To the Graduate Council:

I am submitting herewith a dissertation written by Satinder Pal Bains entitled "Diels-Alder Reactions and Synthetic Methodologies on Alumina and Study of $LiClO_4$/Ether System." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Richard M Pagni

Richard M. Pagni, Major Professor

We have read this dissertation
and recommend its acceptance:

Accepted for the Council:

CW Minkel

Associate Vice Chancellor and
Dean of the Graduate School

DIELS-ALDER REACTIONS AND SYNTHETIC METHODOLOGIES ON ALUMINA AND STUDY OF $LiClO_4$/ETHER SYSTEM

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Satinder Pal Bains

December, 1993

Dedication

This dissertation is dedicated to my parents, Dr. and Mrs. Bains, and to my brother, Tej Bains, for providing the patience and encouragement in life.

Acknowledgements

I would like to acknowledge Dr. R. M. Pagni and Dr. G. W. Kabalka for providing the guidance, patience and financial support during this study. Appreciation is also extended to The University of Tennessee for providing the teaching assistantship, and to my co-workers, especially Jim Green and Cathie Pala, for their help and friendship. Finally, I would like to acknowledge Debbie Willis for her friendship, encouragement, and for holding the fort in Knoxville, Tennessee while I was in Little Rock, Arkansas. Graduation in December 1993 would not have been possible without her help—"tuhaddi mehrbani".

Abstract

The Diels-Alder reactions of dimethyl maleate, dimethyl fumarate, (-)-dimenthyl fumarate and (-)-menthyl methyl fumarate with cyclopentadiene on δ-Aumina and the Diels-Alder reactions of dimethyl maleate, (-)-dimenthyl fumarate and (-)-menthyl methyl fumarate with cyclopentadiene in $LiClO_4$/diethyl ether were examined. The diastereoselectivity of the Diels-Alder reactions increases with increasingly activated alumina. The diastereoselectivity for the Diels-Alder reactions carried out in $LiClO_4$/diethyl ether appears to be moderated due to complexation of the Li^+ with ether and ClO_4^-.

The Tolbert-Ali test was applied to the results of the Diels-Alder reactions of (-)-dimenthyl fumarate and (-)-menthyl methyl fumarate with cyclopentadiene which were carried out on alumina and in $LiClO_4$/diethyl ether.

A chemical, spectroscopic, and theoretical investigation was carried out to determine the Lewis acidity of $LiClO_4$ in diethyl ether. The chemical investigation was done by carrying out the Diels-Alder reaction of dimethyl maleate, (-)-dimenthyl fumarate and (-)-menthyl methyl fumarate with cyclopentadiene in $LiClO_4$/diethyl ether. The spectroscopic investigation (^1H NMR) was carried out by complexing the Lewis acid with crotonaldehyde and measuring the induced chemical shift. The theoretical investigation was carried out using the MNDO calculations and measuring the extent of lowering of energy of the lowest unoccupied molecular Orbital (Lumo). The studies showed that the Li^+ is a strong Lewis acid in the gas-phase but in solution its acidity is moderated due to complexation with ether and ClO_4^-.

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LIST OF ABBREVIATIONS

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MAC	Methyl Acrylate
BQ	1,4-Benzoquinone
DMF	Dimethyl Fumarate
$AlCl_3$	Aluminum Trichloride
AC	Acrolein
ACN	Acrylonitrile
CP	Cyclopentadiene
Al_2O_3	Alumina
e.e.	Enantiomeric Excess
MTA	Methacrolein
DMnF	(-)-Dimenthyl Fumarate
LP/DE	Lithium Perchlorate in Diethyl Ether
MnMF	(-)-Menthyl Methyl Fumarate
DMM	Dimethyl Maleate
d.e.	Diastereomeric Excess
TCNE	Tetracyanoethylene
BBr_3/Al_2O_3	Boron Tribromide Treated Alumina
NMR	Nuclear Magnetic Resonance Spectroscopy
GC/MS	Gas Chromatography/Mass Spectrometry
MAD	Methylaluminum *bis*(2,6-di-*tert*-butyl-4-methylphenoxide)

PART II: A Chemical, Spectroscopic, and Theoretical Assessment of the Lewis Acidity of $LiClO_4$ in Diethyl Ether.

LP/DE	Lithium Perchlorate in Diethyl Ether
e.e.	Enantiomeric Excess
MAC	Methyl Acrylate
d.e.	Diastereomeric Excess
CP	Cyclopentadiene
CA	Crotonaldehyde
DMM	Dimethyl Maleate
MnMF	(-)-Menthyl Methyl Fumarate
DMnF	(-)-Dimenthyl Fumarate
LUMO	Lowest Unoccupied Molecular Orbital
MNDO	Modified Neglect of Differential Overlap
MO	Molecular Orbital

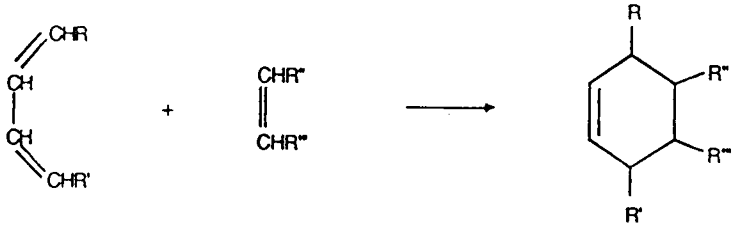
PART I

Diels-Alder Reactions of Dimethyl Maleate, Dimethyl Fumarate, (-)-Dimenthyl Fumarate, and (-)-Menthyl Methyl Fumarate with Cyclopentadiene on γ-Alumina and Diels-Alder Reactions of Dimethyl Maleate, (-)-Dimenthyl Fumarate, and (-)-Menthyl Methyl Fumarate with Cyclopentadiene in $LiClO_4$/Diethyl Ether.

CHAPTER I

INTRODUCTION

The Diels-Alder reaction, which is a ($4\pi + 2\pi$) cycloaddition reaction, is a widely used method[1] for forming carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds. The importance of this reaction lies in the simultaneous, regioselective formation of two bonds leading to the creation of up to four stereogenic centers at the binding sites with largely predictable stereochemistry (Eq. 1).[2]



1 2 3

(1)

The Diels-Alder reaction may be inter- or intramolecular. The diene is the 4π component of the Diels-Alder reaction, and the dienophile, the 2π component, is a molecule containing a double or triple bond and one or more electron withdrawing substituents. The reaction is also reversible, with the reverse process being called the retro-Diels-Alder reaction.

In the transition state of the Diels-Alder reaction, as depicted in Figure I-1, the diene can react only in its cisoid conformation.[3] The cisoid conformation is necessary so that the π-orbitals in the diene and dienophile overlap properly (Figure I-1). The

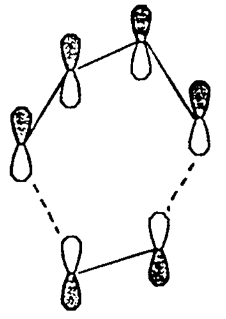
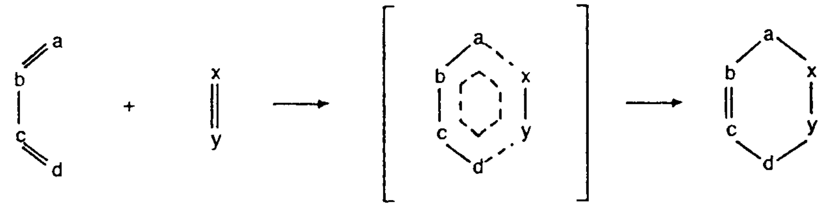


Figure I-1. Transition State of the Diels-Alder Reactions

reactivity of the diene is influenced by the electronic effects of its substituents, with the reactivity increasing with electron-donating substituents and decreasing with electron-attracting groups in a "normal" demand Diels-Alder reaction.[4] Dienophile reactivity is increased when electron-attracting groups are attached to the dienophile.

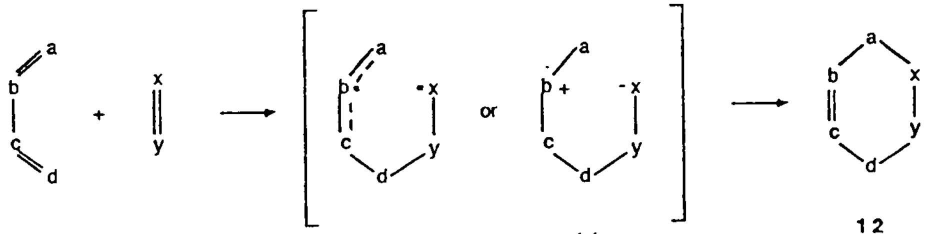
Investigations[5-8] of the Diels-Alder reaction mechanism have shown that not all the cycloadditions can be interpreted by a single mechanism. However, most of the thermal cycloadditions can be explained by a symmetry-allowed, one-step concerted mechanism (Eq.2), where the diene and dienophile approach each other in parallel planes



(2)

4 5 6 7

and interact in the transition state in the manner depicted in Figure I-1. Some cycloaddition reactions, however, proceed via a two-step mechanism (Eq. 3) which involve biradical or zwitterion intermediates. The reaction normally occurs via a

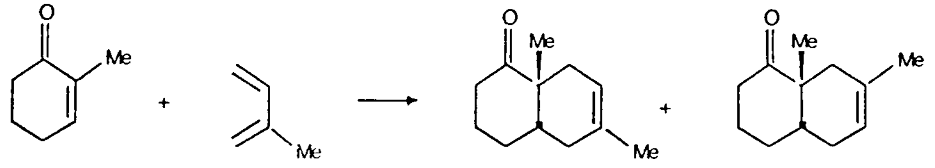


8 9 10 11 12 (3)

concerted mechanism because syn stereospecificity is obtained in the products. There is also an absence of solvent effect on the rate of the reaction, and large negative activation entropies and volumes of activation are obtained. Studies of the secondary α-deuterium isotope effects in retro-Diels-Alder reaction of 9,10-dihydro-9,10-ethanoanthracene and its bridge deuterated analogs; by Thornton *et al.*[9] their results also favor a concerted mechanism.

The concerted Diels-Alder reaction may proceed via a synchronous or asynchronous transition state.[5] A synchronous transition state is one in which bond-breaking and bond-forming processes occur simultaneously and have proceeded to almost the same extent in the transition state.[10] A transition state in which the formation of one σ-bond proceeds entirely or partially in advance of the second one is called asynchronous.[7e] Houk *et al.* have provided experimental and theoretical evidence in favor of a concerted synchronous mechanism for the prototype Diels-Alder reaction of 1,3-butadiene with ethene.[7b]

Wasserman in 1942 was the first person to observe the accelerating effect that acid has on the Diels-Alder reaction,[11] but the influence of the catalyst (trichloroacetic acid) on the reaction rate was small. A remarkable rate acceleration by $AlCl_3$ on the reactions of anthracene with MAC, BQ, and DMF,[12] on the other hand, was reported in 1960 by Yates and Eaton. Since then the use of Lewis acids to catalyze the Diels-Alder reaction has been a common feature of organic chemistry because the reactions can be carried out under very mild conditions of temperature and pressure. For example, whereas the cycloaddition of isoprene to 2-methyl-2-cyclohexenone occurs at 150° in poor yield, the $AlCl_3$-catalyzed reaction proceeds at room temperature in a shorter time and in higher yield[13] (Eq. 4). Lewis acid-catalyzed cycloadditions not only proceed faster than the thermal cycloadditions, but are also more regioselective and stereoselective.



(4)

13 14 15 16

Reaction Conditions	Para/meta Ratio
150 °C, 142 h, 20%	1.9
25 °C, $AlCl_3$, 17 h, 97%	36

Frontier Molecular Orbital (FMO) theory has been used successfully to explain Lewis acid-catalyzed Diels-Alder reactions.[14-16] According to FMO theory the interaction between the dienophile and catalyst lowers the energy of the lowest-unoccupied molecular orbital (LUMO) of the dienophile. Hence, in the case of the normal electron demand cycloaddition, the separation in energy between molecular orbitals (HOMO and LUMO) will decrease, and the stabilization of the transition state will increase (Figure I-2).

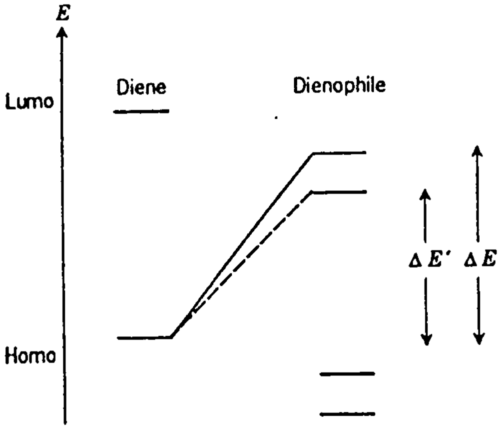


Figure I-2. HOMO (Highest Occupied Molecular Orbital)-LUMO (Lowest Unoccupied Molecular Orbital) interaction for the catalyzed (dashed line) and the uncatalyzed (solid line) normal electron demand Diels-Alder reaction.[4]

Since the Diels-Alder reactions are accompanied by large negative activation volumes, the rates of the reactions can be increased by the use of high pressure. Eckert and co-workers[17] have used high pressure kinetic studies to show that the Diels-Alder reaction occurs by a concerted process.

Solvent effect studies[5] have shown that the reaction rate varies only a little as the polarity of the solvent is altered, and hence the transition state must be only a little more polar than the reactants.

Solid phases like alumina, cellulose and montigel have also been used to carry out the Diels-Alder reactions. Endo/exo diastereoselectivities for the reaction of CP with AC, ACN and MAC,[18] and reported in Table I-1. The results clearly show that solids can greatly influence the diastereoselectivities of the reaction.

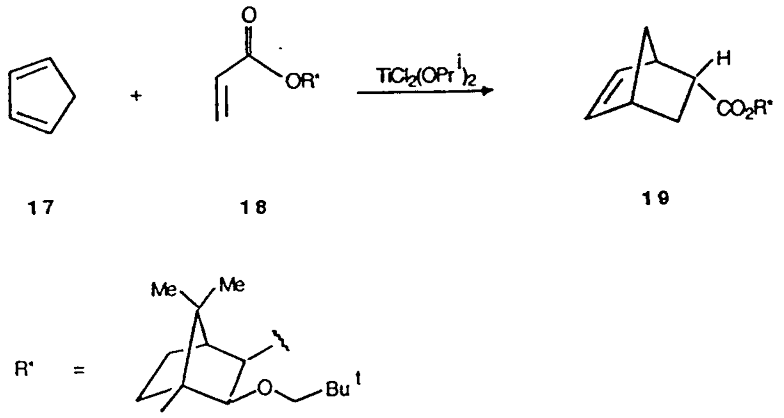
Table I-1. Endo/Exo Ratios for the Reaction of CP and AC, ACN, and MAC on Activated Neutral Al_2O_3, Cellulose, Montigel, and in Homogeneous Phase (HP).

Entry	Dienophile	Al_2O_3	Cellulose	Montigel	HP
1	AC	1.07	2.94	2.5	3
2	ACN	1.63	1.56	2.6	1.45
3	MAC	32.3	2.94	13.7	3

Source: Ref. 4

The Diels-Alder reaction is also important for preparing optically active compounds since two σ-bonds are formed in the process and, therefore, up to four stereogenic centers are produced at the binding sites. Asymmetric induction in the intermolecular process may be achieved by using chiral dienophiles, chiral dienes or chiral catalysts.[19,20]

Chiral conjugated carboxylic esters such as bornyl acrylates and fumarates are the most widely used dienophiles. In the cycloaddition of *cis*-2-neopentyloxyisobornyl acrylate with CP[21] (Eq. 5), for example, asymmetric induction is virtually quantative. The result can be explained by considering the staggered conformation (20) of the neopentyloxy chain in which the re-face is shielded by the *t*-butyl group. Therefore, the reaction occurs almost exclusively on the si face of the alkene.



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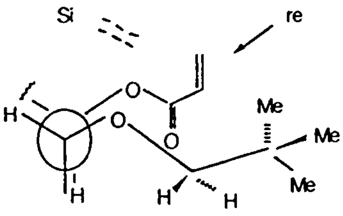

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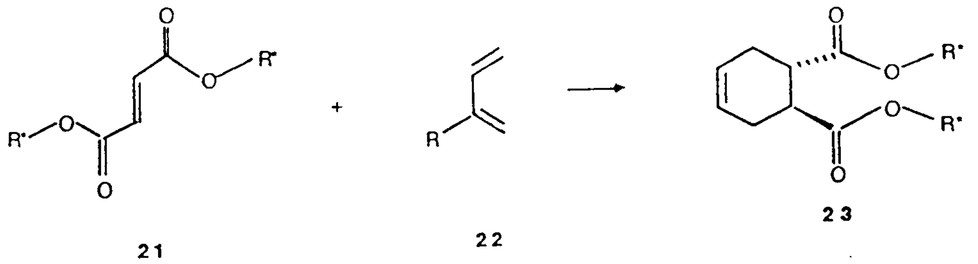
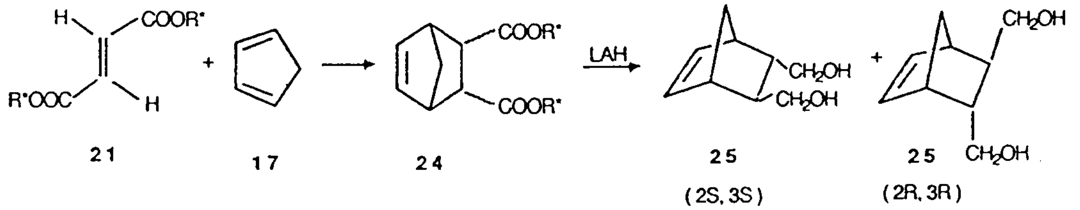
The relationship between pressure and optical yield has been determined for the Diels-Alder reaction of (-)-dimenthyl fumarate with 1,3-butadiene and isoprene[22] (Eq. 6). In all cases the *S*-configuration at C-1 and C-2 is induced and the optical yield increases with increased pressure going from 6.2 to 12.8% for pressures of 4 Kbar and 6.9 Kbar, respectively.



