LiCl and GnCl , respectively, have been attributed to the changes in the hydrophobic effects caused by these salts.²⁰ The enhanced reaction rates in pure water are primarily the result of increased hydrophobic effects. Thus, the increase in the kinetic profiles of Diels–Alder reaction by LiCl implies that the hydrophobic effects are enhanced by this salt. The opposite is applicable to GnCl . Breslow and Connors⁷⁰ used attractive terminology for calling LiCl -type salts as prohydrophobic agents, while GnCl and LiClO_4 as were used as antihydrophobic ones. One can also call GnCl and LiClO_4 chaotropic and LiCl and NaCl antichaotropic agents.^{11d,71} The rate variations with the hydrophobic effects can be explained in terms of hydrophobic packing and a compact transition state.

Systematic information obtained on the concentration dependence of N/X ratios for the reaction of **5** with **34** (Scheme 5) in several prohydrophobic and antihydrophobic salts has been correlated with the hydrophobic effects via salting effects.²³ The increase and decrease in the kinetic profiles in the presence of a salt solution can be ascribed to the salting-out and -in phenomena.⁷² Thus, the increased hydrophobic effects are due to the salting-out phenomena. Accordingly, the solubilities of the reactants decrease in aqueous LiCl , NaCl , NaBr , etc., causing the

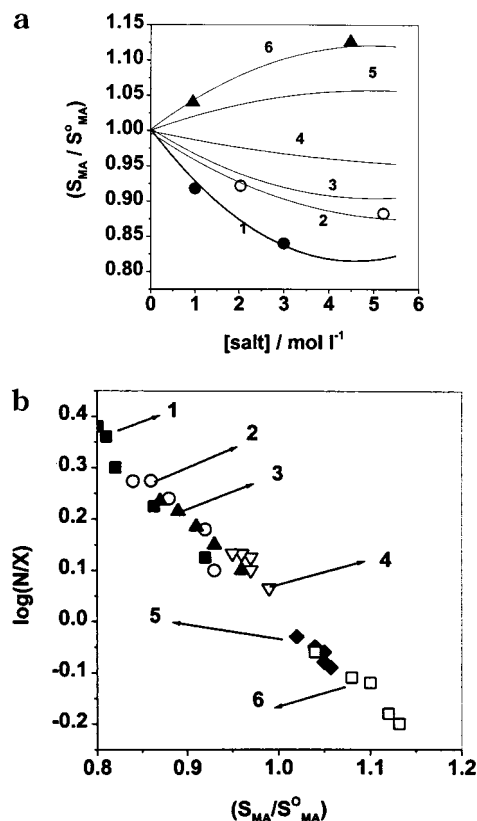


Figure 6. (a) Computed and experimental relative solubilities of methyl acrylate MA, (S_{MA}/S_{MA}^0) as a function of the concentration of salt for different aqueous salt solutions for the reaction of **5** with **34**: (1) LiCl , (2) NaCl , (3) NaBr , (4) CaCl_2 , (5) GnCl , (6) LiClO_4 . Data are from ref 23. (b) Variation of $\log(N/X)$ with respect to the relative solubilities of MA, (S_{MA}/S_{MA}^0) for the reaction of **5** with **34**. Symbols are as in Figure 2. Data are from ref 23).

salting-out of the components. Interactions of Gn^+ and ClO_4^- with water increase the solubilities of the reactants in solutions. Thus, the rates are related to the relative changes in the solubilities of the diene and dienophile in aqueous salt solutions. Figure 6a shows the relative solubilities of methyl acrylate, S_{MA}/S_{MA}^0 as a function of the salt concentration (S and S^0 are the solubilities of methyl acrylate in a salt solution and water, respectively) in different salts for the reaction of **5** with **34**.²³ The relative solubility of methyl acrylate in the salt solutions is less or more than one for the prohydrophobic and antihydrophobic salts, respectively. Figure 6b depicts the impact of S_{MA}/S_{MA}^0 on the $\log N/X$ values for the same reaction. The salting-out and -in coefficients, k_S , of these salts for this reaction have been computed by the scaled particle theory.⁷³ The k_S values for the reaction of **5** with **34** are 0.494, 0.397, 0.374, 0.203, -0.264 , and -0.469 for LiCl , NaCl , NaBr , CaCl_2 , GnCl , and LiClO_4 , respectively. The signs and magnitudes of these values indicate the power of the salts in altering the stereoselectivities in Diels–Alder reactions. The salting behavior and rates can also be understood in terms of the surface tension of the salt solutions.⁷¹ Breslow and Guo⁷¹ suggested that addition of a salt in Diels–Alder reaction leads to changes in the Gibbs energy of solution $\delta(\Delta G^\circ)_{\text{solution}}$ by

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

where $\delta(\Delta G^\circ)_{\text{cavitation}}$ and $\delta(\Delta G^\circ)_{\text{solvation}}$ are the changes in the Gibbs free energy of cavitation and solvation, respectively. The salting-in agents such as GnCl and LiClO_4 make the cavitation easier by breaking the organized structure of water. This effect if true should be reflected in the surface tension data of salt solutions. The changes in the surface tension of water in GnCl and LiClO_4 are positive and smaller than in LiCl and NaCl , which indicates that the formation of cavities in these solutions is not favored with increasing concentrations of GnCl and LiClO_4 , unlike in the case of tetrabutylammonium salts. Thus, in such salt solutions the rate-decreasing effect originates from the solute–solvent interactions with dominating $\delta(\Delta G^\circ)_{\text{solvation}}$ term.

The N/X values for the reaction correlate well with the surface tension data of aqueous ionic solutions. For the rate-enhancing salts, the surface tension of the solution increases steeply with its concentration, thus making the cavitation difficult. How these salts affect the Gibbs free energies of cavitation and solvation in a reaction are discussed both in principle⁷⁰ and in a quantitative way.²³ The approximate calculations of Gibbs free energies as altered by several salts agree well with the theory of the effect of salts on Diels–Alder reactions by Breslow and Guo.^{23,71} The effect of aqueous salt solutions can also be understood in terms of structure-maker (rate-enhancing) and -breaker (rate-decreasing) agents.

It is important to note that the conductance measurements on GnCl indicate ion pairing in the solution phase.⁷⁴ It is not yet known whether the ion pairs of GnCl affect the kinetics of Diels–Alder reaction. The effect of GnCl on the stability of proteins was first studied by von Hippel and co-workers.⁷⁵ It is not possible to state anything quantitative about the role of GnCl in Diels–Alder reaction except its salting-in nature.

In an effort to explain the rate accelerations of Diels–Alder reactions, it was suggested that the internal pressure⁷⁶ of the ionic solutions presses the diene and dienophile (hydrophobic packing) together to realize the reaction.²⁰ The rate data²¹ for the reaction of **8** with **9** (Scheme 2) in 2 M solutions of several sodium and guanidinium salts are observed to be linear with internal pressures of salt solutions.⁷⁷ The Diels–Alder reactions are accompanied by negative activation volumes, indicating a compact transition state.⁷⁸ Salts, like LiCl , NaCl , NaBr , etc., increase the internal pressure of water. The increased internal pressure in conjunction with the negative activation volume gives rise to the rate acceleration. The rate-declining effect by the guanidinium salts can be explained in terms of reduced internal pressures and the negative activation volumes of Diels–Alder reactions.

