

A COMPUTATIONAL ANALYSIS OF SOLVENT EFFECT: THIOL-ENE
REACTIONS AND CaO BOND STRENGTH WITHIN HYDRATED CALCIUM
CLUSTERS

by

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ABSTRACT

A COMPUTATIONAL ANALYSIS OF SOLVENT EFFECT: THIOL-ENE REACTIONS AND CaO BOND STRENGTH WITHIN HYDRATED CALCIUM CLUSTERS

In the first part this thesis, the solvent effect on thiol-ene reaction kinetics is elucidated. The effect of polar media on the reaction kinetics is taken into account by using the transition state theory, the reactivities of the carbon and sulfur radicals have also been rationalized by using conceptual DFT. The results have shown that the solvents have more impact on hydrogen atom transfer reactions and the chain transfer rate constant, k_{CT} , can be increased by using non-polar solvents, while propagation reactions are less sensitive to media. Similarly, the k_P/k_{CT} ratio can be manipulated by changing the environment in order to obtain tailor-made polymers. Regarding the DFT descriptors, the local and global electrophilicity indices are well correlated with the propagation rate constant k_P , whereas global electrophilicity index is associated with the chain transfer rate constant k_{CT} . Overall, electrophilicity indices can be used with confidence to predict the kinetics of thiol-ene reactions.

In the second part, the solvent effect on hydrated calcium clusters are investigated. Calcium ions have significant role on biochemical processes, which makes the enlightenment of hydration of calcium ion crucial. The most stable form of calcium clusters is determined by using vibrational spectroscopy. DFT is used for structural optimizations and local mode analysis (LMA) is utilized in order to obtain the force constants of Ca-O bonds in vacuum and water environment. Bond strength orders are calculated for each bond, and it is concluded that CN of 6 is preferred in aqueous solutions, whereas the bonds get weaker as the cluster size increases in gas phase.

ÖZET

TİYOL-EN REAKSİYONLARINDA ve HİDRATLANMIŞ KALSİYUM KÜMELERİNİN CaO BAĞ KUVVETİNDE ÇÖZÜCÜ ETKİSİNİN HESAPSAL ANALİZİ

Bu tezin ilk bölümünde, çözücü etkisinin tiyol-en reaksiyon kinetiğine etkisi geçiş durum teorisi kullanılarak açıklanmaktadır. Aynı zamanda, karbon ve kükürt radikallerinin reaktiviteleri Yoğunluk Fonksiyonel Teorisi (DFT) kullanılarak hesaplanmaktadır. Sonuçlar, çözücü etkisinin hidrojen atom transferine ilerleme reaksiyonlarına oranla daha belirgin olduğunu göstermektedir. Böylelikle k_P/k_{CT} oranının çözücü değişimi ile kontrolü mümkün olmaktadır. Yoğunluk fonksiyonel teori tanımlayıcıları kullanılarak ilerleme reaksiyonlarının hızını lokal ve global elektrofilisite indeksi ile, zincir transfer reaksiyonlarının hızı ise global elektrofilisite ile açıklanabilmektedir.

Tezin ikinci bölümü hidratlanmış kalsiyum kümelerinde çözücü etkisi incelenmektedir. Kalsiyum iyonlarının biyolojik faaliyetleri rolü sebebiyle hidrat kümelerinin koordinasyon sayılarının öğrenilmesi büyük bir önem taşımaktadır. Bu sebeple Yoğunluk Fonksiyonel Teorisi (DFT) ile optimize edilen yapıların Ca-O bağlarının kuvvet katsayıları gaz ve su ortamında Yerel Mod Analizi (LMA) ile hesaplanmaktadır. Gaz ortamında kompleksin büyüdükçe Ca-O bağlarının zayıfladığı, sulu ortamda ise en kararlı bileşiğin koordinasyon sayısının 6 olduğu tespit edilmiştir.

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LIST OF SYMBOLS

E_{el}	Electronic energy
$E_c[\rho]$	Correlation energy
$E_x[\rho]$	Exchange energy
H	Hamiltonian Operator
h_{KS}	Kohn-Sham Hamiltonian Operator
$J[\rho(r)]$	Coulomb energy
$T[\rho(r)]$	Kinetic energy of interacting electrons
$T_{ni}[\rho(r)]$	Kinetic energy of non-interacting Electrons
$V_{ext}(r)$	External potential
$V_{ee}[\rho(r)]$	Electron-electron interactions
Z	Atomic number
$\Delta H^\ddagger$	Enthalpy of activation
ΔH^o_{rxn}	Enthalpy of reaction
$\Delta G^\ddagger$	Gibbs free energy of activation
ΔG^o_{rxn}	Gibbs free energy of reaction
$\Delta G_{solvation}$	Solvation free energy
k^a	Local stretching force constant
$\rho(r)$	Electron Density
$H(r)$	Energy Density
ψ_i	Kohn-Sham Orbitals
Ψ	Wavefunction

LIST OF ACRONYMS/ABBREVIATIONS

BSO	Bond Strength Order
BP	Bisphosphonate
BLYP	Becke-Lee-Yang-Parr functional
B3LYP	Becke 3-Parameter, Lee, Yang and Parr functional
C-PCM	Conductor-like polarizable continuum model
CN	Coordination Number
DFT	Density Functional Theory
GGA	Generalized Gradient Approximation
GTO	Gaussian Type Orbital
HAP	Hydroxyapatite
HF	Hartree-Fock theory
IEF-PCM	Integral equation formalism polarizable continuum model
IRMPD	Infrared multiple photon dissociation spectroscopy
LC	Long-range Corrected
LCAO	Linear Combination of Atomic Orbitals
LDA	Local Density Approximation
LMA	Local Mode Analysis
MD	Molecular Dynamics
M06-2X	Hybrid meta exchange-correlation functional
NBO	Natural bond orbital analysis
PCM	Polarizable Continuum Model
STO	Slater Type Orbital
TS	Transition State
XC	Exchange-Correlation
ω B97xD	Long-Range Corrected Hybrid Functional with Dispersion Correction

1. INTRODUCTION

This thesis consists of solvent effects on click reactions and on the coordinations of hydrated metal cations by employing the most widely used quantum chemical method, Density Functional Theory (DFT).

In the first part, solvent effect on thiol-ene click reactions are elucidated. The concept of “click chemistry” has attracted attention in the organic synthesis or polymer field due to the philosophy behind this chemistry technique for a long time. It is a common knowledge that carbon-heteroatom bonds (C-X-C) are preferred over carbon-carbon bonds in nature’s chemistry. The building blocks of organisms, nucleic acids, proteins and polysaccharides are the polymers that are combined by carbon-heteroatom bonds. On this basis, ”click chemistry” is developed to acquire reliable and high selective reactions [3]. The main purpose of click reactions is to synthesize polymers of high yields with mild reaction conditions and wide range of functional groups [4]. Moreover, the reactions are highly efficient [5], rapid, insensitive to O₂, [1] and non-chromatographic purification is adequate to purify the few harmless byproducts [6]. Thiol-ene reaction is one of the best known click chemistry that initially focused on photo-curable polymers to generate protective coatings and films, since photoinduced polymerizations are rapid and thiols are induced in mild conditions [1].

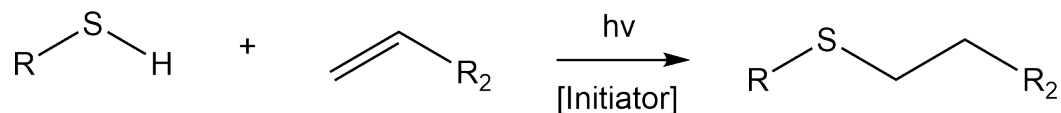


Figure 1.1. Photo-initiated thiol-ene click chemistry [1].

Although solvent usage is undesirable in the area of click chemistry [7–9], Sharpless stated that solvents usually play a critical role on click reactions [3]. It is found

that the rates of Diels-Alder reactions can be increased with the addition of water compared to addition of organic solvents. Hydrophobic aggregates are produced because of the repulsive interactions between hydrophobic species due to the solvation of water. Surface area contact between aggregates and water decreases, thus the reaction accelerates [10]. Sharpless claimed that the click reactions in water are faster than the reactions in organic solvent and explained them with following five factors: First, when organic molecules are poorly solvated in water, their free energies increase, which resulted in increased reactivity. Second, water is the best candidate for reversible carbonyl chemistry because H-bond formation arises as the solvents that can form H-bond prefer nucleophile addition to epoxide and aziridine electrophiles. Third, the use of water on alkene and acetylene click reactions can alter the reactivities of competing "hard" (non-polarizable) and "soft" (polarizable) species. Forth, as the Schotten-Baumann method indicates, a highly favorable reaction is usually faster than low driving force side reaction in solvent water. Fifth, due to water's high heat capacity, it is considered as a great heat sink, which is useful for large-scale processes [3].

In the second part, the solvent effect on hydrated calcium ion is investigated. Calcium (Ca) is the most abundant cation in human body [11] and its ions play important roles in biochemical processes, such as blood coagulation [12], neurotransmission [13], bone formation [14–16], cell division, metabolic control, hormonal activities [17] and muscle contraction [18]. For example, in order to induce muscle contraction, the concentration of free calcium ions within a muscle cell must be in the range of 10^{-6} to 10^{-7} M. Intracellular calcium concentrations are controlled by ion exchange of cells by the use of ATP. Hydrated calcium ions bind to regulating proteins by converting them into semi-hydrated complexes. Studying the hydration and dehydration of calcium ions with water molecules is important to elucidate the ligand exchange reactions [18].

Furthermore, calcium is the major mineral component of the skeletal system as a bivalent metal ion in the form of hydroxyapatite (HAP). The HAP, having the general formula of $\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6$, is similar to the inorganic component of bone matrix, therefore synthetic HAP is used as bone substitutes or replacement agents

in biomedicine [16]. Functional polymers such as HAEPA, EAEPA and MAEPA are synthesized to enhance chemical bonding to calcium of HAP in order to provide dental adhesive systems [19]. Moreover, bisphosphonates (BPs) are synthetic molecules that bind specifically to bone structures, HAP and bone powder. Treatment of osteoporosis, skeletal disorders, as well as usage in bone-imaging are the medical applications of BPs due to their affinity to HAP [20, 21].

1.1. Aim of the Study

In the first part of this thesis, the effect of solvents on thiol-ene click reactions is investigated. Eleven propagation and chain transfer reactions and eight different hydrogen atom transfer reactions are selected in order to elucidate the impact of solvents on the kinetics and on the k_P/k_{CT} ratio. The manipulation of k_P/k_{CT} ratio by polarity differences and by changing the substituents on reactants is carried out in order to obtain tailor-made polymers. Moreover, indices have been selected to determine the best correlated descriptor with propagation and chain transfer rate constants.