(6)

R^* = menthyl; R = H, Me

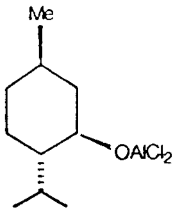
Studies of the reaction of CP with (-)-dimenthyl fumarate (DMnF) (Eq. 7) and other chiral acrylates have shown that generally higher enantiomeric yields are obtained in catalyzed reactions. The uncatalyzed reaction of DMnF (**21**) and CP (**17**) in methylene chloride gave levorotatory **25** in 3.6% e.e., whereas the same reaction at -78 C, catalyzed by $AlCl_3 \cdot OEt_2$, yielded dextrorotatory **25** in 43% e.e.[23] This is analogous



(7)

to Walborsky's observation for the reaction of the same fumarate with 1,3-butadiene.[24]

Relatively few papers have been published on the use of chiral catalysts for asymmetric Diels-Alder reactions since the sensational report by Koga et al.[25] regarding the cycloadditions of CP with AC, MAC, and MTA catalyzed by chiral alkoxyaluminum dichlorides (Eq. 8). The diastereofacial selectivity of these catalysts, as determined for



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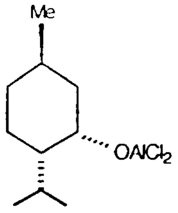

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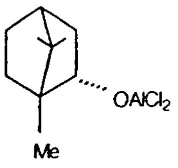

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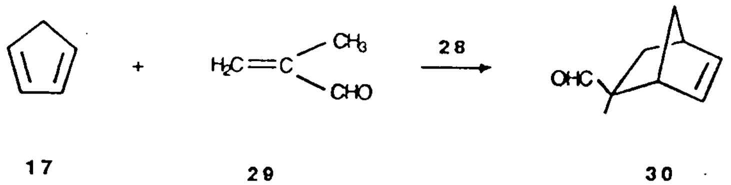
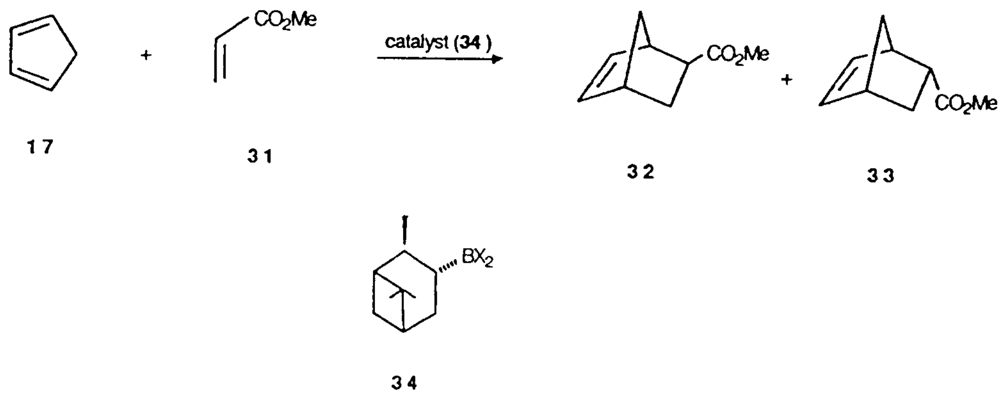
(8)

the cycloaddition of CP with MAC and AC are low (1:1 and 1.7:1), but they become rather significant in the reaction of MTA where the exo adduct predominates (6:1) (Eq. 10).



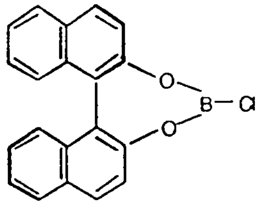
(9)

Bir and Kaufmann[26] reported the use of optically active isocamphenyl haloborane (**34**) as catalyst in the reaction of CP with MAC to afford (**32**) and (**33**) (Eq. 10). The endo



(10)

isomer (**33**) was the major product of the reaction (endo selectivity 99%), with e.e.'s of up to 48.2% being obtained if dimethyl sulfide was added as ligand. Good results can also be achieved with the catalyst derived from β-binaphthyl[27] (**35**). Unfortunately, it is difficult to come up with a rational design of an effective chiral catalyst because knowledge of the exact orientation of the catalyst in the Diels-Alder transition state is lacking.



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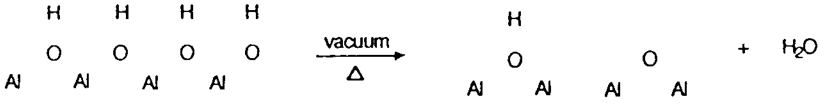
CHAPTER II

BACKGROUND

The Diels-Alder reaction, which is catalyzed by Lewis acids, has been carried out in different systems such as H_2O,[28] LP/DE,[29] in presence of enzymes,[30] and on the surfaces of various solids.[31–35] Not only do these reactions give results which are different from ordinary solutions but also the results tell us about the environments in which the reactions are being carried out.

Solids such as clays,[33] silica gel,[31] zeolites,[32] modified clays,[34] and alumina[35] have also been used to carry out various Diels-Alder reactions.

The reason for using alumina as a catalyst in the Diels-Alder reaction lies in the fact that alumina contains Lewis acidic Al^{+3} ions, as well as Lewis basic O^{-2} ions, which can be exposed to the surface by activating alumina through heating under vacuum. Depending upon the temperature of activation, the surface of alumina loses varying amounts of water, resulting in the exposure of underlying Al^{+3} and O^{-2} ions (Eq. 11).



(11)

36 Unactvated Al_2O_3

37 Activated Al_2O_3

The formation of water is attributed to the reaction of adjacent OH groups on the surface.[36] Higher activation temperature leads to a greater loss of water from the surface and thereby exposing more Lewis acidic and basic sites. The Lewis acid sites, which are exposed on activation of alumina, are not active to the same extent. Unactivated alumina has no Lewis acidic sites, normal Lewis acidic sites are present on alumina activated up to 300 °C, normal Lewis acidic sites and more active defect sites are present on alumina activated above 300 °C, and normal Lewis acidic sites, defect sites and highly active but structurally uncharacterized X-sites are present on alumina activated at still higher temperatures.[37] A schematic of the normal and defect sites are shown below.

Normal Site (Side View)Defect Site (Side View)

O O O......O.......O....Column 2
Al Al Al...Al..(gap)...Al..Column 1

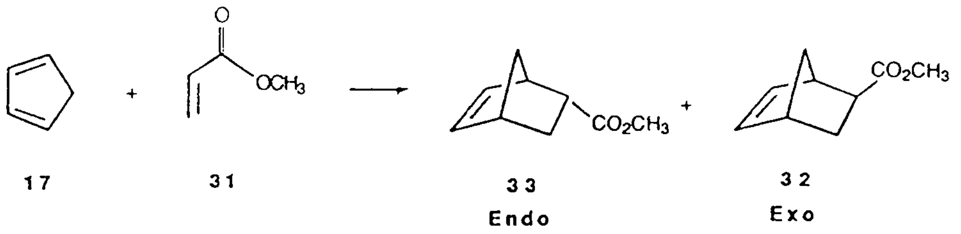
Figure I-3. Normal and Defect Sites in Activated Alumina.
Source: Reference 37.

Carrying out Diels-Alder reactions on the surface of alumina should give results which are different from those obtained in solution. The results should also illuminate the nature of the surface of the alumina and what occurs when the surface is activated by heating.

Pagni, Kabalka, *et al.* have used alumina as a catalyst for the Diels-Alder reaction of CP with MAC[35c] (Eq. 12) and menthyl acrylate[35c] (Eq. 13). For the MAC case, the endo to exo ratio of the adducts go up steadily with respect to activation temperature of alumina up to 400 °C (Fig. I-4). The optimum endo: exo ratio of greater than 50:1 was obtained when 400 °C activated alumina was used, but this selectivity falls when the reaction was carried out on 800 °C activated alumina. Similarly the endo:exo ratio for the menthyl acrylate case went up with respect to the activation temperature of alumina up to 400 °C (Fig. I-4), and, as in the previous case, the optimum endo:exo ratio (of 8.1:1) was obtained when 400°C activated alumina was used. As for the MAC case the ratio dropped when the reaction was carried out on increasingly activated solid. These data can be explained by the fact that highly potent Lewis acidic sites are exposed when alumina is activated beyond 400 °C and these sites also catalyze the retro-Diels-Alder reaction in both cases, thereby lowering the diastereoselectivity of both reactions.

In light of the above results the Diels-Alder reactions of the diesters, dimethyl maleate (DMM), dimethyl fumarate (DMF), optically active (-)-dimenthyl fumarate (DMnF) and optically active (-)-menthyl methyl fumarate (MnMF), with CP on alumina were studied. The diene was restricted to CP so that the new work could be related to the previously reported results.

Boron tribromide-modified alumina[35f] (**44**) is quite acidic, having an $H_o \leq 13.2$. This solid catalyst, which is much more acidic than activated alumina was also used to catalyze the Diels-Alder reaction of CP with DMnF to see the effect of the solid on the diastereoselectivity of the reaction. Since many asymmetric Diels-Alder reactions have been carried out using the chiral catalyst,[25,26,27] the Diels-Alder reactions of CP with DMnF and DMF were also carried out using the chiral solid[35f] (**45**) as catalyst. This



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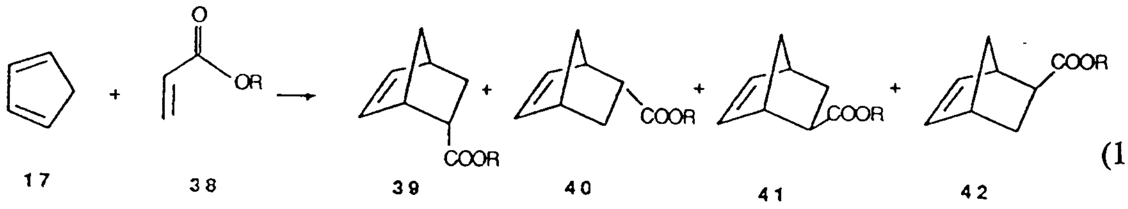
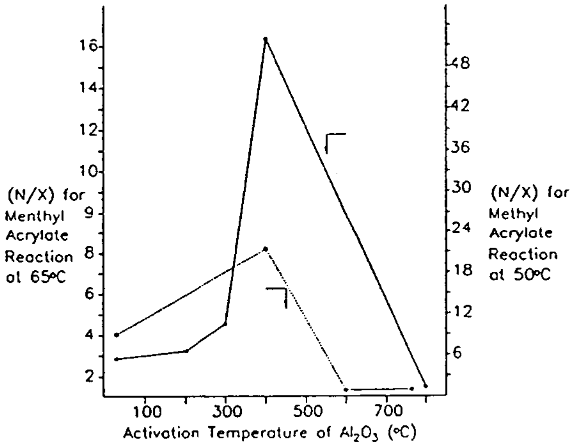


(13)

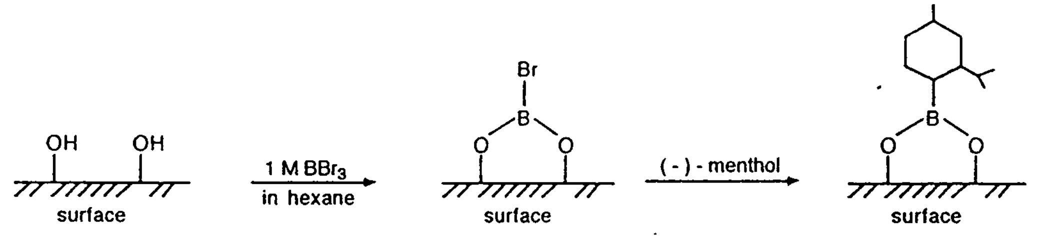
R = (-) - menthyl



Source: Reference 35(f).

Figure I-4. **Selectivities in the Reactions of MAC and Menthyl Acrylate with CP.**

material was prepared by displacing the bromine in **44** with optically active (-)-menthol (Eq. 14).[35f]



43 44 45

(14)

$LiClO_4$ in diethyl ether (LP/DE) has been used extensively to catalyze many reactions.[38,39,40] The system is now known to catalyze the Diels-Alder reaction through the Lewis acidic lithium ion.[41,42] Previous suggestions that the Diels-Alder results were due to a solvent effect[39,40] are now known to be false.

Braun and Sauer studied the Diels-Alder reaction of CP with MAC[40] in LP/DE and got an endo/exo selectivity of 7.3:1 with 38.1 wt% LP in ether. Later, Grieco and co-workers studied the Diels-Alder reaction of CP with ethyl acrylate[39] and got a maximum endo/exo selectivity of 8:1 (5.0 M LP).

In the present work LP/DE was used to catalyze the Diels-Alder reactions of CP with DMM, DMnF, and MnMF. One reason to use MnMF and DMnF for the Diels-Alder reactions with CP in LP/DE and on Al_2O_3 was to apply the Tolbert-Ali test,[43] in which one uses asymmetric induction for probing the transition state structure of the Diels-Alder reaction. This will be discussed further in RESULTS AND DISCUSSION, PART C.

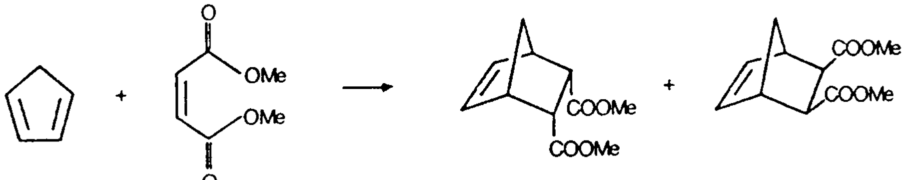
CHAPTER III

RESULTS AND DISCUSSION

A. Diels-Alder Reactions of Dimenthyl Maleate (DMM), Dimethyl Fumarate (DMF), Optically Active (-)-Dimenthyl Fumarate (DMnF), and Optically Active (-)-Menthyl Methyl Fumarate (MnMF) with Cyclopentadiene (CP) on γ-Alumina.

i. Diels-Alder Reactions of DMM and DMF with CP on γ-Alumina.

The Diels-Alder reactions between CP and DMM (Eq. 15) were carried out on γ-alumina. The ratio of grams of γ-alumina to grams of reactants was kept at 10:1 and the mol ratio of reactants was maintained at 1:1. The diendo to diexo ratio increased as



17 46 47 Diendo 48 Diexo (15)

the activation temperature of the alumina was increased (Table I-2). The reaction was also carried out in CH_2Cl_2; the resulting diendo:diexo ratio of 3:1 was lower than that obtained on unactivated alumina. A remarkably large diendo:diexo ratio of 20:1 was obtained when the reaction was carried out in CH_2Cl_2 in presence of $AlCl_3$, which is known to be an excellent Diels-Alder catalyst.

Table I-2. Diendo:Diexo Ratio (47:48) in the Reaction of CP and DMM.[a,b]

Entry	Reaction Conditions	Diendo:Diexo
1	Alumina, Unactivated	4.2
2	Alumina, Activated at 200 °C	5.0
3	Alumina, Activated at 400 °C	7.0
4	Alumina, Activated at 700 °C	15.6
5	Solution (CH_2Cl_2)	3
6	Solution (CH_2Cl_2) + $AlCl_3$	20

Source: Reference 35(e). [a]Run at 20 °C for 20 hours. [b]10:1 Al_2O_3:(CP + DMM) w/w ratio, 1:1 CP:DMM mol/mol ratio.

When the Diels-Alder reaction of CP and DMM was carried out on 700 °C activated alumina, along with the diendo (**47**) and diexo (**48**) adducts, the CP-DMF adduct (**49**) was also formed. Similarly, when the Diels-Alder reaction of CP and DMF was carried out at 55 °C on 700 °C activated alumina the diendo (**47**) and diexo (**48**) adducts were also obtained along with the expected CP-DMF adduct (**49**).

A retro-Diels-Alder explanation wherein the diendo adduct, for example, gives back CP and DMM which re-react to regenerate **47** and **48** would not explain the formation of CP-DMF adduct **49**; hence other epimerization reaction(s) are apparently involved. There are several ways by which these unusual results can be obtained: retro-Diels-Alder reaction, enolate chemistry, and *cis-trans* isomerization.

To study the mechanism of these reactions the diendo (**47**), diexo (**48**) and CP-DMF (**49**) adducts were each loaded onto 700 °C alumina individually and allowed to stir for 20 hours at 55 °C. Analysis of the resulting product mixture by GC/MS and ^{1}H NMR showed the presence of all three adducts in each case (Table I-3).

Table I-3. Epimerization Reactions of Diels-Alder Adducts on 700 °C Activated Alumina.[a]

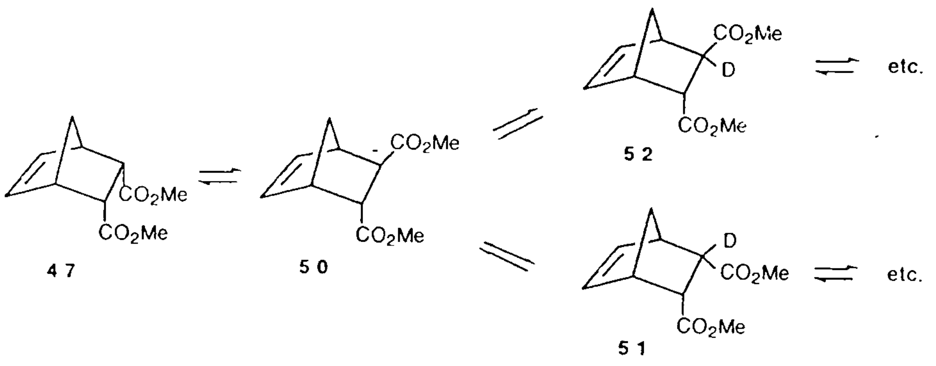
Entry	Adduct Loaded on Alumina	Products (%)		
		Diendo	Diexo	Fumarate (CP-DMF)
1	Diendo Adduct (**47**)	59.1	13.3	27.6
2	Diexo Adduct (**48**)	6.4	84.1	9.5
3	CP-DMF Adduct (**49**)	1.6	2.8	95.6

Source: Reference 35(e). [a]Run at 55 °C for 20 hours.

The epimerization reaction was observed the least for the CP-DMF adduct (**49**) because, of the three adducts, **49** is the most stable. Among the diendo and diexo adducts (**47** and **48**), the diexo adduct, being a thermodynamically more stable adduct than the dieno adduct, epimerized to a lesser extent.