An attempt was also made to divide the salting-out and -in zones on the basis of internal pressure.²³ In the case of the rate-enhancing salts, like LiCl , NaCl , etc., the phenomena of electrostriction caused by the volume contraction on dissolving an electrolyte in water assumes significance.⁷⁹ The electrostriction leads to a decrease in the solubilities of hydrocarbons, thus causing the salting-out and subsequently the

rate enhancement. The antielectrostriction effect in GnCl or LiClO_4 gives rise to exactly the opposite effect. There are, however, opposing reports on the role of internal pressure which will be discussed in a later part of this review.

E. Ionic Solutions in Nonaqueous Solvents

Why does LPDE as a solvent medium accelerate the Diels–Alder reaction? Before attempting to address this issue, it should be appropriate to briefly consider the properties of these solutions.

1. Physicochemical Properties of LPDE

These properties are as follows: (a) LiClO_4 is highly soluble in diethyl ether,⁸⁰ i.e., 53.21% by weight corresponding to a mole fraction of LiClO_4 as 0.44 or 6.06 M; (b) the density of LPDE at 53.21% by weight of LiClO_4 is about 70% higher as compared to that of pure diethyl ether; (c) the viscosity of LPDE solution is very high especially at higher concentrations (for instance, the viscosity of a saturated solution of LPDE is about 800% higher than that of pure ether at room temperature); (d) the vapor pressure of LPDE solution at higher concentrations is lowered by about 30% from that of pure diethyl ether; (e) the molar conductance of LiClO_4 in diethyl ether increases by a factor of several hundred with increasing concentration, while a decrease is noted in its solution with water.

2. Formation of Clathrates and Their Role

First an analysis of the implications of the above solution properties is in order. The analysis of vapor pressure data shows that the activity of diethyl ether in LiClO_4 first increases and then decreases after reaching maxima, indicating the complexes are made up of LiClO_4 and diethyl ether. This is supported by steep rise in both viscosity and molar conductance values.⁸¹ The increased conductance suggests the presence of charged complexes of LiClO_4 –diethyl ether with either excessive Li^+ or ClO_4^- ions. The experimental data show the presence of dietherate, $\text{Li}^+(\text{OEt}_2)_2\text{ClO}_4^-$ below 4.25 M, while a mixture of both the dietherate and monoetherate $\text{Li}^+(\text{OEt}_2)\text{ClO}_4^-$ exists above 4.25 M. Both of these complexes including ion pairs are present simultaneously, and their concentrations vary with the concentration of LiClO_4 in ether. Thus, there is clearly a rapid interchange of ions in the various structures as well as with those in the solvent. Several species in the mixture remain in equilibrium with each other.^{28a} In solution, the electric current is not likely to be transported only by the movement of whole complexes. In fact, the contribution to the conductance from this mechanism must decrease as the complexes get bulkier and solution more viscous. The easier transport of current at high concentrations can be explained by the transport of single ions within the framework of the complexes, consistent with the theory of proton conductance.⁸² According to Ekelin and Sillen,⁸¹ the behavior of Li^+ , ClO_4^- , and their aggregates in diethyl ether can be understood by dividing the solution into three regions. In very dilute solutions, ions are

separated from each other or occasionally in pairs. Thus, Li^+ may have as many as four ether molecules as closest neighbors completely surrounding it. In the moderately concentrated solutions, ions form separate complexes of different sizes. In highly concentrated solutions, the complexes as aggregates come closer together, almost to a coherent lattice. In such conditions ether molecules can hardly suffice for shielding the ions from each other.

It is also suggested that LPDE solution becomes a molten salt below 4.25 M as all the ether molecules are complexed with lithium perchlorate acting as solvent and ether as solute. The molten salts with organic components having very low dielectric constants have been reported in the literature.⁸³

To ascertain the presence of complexes in LPDE, the solubility temperature, heats of solution, and molar dielectric increments have also been studied.^{28a} Though the solubility–temperature diagrams of LPDE do not indicate the presence of any etherates, the heats of solution data favor the presence of both mono- and dietherate. The linear variation of dielectric constant values with the concentration of LiClO_4 up to 0.5 M has also been attributed to the presence of etherates.⁸⁴

Strong support in favor of mono- and dietherates comes from NMR data of LPDE solutions.^{28a} The NMR spectra show a rapidly exchanging ether solvation sphere around the lithium ion. The shift downfield of the methylene and methyl protons of diethyl ether in LPDE mixtures relative to pure ether can be accounted for by an average ether to LiClO_4 ratio of 2:1 below 4.25 M and both 2:1 and 1:1 above 4.25 M LiClO_4 .

The formation of ion pairs and higher aggregates in LPDE is also predicted by the Bjerrum theory of ion-pair formation.⁸⁵ According to this theory, ion pairs and higher species should be available above 2.8×10^{-3} M of LiClO_4 .

The association of LiClO_4 in diethyl ether has also been investigated by studying the refractive indices and dielectric measurements, which indicate the presence of dimers.⁸⁶ These species have further been confirmed by IR and Raman spectroscopic investigations of LPDE solutions.⁸⁷

Pocker and his group^{27,28} successfully demonstrated that the electrostatic catalytic properties due to LiClO_4 clatherates can lead to stabilization of polar transition states by large Coulombic fields in several reactions.

3. Polarity Effects

The polarity effects of the LPDE solutions were investigated several years ago.²⁹ The N/X ratios of the reaction of **5** with **34** increased with the increase of the LPDE concentration. An increase in the polarity by about 20 E_T units was obtained in the concentrated LPDE solutions. The rate enhancement, according to this concept, was attributed to the stabilization of polar transition states. The rate data for some Diels–Alder reactions, however, cannot be correlated successfully with the polarity of solutions.⁸⁸

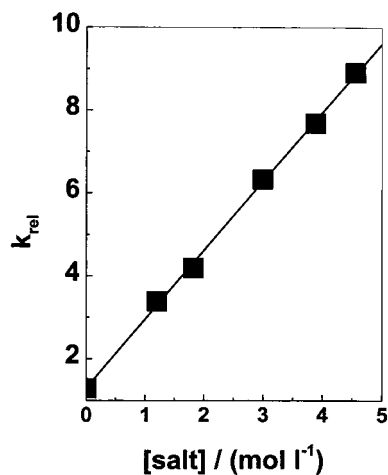


Figure 7. $\log k_{\text{rel}}$ against the concentration of LiClO_4 in diethyl ether for the reaction of **74** and **11**. Data are from ref 89.

