

MODELING THE SELECTIVITY IN PERICYCLIC REACTIONS

by

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*To my grandfather, Hasan Eren
and
my mother, Nurhan Çelebi*

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ABSTRACT

MODELING THE SELECTIVITY IN PERICYCLIC REACTIONS

Pericyclic reactions are very powerful and widely utilized transformations to obtain complex molecules. The selective versions have received remarkable interest and have found extensive use in synthetic organic chemistry to access complex biologically active targets. In this work, the mechanistic details of some highly useful pericyclic reactions have been explored and the origins of the selectivity have been investigated.

The first reaction of interest was the Diels–Alder reactions of α -keto- β,γ -unsaturated phosphonates with cyclopentadiene and 1,3-cyclohexadiene. The reaction constitutes an easy and straightforward method for the synthesis of dihydropyran derivatives, which are efficient substrates in the preparation of chiral building blocks.

Second, diastereoselective cycloadditions of different chiral anthracene templates with maleic anhydride were explored. This reaction serves as the key element in determining the final stereochemistry of the product in the preparation of complex biologically active molecules such as butenolides, α,β -unsaturated lactams and related compounds in their enantiomerically pure forms.

Finally, [3,3]- and [1,3]-sigmatropic rearrangements of allylic acetimidates have been studied. These reactions yield β -amino acid and allyl amine derivatives that are important building blocks found in many bioactive molecules.

In this work, bis-pericyclic, pseudopericyclic and stepwise pathways were shown to play a substantial role in determining the experimental observables such as the product distributions and the selectivity of the reaction, beside the widely accepted concerted pericyclic mechanism. The effect of catalysts on the mechanism and the selectivity have been studied and discussed in detail. The fundamental interactions in the key transition states have been analyzed and the factors affecting the stereoselectivity of the reaction

have been elucidated. Comparative studies on highly selective and non selective variants have allowed us to identify the elements responsible for controlling the selectivity of the reactions of interest.

This work brings a new perspective to the mechanism of pericyclic reactions and provides a deeper insight into the factors that determine the selectivity. However, the scope of the pericyclic reactions is very large and highly useful examples are not limited to the ones discussed in this dissertation. Future work will undoubtedly uncover many other important aspects of selective pericyclic reactions. Several suggestions for prospective studies have been outlined in the final chapter.

ÖZET

PERİSİKLİK TEPKİMELERDE SEÇİCİLİĞİN MODELLENMESİ

Perisiklik tepkimeler, karmaşık moleküllerin elde edilmesinde çok etkili ve yaygın olarak kullanılan kimyasal dönüşümlerdir. Özellikle seçici örneklerinin büyük ilgi gördüğü bu tepkimeler, biyolojik aktif hedeflere ulaşmak için organik kimya alanında geniş kullanım alanı bulmaktadır. Bu çalışmada, çok kullanışlı bazı perisiklik tepkimelerin mekanistik ayrıntıları incelenmiş ve seçiciliğin kaynağı araştırılmıştır.

İlk olarak çalışılan tepkime, α -keto- β,γ -doymamış fosfonatların siklopentadien ve 1,3-sikloheksadien ile Diels–Alder tepkimesidir. Bu tepkime, kiral yapı taşlarının hazırlanmasında aktif bir sübstre olan dihidropiran türevlerinin doğrudan sentezi için kullanılan kolay ve etkili bir yöntemdir.

İkinci olarak, farklı kiral antrasen kalıpları ile maleik anhidritin diastereoseçici çevrimsel eklenme tepkimeleri incelenmiştir. Bu tepkimeler, bütanolidler, α,β -doymamış laktamlar ve türevleri gibi karmaşık biyolojik aktif moleküllerin enansiyomerik saf olarak hazırlanmasında, ürünün stereokimyasını belirleyen anahtar faktörler olarak görev alırlar.

Son olarak, alilik asetimidlerin [3,3]- ve [1,3]-sigmatropik düzenlenme tepkimeleri çalışılmıştır. Bu tepkimeler, birçok biyoaktif molekülün önemli yapıtaşı olan β -amino asit ve alilamin türevlerini verir.

Bu çalışmada, çoğunlukla kabul edilen uyarlanmış perisiklik mekanizmanın yanı sıra, bis-perisiklik, pseudo-perisiklik ve adımsal yolların, ürün dağılımları ve seçicilik gibi deneysel gözlemlenebilirliklerin belirlenmesinde önemli bir rol oynadığı gösterilmiştir. Katalizörlerin mekanizma ve tepkimenin seçiciliği üzerindeki etkisi çalışılmış ve ayrıntılı bir biçimde tartışılmıştır. Anahtar geçiş konumlarındaki temel etkileşimlerin analizi yapılmış ve stereoseçiciliğe etki eden faktörler açıklanmıştır. Seçici ve seçici olmayan

örneklerin karşılaştırmalı çalışması, ilgili tepkimelerde seçiciliği kontrol eden faktörlerin belirlenmesine olanak tanımıştır.

Bu çalışma, perisiklik tepkimelerin mekanizmalarına yeni bir bakış açısı getirmiş ve seçiciliği belirleyen faktörlere daha derin bir anlayış sağlamıştır. Bununla birlikte, perisiklik tepkimelerin kapsamı çok geniştir ve önemli örnekler bu tez kapsamında yer verilenlerle sınırlı değildir. Hiç şüphe yoktur ki, gelecekte yapılacak olan çalışmalar, perisiklik tepkimelerle ilgili daha birçok önemli bilgiyi açığa çıkartacaktır. Son bölümde, ileriye yönelik araştırma önerilerine yer verilmiştir.

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LIST OF SYMBOLS/ABBREVIATIONS

E	Electronic energy
$E[\rho(\mathbf{r})]$	Electronic energy from electron density
$E_C[\rho(\mathbf{r})]$	Correlation energy
E_C^{DFT}	DFT Correlation energy
$E_X[\rho(\mathbf{r})]$	Exchange energy
E_X^{DFT}	DFT exchange energy
E_X^{exact}	Exact exchange energy
E_X^{HF}	Hartree-Fock exchange energy
$E_{\text{xc}}[\rho(\mathbf{r})]$	Exchange correlation energy functional
$\hat{f}_i(1)$	Fock operator
$F(\mathbf{r}_s)$	Electric field perpendicular to the surface
$\hat{H}$	Hamiltonian operator
$\hat{H}^{\text{core}}(1)$	Core-Hamiltonian operator
$\hat{J}_j(1)$	Coulomb operator
$J[\rho(\mathbf{r})]$	Coulomb energy
J_{ij}	Coulomb integral
$\hat{K}_j(1)$	Exchange operator
K_{ij}	Exchange integral
$T[\rho(\mathbf{r})]$	Kinetic energy of interacting electrons
$T_s[\rho(\mathbf{r})]$	Kinetic energy of the non-interacting electrons
U_{xc}^λ	Potential energy of exchange-correlation at intermediate coupling strength
U_x^σ	Exchange energy density
$V_{\text{ee}}[\rho(\mathbf{r})]$	Interelectronic interactions
$V_{\text{ext}}(\mathbf{r})$	External potential
V_{KS}	Kohn-Sham potential
$V_\sigma(\mathbf{r})$	Potential from the surface charge
$V_{\text{xc}}[\mathbf{r}_1]$	Exchange-correlation potential

$\text{\AA}$	Angstrom
$\Delta E_{\text{C}}^{\text{GC}}$	Gradient correction to the correlation energy
$\Delta E_{\text{X}}^{\text{GC}}$	Gradient correction to the exchange energy
$\Delta G^{\ddagger}$	Activation Gibbs free energy
$\Delta H^{\ddagger}$	Activation enthalpy
ε_{C}	Correlation contribution to energy density
ε_{X}	Exchange contribution to energy density
$\varepsilon_{\text{XC}}(\rho(\mathbf{r}))$	Energy density
ϵ	Dielectric constant
λ	Interelectronic coupling strength
$\rho(\mathbf{r})$	Electron density
$\sigma(\mathbf{r}_{\text{s}})$	Charge density on the surface of the cavity
χ_i	Spin orbital
ψ_i	Kohn-Sham orbitals
ACM	Adiabatic connection method
AM1	Austin method 1
B3LYP	Becke-3-Lee-Yang-Parr
B88	Becke 88
B-LYP	Becke-Lee-Yang-Parr
CC	Coupled cluster
CNDO	Complete neglect of differential overlap
CI	Configuration interaction
DA	Diels–Alder
DFT	Density functional theory
GC	Gradient corrected
GGA	Generalized gradient approximation
HDA	Hetero-Diels–Alder
HF	Hartree-Fock
HOMO	Highest occupied molecular orbital
IEFPCM	Integral equation formalism polarized continuum model
INDO	Intermediate neglect of differential overlap

IRC	Intrinsic reaction coordinate
LCAO	Linear combination of atomic orbitals
LDA	Local density approximation
LUMO	Lowest unoccupied molecular orbital
LYP	Lee-Yang-Parr
MCSF	Multiconfiguration self consistent field
MINDO/3	Modified intermediate neglect of differential overlap/3
MNDO	Modified neglect of diatomic overlap
MO	Molecular orbital
MP	Moller-Plesset
MP2	Second order perturbation
MP3	Third order perturbation
MP4	Fourth order perturbation
MRCI	Multi-reference configuration interaction
NBO	Natural bond orbital
NDDO	Neglect of diatomic differential overlap
PCM	Polarizable continuum model
PES	Potential energy surface
PM3	Parameterization method 3
SCF	Self-consistent field
SOI	Secondary orbital interaction
STO	Slater type orbital
TS	Transition state
UEG	Uniform electron gas
VDW	Van der Waals
VRI	Valley-ridge inflection point
VWN	Vosko-Wilk-Nusair

1. INTRODUCTION

Pericyclic reactions represent an important class in organic chemistry besides ionic and radical reactions (Figure 1.1). Radical reactions involve the correlated movement of single electrons, whereas in ionic reactions pairs of electrons move in one direction. Pericyclic reactions also involve the movement of electron pairs but they move in a closed loop and there is no absolute sense in which they flow from one component to the other. As a result, pericyclic reactions have cyclic transition structures in which concerted rearrangement of the electrons causes σ - and π -bonds to simultaneously break and form.

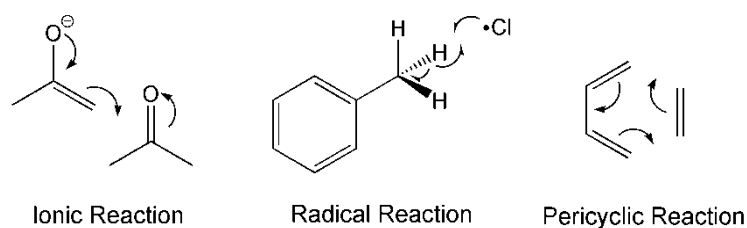


Figure 1.1. Classes of organic reactions.

Pericyclic reactions can be divided into four main subcategories: cycloadditions, electrocyclic reactions, sigmatropic rearrangements and group transfer reactions [1] (Figure 1.2). Cycloadditions consist of the formation of two σ -bonds in dispense of two π -bonds. In group transfer reactions, one π -bond is converted into a σ -bond, as another σ -bond migrates. Electrocyclizations and sigmatropic shifts are unimolecular rearrangements. Electrocyclic reactions involve the translation of one π -bond into a new σ -bond, whereas, in sigmatropic rearrangements, a new σ -bond forms as another σ -bond breaks.

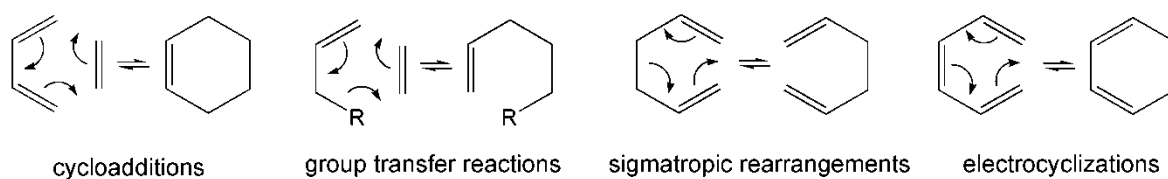


Figure 1.2. Subclasses of pericyclic reactions.

In this dissertation, we focus on modeling the novel examples of highly selective cycloadditions and sigmatropic rearrangements.

Cycloadditions are by far the most abundant and useful of pericyclic reactions [1]. The Diels–Alder reaction [2] is one of the most powerful and widely used carbon-carbon bond formation processes in organic chemistry [3-8]. The driving force of the reaction is the formation of new σ -bonds, which are energetically more stable than the π -bonds, due to the symmetry allowed sigma type overlap between the lowest unoccupied molecular orbital (LUMO) of one reactant and highest occupied molecular orbital (HOMO) of the other as shown in Figure 1.3.

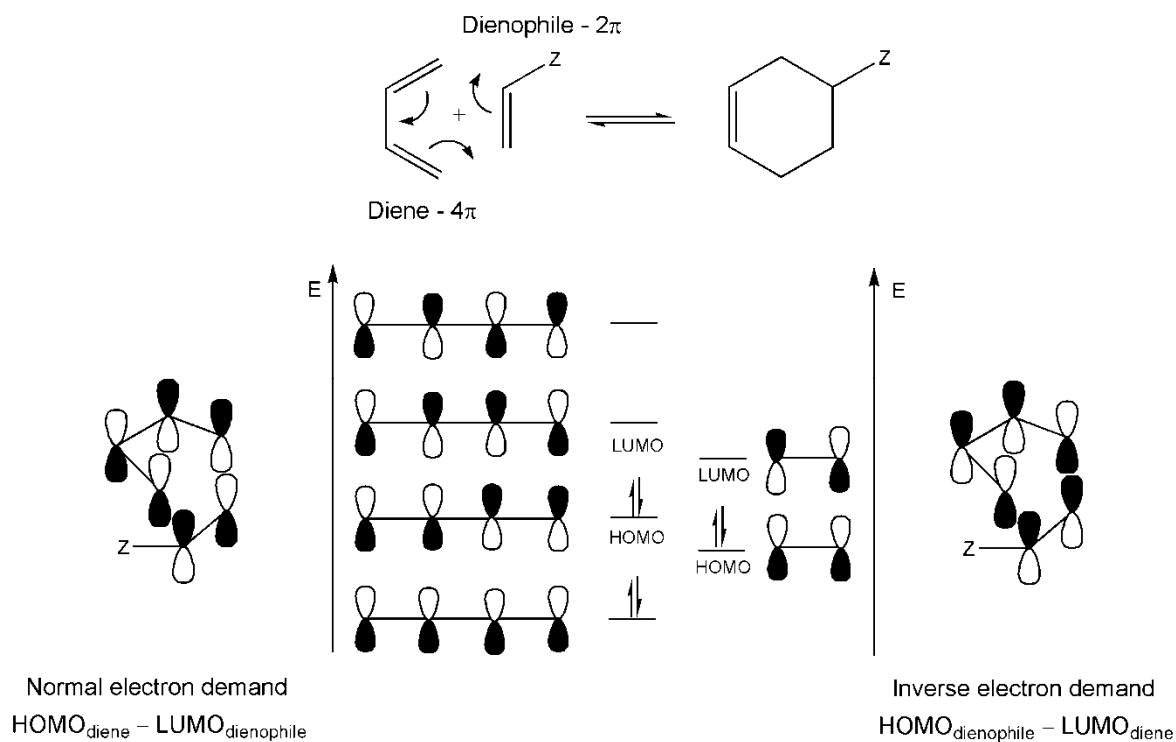


Figure 1.3. Frontier molecular orbital interactions in the Diels–Alder reaction.

Sigmatropic rearrangements are unimolecular isomerizations. They involve the movement of a σ -bond with the simultaneous arrangement of the π -system. As one σ -bond forms another σ -bond breaks. Sigmatropic rearrangements can proceed either through a chair or boat transition state (Figure 1.4).

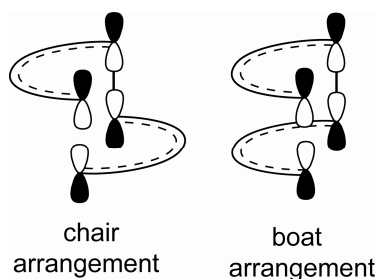


Figure 1.4. Chair and boat arrangements in sigmatropic rearrangements.

The most common sigmatropic rearrangements are [3,3]-sigmatropic shifts, including the Cope rearrangement [9], the Claisen rearrangement [10] and their variants. (Figure 1.5). Cope rearrangement is the thermal isomerization of a 1,5-diene leading to a regioisomeric 1,5-diene, where the main product is the thermodynamically more stable regioisomer. The Claisen rearrangement [10-12] may be viewed as the oxa-variant of the Cope rearrangement. The most recent applications of [3,3]-sigmatropic rearrangements in organic chemistry involve the stereoselective versions [11-13].

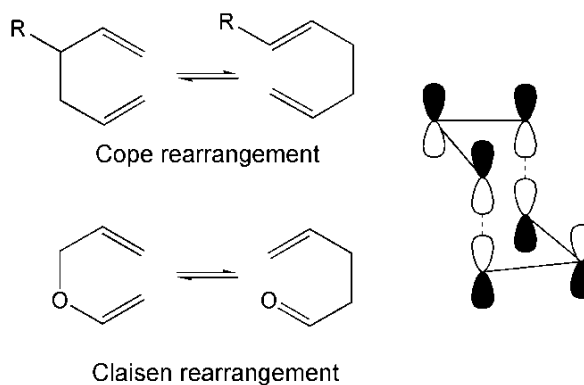


Figure 1.5. Frontier molecular orbital interactions in the Cope and Claisen rearrangements.

The reaction mechanisms are classified in two broad families. Stepwise reactions involve the formation of at least one intermediate, whereas, concerted reactions occur in a single step through concurrent bond making and bond breaking processes (Figure 1.6). Pericyclic reactions, in general, are considered to have concerted cyclic transition structures in which the bonds are formed and broken simultaneously.

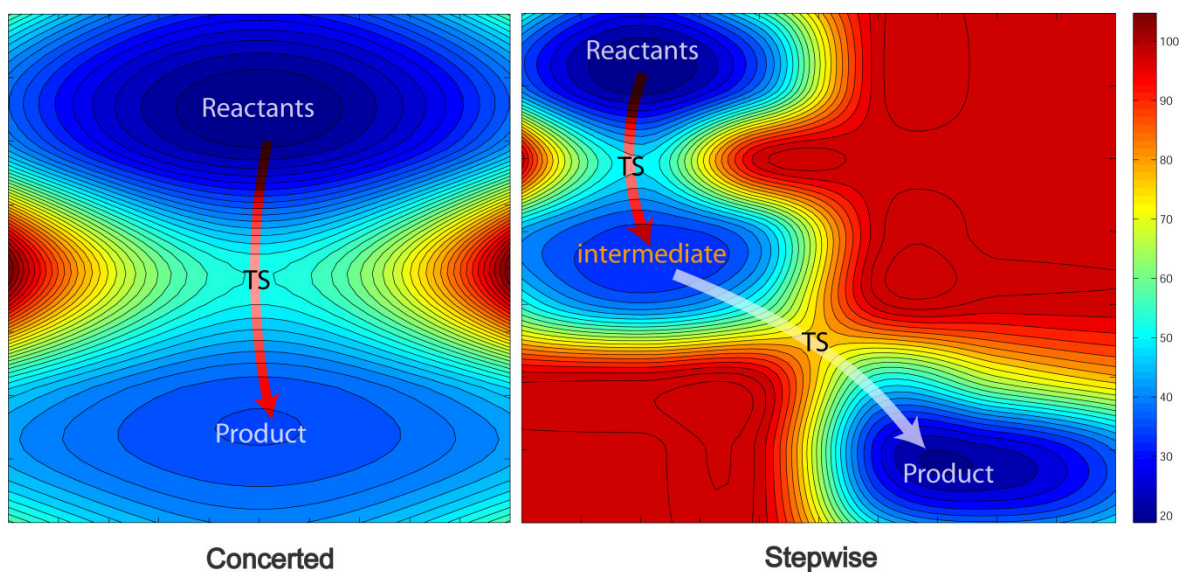


Figure 1.6. Potential energy surfaces of concerted and stepwise reactions.

However, stepwise passes exist in all pericyclic reactions, and compete with the concerted alternatives (Figure 1.7). In the stepwise pathway, the formation of diradical or zwitterionic intermediate is followed by the cyclization step to give the product. The formation of diradical or zwitterionic intermediates is reported to be favored compared to the concerted reaction in a number of examples [6].

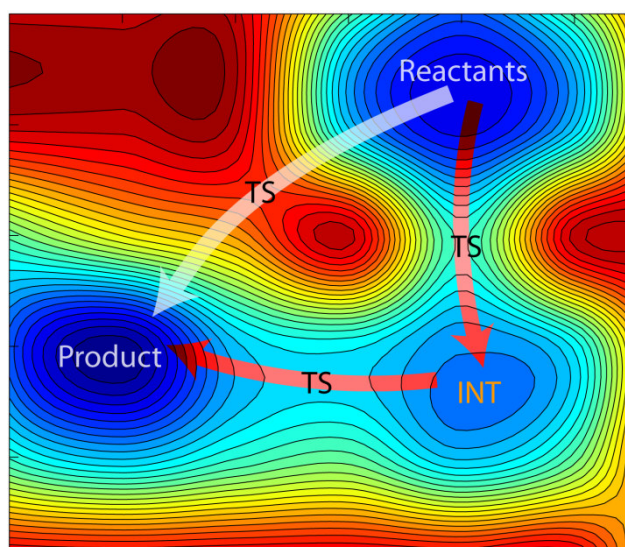


Figure 1.7. Competing concerted and stepwise pathways.

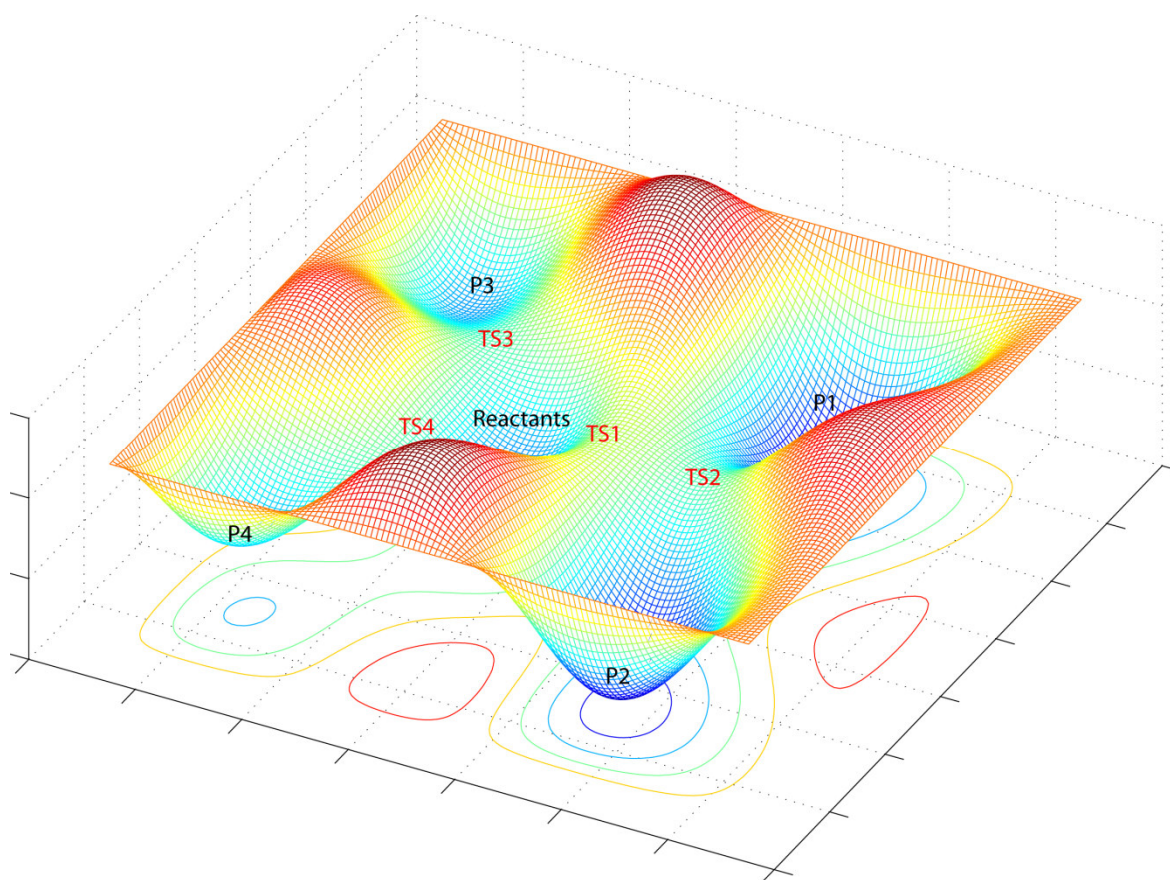


Figure 1.8. Potential energy surface of an hypothetical reaction giving four different products, P1-P4.

The reactions occur on complex potential energy surfaces and the same set of reactants may yield different products and stereoisomers (Figure 1.8). According to transition state theory, the differences in barrier heights towards each product or stereoisomer determine the product distribution, hence the selectivity of the reaction.

However, recent studies have revealed that two transition states can merge into a single transition state that can yield multiple products. This type of potential energy surface describes a two-step no intermediate mechanism [14] (Figure 1.9). The reaction trajectory branches after the transition state towards different products and the selective formation of one product over the other is governed by the surface shape and the dynamic effects rather than the transition state energetics. Reaction path bifurcations have been identified for many complex transformations, but notable number of examples involves the

pericyclic reactions. We, therefore, devoted Chapter 4 to discuss in detail this new type of mechanism and recent examples of “bis-pericyclic” cycloadditions.

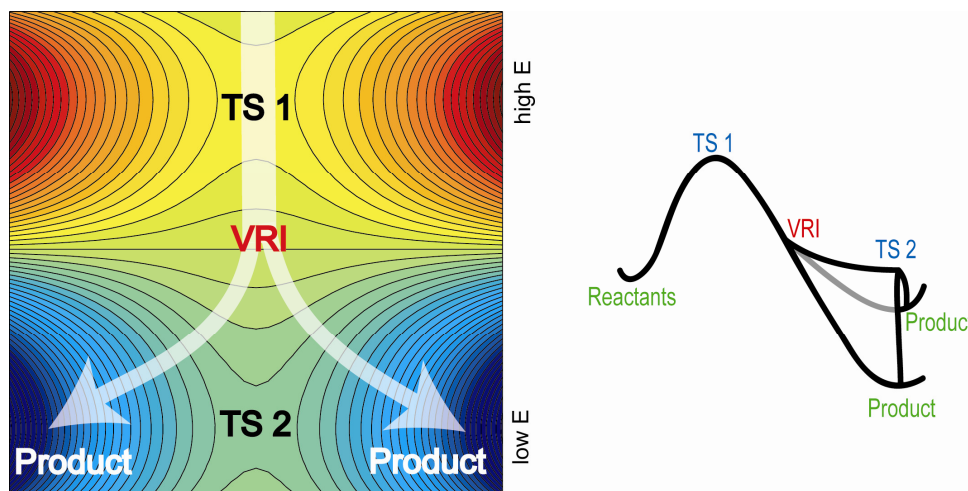


Figure 1.9. Potential energy surface described by the two-step no intermediate mechanism.

Enormous number of examples reveals the widespread use of pericyclic reactions in organic chemistry for the synthesis of complex molecules. There is a considerable effort and ongoing interest for obtaining highly efficient and selective transformations to access biologically active products. Therefore, it is not surprising that the most recent developments in the pericyclic reaction chemistry involve the asymmetric versions [3-8, 11-13]. This interest does not seem to decline in the following years, as pericyclic reactions present one of the most powerful approaches to access complex cyclic molecules.

2. OBJECTIVE AND SCOPE

The general characteristics of pericyclic reactions are described in the previous chapter. Pericyclic reactions are one of the most powerful and widely used methods to synthesize complex molecules in organic chemistry and there is a growing interest to achieve highly selective transformations. The selectivity is determined by the energy differences between competing transition states and therefore is closely related to the reaction mechanism. However, the shape of the potential energy surface on which the pericyclic reactions occur is shown to differ substantially. The correct description of the selectivity, therefore, is only possible by the extensive exploration of the reaction's potential energy surface.

In this work, we aim to elucidate the mechanistic details of novel pericyclic reactions whose products are precursors of biologically active targets and to describe the fundamental interactions in the key transition states that determine the reactivity and selectivity of the reaction. As such, we seek to provide an understanding on the origins of the selective transformations and the factors that act on the loss of selectivity. These results may ultimately allow the synthetic organic chemist to choose the best reagents and conditions to obtain the desired product in high selectivity.

In the following chapter (Chapter 3) the basic principles of theoretical approaches employed throughout this work are presented. Both methodological details and practical aspects of all the computational methods utilized are discussed. The next section (Chapter 4) aims to provide a deeper insight into the features of bifurcating potential energy surfaces and two-step no intermediate mechanism. The mathematical definition is extended by the detailed descriptions of recently identified bifurcations occurring on potential energy surfaces of cycloaddition reactions.

The next four sections (Chapter 5 – Chapter 8) explore the mechanistic details of some highly useful cycloadditions and sigmatropic rearrangements and deal with different aspects of the selectivity encountered in pericyclic reactions, namely periselectivity,

diastereoselectivity and enantioselectivity. Each chapter includes a detailed introduction specific to the topic and computational methodology section summarizing the techniques employed. These chapters are intended to be full articles unless already published.

The periselectivity of cycloadditions occurring on unsymmetrical bifurcating potential energy surfaces and the effect of Lewis acid catalysts on the mechanism and on the periselectivity of the reaction are discussed in Chapter 5. The second topic is based on a comparative analysis of bis-pericyclic and stepwise pathways on the potential energy surfaces of cycloadditions (Chapter 6). The effect of competing bis-pericyclic and stepwise pathways on the periselectivity of the reaction is investigated. Next, the Diels–Alder reactions of different chiral anthracenes with maleic anhydride are studied and the key interactions in the transition states that determine the diastereoselectivity of reaction are discussed in detail (Chapter 7). In Chapter 8, the mechanisms of competing [1,3]- and [3,3]-sigmatropic rearrangements of allylic trichloroacetimidates are explored and the origins of the enantioselective catalytic activity of cinchona alkaloids is explained. In the final chapter (Chapter 9) specific suggestions for future work are presented.

3. COMPUTATIONAL DETAILS

3.1. Quantum Mechanics

The starting point for any discussion of quantum mechanics is simply the Schrödinger equation. The Schrödinger equation can be solved exactly for only a few problems, such as the particle in a box, the harmonic oscillator, the particle on a ring, the particle on a sphere and the hydrogen atom. Unfortunately, no exact solutions can be found for systems that involve three (or more) interacting particles. Therefore, all electronic structure methods search for an approximate solution to the Schrödinger equation for many electron atoms and molecules.

In the most popular kind of quantum mechanical calculations performed on molecules each molecular spin orbital is expressed as a linear combination of atomic orbitals (the LCAO approach) [15]. The molecular orbital calculation simply involves finding the combination of the atomic orbitals that have the proper symmetries and that give the lowest electronic energy.

For molecules, Hartree-Fock (HF) is the central method for all ab initio quantum chemistry methods. The Hartree-Fock method is also called, the self-consistent field (SCF) method because the resulting equations are solved by means of an iterative, fixed-point type algorithm. That is, the orbitals are improved from cycle to cycle until the electronic energy reaches a constant minimum value and the orbitals no longer change.

Within the HF method, the antisymmetric N -body wavefunction is approximated by a single Slater determinant of N -spin orbitals. However, this approximation does not take into account Coulomb correlation, leading to a total electronic energy higher than the exact solution of the non-relativistic Schrödinger equation within the Born-Oppenheimer approximation. That is, the molecular orbitals of the HF method are optimized by

evaluating the energy of an electron in each molecular orbital moving in the mean field of all other electrons, rather than including the instantaneous repulsion between electrons.

However, the probability of finding an electron at a certain position in space depends on the position of the other electron. The motions of the electrons are correlated giving rise to a lower energy than HF formalism would suggest. Post-Hartree-Fock (post-HF) methods are developed to improve the electron correlation on the HF method where electron repulsions are only averaged. There are a number of ways in which the electron correlation effects can be incorporated into *ab initio* molecular orbital calculations. Moller-Plesset perturbation theory, configuration interaction and coupled cluster methods are among the most popular ones. Unfortunately, the added accuracy of the post-HF methods comes with the price of added computational cost.

An alternative approach to the electronic structure of atoms and molecules is density functional theory (DFT). DFT has enjoyed a growing interest due to its reduced computational cost for increased accuracy. DFT is based on the fact that there is a relationship between the total electronic energy and the overall electronic density. Therefore, DFT calculates the overall electronic density distribution, which is a function of only three variables, instead of the complicated many-body wavefunction that depends on three spacial variables for each of the N electrons. A key feature of the density functional theory is the way in which correlation effects are incorporated from the beginning by the term which is known as exchange-correlation potential. The major problem is that the exact functional for exchange and correlation are not known but approximations permit quite accurate calculations. Alterations to the functional or the inclusion of additive terms aim to improve the accuracy of the method and constitute a current research topic.

Semi-empirical methods are based on HF formalism but involve many approximations and some parameters from experimental data. The electron correlation effects are partially taken into account by the use of empirical parameters. They are especially valuable for treating large molecules where higher level of theories bring unaffordable computational cost.

In brief, all ab initio, DFT and semi-empirical calculations treat the linear combination of atomic orbitals (expressed by Gaussian functions) using iterative computations, which establish a self-consistent electric field and minimize the energy of the system. In ab initio and DFT calculations, electron-electron repulsion is specifically taken into account, while the semi-empirical method appears to be an intermediate cost effective approach.

3.2. Ab initio Methods

Ab initio methods are based on quantum mechanics calculations that solve the molecular Schrödinger equation associated with the molecular Hamiltonian. It is very difficult to find an analytical solution to the Schrödinger equation because of the electron-electron interaction terms. Therefore, a particular approximation is rigorously defined on first principles – the quantum theory – and the equation is then solved by numerical iterative methods within an error margin that is defined beforehand. Available computational techniques provide very detailed and reliable numerical solutions for the wavefunctions and energies [16, 17].

The time-independent Schrödinger equation has the form:

$$\hat{H}\psi = E\psi \quad (3.1)$$

where E is the electronic energy, ψ is the wavefunction describing the system and $\hat{H}$ is the Hamiltonian operator, which involves kinetic and potential energy terms.

The masses of the electrons are much smaller than the masses of the nuclei. That is, the electrons can adapt to any changes in the positions of the nuclei instantaneously. The electronic wavefunction then depends on the positions of the nuclei and not on their

momenta, which is known as Born-Oppenheimer approximation. The total wavefunction for the molecule thus can be written in the form:

$$\Psi_{\text{tot}}(\text{nuclei, electrons}) = \Psi(\text{electrons})\Psi(\text{nuclei}) \quad (3.2)$$

The total energy then equals the sum of the nuclear energy and the electronic energy. As the nuclei are considered as fixed, the nuclear energy includes only the electrostatic repulsion between the positively charged nuclei:

$$\sum_{A=1}^M \sum_{B=A+1}^M \frac{Z_A Z_B}{R_{AB}} \quad (3.3)$$

On the other hand, the electronic energy comprises the kinetic and potential energy of the electrons moving in the electrostatic field of the nuclei together with the electron-electron repulsion and it can be approximated by solving the Schrödinger equation associated with the electronic Hamiltonian operator.

The electronic Hamiltonian operator in atomic units is:

$$\hat{H} = -\frac{1}{2} \sum_{i=1}^N \nabla_i^2 - \sum_{i=1}^N \sum_{A=1}^M \frac{Z_A}{r_{iA}} + \sum_{i=1}^N \sum_{j=i+1}^N \frac{1}{r_{ij}} \quad (3.4)$$

where the first term is the kinetic energy operator, the second term is the operator for the attraction between the electrons and the nuclei, and finally the third term is the interelectronic repulsion operator for an N electron M nuclei system.

Ψ can be approximated as an antisymmetrized product of N orthonormal spin orbitals $\chi_1, \chi_2, \dots, \chi_N$ with a Slater determinant, where each spin orbital is the product of a spatial function and a spin function. The expectation value of the energy can be determined by calculating the following integral:

$$E = \frac{\int \Psi^* \hat{H} \Psi d\tau}{\int \Psi^* \Psi d\tau} \quad (3.5)$$

It is possible to write the energy expression in a concise form that distinguishes the three types of interaction that contribute to the total electronic energy of the system. The first contribution is from the kinetic and potential energy of each electron moving in the field of nuclei. The energy associated with this contribution for the molecular orbital χ_i :

$$H_{ii}^{core} = \int \chi_i(1) \left(-\frac{1}{2} \nabla_i^2 - \sum_{A=1}^M \frac{Z_A}{r_{iA}} \right) \chi_i(1) d\tau_1 \quad (3.6)$$

For N electrons in N molecular orbitals this contribution to the total energy is:

$$E_{total}^{core} = \sum_{i=1}^N \int \chi_i(1) \left(-\frac{1}{2} \nabla_i^2 - \sum_{A=1}^M \frac{Z_A}{r_{iA}} \right) \chi_i(1) d\tau_1 = \sum_{i=1}^N H_{ii}^{core} \quad (3.7)$$

The second contribution to the energy is due to the electrostatic repulsion between electron pairs and is calculated from the integrals:

$$J_{ij} = \iint \chi_i(1) \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_i(1) \chi_j(2) d\tau_1 d\tau_2 \quad (3.8)$$

The total electrostatic interaction between the electron in orbital χ_i and the other $N-1$ electrons is a sum of all such integrals, where the summation index j runs from 1 to N , excluding i :

$$\begin{aligned} E_i^{\text{Coulomb}} &= \sum_{j \neq i}^N \iint \chi_i(1) \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_i(1) \chi_j(2) d\tau_1 d\tau_2 \\ &\equiv \sum_{j \neq i}^N \iint \chi_i(1) \chi_i(1) \left(\frac{1}{r_{12}} \right) \chi_j(2) \chi_j(2) d\tau_1 d\tau_2 \end{aligned} \quad (3.9)$$

The total contribution to the electronic energy of the system is obtained as a double summation over all electrons, taking care to count each interaction only once:

$$\begin{aligned} E_{\text{total}}^{\text{Coulomb}} &= \sum_{i=1}^N \sum_{j=i+1}^N \iint \chi_i(1) \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_i(1) \chi_j(2) d\tau_1 d\tau_2 \\ &= \sum_{i=1}^N \sum_{j=i+1}^N J_{ij} \end{aligned} \quad (3.10)$$

The third contribution to the energy is known as exchange ‘interaction’, although this has no classical counterpart. It arises as a result of the correlation of the motions of electrons with parallel spins. Electrons of the same spin tend to ‘avoid’ each other, so they experience a lower Coulombic repulsion leading to a more favorable energy. The exchange interaction involves integrals of the form:

$$K_{ij} = \iint \chi_i(1) \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_j(1) \chi_i(2) d\tau_1 d\tau_2 \quad (3.11)$$

The exchange energy between the electron in spin orbital χ_i and the other $N-1$ electrons is:

$$E_i^{\text{exchange}} = \sum_{j \neq i}^N \iint \chi_i(1) \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_j(1) \chi_i(2) d\tau_1 d\tau_2 \quad (3.12)$$

The total exchange energy is given by:

$$\begin{aligned} E_{\text{total}}^{\text{exchange}} &= \sum_{i=1}^N \sum_{j=i+1}^N \iint \chi_i(1) \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_j(1) \chi_i(2) d\tau_1 d\tau_2 \\ &= \sum_{i=1}^N \sum_{j'=i+1}^N K_{ij} \end{aligned} \quad (3.13)$$

The ground state energy (called HF energy at this level of approximation) in a closed-shell system containing N electrons and $N/2$ orbitals can be expressed by:

$$E = 2 \sum_{i=1}^{N/2} H_{ii}^{\text{core}} + \sum_{i=1}^{N/2} \sum_{j=1}^{N/2} (2J_{ij} - K_{ij}) \quad (3.14)$$

Finally, the variational theorem provides us with a mechanism to find the best solution to the problem, since there is no ‘correct’ solution for many-body systems. The theorem states that energy calculated from an approximation to the exact wavefunction will always be higher than the true energy. This means the better the wavefunction, the lower the energy. The ‘best’ wavefunction is thus obtained when the energy is minimum. This is where the first derivative of energy, δE , will be zero.

The fock operator, $\hat{f}_i(1)$, is an effective one electron Hamiltonian for the electron in a polyelectronic system and has the following form:

$$\hat{f}_i(1) = \hat{H}^{\text{core}}(1) + \left\{ \sum_{j=1}^N \hat{f}_j(1) - \hat{K}_j(1) \right\} \quad (3.15)$$

where three operators that represent the contributions to the energy of the spin orbital χ_i are introduced. These are the core Hamiltonian operator, $\hat{H}^{\text{core}}(1)$:

$$\hat{H}^{\text{core}}(1) = -\frac{1}{2} \nabla_1^2 - \sum_{A=1}^M \frac{Z_A}{r_{1A}} \quad (3.16)$$

the Coulomb operator, $\hat{f}_j(1)$:

$$\hat{f}_j(1) = \int \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_j(2) d\tau_2 \quad (3.17)$$

and the exchange operator, $\hat{K}_j(1)$:

$$\hat{K}_j(1) = \int \chi_j(2) \left(\frac{1}{r_{12}} \right) \chi_i(2) d\tau_2 \quad (3.18)$$

The Hartree-Fock equations then take the standard eigenvalue form:

$$\hat{f}_i \chi_i = \varepsilon_i \chi_i \quad (3.19)$$

The Hartree-Fock equation, however, is based on an assumption that each electron moves in a ‘fixed’ field of the nuclei and the other electrons. Therefore, any solution for one electron will have an effect on the solutions for the other electrons. Moreover, spin functions which have to be the solutions of the equation already appear in the coulomb and exchange operators. The general strategy to solve these equations is self-consistent field approach. An initial set of trial solutions χ_i are used to calculate the Coulomb and exchange operators. Solving the HF equations give a second set of solutions, χ_i , which are used in the next iteration. The SCF method thus gradually refines the individual electronic solutions that correspond to lower and lower total energies. The solutions are said to be self-consistent at the point where the results for all electrons remain unchanged.

Hartree-Fock theory is very helpful for providing initial, first-level predictions for many systems. It performs reasonably well for computing the structures and vibrational frequencies of stable molecules and some transition states. However, the Hartree-Fock method does not take into account the electron correlation resulting from the instantaneous repulsions between electrons. So it is not suitable for the accurate modeling of the energetics of reactions and bond dissociation.