In the second part, the first shell of calcium-water clusters is modeled in vacuum and water environment to determine their structures. $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ clusters with $n=1-8$ are optimized by using DFT and the force constants of Ca-O bonds are analyzed by using Local Mode Analysis (LMA). Bond strength orders are calculated to understand the stability of complexes. Determination of the stability of hydrated calcium clusters in aqueous media may be the first step of designing biological materials that will coordinate with calcium surfaces like HAP and bone tissue.

2. METHODOLOGY

2.1. Density Funtional Theory

Density Functional Theory (DFT) is one of the most widely utilized quantum chemistry method [22], which is proposed by Kohn and Sham in 1964 [23,24]. Hohenberg-Kohn Theorems suggested that the wavefunction is determined in the case the ground state density is known. By this theorem, the electronic structures of molecules can be calculated. Equation 2.1 defines the electron density ($\rho(r)$), where r_i represents the coordinates of the electrons:

$$\rho(r) : N \int \dots \int |\Psi(r_1, r_2, \dots r_n)|^2 dr_1 dr_2 \dots dr_n \quad (2.1)$$

where r_i represents the coordinates of electrons. The second theorem of Hohenberg and Kohn computes the ground state energy by introducing the variational principle. Equation 2.2 describes the ground state electronic energy as functional electron density since the minimized total energy is identified as ground state density [25]:

$$E[\rho(r)] = \int V(r)\rho(r)dr + T[\rho(r)] + V_{ee}[\rho(r)] \quad (2.2)$$

where, $T[\rho(r)]$ represents the kinetic energy of interacting electrons and $V_{ee}[\rho(r)]$ stands for the interelectronic interaction energy. Equation 2.2 can be rewritten as Equation 2.3 because the concept for non-interacting electrons has been introduced by Kohn and Sham:

$$E[\rho(r)] = \int V(r)\rho(r)d(r) + T_{ni}[\rho(r)] + J[\rho(r)] + E_{XC}[\rho(r)] \quad (2.3)$$

where, $T_{ni}[\rho(r)]$ is kinetic energy for non-interacting electrons, $E_{XC}[\rho(r)]$ is exchange-correlation energy functional and $J[\rho(r)]$ is the coulomb energy. The coulomb energy

between the motions of electrons is represented as Equation 2.4:

$$J[\rho(r)] = - \sum_{A=1}^M \int \frac{Z_A}{|r - R_A|} \rho(r) dr + \int \frac{\rho(r_1)\rho(r_2)}{|r_1 - r_2|} dr_1 dr_2 \quad (2.4)$$

in which M stands for the total number of nuclei. The exchange-correlation energy functional $E_{XC}[\rho(r)]$ designated in Equation 2.3 is the sum of exchange functional ($E_X[\rho]$) and correlation functional ($E_C[\rho]$), which defines extra freedom to an electron, shown in Equation 2.5.

$$E_{XC}[\rho(r)] = \int \rho(r) \epsilon_{XC}(\rho(r)) dr \quad (2.5)$$

Equation 2.6 is derived from the derivative of Equation 2.5 with respect to the electron density:

$$V_{XC}[\rho(r)] = \rho(r) \frac{d\epsilon_{XC}(\rho(r))}{d\rho(r)} + \epsilon_{XC}(\rho(r)) \quad (2.6)$$

Kohn-Sham orbitals, which are the independent orbitals (ψ_i) of density functional theory are designated as follows:

$$h_{KS}\psi_i = \varepsilon_i\psi_i \quad (2.7)$$

where the h_{KS} is the Hamiltonian operator, expressed as follows:

$$h_{KS} = -\frac{\nabla^2}{2} - \sum_{A=1}^N \frac{Z_A}{|r - R_A|} + \int \frac{\rho(r_1)\rho(r_2)}{|r_1 - r_2|} V_{XC}[\rho(r)] \quad (2.8)$$

in which $V_{XC}[\rho(r)]$ is the exchange correlation potential associated with the exchange correlation energy defined in Equation 2.6. The exact density of Kohn-Sham orbitals can be generated from the exact form of the exchange-correlation functional, repre-

sented as:

$$\rho(r) = \sum_{i=1}^N |\psi_i|^2 \quad (2.9)$$

On the other hand, the exact forms of exchange-correlation functionals are not known, therefore functionals are used to represent the approximations to obtain the exchange-correlation functional.

2.2. Functionals

In order to attain the exact form of exchange-correlation functional, different approximations have been applied as DFT has developed. Local Density Approximation (LDA) is the one of the approximation to form the base of the exchange-correlation functionals. LDA assumes the electron density of a system as a uniform electron gas and the electrostatic energy of the positivity, E_b is added to make the system neutral by the following equation:

$$E[\rho] = T_{ni}[\rho] + \int \rho(r)v(r)dr + J[\rho] + E_{xc}[\rho] + E_b \quad (2.10)$$

Equation 2.10 can be reduced due to the equivalence of electron density and positive charge density as follows:

$$E[\rho] = T_{ni}[\rho] + E_{xc}[\rho] \quad (2.11)$$

where E_{xc} is defined as an exchange functional and a correlation functional. The equation 2.11 can be rewritten as follows:

$$E[\rho] = T_{ni}[\rho] + E_x[\rho] + E_c[\rho] \quad (2.12)$$

where $T_{ni}[\rho]$ is the kinetic energy functional, defined as:

$$T_{ni}[\rho] = C_F \int \rho(r)^{5/3} dr \quad (2.13)$$

within C_F is being constant equal to 2.8712. The exchange functional can be found by using the following equation:

$$E_x[\rho] = -C_x \int \rho(r)^{4/3} dr \quad (2.14)$$

where C_x constant is equal to 0.7386. Since the electron density varies in a molecule, LDA is not suitable to determine the exact form of the exchange-correlation functional.

Generalized gradient approximation (GGA) method is developed to overcome this issue. According to GGA, the electron density of the system is considered as non-homogenous nature by assuming the exchange and correlation energies to depend on density gradient, defined as:

$$E_{XC}^{GGA}[n] = \int dr n(r) \epsilon_{XC}(n(r), |\nabla n(r)|) \quad (2.15)$$

Hybrid density functional methods are alternative approaches that combine the GGA method with Hartree-Fock (HF) exchange. One of the well-known functional is M06-2X [26], Minnesota 06 generation, based on meta-GGA approximations and double amount of non-local exchange (2X). According to Zhao *et al.*, M06-2X functional improves the calculation of atomization energies, ionization potentials, electron and proton affinities [26]. Moreover, it is used for the calculation of alkyl-bond dissociation energies, proton affinities of conjugates π systems, binding energies of a Lewis acid-base complex and heavy atom transfer barrier heights [27]. The hybrid-change correlation is illustrated as:

$$E_{XC}^{hyb} = \frac{X}{100} E_X^{HF} + (1 - \frac{X}{100}) E_X^{DFT} + E_C^{DFT} \quad (2.16)$$

where X stands for the percentage of Hartree-Fock exchange, it is taken as 54 in the case of M06-2X functional [26].

An alternative approach is the hybrid density functional methods which is a combination of the GGA method with a percentage of Hartree-Fock (HF) exchange. These functionals add the exact exchange calculated through HF functional to DFT exchange and correlation. The most well-known one is B3LYP [24]. It has the form of a mixture of LDA and GGA functionals as illustrated:

$$E_{XC}^{B3LYP} = (1 - a)E_X^{LSDA} + aE_X^{HF} + b\Delta E_X^B + (1 - c)E_C^{LSDA} + cE_C^{LYP} \quad (2.17)$$

where the empirical coefficients are determined to be 0.20, 0.72 and 0.81, respectively.

Long-range corrected (LC) hybrid density functionals are other alternative approaches with 100% HF exchange for long-range electron-electron interactions. ω B97XD [28] is one of the important long-range hybrid functional that employs small fraction of short-range exact exchange. The long range correction improves the features like long-chain polarizability, charge-transfer excitations, optical properties and dissociation of two-centered three electrons bonds [29]. Long range corrected hybrid of a density functional theory approximation (LCDFA) is defined as:

$$E_{XC}^{LCDFA} = E_X^{SR-DFA}(\omega) + E_X^{LR-HF}(\omega) + E_C^{DFA} \quad (2.18)$$

2.3. Basis Sets

Basis sets are described by Slater as orbitals within a system as a set of functions and they are defined to solve the Schrödinger Equation [30]. Basis functions are expanded as linear combination of atomic orbitals (LCAO) with different coefficients as

shown in the following equation:

$$\phi_i = \sum_{\mu=1}^K c_{\mu i} f_{\mu} \quad (2.19)$$

in which i is the number of molecular orbitals, f_{μ} is the number of atomic orbitals, $c_{\mu i}$ being the coefficients and K is being the total number of atomic orbital functions.

Basis sets consist of two major groups: Slater-type Orbitals (STOs) and Gaussian-type Orbitals (GTOs). Even though STOs are more accurate, the high expenses make GTOs preferred over STOs. Slater-type orbitals give the solution to Schrödinger equation for hydrogen-atoms. On the other hand, Gaussian-type orbitals are approximated types of STOs.

Pople developed split-valance basis set method in order to decrease the computational cost. The core and valance orbitals are treated differently by this method. It is known that core electrons are affected less than valance electron by chemical environment, therefore only one basis function is used for each core and larger basis is used for the valance atomic orbitals.

In an effort to get better approximation to the exact electronic energy, basis sets are modified by utilizing two functions, which are polarization and diffuse functions. Polarization functions add higher angular momentum orbital to heavy atoms symbolized by one asteriks * or (d), on the other hand, two asteriks ** or (d,p) are used to include the polarization of light atoms like hydrogen and helium. In addition, diffuse functions allow orbitals to occupy larger spaces. They are represented as plus signs: one plus sign "+" implies the diffuse function addition for heavy atoms and two plus signs "++" indicates the addition of diffuse functions for hydrogen atoms.

2.4. Continuum Solvation Model

In quantum chemical calculations, considering the solvent environment provides a more realistic simulations for systems. Solvent models can be constituted either implicitly or explicitly. In explicit solvent models, discrete numbers of solvent molecules are added into the model explicitly. On the other hand, implicit solvent models describe a continuum solvation model. It is known that these models are the most efficient way to include condensed-phase effect to quantum chemical calculations. Implicit solvation model takes different physical effects into consideration that contribute to overall solvation process. The total solvation free energy is described as:

$$\Delta G_{solvation} = \Delta G_{cavity} + \Delta G_{dispersion} + \Delta G_{electrostatic} + \Delta G_{repulsion} \quad (2.20)$$

where ΔG_{cavity} is the energy of solute addition to system, $\Delta G_{dispersion}$ is dispersion interactions between solute and solvent, which gives stabilization to system. $\Delta G_{electrostatic}$ is the electrostatic interactions energy between solute and solvent and $\Delta G_{repulsion}$ is the exchange solute-solvent interactions that is not considered in the energy of cavitation.

