

MODELING THE SELECTIVITY, CATALYTIC AND BINDING
EFFECTS IN ORGANIC REACTIONS AND PROTEIN ENVIRONMENT

by

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To my family

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ABSTRACT

MODELING THE SELECTIVITY, CATALYTIC AND BINDING EFFECTS IN ORGANIC REACTIONS AND PROTEIN ENVIRONMENT

In this dissertation, quantum chemical tools, in particular density functional methods are used to address problems related with the selectivity, catalytic and binding effects in different fields of chemistry, such as materials science, organic chemistry and biochemistry. The selectivity of photoluminescent polymers towards analytes in the explosive detection field has been investigated by modelling the complexes between the polymers and analytes. The simulated optoelectronic properties of the polymers and their complexes with the analytes highlighted the detection mechanism based on fluorescence quenching. The mechanism and selectivity in the asymmetric desymmetrization of *meso*-cyclic anhydrides induced by cinchona alkaloids have been investigated and base catalysis mechanism has been shown to operate in these reactions. The origins of stereoselectivity have been attributed to the spatial arrangement of the cinchona alkaloid catalyst in the transition state of asymmetric desymmetrization reaction related with the oxyanion stabilization. The inverse electron demand Diels-Alder reaction of phthalazine and siloxy alkyne activated by Ag(I)-bipyridine catalysis have been modeled and the barriers are compared with the uncatalyzed cycloaddition reaction to highlight the catalytic effect of Ag(I)-bipyridine. It has been shown that the primary role of Ag(I)-bipyridine catalyst in an inverse electron demand Diels-Alder reaction is to facilitate the overlap between HOMO of the dienophile and LUMO of the diene by reducing the energy gap. The iron binding-release mechanisms have been investigated in the cluster models of transferrin, iron binding protein. Possible routes for iron release are evaluated on the basis of the thermodynamic stabilities of the models.

ÖZET

ORGANİK REAKSİYONLARDA VE PROTEİN ORTAMINDA SEÇİCİLİĞİN, KATALİTİK VE BAĞLANMA ETKİLERİN MODELLENMESİ

Bu tezde kuantum kimyasal yöntemlerle, özellikle yoğunluk fonksiyoneli teorisi kullanılarak, malzeme kimyası, organik kimya ve biyokimya gibi kimyanın çeşitli alanlarında seçicilik, katalitik ve bağlanma etkileri ile ilintili konular ele alındı. Fotolüminesan polimerlerin analit maddelere seçiciliği polimer ve analit komplekslerinin modellenmesi ile incelendi. Polimerlerin ve analitlerle oluşturdukları komplekslerin optoelektronik özelliklerinin, bu polimerlerin floresans sönümlenmesine dayalı patlayıcı tespit mekanizmalarına olan etkileri araştırıldı. Kınakına alkaloidlerinin katalizlediği mezo-siklik anhidritlerin asimetrik desimetrisasyon tepkimelerinde mekanizma ve seçicilik incelendi. Baz kataliz mekanizmasının bu tepkimelerde etkili olduğu gösterildi. Kınakına alkaloid katalizörlerinin geçiş konumundaki oksianyonun stabilizasyonu ile ilgili konumunun stereoseçiciliğe neden olduğu gözlemlendi. Ag(I)-bipiridin tarafından katalizlenen ftalazin ve siloksi alkinin ters elektron akışı Diels-Alder tepkimeleri modellendi ve Ag(I)-bipiridin'in katalitik önemini anlamak üzere reaksiyon sürecindeki eşik enerjileri katalizörsüz siklik katılım tepkimeleri ile karşılaştırıldı. Ag(I)-bipiridin katalizörünün orbitaller arası enerji farkını düşürerek dienofilin HOMO ve dienin LUMO etkileşimini kolaylaştırdığını gösterildi. Demir bağlayan transferin proteinin de demir bağlama-bırakma mekanizmaları küçük küme modelleri üzerinden incelendi. Olası demir salınımı yolları modellerinin termodinamik kararlılıkları kıyaslanarak değerlendirildi.

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LIST OF SYMBOLS

E	Electronic energy
$E^\ddagger$	Electronic activation energy
$E_{xc}[\rho(r)]$	Exchange-correlation energy
H	Hamiltonian operator
$J[\rho(r)]$	Classical Coulomb energy
$T_{ni}[\rho(r)]$	Kinetic energy of non-interacting electrons
$V(r)$	External potential
Z	Atomic number
ΔG_{sol}	Solvation free energy
ΔG_{elec}	Electrostatic free energy
$\Delta G^\ddagger$	Gibbs free energy of activation
$\nabla^2 \rho(r)$	Laplacian of electron density
f_i	Fock operator
$G(r)$	Kinetic energy density
$H(r)$	Total energy density
χ	Spin-orbital
m_i	Mass of a particle
pK_a	Acid dissociation constant
$\rho(r)$	Electron density
ψ	Wave function

LIST OF ACRONYMS/ABBREVIATIONS

Arg	Arginine
Asp	Aspartic acid
B3LYP	Becke-3-parameter Lee-Yang-Parr functional
C-PCM	Conductor-like polarizable continuum model
DFT	Density functional theory
D-PCM	Dielectric polarizable continuum model
ECP	Effective core potential
FMO	Frontier molecular orbital
GGA	Generalized gradient approximation
GTO	Gaussian type orbital
HF	Hartree-Fock theory
His	Histidine
HOMO	Highest occupied molecular orbital
IEDDA	Inverse electron demand Diels-Alder
IEF-PCM	Integral equation formalism polarizable continuum model
IRC	Intrinsic reaction coordinate
LCAO	Linear combination of atomic orbitals
LDA	Local density approximation
LUMO	Lowest unoccupied molecular orbital
Lys	Lysine
M06-2X	Hybrid meta exchange-correlation functional
MPWB1K	Modified Perdew-Wang-Becke 1 Parameter Method for Kinetic
NPA	Natural population analysis
PCM	Polarizable continuum model
PES	Potential energy surface
SCF	Self consistent field
SD	Slater Determinant
STO	Slater type orbital
TDDFT	Time-dependent density functional theory
Tyr	Tyrosine

1. INTRODUCTION

Computational chemistry today is providing computational techniques capable of addressing and solving a wide range of problems in many different fields of chemistry. From traditional chemistry, such as synthesis and analysis, to modern fields, such as material science and drug development, computational chemistry has demonstrated its usefulness in numerous research areas.

Theoretical modeling of organic molecules and reactions is a powerful tool leading to further insight into these chemical systems. The systems that can be considered in molecular modeling range from small isolated molecules to biological macromolecules like proteins and DNA. Theoretical studies complement the experimental studies and may even offer some advantages. For instance, modeling allows the investigation of the potential energy surfaces. Thus, it is possible to characterize experimentally challenging short-lived intermediates and to locate transition states that cannot be examined experimentally. The transition states enable one to better understand the reactivity of the system. Modeling can also be used to perform analysis that would be time-consuming and tedious experimentally or clarify puzzling experimental results.

In this dissertation, the use of theoretical modeling to examine the selectivity, and catalytic and binding effects in organic systems and in protein environment will be explored.

Selectivity in organic reactions arises either from different ratios of isomers in the reaction products (stereoselectivity) or from preferred reaction sites (regioselectivity). The selectivity in stereoselective and regioselective organic reactions originates from differences in steric effects and electronic effects in the mechanistic pathways leading to the different products. Catalysts providing an alternative reaction pathway of lower activation energy help to differentiate the transition states leading to different isomeric products in stereoselective and regioselective organic reactions. In this dissertation, the stereoselectivity induced by cinchona alkaloid catalysts in the asymmetric desymmetrization of cyclic anhydrides and regioselectivity of the inverse electron demand

Diels-Alder reaction of 1,2-diazines and siloxy alkynes catalyzed by a transition metal complex, namely Ag(I)-bipyridine, have been explored. The selectivity is determined by the energy differences between competing transition states and therefore is closely related to the reaction mechanisms. Therefore, the mechanisms of the aforementioned reactions are also highlighted with the available computational tools.

Binding selectivity, on the other hand, is defined as ligands selectively bind to a substrate forming a complex. Binding selectivity is an important concern for chemosensor applications which are developed for specific target molecules. The sensor is designed to be an excellent match in terms of the size and shape of the target as well as the interactions between the sensor and the target molecule in order to provide maximum binding selectivity. When the target molecule forms a complex with the sensor; it undergoes a change which can be usually observed in absorbance or luminescence spectra generating a signal. Computational chemistry allows the investigation of the nature of the interactions between a sensor and its target in order to design a chemosensor with maximum binding selectivity. The energies of the complexes of the sensor with its target might be used in that case to evaluate the selectivity. In this dissertation, the selectivity of photoluminescent polymers toward analytes for explosive detection based on fluorescence quenching has been explored by modeling the complexes between photoluminescent silafluorene- and silole-containing polymers as sensors and nitro-containing explosives as target molecules. The interactions promoting the binding have been evaluated and the absorption and emission spectra of the polymers and their complexes are simulated to check the efficiency of the polymers as chemosensors.

Proteins consisting of thousands of amino acid residues perform a vast array of functions within living organisms. With the recent advances in the computational power, computational tools can be used to address specific questions about the properties of the protein related with its specific function often more easily than experiments. Computational tools to model the protein environment are generally divided into two groups: molecular dynamics and quantum chemical approaches. Molecular dynamics can provide the ultimate detail on the function of the protein concerning individual particle motions as a function of time. However, the understanding of the catalytic function of

proteins or the mechanisms that trigger the motion of the protein at an atomistic level is of both fundamental and practical interest. Quantum mechanics complement the simulations by highlighting the interactions that trigger that specific motion or by elucidating the reaction mechanisms in the active site of the protein. As a last topic of this dissertation, the active site of iron binding protein, transferrin that controls the level of free iron in human has been investigated with quantum mechanical tools.

2. OBJECTIVE AND SCOPE

The previous chapter was meant to provide a brief overview on several concepts such as selectivity, catalytic effect and mechanisms in organic reactions and in protein environment that will be further tackled in the following chapters within this dissertation.

The dissertation is organized in the following way. In the next chapter (Chapter 3), the fundamental principles of the performed computations are introduced. Starting from the Schrödinger equation we establish the basis of Hartree-Fock and Density Functional Theory and the description of functionals and basis sets associated with the use of these methods. More detailed explanations on the methodologies are presented within the relevant chapters.

After this brief overview of the theoretical methods, the results of the studies related with the selectivity, catalytic effects and mechanisms will be introduced in four chapters. The first topic of interest (Chapter 4) is the selectivity of photoluminescent polymer sensors toward analytes for explosive detection. In Chapter 4, we try to highlight the interactions for binding selectivity as well as the optoelectronic properties of the material itself and the complexes that would form upon binding by means of computational methods. In the following two chapters (Chapters 5 and 6), the catalytic selectivity is explored for some specific organic reactions along with their reaction mechanisms. In Chapter 5, two proposed mechanisms and the origins of stereoselectivity in the asymmetric desymmetrization of cyclic anhydrides catalyzed by cinchona alkaloids have been explored. In Chapter 6, the effect of silver catalyst have been studied in the inverse electron demand Diels-Alder reaction of 1,2-diazines and siloxy alkynes. In Chapter 7, the release mechanism of iron is investigated in a specific protein, namely transferrin. The crucial conclusions drawn from each chapter and concluding remarks are presented in Chapter 8.

3. THEORETICAL BACKGROUND

Quantum chemistry is a wide research field concerned with the general use of the laws of quantum physics to study chemical problems. This chapter provides the basic principles of the theoretical approaches of the most commonly used methods or the ones used in the present study.

3.1. Quantum Mechanics

Quantum mechanics has been developed to describe microscopic systems. The foundation of quantum mechanics is the Schrödinger equation to describe the electronic properties of the molecules:

$$H\psi = E\psi \quad (3.1)$$

where H is the Hamiltonian operator, E is the energy of the system and ψ is the wave function. ψ describes the system and takes as variables the positions of electrons and nuclei in the system. The Hamiltonian operator represents the energy of the system as a sum of kinetic and potential energy terms of the nuclei and the electrons:

$$H = - \sum_i \frac{\hbar^2}{2m_e} \nabla_i^2 - \sum_k \frac{\hbar^2}{2m_k} \nabla_k^2 - \sum_i \sum_k \frac{e^2 Z_k}{r_{ik}} + \sum_{i<j} \frac{e^2}{r_{ij}} + \sum_{k<l} \frac{e^2 Z_k Z_l}{r_{kl}} \quad (3.2)$$

where m_e and m_k are the masses of the electron and the nuclei, respectively, $\hbar$ is the Planck's constant divided by 2π , ∇^2 is the Laplacian operator, e is the charge on the electron, Z is an atomic number and r is the distance between the particles. In Equation 3.2, the first two terms give the kinetic energy of the electrons and the nuclei respectively, the third term gives the attraction of the electrons to the nuclei and the last two terms give the interelectronic and internuclear repulsions respectively.

The Schrödinger equation can be solved exactly for small systems. Unfortunately, no exact solutions can be found for many-particle systems because of the correlated motions of the particles. However, some approximations can be made to overcome this problem. Since the nucleus of the molecule is much more massive than the electrons, its movements compared to the electrons are negligible. In this case, they can be considered to be frozen and their kinetic energy set to zero. Born-Oppenheimer approximation suggests the elimination of the attractive electron-nuclear potential energy term, taking the nuclear kinetic energy term independent of the electrons, and considering the nuclear-nuclear potential energy term constant and hence, the Schrödinger equation with respect to Born-Oppenheimer approximation becomes:

$$(H_{el} + V_{nn})\psi_{el} = E_{el}\psi_{el} \quad (3.3)$$

The eigenfunctions of Equation 3.3 for a molecular system are the molecular orbitals (MO) which are constructed as a linear combination of atomic orbitals (the LCAO approach, [1]).

The variational principle is used to solve Equation 3.3. The variational theorem states that the value calculated for the total energy of a trial wave function can only be greater than or equal to the ground-state energy, E_0 . This method provides a criterion for establishing the “best” wavefunction, subject to a given set of constants. From now on, the two methods based on the variational method (the Hartree-Fock method and Density functional theory) will be described.

3.2. Hartree-Fock Theory

The Hartree-Fock method is the central method for all *ab initio* quantum chemistry methods. Within the HF method, the wave function is approximated by a single Slater determinant:

$$\psi_{SD} = \frac{1}{\sqrt{N!}} \begin{vmatrix} \chi_1(1) & \cdots & \chi_N(1) \\ \vdots & \ddots & \vdots \\ \chi_1(N) & \cdots & \chi_N(N) \end{vmatrix} \quad (3.4)$$

which is constructed from a set of N single-electron wave functions (N being the total number of electrons in the molecule and χ a spin-orbital equal to the spin function multiplied by the spatial wave function). By applying the variational method to a single Slater determinant, the calculation of the lowest possible energy is possible through the optimization of the orbitals χ . The equations formed are called Hartree-Fock equations,

$$f_i \chi_i = \varepsilon_i \chi_i \quad (3.5)$$

and their solution determines the best spin orbitals for which E will reach its lowest value. In Equation 3.5, f_i is the Fock operator, χ_i is an eigenfunction of f_i and ε_i is the corresponding energy of the orbital. The one electron Fock-operator is defined for each electron i as

$$f_i = -\frac{1}{2} \nabla_i^2 - \sum_k^{nuclei} \frac{Z_k}{r_{ik}} + V_{HF}(i) \quad (3.6)$$

where the final term $V_{HF}(i)$ is the Hartree-Fock potential. $V_{HF}(i)$ represents the average repulsive potential experienced by each electron due to the other electrons. Now the interaction of each electron with the static field of all of the other electrons includes exchange effects on the Coulomb repulsion.

The Hartree-Fock method is also called the self-consistent field (SCF) method because the minimum value of energy at which the first derivative of the electronic energy with respect to the molecular orbital is reached by an iterative process. The SCF method starts with an initial guess for molecular orbitals of a given molecular geometry, χ_i is calculated and used to generate a new V_{HF} . This process is repeated until the cycle converges.

The fundamental assumption of HF theory that each electron moves in the average field created by all other electrons, without knowing their instantaneous positions introduces errors that can have profound chemical consequences. There are methods based on the calculation of the wave function including the electron correlation effects, but these methods are computationally very expensive. Instead density functional methods which will be the focus of the following part offer a cheaper solution of this problem.

3.3. Density Functional Theory

Density Functional Theory (DFT), in contrast to Hartree-Fock Theory, is based on the electron density, rather than on wave functions. Hohenberg-Kohn theorems [2] proposed in 1964 are the basic idea of DFT. The first theorem states that the electron density $\rho(r)$ determines the external potential $V(r)$ and the second theorem introduces the variational principle. As a result, for a given electron density, there exists only one particular distribution of nuclei with their given charges and the energy is minimized with respect to $\rho(r)$.

The electron density is defined as:

$$\rho(r) = N \int \dots \int |\psi(r_1, r_2, \dots, r_n)|^2 dr_1 dr_2 \dots dr_n \quad (3.7)$$

where r represents both spin and spatial coordinates of electrons. The ground state electronic energy is a function of electron density function implying the "functional" part of DFT and is expressed as:

$$E[\rho(r)] = \int V(r)\rho(r)dr + T[\rho(r)] + V_{ee}[\rho(r)] \quad (3.8)$$

where the first term describes the interactions of the electrons with the external potential, $T[\rho(r)]$ is the kinetic energy of the interacting electrons and $V_{ee}[\rho(r)]$ is the

interelectronic interaction energy. Although the Hohenberg-Kohn theorems emphasize the existence of a functional relating the electron density and the energy of a system, the form of such functional is not stated.

In 1965, Kohn and Sham [3] developed a formalism which is the foundation for the current application of DFT. They proposed to take as a starting point a fictitious system of non-interacting electrons. According to Kohn and Sham theory, the electronic energy of the ground state of a system can be written as:

$$E[\rho(r)] = \int V(r)\rho(r)d(r) + T_{ni}[\rho(r)] + J[\rho(r)] + E_{xc}[\rho(r)] \quad (3.9)$$

In Equation 3.9, the first term describes the interactions of the electrons with the external potential, $T_{ni}[\rho(r)]$ represents the kinetic energy of the non-interacting electrons, $J[\rho(r)]$ corresponds to the classical Coulomb interaction between electrons and $E_{xc}[\rho(r)]$ is known as the exchange-correlation term which accounts for the correction to the kinetic energy arising from the interacting nature of electrons and nonclassical corrections to the electron-electron repulsion energy. The wave function of this system can be expressed as a Slater determinant of one-electron functions χ_i and the electron density can be represented as:

$$\rho(r) = \sum_{i=1}^N \langle \chi_i | \chi_i \rangle \quad (3.10)$$

The Kohn-Sham orbitals are determined by solving the Kohn-Sham equations.

$$h_i^{KS} \chi_i = \varepsilon_i \chi_i \quad (3.11)$$

where the Kohn-Sham Hamiltonian, h_i , is defined as:

$$h_i^{KS} = -\frac{\nabla^2}{2} - \sum_k^M \frac{Z_k}{|r_i - r_k|} + \int \frac{\rho(r)}{r_{ij}} dr + V_{xc} \quad (3.12)$$

In Equation 3.12, V_{xc} is the exchange-correlation potential and is related to exchange-correlation energy by:

$$V_{xc} = \frac{\delta E_{xc}}{\delta \rho} \quad (3.13)$$

where V_{xc} is divided into two parts: an exchange functional $E_x[\rho]$ and a correlation functional $E_c[\rho]$:

$$E_{xc}[\rho] = E_x[\rho] + E_c[\rho] \quad (3.14)$$

The exchange term is associated with the interactions between electrons of the same spin, whereas the correlation term essentially represents the interactions between electrons of opposite spin. The exchange-correlation energy is the only unknown term in Equation 3.9 and hence should be approximated.

3.3.1. Functionals

$E_{xc}[\rho(r)]$ term does not only include the contributions of exchange and correlation, but also the difference in kinetic energy between the fictitious non-interacting system and the real system. However, the exact form of this functional is not known and the “functionals” described here represent different approximations to this exchange-correlation functional.

Local Density Approximation (LDA) is the base for most of the exchange-correlation functionals. In LDA the electron density is assumed to be the same everywhere (uniform electron gas). However, the constant value of the electronic density is not consistent with the rapid variation of densities in a molecule. Generalized gradient approximation (GGA) methods take into account the inhomogeneous nature of the electron density by making the exchange and correlation energies dependent not only on the density but also on its gradient.

Hybrid density functional methods are alternative approaches that combine the exchange-correlation of GGA method with a percentage of HF exchange. A famous example of hybrid density functional is B3LYP [4,5] which is a mix between LDA and GGA functionals taken from the DFT and HF methods as shown below:

$$E_{XC}^{B3LYP} = (1 - a)E_X^{LSDA} + aE_X^{HF} + b\Delta E_X^B + (1 - c)E_C^{LSDA} + cE_C^{LYP} \quad (3.15)$$

where a , b , and c were optimized to 0.20, 0.72, and 0.81, respectively using a set of atomization energies, ionization potentials, proton affinities and total atomic energies and LSDA (Local Spin Density Approximation), HF (Hartree-Fock), B (Becke) and LYP (Lee-Yang-Parr) are the functionals.

M06-2X [6] is another hybrid functional introduced by Zhao *et al.* and this hybrid functional is extensively used in this thesis. The hybrid exchange-correlation can be written as follows:

$$E_{XC}^{hyb} = \frac{X}{100}E_X^{HF} + \left(1 - \frac{X}{100}\right)E_X^{DFT} + E_C^{DFT} \quad (3.16)$$

where X ($X=54$ in the case of M06-2X functional) is the percentage of Hartree-Fock exchange in the hybrid functional and corresponds to a in Equation 3.15.

3.3.2. Time-Dependent Density Functional Theory

DFT is very successful for the ground state properties of electrons in time-independent potentials. However, properties of excited states cannot be addressed with the ground state density used in DFT. Thus, Time-Dependent Density Functional (TDDFT) extends the discussion of ground state in DFT formalism to time dependent potentials and hence to excited-states. As Hohenberg-Kohn theorem to DFT, Runge-Gross theorem [7] is the fundamental theory of TDDFT. Runge-Gross theorem simply states the existence of a one-to-one correspondence between a given external potential and an associated electronic density up to a purely time-dependent function. Runge and Gross also developed a Kohn-

Sham like scheme for time-dependent electronic densities. TDDFT is an exact theory most widely used in the linear response regime that yields exact excited-state energies and oscillator strengths. For valence excited states, TDDFT offers accuracy with a low cost of computational time [8].

3.4. Basis Sets

A basis set is a set of functions to describe the orbitals within a system. Basis functions are usually expanded as a linear combination of atomic orbitals with the coefficients to be determined. These basis sets can be classified into two main types: Slater-type and Gaussian-type orbitals (STOs and GTOs, respectively), the latter being the extensively studied one in modern DFT.

Valence orbitals can vary widely as a function of chemical bonding, so it is important to have more flexibility in the valence basis functions than in the core. Such basis sets, where the core and valence orbitals are treated differently, are called split valence basis sets and have been developed by Pople.

Basis sets can be further modified with the addition of two functions: polarization and diffuse functions. Polarization functions add higher angular momentum orbital to all heavy atoms designated with a * or (d). Hydrogen atoms can be polarized as well, this would be done by ** or (d,p). Diffuse functions, represented by a “+”, allow orbitals to occupy larger spaces. The inclusion of diffuse functions in the basis sets is important especially in the case of anions, weak interactions and lone pairs.

In the case of transition metals, since the inner core of these atoms is very large and so the number of basis functions used to describe it would be very big; those basis functions can be replaced by an Effective Core Potential (ECP). The effects of the nucleus and the electrons from the inner shell on the valence electrons are modeled as an average effect with ECP allowing the reduction of large systems.

The selection of appropriate functional and basis set for quantum chemical calculations is very important and calculations can often be improved by the addition of diffuse and polarization functions. However, the level of DFT functional and the basis sets should be arranged with respect to the properties of the system modeled as well as to which property of the system we seek for an answer.

3.5. Solvation Models

In quantum chemical calculations, solvation methods are used to mimic the solvent environment of molecular systems in order to obtain more realistic results for reactions in solution phase. Solvent effects can be either taken implicitly and/or explicitly. In explicit solvation models, the molecular nature of the solvent molecules maintained as a discrete number of solvent molecules are explicitly added into the model, whereas in the implicit solvation models a macroscopic (continuous) description is used. An alternative is to choose a combined model in which a limited number of solvent molecules are treated explicitly while the remainder of the solvent is included by a continuum.

In the implicit solvation model, which is also often called continuum solvation model, different physical effects contribute to the overall solvation process and solvation of a free energy of a system is defined as:

$$\Delta G_{sol} = \Delta G_{elec} + \Delta G_{cav} + \Delta G_{disp} \quad (3.17)$$

In this representation, ΔG_{elec} is the electrostatic component of the solute-solvent interaction energy and has a stabilization effect. ΔG_{cav} is the energetic cost of placing the solute in the medium through a cavity. Dispersion interactions between solvent and solute are expressed as ΔG_{disp} which add stabilization to solvation free energy.

Polarizable Continuum Model (PCM) belongs to the class of polarizable continuum solvation models [9]. 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 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. 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) [10] 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) [11,12].

4. SELECTIVITY OF PHOTOLUMINESCENT POLYMERS TOWARDS ANALYTES

Poly(silafluorene-phenylenedivinylene)s and poly((tetraphenyl)-silole-phenylene-divinylene)s are promising materials to be used as chemical sensors for explosives detection. Monomers and dimers of silafluorene- and silole-containing polymers for the detection of nitro containing explosives are modeled with M06-2X/6-31G(d). The geometric features of silafluorene- and silole-containing dimers optimized with M06-2X/6-31G(d) agree well with experimental findings. The binding properties of explosive and non-explosive materials have been differentiated by comparing the relative stabilities of their complexes with silafluorene- and silole-containing dimers. The interactions that promote binding in the complexation of silafluorene- and silole-containing polymers with explosives are studied with a small model to shed light on the origin of the stability of the complexes. The topology of the electron density was analyzed using the QTAIM methodology to understand the nature of the non-covalent interactions that are responsible for analyte-polymer binding. The carbon and germanium analogues of silafluorene-containing dimers are modeled to better understand the role of silicon in these polymeric systems. The calculated HOMO-LUMO energy differences of the complexes of dimers with explosives correlate well with the stability of the complexes; both (HOMO-LUMO and stability) support the selectivities of silafluorene- and silole-containing polymers. The stabilities of the complexes have shown that silafluorene-containing polymer detects the analytes in the order of TNT $\sim$ PA > DNT > RDX > NB while the silole-containing polymer is able to detect the aromatic TNT but is not responsive to the non-aromatic RDX.

The optoelectronic properties of silafluorene- and silole-containing polymers as well as their constituent units have been investigated by modeling the properties of their excited states. Natural Transition Orbital analysis and topological φ_s descriptor assessment have been used to qualitatively and quantitatively characterize the physical nature of the transitions constituting the absorption spectra. The main transitions observed in all oligomers are associated to be a π - π^* transition of the bridging moiety. Lower energy

transitions of charge transfer character are further considered to understand the fluorescence quenching mechanism upon the complexation of these polymers with the analytes. Indeed the charge-transfer character of the first excited state leads to the emergence of thermal deactivation channels and hence to luminescence quenching.

4.1. Introduction

The progress in detection of the explosive materials is of great importance in the fields of forensic investigation, homeland security, military applications, minefield remediation and environmental pollution prevention [13,14]. Besides the physical detection methods, like X-ray imaging, thermal neutron analysis or gas chromatography, which offer high sensitivity and specificity, but some of which are expensive or not easy for field deployment, fluorescence methods are promising because they can be incorporated into portable microelectronic devices and are lower in cost. Therefore, detection based on fluorescence quenching of conjugated photoluminescent polymers in explosive detection is a promising technology to be developed [15]. The use of fluorescent polymers in explosive detection has been adapted for both instrumental and visual imaging approaches. These polymers which constitute highly efficient transport media for electronic excited states (namely excitons) can produce signal gain or amplification in response to interactions with analytes, in that case, with explosives [16]. The amplified signal, mostly in the form of fluorescence quenching, allows the detection of trace explosives that are not sensed by the conventional spectroscopic and imaging techniques employing bulk or trace sampling such as X-ray imaging, thermal neutron analysis or gas chromatography [15].

Hetero- π -conjugated molecules are powerful building blocks for optoelectronic materials. The inclusion of silicon as the heteroatom in these systems can decrease virtual orbitals energy levels substantially due to a strong $\sigma^*-\pi^*$ hyperconjugation effect [17]. This will lead to a general bathochromic shift of both absorption and emission spectra that will easily cover the visible wavelength region. Silafluorenes and siloles are two mostly studied silicon-containing π -conjugated systems to be used as chemical sensors for explosives detection, because of their improved optoelectronic properties [18-25]. The

unique luminescent properties of these molecules are claimed to arise from overlap between the σ^* orbital of the bridging silicon and the π^* orbital of the butadiene moiety, which increases delocalization along the polymer chain [19,25]. Delocalization is further enhanced when silafluorenes and siloles are copolymerized with conjugated organic systems. These polymers show enhanced photoluminescence properties in the solid state, as opposed to most of the luminescent polymers whose emission is quenched by aggregation because of the non-covalent interactions reducing exciton life-time and mobility such as π -stacking [26-28]. As a benefit of this property, silafluorene- and silole-containing polymers (7 and 8, Figure 4.1) can be utilized as thin films where analyte particulates can bind. Any contamination with the explosives can be visualized clearly on these films. These materials are highly sensitive to explosives containing nitroaromatics, nitramines and nitrate esters (Figure 4.2) such as 2,4,6-trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT), picric acid (PA), cyclotrimethylenetrinitramine (RDX), cyclotetramethylene-tetranitramine (HMX), and trinitroglycerine (TNG) [23].

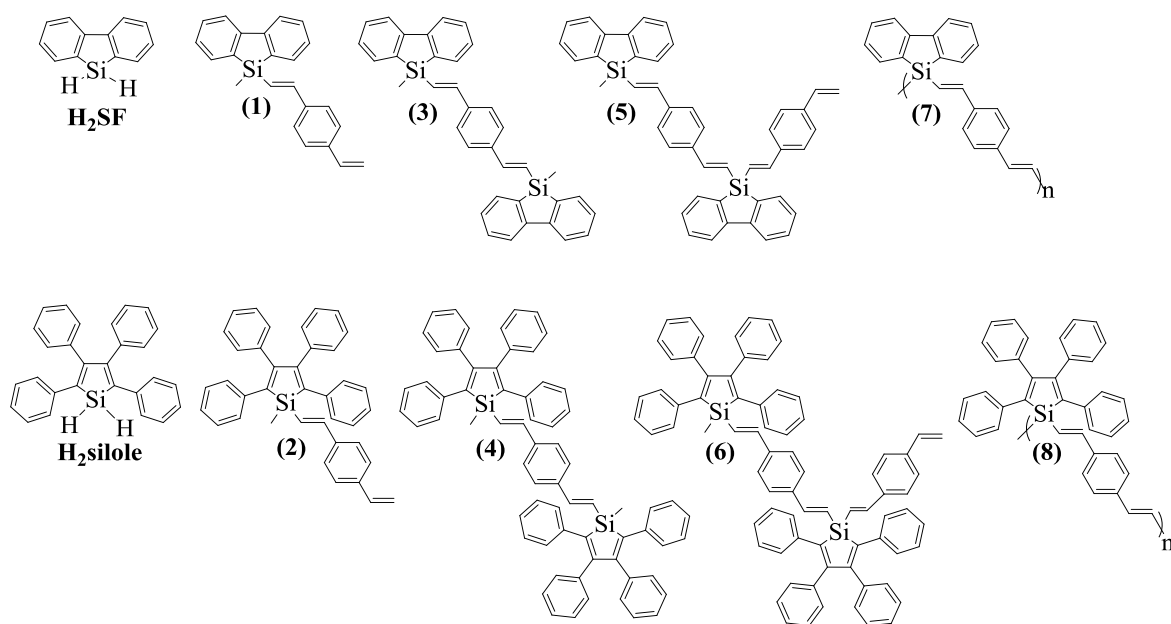


Figure 4.1. Structures of 1,1-dihydrosilafluorene (H_2SF) and 1,1-dihydrido(tetraphenyl)silole ($H_2silole$) and silafluorene- and silole-containing monomers (1 and 2), model dimers (3 and 4), dimers (5 and 6) and polymers (7 and 8).

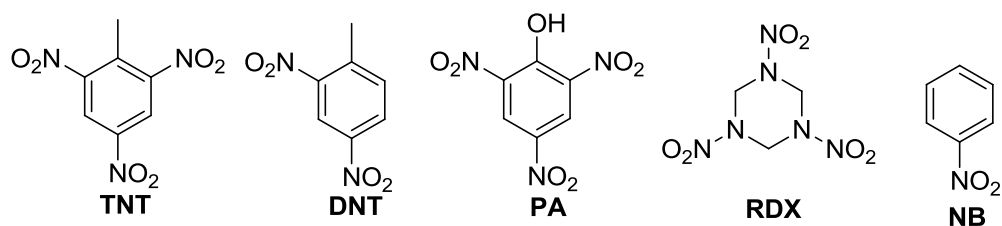


Figure 4.2. Structures of explosives (TNT, DNT, PA, RDX) and non-explosive nitrobenzene (NB).

The syntheses, spectroscopic characterization (Table 4.1), and fluorescence quenching efficiencies of 1,1-silafluorene- and 1,1-silolephenylenedivinylene polymers (**7** and **8**, Figure 4.1) have been reported by Trogler *et al.* [23]. Fluorescence quenching was used as a surface detection method for the analysis of explosives containing nitro groups and the detection limits were reported for the different explosives with these polymers (as low as 0.1 ng/cm² for TNT, Table 4.2). It has been proposed that Lewis acid-base interactions between the lone pairs of the nitro groups of these explosives and the silicon center promotes the binding of explosives in these polymers.

Table 4.1. Summary of photoluminescence data for monomers, dimers, and polymers[23].

	λ_{abs} (nm) ^a	solution λ_{flu} (nm) ^a	thin-film λ_{flu} (nm) ^b
H ₂ SF	288	343	365
3	290	348	380
7	294	359	447
H ₂ silole	305	482	485
4	306	482	482
8	322	487	478

^a UV-Vis and fluorescence taken in toluene. ^b Emission maximum for thin layer of fluorophore absorbed onto TLC plate.

Table 4.2. Summary of solid-state detection limits (ng/cm²) for various explosives by fluorescence quenching of polymers 7 and 8 [23].

Explosive	P _{vap} (Torr)	7		8	
		Porcelain	Filter Paper	Porcelain	Filter Paper
TNT	5.8 x 10 ⁻⁶	0.1 10 ^b	0.1 20 ^b	3 10 ^b	6 30 ^b
DNT	1.1 x 10 ⁻⁴	0.6 20 ^b	0.3 40 ^b	6 20 ^b	13 50 ^b
PA	5.8 x 10 ⁻⁹	2 30 ^b	0.3 30 ^b	1 20 ^b	1 30 ^b
RDX	4.6 x 10 ⁻⁹	3	2	-	-

^a Dashed lines represent no detection at 64 ng/cm² or less. ^b Detection limits (ng/cm²) reported in reference [29].

The aim of this study is first to investigate the binding mechanism of various explosives containing nitro groups (Figure 4.2), to the silafluorene- and silole-containing oligomers (Figure 4.1) at the molecular level and then to examine the fluorescence quenching mechanism to detect the explosives with the use of these oligomers. Binding of TNT, DNT, PA and RDX as well as nitrobenzene (NB), which is a non-explosive analyte, to the silafluorene-containing oligomers and binding of TNT and RDX to the silole-containing oligomers are modeled to understand the binding interactions between analytes and polymers. The non-explosive analyte NB is expected to behave differently than the explosives. The different detection performances of silafluorene- and silole-containing oligomers with the explosives are investigated in terms of binding energies and HOMO-LUMO interactions between the sensor and analyte. In addition to the modeling with oligomers, non-covalent interactions that promote the binding of analytes to polymers are further investigated with a small model to understand the role and weight of each interaction in the binding mechanism. Furthermore the Si atom in the backbone of silafluorene-containing oligomers is replaced by the isovalent Group 4A elements, C and Ge, in order to unravel the role of Si in these polymers. Band gaps of the uncomplexed and complexed polymers with analytes are calculated as HOMO-LUMO energy differences in search of a correlation between band gap energies and detection performances of the polymers. In order to investigate the fluorescence quenching mechanism, the behavior of

excited states are modeled to follow their relaxation in the case of the dimers and of the dimer-explosive complexes. To achieve a good compromise between computational cost and accuracy time-dependent DFT (TD-DFT) techniques are used to assess the properties of the excited states.

4.2. Computational Details and Benchmark Calculations

Geometry optimizations are performed using Density Functional Theory (DFT) [2,3,30] at the M06-2X/6-31G(d) [6] level of theory. All stationary points have been characterized by a frequency analysis. Charge analysis has been carried out by using full natural population analysis (NPA) with M06-2X/6-31G(d) [31]. All calculations have been carried out using the Gaussian 09 program package [32].

A thorough conformational search for silafluorene- and silole-containing monomers and dimers has been carried out. Structures in which Si is replaced by C and Ge in the fluorene ring are optimized by starting from the global minima of the former compounds and this procedure has been followed for consistency.

Energetics are given in kcal/mol. Complexation energies are calculated as the energy difference between the sensor and explosive molecules without any entropy or zero point energy contribution. However, since relative energies are discussed in the present work, these latter effects are not expected to change the general trend.

Time dependent density functional theory (TD-DFT) has been utilized to calculate the excitation energies and the oscillator strengths and to simulate the electronic absorption and fluorescence spectra. Absorption spectra have been calculated as vertical excitation energies from the ground state equilibrium geometry, while fluorescence emission has again been obtained considering vertical transitions taking place from the geometry corresponding to the minimum of the excited state potential energy surface. In order to simulate the band shape, vertical transitions have been convoluted using Gaussian functions of constant fixed-width at half-length of 0.3 eV.

At TD-DFT level, excited states are represented as a linear combination of singly-excited determinants, i.e. as a linear combination of excitations from occupied to virtual Kohn-Sham orbitals. This expression in terms of molecular orbitals can be cumbersome, since many occupied/virtual orbital couples can enter the expansion with similar weight. A possible improvement to get a deeper understanding of the physical nature of the electronic transitions leans on the representation of an excited state in terms of the Natural Transition Orbitals (NTO's) [33]. Indeed, by performing a singular value decomposition of the transition density matrix, one may express the excited state as a transition from occupied to virtual NTOs. The advantage over the Kohn-Sham representation is due to the fact that only one couple of occupied and virtual NTO's has a significant weight, and totally describes the electronic transition [33]. Basically, the transition can be entirely described as electron removal from the occupied natural transition orbital ("hole" density) and electron accumulation into the virtual natural transition orbital ("electron" density). NTO's have been calculated using a post-processing code [34] while they are also attainable, within Gaussian 09 [32].

Wave function files (M06-2X/6-31G(d)) were generated with the Gaussian 09 program prior to the analysis for the electron density contours and topological critical points using the AIM 2000 implementation of Bader's AIMPAC suite of programs [35].

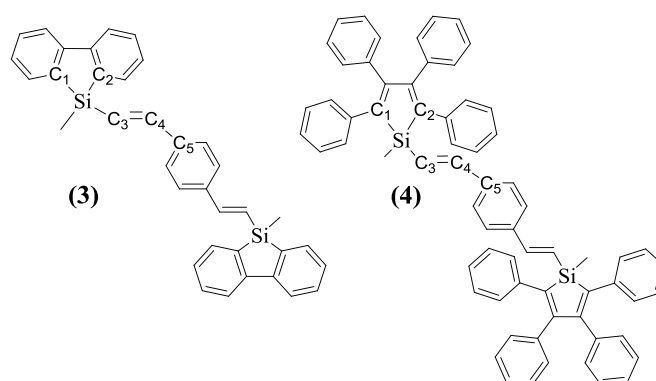
4.2.1. Structural Benchmark Calculations

The B3LYP functional is known to reproduce quite well the geometries of organic species containing Si [36-38]. However, it is also known that B3LYP fails to reproduce weak interactions in most cases [39]. Therefore, energetic and structural benchmark studies have been carried out for a reference structure (model dimer, 3).

Model dimeric compounds, 3 and 4 (Figure 4.1), were synthesized and characterized by single-crystal X-ray diffraction to provide insight into the structural conformation and orbital overlap in these systems [23]. In the structural benchmark, the geometric features of 3 and 4 are compared with the structures obtained by X-ray diffraction (Table 4.3). The bond distances are overestimated with M06-2X, B3LYP and wB97xD functionals but the

bond angles are almost identical to those of the structures obtained by X-ray diffraction.

Table 4.3. Calculated (M06-2X/6-31G(d), B3LYP/6-31G(d) and wB97xD/6-31G(d)) and experimental (X-ray diffraction) geometric parameters of 3 and 4.