Since electrons are correlated, the probability of finding an electron at a certain position depends on the position of other electrons. This requires that the instantaneous electron correlation should be included into the wavefunction. Methods that include electron correlation such as configuration interaction (CI), coupled cluster (CC) and perturbation theory are called post-Hartree-Fock methods [18].

Configuration interaction method uses a variational wavefunction that is a linear combination of configuration state functions built from spin orbitals [19]. Coupled cluster theory is one of the elegant techniques for estimating the electron correlation [20]. Coupled cluster calculations start from the HF molecular orbital method, then a linear combination of excited Slater determinants are produced by acting an excitation operator on the Slater determinant constructed from HF molecular orbitals.

The Møller-Plesset perturbation theory (MP) treats the effect of electronic interactions as a perturbation to a system consisting of non-interacting electrons [21]. The first order perturbation introduces the interaction between the electrons in the ground state and is equal to the Hartree-Fock theory. The second order perturbation (MP2) takes into account the interaction of the doubly excited configurations with the ground state configuration. The third order perturbation (MP3) adds the contribution of doubly excited configurations interacting with each other. The fourth order perturbation (MP4) brings in interactions involving single, double and quadruple excitations.

There are other correlated methods [19], such as multiconfiguration SCF (MCSCF) and multi-reference configuration interaction (MRCI). Although they use a single determinant as reference, they employ similar perturbation or configuration interaction methods to improve the description of electron correlation.

Despite the high accuracy of post-HF methods, they are very expensive methods to treat the correlation energy.

3.3. Semi-empirical Methods

Semi-empirical methods are characterized by their use of parameters derived from experimental data in order to simplify the approximation to the Schrödinger equation. As such, they are relatively inexpensive and can be practically applied to very, very large molecules. The semi-empirical quantum-mechanical methods developed by Dewar and coworkers [22-31] have been successful at reproducing molecular energies, replicating molecular structures and interpreting chemical reactions [32, 33].

To overcome some of the computational difficulties, approximations are made in which several of the integrals involving core orbitals are replaced by parameters. The number of two-electron integrals calculated is reduced, by simply ignoring them or calculating them in an approximate fashion. Three levels of approximation have been defined by Pople and Beveridge, in which certain two-electron integrals are neglected [34].

The first is known as the complete neglect of differential overlap (CNDO) [35, 36]. It assumes the atomic orbitals to be spherically symmetrical when evaluating electron repulsion integrals. The directionality of p-orbitals was included only via the one-electron resonance integrals, the size of which depends on the orientations and distances of the orbitals and on a constant assigned to each type of bond.

The second, known as intermediate neglect of differential overlap (INDO), contains all terms that CNDO contains and includes all one-center two-electron integrals [37]. The third is known as neglect of diatomic differential overlap (NDDO) in which all two-electron two-center integrals involving charge clouds arising from pairs of orbitals on an atom were retained.

In 1975, Dewar and coworkers published the MINDO/3 method, which is a modified version of the INDO method [22-25]. MINDO/3 uses a set of parameters in approximation. These parameters, along with the constants used to evaluate the resonance integrals, allow the results to be fitted as closely as possible to experimental data.

The first practical NDDO method was introduced by Dewar and Thiel in 1977 [26-28] called modified neglect of diatomic overlap (MNDO), the model was parameterized on experimental molecular geometries, heats of formation, dipole moments and ionization potentials. The orbital exponents and the core integral were again treated as empirical parameters to be determined in the fitting procedure.

The inability of MNDO has led to a reexamination of the model, leading to the Austin Model 1 (AM1) [29]. In this model a term was added to MNDO to correct for the excessive repulsions at van der Waals distances. For this purpose, each atom was assigned a number of spherical gaussians, which were intended to mimic long-range correlation effects.

The third parameterization of MNDO is the Parametric Method Number 3 (PM3) [30, 31], AM1 being the second. In PM3, the parameters were optimized using a large set of reference molecular data. This allowed 12 elements to be optimized simultaneously [38]. The PM3 method has been used in this study for conformational search.

Semi-empirical and ab initio methods differ in the trade-off made between computational cost and accuracy of the result. Semi-empirical calculations are relatively inexpensive. They provide reasonable qualitative descriptions of molecular systems and fairly accurate quantitative prediction of energies and structures for systems where good parameter sets exist. Semi-empirical methods may only be used for systems where parameters have been developed for all of their component atoms. In addition to this, semiempirical models have a number of well-known limitations. Types of problems on which they do not perform well include hydrogen bonding, transition structures, and molecules containing atoms for which they are poorly parameterized.

3.4. Density Functional Theory

The density functional theory is based on the Kohn-Hohenberg theorems proposed in 1964 [39, 40]. The first theorem states that the electron density $\rho(\mathbf{r})$ determines the external potential $V_{\text{ext}}(\mathbf{r})$, i.e. the potential due to the nuclei. The second theorem introduces the variational principle. Hence, the electron density can be computed variationally and the position of nuclei, energy, wave function and other related parameters can be calculated.

The electron density is defined as:

$$\rho(x) = N \int \cdots \int |\Psi(x_1, x_2, \cdots, x_n)|^2 dx_1 dx_2 \cdots dx_n \quad (3.20)$$

where x represents both spin and spatial coordinates of electrons.

The electronic energy can be expressed as a functional of the electron density:

$$E[\rho(\mathbf{r})] = \int V_{\text{ext}}(\mathbf{r})\rho(\mathbf{r})d\mathbf{r} + T[\rho(\mathbf{r})] + V_{\text{ee}}[\rho(\mathbf{r})] \quad (3.21)$$

The first term arises from the interaction of the electrons with an external potential $V_{\text{ext}}(\mathbf{r})$, typically due to the Coulomb interaction with the nuclei. $T[\rho(\mathbf{r})]$ is the kinetic energy of the interacting electrons and $V_{\text{ee}}[\rho(\mathbf{r})]$ is the interelectronic interaction energy. The electronic energy may be rewritten as:

$$E[\rho(\mathbf{r})] = \int V_{\text{ext}}(\mathbf{r})\rho(\mathbf{r})d\mathbf{r} + T_s[\rho(\mathbf{r})] + J[\rho(\mathbf{r})] + E_{\text{xc}}[\rho(\mathbf{r})] \quad (3.22)$$

where $J[\rho(\mathbf{r})]$ is the electron-electron Coulomb energy, which is also known as the Hartree electrostatic energy:

$$J[\rho(\mathbf{r})] = \frac{1}{2} \iint \frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_1 d\mathbf{r}_2 \quad (3.23)$$

$T_s[\rho(\mathbf{r})]$ is the kinetic energy of the non-interacting electrons:

$$T_s[\rho(\mathbf{r})] = \sum_{i=1}^N \int \psi_i(\mathbf{r}) \left(-\frac{\nabla^2}{2} \right) \psi_i(\mathbf{r}) d\mathbf{r} \quad (3.24)$$

and $E_{\text{xc}}[\rho(\mathbf{r})]$ contains contributions from exchange and correlation.

The full expression for the energy of an N -electron system within the Kohn-Sham scheme is:

$$\begin{aligned}
E[\rho(\mathbf{r})] = & - \sum_{A=1}^M \int \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} \rho(\mathbf{r}) d\mathbf{r} + \sum_{i=1}^N \int \psi_i(\mathbf{r}) \left(-\frac{\nabla^2}{2} \right) \psi_i(\mathbf{r}) d\mathbf{r} \\
& + \frac{1}{2} \iint \frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_1 d\mathbf{r}_2 + E_{\text{XC}}[\rho(\mathbf{r})]
\end{aligned} \tag{3.25}$$

Equation (3.25) acts to define the exchange-correlation energy functional, $E_{\text{XC}}[\rho(\mathbf{r})]$, which can be expressed as the sum of an exchange functional $E_{\text{X}}[\rho(\mathbf{r})]$ and a correlation functional $E_{\text{C}}[\rho(\mathbf{r})]$, although it contains also a contribution due to the difference between the true kinetic energy of the system and $T_s[\rho(\mathbf{r})]$.

In the Kohn-Sham density functional theory, a reference system of independent non-interacting electrons in a common, one-body potential V_{KS} yielding the same density as the real fully-interacting system is considered. More specifically, a set of independent reference orbitals ψ_i satisfying the following independent particle Schrödinger equation are imagined:

$$\left[-\frac{1}{2} \nabla^2 + V_{\text{KS}} \right] \psi_i = \varepsilon_i \psi_i \tag{3.26}$$

with the one-body potential V_{KS} defined as:

$$V_{\text{KS}} = V_{\text{ext}}(\mathbf{r}) + \frac{\delta J[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})} + \frac{\delta E_{\text{XC}}[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})} \tag{3.27}$$

$$V_{\text{KS}} = - \sum_{A=1}^M \frac{Z_A}{r_{1A}} + \frac{1}{2} \iint \frac{\rho(\mathbf{r}_2)}{r_{12}} d\mathbf{r}_2 + V_{\text{XC}}[\mathbf{r}_1] \tag{3.28}$$

where $V_{\text{xc}}[\mathbf{r}]$ is the exchange-correlation potential and is related to exchange-correlation energy by:

$$V_{\text{xc}}[\mathbf{r}] = \frac{\delta E_{\text{xc}}[\rho(\mathbf{r})]}{\delta \rho(\mathbf{r})} \quad (3.29)$$

The independent orbitals ψ_i are known as Kohn-Sham orbitals and give the exact density by:

$$\rho(\mathbf{r}) = \sum_i^N |\psi_i|^2 \quad (3.30)$$

if the exact form of the exchange-correlation functional is known. However, the exact form of this functional is not known and approximate forms are developed starting with the local density approximation (LDA). This approximation gives the energy of a uniform electron gas (UEG), i.e. a large number of electrons uniformly spread out in a cube accompanied with a uniform distribution of the positive charge to make the system neutral. Because the electron density is constant throughout the space, the total exchange-correlation energy $E_{\text{xc}}[\rho(\mathbf{r})]$ for the system can be obtained by integrating over all the space:

$$E_{\text{xc}}[\rho(\mathbf{r})] = \int \rho(\mathbf{r}) \varepsilon_{\text{xc}}(\rho(\mathbf{r})) d\mathbf{r} \quad (3.31)$$

where $\varepsilon_{\text{xc}}(\rho(\mathbf{r}))$ is the energy density, which can be defined as the exchange-correlation energy per electron as a function of the density in the uniform electron gas. The energy density, ε_{xc} , contains individual exchange, ε_{x} , and correlation, ε_{c} , contributions. The exchange-correlation potential can be obtained by differentiation of expression (3.31):

$$V_{xc}[\mathbf{r}] = \rho(\mathbf{r}) \frac{\delta \varepsilon_{xc}(\rho(\mathbf{r}))}{\delta \rho(\mathbf{r})} + \varepsilon_{xc}(\rho(\mathbf{r})) \quad (3.32)$$

The energy expression can be expressed as:

$$E[\rho(\mathbf{r})] = T_s[\rho(\mathbf{r})] + \int V_{\text{ext}}(\mathbf{r})\rho(\mathbf{r})d\mathbf{r} + J[\rho(\mathbf{r})] + E_{xc}[\rho(\mathbf{r})] + E_b \quad (3.33)$$

where E_b is the electrostatic energy of the positive background. Since the positive charge density is the negative of the electron density due to uniform distribution of particles, the energy expression is reduced to:

$$E[\rho(\mathbf{r})] = T_s[\rho(\mathbf{r})] + E_{xc}[\rho(\mathbf{r})] \quad (3.34)$$

$$E[\rho(\mathbf{r})] = T_s[\rho(\mathbf{r})] + E_x[\rho(\mathbf{r})] + E_c[\rho(\mathbf{r})] \quad (3.35)$$

The kinetic energy functional for a uniform electron gas is derived by Thomas and Fermi [41, 42] and can be written as:

$$T_s[\rho(\mathbf{r})] = C_F \int \rho(\mathbf{r})^{5/3} d\mathbf{r} \quad (3.36)$$

where C_F is a constant equal to 2.8712. Within Slater's derivation [43], the exchange functional under the local density approximation is determined as:

$$E_X [\rho(\mathbf{r})] = -C_x \int \rho(\mathbf{r})^{4/3} d\mathbf{r} \quad (3.37)$$

with C_x being a constant equal to 0.7386. The correlation energy, $E_C[\rho(\mathbf{r})]$, for a homogeneous electron gas comes from the parametrization of the results of a set of quantum Monte Carlo calculations. The correlation energy functional as considered by Vosko, Wilk and Nusair (VWN) [44] is:

$$\begin{aligned} \varepsilon_C [\rho(\mathbf{r})] = \frac{A}{2} \left\{ \ln \frac{x^2}{X(x)} + \frac{2b}{Q} \tan^{-1} \frac{Q}{2x+b} \right. \\ \left. - \frac{bx_0}{X(x_0)} \left[\ln \frac{(x-x_0)^2}{X(x)} + \frac{2(b-2x_0)}{Q} \tan^{-1} \frac{Q}{2x+b} \right] \right\} \end{aligned} \quad (3.38)$$

where $x = r_s^{1/2}$, $X(x) = x^2 + bx + c$, $Q = (4c - b^2)^2$, $A = 0.0621814$, $x_0 = 0.409286$, $b = 13.0720$, and $c = 42.7198$. Vosko, Wilk and Nusair proposed several different fitting schemes, varying the functional forms of Equation (3.38), among which two forms, referred to as VWN and VWN5, have become the most widely used.

The LDA method underestimates the exchange energy by about 10 per cent and does not have the correct asymptotic behavior. The exact asymptotic behavior of the exchange energy density of any finite many-electron system, U_x^σ , is given by:

$$\lim_{x \rightarrow \infty} U_x^\sigma = -\frac{1}{r} \quad (3.39)$$

U_x^σ being related to $E[\rho(\mathbf{r})]$ by:

$$E[\rho(\mathbf{r})] = \frac{1}{2} \sum_{\sigma} \rho_{\sigma} U_x^{\sigma} d\mathbf{r} \quad (3.40)$$

The most common method to correct the asymptotic behavior is to use gradient-corrected (GC), ‘non-local’ functional which depend upon the gradient of the density at each point in space and not just on its value. This approach is known as the ‘generalized gradient approximation’ (GGA). Most gradient corrected functionals are constructed by adding a correction term to the LDA functional:

$$\varepsilon_{X/C}^{\text{GGA}}[\rho(\mathbf{r})] = \varepsilon_{X/C}^{\text{LDA}}[\rho(\mathbf{r})] + \Delta\varepsilon_{X/C} \left[\frac{|\nabla[\rho(\mathbf{r})]|}{[\rho^{4/3}(\mathbf{r})]} \right] \quad (3.41)$$

Becke proposed a gradient-corrected exchange functional, usually abbreviated as ‘B’, which adopts a mathematical form that has correct asymptotic behavior at long range for the electron density, and it incorporates a single empirical parameter:

$$E_X^{\text{B88}}[\rho(\mathbf{r})] = E_X^{\text{LDA}}[\rho(\mathbf{r})] - \beta \sum_{\sigma} \int \rho_{\sigma}^{4/3} \frac{x_{\sigma}^2}{1 + 6\beta x_{\sigma} \sinh^{-1} x_{\sigma}} d\mathbf{r} \quad (3.42)$$

where σ denotes the electron spin, $x_{\sigma} = |\nabla \rho_{\sigma}| / \rho_{\sigma}^{4/3}$ and β is an empirical constant ($\beta=0.0042$). This functional is known as Becke88 (B88) exchange functional [45]. Other exchange functionals similar to B88 have appeared, including CAM [46], FT97 [47], O [48], PW [49], mPW [50], and X [51]. Alternative GGA functionals, such as, B86 [52, 53], LG [54], P [55], PBE [56] and mPBE [57] have been developed, which contain no empirically optimized parameters.

Corrections to correlation energy density following Equation (3.41) include B88 [58], P86 [55], and PW91 [59]. PW91, however, uses a different expression than Equation

(3.38) and does not contain any empirical parameters. Lee, Yang and Parr proposed a GGA correlation functional (LYP) that does not correct the LDA expression, but entirely computes the correlation energy [60]. The closed shell LYP correlation functional is given by:

$$E_C^{\text{LYP}}[\rho(\mathbf{r})] = -a \int \frac{1}{1 + d\rho^{-1/3}} \left\{ \rho + b\rho^{-2/3} \left[C_F \rho^{5/3} - 2t_w + \left(\frac{1}{9} t_w + \frac{1}{18} \nabla^2 \rho \right) e^{-cr^{-1/3}} \right] \right\} d\mathbf{r} \quad (3.43)$$

where

$$t_w(\mathbf{r}) = \sum_{i=1}^N \frac{1}{8} \frac{|\nabla \rho_i(\mathbf{r})|^2}{\rho_i(\mathbf{r})} - \frac{1}{8} \nabla^2 \rho \quad (3.44)$$

and $C_F = \frac{3}{10} (3\pi^2)^{2/3}$, $a=0.04918$, $b=0.132$, $c=0.2533$ and $d=0.349$.

A further step in functional improvement involved the inclusion of the second derivative of the density, the Laplacian. These functionals are termed meta-GGA functionals as they go beyond simply the gradient correction. The examples of meta-GGA functionals for exchange, correlation, or both include B95 [61], B98 [62], PKZB [63], TPSS [64], BMK [65], and M0X-suite of functionals [66-68].

The functional form adopted for the meta-GGA exchange functional in M05 formalism [66] is:

$$E_X^{(0)} = \sum_{\sigma} \int F_{X\sigma}^{\text{PBE}}(\rho_{\sigma}, \nabla \rho_{\sigma}) f(w_{\sigma}) d\mathbf{r} \quad (3.45)$$

where $F_{X\sigma}^{\text{PBE}}(\rho_\sigma, \nabla\rho_\sigma)$ is the exchange energy density of the PBE exchange model [56], and $f(w_\sigma)$ is the kinetic energy density enhancement factor:

$$f(w_\sigma) = \sum_{i=0}^m a_i w_\sigma^i \quad (3.46)$$

where the variable w_σ is a function of t_σ :

$$w_\sigma = (t_\sigma - 1)/(t_\sigma + 1) \quad (3.47)$$

and t_σ is a function of the kinetic energy density τ_σ of electrons with spin σ :

$$t_\sigma = \tau_\sigma^{\text{LSDA}}/\tau_\sigma \quad (3.48)$$

$$\tau_\sigma = \frac{1}{2} \sum_i^{\text{occup}} |\nabla\Psi_{i\sigma}|^2 \quad (3.49)$$

$$\tau_\sigma^{\text{LSDA}} = \frac{3}{10} (6\pi^2)^{2/3} \rho_\sigma^{5/3} \quad (3.50)$$

In the M05 meta-GGA correlation functional, Truhlar and coworkers treated the opposite-spin and parallel-spin correlations differently [66]. The opposite-spins correlation energy of the functional is given by:

$$E_C^{\alpha\beta} = \int e_{\alpha\beta}^{\text{UEG}} g_{\alpha\beta}(x_\alpha, x_\beta) d\mathbf{r} \quad (3.51)$$

where $g_{\alpha\beta}(x_\alpha, x_\beta)$ is:

$$g_{\alpha\beta}(x_\alpha, x_\beta) = \sum_{i=0}^n c_{C\alpha\beta,i} \left[\frac{\gamma_{C\alpha\beta}(x_\alpha^2 + x_\beta^2)}{1 + \gamma_{C\alpha\beta}(x_\alpha^2 + x_\beta^2)} \right]^i \quad (3.52)$$

and x_σ is:

$$x_\sigma = \frac{|\nabla\rho_\sigma|}{\rho_\sigma^{4/3}}, \quad \sigma = \alpha, \beta \quad (3.53)$$

For parallel spins:

$$E_C^{\alpha\beta} = \int e_{\sigma\sigma}^{\text{UEG}} g_{\sigma\sigma}(x_\sigma) \frac{D_\sigma}{2\tau_\sigma} d\mathbf{r} \quad (3.54)$$

where $D_\sigma/2\tau_\sigma$ is the self-interaction correction factor and $g_{\sigma\sigma}(x_\sigma)$ is:

$$g_{\sigma\sigma}(x_\sigma) = \sum_{i=0}^n c_{C\sigma\sigma,i} \left(\frac{\gamma_{C\sigma\sigma} x_\sigma^2}{1 + \gamma_{C\sigma\sigma} x_\sigma^2} \right)^i \quad (3.55)$$

The total correlation energy of the M05 correlation functional is given by:

$$E_C = E_C^{\alpha\beta} + E_C^{\alpha\alpha} + E_C^{\beta\beta} \quad (3.56)$$

The hybrid Hartree-Fock density functional theory involves mixing various amounts of the Hartree-Fock nonlocal exchange operator with local DFT exchange-correlation functionals and gradient-corrected density functions, and optimizing the parameters against a database of thermochemical data.

The adiabatic connection formula connects the non-interacting Kohn-Sham reference system ($\lambda = 0$) to the fully-interacting real system ($\lambda = 1$) and is given by:

$$E_{XC} = \int_0^1 U_{XC}^\lambda d\lambda \quad (3.57)$$

where λ is the interelectronic coupling-strength parameter and U_{XC}^λ is the potential energy of exchange-correlation at intermediate coupling strength. The simplest approximation for the adiabatic connection formula is a linear interpolation when $\lambda = 0$ ($U_{XC}^0 = E_X^{\text{exact}}$) and $\lambda = 1$ ($U_{XC}^1 = U_{XC}^{\text{LDA}}$) [69]:

$$E_{XC} = \frac{1}{2} E_X^{\text{exact}} + \frac{1}{2} U_{XC}^{\text{LDA}} \quad (3.58)$$

U_{XC}^0 is the pure exchange energy of the Slater determinant of the Kohn-Sham orbitals and can be determined exactly, whereas, U_{XC}^1 is the exchange-correlation potential of the full interacting real system. This is so-called ‘half-and-half’ method.

A general form of the adiabatic connection method (ACM) can be written as:

$$E_{\text{XC}} = (1 - a)E_{\text{XC}}^{\text{DFT}} + aE_{\text{X}}^{\text{HF}} \quad (3.59)$$

where a is the fraction of Hartree-Fock exchange, and setting $a = 0.5$ gives the ‘half-and-half’ method.

Empirical 3-paramater hybrids involve the mixing of LDA, Hartree-Fock exchange and the gradient corrected exchange and correlation functionals:

$$E_{\text{XC}} = (1 - a)E_{\text{X}}^{\text{LDA}} + aE_{\text{X}}^{\text{HF}} + b\Delta E_{\text{X}}^{\text{GC}} + E_{\text{C}}^{\text{LDA}} + c\Delta E_{\text{C}}^{\text{GC}} \quad (3.60)$$

where $E_{\text{X}}^{\text{LDA}}$ and $E_{\text{C}}^{\text{LDA}}$ are exchange and correlation energies within LDA formalism, E_{X}^{HF} is the nonlocal Hartree-Fock exchange energy, $\Delta E_{\text{X}}^{\text{GC}}$ and $\Delta E_{\text{C}}^{\text{GC}}$ are the gradient corrections to the exchange and correlation functionals respectively.

Becke developed the 3-parameter functional, B3PW91, using the gradient corrected exchange and correlation functionals B and PW91 [70]:

$$E_{\text{XC}} = (1 - a)E_{\text{X}}^{\text{LDA}} + aE_{\text{X}}^{\text{HF}} + b\Delta E_{\text{X}}^{\text{B}} + E_{\text{C}}^{\text{LDA}} + c\Delta E_{\text{C}}^{\text{PW91}} \quad (3.61)$$

where $\Delta E_{\text{X}}^{\text{B}}$ is the Becke’s gradient correction to the exchange functional, $\Delta E_{\text{C}}^{\text{PW91}}$ is the Perdew-Wang gradient correction to the correlation functional, and the empirical coefficients a , b , and c are 0.20, 0.72 and 0.81 respectively.

Later, Stephens *et al.* [71] modified B3PW91 to use LYP instead of PW91. The B3LYP model is defined by:

$$E_{XC}^{B3LYP} = (1 - a)E_X^{LDA} + aE_X^{HF} + b\Delta E_X^B + cE_C^{LYP} + (1 - c)E_C^{LDA} \quad (3.62)$$

where a , b , and c have the same values as in B3PW91. In the B3LYP functional, the gradient-correction (ΔE_C^{GC}) to the correlation functional is included in LYP. However, LYP contains also a local correlation term which must be subtracted to yield the correction term only:

$$\Delta E_C^{GC} = E_C^{LYP} - E_C^{LDA} \quad (3.63)$$

where E_C^{LDA} is the Vosko-Wilk-Nusair correlation functional (VWN3), a parametrized form of the LDA correlation energy based on Monte Carlo calculations [72].

Both B3PW91 and B3LYP methods contain 20 per cent Hartree-Fock exchange.

A number of one-parameter hybrid methods have been proposed that adjust only the percentage of HF exchange included in the functional. The one-parameter hybrid exchange-correlation energy can be written as follows:

$$E_{XC} = (1 - a)E_X^{DFT} + aE_X^{HF} + E_C^{DFT} \quad (3.64)$$

where E_X^{HF} is the nonlocal Hartree-Fock exchange energy, a is the percentage of Hartree-Fock exchange in the hybrid functional, E_X^{DFT} is the local DFT exchange energy ($E_X^{DFT} = (E_X^{LDA} + \Delta E_X^{GC})$), and E_C^{DFT} is the local DFT correlation energy ($E_C^{DFT} = E_C^{LDA} + \Delta E_C^{GC}$).

Gradient corrected exchange functional mPW, employed with 25 per cent HF exchange and the Perdew-Wang gradient corrected functional PW91, yields a method called mPW1PW91. In the MPW1K ('K' for 'kinetics') functional proposed by Lynch *et*

al. [73] the percentage of HF contribution in the mPW1PW91 is increased from the default value of 25 per cent to 42.8 per cent. Other one-parameter hybrid GGA functionals that employ 25 per cent HF exchange are B1PW91 [74], B1LYP [74], and PBE1PBE [75].

Finally, ACM definitions involving meta-GGA functionals are called hybrid metageneralized gradient approximations (hybrid meta-GGAs). They incorporate electron spin density, density gradient, kinetic energy density, and HF exchange.

M05 one-parameter hybrid meta-GGA functional involves the mixing of M05 meta-GGA exchange and correlation functionals (Equation (3.45) – Equation (3.56)) with 28 per cent of HF exchange, while the fraction of HF exchange in M05-2X is twice as much ($a = 0.56$) [66].

Other examples to hybrid meta-GGA functionals involve B1B95 [61], BB1K [76], BMK [65], MPW1B95 [77], MPWB1K [77], TPSSH [78], PWB6K [79], PW6B95 [79], TPSS1KCIS [80], M06 and M06-2X [67], M08-HX and M08-SO [68].

3.5. Basis Sets

A basis set is the mathematical description of the orbitals within a system, (which in turn combine to approximate the total electronic wavefunction) used to perform the theoretical calculation. Larger basis sets more accurately approximate the orbitals by imposing fewer restrictions on the locations of the electrons in space.

In 1951, Roothaan proposed the Hartree-Fock orbitals as linear combinations of a complete set of known functions, called basis functions. There are two types of set of basis functions for atomic Hartree-Fock calculations, Slater-type functions and Gaussian-type functions.

In the simplest Hartree-Fock model, the number of basis functions on each atom is as small as possible that is only large enough to accommodate all the electrons and still

maintain spherical symmetry. As a consequence, the molecular orbitals have only limited flexibility. If larger basis sets are used, the number of adjustable coefficients in the variational procedure increases, and an improved description of the molecular orbitals is obtained. Very large basis sets will result in nearly complete flexibility. The limit of such an approach termed the Hartree-Fock limit represents the best that can be done with a single electron configuration.

There are numerous different Gaussian basis sets with which SCF calculations can be carried out. The most widely used are those developed by Pople and co-workers. The simplest and lowest basis set is called STO-3G. This means that the Slater-type orbitals are represented by three gaussian functions. It is a minimal basis set which means that it has only as many orbitals as are necessary to accommodate the electrons of the neutral atom.

The next level of basis sets developed by Pople is referred to as the split-valence basis sets. The problem of any minimal basis set is its inability to expand or contract its orbitals to fit the molecular environment. One solution to the problem is to use split valence or double zeta basis sets in which the basis are split into two parts, an inner, compact orbital and an outer, more diffuse one. Thus the size of the atomic orbital that contributes to the molecular orbital can be varied within the limits set by the inner and outer basis functions. Split-valence basis set splits only the valence orbitals in this way, whereas double zeta basis also have split core orbitals.

For greater flexibility the split-valence basis set can be augmented with polarization functions. In polarization basis sets, which are the next level of improvement in basis set, d orbitals are added to all heavy atoms is designated with a * or (d). Polarization can be added to hydrogen atoms as well, this would be done by **.

Diffuse functions are large-size versions of s- and p-type functions (as opposed to the standard valence-size functions). They allow orbitals to occupy a larger region of space. Basis sets with diffuse functions are important for systems where electrons are relatively far from the nucleus: molecules with lone pairs, anions and other systems with significant negative charge, systems in their excited states, and so on. The 6-31+G (d) basis set is the 6-31G (d) basis set with diffuse functions added to heavy atoms. The double plus version,

6-31++G (d), adds diffuse functions to the hydrogen atoms as well. The 6-31+G* and the 6-31+G** split valence basis sets have been used for gas phase calculations in this study, with the addition of polarization and diffused functions on heavy atoms as well as polarization functions on hydrogens for the 6-31+G**.

3.6. Continuum Solvation Models

In continuum solvation models [81, 82], the solvent is represented as a uniform polarizable medium characterized by its static dielectric constant ϵ . In basic continuum solvation models, the solute is described at a homogenous quantum mechanical (QM) level and the solute-solvent interactions are limited to those of electrostatic terms.

The total solvation free energy may be written as

$$\Delta G_{solvation} = \Delta G_{cavity} + \Delta G_{dispersion} + \Delta G_{electrostatic} \quad (3.65)$$

In this representation, ΔG_{cavity} is the energetic cost of creating a cavity in the medium producing a destabilization effect. Dispersion interactions between solvent and solute add stabilization to solvation free energy term expressed as $\Delta G_{dispersion}$. The latter electrostatic term, $\Delta G_{electrostatic}$, has a stabilization effect and furthermore it appears to be responsible for the main structural changes of the solute.

The solute charge distribution within the cavity induces a polarization of the surrounding medium, which in turn induces an electric field within the cavity called the *reaction field*. This field then interacts with solute charges, providing additional stabilization. The effect of the reaction field may be modeled by an appropriately distributed set of induced polarization charges on the surface S of the dielectric. The charge density on the surface of the cavity, $\sigma(\mathbf{r}_s)$, is given by the standard electrostatics in

terms of the dielectric constant, ϵ , and the electric field perpendicular to the surface, $F(\mathbf{r}_s)$, generated by the charge distribution within the cavity

$$4\pi\epsilon\sigma(\mathbf{r}_s) = (\epsilon - 1)F(\mathbf{r}_s) \quad (3.66)$$

Once $\sigma(\mathbf{r}_s)$ is determined, the associated potential is added as an extra term to the Hamiltonian operator

$$H = H_0 + V_\sigma \quad (3.67)$$

$$V_\sigma(\mathbf{r}) = \int \frac{\sigma(\mathbf{r}_s)}{|\mathbf{r} - \mathbf{r}_s|} d\mathbf{r}_s \quad (3.68)$$

The potential of the surface charge V_σ is given by the molecular charge distribution but also enters the Hamiltonian and thus influences the molecular wave function, the procedure is therefore iterative.

In the Polarized Continuum solvation Models (PCM), the solute is embedded in a cavity defined by a set of spheres centered on atoms (sometimes only on heavy atoms), having radii defined by the van der Waals radius of the atoms multiplied by a predefined factor (usually 1.2). The cavity surface is then subdivided into small domains (called tesserae), where the polarization charges are placed. Among the many solutions to the electrostatic problem is the Integrated Equation Formalism (IEF) originally formulated by Cancés and Menucci [83-85]. The IEF-PCM method is a recent development in the polarized continuum models and has been utilized for solvent calculations in this study. It is based on the use of operators largely exploited in the theory of integral equations. The concept of cavity and of its tessellation is conserved. The IEF formalism is in fact able to treat a larger class of electrostatic problems.

Apart from the apparent surface charge (ASC) methods, other solutions for calculating the electrostatic solute-solvent interactions in continuum models have been proposed such as, multipole expansion (MPE) methods, generalized Born approximation (GBA), image charge (IMC) methods, finite element methods (FEM) and finite difference methods (FDM).

4. BIFURCATIONS ON POTENTIAL ENERGY SURFACES OF CYCLOADDITIONS

A typical potential energy surface featuring reaction path bifurcations (Figure 4.1) describes a two-step no intermediate mechanism that is neither stepwise nor concerted. Selective formation of one product over another is governed by the potential energy surface shape and resulting dynamic effects, rather than the transition state energetics. In a recent review, we have shown that such phenomena are surprisingly general and affect experimental observables such as kinetic isotope effects and product distributions [86].

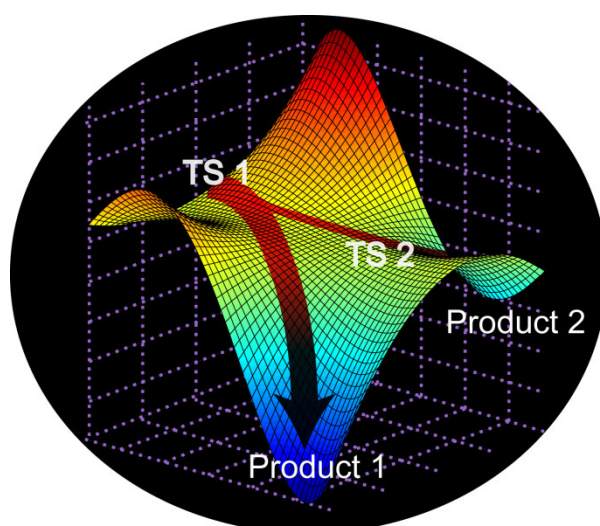


Figure 4.1. An unsymmetrical bifurcating potential energy surface.

Reaction pathway bifurcations have been identified for many complex organic reactions. Early reported examples of bifurcating reactions involved simple isomerizations, rearrangements, and addition reactions. However, recently several complex organic transformations, notably pericyclic reactions, have been shown to involve bifurcating reaction pathways. In this chapter, we explain in detail the features of bifurcating potential energy surfaces and describe the recent examples of cycloaddition reactions that have bis-pericyclic transition states leading to reaction path bifurcations.

4.1. Mathematical Definition

It is possible to identify a stationary point on a molecular potential energy surface in the $3N-6$ dimensional configuration space by all zero energy gradients (forces) with respect to nuclear positions [87]. The evaluation of second derivatives, or force constants allows the characterization of a stationary point as either a minimum or saddle point. When all second derivatives are positive, the stationary point is a minimum, while at the saddle point there is one negative second derivative [88]. In typical quantum mechanical calculations, stationary points are characterized by diagonalizing the matrix of mass-weighted second derivatives (the Hessian matrix) that yields normal vibrational modes (eigenvectors) and the associated force constants (eigenvalues) [87].

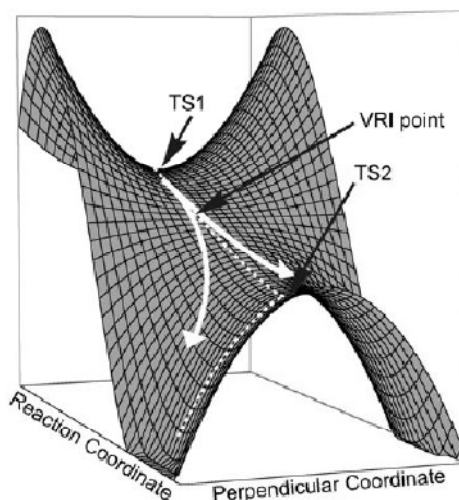


Figure 4.2. The IRC pathway (dotted lines) and expected reaction trajectories (solid lines) on the potential energy surface with sequential transition states.

Along the floor of a downward sloping valley, only one gradient is negative. When two transition states occur sequentially with no intervening energy minimum, the curvature of the energy surface along one direction perpendicular to the reaction valley floor changes into a ridge at some point in this two dimensional configuration space (Figure 4.2). The point where the valley becomes a ridge is the valley-ridge inflection point (VRI). Here the second derivative matrix has one zero eigenvalue that corresponds to a motion

perpendicular to the gradient [88]. Near the VRI, there is no longer a restoring force for molecular motion perpendicular to the reaction coordinate and the single reaction pathway branches into two. However, unlike stationary points, the location of a VRI point is dependent upon the choice of coordinate systems [89].

The most common quantum mechanical reaction pathway description is the intrinsic reaction coordinate (IRC) (Figure 4.1) [90]. This is a mass-weighted steepest descent path where the negative gradient downhill from a transition state is followed. The IRC is typically considered as the theoretical minimum-energy pathway (MEP). However, when the gradient becomes zero or the potential energy surface is flat, a unique preferred reaction trajectory cannot be described by a single IRC [91, 92].

The difference between the IRC pathway (dotted lines) and qualitative dynamics trajectories (white arrows) are shown in Figure 4.2 for a model PES with two sequential transition states (TS1 and TS2) and an intervening VRI point. The IRC corresponds to the steepest descent pathway from TS1 and follows the valley floor in this region. When the valley turns into ridge at the VRI point, the IRC stays on the developing ridge before stopping at TS2. From TS2, the IRC follows the normal coordinate corresponding to the imaginary vibrational frequency, connecting the two products. Representative reaction trajectories that would result from dynamics simulations are shown by the white arrows. Typical trajectories deviate from the IRC in the vicinity of the VRI, bypassing TS2 and branch towards the two products [93]. Several groups are actively investigating alternative theoretical treatments of hypersurfaces to rigorously define bifurcating reaction pathways with VRI points [94]. These methods include reaction-path Hamiltonians [95], reduced gradient following [96, 97], gradient extremals [98-100], transition path sampling [101], and the distinguished coordinate method [102].

4.2. Bifurcations in Cycloaddition Reactions

The query for explaining the *endo* selectivity of cycloadditions has led to the discovery of special features of the reaction's potential energy surface resulting in reaction

path bifurcations. Undoubtedly, the most argued example for more than 40 years is the mechanism of cyclopentadiene dimerization leading to exclusive *endo* selectivity. In 1959, the similarity between cycloaddition transition state and Cope rearrangement transition state (Figure 4.3) let Woodward and Katz to propose a two stage mechanism: “*the reaction proceeds to the Cope transition state after passing a compressed diradicaloid cycloaddition transition state whose branches are kept together by secondary attractive forces which are related to the reaction coordinates of the Cope rearrangement, and thence to the products*” [103]. However, this approach was quickly replaced by a concerted *endo* cycloaddition transition state stabilized by secondary orbital interactions (SOI) (Figure 4.3) [104, 105]. Far after, the appearance of favorable Salem/Houk SOIs [106, 107] and their peculiarity was sufficient to modify this picture again. Different from the other SOIs, this interaction is not only related to the bond shift in the Cope transition state, but more interestingly incorporates the 2+4 perimeter (Figure 4.3). This allowed Caramella *et al.* [108] to rename the Woodward-Katz picture as “bis-pericyclic transition state” which takes advantage of the stabilizing interactions of both the 4+2 and 2+4 cycloaddition pathways.

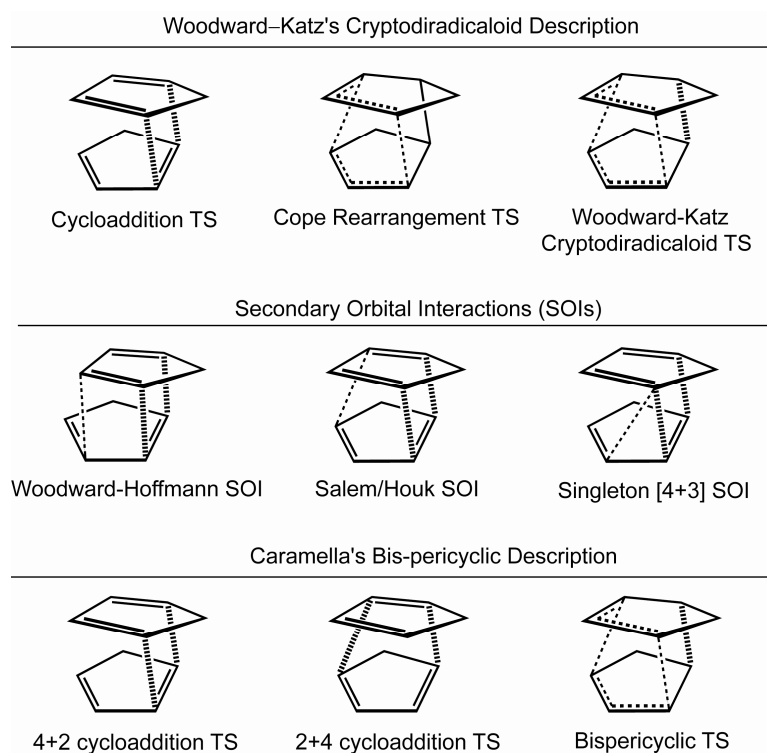


Figure 4.3. *Endo* dimerization of cyclopentadiene.

Caramella used DFT and MCSCF calculations to elucidate the topology of reaction's potential energy surface. They found that cyclopentadiene dimerization proceeds through a concerted, albeit, very asynchronous C_2 symmetric cycloaddition transition state at 21 kcal/mol (Figure 4.4). The $C\cdots C$ bond between the ends of the diene system is distressingly short (1.94 Å). Two other partial bonds of 2.90 Å related to the bond shifts of Cope transition state demonstrate the similarity with the Woodward-Katz picture, yet they also correspond to 4+2 and 2+4 perimeters (See Figure 4.3). The reactant complex, after passing the cycloaddition transition state, proceeds to the Cope transition state retaining its symmetry. These sequential transition states force the reaction pathway to transition from a valley to an unstable ridge region where branching or bifurcation takes place. In the vicinity of this valley-ridge inflection point (VRI), the distortive character of Cope topology break the C_2 symmetry, causing a bifurcation into two different reaction paths which are however equivalent. Despite the diracaloid character of cycloaddition transition state, it is a first order saddle point and the authors could not locate an intermediate along the reaction coordinate. So Caramella concluded that *“in the case of endo approach additional stabilization can be recovered with only minor structural deformations by fully exploiting the highly favorable Salem/Houk SOI, which leads to merging of both geometrically possible 4+2 and 2+4 allowed paths”*. This merging of pericyclic pathways at a single transition state is termed “bis-pericyclic”.