To see if the retro-Diels-Alder reaction is also involved in the epimerization chemistry, attempts were made to trap CP, formed in the retro reaction, with a dienophile more reactive than DMM or DMF. A 3:1 admixture of diendo (**47**) and diexo (**48**) adducts along with MAC, TCNE or BQ, were loaded onto 700 °C activated alumina and then kept for 20 hours at 55 °C. These reactions yield no CP-MAC, CP-BQ, or CP-TCNE adducts. That the retro-Diels-Alder reaction is involved in the epimerization chemistry was proven by another approach wherein a 3:1 admixture of diendo and diexo adducts (**47** and **48**) was loaded onto 700 °C activated alumina and allowed to stir at 55 °C for 20 hours in an open system. Under these circumstances any (volatile) CP formed in the reaction would escape to the atmosphere. Analysis of the reaction mixture indeed showed the presence of approximately 6% DMM. Thus, the retro-Diels-Alder reaction participates in the epimerization chemistry.

Since the retro-Diels-Alder reaction cannot account for the formation of CP-DMF adduct **49** from **47** and **48**, another possibility was tested. A 3:1 admixture of diendo (**47**) and diexo (**48**) adducts was reacted with deuterated 700 °C-alumina[44] (HO groups replaced with DO groups) at ambient temperature. Any epimerization going through an enolate should yield a deuterated adduct (Eq. 16). After 20 hours the reaction mixture showed the presence of deuterated diendo adduct **47**, deuterated diexo adduct **48**, deuterated CP-DMF adduct **49** along with deuterated DMM and DMF (Table I-4). The formation of deuterated adducts prove that enolate chemistry is also involved, along with the retro-Diels-Alder reaction, in the epimerization reactions (Eq. 16). Analysis of the



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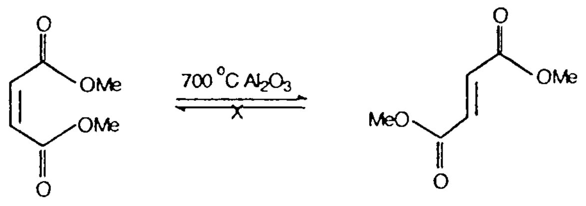
mass spectra of all three deuterated adducts showed that deuterium exchange occurred exclusively at the α-positions to the carbomethoxyl groups (Table I-4). This proves that deuterium incorporation does not occur on CP, a very acidic hydrocarbon, formed in the retro-Diels-Alder reaction. Because the DMM and DMF, which arise from the retro-Diels-Alder reactions, are deuterated to the same extent as the adducts, the enolate mechanism must occur much faster than the retro-Diels-Alder reaction.

Table I-4. Deuterium Exchange of Diendo—Diexo Diesters (3:1) on 700° D/Al_2O_3.

Entry	**Products (Relative % Yield)**	**Deuterium Distribution**		
		d_0	**d_1**	**d_2**
1	Recovered Diesters[a] (92)	11.8	34.5	53.8
2	DMM (6.4)	8.3	35.7	56.9
3	DMF (1.6)	12.2	36.2	51.5

Source: Reference 37. [a]The three diesters were analyzed as a mixture.

Another experiment was carried out wherein DMM was loaded onto 700 °C activated alumina and allowed to stir at RT. After 20 hours, 27.7% DMF had formed via *cis-trans* isomerization (Eq. 17). DMF did not isomerize to DMM under the same



46 53 (17)

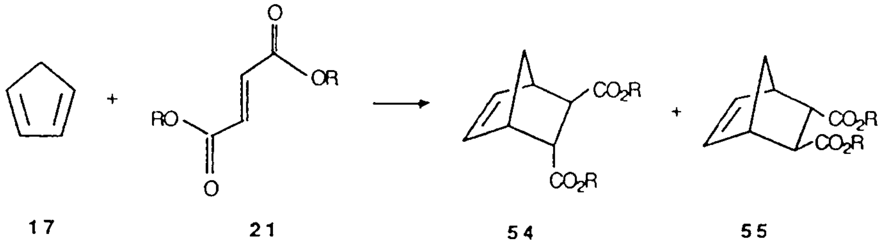
conditions. When 700 °C-D/Al_2O_3 was used for isomerization of DMM to DMF no deuterium was incorporated in either DMM or DMF. Hence we can conclude that there are three competing mechanisms by which epimerization chemistry can occur on 700 °C activated alumina, namely, the enolate mechanism, the retro-Diels-Alder reaction, and the DMM to DMF isomerization. Based on a comparison of the rates of these processes, one can say that the enolate mechanism occurs faster than the retro-Diels-Alder reaction, while the DMM-DMF isomerization occurs the slowest of all.

It is interesting to note that even though the $AlCl_3$-catalyzed Diels-Alder reaction of CP and DMM (Table I-2) gave a higher diendo to diexo ratio than 700 °C activated alumina did, it is on 700 °C activated alumina that the DMM-DMF isomerization occurred. This isomerization did not occur in the presence of $AlCl_3$.

Enolate chemistry participates in the epimerization reactions of the CP-DMM and CP-DMF adducts but not in the case of CP-MAC adducts.[35c] This is probably due to the differences in acidity of the monoester (CP-MAC) and diester adducts (CP-DMM/CP-DMF). Apparently the second ester group decreases the pKa of methine hydrogens at α-positions to the carbomethoxyl groups by inductive stabilization of the anion.

ii. Diels-Alder Reactions of Optically Active (-)-Dimenthyl Fumarate (DMnF) and Optically Active (-)-Menthyl Methyl Fumarate (MnMF) with Cyclopentadiene on γ-Alumina.

The Diels-Alder reactions between DMnF and CP (Eq. 18) were carried out on γ-alumina. The ratio of grams of γ-alumina to grams of reactants was kept at 10:1 and the mol ratio of reactants was maintained 1:1. The ratio of diastereomeric adducts (**54** and **55**) was obtained by a degradation scheme wherein the mixture of diastereomers (**54** and **55**) was saponified in refluxing 70% methanolic KOH, resterified with diazomethane, and the resulting dimethyl esters analyzed for diastereomeric ratio by ^1H NMR spectroscopy using the chiral shift reagent, *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III). The diastereomeric ratio and the d.e. obtained for the reactions carried out on the surface of alumina, and in solution, are reported in Table I-5. Diastereomer **55** predominated in presence of a Lewis acid.



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R = (-)-menthyl

Table I-5. Diastereomeric Ratio and Diastereomeric Excess (d.e.) obtained for the Diels-Alder Reaction of CP with DMnF.

Entry	Reaction Conditions	Diasteromeric Ratio (55:54)	Diastereomeric Excess (d.e.)
1	$AlCl_3/Et_2O$	2.24	38.3%
2	Neat	0.926	-3.84%
3	Unactivated Al_2O_3	1.32	13.8%
4	200° Activated Al_2O_3	1.40	16.8%
5	400° Activated Al_2O_3	1.43	17.7%
6	700° Activated Al_2O_3	1.51	20.3%
7	BBr_3/400° Activated Al_2O_3	1.46	18.7%
8	BBr_3/400° Activated Al_2O_3 with (-)-menthol	1.77	27.8%

Source: Reference 35(f).

The Diels-Alder reaction between DMnF and CP gave a d.e. of 13.8% on unactivated alumina. The d.e. increased steadily as the activation temperature of alumina was increased, with 700 °C activated alumina giving a d.e. of 20.3%. This behavior correlates (Figure I-5) nicely to the results of the previously discussed Diels-Alder reaction of DMM and CP (Table I-2).

When the Diels-Alder reaction of CP with MAC and menthyl acrylate (BACKGROUND, Figure I-3) was carried out on increasingly activated Al_2O_3 (>400 °C), the diastereoselectivity dropped because of increased importance of the retro-Diels-Alder reaction. However, in the case of Diels-Alder reaction of CP and DMnF the diastereoselectivity does not decrease on 700 °C activated alumina, thereby suggesting

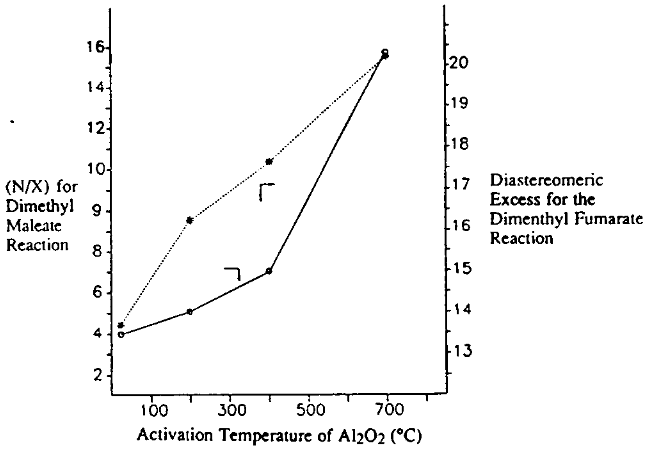

Figure I-5. Selectivities in the Reactions of Dimethyl Maleate and Dimenthyl Fumarate with Cyclopentadiene. Source: Reference 35(f)

that the retro-Diels-Alder reaction of CP with MAC is slower in this case than the Diels-Alder reaction on 700 °C activated alumina.

Because boron tribromide-modified alumina (**44**),[35(f)] as discussed in BACKGROUND, is quite acidic (H_0 of $\leq$ 13.2), it should be an excellent Diels-Alder catalyst. Since BBr_3/Al_2O_3 also possesses no strongly basic sites (O^{-2}), the problem of epimerization of adducts via the enolate mechanism is alleviated (RESULTS AND DISCUSSION, PART A (i)). This modified alumina, when used as a catalyst for the Diels-Alder reaction of CP and DMnF, gave a d.e. of 18.7% which is higher than the d.e. obtained when the same reaction was carried out on 400 °C activated alumina.

Since chiral catalysts can be used for asymmetric Diels-Alder reactions, the Diels-Alder reaction of DMnF and CP was also carried out using the chiral solid catalyst **45** (see BACKGROUND) which afforded a d.e. of 27.8%. This result is superior to that obtained with the boron tribromide-modified catalyst alone. Unfortunately **45** still leaves a lot to be desired. When **45** was used as a catalyst for the Diels-Alder reaction of CP and DMF, where no chiral moiety was present in the dienophile, a 0% e.e. was obtained.

To compare the surface results with the solution counterpart, the Diels-Alder reaction of CP and DMnF gave a -3.84% d.e. when carried out neat (absence of solvent) and a d.e. of 38.3% when carried out with $AlCl_3/Et_2O$.

All the above mentioned reactions were carried out at ambient temperature; these results do not compare favorably to the results obtained at -78 °C in solution by Yamamoto *et al.* for the same reaction.[45] The d.e. in the present cases presumably can be increased also if run at -78 °C.

When the Tolbert test[43] was applied to the Diels-Alder reaction, it was necessary to repeat the reactions of DMnF with CP along with the Diels-Alder reactions of MnMF with CP, both reactions were run on the same batch of Al_2O_3. This insured that the same conditions were used for both cycloaddition reactions.

These latter Diels-Alder reactions between DMnF and CP (Eq. 18) were carried out on γ-alumina at ambient temperature. In these cases the diastereomeric ratio was obtained directly by 400 MHz ^1H NMR spectroscopy by integrating the vinyl protons of the two diastereomers which have different chemical shifts (Figure I-6). Both the old

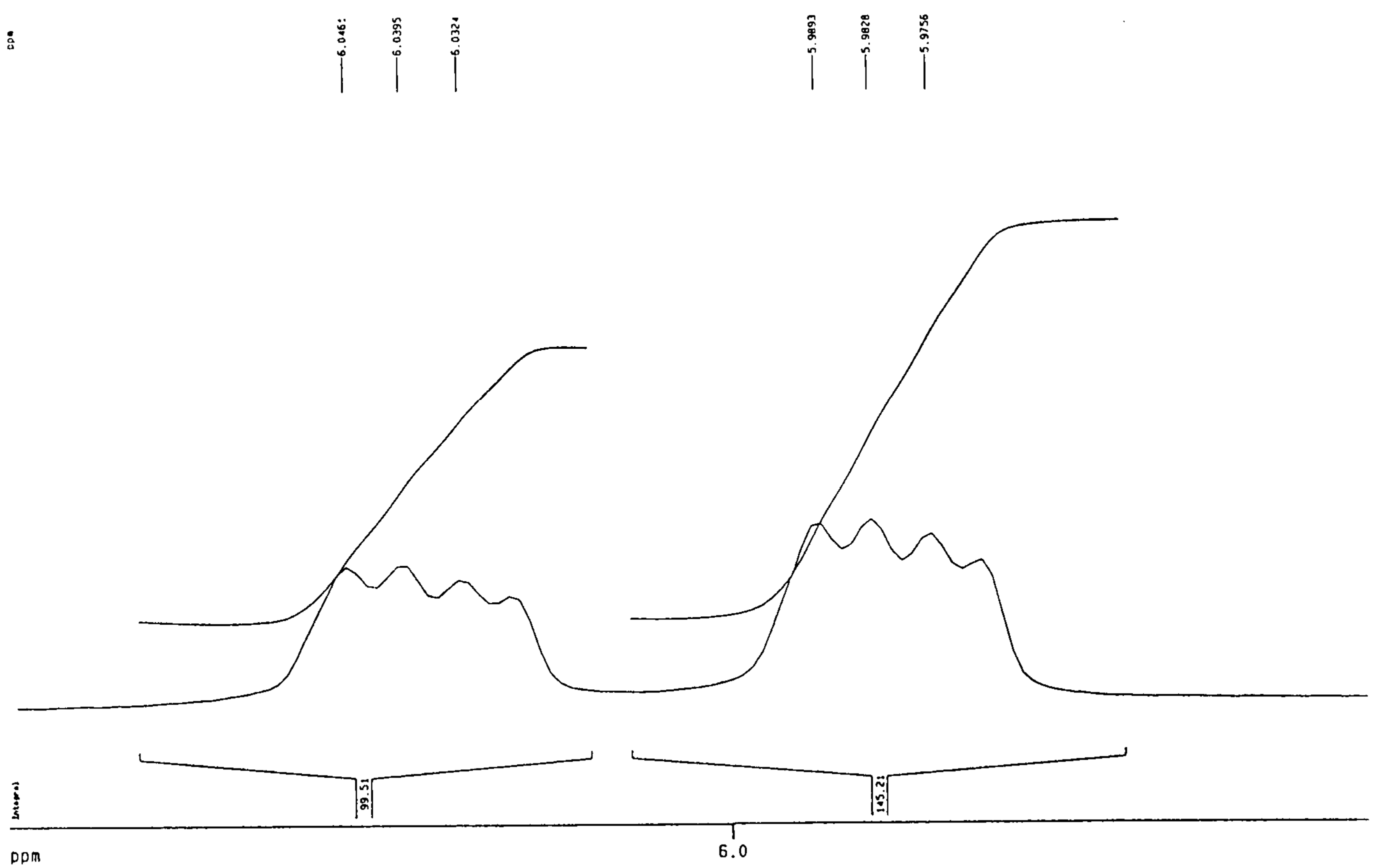

Figure I-6. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of a Mixture of Adducts (55 and 54) Obtained by the Diels-Alder Reaction of CP and DMnF on 700 °C-Al_2O_3.

(degradation) and the new (^{1}H NMR) diastereomeric ratios are listed in Table I-6. It can be seen that the diastereomeric ratios obtained in both studies agree within 1—2% of each other, thereby suggesting that both methods of analysis are reliable.

The Diels-Alder reactions between DMnF and CP (Eq. 18) were also carried out in CH_2Cl_2, ether, and $AlCl_3/CH_2Cl_2$ at ambient temperature, and the diastereomeric ratio determined by ^{1}H NMR, as discussed previously. The results are listed in Table I-7. The $AlCl_3 \cdot Et_2O$ - catalyzed reaction probably gives a lower diastereoselectivity than the $AlCl_3/CH_2Cl_2$ - catalyzed reaction because $AlCl_3$ in $AlCl_3 \cdot Et_2O$ complexes to both Et_2O and the dienophile which is not the case for $AlCl_3/CH_2Cl_2$. An increased steric effect in the transition state and an altered electron distribution in the dienophile will then account for the lower diastereoselectivity.

The error limits, which have an important bearing on the analysis of the Tolbert test results, were obtained by taking known mixtures of methyl benzoate and methyl salicylate, which serve as models for the diester adducts, and subjecting them to ^{1}H NMR (integration and cut-and-weigh) and GC/MS analysis. These results showed that the two NMR methods (integration and cut-and-weigh) are precise (1 Standard deviation) to within 1.4% and accurate to within 2.2%, while the GC/MS data were precise to within 0.4% and accurate to within 2.8%. Furthermore, the ratio of diastereomers obtained for reaction 18 in CH_2Cl_2 (Table I-7) agrees within 1% to that obtained by Sauer[23] for the same reaction, thereby further substantiating the accuracy of the obtained data.

Table I-6. Diastereomeric Ratios Obtained for the Diels-Alder Reactions between CP and DMnF by Different Methods of Analysis

Entry	Reactions Conditions	55:54	
		Degradation Method[a]	^{1}H NMR[b]
1	Unactivated Alumina	1.32	1.34
2	200 °C Activated Al_2O_3	1.40	1.40
3	400 °C Activated Al_2O_3	1.43	1.43
4	700 °C Activated Al_2O_3	1.51	1.46

Source: Reference 46.

[a] Degradation Scheme: Mixture of diastereomers saponified in refluxing KOH/methanol, re-esterified with diazomethane and analyzed for diastereomeric ratio by ^{1}H NMR spectroscopy using chiral shift reagent. [b] Diastereomeric ratio obtained by ^{1}H NMR (400 MHz) by integrating the vinyl protons.

Table I-7. Diastereomeric Ratios Obtained for the Diels-Alder Reactions between CP and DMnF by ^{1}H NMR.

Entry	Reaction Conditions	**55:54**
1	CH_2Cl_2	0.92 ±.03
2	Ether	0.95 ±.03
3	$AlCl_3/CH_2Cl_2$	4.99 ±.14
4	$AlCl_3 \cdot Et_2O$[a]	2.5

[a] Reference 23.

The Diels-Alder reactions between MnMF and CP, which yields four diastereomeric adducts (Eq. 19), were carried out on γ-alumina, CH_2Cl_2, ether and $AlCl_3/CH_2Cl_2$ at ambient temperature. The relative yields of **57-60** obtained in these reactions are shown in Table I-8 (absolute yields are >90%). Also in Table I-8 are the percent diastereomeric excess (% d.e.) [(**57** + **60**) - (**58** + **59**)]/[**57** + **58** + **59** + **60**] X 100 as defined by Yamamoto,[47] and the endo methoxy to exo methoxy ratio (N:X), which is (**57** + **58**):(**59** + **60**).

