

A COMPUTATIONAL APPROACH TO THE CORE OF EUNICELLINS

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A COMPUTATIONAL APPROACH TO THE CORE OF EUNICELLINS

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To my mother, my father and my sister

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ABSTRACT

A COMPUTATIONAL APPROACH TO THE CORE OF EUNICELLINS

The asymmetric Diels-Alder reaction has attracted much interest for decades. Most recently, interest in the use of catalysts in cycloadditions has gained momentum due to their capacity to provide complex stereoselectivity throughout natural product synthesis. In this study, the origin of diastereoselectivity of intramolecular Diels-Alder reaction with chiral imidazolidinones is investigated to construct the skeleton of eunicellin which is a marine metabolite and two of medium ring ethers found in some natural products. The first reaction of interest was the intramolecular Diels-Alder reaction of acyclic precursor, seven, eight and nine membered reactants with and without aldehyde substituent in order to better understand the origin of diastereoselectivity. The *exo* and *endo* selectivity of the cycloaddition reactions, and the rate of thermal reactions are discussed in detail. Secondly, an organocatalyst controlled intramolecular Diels-Alder reaction of seven membered ring to synthesize the tricyclic core is investigated. Lastly, the cycloaddition reactions of eight and nine membered model Diels-Alder precursors are further explored to rationalize the effects of medium ring constraints and to elucidate the difference in diastereoselectivity of the intramolecular Diels-Alder reaction with chiral imidazolidinones. In this work, the effect of MacMillan Catalyst on the mechanism and stereoselectivity of the reaction have been studied with DFT and discussed in detail.

ÖZET

EUNICELLİN'İN MERKEZİNE BİLGİSAYAR DESTEKLİ BİR YAKLAŞIM

Asimetrik Diels-Alder tepkimesi yıllardır oldukça ilgi toplamaktadır. Son zamanlarda siklokatılmalarda katalizörlerin kullanımına olan ilgi, doğal ürün sentezi boyunca karmaşık stereoseçiciliği sağlamadaki kapasitesilerine bağlı olarak ivme kazanmıştır. Bu çalışmada bir deniz metaboliti olan eunicellin'in iskeletini ve bazı doğal ürünlerde bulunan orta büyüklükteki halkalı eterlerin ikisini oluşturmak için moleküli Diels-Alder tepkimesinin kiral imidazolidinonlarla diastereoseçicilikteki kökeni araştırıldı. Diastereoseçiciliğin nedenini daha iyi anlayabilmek için, ilk olarak çalışılan tepkime halkasız öncül, yedi, sekiz ve dokuz üyeli tepkenlerin aldehit substituentli ve aldehit sübstituenti olmadan moleküli Diels-Alder tepkimesiydi. Siklokatılma tepkimesinin *endo* ve *ekzo* seçiciliği ve termal tepkimelerin hızları ayrıntılı olarak tartışılmıştır. İkinci olarak, üç halkalı çekirdeği sentezlemek için yedi üyeli halkanın organokatalizör kontrollü moleküli Diels-Alder tepkimesi incelendi. Son olarak, sekiz ve dokuz üyeli Diels-Alder modeli öncüllerinin siklokatılma tepkimeleri orta büyüklükteki halka kısıtlamalarının etkilerini rasyonelleştirmek ve moleküli Diels-Alder tepkimesinin kiral imidazolidinonlar ile diastereoseçicilikteki farkını aydınlatmak için ilaveten araştırıldı. Bu çalışmada, MacMillan Katalizörünün mekanizma ve tepkimenin seçiciliği üzerindeki etkisi Yoğunluk Fonsiyonları Teorisi (DFT) ile incelenmiş ve ayrıntılı bir biçimde tartışılmıştır.

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LIST OF SYMBOLS

$E^\ddagger$	Electronic activation energy
E_c^{VWN}	Vosko-Wilk-Nusair correlation functional
E_x^{exact}	Exact exchange energy
$E_c[\rho]$	Correlation energy
$E_x[\rho]$	Exchange energy
$G^\ddagger$	Gibbs free energy of activation
$J[\rho]$	Coulomb energy
$T[\rho]$	Kinetic energy of interacting electrons
$T_s[\rho]$	Kinetic energy of non-interacting electrons
U_x^σ	Exchange energy density
$V_{ee}[\rho(\mathbf{r})]$	Interelectronic interactions
$V_{ext}(\mathbf{r})$	External potential
V_{KS}	Kohn-Sham potential
ΔE_x^{B88}	Becke's gradient correction
ΔE_0	Relative electronic energy at 0 K
ΔE_{0+ZPE}	Sum of the change in electronic energy and zero point energy at 0 K
ΔH_{rxn}	Heat of reaction as electronic energy
$v(\mathbf{r})$	External potential
$\rho(\mathbf{r})$	Electron density
ψ_i	Kohn-Sham orbitals

LIST OF ACRONYMS/ABBREVIATIONS

B3LYP	Becke-3-parameter Lee-Yang-Parr functional
B88	Becke 88 Exchange Functional
BMK	Boese-Martin for Kinetics
DFT	Density functional theory
HF	Hartree-Fock theory
LDA	Local density approximation
M062X	Empirical exchange-correlation functionals

1. INTRODUCTION

1.1. Natural Products: Combinational Library

Natural products are compounds produced by living organisms. They have played a significant role in the development of organic chemistry. The major chemical and physical methods of structure elucidation have been developed during the study of natural products. Many reactions of mechanistic importance have their origins in this area of chemistry. Natural products have provided challenging synthetic targets, and their biological activity has given leads for the development of valuable medicines [1].

The interesting chemicals identified as natural products are derived from the phenomenon of biodiversity in which the interactions among organisms and their environment formulate the diverse complex chemical entities within the organism that enhance their survival and competitiveness. [2]. There are literally millions of natural chemical structure types resulting from nature's combinational chemistry effort supplying almost unimaginable chemical diversity. Importantly, nature has been "doing" combinational chemistry, not just for a decade or two, and has been selecting products from that combinational library that have specific biological advantage [3].

In recent years, the use of natural products for drug discovery has declined in favor of combinational methods and the rapid generation of large libraries of potential lead compounds. Natural products offer high potency and selectivity as a result of long evolutionary selection. Taking bioactive natural substances as a starting point, researchers can use the methods of organic synthesis to design targeted modifications of specific structures to create new therapeutic agents [4].

1.1.1. The Classes of Natural Product

Naturally occurring compounds may be divided into three broad categories. Firstly, there are those compounds which occur in all cells and play a central role in the metabolism and reproduction of those cells. These compounds include the nucleic acids and the common amino acids and sugars. They are known as primary metabolites. Secondly, there are the high-molecular-weight polymeric materials such as cellulose, the lignins and the proteins which form the cellular structures. Finally, there are those compounds that are characteristic of a limited range of species. These are secondary metabolites. Most primary metabolites exert their biological effect within the cell or organism that is responsible for their production. Secondary metabolites, on the other hand, have often attracted interest because of their biological effect on other organisms.

At first sight, the structures of secondary metabolites may seem to be confusingly diverse. However, the majority of these compounds belong to one of a number of families, each of which have particular structural characteristics arising from the way in which they are built up in nature, i.e. from their biosynthesis. The class of secondary metabolites are:

- Polyketides and fatty acids
- Terpenoids and steroids
- Phenylpropanoids
- Alkaloids
- Specialized amino acids and peptides
- Specialized carbohydrates [1]

1.1.1.1 Terpenes and Steroids

Terpenes are the largest group of phytochemicals that exhibit diverse functions in mediating antagonistic and beneficial interactions in, and among, organisms. For many years the abundance and distribution of terpenoid compounds in plants have benefitted both nature and human civilization [5].

The terpenes are compounds that are built up from isoprene units. Their structures are divisible into the C_5 isoprene units linked in a head-to-tail manner. This isoprene rule, developed by Ruzicka in 1921, provided a useful guide in structure determination.

The terpenes are classified by the number of these C_5 isoprene units that they contain. The classes are:

- Monoterpenoids, C_{10}
- Sesquiterpenoids, C_{15}
- Diterpenoids, C_{20}
- Sesterterpenoids, C_{25}
- Triterpenoids, C_{30}
- Carotenoids, C_{40}

Most of the terpenes have cyclic structures. The majority of the terpenoid cyclizations which take place in living systems are of an acid-catalyzed type. The branched chain nature of isoprenoid backbone coupled with readily protonated functional groups (e.g. alkenes) lend themselves to acid-catalysed rearrangements during the course of these biosynthetic reactions [1]. Terpenes are vital for life in most organisms exerting metabolic control and mediating inter and intra species interactions. Aside from the facts that, plants manufacture these compounds in response to herbivory or stress factors, it has also been shown that flowers can emit terpenoids to attract pollinating insects and even attract beneficial mites which feed on herbivorous insects [6, 7].

The steroids are derived from tetracyclic triterpenes and possess a cyclopentaperhydrophenanthrene backbone. The availability, crystallinity and well-defined conformation of the steroids have meant that they have become suitable substrates with which to investigate the influence of steric factors on reaction rates and mechanisms. Cholesterol forms an important constituent of lipid membranes and the more highly degraded steroids include the steroid hormones [1].

1.1.1.2. Eunicellin Based Diterpenoids

Diterpenoids are a widespread class of natural products that includes molecules of more than 20 structural types. They are produced mainly by plants, microorganisms, sea algae and sea invertebrates [8].

Soft corals are a rich source of bioactive molecules, such as terpenes, steroids and steroidal glycosides. Soft corals are widely distributed but have marked preference for tropical waters of a depth between 5 and 30 m than temperate reefs. The genera of *Sinularia*, *Lobophytum* and *Sarcophyton* are the most prolific soft corals, whereas species of *Cladiella* (Phylum: Coelenterata, Family: Alcyoniidae, Class: Anthozoa, Order: Alcyonacea) are found on reefs in the Indo-Pacific region [9].

The eunicellins, briarellins, asbestinins, and sarcodyctins are related subclasses of the C₂-C₁₁-cyclized cembranoid diterpenes isolated as secondary metabolites of gorgonian octocoral found in the Caribbean and West Pacific Ocean [10-12].

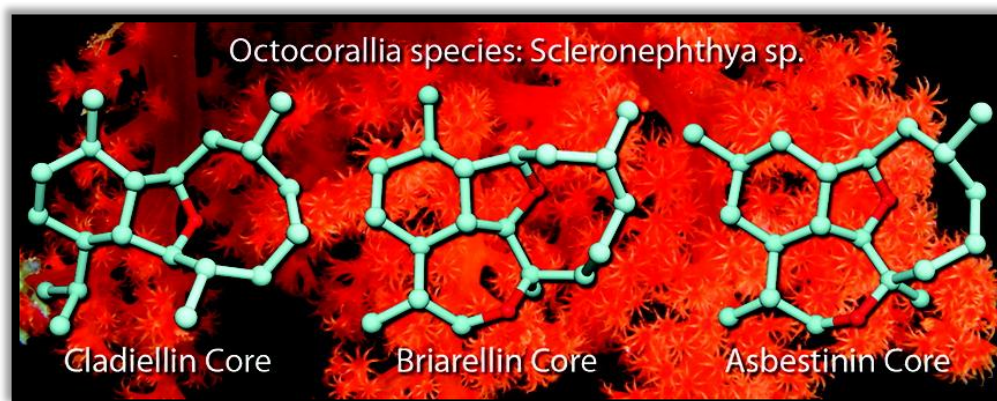


Figure 1.1. The 2-11-Cyclized Cembranoids: Cladiellin, Asbestinin and Briarellin Core.

Eunicellin diterpenes are a family of marine metabolites obtained from gorgonian and soft corals. The eunicellin diterpenes are characterized by a unique tricyclic ring system containing hydroisobenzofuran and oxonane subunit [13]. Eunicellin 1, the first member of this family to be described, was isolated in 1968 by Djerassi, Kennard, and co-workers

from the coral *Eunicella stricta* [14]. The original report of the isolation of eunicellin, extensive investigation of gorgonian soft coral has resulted in the isolation of over 50 novel secondary metabolites in the class [15].

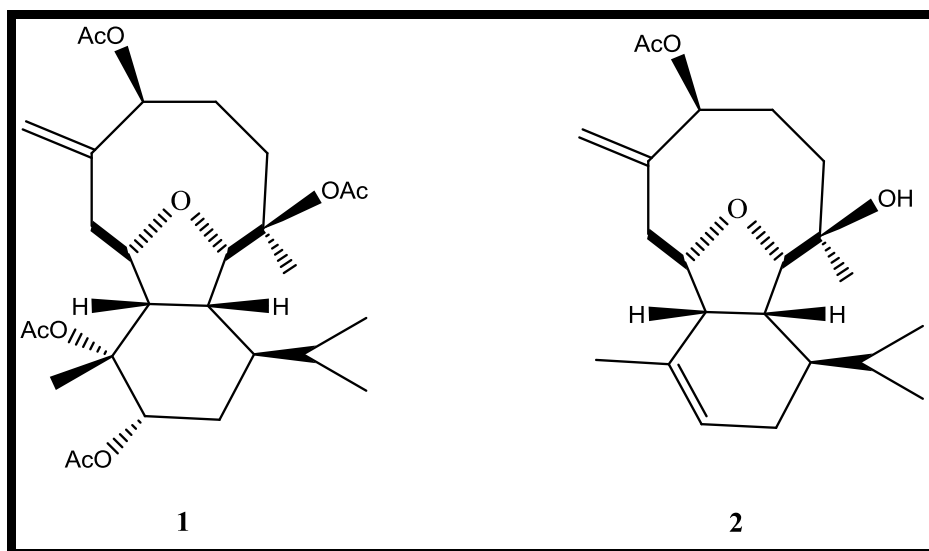


Figure 1.2. Chemical Structure of Eunicellin **1** and (-)-7-deacetoxyalcyonin acetate **2**

Interest in the chemical synthesis of members of these subclasses has piqued in recent years due to their novel structures and diverse biological activities [16-18]. The first total synthesis of a eunicellin diterpene was the synthesis of (-)-7-deacetoxyalcyonin acetate **2** reported by Overman in 1995 [13].

Eunicellin based diterpenoids were found to display a wide range of bioactivities including anti-inflammatory and antitumor activities [11, 19-25].

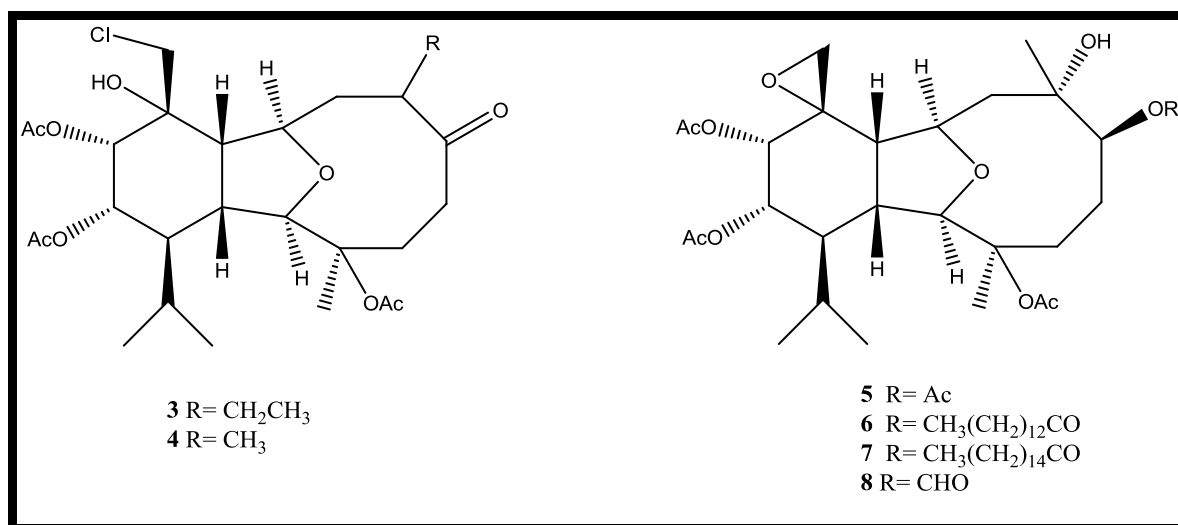


Figure 1.3. Six new eunicellin based diterpenoids isolated from the soft coral *Klyxum molle* [23].

1.2. The Diels -Alder Reactions

The Diels-Alder cycloaddition is the best known organic reaction that is widely used to construct, in region- and stereo-controlled way, a six membered ring with up to four stereogenic centers. The reaction is classified as a $[\pi 4_s + \pi 2_s]$ cycloaddition; 4 and 2 identify both the number of π electrons involved in the electronic rearrangement and the number of atoms originating the unsaturated six-membered ring. The subscript s indicates that the reaction takes place suprafacially on both components. There are other $[\pi 4_s + \pi 2_s]$ reactions, and therefore it is the term Diels-Alder which specifies this particular type of reaction [26].

The Diels-Alder reaction, is a cycloaddition reaction of a conjugated diene with a double or triple bond (the dienophile). For instance an electron rich diene **9** reacts with an electron poor dienophile **10** (e.g. an alkene bearing an electron-withdrawing substituent Z) to yield the unsaturated six-membered product **11**. An illustrative example is the reaction of butadiene **9** with maleic anhydride **12** [27].

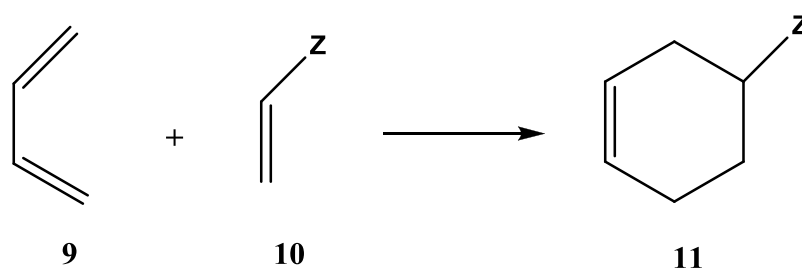


Fig 1.4. [4 + 2] Cycloaddition of diene **9** and dienophile **10** [27].

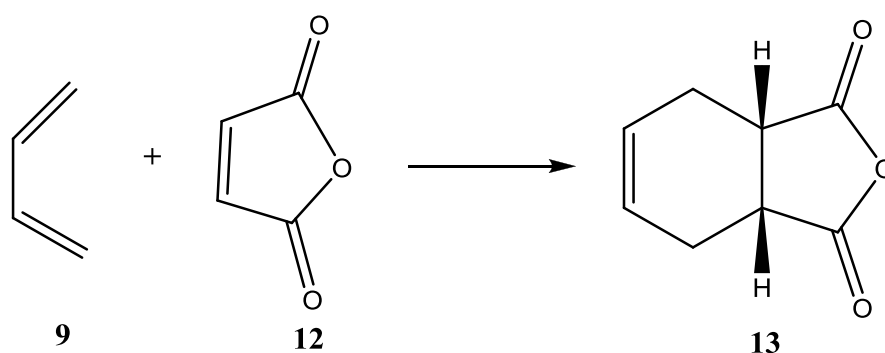


Figure 1.5. The reaction of butadiene **9** with maleic anhydride **12** [27].

The Diels-Alder reaction of a diene with a substituted olefinic dienophile, e.g. **14** and **15** can go through two geometrically different transition states. With a diene that bears a substituent as a stereochemical marker, the two different transition states lead to diastereomeric products which differ in the relative configuration at the stereogenic centers connected by newly formed σ - bonds. The respective transition state as well as the resulting product is termed with prefixes *endo* or *exo*. For example, when cyclopentadiene **14** is treated with acrylic acid **15**, the *endo* product **16** and the *exo* product **17** can be formed. Formation of the *endo* product **16** is kinetically favoured by secondary orbital interactions [28-30]. Under kinetically controlled conditions it is the major product, and the thermodynamically more stable *exo* product **17** is formed in minor amounts only [27].

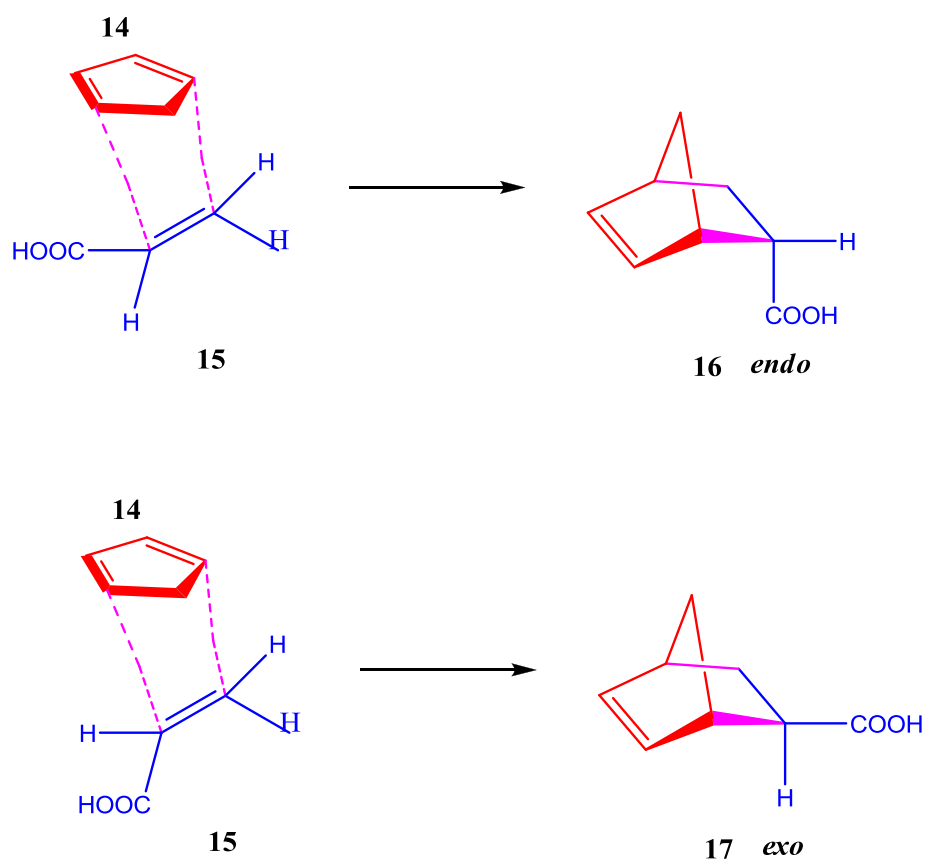


Figure 1.6. The *endo* and *exo* approach in the Diels-Alder Reaction

For most Diels-Alder reactions a concerted mechanism as described above, is generally accepted. If both bonds are formed to exactly the same extent in the transition state, this is called a synchronous concerted reaction; otherwise it is asynchronous [28]. In some cases, the kinetic data may suggest the intermediacy of a diradical intermediate [29]. Furthermore, in certain cases Diels-Alder reactions may proceed by an ionic mechanism [30].

1.2.1. Catalytic Asymmetric Diels Alder Reaction: IMDA (Intramolecular Diels-Alder) Variation

A Diels-Alder reaction can also take place intramolecularly when a molecule incorporates both the diene and dienophile moieties which are connected by a chain [31]. The first reports on the IMDA (Intramolecular Diels-Alder) reaction appeared in the fifties and sixties and were based upon the desire to produce polycyclic structures incorporating this cycloaddition as the key step [32].

The asymmetric Diels-Alder reaction was first investigated more than 40 years ago by introducing a removable chiral auxiliary on the dienophile [33-35]. The ability to generate simultaneously up to four chiral centers in a highly stereoselective and largely predictable fashion has resulted in its applications to numerous synthetic challenges, often difficultly accessible by other means [36]. Over the last 25 years, considerable research efforts have been directed toward the development of enantioselective catalytic variants of the Diels-Alder reaction [37]. During this time, remarkable advances in both catalyst design and substrate tolerance have been accomplished within the intermolecular class of [4 + 2] cycloadditions [38-42]. In contrast, few catalysts have been reported that achieve high levels of enantiocontrol in the intramolecular Diels-Alder (IMDA) reaction [43,44].

In 1999, MacMillan's laboratory introduced a new strategy for asymmetric synthesis based on the capacity of chiral amines to function as enantioselective for a range of transformations, including Diels-Alder and IMDA variation [45].

1.2.1.1. MacMillan Imidazolidinone OrganoCatalysts: Iminium Activation. Iminium catalysis was the first organocatalytic activation mode to be designed and introduced as a general strategy for asymmetric organic synthesis. It is based on the capacity of chiral amines to function as enantioselective catalysts for several transformations that traditionally use Lewis acid catalysts. The concept was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α , β -unsaturated aldehydes

and amines might emulate the equilibrium dynamics and π -orbital electronics that are inherent to Lewis acid catalysis [46].

This strategy, termed iminium activation, was founded on the mechanistic postulate that (i) the LUMO-lowering activation and (ii) the kinetic lability towards ligand substitution that enable the turnover of Lewis acid catalysts might also be available with a carbogenic system that exists as a rapid equilibrium between an electron-deficient and relatively electron rich state.

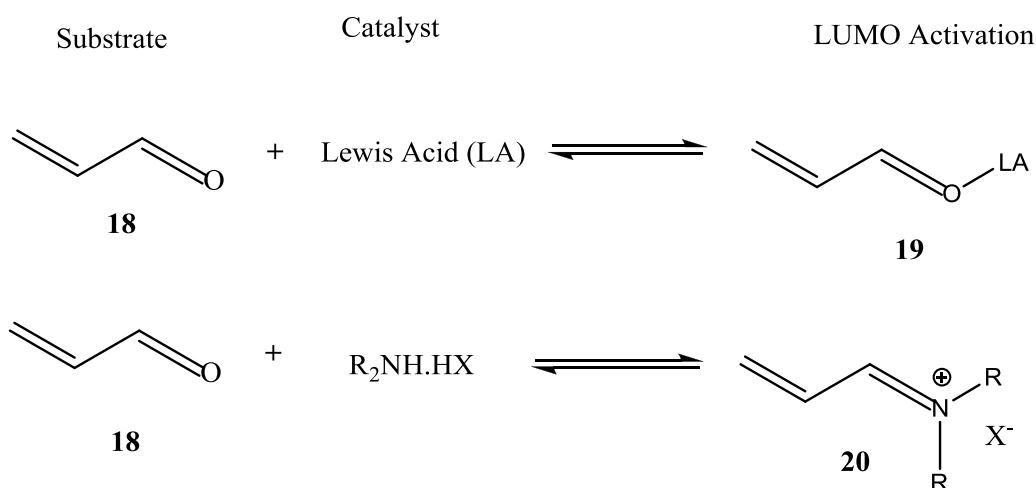


Figure 1.7. LUMO Activation through LUMO Lowering.

Another important application of iminium catalysis concept concerned the development of enantioselective intramolecular Diels-Alder reactions. For these transformations both catalyst **21** and **22** proved to be highly efficient, affording bicyclic aldehyde products in good yields and with excellent enantio- and diastereoselectivities [47].