		Bond lengths (Å)			Bond angles (°)		
		Si-C3	C3-C4	C4-C5	C1-Si-C2	Si-C3-C4	C3-C4-C5
3	X-Ray [23]	1.848	1.337	1.476	91.08	123.14	126.13
	M06-2X	1.864	1.343	1.473	91.26	123.19	127.30
	B3LYP	1.872	1.349	1.470	91.45	124.39	127.91
	wB97xD	1.865	1.342	1.473	91.29	123.65	127.64
4	X-ray [23]	1.846	1.325	1.473	92.57	125.69	127.13
	M06-2X	1.866	1.343	1.473	92.21	123.33	127.41

4.2.2. Energetic Benchmark Calculations

In the energetic benchmark, the absorption wavelength of 3 has been calculated with the hybrid meta-GGA, M06-2X [6] and MPW1B95 [40], the long range corrected functional wB97XD [41] and hybrid GGA B3LYP by employing the 6-31G(d) basis set (Table 4.4). The B3LYP (311 nm) and MPWB95 (308 nm) functionals overestimate the absorption wavelength of 3; on the other hand, the M06-2X (288 nm) and wB97xD (287 nm) functionals reproduce it quite well. The absorption wavelengths in toluene show a bathochromic shift of ~ 6-7 nm with M06-2X (295 nm), MPWB95 (314 nm), and wB97xD (293 nm) and of 21 nm with B3LYP (332 nm) with respect to the absorption wavelengths in vacuum. Notice however that the absorption wavelengths in vacuum are closer to the experimental absorption wavelengths for all methodologies used.

Table 4.4. Benchmark study for λ_{abs} (nm) of 3.^a

	B3LYP	M062X	MPW1B95	wB97xD	Experimental [23]
λ_{abs}^b	311	288	308	287	
λ_{abs}^c	332	295	314	293	290

^a The basis set is 6-31G(d) for all methodologies ^b Gas phase ^cToluene

The influence of the basis set has been carefully analyzed by systematically adding diffuse and polarization functions (Table 4.5). Since the effect of basis set size is rather negligible (not exceeding 10 nm) excited state geometry optimizations were performed at M06-2X/6-31G(d) level of theory. Moreover, we have also shown that the absorption wavelengths in vacuum are closer to the experimental absorption wavelengths for all methodologies used. Nevertheless the absorption and emission spectra have been simulated both in gas phase and in toluene. Throughout, solvent effects have been modeled by using linear response polarizable continuum method (PCM) for absorption as implemented in Gaussian 09 code [42]. In the case of emission we used the state-specific equilibrium version of the PCM methodology to take into account the effects of the solvent reorganization on emission wavelengths. The absorption bands in toluene are only slightly red shifted with higher intensities than those of the ones in gas phase but they have the same characteristics (Figure 4.3) with differences not exceeding 15-20 nm. Also in the case of emission no substantial difference in the behavior of the fluorophore was evidenced when solvent was taken into account.

Table 4.5. Benchmark study for λ_{abs} (nm) of 3 with M06-2X using various basis sets in vacuum and toluene.

	6-31G(d)	6-31+G(d)	6-31+G(d,p)	6-31++G(d,p)	6-311+G(d)
λ_{abs}^a	288	296	297	297	298
λ_{abs}^b	295	303	303	303	304

^a Gas phase ^b Toluene

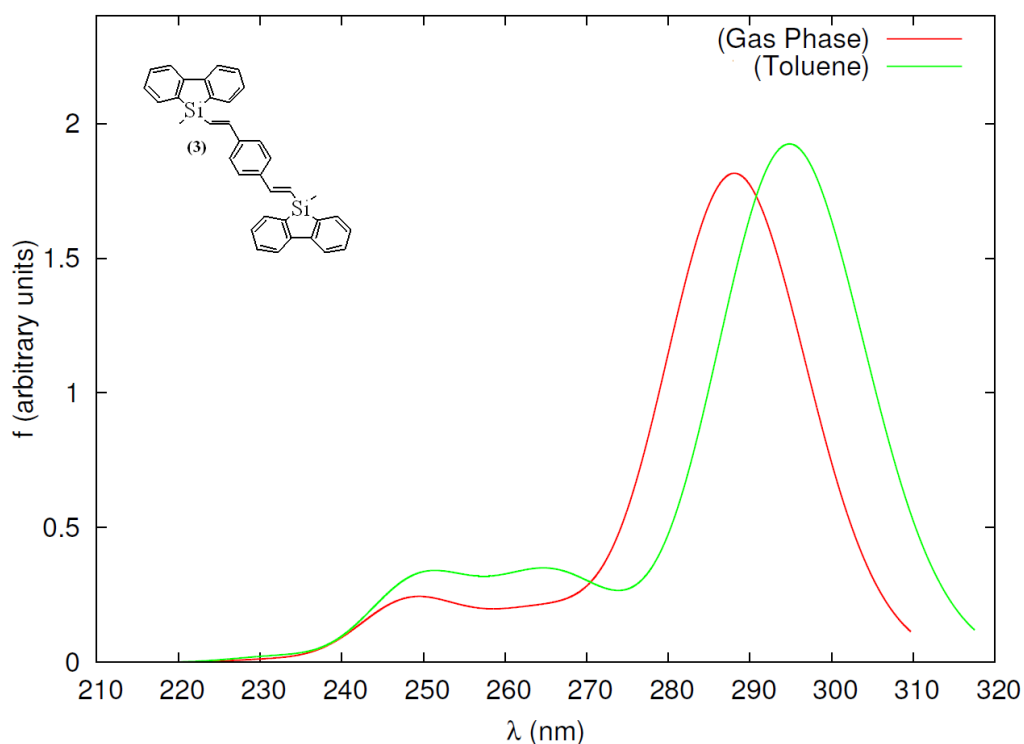


Figure 4.3. The absorption spectra of 3 in vacuum and in toluene (M06-2X/6-31G(d)).

The M06-2X and wB97xD functionals give very similar results but M06-2X/6-31G(d) is shown to reproduce the experimental results best and is employed in all of the geometry optimizations in the rest of the study presented in Chapter 4. Single point TD-DFT calculations have also been performed with M06-2X/6-31+G(d) and M06-2X/6-31G(d) since M06-2X/6-31G(d) is shown to reproduce the experimental absorption wavelength of 3 quite well (Table 4.4).

4.3. Results and Discussion

4.3.1. Geometrical Features of Oligomers

Silafluorene- and silole-containing monomers (1 and 2) can be either cis or trans around the ethylene moiety leading to two different conformations (Figure 4.4). For 1, the trans and cis conformers are almost isoenergetic with an energy difference of 0.1 kcal/mol only. The aromatic rings of silafluorene and the phenyl moieties in the cis monomer are

face-to-face displaying a sandwich-like structure. These features have been detected with the M06-2X functional which provides a satisfactory description of π -stacking interactions [43]. For monomer 2, the energy difference between cis and trans conformations is 1.8 kcal/mol favoring the cis conformer probably due to stronger π - π stacking interactions between the phenyl group of the bridging phenylene-divinylene and the silole ring as well as the phenyl groups around the silole ring. In the cis configuration of 2, there is interplay between non-covalent interactions such as π -stacking and hydrogen bonding and steric effects due to the presence of bulky phenyl rings, the former interactions being favored over the latter.

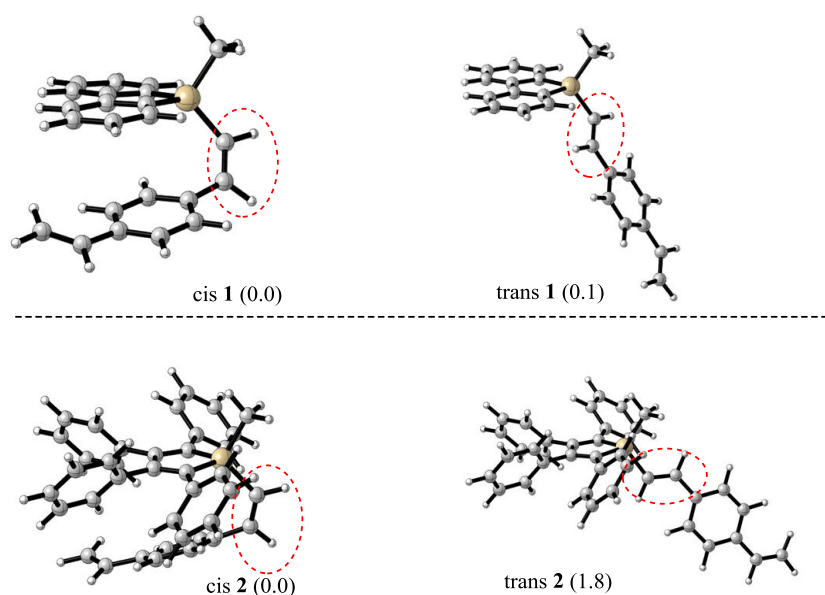


Figure 4.4. Cis and trans monomers 1 and 2 with the relative energies (kcal/mol) in parenthesis (M06-2X/6-31G(d)).

The lowest energy cis and trans conformers of model dimer 3 and dimer 5 that are located as global minima after a thorough conformational search are depicted in Figure 4.5. The trans conformations of 3 and 5 are favored over the corresponding cis conformations by 3.0 and 4.0 kcal/mol, respectively. The cis addition of trans monomers in 5 is also modeled and this conformation is found to be 0.9 kcal/mol less stable than the corresponding trans 5 (Figure 4.6). In the case of 4 and 6, the trans conformations have been located only since their cis counterparts would be very unstable due to steric reasons

(Figure 4.7). The energy difference between cis and trans conformations for silafluorene derivatives (1, 3, 5) increases as the number of repeating units (Figure 4.5) increases favoring the trans structure due to increased conjugation in agreement with the trans product characterized by X-ray diffraction during the catalytic hydrosilylation reaction [23]. The C1-Si-C2 bond angles in the silacycles of 3 and 4 (Table 4.3) are calculated as 91.26° and 92.21° respectively, in remarkably good agreement with the experimental data. These strained silacycles expose the silicon center to attack by Lewis bases making them good candidates as Lewis acids. Furthermore, the trans isomer provides the best orbital overlap between comonomers as compared to cis and geminal isomers allowing enhanced electron delocalization and making these copolymers to be better candidates for explosives detection applications [21].

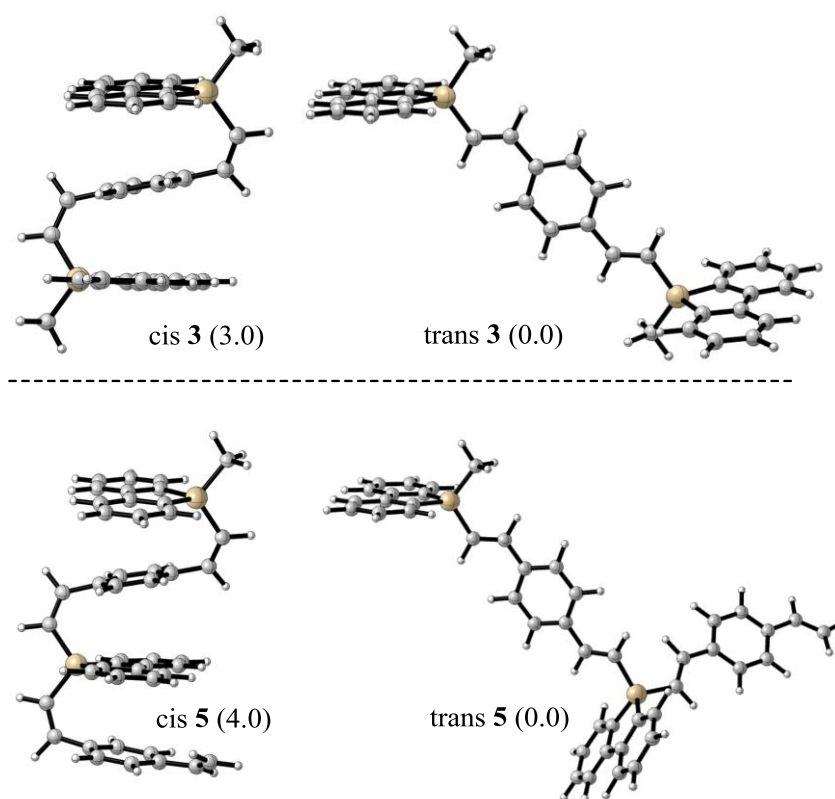


Figure 4.5. Cis and trans conformers of 3 and 5 with the relative energies (kcal/mol) in parenthesis (M06-2X/6-31G(d)).

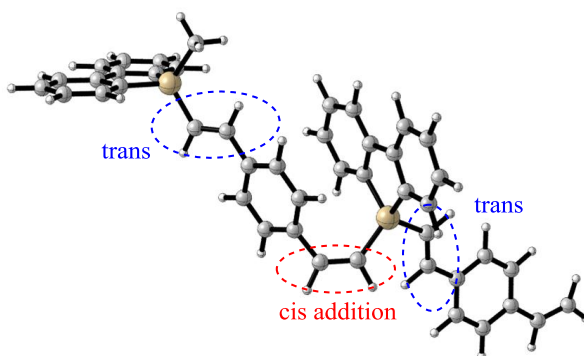


Figure 4.6. Cis addition of trans monomers.

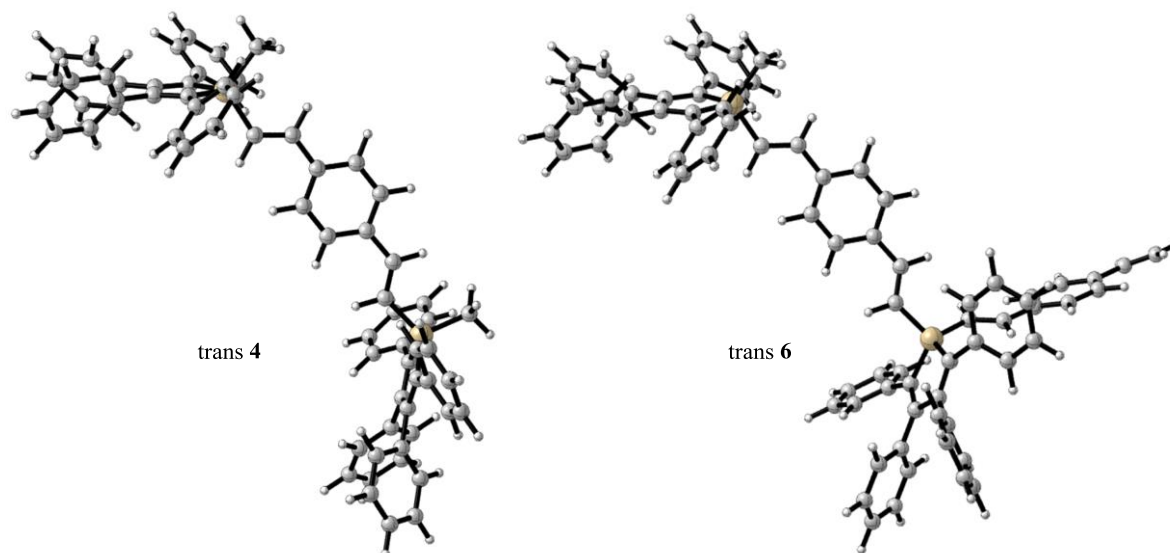


Figure 4.7. Optimized structures of trans 4 and 6 (M06-2X/6-31G(d)).

Monomers, model dimers and dimers of the silafluorene-containing polymer 7 are also modeled with the B3LYP/6-31G(d) methodology (Figure 4.8). Though the trans conformers optimized with B3LYP and M06-2X are similar, there is a significant difference in the geometries for the cis conformations optimized with B3LYP and M06-2X. The silafluorene and phenyl aromatic rings of cis conformations of 1, 3 and 5 optimized with B3LYP tend to be away from each other due to the steric hindrance created by the rings to each other. However, these aromatic rings are stacked in the cis conformations of 1, 3 and 5 optimized with M06-2X. Also it is worth discussing the

difference in energetics of the structures optimized with B3LYP and M06-2X since B3LYP is used in most of the computational studies similar to these systems. The energy difference between cis and trans conformations of 1, 3 and 5 is always greater for B3LYP than the one for M06-2X as a result of the lack of prediction of weak interactions by B3LYP and this difference increases as the chain length increases. Furthermore, the M06-2X methodology predicts the bond distances and bond angles closer to the experimental values (Table 4.3).

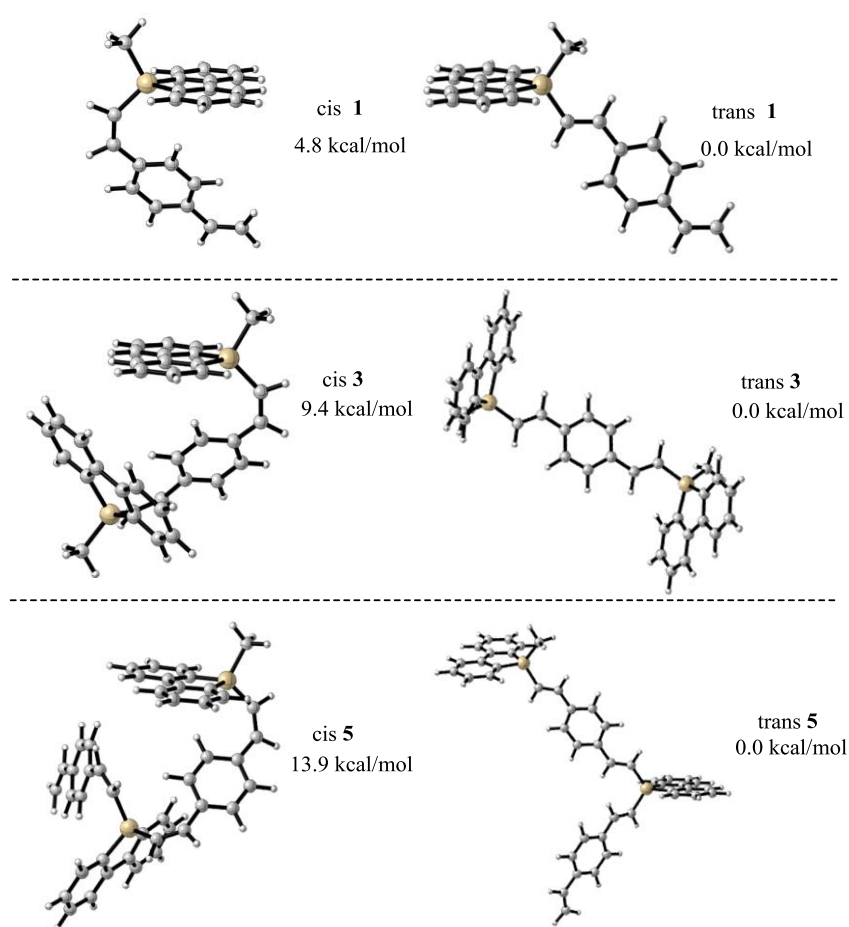


Figure 4.8. Cis and trans conformers of 1, 3 and 5 with the relative energies (kcal/mol, B3LYP/6-31G(d)).

4.3.2. Complexes of Oligomers with Analytes

Different complexation modes have been investigated for the binding between dimer **5** and the analytes. The potential π - π stacking interaction sites (Figure 4.9) for the phenyl group of TNT to bind to **5** have been explored; these are located on the upper side of silafluorene (blue), the center of phenylene-divinylene (red) and the lower part of phenylene-divinylene moieties (green). On the other hand, the nitro oxygen atoms of TNT can bind to the Si atoms of **5** via Lewis acid-base interactions. The complexes with most favorable interactions, in which the binding is promoted by π - π stacking interactions as well as the Lewis acid-base interactions, are depicted in Figure 4.10. The relative complexation energies for the complexes are within the range of 2.4 kcal/mol. Among these complexes, the complex formed between TNT and **5** is best stabilized when TNT binds to both of the Si atoms of **5** and the phenyl ring of TNT faces the phenylene-divinylene moiety of **5** giving rise to π - π stacking interactions.

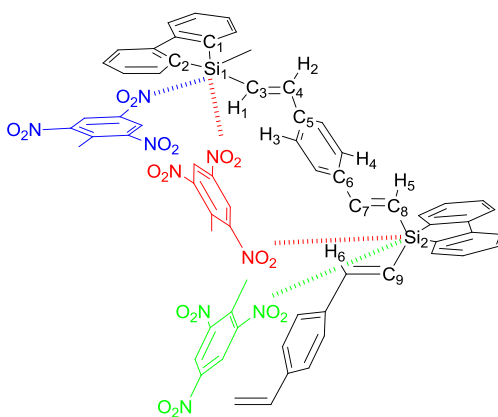


Figure 4.9. Alternative binding modes of **5** with TNT.

Complexes between **5** and different types of analytes, TNT, DNT, PA, RDX and NB, have been modeled taking into account the above mentioned π - π stacking interactions (Figure 4.11). The complexation energies of the complexes formed between analytes and **5** vary between -14.5 and -22.8 kcal/mol and the ranking, from highest to lowest, is TNT, PA, DNT, RDX and NB. The complex of NB which is a non-explosive analyte has the lowest complexation energy among the others and is differentiated from the complex of

RDX, 5-RDX2eq (Figure 4.11), which is already detected with quite low sensitivity, by 3.1 kcal/mol. The lowest complexation energy for the NB complex is in favor of the correlation between the experimental detection limits and the complexation energies. Considering the only two available O atoms of NB that will bind to Si atoms of **5**, the lowest complexation energy for 5-NB complex can be expected. TNT with the highest number of O atoms that will facilitate Lewis acid-base interactions forms the most stable complex (5-TNT) and is closely followed by the PA complex, 5-PA, with the same number of O atoms. DNT with fewer O atoms has lower complexation energy than TNT and PA. 5-RDX2eq complex has the lowest complexation energy among the explosives group and this is consistent with the experimentally reported detection limit for RDX (Table 4.2). The complexes with aromatic explosives (5-TNT, 5-DNT and 5-PA) are more stabilized and have higher exothermicities. For the aromatic explosives, the number of available O atoms that will facilitate the binding mechanism through Lewis acid-base interactions is important. Though RDX is not an aromatic explosive, it still can be detected with a lower sensitivity than the aromatic explosives TNT, DNT and PA, due to the presence of six O atoms. Although TNT and RDX bear the same number of O atoms, the difference in the complexation energies for these two explosives is 5.2 kcal/mol in favor of TNT. This difference probably stems from the absence of π - π stacking interactions between RDX and the phenyl moiety of dimer **5** in 5-RDX2eq complex. This result suggests that π - π stacking interactions are important in the binding in addition to Lewis acid-base interactions which were already proposed by Trogler *et al.* [23]. The computed order of stability of the complexes is remarkably consistent with the detection limits reported for *filter paper experiments*; the calculated results are also in agreement with the trend detected by *in porcelain experiments* except for PA [23]. In another experimental study the detection sensitivity of silafluorene-containing polymer, **7**, towards explosives was reported to rank in the order of PA, TNT and DNT from highest to lowest (Table 4.2) [29]. In the current study, the affinity of the silafluorene-containing polymer, **7**, is found to change as TNT $\sim$ PA > DNT > RDX > NB with the calculated binding energies of the complexes of silafluorene-containing dimer, **5**, and this agrees well with the reported detection limits (Table 4.2).

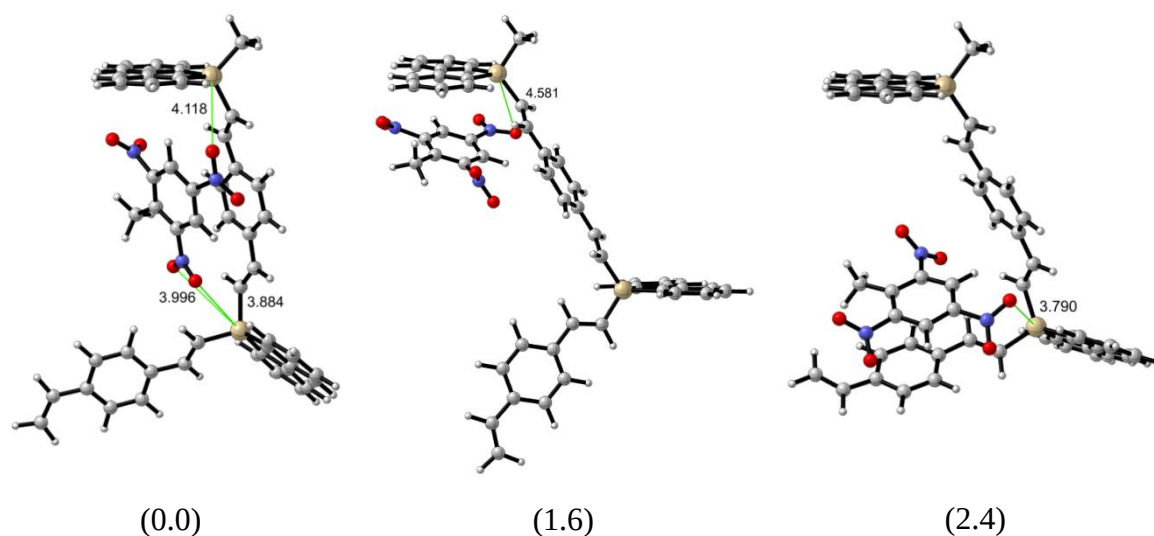


Figure 4.10. Binding of TNT to 5 from different π - π stacking sites as represented in Figure 4.9 and the relative energies of the complexes in kcal/mol (M062X/6-31G(d)).

Among the explosive molecules studied, RDX required further attention for having relatively large number of conformers. A conformational search has been performed for RDX as displayed in Figure 4.12. The three nitro groups on the cyclic RDX structure can be either axial or equatorial and this leads to four different conformations of RDX (Figure 4.12). The lowest energy conformer (RDX3ax) has the nitro groups in the axial position; the next stable conformer (+0.3 kcal/mol) has the two nitro groups in the axial and one in the equatorial positions. The stability of the lowest energy conformer (RDX3ax) may be due to the high number of stabilizing interactions of the positively charged nitrogen atom with the negatively charged oxygen atoms. When any one of the nitro groups adopts an equatorial position, the oxygen atoms of that nitro group in the equatorial position cannot interact with other nitrogen atoms of RDX. 5-RDX3ax modeled with the lowest energy conformer of RDX (RDX3ax) is, however, less stable than 5-RDX2eq by 5.6 kcal/mol (Figure 4.11). In 5-RDX2eq, RDX2eq which has one axial and two equatorial nitro groups can reach both the upper and lower Si atoms of 5 thanks to the equatorial orientation of the nitro groups.

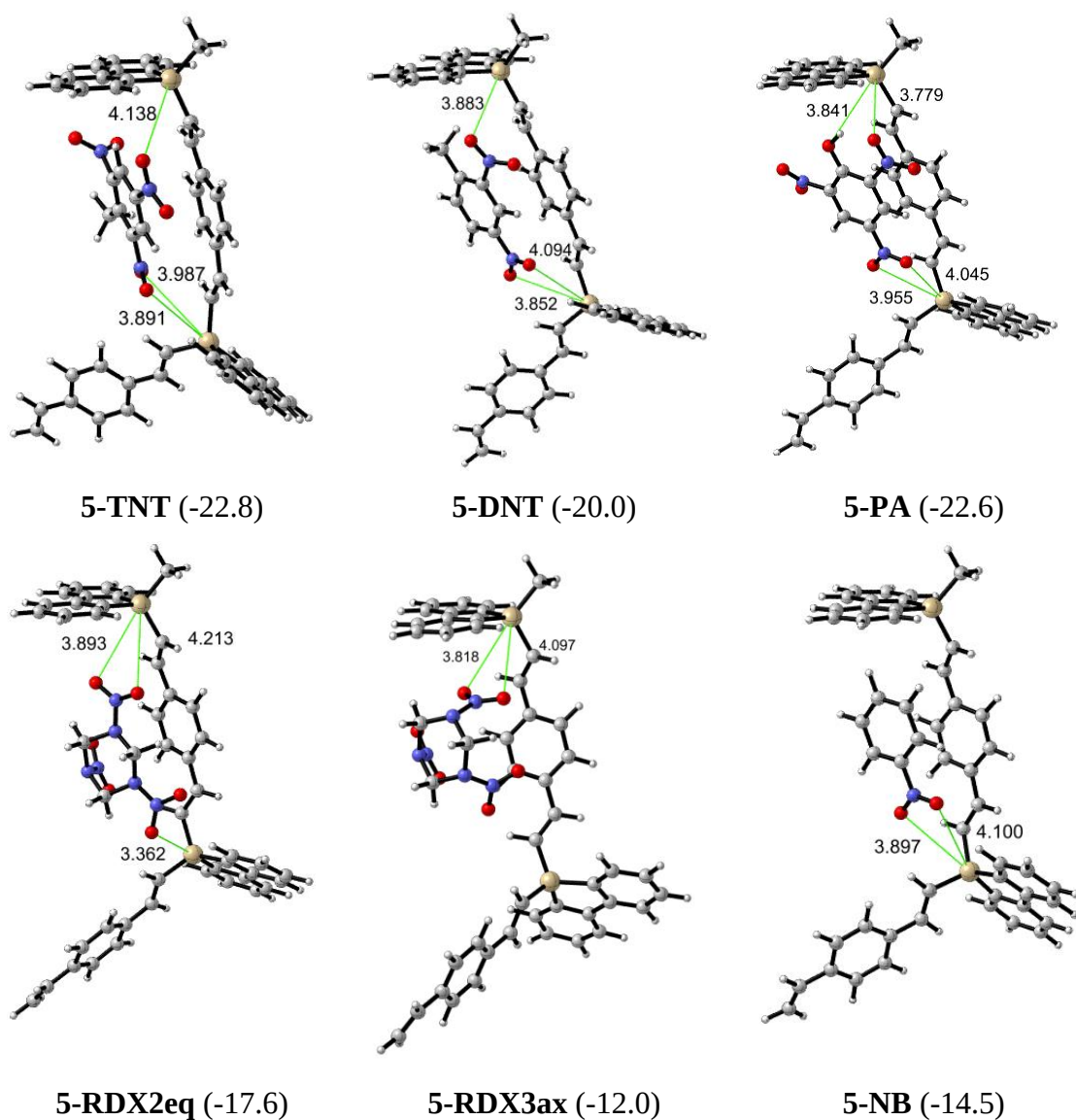


Figure 4.11. Complexes of TNT, DNT, PA, RDX and NB with 5 (M06-2X/6-31G(d)).

Binding energies (kcal/mol) are given in parenthesis.

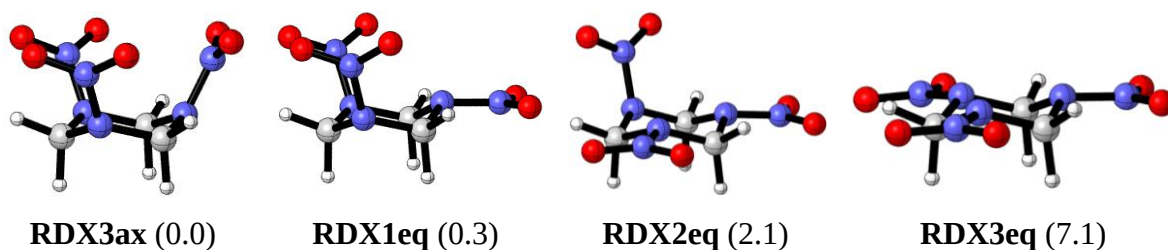


Figure 4.12. Conformations of RDX with the relative energies (kcal/mol) in parenthesis (M06-2X/6-31G(d)).

Complexes of one aromatic (PA) and one non-aromatic (RDX) explosive with dimer 6 are modeled (Figure 4.13) keeping in mind that silole-containing polymers are less responsive than silafluorene-containing polymers in regard to the explosives chosen; the former are even not responsive to non-aromatic explosives (Table 4.2). The experimental result is quite well justified with the complexation energies of the aromatic PA complex, 6-PA, and the non-aromatic RDX complex, 6-RDX, which is 4.0 kcal/mol less stable than 6-PA complex. The stability of the aromatic PA complex, 6-PA, corroborates the importance of π - π stacking interactions for the binding mechanism between polymers and analytes. Furthermore, the planarity of PA enables the oxygen atoms of the nitro groups of PA to reach the Si centers of 6 resulting in closer interactions in 6-PA complex. However, the repulsion between RDX and 6 in 6-RDX complex results in looser interactions between the oxygen atoms of RDX and Si atoms of 6.

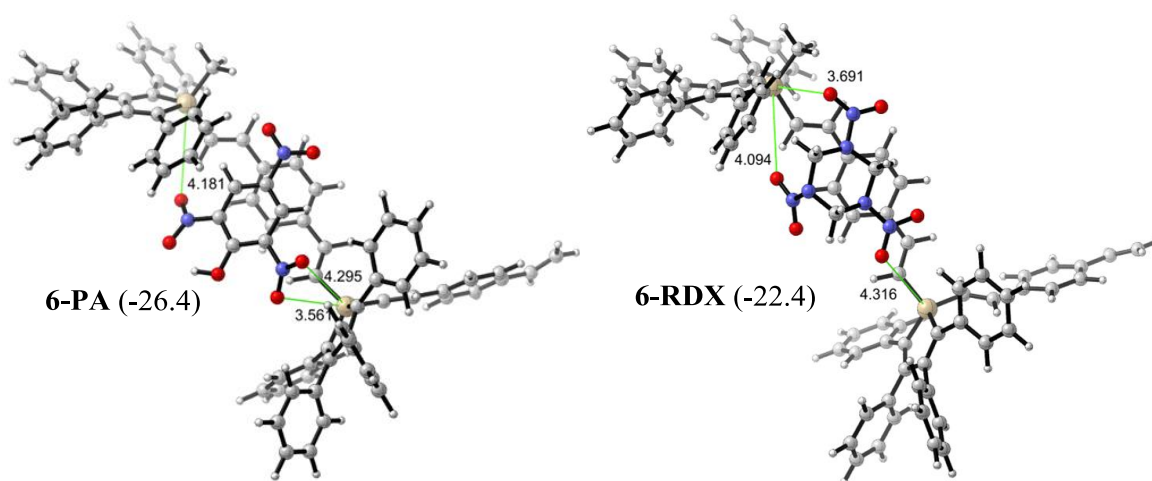


Figure 4.13. Complexes of PA and RDX with 6 (M06-2X/6-31G(d)).

Binding energies (kcal/mol) are given in parenthesis.

Selectivity and *sensitivity* are the two major criteria for the design of a good sensor. Taking into account the correlation between the calculated complexation energies and experimental detection limits reported with >95% accuracy [23], it can be concluded that the *selectivity* of the polymers under discussion towards explosive molecules is

successfully reproduced computationally in the current study. Modeling *sensitivity*, on the other hand, will require future work.

4.3.2.1. The Role of Heteroatom. To understand the role of the heteroatom in the backbone of the polymers, Si is replaced by its isovalent neighbors in the periodic table, C (5C) and Ge (5Ge) atoms, in the fluorene ring of dimer, 5. Ge has been chosen on the basis of the explosive detection studies with the use of polygermole and poly(1,4-diethynylbenzene)2,3,4,5-tetraphenylgermole [29]. From C to Si and Ge, the internal angle of the central ring of fluorene moiety ($C_1-X_1-C_2$) decreases from 101° to $\sim 90^\circ$ from 5C to 5 and 5Ge (Table 4.6). As the covalent radius of metallole in the fluorene ring increases, the internal angle decreases, thus, the stress of the central ring of fluorene moiety increases as stated in experimental studies [44,45]. The strained silafluorene ring of 5 and fluorene ring of 5Ge render these polymers better Lewis acids, promoting the binding of analytes to these polymers. On the other hand, planarity of the backbone is supposed to be the other criteria to provide better π - π stacking interactions between the bridging phenylene-divinylene moiety of the polymers and the analytes. The dihedral angles (τ_1 and τ_2) are selected in a way to reflect the position of the vinyl groups with respect to the phenyl groups in the bridging moiety: the dihedral angles become smaller as one goes from 5C to 5Ge resulting in more planar structures (Table 4.6). This is due to the larger covalent radius of Si and Ge atoms both creating a space around the X_1 and X_2 centers. The bond distances related with these two centers, d_1 , d_2 and d_3 , are around 1.51 Å, 1.86 Å and 1.92 Å for 5C, 5 and 5Ge, respectively (Table 4.6). In 5C, the hydrogen atoms of the methyl group attached to X_1 and H_6 create steric hindrance for H_2 and H_5 , respectively, disrupting the planarity of the bridging moiety of 5C, thus, the delocalization. On the other hand, 5 and 5Ge experiencing to a less extent of such steric hindrance have higher delocalization than 5C. This increased delocalization is confirmed with the calculated absorption wavelengths for these dimers (Table 4.6). From 5C to 5, the absorption wavelength is red shifted by 11 nm with an increase in the oscillator strength which corresponds to an increase in the intensity of the absorption. From 5C to 5Ge, the absorption wavelength is again red shifted but to a smaller extent than in compound 5.

Table 4.6. Bond angles ($^{\circ}$), dihedral angles ($^{\circ}$), bond lengths ($\text{\AA}$) and absorption wavelengths (nm) with the oscillator strengths (f) of dimers 5C, 5 and 5Ge (M06-2X/6-31G(d)).*

	θ_1	τ_1	τ_2	d_1	d_2	d_3	λ_{abs}	f
5C	101	-18	20	1.511	1.514	1.516	280	1.76
5	91	12	6	1.864	1.865	1.862	291	1.91
5Ge	90	-5	-2	1.924	1.924	1.923	288	1.85

* θ_1 : C₁-Si₁-C₂, τ_1 : H₁-C₄-C₅-H₃, τ_2 : H₄-C₆-C₇-H₅, d_1 : Si₁-C₃, d_2 : C₈-Si₂, d_3 : Si₂-C₉ (Labeling system of Figure 4.9 was adopted.)

Complexes of 5C and 5Ge are also modeled with TNT (Figure 4.14). The complexation energy of 5C-TNT (-22.1 kcal/mol) is close to 5-TNT (-22.8 kcal/mol). On the other hand, 5Ge-TNT complex is highly stabilized (-28.4 kcal/mol) by the presence of stronger interactions between Ge and O atoms probably due to the increase in the planarity of the bridging moiety. As the planarity of the bridging moiety increases, stronger and closer π - π stacking interactions also allow better Lewis acid-base interactions.

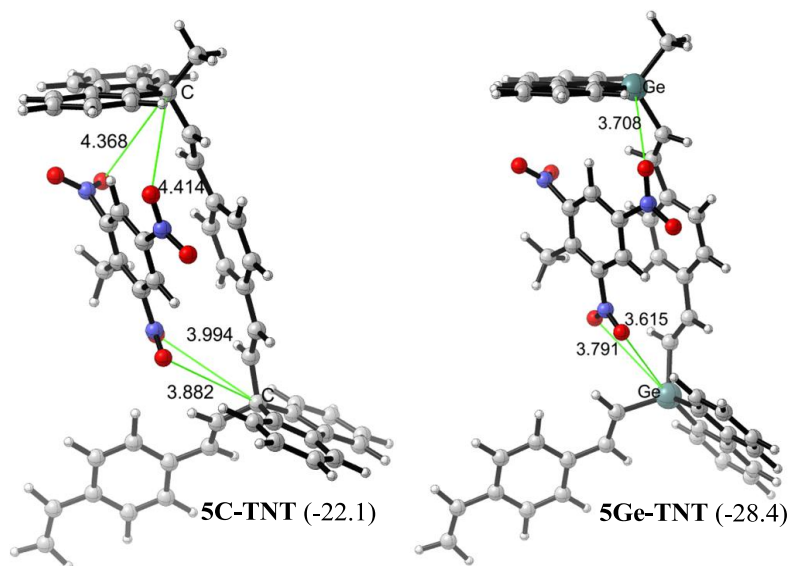


Figure 4.14. Complexes of 5C and 5Ge with TNT (M06-2X/6-31G(d)).

Binding energies (kcal/mol) are given in parenthesis.

4.3.2.2. Analysis of Interactions in the Complexes. In this part of the study, the interactions that promote binding of analytes to silafluorene- and silole-containing polymers is first analyzed in a small model and then the nature of the interactions in the complexes shown in the previous part of the study are characterized by Quantum Theory of Atoms-in-Molecules (QTAIM) theory [35].

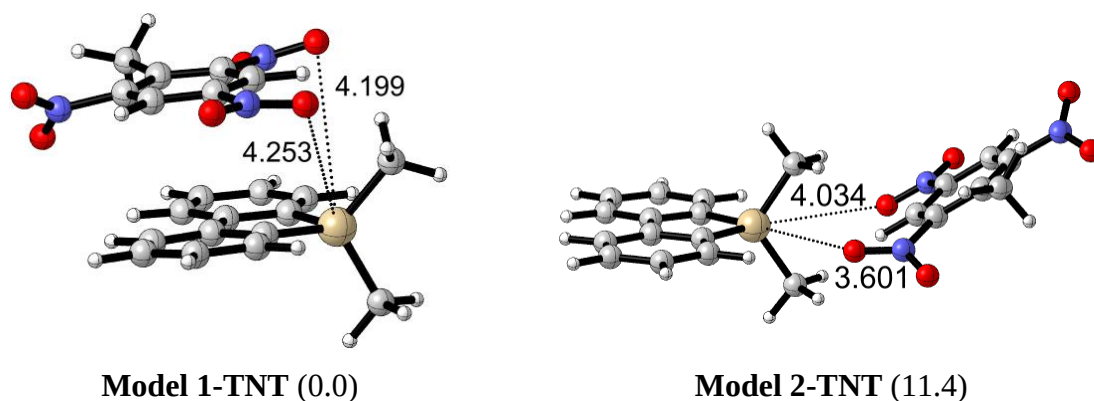


Figure 4.15. Binding of TNT to 9,9-dimethyl-9-silafluorene through π - π stacking on the left and Lewis acid-base interaction on the right with the relative binding energies (kcal/mol, M06-2X/6-31G(d)).