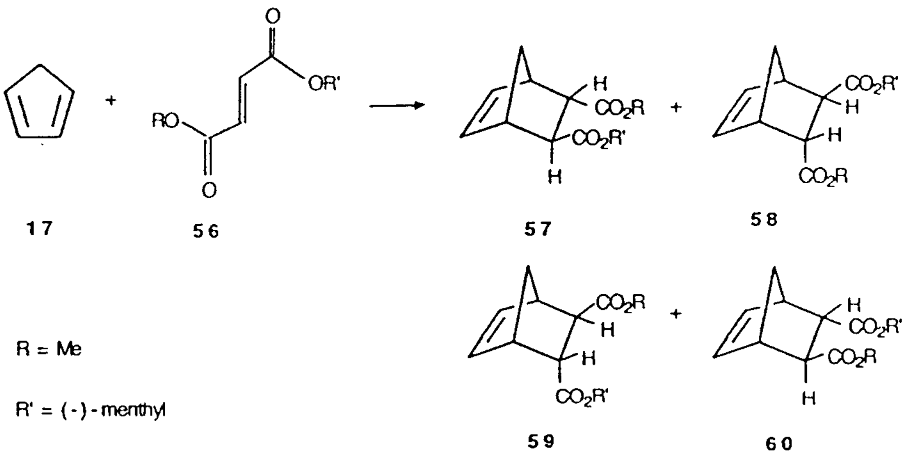

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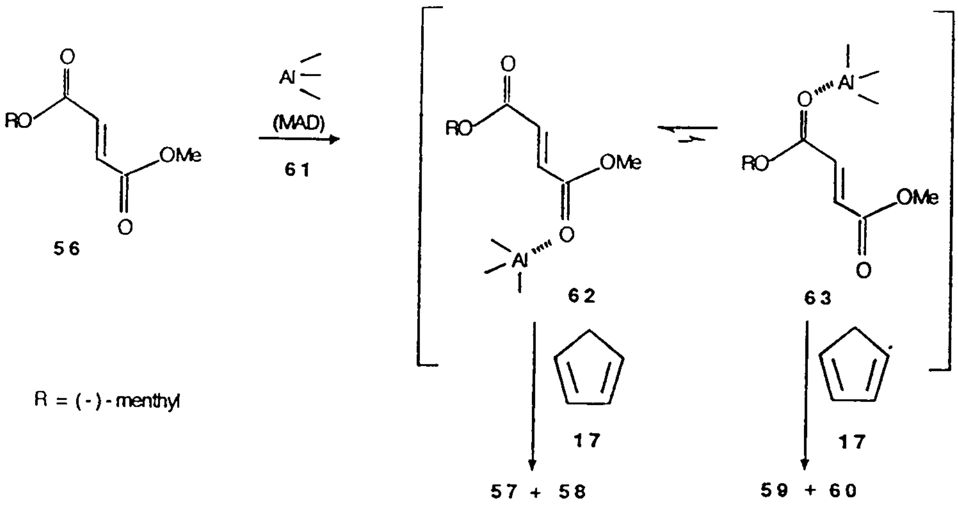
Table I-8. Relative Yields of 57—60, % d.e. and N:X Ratio for the Diels-Alder Reaction of MnMF and CP.

Entry	**Reaction Conditions.**[a]	**Relative Percentage**				**% d.e.**[b]	**N:X**[c]
		57	**58**	**59**	**60**		
1	Methylene chloride	21.8	27.3	28.2	22.7	-11.0	49:51
2	Ether	22.1	27.7	26.3	23.9	-8.0	50:50
3	$AlCl_3/CH_2Cl_2$	35.2	18.0	14.7	32.1	+34.6	53:47
4	Unactivated Al_2O_3	30.7	29.9	20.2	19.2	-0.2	61:39
5	200 °C —Activated Al_2O_3	32.0	33.9	17.4	16.7	-2.6	66:31
6	400 °C —Activated Al_2O_3	34.4	36.4	13.9	15.3	-0.6	71:29
7	700 °C —Activated Al_2O_3	35.4	39.3	12.4	12.9	-3.4	75:25
8	700 °C —Activated Al_2O_3[d]	40.7	42.4	7.8	9.1	-0.4	83:17
9	MAD[e,f,g]	91.4	7.0	0.2	1.4	+85.6	>98:2

Source: Reference 46. [a]Reactions were run at 22 °C unless noted otherwise. [b]%d.e. = [**57** + **60**) - (**58** + **59**)]/[**57** + **58** + **59** + **60**] x 100 as defined by Yamamoto.[47] [c](**57** + **58**):(**59** + **60**). [d]Reaction run at -5 °C. [e]Reference 67. [f]Reaction run at -78 °C. [g]MAD = Methylaluminum *bis*(2,6-di-*tert*-butyl-4-methylphenoxide).

It can be seen from the results in Table I-8 that the % d.e.'s are small as compared to the % d.e. of 85.6 obtained by Yamamoto[47] using MAD [methylaluminum *bis*(2,6-di-*tert*-butyl-4-methylphenoxide)] as a catalyst for the same reaction (at -78 °C). For the reactions run on alumina the percentages of both **57** and **58** increased as the activity of the alumina increased. However, the selectivities between **57** and **58** and **59** and **60** are both small. Even though the % d.e.'s on alumina were quite small the N:X ratios were large and increased as the activity of the alumina increased. The largest N:X ratio of 83:17 was obtained when the reaction was carried out at -5 °C on 700 °C alumina. This ratio is not too much less than the ratio of 96:4 obtained by Yamamoto at -78 °C using MAD as a catalyst.[47]

The reason why N:X ratios are large on alumina and in presence of MAD catalyst is probably because, in both the alumina and MAD, the Lewis acidic sites are in stereically demanding environments and hence prefer to bind to the carbonyl oxygen of the methyl ester in MnMF, thereby leading to complexes which form **57** and **58** more favorably than **59** and **60**.



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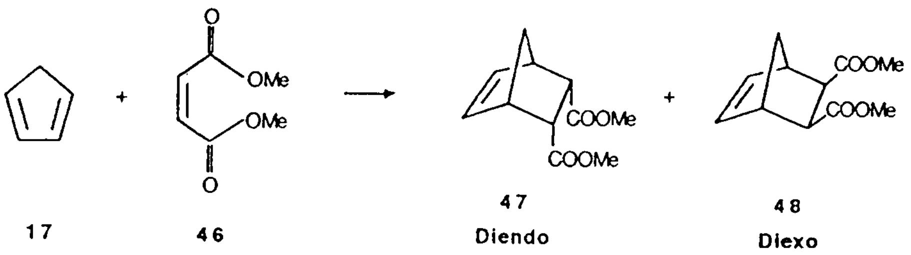
B. Diels-Alder Reactions of Dimethyl Maleate (DMM) Optically Active (-)-Dimenthyl Fumarate (DMnF), and Optically Active (-)-Menthyl Methyl Fumarate (MnMF) with Cyclopentadiene (CP) in LiClO$_4$/Ether (LP/DE).

The Diels-Alder reaction between DMM and CP (Eq. 15) in ether gave a diendo (47): diexo (48) ratio of 3:1, but increased in the presence of LP, giving a limiting value of 8:1 when the reaction was carried out in 6 M LP/DE.



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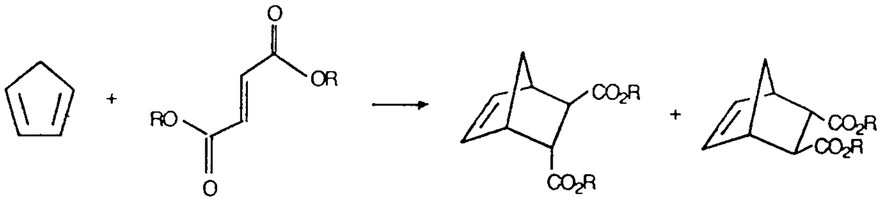
The Diels-Alder reactions involving a chiral dienophile also were influenced by LP/DE. The Diels-Alder reactions between DMnF and CP (Eq. 18) which forms two diastereomeric adducts were carried out in 0.950 M LP/DE, 2.80 M LP/DE, and 4.50 M LP/DE. The % d.e.'s were obtained by the same degradation scheme as mentioned in RESULTS AND DISCUSSION, PART I, A(ii). As can be seen in Table I-9, the % d.e. also increased as the concentration of LP increased as expected from the results with methyl acrylate and dimethyl maleate.



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R = (-)-menthyl

Table I-9. The % d.e. for the Reaction of CP and DMnF

Entry	Reaction Conditions	% d.e.[a]
1	Neat	-3.8
2	0.950 M LP/DE	14.7
3	2.80 M LP/DE	20.6
4	4.50 M LP/DE	16.8
5	10 mmol $AlCl_3$/ether[b]	38.3
6	Unactivated Al_2O_3[b]	13.8
7	Activated (200 °C) Al_2O_3[b]	16.8
8	Et_2AlCl in toluene (-20 °C)[c]	91

Source: Reference 48. [a]Major diastereomer is **55** (Eq. 18) in presence of a Lewis acid. [b]Reference 35(f). [c]Reference 49.

The diastereoselectivity with 4.50 M LP/DE was, however, somewhat less than that obtained when the reaction was carried out in 2.80 M LP/DE. The decreased diastereoselectivity in 4.50 M LP/DE may be due to the presence of higher aggregates of LP and DMnF in the more concentrated media. These data suggest that LP/DE system is a modest Lewis acid catalyst as compared to $AlCl_3$/ether and Et_2AlCl/toluene (Table I-9) which give much higher % d.e.'s for the same reaction. Even unactivated alumina, which is not Lewis acidic, gives a % d.e.[35(f)] comparable to the LP/DE system. The moderation of the Lewis acidity of Li^+ in the LP/DE system is probably due to complexation with both ether and the ClO_4^- ion.

Even though the Diels-Alder reactions of DMnF with CP had already been carried out in LP/DE, as described above, it was necessary to repeat them, along with the Diels-Alder reactions of MnMF with CP, so that both cycloaddition reductions could be run under identical conditions. This was essential for applying the Tolbert test to the LP/DE system. It was hoped that the structure of the transition state of the LP-catalyzed Diels-Alder reaction could be charaterized in this manner. The results of these experiments will be discussed in RESULTS AND DISCUSSION, PART C.

After the Diels-Alder reactions between DMnF and CP (Eq. 18) were carried out again in LP/DE at ambient temperature, the diastereomeric ratios were determined directly by high field ^1H NMR (400 MHz) spectroscopy, as described in RESULTS AND DISCUSSION, PART A (ii). The new diastereomeric ratios are reported in Table I-10.

Table I-10. Diastereomeric Ratios Obtained for the Diels-Alder Reaction Between CP and DMnF (Analysis by ^{1}H NMR).

Entry	Reaction Conditions	55:54
1	0.950 M LP/DE	1.28
2	2.80 M LP/DE	1.37
3	4.50 M LP/DE	1.35

The Diels-Alder reactions between MnMF and CP (Eq. 19) which yields four adducts (**57**-**60**) were also carried out in 0.980 M LP/DE, 2.80 M LP/DE and 4.60 M LP/DE at ambient temperature. The relative yields of **57**—**60** are listed in Table I-11. Also in Table I-11 are the percent diastereomeric excess (% d.e.) = [(**57** + **60**) - (**58** + **59**)]/[**57** + **58** + **59** + **60**] X 100, as defined by Yamamoto,[47] and the endo methoxy to exo methoxy ratio (N:X), which is (**57** + **58**):(**59** + **60**).

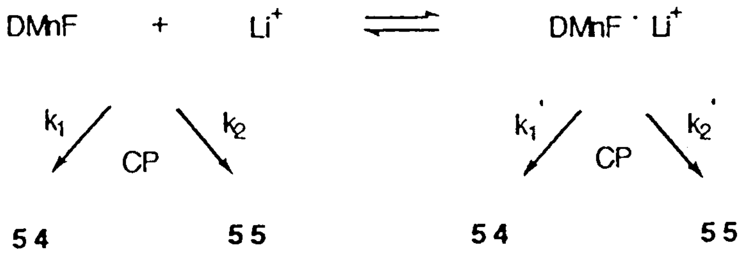
Table I-11. Relative Yields of 57—60, %d.e. and N:X Ratio for the Diels-Alder Reaction of MnMF and CP in LP/DE.

Entry	Reaction Conditions[a]	Relative Percentage				% d.e.[b]	N:X[c]
		57	58	59	60		
1	0.980 M LP/DE	24.7	24.8	26.8	23.7	-3.2	50:50
2	2.80 M LP/DE	26.0	23.6	25.5	24.9	1.8	50:50
3	4.60 M LP/DE	26.7	24.5	24.0	24.8	3.0	51:49

[a] Reactions were run at 22 °C. [b] %d.e. = [(**57** + **60**) + (**58** + **59**)]/[**57** + **58** + **59** + **60**] X 100 as defined by Yamamoto.[47] [c] (**57** + **58**):(**59** + **60**).

The % d.e.'s increase with increasing concentration of LP/DE as expected. (The % d.e.'s are much greater as compared to the reaction being carried out in ether alone (-8.0%)). However, the % d.e.'s are still lower than for the same reaction carried out in presence of $AlCl_3$ or MAD. Furthermore, there is no N:X selectivity in LP/DE which is in contrast to the reaction on Al_2O_3 where N:X was large. Because the Diels-Alder reaction in LP/DE appeared to arise from uncomplexed and complexed dienophile, it was necessary to extrapolate the data to infinite LP concentration in order to get the % d.e. for the complexed reaction alone. This extrapolation yielded a %d.e. = 10 ± 2% for the catalyzed reaction. This value is much lower than the %d.e.'s obtained when the reaction is catalyzed by MAD/CH_2Cl_2 at -78 °C or $AlCl_3/CH_2Cl_2$ at 22 °C.

Pagni, Kabalka, *et al.*[46] have also described the LP/DE-catalyzed Diels-Alder reactions of DMnF and MnMF with CP in a mathematical model wherein the Diels-Alder reaction occurs by catalyzed and uncatalyzed reactions, and the catalyzed reaction occurs via a 1:1 complex of dienophile and Li^+ formed reversibly (Eq. 21).



(21)

For the reaction of DMnF and Li^+ it can be shown[46] that,

$$\frac{\text{Amount of } \mathbf{55}}{\text{Amount of } \mathbf{54}} = \frac{Q_1 + Q_2 a[\mathrm{Li}^+]}{1 + a[\mathrm{Li}^+]} \tag{22}$$

where $a = \frac{k_1' K_{eq}}{k_1}$, Q_1 is the ratio of **55**:**54** at zero $LiClO_4$ concentration, Q_2 is the ratio of **55**:**54** at infinite $LiClO_4$ concentration, and Keq is the equilibrium constant for the reversible reaction of $LiClO_4$ with the dienophile. The theoretical ratios of **55**:**54** so obtained are listed in Table I-12, and they closely agree with the experimental ratios.

The model was also applied to the LP/DE-catalyzed Diels-Alder reaction of MnMF and CP and the resulting theoretical ratios of **57**:**58** and **60**:**59** at various LP concentrations are also given in Table I-12 and they agree with the experimental ratios except for the case of ether where **60**:**59** ratio in the theoretical and experimental ratios differ.

The model was also extended to the alumina—catalyzed Diels-Alder reaction of DMnF and CP. Hence the LP concentrations are replaced by Al^{+3} concentrations in the appropriate equations (Eq. 23). These values are available from the work of Knözinger and Ratnasamy.[49] The theoretical ratios of **55**:**54** so obtained are also given in Table I-12, and they agree closely with the experimental value. The model was not used to obtain the theoretical ratios of **57**:**58** and **60**:**59** because it can be seen from Table I-12, that the experimental diasteromeric ratios of **57**:**58** and **60**:**59** do not change in a regular fashion as the activity of the alumina is increased.

$$\frac{\text{Amount of } \mathbf{55}}{\text{Amount of } \mathbf{54}} = \frac{Q_1 + Q_2 a(Al^{+3})}{1 + a(Al^{+3})} \qquad (23)$$

Table I-12. Selected Diastereomeric Ratios for Reactions of CP with DMnF and MnMF.

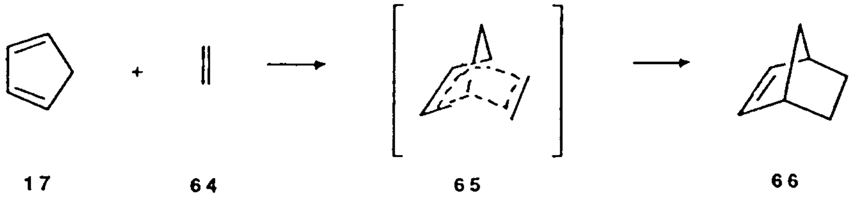
Entry	Reaction Conditions	55:54		57:58		60:59	
		Exp.[b]	Theo.[c]	Exp.[b]	Theo.[c]	Exp.[b]	Theo.[c]
1	Ether	0.95	0.95	.797	.797	.909	.805
	$LiClO_4$/Ether						
2	.950 M .980 M	1.28	1.28	.966	.994	.884	.886
3	2.80 M 2.80 M	1.37	1.35	1.10	1.08	.976	.977
4	4.50 M 4.60 M	1.35	1.37	1.09	1.11	1.03	1.03
5	∞^c ∞^c		1.41		1.17		1.24
	Alumina						
6	Room Temp.[e,f]	1.34	1.34[g]	1.03		.950	
7	200 °C[e]	1.40	1.40[g]	.944		.960	
8	400 °C[e]	1.43	1.43[g]	.945		1.10	
9	700 °C[e]	1.46	1.46[g]	.901		1.04	
10	700 °C[e,h]	1.48		.960		1.17	

Source: Reference 46. [a]Reaction run at 22 °C unless otherwise noted. [b]Experimental results. [c]See text for explanation. [d]Column 1 = concentrations for reaction (18) and
Column 2 = concentrations for reaction (19). [e]Temperature at which alumina is activated. [f]Room temp = unactivated alumina. [g]55:54 ratios calculated assuming $Q_1 = 1.34$, $Q_2 = 1.87$ and $a = 0.177\ M.^{-1}$
[h]Reaction run at -5 °C.