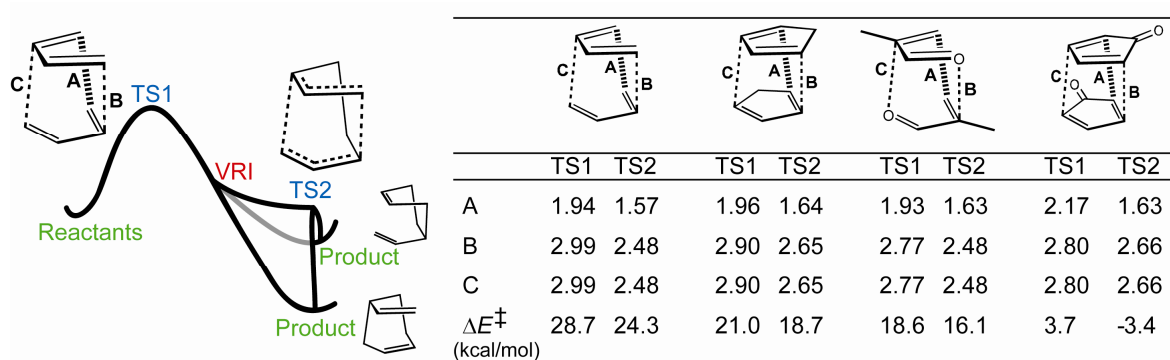


Figure 4.4. Transition state geometries and activation energies ($\Delta E^\ddagger$, kcal/mol) of bis-pericyclic *endo* dimerizations (B3LYP/6-31G(d)).

Similar results have been reported (Figure 4.4) for other dimerization reactions such as dimerizations of butadiene [109], cyclopentadienone [110], methacrolein [111] and phospholes [112]. Enhanced reactivity and selectivity of cyclopentadienone was explained by the more efficient relief of antiaromaticity in the bis-pericyclic array. Bis-pericyclic transition state for butadiene dimerization contrarily has a much higher activation barrier and diradical passes are competitive by only 0.2 kcal/mol. This destabilization of the transition state is accounted for by the significant twisting of the forming bonds (20.3°) between butadiene moieties in the dimerization transition state from the coplanar rearrangement to take more advantage of the Salem/Houk SOI.

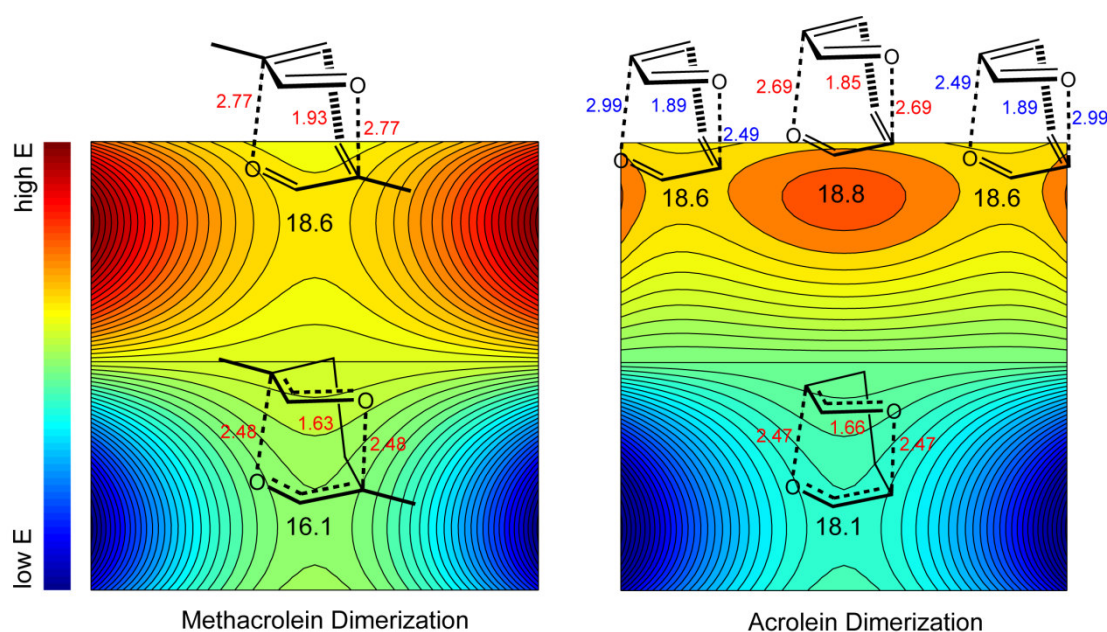


Figure 4.5. Hypothetical potential energy surfaces for *endo* methacrolein and acrolein dimerizations (B3LYP/6-31G(d)). Energies of the transition states are given in kcal/mol with respect to the reactants.

Nevertheless, the PES of acrolein dimerization differs from the other reported dimerization reactions as shown in Figure 4.5 [111]. It involves two distinct and slightly more synchronous transition states corresponding to two cycloaddition modes. However, these transition states lie on a quite flat plateau and are connected via a second order saddle point which is only 0.2 kcal/mol higher in energy. This second order saddle point has

similar geometrical characteristics with the above mentioned first order bis-pericyclic saddle points.

Ess *et al.* have recently studied the dimerization of 1,3-cyclohexadiene [113] and predicted highly competitive concerted and stepwise pathways leading to [4+2] and [2+2] cycloaddition products as well as [6+4] ene product (Figure 4.6). The *endo*-[4+2] transition state is found to have non-degenerate primary and secondary orbital interactions; therefore it is not bis-pericyclic.

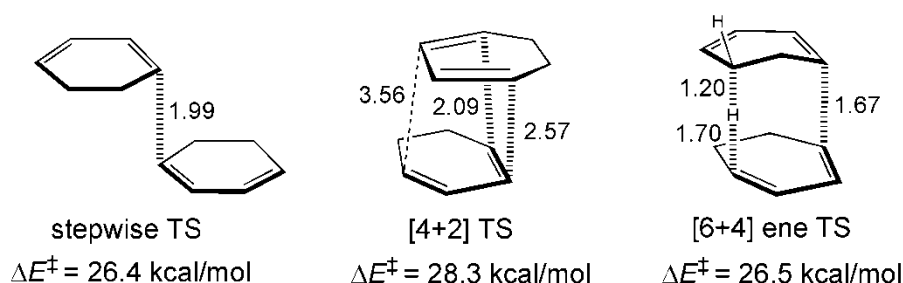


Figure 4.6. Competing reaction pathways in the dimerization of 1,3-cyclohexadiene (B3LYP/6-31G(d)).

There have been some attempts to locate the VRI. Recently Kraka *et al.* identified the bifurcation points before and after the concerted transition state along the C_s symmetrical reaction path of *s*-cis butadiene and ethylene cycloaddition using a newly developed unified reaction valley approach (URVA) to the reaction path following [114]. On the reactant side, the first bifurcation point is the planar C_{2v} *cis*-1,3-butadiene structure that connects the enantiomeric forms of *cisoid*-1,3-butadiene. After the concerted transition state, the reaction pathway leads to a second bifurcation point at the boat cyclohexene saddle-point structure connecting the two enantiomeric C_2 symmetrical twist-boat conformations.

Zhou and Birney were also able to locate the VRI for the formation of semibullvalene where the vibration of the Cope rearrangement was closest to zero [115]. They suggested that the novel consequence of sequential transition states is the stabilization of the first transition state by the following one, more so than by the final products.

However, all the examples presented above lead to two equivalent products. A direct consequence of the two products being indistinguishable is obviously the lack of selectivity. From the aspect of diene/dienophile role selectivity or periselectivity in more general terms, the bifurcations on unsymmetrical potential energy surfaces are far more interesting but much less explored.

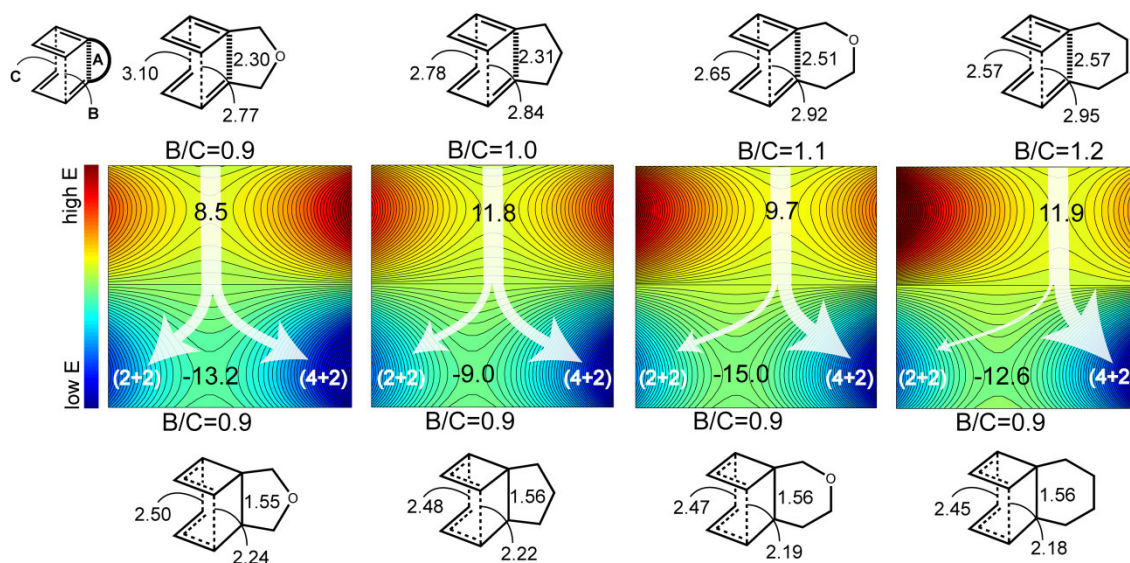
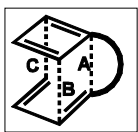
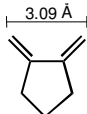


Figure 4.7. The effect of tether length on intramolecular cycloaddition of cyclobutadiene to s-cis butadiene (B3LYP/6-31G(d)). Energies of the transition states are given in kcal/mol with respect to the reactants.

Intramolecular cycloadditions of cyclobutadiene to several s-cis dienes are reported to have merged (4+2) and (2+2) modes in single transition state (Figure 4.7) [116]. The C...C bond between the ends of the diene system is more developed than the two other partial bonds, corresponding to the bond shifts of the Cope transition state or in other words (4+2) and (2+2) perimeters. However, these two relatively long partial bonds are not equidistant. Located transition states are intermediate in character between the (2+2) and the (4+2) modes depending on the geometric constraints of the tethers. It can be considered that when partial bond B is shorter than partial bond C, the transition state looks more like an asynchronous (2+2) cycloaddition transition state stabilized by Salem/Houk SOI, which is in fact the (4+2) perimeter. Then instinctively it is straightforward to conclude that the major product will be the (2+2) cycloadduct. Accordingly, in this work, relative bond lengths of B and C are shown to be good predictors of periselectivity, shorter bond

yielding the major product, and the formation of minor products are described by bis-pericyclic transition states. The tether length has a crucial role on the extent of overlap between the terminal end of diene and cyclobutadiene, so on the geometry of the cycloaddition transition state. But since bond A is totally formed in Cope rearrangement transition state, the length of tether has no effect on Cope transition state. This particularly means that the differences in B/C ratios of cycloaddition transition state (TS1) and Cope rearrangement transition state (TS2) significantly vary with the tether length, so does the shape of the PES. With 2-oxamethylene as tether the geometries of TS1 and TS2 are similar, both with a B/C ratio of 0.9. Interestingly, despite the asymmetry of the transition states, the similarity in the geometries of two sequential transition states results in an almost symmetrical energy surface. Comparing with the experimental results it is predicted that the shape of the PES (alignment of the s-cis transition state and the Cope transition state as well as the slopes of the surface) and dynamic behaviour of the system would determine the relative amounts of (2+2) and (4+2) product formed. The obtained results with several dienes have also revealed a relationship between the periselectivity and the distance between the ends of the diene system: closer the two ends, better the (4+2) pericyclic overlap (Table 4.1).

Table 4.1. Effect of diene on intramolecular cycloaddition of cyclobutadiene to s-cis dienes (B3LYP/6-31G*).

						
	TS1	TS2	TS1	TS2	TS1	TS2
A	2.26	1.56	2.36	1.57	2.15	1.57
B	2.82	2.24	2.80	2.28	2.88	2.37
C	3.08	2.51	2.81	2.47	2.53	2.49
$\Delta H^\ddagger$ (kcal/mol)	5.9	-15.4	5.1	-13.0	8.3	-0.9
$\Delta G^\ddagger$ (kcal/mol)	9.6	-10.4	8.2	-8.8	12.0	3.7
Major	(2+2)		(4+2)		(4+2)	

Similarly, Dinadabayene *et al.* have found that phospholes add to s-cis butadiene in an *endo* fashion through a bis-pericyclic transition state [117]. Although the *endo* transition state of 1H-phosphole and 2H-phosphole have merged into a single transition state at B3LYP level using both 6-31G(d) and 6-31+G(d,p) basis sets, two different transition states have been obtained in which the 3H-phosphole act as diene and dienophile using 6-31G(d) basis set. With the use of a larger basis set these two transition states have collapsed into one. However, there might exist a terminology confusion in this work as some Cope rearrangement transition states are labelled as akin to bis-pericyclic transition states.

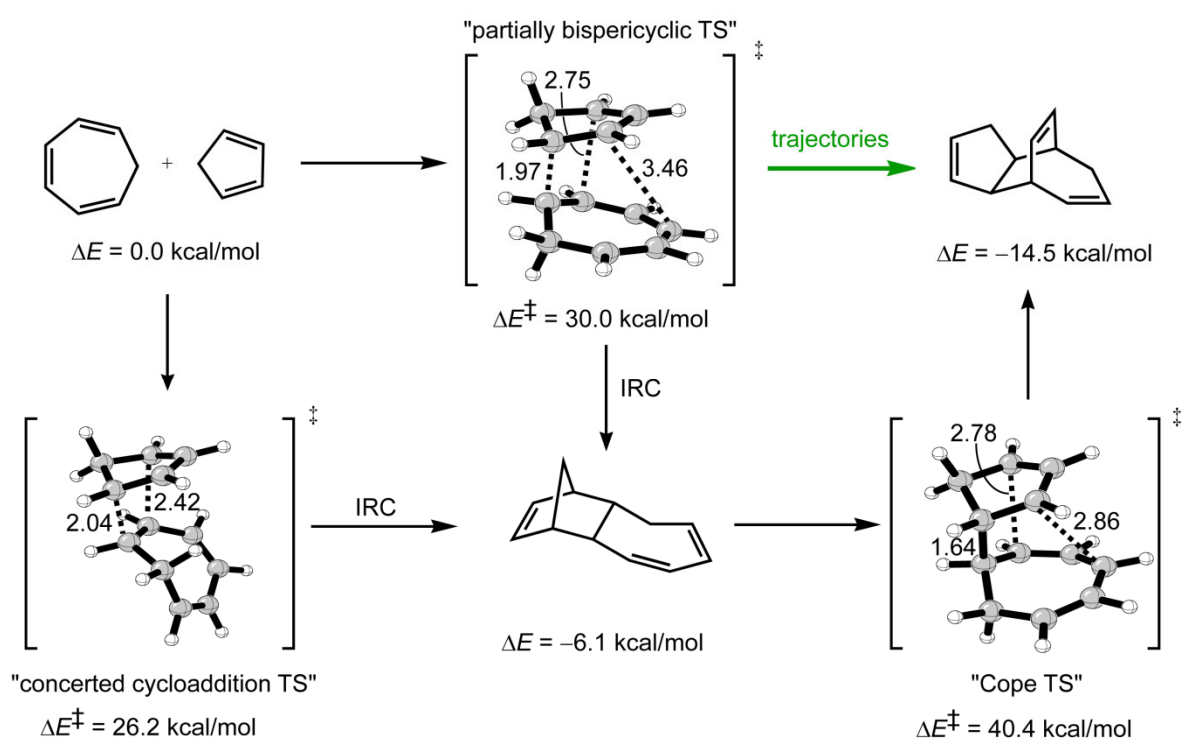


Figure 4.8. Bifurcation to two different [4+2] products through a desymmetrized potential energy surface in the cycloaddition of cycloheptatriene and cyclopentadiene (B3LYP/6-31G(d)).

Another interesting example from Leach, Goldstein and Houk shows that conformation of reactants in the transition state can lead to two concerted transition states, one is directly connected to the Cope rearrangement transition state and the other is to the product [118]. They have located a "partially" bis-pericyclic transition state for the

cycloaddition of cycloheptatriene and cyclopentadiene in which two [4+2] modes have merged. (Figure 4.8) This transition state at 30 kcal/mol using B3LYP/6-31G(d) has the two rings pushed toward one another, allowing it to be partially bis-pericyclic. It may lead to two different [4+2] products and the dynamic behavior of the system determines the exact product distribution ratio. However, they also located another *endo* transition state at 26.2 kcal/mol. It differs in the conformation of the cycloheptatriene ring, having the ring folded away from the cyclopentadiene ring. At B3LYP level of theory, these transition states are of minor importance as the diradical formation transition state is lower in energy at 24.7 kcal/mol. However, single point CASPT2 energies favor the concerted transition states by 4.5 kcal/mol for the non-bis-pericyclic transition state and 1.1 kcal/mol for the bis-pericyclic transition state.

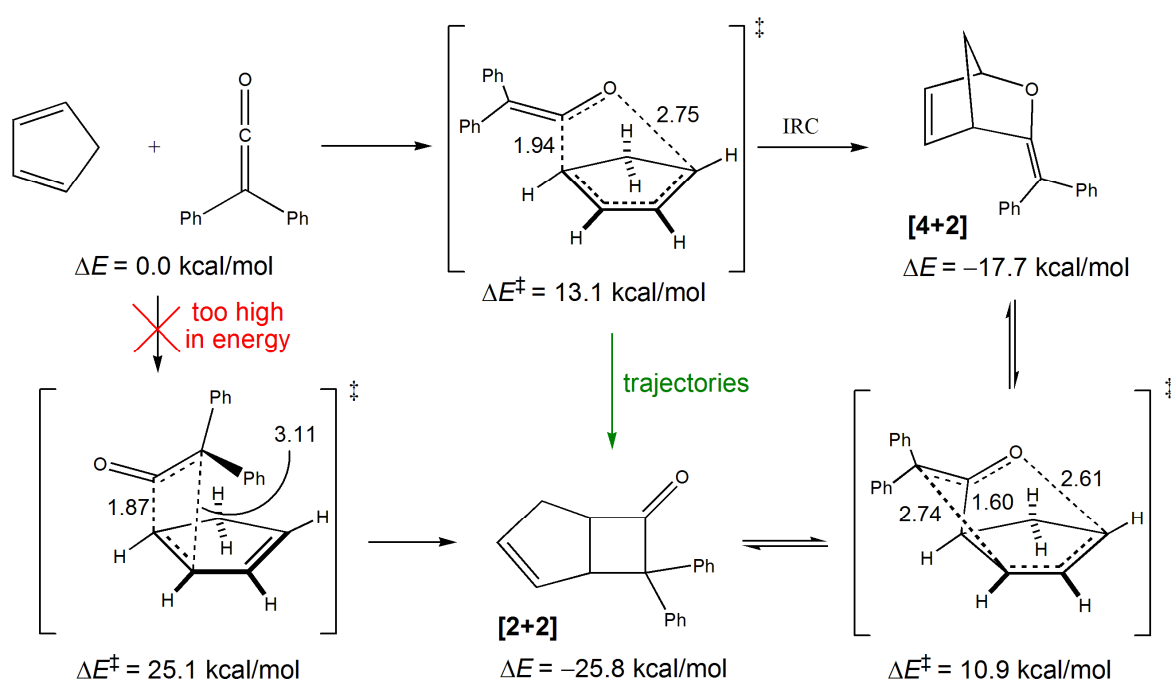


Figure 4.9. Bifurcation to [4+2] and [2+2] products through a desymmetrized potential energy surface in the cycloaddition of diphenylketene and cyclopentadiene (MPW1K/6-31G(d)).

Singleton and co-workers have elegantly shown that the cycloaddition of cyclopentadiene with diphenylketene and dichloroketene affords directly the [4+2] and [2+2] cycloadducts from a single transition state (Figure 4.9) [119]. They confirmed their

results by quassiclassical dynamics and ^{13}C and ^2H kinetic isotope effects. Although their calculated B3LYP and MPW1K surfaces differ, they reveal qualitatively the same mechanism.

We have described the effect of Lewis acid catalysts on unsymmetrical bifurcating potential energy surfaces and on the periselectivity of the reaction [120, 121]. Our results are discussed in detail in the next chapter (Chapter 5).

Thomas *et al.* have recently investigated the control elements in dynamically determined selectivity on a bifurcating potential energy surface [122]. The bis-pericyclic additions of 3-methoxycarbonyl cyclopentadienone with 1,3-dienes were studied by a combination of product studies, experimental kinetic isotope effects, standard theoretical calculations and quassiclassical trajectory calculations (Figure 4.10). They found that the geometry of the transition state can be used as a useful predictor of the periselectivity of the reaction; that is, shorter interactions lead to the major product.

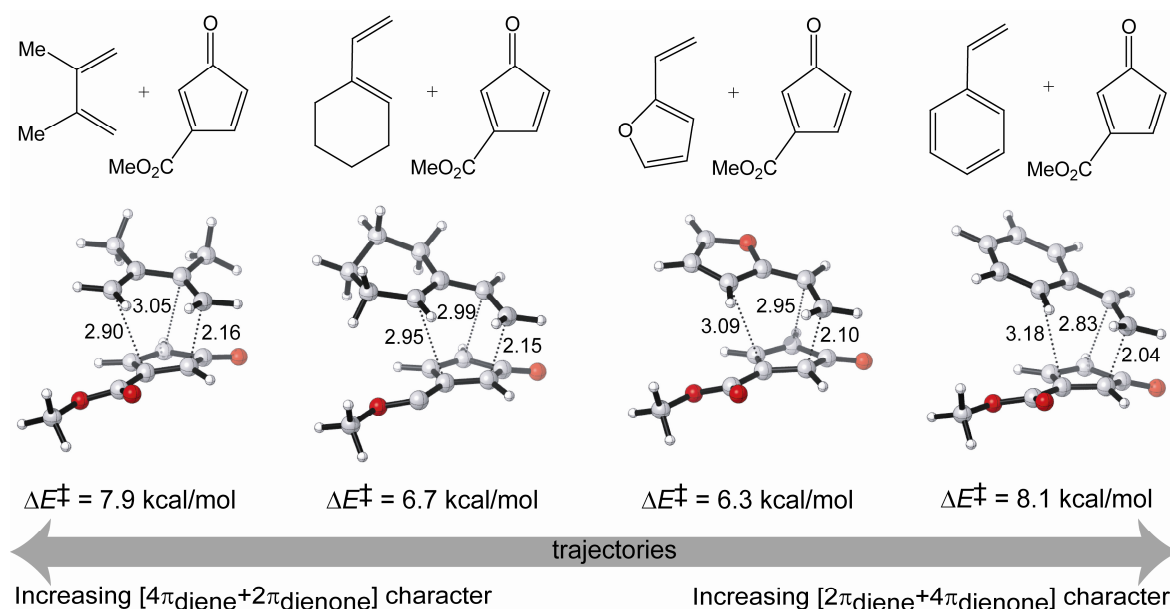


Figure 4.10. Dynamically determined product selectivity in Diels–Alder cycloadditions of 3-methoxycarbonylcyclopentadienone with 1,3-dienes (MPW1K/6-31+G(d,p)).

4.3. Conclusion

The possibility that multiple intermediates and products can be formed from a single transition state blurs the classical distinction between stepwise and concerted mechanisms. When a reaction path bifurcation occurs, a qualitative understanding is only possible by the analysis of the entire potential energy surface. Classical transition state theory fails to describe this type of potential energy surface, and quantitative predictions of selectivity can only be obtained by molecular dynamics simulations.

The flurry of reports precipitated in the last decade shows that reaction path bifurcations are common for many types of reactions, and future work will undoubtedly uncover many more examples.

5. EFFECT OF LEWIS-ACID CATALYSTS ON DIELS–ALDER AND HETERO-DIELS–ALDER CYCLOADDITIONS SHARING A COMMON TRANSITION STATE

The periselectivity of competing reactions is typically accounted for by the difference in barrier heights between two pericyclic addition channels (Figure 5.1, TS 1a and TS 1b). However, when these two distinct transition states merge into a single transition state (Figure 5.1, TS1), the preferential formation of one product is controlled by the branching ratio from a single unsymmetrical bis-pericyclic transition state leading to two distinguishable products as illustrated in Figure 5.1. We have discovered that competing Diels–Alder reactions including two different dienes can have a very unsymmetrical bis-pericyclic transition state that leads predominantly to one of the possible products and the shape of the potential energy surface and the major product are both reversed by Lewis acid catalysts [120, 121].

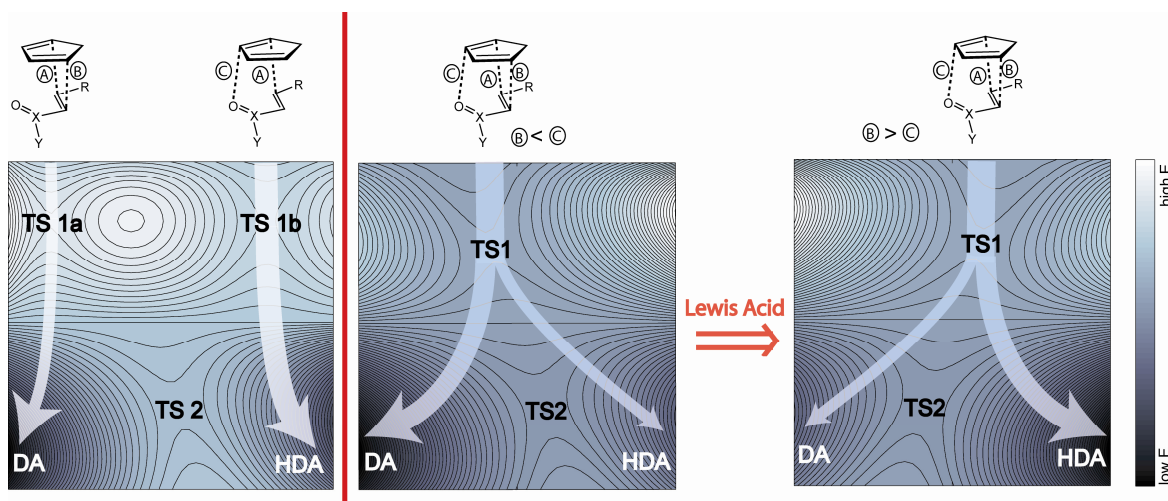


Figure 5.1. Possible reaction pathways in the cycloaddition of β,γ -unsaturated- α -ketophosphonates with cyclopentadiene yielding both Diels–Alder (DA) and hetero-Diels–Alder (HDA) products.

The thermal and Lewis-acid catalyzed cycloadditions of β,γ -unsaturated- α -ketophosphonates with cyclopentadiene have been explored using density functional theory (DFT) methods. In both cases, only a single highly asynchronous bis-pericyclic transition state yielding both Diels–Alder and hetero-Diels–Alder cycloadducts could be located. Stepwise pathways were found to be higher in energy. On the potential energy surface, the bis-pericyclic cycloaddition transition state is followed by the Claisen rearrangement transition state. No intermediates were located between these transition states. Claisen rearrangement transition states are also highly asynchronous, but bond lengths are skewed in the opposite direction compared to the bis-pericyclic transition states. The relative positions of the bis-pericyclic and Claisen rearrangement transition states may control periselectivity due to the shape of the potential energy surface and corresponding dynamical influences. Inspection of the thermal potential energy surface (PES) indicates that a majority of downhill paths after the bis-pericyclic transition state lead to the Diels–Alder cycloadducts, whereas smaller number of downhill paths reach to the hetero-Diels–Alder products with no intervening energy barrier. Lewis-acid catalysts alter the shape of the surface by shifting the cycloaddition and the Claisen rearrangement transition states in opposite directions. This topographical change qualitatively affects the branching ratio after the bis-pericyclic transition state and ultimately reverses the periselectivity of the cycloaddition giving a preference for hetero-Diels–Alder cycloadducts.

5.1. Introduction

Two or more reaction pathways sharing a single transition state has been described in a variety of organic reactions [88, 91, 92, 123]. Ess *et al.* have recently reviewed several examples for organic reactions having these so-called bifurcating potential energy surfaces (PESs) [86]. Briefly, on this type of PES (Figure 5.2), two distinct reaction coordinates give rise to consecutive transition states with no intervening intermediate, and the mechanism is a composite of two-steps, although concerted [14]. After the first transition state (TS1, Figure 5.2), the valley region changes into a ridge region via a valley-ridge inflection point (VRI) [93, 96-100, 124-128], due to the requirement of a negative force

constant in the orthogonal direction for the subsequent transition state (TS2, Figure 5.2). The ridge region divides the PES into two separate reaction channels. On a symmetrical surface, the common average reaction trajectory branches (bifurcates) from the valley region to follow one of two equivalent reaction pathways near the valley-ridge inflection point, because there is little or no restoring force perpendicular to first reaction coordinate. It should be noted that the statistical average intrinsic reaction coordinate does not split until the second transition state. However, on such surfaces it is unlikely that any trajectories actually follow the intrinsic reaction coordinate (IRC). In fact, even without a VRI after a transition state, dynamics can allow a reaction path [86] to access multiple products [129-131], and the Boltzmann distributions of states at TS1 determine the product distribution ratio.

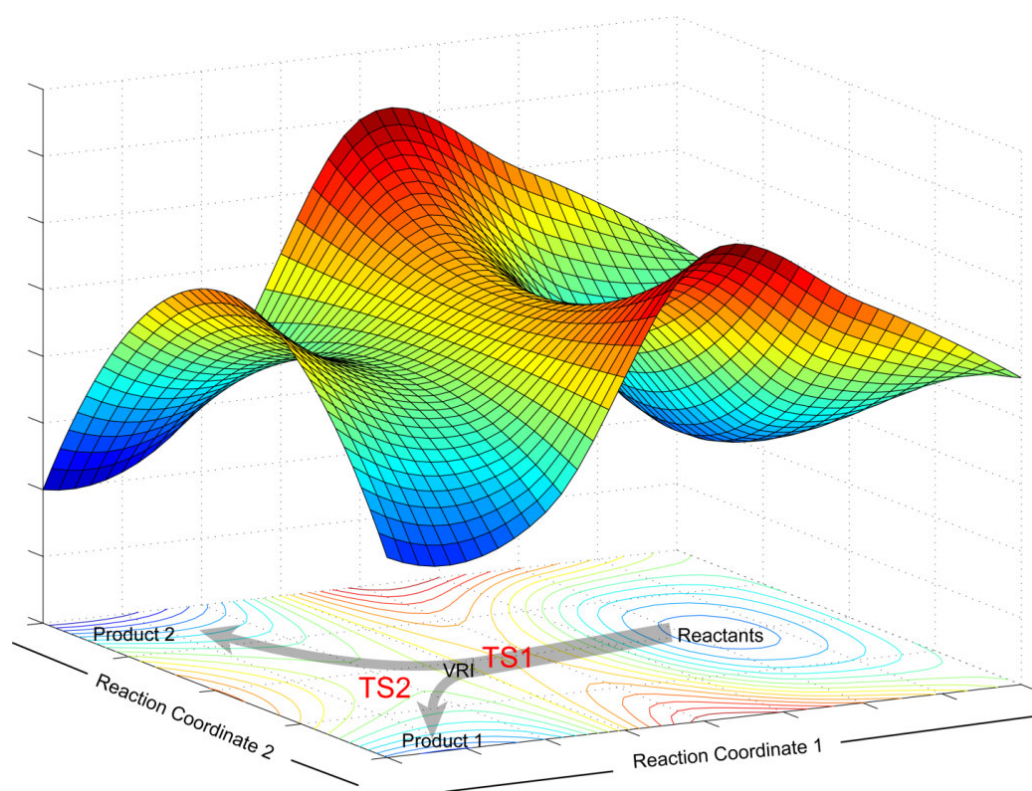


Figure 5.2. Generalized bifurcating potential energy surface.

Generally, when multiple symmetry-allowed processes are possible for a cycloaddition reaction, the periselectivity is classically determined by the difference in activation free energies between the addition channels. Figure 5.3 shows a hypothetical PES with two distinct reaction pathways for the [4+2] and [2+4] cycloaddition modes of

cyclopentadiene dimerization. However, Caramella and co-workers discovered that the actual PES corresponds to a bifurcating surface with a single “bis-pericyclic transition state” where the [4+2] and [2+4] addition modes for cyclopentadiene dimerization have merged (Figure 5.3) [108]. On this C_s symmetrical hypersurface, the relative abundance of each cycloadduct (periselectivity, although equivalent in this reaction) is controlled by the branching ratio after the bis-pericyclic transition state. After the cycloaddition transition state (TS1, Figure 5.3), the downhill IRC leads toward the Cope rearrangement transition state (TS2, Figure 5.3) until near the VRI. In the vicinity of the VRI, dynamic influences may then dictate the branching ratio from the IRC path. Because the PES of cyclopentadiene dimerization is symmetrical, there will be exact equal amount of reaction trajectories that take one of two equivalent downhill pathways.

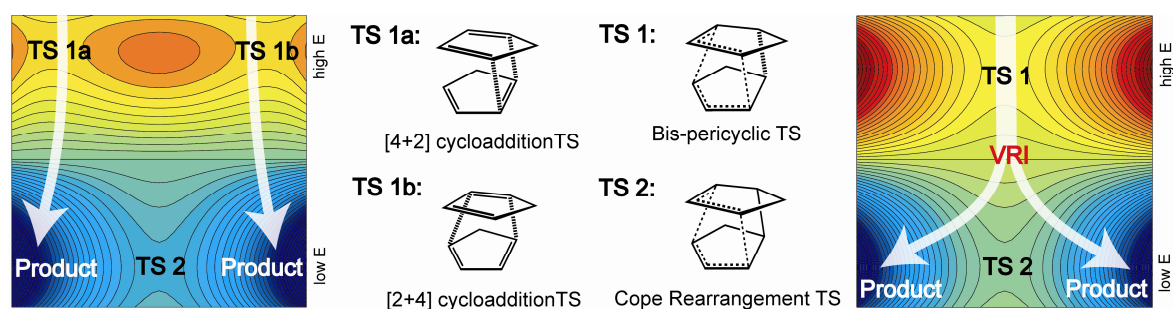


Figure 5.3. Two possible cycloaddition channels for cyclopentadiene dimerization and Caramella’s “bis-pericyclic TS” stabilized by merged [4+2] and [2+4] cycloaddition pathways.

The discovery by Caramella *et al.* [108-111] that the dimerization of several dienes occurs by a single “bis-pericyclic” transition state leading to two products has prompted a flurry of activity to find other reactions with similar potential energy surfaces (PES) featuring reaction path bifurcations [112-119]. Many of the previously reported *endo* dimerization reactions that involve bis-pericyclic transition states lead to equivalent forms of the same product [108-112]. Bis-pericyclic reactions yielding distinguishable products have unsymmetrical PESs. Houk and co-workers reported cycloaddition bifurcations for the reaction of cycloheptatriene and cyclopentadiene [118], and for the intramolecular cycloaddition of cyclobutadiene with butadiene [116]. Sastry and co-workers have identified the reaction of cyclopentadiene with phospholes as being akin to bis-pericyclic

[117]. Recently, Singleton and co-workers have elegantly shown that the periselectivity ([4+2] versus [2+2]) in the cycloaddition of cyclopentadiene with ketenes is controlled by an unsymmetrical bifurcating PES [119], rather than the result of two concerted pericyclic processes ([4+2] cycloaddition followed by [3,3]-rearrangement) [132, 133].

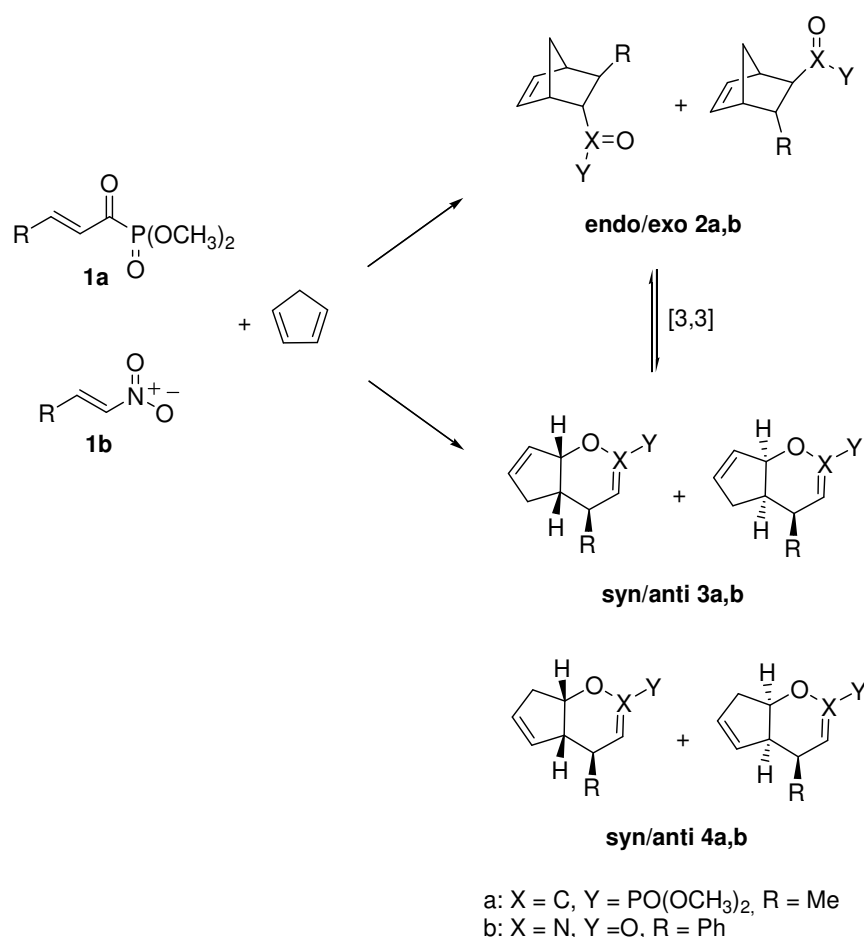


Figure 5.4. Possible Diels–Alder and hetero-Diels–Alder reactions of cyclopentadiene with crotonoyl phosphonates and nitroalkenes.

The highly useful Diels–Alder reactions between dienes and hetero-dienes often yield two different pericyclic products. Hanessian *et al.* [134] and Denmark [135] have shown experimentally that the reactions between crotonoyl phosphonates (**1a**) and nitroalkenes (**1b**) with cyclopentadiene (**Cp**) can lead to mixtures of Diels–Alder (**2a,b**) and hetero-Diels–Alder (**3a,b**) cycloadducts (Figure 5.4). In the thermal reactions, cyclopentadiene acts as a 4π component and gives mainly the *endo* and *exo* Diels–Alder cycloadducts, with only minor amounts of the hetero-Diels–Alder cycloadducts (*anti* and

syn). Lewis acids, such as SnCl_4 , reverse the periselectivity. Cyclopentadiene now acts as the dienophile. The major products formed are the hetero-Diels–Alder cycloadducts with only minor amounts of Diels–Alder products. This change in periselectivity has also been reported by Evans and coworkers for the reaction between cyclopentadiene and **1a** in the presence of Cu-bisoxazoline catalyst [136, 137].

Besides the classical concerted and stepwise mechanisms leading to each product, a two-step no intermediate mechanism, giving both *endo* Diels–Alder and *anti* hetero-Diels–Alder cycloadducts is also possible. There is no possibility for a composite *exo* Diels–Alder and *syn* hetero-Diels–Alder transition state. We report that the possible *endo* Diels–Alder and *anti* hetero-Diels–Alder transition states merge into a single bis-pericyclic transition state (Figure 5.5, Bonds A, B, and C will be referred to throughout the text). The position of the Claisen rearrangement transition state relative to the bis-pericyclic transition state dictates the PES landscape and branching ratio of the bifurcating reaction pathway. Lewis acid catalyst alters the shape of the PES, shifting the product distribution toward the hetero-Diels–Alder product. We describe details of the possible transition states for concerted and stepwise pathways. We also illustrate the effect of various Lewis acid strengths on the nature of the bis-pericyclic transition state and the shape of the PES.

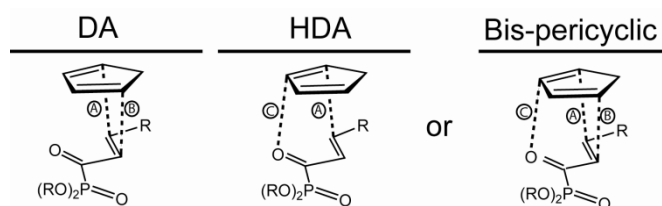


Figure 5.5. Merging of Diels–Alder and hetero-Diels–Alder transition states.

5.2. Computational Methodology

All gas phase geometry optimizations were carried out using Gaussian 03 [138]. Stationary points were verified as minima or saddle points by calculation of the full Hessian. All thermodynamic data (see Appendix, Table A.1 – Table A.5) used for zero-

point, thermal, and entropy corrections were computed at 298 K. Minimum energy paths were followed using the intrinsic reaction coordinate as implemented in Gaussian 03 [139, 140]. Diradical stationary points were located using the unrestricted B3LYP formalism. Spin projection energy corrections were done using the procedure described by Yamaguchi and co-workers [141, 142]. The B3LYP functional was employed with the 6-31+G(d) basis set. The effective core potential and basis set LANL2DZ was used for all transition metals. Comparative MPW1K/6-31+G(d) distances and enthalpies are given in parenthesis. The potential energy surface for the thermal and Lewis acid catalyzed reactions of cyclopentadiene to **1a** were scanned at 0.05 Å intervals for the formation of bond A and at 0.1 Å intervals for either the formation of bond B or the formation of bond C (see Figure 5.5 for definition); in the text this is referred to as the grid of scanned points and the surface scans are pictorially presented in the Appendix B, Figure B.1. Unless noted all values refer to B3LYP geometries, enthalpies (kcal/mol) and NPA charges. In the figures, carbon atoms are shown in light grey, hydrogens in white, oxygens in red, phosphorous in orange, chlorines in green and tin in pink.

5.3. Results and Discussion

5.3.1. Thermal Cycloaddition

One stepwise, and seven concerted cycloaddition transition states, and the Claisen rearrangement transition state that interconvert *endo*-Diels–Alder and *anti*-hetero-Diels–Alder products were located for the reaction of cyclopentadiene with *s-cis* and *s-trans-1a* (Figure 5.6).