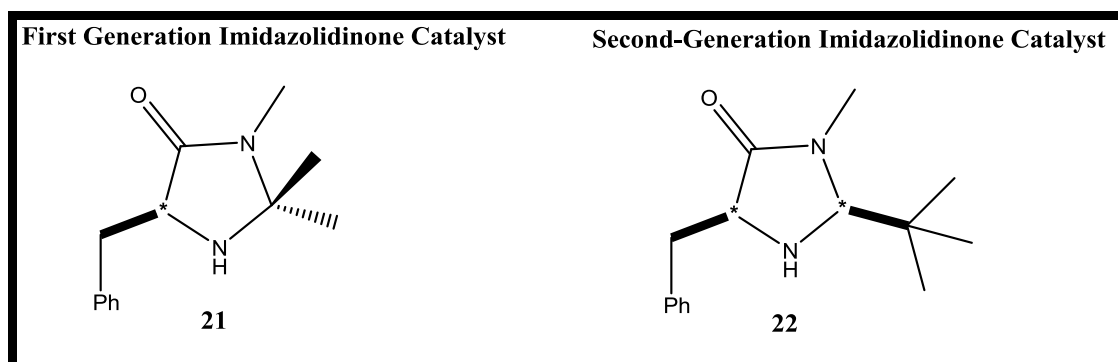


Figure. 1.8. Chemical structures of first- and second- generation imidazolidinone catalyst [47].

2. AIM OF THE STUDY

Pharmaceutical discovery is a numbers game. Thousands of chemicals must be evaluated to find a hit. Natural products are one of the most reliable source of new therapeutic entities. Especially, marine secondary metabolites are on considerable interest due to the highly diversified structures and wide range of biological activities. One of the main stimuli to study marine metabolites, in particular diterpenoids, is no doubt the search for molecules that not only have a high biological activity, but also supplement databanks used for designing new structures.

The eunicellin-based diterpenoids are secondary metabolites that have been shown to exhibit cytotoxic activity against the growth of various cancer cell lines. Cancer chemotherapy, in particular, presents an ideal opportunity for natural product-inspired drug discovery and development. Unfortunately, many of the most promising natural lead compounds are available only in extremely small quantities. Most of the secondary metabolites, eunicellins, have cyclic structures. Intramolecular Diels-Alder reaction is arguably one of the most forceful methods to synthesize these cyclic structures. However, stereocontrol of the reaction is quite tricky. Chiral imidazolidinones are a remarkable platform to build this complex multi-stereogenic architecture. In this respect, understanding the origin of the diastereoselectivity of the reaction is significant. The present study attempts to address the origins of diastereoselectivity of the intramolecular Diels-Alder reaction of nine membered ring (the core of eunicellin) and also eight and seven membered rings which are widely found in marine metabolites, catalyzed by chiral imidazolidinones to further investigate the medium size effect on the diastereoselectivity of the reaction. The results of this study will encourage the organic chemists to synthesize this class of biologically active marine diterpenoids and their new classes, and also to design new set of imidazolidinones.

3. COMPUTATIONAL DETAILS

3.1. Density Functional Theory

Kohn-Hohenberg theorems proposed in 1964 [48-49] are the basic idea of the density functional theory (DFT) [50] which is the quantum mechanical approach of the electronic structure of atoms and molecules. The first theorem states that the electron density $\rho(\mathbf{r})$ determines the external potential $V_{\text{ext}}(\mathbf{r})$ and the second theorem introduces the variational principle. As a result, the electron density can be computed variationally and the position of nuclei, energy, wave function and other related parameters can be calculated [50-51].

The electron density is defined as:

$$\rho(x) = N \int \cdots \int |\Psi(x_1, x_2, \cdots, x_n)|^2 dx_1 dx_2 \cdots dx_n \quad (3.1)$$

where x represents both spin and spatial coordinates of electrons.

The theorem indicates that this density determines a candidate wavefunction and Hamiltonian. That being the case we can evaluate the energy expectation value

$$\langle \Psi_{\text{cand}} | H_{\text{cand}} | \Psi_{\text{cand}} \rangle = E_{\text{cand}} \geq E_0 \quad (3.2)$$

which, by variational principle of the MO theory, must be greater than or equal to the true ground-state energy [52].

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

$$E[\rho] = \int v(r)\rho(r)dr + T[\rho] + V_{ee}[\rho] \quad (3.3)$$

where $T[\rho]$ is the kinetic energy of the interacting electrons and $V_{ee}[\rho]$ is the interelectronic interaction energy. The electronic energy may be rewritten as

$$E[\rho] = \int v(r)\rho(r)dr + T_s[\rho] + J[\rho] + E_{xc}[\rho] \quad (3.4)$$

with $J[\rho]$ being the coulomb energy, $T_s[\rho]$ being the kinetic energy of the non-interacting electrons and $E_{xc}[\rho]$ being the exchange-correlation energy functional. The exchange-correlation functional is expressed as the sum of an exchange functional $E_x[\rho]$ and a correlation functional $E_c[\rho]$, although it contains also a kinetic energy term arising from the kinetic energy difference between the interacting and non-interacting electron systems. The kinetic energy term, being the measure of the freedom, and exchange-correlation energy, describing the change of opposite spin electrons (defining extra freedom to an electron), are the favorable energy contributions. The Coulomb energy term describes the unfavorable electron-electron repulsion energy and therefore disfavors the total electronic energy [53].

The discussion above has revealed that the density determines the external potential, which determines the Hamiltonian, which determines the wave function in hand, the energy can be computed. However, the difficulty derives from the electron-electron interaction term in the correct Hamiltonian. In the language of DFT, electrons interact with one another and with an “external potential”. In 1965, Kohn and Sham realized that things would be considerably simpler if only the Hamiltonian operator one for a non-interacting system of electrons.

In 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. The energy functional divided into specific components to facilitate further analysis, in particular

$$E[\rho(r)] = T_{ni}[\rho(r)] + V_{ne}[\rho(r)] + V_{ee}[\rho(r)] + \Delta T[\rho(r)] + \Delta V_{ee}[\rho(r)] \quad (3.5)$$

where the terms on the Equation 3.5 refer, respectively, to the kinetic energy of the non-interacting electrons, the nuclear-electron interaction, the classical electron-electron repulsion, the correction to the kinetic energy deriving from interacting nature of the electrons, and all non-classical corrections to the electron-electron repulsion energy [52].

Within an orbital expression for the density, Equation 3.5 may then be rewritten as

$$E[\rho(r)] = \sum_i^N \left(\langle X_i | -\frac{1}{2} \nabla_i^2 | X_i \rangle - \langle X_i | \sum_k^{nuclei} \frac{Z_k}{|r_i - r_k|} | X_i \rangle \right) + \sum_i^N \langle X_i | \frac{1}{2} \int \frac{\rho(r')}{|r_i - r'|} dr' | X_i \rangle + E_{xc}[\rho(r)] \quad (3.6)$$

where N is the total number of electrons and the density has been used for a Slater determinantal wave function which is an eigenfunction for the non-interacting system

$$\rho(r) = \sum_i^N |\psi_i|^2 \quad (3.7)$$

if the exact form of the exchange-correlation functional is known. It should be noted that the difficult terms ΔT and ΔV_{ee} have been lumped together in a term E_{xc} , typically referred to as the exchange-correlation energy. 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, 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. The energy expression is

$$E[\rho] = T_s[\rho] + \int \rho(r) V(r) dr + J[\rho] + E_{xc}[\rho] + E_b \quad (3.8)$$

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 [48]

$$E[\rho] = T_s[\rho] + E_{xc}[\rho] \quad (3.9)$$

$$E[\rho] = T_s[\rho] + E_x[\rho] + E_c[\rho] \quad (3.10)$$

Among the ever increasing number of DFT methods, the hybrid functional B3LYP [54] first developed to study vibrational absorption and circular dichroism, has become a standart method to study organic chemistry in gas phase. This functional is a hybrid of exact (Hartree-Fock) exchange with local and gradient-corrected exchange and correlation terms as first suggested by Becke [55]. B3LYP model is defined by

$$E_{xc}^{B3LYP} = (1 - a)E_x^{LSDA} + aE_x^{HF} + b\Delta E_x^B + (1 - c)E_c^{LSDA} + cE_c^{LYP} \quad (3.11)$$

where a , b , and c were optimized to, based on fitting to heats of formation of small molecules, 0.20, 0.72 and 0.81, respectively.

The continued development of improved exchange-correlation functional is essential for expanding applicability of Kohn-Sham density functional theory (DFT). Much progress has been made, primarily due to the exploitation of kinetic energy density and systematic optimization of exchange-correlation functional against broad and diverse databases [56-61].

The highly parametrized empirical exchange correlation functional, M05-2X and M06-2X [62] developed by Zhao and Truhlar have been shown to describe noncovalent interactions better than functionals which are currently in common use. In the design of these functionals they had the goal or objective that specifies the area or areas of application for which it is designed. Five broad areas which they refer are;

- TC: main group chemistry
- BH: barrier heights
- NC: noncovalent interactions
- ES: electronic spectroscopy and
- TM: transition metal bonding.

The M06 and M06-2X are hybrid meta exchange-correlation functionals. In particular, the hybrid exchange-correlation energy can be written as follows:

$$E_{xc}^{hyb} = \frac{X}{100} E_X^{HF} + \left(1 - \frac{X}{100}\right) E_X^{DFT} + E_C^{DFT}$$

where E_X^{HF} is the nonlocal Hartree-Fock (HF) exchange energy, X is the percentage of Hartree-Fock exchange in the hybrid functional, E_X^{DFT} is the local DFT exchange energy, and E_C^{DFT} is the local correlation energy [62].

The M06-2X functional is recommended for main group thermochemistry and kinetics; for systems where main group thermochemistry, kinetics and non-covalent interactions are all important. However, B3LYP functional, which is a hybrid GGA, does have unsatisfactory performance issues: B3LYP approach fail in locating minima on the potential energy surfaces for π - π stacking interactions, which are one of the most important non-covalent interactions in biological systems, while M06 and M06-2X functional of Zhao and Truhlar offer good performance for π - π stacking energies. B3LYP was found to underestimate barrier heights. It is also unable to describe van der Waals complexes bound by medium range interactions. Another point is that, B3LYP has been found to give unreliable results for transition metal chemistry [62-64].

M06-2X is used for single point calculations by Houk *et. al.* in computational investigation of Diels-Alder reactions to deliver more accurate medium-range correlation effects [65-66].

3.2. Continuum Solvation Models

Continuum solvation models are the most efficient way to include condensed-phase effects into quantum mechanical calculations [67]. The advantage of these models is that they decrease the number of the degrees of freedom of the system by describing them in a continuous way, usually by means of a distribution function [68-70]. In continuum solvation models, the solvent is represented as a polarizable medium characterized by its static dielectric constant ϵ and the solute is embedded in a cavity surrounded by this dielectric medium. The total solvation free energy is defined as

$$\Delta G_{\text{solvation}} = \Delta G_{\text{cavity}} + \Delta G_{\text{dispersion}} + \Delta G_{\text{electrostatic}} + \Delta G_{\text{repulsion}} \quad (3.19)$$

where ΔG_{cavity} is the energetic cost of placing the solute in the medium. Dispersion interactions between solvent and solute are expressed as $\Delta G_{\text{dispersion}}$ which add stabilization to solvation free energy. $\Delta G_{\text{electrostatic}}$ is the electrostatic component of the solute-solvent interaction energy. $\Delta G_{\text{repulsion}}$ is the exchange solute-solvent interactions not included in the cavitation energy.

Polarizable Continuum Model (PCM) belongs to the class of polarizable continuum solvation models [71]. In 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 radii 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. There are three different approaches to carry out PCM calculations. The original method is called Dielectric PCM (D-PCM), the second model is the Conductor-like PCM (C-PCM) [72] in which the surrounding medium is modeled as a conductor instead of a dielectric, and the third one is an implementation whereby the PCM equations are recast in an integral equation formalism (IEF-PCM).

4. ORIGINS OF DIASTEREOSELECTIVITY IN ACYCLIC PRECURSOR, SEVEN, EIGHT AND NINE MEMBERED RING MODELS

Intramolecular cycloadditions are powerful methods to synthesize poly-cyclic natural products that often resulted in high yields and good regio- and stereoselectivities. In the light of this repertoire, we present a computational investigation for the *endo/exo* stereochemical outcome of the intramolecular cycloadditions of three medium ring ethers that are found in marine natural products. The origins of diastereoselectivity of seven, eight and nine membered ring models catalyzed by chiral imidazolidinones have been assessed with density functional methods. Firstly, the intramolecular Diels-Alder reaction of acyclic precursor is investigated. After that, the diastereoselective preference of all rings is studied. The rate of thermal cycloaddition, and the effect of aldehyde substituent has also been considered. Organocatalytic Intramolecular Diels-Alder reaction of all ring models with (R)- and (S)- enantiomers of MacMillan's Catalyst has been taken into account. Preferred conformations of transition structures and reaction intermediates have been located. The different reactivities and diastereoselectivities stemmed from medium rings and two chiral imidazolidinones are rationalized.

4.1. Introduction

The introduction of specific chirality into organic synthesis using metal-free chiral organocatalysts has attracted great interest in recent years [73-75]. In 2000, MacMillan and coworkers reported the first highly enantioselective Diels-Alder reaction of cyclopentadiene with α,β -unsaturated aldehydes catalyzed by chiral imidazolidinone 21, derived from phenylalanine. The authors demonstrated the power of the reaction by using a variety of aldehydes with good yield and enantioselectivity.

Catalyst 21 was also successful for 1,3-dipolar cycloaddition reactions between nitrones and α,β -unsaturated aldehydes [76], alkylation reactions of pyrroles by olefinic aldehydes [77] and α -chlorination of aldehydes [78].

For asymmetric alkylations of indoles, enantioselectivities were improved by using 22 [79]. In 2004, MacMillan *et. al.* reported the enantioselective synthesis of (-)-flustrami-

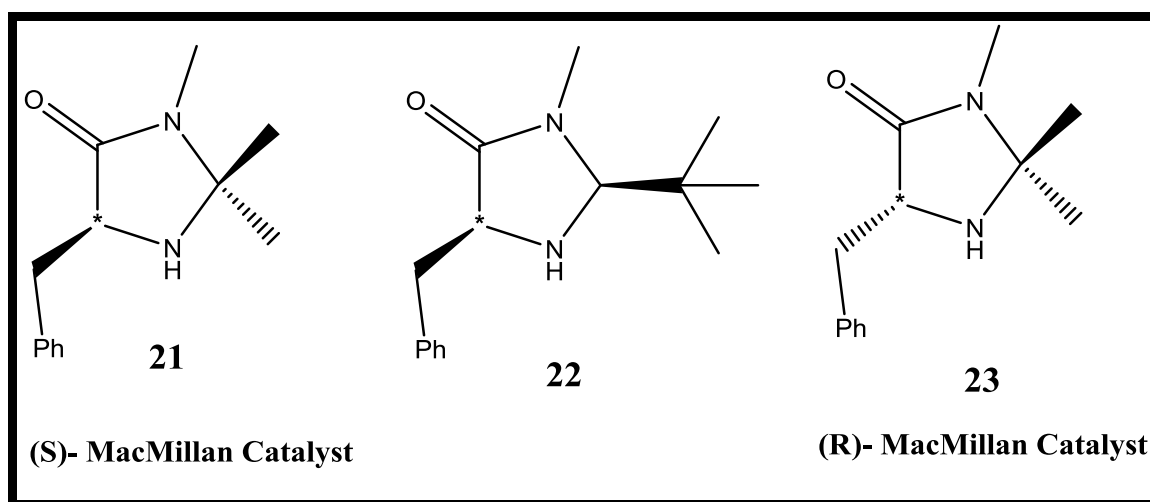


Figure 4.1. Chemical structures of chiral imidazolidinone organocatalysts.

ne B, by using 6-bromotryptamine and acrolein as starting materials and compound 22 as organocatalyst [80]. Imidazolidinone 22 was, also used for aldehyde-aldehyde aldol reactions by the same research group [81]. In 2005, MacMillan's laboratory demonstrated the utility of catalysts 21 and 22 via the total synthesis of the marine metabolite solanapyrone D [82].

In 2004, Holmes's group synthesized the skeleton of Eunicellin based on the use of an intramolecular Diels-Alder reaction of nine-membered ether. Under the conditions employed 9-r-PRO-ter underwent an in situ intramolecular Diels-Alder reaction to afford two diastereomeric tricyclic adducts in a 3:1 *endo:exo* ratio and a combined overall yields of %84 [83]. In 2007, the same laboratory applied the new organocatalytic technology to construct the tricyclic core of eunicellin which is a marine diterpenoid. The synthesis featuring diastereoselective Diels-Alder reaction as one of the key steps, resulted with desired diastereoselectivity depending on the enantiomer of the organocatalyst used; (S)

enantiomer 21 afforded predominantly the *exo*-adduct corresponding to the natural stereochemistry of this nine membered compound, whereas the (R)-enantiomer, 23, favoured the *endo*-adduct [84] (See Figure 4.2 and Table 4.1).

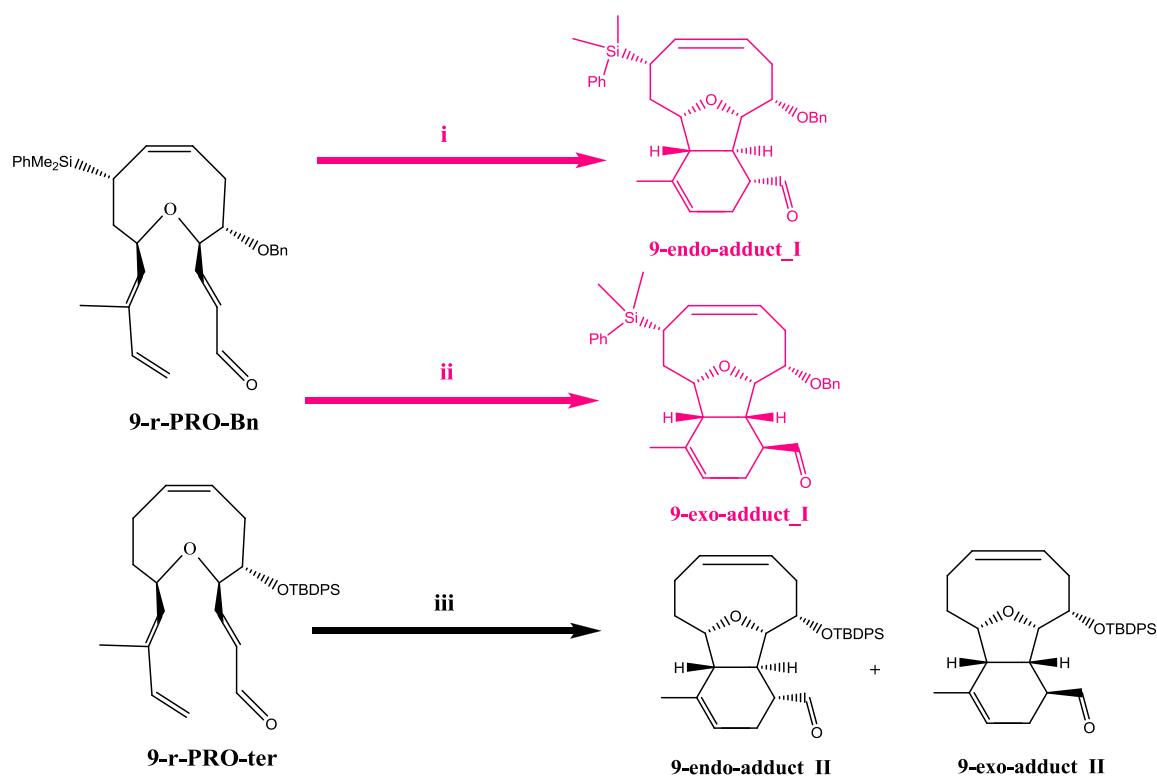


Figure 4.2. Intramolecular Diels-Alder Reaction of nine membered ring with/without organocatalyst.

Table 4.1. Intramolecular Diels-Alder Cycloaddition's experimental results for the nine membered ring with/without chiral imidazolidinones.

	Conditions	Yield	Endo/Exo
i	(R)-MacMillan.HCl, MeCN/H ₂ O	62%	15:1
ii	(S)-MacMillan.HCl, MeCN/H ₂ O	67%	0:100
iii	heat	84%	75:25

In 2009, Joel Hooper carried out an experimental study to further explore the effects of medium-ring constraints on the intramolecular Diels-Alder reaction by using

chiral imidazolidinones. According to his results, intramolecular Diels-Alder reaction of seven membered ring produced the *endo*-adduct exclusively with both enantiomers of the organocatalyst and without catalyst. On the other hand, the treatment of eight membered ring with (R)-imidazolidinone favoured the *endo* product while the (S)-enantiomer gave a mixture 1:1 of the *endo/exo* products (See Figure 4.3 and Table 4.2) [85].

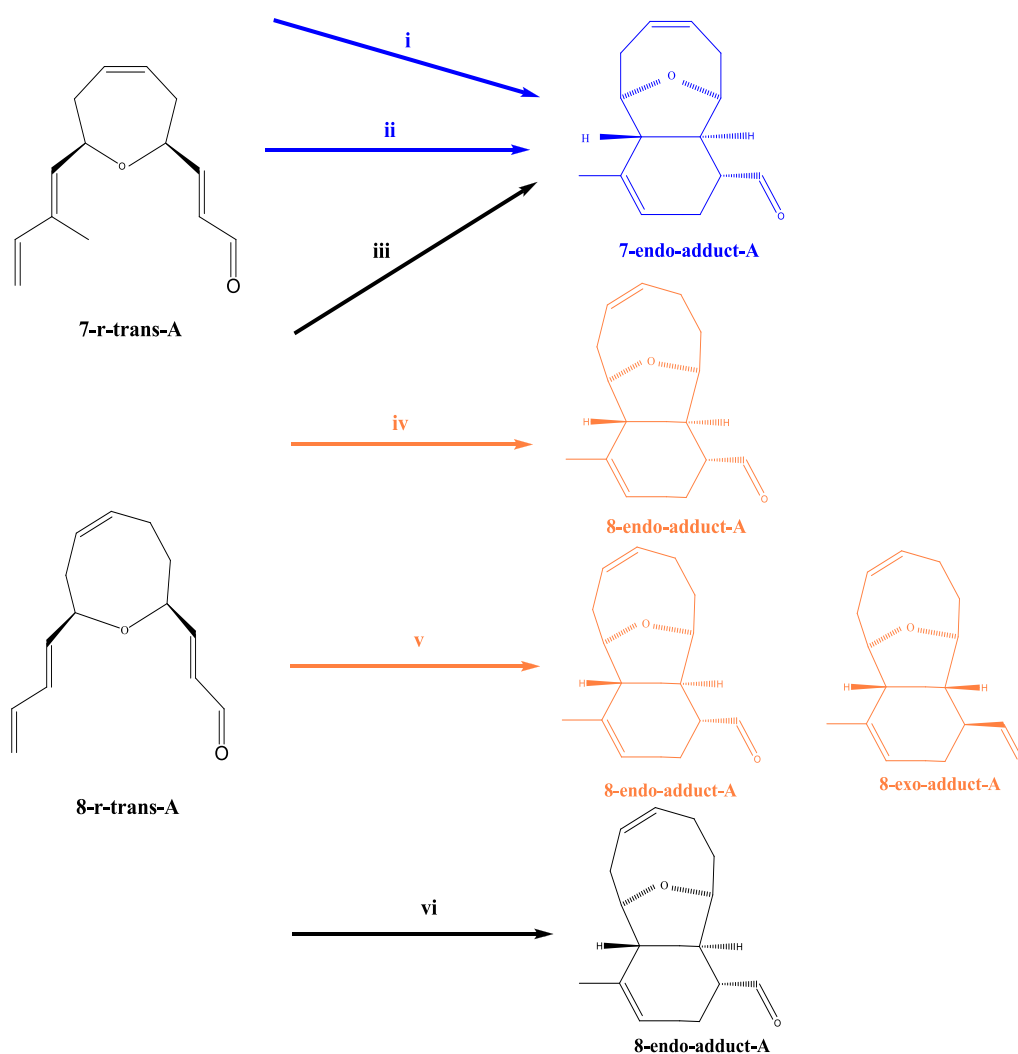


Figure 4.3. Intramolecular Diels-Alder reactions of seven and eight membered rings with/without organocatalyst.

With the aim to adjust the *endo* bias derived from rings' structures and secondary chiral amines as organocatalysts, the transition structures corresponding to uncatalyzed

intramolecular Diels-Alder reaction of all ring models and acyclic precursor have been also computed.

Table 4.2. Intramolecular Diels-Alder Cycloaddition's experimental results for the seven and eight membered rings with/without chiral imidazolidinones.

	Conditions	Yield	Endo/Exo
i	(R)-MacMillan.HCl, TFA, MeCN/H ₂ O, -15 C°, 7h	61%	100:0
ii	(S)-MacMillan.HCl, TFA, MeCN/H ₂ O, -15 C°, 7h	63%	100:0
iii	Rt, 24h, CDCl ₃	50%	100:0
iv	(R)-MacMillan.HCl, TFA, MeCN/H ₂ O, 0 C°, 24h	65%	100:0
v	(S)-MacMillan.HCl, TFA, MeCN/H ₂ O, 0 C°, 24h	72%	50:50
vi	100 C°, 3h, microwave	40%	2.5:1

4.2. Computational Methods

Gaussian 09 [50] is used to perform all DFT calculations. The geometries of reactants and transition states were optimized using the B3LYP/6-31+G(d) and M06-2X/6-311+G** for uncatalyzed reactions, and the B3LYP functional with 6-31+G(d) basis set for all organocatalyzed reactions. The solvent effects were considered by single points calculations on the gas phase stationary points with the polarizable continuum model (Conductor-like PCM). Chloroform, toluene, water and acetonitrile were the solvents. The solute surface was defined as Pauling radii in each case. The thermodynamic corrections were computed at 298 K. Relevant distances are given in angstroms. All calculated reaction barriers given in tables are in kcal/mol and relative Gibbs free energies for the gas phase are shown in parentheses.

Frequency analysis has been performed in order to identify the nature of the stationary points and also to have zero point energies and thermal corrections. Transition states were identified by the presence of a single imaginary vibrational frequency.

The population of diastereoisomers has been evaluated by using the Boltzmann distribution at room temperature. In the Boltzmann distribution equation:

$$\frac{n_b}{n_a} = e^{-\frac{\Delta(\Delta G^\ddagger)}{RT}} \quad (4.1)$$

$\Delta(\Delta G^\ddagger)$ is the energy difference between diastereomer A and diastereomer B in terms of Gibbs free energies, R is the Boltzmann constant and T is the temperature.

4.3. Uncatalyzed Intramolecular Diels-Alder Reaction of Acyclic Precursor with and without Aldehyde Substituent.

In this part, the intramolecular Diels-Alder reaction is explored without ring in order to gain better insight in terms of diastereoselectivity (Figure 4.4 and 4.5). The effect of aldehyde substituent is also assessed. The expected four diastereoisomers of all reactions are optimized, however only the ones whose relative Gibbs free energies are up to 5 kcal/mol are included.