C. Application of the Tolbert-Ali Test to the Diels-Alder Reactions of DMnF and MnMF with CP in LP/DE and on Al_2O_3.

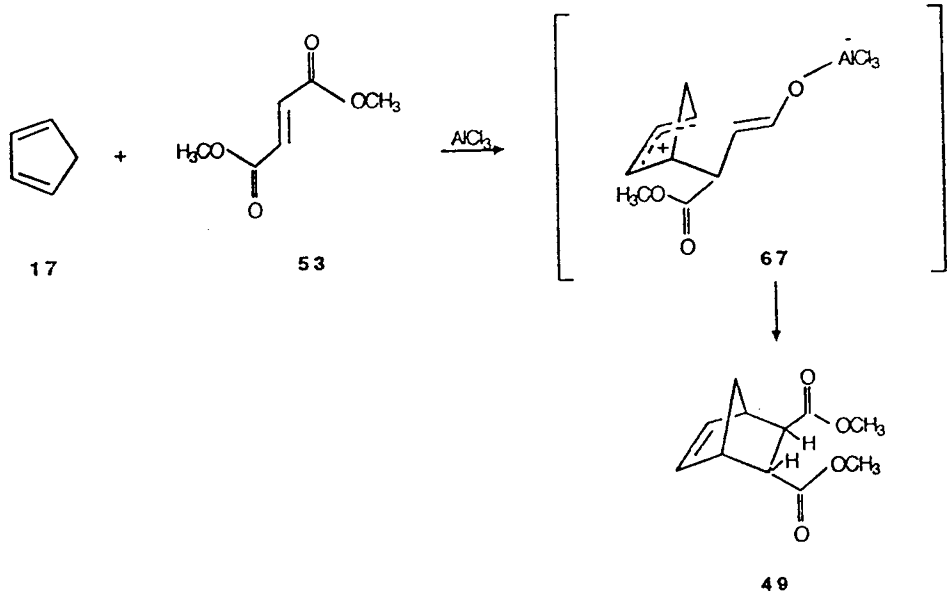
According to Tolbert and Ali[43] and earlier workers,[5,10] a ($4\pi + 2\pi$) cycloaddition reaction with no substituents on the diene and dienophile occurs via a synchronous, symmetric transition state (Figure I-7), whereas Lewis acid catalyzed reaction, where the dienophile is complexed to a Lewis acid, occurs via an asychronous transition state (Figure I-8).

The Tolbert-Ali test[43] uses asymmetric induction to probe the geometry of the transition state of the Diels-Alder and other cycloaddition reactions. According to them, the diastereomeric ratio produced when the dienophile contains two independent chiral moieties can be predicted on the basis of the asymmetric induction resulting when a single chiral moiety is used. For the Diels-Alder reaction wherein the dienophile contains two chiral moieties the asymmetric induction will be caused by the cumulative power of both chiral moieties which will correspond to the square of the monochiral



(24)

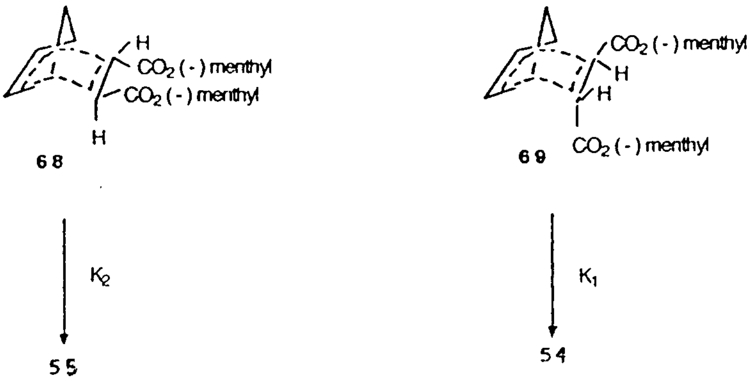
Figure I-7. Synchronous Symmetric Transition State in the Diels-Alder Reaction.



(25)

Figure I-8. Asynchronous Transition State in Lewis Acid-Catalyzed Diels-Alder Reaction.

ratio. This statement is valid only when each chiral moiety influences the reaction in exactly the same manner, as is the case for a synchronous reaction. For reactions 18 and 19 (See RESULTS AND DISCUSSION, PART I-A), the Tolbert-Ali theory predicts that (**55**:**54**) = (**57**:**58**) (**60**:**59**) if the reactions occur via a synchronous transition state, for example. This prediction can be explained as follows:[46] In reaction 18, **55** and **54** are produced via transition states **68** and **69**. For **55**, the endo (N) menthyl group which is



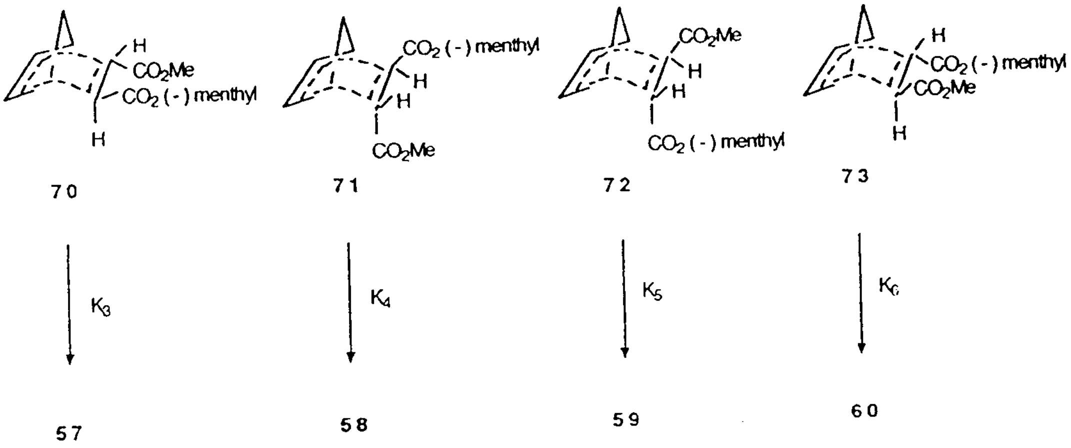
(26)

back (N_BMn), where N_BMn refers to a menthyl group (Mn) which is both endo (N) and bck (B), and the exo (X) menthyl group which is forward (X_FMn) will influence the asymmetric induction. For **54** the asymmetric induction will be influenced by N_FMn and X_BMn.

$$\frac{55}{54} = \frac{k_2\,(N_BMn, X_FMn)}{k_1\,(N_FMn, X_BMn)} \qquad (27)$$

Thus, where k_2 and k_1 are the rate constants of the reactions which lead, to the formation of **55** and **54**, respectively.

For reaction 19, the four adducts **57-60**, are produced via the four transition states **70-73**. For adduct **57** the asymmetric induction will be influenced by X_FMn and



(28)

N_BMe; for **58** the asymmetric induction will be influenced by X_FMe and X_BMn; for **59** the asymmetric induction will be influenced by N_FMn and X_BMe and for **60**, the asymmetric induction will be influenced by X_FMe and N_BMn. Thus,

$$\frac{57}{58} = \frac{k_3\ (N_BMe, X_FMn)}{k_4\ (N_FMe, X_BMn)} \tag{29}$$

and

$$\frac{60}{59} = \frac{k_6\ (X_FMe, N_BMn)}{k_5\ (X_BMe, N_FMn)} \tag{30}$$

where k_3-k_6 are the rate constants of the Diels-Alder reactions which lead to the formation **57**-**60**. If the methyl groups have a constant effect on the asymmetric induction, i.e. $N_BMe = N_FMe$ and $X_BMe = X_FMe$ then we have,

$$\frac{57}{58} = \frac{k_3\ (X_FMn)}{k_4\ (X_BMn)} \tag{31}$$

and

$$\frac{60}{59} = \frac{k_6\ (N_BMn)}{k_5\ (N_FMn)} \tag{32}$$

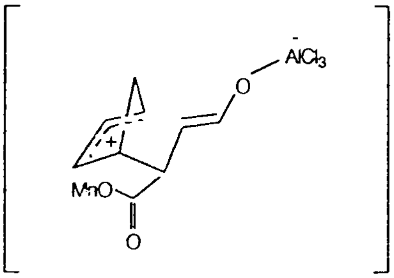
It follows that,

$$\left(\frac{57}{58}\right)\left(\frac{60}{59}\right) = \frac{k_3\,(X_FMn)}{k_4\,(X_BMn)} \times \frac{k_6\,(N_BMn)}{k_5\,(N_FMn)} \qquad (33)$$

because k_3 (X_FMn) x k_6 (N_BMn) should be similar in value to k_2 (N_BMn, X_FMn) because the influences on asymmetric induction in both cases are the same and because k_4 (X_BMn) x k_5 (N_FMn) should be similar in value to k_1 (N_FMn, X_BMn) for the same reason, it follows that,

$$\left(\frac{55}{54}\right) \approx \left(\frac{57}{58}\right)\left(\frac{60}{59}\right) \qquad (34)$$

For asynchronous transition states the influence of X_BMn and N_FMn will not be identical because the menthyl group that perturbs the transition state when close to an incipient bond will have a greater effect at one site than the other (74).[43] Thus, the relationship in equation 34 will not be applicable for Lewis acid-catalyzed Diels-Alder reactions.



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The previously described data for the alumina and LP/DE-catalyzed reactions are shown in Table I-13 as the ratio **55**:**54**, the product of ratios (**57**:**58**)(**60**:**59**) and the difference between these quantities Δ. If Δ is approximately zero, i.e. (**55**:**54**) ≈ (**57**:**58**)(**60**:**59**) the reactions occur synchronously. If Δ deviates significantly from zero, the transition states for this set of reactions are asynchronous. For the LP-catalyzed Diels-Alder reaction it is of course necessary to extrapolate the data to infinite [LP] to obtain Δ for the catalyzed reaction alone. It should be noted that each value of Δ comes from the percentages of six compounds, each of which has an associated error. Hence, even a small error in each percentage will lead to a large total error due to propagation of errors.

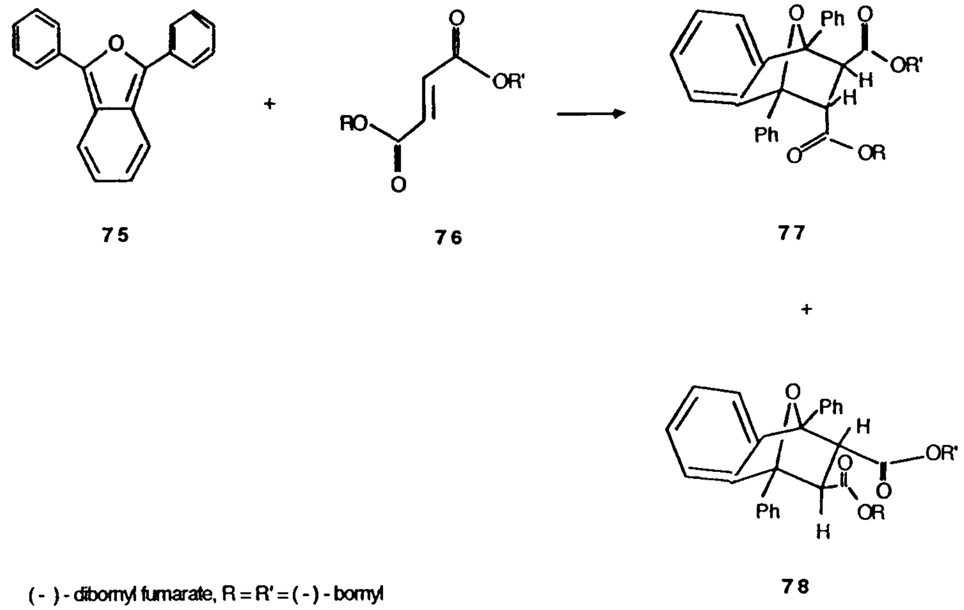
Tolbert and Ali performed their studies for uncatalyzed Diels-Alder reactions of (-)-dibornyl fumarate and (-)-bornyl methyl fumarate with diphenylisobenzofuran in benzene and xylene (both non-polar solvents) at various temperatures (ranging from ambient to 75 °C) and found Δ ≅ 0.

Table I-13. Tolbert-Ali Test as Applied to Reactions 18 and 19 and the Difference (Δ) in the Predicted and Experimental Diastereomeric Ratio.

Entry	Reaction Conditions[a]	Predicted Diastereomeric Ratio According to Tolbert-Ali Test.[43] (57:58)(60:59)	Experimental Diastereomeric Ratio 55:54	Difference Δ = (55:54)-(57:58)(60:59) (error limits)[b]
1	CH_2Cl_2	0.64	0.92	0.28 (.04, .06)
2	Ether	0.72	0.95	0.23 (.04, .06)
3	$AlCl_3/CH_2Cl_2$	4.27	4.99	0.72 (.23, .33)
	LP/DE			
4	0.950 M	0.88	1.28	0.40 (.05, .07)
5	2.80 M	1.07	1.37	0.30 (.06, .09)
6	4.50 M	1.12	1.35	0.23 (.06, .09)
7	∞[c]	1.47	1.41	-0.06 (.07, .11)
	Alumina			
8	Unactivated	0.98	1.34	0.36 (.06, .08)
9	200 °C Activated	0.91	1.40	0.49 (.05, .08)
10	400 °C Activated	1.04	1.43	0.39 (.06, .08)
11	700 °C Activated	0.94	1.46	0.52 (.06, .08)
12	700 °C Activated	1.12	1.48	0.36 (.06, .09)

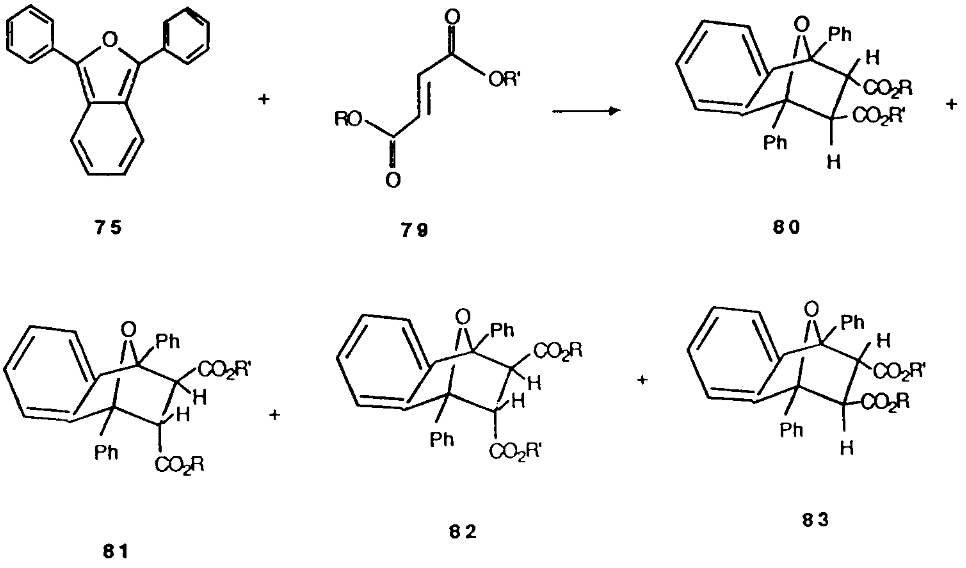
[a] Reactions were carried out at ambient temperature except entry 12 which was carried out at -5 °C [b] (± 2% error limits, ± 3% error limits).
[c] Extrapolated values.

(Eq. 35 and 36) in all cases. However, as can be seen in Table I-13, Δ has a value of



(35)

(-) - dibornyl fumarate, R = R' = (-) - bornyl



(36)

(-) - bornyl methyl fumarate, R = methyl, R' = (-) - bornyl

0.28 in CH_2Cl_2 and a value of 0.23 in ether for the reactions in the present study. These results are not in agreement with the results of Tolbert and Ali. These differences in Δ are probably due to the differences in solvent character, with ether and CH_2Cl_2 being more polar than benzene and xylene. Further work will have to be done to clarify this point.

If one looks at entries 11 and 12 in Table I-13, one sees that reactions 18 and 19 were carried out using the same solid (700 °C - Al_2O_3) but at different temperatures (22 °C and -5 °C). The Δ values for these two reactions, Δ= 0.52 at 22 °C and Δ = 0.36 at -5 °C, differ. For the present case Δ apparently not only depends on solvent but also on reaction temperature. This result is again at odds with that obtained by Tolbert and Ali, who found Δ ≅ 0 for reactions of (-)-dibornyl fumarate and (-)-bornyl methyl fumarate with diphenylisobenzofuran at different temperatures. Even though Tolbert and Ali contend that Δ should always be temperature independent for synchronous reactions, it is clear from the present results that this need not be so.

A Δ value of 0.72 was found when reactions 18 and 19 were carried out in $AlCl_3/CH_2Cl_2$. This Δ value is much higher than that obtained in CH_2Cl_2 in the absence of the Lewis acid. Even if one corrects for the solvent effect of CH_2Cl_2, the resulting Δ value of 0.44 (0.72-0.28) clearly shows that the $AlCl_3/CH_2Cl_2$ -catalyzed cycloaddition reactions proceed via asynchronous transition states.

The Δ values obtained for LP/DE-catalyzed reactions 18 and 19 decrease with increasing LP/DE concentration, until a limiting Δ value of -0.06 is obtained. This near zero value of Δ suggests that these LP-catalyzed reactions occur via synchronous transition states. One must, however, take into account the solvent effect on Δ. If one corrects for the solvent effect of ether the resulting Δ value of -0.29 (-.06 -.23) points towards asynchronous transition states for the LP-catalyzed reactions in this medium.

There is no clear trend for the Δ values obtained when reactions 18 and 19 were carried out on alumina which had been activated at different temperatures. However, all the Δ values deviate significantly from zero. Thus, all these reactions also proceed via asynchronous transition states. Even on unactivated alumina where there are no Lewis acid sites available to catalyze the reactions, they still proceed via asynchronous transition states, probably because the surface OH groups influence the symmetry of the transition state by interacting with the dienophile through hydrogen bonding.[46]

CHAPTER IV

EXPERIMENTAL SECTION

A. Materials

i. Solvents

Anhydrous Ethyl Ether, Mallinckrodt, ACS grade.
Hexanes, Mallinckrodt, ACS grade.
The solvents ware used as purchased.

ii. Gases

Prepurified Argon, MG Industries, was used as received.

iii. Reagents

Dimethyl Maleate, Aldrich Chemical Co.**
Dimethyl Fumarate, Aldrich Chemical Co.**
Aluminum Trichloride, Aldrich Chemical Co.**
Dicyclopentadiene, Aldrich Chemical Co.**
(1R, 2S, 5R)-(-)-Menthol, Aldrich Chemical Co.**
Alumina, Neutral Brockmann Activity Grade 1, Fisher Scientific, used as received.
Activated alumina, Neutral Brockmann Activity Grade 1, Fisher Scientific, was prepared using the method and apparatus described by Pagni, *et al.*[44]
Deuterated alumina was prepared according to the procedure described by Pagni, *et al.*[44]
Diazald, Aldrich Chemical Co.**
Lithium Perchlorate, Aldrich Chemical Co., was dried by the procedure described in Experimental Part II.