The lowest energy transition state is the bis-pericyclic transition state **6** ($\Delta H^\ddagger = 17.7$ kcal/mol) that can lead to either *endo-2a* ($\Delta H = -8.1$ kcal/mol, $\Delta H_{MPW1K} = -25.9$ kcal/mol) or *anti-3a* ($\Delta H = -8.2$ kcal/mol, $\Delta H_{MPW1K} = -24.0$ kcal/mol), although the IRC path connects **6** to *endo-2a*. Several phosphonate transition state conformations were explored. All others were 1 kcal/mol higher than **6**. No other transition state was found for direct

formation of **anti-3a**. The alternative route to **endo-2a** via transition state **5** is 5.6 kcal/mol higher than **6**. The third “*endo*” transition state, **7**, leads to **anti-4a** ($\Delta H = -9.1$ kcal/mol), but again is significantly higher than **6** (8.4 kcal/mol higher).

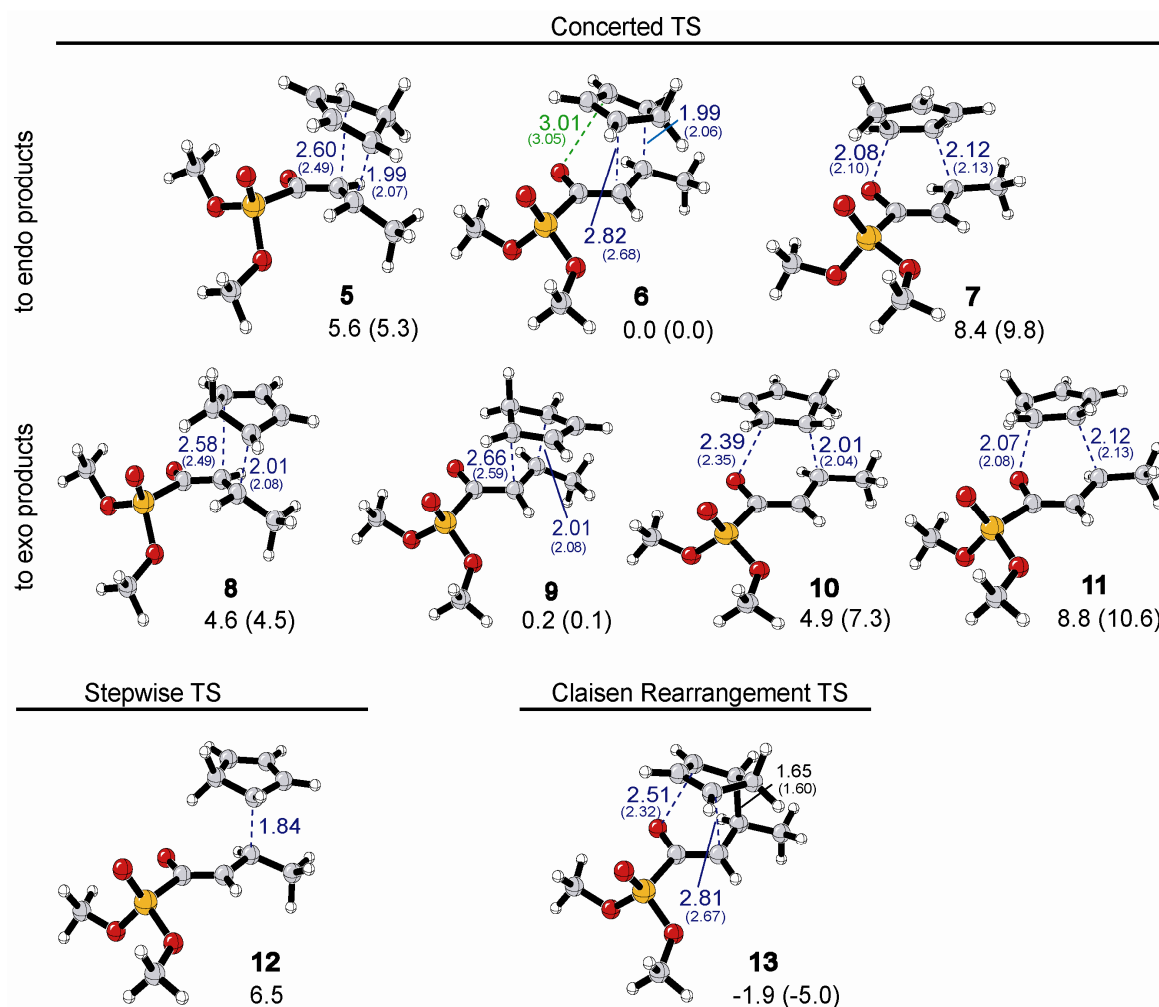


Figure 5.6. Transition state geometries and relative enthalpies ($\Delta\Delta H$, kcal/mol) for the reaction of cyclopentadiene with crotonoyl phosphonate. $\Delta H^\ddagger(\mathbf{6}) = 17.4$ (13.4) kcal/mol.

The lowest energy *exo* transition state is the addition of cyclopentadiene to *s-cis-1a* via transition state **9** ($\Delta H^\ddagger = 17.9$ kcal/mol) to give **exo-2a** ($\Delta H = -8.5$ kcal/mol, $\Delta H_{MPWIK} = -26.3$ kcal/mol). The transition state, **8**, with *s-trans-1a* also gives **exo-2a** and is 4.4 kcal/mol higher than **9**. The two other *exo* transition states, **10** and **11**, that give **syn-3a** and **syn-4a**, respectively ($\Delta H = -9.0$ and -9.1 kcal/mol, $\Delta H_{MPWIK} = -24.6$ and -24.7 kcal/mol), are 4.7 and 8.6 kcal/mol higher than transition state **9**.

The difference between the lowest *endo* and lowest *exo* transition state is only 0.2 kcal/mol. Experimentally, Hanessian and Compain [134] observed an *endo/exo* ratio of 6/1 in neat cyclopentadiene at room temperature during an eight hour reaction time period. They also reported a 7/1 ratio of **endo-2a/anti-3a**, which obviously cannot be account for by a difference in activation enthalpies, since separate transition states were not located. In accord with the larger activation enthalpies, due to the mismatch of frontier orbital coefficients, neither **syn-4a** nor **anti-4a** was observed.

A diradical transition state, **12** ($\langle S^2 \rangle = 0.27$), 8.9 kcal/mol higher in energy than **6**, was also located. The energy difference after spin projection is 6.5 kcal/mol. The resulting diradical intermediate is 4.4 kcal/mol higher in energy than **6** (7.3 kcal/mol before spin correction). No other stepwise pathways could be located.

Transition state **6** resembles an asynchronous Diels–Alder transition state with one short partial C–C bond ($r_A = 1.98 \text{ \AA}$) and two longer partial C–C and C–O bonds ($r_B = 2.82 \text{ \AA}$ and $r_C = 3.01 \text{ \AA}$). Additional stabilizing secondary orbital overlaps are common to *endo* transition states and set up a rationale for the *endo* selectivity of a variety of Diels–Alder reactions. Generally, the shorter bonds are expected to lead to the major product via the minimum energy pathway while other possible secondary orbital interactions (SOI) [104-107] are considered to provide additional stabilization to the transition state. However, stabilization of the *endo* transition states via SOIs presumably plays a minor role in this case and competes with the stereoelectronic factors, since no *endo/exo* selectivity is predicted. Bond C is about 3 $\text{\AA}$ and probably is insufficient to provide substantial stabilization to **6** which is highly asynchronous and has zwitterionic character (charge separation of 0.3e).

This well known SOI depicted in bond C, on the other hand, with a distance competitive to bond B, may lead to a more interesting consequence: the merging of the Diels–Alder and hetero-Diels–Alder pathways into **6**.

The displacement vectors associated with the imaginary frequency indicate motion along both bonds B and C besides the major vibration along bond A (see Figure 5.7 and Figure 5.5). However, the vibration along the partial C–C bond is more pronounced than

the vibration along the partial C–O bond in accordance with the Diels–Alder product obtained from the IRC calculations.

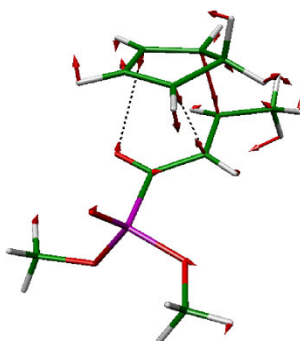


Figure 5.7. Displacement vectors associated with the imaginary frequency of the non-catalyzed bis-pericyclic transition state (**6**).

A detailed exploration of the PES starting from **6** over a grid of approximately 300 points (see the section 5.2 for details) shows that the steepest descent leads to *endo-2a*, indicative of the bond distance B being smaller than the bond distance C. However, it also shows the presence of alternative downhill paths toward *anti-3a*. Although **6** is highly asynchronous and has zwitterionic character, the mechanism is still concerted, since no intermediate exists on the PES and other factors beyond this transition state influence the product distribution.

The Claisen rearrangement transition state, **13**, is 2 kcal/mol lower in energy than **6**. Compared to the cycloaddition transition state, the Claisen rearrangement transition state has bond lengths skewed in the opposite direction on the PES. Bond length r_C is shorter than r_B ($r_B = 2.81 \text{ \AA}$, $r_C = 2.51 \text{ \AA}$).

Figure 5.8 shows a qualitative PES, based on the grid scan, showing the relative positions of the bis-pericyclic Diels–Alder and Claisen rearrangement transition states (TS1 and TS2). The PES clearly bifurcates in an unsymmetrical fashion (the VRI on this surface is on the path connecting **6** to **13** [100]). Qualitative inspection of the PES indicates that a larger number of downhill reaction pathways passing through TS1 reach *endo-2a* and are probably followed by the majority of reaction trajectories. It is possible that some

reaction trajectories passing through TS1 may also follow smaller number of downhill paths that lead directly to the hetero-Diels–Alder cycloadduct. Ultimately, periselectivity and the product distribution ratio will be mainly determined by the branching ratio from **6**, controlled by the Boltzmann distribution of states at the bis-pericyclic transition state, the exact PES shape and dynamics on the surface. The amount of hetero-Diels–Alder to Diels–Alder rearrangement may also affect the final product distribution of the cycloaddition. Singleton and co-workers have identified a similar unsymmetrical bifurcating type of PES for the cycloaddition of cyclopentadiene with ketenes and have shown that on such surfaces significant amounts of reaction trajectories can deviate from the statistical average pathway [119].

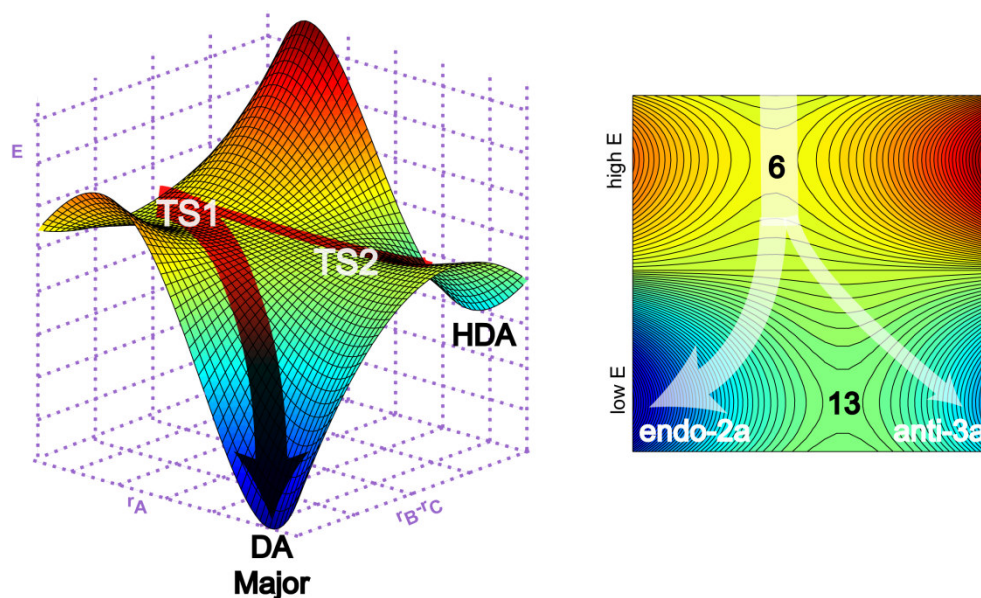


Figure 5.8. Hypothetical potential energy surface of the thermal reaction.

5.3.2. Lewis-acid Catalyzed Cycloaddition

There are several possibilities for the coordination of SnCl_4 to the dienophile **1a** (Figure 5.9). In their experimental work, Telan *et al.* [143] have studied the coordination of SnCl_4 to **1a** using low temperature ($-78\text{ }^\circ\text{C}$) ^{31}P and ^{119}Sn NMR spectroscopy. They reported that, up to 0.5 equivalent of SnCl_4 , a bridged structure (**14**) is formed in which

SnCl_4 is coordinated with two acylphosphonates via the phosphoryl oxygen to form an octahedral complex. With further addition of SnCl_4 , **15** is observed in which SnCl_4 is coordinated to both phosphoryl and carbonyl oxygens.

Complexes **15** and **16** (as a model for **14**) are used in the calculations. In **16**, SnCl_4 coordinates to the dienophile via only the phosphoryl oxygen like in **14**, but occupies a trigonal bipyramidal geometry. In both **15** and **16**, Sn is coordinated to the phosphoryl oxygen with a distance of about 2.2 Å (2.22 Å in **15** and 2.15 Å in **16**), whereas in **15**, Sn coordinates also to the carbonyl oxygen but more loosely (2.48 Å). Complex **15** is found to be about 3 kcal/mol destabilized with respect to **16**, presumably due to the loss of flexibility around the C-P bond. The dihedral angle between the carbonyl oxygen and phosphoryl oxygen, which is 96° in **1a**, is 4° in **15** and 114° in **16**.

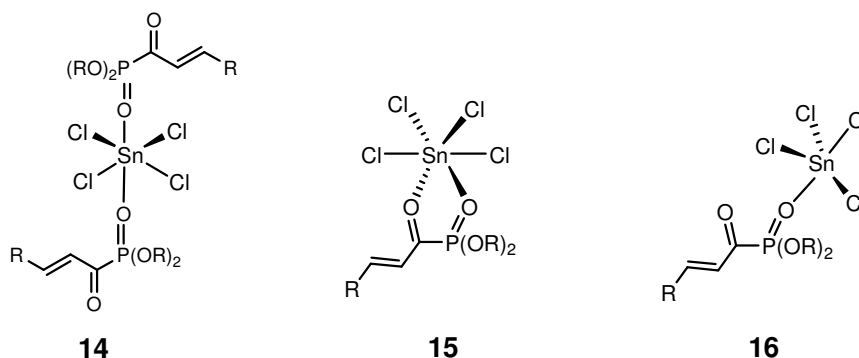


Figure 5.9. Complexes of crotonoyl phosphonate and SnCl_4 .

The destabilization of **15**, however, reverses in the transition state. The distance between Sn and the phosphoryl oxygen does not change much (2.21 Å in **15** and 2.11 Å in **16**), but in **15**, Sn coordinates to the carbonyl oxygen much more tightly (2.24 Å). Accordingly, 0.2e of a total of 0.5e charge transferred (Mulliken) in the transition state is withdrawn by the Lewis acid. On the other hand, no additional charge-transfer occurs in the transition states of **16**. The delocalization effect caused by the direct coordination of the Lewis acid to the reaction center in **15** polarizes and eventually stabilizes the transition states. The transition states of **16** lie significantly above the ones obtained from **15** (more than 3.3 kcal/mol), but follow exactly the same trend (see Appendix, Table A.5). In both

cases, only a single bis-pericyclic transition state could be located yielding both *endo-2a* and *anti-3a*.

In the products, like in the reactants, the distance between Sn and the phosphoryl oxygen stays around 2.2 Å in all cases. The distance between Sn and the carbonyl oxygen in **15**, however, is 2.49 Å for *endo-2a*, and is as long as 2.66 Å as expected for the hetero-Diels–Alder product, *anti-3a*.

Complex **15** is discussed here, since 60 mol per cent of the catalyst was used during the experiments.

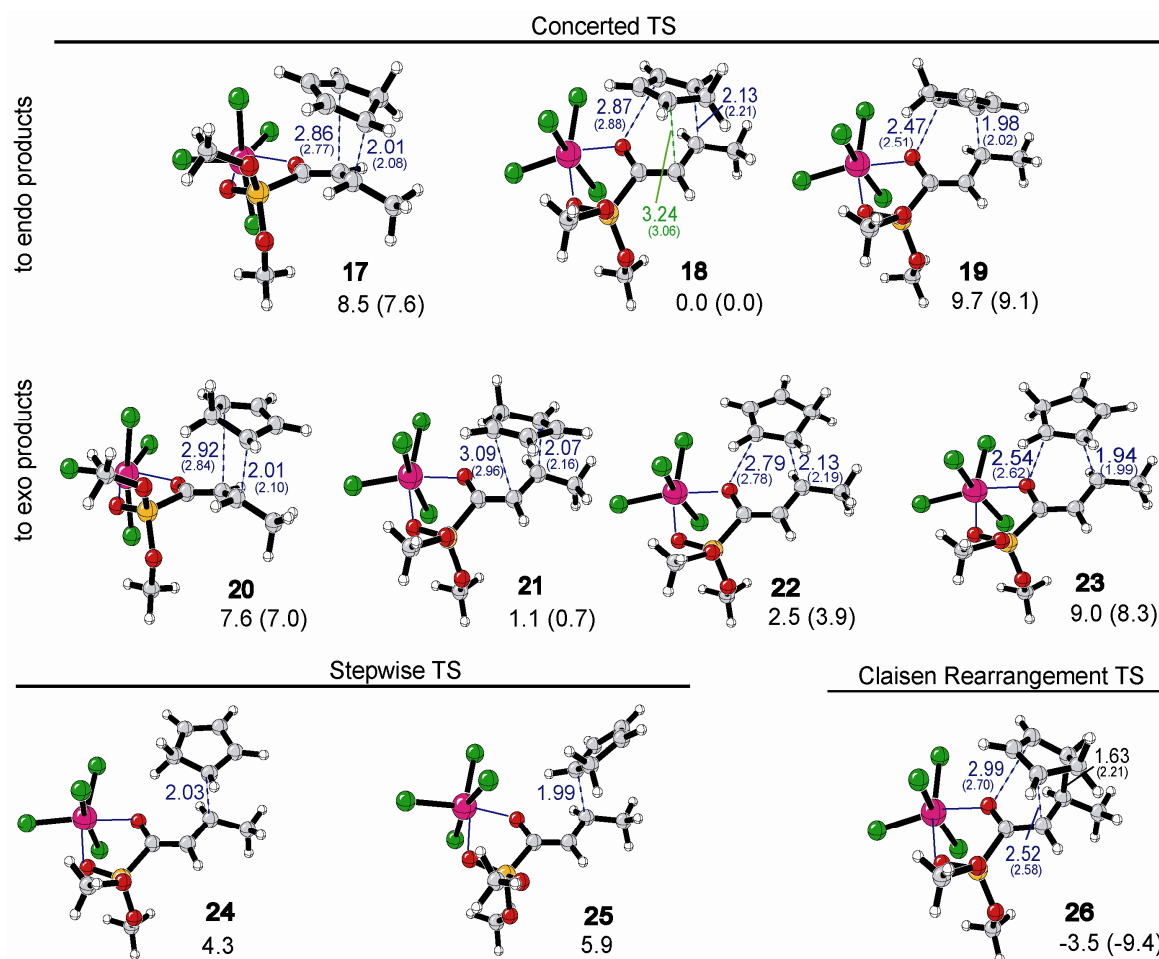


Figure 5.10. Transition state geometries and relative enthalpies ($\Delta\Delta H$, kcal/mol) for the SnCl_4 catalyzed reaction of cyclopentadiene with crotonyl phosphonate. $\Delta H^\ddagger(\mathbf{18}) = 9.0$ (3.8) kcal/mol.

Figure 5.10 shows the transition states and the corresponding relative enthalpies in kcal/mol for the potential energy surface of the SnCl_4 catalyzed reaction. Similar to the thermal reaction, the lowest energy transition state is the bis-pericyclic transition state **18** ($\Delta H^\ddagger = 9.0$ kcal/mol) that may lead to *anti*-**3a** (via the minimum energy pathway) or *endo*-**2a** via an alternative downhill pathway; there is no separate catalyzed transition state directly leading to *endo*-**2a** along a minimum energy pathway. In this bis-pericyclic transition state, bond C is 0.37 Å shorter than bond B, indicative of mostly hetero-Diels–Alder character. Experimentally, Hanessian and Compain found a 1/ 8 ratio of *endo*-**2a**/*anti*-**3a**. The displacement vectors associated with the imaginary frequency in the bis-pericyclic transition state still show motion along both bonds B and C together with the major vibration along bond A (see Figure 5.11 and Figure 5.5). However, the vibration along the C–O bond is more pronounced than the vibration along the C–C bond. Accordingly the IRC path connected the reactants to hetero-Diels–Alder products.

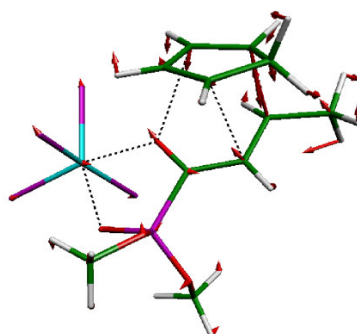


Figure 5.11. Displacement vectors associated with the imaginary frequency of the SnCl_4 catalyzed bis-pericyclic transition state (**18**).

The change in the direction of the cycloaddition toward the hetero-Diels–Alder reaction (see **18** compared to **6**) is consistent with the change in the LUMO profiles of *s-cis*-**1a** and its corresponding SnCl_4 complex. Coordination of SnCl_4 causes a significant decrease in the coefficient of the dienophile α -carbon adjacent to the ketophosphonate group (-0.4 to -0.2), and increases the carbonyl-oxygen coefficient (0.7 to 0.8). SnCl_4 lowers the activation enthalpy of the bis-pericyclic transition state by 8.4 kcal/mol compared to the uncatalyzed reaction.

The alternative reaction pathway giving **endo-2a** occurs via transition state **17** which is significantly higher than **18** (8.5 kcal/mol). Only transition states **21** ($\Delta H^\ddagger = 10.1$ kcal/mol) and **22** ($\Delta H^\ddagger = 11.5$ kcal/mol) have barriers that are predicted to be reasonably competitive with **18**. These transition states give **exo-2a** and **syn-3a**. The *endo/exo* ratio for this reaction, run in CH₂Cl₂ solvent at -78 °C with 0.6 equivalent of SnCl₄, is 20/1. The computed $\Delta\Delta H$ of 1.1 kcal/mol between **18** and **21** qualitatively agrees with this larger *endo/exo* ratio compared to the $\Delta\Delta H$ of only 0.2 kcal/mol between transition states **6** and **9** for the thermal reaction. The degree of diastereocontrol may again be due to steric and electronic factors, since the SOI displayed in **B** is too long (3.24 Å) to provide extra stabilization to the transition state. Transition states leading to **anti-4a** and **syn-4a**, **19** and **23**, are 9.7 and 9.0 kcal/mol higher than **18**, and not observed experimentally.

Transition states **24** and **25** lie 4.3 and 5.9 kcal/mol above **18**, respectively. These transition states are found to be zwitterionic, with $\langle S^2 \rangle$ values of 0. The corresponding intermediates are 0.5 and 0.9 kcal/mol above **18** (see Appendix, Table A.3).

In the Claisen rearrangement transition state, **26**, bond B is shorter ($r_B = 2.52$ Å) than bond C ($r_C = 2.99$ Å). The energy difference between **18** and **26** is more pronounced ($\Delta\Delta H_{B3LYP} = 3.5$ kcal/mol and $\Delta\Delta H_{MPW1K} = 9.4$ kcal/mol) than in the thermal reaction, so the potential energy surface is steeper in this region. A potential energy surface scan on a grid of 400 points shows that only transition state **18** separates reactants and **anti-3a** and **endo-2a**; the steepest descent from the Lewis acid catalyzed bis-pericyclic transition state leads to **anti-3a**. Although the charge transfer in **18** (0.4e) is larger than in **6**, due to the presence of Lewis acid, the PES shows no intermediates.

Figure 5.12 shows a qualitative representation of the computed Lewis acid catalyzed PES. Here, the cycloaddition and the Claisen rearrangement transition states are again skewed, but the Lewis acid has shifted the cycloaddition and the Claisen rearrangement transition states in opposite directions (compare to Figure 5.8). Now most of the reaction trajectories that pass through transition state **18** (also labeled as TS1) may lead to the hetero-Diels–Alder cycloadduct owing to the shape of the PES with surface dynamics allowing reactions to be funneled to the minor Diels–Alder cycloadduct. However, only dynamics simulations would be able to quantitatively give the branching ratio on this PES.

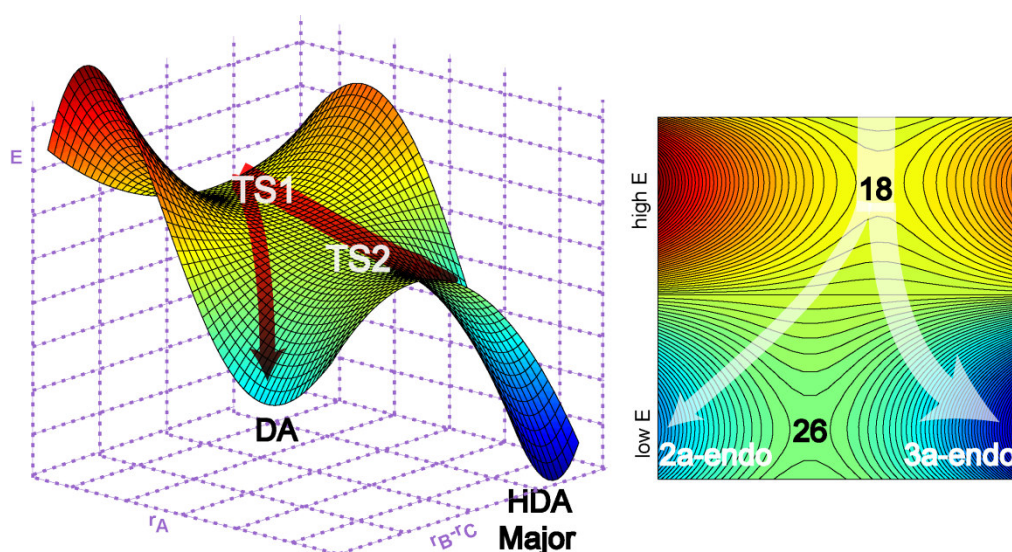


Figure 5.12. Hypothetical potential energy surface of the catalyzed Diels–Alder reaction.

5.3.3. Effect of Lewis Acid Strength on the PES

In order to understand the effect of Lewis acids on the shape of bifurcating PESs, we have compared the position of the bis-pericyclic transition state (TS1) and Claisen rearrangement transition state (TS2) using varying strengths of Lewis acidity. Table 5.1 gives the activation enthalpies, transition state bond lengths (bonds A, B, and C), and charge-separation for the uncatalyzed bis-pericyclic and Claisen rearrangement transition states, SnCl_4 catalyzed transition states, in which the Lewis acid coordinates to the dienophile either via only the phosphoryl oxygen (monodentate) or via both phosphoryl and carbonyl oxygens (bidentate) and bidentate BiCl_3 coordinated transition states.

The activation barriers show that the most effective catalyst is the bidentate coordinated SnCl_4 , lowering the barrier by 8.4 kcal/mol. Monodentate coordination only lowers the activation enthalpy by 2.0 kcal/mol while BiCl_3 lowers it by 3.8 kcal/mol. As can be seen from the changes in TS1 bond distance A, catalyzed transition states have longer C–C bond distances corresponding to slightly earlier transition states. With increasing charge separation, the TS1 bond distance B increases gradually from 2.82 Å to 3.24 Å, while bond distance C decreases from 3.01 Å to 2.87 Å. In TS2, however, bond

distance B decreases from 2.81 Å to 2.52 Å while bond distance C increases from 2.51 Å to 2.99 Å.

Table 5.1. Properties of the bis-pericyclic (TS1) and Claisen rearrangement (TS2) transition states catalyzed by different Lewis acids.

Structure	TS1					TS2			
	Charge Separation ^a	ΔH^b	A	B	C	ΔH^b	A	B	C
Thermal (6 and 13)	0.37 (0.30)	17.4	1.99	2.82	3.01	15.4	1.65	2.81	2.51
SnCl ₄ catalyzed (monodentate complex)	0.43 (0.31)	15.4	2.02	3.01	2.94	12.8	1.64	2.79	2.84
BiCl ₃ catalyzed	0.46 (0.34)	13.6	2.07	3.16	2.80	10.4	1.64	2.63	2.80
SnCl ₄ catalyzed (18 and 26) (bidentate complex)	0.50 (0.36)	9.0	2.13	3.24	2.87	5.5	1.63	2.52	2.99

^aMulliken (NPA) charges, ^b ΔH (kcal/mol) with respect to the reactants.

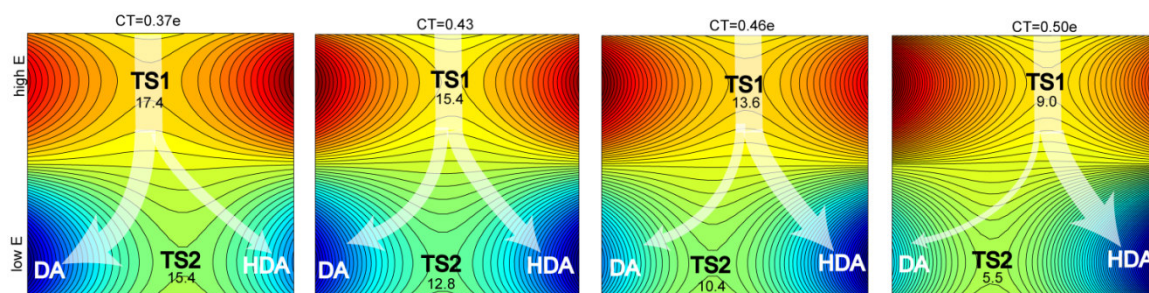


Figure 5.13. Evolution of the potential energy surface with increasing charge-transfer (CT) and increasing Lewis acid strength. Transition state enthalpies are given with respect to the reactants (kcal/mol).

Figure 5.13 shows a qualitative relationship for these four reactions and the position of their bis-pericyclic and Claisen rearrangement transition states. With increasing polar character, the position of TS2 relative to TS1 shifts. In the uncatalyzed reaction TS2 is skewed significantly compared to the position of TS1. However, with monodentate coordination, TS2 becomes skewed in the opposite direction. BiCl_3 and bidentate coordination further exacerbates this skewing. Also, as the strength of the Lewis acid increases, the energy difference between TS1 and TS2 increases, indicating a steeper descent along the minimum energy pathway.

5.4. Conclusion

The reactions of cyclopentadiene with crotonoyl phosphonates proceed through a highly asynchronous bis-pericyclic transition state to give both Diels–Alder and hetero Diels–Alder cycloadducts. Lewis acids alter the PES landscapes by shifting the relative positions of the cycloaddition and Claisen rearrangement transition states in opposite directions. This change in the shape of the PES ultimately affects the branching ratio and reverses the periselectivity of these bis-pericyclic reactions.

6. PERISELECTIVITY IN THE REACTIONS OF CROTONOYL PHOSPHONATE: 1,3-CYCLOHEXADIENE VERSUS CYCLOPENTADIENE

In the previous chapter, we explained the origins of the periselectivity in the Lewis acid catalyzed reaction of crotonoyl phosphonate with cyclopentadiene. The SnCl_4 catalyzed reaction of crotonoyl phosphonate with 1,3-cyclohexadiene, however, proceeds with a much lower selectivity ($\text{HDA:DA} = 1.2:1$ in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$, 1 equivalent of SnCl_4) and yields almost equal amounts of Diels–Alder (DA) and hetero-Diels–Alder (HDA) products unlike with cyclopentadiene ($\text{HDA:DA} = 30:1$ in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$, 0.6 equivalent of SnCl_4) [134]. 1,3-cyclohexadiene is known to show a different behavior compared to cyclopentadiene in cycloaddition reactions. In contrast to cyclopentadiene, dimerization of 1,3-cyclohexadiene is not bis-pericyclic and the stepwise pathways are predicted to be competitive with the concerted cycloaddition [113]. In this section, we seek to understand the factors that act on the loss of periselectivity in the SnCl_4 catalyzed reaction of 1,3-cyclohexadiene with crotonoyl phosphonate.

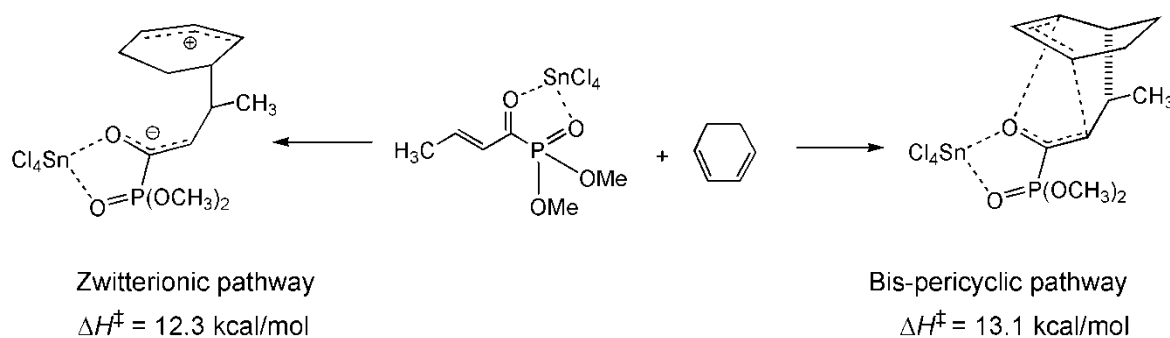


Figure 6.1. Competing reaction pathways in the SnCl_4 catalyzed reaction of crotonoyl phosphonate with 1,3-cyclohexadiene.

Density functional theory was used to explore the mechanism of the Diels–Alder reaction of 1,3-cyclohexadiene with crotonoyl phosphonate. As shown in Figure 6.1, the reaction proceeds either via the bis-pericyclic pathway ($\Delta H^\ddagger = 13.1 \text{ kcal/mol}$) or through

the formation of a zwitterionic intermediate ($\Delta H^\ddagger = 12.3$ kcal/mol). No separate channels exist for the cyclization after the intermediate, but the reaction trajectories may branch to give both hetero-Diels–Alder and Diels–Alder products. In the bis-pericyclic and stepwise pathways, the steepest descent paths lead to the less stable hetero-Diels–Alder product ($\Delta H = -6.2$ kcal/mol), that can later rearrange into the more stable Diels–Alder product ($\Delta H^\ddagger = -11.2$ kcal/mol) via the Claisen rearrangement pathway ($\Delta H^\ddagger = 15.5$ kcal/mol).

6.1. Introduction

In the last decade, the general classification of reaction mechanisms as concerted and stepwise has been broadened by the introduction of the “two-step no intermediate” mechanism [14] occurring due to post-transition state reaction path bifurcations. On this type of potential energy surface, two transition states connect with no intervening energy minimum, and the branching of the reaction trajectory past the first transition state allows the formation of multiple intermediates and products. Houk and co-workers have recently reviewed bifurcations occurring on potential energy surfaces of organic reactions, and have shown that such phenomena are surprisingly common [86]. The examples include many complex organic transformations, such as, isomerisation reactions, substitution reactions and particularly pericyclic reactions.

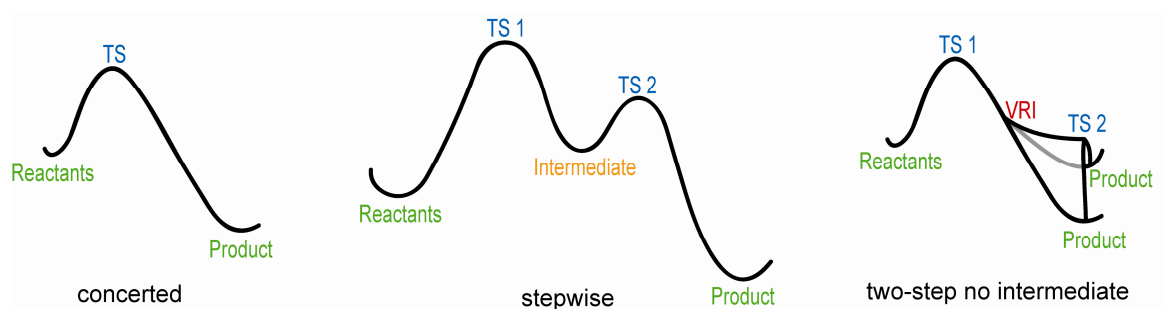


Figure 6.2. Reaction mechanisms.

In the field of cycloadditions, the pioneering work of Caramella on “bis-pericyclic” *endo* dimerizations [108-111] has been followed by several interesting reports on

unsymmetrical bifurcating potential energy surfaces leading to distinguishable products [116-122]. One example is the cycloaddition of cyclopentadiene with crotonoyl phosphonate yielding both Diels–Alder and hetero-Diels–Alder products via a single, highly asynchronous bis-pericyclic transition state [120]. We have shown that Lewis acid catalysts alter the shape of the potential energy surface of the reaction by shifting the consecutive bis-pericyclic and Claisen rearrangement transition states in opposite directions and favor the more stable hetero-Diels–Alder product [121].

We now report that in the SnCl_4 catalyzed reaction of crotonoyl phosphonate with 1,3-cyclohexadiene, stepwise passes are favored compared to the bis-pericyclic transition state and no separate cyclization transition state exists after the zwitterionic intermediate towards Diels–Alder and hetero-Diels–Alder products. However, the reaction trajectories may branch after the intermediate to give both cycloadducts.

6.2. Computational Methodology

Gaussian 03 [138] is used to perform all DFT calculations. The geometries of all reactants, transition states and products were optimized using the B3LYP functional with the 6-31+G(d) basis set. The effective core potential LANL2DZ was used for Sn. Stepwise pathways were explored using the unrestricted B3LYP formalism. Located stationary points were characterized as minima or saddle points using the frequency calculations. The thermodynamic corrections were computed at 298 K. Gas phase enthalpies are reported in kcal/mol relative to the reactants throughout the text and in the figures. Complete energetics for all reactants, transition states and products are given in Appendix, Table A.6. The minimum energy paths were followed using the intrinsic reaction coordinate method (IRC) [139, 140]. The potential energy surface for the cyclization after the intermediate was explored using relaxed potential energy surface scan. Twenty five points were located on the potential energy surface constraining the forming C–C and C–O bond distances. Spline interpolation is employed to smooth the surface. In the figures, carbon atoms are shown in light grey, hydrogens in white, oxygens in red, phosphorous in orange, chlorines in green and tin in dark grey.

6.3. Results and Discussion

SnCl_4 catalyzed Diels–Alder reactions of crotonoyl phosphonate with cyclopentadiene and 1,3-cyclohexadiene both yielded mixtures of Diels–Alder and hetero-Diels–Alder products (Figure 6.3) [134]. The formation of hetero-Diels–Alder product is highly favored with cyclopentadiene (HDA:DA 30:1 in CH_2Cl_2 at -78°C , 0.6 equivalent of SnCl_4), whereas the catalyzed reaction of 1,3-cyclohexadiene gave almost equal amounts of Diels–Alder and hetero-Diels–Alder products (HDA:DA 1.2:1 in CH_2Cl_2 at -78°C , 1 equivalent of SnCl_4).

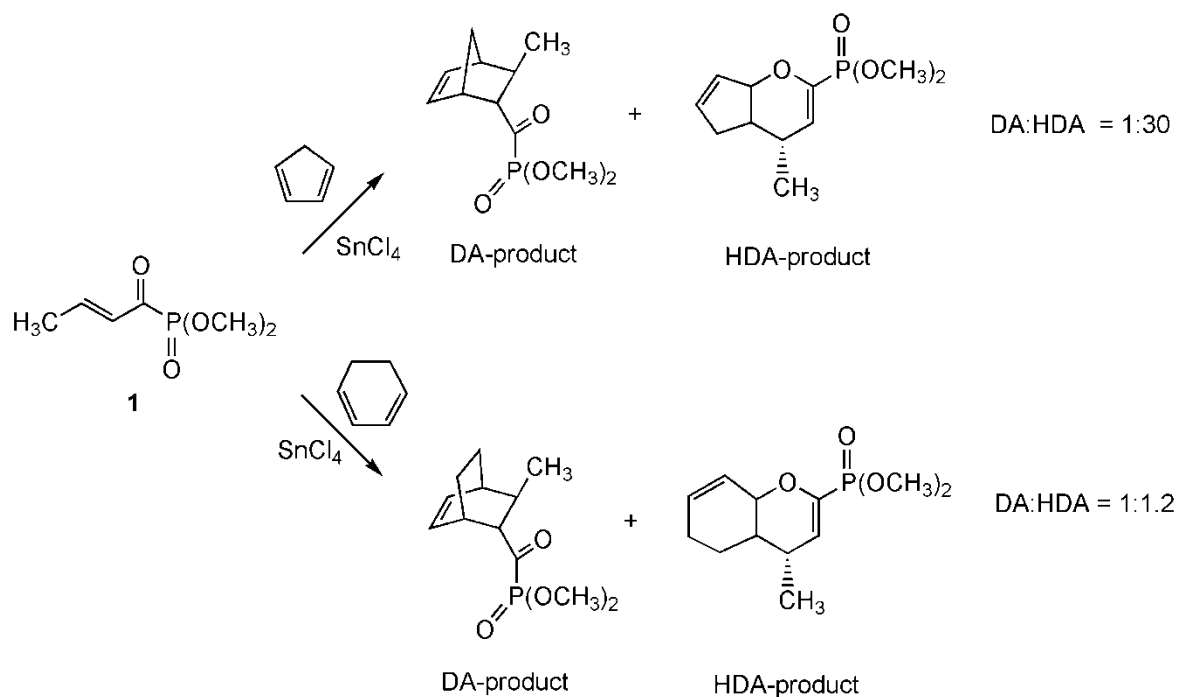


Figure 6.3. The reactions of crotonoyl phosphonate with cyclopentadiene and 1,3-cyclohexadiene.

Ess *et al.* have shown that the cycloaddition mechanism of 1,3-cyclohexadiene may differ from the one with cyclopentadiene [113]. They found that unlike the cyclopentadiene dimerization, dimerization of 1,3-cyclohexadiene is not bis-pericyclic and the stepwise pathways are predicted to be competitive with the concerted cycloaddition.

We, therefore, studied in detail the concerted and stepwise pathways in the Lewis acid catalyzed reaction of 1,3-cyclohexadiene with crotonoyl phosphonate.

6.3.1. Bis-pericyclic Reaction Pathway

A single *endo* transition state, **27**, exists on the potential energy surface of the reaction (Figure 6.4). It has an activation enthalpy of 13.1 kcal/mol. **27** is highly asynchronous and unsymmetrical. The distances between two partial C–C bonds are 2.09 and 3.43 Å respectively, and the C–O distance is 2.79 Å. The partial C–O bond is 0.64 Å shorter than the partial C–C bond. This more pronounced difference compared to cyclopentadiene can be partly explained by the deterioration of the [4+2] pericyclic overlap (Figure 6.5). The forward IRC path led to the hetero-Diels–Alder product accordingly. No other transition state towards the Diels–Alder product could be located. **27** has a zwitterionic character with a charge separation of 0.5e.