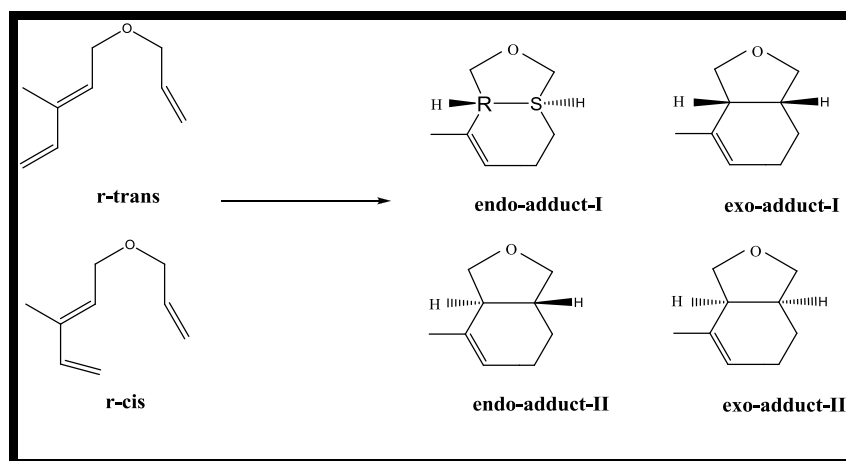


Figure 4.4. Reaction 1: Cycloaddition reaction of acyclic precursor without aldehyde substituent.

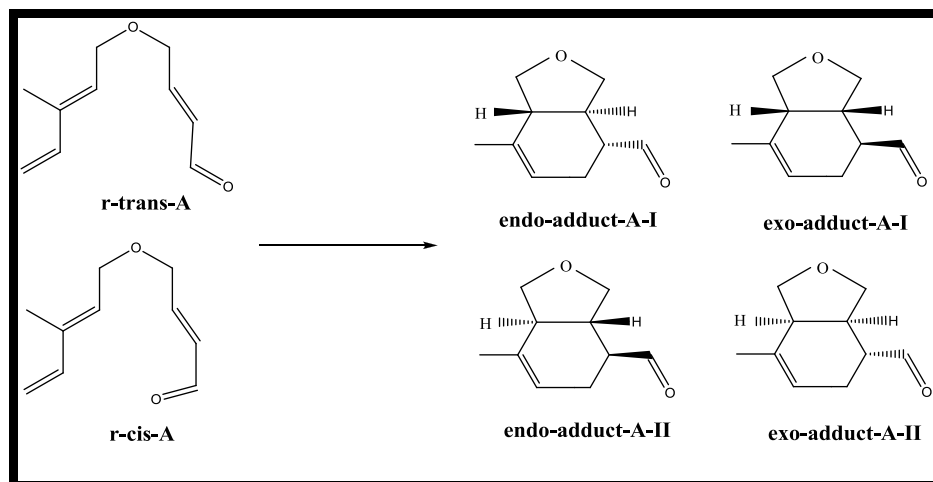


Figure 4.5. Reaction 2: Cycloaddition reaction of acyclic precursor with aldehyde substituent.

4.3.1. Thermal Cycloaddition of Acyclic Precursor

Figure 4.7 and 4.8 show the *cis*- and *trans*- conformers of acyclic precursor and their endo- and exo- transition structures. The *trans* isomer of the diene and the dienophile is more stable than the *cis*- isomers, by 2.2 and 2.0 kcal/mol respectively. The *cis* isomer of diene is not preferred due to the close H-H distance: 2.45 Å (Figure 4.7). The energy difference between the *cis*- and *trans*- isomers of dienophile can be attributed to the torsional strain which originates from the eclipsing C-H bonds as illustrated below.

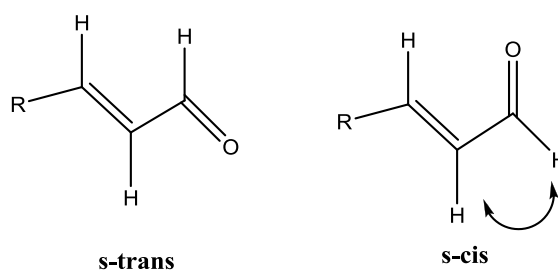


Figure 4.6. *s-cis* and *s-trans* isomers of unsaturated aldehyde.

For the reaction of the acyclic precursor without aldehyde substituent the *endo:exo* ratio is predicted 73:27 while it is 98:2 for the reaction with aldehyde substituent in gas phase.

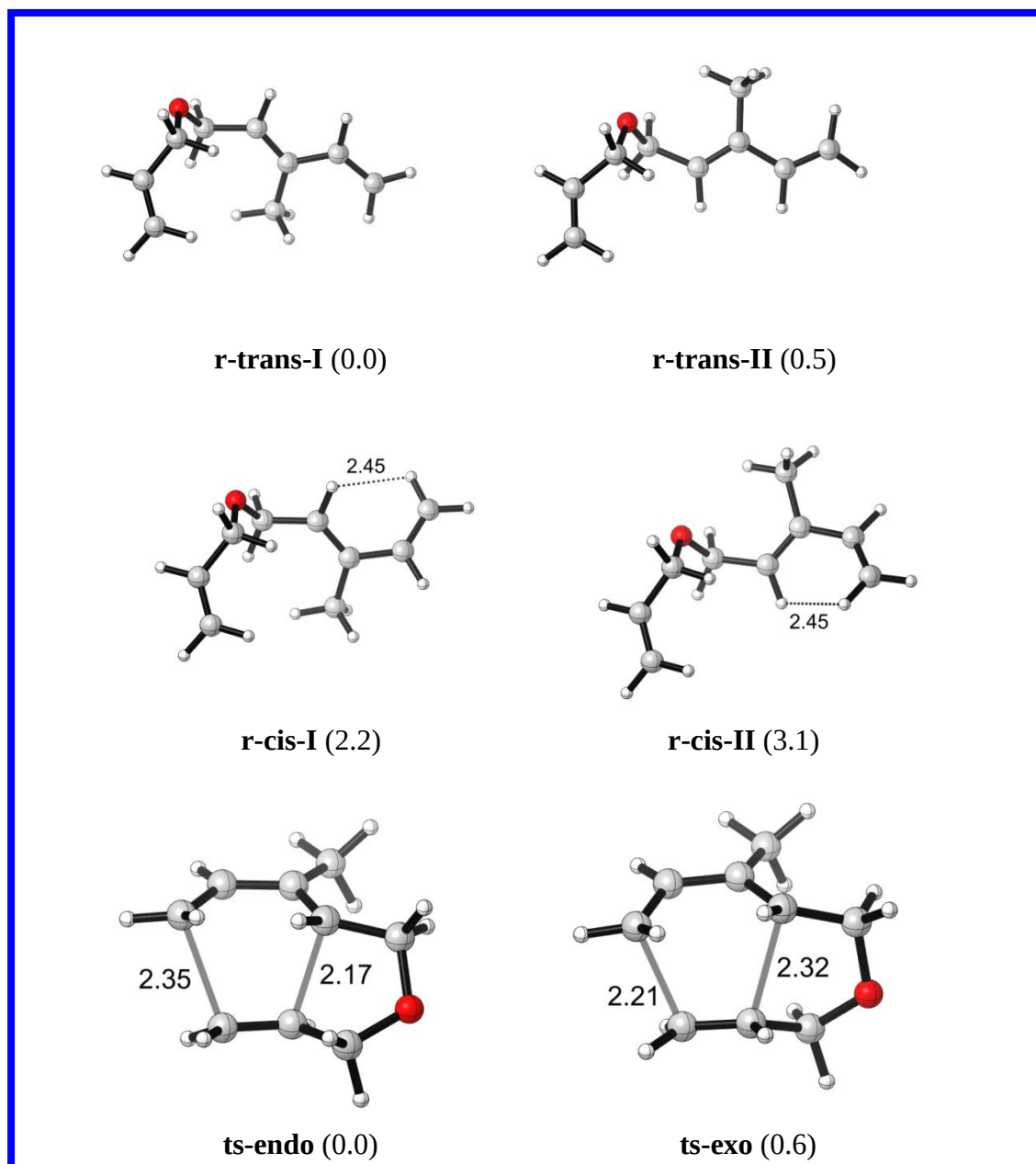


Figure 4.7. Acyclic precursor's conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent.

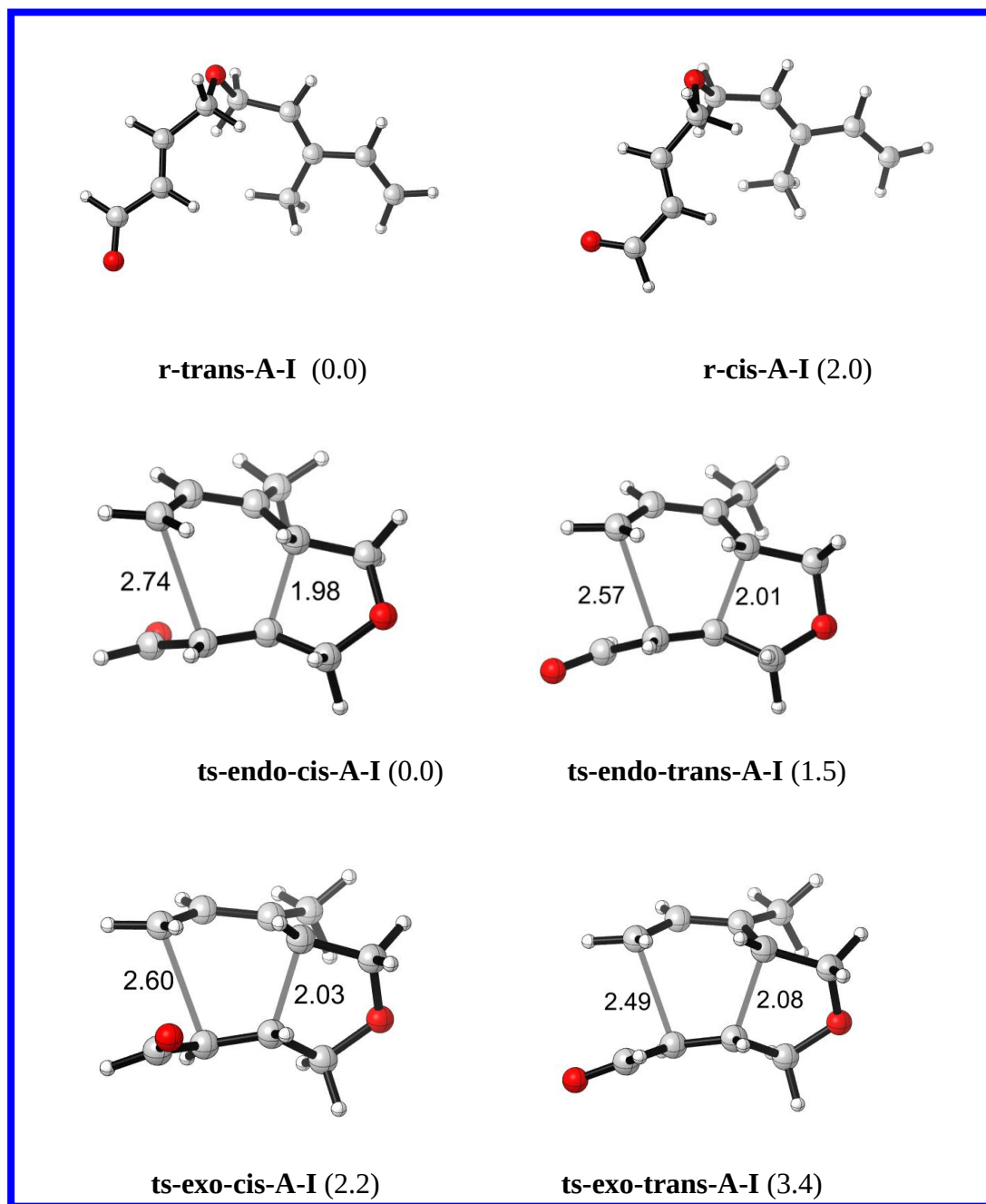


Figure 4.8. Acyclic precursor's conformers and calculated transition structures for intramolecular Diels-Alder reaction with aldehyde substituent.

Although several reasonable suggestions have been proposed to explain the observed *endo* selectivity in cycloaddition reactions, one of the most popular explanations attributes

the *endo* preference to secondary pi-orbital overlap in the transition state [86-88]. In the *endo* TS the dienophile is oriented toward the pi orbitals of the diene. In this study, the reason of *endo* preference may be the existing SOI between the pi orbital of diene and ester's ring oxygen, and interaction between the aldehyde substituent and pi electrons of diene in the HOMO (Figure 4.9).

B3LYP/6-31+G(d) calculations predict that the activation energies are lowered by substitution with the aldehyde group. The overall increase of *endo* selectivity can be clarified with the effect of electron withdrawing aldehyde substituent which makes frontier orbital interactions dominant. It is known that conjugating substituents compress the frontier orbital separation and electron withdrawing substituents lower frontier orbital energies [89]. Aldehyde is a conjugating and electron withdrawing substituent so that the overall lowering the HOMO is much less than of the LUMO. The HOMO-LUMO separation is minimized (Figure 4.9).

Table 4.3. Calculated Energy barriers for the intramolecular Diels-Alder reaction of acyclic precursor with/without aldehyde substituent in gas phase and in solution.

	B3LYP/6-31+G*			M062X/6-31+G*// B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{(\text{gas})}$	$\Delta G^\ddagger_{(\text{CHCl}_3)}$	$\Delta G^\ddagger_{(\text{H}_2\text{O})}$
ts-endo	31.0	27.5	28.4	25.4	25.6	25.6
ts-exo	31.6	27.7	28.5	25.2	25.4	25.4
ts-endo-cis-A-I	26.4	22.5	23.2	19.5	18.1	17.9
ts-endo-trans-A-I	27.9	23.6	24.3	20.9	19.2	18.4
ts-exo-cis-A-I	28.6	24.3	24.9	21.1	20.6	20.4
ts-exo-trans-A-I	29.8	25.6	26.4	22.1	21.1	20.6

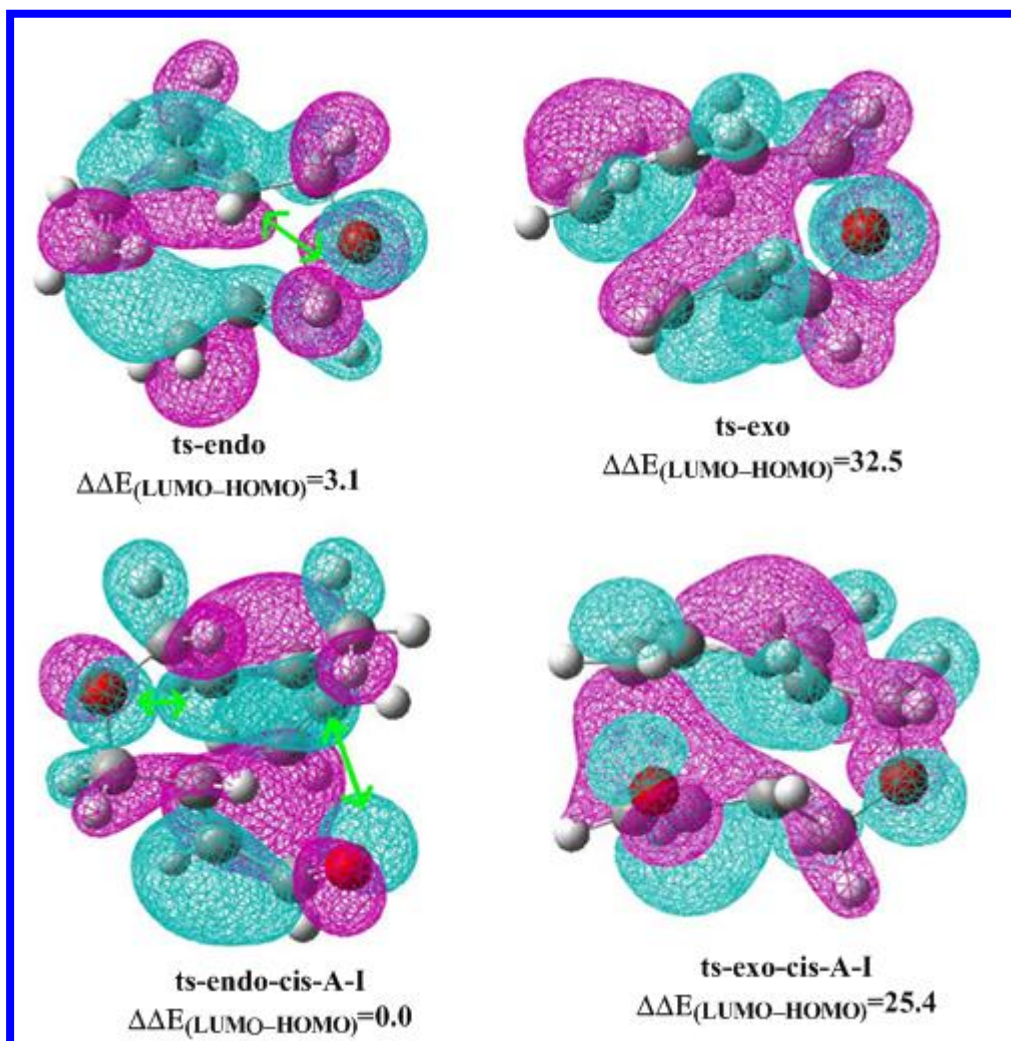


Figure 4.9. Representation of HOMO orbitals of the most stable transition structures of acyclic precursor.

4.4. Uncatalyzed Intramolecular Diels-Alder Reaction of Seven Membered Ring with and without Aldehyde Substituent.

The second reaction of interest is the cycloaddition of seven membered ring with/without aldehyde substituent. The effect of ring to the rate of thermal reaction is discussed and compared with the acyclic precursor.

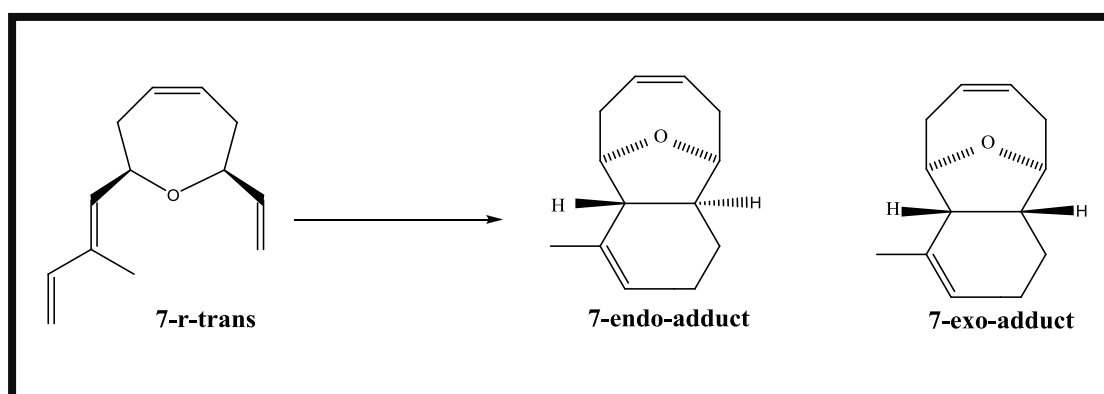


Figure 4.10. Reaction 3: Cycloaddition reaction of seven membered ring without aldehyde substituent.

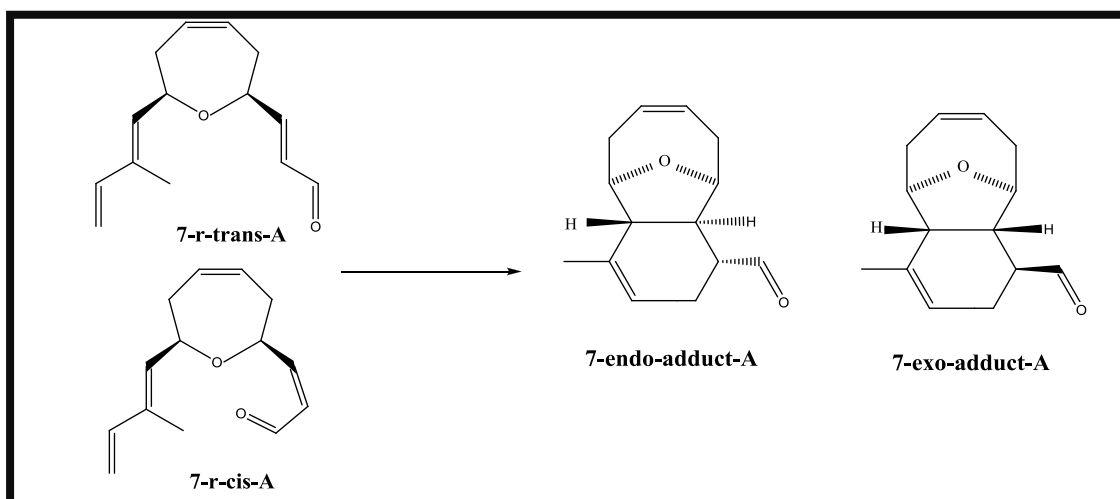


Figure 4.11. Reaction 4: Cycloaddition reaction of seven membered ring with aldehyde substituent.

4.4.1. Thermal Cycloaddition of Seven Membered Ring

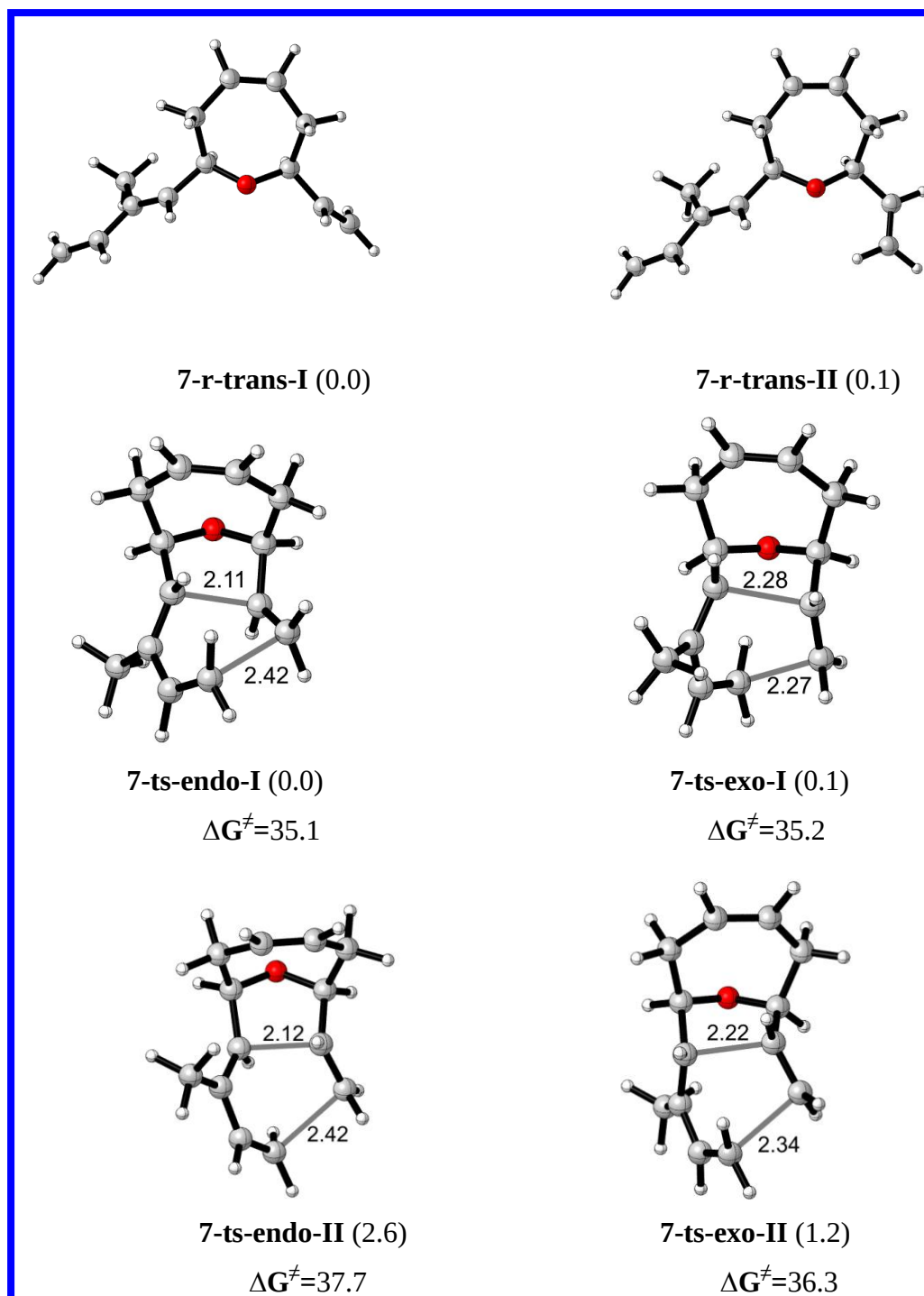


Figure 4.12. Seven membered ring conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent (B3LYP/6-31+G*).

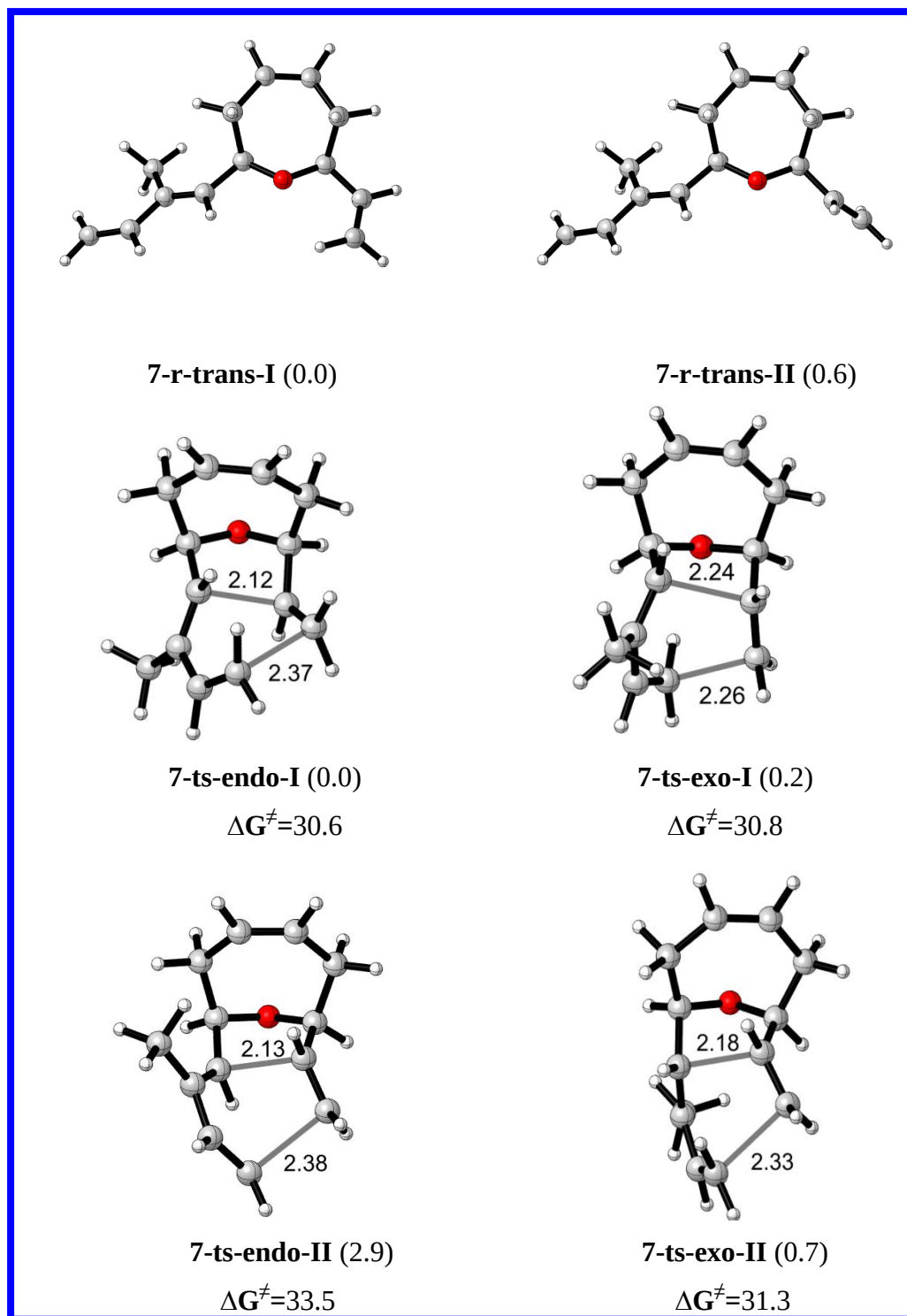


Figure 4.13. Seven membered ring conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent (M06-2X/6-311+G**).