Binding of analytes to silafluorene- and silole-containing polymers was proposed to proceed through Lewis acid-base interactions [21,23]. The strained silacycle of both the silafluorene and (tetraphenyl)silole comonomers acts as a Lewis acid center that promotes the binding of nitro- and nitrate-containing explosive analytes [23]. On the other hand the complexes modeled in Figures 4.11 and 4.13 showed that π - π stacking interactions also play an important role in the binding mechanism. A small model has been chosen in which TNT can bind to 9,9-dimethyl-9-silafluorene through Lewis acid-base interactions between the nitro oxygen atoms of TNT and the Si atom of 1,1-dimethylsilafluorene (Figure 4.15). The binding is facilitated mostly by π - π stacking and Lewis acid-base interactions in Model 1-TNT complex and by Lewis acid-base interactions in Model 2-TNT complex. There is a high charge transfer of 0.0118 from TNT to 9,9-dimethyl-9-silafluorene for Model 2-TNT promoted by Lewis acid-base interactions while this charge transfer is only 0.0033 from 9,9-dimethyl-9-silafluorene to TNT for the complex Model 1-TNT triggered by π - π stacking interactions. There is a significant difference in the complexation energies

of the two complexes (11.4 kcal/mol), showing that π - π stacking interactions dominate in the binding mechanism.

QTAIM theory has been employed to reveal the nature of the non-covalent interactions between the oligomers and analytes in the complexes as well as to understand the effect of isovalent heteroatoms. Inter-atomic interactions can be classified as shared or closed-shell interactions using AIM theory parameters [46,47]. Accordingly, a shared (covalent) interaction is one where the Laplacian of electron density, $\nabla^2\rho(r)$, at the (3, -1) bond critical point (bcp) of the electron density topology is negative (electron concentration) with a $\rho(r)$ value of the order 10^{-1} au ($0.675 \text{ e } \text{\AA}^{-3}$) [46]. A closed-shell (non-covalent) interaction is one where $\nabla^2\rho(r)$ is positive (electron depletion) with a $\rho(r)$ value of the order 10^{-2} au ($0.068 \text{ e } \text{\AA}^{-3}$), which is lower than the former case. There are also intermediate interactions where there is a positive $\nabla^2\rho(r)$ value with a reasonably high $\rho(r)$. Therefore, in search for a proper classification of the interactions in the present systems, QTAIM parameters such as $\rho(r)$, $\nabla^2\rho(r)$, kinetic energy density $G(r)$, potential energy density $V(r)$, and total energy density $H(r)$ corresponding to the bcp observed between two centers are tabulated in Table 4.7.

$\rho(r)$ and $\nabla^2\rho(r)$ data show that as the heteroatom changes from C to Ge and then to Si in the dimer, there is a decrease in the covalency of the bond between the heteroatom and neighboring carbon atoms. In 5C, high $\rho(r)$ values and negative Laplacian point out at a regular covalent bond. In 5Ge, however, electron density value decreases to the half and Laplacian becomes positive, suggesting a non-covalent interaction or a very polar bond between Ge and neighboring C. In 5, electron density value is lower and Laplacian is more positive for Si-C bonds. The increase in the $G(r)$ values going from 5C to 5Ge and then to 5 also suggests a decrease in the covalent bond character and an increase in the polarity. Therefore, it is possible to conclude that the Ge and Si centers in the metalofluorene group are capable of acting as Lewis acids due to the charge transfer and polar bonds they make with their neighbors. Laplacian maps in Figure 4.16 show the change in the electron density in the region connecting heteroatom to the neighboring

carbons. The charge transfer and depletion of electron density between the heteroatom and carbon atoms is obvious for the Si and Ge cases in these maps.

Table 4.7. QTAIM parameters of electron density $\rho(r)$, Laplacian of electron density $\nabla^2\rho(r)$, kinetic energy density, $G(r)$, potential energy density, $V(r)$, and total energy density, $H(r)$ in a.u (Labeling system of Table 4.6 was adopted).

		$\rho(r)$	$\nabla^2\rho(r)$	$G(r)$	$V(r)$	$H(r)$
5	X1-C1	0.11581	0.07371	0.13899	-0.20428	-0.06529
	X1-C3	0.11622	0.08124	0.14397	-0.20670	-0.06273
	X2-C8	0.11628	0.08052	0.14347	-0.20641	-0.06295
	X2-C9	0.11682	0.08117	0.14460	-0.20802	-0.06343
5+TNT	X1-C1	0.11567	0.07363	0.13884	-0.20405	-0.06521
	X1-C3	0.11458	0.07947	0.14096	-0.20246	-0.06150
	X2-C8	0.11560	0.08047	0.14279	-0.20511	-0.06232
	X2-C9	0.11756	0.08064	0.14509	-0.20954	-0.06445
	C8-O	0.00830	0.00681	0.00605	-0.00528	0.00077
	(rings)	0.00799	0.00568	0.00471	-0.00374	0.00097
5+NB	X1-C1	0.11456	0.07334	0.13745	-0.20156	-0.06411
	X1-C3	0.11683	0.08151	0.14493	-0.20836	-0.06342
	X2-C8	0.11627	0.08016	0.14327	-0.20638	-0.06311
	X2-C9	0.11721	0.08019	0.14432	-0.20845	-0.06413
	C8-O	0.00862	0.00670	0.00604	-0.00539	0.00066
	(rings)	0.00792	0.00573	0.00482	-0.00391	0.00091
5C	X1-C1	0.24707	0.13884	0.05964	0.01956	0.07920
	X1-C3	0.25092	-0.14457	0.06008	-0.26474	-0.20465
	X2-C8	0.24839	-0.14167	0.05919	-0.26004	-0.20086
	X2-C9	0.24808	-0.14106	0.05963	-0.26033	-0.20069
5Ge	X1-C1	0.12428	0.04492	0.11225	-0.1958	-0.06733
	X1-C3	0.12588	0.04827	0.11604	-0.18381	-0.06777
	X2-C8	0.12616	0.04682	0.11515	-0.18347	-0.06833
	X2-C9	0.12648	0.04696	0.11559	-0.18422	-0.06863
5Ge+TNT	X1-C1	0.12395	0.04467	0.11170	-0.17874	-0.06703
	X1-C3	0.12415	0.04720	0.11365	-0.18010	-0.06645
	X2-C8	0.12594	0.04768	0.11570	-0.18371	-0.06802
	X2-C9	0.12664	0.04535	0.11436	-0.18338	-0.06901
	C8-O	0.01109	0.00942	0.00842	-0.00743	0.00099
	(rings)	0.00781	0.00563	0.00478	-0.00392	0.00086

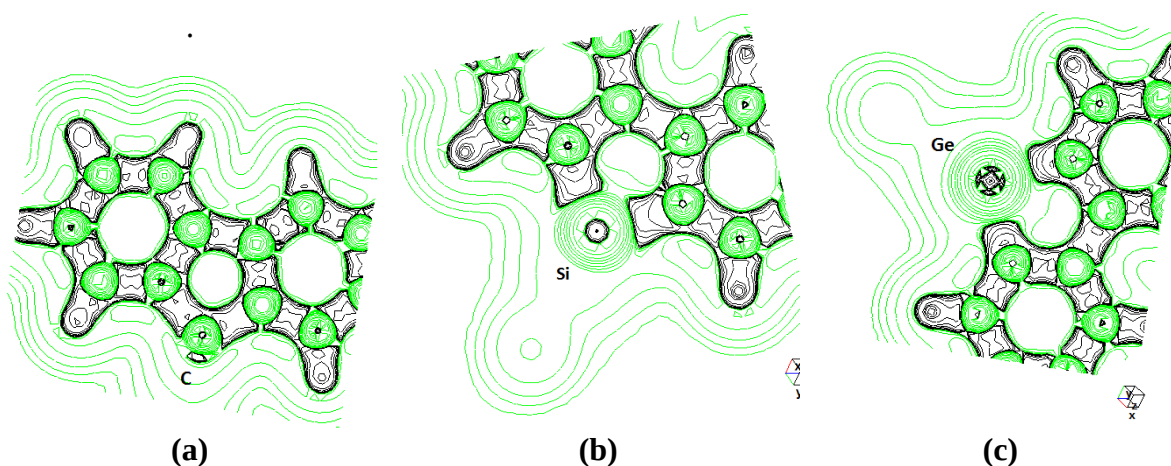


Figure 4.16. Laplacian maps of electron density for (a) 5C, (b) 5 and (c) 5Ge molecules showing heteroatom's interactions with the neighbors.

Electron density topology analyses were also performed for the complexes of **5** with an explosive (TNT) and non-explosive (NB) molecules (Table 4.7). 5Ge-TNT complex was also studied for a comparison of binding mechanisms with Si and with Ge. Figure 4.17 shows the bond critical points observed for the complexes of **5**. These interactions mostly correspond to hydrogen bonds and π - π stacking interactions. No Lewis acid-base type interaction was observed between Si and TNT or NB in the complex. On the other hand, it might be possible that Lewis acid-base interactions are related to the primary binding interaction or “first recognition”. Once two molecules come to close proximity by this type of interactions, secondary non-covalent interactions such as π - π stacking take over and govern the final or equilibrium structure of the complex molecule.

When $V(r)$ values are compared for the complexes of **5**; the strengths of π - π interactions (C8-O or ring-ring interactions) are found to be comparable for the TNT and NB cases. However, there is a difference between their occurrence numbers. Number of bond critical points related to the non-covalent intermolecular interactions almost doubles as one goes from NB to TNT complex, which means that although both TNT and NB are held by interactions with similar strength, there are more such interactions in the case of TNT. This might explain the better binding and higher complexation energy of TNT.

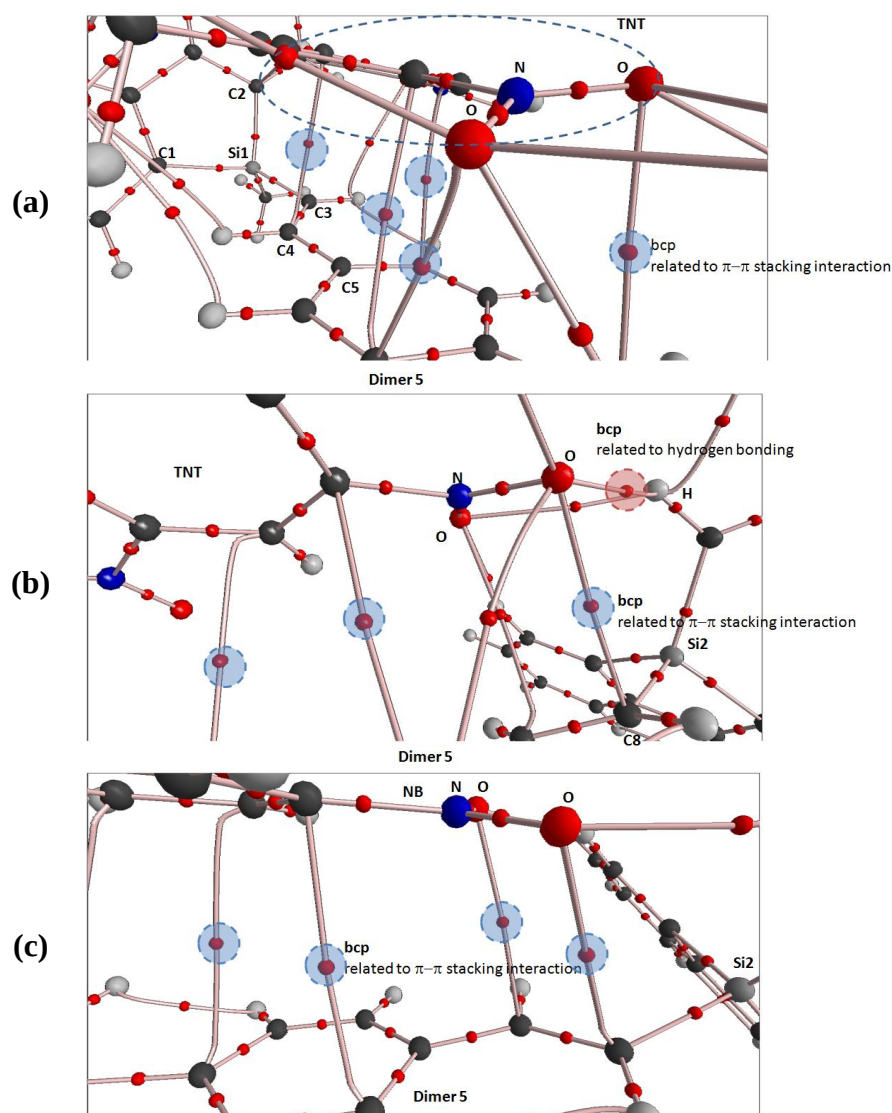


Figure 4.17. Bond critical points (bcp) corresponding to the interactions in (a)-(b) 5-TNT and (c) 5-NB complexes.

bcps are represented by red smaller globes. bcp corresponding to a non-covalent interaction is further encircled with dashed lines. Ring and cage critical points are omitted for clarity.

One interesting observation related to the $V(r)$ values of 5Ge-TNT complex is that, π - π interaction between the dimer (C8) and oxygen of TNT are stronger than the one present in 5-TNT complex. This suggests the polymer of 5Ge a good candidate for the detection of explosives with nitro group.

4.3.2.3. Frontier Molecular Orbital Analysis. To see whether the electron accepting ability of explosives correlate with ease of detection of poly(tetraphenylsilole-vinylene), poly(tetraphenylsilole-silafluorene-vinylene), and poly(silafluorene-vinylene), theoretical calculations at the B3LYP/6–31G* level of theory were used in the literature to determine the HOMO and LUMO energies for various explosives [20]. In the above-mentioned study it has been proposed that frontier orbital energy matching of explosives with silafluorene- and silole containing polymers is a dominant factor that determines explosives detection in the solid state. Thus in this study, the HOMO-LUMO energies of explosives and uncomplexed dimers as well as the frontier orbital energy matching of the complexes that will form between explosives and dimers are investigated (Figure 4.18).

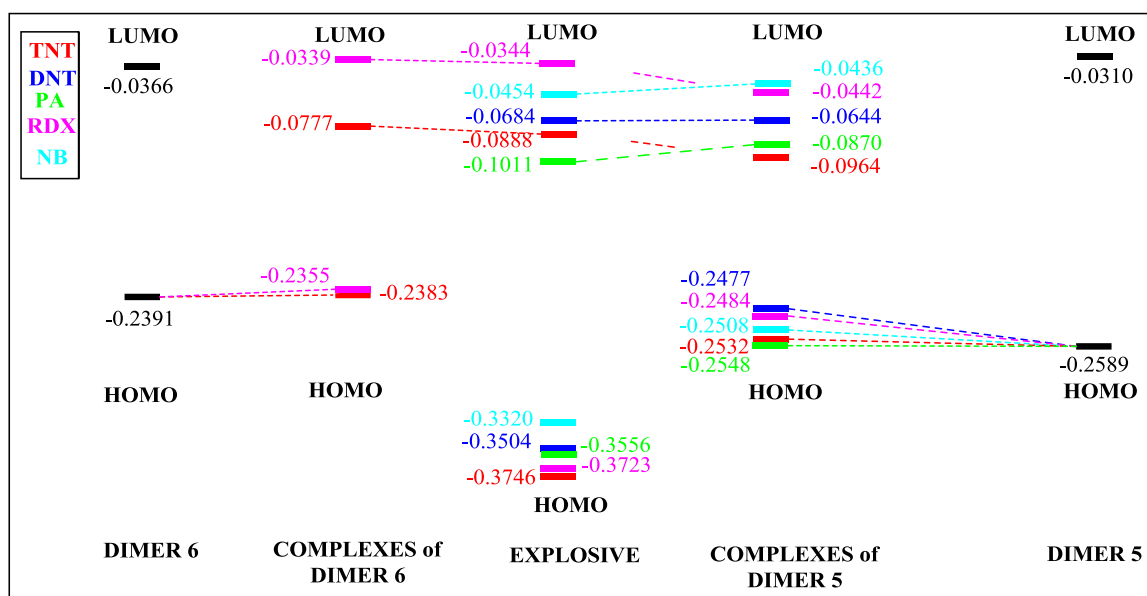


Figure 4.18. HOMO-LUMO map (in atomic units) for dimer 5, dimer 6 and explosives (M06-2X/6-31G(d)).

The HOMO and LUMO energies of the complexes are closer to the HOMO energies of the dimers and the LUMO energies of explosives, respectively. This might indicate a possible charge transfer from the polymer to the analyte. The band gaps calculated as the HOMO-LUMO energy difference correlate well with ease of detection for dimer 5 and dimer 6 (Table 4.8). The band gap of the uncomplexed dimer 5 is calculated as 6.201 eV.

Upon complexation of dimer 5 with the analytes, the band gaps decrease, even to 4.267 eV for 5-TNT complex, and the degree of the decrease in the band gaps of complexes with different analytes are in accordance with selectivity of dimer 5 towards the analytes. The higher the decrease in the band gaps of dimers upon complexation with the analytes, the more discernible signals for explosives detection would be obtained with these polymers. The trend observed in the calculated band gaps upon complexation is valid for dimer 6. The calculated band gap of the uncomplexed dimer 6 (5.510 eV) does not change much upon complexation with RDX (5.486 eV), to which dimer 6 is not responsive. However complexation of dimer 6 with TNT significantly decreases the band gap to 4.370 eV which actually suggests that the calculated band gaps of complexes reflect quite well the ease of detection.

Table 4.8. Band gap energies (eV) calculated as the HOMO-LUMO energy difference for the complexes of dimers 5, 5C, 5Ge and 6 and the explosive analytes (M06-2X/6-31G(d)).

	Band gap		Band gap
5	6.201	6	5.510
5 + TNT	4.267	6 + TNT	4.370
5 + DNT	4.988	6 + RDX	5.486
5 + PA	4.566	5C	6.403
5 + RDX	5.556	5Ge	6.267
5 + NB	5.638	5C + TNT	4.615
		5Ge + TNT	4.740

The band gap of uncomplexed dimer 5C (6.403 eV) decreases to 6.201 and 6.267 eV, respectively, with the inclusion of Si and Ge in dimer 5. This decrease in the band gaps explains the suitability of Si and Ge in the backbone of these polymers for explosives detection methods with improved optoelectronic properties. HOMO energies of dimer 5 and dimer 5Ge are both stabilized by 0.272 eV, for both, compared to the HOMO energy of dimer 5C. In the case of LUMO energies, stabilization of the LUMO of dimer 5 and the dimer 5Ge is 0.473 eV and 0.065 eV respectively. The higher degree of stabilization of LUMO of dimer 5 results in a smaller band gap for dimer 5 than dimer 5Ge which leads to higher delocalization in dimer 5. Note that higher delocalization in dimer 5 was also shown by the calculated absorption wavelength of dimer 5 (291 nm, Table 4.6). The difference in

absorption wavelengths between dimer 5 and 5Ge is expected to increase much more at the polymer level.

The calculated band gaps of the uncomplexed dimer 5C (6.403 eV) and dimer 5Ge (6.267 eV) decrease drastically upon complexation with TNT. However, the degree of the decrease in the calculated band gaps upon complexation does not reflect the trend expected. This decrease in the calculated band gap is higher for dimer 5C (1.788 eV) than dimer 5Ge (1.527 eV) suggesting that dimer 5 is more prone to undergo a change that can be detected more easily. The decrease in the calculated band gaps of dimers upon complexation might be a good indicator to determine the potential use of dimer 5 for explosives detection since a thorough conformational search has been employed for dimer 5. On the other hand, for the complexes of dimer 5C and 5Ge, the structure corresponding to the global minimum has been considered, Si has been replaced by C and Ge and the corresponding structures have been optimized. For the complexes of dimer 5C and 5Ge, there may still be structures with energies lower than the ones reported in this study. This issue, being of minor importance in the context of this study, is to be investigated further if firm relationships between band gap and complexation are of interest for 5C and 5Ge.

4.3.3. Optical Properties

4.3.3.1. Monomers and Dimers. The computed absorption spectra of H₂SF, model dimer (3) and dimer (5) convoluted using gaussian functions are reported in Figure 4.19, together with the calculated spectrum of the phenylenedivinylene bridging moiety, 1,4-divinylbenzene. The dimer and model dimer both give an intense absorption at around 300 nm that compares very well with experimental results (Table 4.1). For comparison the spectrum of the dimer's constituent units H₂SF and 1,4-divinylbenzene are also reported. The oscillator strengths of the two constituents are much lower than the ones of the dimer and model dimer. The lowest energy transition of H₂SF happens at about 265-270 nm with a low intense and very large band. This is once again in good agreement with the experimental values (Table 4.1). The phenylenedivinylene bridge on the contrary is characterized by a relatively stronger absorption maximum appearing at 280 nm. It has to be noted the relative good agreement with the experimental results [23], indeed the main

transition was modeled with a relative error of only about 10-15 nm, moreover also the position of the shoulder due to the absorption of the second unit was correctly previewed as compared to the experiment.

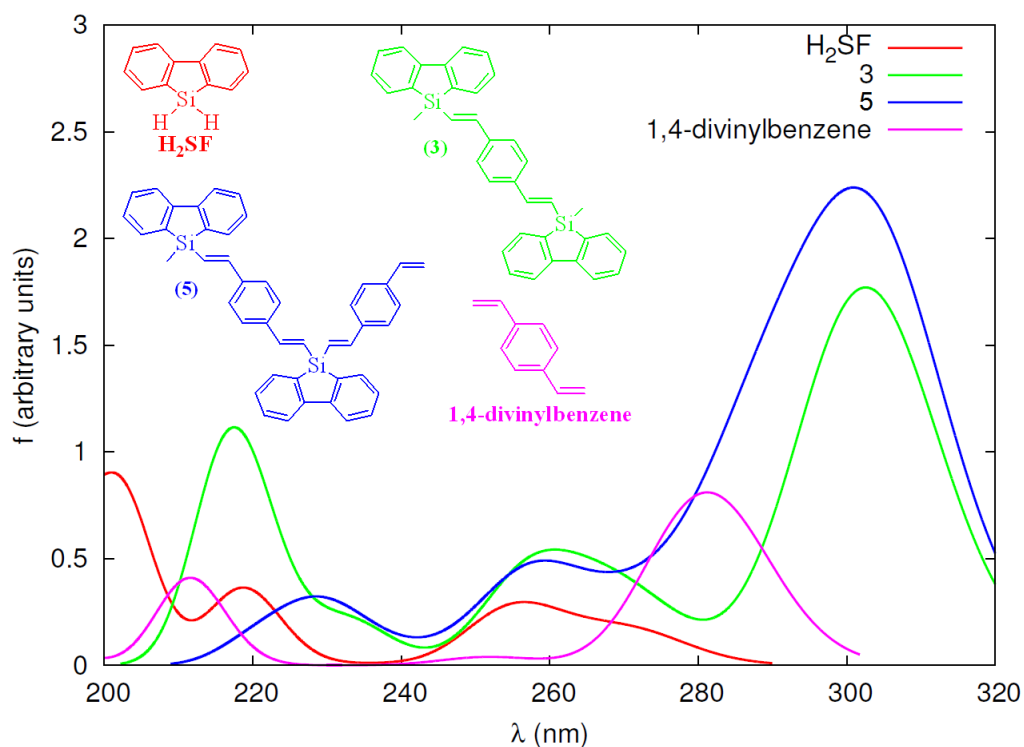


Figure 4.19. TD-DFT (M06-2X/6-31+G(d)) predicted absorption spectra for H_2SF , 3, 5 and 1,4-divinylbenzene in toluene.

The nature of the different excited states can be easily determined by analyzing the corresponding NTO's (Figure 4.20). Indeed, and as expected, both H_2SF and 1,4-divinylbenzene give local transitions that are mainly of $\pi-\pi^*$ nature. It is also interesting to note the important participation of the Si atom in the case of H_2SF . Obviously the case of the dimers can be much more complex. The occupied and virtual NTO's for the first transition responsible for the ~ 300 nm absorption band shows that the transition is mainly ascribed to be a $\pi-\pi^*$ localized in the bridging moiety (phenylenedivinylylene). The silafluorene rings are not only innocent spectators. Indeed some density delocalization over the Si atoms is noticeable both in the occupied and virtual NTO's for the first transition of 3 and 5 (Figure 4.20). The coupling between the bridging and silafluorene units may

explain the red shift of the transition (~ 20 nm), compared to the pure π - π^* one obtained for 1,4-divinylbenzene alone. The reasons for the important difference in intensities between monomers and oligomers can be related to the difference in the local environment of the chromophoric units that result in an important increase of transition dipole moments value and hence of absorption intensity.

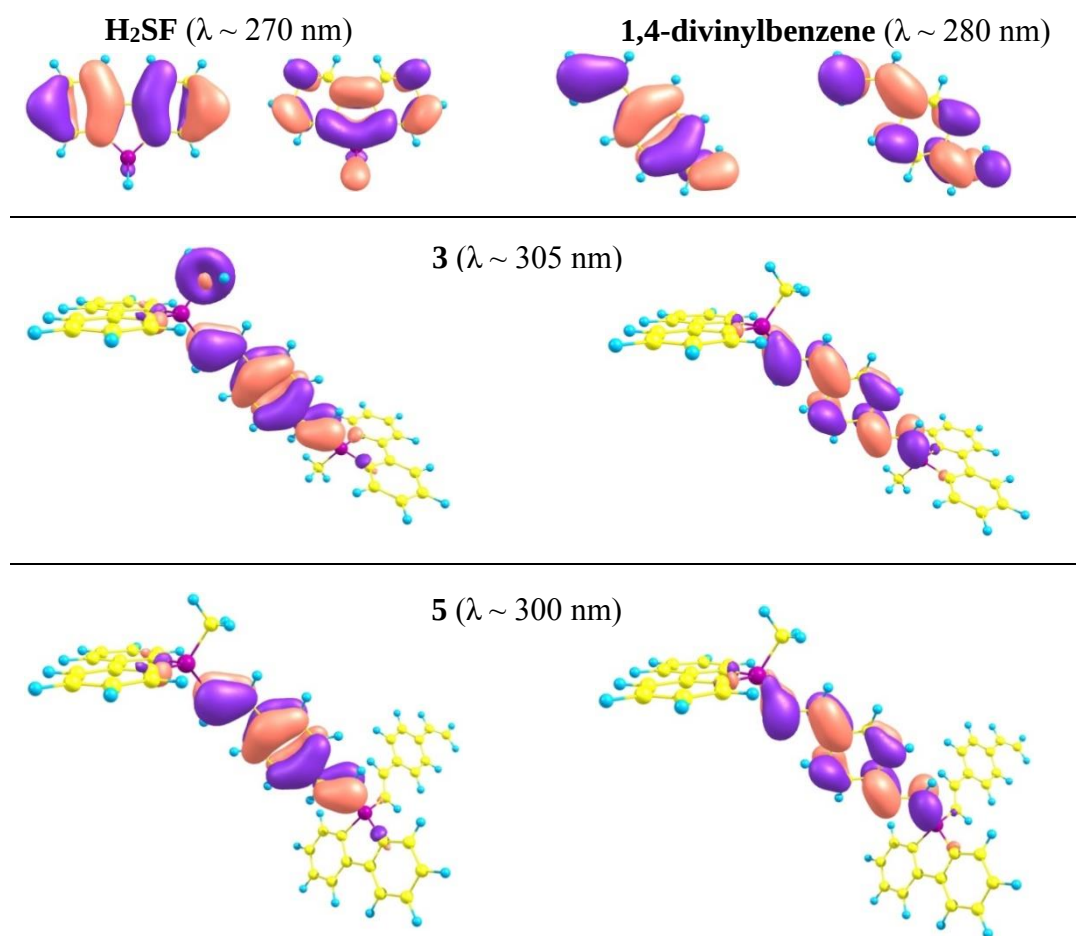


Figure 4.20. First transition NTO's couples (M06-2X/6-31+G(d)) of H₂SF, 1,4-divinylbenzene, 3, and 5 in toluene.

Left NTO is the occupied and the right one is the virtual.

The same tendencies in the absorption spectra as before can be observed in the case of the silole-containing monomer (H₂silole), model dimer (4) and dimer (6) (Figure 4.21). Once again the main absorption peak (~ 300 nm) of dimer and model dimer is significantly red shifted compared to the 1,4-divinylbenzene equivalent one (280 nm). As well as in the

previous case, the oscillator strengths are much higher upon dimerization. Interestingly enough for this class of compounds we can also notice a lower energy, and much less intense band appearing for the monomer as well as the dimer and model dimer at around 360 nm. The analysis of the NTO's can elucidate the nature of the transitions, in particular the 300 nm transition of 4 and 6 is ascribed to be a mainly π - π^* excitation centered on the bridging unit, again some participation of the silole ring is evidenced (Figure 4.22). The lowest energy transition ($\sim$ 360 nm) on the contrary appears totally localized on the silole ring, an occurrence that perfectly explains the fact that this transition is almost unaltered upon dimerization.

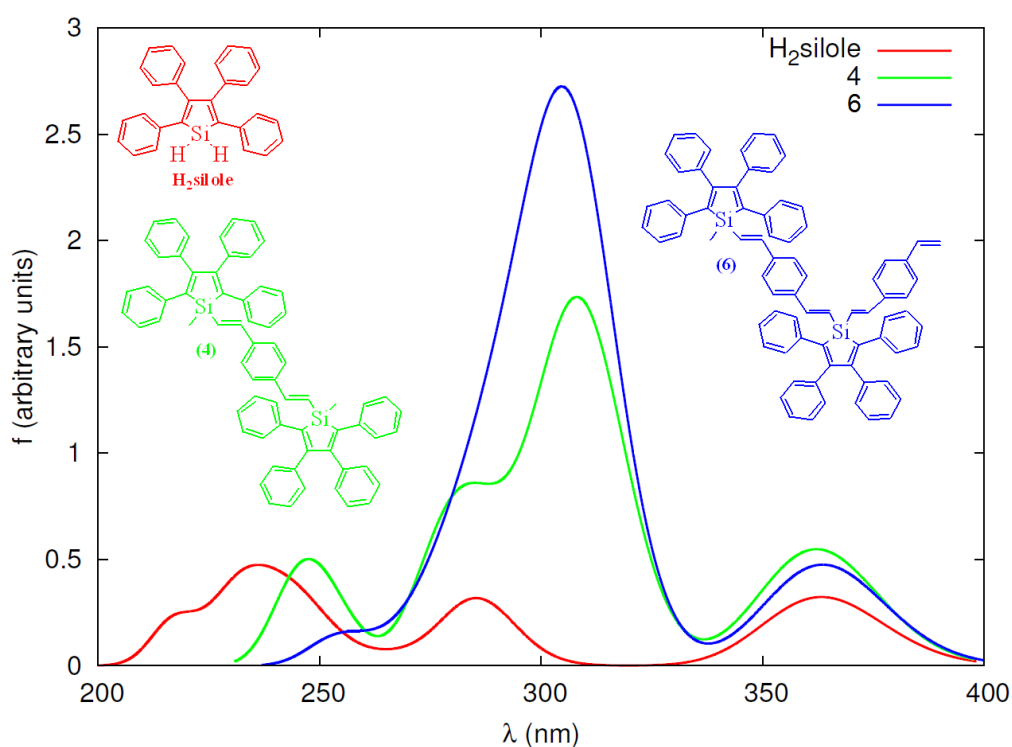


Figure 4.21. TD-DFT (M06-2X/6-31+G(d)) predicted absorption spectra for H₂silole, 4 and 6 in toluene.

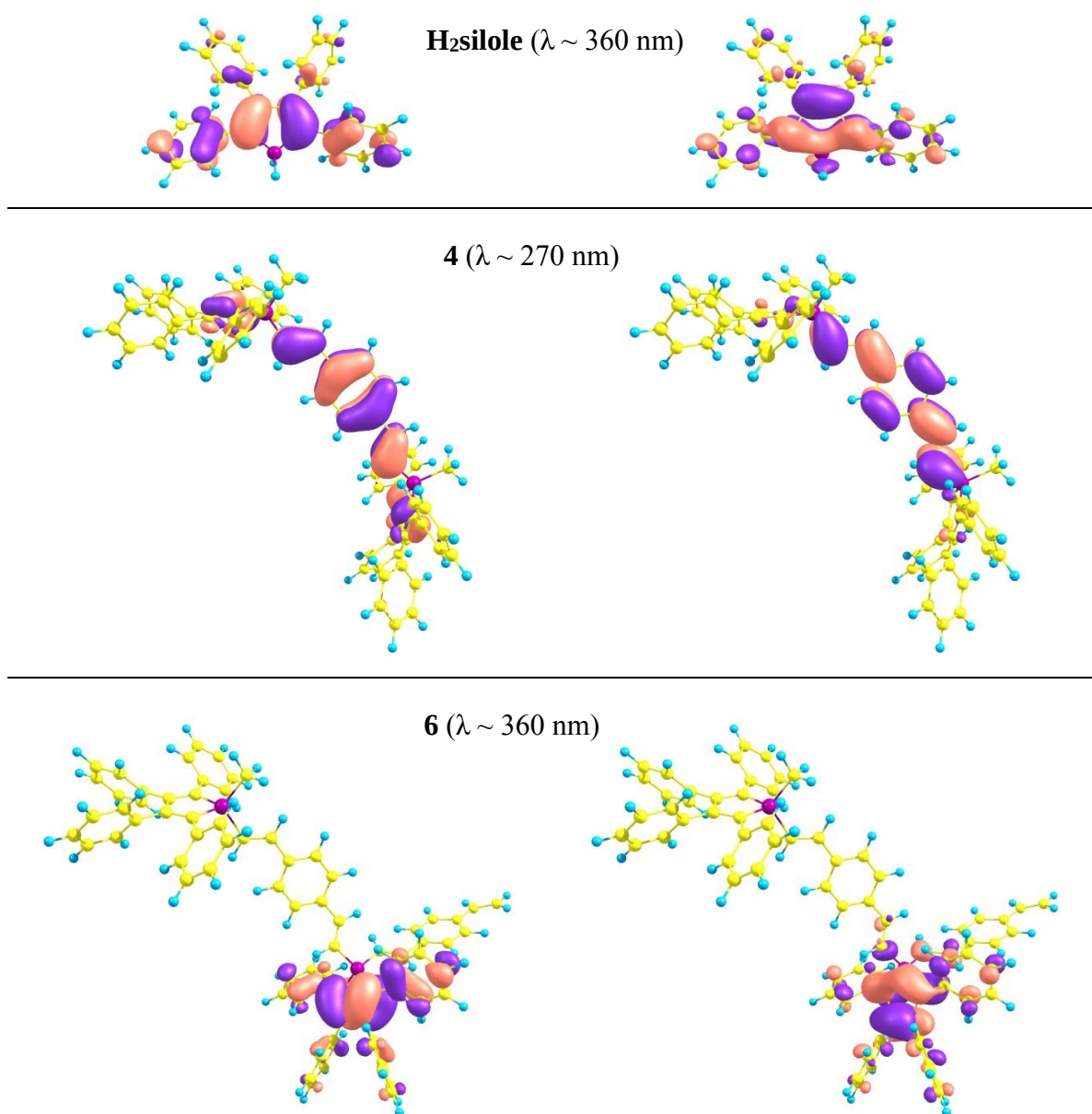


Figure 4.22. First and main transition NTO's couples (M06-2X/6-31+G(d)) of H₂silole, 4 and 6 in toluene.

Left NTO is the occupied and the right one is the virtual.

4.3.3.2. Complexes. Absorption spectra of different analytes are given in Figure 4.23. In particular and coherently with previous work we considered four aromatic (TNT, PA, DNT, NB) analytes, and one non aromatic (RDX). In all the cases they show intense absorption in the UV, with weak but not negligible tail at around 320 nm (Figure 4.23). Binding of silafluorene- and silole-containing polymers to explosives was investigated by

modeling the complexes between nitro containing explosives and dimers of these polymers [17].

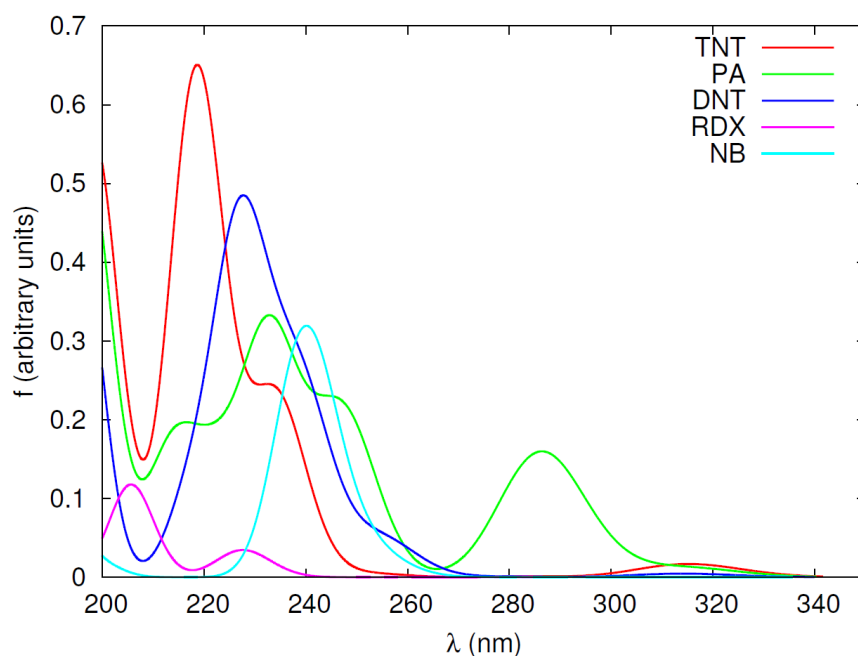


Figure 4.23. TD-DFT (M06-2X/6-31+G(d)) predicted absorption spectra for TNT, PA, DNT, RDX and NB in toluene.

As an illustrative example, the spectra of individual dimer 5, TNT and their complex, 5-TNT, are shown in Figure 4.24. The main absorption of TNT is centered in the UV region. On the contrary, upon complexation, one can observe an evident modification of the ~ 300 nm absorption band characteristic of dimer (5). In particular the intensities are lowered and the absorption maxima are very slightly red shifted with a double maxima structure. Interestingly enough one can now see a low intense tail centered around 375 nm that was not present neither in the spectrum of TNT alone nor in the one of the dimer. Spectra of the complexes with other explosives (Figure 4.25) show the same tendency as the spectrum of 5-TNT; strong absorption around 300 nm and low absorption tail at longer wavelengths (~ 370 nm).

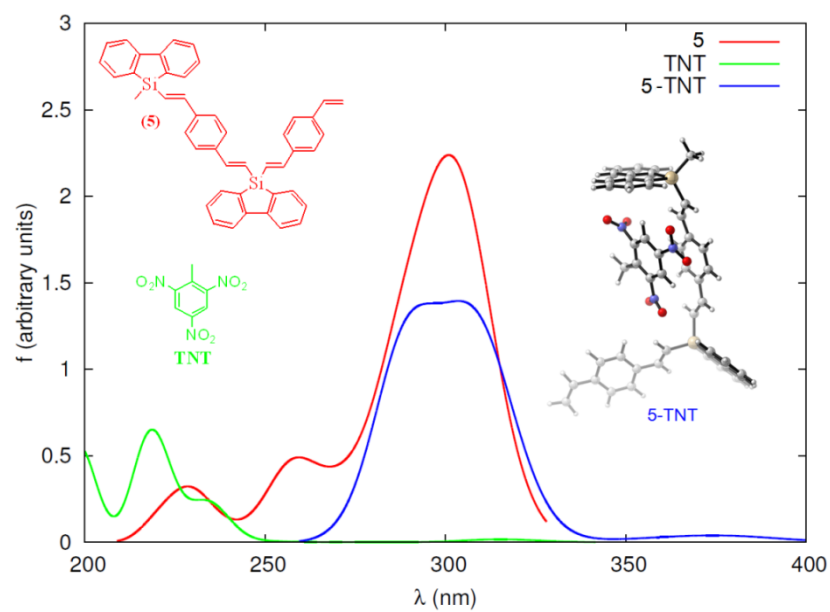


Figure 4.24. TD-DFT (M06-2X/6-31+G(d)) predicted absorption spectra for 5, TNT and 5-TNT in toluene.