Polarizable Continuum Model (PCM) is one of the polarizable continuum solvation model defined by Tomasi *et al.* [31]. PCM describes the solvent as homogeneous, dielectric continuum rather than individual molecules. The solute is placed into the cavity of solvent medium and exposed to reaction field of solvent. This approach distinguishes solute from solvent and provides modeling with bulk solvation effects [32]. PCM has 3 major approaches, such as Dielectric PCM (D-PCM), Conductor-like PCM (C-PCM) and Integral Equation Formalism of PCM (IEF-PCM). D-PCM is the first PCM model that developed [33]. C-PCM considers the surrounding medium as a conductor rather than dielectric and the third model IEF-PCM is the revision of PCM by using integral formalism variant [34,35]. The C-PCM and IEF-PCM methods are used in this thesis.

3. SOLVENT EFFECT ON THIOL-ENE REACTIONS

3.1. Background

Thiol-ene chemistry, which is found by Posner in 1905 [36] is the one of the most important click reactions [37]. Thiol-ene reactions have come to forefront due to the anti-Markovnikov addition mechanism and the formation of carbon-sulfur bond, which is present in natural products and drug molecules [38]. Thiol-ene chemistry is widely used in polymer chemistry [39,40], material chemistry [41,42], drug delivery systems [43], dendrimer chemistry [5,44], disaccharides [45] and bioconjugate chemistry [46,47]. Some areas of bioconjugate chemistry prefer thiol-ene chemistry over copper-catalyzed alkyne-azide click chemistry (CuAAC)² [1], since it does not involve the usage of potentially toxic metal catalysts. Hence, the reactions are environmentally friendly [40,48].

Radical-catalyzed thiol-ene click reactions involve three steps; initiation, propagation and chain transfer, displayed in Figure 3.1. In the initiation step, a hydrogen atom is abstracted from thiol in order to form a thiyl radical by photochemical or thermal initiation under mild reaction conditions. It is claimed that photochemical initiation is more efficient and requires shorter reaction time than thermal initiation [39]. In the propagation step, a carbon-centered radical intermediate is generated by the addition reaction of thiyl radical to alkene substrate by following the anti-Markovnikov rule [49]. Thereafter, the resulted carbon-centered radical intermediate can follow either homopolymerization or chain transfer. In homopolymerization, the carbon-centered radical intermediate attacks to an alkene substrate (chain-growth). On the other hand, the chain transfer step consists of the hydrogen abstraction of carbon-centered radical intermediate from another thiol, resulting in the formation of thioether and a new thiyl radical. The new thiyl can initiate another propagation step. The chain transfer step terminates the polymerization (step growth). The pathway is determined by the relative rates of propagation and chain transfer steps and based on

this preference, the nature of the product varies [1, 49].

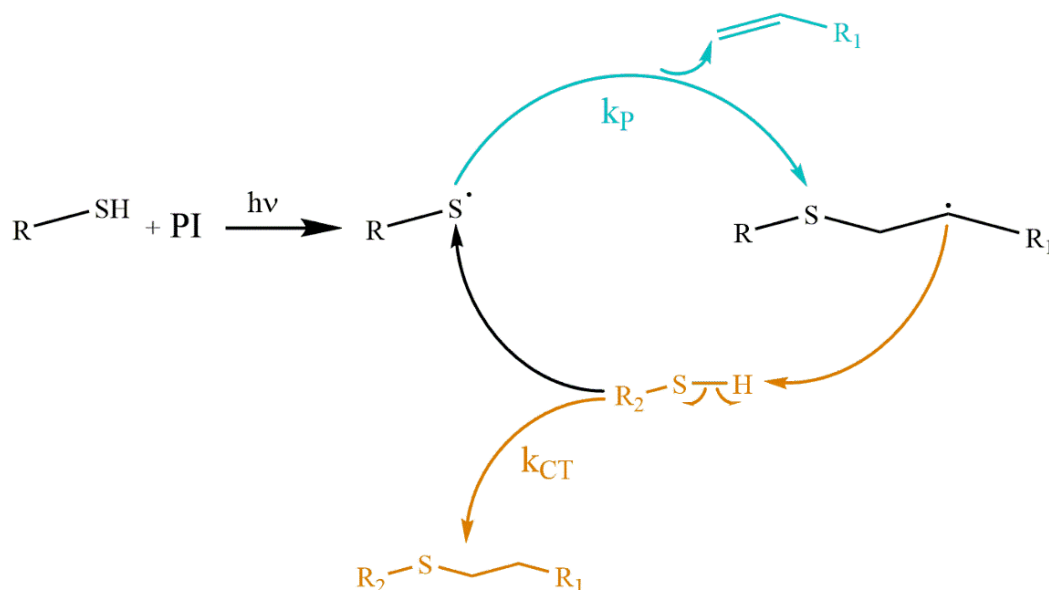


Figure 3.1. Thiol-ene reaction mechanism [1].

The ratio of propagation rate constant (k_P) to chain transfer rate constant (k_{CT}) determines the thiol-ene reaction mechanism and reaction kinetics [49]. By the manipulation of k_P/k_{CT} ratio, tailor-made polymers can be obtained. When the propagation rate constant is larger than chain transfer rate constant ($k_P \gg k_{CT}$), the high k_P/k_{CT} ratio indicates the chain transfer step is rate limiting step. The overall reaction rate is first order with respect to thiol functional group concentration and the reaction rate is not correlated with the ene functional group concentration. Similarly, in the case of higher chain transfer rate constant than propagation rate constant ($k_P \ll k_{CT}$), the low k_P/k_{CT} ratio indicates the rate limiting step as propagation step. The reaction rate is first order with respect to ene functional group concentration and is independent on the thiol functional group. When propagation rate constant is equal to chain transfer rate constant ($k_P \approx k_{CT}$), the overall reaction rate is determined by half order thiol functional group concentration and half order ene functional group concentration, shown in Figure 3.2 [1, 49].

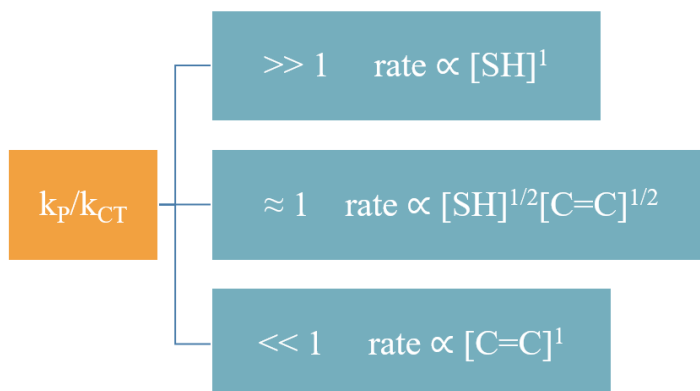


Figure 3.2. The ratio of propagation rate constant (k_P) to chain transfer rate constant (k_{CT}) [1].

Previous studies report on the contribution of alkene, carbon-centered radical [1, 49, 50] and thiol functionalities [51] on thiol-ene reactions kinetics in vacuum environment. It has been claimed that electron density of alkenes is an important aspect on overall thiol-ene reaction rates, because electron-rich enes react faster than electron-poor enes [51, 52]. Therefore, alkene functionality and the stability of carbon-centered radical have crucial roles on the thiol-ene reaction kinetics. Similarly, the overall rate is expected to be dependent on the thiol functionality and the stability of sulfur-centered radical. Accordingly, the k_P/k_{CT} ratio can be altered by changing the substituents and their positions on thiol substituents and by modifying the alkene and thiol functionalities. Apart from the substituent effect, it is well known that, radical initiated reactions are greatly affected by solvent effects [53–55].

The effect of solvents on the thiol-ene polymerization has not been well elaborated yet. There are a few studies about the solvent effect on the thiol-ene polymerization [56, 57]. Therefore, in this study, we aim to investigate the effect of solvents on thiol-ene click reaction kinetics. The reactions studied by Findik *et al.* [51] have been chosen to evaluate the solvent effect since the set of reactions chosen includes various alkene and

thiol functionalities. The first part of this study focuses on modeling the propagation and chain transfer reaction steps of 11 different reactions shown in Figure 3.3 and eight hydrogen atom transfer reactions shown in Figure 3.4 by using Density Functional Theory (DFT) in vacuum and in solution. For this purpose, the implicit solvation model is used, two solvents have been selected because of their polarity differences such as dichloromethane (DCM, $\epsilon=8.93$) [58] and water ($\epsilon=78.36$) [59]. Moreover, the reactivities of carbon and sulfur radicals are predicted by the use of descriptors and the results have been correlated with the transition state theory analysis.

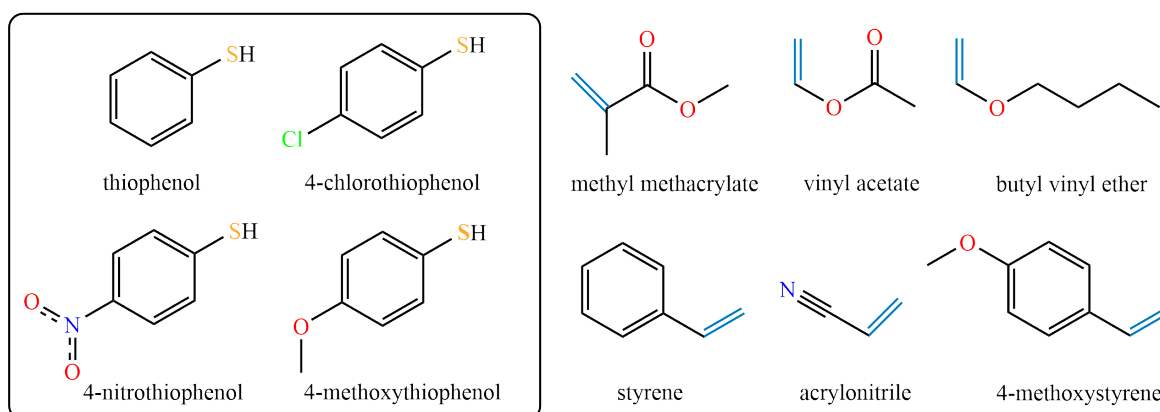


Figure 3.3. Chemical structures of thiols (in frame) and alkenes used to study the solvent effect on propagation and chain transfer steps of thiol-ene reactions.

The studies on hydrogen atom transfer reactions has shown that solvents have significant effect on reaction kinetics [55,60,61]. Therefore, in this dissertation, various hydrogen atom transfer reactions, which are displayed in Figure 3.4 are modeled in vacuum and non-polar solvents and the reactivity of thiyl radical and hydroxyl radical is studied in non-polar environment.