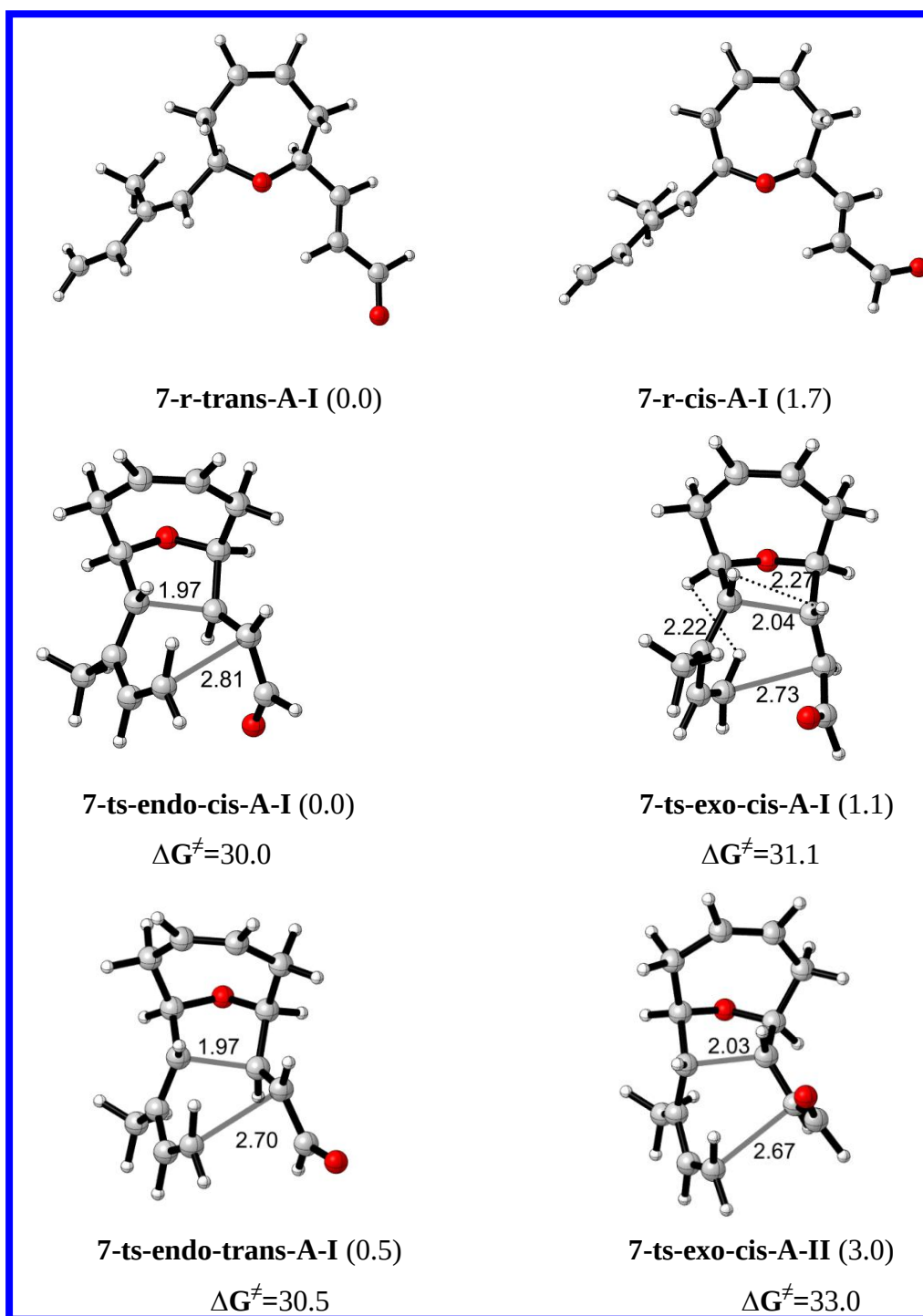


Figure 4.14. Seven membered ring conformers and transition structures for intramolecular Diels-Alder reaction with aldehyde substituent (B3LYP/6-31+G*).

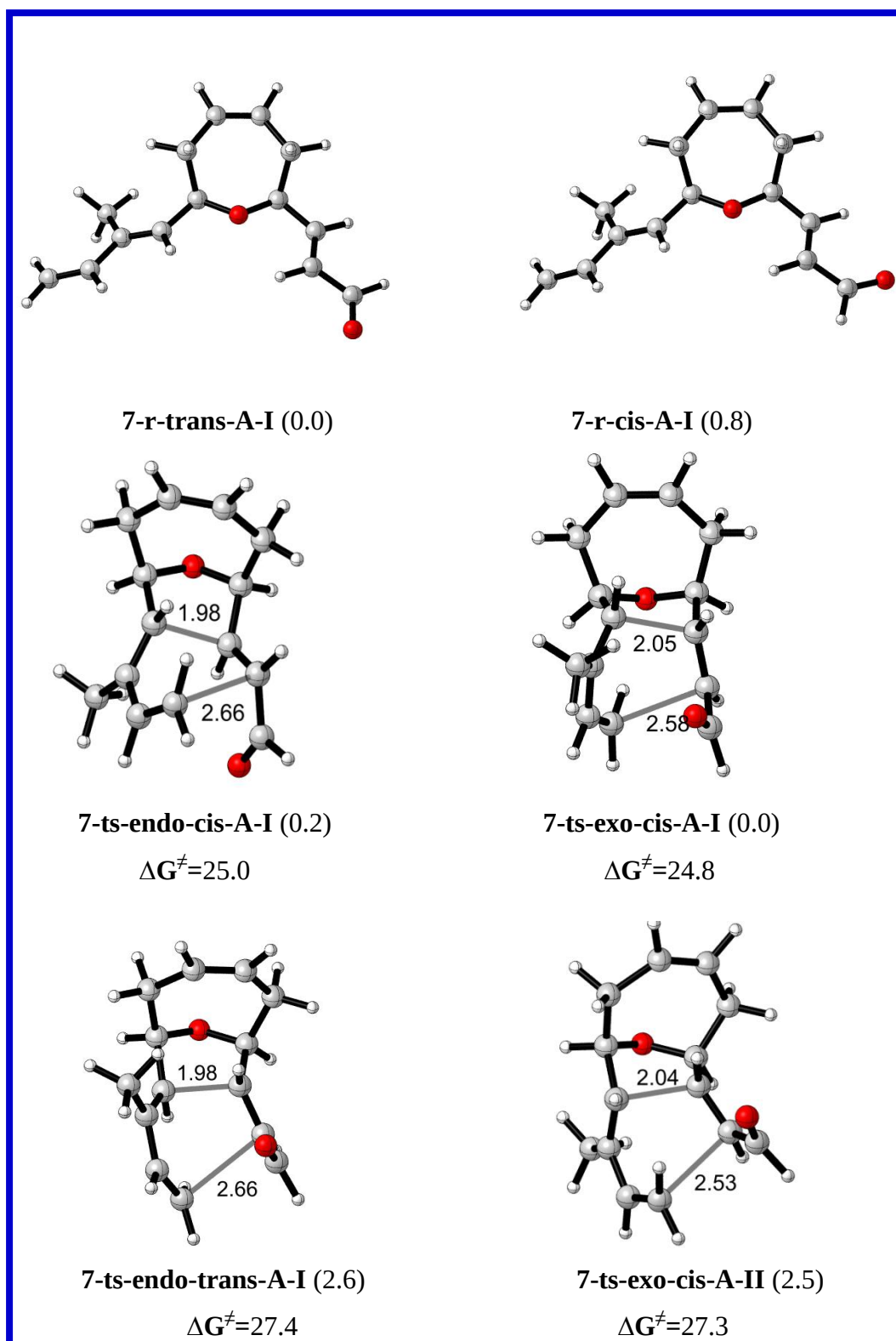


Figure 4.15. Seven membered ring conformers and transition structures for intramolecular Diels-Alder reaction with aldehyde substituent (M06-2X/6-311+G**).

Table 4.4. Calculated barriers for the intramolecular Diels-Alder reaction of seven membered ring with/without aldehyde substituent in gas phase and in solution.

B3LYP/6-31+G*				M062X/6-31+G*//B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger$	$\Delta G^\ddagger_{(\text{CHCl}_3)}$	$\Delta G^\ddagger_{(\text{H}_2\text{O})}$
7-ts-endo-I	35.1	30.9	31.3	26.5	27.4	27.8
7-ts-exo-I	35.2	31.3	31.8	26.7	28.3	28.8
7-ts-endo-cis-A-I	30.0	25.6	25.9	21.2	20.3	19.8
7-ts-exo-cis-A-I	31.1	26.7	27.1	21.6	22.0	22.3

Table 4.5. Calculated barriers for the intramolecular Diels-Alder reaction of seven membered ring with/without aldehyde substituent in gas phase and in solution.

M062X/6-311+G**				M062X/6-311+G**// M062X/6-311+G**
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta G^\ddagger_{(\text{CHCl}_3)}$
7-ts-endo-I	30.6	26.7	27.6	28.0
7-ts-exo-I	30.8	27.5	27.9	29.1
7-ts-endo-cis-A-I	25.0	21.1	21.4	20.5
7-ts-exo-cis-A-I	24.8	20.5	20.9	22.3

The insertion of ring increases the activation energy barrier of the reactions: 4.1 kcal/mol for the reaction without aldehyde substituent and 3.6 kcal/mol for the reaction including aldehyde substituent. To determine the reason for the rate decrease of the reaction we considered the strain in the chain connecting the diene and dienophile, since, the ring should have created a difference in the transition structure. Accordingly, we compared the interested angles; 1-2-3, 5-4-3 of acyclic precursor, *ts-endo-I* and *ts-endo-A-I*, and 1-2-3, 5-4-3, and of the seven membered ring, *7-ts-endo-I* and *7-ts-endo-A-I*. As it could be seen from Figure 4.16, angle compression in seven membered ring, for the angle 5-4-3 in *7-ts-endo-I* 3° and in *7-ts-endo-A-I* almost 4°, leads to a strain and probably increases the activation barrier.

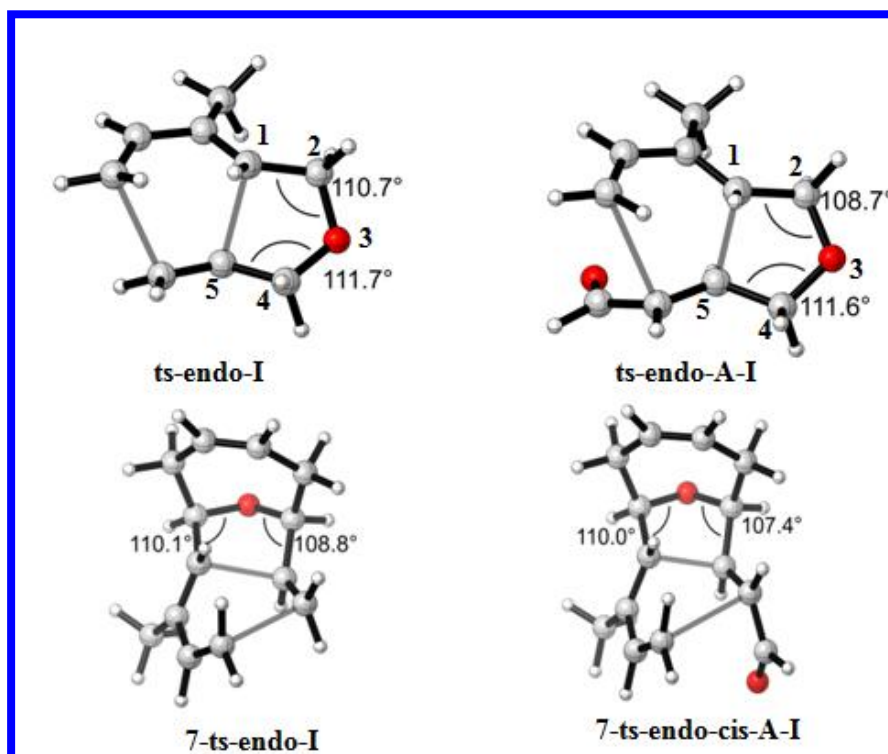


Figure 4.16. Most stable transition structures of acyclic precursor and seven membered ring showing the angle compression.

The predicted *endo:exo* ratio for the reaction without aldehyde substituent is 54:46; 86:14 for the reaction with aldehyde substituent. For the fourth reaction (Figure 4.14 and Figure 4.15) experimental *endo:exo* ratio is 100:0 [85]. The *endo/exo* selectivity of the reaction and the position of the methyl group on the ring can be rationalized with transannular interactions. For the *exo*- transition structure, one of the hydrogens of axial methyl group has a very close distance 2.2 Å, while this distance is longer in the case of equatorial methyl group, 2.4Å. For the *endo* transition structure there are two close H-H distances belonging to the two axial methyl group's hydrogens: 2.3 Å and 2.4 Å (Figure 4.17). Whereas, there are two close H-H distances (2.27 Å and 2.22 Å) which disfavour, 7-*ts-exo-cis-A-I*, *exo* transition structure (Figure 4.14).

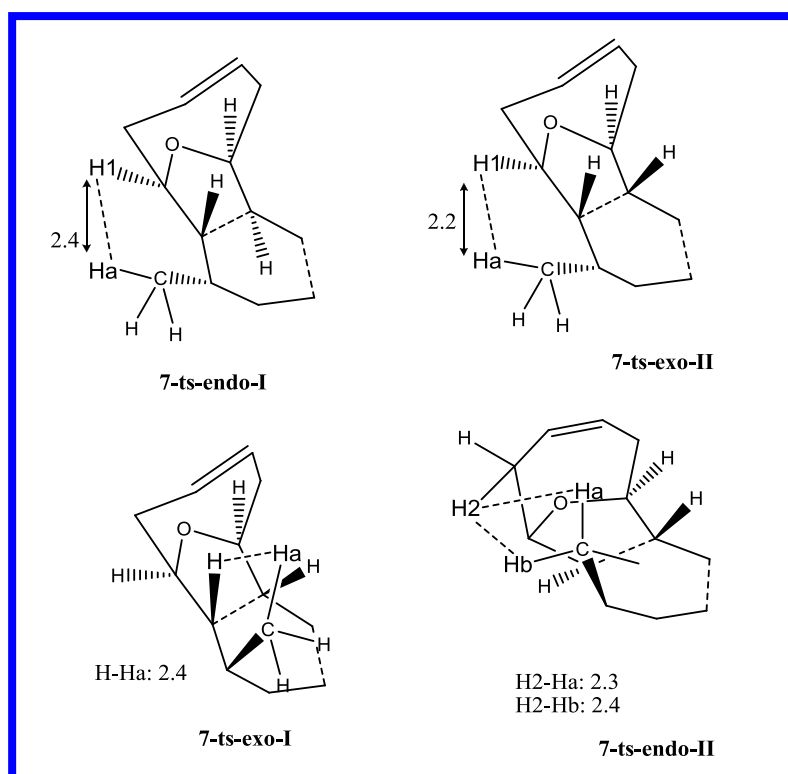


Figure 4.17. Most stable transition structures of seven membered ring showing transannular interactions.

Previous experimental results showed that *endo* orientation of carbonyl group is favoured and this tendency increases in polar solvents [86-88]. In solvent, especially in water, the *endo* selectivity increases due to the hydrophobic interactions between diene and dienophile [89-93].

All the located transition structures correspond to an asynchronous, but concerted pathway (carbon-carbon bond-forming distance differences between 0.1 and 0.8) (Figure 4.7, Figure 4.8, Figure 4.13 and Figure 4.14). Substitution of an electron withdrawing specie on the dienophile necessarily renders the transition structure asynchronous [94]. In this study, reactions including aldehyde substituent are more asynchronous than the other reactions because of the electron withdrawing capacity of aldehyde group on the dienophile. Furthermore, our results show that the *endo* transition structures of acyclic precursor and seven membered ring are more asynchronous than the *exo* ones. For *ts-endo-A-I*, *endo* forming bonds are 1.98 Å and 2.74 Å (Figure 4.8); for *7-ts-endo-cis-A-I*, the forming bonds are 1.97 Å and 2.81 Å (Figure 4.14). The *endo* transition structures

appears earlier along the reaction pathway and results in an activation energy lower than that of *exo* structures.

4.5. Uncatalyzed Intramolecular Diels-Alder Reaction of Eight Membered Ring with and without Aldehyde Substituent.

In order to discriminate the stereo-preference of medium rings, the procedure that has been followed for seven membered ring, was applied to the eight membered ring.

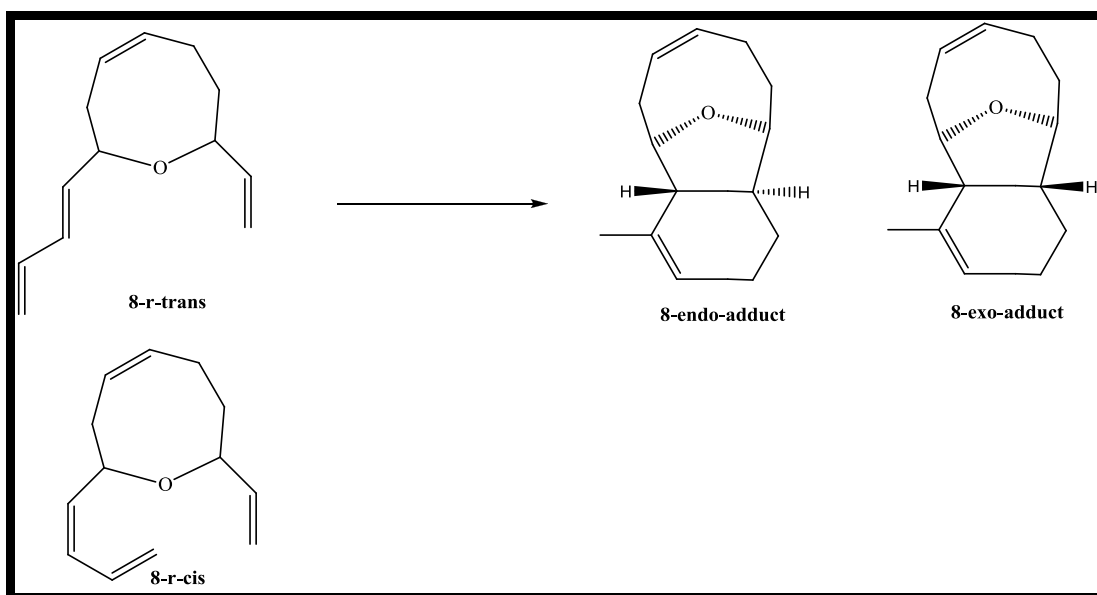


Figure 4.18. Reaction 5: Cycloaddition reaction of eight membered ring without aldehyde substituent.

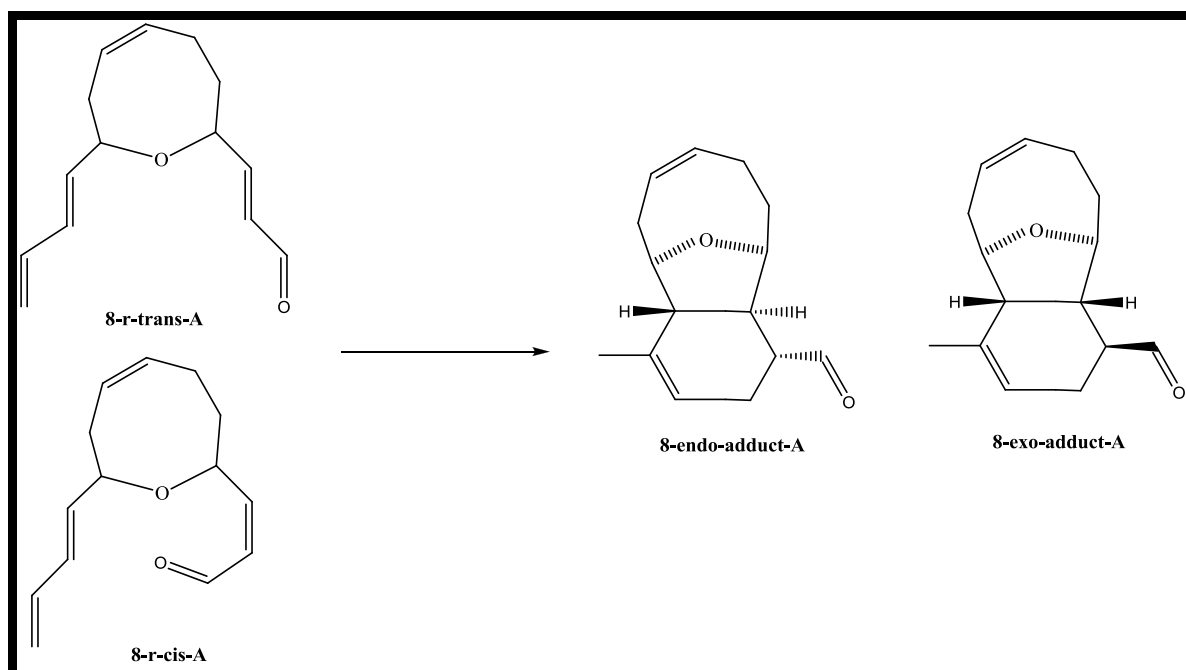


Figure 4.19. Reaction 6: Cycloaddition reaction of eight membered ring with aldehyde substituent.

4.5.1. Thermal Cycloadditions of Eight Membered Ring

In this part, cycloadditions of eight membered ring have been modelled with and without aldehyde substituent. The experimental torsional angles around the bonds of the eight membered ring are in close agreement with the computed ones. Small differences necessarily arise from the substitution on the eight membered ring of (+)-Laurencin compound [94].

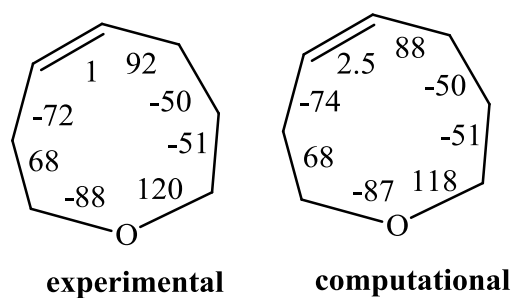


Figure 4.20. Calculated and experimental torsional angles of eight membered ring [94].

In transition states the eight membered ring adopts two different conformations denoted as “up” and “down” based on the location of the segment containing ester oxygen. The endo transition state adopts the down conformation, since the up conformation has a very close H-H distances between two of the hydrogens on the eight membered ring and one of the hydrogens of the forming six membered ring. The exo transition structure adopts the up the conformation, since the down conformation there would have steric repulsions between the hydrogens on the forming ring and the eight membered ring.

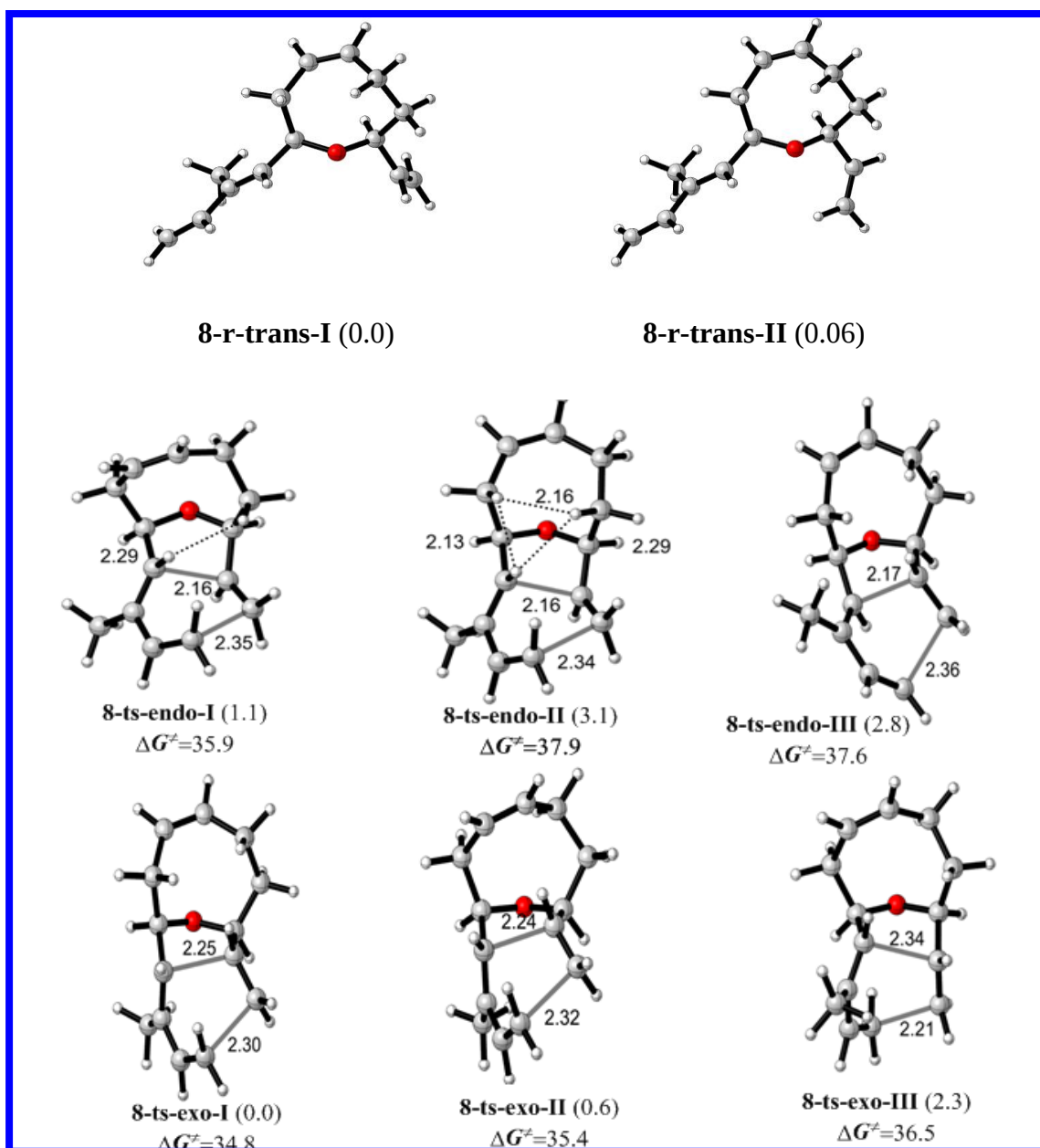


Figure 4.21. Eight membered ring conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent.