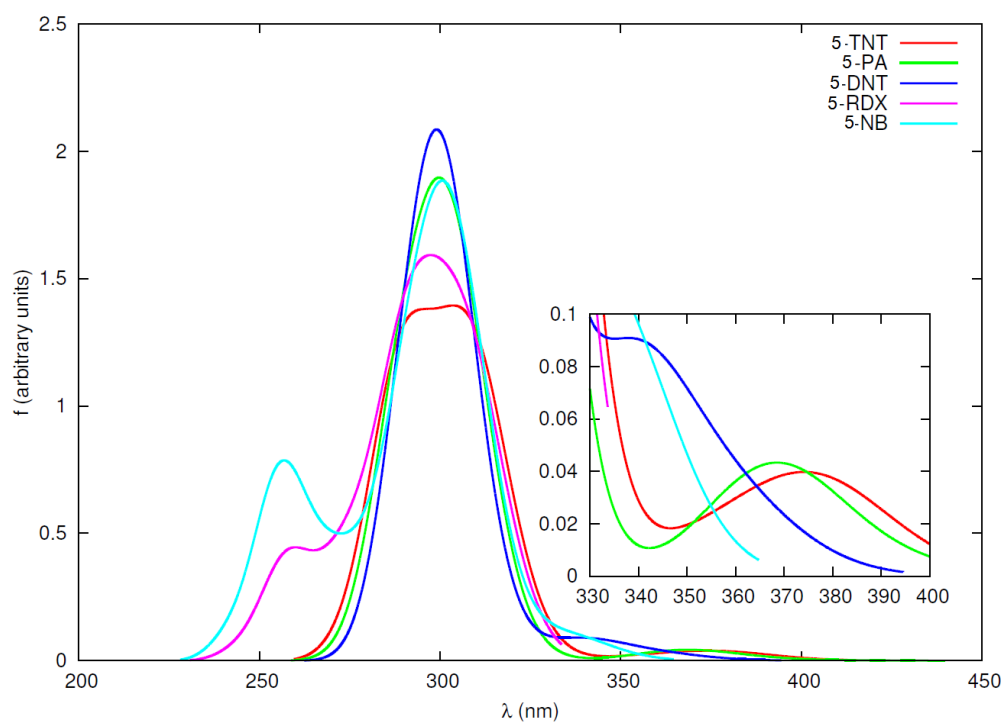


Figure 4.25. TD-DFT (M06-2X/6-31+G(d)) predicted absorption spectra for the complexes between 5 and analytes in toluene.

As far as the NTO analysis (Figure 4.26) is concerned we may first recognize that the most intense transition (~ 300 nm) is invariantly characterized as π - π^* and is always localized on the dimer and in particular on the phenylenedivinylene bridge. The participation of the aromatic analyte to this transition is always extremely weak. An important exception is the case of RDX for whom charge-transfer nature can be evidenced going from the bridge of the dimer to the acceptor nitramine group. The fact that in almost all the cases the most intense transition is keeping a local nature explains the small change on the absorption spectra maxima upon complexation. It is however interesting to analyze the lowest energy transition that gives the small intense absorption tail. Indeed since this tail is due to the first excited state it will be extremely important to modulate the emission properties of the aggregate since following Kasha's rule emission can be modeled as taking place from the lowest energy excited state, only.

In Figure 4.27 NTO's for the first excited state are reported. Contrary to the previous transition an impressive charge transfer from the phenylenedivinylene bridge of the dimer to the explosive is observed. Charge transfer is present for all the analytes concerned, especially when they present an aromatic core. Note also that the geometry of the complex is ideal to favor an important charge transfer since it allows a good overlap between the π systems of the bridge and of the analyte in the case of the aromatic explosives or between the bridge and the acceptor nitramine group in the case of 5-RDX.

From a more quantitative point of view, charge transfer is evidenced by calculating the charges of the analytes in the complexes for both first and main excited states and the charge-transfer character of these transitions is also evaluated with a descriptor, ϕ_S [48,49], that allows to quantitatively represent the charge-separation nature of a chromophore upon light-absorption (Table 4.9). All aromatic explosives follow the main trend with the most intense transition showing almost no charge transfer while already at the Franck-Condon region almost one full electron is transferred to the analyte for the first excited state. On the other hand in the case of 5-RDX the first and the main excited state can be classified as a charge-transfer state with a lesser amount of charge (about half an electron) transferred. The less amount of electronic charge transferred for this last case can be due to the fact that

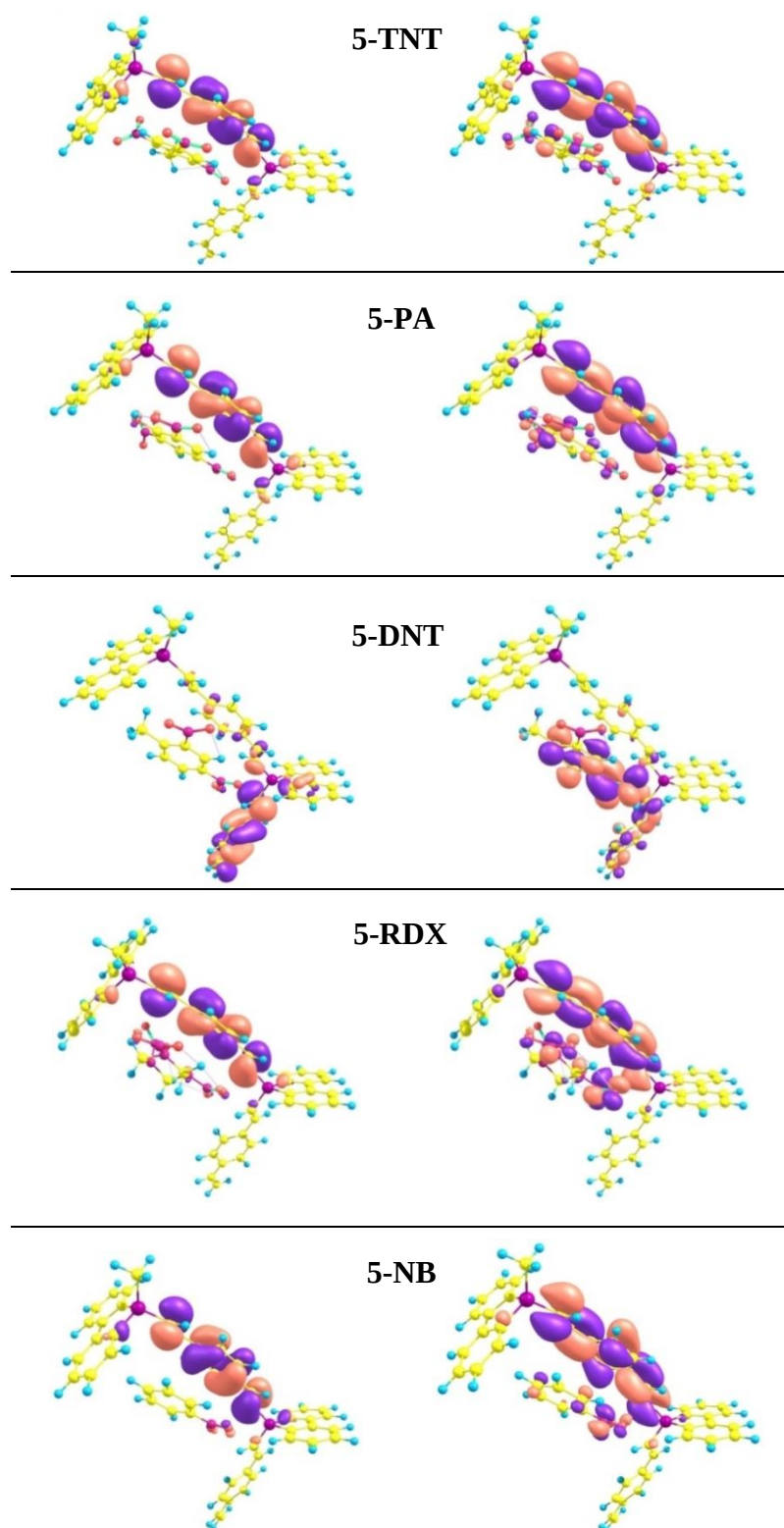


Figure 4.26. NTO's (M06-2X/6-31+G(d)) of complexes in the main excited state in toluene.

Left NTO is the occupied and the right one is the virtual.

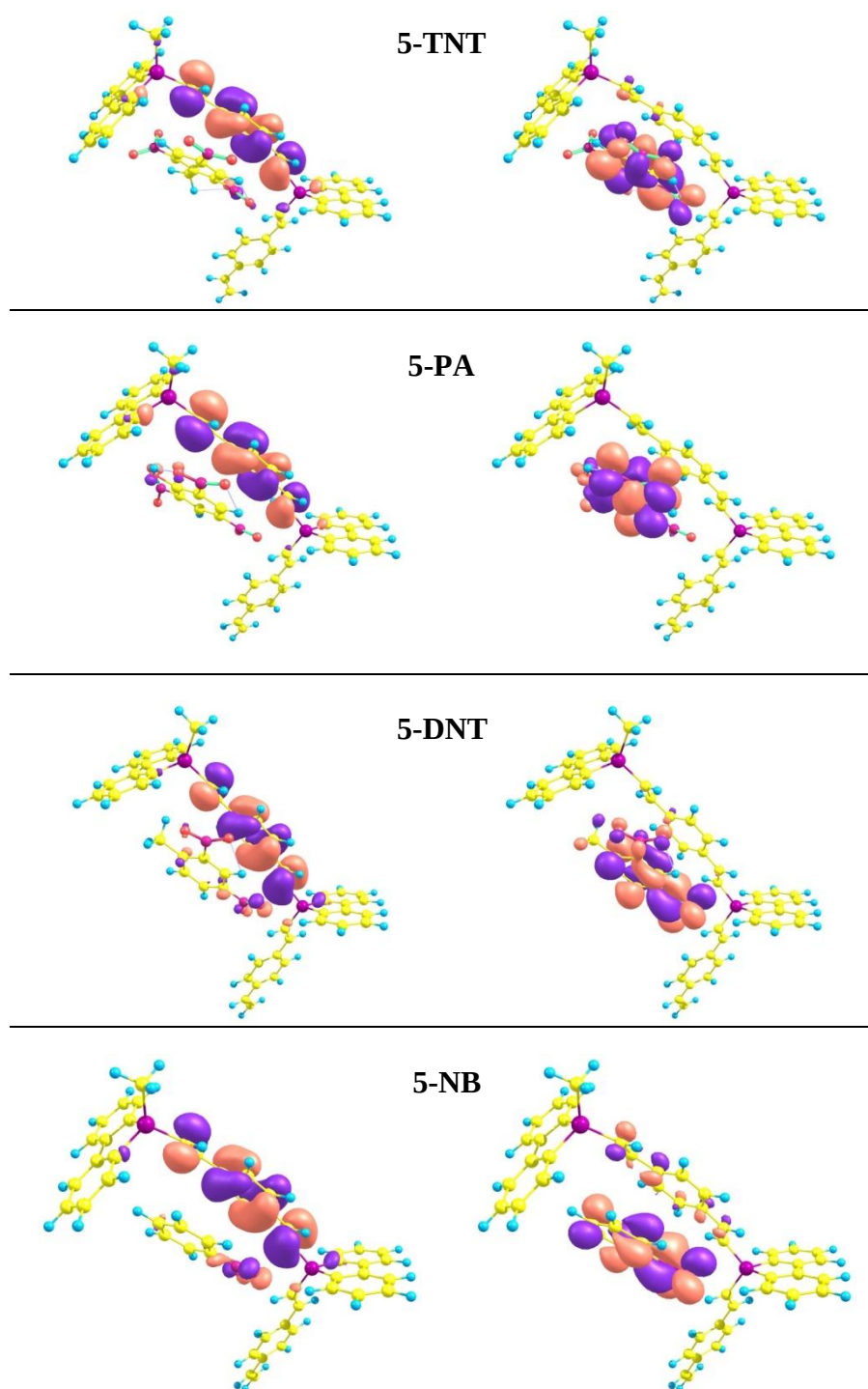


Figure 4.27. NTO's (M06-2X/6-31+G(d)) of complexes in the first excited state in toluene. Left NTO is the occupied and the right one is the virtual. The main excited state of 5 and 5-RDX corresponds to the first transition and the related NTO's are depicted in Figures 4.20 and 4.26, respectively.

in the case of aromatic explosives the whole π system of the analyte was participating to the charge transfer that is now only restricted to the acceptor group.

Table 4.9. NPA charges of the analytes in the complexes for the ground state (S_0), the first excited state (S_1) and the main excited state (ES_{main}) and the overlap descriptor, φ_s , of the first and main excited states.

	q			φ_s	
	S_0	S_1	ES_{main}	S_1	ES_{main}
5-TNT	-0.001	-0.869	-0.124	0.357	0.856
5-PA	0.004	-0.922	-0.084	0.260	0.867
5-DNT	0.015	-0.847	-0.210	0.416	0.733
5-RDX	0.029	-0.414	*	0.804	*
5-NB	0.007	-0.728	-0.052	0.493	0.869

* The first excited state of 5-RDX corresponds to the main transition.

4.3.3.3. Fluorescence Quenching. The fluorescence quenching process of silafluorene- and silole-containing polymers occurs due to the formation of complexes in the ground state mentioned earlier. The perturbation of the absorption spectrum of the fluorophore also indicates a ground-state complex formation. There is a significant change in the spectrum of free dimer 5 (red spectrum in Figure 4.24) when it is complexed with TNT (blue spectrum in Figure 4.24) indicating a static mechanism. Thus, the complexes formed by the fluorophores have been considered to understand the nature of the excited states.

According to the Kasha's rule [50,51], the emission from the excited fluorophore is exclusively happening from the lowest singlet excited state (S_1). Any excitation to higher electronic state will lead to a fast relaxation to the S_1 state before the possible emission to the ground state (S_0). This can be basically interpreted by the fact that the energy differences between excited states are much lower than the one between S_1 and S_0 state. As an example, in Figure 4.28 the excited state energies of the individual dimer, 5, and its complex with DNT, 5-DNT are reported. Since the energy difference between S_1 and S_0 is of the order of 3.5-4.0 eV while the energy difference between the other excited states is at most of the order of some fraction of eV the validity of Kasha's rule can be safely assumed.

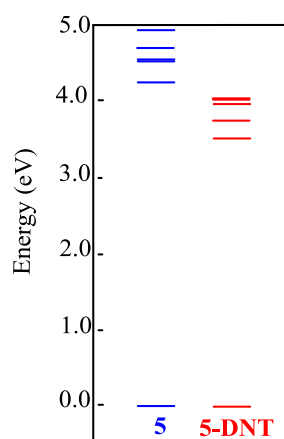


Figure 4.28. Vertical excitation energies (eV) for 5 and 5-DNT.

In Table 4.10 the emission wavelengths for the dimer (5) and different complexes with explosives obtained upon the first excited state geometry optimization using TD-DFT are reported both in toluene and gas phase. The fluorescence wavelength of 3 alone is calculated at about 340 nm (Table 4.10) which is close to the experimental λ_{flu} taken in toluene (Table 4.1). Moreover the emission oscillator strength is quite high suggesting a fully allowed fluorescence, again in agreement with experimental evidences. This is due to π - π^* character of the transition. On the contrary, when we consider the case of explosive-dimer complexes we invariably see that emission wavelength is shifted in the red or infra-red region of the spectrum. Moreover the oscillator strengths become extremely close to zero which implies that upon complexation with explosives (whether aromatic or not) and because of the presence of a charge-transfer for the first excited state the fluorescence should be quenched. The fluorescence intensities not only depend on the radiative rate (proportional to the oscillator strengths), but also to non-radiative rate. In the present case, especially for the charge-transfer states characterized by very low energy emission, the latter can be competitive with the radiative pathways, hence giving rise to even more important quenching phenomena. The photophysical and analytical properties of the complexes can therefore be easily interpreted on that basis. Indeed as soon as one molecule of explosive complexes with the detecting polymer it totally quenches emission from one of the emitting units of the polymer (the phenylenedivinylene bridges). This can also explain the linear law relating quenching to the explosive concentration. In addition since

the quenching happens to be total for every explosive tested here the sensitivity of the polymer will mostly depend on the complexation affinity with different explosives; the higher the affinity the better the sensitivity.

Table 4.10. Fluorescence wavelengths (nm) of 5, 5-DNT, 5-RDX with the oscillator strengths in parenthesis.*

	λ_{flu} (nm) gas-phase	λ_{flu} (nm) toluene
5	342 (1.697)	341 (1.778)
5-DNT	622 (0.110)	718 (0.009)
5-RDX	739 (0.047)	807 (0.004)

* The fluorescence wavelengths of 5-TNT, 5-PA and 5-NB show the same tendency (shift to ~ 600 - 700 nm and an intense decrease of the oscillator strength) as 5-DNT and 5-RDX. However, these numerical values are not reported because of the extremely flat potential energy surface of these compounds only loose convergence criteria were met.

4.4. Conclusions

Silafluorene and silole phenylene-divinylenes studied herein are promising candidates to be used as chemical sensors for explosives detection in accord with experimental studies. Trans structure for silole and silafluorene phenylene-divinylenes is found to be more stable than cis one as confirmed by X-ray diffraction analysis [23]. Selected bond lengths and bond angles agree well with the X-ray structure confirming the suitability of the M06-2X/6-31G(d) methodology for these systems. The stabilities of the complexes between polymers and analytes correlate with ease of detection. Two types of interactions, π - π stacking and Lewis acid-base, have been shown in a model system to promote the binding of analytes to polymers. π - π stacking interactions are found to be dominant in this model suggesting that the bridging phenylene-divinylene moiety from where π - π stacking interactions proceed is important. Thus new polymers synthesized with different bridging moieties would be better chemical sensors for explosives detection than silafluorene and silole phenylene-divinylenes. In the electron density topology analyses by QTAIM, π - π stacking interactions were found to govern the complex structure in cooperation with the hydrogen bonding interactions. The substitution of Si with Ge in the

polymer backbone suggested the suitability of Ge in the backbone as well as Si. Band gaps calculated as HOMO-LUMO energy differences support the selectivity trends observed with the calculated stabilities of the complexes in accord with experimental studies. Experimental selectivity trends have been reproduced computationally. However, modeling sensitivity needs further investigation.

The improved optoelectronic properties of silafluorene- and silole-containing polymers have been shown to arise from the increased delocalization of the conjugated bridge through the silicon centers in the silafluorene and silole moieties. The complexation of silafluorene containing polymers with the analytes produces a tail in the absorption spectrum of the complexes. This tail has been shown to be responsible for the charge transfer from the polymer to the analyte as should be the case for static quenching mechanism. The shift of the fluorescence signal of the complexes out of the Vis range and the extreme lowering of the oscillator strengths, prove the suitability of the silafluorene containing polymers as chemical sensors for the analytes based on the fluorescence quenching technique.

5. SELECTIVITY IN CINCHONA ALKALOID CATALYZED ASYMMETRIC DESYMMETRIZATION OF *meso*-CYCLIC ANHYDRIDES

Cinchona alkaloids catalyze a broad range of organic reactions one of which is the asymmetric desymmetrization (AD) of *meso*-cyclic anhydrides. In this chapter, the mechanism of AD of *meso*-cyclic anhydrides is highlighted in the presence of β -amino alcohols resembling cinchona alkaloids and the origins of stereoselectivity in cinchona alkaloids catalyzed AD of *meso*-cyclic anhydrides is investigated.

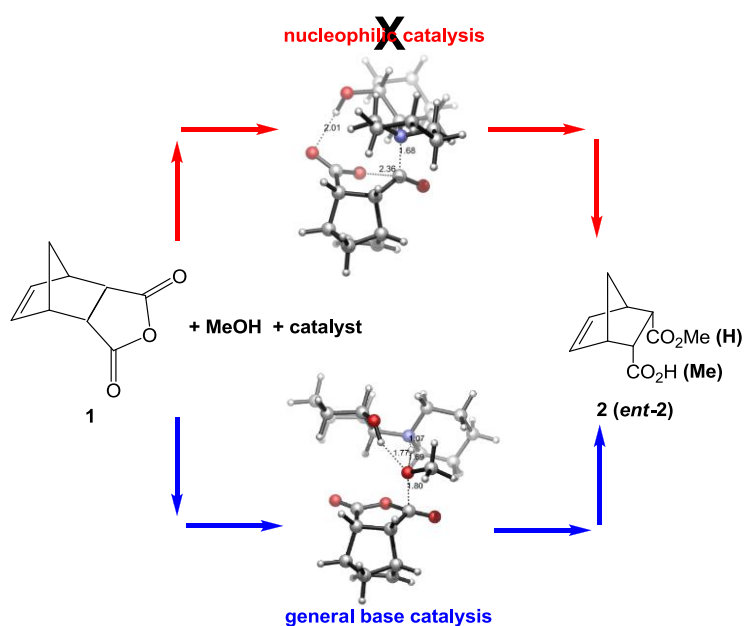


Figure 5.1. Nucleophilic and general base catalysis pathways for asymmetric desymmetrization of *meso*-cyclic anhydrides.

The alcoholysis of *meso*-cyclic anhydrides catalyzed by β -amino alcohols has been investigated with DFT quantum mechanics to determine the mechanism of this reaction. Both nucleophilic catalysis and general base catalysis pathways are explored for methanol-induced ring opening of an anhydride catalyzed by a chiral amino alcohol. The nucleophilic pathway involves a late transition state with a high energy barrier. In this

mechanism, methanolysis is expected to take place following the amine-induced ring opening of the anhydride. In the base-catalyzed mechanism, methanol attack on one carbonyl group of the *meso*-anhydride is assisted by the β -amino alcohol; the amine functionality abstracts the methanol proton. The chiral amino alcohol also catalyzes the reaction by stabilizing the oxyanion that forms upon ring opening of the anhydride by hydrogen bonding with its alcoholic moiety. Both stepwise and concerted pathways have been studied for the general base catalysis route. Transition structures for both are found to be lower in energy than in the nucleophilic mechanism. Overall this study has shed light on the mechanism of the β -amino alcohol-catalyzed alcoholysis of *meso*-cyclic anhydrides, showing that the nucleophilic pathway is approximately 25 kcal/mol higher in energy than the general base pathway (Figure 5.1).

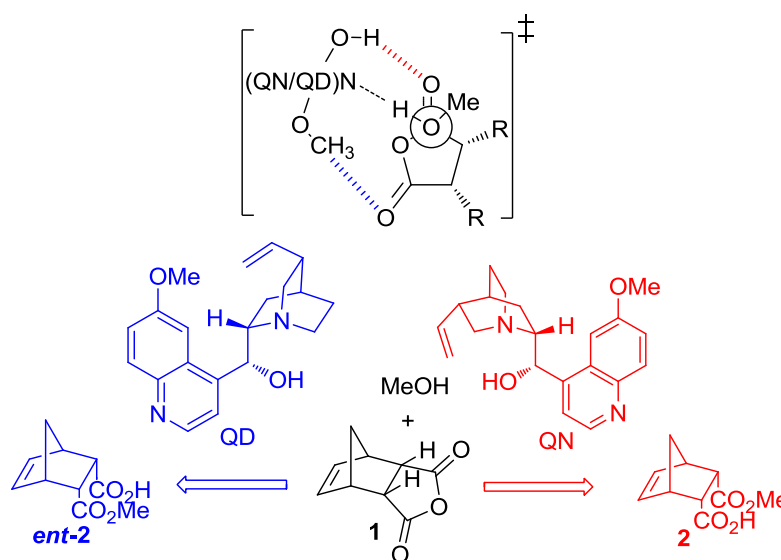


Figure 5.2. Asymmetric desymmetrization (AD) of *meso*-cyclic anhydrides catalyzed by quinine (QN) and quinidine (QD).

The asymmetric desymmetrization of *meso*-cyclic anhydrides catalyzed by the pseudoenantiomeric pairs of cinchona alkaloids, quinine (QN) and quinidine (QD), has been subject to a computational study employing density functional theory to understand the origin of the experimentally observed stereoselectivity (Figure 5.2). The spatial placement of the catalyst with respect to the anhydride, which resembles a molecular

tweezer, was found to be the primary reason for the stabilization of the oxyanion forming in the transition states, as well as the oxyanion intermediate observed along the reaction coordinate. The distortion-interaction model has been employed to rationalize the experimentally observed enantiomeric ratios. The assistance of solvent molecules was essential in prediction of experimental enantioselectivities.

5.1. Introduction

Cinchona alkaloids (Figure 5.3) have demonstrated widespread potential in chiral molecular recognition as well as enantioselective catalysis [52-55]. Their versatility is commonly attributed to the presence of several functionalities and their ability to act as multisite receptors. Several conformational investigations have been carried out both with computational tools, NMR and X-Ray analysis [56-63]. Assessing the conformational dynamics of cinchona alkaloids is important in developing a comprehensive understanding of the catalytic mechanism leading to enantiodifferentiation.

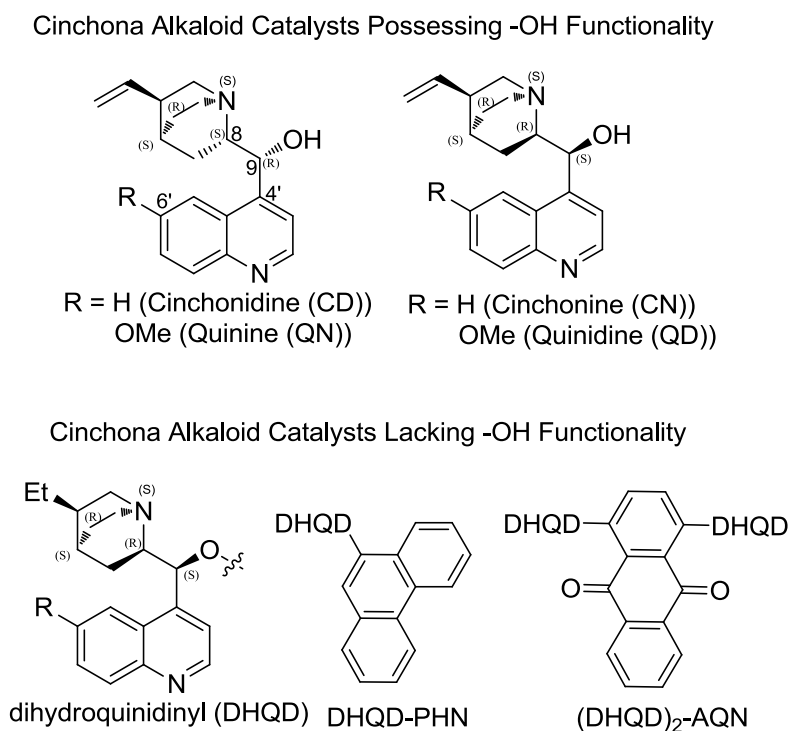


Figure 5.3. Widely used cinchona alkaloids and their derivatives.

Cinchona alkaloid-derived catalysts are central to many catalytic asymmetric reactions today, one of which is the asymmetric desymmetrization (AD) of *meso*-cyclic anhydrides (Figure 5.4). AD with cinchona alkaloids has attracted considerable attention, since many *meso*-cyclic anhydrides are available through the Diels-Alder reactions of maleic anhydride. The desymmetrized products can be readily transformed to a variety of chiral building blocks [64-66]. Although the cinchona alkaloid catalysts, quinine and quinidine, are diastereomers (Figure 5.3), the reactions catalyzed by these two compounds often yield opposite enantiomers as products by virtue of the opposite absolute configurations at C8 and C9 of the alkaloids. In Bolm's asymmetric desymmetrization, the ring-opening reaction of **1** affords hemiester **2** in 96% ee when catalyzed by quinidine and *ent*-**2** in 99% ee when catalyzed by quinine (Figure 5.4).

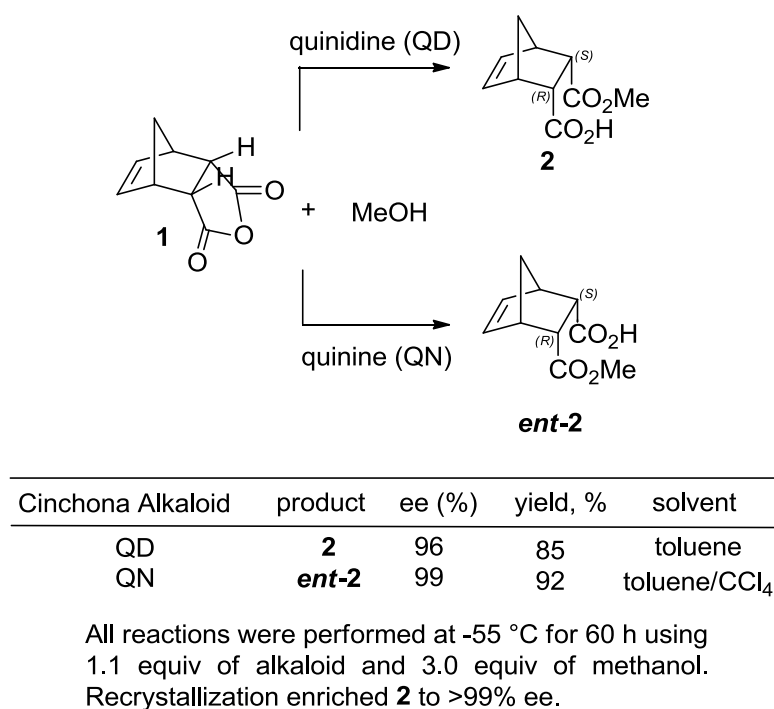


Figure 5.4. Experimental products, enantiomeric excess ratios and yields in Asymmetric Desymmetrization (AD) of a *meso*-cyclic anhydride with pseudoenantiomeric pairs of cinchona alkaloids [67].

Oda and co-workers were first to carry out desymmetrization of *meso*-cyclic anhydrides catalyzed by 0.1 eq of cinchona alkaloids, however, with moderate enantioselectivities, this report was followed by various studies on the enantioselectivity of the ring-opening processes [68,69]. Aitken *et al.* observed that increasing the catalyst (cinchonidine or quinidine) load led to a significant increase in the enantioselectivity in the reaction of tetracyclic anhydrides with methanol [70]. Bolm and co-workers have worked extensively on the development of a simple and highly enantioselective methanolysis of *meso*-cyclic anhydrides and obtained up to 99% ee in the opening of prochiral anhydrides by methanol, even though stoichiometric amounts of quinine or quinidine were required (Figure 5.4). In solvents of low polarity and at low temperatures the highest enantioselectivities were observed [67,71,72]. In order to identify the key structural components for the catalytic and enantioselective effects of the generally rather complex alkaloids, Bolm and co-workers started to evaluate the use of low molecular weight amino alcohols and investigated their efficiency as catalysts in asymmetric anhydride openings. Applying advanced variations of their early protocols [67,71-75], they were able to identify structurally simple β -amino alcohols such as **3**, which provided products with very good enantioselectivities in excellent yields (Figure 5.5) [64,76]. In parallel with Bolm's studies, Deng *et al.* developed a general and highly enantioselective catalytic alcoholysis of *meso*-cyclic anhydrides with modified cinchona alkaloids ((DHQD)₂AQN or (DHQ)₂AQN) [77].

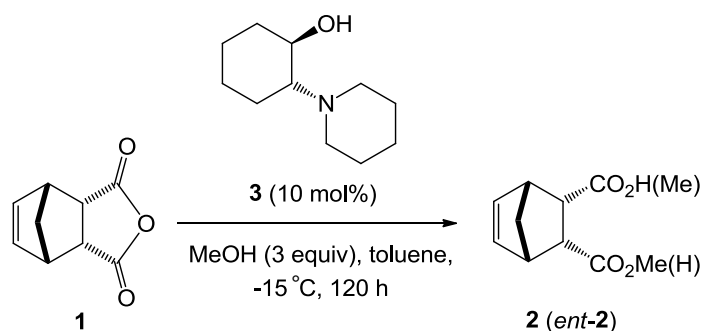


Figure 5.5. β -Amino alcohol-catalyzed enantioselective anhydride alcoholysis.

Two possible mechanisms have been proposed for the AD of cyclic anhydrides: nucleophilic and general base catalysis (Figure 5.6) [68,78]. In nucleophilic catalysis, the nucleophilic attack of the catalyst quinuclidine nitrogen on the anhydride is expected to form a reactive chiral acylammonium salt. Nucleophilic attack on this salt by an alcohol gives the ester product and regenerates the amine. In the general base catalysis mechanism, in which the catalyst acts as a chiral general base rather than a nucleophile, the methanol attack on the anhydride carbonyl is assisted by the catalyst nitrogen through deprotonation of the methanol. The resulting methoxide is far more nucleophilic than methanol, enhancing the nucleophilic attack that leads to the ring opening of the anhydride. Evidence has been found for both mechanisms [69,70,78-80]. Both Oda [69] and Deng [80] observed a first-order dependence of the rate of the alcoholysis on alcohol and their kinetic isotope effect investigations were consistent with a general base catalysis mechanism. On the other hand, Aitken and co-workers [70,78] suggested the formation of an acylammonium-type intermediate pointing out a nucleophilic mechanism which was also supported with Carloni's detection of an anhydride-quinidine adduct by mass spectroscopy [79]. Both mechanisms are computationally explored in order to identify the most plausible pathway in the first part of this chapter.

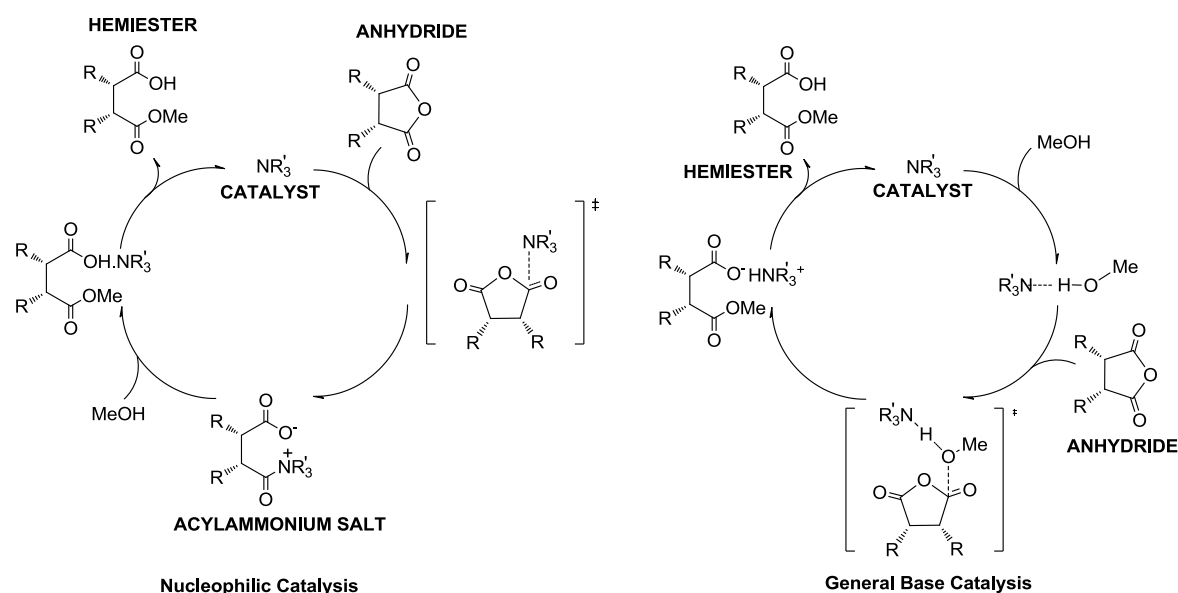


Figure 5.6. Nucleophilic and general base catalysis pathways for AD of cyclic anhydrides as previously proposed by Aitken [70,78] and Oda [68,69].

The origin of stereoselectivity in AD of cyclic anhydrides has been recently subject to several studies. Deng *et al.* have identified the active conformation of cinchona alkaloid catalyst as the *app*-closed conformation of DHQD derivatives, a cinchona alkaloid derivative (Figure 5.3), in the enantioselective methanolysis of *cis*-2,3-dimethylsuccinic anhydride [81]. In Deng's study, the enantioselectivity has been attributed to steric factors caused by the bulky substituent at the C9-O position of the catalyst (Figure 5.3) which helps to differentiate the conformation of the catalyst in their transition-state model. Deng *et al.* have also reported kinetic studies in accordance with the general base catalysis mechanism for the cinchona alkaloid-catalyzed alcoholysis [81]. Thereafter, it has been suggested in a conformational and mechanistic NMR study by Balzano *et al.* that C9-O substituent of the catalyst should have a more active role than merely enforcing the chiral fragments to adopt a preferential reactive conformation, since no obvious correlation could be found between the propensity of the different chiral derivatives to attain a Closed(2) conformation and their catalytic properties [82]. In a combined experimental and theoretical study, the stability of the pro-*R* and pro-*S* conformers rather than the transition states in the quinine catalyzed desymmetrization of glutaric *meso*-anhydrides was investigated and it has been suggested that the stabilization of the pro-*R* conformer that will lead to the observed product, stems from steric interactions between methanol and the anhydride hydrogen atoms in the axial position [83]. In a more recent theoretical study, much effort has been invested by Yang and Wong to shed light on the origin of stereoselectivity in asymmetric methanolysis of *meso*-cyclic anhydrides catalyzed by a sub-class of cinchona alkaloid catalysts, which lack the -OH functionality (Figure 5.3), namely DHQD derivatives [84]. This systematic study comprises the location of the possible transition states of asymmetric methanolysis of *meso*-cyclic anhydrides in a small model catalyst system, the results are later extrapolated to the full catalyst system. A transition state model in which the developing oxyanion is stabilized via C-H...O hydrogen bonds has been proposed and predicted enantioselectivities have been reported in conjunction with Deng's experimental findings for the asymmetric methanolysis of *meso*-cyclic anhydrides with cinchona alkaloid catalyst (DHQD derivatives), which does not incorporate the N-H or O-H functionality to stabilize the oxyanion.

This chapter aims to understand the mechanistic aspects of the alcoholysis of *meso*-anhydrides catalyzed by chiral amines, through a computational evaluation of the probable reaction pathways mentioned earlier (Figure 5.6) and to gain insight into the observed stereoselectivities based on Bolm's experimental findings (Figure 5.4) in the ring-opening reactions of *meso*-cyclic anhydrides catalyzed by cinchona alkaloids, QN and QD which possess the -OH functionality that is believed to play a much more active role in the stabilization of the oxyanion than C-H...O hydrogen bonds that were highlighted in Yang and Wong's study. Though the previous studies revealed the importance of Open(3) conformation for the cinchona alkaloid catalyst in these reactions, a systematic conformational search was conducted to locate the lowest-energy conformations utilizing a dispersion-corrected DFT functional. The Open(3) conformation was further used to study the base catalyzed AD of *meso*-cyclic anhydrides with methanol. In the first part of this chapter that aims to clarify the operative mechanism for the AD of *meso*-cyclic anhydrides the increased conformational space with methanol for the base catalyzed mechanism is not fully investigated but the preliminary results on stereoselectivity in base catalysis are attributed to the relative orientation of the catalyst with respect to the anhydride and methanol. In the second part of this chapter, transition state conformations including the various spatial position of the -OH functionality of the catalyst with respect to the anhydride have been modeled to highlight the interactions contributing to the stabilization of the oxyanion forming in the transition state and to understand the stereoselectivities with methanol acting as the reaction partner. The distortion/interaction analysis, which has been shown to reveal the origin of selectivities in many organic and organometallic reactions [85-89], was employed, herein, to evaluate the distortion of the catalyst and its relation to stereoselectivity. Bolm's experimental findings (Figure 5.4) have been modeled taking into account the effect of the assistance of solvent molecules that can significantly alter the calculated enantiomeric ratios [67].

5.2. Computational Details

Geometry optimizations were performed using density functional theory (DFT) [32]. All stationary points have been characterized by a frequency analysis from which thermal corrections have also been obtained. Local minima and first order saddle points were

identified by the number of imaginary vibrational frequencies. The intrinsic reaction coordinate (IRC) calculations were used to determine the species connected by each transition structure [90].

All calculations for the mechanism of small amino alcohol catalyzed AD (Chapter 5.3.1) have been carried out using the Gaussian 03 program package, an earlier version of Gaussian 09 [32]. The effect of a polar environment has been taken into account via the integral equation formalism-polarizable continuum (IEF-PCM) model [11,42,91], utilizing toluene ($\epsilon = 2.38$) as the solvent. B3LYP functional and 6-31+G(d,p) basis set was employed for this part. The B3LYP functional is known to be adequate for geometries. However, it usually overestimates energy barriers; therefore, energies were further checked with the hybrid meta-GGA's MPW1B95 [40], MPWB1K [40] and hybrid GGA M05-2X [92], each known to perform well for thermochemical kinetics. However, a high energy difference between the barriers of the proposed mechanisms allowed us to safely predict the plausible mechanism. The rest of the calculations where we have dealt with the small energy differences to predict the stereoselectivity of the cinchona alkaloid catalyzed AD have been carried out with a more up-to-date hybrid GGA functional, M06-2X [6], with 6-31+G(d,p) basis set using Gaussian 09 program package [32]. The free energies reported include the thermal free energy corrections obtained from gas phase calculations at the M06-2X/6-31+G(d,p) level at 218.15 K and 1 atm.

5.3. Results and Discussion

5.3.1. Mechanism of the Desymmetrization of *meso*-Cyclic Anhydrides by Chiral Amino Alcohols

The amine-catalyzed methanolysis of cyclic anhydride **1** has been subject to a computational investigation in order to identify the mechanism in operation. For this purpose, *base-catalyzed* and *nucleophile-catalyzed* pathways (Figure 5.6) have been modeled, utilizing (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexanol (**3**) as a chiral catalyst (Figure

5.5). Prior to calculations on reaction pathways, the conformational space of the catalyst has been studied.

Conformers of **3** with axial or equatorial groups at the piperidine N are depicted in Figure 5.7. Among these conformers, 3-ax and 3-eq are both capable of forming intramolecular hydrogen bonds as shown in Figure 5.8. Conformer 3-eq which has all substituents at the piperidinyll and the cyclohexyl ring in equatorial position is 4 kcal/mol more stable than 3-ax. A potential energy surface (PES) scan has been carried out for possible conformers of 3-eq, and the lowest energy conformer (shown in Figure 5.8) has subsequently been utilized for reaction path calculations in the methanolysis of cyclic anhydride **1**.