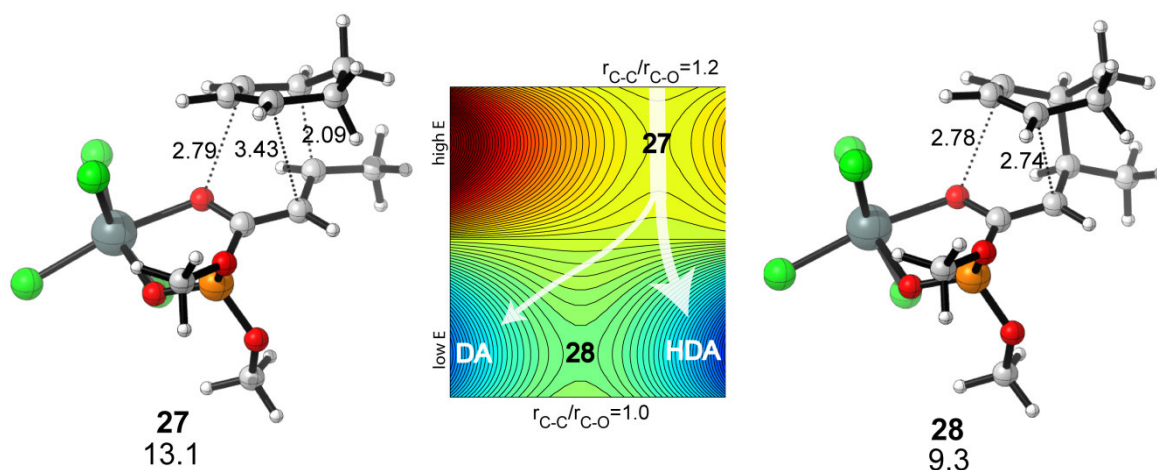


Figure 6.4. The geometries and enthalpies (ΔH , kcal/mol with respect to the reactants) of the cycloaddition and Claisen rearrangement transition states for the reaction of crotonoyl phosphonate with 1,3-cyclohexadiene.

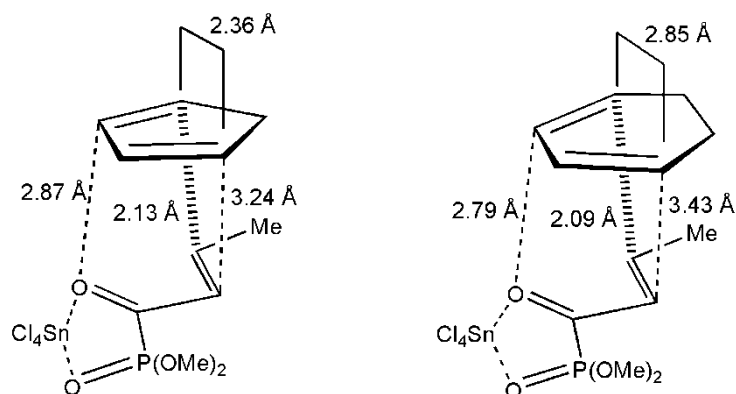


Figure 6.5. [4+2] pericyclic overlap of crotonoyl phosphonate with cyclopentadiene and 1,3-cyclohexadiene.

The Claisen rearrangement transition state, **28**, interconnects the hetero-Diels–Alder and Diels–Alder products and is 3.8 kcal/mol downhill from **27** (Figure 6.4). **28** is synchronous with forming and breaking bond distances of 2.74 and 2.78 Å. The C–O distance is only 0.01 Å different from **27**; progressive formation of two C–C bonds connects **27** to **28**. The resulting potential energy surface involves only a single cycloaddition transition state (**27**) connected to the Claisen rearrangement transition state (**28**) with no intervening energy minimum, but it is highly unsymmetrical (Figure 6.4). The steepest descent path, on the other hand, leads to thermodynamically less stable hetero-Diels–Alder product ($\Delta H = -6.2$ kcal/mol) that can further rearrange to the more stable Diels–Alder product ($\Delta H = -11.2$ kcal/mol).

6.3.2. Stepwise Reaction Pathway

The stepwise pathway is competitive with the bis-pericyclic transition state. Transition state, **29**, involves the formation of the terminal C–C bond and the IRC calculations have connected **29** to the zwitterionic intermediate **30** (Figure 6.6). **29** has an activation enthalpy of 12.3 kcal/mol, which is 0.8 kcal/mol lower in energy than the bis-pericyclic alternative **27**. The charge separation is found to be 0.8e in **29** and 0.6e in **30**. Zwitterionic intermediate is 2.9 kcal/mol lower in energy than **29**.

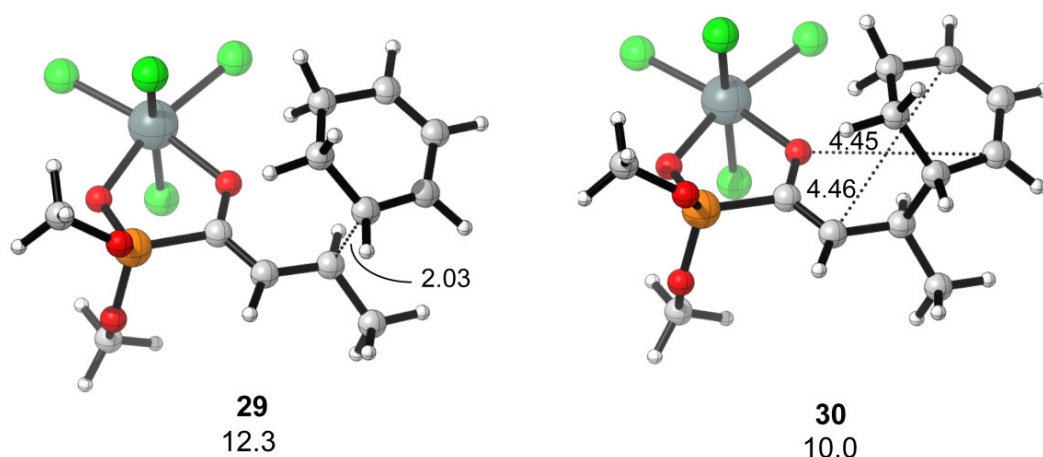


Figure 6.6. The geometries and enthalpies (ΔH , kcal/mol with respect to the reactants) of the zwitterionic transition state and the intermediate for the reaction of crotonoyl phosphonate with 1,3-cyclohexadiene.

From the intermediate, the cyclization may occur by the formation of the C–O bond to give the hetero-Diels–Alder product or by the formation of the C–C bond to yield the Diels–Alder product. The concurrent development of C–O and C–C bonds also connects the intermediate **30** ($r_{\text{C-O}} = 4.45 \text{ \AA}$, $r_{\text{C-C}} = 4.46 \text{ \AA}$) to the Claisen rearrangement transition state **28** ($r_{\text{C-O}} = 2.78 \text{ \AA}$, $r_{\text{C-C}} = 2.74 \text{ \AA}$). The potential energy surface for the cyclization process after the intermediate may either involve two separate cyclization channels yielding Diels–Alder and hetero-Diels–Alder cycloadducts (TSa and TSb, Figure 6.7) or two different cyclization transition states can merge into a single valley (TS, Figure 6.7) from which downhill trajectories may reach to both products.

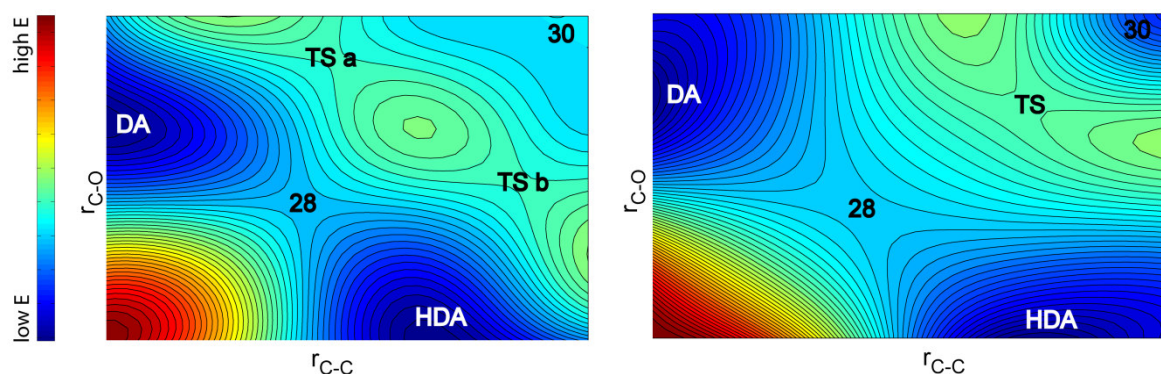


Figure 6.7. Possible reaction paths for the cyclization after the intermediate.

No cyclization transition states after the intermediate could be located presumably due to the flat nature of the energy surface past **30**. Figure 6.8 shows the contour plot of potential energy surface for the formation of C–C and C–O bonds after the intermediate obtained by constraint geometry optimizations. The surface closely resembles Figure 6.7. The intermediate lies in a shallow well. A small barrier of about 5 kcal/mol is found to connect **30** with the Claisen rearrangement transition state, **28**, and the Diels–Alder and hetero-Diels–Alder products with no intervening energy minimum or barrier. The geometry of the complex around this valley region (TS, Figure 6.8) is very similar to the intermediate with C–C and C–O bonds 0.3 – 0.4 Å more advanced as compared to **30**. The C–C and C–O distances are still around 4.0 Å, the cyclohexadienyl group has slightly rotated towards the heterodienyl moiety. This valley region presumably corresponds to a rotational barrier rather than a cyclization transition state. No separate cyclization transition states could be identified on the scanned surface. The reaction trajectories may branch in the flat potential energy region connecting the valley floor to **28**, leading to the formation of both products. Steepest descent path again favors the formation of hetero-Diels–Alder product, which may eventually rearrange into more stable Diels–Alder product.

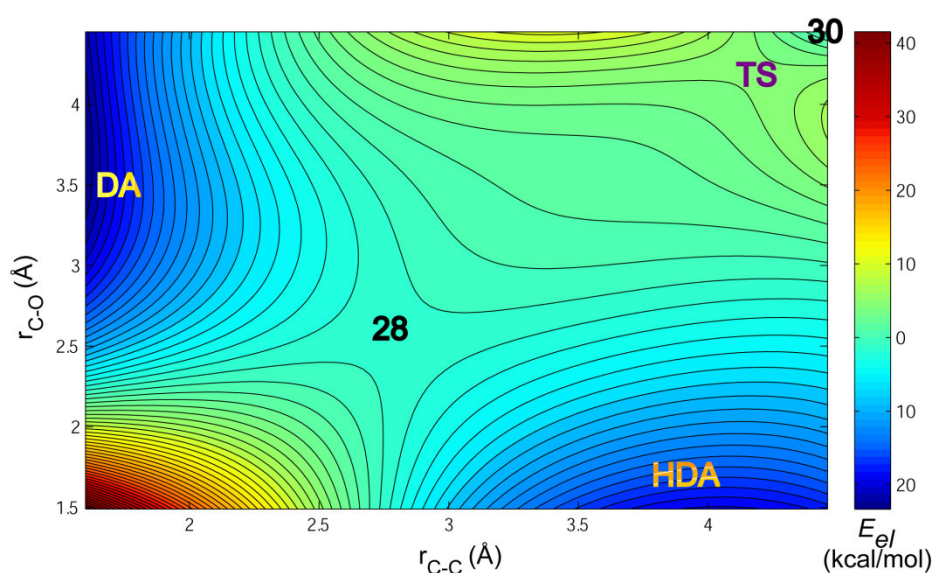


Figure 6.8. Scanned potential energy surface for the formation of C–C and C–O bonds after the intermediate.

6.4. Conclusion

Stepwise passes compete with the bis-pericyclic pathway in the SnCl_4 catalyzed reaction of crotonoyl phosphonate with 1,3-cyclohexadiene. In the stepwise pathway, the intermediate occupies a shallow well and no separate cyclization transition states exist after the intermediate. A small energy barrier connects the intermediate with the Claisen rearrangement transition state and the products. The reaction trajectory may branch on the flat potential energy surface to give Diels–Alder and hetero-Diels–Alder cycloadducts. Both mechanisms favor the formation of the hetero-Diels–Alder product, which can further rearrange to the more stable Diels–Alder product by the Claisen rearrangement pathway.

7. UNDERSTANDING THE STEREOSELECTION INDUCED BY CHIRAL ANTHRACENE TEMPLATES

In this chapter, we turn our attention from periselectivity to diastereoselectivity of cycloaddition reactions. Recyclable chiral anthracene templates have emerged as an effective and well-designed approach in preparing complex biologically active molecules such as butenolides, α,β -unsaturated lactams and related compounds in their enantiomerically pure forms. Highly diastereoselective initial cycloaddition serves as the key element of the total process, as it determines the final stereochemistry of the product. We explored the diastereoselectivity of four different chiral anthracene templates by using density functional theory (DFT) methods (Figure 7.1) and discussed in detail the steric and electronic factors that determine the stereochemical outcome of the cycloaddition [144]. The reliability and applicability of the previously proposed models, mostly based on steric arguments, are also tested by mechanistic means.

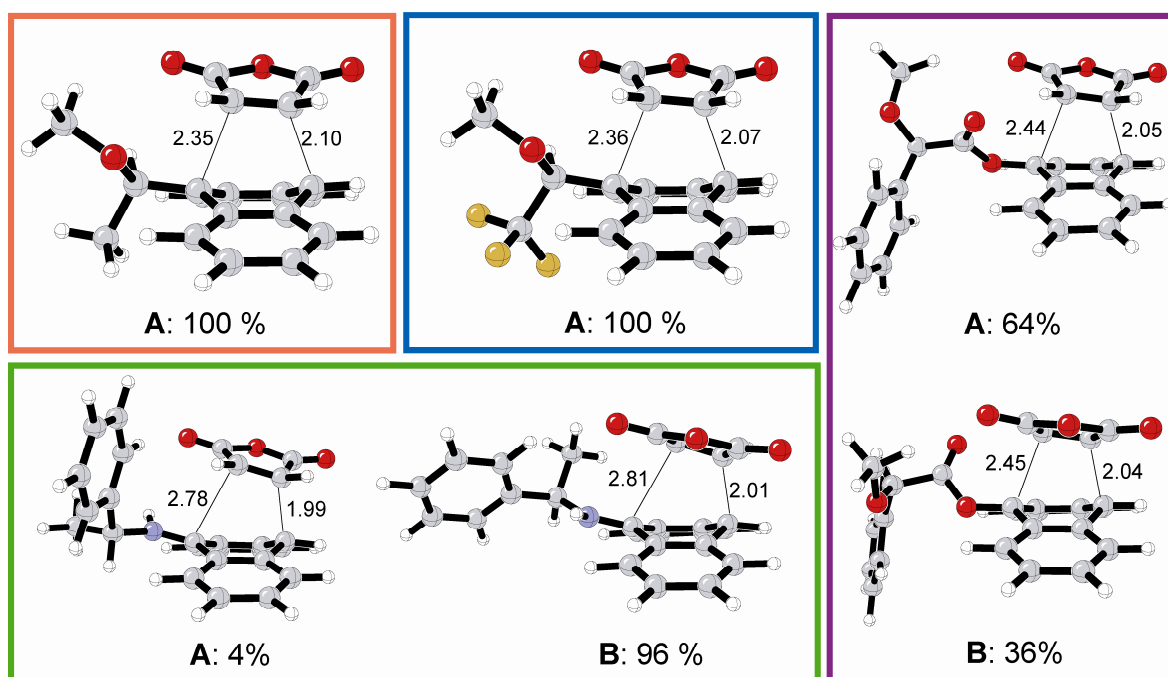


Figure 7.1. Lowest energy transition states and product distributions for the Diels–Alder additions of different chiral anthracene templates to maleic anhydride.

The diastereomers **A** and **B** are identified according to the stereochemistry around the formed stereocenter on the dienophile attached to C9, as being (*R*) or (*S*) respectively. The reactions of (*R*)-9-(1-methoxyethyl)anthracene and (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene with maleic anhydride both give exclusively diastereomer **A** via a similar transition state in which the CH₃/CF₃ group is antiperiplanar to the approaching dienophile. The major product of the reaction between (*R*)-9-(1-phenylethyl)aminoanthracene and maleic anhydride is diastereomer **B**. The geometry around nitrogen is close to planar in the transition state (10-25° out of plane) and the nitrogen lone pair is antiperiplanar to the incoming dienophile. Both of the lowest energy diastereomeric transition states giving **A** and **B** benefit from the favorable interaction between the carbonyl oxygen and the amine hydrogen; this interaction does not play a substantial role in the selectivity of the reaction as previously proposed. The diastereomeric transition states leading to **A** and **B** for the reaction between (*R*)-9-acyloxanthracene and maleic anhydride have very similar interactions around the reaction center, leading to a very small energy difference between the diastereomeric transition states. The product distribution ratios for all templates calculated from Boltzmann distributions agree very well with the experimental results.

7.1. Introduction

One of the most common approaches in the synthesis of enantiomerically pure substances utilizes the concept of asymmetric induction [145-149]. The key idea is to form non-equivalent diastereomeric trajectories that selectively yield a single product. This can be achieved by incorporating a stereocenter to the reagents or catalyst, for example via use of chiral auxiliaries or chiral ligands.

Among the chiral auxiliary based approaches, the use of chiral dienes as a ‘template’ in asymmetric synthesis has emerged as an elegant and powerful methodology and has been applied towards the synthesis of numerous stereochemically complex molecules in their enantiomerically pure forms [150]. The methodology involves a Diels–Alder reaction of an achiral dienophile with the chiral diene to furnish a diastereomerically pure

cycloadduct. Thereafter the stereocenters on the cycloadduct allow stereocontrolled modifications of the dienophile subunit. Finally a cycloreversion step regenerates the chiral diene template and releases the desired enantiopure product.

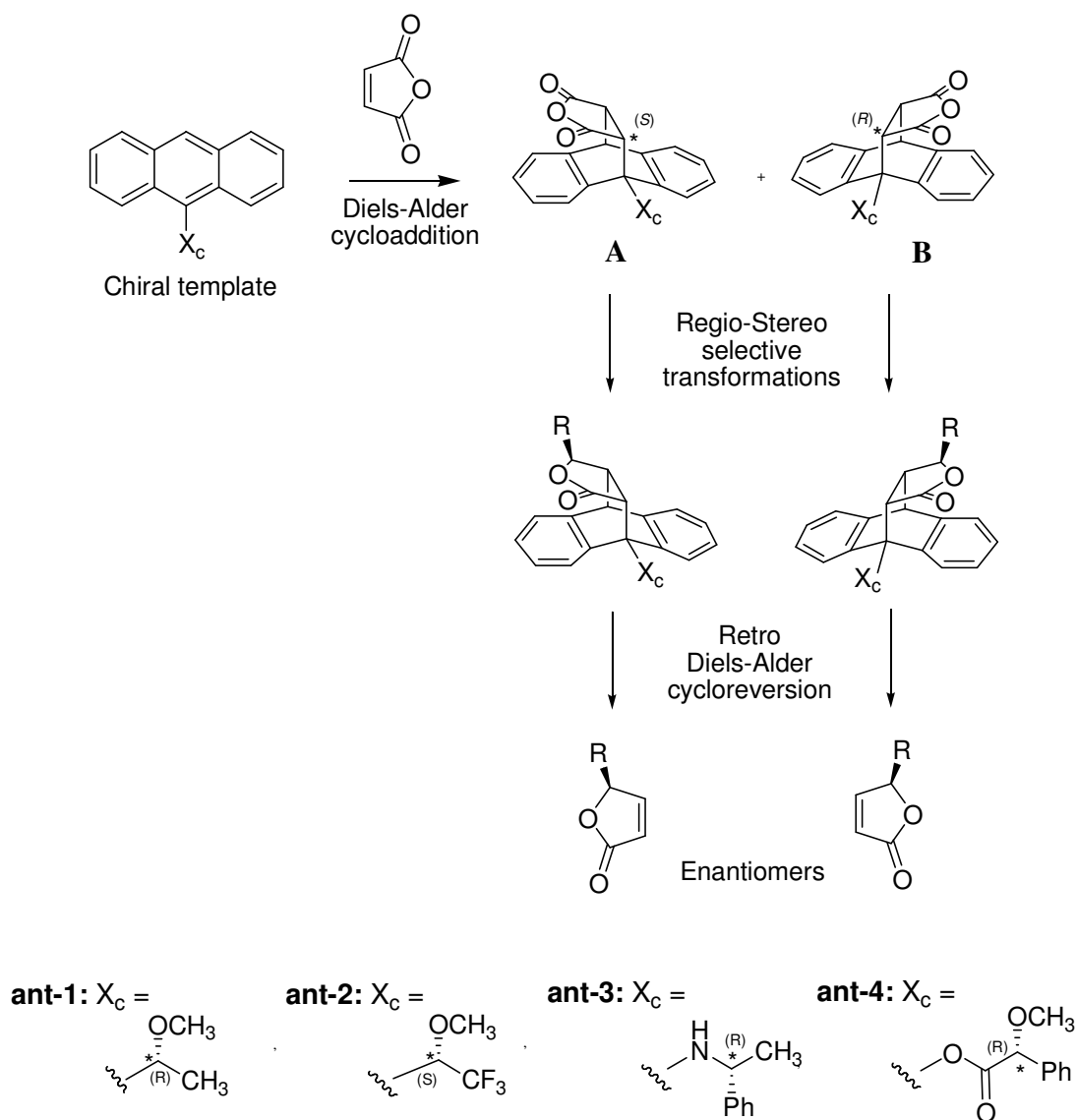


Figure 7.2. Stereoselective functionalization of the dienophile using chiral anthracene template.

One such strategy, developed by Snyder *et al.* [151-155] and Jones *et al.* [156-162] employs chiral anthracene templates in Diels–Alder/retro-Diels–Alder sequences to stereoselectively functionalize the dienophile (Figure 7.2). Biologically active substances such as butenolides, α,β -unsaturated lactams and related compounds were successfully

prepared from achiral dienophiles using chiral and recyclable anthracene templates with this strategy [151-155]. More recently, Liu and Snyder demonstrated that chiral anthracene based cycloadducts provide access to a valuable class of chiral auxiliaries that allow excellent diastereocontrol in a variety of reactions such as Diels–Alder cycloadditions, conjugate additions and Aldol reactions [163]. In this method, highly diastereoselective initial cycloaddition determines the final stereochemistry of the product (Figure 7.2). So, much effort has been devoted to develop benchtop stable chiral anthracenes with improved reactivity and diastereoselectivity [151-162].

The Diels–Alder reactions of several dienophiles with various chiral anthracene templates substituted at C9 position with a stereogenic center have been extensively explored [151-162]. These cycloadditions can give two diastereomers, **A** and **B**, which can be identified with the stereocenter on the dienophile attached to C9 as being (*R*) or (*S*) respectively. Exclusive diastereoselectivity has been successfully obtained with (*R*)-9-(1-methoxyethyl)anthracene (**ant-1**) and (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene (**ant-2**) when reacted with maleate derivatives [151, 153, 156, 158]. Snyder and coworkers have then prepared anthracenes with electron donating chiral substituents at C9 position to obtain enhanced reactivity and cycloreversion at lower temperatures [155]. While (*R*)-9-acyl-oxyanthracene (**ant-4**) has produced the diastereomers in a very low ratio (3:2), promising diastereoselectivity (>10:1) with (*R*)-9-(1-phenylethyl)aminoanthracene (**ant-3**) together with improved reactivity has been achieved. Recent results of Adams *et al.* [162] supported the encouraging stereoselectivity obtained for **ant-3**, however, they showed the stereochemical outcome of the reaction to be the opposite to that had previously been reported.

Asymmetric induction is usually explained by steric and electronic effects that determine the facial recognition. Steric interactions in the transition state can be used to derive models to predict the absolute stereochemistry of the products. When steric interactions are close to the reaction center, it is usually possible to explain the experimental outcome of the reaction with simple and reliable models based on steric arguments. This task is more demanding when the stereogenic center does not lie in the immediate proximity of the reaction center and even harder when the transition state is conformationally flexible. The degree of stereocontrol exerted by the chiral group depends

on small energy differences between the diastereomeric transition state conformers and can easily be affected by minor changes.

Some models have already been proposed to explain the diastereoselectivity [151-162] of chiral anthracenes. The reaction of maleic anhydride (MA) with (*R*)-9-(1-methoxyethyl)anthracene (**ant-1**) proceeding with exclusive diastereoselectivity has perhaps one of the most reliable models, since the stereogenic center with well known electronic characteristics is directly attached to the carbon involved in the bond formation process. However, the same model may not explain the product distribution when the electronic properties of the system are modified as in the case of compound **ant-2**. Similarly, simple steric arguments are insufficient to explain the degree of stereocontrol caused by (*R*)-9-(1-phenylethyl)aminoanthracene (**ant-3**) and (*R*)-9-acyl-oxyanthracene (**ant-4**). In **ant-3** and **ant-4**, even though the location of the chiral center is similar – one bond away from C9 – there is a substantial difference in their experimental diastereoselectivities. Overall, the factors influencing the selectivities of Diels–Alder reactions of chiral fluoro-substituted anthracenes, aminoanthracenes and acyloxyanthracenes require deeper mechanistic exploration.

In this study we focus on the initial diastereoselectivity of the Diels–Alder cycloaddition and investigate the diastereoselection process of the chiral anthracene templates **ant-1**, **ant-2**, **ant-3** and **ant-4** using Density Functional Theory. We also examine the reliability of the previously proposed models. We first explore the reaction of MA with (*R*)-9-(1-methoxyethyl)anthracene (**ant-1**) to validate our methodology and to provide a deeper insight into the stereoelectronic features of the transition states leading to the diastereomers. We then model the reaction of MA with (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene (**ant-2**). As such, the aim is to understand the selectivity of similar systems but with very different electronic properties. Finally, we focus our attention to the reactions of MA with (*R*)-9-(1-phenylethyl)aminoanthracene (**ant-3**) and (*R*)-9-acyl-oxyanthracene (**ant-4**) giving two diastereomeric products **A** and **B**, with very different diastereoselectivities that cannot be explained by simple steric models.

7.2. Computational Methodology

All DFT calculations were carried out with Gaussian 03 [138]. The Becke three parameter exchange functional and the nonlocal correlation functional Lee, Yang and Parr (B3LYP) have been employed with the 6-31+G(d) basis set. Geometry optimizations were performed for all reactants, transition states and products. Frequency calculations were used to characterize the stationary points as minimum or saddle point and to provide thermal and zero point corrections. The minimum energy paths were followed by the intrinsic reaction coordinate method (IRC) [139, 140]. Solvent effects were considered using the IEFPCM methodology with the UA0 cavity model as implemented in Gaussian 03. Toluene is used as the solvent to represent the experimental conditions.

Gas phase enthalpies are reported throughout the text unless otherwise specified. In figures, the relative enthalpies (ΔH) for the reactants, and activation enthalpies ($\Delta H^\ddagger$) for the transition states are given in kcal/mol. Mulliken charges of interacting atoms are shown in italics. In the figures, carbon atoms are shown in light grey, hydrogens in white, oxygens in red, nitrogen in blue and fluorines in yellow. Complete energetics, including the free energies and solvent energies of all reactants, transition states and products are given in the Appendix, Table A.7.

The conformational space was initially explored systematically with 3-fold rotation around the single bonds using the semi-empirical PM3 method. The conformers within 3 kcal/mol energy range were then optimized with B3LYP/6-31+G(d) to get a more accurate description of the conformer distribution. Single point energies of these conformers in toluene were calculated. For **ant-1** and **ant-2**, an additional relaxed potential energy surface scan was performed with 60° increments around the C9-C* bond connecting C9 with the chiral carbon atom at the B3LYP/6-31+G(d) level of theory.

Natural bond orbital analysis (NBO) was performed on the conformers of **ant-1** and **ant-2** [164-168]. The role of electronic delocalizations was quantitatively assessed by deleting all non-Lewis NBOs from the basis set. The net energy difference between the original electronic energy (E_{el}) and the energy of the perfectly localized Lewis-type

wavefunction ($E_{(L)}$) gives the electronic delocalization energy ($E_{(NL)}$) and describes the stabilizing effect of the delocalizing (non-Lewis) contributions (Equation (7.1)).

$$E_{(NL)} = E_{el} + E_{(L)} \quad (7.1)$$

To understand specific interactions responsible for the conformational preferences, all hyperconjugative delocalizations between ‘filled’ (donor) Lewis-type NBOs and ‘empty’ (acceptor) non-Lewis NBOs were examined and their energetic importance was estimated by second order perturbation theory. It has been shown that the use of diffuse functions in NBO calculations lead to erroneous results originating from the augmented Rydberg orbital’s extension [169]. The NBO calculations were, therefore, performed by using the B3LYP methodology and 6-31G(d) basis set and the electronic energies are reported in the text.

7.3. Results and Discussion

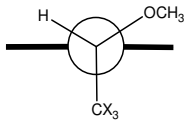
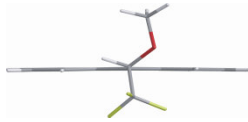
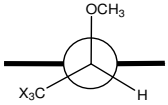
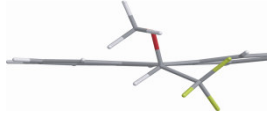
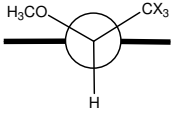
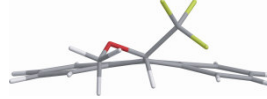
7.3.1. Reactions of (*R*)-9-(1-methoxyethyl)anthracene and (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene with Maleic Anhydride

The conformational analysis of **ant-1** and **ant-2** has shown a strong energetic bias towards structures in which the methyl and trifluoromethyl groups on the stereogenic center occupy a position perpendicular to the anthracene plane. This conformational preference is justified by a relaxed potential energy surface scan around the bond connecting C9 with the chiral carbon atom (C9-C*).

The conformations obtained from the PES scan (**a**, **b** and **c**) have been analyzed to understand the factors contributing to the stabilization of **ant-1a** and **ant-2a** (Table 7.1). In structures **ant-1a** and **ant-2a** the anthracene ring is completely planar. The significant

distortions of the anthracene ring in structures **ant-1b**, **ant-2b**, **ant-1c** and **ant-2c** can be accounted for by the steric repulsions between the anthracene ring and the bulky *syn* substituents.

Table 7.1. Natural bond orbital (NBO) analysis of the conformers of (*R*)-9-(1-methoxyethyl)anthracene and (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene.

Conformation	ant-1 (X = H)			ant-2 (X = F)			3D Structure
	ΔE_{el}	$\Delta E_{(L)}$	$\Delta E_{(NL)}$	ΔE_{el}	$\Delta E_{(L)}$	$\Delta E_{(NL)}$	
 a	0.0	0.0	0.0	0.0	0.0	0.0	
 b	8.0	5.5	2.5	7.4	4.8	2.6	
 c	11.3	2.9	8.4	15.2	7.8	7.4	

Relative electronic energies (ΔE_{el}), Lewis ($\Delta E_{(L)}$) and non-Lewis ($\Delta E_{(NL)}$) contributions to the electronic energies (kcal/mol)

The localized $E_{(L)}$ contributions strongly favor **ant-1a** and **ant-2a** in accordance with the expected steric and electrostatic effects. Energy differences between conformers are further amplified by the delocalization contributions $\Delta E_{(NL)}$. **Ant-1c** is 2.6 kcal/mol lower in energy than **ant-1b** in the absence of electronic delocalizations, this difference can be attributed to an electrostatically more favorable arrangement of the methyl and methoxy groups ($\Delta E_{(L)}$ (**ant-1b**) = 5.5 kcal/mol, $\Delta E_{(L)}$ (**ant-1c**) = 2.9 kcal/mol). However, **ant-1b** is highly stabilized by the electronic delocalization energy and favored overall by 3.3 kcal/mol as compared to **ant-1c** ($\Delta E_{(NL)}$ (**ant-1b**) = 2.5 kcal/mol, $\Delta E_{(NL)}$ (**ant-1c**) = 8.4 kcal/mol).

In the case of compound **ant-2**, the electrostatic repulsions between the trifluoromethyl and methoxy groups destabilize **ant-2c** by 3.0 kcal/mol as compared to **ant-2b** when electronic delocalizations are not taken into account, ($\Delta E_{(L)}$ (**ant-2b**) = 4.8 kcal/mol, $\Delta E_{(L)}$ (**ant-2c**) = 7.8 kcal/mol). **Ant-2c** is further disfavored by lack of delocalizations leading to very large total energy differences with **ant-2a** and **ant-2b** ($\Delta E_{(NL)}$ (**ant-2b**) = 2.6 kcal/mol, $\Delta E_{(NL)}$ (**ant-2c**) = 7.4 kcal/mol). The relative stability of **ant-1c** (3.9 kcal/mol) relative to **ant-2c**, can be explained by the differences in the electrostatic interactions between the substituents, whereas the relative energies of **ant-1b** and **ant-2b** are very close due to similar Lewis and non-Lewis contributions.

To understand specific interactions responsible for the energy difference, hyperconjugative delocalizations involving the acceptor and donor NBOs on the chiral carbon (CH, $CC_{(CX3)}$ and CO) are explored in detail. The most important contributions to the stabilization of **a** compared to both **b** and **c** is found to be the vicinal hyperconjugative interactions between the donor/acceptor $CC_{(CX3)}$ NBOs on the chiral carbon with the acceptor/donor OC NBOs on the methoxy group that shows a favorable antiperiplanar arrangement in **a** (Table 7.2). The hyperconjugative interactions between the anthracene aromatic system and the CH, $CC_{(CX3)}$ and CO antibonds on the chiral carbon give an extra stabilization of about 2.5 kcal/mol to both **a** and **b** as compared to **c**. A detailed list of donor-acceptor interactions and their stabilization energies are given in the Appendix (Table C.1 – Table C.6).

Table 7.2. Important donor-acceptor interactions and their stabilization energies.

	Acceptor NBO	Donor NBO	$E(2)$ (kcal/mol)
ant-1a	BD ($CC_{(CX3)}$)	BD* (OC)	2.44
ant-1a	BD (anthracene)	BD* (CH, $CC_{(CX3)}$, CO)	7.82
ant-1b	BD (anthracene)	BD* (CH, $CC_{(CX3)}$, CO)	7.39
ant-1c	BD (anthracene)	BD* (CH, $CC_{(CX3)}$, CO)	5.93
ant-2a	BD ($CC_{(CX3)}$)	BD* (OC)	2.37
ant-2a	BD (anthracene)	BD* (CH, $CC_{(CX3)}$, CO)	9.07
ant-2b	BD (anthracene)	BD* (CH, $CC_{(CX3)}$, CO)	8.21
ant-2c	BD (anthracene)	BD* (CH, $CC_{(CX3)}$, CO)	6.09

Figure 7.3 shows model transition states leading to diastereomers **A** and **B** for the cycloadditions of MA with **ant-1** and **ant-2**. When MA approaches from the face opposite to the CH₃/CF₃ group, the diastereoselection occurs between **I** and **II**. The approach of MA from the face hindered by the CH₃/CF₃ groups results in the transition state models **III**, **IV**, **V** and **VI**.

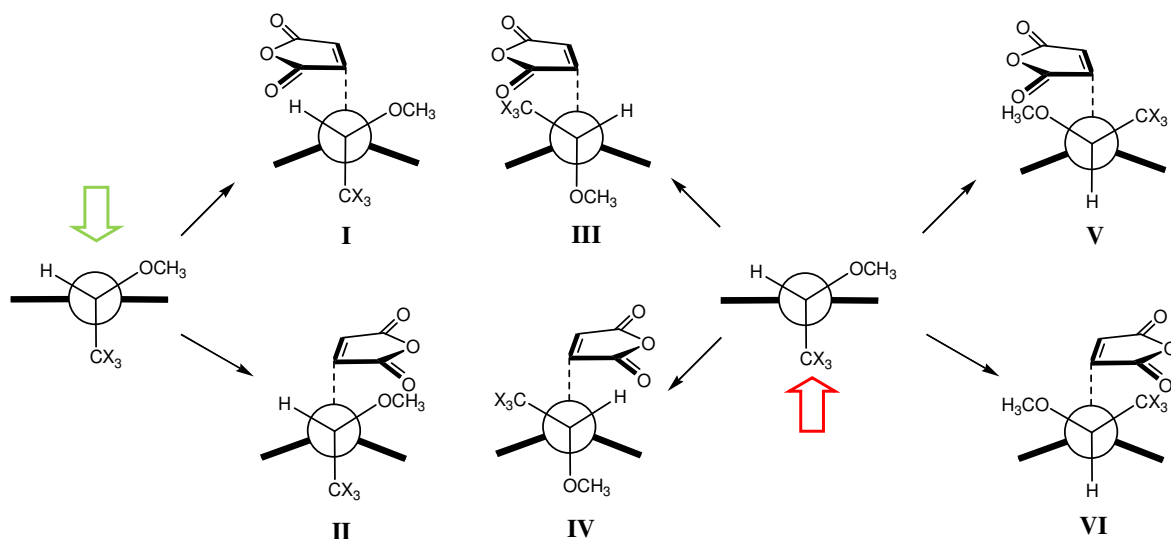


Figure 7.3. Model transition states for the reactions of maleic anhydride with (*R*)-9-(1-methoxyethyl)anthracene (X=H) and (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene (X=F).

In Figure 7.4, transition state conformers yielding diastereomers **A** and **B** are shown. Charge distributions and distances between repulsive and attractive centers are also displayed. Even though the strength of CH–O interactions cannot be solely predicted based on the CH···O distances especially in gas phase optimized geometries, assessment of such interactions may pave the way for rationalizing the relative stabilities of the alternative transition state conformations.

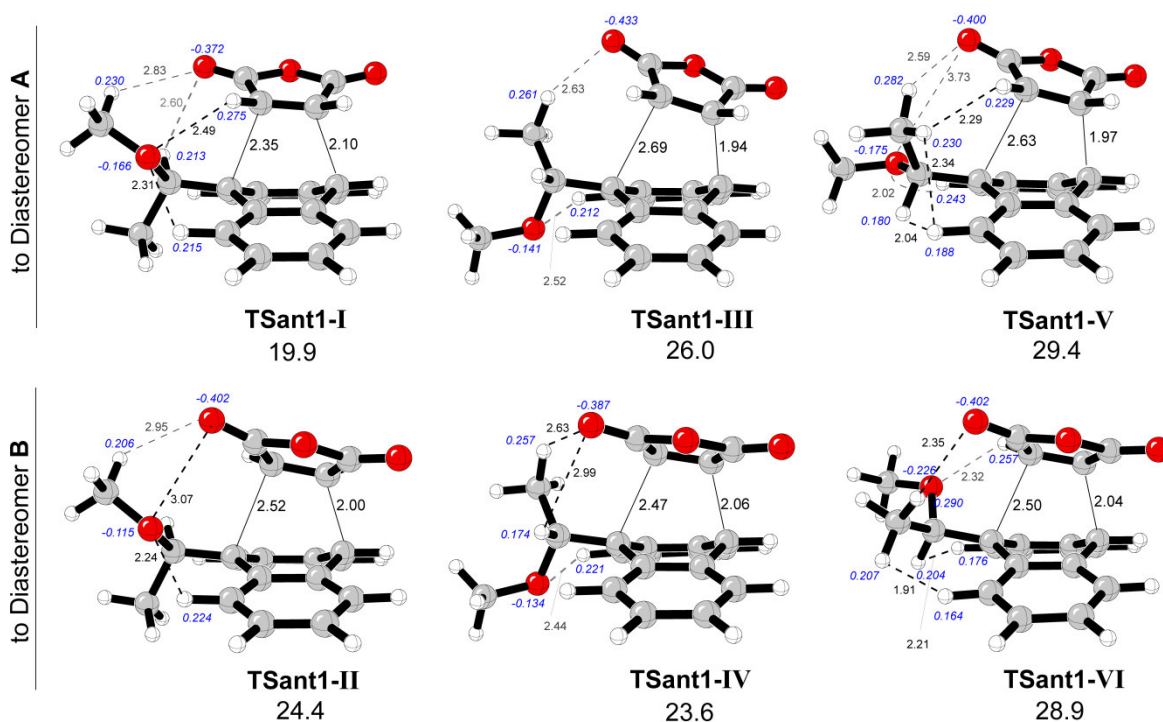


Figure 7.4. Transition state geometries and activation enthalpies ($\Delta H^\ddagger$, kcal/mol) corresponding to models **I–VI** for the reaction of maleic anhydride with (R)-9-(1-methoxyethyl)anthracene.

The most stable transition state for the reaction between **ant-1** and MA, **TSant1-I**, leads to **A** with an activation enthalpy of 19.9 kcal/mol. In this transition state the carbonyl oxygen fits into the hydrogen pocket. The charge distribution reveals an electrostatically more favorable arrangement compared to the other transition state alternatives given in Figure 7.4. The methoxy oxygen favorably interacts with the hydrogen on MA (2.49 Å) and the hydrogen on the bent anthracene (2.31 Å). The carbonyl oxygen on MA seems to be stabilized mostly by the hydrogen atom on the stereogenic center (2.60 Å) and on the methoxy substituent (2.83 Å). The minimum energy transition state leading to diastereomer **B**, **TSant1-IV**, is 3.6 kcal/mol above **TSant1-I**. The carbonyl moiety also nicely fits into the hydrogen pocket although at a larger distance (2.99 Å) than in the previous case (2.60 Å). The methyl group of the methoxy is tilted toward the hydrogen on the stereogenic center in order to avoid steric repulsions between the two large methyl groups. **TSant1-II** also leads to **B**, but is 0.9 kcal/mol higher in energy than **TSant1-IV**. It suffers from electrostatic repulsion between the oxygens although the oxygen of the methoxy group interacts favorably with the hydrogen on the anthracene ring (2.24 Å).

TSant1-III has an activation enthalpy of 26.1 kcal/mol, and is the most asynchronous transition state with destabilizations due to repulsive steric interactions. **TSant1-V** and **TSant1-VI** are strongly destabilized by both steric and electrostatic repulsions of the methyl and the methoxy groups with the anthracene ring similar to the repulsions in **2c** (Table 7.1) and have high activation enthalpies, 29.4 and 28.9 kcal/mol respectively.

TSant1-I, the lowest energy transition state, gives **A** as the major product. The origin of the experimentally observed exclusive selectivity in the reaction between **ant-1** and MA stems from the difference in the activation enthalpies between **TSant1-I** and **TSant1-IV**.