**The reagent was used as received.

B. Experimental Methods

i. Analytical Methods

Gas chromotography was performed on a Hewlet-Packard 5890A GC instrument equipped with a 30 m x 1/8" column packed with 30% SE-30 by weight on Chromosorb W as the solid support. Gas chromatograph/Mass spectrometry (GC/MS) was performed using a Hewlett-Packard 5970 Gas chromatograph/mass spectrometer. For the analysis of adducts obtained by the Diels-Alder reaction of cyclopentadiene and MnMF the GC/MS was carried out on a 25-m crosslinked polyethylene glycol-TPA capillary column at 170 °C.

Nuclear magnetic resonance spectra were recorded either on a 90 MHz JEOL FX-90Q spectrometer, a 250 MHz Bruker spectrometer, or a 400 MHz Bruker spectrometer. Samples were run in $CDCl_3$ with 1% tetramethylsilane (TMS) as the internal standard ($\delta=0$). Chemical shifts are reported in parts per million downfield from TMS.

ii. Apparatus and Manipulation of Reagents

Due to moisture sensitivity of activated Al_2O_3 and BBr_3/Al_2O_3, all manipulations were performed under a dry argon atmosphere in a glove bag. All glassware, syringes and needles were oven-dried at 100 °C for 6 hours, assembled hot, and cooled under a stream of argon before use. The reactions were performed under an argon atmosphere.

C. Experimental Procedures

i. Diels-Alder Reaction of Dimethyl Maleate and Cyclopentadiene on 400 °C - Al_2O_3. General Procedure A.

To a 250-mL round bottomed flask containing 22.3 g of 400 °C activated alumina under argon was added 1.25 mL of dimethyl maleate (10.0 mmol) with stirring. After 20 minutes 1.00 mL of cyclopentadiene (12.0 mmol) was injected onto the solid and the reaction stirred for 20 h at room temperature. The reaction mixture was then extracted with ether, filtered through $MgSO_4$, and concentrated *in vacuo* to afford a mixture of diendo and diexo adducts, **47** and **48** respectively as a colorless oil. (92% overall yield). It was possible to separate the diendo and diexo adducts through preparative GC using 30 m x 1/8" column packed with 30% SE-30 by weight on chromosorb W as the solid support. Analysis of the mixture was accomplished by ^1H and ^{13}C NMR spectroscopy and GC/MS. ^1H NMR ($CDCl_3$) (ppm), diendo (**47**): δ 6.25 (2 H, s, vinyl), 3.60 (6 H, s, OCH_3), 3.20 (4 H, m, CH), 1.40 (2 H, dd, CH_2); diexo (**48**): δ 6.20 (2 H, s, vinyl), 3.65 (6 H, s, OCH_3), 2.80 (4 H, m, CH), 1.58 (2 H, dd, CH_2). ^{13}C NMR ($CDCl_3$) (ppm), diendo (**47**): δ 172.8 (C = O), 134.8 (vinyl), 51.4 (CH_2), 48.6 (CH), 47.9 (OCH_3), 46.2 (CH next to COOMe); diexo (**48**): δ 173.8 (C = O), 137.9 (vinyl), 51.8 (CH_2), 47.2 (CH), 47.2 (OCH_3), 45.5 (CH next to $COOCH_3$).

ii. Diels-Alder Reaction of Dimethyl Fumarate and Cyclopentadiene on 700 °C - Al_2O_3. General Procedure B.

To a 250-mL round bottomed flask containing 22.3 g of 700 °C activated alumina under argon was added 1.44 g (10.0 mmol) of dimethyl fumarate in 25 mL of ether. After removing the ether *in vacuo*, 1.00 mL of cyclopentadiene (12.0 mmol) was injected and the reaction stirred for 20 h at room temperature. The reaction mixture was then extracted with ether, filtered through $MgSO_4$, and concentrated *in vacuo* to afford a mixture of (**47**), (**48**) and the CP-DMF (**49**) adduct as a colorless oil (90% overall yield). Analysis of the mixture was accomplished by ^1H and ^{13}C NMR spectroscopy and GC/MS. ^1H NMR ($CDCl_3$) (ppm), CP-DMF adduct (**49**): δ 6.12 (2 H, s, vinyl), 3.71 (3 H, s, exo OCH_3), 3.64 (3 H, s, endo OCH_3), 3.28 (4H, m, CH), 1.45 (2H, dd, CH_2); ^{13}C NMR ($CDCl_3$) (ppm), CP-DMF adduct (**49**): δ 174.4 (exo C = O), 173.2 (endo C = O), 137.2 (vinyl), 134.8 (vinyl), 51.7 (CH_2), 51.4 (CH), 47.6 (CH), 47.3 (endo OCH_3), 46.9 (exo OCH_3), 46.8 (CH next to $COOCH_3$), 45.3 (CH next to $COOCH_3$).

iii. Epimerization of Diendo (47) to Diexo (48) and CP-DMF adduct (47) on 700 ° - Al_2O_3. General Procedure C.

To a 100-mL round bottomed flask containing 10.0 g of alumina that had been activated at 700° was added dropwise (via syringe), under an argon atmosphere, diendo adduct (**47**) (1.00 g, 4.76 mmol). The reaction was stirred for 20 hours at 55 °C. The reaction mixture was then extracted with ether, filtered through $MgSO_4$, and concentrated *in vacuo* to afford a mixture of diendo (**47**), diexo (**48**) and CP-DMF (**49**) adducts (94% yield). Analysis of the mixture was accomplished by ^1H and ^{13}C NMR spectroscopy and GC/MS.

iv. Epimerization of Diendo (**47**) and Diexo (**48**) (3:1 mixture) on 700° - Deuterated/Al_2O_3.

To a 250-ml round bottomed flask containing 20.0 g of 700° - deuterated alumina[58] was added dropwise (via syringe), under an argon atmosphere, a 3:1 mixture of diendo (**47**) and diexo (**48**) adducts (2.00 g, 9.52 mmol). The reaction was stirred for 20 hours at room temperature. The reaction mixture was then extracted with ether, filtered through $MgSO_4$, and concentrated *in vacuo* to afford a mixture of deuterated diendo (**47**), deuterated diexo (**48**), deuterated CP-DMF (**49**) adducts and deuterated DMM and DMF (94% overall yield). Analysis of the mixture was accomplished by GC/MS.

v. Isomerization of DMM to DMF on 700° - Al_2O_3. General Procedure D.

To a 250-ml round bottomed flask containing 25.0 g of 700 °C activated alumina was added dropwise, under an argon atmosphere, dimethyl maleate (1.25 mmol, 0.180 g). The reaction was allowed to stir for 20 hours at ambient temperature. The reaction mixture was then extracted with ether, filtered though $MgSO_4$, and concentrated *in vacuo*. The product mixture was analyzed by ^1H and ^{13}C NMR spectroscopy and GC/MS. 27.7% DMF was produced from DMM.

vi. $AlCl_3$-Catalyzed Diels-Alder Reaction of Dimethyl Maleate and Cyclopentadiene in CH_2Cl_2.

To a solution of DMM (2.13 mL, 17.0 mmol) in 200 mL of CH_2Cl_2 was added 2.27 g, (17.0 mmmol) of aluminum trichloride. The solution was stirred for 10 min. Cyclopentadiene (1.70 mL, 20.4 mmol) was added and the solution was stirred at ambient temperature for 20 h. The reaction mixture was washed first with water (2 x 200 mL), then with 5% $NaHCO_3$ (2 x 200 mL), and lastly with water again (2 x 200 mL). The organic extract was dried over anhydrous magnesium sulfate and concentrated under vacuum to afford a mixture of diendo (**47**) and diexo (**48**) adducts (>95% overall yield). Analysis of the mixture was accomplished by ^1H and ^{13}C NMR spectroscopy and GC/MS.

vii. Trapping Experiment for Retro-Diels-Alder Reaction. General Procedure E.

To a 250-mL round bottomed flask containing 20.0 g of 700 °C activated alumina under argon was added 0.860 ml of methyl acrylate (9.52 mmol) with stirring. After 20 minutes a 3:1 mixture of diendo (**47**) and diexo (**48**) adducts (2.00 g, 9.52 mmol) was added and the reaction stirred for 20 h at 55 °C. The reaction mixture was then extracted with ether, filtered through $MgSO_4$, and concentrated *in vacuo*. Analysis of the product mixture by ^1H NMR and GC/MS showed no CP-MAC adduct.

viii. Synthesis of (-)-Dimenthyl Fumarate.

To a 250-mL round bottomed flask was added fumaric acid (2.32 g, 20.0 mmol), (1R, 2S, 5R)-(-)-menthol (12.5 g, 80.0 mmol), 25 mL of benzene, and 1 mL of conc. H_2SO_4. The solution was refluxed for 12 hr. After cooling the solution to room temperature, it was washed twice with 20 mL of water, twice with saturated aq $NaHCO_3$, and twice again with 20 mL of water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue on silica with 5% ethyl acetate/hexanes gave (-)-dimenthyl fumarate as a colorless oil in 80% overall yield. ^{1}H NMR ($CDCl_3$) (ppm): δ 6.82 (2 H, s, vinyl), 4.81 (2 H, dt, J = 4.5, 10.8 Hz, methine next to oxygen), 0.7-2.2 (36 H, m, menthyl H); ^{13}C NMR ($CDCl_3$) (ppm): δ 164.7 (C = O), 134.0 (vinyl), 75.4 (menthyl carbon next to oxygen), and 47.1, 40.8, 34.2, 31.5, 26.3, 23.5, 22.1, 20.8 and 16.4 (remaining menthyl).

ix. Synthesis of (-)-Menthyl Methyl Fumarate.

To a 250-mL round bottomed flash was added (1R, 2S, 5R)-(-)-menthol (6.25 g, 40.0 mmol), maleic anhydride (3.92 g, 40.0 mmol), and 100 mL of benzene. The solution was refluxed for 12 hr. After cooling the solution to room temperature, it was extracted with saturated aq $NaHCO_3$ solution (3 x 100 mL). The $NaHCO_3$ extracts were combined and acidified with conc. HCl in an ice bath until the solution was acidic to litmus, after which it was extracted three times with ether (3 x 150 mL). The combined ether extracts were washed with water, dried with $MgSO_4$, and the solvent removed *in vacuo* to give monomenthyl maleic acid as a white solid in 70% yield. ^{1}H NMR

($CDCl_3$) (ppm): δ 10.98 (1 H, br s, COOH), 6.36 (2 H, s, vinyl), 4.84 (1 H, dt, J = 4.8, 10.8 Hz, methine next to oxygen), 0.7-2.1 (18 H, m, menthyl); ^{13}C NMR ($CDCl_3$) (ppm): δ 166.6 and 165.9 (C = O), 133.8 and 130.3 (vinyl), 77.1 (methine next to oxygen), and 46.6, 40.2, 33.8, 31.2, 26.0, 23.1, 21.7, 20.5 and 16.0 (menthyl). The white solid monomenthyl maleic acid so obtained was then dissolved in CCl_4 (10.0 mL CCl_4 for every 1.00 gm of monomenthyl maleic acid) and subjected to the light of a sun lamp while a 0.6 M solution of Br_2/CCl_4 was added dropwise (10-12 drops). The addition was stopped once an orange color persisted in the solution. After the orange color disappeared, more Br_2/CCl_4 was added dropwise until an orange color persisted. Removal of CCl_4 *in vacuo* gave a quantitative yield of monomenthyl fumaric acid as a white solid. ^1H NMR ($CDCl_3$) (ppm): δ 11.28 (1 H, s, COOH) 6.88 (1 H, s, vinyl), 6.86 (1 H, s, vinyl), 4.82 (1 H, dt, J = 4.5, 10.8 Hz, methine next to oxygen), 0.7-2.2 (18 H, m, menthyl); ^{13}C NMR ($CDCl_3$) (ppm): δ 170.3 and 164.4 (C = O), 136.3 and 132.6 (vinyl), 75.7 (methine next to oxygen), and 47.1, 40.3, 34.3, 31.4, 26.6, 23.7, 22.2, 20.7 and 16.5 (remaining menthyl).

The monomenthyl fumaric acid was converted to (-)-menthyl methyl fumarate by treating the acid with diazomethane in ether.[50] The product (a colorless oil) was purified by flash chromatography on silica gel using 10% ethyl acetate in hexanes. ^1H NMR ($CDCl_3$) (ppm): δ 6.88 (2 H, s, vinyl), 4.82 (1 H, dt, J = 4.5. 10.8 H, methine next to oxygen), 3.82 (3 H, s, methoxyl), 0.7-2.1 (18 H, m, menthyl); ^{13}C NMR ($CDCl_3$) (ppm): δ 165.4 and 164.3 (C = O), 134.5 and 132.9 (vinyl), 75.1 (menthyl next to oxygen), 52.3, (OCH_3), and 47.0, 40.8, 34.3, 31.6, 26.4, 23.6, 22.1, 20.6 and 16.2 (remaining menthyl).

x. Diels-Alder Reaction of (-)-Dimenthyl Fumarate and Cyclopentadiene on 400° - Al_2O_3 followed by Determination of Diastereomeric Excess by Chiral Shift Reagent. General Procedure F.

To a 250-mL round bottomed flask containing 47.3 g of 400 °C activated alumina under argon was added (-)-dimenthyl fumarate (3.93 g, 10.0 mmol) dissolved in 50 mL of ether. After stirring for 10 minutes the ether was removed *in vacuo*. Cyclopentadiene (1.00 mL, 12.0 mmol) was then added dropwise and the reaction was allowed to stir for 20 h at room temperature. The reaction mixture was extracted with ether and the solvent removed *in vacuo* to give the Diels-Alder **54** and **55** (> overall 90% yield). Analysis of the liquid mixture was accomplished by ^1H and ^{13}C NMR spectroscopy. ^1H NMR ($CDCl_3$) (ppm): δ 6.02 (2 H, m, vinyl), 4.6 (2 H, dt, $J = 4.5, 10.8$ Hz, methine next to oxygen), 3.20, 2.80 (4 H, m, CH), 1.40 (2 H, m, CH_2), 0.7-2.2 (36 H, m, menthyl H). ^{13}C NMR ($CDCl_3$) (ppm): δ 175.3 (exo C = O), 173.5 (endo C = O), 137.9 (vinyl), 135.2 (vinyl), 74.5 (methine next to oxygen), 53.7 (CH_2), 49.8 (CH), 47.4 (CH), 46.6 (CH next to COOMn), 45.2 (CH next to COOMn), 47.0, 40.2, 34.4, 31.2, 26.7, 23.8, 22.4, 20.7, and 16.4 (remaining menthyl).

The mixture of diesters, **54** and **55** (4.02 g, 8.77 mmol), was saponified in refluxing 70% methanolic KOH (6 h). The reaction mixture was then cooled to room temperature and the solvent removed *in vacuo* to give a white solid which was dissolved in distilled water. The aqueous solution was then extracted three times with ether to remove menthol and then acidified with conc. HCl in an ice bath until the solution was acidic to litmus. The solution ws then extracted several times with ether. The ether extracts were combined, washed with distilled water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield 1.52 g of the diacid. The diacid was then re-esterfied with diazomethane[50] in ether and the resulting colorless oil of the dimethyl ester was purified by flash chromatography on silica gel using 5% ethyl acetate in hexanes. ^1H NMR ($CDCl_3$) (ppm): δ 6.12 (2H, s, vinyl), 3.71 (3H, s, exo OCH_3), 3.64 (3H, s, endo OCH_3), 3.28 (4H, m, CH), 1.45 (2H, dd, CH_2); ^{13}C NMR ($CDCl_3$) (ppm): δ 174.4 (exo C = O), 173.2 (endo C = O), 137.2 (vinyl), 134.8 (vinyl), 51.7 (CH_2), 51.4 (CH), 47.6 (CH), 47.3 (endo OCH_3), 46.9 (exo OCH_3), 46.8 (CH next to OCH_3), 45.3 (CH next to OCH_3). The purified dimethyl ester was analyzed for e.e. by ^1H NMR in $CDCl_3$ using the chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) as follows: A 0.1 M solution of the chiral reagent in $CDCl_3$ was added dropwise to the dimethyl ester in $CDCl_3$ under argon and the complexed mixture was subjected to ^1H NMR analysis wherein the areas under the endo methoxy peaks of the two enantiomers were determined by integration (or the cut and weight) method to obtain the e.e. (More of the chiral reagent in $CDCl_3$ was added to the dimethyl ester at times when the endo methoxy peaks were not separated in the ^1H NMR). The assignments for the endo methoxy peaks were based on a comparison to those of previously published results.[23]

xi. Synthesis of BBr_3/Aluminas.[35(f)]

Hexane (50 mL) was added under argon to a 60-g sample of Al_2O_3, which had previously been activated at 400°, in a 250-mL round bottomed flask with side arm and stir bar. After cooling to 0°, 60 mmol of BBr_3 (1.0 M solution) in hexane was added through a double-ended 18 gauge needle. HBr gas is released during this operation. After stirring for 30 min, the liquid phase was removed *in vacuo*, leaving behind a free flowing powder **44**.

To 33 g of the above solid contained in an argon flushed 500-mL round bottomed flask, fitted with septum inlet and stir bar, was added dry hexane (33 mL) via a double-ended needle. After cooling in ice, a solution of 5.17 g (0.033 mol) of (-)-menthol in 33 mL of dry hexane was added under argon with stirring over 10 min. Some gas evolution was observed during the first half of the addition. After an additional 20 min, the solution was separated from the alumina by filteration through a fritted funnel under Ar. The resulting solid was washed three times under argon with 30-mL aliquots of dry hexane and then dried *in vacuo* to give **45**. (^{11}B SS NMR: broad singlet at 7.1 ppm relative to $NaBPh_4$ at δ = O ppm).

xii. Diels-Alder Reaction of Dimethyl Maleate and Cyclopentadiene in $LiClO_4$/Ether.