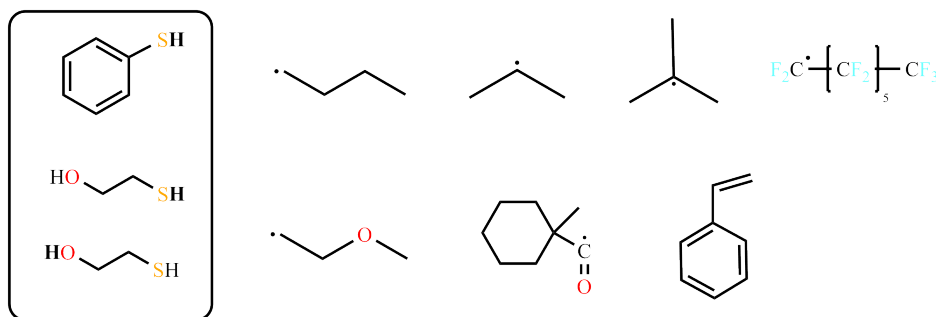


Figure 3.4. Chemical structures of hydrogen atom donors (in frame) and alkyl radicals used to study the solvent effect of hydrogen atom transfer reactions.

3.2. Computational Procedure

In this study, transition state analysis is carried out by using Density Functional Theory (DFT). All thermodynamic and kinetic calculations and conformer search on all reactants, transition states and products are performed within the Gaussian09 software package [62]. The optimizations take place at M06-2X meta-hybrid functional employing the 6-31++G(d,p) basis set. M06-2X/6-31++G(d,p) methodology has been used by Findik *et al.* in gas phase thiol-ene reactions, it has shown good agreement with experimental data and CBS-QB3 calculations [51]. Therefore, the same methodology has been chosen in order to perform geometry optimizations, conformational analysis, frequency calculations in vacuum and solvent environments.

Free energies are reported in kcal/mol at 1.0 atm. The geometry optimizations and conformational analysis of reactants, transition states and products are carried out in vacuum, then the structures are re-optimized in solvent environments. The conductor-like polarizable continuum model (C-PCM) is applied as implicit solvation model [34, 63, 64].

The Charge Model 5 (CM5) is used to analyze charge populations of carbon atoms and sulfur radicals of propagation step transition state geometries. The CM5 analysis is

based on partial atomic charges which are derived from Hirschfield population analysis [65].

The rate constants (k) are calculated by using Equation 3.1:

$$k(T) = \kappa(T) \frac{k_B T}{h} (c^\circ)^{1-m} e^{-\Delta G^\ddagger / RT} \quad (3.1)$$

where, $k(T)$ is reaction rate constant, $\kappa(T)$ is the tunneling correction (it has taken as 1 for propagation reactions), k_B is Boltzmann constant ($1.380658 \times 10^{-23} \text{ J K}^{-1}$), R is the universal gas constant ($8,314 \text{ J mol}^{-1} \text{ K}^{-1}$), T is the temperature, h is Planck's constant ($6.6260755 \times 10^{-34} \text{ J s}$), c° is the standard unit of concentration (mol L^{-1}), where ($n/V = P^\theta / RT$), m is the molecularity of the reaction and $\Delta G^\ddagger$ is the change in the Gibbs free energy between the activated complex and the reactants.

Wigner correction for tunneling [66] κ has been calculated for chain transfer reactions by using Equation 3.2:

$$\kappa(T) = 1 + \frac{1}{24} \left| \frac{h\omega^\ddagger}{k_B T} \right|^2 \quad (3.2)$$

where $\omega^\ddagger$ is the imaginary frequency of the transition states of chain transfer reactions, k_B is Boltzmann constant ($1.380658 \times 10^{-23} \text{ J K}^{-1}$), h is Planck's constant ($6.6260755 \times 10^{-34} \text{ J s}$), T (K) is the temperature.

The Bell-Evans-Polanyi (BEP) relation used is given by Equation 3.3:

$$E_a = E_0 + \alpha \Delta H_{rxn} \quad (3.3)$$

where E_a is activation energy, ΔH_{rxn} is the reaction enthalpy, α is slope and E_0 is the intercept.

The activation Energy (E_a) is calculated for bimolecular reaction in solution by

Equation 3.4:

$$E_a = E_0 + \Delta H^\ddagger + RT \quad (3.4)$$

where $\Delta H^\ddagger$ is the enthalpic activation barrier, R is the universal gas constant (8,314 J.mol⁻¹ K⁻¹), T (K) is the temperature.

DFT descriptors are used to characterize the reactivities of the sulfur and carbon centered radicals in thiol-ene reactions. For the descriptors, geometry optimizations were performed in the gas phase, DCM and water at the B3LYP/6-311+G(d,p) level of theory using the integral equation formalism (IEF-PCM). B3LYP/6-311+G(d,p) has been chosen because of its previous success on the calculation of the vertical ionization energies (IE) and electron affinities (EA) [67,68]. The geometries of the neutral radicals are used to calculate the energetics of the cations and the anions.

Global electrophilicity index ω [69] is calculated by Equation 3.5

$$\omega = \frac{\mu^2}{2\eta} \quad (3.5)$$

where μ is the electronic chemical potential [70] and η is the chemical hardness. [71]

The local electrophilicity index (ω^+_{rc}) [72] and the nucleophilicity index (ω^-) [73] are calculated according to Equations 3.6, 3.7, 3.8, respectively. The Fukui function for nucleophilic attack, $f^+(r)$ [74] makes use of ρ_{N+1} and ρ_{N_o} which are the atomic charges in cationic and neutral species condensed to radical centers respectively; the atomic populations with the NPA methodology has been used [74,75]. In Equation 3.8 A represents the nucleophile and B represents the electrophile. In this study, fluorine is chosen as an electrophile and the radicals as nucleophiles.

$$f^+(r) \approx \rho_{N+1}(r) - \rho_{N_o} \quad (3.6)$$

$$\omega_{rc}^+ = \omega f^+(r) \quad (3.7)$$

$$\omega^- = \frac{1}{2} \frac{(\mu_A - \mu_B)^2}{(\eta_A - \eta_B)^2} \eta_A \quad (3.8)$$

3.3. Solvent Effect on Propagation Step

In this dissertation, the factors that affect the rates of thiol-ene reactions described in Table 3.1 are investigated. The reactions are modeled in polar and non-polar solvents to elucidate their influences on the reactions of thiyl radicals and alkene derivatives.

Table 3.1. Propagation step reactions considered in this study.

Reaction	Radical	Alkene
1	$\text{C}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{CHPh}$
2	$\text{C}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{C}(\text{Me})\text{CO}_2\text{Me}$
3	$\text{C}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{CH}(\text{CN})$
4	$\text{C}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{CH}(\text{OBu})$
5	$\text{C}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{CH}(\text{OC}(\text{O})\text{Me})$
6	$p\text{-MeOC}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{C}(\text{Me})\text{CO}_2\text{Me}$
7	$p\text{-NO}_2\text{C}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{C}(\text{Me})\text{CO}_2\text{Me}$
8	$p\text{-ClC}_6\text{H}_5\text{S}\bullet$	$p\text{-MeO-PhCH}=\text{CH}_2$
9	$p\text{-ClC}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{C}(\text{Me})\text{CO}_2\text{Me}$
10	$p\text{-ClC}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{CH}(\text{OC}(\text{O})\text{Me})$
11	$p\text{-ClC}_6\text{H}_5\text{S}\bullet$	$\text{CH}_2=\text{CH}(\text{CN})$

Beuermann [76] stated that radical polymerization kinetics is influenced by the reaction medium. The propagation rates are affected differently by the reaction environment such as organic solvents, water, ionic liquids, etc. For example, solvents may cause hindering of rotational modes, hydrogen bonds and electron pair donor/acceptor

interactions [76]. Andrzejewska has demonstrated that for thiol-ene polymerizations, ionic liquid or non-ionic liquids environments can increase the reaction rate up to 2 times [56, 57].

In this study, based on the calculated Gibbs free energy activation barriers for propagation step ($\Delta G^\ddagger_P$), it can be observed that the polarity differences of solvents may cause fluctuations in reaction barriers shown in Table 3.2. The activation Gibbs energies of propagation step vary from 7.1 kcal/mol (8) to 13.3 kcal/mol (11) in vacuum, 7.1 kcal/mol (8) to 13.5 kcal/mol (6) in DCM and 7.1 kcal/mol (8) to 13.7 kcal/mol (6) in water (Table 3.3). Furthermore, the dipole moments of reactants increase as the solvent becomes more polar (Table 3.2).

The Gibbs free energy activation barriers ($\Delta G^\ddagger_P$) in the propagation step increase in water as compared to DCM except for reaction 4, which has the reactant butyl vinyl ether, less polar than the majority of the alkenes (Table 3.3). Even though the $\Delta G^\ddagger_P$ difference between the reactions in DCM and water is in the range of ± 0.4 kcal/mol, reactions 5 and 10, which have the same alkene, vinyl acetate and two distinct thiol radicals, phenylthio radical (5) and 4-chlorophenylthio radical (10), have $\Delta G^\ddagger_P$ differences of 1.6 kcal/mol and 2.5 kcal/mol respectively. Vinyl acetate may have been stabilized by water and the Gibbs free activation barrier may have increased. Styrene (1) is less polarized in solution (Table 3.2) and the solvent does not alter the barriers. Similarly, 4-methoxystyrene (8) has the same dipole moments both in DCM and water and the Gibbs free barriers of reaction 8 are not media dependent (Table 3.2, Table 3.3).

Table 3.2. Dipole moments, μ (D) of the alkenes in vacuum, DCM and water
(M06-2X/6-31++G(d,p)).

Reaction	Dipole Moment		
	Vacuum	DCM	Water
1	0.17	0.20	0.20
2	1.76	2.37	2.47
3	4.03	4.97	5.11
4	1.11	1.40	1.45
5	1.97	2.52	2.60
8	1.49	1.91	1.91

Table 3.3. Calculated activation barriers ($\Delta G^\ddagger_P, \Delta H^\ddagger_P$) and reaction energies ($\Delta G^o_P, \Delta H^o_P$) for propagation step in vacuum, DCM and water at 1.0 atm and 298.15 K (kcal/mol) (M06-2X/6-31++G(d,p)).