It is possible to alter the electronic features of the chiral anthracene template simply by changing the hydrogens on the electron donating methyl group with highly electronegative fluorine atoms. As such, a high electron density region is introduced next to the reaction center. The electron withdrawing trifluoromethyl group is well-known to exhibit unusual steric effects attributed to the very large effective negative charge it carries. Accordingly, with **ant-2**, the transition state model **V** – rather than **I** – has been proposed to explain the obtained diastereoselectivity of the reaction [152].

Figure 7.5 summarizes the transition states, activation enthalpies as well as favorable and unfavorable electrostatic interactions in the transition states for the reaction between **ant-2** and MA. The lowest energy transition state is again obtained from model **I** that yields **A** as the product. The activation enthalpy of **TSant2-I** is 21.8 kcal/mol; 1.9 kcal/mol higher enthalpy barrier compared to **TSant1-I**. This fact can be rationalized by the electron withdrawing character of the CF₃ substituent on the diene. In **TSant2-I**, MA approaches *syn* to the hydrogen and the methoxy group and the carbonyl group nicely fits into the pocket of the small hydrogen atom. The approach of MA in **TSant2-I**, not only prevents the steric and electrostatic repulsions but also accounts for a large number of favorable electrostatic interactions. The hydrogen on the stereogenic center and the carbonyl oxygen seem to interact favorably (2.57 Å). The electronegative fluorine atoms are squeezed between the partially positively charged hydrogens on the bent anthracene ring (2.31 Å and 2.60 Å). The hydrogen on MA and the hydrogen on the anthracene ring interact favorably with the methoxy oxygen (2.45 Å, 2.30 Å), while the hydrogen on the methoxy group electrostatically stabilizes the electron rich fluorine atom (2.62 Å).

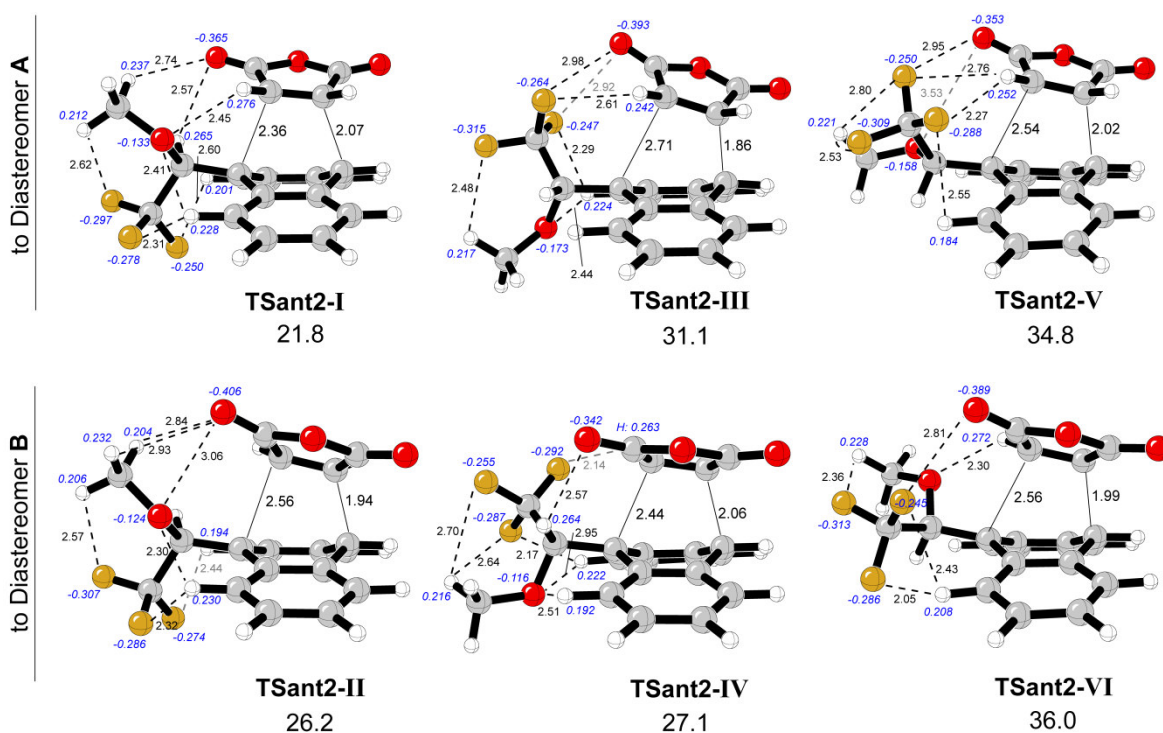


Figure 7.5. Transition state geometries and activation enthalpies ($\Delta H^\ddagger$, kcal/mol) corresponding to models **I-VI** for the reaction of maleic anhydride with (S)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene.

TSant2-IV is a potential transition state yielding **B** with no unfavorable electrostatic interactions. **TSant2-II** also yields **B** as the product, but it suffers from electrostatic repulsions between the lone pairs of the methoxy-oxygen and the carbonyl oxygen. Despite this destabilizing interaction, **TSant2-II** is stabilized with respect to **TSant2-IV** by 1 kcal/mol presumably because of the repulsive interactions between the electron density on the dienophile and the one around CF_3 in the latter. **TSant2-II** is 4.4 kcal/mol higher in energy than **TSant2-I**. The electrostatic repulsion between the oxygens is partly diminished by the favorable interaction between the oxygen on methoxy group and the hydrogen on the anthracene ring (2.30 Å). Electrostatic stabilizing interactions between the fluorine atom and the hydrogen on the methoxy substituent can also be expected (2.57 Å). The electronegative fluorine atoms also favorably interact with the hydrogens of the bent anthracene (2.32 and 2.44 Å).

The activation enthalpy for **TSant2-IV** is 27.1 kcal/mol. The electronegative fluorine atoms are stabilized by the hydrogen on MA and the hydrogen on the anthracene ring (2.17 and 2.13 Å). As in **TSant2-I**, there seems to be a stabilizing interaction between the carbonyl oxygen and the hydrogen on the stereogenic center (2.57 Å). The lone pairs of the methoxy oxygen interact favorably with the hydrogen on the anthracene ring (2.51 Å) and the methoxy hydrogen interacts with two fluorine atoms on CF₃ (2.70 Å, 2.64 Å). Although there seems to be no unfavorable interaction between the diene and the dienophile in **TSant2-IV**, the number of stabilizing interactions is smaller as compared to the ones in **TSant2-I** and the high electron density region around CF₃ unfavorably interacts with the negative charge on the dienophile.

TSant2-III yields **A** and is destabilized by 9.5 kcal/mol as compared to **TSant2-1**. There are large steric and electrostatic repulsions between the oxygen lone pairs and the highly electronegative fluorine atoms. In **TSant2-V**, the dienophile is *syn* to the CF₃ and the OCH₃ substituents and *anti* to the hydrogen. This model has been previously proposed to explain the observed stereoselectivity of the reaction. According to Corbett *et al.* [152], **ant-2** at a conformation with the hydrogen perpendicular to the anthracene plane (**ant-2c**) should be the most reactive conformer. In this conformation maximum σ -donation due to the alignment of the relatively acidic C-H bond of the stereogenic center with the anthracene orbitals has been anticipated, raising the HOMO_{diene}. The dienophile is suggested to approach **ant-2c** as in model **V** to avoid the stronger electrostatic repulsion of the CF₃ group as compared to the neighborhood of the methoxy oxygen. However, the conformational analysis results have shown that starting from the minimum energy conformer **ant-2a**, the energy increases gradually as rotation around the C9-C* bond proceeds: **ant-2c** is 15.2 kcal/mol higher in energy than **ant-2a** (Table 7.1) Thus, the frontier orbitals can not be used to set up a reliable model as proposed earlier [152]. As expected, the optimized transition state geometry, **TSant2-V**, is found to be much higher in energy than the transition states obtained from models **I-IV**.

The activation enthalpy of **TSant2-V** is 34.8 kcal/mol. It contains only a few favorable electrostatic contacts, all between the fluorine atoms and the hydrogens. One fluorine atom interacts with the hydrogen on MA and the hydrogen on the bent anthracene

(2.27 Å, 2.55 Å), the hydrogen on MA also interacts with another fluorine atom (2.74 Å) and the hydrogen of the methoxy group interacts with two fluorine atoms (2.53 Å, 2.80 Å).

TSant2-VI leads to **B** with an activation enthalpy of 36.0 kcal/mol. Despite the seemingly favorable electrostatic interactions between the hydrogen on MA and the methoxy oxygen (2.30 Å), the hydrogen on the bent anthracene with two fluorine atoms (2.43 Å, 2.05 Å), and the hydrogen on the methoxy group with the fluorine atom (2.36 Å), this transition state is 14.6 kcal/mol higher than **TSant2-I**. Unfavorable steric contacts cause a large destabilization. The highest electron density regions of the diene and the dienophile are in very close contact contributing to the expected high energy barrier.

As confirmed by the calculations in the gas phase and in toluene, the exclusive product of the reaction is **A**. The reaction proceeds through the transition state model **I**. **TSant2-I** is 1.9 kcal/mol higher in energy than **TSant1-I**, in accordance with the experimentally observed rate deceleration. The building negative charge on the dienophile and the high effective negative charge around the CF₃ group unfavorably interact and lead to higher activation enthalpies when the dienophile is syn to the CF₃ group.

7.3.2. Reaction of (*R*)-9-(1-phenylethyl)aminoanthracene with Maleic Anhydride

In **ant-3**, the electron donating chiral amino group attached to the anthracene ring is expected to increase the rate of the reaction [155]. The diastereoselectivity of the reaction is found to be interestingly high although the stereogenic center was not in the immediate proximity of the reaction center. Adams *et al.* [162] have identified **B** as the major product by X-ray crystallography.

Amines with three different but independent R groups do not show chirality due to rapid Walden inversion around nitrogen. Compound **ant-3** is found to be present in two dominating conformations, **ant-3a** and **ant-3b**. The optimized geometries of **ant-3a** and **ant-3b** are shown in Figure 7.6.

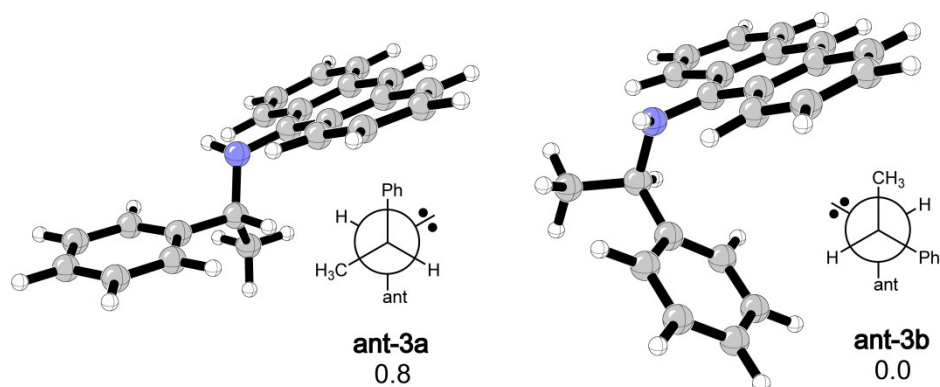


Figure 7.6. Conformers of (*R*)-9-(1-phenylethyl)aminoanthracene and their relative enthalpies (ΔH , kcal/mol).

In both conformers, the amine hydrogen and the hydrogen on the stereogenic center prefer to occupy *anti* positions to each other. In **ant-3a**, the phenyl group points away from the anthracene ring whereas in **ant-3b**, the phenyl group points towards the anthracene ring. The crystal structure obtained by Adams *et al.* [162] strongly agrees with conformer **ant-3b**. The enthalpy difference between **ant-3a** and **ant-3b** is found to be only 0.8 kcal/mol in the gas phase. The difference between their energies in toluene is as low as 0.1 kcal/mol, indicating that a diastereomeric mixture is present in the reaction medium (See Appendix, Table A.7).

Adams *et al.* [162] have proposed that the diastereoselection occurs as the dienophile approaches the anthracene ring *anti* to the chiral carbon in two different ways. In the favored approach the carbonyl oxygen is oriented towards the amine hydrogen and in the disfavored approach the carbonyl oxygen is oriented towards the nitrogen lone pair. As such, they underlined the importance of a combination of electrostatic repulsion and attractive hydrogen bonding in establishing high levels of diastereoselectivity giving **B** as the major product. This model, however, is based on the assumption that a single conformation dominates over the other and fails to explain the product distribution in the presence of both **ant-3a** and **ant-3b**: As shown in Figure 7.7, a mixture of **ant-3a** and **ant-3b** would favorably yield both **A** and **B** contradicting the observed levels of diastereoselectivity.

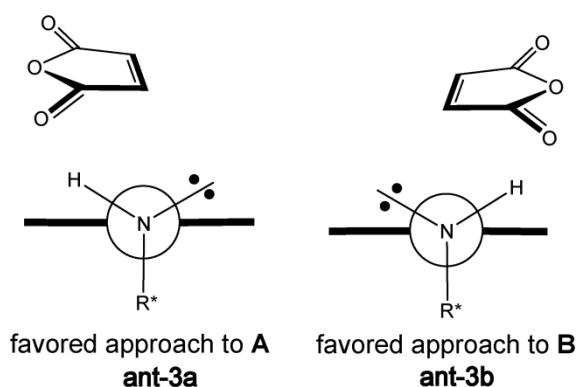


Figure 7.7. Favoured approaches of maleic anhydride to (*R*)-9-(1-phenylethyl)aminoanthracene as proposed by Adams *et al.* [162].

It has also been assumed that the most stable conformation of the chiral anthracene template is maintained in the transition state. In fact, a conformation with the stereodirecting group *syn* and the nitrogen lone pair *anti* to the dienophile in the transition state may lead to a better stabilization and a more pronounced stereocontrol exerted by the chiral group.

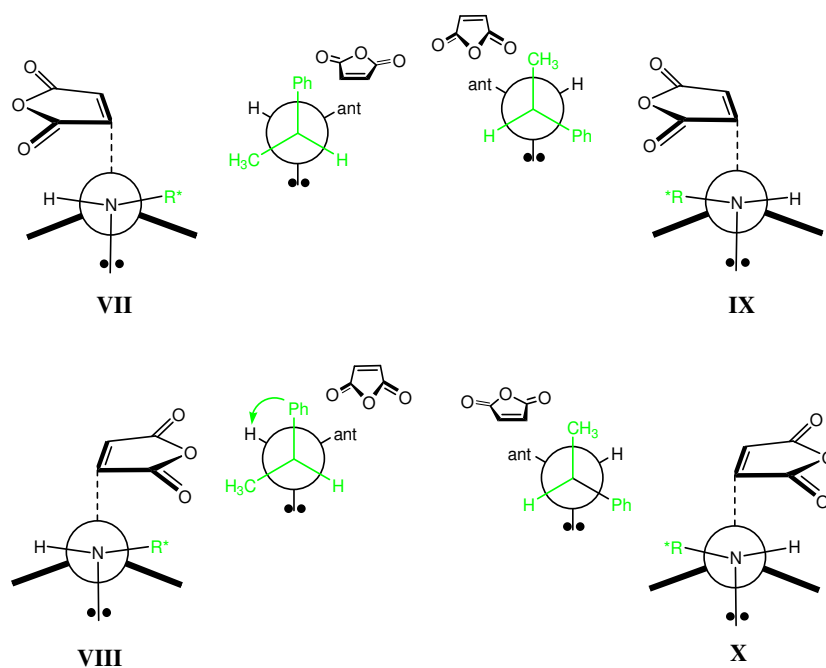


Figure 7.8. Model transition states for the reaction between maleic anhydride and (*R*)-9-(1-phenylethyl)aminoanthracene.

We, therefore, propose transition state models **VII-X** (Figure 7.8), in which the nitrogen lone pair is *anti* to the dieneophile. The free rotation around the C–N bond can additionally assist to diminish the unfavorable steric interactions. In model **VIII**, for example, the phenyl group can rotate towards the amine hydrogen to diminish the electrostatic repulsions with the carbonyl oxygen.

Optimized transition state geometries shown in Figure 7.9 have confirmed the suggested models (**VII-X**). All calculated structures predict that the lone pair on nitrogen is *anti* to MA and the geometry around nitrogen is close to planar (10–25° out of plane). Attempts to locate transition states with a nitrogen lone pair *syn* to MA as proposed by Adams *et al.* resulted in structures **TSant3-VII** to **TSant3-X**.

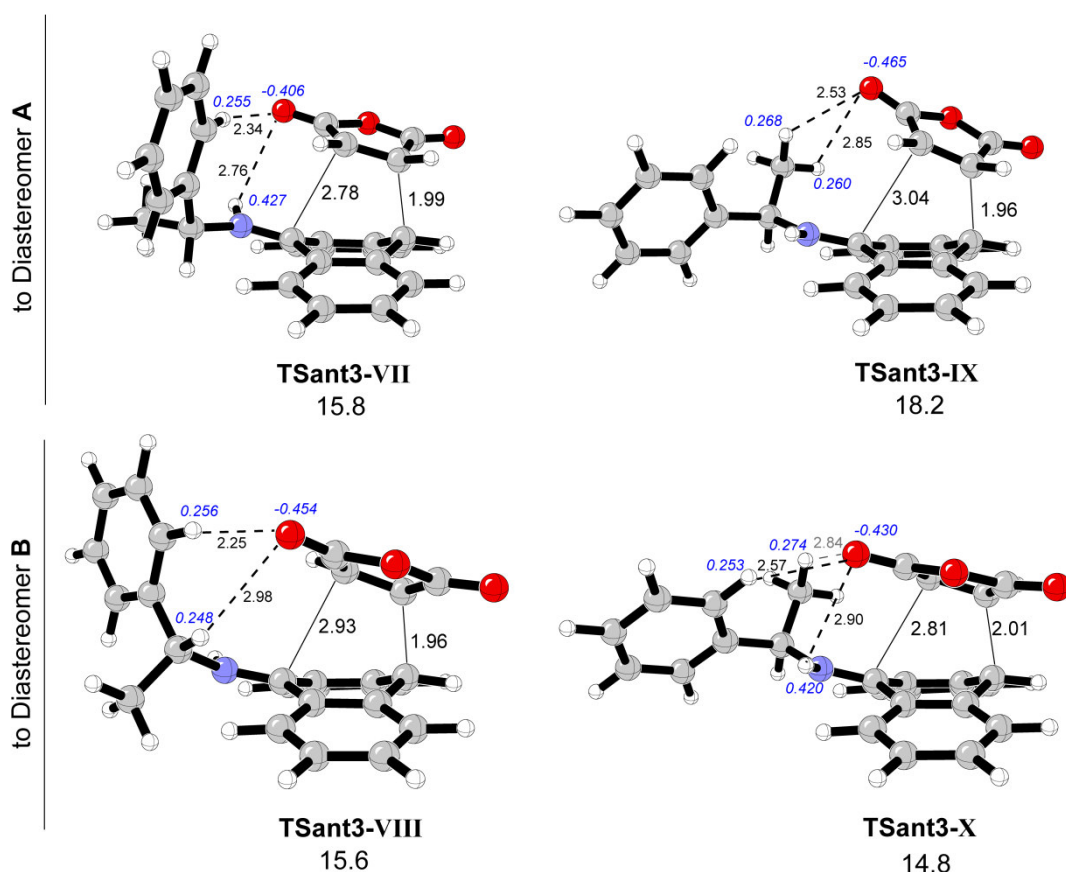


Figure 7.9. Transition state geometries and activation enthalpies ($\Delta H^\ddagger$, kcal/mol) for the reaction of maleic anhydride with (*R*)-9-(1-phenylethyl)aminoanthracene.

The lowest activation barrier is predicted for **TSant3-X** (14.8 kcal/mol), and the IRC path connects the reactants to **B** in agreement with the results of Adams *et al.* [162]. The activation enthalpy of this transition state is 5.1 kcal/mol lower than **TSant1-I**. The lower activation enthalpies for the reaction of chiral amino anthracene (**ant-3**) and MA can be attributed to the electron donor character of the amine group attached to the diene. However, the energy differences giving rise to stereoselectivity are not high; the chiral center is not close to the reaction site resulting in weaker steric and electrostatic effects. **TSant3-VIII** and **TSant3-X** both lead to **B**, in the latter the carbonyl group is in the pocket hindered by the chiral group instead of favorably interacting with the amine hydrogen. The loss of stabilization due to this interaction is only 0.8 kcal/mol.

TSant3-IX yields **A**, and has the highest activation enthalpy (18.2 kcal/mol). The absence of an interaction between the dienophile and the aromatic hydrogen of the phenyl ring in **TSant3-IX**, in contrast to the other alternative transition states, suggests the importance of this interaction in stabilizing a transition state conformation. Increased asynchronicity and steric effects also contribute to the destabilization of this transition state. The other transition state giving **A**, **TSant3-VII**, is 2.4 kcal/mol lower in energy than **TSant3-IX**, however it is still 1.0 kcal/mol higher in energy than the most stable transition state, **TSant3-X**, leading to **B**. Although in **TSant3-VII** the carbonyl oxygen interacts favorably with the hydrogen on the amino group, its energy is comparable to **TSant3-VIII** which lacks this interaction.

All located transition states are very asynchronous; the forming C–C bond next to the chiral amino-substituent is 2.8–3.0 Å, as the other forming C–C bond is about 2.0 Å. Hydrogen bonding is found to have no considerable effect on the diastereoselection process, since both of the lowest energy transition states leading to **A** and **B** benefit from this interaction. In **TSant3-VII**, the distance between carbonyl oxygen and amine hydrogen is 2.76 Å, whereas in the lowest energy transition state, **TSant3-X**, it increases to 2.90 Å. The crystal structures of the major and minor products reported by Adams *et al.* [162] agree very well with the products of **TSant3-X** and **TSant3-VII** obtained from IRC calculations and show the hydrogen attached to the amino group interacting with the carbonyl oxygen in both of the structures. In transition states **TSant3-VII**, **TSant3-VIII** and **TSant3-X**, the *ortho* hydrogen on the phenyl substituent interacts with the oxygen on

the carbonyl group (2.34 Å, 2.57 Å, 2.25 Å). In **TSant3-IX**, the negative charge on the carbonyl oxygen is stabilized by the methyl hydrogens (2.53 Å, 2.85 Å).

The minimum energy transition state **TSant3-X** leads to stereoisomer **B**. The major product of the reaction is predicted to be **B** with two low energy transition states **TSant3-X** and **TSant3-VIII** giving this product. The lowest energy transition state yielding **A** is 1.0 kcal/mol higher in energy than **TSant3-X**. In all transition states, the nitrogen lone pair is anti to the dienophile. Hydrogen bonding has no substantial effect on the obtained diastereoselectivity since both of the transition states leading to the diastereomeric products benefit from this interaction. The calculated product distribution ratio (**B:A** 88:12 in gas phase and 96:4 in toluene) agrees well with the experimental results (**B:A** 91:9) (See 7.3.4 Product Distributions).

7.3.3. Reactions of (*R*)-9-acyloxyanthracenes with Maleic Anhydride

O-methylmandelic acid has been successfully employed by Trost and co-workers [170] as a covalent chiral auxiliary in the Diels–Alder reactions of their dienol esters to give moderate to high diastereoselectivities, despite the fact that the stereogenic center is located three bonds away from the site of bond formation. (*R*)-9-acyloxyanthracene (**ant-4**), however, gave very low diastereoselectivity in the cycloaddition process. The low diastereoselectivity of **ant-4** also contrasts the remarkable diastereoselectivities obtained with chiral amino-anthracene **ant-3**. This selectivity difference cannot be rationalized with simple steric arguments because in both of the compounds the stereogenic center is more than one bond away from the reaction center. Even though it has been suggested that hydrogen bonding can provide a diastereoselective improvement in **ant-3** as compared to **ant-4** [162], our results have shown that the hydrogen bonding between the diene and the dienophile in **ant-3** had no effect on the diastereoselection process.

Ant-4 is a highly flexible substrate with five rotatable bonds. The conformational preferences of **ant-4** are shown in Figure 7.10. **Ant-4a** and **ant-4b** are found to be the dominating conformers in the gas phase and in toluene (See Appendix, Table A.7). In the

minimum energy conformer **ant-4a**, the phenyl group is perpendicular to the anthryl group with one face toward the anthracene ring. The carbonyl and the methoxyl oxygens are in an eclipsed arrangement as shown previously for α -alkoxy esters [171]. However, the dienyl and carboxyl groups are perpendicular to each other due to the steric constraints imposed by the anthracene ring rather than being in a coplanar arrangement as reported for the dienol esters of *O*-methylmandelic acid [171]. **Ant-4b** is 1.2 kcal/mol higher in energy than **ant-4a** in the gas phase and 1.0 kcal/mol in toluene (See Appendix, Table A.7). In **ant-4b** the carbonyl group is eclipsed to the CH bond instead of the methoxy oxygen. Two other conformers (**ant-4c** (+5.6 kcal/mol) and **ant-4d** (+8.5 kcal/mol)) where the phenyl ring and the anthracene ring are face to face, have also been located.

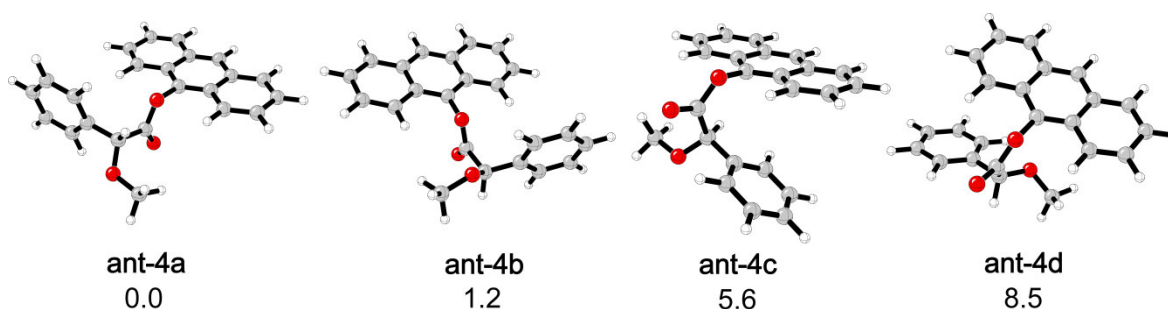


Figure 7.10. Minimum energy conformations of (*R*)-9-acyloxyanthracenes and their relative enthalpies (ΔH , kcal/mol).

To be able to explain the low diastereoselectivity of **ant-4**, we located the transition states of the cycloaddition process between **ant-4** and MA. The relative activation enthalpies of the transition states (Figure 7.11) show that the diastereoselection occurs between **TSant4-XIII** and **TSant4-XIV**. The arrangement of the dienophile in these transition states allows the stabilization of the hydrogen on MA with the carbonyl oxygen on the template. This favorable interaction stabilizes **TSant4-XIII** and **TSant4-XIV** by about 2 kcal/mol as compared to the transition states obtained from the *syn* approach to the oxygen lone pairs (**TSant4-XI** and **TSant4-XII**). However, the energy difference between **TSant4-XIII** and **TSant4-XIV** is very small ($\Delta H^\ddagger = 21.7$ and $\Delta H^\ddagger = 21.8$ kcal/mol respectively), in agreement with the observed lack of diastereoselectivity [155]. The geometries of these two transition states are very similar especially around the reaction center. In both transition states the carbonyl oxygen on the anthracene template is tilted

toward the hydrogen on MA, taking advantage of the stabilizing electrostatic attraction between the negatively charged oxygen and the positively charged hydrogen (2.29 Å, 2.26 Å) and also interacts favorably with the hydrogen on the bent anthracene ring (2.68 Å, 2.70 Å). The hydrogen on the methoxy substituent interacts with the carbonyl oxygen on MA (2.46 Å, 2.86 Å).

TSant4-XI and **TSant4-XII**, on the other hand, have higher activation enthalpies, ($\Delta H^\ddagger = 23.5$ and 23.3 kcal/mol respectively) and less favorable interactions. The carbonyl oxygen on MA interacts with the *ortho* hydrogen on the phenyl substituent in **TSant4-XI** (2.71 Å). The carbonyl group is favorably squeezed between the hydrogens on the bent anthracene in **TSant4-XI** (3.04 Å, 2.95 Å) and in **TSant4-XII** (2.97 Å, 3.02 Å).

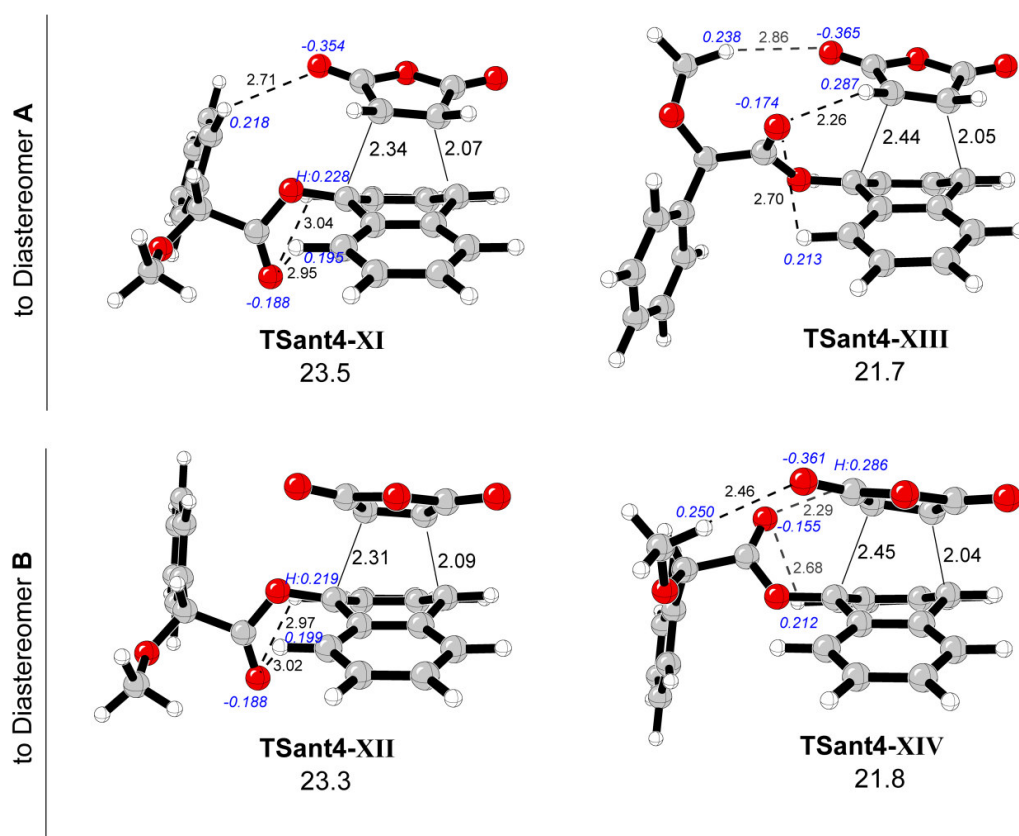


Figure 7.11. Transition state geometries and activation enthalpies ($\Delta H^\ddagger$, kcal/mol) for the reaction of maleic anhydride with (*R*)-9-acyloxanthracenes.

In the lowest energy conformations of **ant-4**, the carboxyl and the anthryl groups are in a perpendicular arrangement and MA preferably attacks **ant-4** from the face of the carboxyl group. This attack allows the favorable interaction between the carbonyl oxygen on the acyl-oxyanthracene and the hydrogen on MA in both of the diastereomeric transition states. The interactions around the reaction site are very similar leading to a very small energy difference between the diastereomeric transition states. This can originate from the conformational differences around the stereogenic center.

The calculated product distribution ratios (**A:B** 57:43 in gas phase and 64:36 in toluene) are in close agreement with the experimentally observed low diastereoselectivity (**A:B** 60:40) (See 7.3.4 Product Distributions).

7.3.4. Product Distributions

Experimental and predicted product distributions in the gas phase and in toluene (Table 7.3) are in close agreement with each other. The reactions of MA with **ant-1** and **ant-2** proceed with exclusive diastereoselectivity via transition state **TS1-I**. In the reaction of **ant-3** and MA both **TSant3-VIII** and **TSant3-X** contribute to the formation of **B** as the major product in the gas phase, whereas, the contribution of **TSant3-VIII** is found to be much less important in toluene and the majority of the reaction trajectories pass through **TSant3-X**. For the reaction between **ant-4** and MA, the diastereoselection process occurs through competition among **TSant4-XIII** and **TSant4-XIV**. Due to very similar interactions in diastereomeric transition states, the stereoselectivity is found much lower in agreement with the experimental results.

Table 7.3. Predicted and experimental product distributions.

		Activation Enthalpies (Gas Phase)			Activation Free Energies (Gas Phase)		Activation Energies (Toluene)		Activation Energies with non-electrostatic terms (Toluene)	
		Expl.Prod. Dist.	Boltzmann Dist.	Pred.Prod Dist.	Boltzmann Dist.	Pred.Prod Dist.	Boltzmann Dist.	Pred.Prod Dist.	Boltzmann Dist.	Pred.Prod Dist.
ant-1 + MA	TSant1-I		1.00		1.00		1.00		1.00	
	A TSant1-III	100%	0.00	100%	0.00	100%	0.00	100%	0.00	100%
	TSant1-V		0.00		0.00		0.00		0.00	
	TSant1-II		0.00		0.00		0.00		0.00	
	B TSant1-IV	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%
	TSant1-VI		0.00		0.00		0.00		0.00	
ant-2 + MA	TSant2-I		1.00		1.00		1.00		1.00	
	A TSant2-III	100%	0.00	100%	0.00	100%	0.00	100%	0.00	100%
	TSant2-V		0.00		0.00		0.00		0.00	
	TSant2-II		0.00		0.00		0.00		0.00	
	B TSant2-IV	0%	0.00	0%	0.00	0%	0.00	0%	0.00	0%
	TSant2-VI		0.00		0.00		0.00		0.00	
ant-3 + MA	TSant3-VII	<10%	0.12	12%	0.07	7%	0.13	14%	0.03	4%
	TSant3-IX		0.00		0.00		0.01		0.01	
	TSant3-VIII	>90%	0.18	88%	0.35	93%	0.27	86%	0.03	96%
	TSant3-X		0.70		0.58		0.59		0.93	
ant-4 + MA	TSant4-XI	60%	0.03	57%	0.02	70%	0.04	54%	0.02	64%
	TSant4-XIII		0.54		0.68		0.50		0.62	
	TSant4-XII	40%	0.03	43%	0.13	30%	0.07	46%	0.01	36%
	TSant4-XIV		0.40		0.17		0.39		0.35	

7.4. Conclusion

For substrates with high degrees of rotational freedom and flexible chiral groups, models based on the conformations of the reactants and related facial recognition may not be sufficient to determine the most favorable transition state conformation and thus the selectivity. The arguments based on frontier molecular orbital theory and facial recognition due to stereoelectronic effects have to be dealt with care. Eventually, a thorough analysis of the transition state conformations leading to each diastereomer is necessary in order to elucidate the selectivity of the reaction.

For the reactions of chiral anthracenes **ant-1** – **ant-4** with MA, our results have shown that, **ant-1** and **ant-2** exclusively give **A** via a similar transition state in which the CH₃/CF₃ group is *anti* to the dienophile. The high diastereoselectivity obtained with **ant-3** is found to depend on the stereoelectronic effects of the chiral substituent rather than the hydrogen bonding between the dienophile and the amine hydrogen on C9 of the diene. The loss of diastereoselectivity in **ant-4** can be based on the presence of similar interactions –favorable interaction of the carbonyl group on the diene with the hydrogen on MA– around the reaction center in both diastereomeric transition states. The calculated product distributions in the gas phase and in toluene are in very close agreement with the experimental results.

The experimentally observed rate deceleration for the cycloaddition of **ant-2** is well predicted with a 1.9 kcal/mol higher enthalpy barrier as compared to that of **ant-1**. The calculations reproduce remarkably well the experimentally obtained rate enhancement for the reaction of **ant-3** and MA having a 5.1 kcal/mol lower enthalpy barrier than that of **ant-1**. The enthalpy barrier for the cycloaddition of **ant-4** is predicted to be comparable to that of **ant-1**.

Finally, this work has pointed out the limitations of the previously proposed models for the diastereoselectivity of chiral anthracene templates and has allowed us to propose new models based on the energy differences between the diastereomeric transition states and their geometries.

8. MECHANISM AND SELECTIVITY OF CINCHONA ALKALOID CATALYZED [1,3]-SHIFTS OF ALLYLIC TRICHLOROACETIMIDATES

Cinchona alkaloids catalyze a broad range of organic reactions leading to products of biological interest [172-196]. However, their catalytic proficiency seems to depend on many factors. Understanding the origins of their catalytic efficiency constitutes an important step towards the design of more powerful cinchona derivatives. In this chapter, we describe the mechanism and selectivity of symmetry forbidden [1,3]-rearrangements of allylic trichloroacetimidates in the presence of cinchona alkaloids (Figure 8.1).

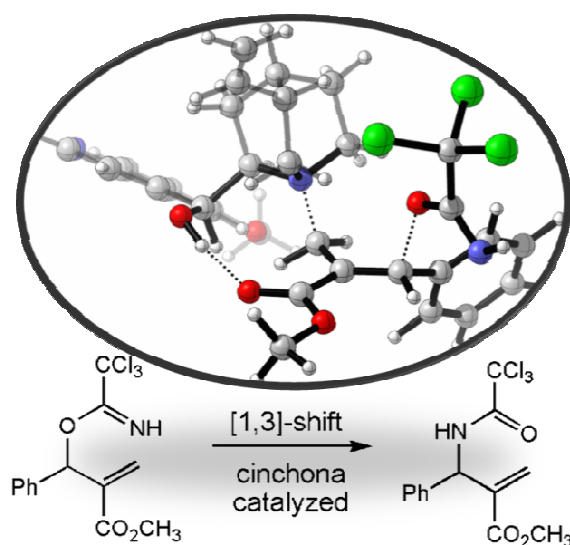


Figure 8.1. Cinchona catalyzed [1,3]-rearrangements of allylic trichloroacetimidate derivatives.

Density Functional Theory calculations were used to investigate the competing [3,3]- and [1,3]-rearrangement pathways of *O*-allylic trichloroacetimidates to trichloroacetamides (Figure 8.2). Thermal [1,3]- and [3,3]-rearrangements proceed through concerted pseudopericyclic transition states to give the corresponding rearranged products. [1,3]-rearrangement is catalyzed via a double S_N2' mechanism in which *syn* addition of the

amine nucleophile is exclusively preferred in both steps. The catalyzed mechanism is favored by a 6.3 kcal/mol free energy difference compared to the alternative [3,3]-rearrangement pathway. The fast-reacting enantiomer is predicted to be determined by the availability of the H-bonding interaction between the cinchona catalyst and the substrate.

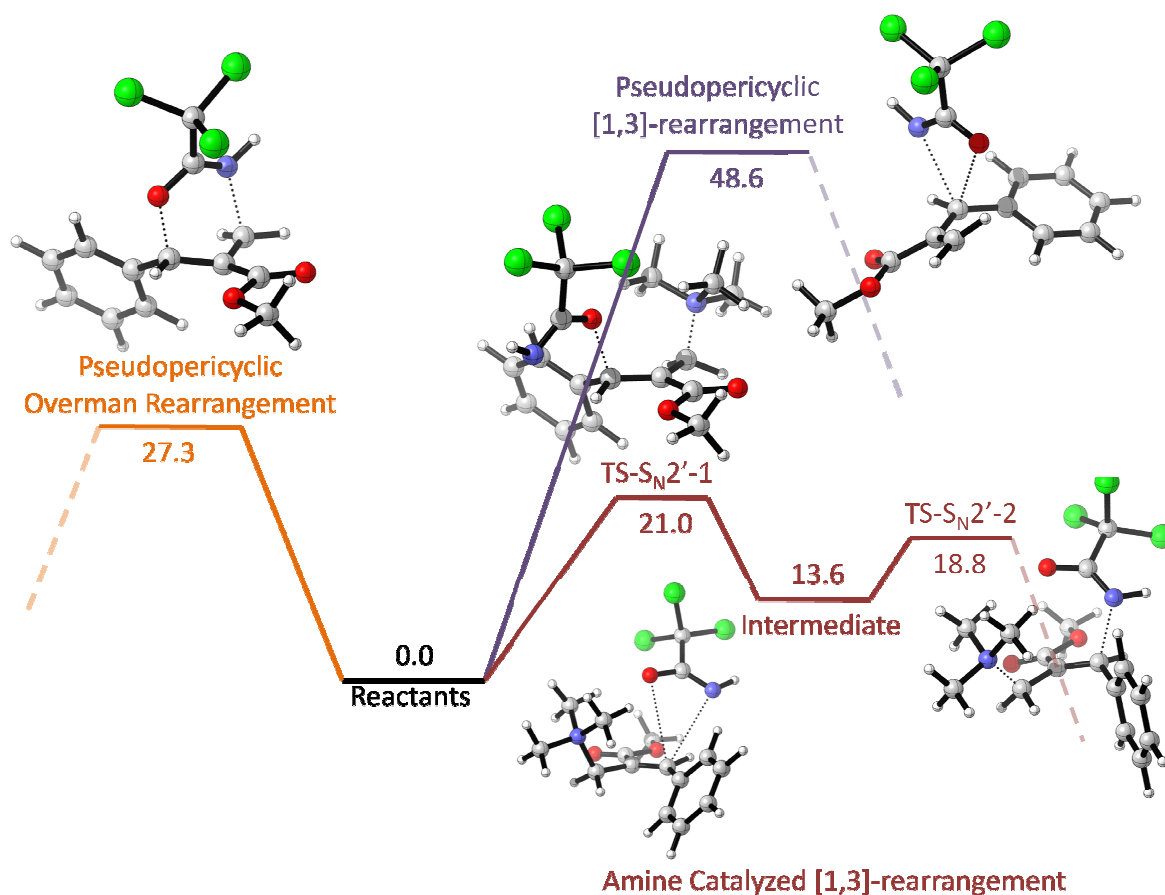


Figure 8.2. Competing reaction pathways for the [3,3]- and [1,3]-rearrangements of *O*-allylic trichloroacetimidates to trichloroacetamides.

8.1. Introduction

Cinchona alkaloids have found extensive use in organic chemistry as organocatalysts in asymmetric synthesis [172-196]. The success is also related to their tailorability for specific reactions. Asymmetric primary amine derivatives of cinchona alkaloids are shown

to be excellent activators of carbonyl compounds [172-176]. The 6'-hydroxy [177-180], 9-thiourea [181-186] and 6'-thiourea [187-189] derivatives have emerged as powerful bifunctional organocatalysts. Dimeric cinchona alkaloids linked with various aromatic linkers provided very high enantioselectivities and are proposed to form enzyme like binding pockets for substrates [190-195].