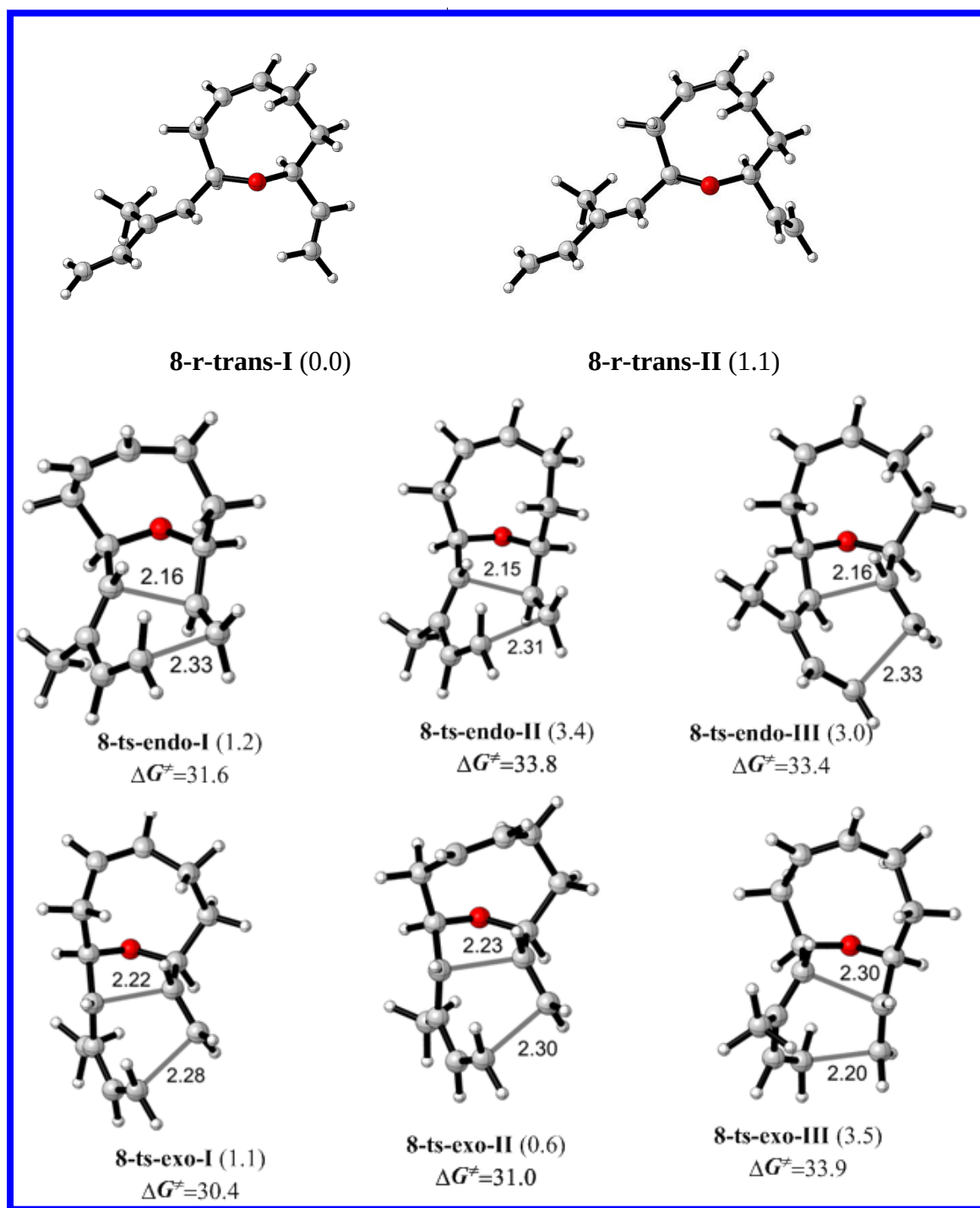


Figure 4.22. Eight membered ring conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent (M062X/6-311+G**).

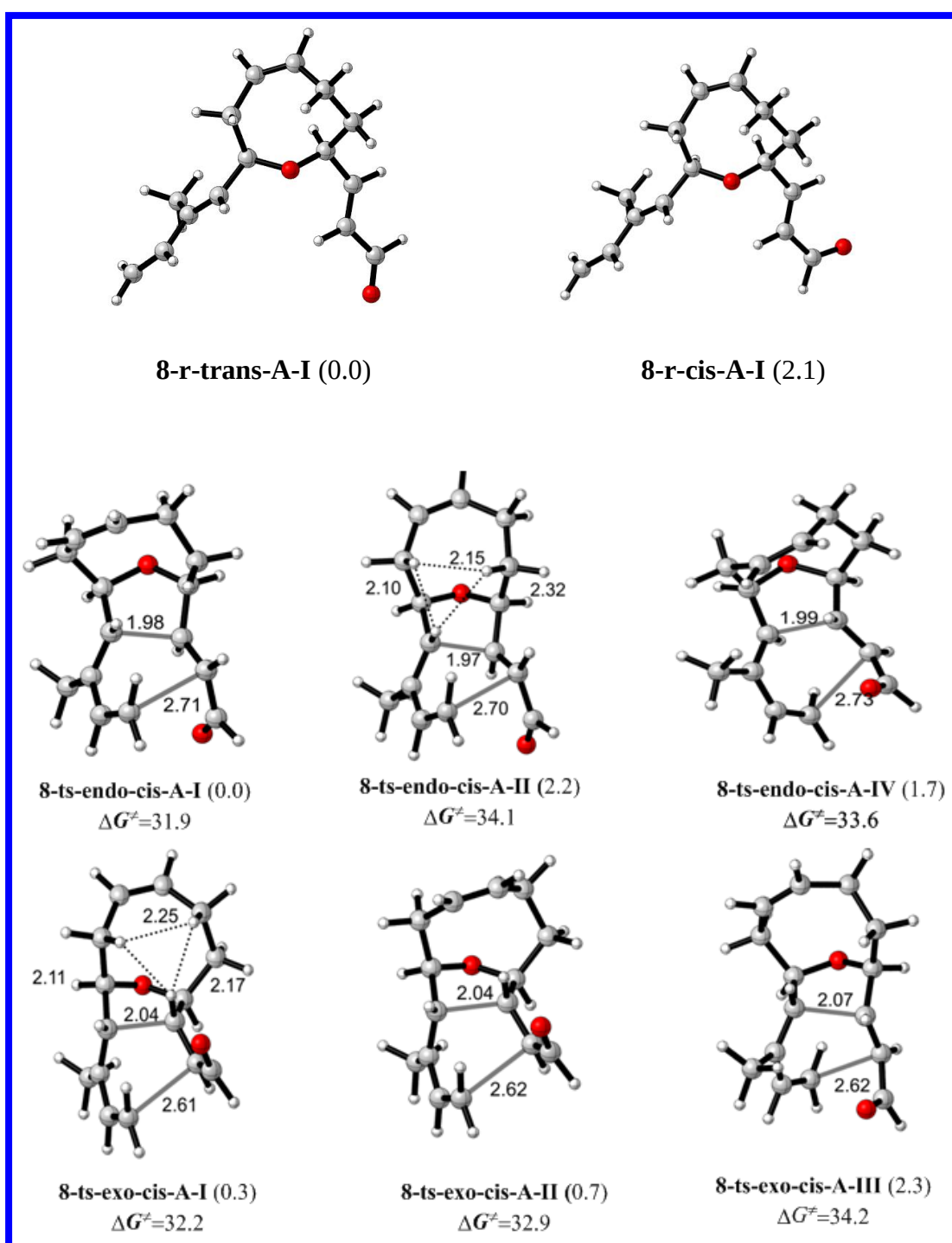


Figure 4.23. Eight membered ring conformers and transition structures for intramolecular Diels-Alder reaction with aldehyde substituent (B3LYP/6-311+G**).

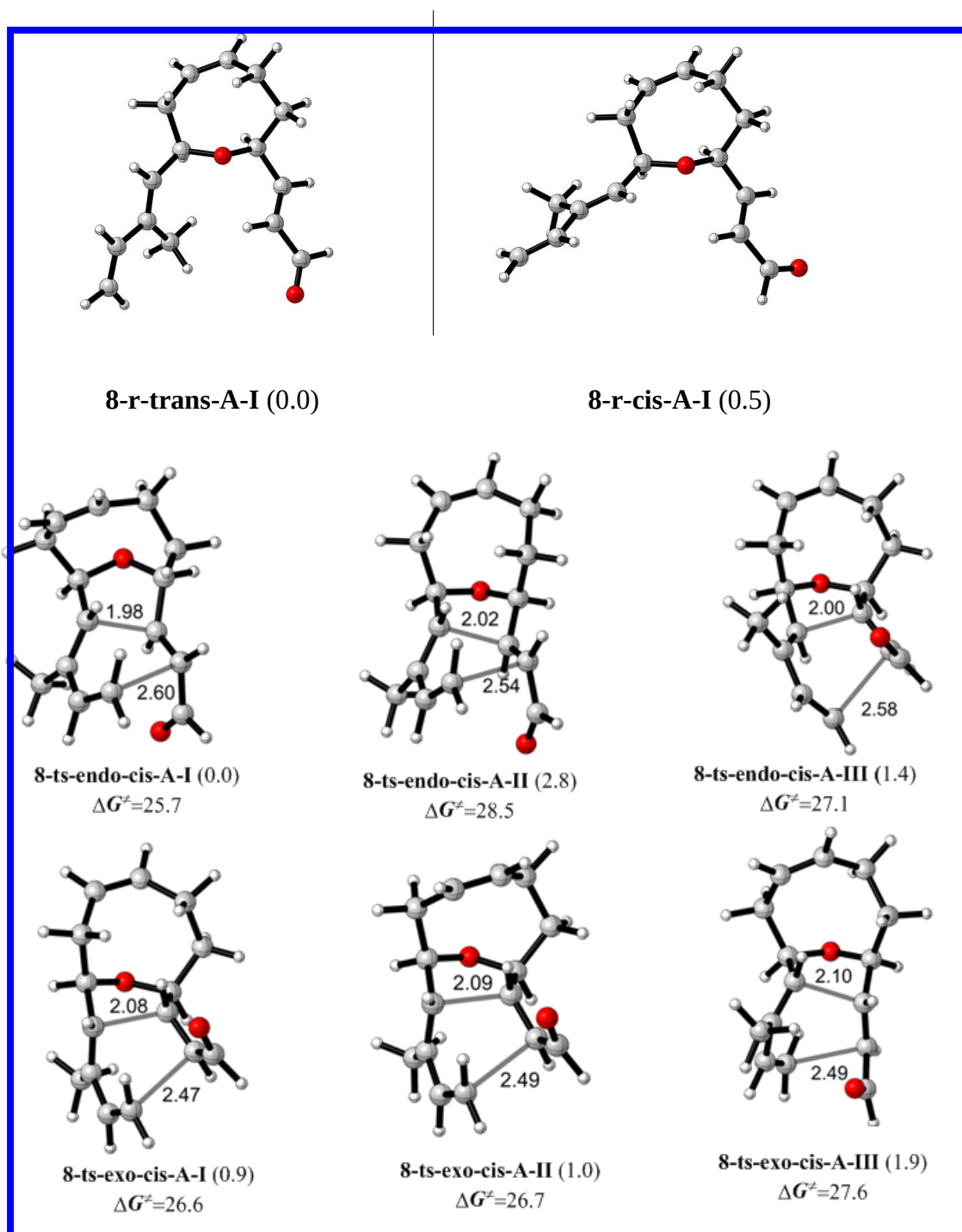


Figure 4.24. Eight membered ring conformers and transition structures for intramolecular Diels-Alder reaction with aldehyde substituent (M062X/6-311+G**).

Table 4.6. Calculated barriers for the intramolecular Diels-Alder reaction of eight membered ring with/without aldehyde substituent in gas phase and solution.

B3LYP/6-31+G*				M062X/6-31+G**//B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{\text{gas}}$	$\Delta G^\ddagger(\text{CHCl}_3)$	$\Delta G^\ddagger(\text{H}_2\text{O})$
8-ts-endo-I	35.9	31.8	32.2	27.2	28.4	24.7
8-ts-exo-I	34.8	30.4	31.2	26.0	26.2	22.0
8-ts-endo-cis-A-I	31.9	27.5	28.0	23.7	22.5	22.3
8-ts-exo-cis-A-I	32.2	27.4	28.7	24.0	22.9	22.9

Table 4.7. Calculated barriers for the intramolecular Diels-Alder reaction of eight membered ring with/without aldehyde substituent in gas phase and solution.

M062X/6-311+G**				M062X/6-311+G** // M062X/6-311+G**
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta G^\ddagger(\text{CHCl}_3)$
8-ts-endo-I	31.6	28.3	28.8	29.2
8-ts-exo-I	30.4	26.7	27.4	26.8
8-ts-endo-cis-A-I	25.7	22.2	22.8	22.8
8-ts-exo-cis-A-I	26.6	22.0	23.4	23.1

The predicted *endo:exo* ratio for the reaction without aldehyde substituent is 14:86; 62:38 for the reaction with aldehyde substituent with the B3LYP functional. M06-2X optimizations predict the *endo:exo* ratio of the first one as 18:82 and 62:38 for the latter one.

4.6. Uncatalyzed Intramolecular Diels-Alder Reaction of Nine Membered Ring with and without Aldehyde Substituent.

The conformational behavior of oxonene ring was studied by Tachibana et. al. Molecular mechanic calculations suggested the existence of only two conformers, the “up” and “down” ones, which differ in the location of the olefinic bond with regard to the ring plane. The same group also reported that the ring exhibits a preference for the up conformation over the down one. It was explained that the most remarkable structural feature of oxonene ring is that it undergoes a conformational change in solution. Thus the ring functions as a hinge in the conformational flexibility of the molecule [95].

4.6.1. Thermal Cycloadditions of Nine Membered Ring

The located nine membered reactants show a preference for the up conformation which is in agreement with the previous findings on Ciguatoxin molecule [95]. In our case the up conformation is preferred in order to prevent electrostatic repulsion between ester oxygen and olefinic bond.

The nine membered ring's *endo*- and *exo*- transition structures prefer the “down” conformation due to electrostatic repulsion. The up conformation has steric interactions between the nine membered ring's hydrogens and the forming six membered ring.

The observed *exo* selectivity of cycloaddition reaction without aldehyde substituent similar to the eight membered ring's case: one of the diene's hydrogens and one of nine membered ring's crash into each other. The calculated *endo:exo* ratio is 34:66 in gas phase. The introduction of aldehyde substituent shifts the selectivity towards the *endo* structure due to the secondary orbital interactions. The *endo:exo* ratio for this reaction is 79:21 and in good agreement with the experimental data which is 75:25.

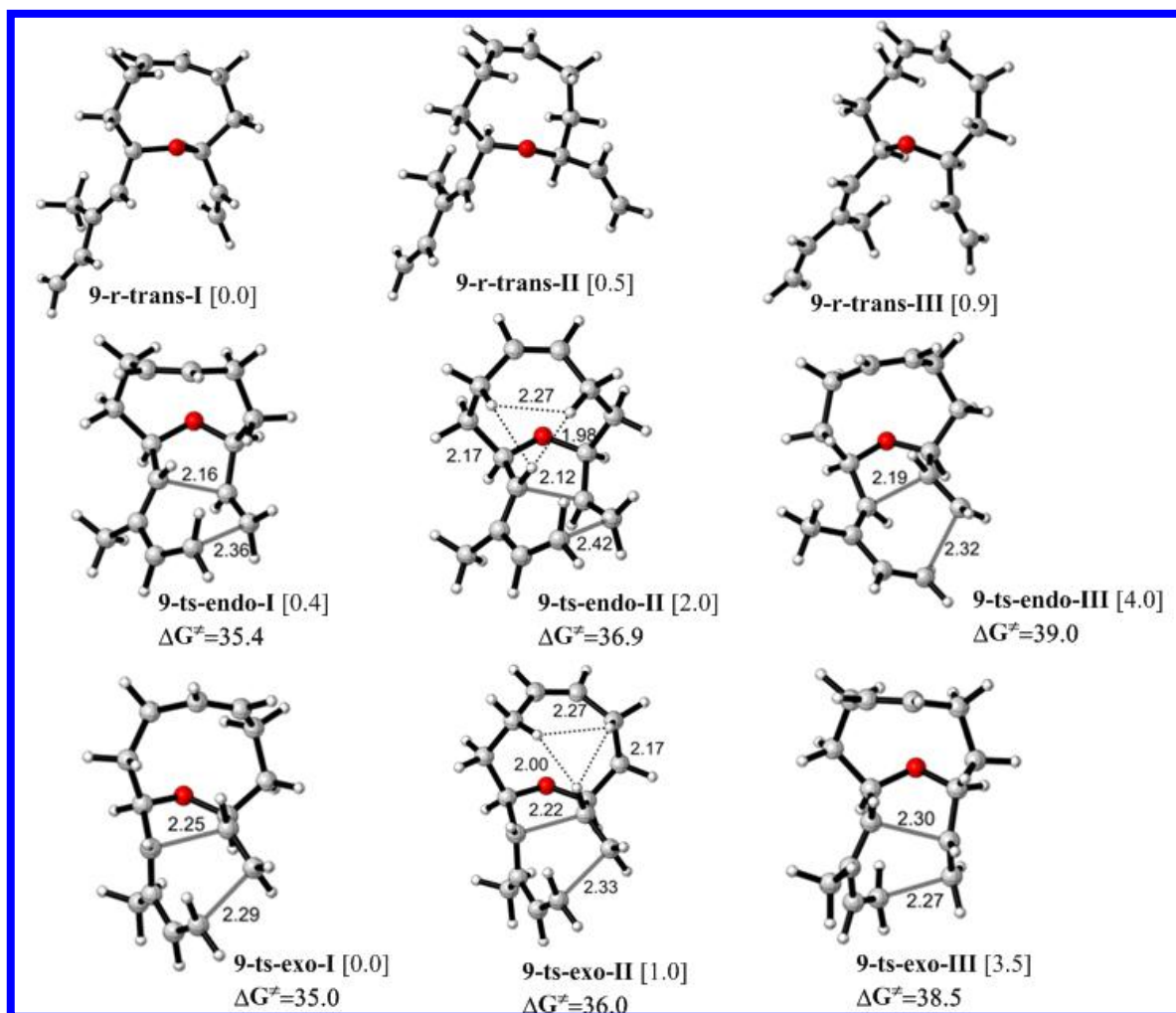


Figure 4.25. Nine membered ring conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent.

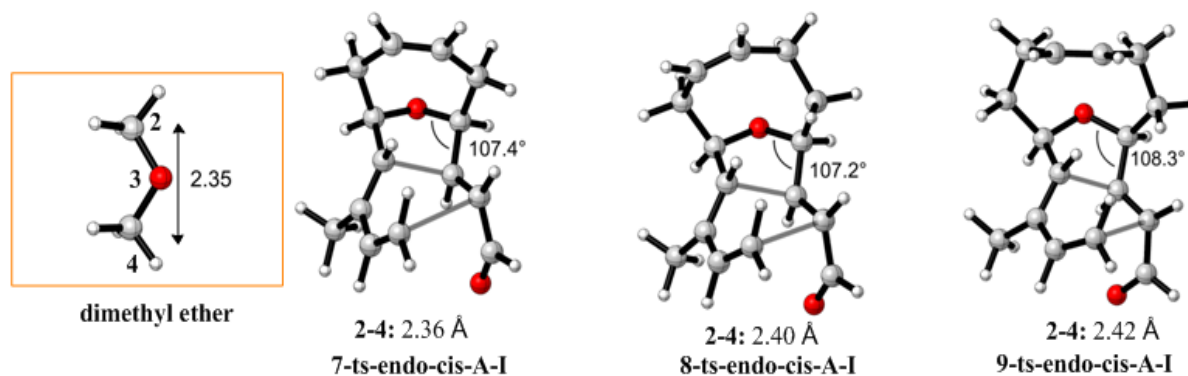


Figure 4.26. Most stable transition structures of all ring models for Intramolecular Diels-Alder reactions showing tether lengths and angles.

Table 4.8. Calculated barriers for the intramolecular Diels-Alder reaction of nine membered ring without organocatalyst.

B3LYP/6-31+G*				M062X/6-31+G*//B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{\text{gas}}$	$\Delta G^\ddagger_{\text{toluene}}$	$\Delta G^\ddagger_{\text{H}_2\text{O}}$
9-ts-endo-I	36.3	32.0	32.7	27.5	28.4	29.0
9-ts-exo-I	35.0	30.7	31.5	26.5	27.6	28.4
9-ts-endo-cis-A-I	30.9	26.8	27.4	21.3	21.2	20.8
9-ts-exo-cis-A-I	31.6	27.7	28.4	23.4	23.7	23.8

Table 4.9. Calculated energy barriers for the intramolecular Diels-Alder reaction of nine membered ring without organocatalyst.

M062X/6-311+G**				M062X/6-311+G** // M062X/6-311+G**
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta G^\ddagger_{\text{(toluene)}}$
9-ts-endo-I	31.2	27.3	27.8	28.4
9-ts-exo-I	29.9	26.1	26.7	27.6
9-ts-endo-cis-A-I	25.5	20.8	21.2	21.7
9-ts-exo-cis-A-I	27.2	23.1	23.6	24.5

The predicted *endo:exo* ratio for the reaction without aldehyde substituent is 10:90; 76:24 for the reaction with aldehyde substituent by B3LYP functional. M06-2X optimizations predict the *endo:exo* ratio of the first one as 10:90 and 98:2 for the latter one.

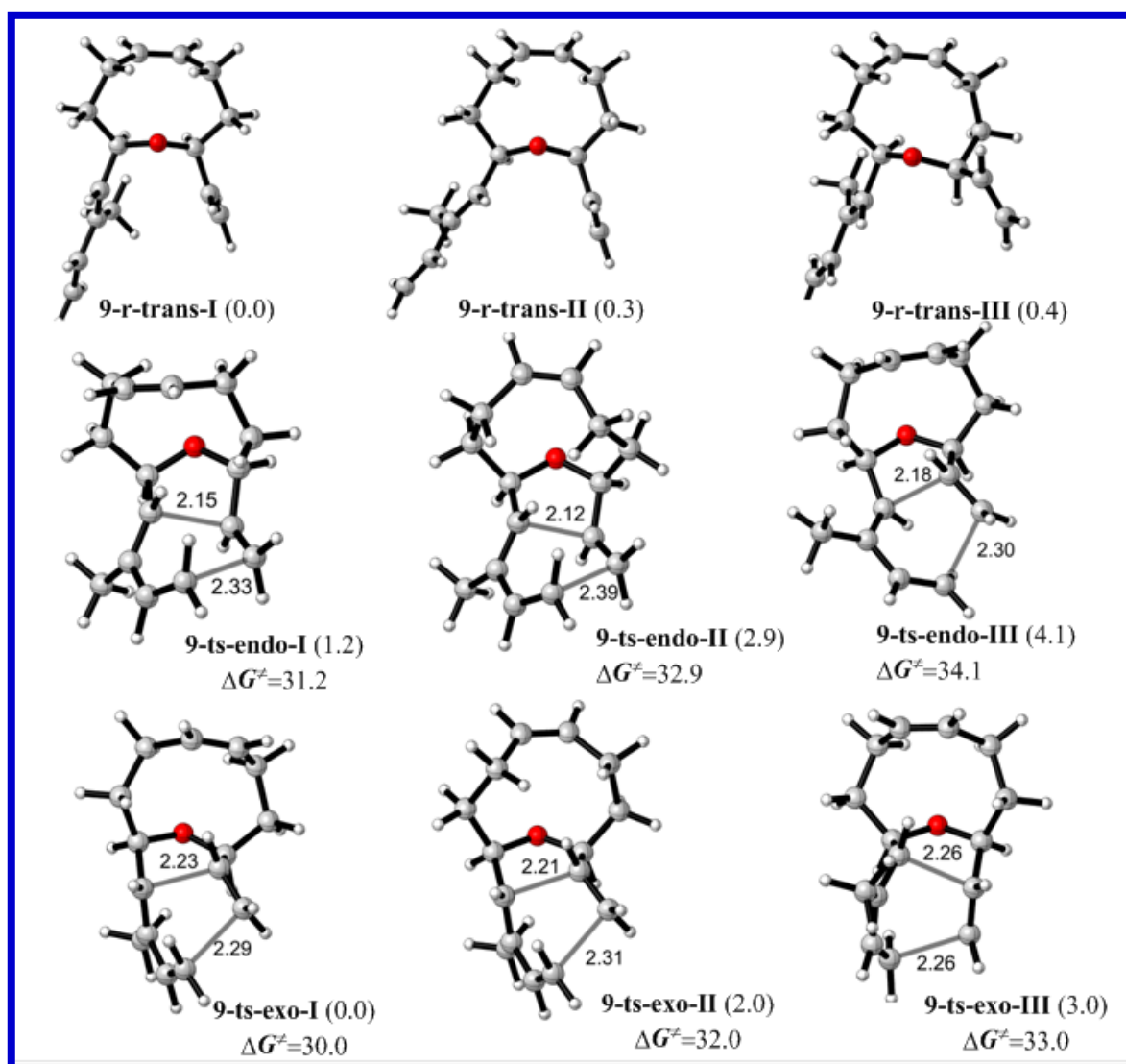


Figure 4.27. Nine membered ring conformers and transition structures for intramolecular Diels-Alder reaction without aldehyde substituent (M06-2X/6-311+G**).