Reaction	Vacuum				DCM				Water			
	$\Delta G^\ddagger_P$	$\Delta H^\ddagger_P$	ΔG^o_P	ΔH^o_P	$\Delta G^\ddagger_P$	$\Delta H^\ddagger_P$	ΔG^o_P	ΔH^o_P	$\Delta G^\ddagger_P$	$\Delta H^\ddagger_P$	ΔG^o_P	ΔH^o_P
1	9.0	-3.8	0.2	-13.1	8.9	-3.3	0.5	-12.3	8.9	-3.3	0.7	-12.2
2	10.3	-1.6	0.4	-11.9	11.3	-0.9	1.4	-11.8	11.4	-0.8	1.1	-11.0
3	12.6	1.2	1.1	-9.7	12.9	2.0	2.1	-9.0	13.2	2.1	2.3	-8.9
4	9.2	-2.0	7.8	-4.6	10.2	-2.1	8.6	-3.3	9.8	-1.8	8.7	-3.2
5	12.7	-0.6	6.5	-7.6	11.9	0.5	6.0	-6.2	13.5	-0.1	7.6	-6.7
6	12.5	-0.6	3.0	-10.2	13.5	0.6	4.3	-8.7	13.7	0.9	4.4	-8.5
7	8.2	-3.6	-1.4	-13.8	8.7	-3.2	-1.4	-13.6	8.5	-3.2	-1.0	-13.6
8	7.1	-6.6	-0.7	-13.8	7.1	-6.0	-1.0	-13.6	7.1	-5.9	-0.9	-13.4
9	10.5	-2.2	0.9	-12.2	10.7	-1.5	0.9	-11.7	10.8	-1.5	1.0	-11.6
10	12.5	-1.0	6.2	-7.7	10.7	-2.0	4.2	-8.6	13.2	-0.5	6.7	-7.1
11	13.3	1.4	2.0	-9.3	12.8	2.0	2.3	-9.0	13.0	2.0	2.3	-8.9

The solvent influence on sulfur-centered radicals is traced with the correlation between C-S bond distances of the transition state geometries and their correlation with the enthalpy of propagation step shown in Table 3.5 and Figure 3.5. The formation of a σ (C-S) bond in the propagation step involves the attack of the thiyl radical to the alkene while breaking the π (C-C) bond. The C-S bond distances are well correlated with enthalpy in DCM ($R^2 = 0.92$) and water ($R^2 = 0.95$). The addition of phenylthio radical to the electron donating butyl vinyl ether (4), decelerates the reaction with the latest transition state both in DCM and water (C-S bond distance 2.25 Å) the heat evolved (ΔH_P°) is relatively small ($\Delta H_P^\circ = -9.0$ kcal/mol in DCM, $\Delta H_P^\circ = -8.9$ kcal/mol in water). On the other hand, the addition of the electron withdrawing 4-nitrophenylthio radical to methyl methacrylate (7) has the earliest transition state and the lowest reaction enthalpy (C-S bond distance 2.48 Å, $\Delta H_P^\circ = -13.6$ kcal/mol in DCM and water). The CM5 charges on the carbon atom and sulfur radicals on transition states as shown in Table 3.4, being almost equal in different media suggests the solvent effect to be negligible on the transition structures.

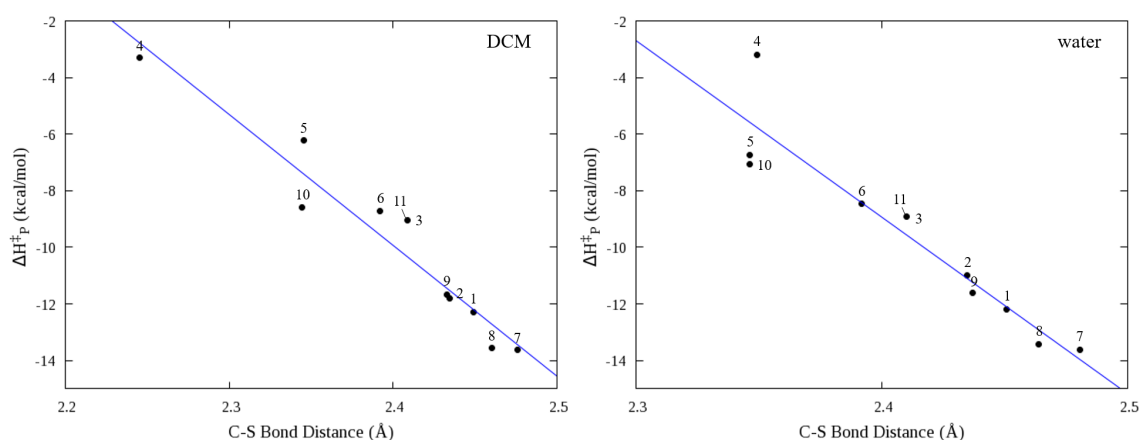


Figure 3.5. Correlation between ΔH_P° (kcal/mol) and the carbon-sulfur bond distances (Å) of propagation transition states in DCM ($R^2 = 0.92$) and water ($R^2 = 0.95$).

Table 3.4. CM5 charges of carbon and sulfur atoms of the propagation transition step geometries calculated in DCM and water (M06-2X/6-31++G(d,p)).

Reactions	DCM		Water	
	C	S	C	S
1	-0.14	-0.17	-0.14	-0.18
2	-0.13	-0.12	-0.13	-0.12
3	-0.11	-0.10	-0.11	-0.10
4	-0.16	-0.20	-0.16	-0.20
5	-0.15	-0.16	-0.15	-0.16
6	-0.13	-0.13	-0.13	-0.13
7	-0.13	-0.09	-0.13	-0.09
8	-0.15	-0.18	-0.15	-0.19
9	-0.13	-0.11	-0.13	-0.11
10	-0.15	-0.15	-0.15	-0.16
11	-0.11	-0.09	-0.11	-0.09

Table 3.5. Propagation step transition state geometries and bond distances ($\text{\AA}$) of carbon and sulfur atoms of 11 thiol-ene reactions (M06-2X/6-31++G(d,p)) in DCM and water.

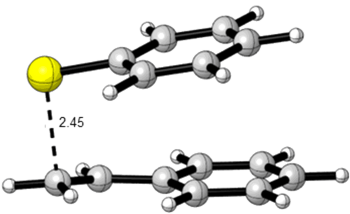
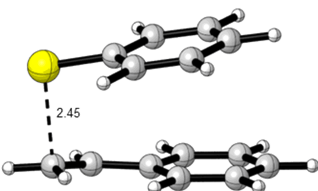
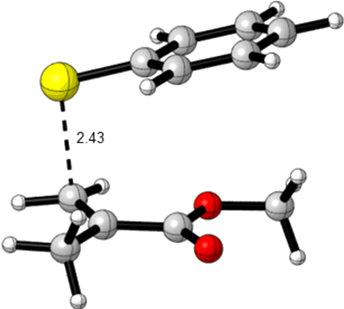
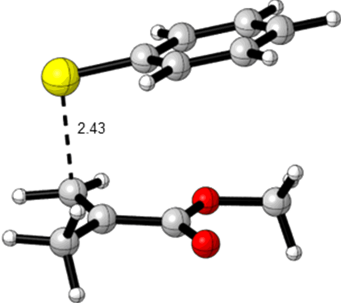
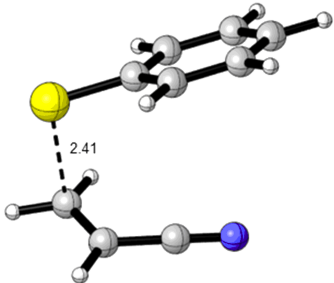
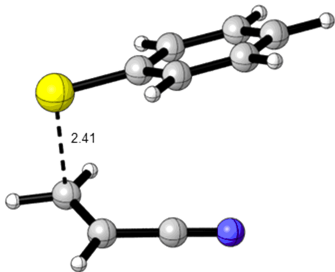
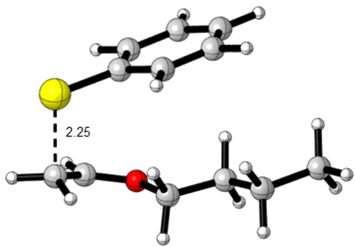
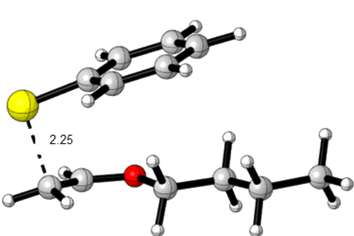
Reaction	DCM	Water
1		
2		
3		
4		

Table 3.5 Propagation step transition state geometries. (cont.)

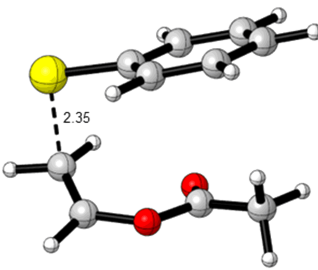
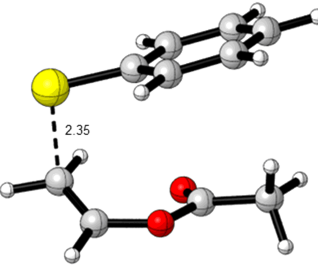
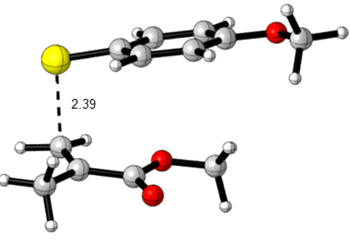
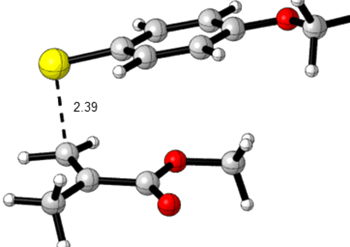
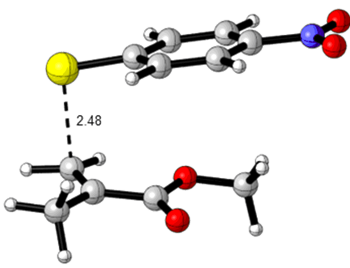
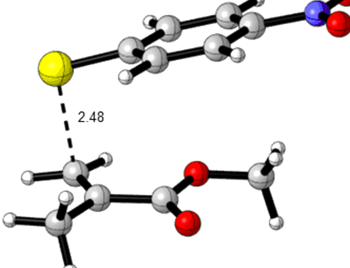
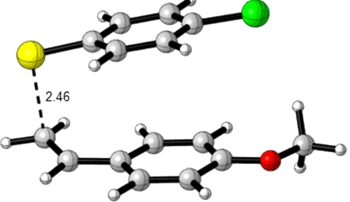
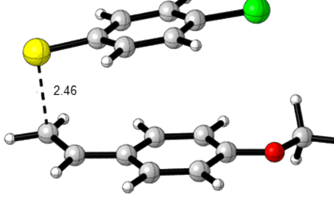
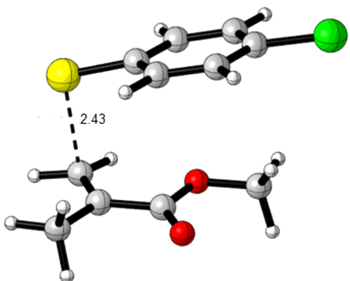
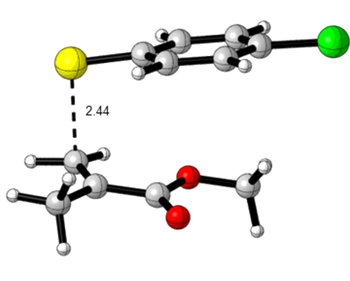
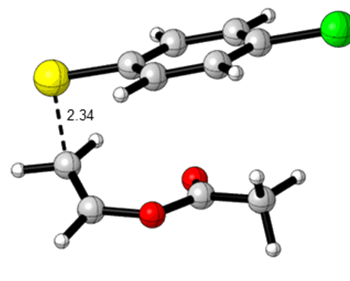
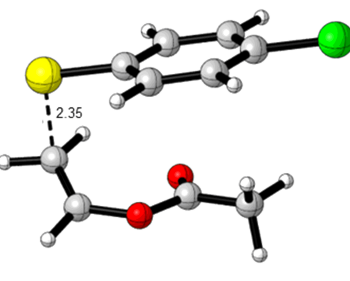
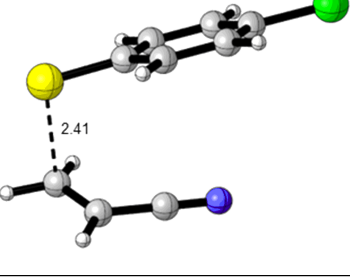
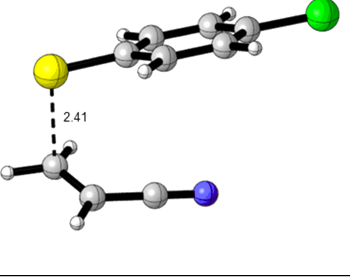
Reaction	DCM	Water
5		
6		
7		
8		