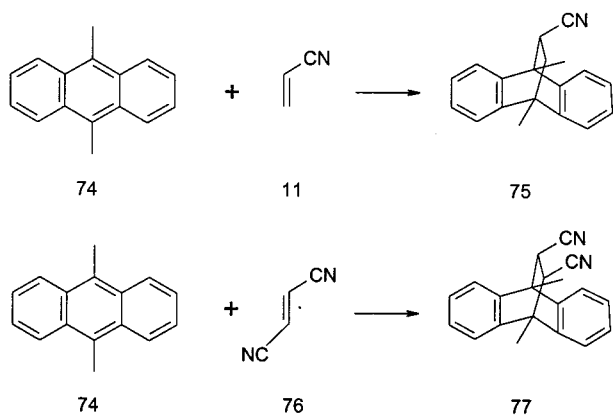
4. Lewis-Acid Catalysis

Though the stabilization of the polarized transition state of a Diels–Alder reaction in the concentrated solutions of LiClO_4 in organic solvents cannot be disregarded, it cannot explain the dramatic rate accelerations of Diels–Alder reactions in LPDE type of medium. An explanation was, therefore, proposed in which the huge rate accelerations were attributed to the Lewis-acid catalysis of Li^+ in solution.

Forman and Dailey⁸⁹ were the first to put forward evidence that the unusual effect of LPDE in accelerating Diels–Alder reactions as reported by Grieco, Nunes, and Gaul³⁰ originated by the Lewis-acid catalysis due to the presence of lithium ion. To support their findings, they measured the second-order rate constants for the reaction of 9,10-dimethylanthracene (**74**) with **11** (Scheme 11) in the presence of different concentrations of LPDE. In Figure 7 is shown the concentration dependence of k_{rel} , which is linear indicating the first-order dependence on LiClO_4 . According to the authors, the Diels–Alder reactions being sensitive to Lewis-acid catalysis should accelerate with the increase in the concentration of lithium cation. The reactions of fumaronitrile (**75**) with **74** (Scheme 11) and **49** with **50** (Scheme 6) were also studied in LPDE. In these reactions, two sites for lithium ion complexation are possible, as both fumaronitrile and dimethyl acetylenedicarboxylate contain two activating groups. Both these reactions showed linear dependence of the second-order rate constant on the concentration of LPDE. No enhancement in the reaction rates was observed in the presence of perchlorate salt lacking Lewis acidity.

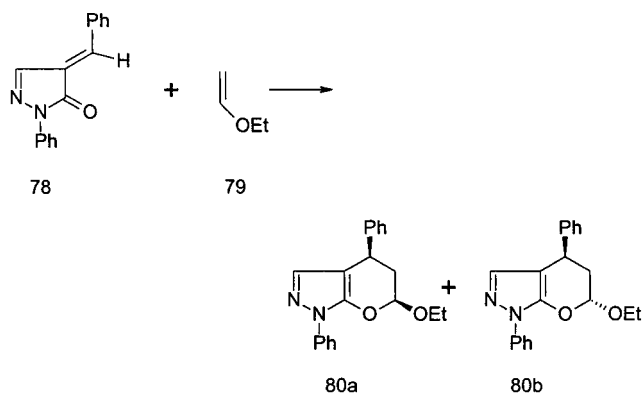
The school of Righetti⁸⁸ was the next to put forward evidence in favor of Lewis-acid catalysis by LPDE solvent in Diels–Alder reactions. In this regard, the hetero-Diels–Alder reaction of 1-phenyl-4-benzylidene-5-pyrazolone (**78**) with ethyl vinyl ether (**79**) (Scheme 12) was investigated in LPDE, LPAC, LiClO_4 –acetonitrile (LPAN), LiClO_4 –methanol (LPME), and LiClO_4 –2-propanol (LPIP) solutions. In the case of LPDE, an acceleration in the reaction rates was noted to be ~ 308 times the maximum concentration of 2.16 M of LiClO_4 . Very low concentrations of

Scheme 11



LiClO_4 in other solvents were used in the reaction owing to the salt solubilities in these solvents. In Figure 8 are shown the $\log k_{\text{rel}}$ as a function of $\log x$, where x is the molar fraction of LiClO_4 in solution. The linear plots shown in the figure confirm the Lewis-acid catalysis by lithium ion. The slopes of these plots indicate the catalytic power of lithium ion in different solvents. The catalytic power of lithium ion depends on the extent of solvating power of solvent and follows the order of diethyl ether > acetonitrile > acetone > methanol \approx 2-propanol.

Scheme 12



Further support of the catalysis by lithium ion was obtained by carrying out the above reaction in the presence of [12]-crown-4, a crown ether specific for Li^+ complexation. The results showed that the effect was significant compared to blank experiments as the rate was lowered indicating the loss of catalytic activity by lithium ion. These studies concluded that those Diels–Alder reactions are strongly accelerated in the presence of the metal ion whose rates increase with the increasing electrophilic character of the solvent. Very mild acceleration in the rates is noted in the Diels–Alder reactions characterized by nucleophilic or nonspecific solvent effects. Similarly, the reaction of 54 with 4-bromonitrosobenzene (81) (Scheme 13) is poorly affected by these salt solutions. The solvent in these cases behaves as a nucleophile, the HOMO of which interacts and destabilizes the LUMO of 60 (Scheme 7). As pointed out by Casaschi et al.,⁴⁰ the HOMO of a cation is a highly stabilized MO insensitive to any reasonable interactions. No coordination between cation and 60 was observed

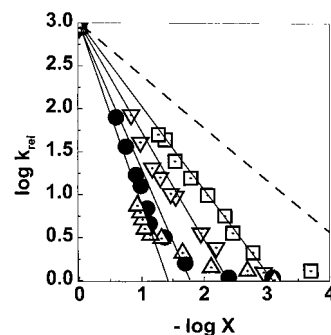
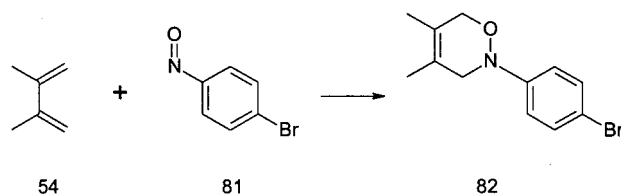


Figure 8. Plots of $\log k_{\text{rel}}$ against $(-\log x)$ for the reaction of 78 and 79 in solutions of LiClO_4 : (\square) LPAN, (∇) LPAC, (\bullet) LPME, (\triangle) LPIP. A dashed line without any symbols shows the results of LPDE. Data are from ref 88.

Scheme 13



during the ^{13}C NMR studies on the effect of perchlorate–acetone solutions on the carbonyl carbon atom of 60. Very small variations in the reaction rates in the case of 54 and 81 (Scheme 13) are possible due to nonspecific interactions. The absence of any specific interactions between cation and 81 indicates that these small changes in the reaction rates had originated from weak or nonbonding interactions present in the reaction mixtures.

In the reactions with electron demand described above, the cation acts as an electrophile and its LUMO interacts with the HOMO of 55. The LUMO of 55 is stabilized by electrostatic interactions resulting into a lower energy separation between the FMOs of 54 and 55. This leads to the enhancement of the reaction rates. The electrophilic character of these cations is supported by MO calculations.

Subsequent detailed studies on the use of LPDE, LPAC, LPME, LPAN, and LiClO_4 –DMSO (LPDM) on the reactions of 81 with 54 (Scheme 13), 54 with 55 (Scheme 7), and 78 with 79 (Scheme 12) have further confirmed the correlation between the reaction rates and catalytic activities in the LiClO_4 -containing solvent media.