Despite the experimental reports on the use of cinchona alkaloid derivatives as organocatalysts, the origins of their enantioselective catalytic activity still remain unexplored. Elucidating the catalytic mechanisms of cinchona alkaloids is necessary to largely understand their catalytic efficiency.

In this study, we describe in detail the mechanism of the thermal and cinchona catalyzed rearrangements of allylic acetimidates yielding β -amino acid and allyl amine derivatives that are important building blocks found in many bioactive molecules. The experimental work by Jorgensen's group is an excellent example of cinchona catalysts; and here we describe how their reactions occur [196].

Allylic trichloroacetimidate **r-1** undergoes either the well-known [3,3]-sigmatropic rearrangement (Overman rearrangement) [197, 198] or a less known [1,3]-sigmatropic *O*-to *N*-rearrangement [199, 200] to give the corresponding trichloroacetamides, **p-[3,3]** and **p-[1,3]** (Figure 8.3). The symmetry forbidden [1,3]-rearranged product has been exclusively obtained in the presence of cinchona alkaloids, whereas the sterically hindered alkenes gave only the [3,3]-rearranged products [196].

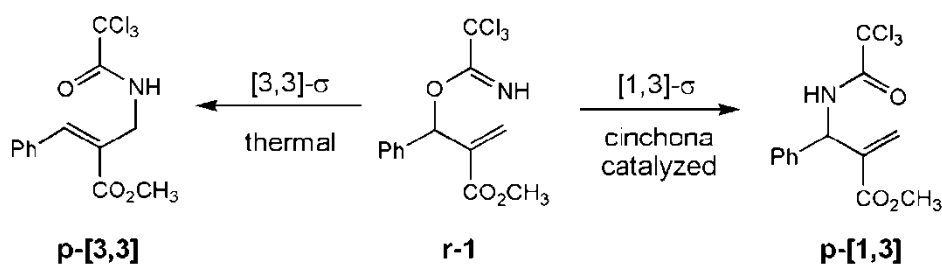


Figure 8.3. [3,3]- and [1,3]-sigmatropic rearrangements of *O*-allylic trichloroacetimidates.

8.2. Computational Methodology

The geometries of reactants, transition states and products were optimized using B3LYP/6-31G(d) with Gaussian 03 [138]. Concerted and stepwise pathways for the thermal [1,3]-rearrangement were explored using UB3LYP/6-31G(d). Frequency calculations were used to verify the stationary points as minima or saddle points. Single point energies were computed using M05-2X/6-31+G(d) level of theory. All energetics reported throughout the text are given in terms of free energies in kcal/mol. Intrinsic reaction coordinate (IRC) method as implemented in Gaussian 03 was used to follow minimum energy paths from the transition states and to verify the nature of the reactants and products [139, 140]. In the figures, carbon atoms are shown in light grey, hydrogens in white, oxygens in red, nitrogen in blue, and chlorines in green.

Potential energy surface (PES) scans were used to explore the conformational space of reactants, transition states and products. An initial systematic conformational search with three fold rotation around the single bonds was performed for the reactants and products using semi-empirical PM3 methodology. The conformers within 3 kcal/mol energy range were then optimized using B3LYP/6-31G(d) for a more accurate description of the conformer distribution. A rigid PES scan was performed with B3LYP/6-31G(d) on the transition states using the dihedrals as specified in the results and discussion section. The low energy conformers of the transition states were later optimized using the same level of theory.

8.3. Results and Discussion

8.3.1. Conformational Flexibility of the Substrate

The conformational analysis of *O*-allylic trichloroacetimidate **r-1** has revealed the significant flexibility of the substrate with six conformers within 1.1 kcal/mol energy range

(Figure 8.4). The energy differences between the *s-cis* and *s-trans* conformers are very small (0.2-0.6 kcal/mol). The terminal alkene can either adopt an eclipsed conformation or a perpendicular arrangement with the C–O bond. The lowest energy conformer shows an eclipsed rearrangement of the terminal alkene and the C–O bond, but it is close in energy (0.6-0.8 kcal/mol) to the conformers with the perpendicular arrangement.

A thorough conformational search was performed on all transition states, whereas only lowest energy ones are discussed in the following sections.

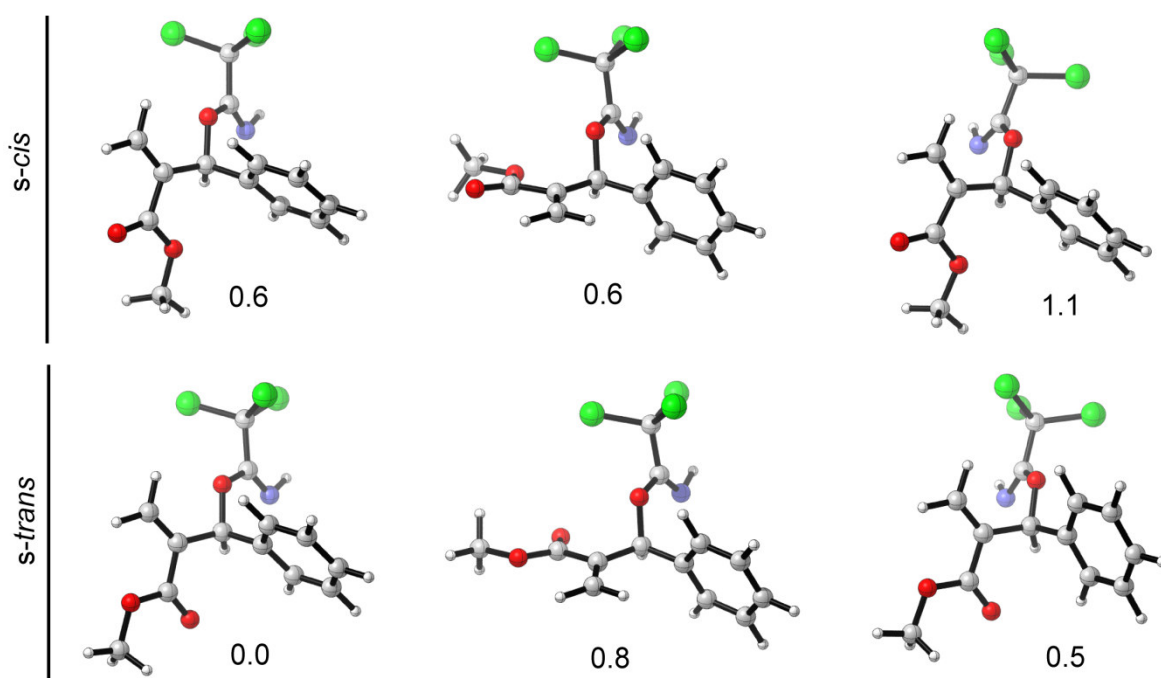


Figure 8.4. Conformational preferences (ΔG , kcal/mol) of allylic trichloroacetimidate.

8.3.2. Thermal Sigmatropic Rearrangement Pathways

Overman rearrangement occurs via transition states **TS-[3,3]-1** and **TS-[3,3]-2**, with activation free energies 26.7 and 26.9 kcal/mol respectively (Figure 8.5). **TS-[3,3]-1** and **TS-[3,3]-2** are very close in energy ($\Delta\Delta G^\ddagger = 0.4$ kcal/mol) and differ in the *s-cis* and *s-trans* arrangements of the ester substituent. They can be described as pseudopericyclic

[201-207] as evidenced by the disconnections in orbital overlap; orthogonal sets of orbitals meet, but there is no continuous overlap around the ring of forming and breaking bonds. The process is concerted but asynchronous ($d_{C-O} = 1.71 \text{ \AA}$, $d_{C-N} = 1.97 \text{ \AA}$). The charge separation is found to be 0.28e. No pericyclic alternative could be located at this conformation presumably due to unfavorable steric interactions of the trichloromethyl group with the phenyl and ester substituents. The process is highly exothermic by 19.9 kcal/mol.

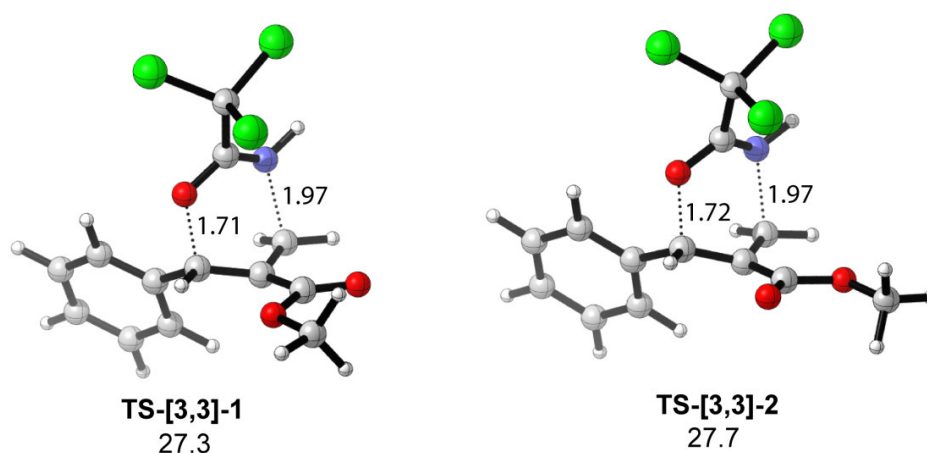


Figure 8.5. Lowest energy transition states and their activation free energies ($\Delta G^\ddagger$, kcal/mol) for the thermal [3,3]-rearrangement.

An equatorial arrangement of the phenyl ring leads to destabilizing interaction between the ester and the phenyl groups; the transition states putting the phenyl ring at an equatorial position are found to be more than 4.5 kcal/mol higher in energy (Figure 8.6). Although we were able to locate a chair pericyclic transition state at this conformation (TS-[3,3]-4), it is 4.4 kcal/mol higher in energy than its pseudopericyclic alternative TS-[3,3]-3.

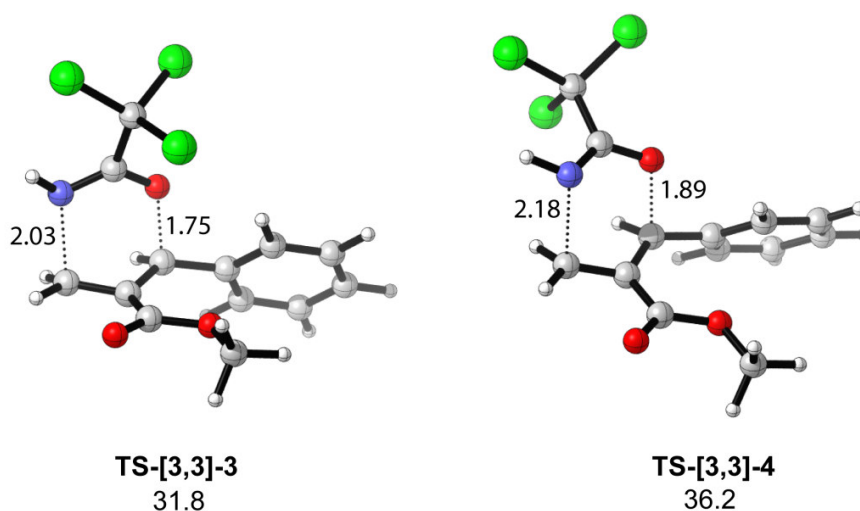


Figure 8.6. Transition state alternatives and their activation free energies ($\Delta G^\ddagger$, kcal/mol) for the thermal [3,3]-rearrangement.

According to Woodward-Hoffman rules, pericyclic transition structures are symmetry forbidden for [1,3]-sigmatropic rearrangements [104, 105, 208, 209]. However, we found that the thermal [1,3]-rearrangement of **r-1** to **p-[1,3]** can occur via four membered pseudopericyclic transition states **TS-[1,3]-1** and **TS-[1,3]-2** (Figure 8.7). Houk and Danishefsky have recently reported similar pseudopericyclic transition states for symmetry forbidden [1,3]-acyl rearrangements [210].

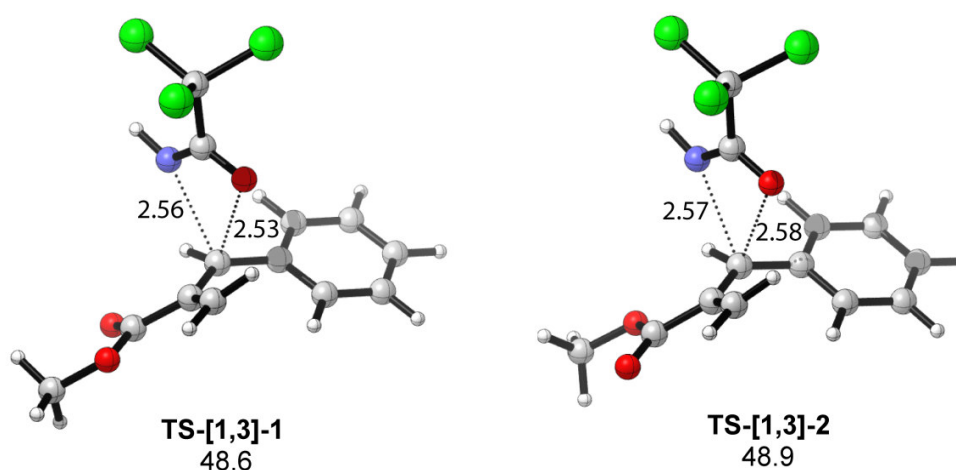


Figure 8.7. Lowest energy transition states and their activation free energies ($\Delta G^\ddagger$, kcal/mol) for the thermal [1,3]-rearrangement.

In contrast to the relatively easy thermal [3,3]-rearrangement process, 48.6 kcal/mol is required for the thermal [1,3]-rearrangement of **r-1** to **p-[1,3]**. **TS-[1,3]-1** is concerted and synchronous ($d_{\text{C-N}} = 2.56 \text{ \AA}$, $d_{\text{C-O}} = 2.53 \text{ \AA}$), but, it is highly polar with a charge separation of 0.61e. No evidence of diradical character in the transition state is found ($S^2 = 0$) even for unrestricted calculations. The *s-cis* arrangement of the ester, **TS-[1,3]-2**, is very close in energy ($\Delta G^\ddagger = 48.9 \text{ kcal/mol}$) and also very similar in character to **TS-[1,3]-1**. We were not able to find any evidence for alternative stepwise pathways involving polar or radical pair intermediates. The homolytic or the heterolytic cleavage of the C–O bond of **r-1** is highly endothermic by 52.5 kcal/mol and 131.7 kcal/mol respectively. These large endothermicities imply that formation of the completely separated radicals or ions through these fragmentation processes are quite unlikely.

8.3.3. Mechanism of the Catalyzed Reaction

The proposed catalytic mechanism for [1,3]-rearrangement of imidates to amides consists of a two step S_N2' addition (Figure 8.8). The attack of the nucleophilic amine is accompanied by loss of the trichloroacetimidate anion (**TS-S_N2'-1**). This establishes an ion pair intermediate (**INT**). Subsequent attack of the nitrogen nucleophile of the anionic trichloroacetamide proceeds with the release of the catalyst in the second addition step (**TS-S_N2'-2**).

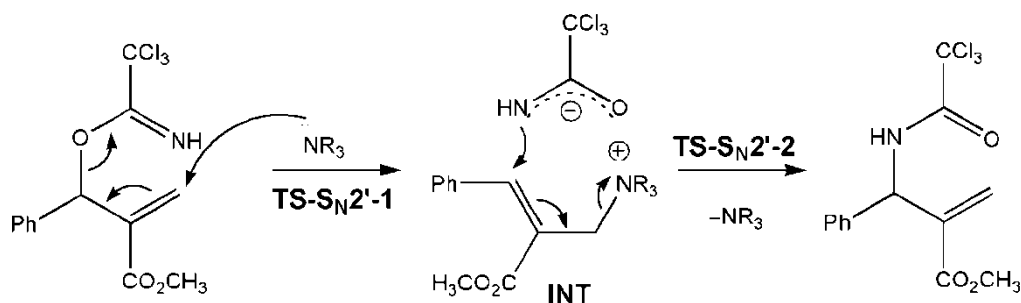


Figure 8.8. Proposed mechanism for the cinchona catalyzed [1,3]-shifts.

In order to reduce the computational cost, the mechanism was first investigated by using trimethylamine as the model catalyst. Both *syn* and *anti* attacks of trimethylamine to **r-1** were considered (Figure 8.9). Due to the flexibility of the substrate, all transition state conformers obtained by rotation around τ_1 , τ_2 and τ_3 were analyzed. The lowest energy *syn* and *anti* transition state conformations are shown in Figure 8.9.

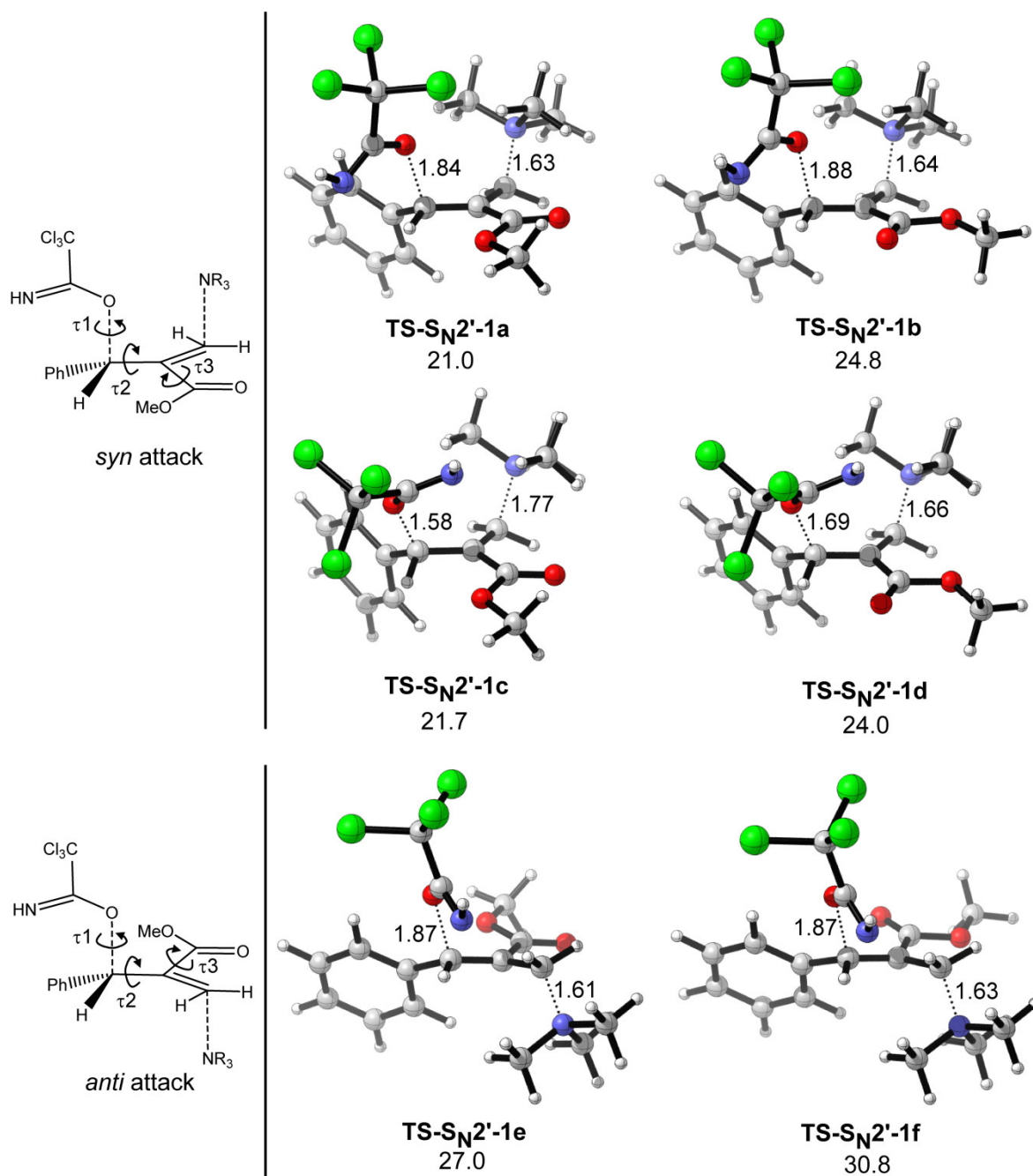


Figure 8.9. Lowest energy *syn* and *anti* transition states and their activation free energies ($\Delta G^\ddagger$, kcal/mol) for the S_N2' reaction.

TS-S_N2'-1a is the lowest energy transition state, with an activation free energy of 21.0 kcal/mol. The *anti* transition states, **TS-S_N2'-1e** and **TS-S_N2'-1f** are 6.0 kcal/mol and 9.8 kcal/mol higher in energy than **TS-S_N2'-1a** respectively. All other *anti* transition states have activation free energies above 30.8 kcal/mol. Houk and coworkers have also shown and discussed in detail the preference of the *syn* attack in S_N2' reactions [211]. **TS-S_N2'-1a** and **TS-S_N2'-1c** differ in τ_3 resulting in 0.7 kcal/mol free energy difference ($\tau(\text{C}-\text{C}-\text{O}-\text{C})_{\text{TS-S}_{\text{N}}2'-1a} = -130.4^\circ$, $\tau(\text{C}-\text{C}-\text{O}-\text{C})_{\text{TS-S}_{\text{N}}2'-1c} = -60.3^\circ$). A notable preference for the *s-cis* conformation in the transition state is found, unlike that in the reactant (**TS-S_N2'-1a**/**TS-S_N2'-1b** ($\Delta\Delta G^\ddagger = 3.8$ kcal/mol), **TS-S_N2'-1c**/**TS-S_N2'-1d** ($\Delta\Delta G^\ddagger = 2.3$ kcal/mol) and **TS-S_N2'-1e**/**TS-S_N2'-1f** ($\Delta\Delta G^\ddagger = 3.8$ kcal/mol)). The energy difference (see Figure 8.9) between **TS-S_N2'-1a** and the other alternative transition state conformations suggests that **TS-S_N2'-1a** controls the subsequent steps of the rearrangement process.

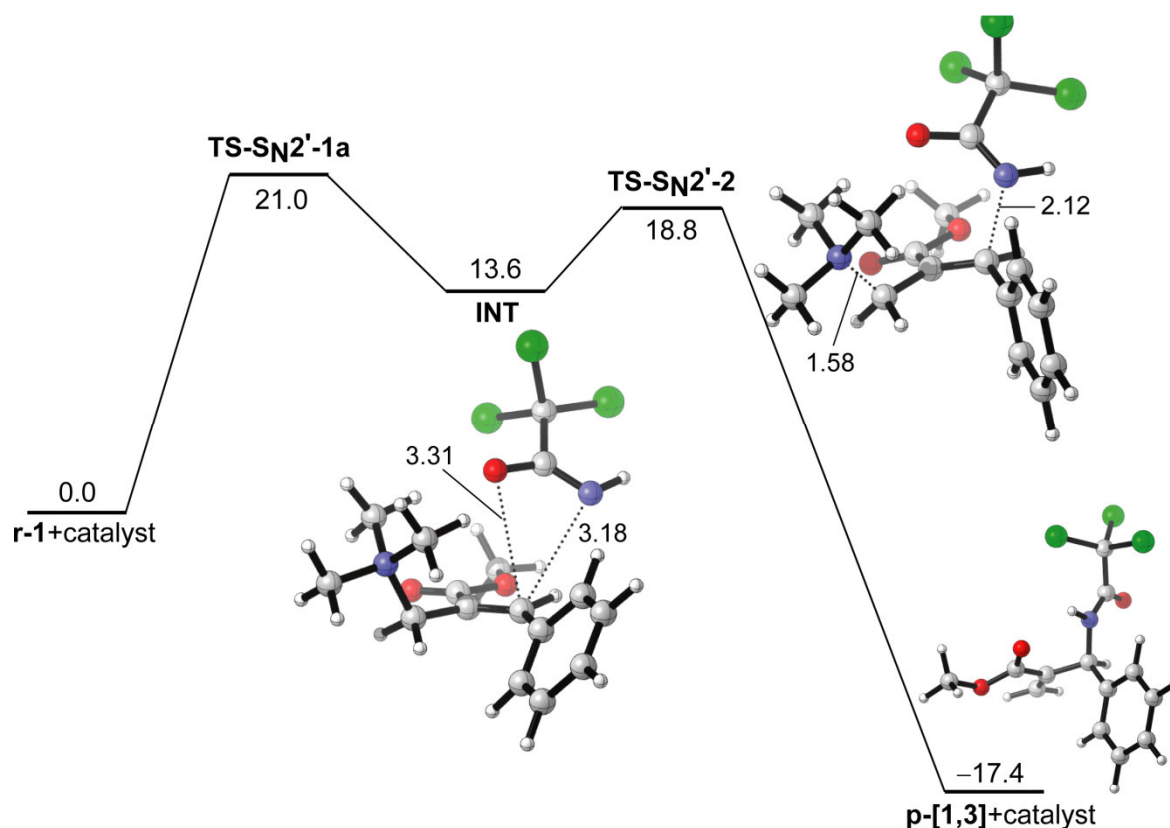


Figure 8.10. Free energy profile (kcal/mol) for the catalyzed [1,3]-shift of allylic trichloroacetimidate **r-1**.

Figure 8.10 shows the reaction profile predicted from the IRC calculations. The IRC path connects **TS-S_N2'-1a** to the ion pair intermediate, **INT**, and to the reactant complex. **INT** is 7.4 kcal/mol downhill from **TS-S_N2'-1a**. The charge separation in the intermediate is found to be 0.85e in the gas phase. **INT** already shows a favorable arrangement for the subsequent attack of the nitrogen nucleophile of the anionic trichloroacetamide to the quaternary ammonium bound substrate. A small energy barrier of 5.2 kcal/mol to **TS-S_N2'-2** initiates the second S_N2' reaction. The IRC calculations have demonstrated that the addition-elimination process is concerted although very asynchronous with the forming and breaking C–N bond distances of 2.12 Å and 1.58 Å respectively. The total process is exothermic by 17.4 kcal/mol. We were not able to locate any transition state for an *anti* attack of trichloroacetamide anion in the second step.

The 6.3 kcal/mol free energy difference between the Overman rearrangement transition state **TS-[3,3]-1** and **TS-S_N2'-1a** explains the exclusive formation of the [1,3]-rearranged product in the presence of cinchona alkaloids, whereas high activation free energies rule out the possibility of a thermal [1,3]-rearrangement.

8.3.4. Reactions of Hindered *O*-allylic trichloroacetimidates

In contrast to **r-1**, the terminal alkene in acetimide **r-2**, is sterically hindered, hence less prone to nucleophilic attack (Figure 8.11). Accordingly, **r-2** gave only the Overman rearranged acetamide and provided evidence on nucleophilic catalysis [196].

We found that [3,3]-rearrangement occurs via a concerted pseudopericyclic transition state with an activation free energy of 29.1 kcal/mol. The energetic penalty due to steric effects is much more significant for the competing S_N2' addition as expected. A 7.5 kcal/mol higher energy barrier for the addition of the amine nucleophile shows why the exclusive formation of the Overman product is observed experimentally. Unlike **r-1**, **r-2** failed to give the [1,3]-rearranged product upon attempted nucleophilic catalysis.

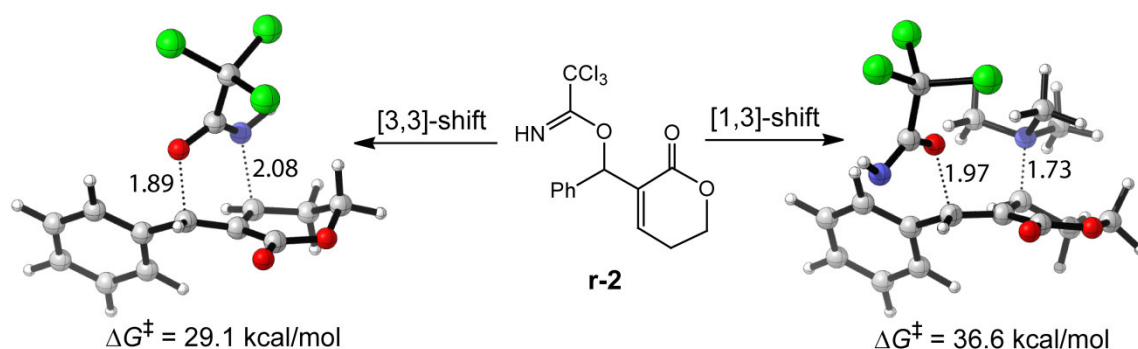


Figure 8.11. [3,3]- and [1,3]-rearrangements of hindered *O*-allylic trichloroacetimidates.

8.3.5. Selectivity of the Catalyzed Reaction

Figure 8.12 summarizes the possible pathways for formation of the (*R*) and (*S*) products starting from a racemic mixture of allylic trichloroacetimidates. Our calculations with the model catalyst (NMe₃) have shown that the *syn* addition-elimination mechanism is highly preferred in both steps (see Figure 8.9). The formation of *anti* ion pairs and the possibility of a concomitant *anti* attack of another nucleophile are both strongly disfavored. These results suggest that the (*R*) and (*S*) enantiomers will react at different rates with the chiral amine nucleophile to form diastereomeric *syn* ion pairs in the first step. As the intermediate concentrations build up, the diastereomeric *syn* ion pairs will be engaged in a chemical equilibrium via dissociation-recombination process. The selective *syn* addition of the nitrogen nucleophile of the anionic trichloroacetamide in the second step then designates the stereochemical outcome of the reaction. However, due to the high exothermicity of the reaction and the reversibility of the first step (see Figure 8.10), significant differences in the initial reaction rates may also affect the product distribution and the major product of the rearrangement process.

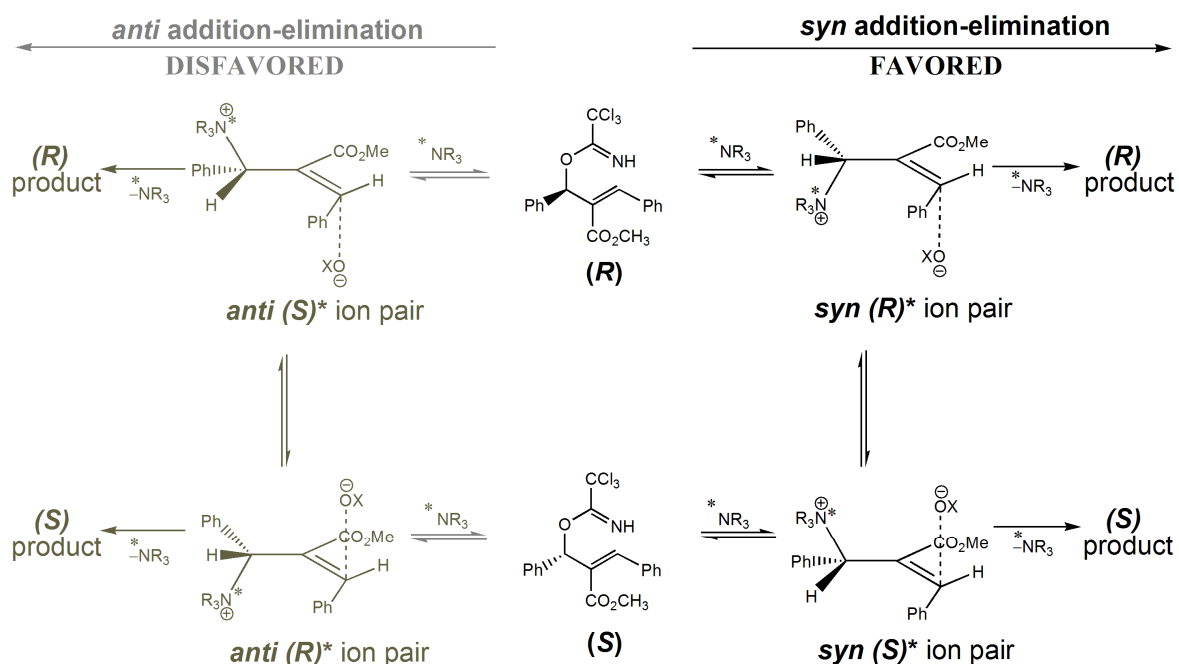


Figure 8.12. Possible pathways of cinchona catalyzed [1,3]-shifts of allylic trichloroacetimidates.

8.3.6. Cinchona Alkaloid Catalyzed Reactions

Kobbelgaard *et al.* [196] have screened different cinchona alkaloids and have shown that the choice of the cinchona alkaloid has a remarkable impact on the enantioselectivity of the reactions with enantiomeric excess values ranging from zero per cent to 83 per cent (Figure 8.13). The selectivity of quinine (**QN**) is found to be very poor, whereas quinidine (**QD**) gave more promising enantioselectivities and favored the opposite enantiomer, as expected. The best results are obtained with the dimeric cinchona alkaloid **(DHQD)₂PHAL**, which resulted in enantiomeric excess values higher than 80 per cent. However, a reversal of enantioselectivity occurred between **QD** and **(DHQD)₂PHAL**, although these two catalysts have identical stereochemistries of the binding site. More interestingly, dimeric cinchona alkaloids with different linkers such as **(DHQD)₂PYR** yielded a racemic mixture in toluene in contrast to the high enantioselectivities obtained with **(DHQD)₂PHAL**.

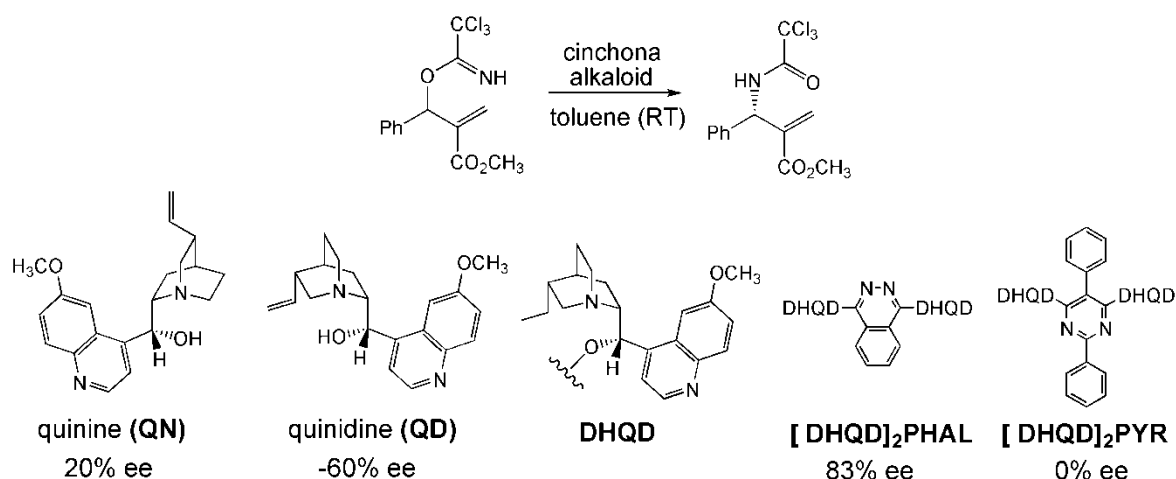


Figure 8.13. Cinchona catalyzed [1,3]-sigmatropic rearrangements.

Quinidine and quinine catalyzed rearrangements of the racemic *O*-allyl trichloroacetimidate **r-1** are investigated here in order to elucidate the factors affecting the stereoselectivity of the real system. Previous experimental and computational studies have shown that cinchona alkaloids exist in solution as a mixture of rapidly interconverting conformers and their conformational preferences have been extensively investigated [212-215]. These reports have shown that open-(3) and closed-(1) conformations, defined by the rotation around τ_4 and τ_5 , dominate in most of the solvents usually favoring the open-(3) conformer (Figure 8.14). We, therefore, used open-(3) conformer of the catalyst in our calculations. We have chosen **TS-S_N2'-1a** and its enantiomer to serve as transition state templates. The dimensions of the conformational space are, thus, reduced with the help of the preceding knowledge on τ_1 - τ_5 .

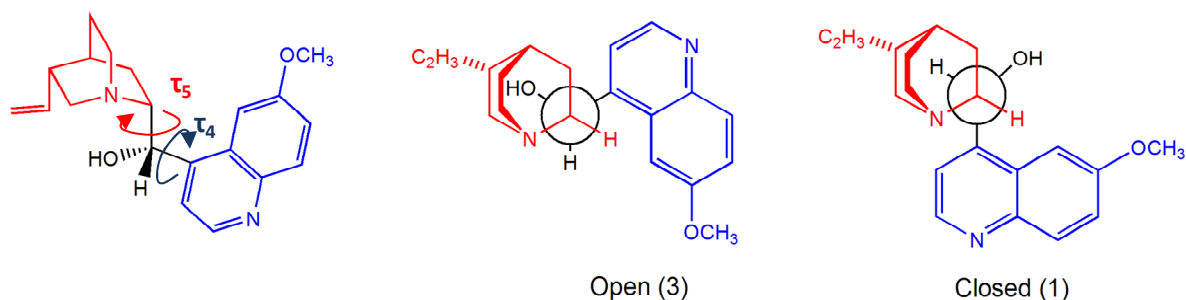


Figure 8.14. Open (3) and Closed (1) conformations of quinidine, defined by the rotation around τ_4 and τ_5 .

Transition states **(R)-TS-QD-I**, **(R)-TS-QD-II** and **(S)-TS-QD** (Figure 8.15), were located by substituting the model catalyst with **QD-open3** in the transition state templates. The critical distances in all transition states are in close agreement with the model transition state **TS-S_N2'-1a**. **(R)-TS-QD-II** is 2.2 kcal/mol stabilized compared to **(R)-TS-QD-I** due to H-bonding interaction between the hydroxyl proton of the catalyst and the carbonyl oxygen on the substrate (1.81 Å). **(R)-TS-QD-II** is also 0.9 kcal/mol lower in energy than **(S)-TS-QD**. This clearly contrasts to the stability of **(S)-TS-QD** compared to **(R)-TS-QD-I** and suggests the importance of H-bonding interactions in determining the fast-reacting enantiomer. The lowest energy transition state **(R)-TS-QD-II** reveals the selective transformation of the *R* enantiomer in the first step.

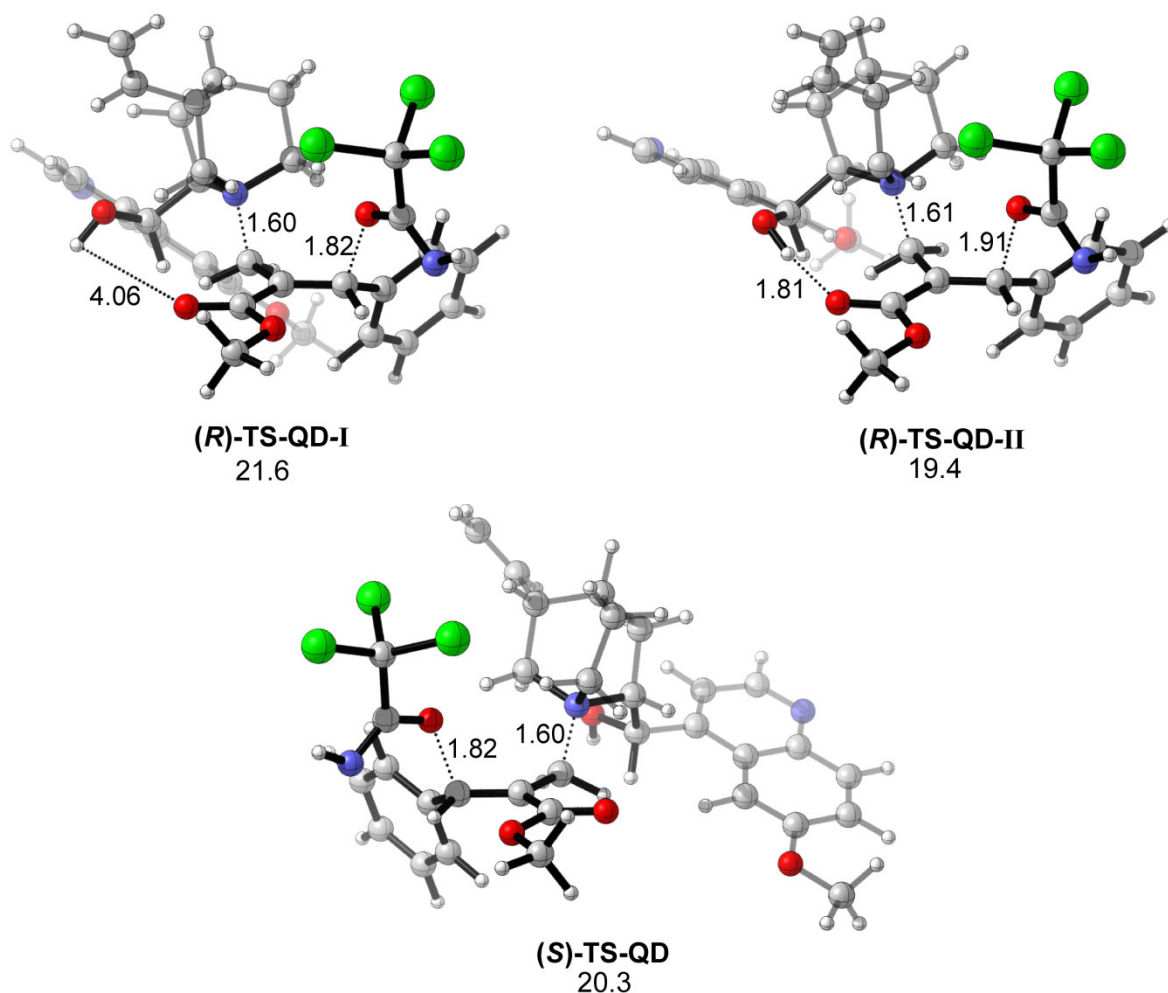


Figure 8.15. Transition state geometries and the activation free energies ($\Delta G^\ddagger$, kcal/mol) of the first S_N2' step for the quinidine (**QD**) catalyzed transformations of (*R*) and (*S*) allylic trichloroacetimidates.

The rigid PES scan on the transition state geometries around the dihedrals τ_6 , τ_7 and τ_8 (Figure 8.16) showed that there are no other low energy transition state alternatives. All geometries obtained from the rotation around τ_6 are found to be higher in energy. The energy contour plots for the scan of τ_7 versus τ_8 are displayed in Figure 8.16. The PES obtained for (*S*)-**TS-QD** has verified the existence of a single minimum corresponding to the located transition state geometry for the transformation of the *S* enantiomer. Two alternative transition states for the *R* enantiomer are disclosed by two minima (**I** and **II**) on the PES corresponding to (*R*)-**TS-QD-I** and (*R*)-**TS-QD-II**.