Table 3.5 Propagation step transition state geometries. (cont.)

Reaction	DCM	Water
9		
10		
11		

The singlet-triplet gap illustrates the π - π^* excitation energy of alkenes: it is known that alkenes with lower S-T energy gaps have lower energy barriers for propagation reactions because of the weaker π -bonds [77,78] shown in Figure 3.6. Reactions 1, 2, 3 and 8 which have electron withdrawing groups show high correlation between ΔG_P° and the S-T gap in DCM ($R^2 = 0.98$) and water ($R^2 = 0.99$). Butyl vinyl ether (4) and vinyl acetate (5) are the outliers and they differ from the other alkenes since they contain an electron donor oxygen atom next to the C=C double bond. 4-methoxystyrene (8) has the lowest S-T gap and lowest activation Gibbs free energy

barrier (ΔG^o_P) in DCM and water (S-T gap and ΔG^o_P are identical in both solvents 3.55 eV and 7.1 kcal/mol respectively). Acrylonitrile (3) has the highest S-T gap (4.01 eV in DCM and water) and the highest activation Gibbs free energy barrier (ΔG^o_P) (12.9 kcal/mol in DCM, 13.2 kcal/mol in water). Reaction 3 has lower barrier in DCM than water, due to stabilization of the electron withdrawing group (-CN) of acrylonitrile by polar solvent. Overall, the S-T gap of alkenes is directly correlated with the activation barrier for propagation reactions.

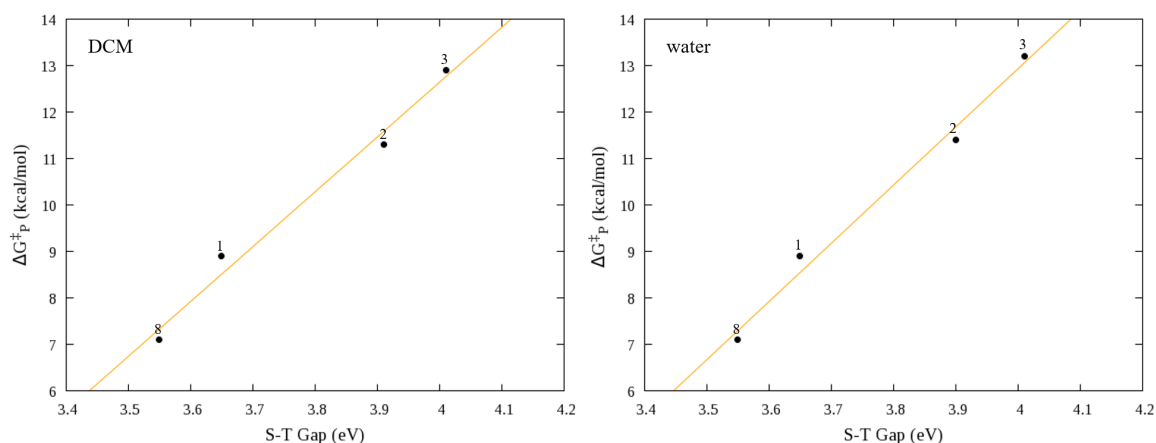


Figure 3.6. Correlation between $\Delta G^{\ddagger}_P$ (kcal/mol) and the S-T gap (eV) of alkenes in DCM ($R^2 = 0.98$) and water ($R^2 = 0.99$).

Fındık *et al.* [51] have suggested that the diversity in the alkene groups has a remarkable impact on the energetics of thiol-ene reactions in vacuum. The reactions that possess the phenylthio and 4-chlorophenylthio radical (reactions 1-5 and reactions 8-11) indicate that, as the delocalization ability of the intermediate carbon-centered radical increases, the activation barrier of the propagation step decreases. The variety of thiol groups has shown that the electrophilic nature of the sulfur-centered radical causes a decrease in the activation barriers, since the radical is stabilized by the electron donating groups. Moreover, the substituent effect on thiol-ene reaction reactivity can be traced by four different groups (-NO₂, -OMe, -Cl, -H) at the para position of the

thiols. As the electron withdrawing abilities of the substituents rank in the order $-\text{NO}_2 > -\text{Cl} > -\text{H} > -\text{OMe}$ in DCM, ΔG_P° is correlated with the nature of the substituents. The reaction of 4-nitrophenol (7) has the lowest barrier (8.7 kcal/mol), the reaction with 4-methoxythiophenol (6) has the highest barrier (13.5 kcal/mol), 4-chlorothiophenol (9) ranks in between (10.7 kcal/mol) (3.3). The Gibbs free energy barriers are higher in water than in DCM as compared to the ones in vacuum. Reaction 7 is an exception to this trend, the transition state being polarizable in water (5.62 D) it may be stabilized by water thus the Gibbs free activation barrier decreases as shown in Table 3.6.

Table 3.6. Dipole moment μ (D) of propagation step transition step geometries in DCM and water (M06-2X/6-31++G(d,p)).

Reactions	DCM	Water
1	4.28	4.51
2	2.86	3.00
3	2.05	2.16
4	4.31	4.93
5	4.01	4.19
6	2.92	3.04
7	5.45	5.62
8	4.30	4.54
9	2.43	2.54
10	3.14	3.27
11	4.15	4.34

3.4. Solvent Effect on Chain Transfer Reactions

Chain transfer consists of the abstraction of hydrogen atom from thiol derivatives, generating thioether and thiyl radical. The barrier of chain transfer reactions is directly correlated with the stability of the carbon-centered radical intermediate [49] and the

reactivity is known to be controlled by the dissociation energy of the sulfur-hydrogen bond (S-H) of thiols [79]. The chain transfer reactions which are considered in this dissertation are shown in Table 3.7. The transition state geometries and the bond lengths of carbon and sulfur bonds are displayed in Table 3.8. Quantum tunneling corrections are applied to chain transfer rate constants using Equation 3.2, because at low temperatures tunneling dominates the barriers of hydrogen-transfer reactions [80]. The chain transfer reactions are exergonic in DCM and in water (Table 3.9, Figure 3.7). $\Delta G^\ddagger_{CT}$ is the Gibbs free activation barrier and $\Delta H^\ddagger_{CT}$ is the enthalpy barrier of chain transfer reactions consisting of the termination of the polymerization by hydrogen abstraction of carbon-centered radical intermediate from a thiol substituent. $\Delta G^\ddagger_{CT}$ and $\Delta H^\ddagger_{CT}$ refer to the activation Gibbs free energy and enthalpy of thioether formation, respectively. The activation Gibbs energy barriers vary from 7 kcal/mol (4) to 13.5 kcal/mol (3) in vacuum, whereas the activation Gibbs energy is in the range of 8.3 kcal/mol (5) to 15.2 kcal/mol (7) in DCM shown in Table 3.9 and 8.4 kcal/mol (5) to 15.1 kcal/mol (7) in water are displayed in Figure 3.7 and Table 3.9. The reactions are slightly decelerated in polar media.

Table 3.7. Chain transfer step reactions that considered.

Reaction	Thiol	Radical
1	$\text{C}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet\text{Ph}$
2	$\text{C}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{Me})\text{CO}_2\text{Me}$
3	$\text{C}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{CN})$
4	$\text{C}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{OBu})$
5	$\text{C}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{OC}(\text{O})\text{Me})$
6	$p\text{-MeOC}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{Me})\text{CO}_2\text{Me}$
7	$p\text{-NO}_2\text{C}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{Me})\text{CO}_2\text{Me}$
8	$p\text{-ClC}_6\text{H}_5\text{SH}$	$p\text{-MeO-PhC}^\bullet=\text{CH}_2\text{-R}$
9	$p\text{-ClC}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{Me})\text{CO}_2\text{Me}$
10	$p\text{-ClC}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{OC}(\text{O})\text{Me})$
11	$p\text{-ClC}_6\text{H}_5\text{SH}$	$\text{R-CH}_2=\text{C}^\bullet(\text{CN})$

The majority of the reactions have ± 0.2 kcal/mol Gibbs free energy differences in DCM and in water. This difference is slightly larger (1 kcal/mol) for the reactions of methyl methacrylate with thiophenol (2) and 4-chlorothiophenol (9) (0.4 kcal/mol). Water may have stabilized the carbon centered radical intermediate more than DCM to increase the barrier displayed in Table 3.9.

Table 3.8. Chain transfer step transition state geometries and bond distances ($\text{\AA}$) of carbon and sulfur atoms of 11 thiol-ene reactions (M06-2X/6-31++G(d,p)) in DCM and water.