The Lewis-acid catalysis of LPDE is applicable to those Diels–Alder reactions in which Li^+ coordinates with suitable functional groups in the substrate. Studies have also been conducted without and with LPDE under pressure to investigate the Lewis-acid catalysis.⁹⁰

An assessment of the Lewis acidity of LPDE has been made by comparing its performance with that of AlCl_3 or BF_3 . The N/X selectivities for the reaction of cyclopentadiene with methyl acrylate in 5 M LPDE are 8:1 as compared to those in AlCl_3 (99:1).⁹¹ Similarly, a ratio of 20:1 for N/X selectivities is obtained in AlCl_3 -catalyzed reaction of 5 with 65 (Scheme 8).⁹² LPDE, on the other hand, offers a ratio of 8:1 for the same reaction.

Several attempts have been made to describe the Lewis-acid scale on the basis of theoretical calculations. In principle, when a Lewis acid complexes with the electron-withdrawing group of a dienophile, it removes the electron density from the carbon–carbon double bond. This lowers the energy of the LUMO of the resultant complexes and thus favors the interaction with the HOMO of the diene. The energy of the transition state of a bimolecular reaction is therefore lowered. Considering the changes in MO calculations under the environment of Lewis acidity and their correlations with the NMR spectroscopy, empirical Lewis acidity scales were developed. For instance, an empirical Lewis acidity scale was proposed by studying the magnitude of the induced ^1H and ^{13}C chemical shifts of α,β -unsaturated aldehydes and ketones in methylene chloride.⁹³ The MNDO (modified neglect of diatomic overlap) calculations of 1:1 complexes derived from crotonaldehyde and a Lewis acid have also been employed in developing the Lewis-acidity scale.^{94,95}

The methodology of Childs has been employed to determine the Lewis acidity of the medium.⁹⁶ The results show that the induced shifts for BBr_3 , BF_3 , and AlCl_3 in CH_2Cl_2 are considerably larger than LPDE, confirming that LPDE is a weaker Lewis acid than BBr_3 , BF_3 , and AlCl_3 . The research group of Pagni and Kabalka showed that Li^+ is an intrinsically strong Lewis acid, a conclusion drawn based on the MO calculations and gas-phase experiments.⁹⁶ This strong Lewis-acid effect of Li^+ is considerably moderated in diethyl ether due to solvation effects and the perchlorate ion interactions. The catalytic activity of Li^+ depends on the counterion of its salt.⁹⁶ The moderate Lewis-acid effect of LPDE was further confirmed by polarimetric studies on camphor and IR studies on crotonaldehyde and benzonitrile. The weak binding of LiClO_4 to probe bases in diethyl ether is due to the fact that the Li^+ competitively binds to ether and the added base.⁹⁷ Earlier, the kinetic data of the reaction of **5** with **67** (Scheme 9) in LPDE also showed the modest catalytic effect.⁹⁸ The variations in dielectric constants of LPDE solutions⁸² do not conform to the steep rate enhancement observed in the above LPDE-mediated Diels–Alder reactions. Though the dielectric constant data of LPDE show a possibility of the salting-out phenomena, one should not consider the dielectric constant to be a sensitive probe to analyze the kinetics of Diels–Alder reactions.

5. Internal Pressure Effects

The suggestion of Breslow²⁰ and Grieco³⁰ on the possible role of the induced inner pressure or internal pressure of the ionic solutions led to the development of correlations between reaction profiles and internal pressure for several Diels–Alder reactions.⁹⁹ According to this development, the internal pressure generated by the LPDE type of solvent media presses the diene and dienophile in order to realize a reaction. Further, since LPDE is a substitute for ultrahigh pressure in the cantharidin synthesis,³⁰ it can be attributed to very high internal pressure generated by 5 M LPDE. It would seem that internal pressure

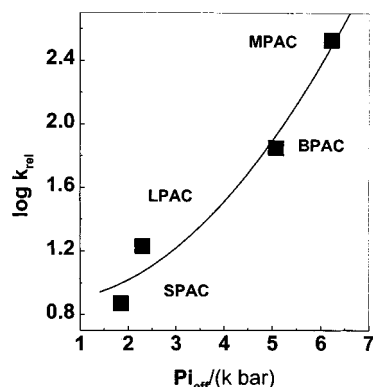


Figure 9. $\log k_{\text{rel}}$ as a function of $P_{i,\text{eff}}$ (difference of P_i of solution and acetone with P_i being internal pressure) induced by MPAC, BPAC, LPAC and SPAC for the reaction of **54** with **55**; data are from ref 40.

acts as an externally applied high pressure and influences the rates of Diels–Alder reactions in the same direction.

The internal pressures of LPDE, LPAC, and other solutions of LiClO_4 –ethyl acetate (LPEA) and LiClO_4 –tetrahydrofuran (LPTF)¹⁰⁰ are surprisingly very high.⁹⁹ For instance, a 5 M solution of LPDE, LPAC, and LPEA induces internal pressures between 16 and 20 kbar, a range used in the cantharidin synthesis.³⁴

The increased internal pressure at higher LiClO_4 concentrations in the above solution, in conjunction with the negative activation volume, has been considered as the rate-enhancing parameter. A direct correlation between the yields of cantharidin and internal pressures of LPDE solutions at different concentrations points out that the maximum yield is obtained at 5 M LPDE, a concentration at which a maximum internal pressure is induced.

The experimental kinetic data on several Diels–Alder reactions have been analyzed by the concept of internal pressure. Different magnitudes of rate accelerations of the reaction of **54** with **55** (Scheme 7) in acetone solutions of NaClO_4 , LiClO_4 , $\text{Ba}(\text{ClO}_4)_2$, and $\text{Mg}(\text{ClO}_4)_2$ at a given concentration, for example at 1.4 M (shown in Figure 9), have been interpreted on the basis of different internal pressures induced by these salt solutions. In general, the solvent medium with high internal pressure at a specified concentration and with lower activation volumes can enhance the reaction rate with greater magnitude than one with lower activation volume. The procedures to calculate the rate constants from the knowledge of fundamental quantities⁹⁹ and the activation volumes from the pressure dependence of the rate constants¹⁰¹ have been discussed.