See Experimental Part II, General Procedure A, page 89.

xiii. Diels-Alder Reaction of (-)-Dimenthyl Fumarate and Cyclopentadiene in $LiClO_4$/Ether followed by Determination of Diastereomeric Excess by Chiral Shift Reagent.

See Experimental Part II. General Procedure B., page 90.

xiv. Diels-Alder Reaction of (-)-Dimenthyl Fumarate and Cyclopentadiene on 400°-Al_2O_3 followed by Determination of Diastereomeric Excess by 400 MHz ^1H NMR Spectroscopy. General Procedure G.

The reaction was carried out as described in Experimental Part I, General Procedure F. The diastereomeric ratio of adducts was determined by using high field (400 MHz) ^1H NMR spectroscopy wherein the vinyl resonances of the two diastereomers at $\delta = 5.98$ for **55** (1H, m, vinyl γ to exo COOMn) and $\delta = 6.04$ for **54** (1H, m, vinyl γ to exo COOMn) were used for the analysis. The areas under these peaks were determined by integration (or the cut and weigh) method.

xv. Diels-Alder Reaction of (-)-Menthyl Methyl Fumarate and Cyclopentadiene on 400° - Al_2O_3. General Procedure H.

To a 250-mL round bottomed flask containing 36.0 g of 400 °C activated alumina under argon was added (-)-menthyl methyl fumarate (2.68 g, 10.0 mmol) dissolved in 50 mL of ether. After stirring for 20 minutes the ether was removed *in vacuo*. Cyclopentadiene (1.0 mL,12 mmol) was then added dropwise and the reaction was allowed to stir for 20 h at room temperature. The reaction mixture was then extracted with ether and the solvent removed *in vacuo* to give the Diels-Alder adducts **57-60** (90% overall yield). Analysis of the diastereomeric mixture was accomplished by a combination of high field (400 MHz) ^{1}H NMR spectroscopy and GC/MS. The endo:exo ratio (**57+58**:**59+60**) was obtained by integration (or cut and weigh) of the methoxyl resonances at δ 3.61 ppm and δ 3.68 ppm, respectively. GC/MS was carried out on a 25-m crosslinked polyethylene glycol-TPA capillary column at 170 °C: t_R (**58+59**) = 74.7 min, t_R (**57**) = 78.6 min t_R (**60**) = 81.1 min (assignments are based on the work of Yamamoto).[47]

xvi. Diels-Alder Reaction of (-)-Dimenthyl Fumarate and Cyclopentadiene in 2.8 M $LiClO_4$/Ether followed by Determination of Diastereomeric Excess by High Field (400 MHz) ^{1}H NMR Spectroscopy. General Procedure I.

To a 100-mL round bottomed flask containing 15.98 g (150.2 mmol) $LiClO_4$ in 50.0 mL of anhydrous ether was added (-)-dimenthyl fumarate (3.93 g, 10.0 mmol). After stirring for 10 minutes, cyclopentadiene (1.0 mL, 12 mmol) was then added dropwise (total volume of the reaction mixture = 54.0 mL) and the reaction was allowed to stir for 20 h at room temperature (22 °C ± 1 °C). The reaction mixture was then washed with water (2 x 50 mL), 5% $NaHCO_3$ (2 x 50 mL), and water (2 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a diastereomeric mixture of **54** and **55** in 94% overall yield). Analysis of the mixture was accomplished by high field ^{1}H NMR spectroscopy as described in Experimental Part I, General

Procedure G, wherein the diastereomeric ratio (**55**:**54**) was obtained by integrating the vinyl resonances of the two diastereomers.

xvii. Diels-Alder Reaction of (-)-Menthyl Methyl Fumarate and Cyclopentadiene in 2.8 M $LiClO_4$/Ether. General Procedure J.

To a 100 mL round bottomed flask containing 15.98 g (150.98 mmol) $LiClO_4$ in 50.0 mL of anhydrous ether was added (-)-menthyl methyl fumarate (2.68 g, 10 mmol). After stirring for 10 minutes, cyclopentadiene (1.0 mL, 12 mmol) was then added dropwise (total volume of the reaction mixture = 53.0 ml) and the reaction was allowed to stir for 20 h at room temperature (22 °C ± 1 °C). The reaction mixture was then washed with water (2 x 50 mL), 5% aq $NaHCO_3$ (2 x 50 mL), and water (2 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give four diastereomeric adducts **57-60** in 92% overall yield). The mixture of diasteromeric adducts was analyzed by a combination of high field ^1H NMR spectroscopy and GC/MS as described in Experimental Part I, General Procedure H.

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PART II

A Chemical, Spectroscopic, and Theoretical Assessment of the Lewis Acidity of $LiClO_4$ in Diethyl Ether.

CHAPTER I

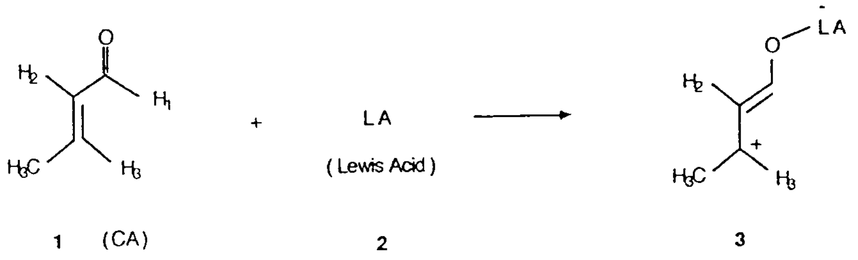
INTRODUCTION

As previously discussed in BACKGROUND, Part I, $LiClO_4$ in diethyl ether (LP/DE) is known to accelerate the rates of the Diels-Alder reactions by lithium ion catalysis[1,2] and not by a solvent effect.[3,4]

Braun and Sauer studied the Diels-Alder reaction of CP with MAC[4] in LP/DE and got an endo/exo selectivity of 7.3:1 (38.1 wt % LP). Later, Grieco and co-workers studied the Diels-Alder reaction of CP with ethyl acrylate[3] and got an endo/exo selectivity of 8:1 (5.0 M LP). The selectivity of both reactions is considerably less in the absence of LP, being 3:1 for the reaction of CP with MAC in ether[4] and 4:1 for the reaction of CP with ethyl acrylate in H_2O.[3]

Since LP/DE system has been used extensively as a catalyst in the Diels-Alder reactions including the ones just mentioned and other reactions,[5,6] it would be helpful to quantitate the Lewis acidity of LP/DE. The Lewis acidity of Li^+ in LP/DE system can be interpreted in many ways: kinetically, stereo- and regiochemically, thermodynamically, and others. Thus, the acidity can be studied by various methods, including chemical approaches, an NMR method, and MO calculations. In the chemical approach the regio- and stereoselectivity of a given reaction being carried out in LP/DE system is compared to the results obtained using other Lewis acids such as $AlCl_3$ and BBr_3 which are believed to be "strong" Lewis acids.

In the NMR method, as described by Childs and co-workers,[7] the effect that Lewis acids have on the ^1H and ^{13}C chemical shifts of α,β-unsaturated aldehydes and (ketones) such as crotonaldehyde (CA) (1) in methylene chloride is assessed at -20°C (Table II-1, II-2). They defined an empirical Lewis acidity scale based on the ability of the Lewis acid to shift the H_3 resonance to lower field. They proposed that the magnitude of the H_3 resonance shift of **1** (CA) on complexation with the Lewis acids ($\Delta\delta$) was proportional to the acid strength. This experimental method works because of the linear dependence of the H_3 chemical shift on the energy of the lowest π^* MO in the complex (3).[8] The shifts of H_2 and CH_3 resonances were small on complexation and the shifts for H_1 was found to be both upfield and downfield. Based upon the induced shift ($\Delta\delta$) of H_3 resonance of CA (1) on complexation with various Lewis acids, a Lewis acid scale was developed (Table II-3). On this scale BBr_3 is the strongest Lewis acid because it shifts H_3 the greatest and Et_3Al is comparatively a weaker Lewis acid.



(1)

Table II-1. ^1H Chemical Shift Differences ($\Delta\delta$) of Crotonaldehyde 1 on Complexation with Various Lewis Acids[a]

	Proton $\Delta\delta$ (ppm)			
Lewis acid	H1	H2	H3	CH_3
BBr_3	0.11	0.93	1.49	0.51
BCl_3	-0.65	0.85	1.35	0.49
$SBCl_5$	0.17	0.78	1.32	0.48
$AlCl_3$	-0.20	0.76	1.23	0.47
$EtAlCl_2$[b,c]	-0.20	0.77	1.25	0.47
BF_3	-0.27	0.74	1.17	0.44
$EtAlCl_2$[b,c,d]	-0.17	0.67	1.15	0.38
Et_3AlCl_3[b]	-0.15	0.69	1.14	0.39
$TiCl_4$	0.03	0.60	1.03	0.36
Et_3AlCl[b,c]	-0.15	0.55	0.91	0.30
$SnCl_4$	0.02	0.50	0.87	0.29
Et_3Al[b,c]	-0.34	0.42	0.63	0.23

Source: Reference 7.

[a] In ppm (± 0.01). Chemical shifts of uncomplexed base are: δ = 9.47 (d, 1H, H1), 6.10 (ddq, 1H, H2), 6.93 (m, 1H, H3), 2.02 (dd, 3H, H4 $\Delta\delta$ is positive for a downfield shift. Approximately 0.3 *M* solution in dichloromethane at -20 °C, unless otherwise stated.

[b] At =60°C. Chemical shifts of uncomplexed base: δ 9.84 (H1), 6.12 (H2), 6.98 (H3), 2.05 (H4) at this temperature.

[c] Written in monomeric form for simplicity.

[d] 2:1 in crotonaldehyde—$EtAlCl_2$.

Table II-2. ^{13}C Chemical Shift Differences ($\Delta\delta$) of Crotonaldehyde 1 on Complexation with Various Lewis Acids[a]

Lewis acid	Carbon $\Delta\delta$ (ppm)			
	C1	C2	C3	C4
BF_3	8.3	-3.3	26.1	3.1
BCl_3	6.8	-3.7	31.7	4.3
$SbCl_5$	6.9	-4.0	27.6	3.7
Et_2AlCl[b]	9.4	-2.0	20.1	2.3
$SnCl_4$	7.8	-2.8	19.2	2.3

Source Reference 7.

[a] In ppm (± 0.01). Chemical shifts of uncomplexed base are: δ = 194.7 (CL), 134.4 (C2), 155.2 (C3), 10.0 (C4). As approximately 0.3 *M* solution in dichloromethane at -20 °C. [b] Acid written in monomeric form for simplicity.

Table II-3. Lewis Acid Scale Based On $\Delta\delta$-values of H3 Resonance of Crotonaldehyde (CA, 1).

Lewis acid	Relative power
BBr_3	1.00 ± 0.005
BCl_3	0.93 ± 0.02
$SbCl_5$	0.85 ± 0.03
$AlCl_3$	0.82
BF_3	0.77 ± 0.02
$EtAlCl_2$	0.77
$TiCl_4$	0.66 ± 0.03
Et_2AlCl	0.59 ± 0.03
$SnCl_4$	0.52 ± 0.04
Et_3Al	0.44 ± 0.02

Source: Reference 7.

In the MO calculation approach, as described by Laszlo and Teston,[8] a Lewis acid scale can be generated based on the orbital properties of 1:1 complexes of CA and Lewis acid (Table II-4) as determined by MNDO calculations. They propose that since the complexation by a Lewis acid will lower all the molecular orbitals in α,β-unsaturated carbonyl compounds, there ought to be a relationship between the extent of this lowering and the catalytic activity. Hence, the calculated LUMO (π^*) (Lowest Unoccupied Molecular Orbital) energy of a 1:1 complex correlates with the strength of the given Lewis acid. Here the lower the LUMO energy is, the stronger the Lewis acid is. The results obtained by Laszlo and Teston (Table II-4) correlate reasonably well to the NMR results obtained by Childs and co-workers, wherein BBr_3 is a stronger Lewis acid than $AlCl_3$ and Et_2AlCl_3.

Because of the importance of LP/DE in organic reactions, both the NMR and MNDO methods were used, in conjunction with diastereoselectivities of Diels-Alder reactions, to determine the Lewis acidity of LP/DE.

Table II-4. Sequence of Lewis Acidities Obtained by the MNDO Method and Comparison with Other Methods[e]

Lewis acids	MNDO			
	ΔH_{int}[c] kcal · mol^{-1}	π^*, eV	relative Lewis acidity[d]	NMR[b] $\Delta\delta$, ppm
BCl_3	-6.63	-2.52	1.00	1.35
BBr_3	-8.17	-2.50	0.99	1.49
$SiCl_4$	-0.26	-2.43	0.96	
$AlBr_3$	-26.28	-2.37	0.94	
$AlCl_3$	-25.57	-2.31	0.91	1.23
$EtAlCl_2$	-19.97	-2.03	0.80	1.15
BF_3	+4.13	-1.93	0.76	1.17
Et_2AlCl	-15.56	-1.82	0.71	0.91
AlF_3	-16.25	-1.77	0.69	
$Me(OPh)_2Al$	-11.40	-1.76	0.68	
$HgCl_2$	-2.49	-1.74	0.68	
$HgBr_2$	+4.38	-1.72	0.67	
HgF_2	-0.47	-1.71	0.66	
HgI_2	+9.78	-1.66	0.64	

Table II-4 (continued).

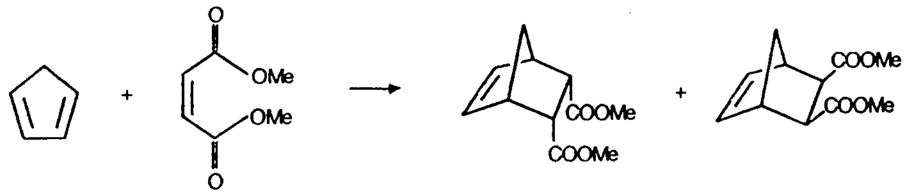
Lewis acids	**MNDO** ΔH_{int}[c] kcal · mol^{-1}	π^*, eV	relative Lewis acidity[d]	**NMR[b]** $\Delta\delta$, ppm
Et_3Al	-10.09	-1.62	0.63	0.63
$SnCl_4$	+10.05	-1.58	0.61	0.87
AlH_3	-16.86	-1.56	0.60	
HgH_2	+16.76	-0.99	0.36	

Source: Reference 8.
[a] Shifts of the carbonyl stretching frequency in ethyl acetate complexes.[9]
[b] Variations of H-3 chemical shift in crotonaldehyde.[7] [c] Calculated MNDO values for the energies of interaction (heat of formation of the complexes—sum of heats of formation of the reactants). [d] BCl_3 = 1.00 and the π^* energy of uncomplexed crotonaldehyde (—0.11 eV) used to define the zero of the Lewis acidity scale.
[e] Comparison with the compilation by Satchell[10] is made difficult by the variety of the bases against which Lewis acids are pitted and by solvent effects.

CHAPTER II

RESULTS AND DISCUSSION

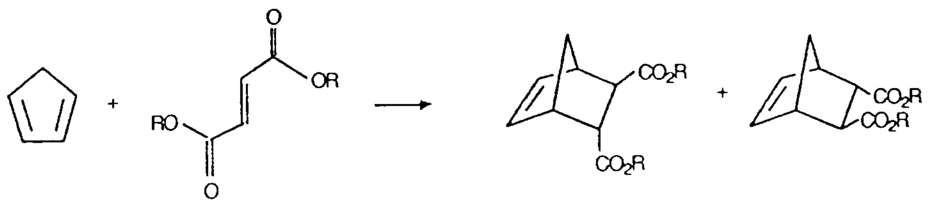
As discussed previously in RESULTS AND DISCUSSION, PART I-B, moderate diastereoselectivities are obtained for the LP/DE catalyzed Diels-Alder reactions of DMM, DMnF and MnMF with CP. The 6 M LP/DE-catalyzed Diels-Alder reaction of DMM with CP (Eq. 2) gave an diendo:diexo ratio of 8:1 which is much lower than the ratio of 20:1 obtained for the $AlCl_3/CH_2Cl_2$-catalyzed reaction. The LP/DE-catalyzed



4 5 6 Diendo 7 Diexo

(2)

Diels-Alder reaction of DMnF and CP (Eq. 3) gave an optimum d.e. of 20.6% (9

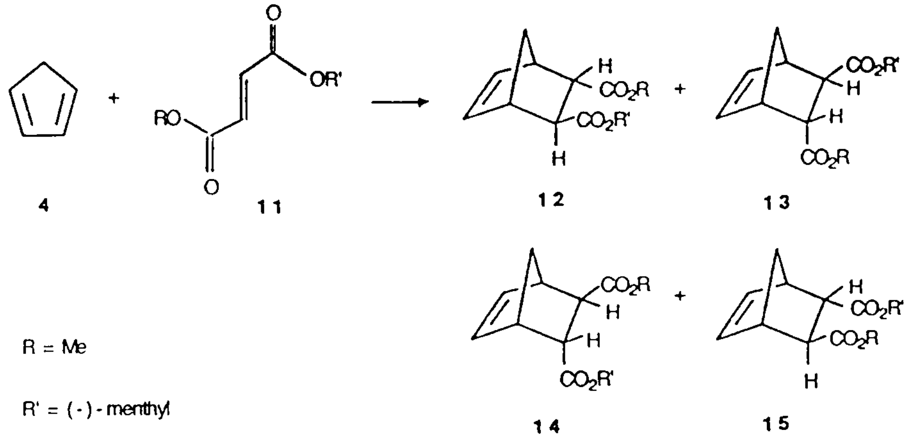


4 8 9 10

(3)

R = (-) - menthyl

predominating) which is much lower as compared to the d.e. of 91 % for the Et_2AlCl-catalyzed reaction.[15] The LP/DE-catalyzed Diels-Alder reaction of MnMF with CP (Eq. 4) did not show any selectivity in the endo:exo methoxy ratio (N:X), which is (**12** + **13**):(**14**+**15**), whereas the N:X selectivity is >98:2 for the MAD-catalyzed reaction.[16] The moderate diastereoselectivity obtained for the above mentioned reactions can be traced to the fact that Li^+ is highly solvated with ether and ClO_4^-. The moderate diastereoselectivity infers that LP/DE is a moderate Lewis acid.



(4)

The NMR method to assess the Lewis acidity of LP/DE was carried out by using the procedure described by Childs and co-workers,[7] wherein the induced downfield shift of H_3 of CA (**1**) in various LP/DE concentrations was measured at -20 °C (Table II-5). It should be noted that CH_2Cl_2 could not be used as a solvent to compare the results to that obtained by Childs and co-workers as LP is not soluble in CH_2Cl_2. Besides it is the acidity of LP/DE which needed to be assessed.