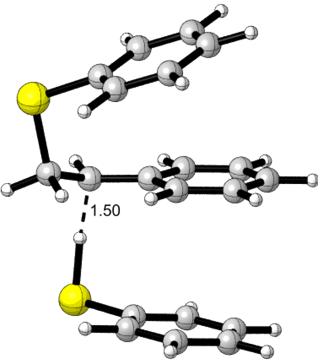
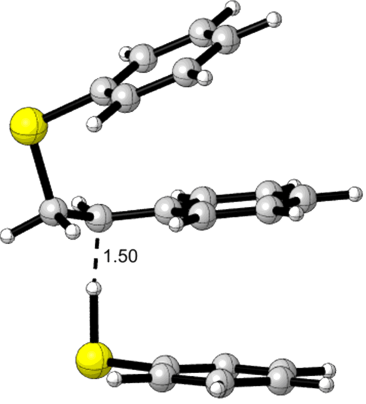
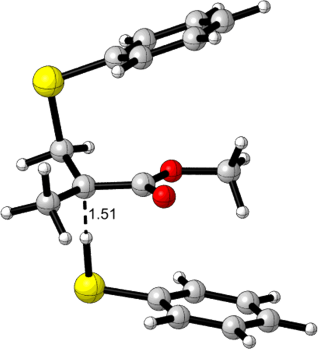
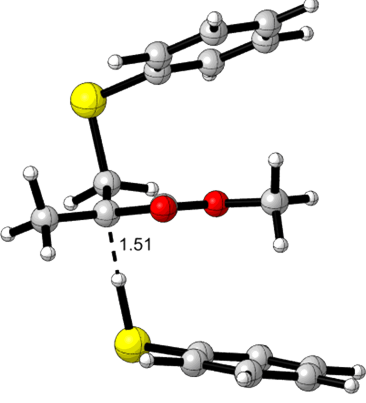
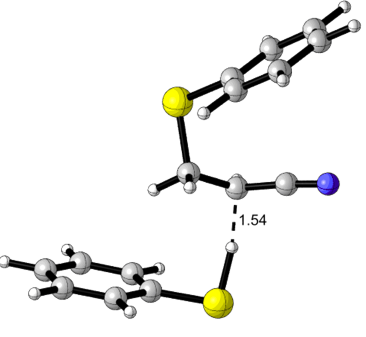
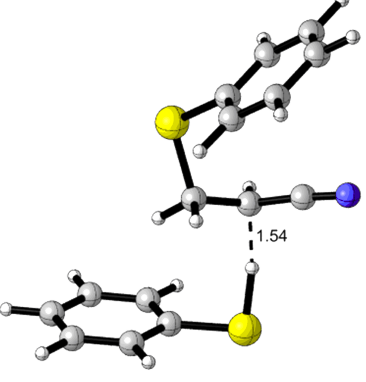
Reaction	DCM	Water
1		
2		
3		

Table 3.8 Chain transfer step transition state geometries. (cont.)

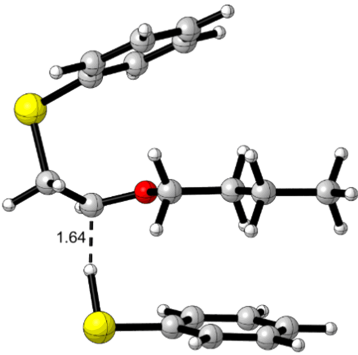
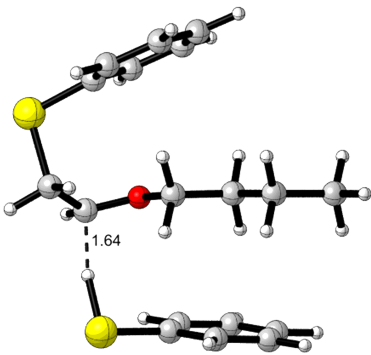
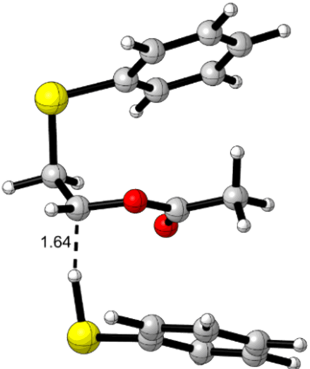
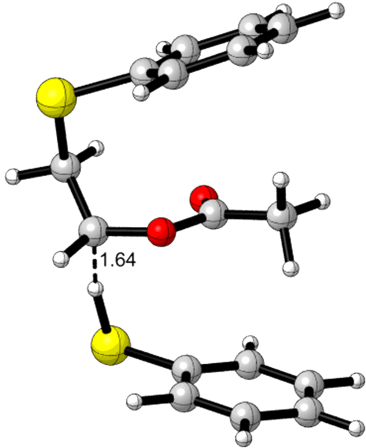
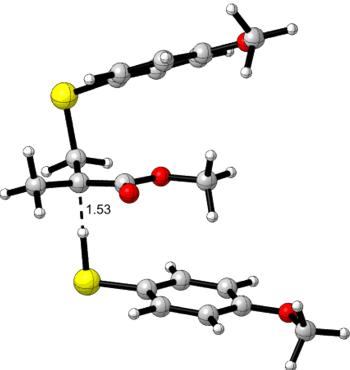
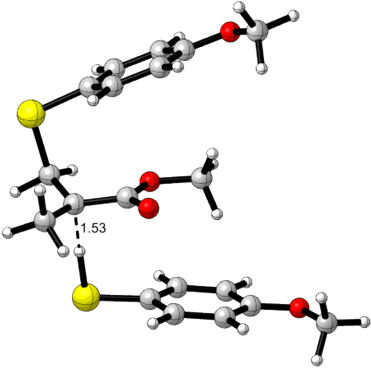
Reaction	DCM	Water
4		
5		
6		

Table 3.8 Chain transfer step transition state geometries. (cont.)

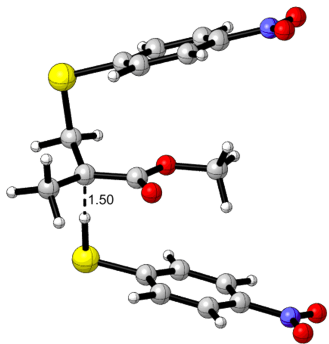
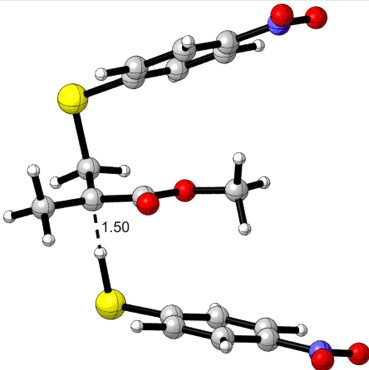
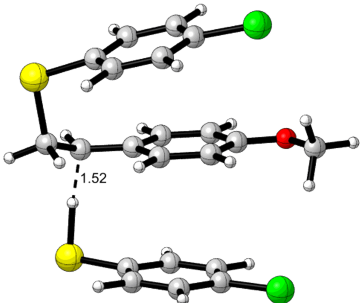
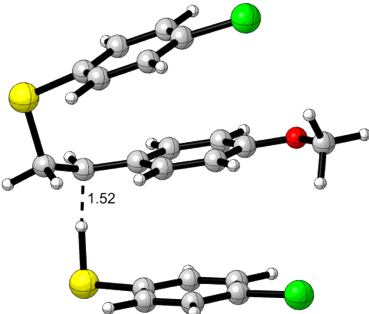
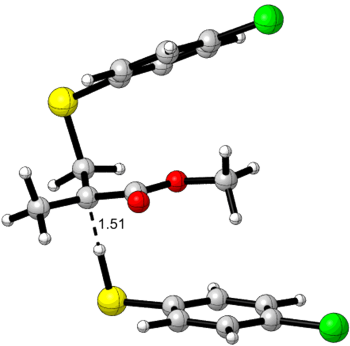
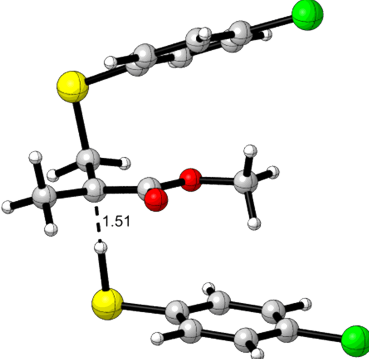
Reaction	DCM	Water
7		
8		
9		

Table 3.8 Chain transfer step transition state geometries. (cont.)

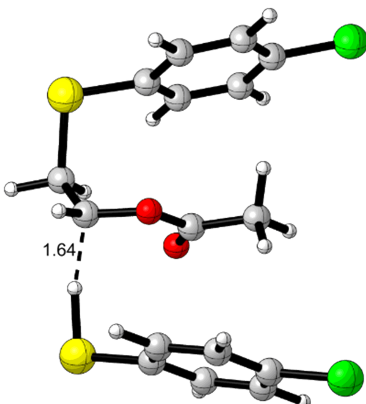
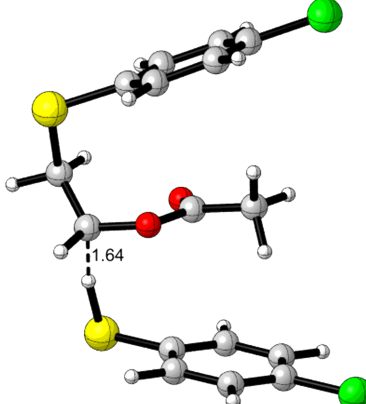
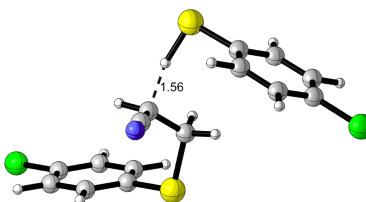
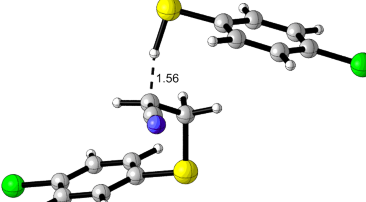
Reaction	DCM	Water
10		
11		

Table 3.9. Calculated activation barriers ($\Delta G^\ddagger_{CT}, \Delta H^\ddagger_{CT}$) and reaction energies ($\Delta G^o_{CT}, \Delta H^o_{CT}$) for chain transfer in vacuum, DCM and water at 1.0 atm and 298.15 K (kcal/mol) (M06-2X/6-31++G(d,p)).