As pointed out in a recent work,⁹⁷ the mode by which these solvent media function and enhance the kinetic profiles is a matter of controversy and uncertainty. No general agreement on the origin of forces responsible for the impressive rate acceleration of Diels–Alder reactions is reached among various workers. Forman and Dailey⁸⁹ observed that the reaction of 1,3-diphenylisobenzofuran and styrene was insensitive to LPDE. According to the concept of internal pressure and activation volume, the poor response of the solvent medium was due to nearly zero activation volume of the reaction, rendering even

the high internal pressure of 5 M LPDE ineffective.⁹⁹ There are, however, contrasting views on the role of internal pressure of these solvent media. It is suggested that if a reaction shows a mild rate enhancement, it could be explained on the basis of internal pressure.⁴⁰ Faita and Righetti¹⁰² studied the rate enhancements of several Diels–Alder reactions in different ionic solutions and concluded that both internal pressure and Li^+ catalysis contribute to speeding up the reactions. The observed rate accelerations are the result either of specific solute–cation interactions or the increased internal pressure of the media, depending on substrates, solvents, and metal cations. The rate acceleration for the reaction of (*E*)-1,3-pentadiene with methyl acrylate in LPDE has recently been credited to the Lewis-acid catalysis and not to the polarity and internal pressure.⁹⁷ These authors, however, have maintained that Li^+ , a strong Lewis acid in the gas phase, is moderated in diethyl ether due to complexation to the solvent and counterion. Can a moderate Lewis-acid catalysis explain dramatic and the enormous rate acceleration of the Diels–Alder reactions? By conducting some reactions in LPDE, it has been demonstrated that internal pressure cannot mimic the external pressure applied for realizing a Diels–Alder reaction.^{97,103} A methodology based on the combination of LPDE and high pressure has been suggested to be a more effective tool to catalyze a reaction.¹⁰³

F. Ionic Liquids

From the limited number of studies made in ionic melts to date, it is not possible to point out the possible cause of the enhancement in the kinetic profiles of Diels–Alder reactions in the presence of these solvent media. Tentative suggestions, however, include solvophobic associations and the role of internal pressure. More kinetic data are required in order to ascertain the origin of special effects arising from the use of ionic melts. The properties of ionic liquids that are said to render this class of compounds as effective media have been described in detail.⁹

V. Theoretical Developments

A large number of papers have been published on theoretical calculations to describe the mechanism of Diels–Alder reactions. The success of these calculations depends on the theoretical level and the solvation models employed in the computations. Both semiempirical and *ab initio* calculations have been performed to examine solvent effects on Diels–Alder reactions. Cativiela et al.^{1f} and Houk et al.⁵ have provided a good description of these methods. Herein, only significant developments after the publication of these two reviews have been summarized. The Monte Carlo simulations have been performed to obtain the gas-phase reaction paths and partial charges for the reaction and then the Gibbs free energies of solvation. The results of these studies provide a reasonable picture of hydrophobic effects in aqueous Diels–Alder reactions.⁶¹ These simulation studies, however, do not consider the nuclear and electronic relaxation induced by the solvent medium.

The molecular dynamics and reactive flux simulations of cyclopentadiene with methyl vinyl ketone in water were carried out to calculate the activation free energy and transmission coefficients using an empirical potential surface. The reaction barrier height in the gas phase predicted by this method is 16 kcal mol⁻¹ with a reduction by 2.2 kcal mol⁻¹ in water medium.¹⁰⁴

The initial computations based on the SCRF models on the investigation of polarity effects on the rate data were later improved by using AM1 and PM3 semiempirical models.^{105,107} The structural, kinetic, and thermodynamic parameters for Diels–Alder reaction were computed using Hartree–Fock (HF), post-HF (MP2), and density functional methods.¹⁰⁸ According to this study, the substitution of aminic hydrogen in thioamides by acceptor groups provides effective reagents even in the absence of Lewis-acid catalysis. The pre-reactive van der Waals complexes located on the potential surfaces have been employed to describe the N/X ratios in these reactions.¹⁰⁹ The dominant role of the electrostatic solvent effects was determined also by *ab initio* methods.¹¹⁰ The semiempirical calculations (AM1, PM3) have been used in the framework of SCRF in order to analyze the solvent effects on several cyclopentadiene-dienophile reactions.^{110d}

Efforts by Houk⁵ helped to delineate the controlling elements for the N/X values of Diels–Alder reactions. The transition states for Diels–Alder reaction of butadiene and cyclopentadiene with methyl acrylate coordinated with BH_3 have been located with *ab initio* calculations and the B-21G basis set. The computations were performed to determine the activation energies in a solvent with a dielectric constant of 9.08. The method has been found to be successful in both the uncatalyzed and catalyzed reactions.¹¹¹

The calculations based on density functional theory (DFT) appear to give a good description of the basic features of Diels–Alder reactions. The decisive role played by the Lewis-acid catalyst in reducing the reaction barrier and increasing the N/X values was quantified. It has been shown that the Lewis-acid coordination to the dienophile significantly changes the geometrical and electronic character of the transition structure.¹¹² The DFT has also been used to determine the influence of the reactant polarity on Diels–Alder reactions.¹¹³ In a very recent work, four transition-state structures of the reaction between butadiene and acrolein both uncatalyzed and catalyzed by BF_3 have been theoretically studied. In these studies, the electron correlation effects have been accounted for by means of DFT calculations.¹¹⁴ There are many other papers in this area, but in view of the scope of this review, it will not be possible to discuss them all.

VI. Miscellaneous

The Diels–Alder reactions have also been accelerated by the application of high pressure, ultrasound, common Lewis acids such as ZnCl_2 and TiCl_4 , and polymer-bound dienophiles, which are summarized by Pindur,⁵ who covered a vast amount of literature on Lewis acids up to 1992. Another review¹¹⁵ pub-

lished simultaneously focused on the synthetic and mechanistic aspects of catalyzed, asymmetric Diels–Alder reactions also covering the chiral aluminum catalysts, chiral titanium catalysts, chiral lanthanide complexes, transition complexes, and base-catalyzed reactions. These aspects are excluded from this article to remain within the scope of the review.

VII. Conclusion and Future Outlook

In summary, the special effects of salt solutions in altering the reaction rates and stereoselectivity products of Diels–Alder reactions have been reviewed. It is observed that a solvent medium like LPDE can drastically reduce the reaction time and enhance the yield of product. High-pressure conditions required for the synthesis of cantharidin can be obviated by using LPDE. Aqueous salt solutions can increase or decrease the reaction rates and stereoselectivity ratios depending on the nature of the salt and its concentration. Though several explanations are available to describe the effect of salt solutions on Diels–Alder reactions as discussed above, no single theory is adequate to account for the powerful role of these solutions in Diels–Alder reactions. Nevertheless, hydrophobic interactions and Lewis-acid catalysis appear to be useful concepts to understand the salt effect on Diels–Alder reactions. Systematic experimental kinetic data on the influence of different types of ions on the reaction rates and stereoselectivities are not available in the literature. Once these data on a variety of dienes and dienophiles become available, it will be possible to use the concepts of physical organic chemistry to understand the effects of these ions on the reaction kinetics. In view of a substrate being poorly soluble in a solvent, it is likely that the Diels–Alder reaction takes place at the interface of solvent. The experimental data should be collected to determine the energetics involved in such a reaction. There is no definite way to accurately quantify the hydrophobic effects from the experimental physical chemistry as applied to these organic reactions, though computer simulations have provided a combined role of hydrophobicity and hydrogen bonding. More kinetic data in this direction should be collected. No work is reported on the comparison of different theoretical methods as applied to the same reaction, thus preempting the selection of a method that will describe a majority of characteristics of the reactions. At a macro level, no empirical treatment is available to directly quantify the effect of salt solutions on Diels–Alder reactions. It is interesting to note that the rate accelerations of the Diels–Alder reaction in salt solution cannot be explained on the basis of a single concept or theory. Very recently, ionic liquids were also shown to be effective solvent media in Diels–Alder reactions. However, it is hoped that the use of these salt solutions will help us in accelerating the sluggish reactions and minimizing the high-pressure Diels–Alder reactions.