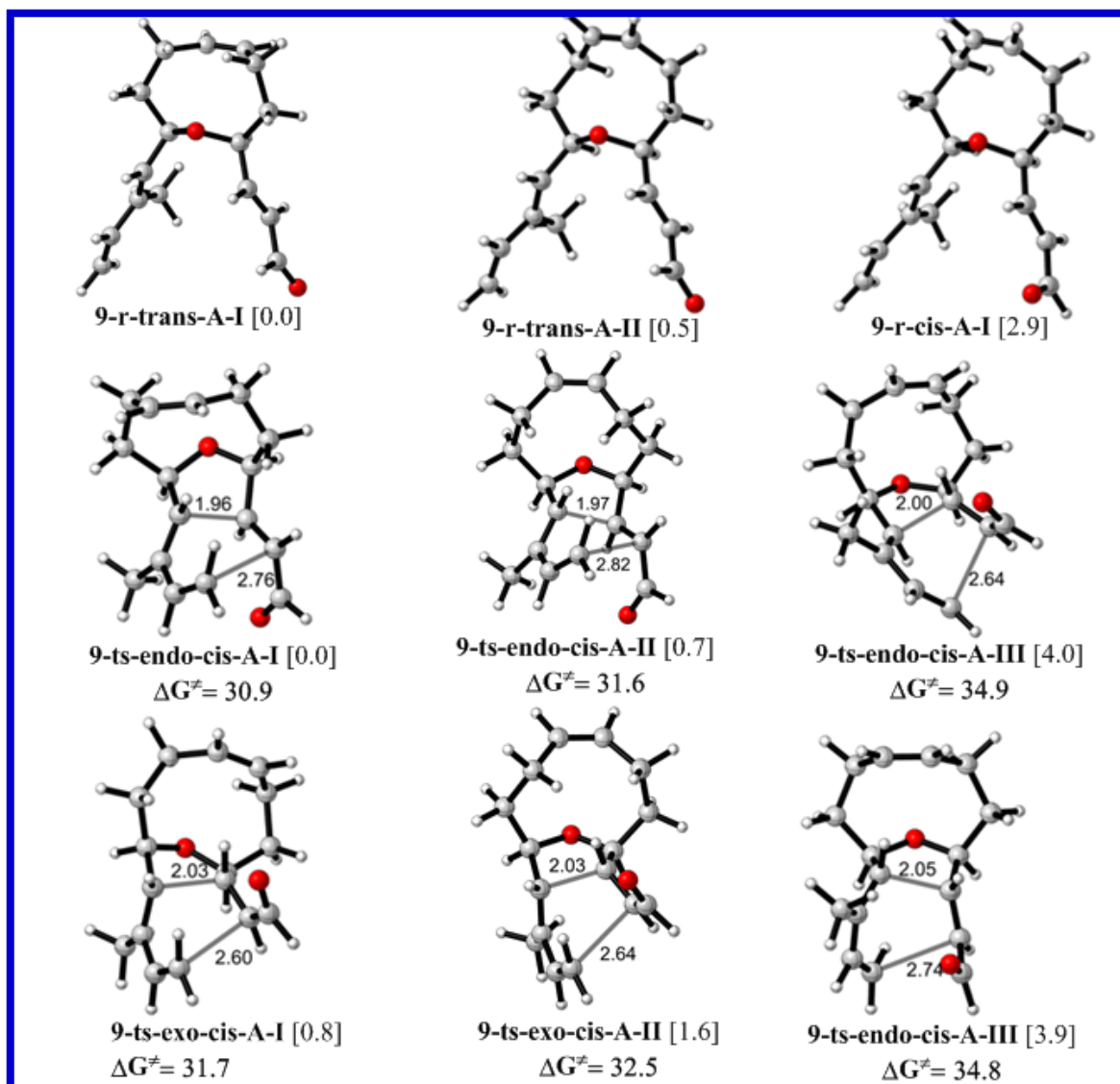


Figure 4.28. Nine membered ring conformers and transition structures for intramolecular Diels-Alder reaction with aldehyde substituent.

The experimental data reveals that the rate of thermal reaction decreases as the ring size increases. Thermal cycloaddition of the seven membered ether proceeded at room temperature, while eight membered ether must be heated to 100 °C for 3 hours. The nine membered ether was heated to reflux in toluene for 24 hour. Our computational results show that rate of thermal reaction decreases from seven membered ring ether to the eight membered ring ether as expected. However, for the nine membered ring ether, the activation barrier is lower than expected.

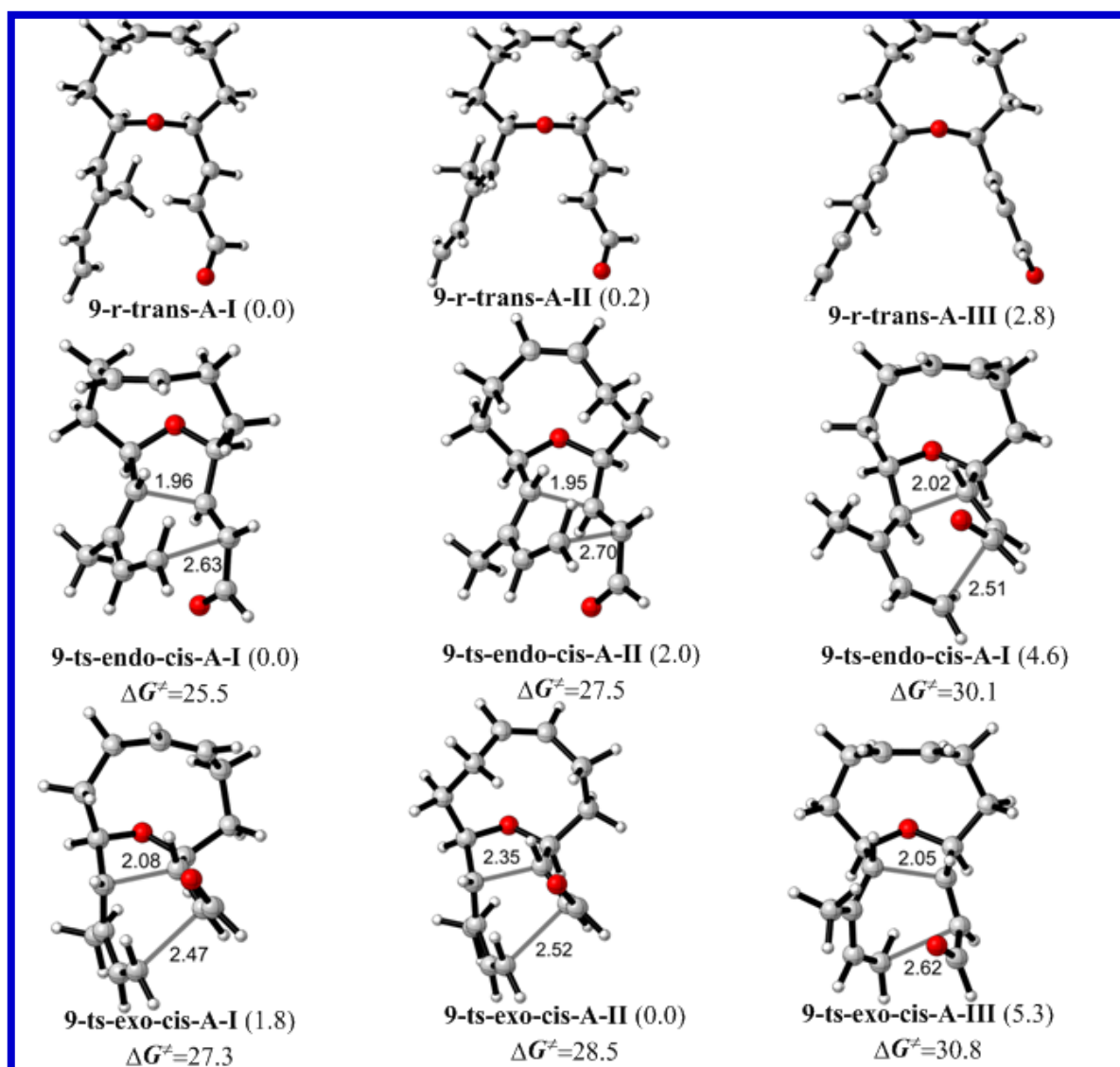


Figure 4.29. Nine membered ring conformers and transition structures for Intramolecular Diels-Alder reaction with aldehyde substituent (M06-2X/6-311+G**).

Figure 4.26 compares the geometries of the intramolecular transition structures of ring models. The proposed explanation for the rate decrease of seven membered ring holds for eight and nine membered rings. The tether length is crucial to adjust the rate decrease of thermal reactions. The intramolecular cycloadditions with butadiene do prefer shorter tethers as noted by Houk, because it allows exceptionally good orbital overlap without introducing any strain [96].

5. INTRAMOLECULAR DIELS-ALDER REACTIONS OF ALL RING MODELS WITH THE (R)- AND (S)- ENANTIOMERS OF MACMILLAN'S CATALYST

5.1. First Generation Imidazolidinone Catalyst

As suggested from computational modeling, catalyst-activated E isomer, about +N=C bond of the iminium ion, was expected to form selectively to avoid nonbonding interactions between the substrate olefin and the gem-dimethyl substituents on the catalyst. In terms of enantioselective discrimination, iminium structure revealed that benzyl group of imidazolidinone moiety would effectively shield the Si face of the iminium ion and leave Re face exposed for selective bond formation. Our results affirm the previous computational findings that (E)- iminium geometry is favoured to avoid nonbonding interactions [97-99].

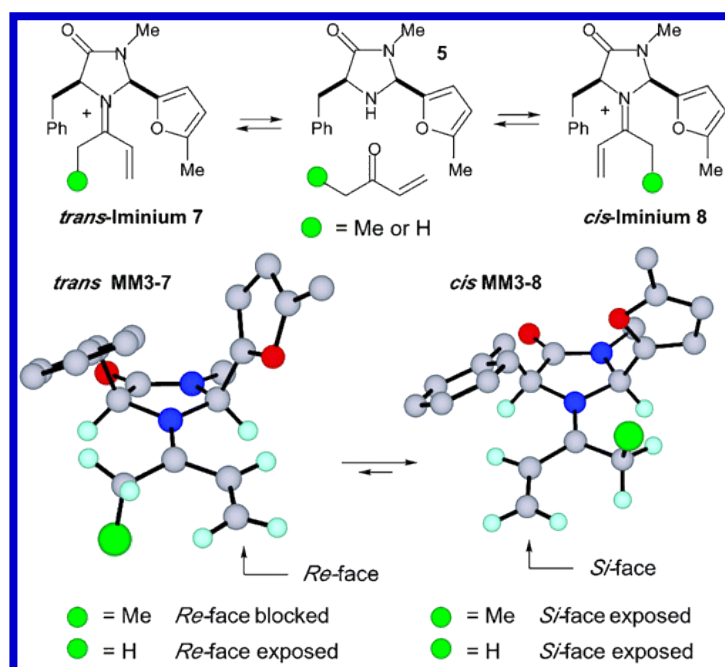


Figure 5.1. Computational models for the first generation imidazolidinone catalyst and of the corresponding iminium ions [98].

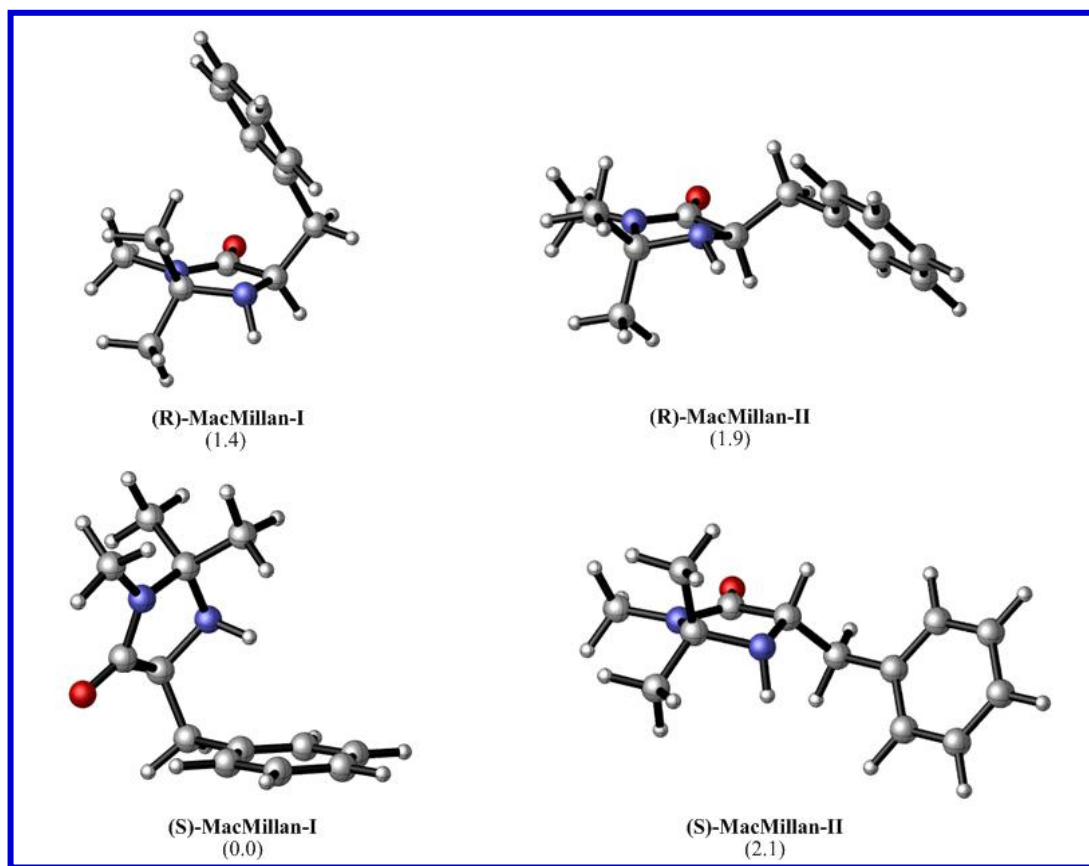


Figure 5.2. Optimized conformers of (R)- and (S)- enantiomers of organocatalysts showing most stable structures (M06-2X/6-31+G*).

Figure 5.2 shows the optimized conformers of organocatalysts with M062X/6-31+G*. The (S)-enantiomer, is favoured over the (R)- one. Both enantiomers, (S)-MacMillan-I and (R)-MacMillan-I, include C-H... π stabilizing interaction. Additionally, the lone pair of nitrogen atom is away from the benzyl ring in (S)-MacMillan-I, however in (R)-MacMillan-I the lone pair of nitrogen is oriented towards the aromatic ring which leads an electrostatic repulsion and destabilization.

In 2006, chiral imidazolidinones were studied by Houk et. al. in the context of the origins of stereoselectivity in Diels-Alder cycloadditions. It was concluded that the preference of attack in a sterically unencumbered fashion leads to preferred transition structures and stereoselectivity [100].

5.2. Cycloaddition Reactions of Seven Membered Ring

5.2.1. Reaction of Seven Membered Ring with (R)- MacMillan's Catalyst

B3LYP/6-31+G* gas phase calculations confirm the *endo: exo* ratio, 100:0, and it's reported as 100:0 by experiment [85] for the reaction with (R)- MacMillan's Catalyst (Table 4.2).

Contrary to previous force field energy minimizations, conformer 7-r-(R)-N-I which includes a stabilizing C-H... π interaction between one of the methyl groups of the imidazolidinone ring and phenyl ring of the benzyl group was found to be global minimum as noted by Houk [100].

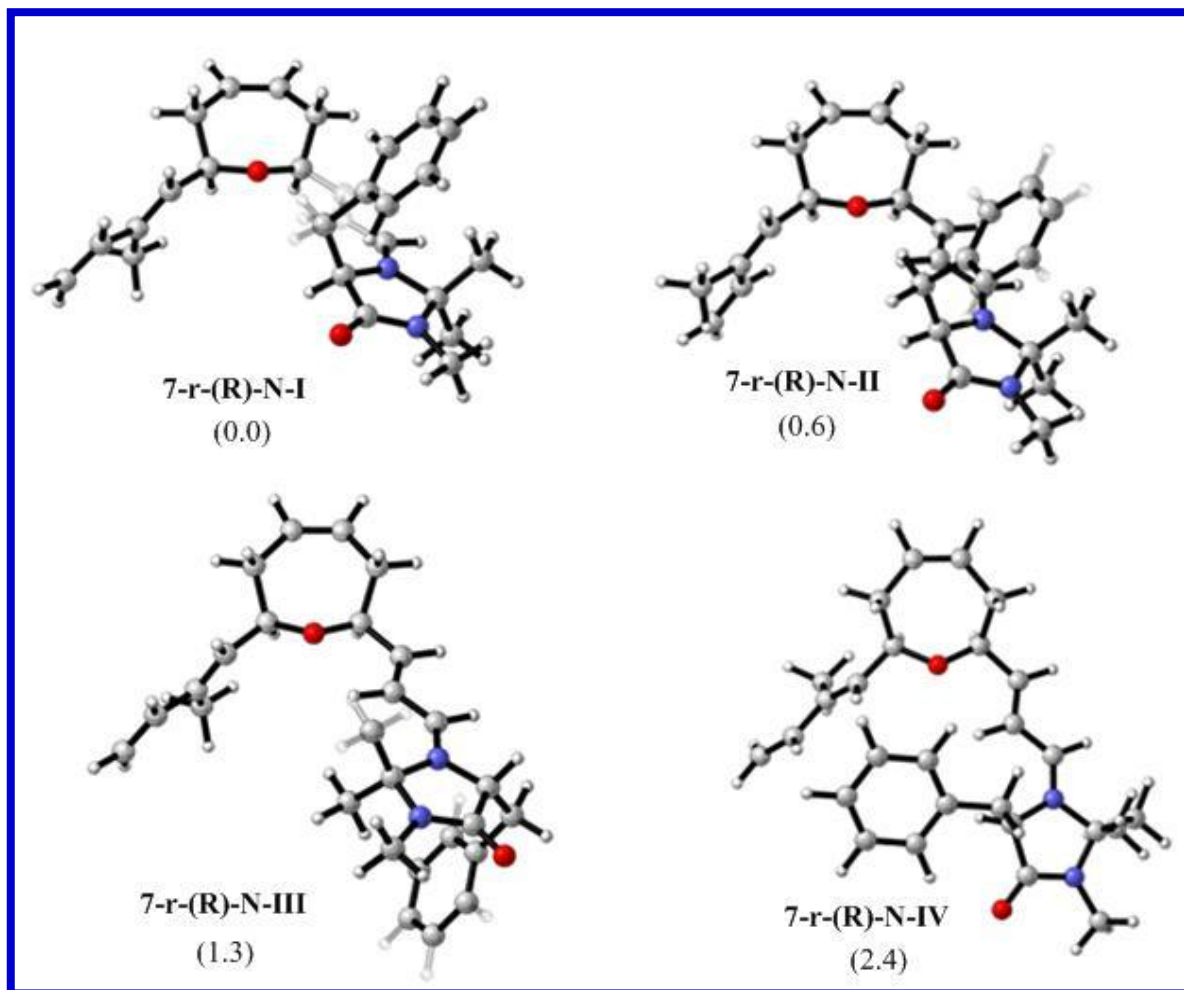


Figure 5.3. Seven membered ring's reactant conformers with (R)- enantiomer of MacMillan's Catalyst.

B3LYP fails to predict the barrier height of (R)- catalyzed reaction when compared to (S)- catalyzed reaction. It can be seen from Table 4.2 that both (R)- catalyzed reaction and (S)-catalyzed reaction were carried out in 7 hours.

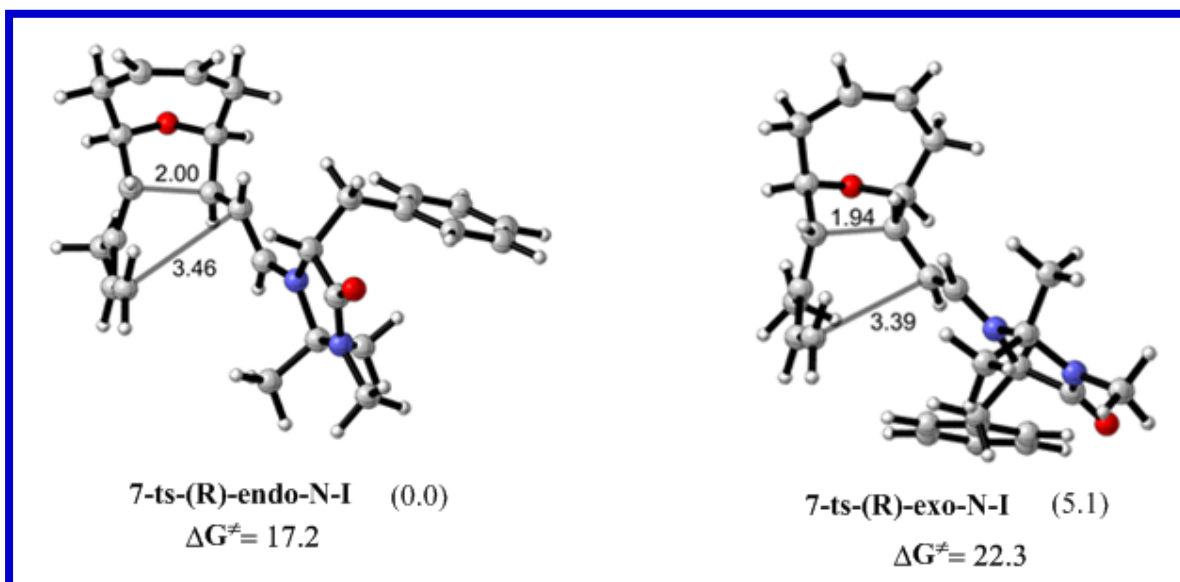


Figure 5.4. Most stable *endo* and *exo* transition structures of seven membered ring with the (R)- enantiomer of MacMillan Catalyst.

Table 5.1. Calculated barriers for the intramolecular Diels-Alder reaction of seven membered ring with (R)-enantiomer of the MacMillan Catalyst in gas phase and in solution.

B3LYP/6-31+G*				M062X/6-31+G*// B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{(\text{GAS})}$	$\Delta G^\ddagger_{(\text{MeCN})}$	$\Delta G^\ddagger_{(\text{H}_2\text{O})}$
7-ts-(R)-endo-N-I	17.2	14.2	14.6	10.1	11.5	11.6
7-ts-(R)-exo-N-I	22.3	20.6	21.2	17.8	20.4	20.5

5.2.2. Reaction of Seven Membered Ring with (S)- MacMillan's Catalyst

Diastereoselectivity of the (S)- MacMillan catalyzed reaction is also in good agreement with the experiment; 100:0 (Table 4.2) and 99:1 by B3LYP/6-31+G. All transition structures are concerted but very asynchronous and very similar to those previously reported by Houk and Gordilla [100].

The stereoselectivity rule [101] for ionic cycloadditions states that “If two geometrical isomers are possible for the transition states differ in distances between the centers of receding and developing positive charge, then the geometrical isomer formed in the larger amount will be that with the greater distance between the charge centers in the transition state”. According to this rule in the present case where endo adduct is preferentially formed, calculated distances between the charge centers in *exo* and *endo* of (R)-enantiomer, are 3.39 and 3.46 Å (Figure 4.20), of (S)-enantiomer 3.37 and 3.59 Å (Figure 4.23) , respectively. This is in total accordance with the stereoselectivity rule mentioned above.

Both (R)- and (S)- enantiomers of the Catalyst lowers the activation barrier of the reaction, 12.8 kcal/mol (Table 5.1) and 11.5 kcal/mol (Table 5.2) , respectively. The result can be attributed to the LUMO activation (LUMO-lowering) strategy of the catalyst. The formation of the iminium complex produces a much more reactive dienophile [100].

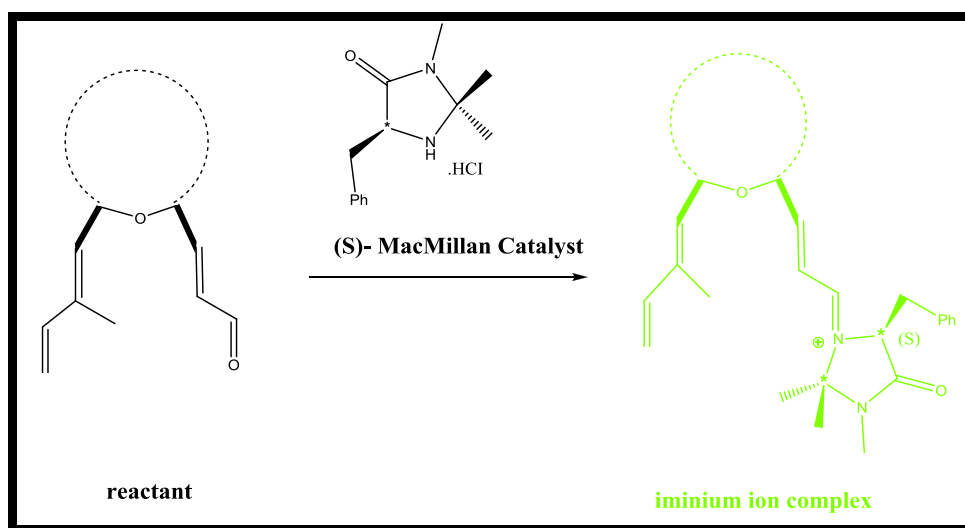


Figure 5.5. Formation of E-iminium ion intermediate with (S)-MacMillan's Catalyst.

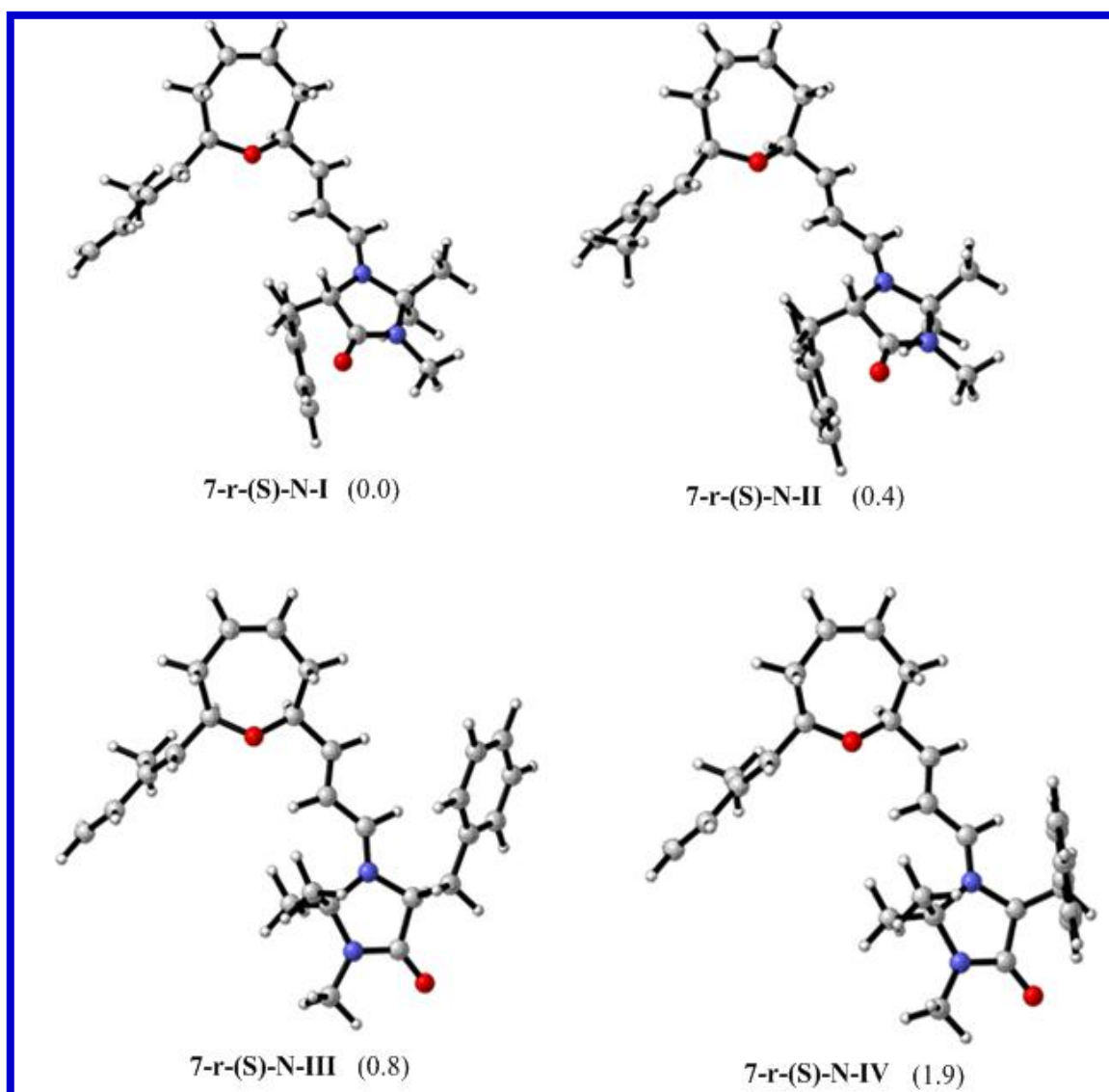


Figure 5.6. Seven membered ring reactant conformers with (S)- enantiomer of MacMillan's catalyst.