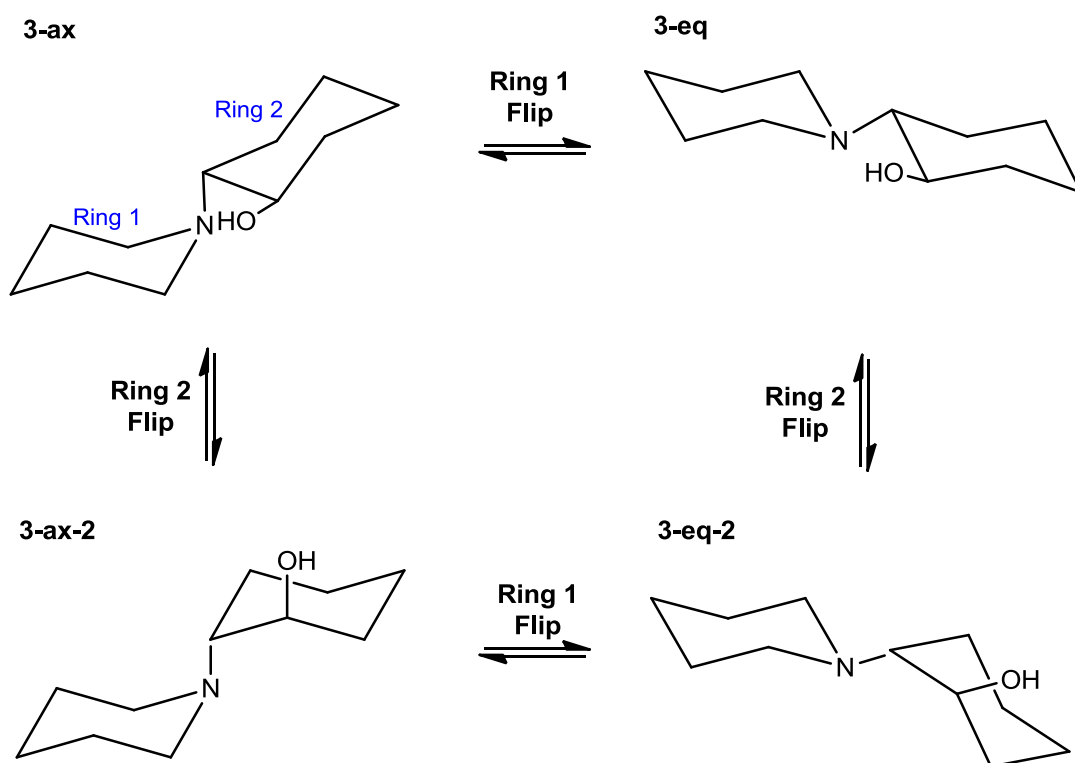


Figure 5.7. Conformers of **3** for the amine-catalyzed methanolysis of cyclic anhydride **1**.

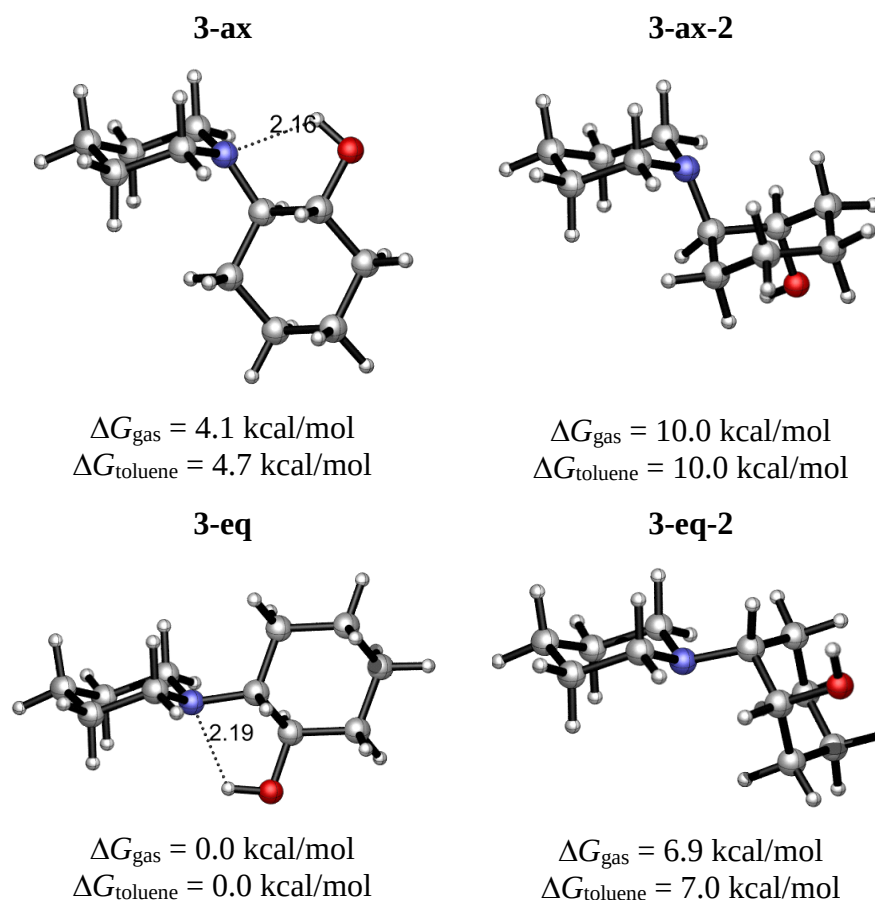


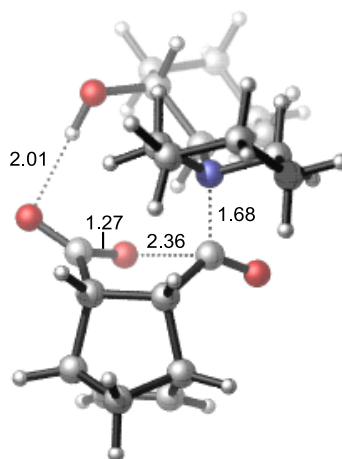
Figure 5.8. Conformers of 3 with relative free energies in gas-phase (ΔG_{gas}) and toluene ($\Delta G_{\text{toluene}}$).

Thermal free energy corrections for solvent calculations from B3LYP/6-31+G(d,p) calculations at 1atm and 298K.

5.3.1.1. Proposed Mechanisms. Nucleophilic Catalysis vs General Base Catalysis. Two possible mechanisms- *general base catalysis* and *nucleophilic catalysis* -have been previously proposed for asymmetric ring opening reactions [68-70,78,79,93-96]. Both mechanisms have been modeled in order to identify the most plausible pathway for the amine-catalyzed methanolysis of cyclic anhydride 1.

In the nucleophilic catalysis mechanism, the amine nitrogen of the catalyst attacks the anhydride to form a reactive chiral acylammonium salt. Next, methanol reacts with this salt leading to the product and regenerating the amine. As the catalyst nitrogen (TS-Nuc, Figure 5.9) approaches the carbonyl of anhydride 1, the C-O bond of the substrate

elongates from 1.39 Å to 2.36 Å and the cyclic anhydride is cleaved. The reaction is assisted by the -OH group of the catalyst, which stabilizes the carboxylate moiety that forms upon ring opening.



TS-Nuc

$$\Delta G_{\text{gas}}^{\ddagger} = 62.7 \text{ kcal.mol}^{-1}$$

$$\Delta G_{\text{toluene}}^{\ddagger} = 59.5 \text{ kcal.mol}^{-1}$$

Figure 5.9. Transition structure for nucleophilic catalysis of anhydride 1 and free energies of activation (in kcal/mol) in gas-phase ($\Delta G_{\text{gas}}^{\ddagger}$) and toluene ($\Delta G_{\text{toluene}}^{\ddagger}$) calculated by B3LYP/6-31+G(d,p).

Carloni *et al.* proposed that the desymmetrization of *meso*-anhydrides, catalyzed by cinchona alkaloids, proceeds through the formation of an adduct between quinidine and anhydride (Figure 5.10) [79]. The hypothetical structure proposed by Carloni forms through the nucleophilic attack of quinidine that leads to ring opening of anhydride. The ring openings of TS-Nuc and Carloni's intermediate are assisted by hydrogen bonds between the -OH of the catalyst and the anhydride. The structure proposed by Carloni is very similar to TS-Nuc, nevertheless different catalysts and anydrides have been used in the latter, so the stability of TS-Nuc cannot be argued based on this finding.

The transition state is late with a high energy barrier ($\Delta G_{\text{gas}}^{\ddagger} = 62.7$ kcal/mole, Figure 5.9). In this mechanism, the stereochemistry of the product, 2, is established in the initial

step, before methanol attacks the acylammonium salt. The reaction is likely to be stereoselective, and the transition state in Figure 5.9 leads to the major product. However, in the case of TS-Nuc, the activation free energies are much too high to be operative.

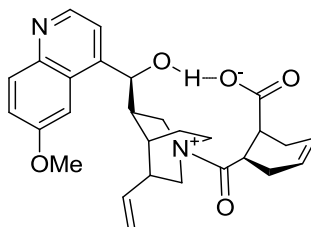


Figure 5.10. Active intermediate proposed by Carloni *et al.* [79].

In the alternative mechanism, the catalyst acts as a chiral general base rather than a nucleophile. The methanol attack on the carbonyl is assisted by the catalyst nitrogen through deprotonation. Deprotonation of the methanol yields methoxide, which is far more nucleophilic than methanol, enhancing the nucleophilic attack that leads to ring opening of the anhydride. The catalyst also stabilizes- through H-bond donation by the alcohol moiety -the oxanion formed as a result of ring opening. The stereochemistry of the final product is determined by which enantiotopic carbonyl is attacked by methoxide. In the base catalyzed mechanism, the ring opening reaction may proceed via a stepwise (TS-Base-Step1) or a concerted pathway (TS-Base-Conc; Figure 5.11).

In the concerted pathway, attack of methanol is accompanied by a simultaneous ring opening of the anhydride in a single step. In the stepwise pathway, nucleophilic attack of methanol on the anhydride leads to the formation of a tetrahedral intermediate (INT), which then undergoes ring opening to yield the final product. The energies computed for these mechanisms are shown in Figure 5.11.

In the transition state of the concerted pathway (TS-Base-Conc; Figure 5.11), as methanol attacks anhydride 1, the forming CO distance is 1.80 Å. Methanol is deprotonated by the basic catalyst; the forming NH distance is 1.07 Å. Finally, product 2 forms and the catalyst is regenerated. The process is endothermic by 4.4 kcal/mol ($\Delta G_{\text{toluene}} = 5.0$ kcal/mol; Figure 5.11).

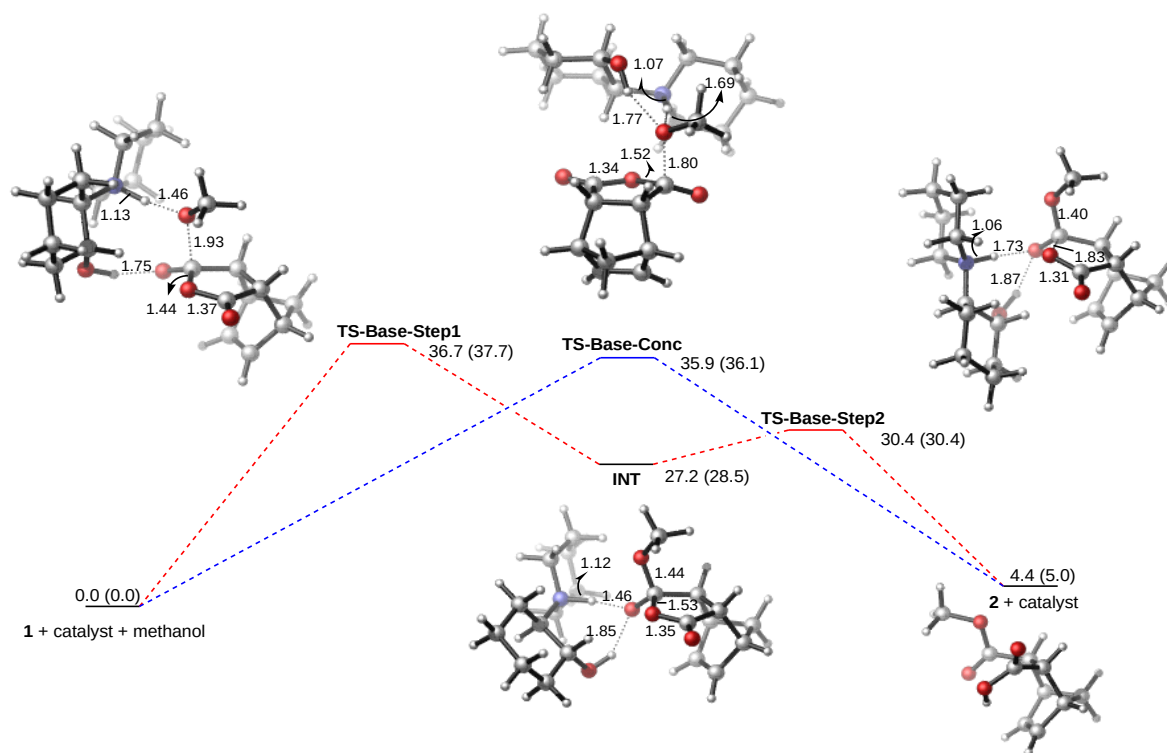


Figure 5.11. B3LYP/6-31+G(d,p) free energy profile, for concerted and stepwise base catalysis pathways.

Numerical values refer to ΔG_{gas} (in kcal/mol). Values in parentheses are $\Delta G_{\text{toluene}}$. Thermal free energy corrections for solvent calculations from B3LYP/6-31+G(d,p) calculations at 1atm and 298K.

The first step in the stepwise general base catalysis mechanism is the same, but a tetrahedral intermediate is formed instead. Transition structure TS-Base-Step1 (Figure 5.11) illustrates the complex between anhydride 1, the catalyst and methanol. This complex is stabilized through a hydrogen bond network between the nitrogen atom of the catalyst and the hydrogen atom of methanol, stabilizing the oxyanion. IRC calculations have verified that TS-Base-Step1 connects the intermediate (INT) to the reactants. The intermediate, INT is 27.2 kcal/mol (28.5 kcal/mol in toluene) higher in energy than the reactants. The second step requires only a small energy barrier of 3.2 kcal/mol (1.9 kcal/mol in toluene) and through TS-Base-Step2 ring opening leads to the final product, and the catalyst is regenerated (Figure 5.11).

The 26.8 kcal/mol free energy difference (23.4 kcal/mol in toluene) between the transition states of the nucleophilic catalysis (TS-Nuc) and base catalysis mechanisms (TS-Base-Conc) shows that the general base catalysis mechanism for asymmetric ring opening reactions is most likely to be the operative pathway. Nevertheless, the computed activation energy is quite high compared to the facility with which the reactions occur.

5.3.1.2. Effect of Excess Methanol on Reaction Energetics. AD reactions with β -amino alcohol 3 were conducted using 1 equivalent of the catalyst and 3 equivalents of methanol [64,76]. In order to better mimic the reaction conditions, three methanol molecules were included in the calculations to explore the concerted base-catalyzed reaction pathway. One methanol acted as the nucleophile and the other two were stabilizing carbonyl oxygens of the anhydride 1 through hydrogen bonds (Figure 5.12).

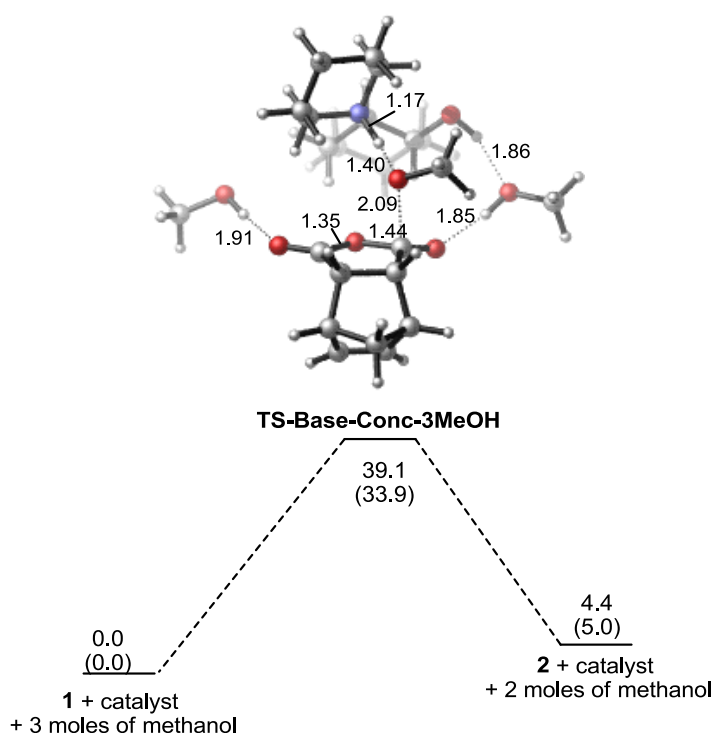


Figure 5.12. B3LYP/6-31+G(d,p) free energy profile for the concerted base catalyzed mechanism with excess methanol (anhydride + 3 methanol + catalyst).

Numerical values refer to ΔG_{gas} (in kcal/mol). Values in parentheses are $\Delta G_{\text{toluene}}$. Thermal free energy corrections for solvent calculations from B3LYP/6-31+G(d,p) calculations at 1atm and 298K.

TS-Base-Conc-3MeOH (Figure 5.12) is very similar to TS-Base-Conc except for additional H-bonds between the catalyst, methanol and anhydride 1. As the nucleophilic methanol approaches, a bond elongation is observed in the anhydride ring, where the carbon oxygen bond lengthens from 1.39 Å to 1.44 Å, and methanol is deprotonated by the catalyst. Peripheral methanols help stabilize the charge developing as the ring opens. TS-Base-Conc-3MeOH and TS-Base-Conc are very similar in terms of free energy, but TS-Base-Conc-3MeOH is better stabilized in toluene compared to the one methanol system, TS-Base-Conc ($\Delta\Delta G_{\text{toluene}}^{\ddagger} = 2.2$ kcal/mol).

5.3.1.3. Effect of Method and Implicit Solvation on Reaction Energetics. Activation free energies for the nucleophilic catalysis and *concerted*-general base catalysis mechanism are given in Table 5.1. The results show a clear preference for the *concerted*-general base catalysis over the nucleophilic catalysis mechanism for all functionals. For all methods, the energy difference between nucleophilic and base catalysis is approximately 25 kcal/mol, both in vacuo and toluene. While the base catalysis barriers are relatively unaffected by the solvent, the nucleophilic catalysis barriers show a slight decrease in barrier, due to the stabilization of the transition state in toluene. Note that M05-2X gives activation barriers quite consistent with experimental results at room temperature [64, 76].

Table 5.1. Free energies of activation for nucleophilic and *concerted*-base catalysis pathways in gas-phase ($\Delta G_{\text{gas}}^{\ddagger}$) and toluene ($\Delta G_{\text{toluene}}^{\ddagger}$) with MPW1B95, MPWB1K and M05-2X on B3LYP/6-31+G(d,p) geometries.^a

	Nucleophilic Catalysis		<i>Concerted</i> -Base Catalysis	
	$\Delta G_{\text{gas}}^{\ddagger}$	$\Delta G_{\text{toluene}}^{\ddagger}$	$\Delta G_{\text{gas}}^{\ddagger}$	$\Delta G_{\text{toluene}}^{\ddagger}$
B3LYP/6-31+G(d,p)	62.7	59.5 (56.3) ^b	35.9	36.1 (39.2) ^b
MPW1B95/6-31+G(d,p)	57.3	53.9	30.5	30.7
MPWB1K/6-31+G(d,p)	77.7	73.9	49.9	50.0
M05-2X/6-31+G(d,p)	51.7 (51.0) ^c	48.2	21.2 (20.0) ^c	21.7

^a Thermal free energy corrections for solvent calculations from B3LYP/6-31+G(d,p) calculations at 1atm and 298K. ^b Acetone as solvent. ^c optimized with M05-2X/6-31+G(d,p).

The energetics of the nucleophilic catalysis and the *concerted*-general base catalysis mechanisms were calculated in toluene ($\epsilon = 2.38$) and in acetone ($\epsilon = 20.56$) (Table 5.1). The free energy of activation for the nucleophilic catalysis becomes smaller as the polarity of the solvent increases. In contrast, in the *concerted*-general base catalysis, the activation energies increase with increasing solvent polarity. Compared to toluene ($\epsilon = 2.38$) TS-Nuc is stabilized by 3.2 kcal/mol in acetone ($\epsilon = 20.56$), which is possibly due to the stabilization of the acylammonium salt, a zwitterionic intermediate in a polar medium. TS-Base-Conc is destabilized as solvent polarity increases.

5.3.1.4. Stereoselectivity. Figure 5.13 depicts the reaction profile for the formation of the product *ent*-2. The transition structure TS-*ent*2-Base-Step1, leading to the formation of *ent*-2, illustrates a complex between anhydride 1, the catalyst and methanol. This complex is again stabilized through a hydrogen bond network between the nitrogen atom of the catalyst and the hydrogen atom of methanol, as in the case of TS-Base-Step1. Once the intermediate has formed, the second step through TS-*ent*2-Base-Step2 requires a minute energy barrier of 0.1 kcal.mol⁻¹ (0.2 kcal.mol⁻¹ in toluene); subsequent ring opening leads to the final product, *ent*-2, and the catalyst is regenerated.

The energy difference of 4.3 kcal.mol⁻¹ (3.4 kcal.mol⁻¹ in toluene) between the transition structures TS-Base-Step1 (Figure 5.11) and TS-*ent*2-Base-Step1 (Figure 5.13) leading to the formation of products, 2 and *ent*2, respectively, mainly stems from the relative orientations of the piperidine and cyclohexanol rings of the catalyst. While in TS-*ent*2-Base-Step1 the catalyst looks like 3-eq (Figure 5.8), this is not the case for the catalyst in TS-Base-Step1, (Figure 5.13). In TS-Base-Conc and TS-*ent*2-Base-Step1 catalyst conformations are almost identical (Figure 5.14). However, there is still an energy difference of 3.5 kcal/mol (1.8 kcal/mol in toluene), which can be attributed to the difference in the nature of hydrogen bonds involved; in TS-Base-Conc, the catalyst assists the reaction by hydrogen bonding to the methanol oxygen via its alcoholic entity, while in TS-*ent*2-Base-Step1 the catalyst OH is hydrogen bonded to the carbonyl oxygen of the anhydride. The location and nature of the hydrogen bonds seem to play an important role, since they render the nucleophilic attack by methanol easier. Figure 5.14 gives a comparative picture of the dihedral angles between the piperidine and cyclohexanol rings

of the catalyst for transition states TS-Base-Conc, TS-ent2-Base-Conc, TS-Base- Step1, and TS-ent2-Base-Step1 against 3-eq.

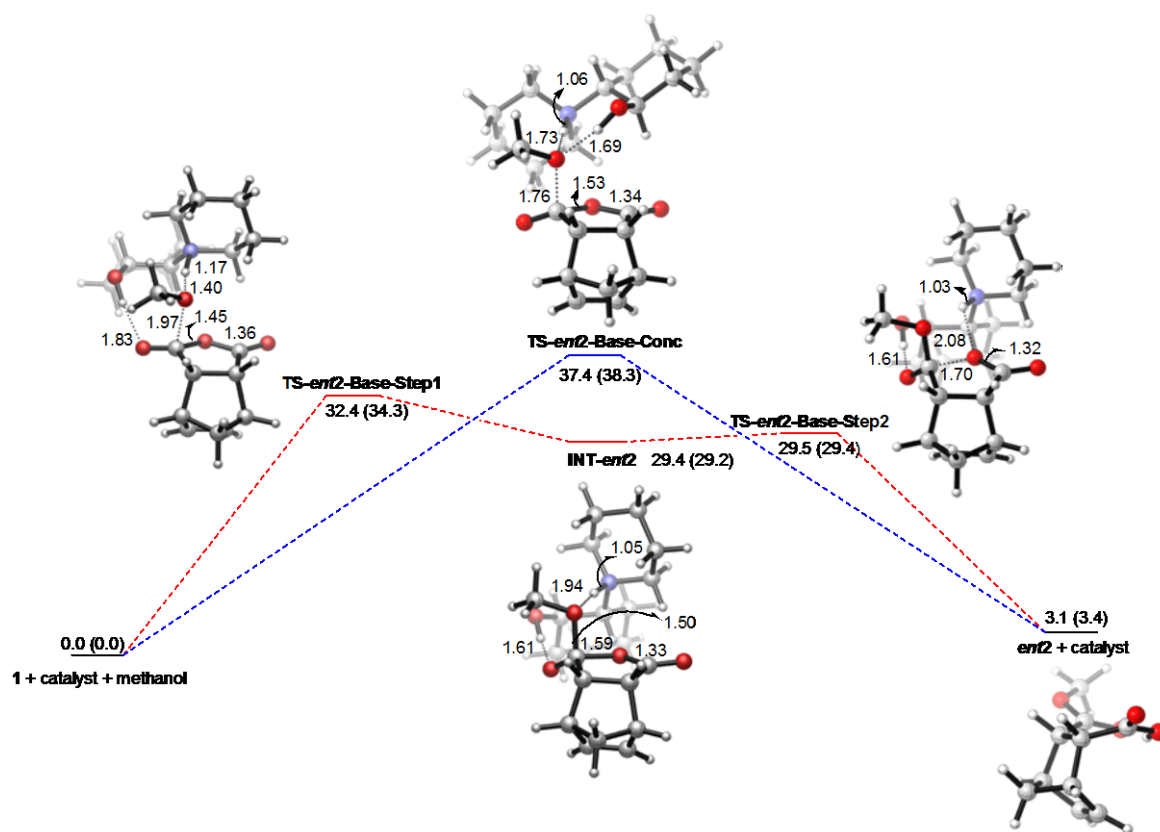


Figure 5.13. B3LYP/6-31+G(d,p) free energy profile for concerted and stepwise base catalysis pathways.

Numerical values refer to ΔG_{gas} (in kcal/mol). Values in parentheses are $\Delta G_{\text{toluene}}$. Thermal free energy corrections for solvent calculations from B3LYP/6-31+G(d,p) calculations at 101325 Pa and 298 K.

Our computational results favor the formation of the product *ent*-2 in contrast to the experimental findings where the formation of 2 is favored. Nevertheless, transition structures that include methanol (base-catalyzed mechanism) have large conformational space and flexibility, therefore, further investigation is beyond the scope of this part of the study, which aims at clarifying the feasibility of nucleophilic versus base-catalyzed pathways for alcoholytic ring opening of cyclic anhydrides. It should be noted that the preliminary results on stereoselectivity in base catalysis are attributed to the relative

orientation of the catalyst with respect to the anhydride and methanol, which will be investigated in detail in the next part of this chapter.

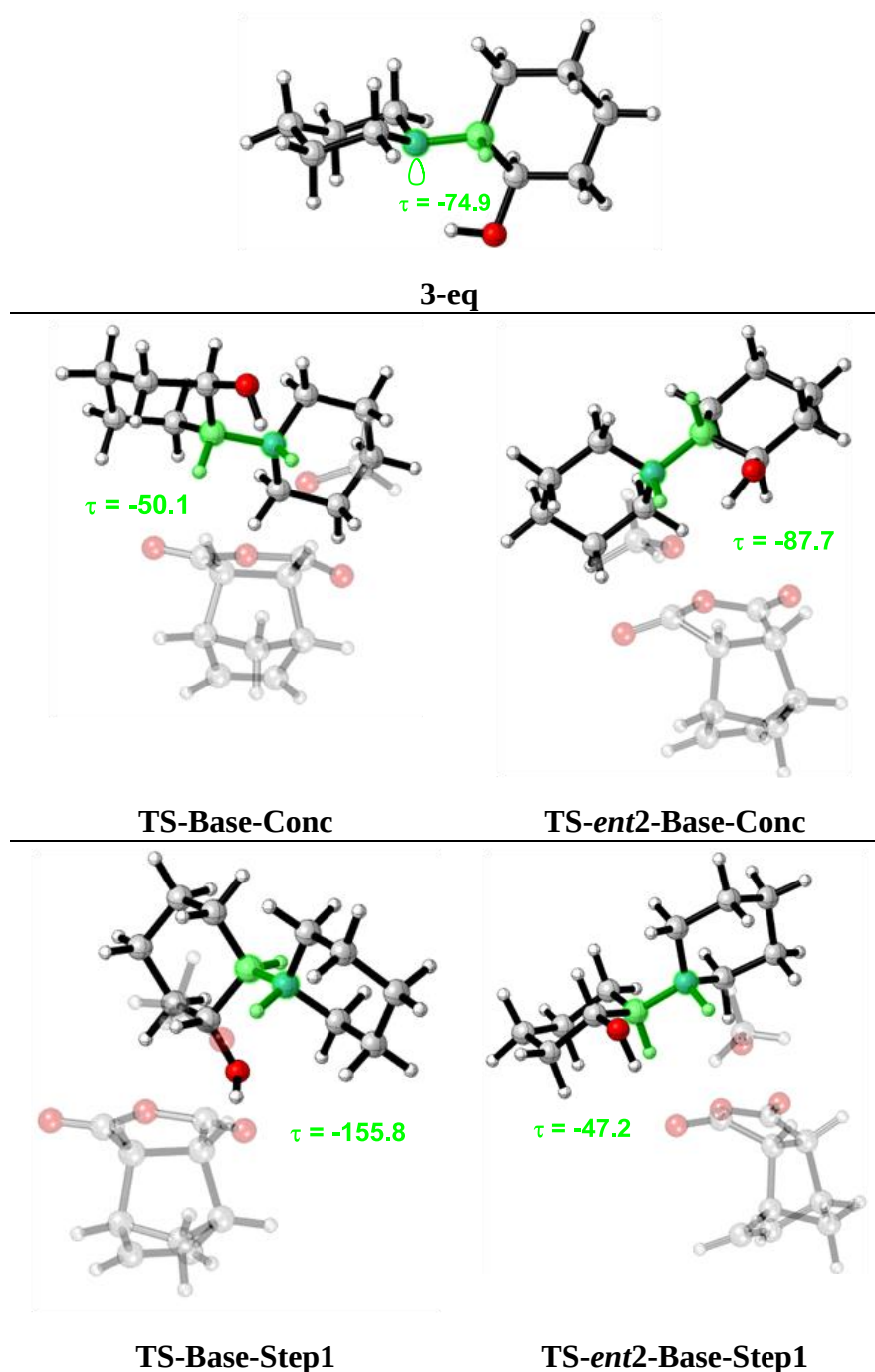


Figure 5.14. Catalyst dihedral angles for 3-eq, TS-Base-Conc, TS-ent2-Base-Conc, TS-Base-Step1, TS-ent2-Base-Step1.

However, the transition structure for the nucleophilic mechanism is very tight and the lack of methanol renders the conformational space of this structure quite limited. Thus we can safely predict that the base-catalysis mechanism is preferred over the nucleophilic mechanism for the desymmetrization of cyclic *meso*-anhydrides by chiral amino alcohols.

5.3.2. Conformational Space of Cinchona Alkaloids, Quinidine and Quinuclidine

In asymmetric processes, cinchona alkaloids induce enantioselectivity owing to the specific interactions between the alkaloid and the reactant molecule. Cinchona alkaloids, with rotational freedom around the C8-C9 and C4'-C9 bonds (Figure 5.15), are effective chiral organic catalysts; their conformation plays a crucial role in determining product stereochemistry [56,97]. Due to their important role as enantioselective catalysts, there have been many studies on the conformational behavior of cinchona alkaloids in literature [56-63]. The first conformational study of cinchona alkaloids by means of NMR spectroscopic and molecular mechanics (MM) calculations have been reported by Dijkstra *et al.* in 1989 [59,98]. Four low-energy conformers (*syn*-closed, *syn*-open, *anti*-closed, and *anti*-open conformers, Figure 5.15) have been located and the first known X-ray structure of a cinchona alkaloid was presented [59,98].

The conformations of several cinchona alkaloids and their derivatives have been the subject of some experimental work [97,99] and some have been combined with theoretical studies [58,100]. Bürgi and Baiker, in 1998, have investigated the solvent-dependent conformational behavior of cinchonidine (CD) using a combined NMR and *ab initio* reaction field approach and located several stable conformations [56]. Open(3), Closed(1) and Closed(2) conformations have been found to be the most stable conformations, with Open(3) being the most stable one (Figure 5.16). However, according to the *ab initio* calculations, when the polarity of the solvent increases, Closed(1) and Closed(2) conformations are stabilized mainly due to their larger dipole moments [56]. In 2008, the same group has found additional stable conformers of CD by a combined NOESY-DFT analysis [63]. According to the latter study, Closed(7) and Open(10) rank among the most stable conformations of CD (Figure 5.16). Overall, it has been suggested that Open(3) is responsible for the observed enantiodifferentiation in apolar solvents.

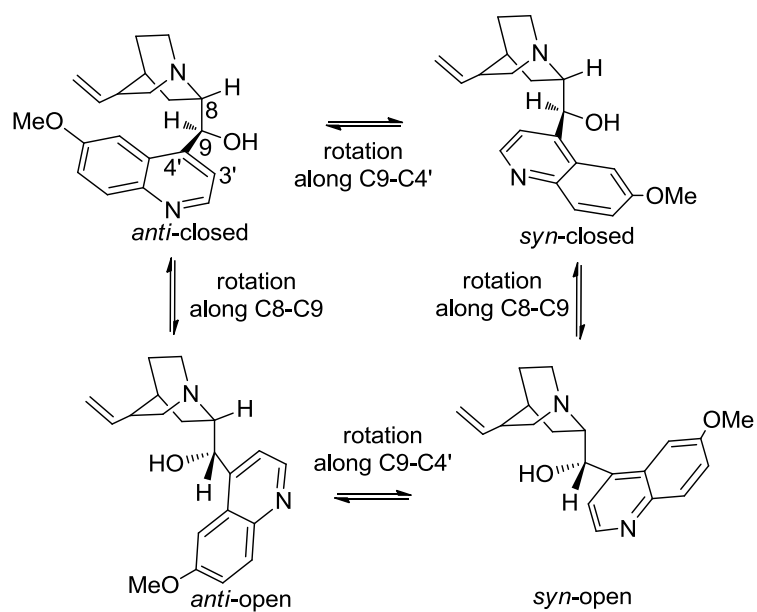


Figure 5.15. The four lowest-energy conformers of quinidine (QD) characterized by molecular mechanics and NMR [59,98].

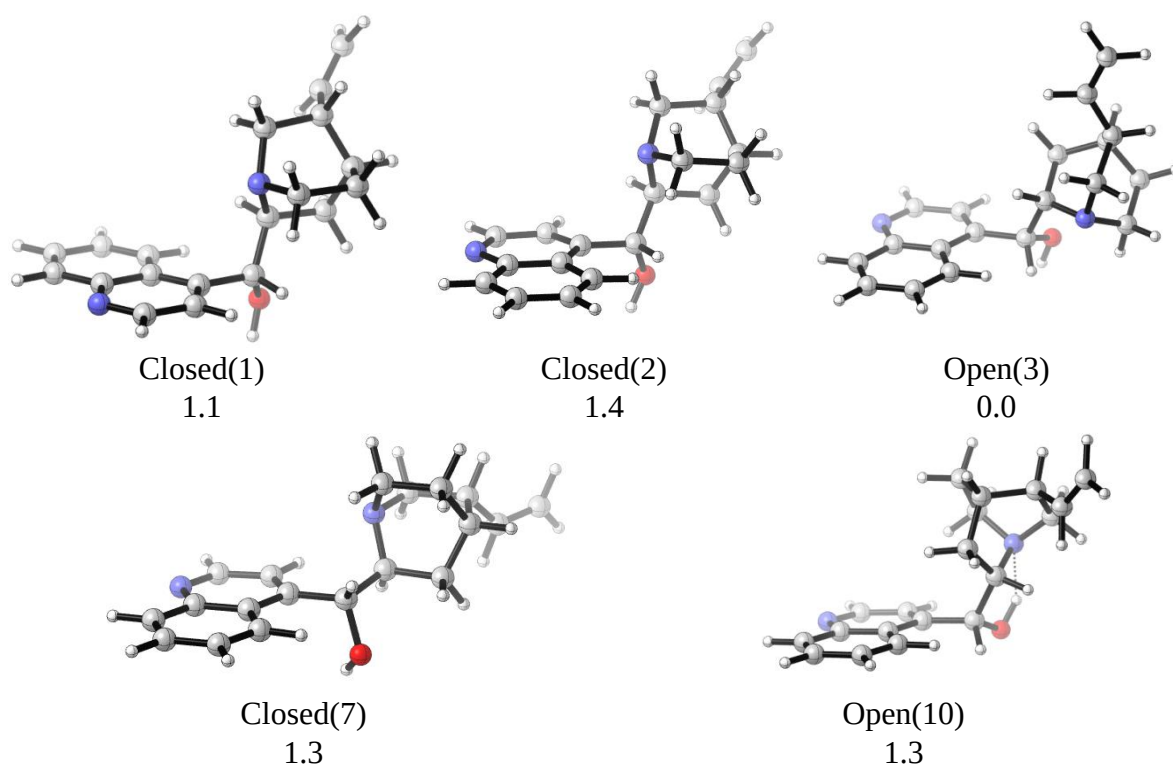


Figure 5.16. Conformations of CD optimized by the BLYP-PW method and their relative energies with respect to Open(3) (kcal/mol) [63].

Cinchona alkaloids consist of two rigid moieties, a quinoline ring and a quinuclidine ring, coupled together by two carbon-carbon bonds (Figure 5.17). The relative position of these two rings determines the conformational diversity of the alkaloid. Mainly, the cinchona alkaloids are found in open and closed conformations. In open conformation, the lone pair of electrons on the quinuclidine N points away from the quinoline ring, whereas it points towards the quinoline ring in closed conformation. The conformers are generally described by three torsional angles, τ_1 (C3' – C4' – C9 – C8), τ_2 (C4' – C9 – C8 – C7) and τ_3 (H9 – C9 – C8 – H8) (Figure 5.17).

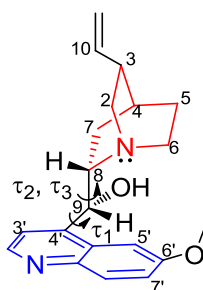


Figure 5.17. Definition of τ_1 , τ_2 and τ_3 in quinine. The quinoline and quinuclidine moieties of QN are highlighted in blue and red, respectively.

All conformations of CD previously optimized with BLYP-PW method in the study of Urakawa *et al.* [63] have been used as initial structures to optimize the conformations of QN since CD and QN have chiral carbons with the same stereochemistry, they only differ in the C6' substitution (Figure 5.3) in QN. In the case of QD, the characteristic dihedral angles of CD were first subtracted from 360 degrees and then applied to QD in order to generate the initial conformations.

The optimized geometries of QN and QD conformations possess two important structural features: i) the C6'-OMe is coplanar with the quinoline ring; ii) the methyl group is trans to C7' of quinoline (Figure 5.18). The characteristic dihedral angles and their relative free energies are given in Table 5.2. For Open(3)-QN, a *cis*-coplanar structure of the C6'-OMe is 1.7 kcal/mol higher in energy than the preferred *trans*-coplanar structure, while this energy difference has been reported to be 1.46 kcal/mol in chloroform with

B3LYP/6-31+G(d,p).[61] Another conformational feature of QN and QD is the relative position of the C3-vinyl of the quinuclidine moiety with respect to the quinuclidine ring. The preferred orientation of the vinyl group H10 is *trans* to H3 of the quinuclidine ring and this conformation is stabilized over its *cis* counterpart by 0.8 kcal/mol for Open(3)-QN.

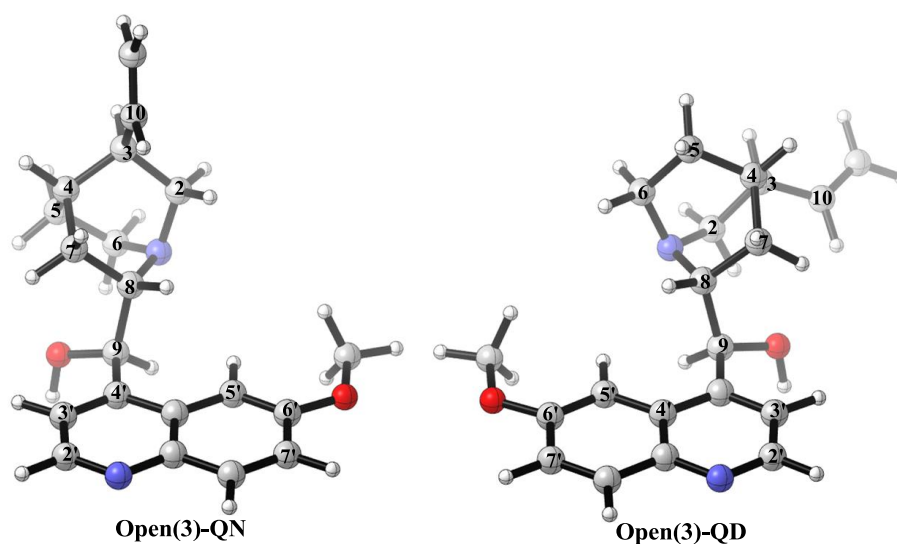


Figure 5.18. Optimized geometries of Open(3)-QN and Open(3)-QD.

Table 5.2. Characteristic dihedral angles (τ_1 , τ_2 and τ_3 , in Degrees) and relative energies (RE, kcal/mol) of QN and QD conformers.