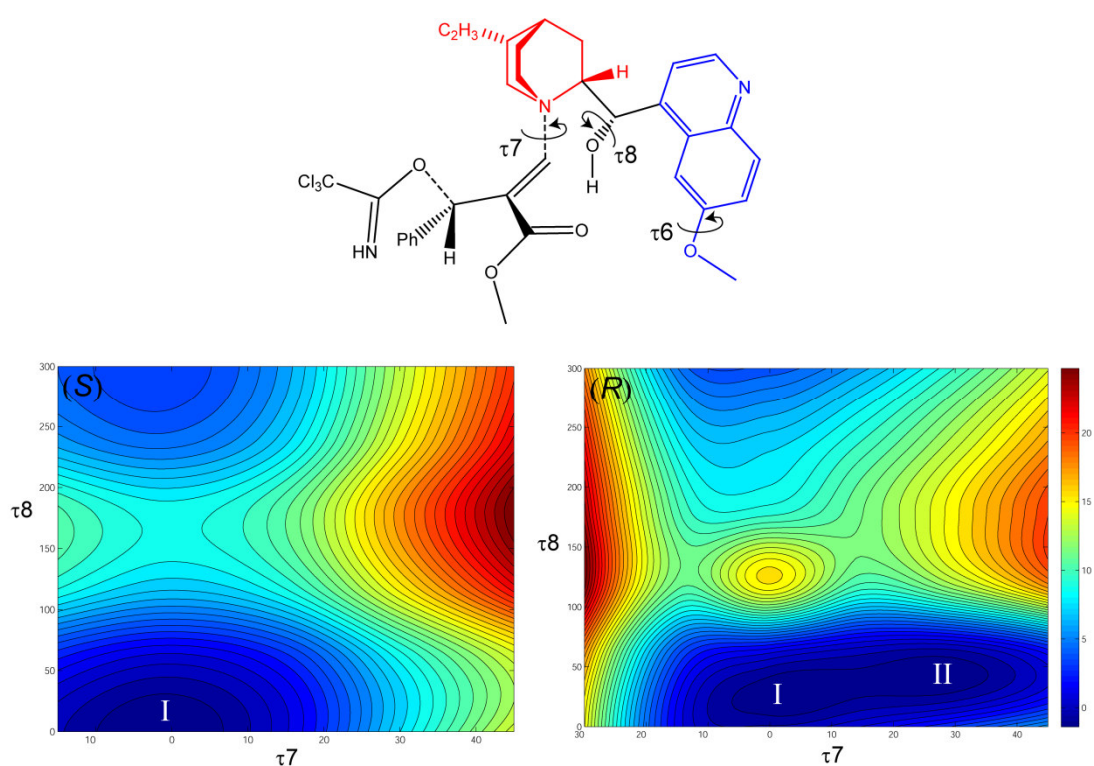


Figure 8.16. Energy contour plots for the scan of τ_7 versus τ_8 .

Next, the reaction catalyzed by quinine is considered. In this case, (*S*)-**TS-QN** profits from the H-bonding interaction and only slightly favors the transformation of the *S* enantiomer by 0.2 kcal/mol compared to (*R*)-**TS-QN** (Figure 8.17). The relay of stereochemical information from the vinyl group seems negligible; quinine and quinidine catalyzed reactions have very close activation energies.

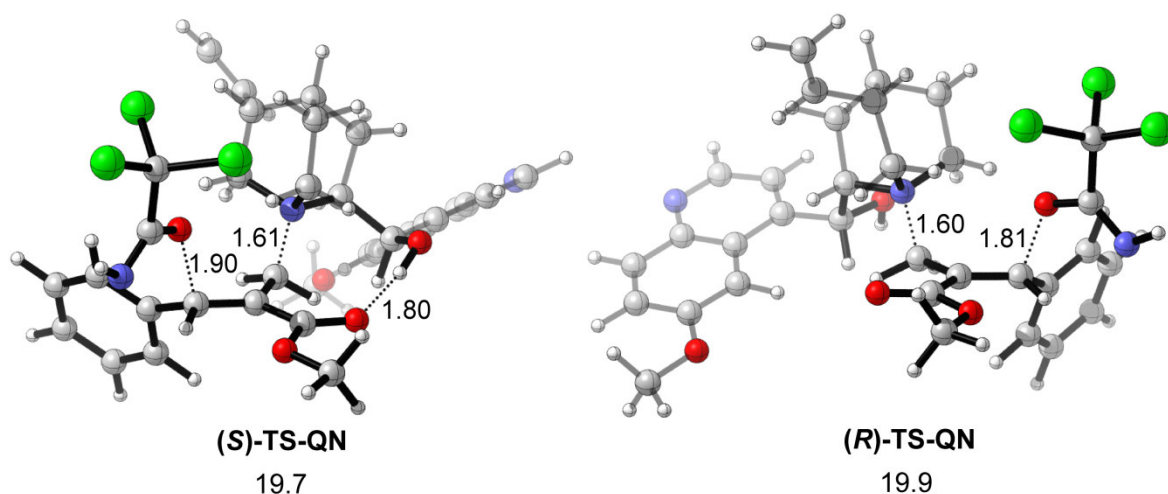


Figure 8.17. Transition state geometries and the activation free energies ($\Delta G^\ddagger$, kcal/mol) of the first S_N2' step for the quinine (QN) catalyzed transformations of (*R*) and (*S*) allylic trichloroacetimidates.

The free energies for the complete processes are given in Figure 8.18. The geometries of intermediates and transition states are very similar to **INT** and **TS- S_N2' -1a**. The fast-reacting enantiomer is determined by the H-bonding interaction between the catalyst and the substrate. Indeed, from the activation barriers of the first and the second S_N2' steps, the major product is predicted as the *R* enantiomer with quinidine and the *S* enantiomer with quinine, quinine giving lower enantioselectivity in agreement with the experimental results [196].

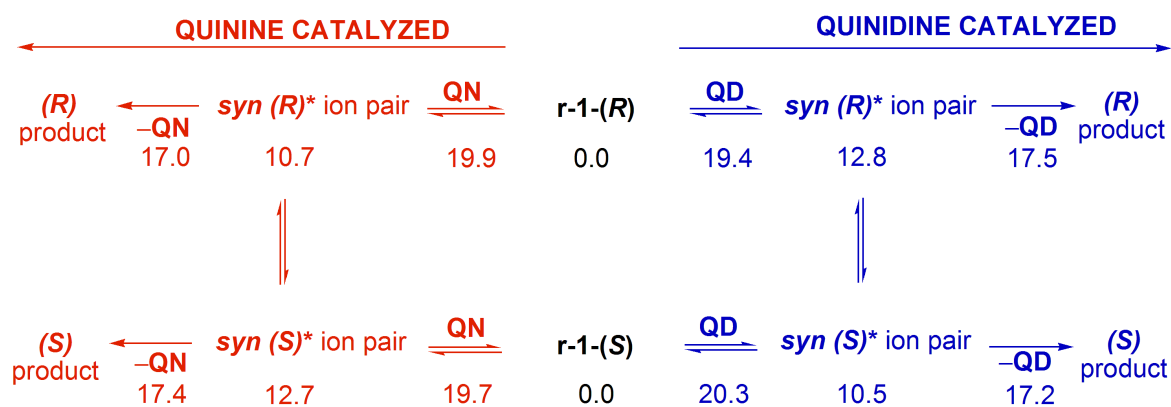


Figure 8.18. Energetics of quinine (QN) and quinidine (QD) catalyzed [1,3]-shifts.

The switch in the fast-reacting enantiomer due to hydrogen bonding has prompted us to verify our results by substituting the hydroxyl proton with a methyl group. Our results have demonstrated the preferential transformation of the *S* enantiomer as expected ($\Delta G^\ddagger((S)\text{-TS-QD-OCH}_3) = 19.6$ kcal/mol, $\Delta G^\ddagger((R)\text{-TS-QD-OCH}_3) = 21.7$ kcal/mol) (Figure 8.19). These results qualitatively explain the experimentally observed change in the enantioselectivity of the reaction as the hydroxyl group on quinidine is modified by an aromatic linker to connect two dihydroquinidine units. However, the selectivity seems to rely on many other factors depending on the nature of the linkage and the solvent that are still to be explored.

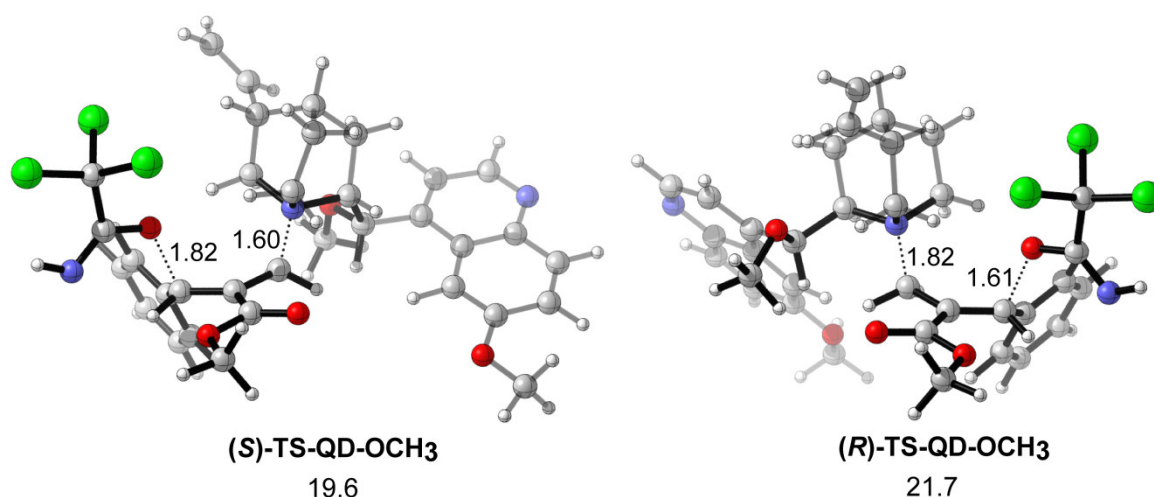


Figure 8.19. Transition state geometries and the activation free energies ($\Delta G^\ddagger$, kcal/mol) of the first S_N2' step for transformations of (*R*) and (*S*) allylic trichloroacetimidates catalyzed by the quinidine methyl ether catalyst.

8.4. Conclusion

The catalyzed [1,3]-rearrangement proceeds via a double S_N2' addition that is favored energetically compared to the competing pseudopericyclic Overman rearrangement pathway. Calculations with a model catalyst have suggested that *syn* addition-elimination is highly favored in both steps. Inclusion of the cinchona alkaloid catalysts has additionally revealed the importance of the H-bonding in accelerating the

reaction. These results provide an initial but important understanding of the factors affecting the enantioselective catalytic activity of cinchona alkaloids as nucleophilic catalysts. However, the conformational space of the substrate and cinchona alkaloids is large and the selectivity seems to depend on many factors that are still to be explored.

9. FUTURE WORK

Pericyclic reactions have been a major area of interest for both experimental and computational chemists for almost a century. This work provides a deeper insight into the mechanism of pericyclic reactions and the factors that determine the selectivity. However, the scope of the pericyclic reactions is very large and the selectivity seems to depend on many factors.

In this work, we have qualitatively explained the origins of the periselectivity in the thermal and Lewis acid catalyzed Diels–Alder reactions of crotonoyl phosphonate with cyclopentadiene and 1,3-cyclohexadiene on unsymmetrical potential energy surfaces. However, it is not possible to obtain a quantitative description of the product distribution using quantum mechanics calculations on such surfaces. Further studies may involve quasiclassical dynamics calculations in order to attain a quantitative insight into the periselectivity of these reactions. These calculations involve sampling the Boltzmann distributions of states at the bis-pericyclic transition state from which a number of dynamic trajectories are generated towards the products. A statistical average of the trajectories leading to each product may ultimately allow calculation of the product distribution ratio for the reaction of interest whose selectivity is controlled by surface shape and resulting dynamic effects.

Our calculations with different chiral anthracene templates revealed a fine balance between steric and electronic effects in the transition states that determine the diastereoselectivity of the cycloaddition process. Conformational analysis of the anthracene templates showed a substantial increase in energy because of the distortion of the anthracene ring due to stereoelectronic effects caused by the substituents on the chiral carbon. It is possible to analyze the distortion/interaction energies at the transition state in order to evaluate the contributions of the unfavorable distortion energy in the reactants and the favorable electrostatic interaction between the diene-dienophile pairs to the activation barriers. Partitioning the energy components for the competing diastereomeric transition state conformations will allow us to quantify the contributions causing the energy

differences between the competing transition states and eventually to understand the major factor that determines the selectivity of the reaction. In the light of work described in this dissertation, prospective studies may also include investigating the cycloadditions of chiral anthracene templates with hydrogen bond donating substituents. As such, the effect of hydrogen bonding interaction between the diene and the dienophile on the rate enhancement and on the degree of stereocontrol exerted by the template can be evaluated and quantified. This will require a quantum mechanical approach analyzing differences in reaction barriers as well as distortion/interaction analysis.

Finally, we described the mechanism and selectivity of cinchona alkaloid catalyzed [1,3]-shifts of allylic trichloroacetimidates and competing thermal rearrangement pathways. The results provide an important understanding of the enantioselective catalytic activity of cinchona alkaloids as nucleophilic catalysts and interestingly reveal that the Overman and thermal [1,3]-rearrangements have pseudopericyclic type geometry. However, conformational space of the substrate and the cinchona alkaloids is large and the selectivity seems to depend on many factors that are still to be explored. The studies can be extended to include transition state templates, **TS1-S_N2'-1c** and **TS1-S_N2'-1e**, and other accessible catalyst conformers such as **QD-closed-(1)** in order to obtain a more complete and quantitative description of the origins of the enantioselective catalytic activity of cinchona alkaloids. Future work may involve the inclusion of the solvent effects and the exploration of the catalytic activity of different dimeric cinchona alkaloids linked with different aromatic linkers.

APPENDIX A: COMPLETE ENERGETICS FOR ALL REACTANTS, TRANSITION STATES AND PRODUCTS

Table A.1. B3LYP/6-31+G(d) energetics (kcal/mol) for the thermal reaction of cyclopentadiene and crotonoyl phosphonate.

Structure	ΔE	ΔE_0	ΔH	ΔG
Cp + <i>s-trans</i>-1a	0.0	0.0	0.0	0.0
Cp + <i>s-cis</i>-1a	0.4	0.3	0.4	-0.1
5	22.1	24.1	23.3	37.4
6	16.5	18.5	17.7	31.6
7	25.2	27.0	26.2	40.4
8	21.3	23.2	22.4	36.7
9	16.7	18.7	17.9	32.1
10	21.6	23.3	22.6	36.4
11	25.6	27.3	26.5	40.4
12	25.4	26.5	25.9	40.3
13	14.1	17.1	15.8	31.4
<i>endo</i>-2a	-11.7	-6.8	-8.1	6.8
<i>exo</i>-2a	-12.2	-7.2	-8.5	6.4
<i>anti</i>-3a	-11.9	-7.0	-8.2	6.3
<i>syn</i>-3a	-12.7	-7.0	-9.0	5.6
<i>anti</i>-4a	-11.5	-6.6	-7.8	6.7
<i>syn</i>-4a	-12.7	-7.9	-9.1	5.2
Intermediate-12	23.9	25.4	25.0	37.6

Table A.2. MPW1K/6-31+G(d) energetics (kcal/mol) for the thermal reaction of cyclopentadiene and crotonoyl phosphonate.

Structure	MPW1K/6-31+G*				MPW1K/6-31+G*// B3LYP/6-31+G*			
	ΔE	ΔE_0	ΔH	ΔG	ΔE	ΔE_0	ΔH	ΔG
Cp + <i>s-trans</i>-1a	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cp + <i>s-cis</i>-1a	0.5	0.5	0.6	0.0	0.6	0.5	0.6	0.5
5	17.9	19.8	19.0	33.1	18.4	19.9	19.3	33.6
6	12.5	14.5	13.7	27.7	13.0	14.7	14.0	28.1
7	22.6	24.3	23.5	37.6	22.8	24.3	23.5	37.9
8	17.2	19.1	18.2	32.7	17.5	19.2	18.4	32.8
9	12.6	14.7	13.8	28.2	12.9	14.7	14.0	28.3
10	20.0	21.7	21.0	34.6	20.3	21.9	21.1	35.2
11	23.3	25.0	24.3	38.1	23.5	25.1	24.3	38.6
13	6.8	10.2	8.7	24.7	7.8	10.5	9.3	24.7
<i>endo</i>-2a	-29.8	-24.6	-25.9	-11.1	-29.3	-24.6	-25.8	-10.6
<i>exo</i>-2a	-30.2	-25.0	-26.3	-11.5	-29.8	-24.9	-26.2	-10.9
<i>anti</i>-3a	-28.1	-22.8	-24.0	-9.8	-27.7	-22.8	-24.0	-8.7
<i>syn</i>-3a	-28.6	-23.4	-24.6	-10.1	-28.3	-23.4	-24.6	-9.3
<i>anti</i>-4a	-27.9	-22.6	-23.9	-9.0	-27.5	-22.6	-23.8	-8.5
<i>syn</i>-4a	-28.7	-23.5	-24.7	-10.4	-28.4	-23.5	-24.7	-9.5

Table A.3. B3LYP/6-31+G(d) energetics (kcal/mol) for the SnCl_4 catalyzed reaction of cyclopentadiene and crotonoyl phosphonate.

Structure	ΔE	ΔE_0	ΔH	ΔG
Cp + <i>s-trans</i>-15	0.1	0.2	0.2	0.7
Cp + 15	0.0	0.0	0.0	0.0
17	16.2	18.4	17.5	32.4
18	7.8	9.7	9.0	23.3
19	18.0	19.6	18.8	33.5
20	15.4	17.5	16.7	31.7
21	8.9	10.9	10.1	24.8
22	10.4	12.1	11.5	25.6
23	17.3	18.8	18.0	32.5
24	12.3	14.0	13.4	27.0
25	13.9	15.6	14.9	29.1
26	3.4	7.0	5.5	21.9
<i>endo</i> -2a	-9.6	-4.7	-6.0	8.9
<i>exo</i> -2a	-9.8	-4.9	-6.1	8.4
<i>anti</i> -3a	-15.3	-11.4	-11.4	4.2
<i>syn</i> -3a	-15.7	-10.5	-11.8	5.4
<i>anti</i> -4a	-14.5	-9.4	-10.7	4.8
<i>syn</i> -4a	-16.3	-11.4	-12.4	0.5
Intermediate-24	8.0	10.3	9.5	24.0
Intermediate-25	8.8	10.7	10.0	24.4

Table A.4. MPW1K/6-31+G(d) energetics (kcal/mol) for the SnCl₄ catalyzed reaction of cyclopentadiene and crotonoyl phosphonate.

	MPW1K/6-31+G*				MPW1K/6-31+G*// B3LYP/6-31+G*			
	ΔE	ΔE_0	ΔH	ΔG	ΔE	ΔE_0	ΔH	ΔG
Cp + <i>s-trans</i>-15	0.1	0.2	0.1	0.5	0.1	0.1	0.1	0.3
Cp + 15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
17	10.2	12.3	11.4	26.4	10.4	12.3	11.5	26.3
18	2.7	4.5	3.8	18.1	3.0	4.6	4.0	18.5
19	12.2	13.7	12.9	27.6	12.4	13.7	12.9	27.8
20	9.8	11.6	10.8	25.7	9.9	11.7	10.9	25.7
21	3.5	5.3	4.5	19.5	3.6	5.3	4.6	19.2
22	6.8	8.3	7.7	21.7	6.8	8.4	7.7	22.3
23	11.4	23.8	12.0	26.6	11.3	12.7	11.9	26.8
26	-7.7	-4.1	-5.6	10.8	-7.3	-4.1	-5.4	10.7
<i>endo</i>-2a	-28.6	-23.5	-24.8	-9.5	-28.2	-23.4	-24.7	-9.1
<i>exo</i>-2a	-28.8	-23.8	-26.2	-10.7	-28.4	-23.5	-24.7	-9.5
<i>anti</i>-3a	-33.5	-28.0	-29.3	-13.4	-32.9	-27.8	-29.1	-13.4
<i>syn</i>-3a	-33.7	-28.2	-29.6	-13.9	-33.2	-28.1	-29.4	-13.8
<i>anti</i>-4a	-32.5	-27.1	-28.5	-12.6	-31.9	-26.9	-28.2	-12.7
<i>syn</i>-4a	-32.5	-27.4	-28.4	-15.6	-32.3	-27.4	-28.5	-13.9

Table A.5. B3LYP/6-31+G(d) energetics (kcal/mol) for the SnCl_4 catalyzed transition states of cyclopentadiene and crotonoyl phosphonate.

	ΔE	ΔE_0	ΔH	ΔG
Cp+15 (octahedral complex)	0.0	0.0	0.0	0.0
Cp+16 (trigonal bipyramidal complex)	-3.1	-3.5	-3.1	-5.9
17 – trigonal bipyramidal complex	18.2	20.0	19.4	32.8
18 – trigonal bipyramidal complex	11.2	12.8	12.3	24.7
19 – trigonal bipyramidal complex	21.6	23.0	22.5	35.2
20 – trigonal bipyramidal complex	17.5	19.1	18.5	31.6
21 – trigonal bipyramidal complex	12.3	14.0	13.5	25.8
22 – trigonal bipyramidal complex	15.3	16.9	16.4	28.7
23 – trigonal bipyramidal complex	21.0	22.4	21.9	33.7
26 – trigonal bipyramidal complex	7.9	10.7	9.7	24.0

Table A.6. B3LYP/6-31+G(d) energetics (kcal/mol) for the SnCl_4 catalyzed cycloaddition of 1,3-cyclohexadiene and crotonoyl phosphonate.

Structure	ΔE	ΔE_0	ΔH	ΔG
1,3-cyclohexadiene + 15 (octahedral complex)	0.0	0.0	0.0	0.0
27	11.8		13.1	28.3
28	7.3		9.3	26.2
29	11.4		12.3	27.3
30	8.4		10.0	25.2
Diels–Alder product	-14.8		-11.2	4.1
Hetero-Diels–Alder product	-10.0		-6.2	10.4

Table A.7. Energetics (kcal/mol) for the reactions of maleic anhydride (MA) with chiral anthracene templates.

	B3LYP/6-31+G*(gas phase)				B3LYP/6-31+G*(in toluene)	
	ΔE	ΔE_0	ΔH	ΔG	SCF with PCM corr.	ΔE in soln. with all electrostatic terms
ant-1 + MA	0.0	0.0	0.0	0.0	0.0	0.0
TSant1-I	19.4	20.3	19.9	34.7	20.5	19.7
TSant1-II	23.9	24.6	24.4	38.6	24.5	23.6
TSant1-III	25.5	26.2	26.0	39.7	25.9	25.1
TSant1-IV	22.9	23.9	23.6	38.1	23.8	24.2
TSant1-V	28.8	29.8	29.4	43.7	29.1	28.2
TSant1-VI	28.4	29.3	28.9	43.6	29.1	27.8
A-ant-1	-13.2	-9.5	-10.2	5.3	-11.6	-12.7
B-ant-1	-13.0	-9.2	-10.1	5.8	-11.5	-12.5
ant-2 + MA	0.0	0.0	0.0	0.0	0.0	0.0
TSant2-I	21.1	22.2	21.8	36.5	23.0	22.2
TSant2-II	25.7	26.5	26.2	40.7	26.9	25.8
TSant2-III	30.6	31.4	31.1	45.6	30.9	30.4
TSant2-IV	26.6	27.5	27.1	42.3	28.1	27.4
TSant2-V	34.5	35.2	34.8	49.2	35.2	34.3
TSant2-VI	35.6	36.4	36.0	51.1	36.2	35.2
A-ant-2	-11.4	-7.7	-8.6	7.6	-9.1	-10.1
B-ant-2	-5.2	-1.5	-2.5	13.9	-3.4	-5.0
ant-3 + MA	0.0	0.0	0.0	0.0	0.0	0.0
TSant3-VII	14.9	16.2	15.8	30.9	15.4	15.0
TSant3-VIII	14.6	15.8	15.6	29.9	14.9	15.2
TSant3-IX	17.2	18.4	18.2	32.2	16.7	15.5
TSant3-X	13.8	15.1	14.8	29.6	14.5	13.1
A-ant-3	-9.0	-5.3	-6.1	9.5	-6.8	-7.2
B-ant-3	-6.6	-2.7	-3.5	12.3	-4.4	-5.5
ant-4 + MA	0.0	0.0	0.0	0.0	0.0	0.0
TSant4-XI	22.9	23.8	23.5	38.5	24.4	24.3
TSant4-XII	22.8	23.6	23.3	37.4	24.2	24.8
TSant4-XIII	21.1	22.0	21.7	36.4	23.0	22.3
TSant4-XIII	21.1	22.0	21.8	37.2	23.2	22.7
A-ant-4	-14.0	-10.2	-11.0	4.5	-11.8	-12.1
B-ant-4	-14.0	-10.0	-10.9	5.5	-11.5	-12.1

APPENDIX B: POTENTIAL ENERGY SURFACE SCAN RESULTS

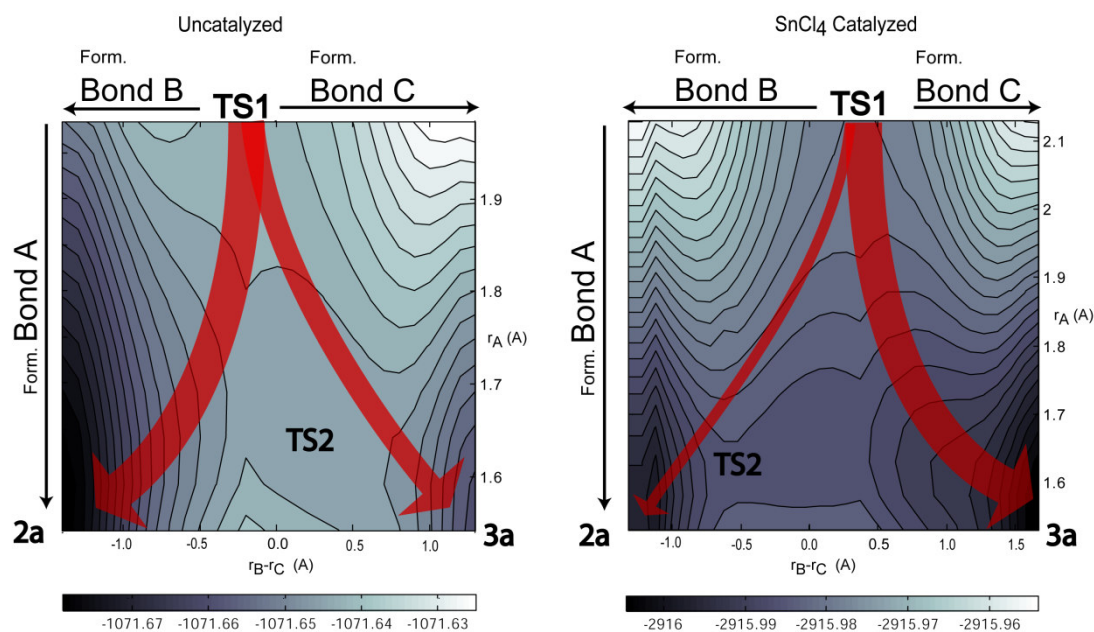


Figure B.1. Potential energy surface scan results. The contour plots are drawn by Matlab 7.0.4 program using a step level of 0.0020 a.u.

APPENDIX C: NATURAL BOND ORBITAL (NBO) ANALYSIS RESULTS

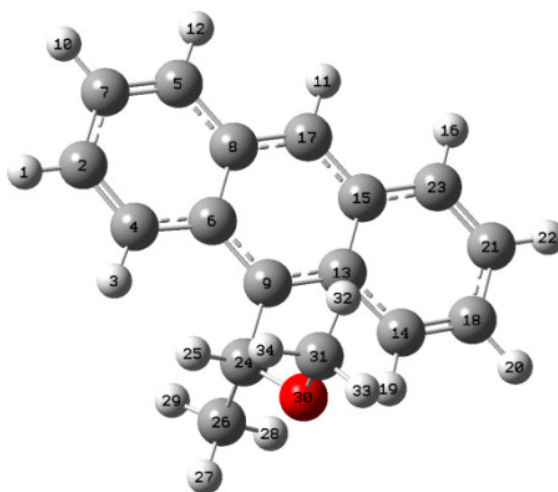


Figure C.1. Numbering scheme used in Natural Bond Orbital (NBO) analysis for (*R*)-9-(1-methoxyethyl)anthracene.

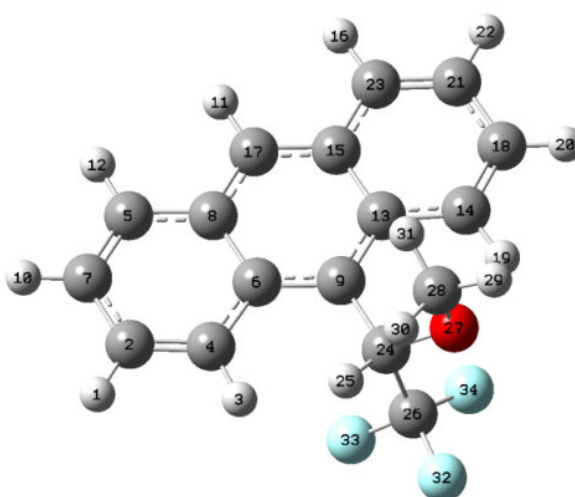


Figure C.2. Numbering scheme used in Natural Bond Orbital (NBO) analysis for (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene.

Table C.1. Natural Bond Orbital (NBO) analysis results for (*R*)-9-(1-methoxyethyl)anthracene conformer **a**.

Energy of deletion :				-731.089133035	
Total SCF energy :				-732.668280753	
Energy change :				1.579148 a.u.,	990.931 kcal/mol
BD (anthracene)	→	BD* (CH – CC – CO)		E(2) (kcal/mol)	
5 BD (1) H 3 - C 4	/293.	BD*(1) C 24 - H 25		1.31	
12 BD (1) C 6 - C 9	/295.	BD*(1) C 24 - O 30		0.92	
13 BD (2) C 6 - C 9	/295.	BD*(1) C 24 - O 30		2.97	
13 BD (2) C 6 - C 9	/294.	BD*(1) C 24 - C 26		2.62	
		TOT		7.82	
BD (CH – CC – CO)	→	BD* (anthracene)		E(2)	
33 BD (1) C 24 - H 25	/265.	BD*(1) H 3 - C 4		0.84	
33 BD (1) C 24 - H 25	/277.	BD*(1) C 9 - C 13		3.66	
34 BD (1) C 24 - C 26	/273.	BD*(2) C 6 - C 9		2.07	
34 BD (1) C 24 - C 26	/272.	BD*(1) C 6 - C 9		0.79	
35 BD (1) C 24 - O 30	/272.	BD*(1) C 6 - C 9		0.97	
		TOT		8.33	
BD (CH – CC – CO)	→	Other acceptor		E(2)	
33 BD (1) C 24 - H 25	/297.	BD*(1) C 26 - H 28		2.65	
34 BD (1) C 24 - C 26	/299.	BD*(1) O 30 - C 31		2.44	
35 BD (1) C 24 - O 30	/298.	BD*(1) C 26 - H 29		1.14	
35 BD (1) C 24 - O 30	/301.	BD*(1) C 31 - H 33		1.05	
		TOT		7.28	
Other donor	→	BD* (CH – CC – CO)			
36 BD (1) C 26 - H 27	/295.	BD*(1) C 24 - O 30		0.61	
37 BD (1) C 26 - H 28	/293.	BD*(1) C 24 - H 25		2.23	
38 BD (1) C 26 - H 29	/295.	BD*(1) C 24 - O 30		4.06	
39 BD (1) O 30 - C 31	/294.	BD*(1) C 24 - C 26		1.64	
41 BD (1) C 31 - H 33	/295.	BD*(1) C 24 - O 30		3.35	
		TOT		11.89	

Table C.2. Natural Bond Orbital (NBO) analysis results for (*R*)-9-(1-methoxyethyl)anthracene conformer **b**.

Energy of deletion :		-731.080298561		
Total SCF energy :		-732.655516997		

Energy change :		1.575218 a.u.,		988.465 kcal/mol

BD (anthracene)		→	BD* (CH – CC – CO)	E(2) (kcal/mol)
13	BD (2) C 6 - C 9	/293.	BD*(1) C 24 - H 25	0.79
13	BD (2) C 6 - C 9	/295.	BD*(1) C 24 - O 30	5.16
17	BD (1) C 9 - C 13	/294.	BD*(1) C 24 - C 26	1.44
			TOT	7.39
BD (CH – CC – CO)		→	BD* (anthracene)	E(2)
33	BD (1) C 24 - H 25	/273.	BD*(2) C 6 - C 9	2.02
33	BD (1) C 24 - H 25	/272.	BD*(1) C 6 - C 9	3.36
34	BD (1) C 24 - C 26	/277.	BD*(1) C 9 - C 13	1.62
35	BD (1) C 24 - O 30	/273.	BD*(2) C 6 - C 9	0.97
35	BD (1) C 24 - O 30	/272.	BD*(1) C 6 - C 9	0.67
			TOT	8.64
BD (CH – CC – CO)		→	Other acceptor	E(2)
33	BD (1) C 24 - H 25	/297.	BD*(1) C 26 - H 28	2.92
35	BD (1) C 24 - O 30	/298.	BD*(1) C 26 - H 29	0.91
35	BD (1) C 24 - O 30	/301.	BD*(1) C 31 - H 33	1.02
			TOT	4.85
Other donor		→	BD* (CH – CC – CO)	E(2)
37	BD (1) C 26 - H 28	/293.	BD*(1) C 24 - H 25	1.36
37	BD (1) C 26 - H 28	/295.	BD*(1) C 24 - O 30	0.87
38	BD (1) C 26 - H 29	/295.	BD*(1) C 24 - O 30	3.91
41	BD (1) C 31 - H 33	/295.	BD*(1) C 24 - O 30	3.36
			TOT	9.50

Table C.3. Natural Bond Orbital (NBO) analysis results for (*R*)-9-(1-methoxyethyl)anthracene conformer **c**.

Energy of deletion :				-731.084498568	
Total SCF energy :				-732.650227610	
Energy change :				1.565729 a.u.,	982.511 kcal/mol
BD (anthracene)		→	BD* (CH – CC – CO)		E(2) (kcal/mol)
13	BD (2) C 6 - C 9	/293.	BD*(1) C 24 - H 25		2.47
12	BD (1) C 6 - C 9	/294.	BD*(1) C 24 - C 26		0.51
13	BD (2) C 6 - C 9	/294.	BD*(1) C 24 - C 26		1.34
13	BD (2) C 6 - C 9	/295.	BD*(1) C 24 - O 30		0.62
17	BD (1) C 9 - C 13	/294.	BD*(1) C 24 - O 30		0.99
TOT					5.93
BD (CH – CC – CO)		→	BD* (anthracene)		E(2)
33	BD (1) C 24 - H 25	/273.	BD*(2) C 6 - C 9		2.19
33	BD (1) C 24 - H 25	/272.	BD*(1) C 6 - C 9		0.97
34	BD (1) C 24 - C 26	/273.	BD*(2) C 6 - C 9		1.63
34	BD (1) C 24 - C 26	/272.	BD*(1) C 6 - C 9		1.80
35	BD (1) C 24 - O 30	/277.	BD*(1) C 9 - C 13		1.49
TOT					8.08
BD (CH – CC – CO)		→	BD* (subsituents)		E(2)
33	BD (1) C 24 - H 25	/297.	BD*(1) C 26 - H 28		2.20
35	BD (1) C 24 - O 30	/298.	BD*(1) C 26 - H 29		1.42
35	BD (1) C 24 - O 30	/301.	BD*(1) C 31 - H 33		1.01
TOT					4.63
Other donor		→	Other acceptor		E(2)
36	BD (1) C 26 - H 27	/295.	BD*(1) C 24 - O 30		0.99
37	BD (1) C 26 - H 28	/293.	BD*(1) C 24 - H 25		2.98
38	BD (1) C 26 - H 29	/295.	BD*(1) C 24 - O 30		2.64
41	BD (1) C 31 - H 33	/295.	BD*(1) C 24 - O 30		3.46
TOT					10.07

Table C.4. Natural Bond Orbital (NBO) analysis results for (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene conformer **a**.

Energy of deletion :				-1028.304433464	
Total SCF energy :				-1030.385842297	
Energy change :				2.081409 a.u.,	1306.105 kcal/mol
BD (anthracene)	→	BD* (CH – CC – CO)		E(2) (kcal/mol)	
5 BD (1) H 3 - C 4	/332.	BD*(1) C 24 - H 25		1.27	
13 BD (2) C 6 - C 9	/333.	BD*(1) C 24 - C 26		4.00	
12 BD (1) C 6 - C 9	/334.	BD*(1) C 24 - O 27		1.12	
13 BD (2) C 6 - C 9	/334.	BD*(1) C 24 - O 27		2.68	
		TOT		9.07	
BD (CH – CC – CO)	→	BD* (anthracene)		E(2)	
33 BD (1) C 24 - H 25	/304.	BD*(1) H 3 - C 4		0.59	
33 BD (1) C 24 - H 25	/315.	BD*(1) C 9 - C 13		3.55	
34 BD (1) C 24 - C 26	/312.	BD*(2) C 6 - C 9		1.45	
34 BD (1) C 24 - C 26	/311.	BD*(1) C 6 - C 9		0.60	
35 BD (1) C 24 - O 27	/311.	BD*(1) C 6 - C 9		0.91	
		TOT		7.10	
BD (CH – CC – CO)	→	Other acceptor		E(2)	
33 BD (1) C 24 - H 25	/335.	BD*(1) C 26 - F 32		0.66	
33 BD (1) C 24 - H 25	/337.	BD*(1) C 26 - F 34		4.83	
34 BD (1) C 24 - C 26	/338.	BD*(1) O 27 - C 28		2.37	
35 BD (1) C 24 - O 27	/336.	BD*(1) C 26 - F 33		1.86	
35 BD (1) C 24 - O 27	/339.	BD*(1) C 28 - H 29		0.94	
		TOT		10.66	
Other donor	→	BD* (CH – CC – CO)		E(2)	
37 BD (1) C 26 - F 33	/334.	BD*(1) C 24 - O 27		1.39	
38 BD (1) C 26 - F 34	/332.	BD*(1) C 24 - H 25		0.78	
39 BD (1) O 27 - C 28	/333.	BD*(1) C 24 - C 26		1.76	
40 BD (1) C 28 - H 29	/334.	BD*(1) C 24 - O 27		3.36	
		TOT		7.29	

Table C.5. Natural Bond Orbital (NBO) analysis results for (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene conformer **b**.

Energy of deletion :		-1028.296821039		
Total SCF energy :		-1030.374035780		
Energy change :		2.077215 a.u.,		1303.473 kcal/mol
BD (anthracene)		→	BD* (CH – CC – CO)	E(2) (kcal/mol)
13	BD (2) C 6 - C 9	/332.	BD*(1) C 24 - H 25	0.88
13	BD (2) C 6 - C 9	/334.	BD*(1) C 24 - O 27	5.46
17	BD (1) C 9 - C 13	/333.	BD*(1) C 24 - C 26	1.87
			TOT	8.21
BD (CH – CC – CO)		→	BD* (anthracene)	E(2)
34	BD (1) C 24 - H 25	/310.	BD*(1) C 6 - C 9	3.59
34	BD (1) C 24 - H 25	/311.	BD*(2) C 6 - C 9	1.25
35	BD (1) C 24 - C 26	/315.	BD*(1) C 9 - C 13	1.33
36	BD (1) C 24 - O 27	/310.	BD*(1) C 6 - C 9	0.60
36	BD (1) C 24 - O 27	/311.	BD*(2) C 6 - C 9	1.22
			TOT	7.99
BD (CH – CC – CO)		→	Other acceptor	E(2)
34	BD (1) C 24 - H 25	/335.	BD*(1) C 26 - F 32	1.79
34	BD (1) C 24 - H 25	/337.	BD*(1) C 26 - F 34	4.30
36	BD (1) C 24 - O 27	/336.	BD*(1) C 26 - F 33	1.57
36	BD (1) C 24 - O 27	/341.	BD*(1) C 28 - H 31	0.78
			TOT	8.44
Other donor		→	BD* (CH – CC – CO)	E(2)
38	BD (1) C 26 - F 33	/334.	BD*(1) C 24 - O 27	1.03
39	BD (1) C 26 - F 34	/332.	BD*(1) C 24 - H 25	0.56
43	BD (1) C 28 - H 31	/334.	BD*(1) C 24 - O 27	3.48
			TOT	5.07

Table C.6. Natural Bond Orbital (NBO) analysis results for (*S*)-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene conformer **c**.

Energy of deletion :		-1028.292081072		
Total SCF energy :		-1030.361724958		
Energy change :		2.069644 a.u.,		1298.722 kcal/mol

BD (anthracene)		→	BD* (CH – CC – CO)	E(2) (kcal/mol)
13	BD (2) C 6 - C 9	/332.	BD*(1) C 24 - H 25	2.24
13	BD (2) C 6 - C 9	/333.	BD*(1) C 24 - C 26	1.85
16	BD (1) C 9 - C 13	/333.	BD*(1) C 24 - C 26	0.81
12	BD (1) C 6 - C 9	/334.	BD*(1) C 24 - O 27	1.19
			TOT	6.09
BD (CH – CC – CO)		→	BD* (anthracene)	E(2)
33	BD (1) C 24 - H 25	/312.	BD*(2) C 6 - C 9	2.67
33	BD (1) C 24 - H 25	/315.	BD*(1) C 9 - C 13	0.79
34	BD (1) C 24 - C 26	/312.	BD*(2) C 6 - C 9	0.75
34	BD (1) C 24 - C 26	/315.	BD*(1) C 9 - C 13	1.52
35	BD (1) C 24 - O 27	/311.	BD*(1) C 6 - C 9	1.35
			TOT	7.08
BD (CH – CC – CO)		→	Other acceptor	E(2)
33	BD (1) C 24 - H 25	/336.	BD*(1) C 26 - F 33	1.48
33	BD (1) C 24 - H 25	/337.	BD*(1) C 26 - F 34	2.27
34	BD (1) C 24 - C 26	/338.	BD*(1) O 27 - C 28	0.55
35	BD (1) C 24 - O 27	/336.	BD*(1) C 26 - F 33	0.69
35	BD (1) C 24 - O 27	/337.	BD*(1) C 26 - F 34	0.52
35	BD (1) C 24 - O 27	/341.	BD*(1) C 28 - H 31	0.76
			TOT	6.27
Other donor		→	BD* (CH – CC – CO)	E(2)
42	BD (1) C 28 - H 31	/334.	BD*(1) C 24 - O 27	3.43
			TOT	3.43

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