VIII. Acknowledgments

Several years ago, on a suggestion from my wife Vaijayanti Kumar, a synthetic organic chemist at

NCL, I took up the study of the physical-organic aspects of Diels–Alder reactions. I am grateful to her for this very fruitful suggestion. I express my sincere gratitude to Professor P. T. Manoharan, Indian Institute of Technology, Madras, for advising me to widen my area of research and for being a constant source of inspiration. Mr. Sanjay S. Pawar of this laboratory has not only carried out several reactions, but has also freely given his unstinted cooperation in assembling the required literature to write this review. I thank Mr. Pawar for his sincerity and dedication. A grant-in-aid extended by the Department of Science and Technology, New Delhi, for carrying out research in this area is gratefully acknowledged. I also appreciate fruitful comments from the reviewers, which helped me in finalizing this manuscript.

IX. References

- (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990 and references therein. (b) Desimoni, G.; Tacconi, G.; Barco, A.; Polloni, G. P. *National Product Synthesis through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society: Washington, D.C., 1983 and references therein. Fringuelli, F.; Tatichi, A. *Dienes in the Diels–Alder Reactions*; Wiley: New York, 1990. (d) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. (e) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (f) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, 209. (g) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (h) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (i) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (j) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (k) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie: Glasgow, 1998. (l) Li, C.-J.; Chan, T.-H. *Organic Synthesis in Aqueous Media*; John Wiley: New York, 1977. (m) Laschat, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 289. (n) Stipanovic, R. D. *Environ. Sci. Res.* **1992**, *44*, 319. (o) Ressig, H.-U. In *Organic Synthesis Highlights*; VCH: Weinheim, 1991; p 71.
- Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, 460, 98.
- Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970. Also see: *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
- Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
- Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Intl. Ed. Engl.* **1992**, *31*, 682.
- Burrage, M. E.; Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1325.
- (a) Konovalov, A. I.; Breus, J. P.; Sharagin, I. A.; Kieslev, V. D. *J. Org. Chem., USSR* **1979**, *15*, 315; *Chem. Abstr.* **1979**, *90*, 203134 (b) Brown, P.; Cookson, R. C. *Tetrahedron* **1965**, *21*, 1977.
- For a recent review on this topic; see: ref 1f.
- Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
- (a) Diels, O.; Alder, K. *Ann. Chem.* **1931**, *390*, 243. (b) Eggelte, T. A.; de Konig, H.; Huisman, H. O. *Tetrahedron* **1973**, *29*, 2491. (c) Berson, J. A.; Swodler, R. *J. Am. Chem. Soc.* **1953**, *75*, 1721.
- (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901. (c) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239. (d) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5612. Breslow, R. *Water as Solvent for Chemical Reactions*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998.
- (a) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. (b) Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.
- Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897.
- (a) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137. (b) Grieco, P. A.; Larsen, S.; Fobare, W. F. *Tetrahedron* **1986**, *27*, 1975.
- (a) Grieco, P. A.; Yoshida, K.; He, Z. *Tetrahedron Lett.* **1984**, *25*, 5715. (b) Yoshida, K.; Grieco, P. A. *Chem. Lett.* **1985**, 155. (c) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (d) Drewes, S. E.; Grieco, P. A.; Huffman, J. C. *J. Org. Chem.* **1985**, *50*, 1309. (e) Grieco, P. A.; Garner, P.; Yoshida, K.; Huffman, J. C. *Tetrahedron Lett.* **1983**, *24*, 3807. Yoshida, K.; Grieco, P. A. *J. Org. Chem.* **1984**, *49*, 5257. (g) Grieco, P. A.; Brades, E. B.; Garner, P. *J. Chem. Soc., Chem. Commun.* **1988**, 500.