	Quinine (QN)				Quinidine (QD)			
	τ_1	τ_2	τ_3	RE	τ_1	τ_2	τ_3	RE
Closed(1)	252.6	53.4	179.4	1.6	106.2	302.9	176.9	0.5
Closed(2)	85.2	67.1	190.2	2.0	275.8	294.9	172.1	1.0
Open(3)	103.6	151.9	279.7	0.0	255.0	211.7	83.9	0.0
Open(4)	258.2	134.3	265.6	3.0	102.7	227.5	96.3	2.7
Open(5)	85.1	312.9	77.8	5.5	273.7	46.9	282.2	3.5
Open(6)	259.8	302.9	72.0	3.5	99.7	58.5	289.7	2.2
Closed(7)	6.9	58.8	180.5	1.9	353.8	300.2	178.7	1.7
Open(8)	12.4	155.6	283.5	3.4	346.6	207.4	79.1	3.0
Open(9)	3.0	273.8	45.8	7.3	358.2	86.1	314.4	8.4
Open(10)	100.7	276.7	45.6	1.9	259.5	82.3	321.4	0.1
Open(11)	271.3	279.2	51.9	3.4	90.2	78.0	305.9	2.0

5.3.3. QN- and QD-Catalyzed Asymmetric Desymmetrization Reaction

The progress of AD reactions with small amino alcohols has been reported to proceed through general base catalysis (Figure 5.6) [101]. In the base-catalyzed mechanism, there are three stages in the transition-state that can either take place simultaneously or consecutively and can occur to different extents (Figure 5.19): (s1) Proton transfer from methanol to the catalyst, (s2) Nucleophilic attack of methoxide to the pro-ester site (O_a), (s3) Ring opening of the anhydride through nucleophilic attack forming the pro-acid (O_b and O_c are the oxygens of the pro-acid site). The first two stages, proton transfer (s1) and nucleophilic attack (s2), occur concurrently. A recent study by Yang and Wong indicated that a protonated trimethylamine-methoxy anion complex does not exist in the stepwise pathway [84]. However, the ring opening reaction (s3) may also proceed via a stepwise or a concerted pathway. In the concerted pathway, attack of methoxy is accompanied by a simultaneous ring opening of the anhydride in a single step. In the stepwise pathway, nucleophilic attack of methoxy on the anhydride leads to the formation of a tetrahedral intermediate, which then undergoes ring opening to yield the final product. The concerted pathway for the ring opening step was slightly stabilized over the stepwise pathway by 0.8 kcal/mol at B3LYP/6-31+G(d,p) level for AD of small amino alcohols [101]. All of the transition-states located in this study support the existence of a stepwise mechanism for the ring opening of the anhydride. Note also that the transition-states which point to a concerted mechanism with B3LYP/6-31+G(d,p) turned out to point to a stepwise mechanism at M06-2X/6-31+G(d,p), this is a consequence of further stabilization of charged intermediates with the dispersive interactions that are effectively accounted for with the M06-2X functional.

The free energy profile for the ‘stepwise’ base-catalyzed mechanism of QN-catalyzed AD of **1** is shown in Figure 5.20. Transition structure, TS-QN-I, which requires an energy barrier of 8.1 kcal/mol, leads to the tetrahedral intermediate (INT). The intermediate, INT, is 4.0 kcal/mol higher in energy than the reactants. The second step requires only a small energy barrier of 1.0 kcal/mol and through TS2-QN-I ring opening leads to the final product, and the catalyst is regenerated (Figure 5.20).

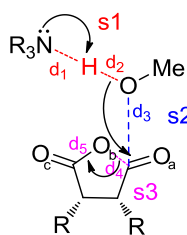


Figure 5.19. Schematic representation of the three stages and the critical distances in the transition-state of the base-catalyzed mechanism for AD of cyclic anhydrides.

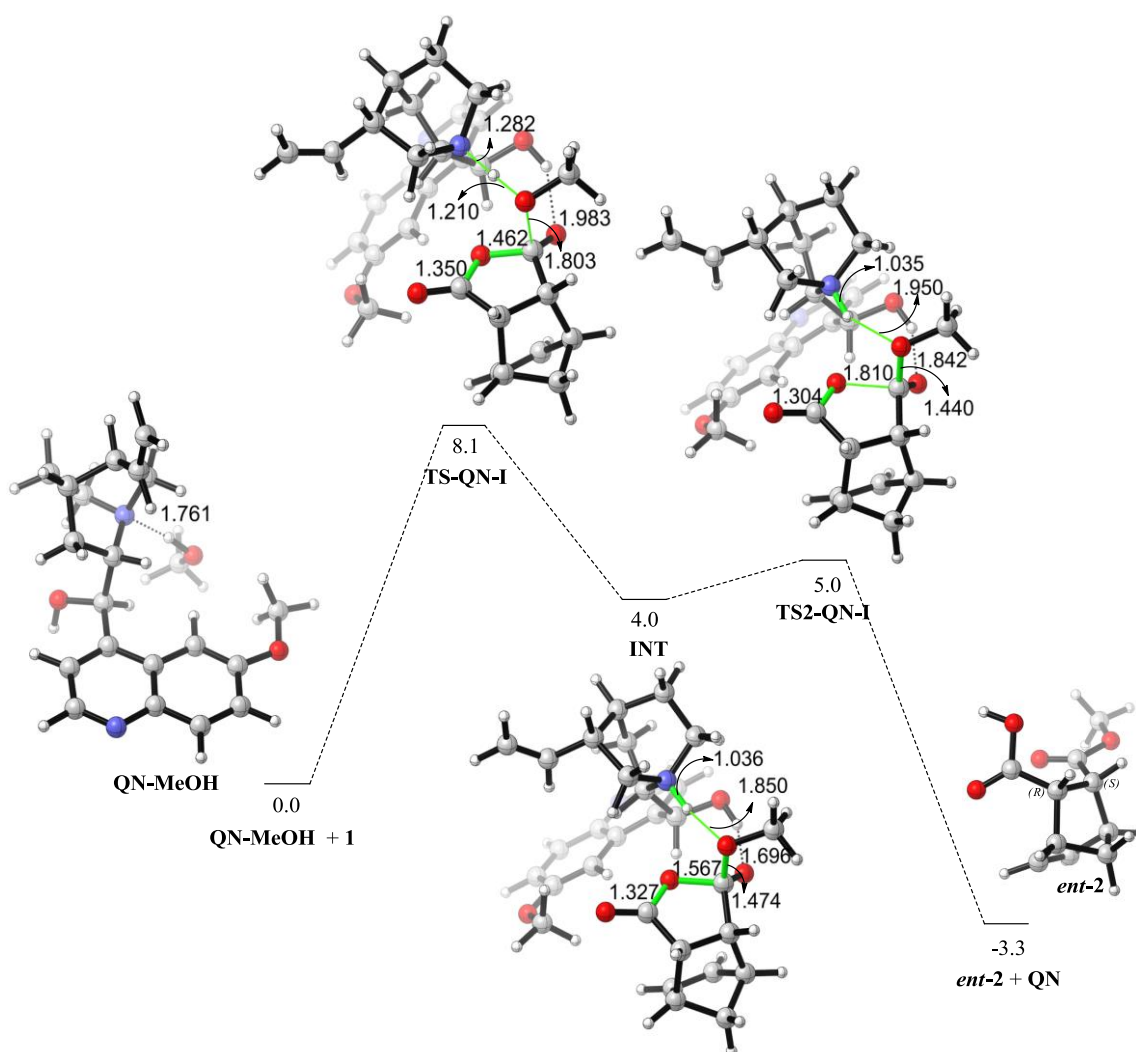


Figure 5.20. Free energy profile for stepwise base catalyzed pathway for QN catalyzed AD of 1.

All energies with respect to quinoline-MeOH complex and anhydride 1. Thermal free energy corrections from M06-2X/6-31+G(d,p) calculations at 218 K.

In the aforementioned computational study of the trimethylamine-catalyzed methanolysis of cyclic anhydrides by Yang and Wong, six staggered transition states with respect to the forming C–O bond were considered, and the most stable transition states were used to construct the transition structures involving the full catalysts, the DHQD derivatives (Figure 5.3) [84].

The transition states modeled for small amino alcohols-catalyzed methanolysis of cyclic anhydride were found to be analogous to those reported by Yang and Wong [17,84]. These transition states were, thus, used as input geometries in the transition structure searches for the QN- and QD-catalyzed methanolysis of **1** herein. However, in the larger catalysts, QN and QD, there are two additional points to consider in the staggered transition states: i) the C6'-OMe of the quinoline moiety, which has been proposed to stabilize the forming oxanion [84], and ii) the C9-OH group, which can potentially form H-bonds with one of the three anhydride oxygens. When these two critical points are taken into account, the 'staggered' transition state has six different variations with respect to the forming C–O bond (Figure 5.21).

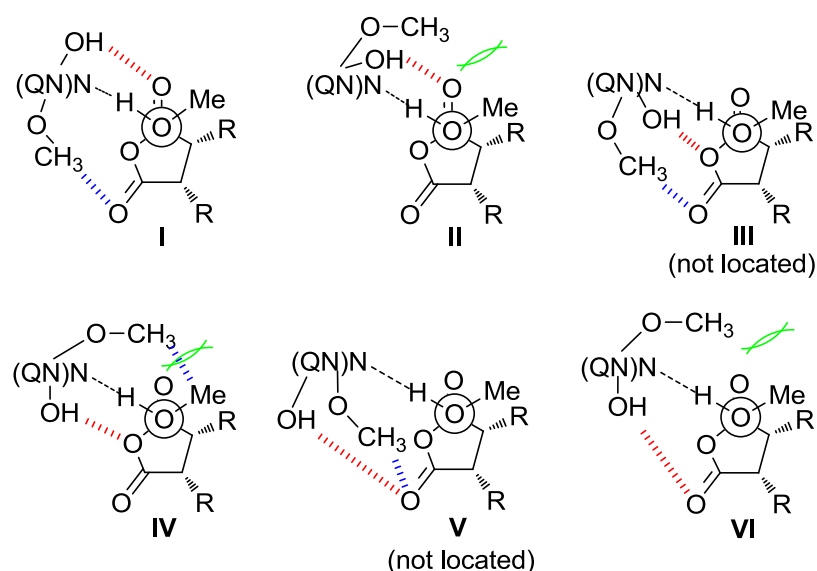


Figure 5.21. Plausible 'staggered' transition states for QN/QD-catalyzed methanolysis of cyclic anhydride **1**.

Four out of six transition-state conformations (Figure 5.21) for QN- and QD-catalyzed asymmetric desymmetrization reaction were located: I, II, IV and VI (Figures 5.22 and 5.23). Transition state III could not be located due to the inconvenient approach of the catalyst, while TS V converted to TS I upon optimization. Interactions between the anhydride and the C9-OH and C6'-OMe of the catalyst enable the quinoline and/or the quinuclidine rings to stabilize the oxyanion hole of the anhydride.

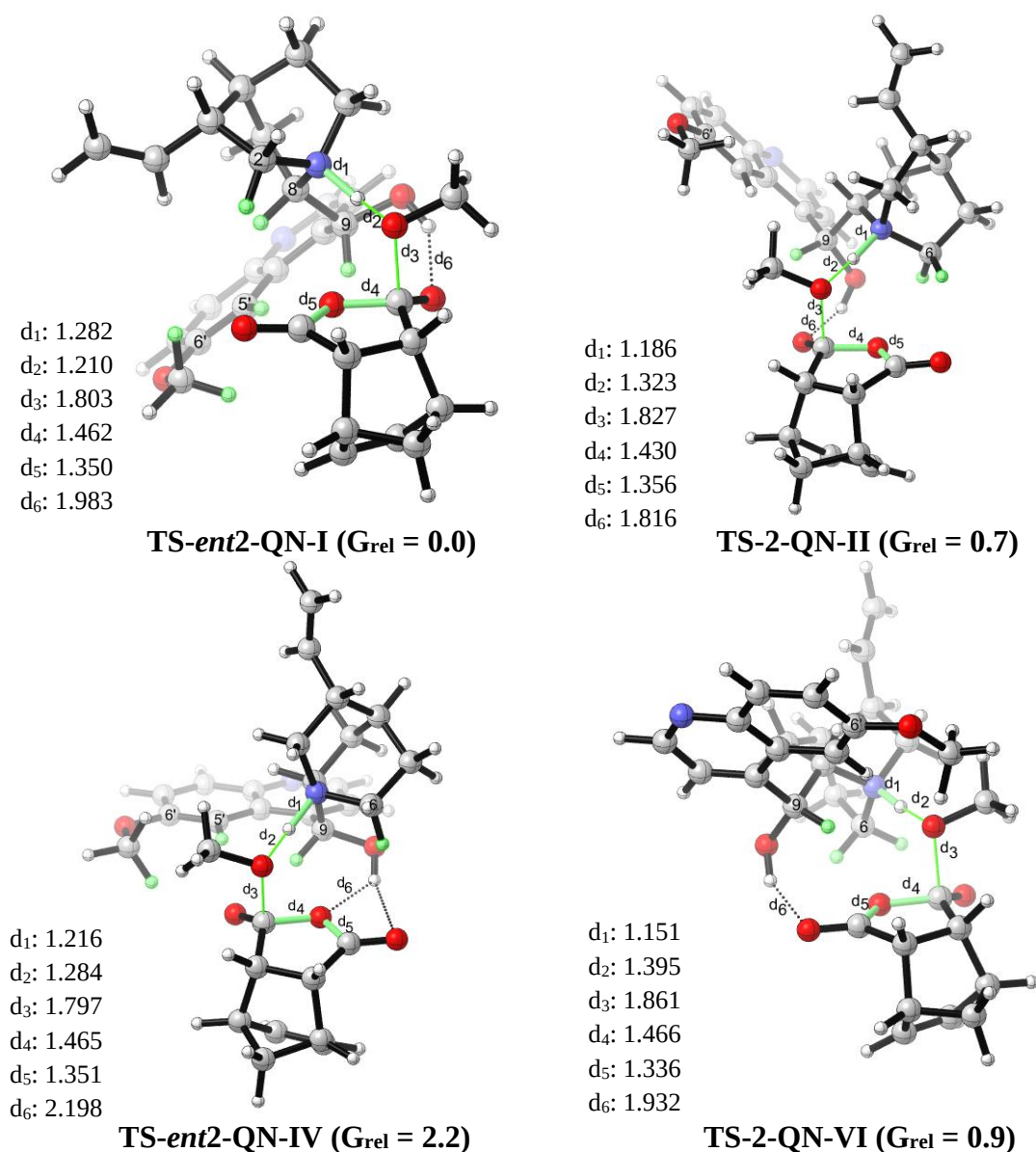


Figure 5.22. Transition state geometries for QN-catalyzed methanolysis of 1.

The H atoms of the catalyst are highlighted in green for C-H...O interactions (Table 5.3). Thermal free energy corrections from M06-2X/6-31+G(d,p) calculations at 218 K (kcal/mol).

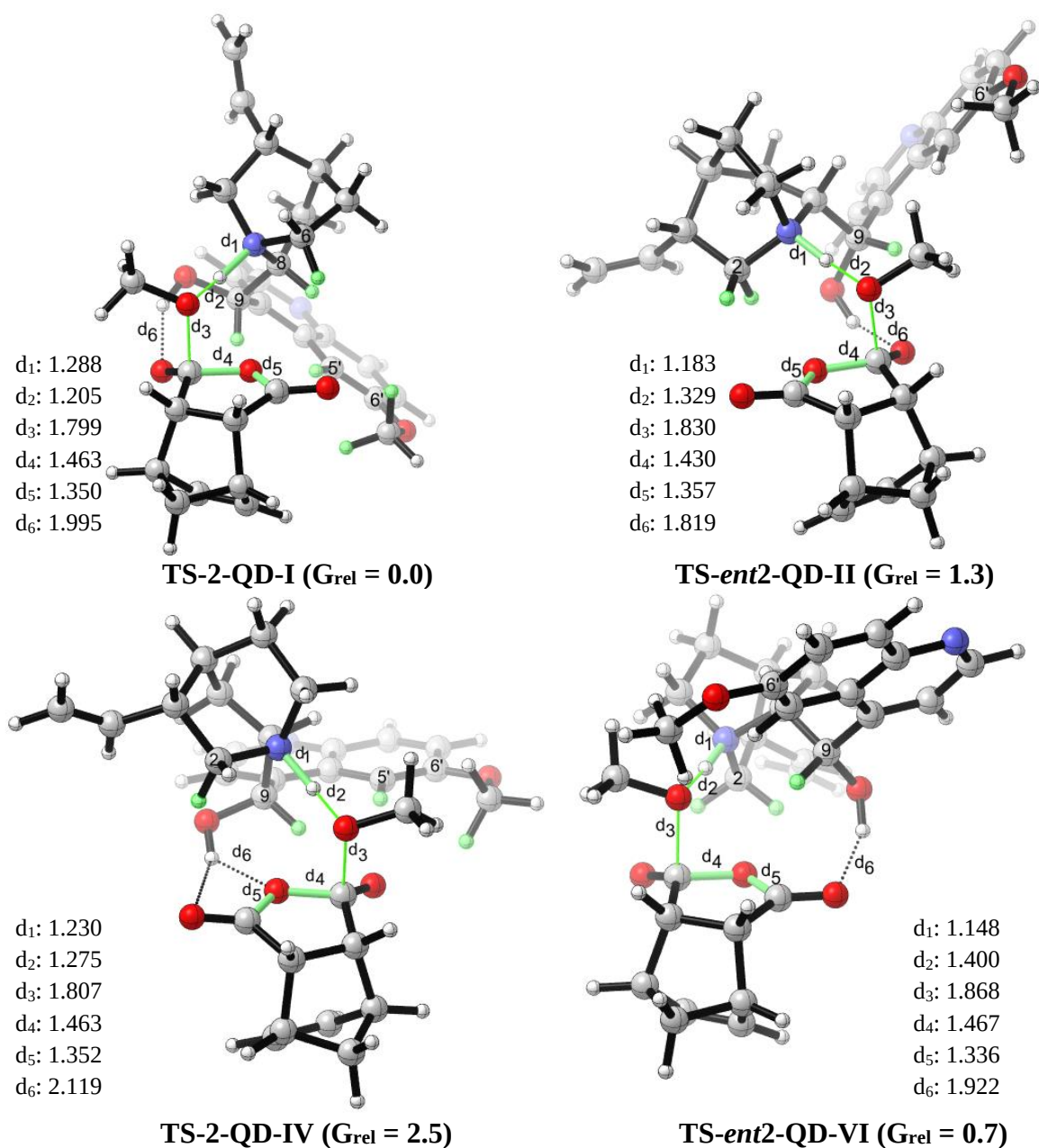


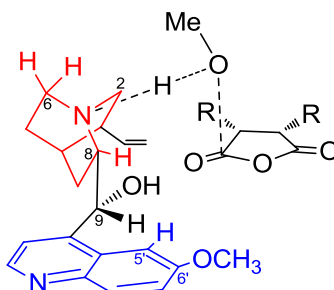
Figure 5.23. Transition state geometries for QD-catalyzed methanolysis of 1. The H atoms of the catalyst are highlighted in green for C–H...O interactions (Table 5.3). Thermal free energy corrections from M06-2X/6-31+G(d,p) calculations at 218 K (kcal/mol).

In the lowest energy transition-state I (TS-*ent*2-QN-I, Figure 5.22) leading to the observed product *ent*-2 the interactions formed between the anhydride and the C9-OH and C6'-OMe of the catalyst enable the quinoline ring to face the oxyanion hole of the anhydride in a molecular tweezer-like fashion and a maximum number of catalyst

hydrogens can stabilize the oxyanion hole (NBO stabilization energies of each catalyst hydrogen is given in Table 5.3). TS II (TS-2-QN-II, Figure 5.22) leading to product 2 has the same type of C9-OH hydrogen-bonding interactions as its TS I counterpart. The key sites on the catalyst, C6'-OMe and C9-OH, interact with the same site of the anhydride; therefore in TS II, the quinoline ring is situated away from the oxyanion hole creating a steric hindrance for methanol due to the position of C6'-OMe and the only stabilization comes from the hydrogens of the quinuclidine ring (Table 5.3). These features result in a penalty of 0.8 kcal/mol for TS-2-QN-II. In TS IV (TS-*ent*2-QN-IV, Figure 5.22), the catalyst adopts a conformation similar to TS I, however, a shift of the catalyst from the front face of the oxyanion hole leads to a penalty of 2.2 kcal/mol due to the bifurcated H-bonding in TS-*ent*2-QN-IV leading to the observed product *ent*-2. On the other hand, TS VI for the product 2 is 0.9 kcal/mol less stable than TS I since these transition states suffer from the stabilization of the oxyanion hole due to the catalyst's spatial position with respect to the anhydride. TS VI (TS-2-QN-VI, Figure 5.22), in which O_c is stabilized by C9-OH H-bonds, still experiences a strong repulsion with methanol due to C6'-OMe. The transition states of QD catalyzed AD (Figure 5.23) follow the same trend as QN and the relative free energies for QD transition states I, II, IV and VI are 0.0, 1.3, 2.5 and 0.8 kcal/mol.

In TS-*ent*2-QN-I and TS-2-QN-II, C9-OH both stabilizes O_a (with a quiet high interaction energy for TS II), TS-*ent*2-QN-I is stabilized over TS-2-QN-II by 0.7 kcal/mol. NBO analysis indicates that the contribution from C9-OH is orders of magnitude greater than the C-H...O interaction via C6'-OMe (only 0.6 kcal/mol in TS-*ent*2-QN-I, Table 5.3). C6'-OMe might not be crucial for the stabilization of the oxyanion in the transition state, but indeed, of importance for the stabilization of the intermediate (Figure 5.20) where the negative charge increases on each one of the oxygen atoms of the anhydride. The role of the C6'-OMe actually seems, according to Hammond-Leffler postulate [102,103], to determine the extent of propagation along the reaction path through less reactive intermediates. The intermediate through TS-2-QN-II which lacks the stabilization of the *pro*-acid site through C6'-OMe is 7.7 kcal/mol higher in energy than the reactants.

Table 5.3. NBO second-order perturbation energy analysis (HF/6-31G(d,p)) of C–H...O and O–H...O interactions in the transition states.^a



			quinoline ring		quinuclidine ring		
	C9-OH	C9H	C5'H	C6'-OMe	C2H	C6H	C8H
TS- <i>ent</i> 2-QN-I	12.0	5.1	0.9	0.6	1.64	-	0.2
TS-2-QN-II	22.8	1.3	-	-	-	2.1	-
TS- <i>ent</i> 2-QN-IV	3.9	5.6	3.7	2.1	-	2.9	-
TS-2-QN-VI	14.8	1.8	-	-	-	3.0	-

^a NBO interaction energies are in kcal/mol.

When the interactions through the C9-OH and C6'-OMe of the catalyst operate on the remote sites of the anhydride oxygens (O_a and O_c) in a molecular tweezer-like fashion (as in the cases of TS I and IV) a maximum number of catalyst hydrogens (highlighted in green in Figures 5.22 and 5.23) can stabilize the oxyanion hole. Deng *et al.* proposed that C6'-OMe acts as a repulsive group that controls the stereochemistry [81] while it has been recently shown to be part of the oxyanion hole via attractive C–H...O interactions [84]. However, both implications are present in our study. However, both implications are present in our study: while TS I leading to the experimentally observed product enjoys the stabilization of C6'-OMe with O_c, C6'-OMe along the *pro*-ester site, O_a, engages in repulsive steric interactions in TS II leading to the other enantiomeric product.

5.3.4. Assistance of Methanol in the Stereoisomeric Transition States

The methanolysis of cyclic *meso* anhydride 1 yields products 2 and *ent*-2 with up to 99% of enantiomeric excess (Figure 5.4), in the presence of QD and QN, respectively [67].

The stereochemistry of the final product is determined by methanol attack on the enantiotopic carbonyl (Figure 5.24). The lower energy transition states I and II for QN- and QD-catalyzed AD with 1 equivalent of methanol were further modeled with the assistance of methanol in order to better mimic the reaction conditions (Figure 5.25) [67]. Therefore, 3 methanol molecules were included in the calculations of the stepwise pathway for base-catalyzed reaction. One of the methanol molecules serves as the nucleophile; another methanol molecule is hydrogen-bonded to the catalyst hydroxyl group and the oxygen of the attack site, O_a , of **1**, while a third methanol molecule is associated with the carbonyl oxygen of the *pro*-acid site, O_c (Figure 5.25).

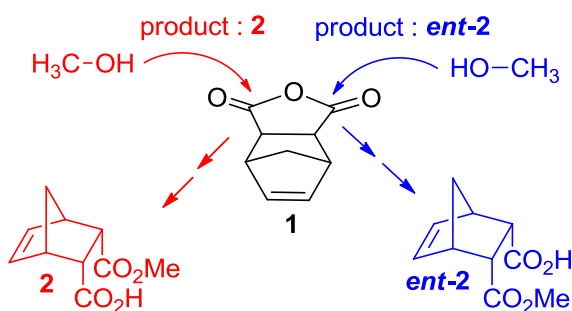


Figure 5.24. Attack of methanol to *meso*-cyclic anhydride **1**.

Figure 5.26 illustrates the manner by which the enantiotopic carbonyl groups of **1** are distinguished by the chiral pocket of the catalyst, using quinidine as an example. As highlighted in the box in Figure 5.26, the major transition structure (yellow) enjoys stabilizing C-H...O interactions between the C5' hydrogen of the quinoline ring and the middle oxygen of **1** (O_b), as well as between the quinoline's methoxy group and the *pro*-acid carbonyl oxygen (O_c). In the minor transition structure (magenta), these stabilizing interactions are absent, and the quinoline group sterically clashes with the nucleophilic methanol molecule. The energy difference between the transition states with excess methanol that will lead to different enantiomeric products has increased from 0.7 and 1.3 kcal/mol up to 3.7 and 4.6 kcal/mol, respectively, for QN- and QD-catalyzed AD, in agreement with experimental enantiomeric ratios. The distortion and/or the relaxation of the catalyst in the transition states via the assistance of methanol might be used to reveal the origins of the observed stereoselectivities and to understand the increase in the

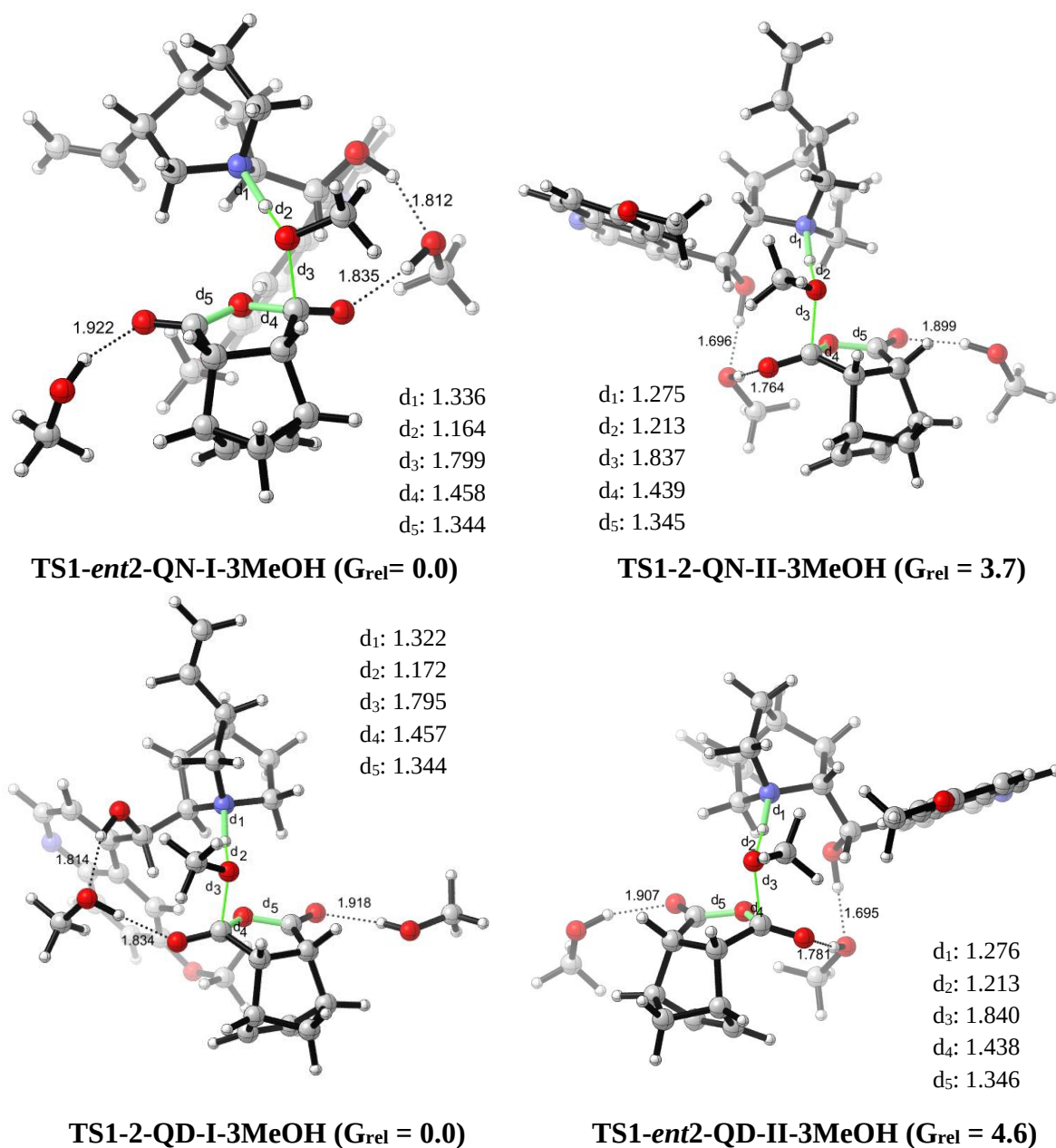


Figure 5.25. Transition state geometries of QN- and QD-catalyzed methanolysis of 1 in the presence of 3 explicit MeOH.

Thermal free energy corrections from M06-2X/6-31+G(d,p) calculations at 218 K (kcal/mol).

enantiomeric ratios. It should be noted that 3 equivalents of methanol is expected to polarize the micro environment of the transition state increasing the dielectric constant of the medium immediately surrounding the catalyst and the anhydride. This leads to a significant change in the calculated enantioselectivities. The distortion and/or the

relaxation of the catalyst in the transition states via the assistance of methanol are proposed to be the origins of the observed stereoselectivities.

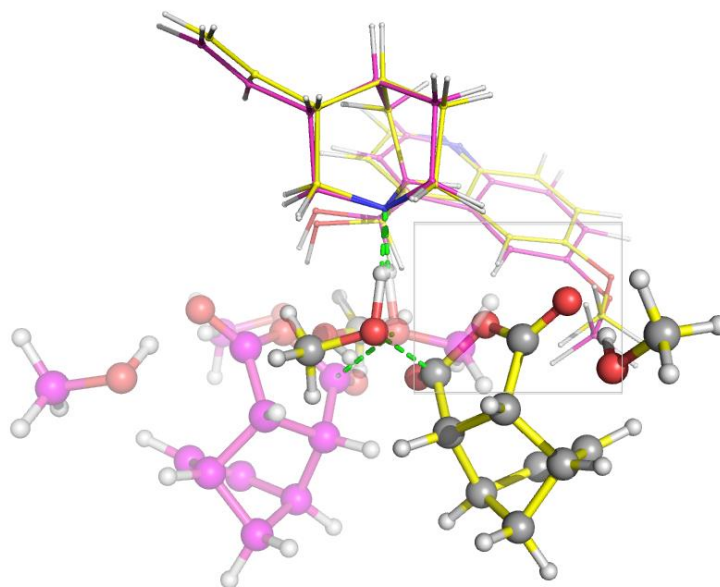


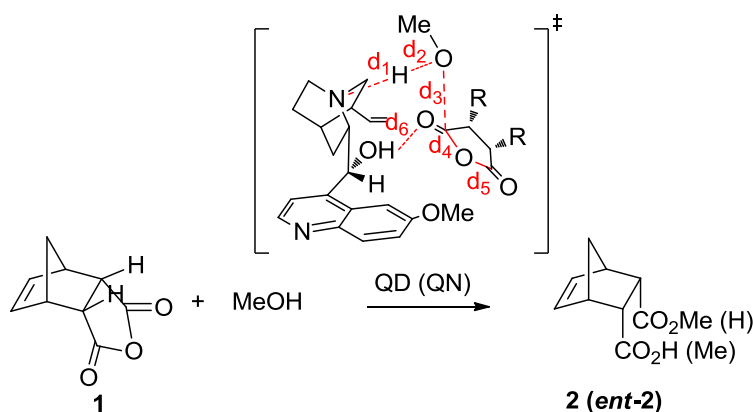
Figure 5.26. Overlay of two stereoisomeric transition structures for the quinidine-catalyzed methanolysis of 1.

Yellow: TS-1-2-QD-I-3MeOH. Magenta: TS1-ent2-QD-II-3MeOH. The green dashes indicate the bonds being broken or formed. For clarity, the catalyst moieties are represented by thinner lines and the minor transition structure is rendered more transparent.

The location of the transition state along the reaction coordinate has a large effect on the distortion and interaction energies and is an important consideration for understanding the energy barriers. We explored the extent of reaction and the origins of stereoselectivities in QN- and QD-catalyzed methanolysis of cyclic anhydride 1. The distortion/interaction model, also known as activation-strain model [104] is used starting from the ‘staggered’ transition states with one methanol extending to the transition states with excess methanol (Table 5.4). The $\Delta E_{\text{dist}}^{\ddagger}(\text{cat.})$ is the energy to distort the catalyst (QN/QD) into the transition state geometry and can be used to discriminate the stereoisomeric transition states. The $\Delta E_{\text{dist}}^{\ddagger}(\text{cat.})$ is the focus of this study as explained further below.

The $\Delta E_{\text{dist}}^{\ddagger}(\text{MeOH})$ and $\Delta E_{\text{dist}}^{\ddagger}(1)$ are a measure of the polarization of methanol and anhydride 1 in the transition state geometries and indicate the extent of propagation along the reaction profile. The energy required to polarize methanol correlates with the proton transfer distances between the quinuclidine nitrogen and methanol (d_1 and d_2) in the transition states (Figure 5.27). Hence, the distortion energy is mainly controlled by the position of the transition state on the reaction coordinate and the transition states of type I are early while the transition states of type II are late.

Table 5.4. Dihedral angles ($^{\circ}$) of the catalyst in the transition states and distortion energies (kcal/mol) of the catalyst, methanol and cyclic anhydride 1 in the transition states and relative free energies (kcal/mol) of the transition states.



	$[\tau_1, \tau_2, \tau_3]$	$\Delta E_{\text{d}}^{\ddagger}$ (cat.)	$\Delta E_{\text{d}}^{\ddagger}$ (MeOH)	$\Delta E_{\text{d}}^{\ddagger}(1)$	$\Delta \Delta G^{\ddagger}$
QN-Open(3)	[104, 152, -80]				
TS-ent2-QN-I	[109, -165, -36]	6.9	23.7	14.4	0.0
TS-2-QN-II	[106, 180, -53]	4.9	41.3	13.1	0.8
TS1-ent2-QN-I-3MeOH	[106, 178, -54]	3.5	16.4	15.1	0.0
TS1-2-QN-II-3MeOH	[105, 172, -61]	5.0	24.2	13.4	3.7
QD-Open(3)	[-104, -148, 84]				
TS-2-QD-I	[-107, 166, 37]	7.1	23.0	14.7	0.0
TS-ent2-QD-II	[-104, -179, 54]	4.9	42.2	13.1	1.3
TS1-2-QD-I-3MeOH	[-102, -179, 54]	3.7	17.8	15.3	0.0
TS1-ent2-QD-II-	[-103, -171, 63]	3.4	24.2	13.3	4.6

Meanwhile, $\Delta E_{\text{dist}}^{\ddagger}(\text{cat.})$ is very closely related to the extent of deviation in the characteristic dihedral angles of the catalyst (transition state versus Open(3); Table 5.4).

The dihedral angle of the catalyst, τ_1 , does not change significantly in the transition state; however, there is a large deviation for τ_2 and τ_3 . Once the catalyst-methanol complex and the anhydride come to close proximity for the nucleophilic attack, C6'-OMe and C9-OH play a decisive role for the deviations of τ_2 and τ_3 , allowing the arrangement of the quinoline ring to face the oxyanion hole.

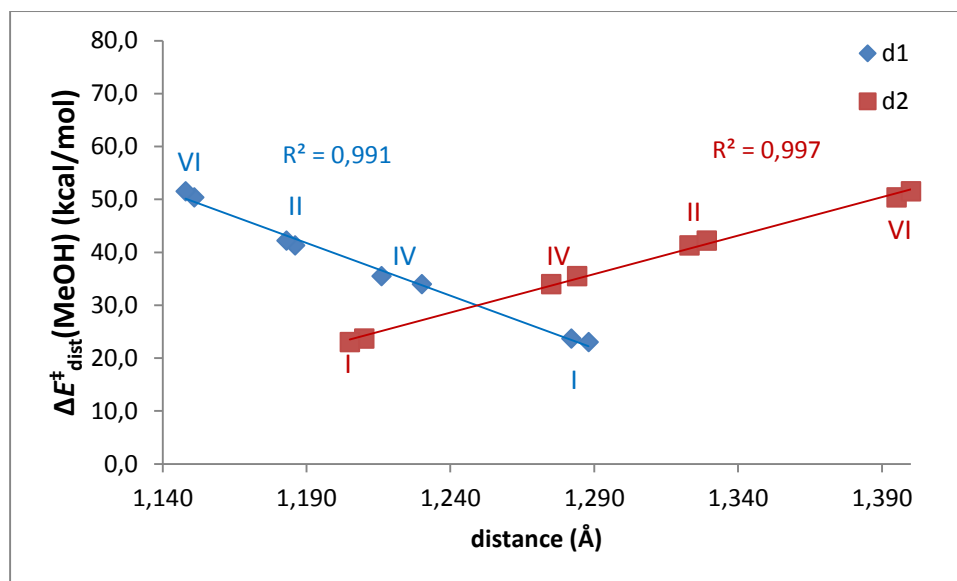


Figure 5.27. Plot of the distortion energy of methanol ($\Delta E_{\text{dist}}^{\ddagger}(\text{MeOH})$) vs the critical d_1 and d_2 distances in the transition states for AD of 1.

Early transition states are located via the assistance of peripheral methanol molecules in the AD reaction catalyzed by QN and QD due to the stabilization of charge developing as the ring opens along the reaction coordinate. This was also observed in the AD reaction catalyzed by small amino alcohols [101]. The relaxation of the catalyst with the flexibility created by the assistance of excess methanol, however, leads to a substantial increase in the calculated enantiomeric ratios for the transition states of type I. The catalysts in the transition states of type I with excess methanol (TS1-ent2-QN-I-3MeOH and TS1-2-QN-I-3MeOH) relax with a 3.4 kcal/mol decrease in the distortion energy of the catalyst (Table 5.4). Whereas in the transition states of type II which are already less distorted due to the freedom of the quinoline ring, the distortion energy of the catalyst does not change much ($\Delta\Delta E_{\text{dist}}^{\ddagger}(\text{cat.}) = 0.1$ kcal/mol) as more methanol molecules are introduced. Assistance of

methanol also decrease the distortion of methanol in the transition states of type I and II by 5-7 and 17 kcal/mol respectively. Note that though the decrease of the distortion energies of methanol are more pronounced for the transition states of type II, the distortion energies of methanol in the transition states of type I are still lower.

5.4. Conclusions

The asymmetric ring opening of *meso*-cyclic anhydride 1 catalyzed by amino alcohol 3 is proposed to proceed by the general base catalysis pathway. The general base catalysis pathway is favored energetically (B3LYP/6-31+G(d,p)) by 26.8 kcal/mol (23.4 kcal/mol in toluene) over the nucleophilic catalysis. These results have also been confirmed with the MPW1B95, MPWB1K and M05-2X methodologies. The addition of 3 equivalents of methanol stabilizes the reaction by 2.2 kcal/mol through the formation of hydrogen bonds of the peripheral methanols. These reactions have also been modeled in two solvents (toluene and acetone) with different polarities. Overall the results suggest that the concerted general base catalysis is favored over the nucleophilic catalysis mechanism.

Enantioselective alcoholysis of *meso*-cyclic anhydrides induced by pseudoenantiomeric pairs of cinchona alkaloids, quinine and quinuclidine, has been subject to a computational investigation to shed light on the origin of the catalytic activity and the stereoselectivity. A conformational analysis of QN and QD reveals Open(3) as the most stable conformation with M06-2X/6-31+G(d,p). For AD reactions catalyzed by QN and QD, various transition states have been located based on the two key features of the catalyst, the C9-OH and C6'-OMe groups. For the transition states where the remote sites of the oxyanion are stabilized through C9-OH, H-bonding and C6'-OMe weak interactions, lower free energy barriers are required. Full analysis of the reaction path has revealed that the stepwise mechanism is valid for the ring opening of the anhydride induced by the nucleophilic attack of methanol. The stepwise mechanism leads to an intermediate where the negative charge increases and the stabilization of the intermediate determines the stage of the transition state. The stabilization of the distant sites of the oxyanion in the transition states enables the catalyst to act like a molecular tweezer allowing H atoms in the quinoline ring of the catalyst to stabilize the oxyanion of the anhydride. However this

clamp-like stabilization distorts the catalyst. The flexibility created by excess methanol relieves the catalyst and the enantioselectivities increase up to 100% in accordance with the experimental results. High enantioselectivities with the assistance of methanol also indicate the importance of explicit solvation model used in this study.