Inclusion of solvent effects through single point PCM calculations with acetonitrile and water as solvent did, do not alter *endo/exo* selectivity. Remarkably, the presence of water exhibited beneficial effects on reaction rates and stereoselectivity, while facilitating the iminium ion hydrolysis step [100].

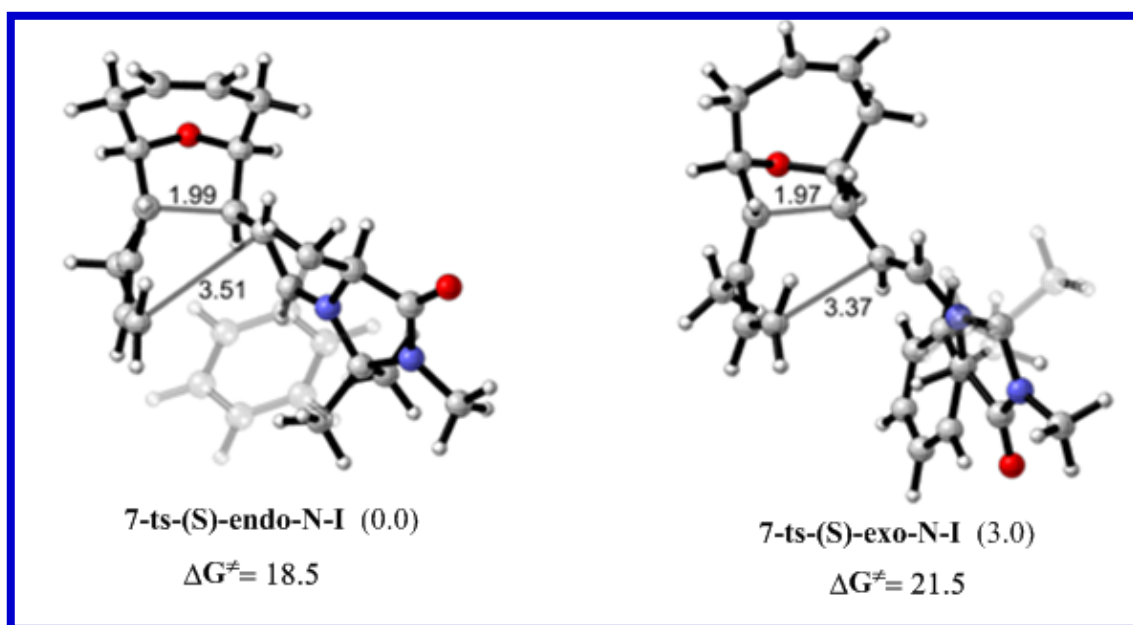


Figure 5.7. Most stable *endo* and *exo* transition structures of seven membered ring with (S)- enantiomer of MacMillan's Catalyst.

Table 5.2. Calculated barriers for the intramolecular Diels-Alder reaction of seven membered ring with (S)-Enantiomer of the MacMillan Catalyst in gas phase and solution.

B3LYP/6-31+G*				M062X/6-31+G*// B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{(\text{GAS})}$	$\Delta G^\ddagger (\text{MeCN})$	$\Delta G^\ddagger (\text{H}_2\text{O})$
7-ts-(S)-endo-N	18.5	15.5	15.8	10.6	13.5	13.6
7-ts-(S)-exo-N	21.5	19.6	20.2	17.3	20.7	20.8

The *endo* preference of seven membered ring with (R)- MacMillan Catalyst can be clarified with the attack of dienophile in a sterically unhindered way; attack from bottom away from benzyl group is favoured as explained by MacMillan [98]. Also, 7-ts-R-*endo*-N-I includes a stabilizing C-H... π interaction between one of the methyl groups of imidazolidinone ring and the phenyl ring of benzyl group as explained by Houk [100]. For (S)- MacMillan catalyzed reaction, the iminium intermediate attacks from the bottom, the

endo selectivity is favoured. It's favoured since in both of the transition structures stabilizing C-H... π interaction is present.

A second contribution may arise from the angles of 2-3-4 and 2-1-5. These two angles include the contribution of ester oxygen in the chain connecting diene and dienophile and, presumably play an important role in stereoselectivity. For 7-*ts1-(R)-endo-N-I* and 7-*ts1-(S)-endo-N-I* structures these angles are 108.7° and 108.5°, 108.5° and 108.5°, respectively. Being almost identical and being equal in both transition structures, may create a balance on forming tetrahydrofuran ring and therefore may favour *endo* transition state. It has something to do with the stereo-preference, since it seems like the design of organocatalyst is not only crucial for its geometry control, but also crucial for *endo* approach tendency of seven membered ring. It adjusts the critical angle and dihedrals through +N=C bond. The above mentioned angles are not identical and equal for *exo* ones. For example, 2-3-4 and 2-1-5 angles are 106.6° and 111.7° for 7-*ts-(R)-exo-N-I*.

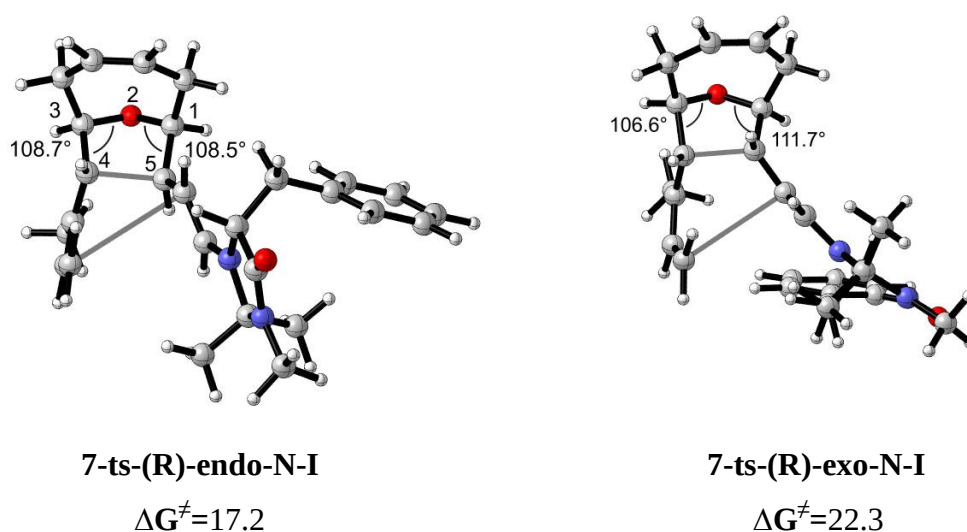


Figure 5.8. Most stable *endo* and *exo* transition structures of seven membered ring with (R)- enantiomer of MacMillan's Catalyst showing critical angles.

5.3. Cycloaddition Reactions of Eight Membered Ring

5.3.1. Reaction of Eight Membered Ring with (R)- MacMillan's Catalyst

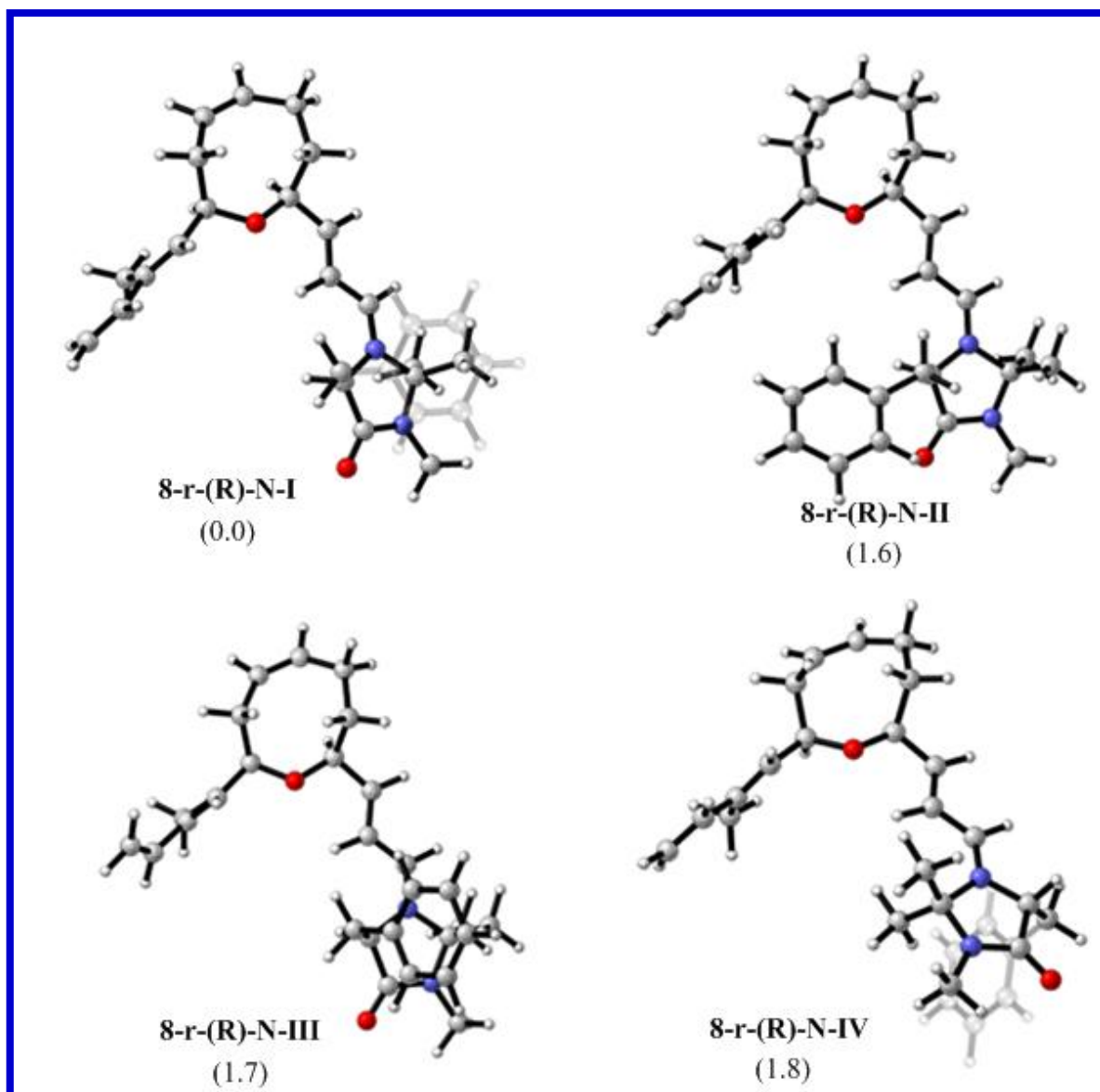


Figure 5.9. Eight membered ring reactant conformers with the (R)- enantiomer of MacMillan's Catalyst.

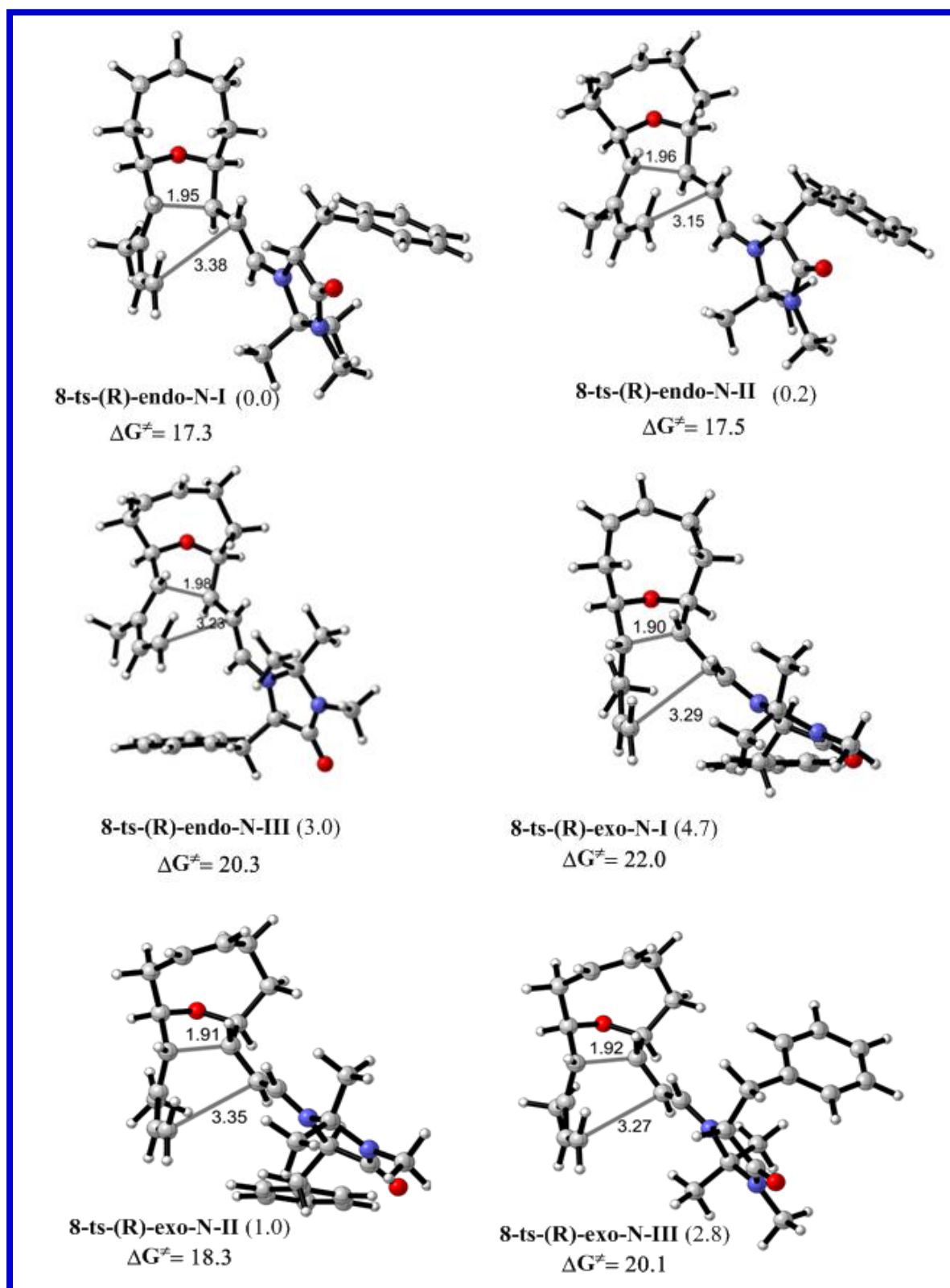


Figure 5.10. Most stable transition structures of eight membered ring corresponding to *endo* and *exo* ones with the (R)- enantiomer of MacMillan's Catalyst.

5.3.2. Reaction of Eight Membered Ring with the (S)- MacMillan's Catalyst.

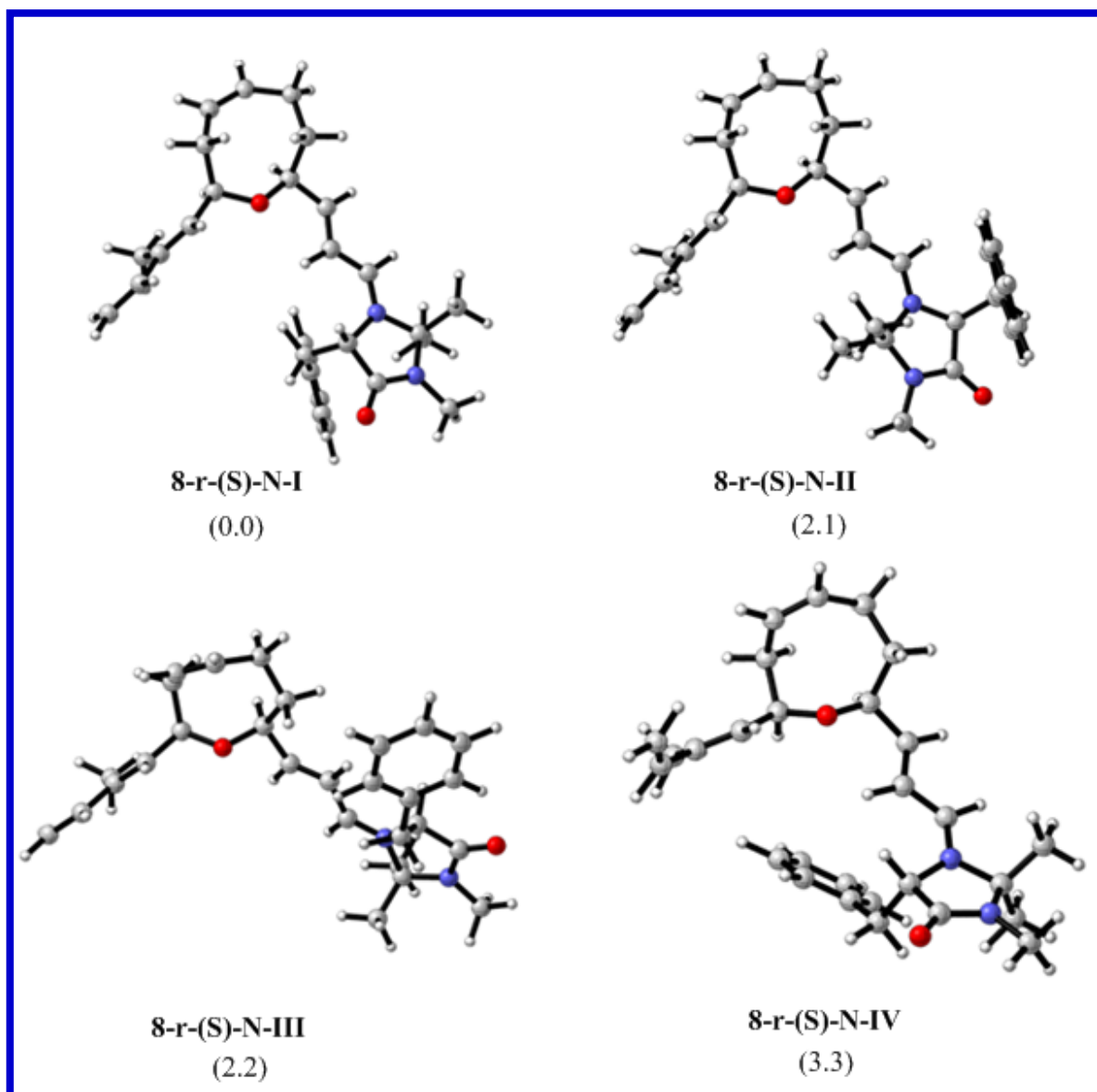


Fig. 5.11. Eight membered ring reactant conformers with the (S)- enantiomer of MacMillan's catalyst.

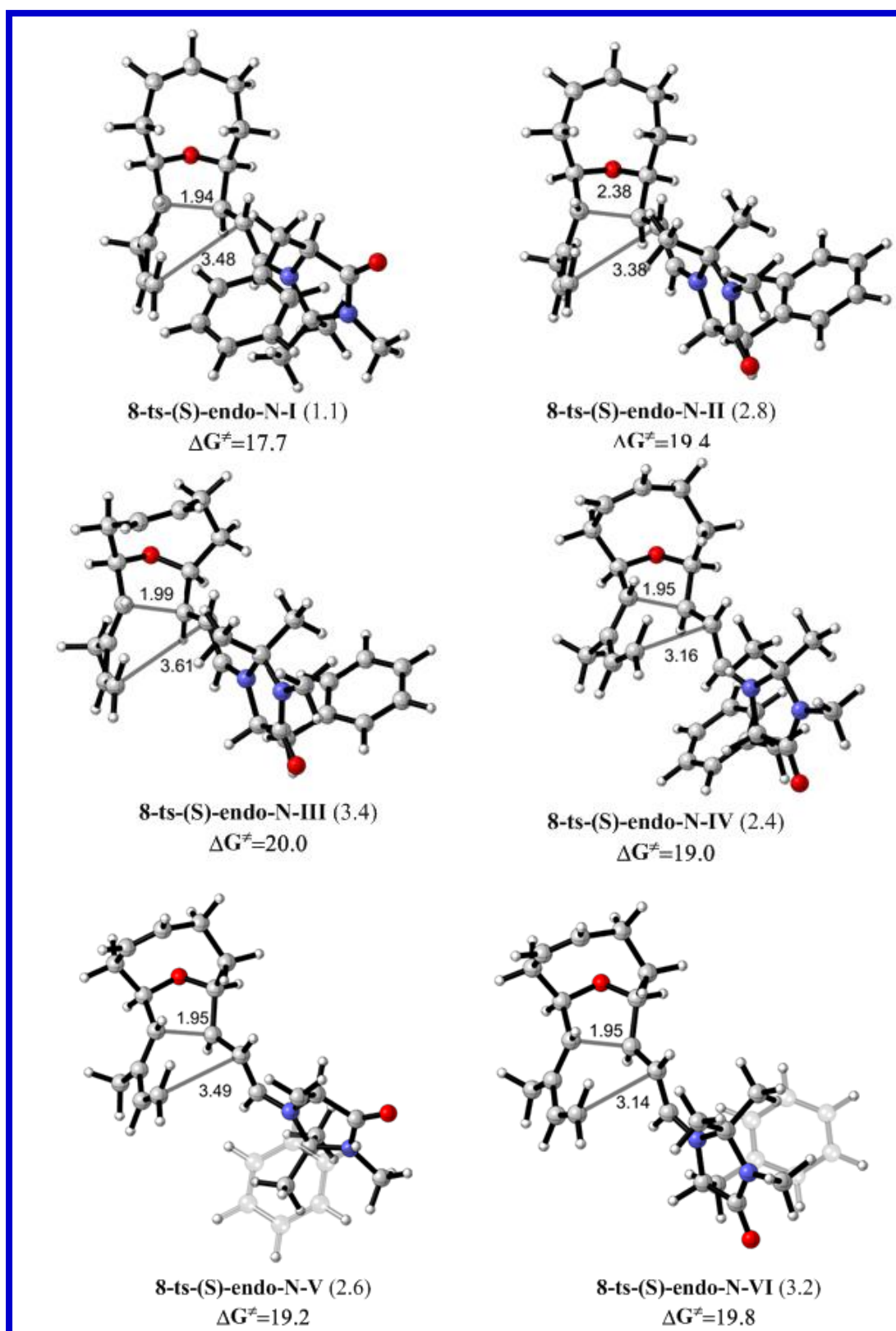


Figure 5.12. Most stable *endo* transition structures of eight membered ring (S)- enantiomer of MacMillan's Catalyst.

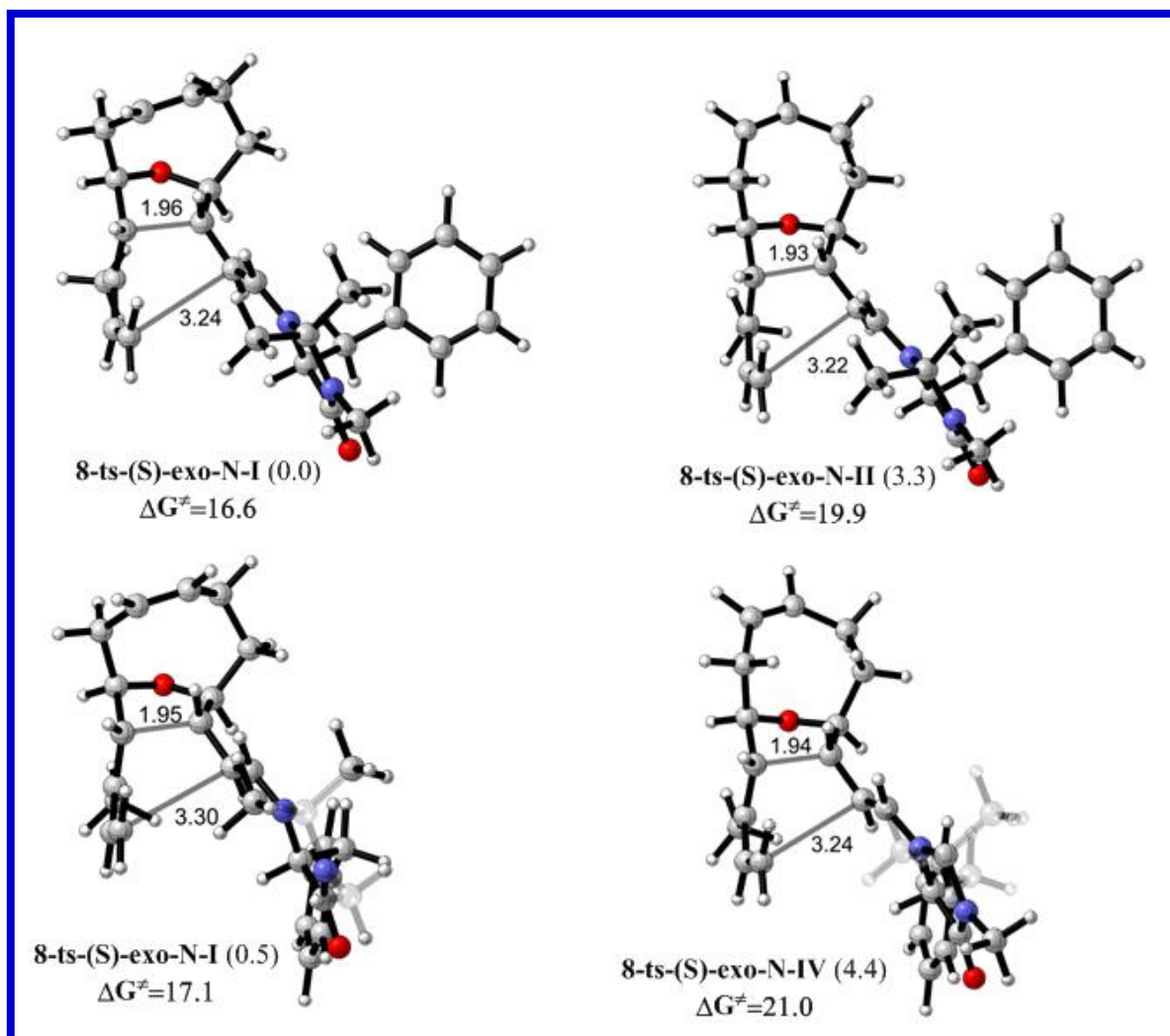


Figure 5.13. Most stable *exo* transition structures of eight membered ring with the (S)- enantiomer of MacMillan's Catalyst.