- (16) (a) Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 274. (b) Waldmann, H. *Liebigs Ann. Chem.* **1989**, 231.
- (17) (a) Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.
- (18) Garner, P. P. *Diels–Alder Reactions in Aqueous Media*, Chapter 1, in ref 17b.
- (19) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340.
- (20) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. The experimental data and the conclusions drawn refer to the work reported up to 1990.
- (21) Rizzo, C. J. *J. Org. Chem.* **1992**, *57*, 6382.
- (22) (a) Holfmeister, F. *Ach. Exptl. Pathol. Pharmacol.* **1888**, *24*, 247. (b) For details, see: Collins, K. D.; Washabaugh, M. W. *Quart. Rev. Biophys.* **1985**, *18*, 323.
- (23) Pawar, S. S.; Phalgune, U.; Kumar, A. *J. Org. Chem.* **1999**, *64*, 7055.
- (24) Kumar, A.; Phalgune, U.; Pawar, S. S. *J. Phys. Org. Chem.* **2000**, *13*, 555.
- (25) Breslow, R. In *Structure and Reactivity in Aqueous Solutions*; Cramer, C. J., Truhlar, D. G., Eds.; ACS Symposium Series 568; American Chemical Society: Washington, D.C., 1994.
- (26) (a) Weinstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, *81*, 5511. (b) Weinstein, S.; Friedrich, E. C.; Smith, S. *J. Am. Chem. Soc.* **1964**, *86*, 305.
- (27) Pocker, Y.; Ellsworth, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 2276.
- (28) (a) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 2075. (b) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 4033. (c) Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 2905. (d) Pocker, Y.; Ellsworth, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 2284. (e) Pocker, Y.; Ciula, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2904. (f) Pocker, Y.; Ciula, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4728.
- (29) Braun, R.; Sauer, J. *Chem. Ber.* **1986**, *119*, 1269.
- (30) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.
- (31) Rivera, M.; Lany-Schalkens, H.; Sainte, F.; Mbiya, K.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 4573.
- (32) Srivastava, S.; Marchand, A. P.; Vidyasagar, V.; Flippen-Anderson, J. L.; Gilard, R.; George, C.; Zachwieja, Z.; Le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 247.
- (33) (a) Grieco, P. A. *Organic Chemistry in Lithium Perchlorate/Diethyl ether*. In *Organic Chemistry, Its language; Its State of Art*; Kisakuerek, M. V., Ed.; Verlag Helvetica Chim. Acta: Basel, 1993; p 133. (b) Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1306.
- (34) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893.
- (35) Dauben, W. G.; Krabenhof, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992.
- (36) (a) Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2662. (b) Grieco, P. A.; Moher, E. D. *Tetrahedron Lett.* **1993**, *34*, 5567. (c) General salt effects in organic reactions are documented in Loupy, A.; Tchoubar, B. *Salt Effects in Organic and Organometallic Chemistry*; VCH: Weinheim, 1992.
- (37) Grieco, P. A.; Collins, J. L.; Handy, S. T. *Syn Lett.* **1995**, 1155.
- (38) Henry, K. J.; Grieco, P. A. *J. Org. Chem.* **1992**, *57*, 1817.
- (39) Handy, S. T.; Grieco, P. A.; Mineur, C.; Ghosez, L. *Synlett* **1995**, 565.
- (40) Casashi, A.; Desimomi, G.; Faita, G.; Ivernizzi, A. G.; Lanati, S.; Righetti, P. P. *J. Am. Chem. Soc.* **1993**, *115*, 8002.
- (41) Wong, M. K.; McKinney, W. J.; Popov, A. I. *J. Phys. Chem.* **1971**, *75*, 56.
- (42) (a) Desimomi, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1993**, *49*, 6025. (b) Desimomi, G.; Giuseppe, I.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1996**, *52*, 12009. (c) Desimomi, G.; Faita, G.; Righetti, P. P.; Vietti, F. *Heterocycles* **1995**, *40*, 817.
- (43) Fukuzumi, S.; Okamoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1160.
- (44) Ayerbe, M.; Cossio, F. *Tetrahedron Lett.* **1995**, *36*, 4447.
- (45) Chiba, K.; Tada, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2485.
- (46) Reetz, M. T.; Gansaeur, A. *Tetrahedron* **1993**, *49*, 6025.
- (47) (a) Shtyrilin, Y. G.; Murzin, D. G.; Luzanova, N. A.; Iskhakova, G. G.; Kiselev, V. D.; Konovalov, A. I. *Tetrahedron* **1998**, *54*, 2631. (b) Shtyrilin, Y. G.; Kiselev, V. D.; Murzin, D. G.; Sadyukova, D. N.; Konovalov, I. *Zh. Org. Khim.* (Russian) **1993**, *29*, 1713; *Chem. Abstr.* **1993**, *121*, 178915. (c) Kiselev, V. D.; Shtyrilin, Yu. G.; Murzin, D. G.; Konovalov, A. I. *Dokl. Akad. Nauk* (Russian) **1995**, *64*, 345; *Chem. Abstr.* **1995**, *127*, 65370. (d) Shtyrilin, Yu. G.; Fedorenko, V. Yu.; Iskhakova, G. G.; Kiselev, V. D.; Konovalov, A. I. *Zh. Obshch. Khim.* (Russian) **1996**, *66*, 499; *Chem. Abstr.* **1996**, *126*, 7553.
- (48) (a) Freemantle, M. *Chem. Eng. News* **1998** (March 30), 32. (b) Olivier-Bourbigou, H. In *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998. (c) Chauvin, Y.; Olivier-Bourbigou, H. *CHEM TECH* **1995**, *25*, 26. (d) Seddon, K. R. *Kinet. Catal.* **1996**, *37*, 693. Carlin, R. T.; Wilkes, J. S. In *Advances in Non-Aqueous Chemistry*; Mamantov, G., Popov, A., Eds.; VCH Publishing: New York, 1994.
- (49) (a) Walden, P. *Bull. Acad. Imper. Sci. (St. Petersburg)* **1914**, 1800. (b) Sugden, S.; Wilkins, H. *J. Chem. Soc.* **1929**, 1291.
- (50) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785.
- (51) Samii, A. A.; de Savignac, A.; Rico, I.; Lattes, A. *Tetrahedron* **1985**, *41*, 3683.
- (52) (a) Evans, D. F.; Chen, S.-H.; Schriever, G. W.; Arnett, E. M. *J. Am. Chem. Soc.* **1981**, *103*, 481. (b) Allen, M.; Evans, D. F.; Lumry, R. *J. Solution Chem.* **1985**, *14*, 549. (c) Evans, D. F.; Yamauchi, A.; Roman, R.; Casassa, E. Z. *J. Colloid Interface Sci.* **1982**, *88*, 89. (d) Evans, D. F.; Yamauchi, A.; Wei, G. J.; Bloomfield, V. A. *J. Phys. Chem.* **1983**, *87*, 3537.
- (53) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097.
- (54) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.
- (55) Lee, C. W. *Tetrahedron Lett.* **1999**, *40*, 2461.
- (56) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23.
- (57) Desimoni, G.; Faita, G.; Righetti, P. P.; Tornaletti, N.; Visigalli, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 437.
- (58) (a) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1787. (b) Schneider, H.-J.; Sangwan, N. K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 896. (c) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223.
- (59) Kamlet, M. J.; Abboud, J.-L.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877. For its application, see: ref 1f.
- (60) For definition and discussion on hydrophobicity, see: (a) Tanford, C. *The Hydrophobic Effect*, 2nd ed.; Wiley: New York, 1980. (b) Ben-Naim, A. *Hydrophobic Interactions*; Plenum Press: New York, 1980. For an informative review, see: (c) Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545.
- (61) Breslow, R.; Groves, K.; Mayer, M. U. *Pure Appl. Chem.* **1998**, *70*, 1933.
- (62) For example, see: (a) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241. (b) Blokzijl, W.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1992**, *114*, 5440.
- (63) Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923.
- (64) (a) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430. (b) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966. (c) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, *59*, 803. (d) Jorgensen, W. L.; Blake, J. F.; Lim, D.; Severance, D. L. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1727.
- (65) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381 and references therein.
- (66) (a) Otto, S.; Blokzijl, W.; Engberts, J. B. F. N. *J. Org. Chem.* **1994**, *59*, 5372. (b) Blokzijl, W.; Engberts, J. B. F. N. *ACS Symp. Ser.* **1994**, *568*, 303. (c) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823. (d) Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1997**, *62*, 2039. (e) Mersbergen, D.; van Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801. (f) Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989.
- (67) Furlani, T. R.; Gao, J. *J. Org. Chem.* **1996**, *61*, 5492.
- (68) Lattes, A.; Ricco, I.; de Savignac, A.; Samii, A.-Z. A. *Tetrahedron* **1987**, *43*, 1725.
- (69) Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3745.
- (70) (a) Breslow, R.; Connors, R. V. *J. Am. Chem. Soc.* **1995**, *117*, 6601. (b) Breslow, R.; Zu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923.
- (71) Breslow, R.; Guo, T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 167.
- (72) (a) Long, F. A.; McDevitt, W. F. *Chem. Rev.* **1952**, *52*, 119. (b) McDevitt, W. F.; Long, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 1773. (c) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975.
- (73) (a) Though the reactant solubilities in the salt solution can be estimated by several other methods, the use of the scaled particle theory enables separate calculations of the cavitation and solvation. For details, see ref 23. (b) Reiss, H.; Frisch, H. L.; Lebowitz, J. L. *J. Chem. Phys.* **1959**, *31*, 369. (c) Masterton, W. L.; Lee, T. P. *J. Phys. Chem.* **1970**, *74*, 1776. (d) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717 and references therein. (e) For application to mixture containing components of different sizes, see: Kumar, A. *J. Am. Chem. Soc.* **1993**, *115*, 9243.
- (74) Alin, B.; Evers, L.; Sillen, L. G. *Acta Chem. Scand.* **1952**, *6*, 759.
- (75) (a) von Hippel, P. H.; Wong, K.-Y. *Science* **1964**, *145*, 577. (b) von Hippel, P. H.; Schleich, T. *Acc. Chem. Res.* **1969**, *9*, 257. (c) Castellino, F. J.; Barker, R. *Biochemistry* **1968**, *7*, 3439. (d) Makhatadze, G. I. *J. Phys. Chem. B* **1999**, *103*, 4781.
- (76) For definition of internal pressure, see (a) Dack, M. R. *J. Chem. Soc. Rev.* **1975**, *4*, 211 and references therein. (b) Support to internal pressure is provided by equation of state, see: Ouellette, R. J.; Williams, S. H. *J. Am. Chem. Soc.* **1971**, *93*, 466. (c) Hildebrand, J. H.; Scott, R. L. *Regular Solution*; Prentice-Hall: Englewood Cliffs, 1962. (d) Kumar, A. *J. Phys. Org. Chem.* **1996**, *9*, 287. An application to polar and nonpolar solvents in Diels–Alder reactions is given also for the use of transition state theory in this context.
- (77) Kumar, A. *J. Org. Chem.* **1994**, *59*, 230.