6. CATALYTIC EFFECT OF SILVER IN DIELS-ALDER REACTION OF 1,2-DIAZINES AND SILOXY ALKYNES

The Diels-Alder reaction has been established as one of the most utilized reaction type and offers a great advantage of installing up to four stereocenters at once (Figure 6.1) [105]. Diels-Alder reaction, a [4+2] pericyclic reaction, involves four π -electrons on the diene and two on the dienophile forming a six membered cycloadduct. They are thermodynamically favored associated with the carbon-carbon bond formation; however, they require high temperatures due to a large activation barrier.

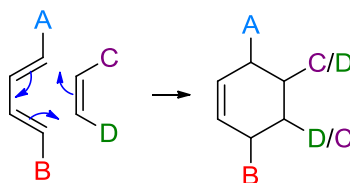


Figure 6.1. Schematic representation of the Diels-Alder reaction.

Orbital symmetry considerations provide a fundamental insight into the electronic nature of the cycloaddition reactions. Woodward and Hoffmann presented their symmetry rules for pericyclic reactions based on molecular orbital theory [106,107]. Fukui used the frontier molecular orbitals to analyze pericyclic reactions. Frontier orbitals, the highest occupied molecular orbital (HOMO) and the lowest unoccupied orbital (LUMO), are considered to have a significant influence on the interactions between two molecules and the strength of an interaction is determined by the extent of HOMO-LUMO overlap. In a normal Diels-Alder reaction, electrons move from the highest occupied molecular orbital of the diene to the lowest unoccupied orbital of the dienophile, while in an inverse electron demand Diels-Alder (IEDDA) reaction a reverse electron motion takes place (Figure 6.2).

Diels-Alder reaction is activated by the addition of substituents to the diene and/or dienophile. In a normal electron demand DA reaction, the reaction barrier is lowered by electron-donating groups (EDGs) on the diene and electron-withdrawing groups (EWGs)

on the dienophile facilitating HOMO-LUMO interaction. In an inverse electron demand DA reaction, introduction of an electron withdrawing group (EWG) to the diene can render it more electron deficient so that an affordable reaction between the more electron deficient diene and electron rich dienophile occurs.

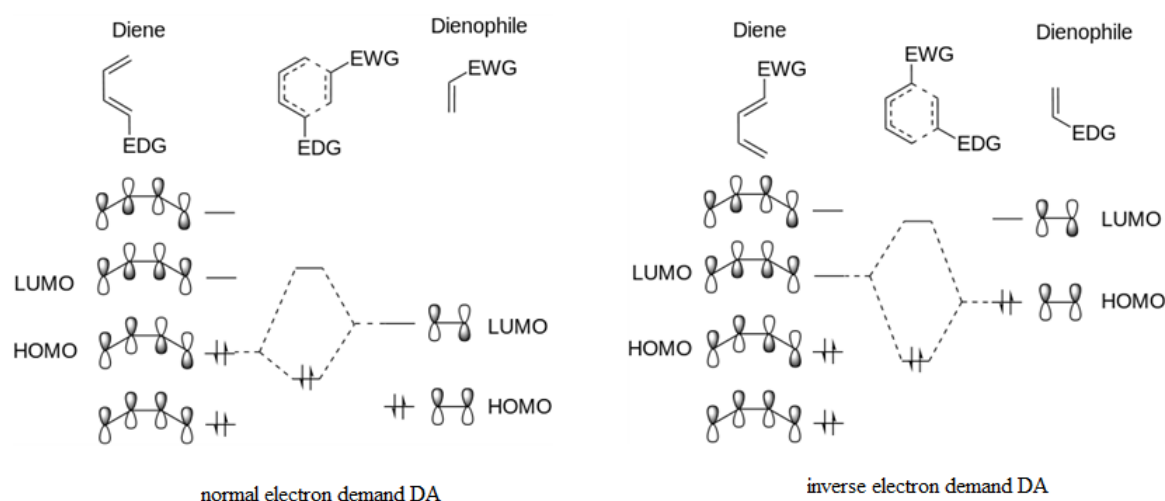


Figure 6.2. Frontier molecular orbital depictions for normal and inverse DA reactions.

There are several strategies to catalyze a Diels-Alder reaction when thermal conditions or substitution on the diene/dienophile do not yield a cycloadduct. In a transition state of a DA reaction, a partial negative charge is built up and, hence, stabilized by a catalyst that is able to carry the excess charge. From a frontier molecular orbital point of view, the coordination of the catalyst to the diene or dienophile lowers the energy of the frontier orbitals compared to uncatalyzed reaction, thus increasing the total charge transfer in the transition state. Transition state stabilization or the lowering of the frontier orbitals can be achieved using strong electron acceptors (Lewis acids) or transition metals.

Diels-Alder reactions of substituted dienes and dienophiles have been found to occur by both concerted and stepwise mechanisms. Concerted mechanism (Figure 6.3) involves a cyclic aromatic transition state in which both bonds are formed to the same extent. However, asynchronicity arises if substituents deform the FMOs giving better overlap between certain region leading to one bond forming 'earlier' on the reaction coordinate.

Though some DA reactions are asynchronous, they may still be concerted with no intermediates located between transition states [108]. Two-stage mechanism or stepwise mechanism involves a biradicalic or zwitterionic intermediate (Figure 6.3). In Chapter 6, we try to highlight the catalytic effect of silver(I)-bipyridine in the inverse electron demand DA reaction of 1,2-diazine and siloxy alkyne as well as the mechanism of this reaction.

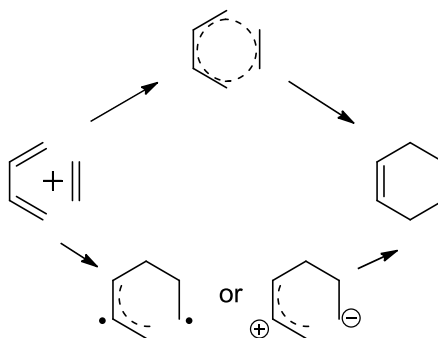


Figure 6.3. One step and two step mechanism of Diels-Alder cycloaddition.

6.1. Introduction

The Diels-Alder reaction plays an important role in organic synthesis. Lewis acid catalysis has found great use in the acceleration of normal electron-demand DA reactions, those between electron-rich dienes and electron-deficient dienophiles; however, limited success has been achieved in the case of the complementary process, the inverse electron-demand Diels-Alder (IEDDA) reaction, between an electron-deficient diene and an electron-rich dienophile [109,110].

Heterocyclic azadienes including 1,2-diazines provide a broad application of IEDDA reactions in the synthesis of useful heterocyclic compounds [111,112]. However, the IEDDA of such azadienes most often require harsh reaction conditions and enhancement of their activity by a variety of substituents since only a few dienophiles react with unsubstituted phthalazines [113-115]. Oishi *et al.* reported the formation of 1-substituted naphthalenes in the IEDDA reactions of 1-substituted phthalazines with enamines or ynamines at elevated temperatures and in the presence of electron-withdrawing groups on the

phthalazines (Figure 6.4) [112]. The work of Wegner *et al.* described, for the first time, Lewis acid catalyzed IEDDA reactions of 1,2-diazines, however, at relatively high temperatures [116-118]. Moreover, alkynes were shown to be unreactive towards unsubstituted phthalazines even in the presence of Lewis acids in their work.

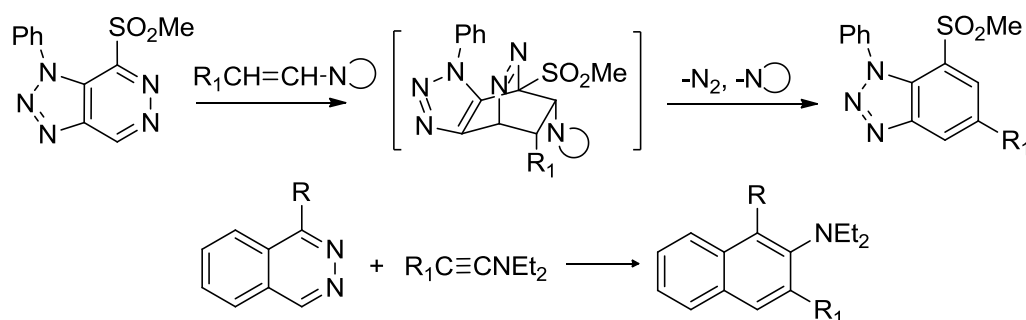


Figure 6.4. Cycloaddition of 1-substituted phthalazine with enamine and ynamine.

Silicon-functionalized building blocks are finding more and more applications in carbon-carbon bond formation processes. The interest arises not only from the low toxicity, ease of handling, and stability of the silicon-functionalized compounds but also from the increasing number of methodologies available for their synthesis and use in follow-up reactions. Nevertheless, Hilt *et al.* reported that the use of silicon-functionalized compounds in DA reactions is generally restricted to the use of silicon-functionalized dienes since trialkyl-silyl functionalized dienes and dienophiles do not have high activation towards both normal and inverse DA reactions [119].

Recently, Rawal *et al.* and Kozmin *et al.* described the development of a highly effective silver-catalyzed formal inverse electron-demand Diels-Alder reaction of 1,2-diazines and siloxy alkynes (Figure 6.5) [120]. They have also extended their research with the use of copper(I) and nickel(0) complex catalysts [121]. In their work, IEDDA reactions can be enhanced by transition metals possessing π acceptor properties like Lewis acids but not by traditional Lewis acids themselves [120].

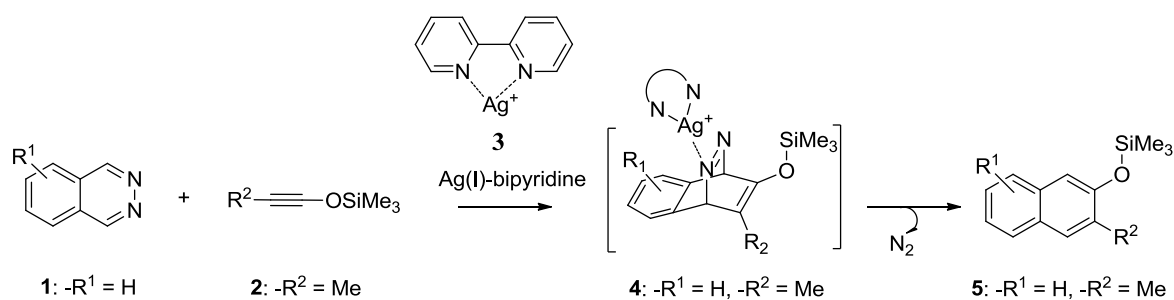


Figure 6.5. 1,2-diazine and siloxy alkyne [4+2] cycloaddition reaction in the presence of silver-bipyridine.

In this study, we focus on the silver (I) catalyst complexing with bipyridine ligand and its effect on reaction kinetics in IEDDA reactions of 1,2-diazine and siloxy alkyne derivatives (Figure 6.5). The complexation reactions of Ag(I)-bipyridine with 1,2-diazine and siloxy alkyne are modeled to understand the affinity of the catalyst prior to the reaction. In order to highlight the catalytic effect of Ag(I)-bipyridine, the uncatalyzed IEDDA reaction is also modeled and frontier molecular orbitals are analyzed to unravel how the catalyst change the reaction kinetics. We aimed to shed light on the mechanism of 1,2-diazine and siloxy alkyne cycloaddition in the presence of silver catalyst with quantum mechanical tools. However, the mechanism is still under investigation.

6.2. Computational Details

All calculations were performed using the hybrid density functional M06-2X [6] as implemented in Gaussian 09 [32]. For silver effective core potential (SDD) [121], and for the rest of the atoms the 6-311+G(d,p) basis set were used. Frequency analyses were performed to confirm the nature of the stationary points as the minima (with all real frequencies) or transition states (with only one imaginary frequency). The intrinsic reaction coordinate (IRC) calculations were used to determine the species connected by each transition structure [91]. Charge analysis has been carried out by using full natural population analysis (NPA) [31].

6.3. Results and Discussion

6.3.1. Silver Catalyzed Inverse Electron-Demand Diels-Alder Reaction of 1,2-Diazine and Siloxy Alkyne

6.3.1.1. Coordination of Ag(I)-bipyridine. Experimental studies on the catalytic effect of silver in IEDDA reactions of 1,2-diazines and siloxy alkynes underscored the importance of bidentate chelating ligands for effective catalysis. Because of its simplicity and high catalytic effect, bipyridine was selected for further study the scope of the catalyzed cycloaddition reaction under the optimized conditions [120].

In this study, Ag(I)-bipyridine complex was used as catalyst to model IEDDA reaction of phthalazine and trimethyl(prop-1-yn-1-yloxy)silane as siloxy alkyne. Silver based catalysts are known to show high affinity for alkynes. On the other hand, 1,2-diazines are appropriate as bidentate chelating ligands for silver cation. Silver ion coordination of the 1,2-diazine and siloxy alkyne, thus, seem to be equally probable and for this reason two possible complexes of silver with phthalazine and siloxy alkyne are modeled (Figure 6.6).

The bidentate nature of phthalazine, though similar to bipyridine, does not lead to the bifurcated coordination of Ag(I) with the vicinal diazine nitrogens as in the case of bidentate ligands. Ag(I) coordinated only with one of the diazine nitrogens, instead of both, possibly due to the face away lone pairs of N-donors in phthalazine. Hence, in the Ag(I)-bipyridine and phthalazine complex (6), only one N-donor is accessible to share its lone pair electrons. In the case of Ag(I)-bipyridine and siloxy alkyne complex (7), Ag(I)-bipyridine coordinates to the siloxy alkyne with two asymmetric C-Ag(I) distances in accordance with the polarization of the triple bond allowing to the formation of hydrogen bond with the oxygen of the siloxy alkyne. A potential energy surface scan was carried out around the coordination bond of Ag(I) to phthalazine and siloxy alkyne for possible conformers of 6 and 7. Ag(I)-bipyridine coordinates to phthalazine either from the equatorial or the axial plane with respect to the plane of phthalazine resulting in two isoenergetic conformers (Figure 6.6). However, we were not able to locate any conformer

other than the one in Figure 6.6 for Ag(I)-bipyridine siloxy alkyne complex(7). In both cases, 6 and 7, silver forms a ternary complex.

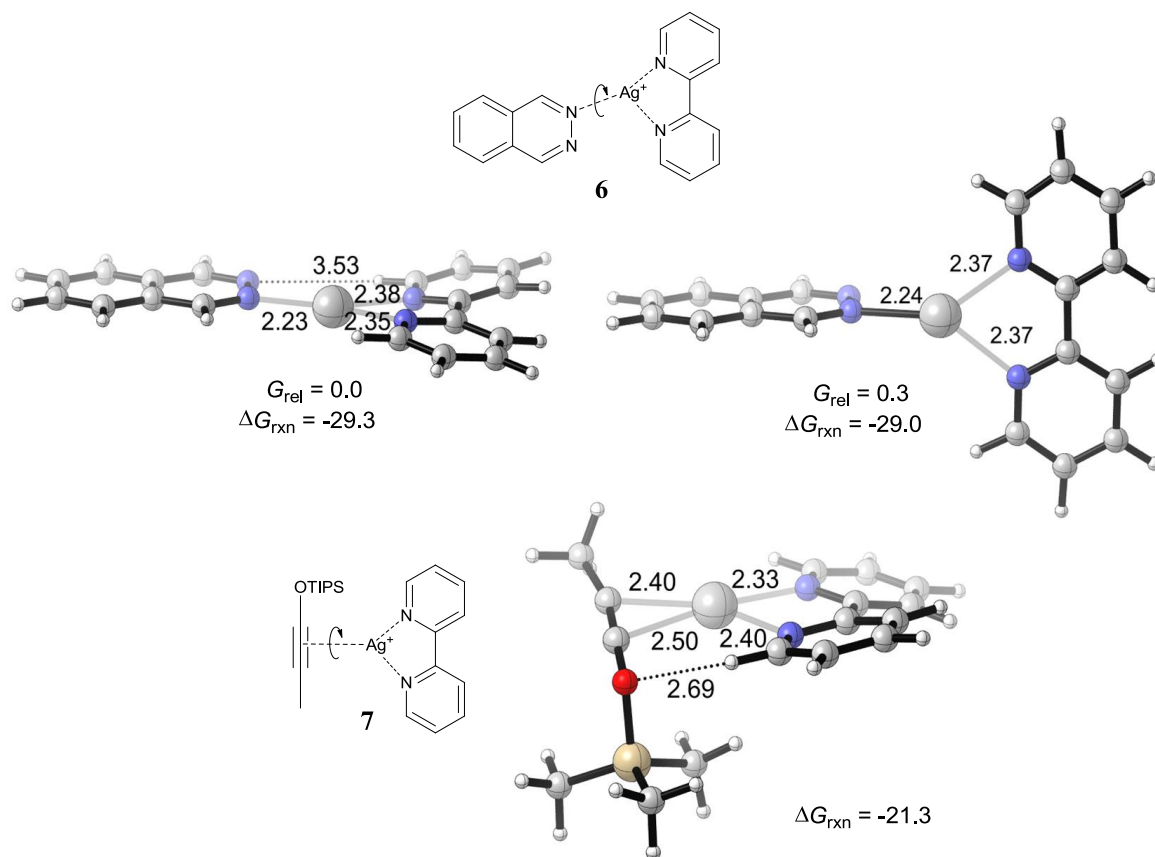


Figure 6.6. Silver-phthalazine and silver-siloxy alkyne complexes (6 and 7). Relative and reaction Gibbs free energies are in kcal/mol.

The Ag(I)-bipyridine and phthalazine complex (6) is more favorable in comparison to Ag(I)-bipyridine and siloxy alkyne complex (7) (Figure 6.6). There is 8 kcal/mol difference in the Gibbs free reaction energies of 6 and 7 suggesting that Ag(I)-bipyridine forms silver-phthalazine complex rather than silver-siloxy alkyne complex. Thus in the following section we have considered the IEDDA reaction of silver-phthalazine complex (6) and siloxy alkyne.

6.3.1.2. Regioselectivity. Asymmetric dienophiles such as siloxy alkyne, tend to attack from the electron rich site to the more electron deficient site in the diene, phthalazine in our case, in IEDDA reaction. Charge analysis of the reactants has been carried out to

unravel the reactive site prior to cycloaddition reaction of asymmetric siloxy alkyne with phthalazine (Figure 6.7). The coordination of Ag(I)-bipyridine acting as a Lewis acid withdraws electron density from phthalazine. The electron withdrawing effect of the catalyst is more pronounced for the vicinal carbon atom (C1) of phthalazine. Nevertheless, we have modeled the two possible types of regioselective transition states for the nucleophilic attack of siloxy alkyne to the electron deficient carbon atoms (C1 and C4) of phthalazine (Figure 6.8).

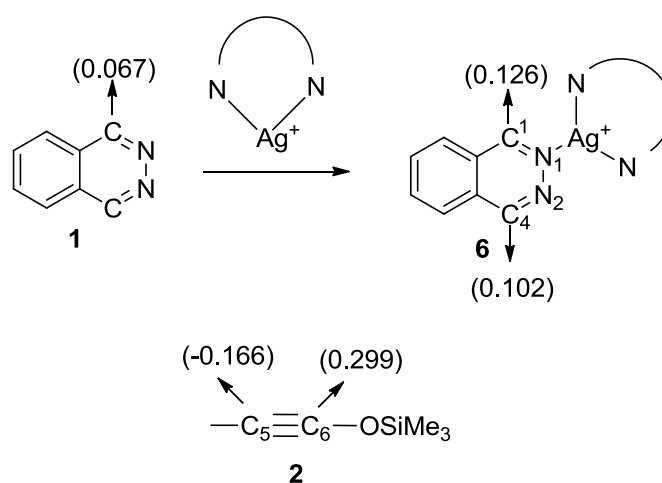


Figure 6.7. NPA charges of 1, 2 and 6.

The transition states related with the nucleophilic attack of siloxy alkyne to the vicinal carbon atom (C1) of phthalazine with respect to the coordination of Ag(I)-bipyridine are more stabilized over the ones related with the nucleophilic attack of siloxy alkyne to C4 of phthalazine consistent with the charge analysis (Figure 6.8). For each regioselective transition state type, there are two conformations related with the position of the sterically hindered triisopropylsilyl (TIPS) group of the siloxy alkyne with respect to the position of the catalyst. The transition states with opposite configuration of the catalyst and TIPS group of the siloxy alkyne are more favorable with respect to their counterparts. When the catalyst and TIPS group of the siloxy alkyne are on the same side, though this configuration enjoys the stabilization of the non-conventional hydrogen bonding between the hydrogens of TIPS and N2 of the phthalazine, it still suffers from the steric hindrance

created by TIPS group. This steric hindrance results in 1.1 kcal/mol of penalty in this transition state (TSA-N1a). In all types of transition states a highly asynchronous bond formation is observed due to the asymmetric nature of the diene and dienophile as well as the steric hindrance introduced by the catalyst and more importantly by TIPS group of the siloxy alkyne adjacent to the one of the bond formation site. The asynchronicity is also evidenced with the formation of the ketenium ion in the transition states. Notice that the C5-C6-O bond is almost linear in the transition states (Figure 6.8).

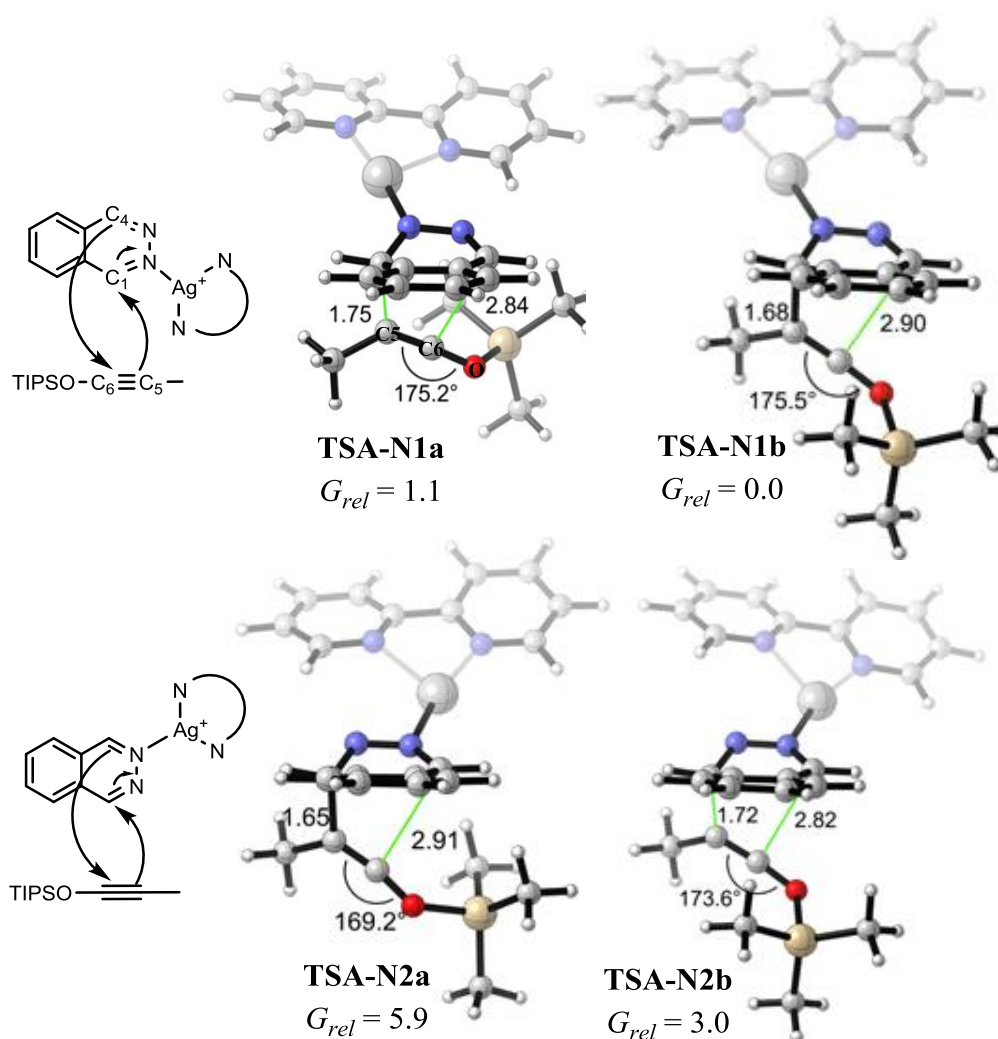


Figure 6.8. Regioselective transition states of IEDDA reaction of 2 and 6 and relative Gibbs free energies (kcal/mol).

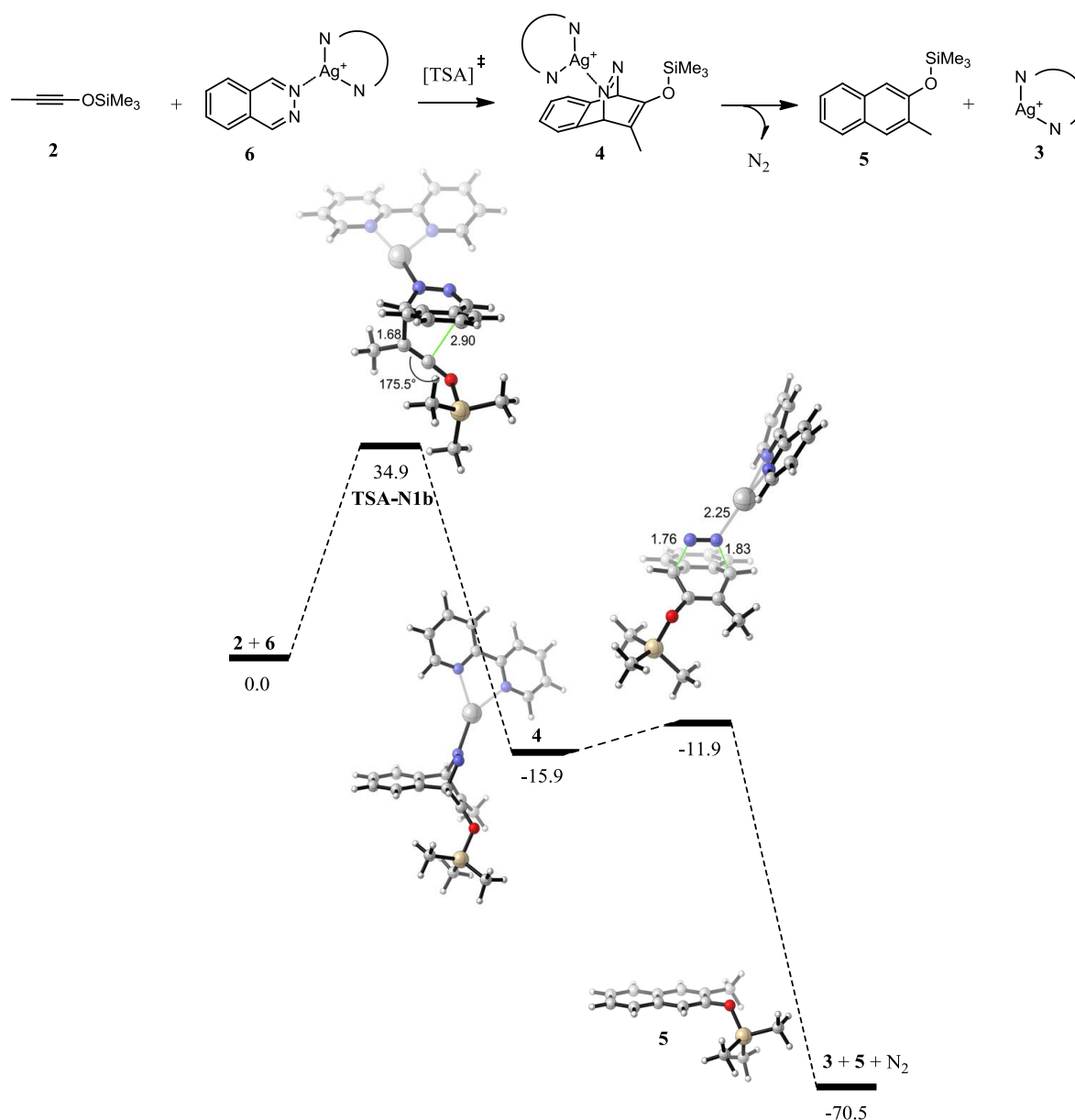


Figure 6.9. The Gibbs free energy (kcal/mol) profile for Ag(I) catalyzed IEDDA reaction of phthalazine and siloxy alkyne.

The Ag(I) catalyzed reaction profile is depicted in Figure 6.9. The transition state, TSA-N1b, for the nucleophilic attack of siloxy alkyne to phthalazine is 34.9 kcal/mol higher in energy than the corresponding reactants. Though the bond formation in TSA-N1b is highly asynchronous, the reaction is still concerted. The formation of the cycloadduct, **4**, is highly exergonic. Nitrogen gas release requires only 4 kcal/mol of Gibbs free energy of

activation yielding silyl-protected 2-naphtol (5). The formation of 5 is remarkably exergonic due to the gain of the aromaticity.

6.3.2. Uncatalyzed Cycloaddition of 1,2-Diazine and Siloxy Alkyne

Phthalazine, 1, was reported to be unreactive toward siloxy alkynes at room temperature and the expected cycloadduct was obtained in only 5% yield at 150°C without silver catalysis. However, the silver catalyzed cycloaddition of 1,2-diazines and siloxy alkynes proceeded at relatively much more milder conditions (at room temperature) giving the expected cycloadduct in up to 92% yield depending on the substituents of 1,2-diazine and the siloxy alkyne [121]. In order to understand the silver catalyst effect on 1,2-diazine and siloxy alkyne cycloaddition, the uncatalyzed cycloaddition reaction has been modeled.

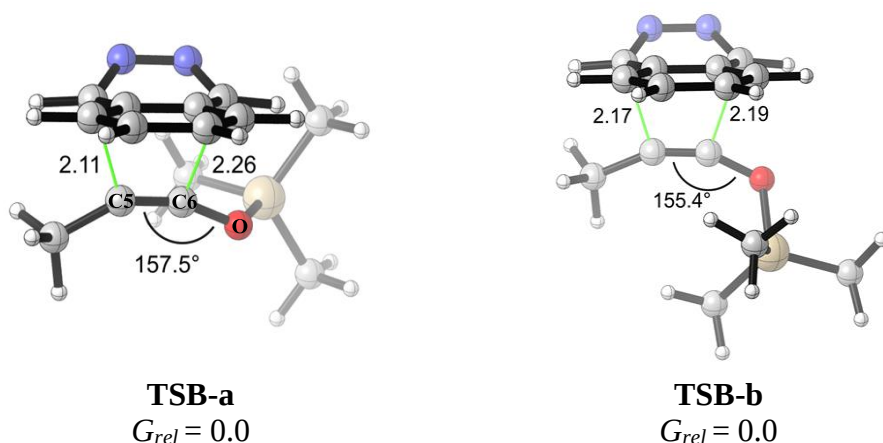


Figure 6.10. Transition states of uncatalyzed cycloaddition of phthalazine and siloxy alkyne and relative Gibbs free energies (kcal/mol).

The transition states of the uncatalyzed cycloaddition of phthalazine and siloxy alkyne are depicted in Figure 6.10. The two transition states, TSB-a and TSB-b, differing in the conformation of TIPS group of the siloxy alkyne are isonergetic. While, in TSB-a, a more asynchronous bond formation is observed compared to TSB-b, it is still synchronous compared to the transition states of the silver catalyzed cycloaddition reaction (Figure 6.8). In the case of uncatalyzed cycloaddition, no ketenium ion is observed in the transition states indicating a concerted mechanism. The C5-C6-O angle decreases from 175° to

$\sim 156^\circ$ in harmony with the sp^2 hybridization of C6 of the siloxy alkyne in the transition states of uncatalyzed cycloaddition reaction.

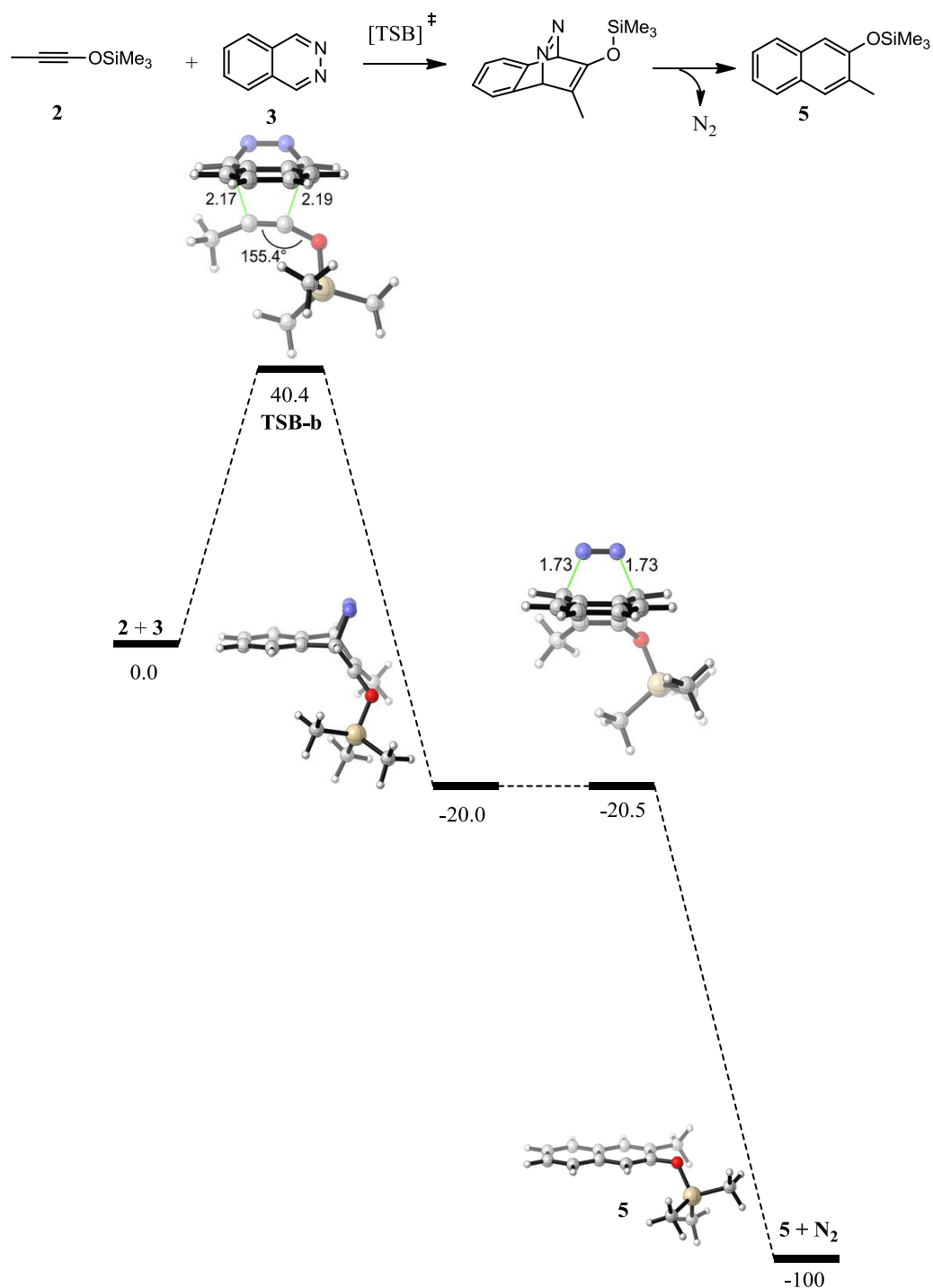


Figure 6.11. The Gibbs free energy (kcal/mol) profile for the uncatalyzed IEDDA reaction of phthalazine and siloxy alkyne.

The Gibbs free energy profile of the uncatalyzed cycloaddition of phthalazine and siloxy alkyne is depicted in Figure 6.11. The potential energy surface of the uncatalyzed cycloaddition of phthalazine and siloxy alkyne is similar with silver catalyzed cycloaddition (Figure 6.9) yielding the expected cycloadduct via the transition state (TSB-b). Upon spontaneous extrusion of N_2 , highly stable product (5) is obtained. Though TSB-b is highly synchronous compared to TSA-N1b; both pathways end up with the corresponding cycloadducts. However, catalysis of the phthalazine and siloxy alkyne in the presence of Ag(I) endorses the cycloaddition by 5.5 kcal/mol difference in comparison to the uncatalyzed reaction.

6.3.3. Frontier Molecular Orbital Analysis

Frontier molecular orbitals are considered to play an important role on the outcome of Diels-Alder reactions. In this section we, thus, elaborated the motives of the uncatalyzed and catalyzed IEDDA reactions through a molecular orbital analysis approach.

Ag(I)-bipyridine acting as a Lewis acid may complex one of the nitrogen atoms of phthalazine or the triple bond of the siloxy alkyne, however, formation of the former complex have been shown to be more favorable over the latter in Section 6.3.1.1. Nevertheless, we have analyzed the molecular orbitals of phthalazine, siloxy alkyne as well as their complexes with Ag(I)-bipyridine (Figure 6.12). Ag(I)-bipyridine significantly lowers the LUMO of both phthalazine (1) and the siloxy alkyne (2) when coordinated to either one of them (6 and 7). However, the coordination of Ag(I)-bipyridine to phthalazine (6) brings about the LUMO of complex 6 and HOMO of the siloxy alkyne (2) more close in energy facilitating the charge transfer in IEDDA reaction of the two. The band gap between HOMO of the siloxy alkyne (3) and LUMO of complex 6 is calculated as 3.64 eV while the band gap between HOMO of phthalazine (1) and LUMO of complex 7 is calculated as 4.16 eV. In the absence of Ag(I)-bipyridine, the band gap for the IEDDA of phthalazine (1) and the siloxy alkyne (3) is 6.60 eV. The big band gap of the NEDDA of phthalazine (1) and the siloxy alkyne (3) is also depicted for comparison. Overall, the catalyst withdraws electron density from phthalazine through a complex formation. The

coordination lowers the LUMO of the diene and facilitates the cycloaddition step according to the FMO theory.

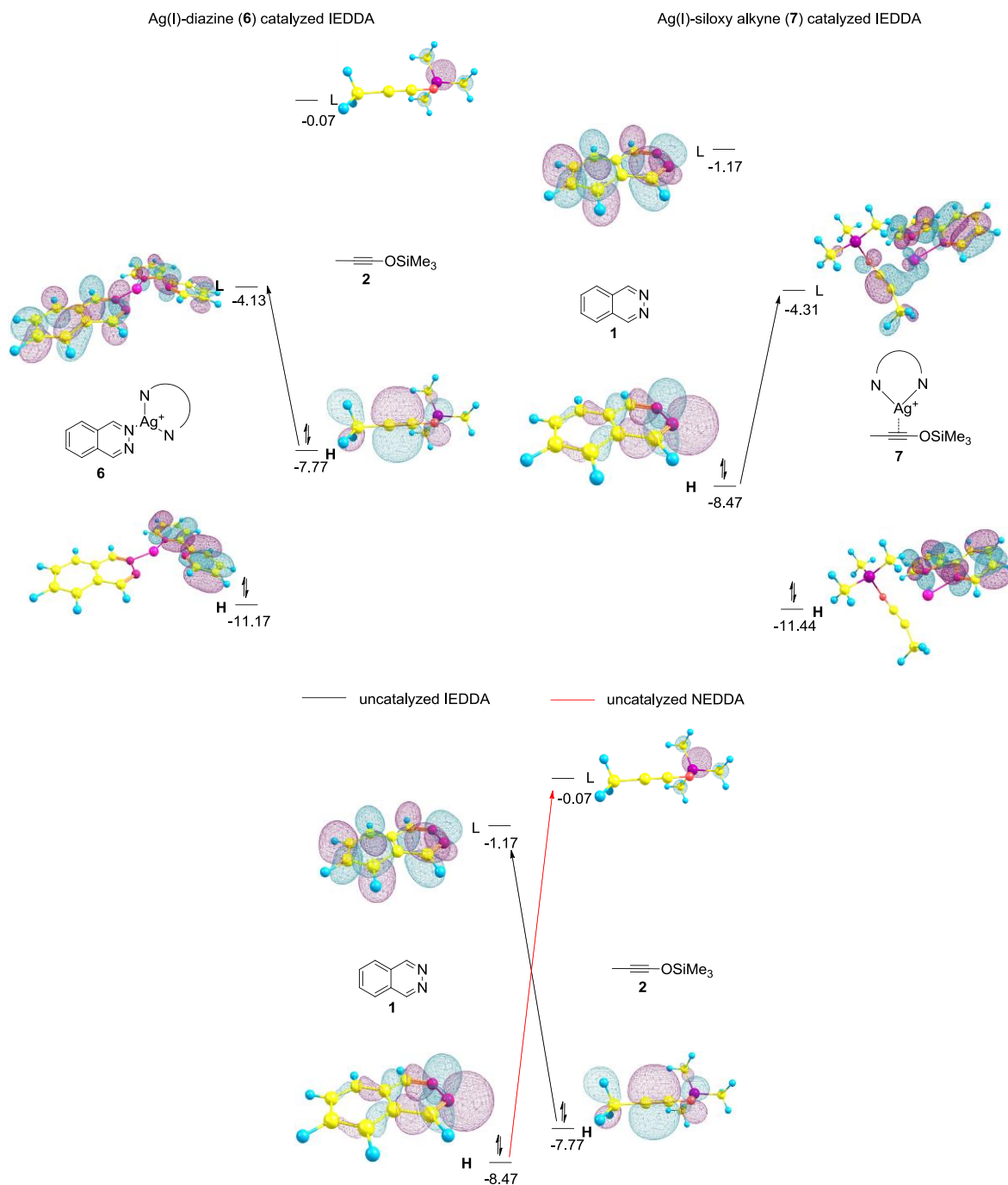


Figure 6.12. Frontier molecular orbitals of **1**, **2**, **6** and **7**.