As can be seen from Table II-5 the induced downfield shift of H_3 of CA increases with increasing LP concentration. Because LP complexes to CA reversibly, the observed chemical shifts are a weighted average of the shifts of complexed and uncomplexed CA. It was thus necessary to extrapolate the data to infinite LP concentration to obtain the shift due to the CA-LP complex alone. To accomplish this, Pagni, *et al.* have developed a mathematical model to accomplish this.[12] In the model CA is assumed to complex to LP reversibly (Eq 5).

$$\mathrm{CA} + \mathrm{LP} \rightleftharpoons \mathrm{CA\text{-}LP} \qquad (5)$$

Therefore,

$$K_{eq} = \frac{[\mathrm{CA\text{-}LP}]}{[\mathrm{CA}]\,[\mathrm{LP}]} \qquad (6)$$

Since $[\mathrm{LP}]_o = [\mathrm{LP}] + [\mathrm{CA\text{-}LP}]$ and $[\mathrm{CA}]_o = [\mathrm{CA}] + [\mathrm{CA\text{-}LP}]$, where $[\mathrm{LP}]_o$ and $[\mathrm{CA}]_o$ are the initial concentrations, one obtains

$$K_{eq} = \frac{([\mathrm{CA}]_o - [\mathrm{CA}])}{[\mathrm{CA}]\,([\mathrm{LP}]_o - [\mathrm{CA}]_o + [\mathrm{CA}])} \qquad (7)$$

Furthermore, if the observed shift is a weighted average of the shifts due to CA and CA-LP, it follows that,

$$\delta = \frac{[\mathrm{CA}]}{[\mathrm{CA}] + [\mathrm{CA\text{-}LP}]}\,\delta_A + \frac{[\mathrm{CA\text{-}LP}]}{[\mathrm{CA}] + [\mathrm{CA\text{-}LP}]}\,\delta_{\mathrm{CA\text{-}LP}} \qquad (8)$$

where δ_A is the shift for H_3 of CA and $\delta_{\mathrm{CA\text{-}LP}}$ is the shift for H_3 of CA-LP complex. The induced shift, $\Delta\delta$, can then be represented as,

$$\delta\Delta = \delta - \delta_A = -\frac{[\mathrm{CA\text{-}LP}]}{[\mathrm{CA}] + [\mathrm{CA\text{-}LP}]} + \frac{[\mathrm{CA\text{-}LP}]}{[\mathrm{CA}] + [\mathrm{CA\text{-}LP}]}\,\delta_{\mathrm{CA\text{-}LP}} \qquad (9)$$

Table II-5. Induced Chemical Shifts of Crotonaldehyde (H_3) and Diethyl Ether in Solutions of CA in LP/DE at -20 °C

			Induced Shifts			
	Initial Concentration		CA		Diethyl Ether	
Entry	$[LP]_0$	$[CA]_o$	$\Delta\delta_{exp}$[a]	$\Delta\delta_{the}$[b]	$\Delta\delta(CH_2)$[c]	$\Delta\delta(CH_3)$[c]
1	0.30	0.24	0.25	0.27	0.01	0.03
2	0.45	0.36	0.33	0.32		
3	0.60	0.48	0.38[d]	0.36	0.05	0.03
4	1.0	0.80	0.44[d]	0.44	0.07	0.04
5	2.0	1.6	0.54	0.53	0.12	0.07
6	5.0	4.0	0.61	0.62	0.28	0.13

Source: Reference 12.

[a] Relative to $CA(H_3)$ in DE at -20°C. [b] Values obtained assuming $K_{eq} = 3.20$ and $\Delta\delta_{\infty} = 0.764$. [c] Chemical shifts relative to those for DE at -20 °C. [d] See reference 11.

Since $[CA]_o$ = [CA] + [CA-LP], rearranging Eq. 9 gives,

$$\Delta\delta = \frac{[CA]_o - [CA]}{[CA]_o} \quad \Delta\delta \tag{10}$$

where $\Delta\delta_\infty$ is the induced shift of the complex ($\delta_{CA\text{-}LP}$-δ_A). From equations 7 and 10, one obtains after considerable manipulation,

$$([CA]_o\Delta\delta\text{-}[LP]_o\Delta\delta_\infty)\ (\Delta\delta\text{-}\Delta\delta_\infty)\ K_{eq} = \Delta\delta\Delta\delta_\infty \tag{11}$$

One then adjusts K_{eq} and $\Delta\delta_\infty$ to fit the experimental data. As shown in Table II-5 K_{eq} = 3.20 and $\Delta\delta_\infty$ = 0.764 yields theoretical $\Delta\delta$ values close to the experimental ones. Because the measured induced shifts are accurate to ±0.02, the induced shift at infinite concentration of LP is 0.76 ± 0.02.

Because Childs and co-workers measured the induced chemical shift of H_3 of CA for various Lewis acids in CH_2Cl_2, and the present data were determined in ether, it was necessary to examine the behavior of several other Lewis acids (BBr_3, BF_3 and $AlCl_3$) with CA in ether to provide a bridge to the data obtained for these Lewis acids in CH_2Cl_2 (Table II-6).

Table II-6. Induced Chemical Shifts of CA(H_3) in CH_2Cl_2 and DE Solutions Containing Lewis Acids[a]

	Lewis acid (concn)			
Solvent	BBr_3	BF_3	LP	$AlCl_3$
CH_2Cl_2[b]	1.49	1.17		1.23
Diethyl Ether (DE)	0.94 (1 *M*)	0.26 (2 *M*)	0.53 (1 *M*)	1.61 (1 *M*)[d]
	1.02 (2 *M*)	0.91 (neat)[c]	0.76 (limiting)	

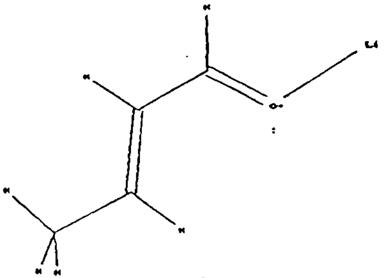
Source: Reference 12.
[a]25% excess Lewis acid relative to CA unless stated otherwise. [b]Data from ref. 7, [c]BF_3Et_2O plus CA in a 4:3 ratio. [d]Two-phase system was obtained wherein CA resided in the lower phase.

It can be seen from Table II-6 that the induced shifts of H_3 of CA in 2 M BBr_3/Et_2O and neat $BF_3 \cdot Et_2O$ (approximately 8 M BF_3) at -20 °C are 1.02 and 0.91, respectively, which are greater than the shift of 0.76 ± 0.02 obtained at infinite LP concentration. The limiting shifts for BBr_3 and BF_3 would undoubtedly be larger still. Thus, BBr_3 and BF_3 are stronger Lewis acids than LP in ether.

When 1 M $AlCl_3/Et_2O$ was treated with CA at -20 °C a two-phase system was obtained in which CA was found only in the lower phase with broad resonances. The induced shift of 1.61 did not change when $AlCl_3$ concentration was increased from 25% excess to 75% excess relative to CA. The induced shifts of ether [0.48 (CH_2) and 0.36 (CH_3)] in the lower layer also did not change when the $AlCl_3$ concentration was increased. However, the induced shifts of ether in the upper layer changed from 0.08 (CH_2) and 0.10 (CH_3) to 0.19 (CH_2) and 0.15 (CH_3) when 75% excess $AlCl_3$ was used.

It appears that the excess $AlCl_3$ went to the upper layer of the two-phase system, probably due to the fact that the lower layer was already saturated in $AlCl_3$ when 25% excess $AlCl_3$ was used. Since the induced chemical shift of H_3 of CA (1.61) is greater in $AlCl_3/Et_2O$ than the corresponding shift in LP/DE (0.76), $AlCl_3$ is also a stronger Lewis acid than LP in ether.

The theoretical method to assess the Lewis acidity of LP/DE, namely the MNDO calculation, was carried out according to the procedure described by Laszlo and Teston,[8] wherein the calculated LUMO energy correlates to the strength of the given Lewis acid. The MNDO calculation was carried out on a 1:1 complex of CA and Li^+ (we acknowledge Dr. J. E. Bartmess for help with the theoretical calculation). The geometry of the complex needed for the MNDO calculation was obtained by molecular mechanics calculation (CA, cisoid, planar; Li^+, in plane, anti to the C_1-C_2 bond of CA, **12**). The MNDO calculation gave a LUMO energy of -4.57 eV for the CA-Li^+ complex (**12**).



12

This value is far more negative than any determined by Laszlo and Teston. This means that Li^+ is a far stronger Lewis acid than BCl_3 (LUMO energy of -2.52 eV, Table II-4), the strongest Lewis acid on the Laszlo-Teston scale. The calculated enthalpy of interaction (ΔH_{int}) for the CA-Li^+ complex formation (-47.92 kcal/mol)is also more exothermic than the ΔH_{int} for various other Lewis acids on the Laszlo-Teston scale (Table II-4).

The MNDO calculation which mimics behavior in the gas phase suggests that Li^+ is a very strong Lewis acid, but the NMR and diastereoselectivity results suggest that the Li^+ in LP/DE is a moderate Lewis acid. The difference clearly lies in the difference between the gas-phase and solution. The "gas-phase" MNDO calculation neglects the counterion (ClO_4^-), which should moderate the acidity of Li^+ by formation of ion pairs in solution due to cation-anion interactions. Also, in ether the Li^+ is complexed to the oxygen of the solvent and transfer of Li^+ from $Et_2O \cdot Li^+$ to CA will be less exothermic than for the corresponding reaciton of Li^+ alone to CA in the gas-phase. This has been verified experimentally (Eq. 12 and 13).[13] In the gas-phase the CA-Li^+ complex is not subjected to solvation, however, in solution, the CA-Li^+ complex will be solvated by ClO_4^- and ether, this will make the LUMO of CA-Li^+ complex less negative thus reducing the Lewis acidity of LP/DE. Ab initio calculations carried out by Lefour *et al.* on various Li^+-acrolein complexes in which the number of solvating water molecules is varied prove this.[14]

	ΔH_{int} (Kcal/mol)	
$Li^+ + CH_2O \rightarrow CH_2OLi^+$	-36	(12)
$MeO \cdot Li^+ + CH_2O \rightarrow CH_2OLi^+ + Me_2O$	+3.5	(13)

CHAPTER III

EXPERIMENTAL SECTION

A. Materials

i. Solvents

Anhydrous Ethyl Ether, Mallinckrodt, ACS grade
Hexanes, Mallinckrodt, ACS grade
Ethyl Acetate, Mallinckrodt, ACS grade
All the solvents were used as purchased.

ii. Gases

Argon, Ar, MG Industries, prepurified Ar ws used without further purfication.

iii. Reagents

Dimethyl Maleate, Aldrich Chemical Co.
(IR, 2S, 5R)-(-)-Menthol, Aldrich Chemical Co.
Fumaric Acid, Aldrich Chemical Co.
Lithium Perchlorate, Aldrich Chemical Co.
Dicyclopentadiene, Aldrich Chemical Co.
Diazald, Aldrich Chemical Co.
Decane, Aldrich Chemical Co.
All the reagents were used as received.

B. Experimental Methods

i. Analytical Methods

Gas chromatography was performed on a Hewlett-Packard 5890A GC instrument equipped with a 30 m x 1/8" column packed with 30% SE-30 by weight on Chromosorb W as the solid support. Gas chromatograph/Mass spectrometry (GC/MS) was performed using a Hewlett-Packard 5970 Gas chromatograph/mass spectrometer.

Nuclear magnetic resonance spectra were recorded either on a 90 MHz JEOL FX-90Q spectrometer or a 250 MHz BRUKER spectrometer. Samples were run in $CDCl_3$ with 1% tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million downfield from TMS.

ii. Apparatus and Manipulation of Reagents

Commercially available (Aldrich) lithium perchlorate was dried under high vacuum (P_2O_5 trap) at 160 °C for 48 h. Lithium perchlorate is thermally stable at or above its melting point of 247 °C. Due to moisture sensitivity of $LiClO_4$ and ether, all manipulations were performed under dry argon in a glove bag. All glassware, syringes and needles were oven-dried at 100 °C for 6 hours, assembled hot, and cooled under a stream of argon before use. The reactions were performed under an argon atmosphere.

C. Experimental Procedures

i. Diels-Alder Reaction of Dimethyl Maleate and Cyclopentadiene in 5.7 *M* $LiClO_4$/Ether. General Procedure A.

To a 100-mL round-bottomed flask containing 63.9 g $LiClO_4$ (601 mmol) in 100 mL of anhydrous ether was added DMM (2.50 mL, 20.0 mmol). After stirring for 10 minutes, cyclopentadiene (2.00 mL 24.0 mmol) was then added dropwise (total volume of the reaction mixture = 105 mL) and the reaction was allowed to stir for 20 h at room temperature. The reaction mixture was then washed twice with 100 mL of water, twice with 100 ml of 5% aq $NaHCO_3$, and twice again with 100 ml of water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a mixture of diendo (**6**) and diexo (**7**) adducts in 94% yield. Analysis of the mixture was accomplished by ^1H and ^{13}C NMR spectroscopy and GC/MS. ^1H NMR ($CDCl_3$) (ppm), diendo (**6**): 6.25 (2 H, s, vinyl), 3.60 (6 H, s, OCH_3), 3.20 (4 H, m, CH), 1.40 (2 H, dd, CH_2); diexo (**7**): 6.20 (2 H, s, vinyl), 3.65 (6 H, s, OCH_3), 2.80 (4 H, m, CH), 1.58 (2 H, dd, CH_2). ^{13}C NMR ($CDCl_3$ (ppm), diendo (**6**): 172.8 (C = O), 134.8 (vinyl), 51.4 (CH_2, 48.6 (CH), 47.9 (OCH_3), 46.2 (CH next to COOMe); diexo (**7**): 173.8 (C = O), 137.9 (vinyl), 51.8 (CH_2), 47.2 (CH), 47.2 (OCH_3), 45.5 (CH next to $COOCH_3$).

ii. Diels-Alder Reaction of (-)-Dimenthyl Fumarate with Cyclopentadiene in 2.8 M $LiClO_4$/Ether followed by Determination of Diastereomeric Excess by Chiral Shift Reagent. General Procedure B.

To a 100-mL round-bottomed flask containing 15.98 g (150.2 mmol) $LiClO_4$ in 50.0 mL of anhydrous ether was added (-)-dimenthyl fumarate (3.93 g, 10.0 mmol, See Experimental Part I, viii). After stirring for 10 minutes, cyclopentadiene (1.00 mL, 12 mmol) was then added dropwise (total volume of the reaction mixture = 54.0 mL) and the reaction was allowed to stir for 20 h at room temperature. The reaction mixture was then washed twice with 50 mL of water, twice with 50 mL of 5% $NaHCO_3$, and twice again with 100 mL of water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a diastereomeric mixture of **9** and **10** in 92% yield. Analysis of the mixture was accomplished by ^1H and ^{13}C NMR spectroscopy. ^1H NMR ($CDCl_3$) (ppm): δ 6.02 (2 H, m, vinyl), 4.6 (2 H, dt, J = 4.5, 10.8 Hz, methine next to oxygen), 3.20, 2.80 (4 H, m CH), 1.40 (2 H, m, CH_2), 0.7—2.2 (35 H, m menthyl H).

The mixture of diesters **9** and **10** (4.00 g, 8.73 mmol) was saponified in refluxing 70% methanolic KOH (231 mL, 6 h). The reaction mixture was then cooled to room temperature and the solvent removed *in vacuo* to give a white solid which was dissolved in distilled water. The aqueous solution was then extracted three times with ether to remove menthol and then acidified with conc. HCl in an ice bath until the solution was acidic to litmus paper. The solution was then extracted several times with ether. The ether extracts were combined, washed with distilled water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield 1.49 g of the diacid. ^1H NMR ($CDCl_3$): δ 8.48 (2

H, br s, COOH), 6.20 (2 H, m, vinyl), 3.28 (4 H, m, CH), 1.52 (2 H, dd, CH_2). ^{13}C NMR ($CDCl_3$): δ 180.1 (exo COOH), 178.9 (endo COOH), 138.1 (vinyl), 135.2 (vinyl), 52.3 (CH_2), 52.1 (CH), 47.6 (CH next to COOH), 46.9 (CH next to COOH), 45.4 (CH next to COOH). The diacid was then re-esterfied with diazomethane in ether and the resulting dimethyl ester was purified by flash chromatography on silica gel using 5% ethyl acetate in hexanes. The purfied dimethyl ester was analyzed for e.e. by ^1H NMR in $CDCl_3$ using the chiral shift reagent *tris*-(3-heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III) (see Experimental Part I (x) for detailed analysis).

iii. NMR Experiment to Determine the Chemical Shift of H_3 in Crotonaldehyde (1).

To a 50-mL round-bottomed flask, which was flame dried under argon, was added at -78 °C, the Lewis acid, ether, and crotonaldehyde. After allowing the solution to stir for 15 minutes, the mixture was transferred under argon to a 5 mm NMR tube which was fixed in a 10 mm NMR tube containing $CDCl_3$/TMS as the standard and the spectrum was recorded at -20°C.

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11. For entries 3 and 4 $\Delta\delta_{exp}$ values of 0.51 and 0.53 were obtained, however these values did not correlate to the $\Delta\delta_{the}$ values in any scheme, including the scheme where $K = 3.20$ and $\Delta\delta_{\infty} = 0.764$. Repeating the experiment gave the values of 0.38 and 0.44 for entries 3 and 4 which correlate to the $\Delta\delta_{the}$ values. No explanation for the discrepancy in the original data is being offered.

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Vita

Satinder Bains was born in Bombay, India. He completed his schooling from Fatima High School, Bombay, India. He then attend the University of Bombay, India and received a Bachelor of Science degree in Chemistry in May 1984, and a Master of Science degree in Organic Chemistry in May 1986. In August 1987, he accepted a teaching assistantship from Southern Illinois University at Edwardsville, Illinois and received a Master of Science degree in Chemistry in August 1989. In August 1989, he began his study with a teaching assistantship toward a Ph.D. in Organic Chemistry at The University of Tennessee, Knoxville, Tennessee. In August 1993, he was employed by Arkansas State University, Beebe, Arkansas as Assistant Professor of Chemistry. He graduated with a Doctor of Philosophy degree in December 1993.