- (78) (a) Drljaca, A.; Hubbard, C. D.; van Eldik, R.; Asono, T.; Basilevsky, M. V.; Lenoble, W. J. *Chem. Rev.* **1998**, *98*, 2167. (b) van Eldik, R.; Asono, T.; Le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549. (c) Le Noble, W. J. *Progress in Physical Chemistry*; Interscience: New York, 1967, vol. 5, p 207.
- (79) (a) Kumar, A. *Biochemistry* **1995**, *34*, 12921. (b) Millero, F. J. In *Water and Aqueous Solutions*; Horne, R. A.; Ed.; Wiley-Interscience: New York, 1972; Chapter 13.
- (80) Willard, H. H.; Smith, G. F. *J. Am. Chem. Soc.* **1923**, *45*, 286.
- (81) Ekelin, K.; Sillen, L. G. *Acta Chem. Scand.* **1953**, *7*, 987.
- (82) Bernel, J. D.; Fowler, C. A. *J. Chem. Phys.* **1933**, *1*, 542.
- (83) (a) Kraus, C. A.; Strong, L. E. *J. Am. Chem. Soc.* **1950**, *72*, 166. (b) Pitzer, K. S. *J. Am. Chem. Soc.* **1980**, *102*, 2902. (c) Also see: ref 71e.
- (84) Markowitz, M. M.; Hawley, W. N.; Boryta, D. A.; Harris, R. F. *J. Chem. Eng. Data* **1961**, *6*, 325.
- (85) Davies, C. W. *Ion Association*; Butterworths: London, 1962.
- (86) Menard, D.; Chabanel, M. *J. Phys. Chem.* **1975**, *79*, 1081.
- (87) Chabanel, M.; Legoff, D.; Touaj, K. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 4199.
- (88) Desimoni, G.; Faita, G.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1991**, *47*, 8399.
- (89) Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 2761.
- (90) (a) Papadopoulos, M.; Jenner, G. *Tetrahedron* **1982**, *23*, 317. (b) Papadopoulos, M.; Jenner, G. *New J. Chem.* **1983**, *7*, 463. (c) Jenner, G.; Papadopoulos, M.; Le Noble, W. J. *New J. Chem.* **1983**, *7*, 687. (d) Jenner, G.; Papadopoulos, M.; Jurczak, J.; Kozluk, T. *Tetrahedron Lett.* **1984**, *25*, 5744. (e) Jenner, G. *High-Pressure Res.* **1995**, *13*, 1321. (f) Rimmelin, P.; Jenner, G. *Tetrahedron* **1997**, *53*, 4617.
- (91) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 731.
- (92) Bains, S.; Pagni, R. N.; Kabalka, G. *Tetrahedron Lett.* **1991**, *32*, 5663.
- (93) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.
- (94) Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750.
- (95) Laszlo, P.; Teston, M. *Tetrahedron Lett.* **1991**, 3837.
- (96) Pagni, R. M.; Kabalka, G. W.; Bains, S.; Plesco, M.; Wilson, J.; Bartmess, J. *J. Org. Chem.* **1993**, *58*, 3130.
- (97) Springer, G.; Elam, C.; Edwards, A.; Bowe, C.; Boyles, D.; Bartmess, J.; Chandler, M.; West, K.; Williams, J.; Green, J.; Pagni, R. M.; Kabalka, G. W. *J. Org. Chem.* **1999**, *64*, 2202.
- (98) Bains, S.; Pagni, R. M.; Kabalka, G. W.; Pala, C. *Tetrahedron Asymmetry* **1994**, *5*, 821.
- (99) (a) Kumar, A. *J. Org. Chem.* **1994**, *59*, 4612. (b) Kumar, A. *Pure Appl. Chem.* **1998**, *70*, 615.
- (100) The limited internal pressure in LPTF is due to the low solubility of LiClO₄ in tetrahydrofuran.
- (101) (a) Eckert, C. A. *Annu. Rev. Phys. Chem.* **1972**, *23*, 249. (b) Backman, C.-M.; Claesson, S.; Szwarc, M. *Trans. Faraday Soc.* **1970**, *66*, 3061. (c) McCabe, J. R.; Eckert, C. A. *Acc. Chem. Res.* **1974**, *7*, 251.
- (102) Faita, G.; Righetti, P. P. *Tetrahedron* **1995**, *51*, 9091.
- (103) Jenner, G.; Salem, R. B. *Tetrahedron* **1997**, *53*, 4617.
- (104) Pak, Y.; Voth, G. A. *J. Phys. Chem. A* **1999**, *103*, 925.
- (105) Pardo, L.; Branchadell, V.; Oliva, A.; Bertran, J. *J. mol. Struct. (THEOCHEM)* **1983**, *93*, 256.
- (106) Sustmann, R.; Sicking, W. *Tetrahedron* **1992**, *48*, 10293.
- (107) Hunt, I. R.; Rank, A.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 751.
- (108) Barone, V.; Arnaud, R.; Chavant, P. Y.; Vallee, Y. *J. Org. Chem.* **1996**, *61*, 5121.
- (109) Suarez, D.; Sordo, J. A. *J. Chem. Soc., Chem. Commun.* **1998**, 385.
- (110) (a) Suarez, D.; Assfeld, X.; Gonzalez, J.; Ruiz-Lopez, M. F.; Sordo, T. L.; Sordo, J. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1683. (b) Salvatella, L.; Mokrane, A.; Cartier, A.; Ruiz-Lopez, M. F. *Chem. Phys. Lett.* **1998**, *296*, 239. (c) Assfeld, X.; Ruiz-Lopez, M. F.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Chem. Soc., Chem. Commun.* **1995**, 1371. (d) Ruiz-Lopez, M. F.; Salvatella, L. *THEOCHEM* **1995**, *331*, 37.
- (111) (a) de Pasual-Teresa, B.; Gonzalez, J.; Asensio, A.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 4347. (b) Gonzalez, J.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3031. (c) Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378. (d) For a review, see: Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H.-Y.; Wilsey, S.; Lee, J. *THEOCHEM* **1997**, *398*, 169.
- (112) Venturini, A.; Jogle, J.; Fustero, S.; Gonzalez, J. *J. Org. Chem.* **1997**, *62*, 3919.
- (113) (a) Domingo, L. R.; Arno, M.; Andres, J. *J. Org. Chem.* **1999**, *64*, 5867. (b) Sheng, Y. H.; Fang, D. C.; Wu, Y. D.; Fu, X. X.; Jiang, Y. S. *Theochem- J. Mol. Struct.* **1999**, *488*, 187.
- (114) Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415.
- (115) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

CR990410+