H and L designate HOMO and LUMO, respectively. The energies of HOMO and LUMO are in eV.

6.4. Conclusions

In this study we have modeled the IEDDA reaction of phthalazine and siloxy alkyne enhanced by Ag(I)-bipyridine catalysis. We have first investigated the complexation of the catalyst with the two reactant partners separately. Since the complexation of Ag(I)-bipyridine with phthalazine is more favorable, it is assumed that IEDDA reaction proceeds with the initial attack of siloxy alkyne to the previously formed complex between Ag(I)-bipyridine and phthalazine. The full reaction path of this reaction is highlighted. Though the bond formation of the cycloadduct in the rate determining step is highly asynchronous, IRC calculations did not yield a zwitterionic intermediate that would form through a stepwise mechanism. Without the catalyst, the IEDDA reaction proceeds in a similar manner, however, this time synchronous bond formation is observed in the transition state of the cycloadduct with a higher barrier compared to that of Ag(I)-bipyridine catalysis. In order to highlight the catalytic effect of Ag(I)-bipyridine, frontier molecular orbital analysis has been conducted. The coordination of Ag(I)-bipyridine to phthalazine decreases the energy of the LUMO of phthalazine promoting the charge transfer from HOMO of the siloxy alkyne. This result fully supports the initial idea for catalysis of the IEDDA reaction of phthalazine and siloxy alkynes.

6.5. Future Work

The mechanism of IEDDA of phthalazine and siloxy alkyne catalyzed by Ag(I)-bipyridine was found to proceed through a highly asynchronous but concerted mechanism in Section 6.3.1.2. Though we observed the formation of the ketenium ion in the transition state of the cycloadduct, IRC calculations with default parameters as implemented in Gaussian09 pointed out a concerted mechanism. Thus, we are still suspicious about the mechanism and the reaction path will be traced more carefully. Moreover, the concerted mechanism through synchronous transition states and stepwise mechanism involving a biradicalic intermediate will be also investigated.

IEDDA reaction of phthalazine and siloxy alkyne was not facilitated experimentally by the traditional Lewis acids. We are going to model this reaction in the presence of

Lewis acids such as SnCl_4 in order to better highlight the importance of the catalytic effect of Ag(I) -bipyridine.

7. INVESTIGATION OF IRON BINDING-RELEASE DYNAMICS IN TRANSFERRIN

7.1. Introduction

Iron is an important element for almost all living organisms for its role in many biological processes due to its redox ability to shift between two oxidation states i.e. ferrous (Fe^{2+}) and ferric (Fe^{3+}) [123]. In unbound form, Fe^{3+} is not soluble in water, and the reduced Fe^{2+} is toxic. For this reason, iron is regulated strictly when it enters the organism to prevent the formation of superoxide radicals, which will disrupt the proteins, lipids and nucleic acids via Fenton reactions, or growth of pathogens [124]. To prevent these, iron is stored in ferritin and transported via transferrin where it is solubilized as Fe^{3+} .

The main role of human serum transferrin (hTf) is to bind ($\sim 10^{22}$ M) and carry the Fe^{3+} via transferrin receptors (TfR) into the intracellular domain where the complex is internalized by receptor-mediated endocytosis [125,126]. In the cytoplasm, the iron is released as the pH decreases from 7.4 (serum pH) to 5.5 in the endosome. Iron is then transported out of the endosome and stored in ferritin whereas hTf and its receptor are recycled.

hTf has two distinct lobes, N-lobe and C-lobe, which are structurally similar and capable of binding to iron reversibly [127]. Both lobes are further divided into two subdomains that are bound to each other by two antiparallel beta strands, N1, N2 and C1, C2 [127]. Iron coordination is mediated by similar residues in both lobes (Figure 7.1): an aspartic acid, two tyrosines, and a histidine. The distorted octahedral coordination of the iron in both lobes is completed with a synergistic anion, which is identified as either carbonate or bicarbonate. Although carbonate is the physiologically relevant synergistic anion [128], other anions (oxalate, glycolate, malonate, etc.) have also been reported to promote high affinity Fe^{3+} binding to hTf [129]. The synergistic anion has been shown to preorganize the binding site prior to iron coordination [130-132].

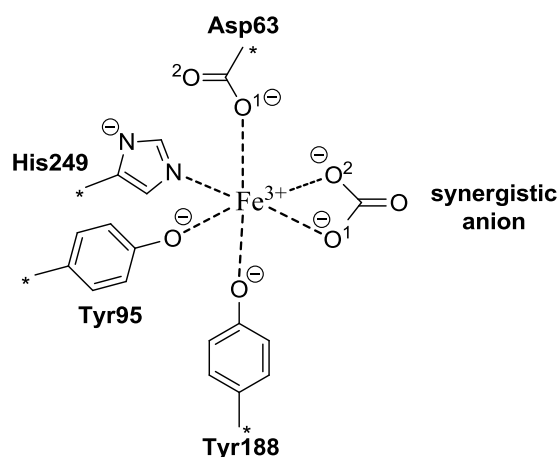


Figure 7.1. Schematic representation of Fe^{3+} binding site in the N-lobe of transferrin considered in this work.

The metal-binding and release result in significant conformational changes of the transferrin: a closed conformation in the holo-form [133-136] and an open conformation in the apo-form [127,137,138]. A 'partially-opened' conformation between those of the apo-hTF and holo-hTF has also been resolved recently [139]. Iron release mechanism of transferrin molecule is not known completely, yet it is thought that the pH change from physiological to endosomal triggers a series of protonation events resulting in the opening of the binding cleft and release of iron consequentially. The commonly accepted mechanism for the N-lobe starts with the protonation of carbonate, which results in conformational change in Arg124 and is followed by the protonation of His249. Finally, proton transfer from Lys296 to Tyr188 occurs via the protonation of Lys206. The two lysine residues, which are called "dilysine trigger", are on the opposite sides of the iron binding domain modulating the opening of the binding cleft [140]. Even though the C and N-lobes have ~56% sequence similarity and 45% sequence identity and the residues for iron coordination and iron binding are similar, C-lobe releases iron at a relatively slower rate when the pH is at the endosomal level [127,141]. In addition, while Fe^{3+} release from N-lobe occurs at $\text{pH} \sim 5.4$, C-lobe can stay bound to iron up to $\text{pH} \sim 4.8$ [140]. It has been proposed that the difference in the composition of dilysine trigger is the underlying reason for the difference in iron release rates [142]. In the C-lobe, on the other hand, the dilysine trigger is replaced by Lys534, Arg632 and Asp634 residues [143].

Mutation studies and molecular dynamics simulations showed that protonation of Lys206 is not sufficient to trigger the domain opening [144,145]. Instead the protonation of Lys206 prompts the protonation of Tyr188 by Lys296, which would lead to a weakening of the iron binding site is hypothesized. This hypothesis was also confirmed by quantum chemical calculations reporting that Tyr188 is readily protonated resulting in its departure from the first coordination shell of iron [146]. The requirement of the protonation of Tyr188 for the release of iron from the iron loaded transferrin has also been evidenced with molecular dynamics simulations considering various protonation states by Mujika *et al.* [147]. In their early work, the protonation of His249 has led to the leaving of this residue from the metal coordination shell to the second coordination sphere during the MD simulations [148].

In this study, the binding site of iron in the N-lobe of hTf is investigated in detail quantum mechanically. Simple cluster models of the iron-binding site consisting of the ferric ion and its first shell ligands are optimized considering the effect of protonation of various ligands. The optimized structures are compared with the crystal structure in search of a representative model of the binding site of the N-lobe of hTf which is further used to investigate the effect of protonation on the release of iron. The formation of thermodynamically stable complex upon the protonation of Tyr188 is evaluated as the possible route for the disruption of the octahedral coordination around iron and, thus, for its release.

7.2. Computational Details

The quantum chemical methods are applied on the Transferrin crystal structure with a resolution of 2.1 Å (3v83) [136]. The models employed for computations of the iron-binding site of transferrin are truncated from the β -Carbon of the residues involved in the first solvation shell of iron. The residues are frozen at the atom of truncation to preserve the structural integrity of the active site. The spin state of iron (Fe^{3+}) is $S=5/2$.

All calculations were performed using the hybrid density functional B3LYP [4,5] as implemented in Gaussian 09 [32]. For iron effective core potential (SDD) [122], and for

the rest of the atoms the 6-311+G(d) basis set were used. Geometry optimizations were performed with the implicit solvent model IEFPCM (water) [11,12,42,91] with $\epsilon=4.0$ corresponding to an approximate dielectric constant of a protein active site [149].

7.3. Results and Discussion

7.3.1. Model of the First Binding Shell of Iron

The iron binding site of N lobe of transferrin consists of four ionizable residues namely Asp63, Tyr95, Tyr188 and His249 and a synergistic anion, (bi)carbonate as mentioned earlier. pK_a calculations on the various forms of N lobe transferrin showed that the pK_a values of all residues in the coordination shell of iron undergo high pK_a shifts to lower pH when iron is bound [144]. However, different methodologies to predict the protonation states of residues in protein environment may give different pK_a values. In this study, the first coordination shell of iron considering the different protonation states of the ionizable residues (Table 7.1) is modeled quantum mechanically and the root-mean square deviations of the complexes are calculated in order to find out the more probable structure as a representative model of the crystal structure, 3v83 (Table 7.2). Only the high-spin complexes are considered since the high-spin complexes are lower in energy than the low-spin ones [146] and since the iron in transferrin is known to be in the high-spin state [150].

Aspartate is assumed to be the easiest deprotonatable residue and thus the formal charge of Asp63 is assigned as (-1) in all cases. Furthermore, the pK_a value of Asp63 was calculated as almost 0 in all forms of transferrin [144]. For the complexes in which axial tyrosine (Tyr188) is protonated or bicarbonate/carbonic acid is used as the synergistic anion, the octahedral coordination around iron is mostly disrupted. Tyr188 when protonated, left the coordination in the complexes such as in TfN5, TfN6a, TfN17 and TfN18. On the other hand, the protonation of the synergistic anion resulted in its monodentate coordination to iron (TfN2, TfN5, TfN7, TfN14 and TfN16) or even the complete loss of coordination in the case of carbonic acid (TfN13).

Table 7.1. Complexes with different protonation states of residues in the first binding shell of iron.

	Asp63	His249	Tyr95	Tyr188	Synergistic Anion
TfN1	(-1)	(-1)	(-1)	(-1)	(0)
TfN2	(-1)	(-1)	(-1)	(-1)	(-1)
TfN3	(-1)	(-1)	(-1)	(-1)	(-2)
TfN4	(-1)	(-1)	(-1)	(0)	(0)
TfN5	(-1)	(-1)	(-1)	(0)	(-1)
TfN6	(-1)	(-1)	(-1)	(0)	(-2)
TfN7	(-1)	(-1)	(0)	(-1)	(0)
TfN8	(-1)	(-1)	(0)	(-1)	(-1)
TfN9	(-1)	(-1)	(0)	(-1)	(-2)
TfN10	(-1)	(-1)	(0)	(0)	(0)
TfN11	(-1)	(-1)	(0)	(0)	(-1)
TfN12	(-1)	(-1)	(0)	(0)	(-2)
TfN13	(-1)	(0)	(-1)	(-1)	(0)
TfN14	(-1)	(0)	(-1)	(-1)	(-1)
TfN15	(-1)	(0)	(-1)	(-1)	(-2)
TfN16	(-1)	(0)	(-1)	(0)	(0)
TfN17	(-1)	(0)	(-1)	(0)	(-1)
TfN18	(-1)	(0)	(-1)	(0)	(-2)
TfN19	(-1)	(0)	(0)	(-1)	(0)
TfN20	(-1)	(0)	(0)	(-1)	(-1)
TfN21	(-1)	(0)	(0)	(-1)	(-2)
TfN22	(-1)	(0)	(0)	(0)	(0)
TfN23	(-1)	(0)	(0)	(0)	(-1)
TfN24	(-1)	(0)	(0)	(0)	(-2)

The calculated structures reasonably reproduce the crystal structure (3v83) with an average root-mean square deviation of 0.21 Å for the iron-ligand coordination distances in the complexes with octahedral coordination preserved around iron. The largest iron-ligand deviations occur for the iron-histidine distances without showing much dependence on the charge of the histidine residue. The average histidine-iron distance in its imidazole form is 2.14 Å, 0.1 Å longer than its imidazolate counterpart, however, still quite shorter than the crystal structure (2.40 Å). We have attributed this large deviation to the absence of water molecules that form hydrogen-bonds to the Nδ1 of His249. However, we have not observed an elongation in iron-histidine distance when two water molecules are included

in our model (Figure 7.2). The other iron-ligand distances are within 0.2 Å of the reference crystal structure (3v83). For the complexes with the loss of coordination of at least one of the residues (Tyr188 or the synergistic anion), root-mean square deviations for the iron-ligand distances as high as 1.89 Å have been observed.

Table 7.2. Distances between iron and its first shell ligands in the optimized structures and the root mean square deviation values.

	O ¹ Asp63	NHis249	OTyr95	OTyr188	O ¹ CO ₃	O ² CO ₃	RMSD ^a	RMSD ^b
3v83	2.21	2.40	2.13	2.19	2.28	2.26		
TfN2	2.03	2.08	1.91	1.92	2.07	3.50	0.55	0.91
TfN3	2.13	2.14	1.99	2.01	2.08	2.12	0.18	0.50
TfN5	1.90	1.98	1.86	5.75	1.94	3.29	1.54	1.12
TfN6a	1.95	2.05	1.91	4.11	2.06	2.07	0.82	1.12
TfN7	1.91	1.97	2.24	1.86	3.48	2.24	0.55	1.15
TfN9a	2.04	2.10	2.32	1.94	2.13	2.02	0.22	0.86
TfN10	1.91	2.10	2.31	2.13	2.38	2.2	0.49	1.11
TfN11	1.90	1.96	2.19	2.27	2.34	2.03	0.24	0.62
TfN12	1.94	2.05	2.29	2.38	2.01	1.98	0.26	0.47
TfN13	1.90	2.09	1.85	1.85	5.91	5.08	1.89	2.02
TfN14	1.98	2.22	1.88	1.90	2.04	3.32	0.49	0.88
TfN15	2.11	2.23	1.96	2.00	2.03	2.12	0.18	0.53
TfN16	1.89	2.08	1.85	2.18	3.39	2.14	0.50	0.81
TfN17	1.88	2.10	1.86	4.77	2.11	2.20	1.08	0.70
TfN18	1.95	2.16	1.88	5.57	2.02	2.03	1.40	1.10
TfN19	1.92	2.08	2.14	1.85	3.41	2.23	0.51	0.78
TfN20	1.98	2.14	2.19	1.86	2.19	2.16	0.20	0.68
TfN21	2.00	2.23	2.33	1.92	2.08	2.02	0.22	0.86
TfN23	1.86	2.08	2.14	2.20	2.11	2.10	0.22	0.60

^aRoot mean square deviation for the coordination distances between iron and its first shell ligands with respect to the reference crystal structure (3v83). ^bAll-atom root mean square deviation with respect to the reference crystal structure (3v83).

The lowest iron-ligand deviations occur for TfN3 and TfN15 with an RMSD of 0.18 Å. The charges of the residues in these two complexes, TfN3 and TfN15, are almost the same with a (-1) charge for Asp63, Tyr95, Tyr188 and a (-2) charge for the synergistic

anion except the protonation state of His249. In TfN3, His249 is in its imidazolate form where in TfN15 the imidazole form is modeled. Though TfN3 and TfN15 show the lowest RMSD values, they are still close to the average RMSD value (0.21 Å) for the complexes with octahedral coordination around iron. Root-mean square deviations for heavy atoms with respect to the reference crystal structure are also calculated. The lowest RMSD values around 0.50 Å are obtained for TfN3 (0.50 Å), TfN12 (0.47 Å) and TfN15 (0.53 Å). The optimum model for the iron-binding site seems to be TfN3. Furthermore, TfN3, consisting of deprotonated forms of Asp63, Tyr95, Tyr188, His249 and the synergistic anion is consistent with the calculated pK_a values of these residues at the physiological pH [144]. Thus, TfN3 (Figure 7.3) is chosen on the basis of both the pK_a 's and RMSD calculations to further model the release mechanism in transferrin.

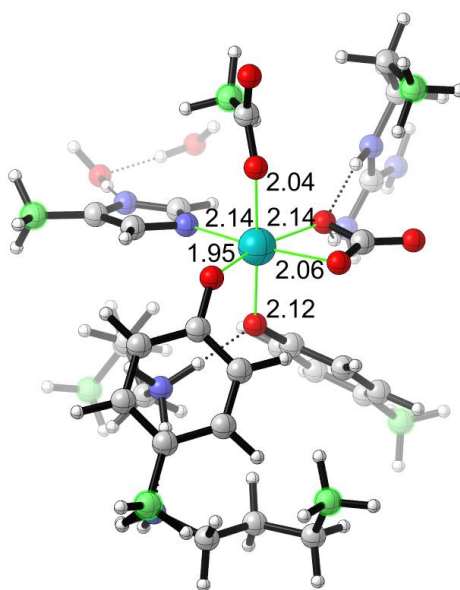


Figure 7.2. The complex including Arg124, Lys206 and Lys296 as second shell residues as well as two water molecules in close proximity to N δ 1 of His249.

The truncated atoms are frozen and highlighted in green.

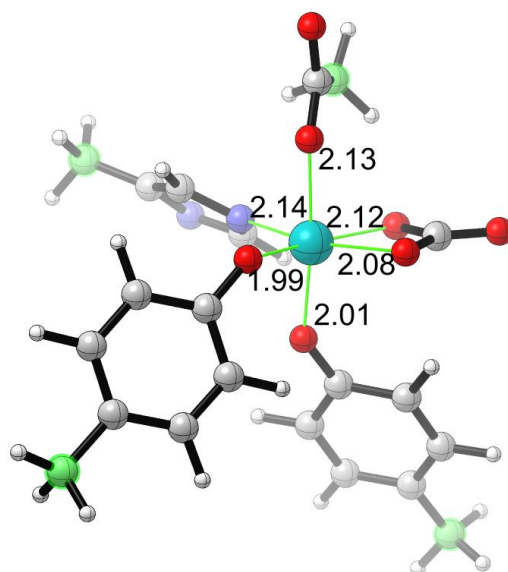


Figure 7.3. The optimized structure of TfN3.
The truncated atoms are frozen and highlighted in green.

7.3.2. Release of Iron in the N-lobe of Transferrin

In the release mechanism, several protonation events are proposed to be effective upon the decrease of the pH in the endosome where iron is released. These protonation events are associated with the protonation of carbonate, His249 and Tyr188 as mentioned previously. Among these proposed protonation events leading to the opening of the domain and thus resulting in the iron release, the protonation of the axial tyrosine is proposed to be the key event in the iron release by recent molecular dynamics simulations and experimental studies [139,147]. In this work, we have considered the protonation of each residue separately in the first iron binding shell of TfN3 to see how the protonation of each residue affects the coordination mode in the first binding site (Figure 7.4). The geometries associated with the protonation of each coordinating residue in TfN3, namely TfN2, TfN6, TfN9 and TfN15 are depicted in Figure 7.5.

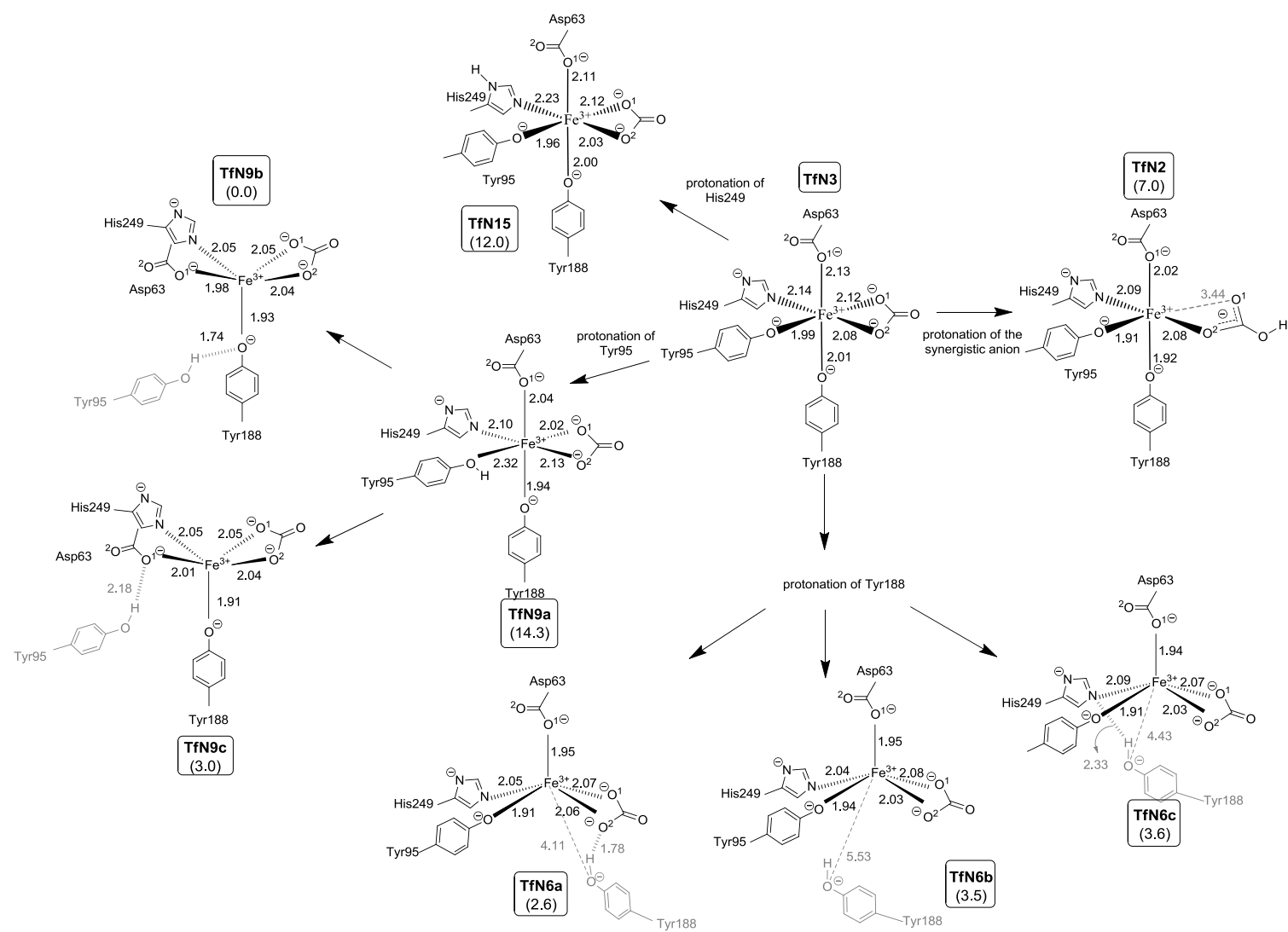


Figure 7.4. The protonation of His249, Ty95, Tyr188 and the synergistic anion in TfN3. Relative free energies are given in kcal/mol.

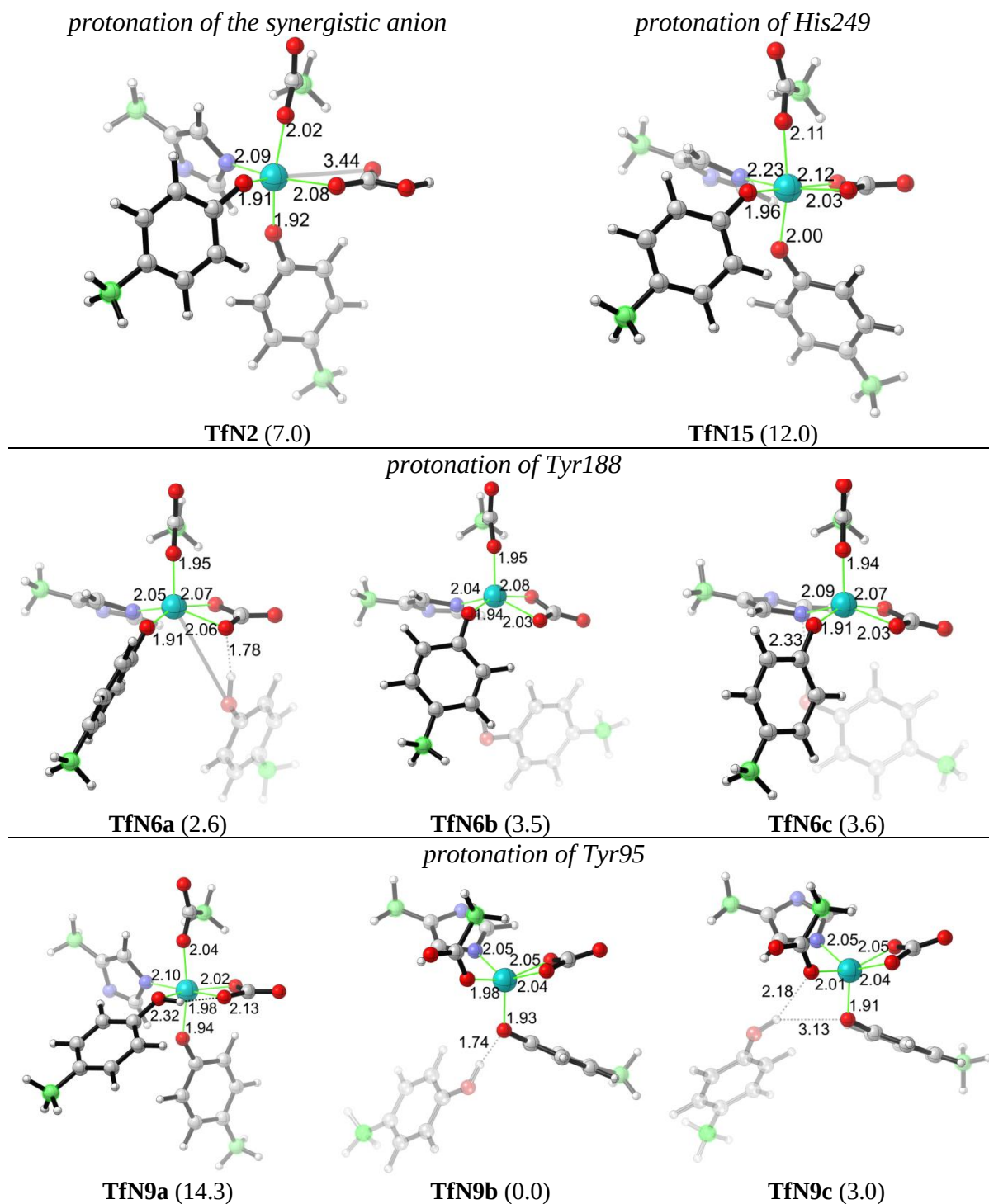


Figure 7.5. The complexes associated with the protonation of each residue in TfN3 and their relative free energies (kcal/mol).

The truncated atoms are frozen and highlighted in green.

The protonation of Tyr188 leads to the detachment of this residue from the first coordination shell adopting a square pyramidal coordination. The protonated Tyr188 may form hydrogen bond with Asp63-O² (TfN6a) or His249-Nε2 (TfN6c) or interact with the π -system of Tyr95 (TfN6b). The relative free energies of these complexes are in the range of 1 kcal/mol. The positions of the other coordinating residues are preserved in all the three complexes related with the protonation of Tyr188 (TfN6a, TfN6b and TfN6c).

The coordination of the synergistic anion changed from bidentate to monodentate as the anion is protonated (TfN2). The distance between the iron and the second coordinating oxygen (O¹) of bicarbonate increases to 3.44 Å resulting in the weakening of this coordination. The loss of the coordination of one of the oxygen of bicarbonate in the equatorial plane results in a trigonal bipyramidal coordination around iron consistent with the previously reported studies [144,148].

The protonation of Tyr95 results in two different types of coordination modes around iron: octahedral (TfN9a) and square pyramidal (TfN9b and TfN9c). In TfN9a, the proton of Tyr95 forms H-bond to the O² of carbonate. Since these two residues are in the same equatorial plane of the coordination shell, the octahedral arrangement around iron is preserved. When Tyr95 is protonated in the axial plane direction, either up or down, the protonated Tyr95 is capable of forming H-bonds with the axial residues, Asp63 and Tyr188, depending on the upwards/downwards direction of the incoming proton. The axial protonation of Tyr95 leads to the leaving of this residue from the first iron coordination shell to the second coordination sphere. Iron with the loss of coordination of Tyr95 in TfN9b and TfN9c presents a square pyramidal coordination mode: O¹ and O² of carbonate, Asp63 and His249 in the square plane and Tyr188 in the axial position. However, the movement of Asp63 from the axis of the octahedral arrangement in TfN3 to the square plane in TfN9b or TfN9c is questionable/irrelevant in the absence of the second shell residues. The distance between the oxygen of Ser125 and O² of Asp63 is 3.3 Å in the crystal structure indicating a hydrogen bond between the two residues which will presumably prevent the shift of Asp63 to the square plane.

The protonation of Tyr95 in TfN9b results in the most thermodynamically stable complex among the protonated complexes closely followed by the complexes with protonated Tyr188 (TfN6a, TfN6b and TfN6c) and TfN9c. The protonation of the carbonate (TfN2, 7.0 kcal/mol) as well as the protonation of His249 (TfN15, 12.0 kcal/mol) in the acidic environment are energetically less favorable compared to TfN9b. Though the equatorial protonation of Tyr95 (TfN9a, 14.3 kcal/mol) is less favorable with respect to its counterparts, this complex with the preserved octahedral coordination mode would form in a shorter time interval. Even if these two complexes (TfN9b and TfN9c) exist, the drastic change in the coordination mode associated with the movement of the first binding shell residues probably occurs on a longer time scale. This will be further discussed in the following section with the models including second shell residues.

7.3.3. Effect of Second Shell Residues

The effect of groups outside the immediate coordination shell of the iron is investigated on a larger cluster model in which ethanol, 1-methyl guanidium, methanol, methyl amine, methyl ammonia groups are added to represent Thr120, Arg124, Ser125,

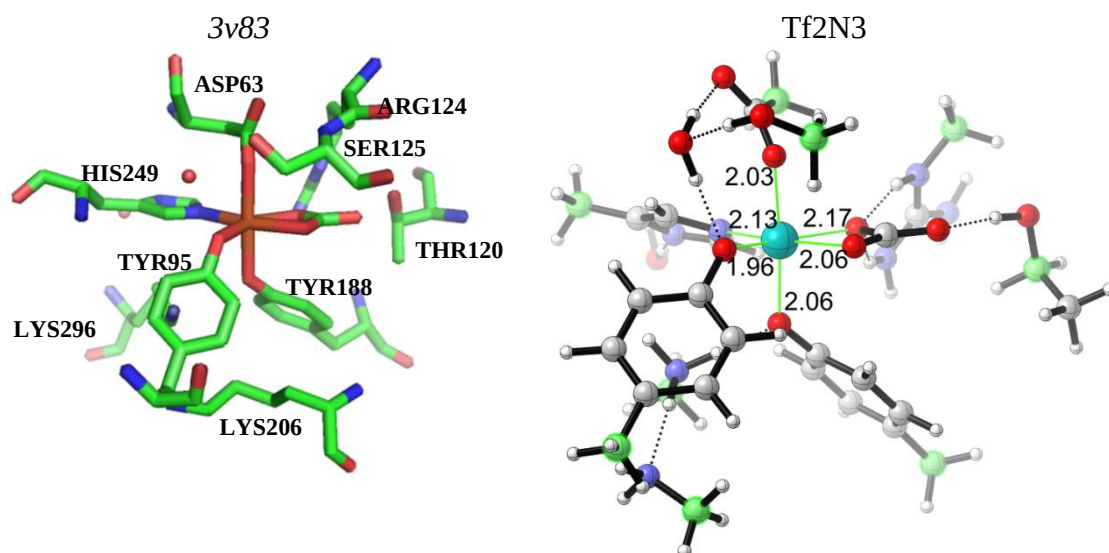


Figure 7.6. The iron binding site of N-lobe of transferrin (3v83) including the first and the second sphere ligands (left) and its optimized structure (Tf2N3, right).

The truncated atoms are frozen and highlighted in green.

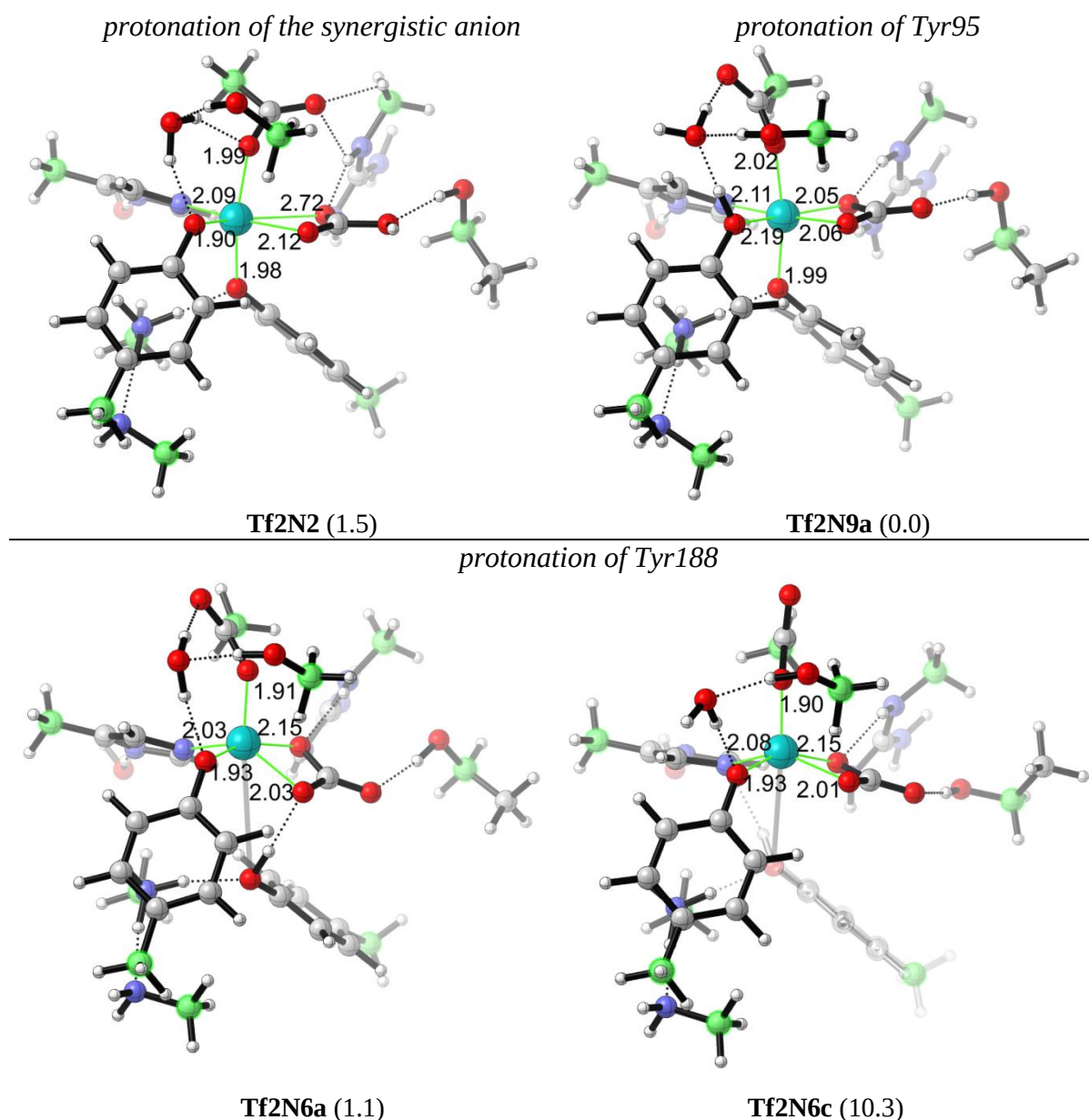


Figure 7.7. The complexes associated with the protonation of each residue in Tf2N3 and their relative free energies (kcal/mol).

The truncated atoms are frozen and highlighted in green.

Lys206 and Lys296 respectively and two water molecules are included: one in close proximity to His249 and one playing a bridge role between Tyr95 and Ser125 (Figure 7.6). The ammonia corresponding to Lys296 is protonated whereas that corresponding to Lys206 is not, in agreement with the predictions of pK_a calculations [144]. The iron-ligand distances remain similar to those of TfN3 (Figure 7.3) including only the first solvation

shell of iron. The all-atom RMSD value of Tf2N3 is 0.49 close to that of TfN3 (0.50) showing the appropriateness of the models chosen.

The protonation of each residue in Tf2N3 in the presence of the second solvation shell (Figure 7.7) does not change the geometries much with respect to that of TfN3 including first solvation shell only. To this end, we were able to model the complexes of the protonated synergistic anion (Tf2N2), Tyr95 (Tf2N9a) and Tyr188 (Tf2N6a and Tf2N6c). The monodentate coordination of the synergistic anion upon its protonation is still observed in the presence of Arg124 (Tf2N2) though with a shorter Fe-O¹ of bicarbonate distance (2.72 Å). The protonation of Tyr95 (Tf2N9a) leads to the thermodynamically stable complex with the octahedral coordination around iron preserved. This complex is energetically followed by the complex formed through the protonation of Tyr188 (Tf2N6a), however, the departure of the protonated residue from the coordination shell of iron is observed.

7.4. Conclusions

The optimum model for the iron binding site of transferrin is chosen on the basis of the RMSD values of the complexes modeled with various protonation states of the coordinating ligands around iron. The model in which all of the coordinating ligands are in their deprotonated states is evaluated as the representative of the iron binding site of transferrin at the physiological pH. Each of the coordinating ligands in this model complex is protonated to study the release of iron upon acidification in the absence and presence of the second shell residues. The protonation of the axial tyrosine leading to thermodynamically stable complexes is evaluated as the possible route for the release of iron. The complex in which equatorial tyrosine is protonated is also thermodynamically stable, however, formation of this complex in the presence of the second shell residues is not supposed to be relevant. The study of the protonated complexes in the presence of the second shell residues is currently in progress.

7.5. Future Work

N and C-lobes of transferrin are structurally similar; however, the rate at which they release iron is different from each other. The difference in the release rates was attributed to the nature of the second shell residues in the two lobes as mentioned earlier. In order to highlight the different release rates of iron in the two lobes and the effect of the second shell residues on the release mechanism, the iron binding site of the C-lobe of transferrin including the second solvation shell will be modeled.

8. CONCLUDING REMARKS

This dissertation presents different examples which span over rather different areas of chemistry including either ground or excited state topics. In particular, the use of silafluorene and silole phenylene-divinylenes as chemical sensors for explosives detection based on the fluorescence quenching technique upon the formation of complexes between the polymer and the analyte is investigated. The nature of the interactions is analyzed as these polymers form complexes with the target molecules, namely nitro containing explosive materials. The results pointed out the importance of the bridging phenylene-divinylene moiety in these polymers for the ease of charge transfer during the fluorescence quenching process. The spectra of the complexes are simulated and the fluorescence quenching mechanism is highlighted as the charge transfer from the bridge of the polymer to the analyte. These results are supposed to contribute to the field to design new polymeric materials with improved properties as chemical sensors.

We described the mechanism and enantioselective catalytic activity of cinchona alkaloids in the asymmetric desymmetrization of *meso*-cyclic anhydrides. Among the two proposed mechanisms, nucleophilic and general base catalysis, our results confirmed the feasibility of the latter mechanism. The enantioselectivity is shown to arise from the extent of stabilization of the transition states by cinchona alkaloid catalysts acting as bases in this mechanistic pathway.

Our calculations highlighted the catalytic effect of Ag(I)-bipyridine in the inverse electron demand Diels-Alder reaction of phthalazine and siloxy alkyne. Ag(I)-bipyridine through its coordination lowers the LUMO of phthalazine facilitating the charge transfer between the reactant partners. The mechanism of this reaction is still under investigation.

Finally, the iron binding-release mechanism is quantum mechanically investigated in the cluster model of iron binding protein, transferrin. The model for iron bound form of transferrin is evaluated on the basis of the RMSD values and then the release of iron in this

model is studied. Possible routes for iron release upon acidification are evaluated in terms of the thermodynamic stabilities of the models.

Overall, throughout this dissertation we tried to address specific problems including the mechanisms, the selectivity and the effect of catalysts in some specific organic reactions and in the polymer or protein environment. The detailed conclusions related with the specific problems are drawn within the relevant chapters. Standard quantum mechanical methods have been employed in the study of organic reactions to simulate the behavior of molecular systems. The calculations helped to rationalize the experimental data and to investigate various mechanistic hypotheses.

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