For the (R)- and (S)- catalyzed reactions, in the most stable *endo* transition structures the eight membered ring adopts the “up” conformation (Figure 5.10 and Figure 5.12), while in the most stable *exo* transition structures, the eight membered ring adopts the “down” conformation to minimize the transannular interactions. C-H... π stabilizing effect is present in *8-ts-(R)-endo-N-I* which favours *endo* diastereoisomer in gas phase. For the (S)- catalyzed reaction, the observed diastereomeric mixture can be attributed to the present C-H... π stabilizing effect of both *endo* and *exo* transition structures.

Table 5.3. Calculated barriers for the intramolecular Diels-Alder reaction of eight membered ring with the (R)- enantiomer of the MacMillan's Catalyst in gas phase and solution.

B3LYP/6-31+G*				M062X/6-31+G*// B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{(GAS)}$	$\Delta G^\ddagger_{(MeCN)}$	$\Delta G^\ddagger_{(H_2O)}$
8-ts-(R)-endo-N-I	17.3	14.4	14.8	8.8	11.9	12.0
8-ts-(R)-exo-N-I	18.3	16.3	17.0	12.9	17.0	17.1

Table 5.4. Calculated barriers for the intramolecular Diels-Alder reaction of eight membered ring with the (S)- enantiomer of the MacMillan's Catalyst in gas phase and solution.

B3LYP/6-31+G*				M062X/6-31+G*// B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{(GAS)}$	$\Delta G^\ddagger_{(MeCN)}$	$\Delta G^\ddagger_{(H_2O)}$
8-ts-(S)-endo-N-I	17.7	15.7	16.1	10.9	13.4	13.4
8-ts-(S)-exo-N-I	16.6	14.2	14.9	9.1	13.7	13.8

5.4. Cycloaddition Reactions of Nine Membered Ring

5.4.1. Reaction of Nine Membered Ring with (R)- MacMillan's Catalyst

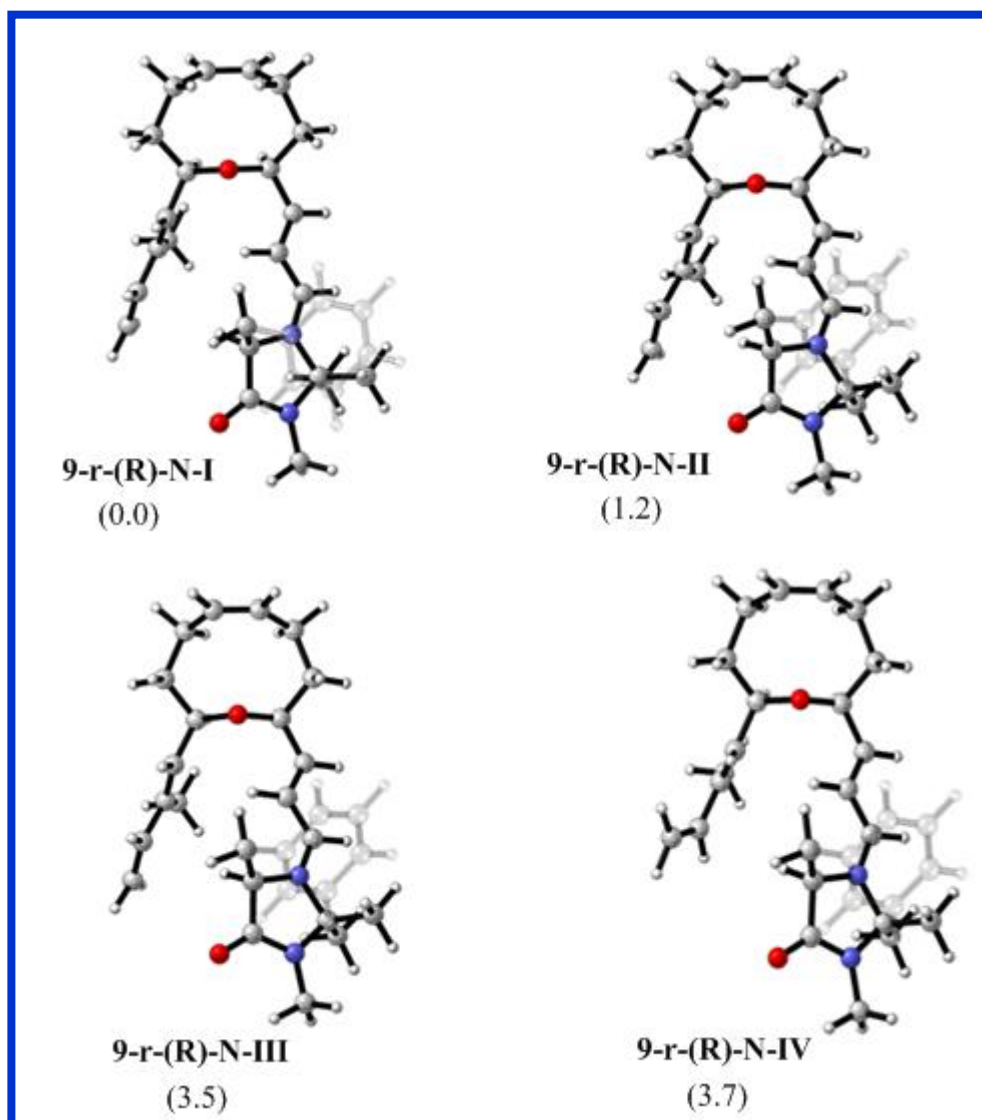


Fig. 5.14. Nine membered ring reactant conformers with the (R)- enantiomer of MacMillan's Catalyst.

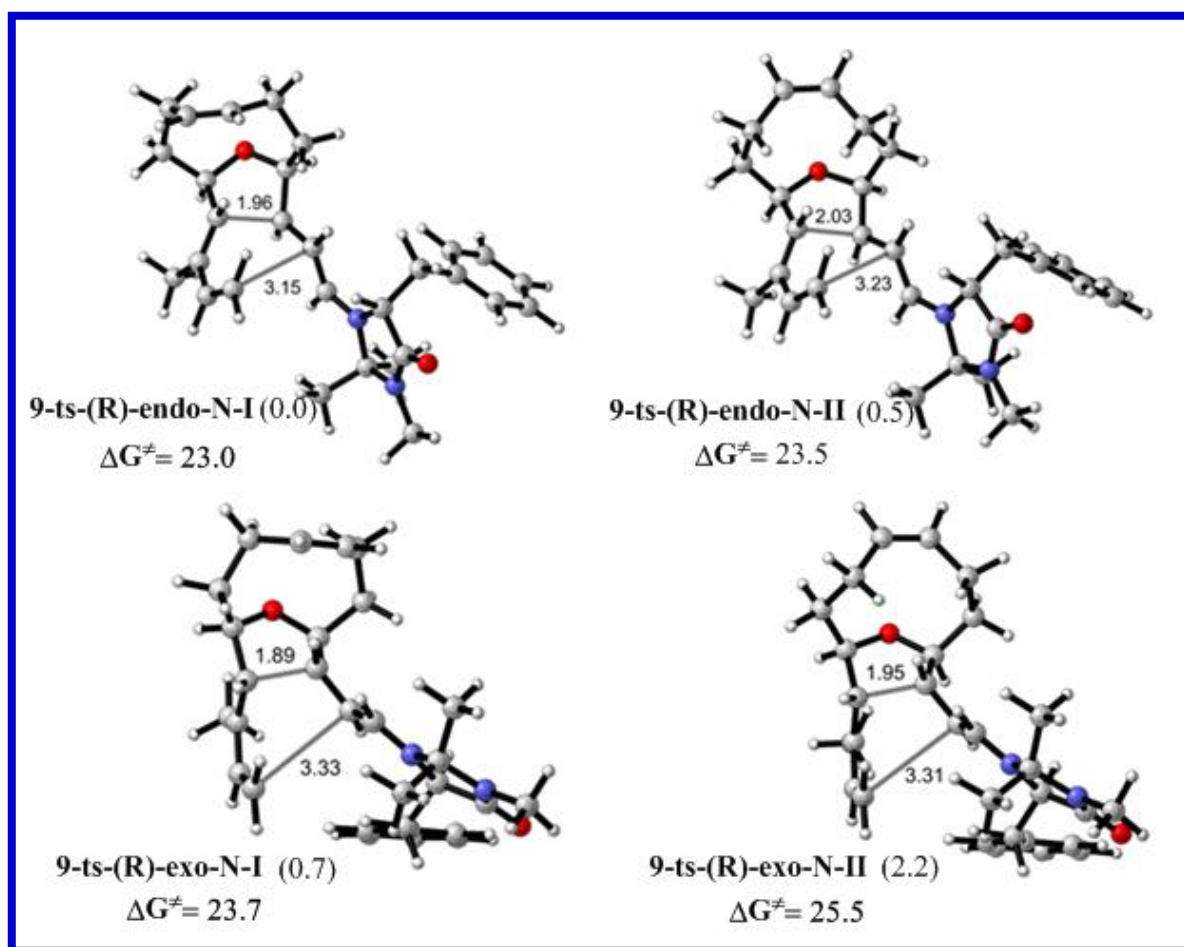


Figure 5.15. Most stable *endo* and *exo* transition structures of nine membered with the (R)- enantiomer of MacMillan's Catalyst.

Table 5.5. Calculated barriers for the intramolecular Diels-Alder reaction of nine membered ring with (R)-enantiomer of the MacMillan Catalyst in gas phase and solution.

	B3LYP/6-31+G*			M062X/6-31+G*// B3LYP/6-31+G*		
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger$ (GAS)	$\Delta G^\ddagger$ (MeCN)	$\Delta G^\ddagger$ (H ₂ O)
9-ts-(R)-endo-N-I	23.0	20.2	20.9	19.5	18.9	19.0
9-ts-(R)-exo-N-I	23.7	22.2	23.0	22.1	23.3	23.4

5.4.2 Reaction of Nine Membered Ring with the (S)- MacMillan's Catalyst

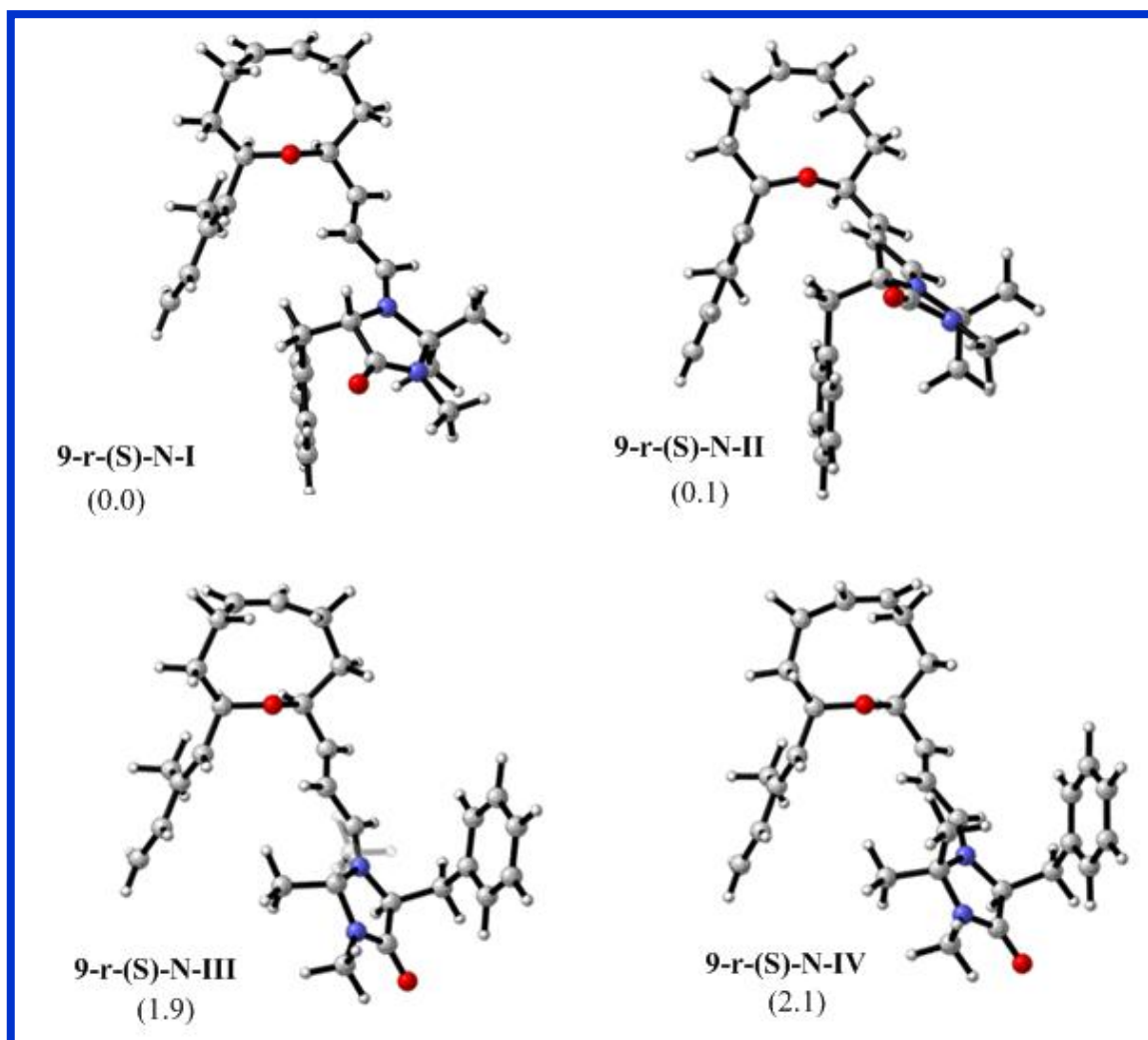


Figure 5.16. Nine membered ring reactant conformers with the (S)- enantiomer of MacMillan's Catalyst.

The observed stereoselectivities of organocatalyzed reactions of nine membered ring are in very nice agreement with the experimental data. The results can be attributed to the presence of CH... π stabilizing interaction which is available in *9-ts-(R)-endo-N-I* and *9-ts-(S)-exo-N-I*.

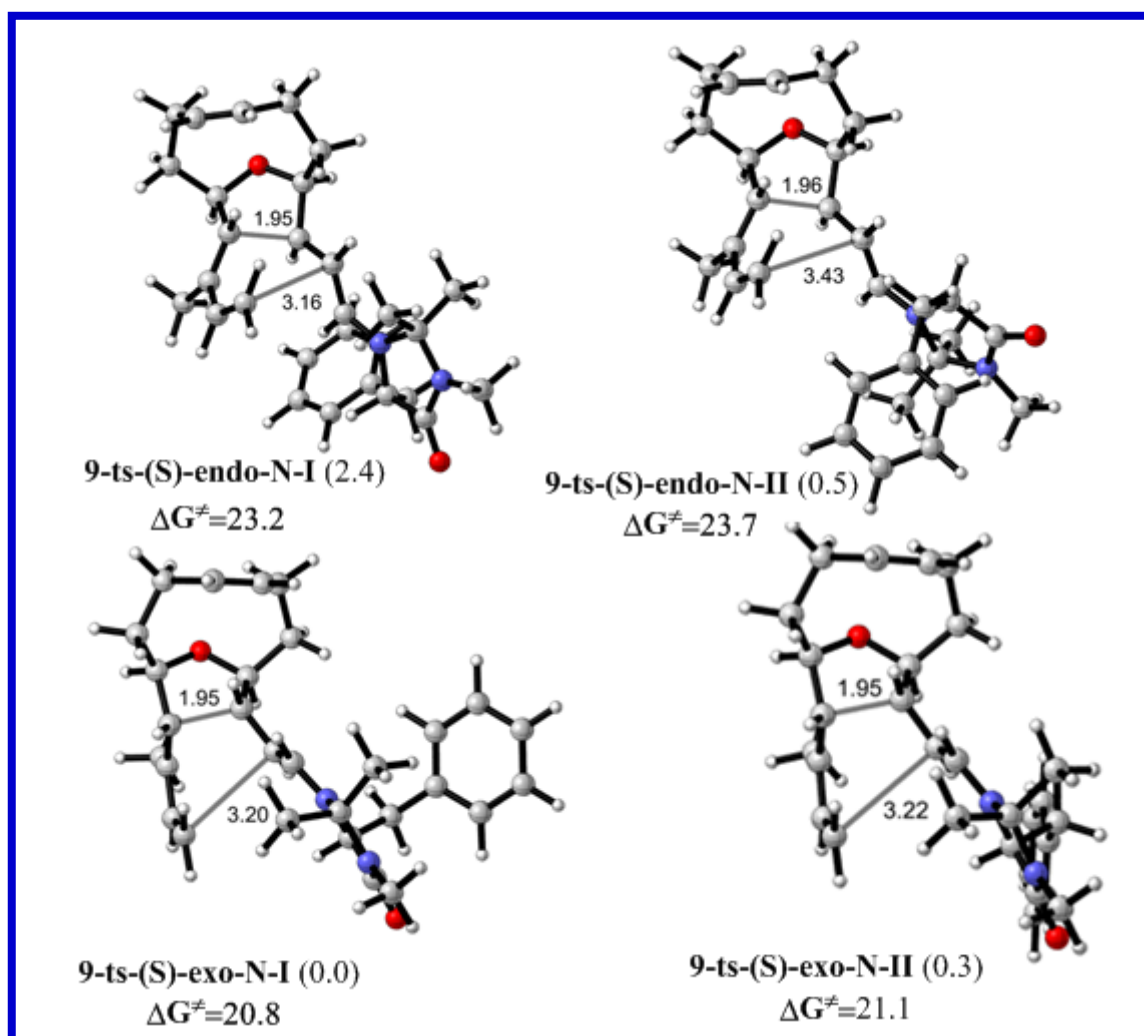


Figure 5.17. Most stable *endo* and *exo* transition structures of nine membered ring with the (S)- enantiomer of MacMillan's Catalyst

Table 5.6. Calculated barriers for the intramolecular Diels-Alder reaction of nine membered ring with (S)-enantiomer of the MacMillan's Catalyst in gas phase and solution.

	B3LYP/6-31+G*				M062X/6-31+G*// B3LYP/6-31+G*	
	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta E^\ddagger$	$\Delta E^\ddagger_{(\text{gas})}$	$\Delta G^\ddagger (\text{MeCN})$	$\Delta G^\ddagger (\text{H}_2\text{O})$
9-ts-(S)-endo-N-I	23.2	21.1	21.8	19.8	23.2	23.3
9-ts-(S)-exo-N-I	20.8	18.6	19.4	16.3	19.3	19.4

5.5. Summary

Figure 5.18 shows the critic dihedrals for the endo diastereoisomers of seven and nine membered rings with the (S)-MacMillan's Catalyst. The dihedral angle of seven and nine membered rings, 3-4-5-1, are compared with the natural tetrahydrofuran ring's. It's clear that the endo transition structure of nine membered ring is distorted, 43.8° , which disfavours the diastereoisomer, while it is 9.5° for the seven membered ring which is planar as tetrahydrofuran ring and it is preferred.

Table 5.7 shows the calculated and experimental *endo:exo* ratios of all cycloaddition reactions in gas phase and in solution. The experimental solvents' results are highlighted with the green box for the reactions of all ring models with aldehyde substituent.

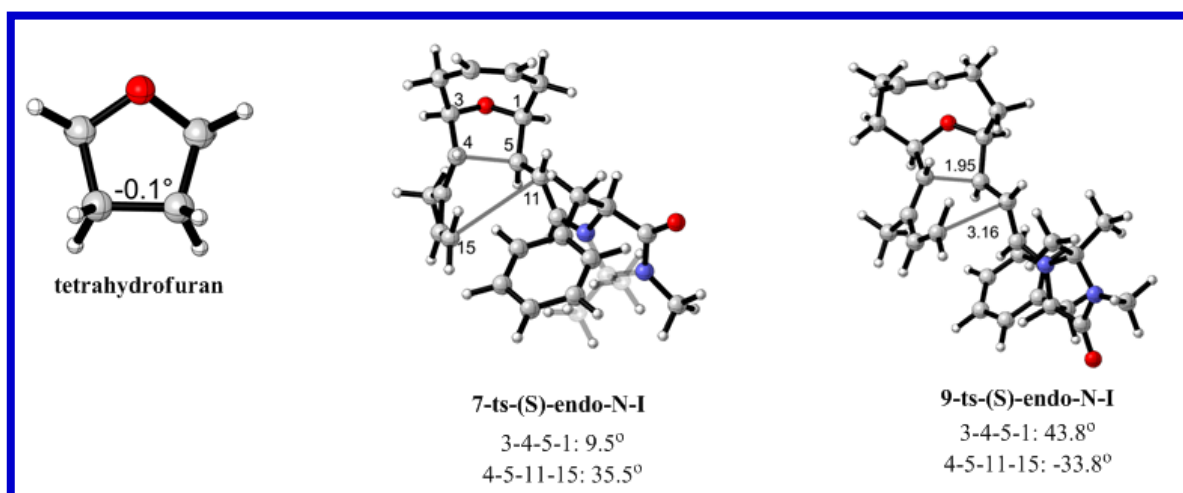


Figure 5.18. The stereo preference of seven and nine membered rings with the (S)-MacMillan's Catalyst (B3LYP/6-31+G*).

Table 5.7. Calculated barriers and *endo/exo* ratios for the all intramolecular Diels-Alder reactions of all ring models.

	$\Delta G^{1\ddagger}_{(gas)}$	$\Delta G^{2\ddagger}_{(gas)}$	$\Delta G^{3\ddagger(a,b)}$	$\Delta G^{3\ddagger}_{(water)}$
7-ts-endo-I	35.1	30.6	27.4	27.8
7-ts-exo-I	35.2	30.8	28.3	28.8
<u>Exp: endo/exo: ---</u>	54:46	58:42	82:28	84:16
7-ts-endo-cis-A-I	30.0	25.0	20.3	19.8
7-ts-exo-cis-A-I	31.1	24.8	22.0	22.3
<u>Exp:endo/exo: 100:0</u>	86:14	42:58	95:5	99:1
7-ts-(R)-endo-N-I	17.2	-	11.5	11.6
7-ts-(R)-exo-N-I	22.3	-	20.4	20.5
<u>Exp:endo/exo:100:0</u>	100:00	-	100:0	100:0
7-ts-(S)-endo-N-I	18.5	-	10.6	13.6
7-ts-(S)-exo-N-I	21.5	-	17.3	20.8
<u>Exp:endo/exo:100:0</u>	99:1	-	100:00	100:00

	$\Delta G^{1\ddagger}_{(gas)}$	$\Delta G^{2\ddagger}_{(gas)}$	$\Delta G^{3\ddagger(a,b)}$	$\Delta G^{3\ddagger}_{(water)}$
8-ts-endo-I	35.9	31.6	28.4	24.7
8-ts-exo-I	34.8	30.4	26.2	22.0
<u>Exp: endo/exo: ---</u>	14:86	12:88	2:98	99:1
8-ts-endo-cis-A-I	31.9	25.7	22.5	22.3
8-ts-exo-cis-A-I	32.2	26.6	22.9	22.9
<u>Exp:endo/exo: 2.5:1</u>	62:38	82:18	66:34	73:27
8-ts-(R)-endo-N-I	17.3	-	11.9	12.0
8-ts-(R)-exo-N-I	18.3	-	17.0	17.1
<u>Exp:endo/exo:100:0</u>	84:16	-	100:0	100:0
8-ts-(S)-endo-N-I	17.7	-	13.4	13.4
8-ts-(S)-exo-N-I	16.6	-	13.8	13.8
<u>Exp:endo/exo:50:50</u>	14:86	-	66:34	66:42

	$\Delta G^{1\#}_{(gas)}$	$\Delta G^{2\#}_{(gas)}$	$\Delta G^{3\#(a,b)}$	$\Delta G^{3\#}_{(water)}$
9-ts-endo-I	36.3	31.2	28.4	29.0
9-ts-exo-I	35.0	29.9	27.6	28.4
<i>Exp: endo/exo: ---</i>	<i>10:90</i>	<i>10:90</i>	<i>18:82</i>	<i>21:79</i>
9-ts-endo-cis-A-I	30.9	25.5	21.2	20.8
9-ts-exo-cis-A-I	31.6	27.2	23.7	23.8
<i>Exp: endo/exo: 75:25</i>	<i>76:24</i>	<i>95:5</i>	<i>99:1</i>	<i>99:1</i>
9-ts-(R)-endo-N-I	23.0	-	18.9	21.1
9-ts-(R)-exo-N-I	23.7	-	23.3	24.0
<i>Exp: endo/exo: 15:1</i>	<i>76:24</i>	-	<i>100:0</i>	<i>100:0</i>
9-ts-(S)-endo-N-I	23.2	-	23.2	23.3
9-ts-(S)-exo-N-I	21.1	-	19.3	19.4
<i>Exp: endo/exo: 0:100</i>	<i>3:97</i>	-	<i>0:100</i>	<i>0:100</i>

¹ indicates the B3LYP/6-31+G* optimization in gas phase,

² indicated M062X/6-311+G** optimization in gas phase

³ indicates M062X/6-31+G*//B3LYP/6-31+G* calculations in the gas phase

^a denotes chloroform for the uncatalyzed reaction of seven and eight membered rings;

^b denotes acetonitrile for the organocatalyzed reactions of all ring models;

^c denotes toluene for the uncatalyzed reaction of nine membered ring

6. CONCLUSIONS

DFT calculations were carried out in order to rationalize the stereoselective preference of seven, eight and nine membered rings with chiral imidazolidinones. The uncatalyzed reactions of all ring models are compared with the organocatalyzed cycloadditions. For the uncatalyzed reaction, the aldehyde substitution increases the rate of thermal reactions: HOMO-LUMO gap is minimized. The rate of reaction of eight membered ring is lower than the seven membered ring due to the angle compression and long tether length. However, the rate of thermal reactions doesn't decrease as the ring size increases when the structures were optimized with B3LYP/6-31+G* and M062X/6-311+G** in gas phase. The rate of thermal reaction of nine membered ring is higher than the eight membered one. Both of the functionals and basis sets predict the *endo:exo* ratios in nice agreement with the experimental data except for the eight membered ring. Calculations with B3LYP/6-31+G* and M062X/6-31+G*//B3LYP/6-31+G* demonstrated that both enantiomers of the MacMillan's Catalysts decrease the activation energies of the intramolecular Diels-Alder reactions of all ring models. The formation of the iminium complex produces a much more reactive dienophile. Different stereoselectivities are observed for the imidazolidinone catalyzed cycloaddition reactions of seven, eight and nine membered rings. Although a number of different conformers of iminium intermediates and transition states are located, steric effects and CH... π stabilizing interaction and distortion of tetrahydrofuran ring are found to play important roles for the preferred diastereoselectivities.

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