Reaction	Vacuum				DCM				Water			
	$\Delta G^\ddagger_{CT}$	$\Delta H^\ddagger_{CT}$	ΔG^o_{CT}	ΔH^o_{CT}	$\Delta G^\ddagger_{CT}$	$\Delta H^\ddagger_{CT}$	ΔG^o_{CT}	ΔH^o_{CT}	$\Delta G^\ddagger_{CT}$	$\Delta H^\ddagger_{CT}$	ΔG^o_{CT}	ΔH^o_{CT}
1	10.7	-2.2	-8.4	-9.2	11.8	-1.0	-7.5	-8.7	12.0	-0.9	-7.4	-8.6
2	11.2	-1.5	-8.2	-10.1	11.8	0.8	-8.1	-9.1	12.8	0.4	-7.6	-9.9
3	13.5	2.2	-10.3	-12.4	14.0	3.2	-11.6	-12.5	14.2	3.4	-11.9	-12.6
4	7.0	-6.6	-12.7	-14.5	8.9	-6.0	-12.5	-14.8	9.1	-5.8	-12.4	-14.9
5	7.2	-4.6	-18.5	-19.8	8.3	-3.4	-18.7	-19.6	8.4	-3.3	-18.7	-19.6
6	9.1	-3.0	-12.1	-13.2	11.6	-1.3	12.0	-13.3	11.8	-1.0	-11.8	-13.3
7	12.4	1.2	-6.2	-7.6	15.2	2.4	-5.4	-6.4	15.1	2.6	-5.6	-6.3
8	7.9	-6.1	-8.3	-10.8	9.8	-3.7	-6.7	-9.0	10.0	-3.4	-6.5	-8.9
9	9.7	-1.8	-8.9	-10.0	13.8	-0.5	-8.4	-9.5	14.2	-0.1	-8.2	-9.4
10	9.2	-5.7	-18.1	-20.0	8.6	-3.7	-18.0	-19.6	8.7	-3.6	-18.1	-19.6
11	13.0	1.0	-11.1	-13.0	14.7	3.3	-13.2	-13.8	14.7	3.5	-12.3	-12.9

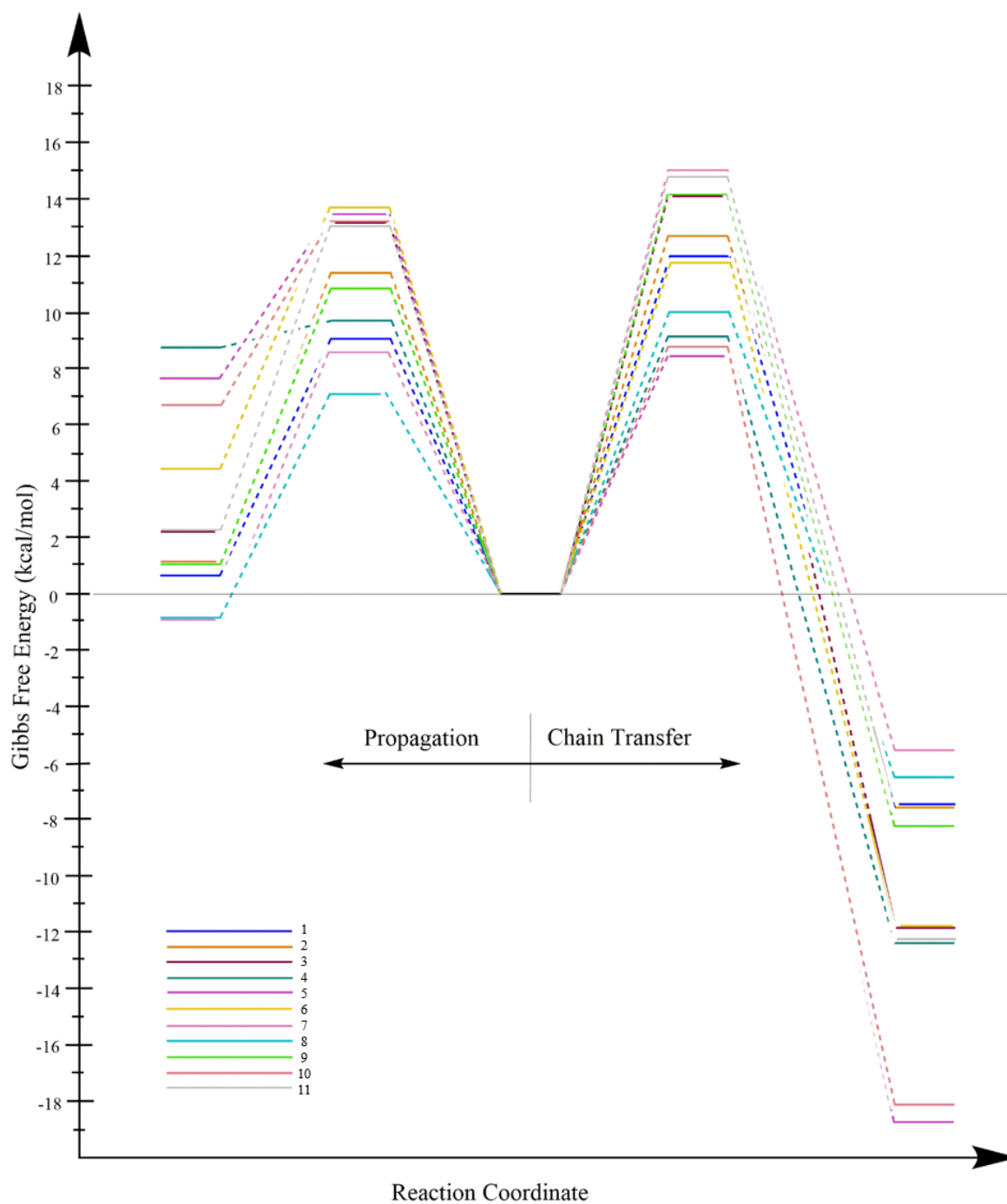


Figure 3.7. Overall propagation and chain transfer reaction profiles of 11 thiol-ene reactions in water.

The Bell-Evans-Polanyi Principle (BEP) correlations can be used to gain insights

on the chemical trends [81]. The reaction enthalpy of the chain transfer (ΔH°_{CT}) is correlated with activation energy (E_a) in DCM ($R^2 = 0.85$) and water ($R^2 = 0.86$), except for the outlier reactions 3, 4, 8 and 11 shown in Figure 3.8. The activation energies are higher than expected for reactions 3 and 11, due to the stabilization of the radical intermediates by the electron withdrawing (-CN) group. On the other hand, reactions 4 and 8 have electron donating groups, the oxygen atom adjacent to carbon centered radical (4) and the methoxy substituent on the phenyl ring attached to carbon radical (8) destabilize the radical intermediate; their activation energies are found to be lower than expected. The slope of BEP correlations indicates the state of transition states. Slopes that are close to zero refer to early transition states and slopes close to one indicate late transition state [82,83]. The slope of hydrogen atom transfer for the reactions studied is 0.37 in both DCM and water, which indicates early transition states and exothermic reactions.

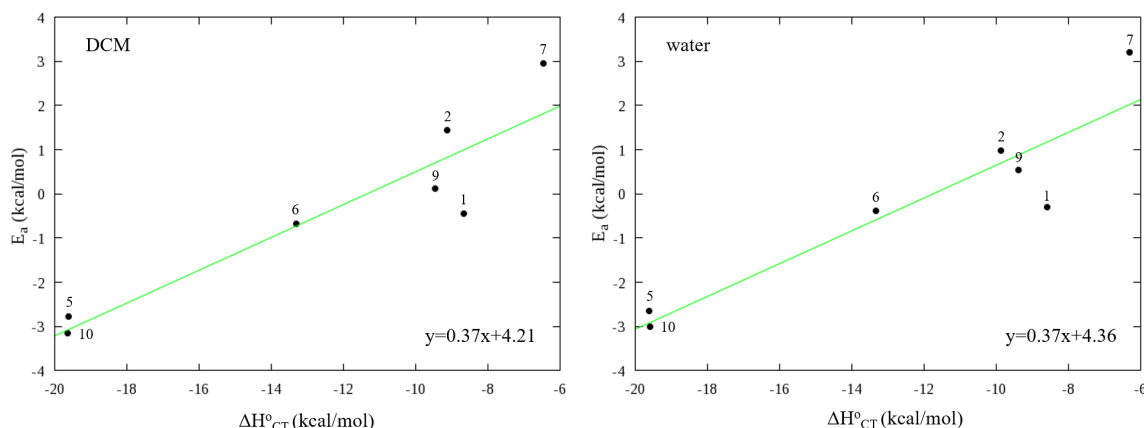


Figure 3.8. Bell-Evans-Polanyi (BEP) relationship between E_a (kcal/mol) and ΔH°_{CT} (kcal/mol) in DCM ($R^2 = 0.85$) and water ($R^2 = 0.86$).

3.5. Solvent Effect on Reaction Rates

Thiols are poor hydrogen-bond donors and they are less sensitive toward hydrogen abstraction in polar media than phenols, which are protic hydrogen atom donors. Dénès

et al. [55] suggested that hydrogen atom transfer from hydrocarbons by an alkyl radical is accelerated in polar solvents, however a negligible difference is observed in non-polar solvents. On the other hand, hydrogen abstractions from thiols by carbon radicals may follow a different behavior.

The propagation rate constants (k_P) vary from 2.6×10^4 (11) to 1.0×10^9 (8) in vacuum, from 1.9×10^4 (6) to 9.7×10^8 (8) in DCM and from 1.4×10^4 (6) to 9.9×10^8 (8) in water as given in Table 3.10. The fastest reaction (8) is the one between 4-chlorothiophenyl radical and 4-methoxystyrene, the electron donating group (-OMe) stabilizes the transition state and increases the reaction rate. On the other hand, the slowest reaction for DCM and water, reaction 6 has an electron withdrawing group on methyl methacrylate, the latter is expected to stabilize the radical and decreases the forward propagation rate (k_P). Rate constants for chain transfer reactions are in the range of 3.7×10^4 (3) – 1.3×10^4 (9) in vacuum, 2.1×10^3 (7) – 1.6×10^8 (5) in DCM and 2.8×10^3 (7) – 1.5×10^8 (5) in water; the width of the range illustrates the major role of the solvent on chain transfer reactions (Table 3.10).

Table 3.10. Reaction rates for the propagation (k_P) [$M^{-1} s^{-1}$], chain transfer (k_{CT}) [$M^{-1} s^{-1}$] and k_P/k_{CT} ratios in vacuum, DCM and water at 1.0 atm and 298.15 K (M06-2X/6-31++G(d,p)).

Reaction	Vacuum			DCM			Water		
	k_P	k_{CT}	k_P/k_{CT}	k_P	k_{CT}	k_P/k_{CT}	k_P	k_{CT}	k_P/k_{CT}
1	3.5×10^7	4.1×10^6	8.4396	4.3×10^7	6.5×10^5	66.0121	4.4×10^7	4.7×10^5	93.4894
2	4.3×10^6	1.9×10^6	2.2484	8.0×10^5	6.9×10^5	1.1609	6.6×10^5	1.4×10^5	4.7070
3	8.2×10^4	3.7×10^4	2.2317	5.2×10^4	1.9×10^4	2.6674	3.2×10^4	1.3×10^4	2.4226
4	2.5×10^7	1.3×10^9	0.0190	5.2×10^6	5.5×10^7	0.0951	9.3×10^6	3.9×10^7	0.2405
5	7.1×10^4	1.1×10^9	0.0001	2.8×10^5	1.6×10^8	0.0018	1.8×10^4	1.5×10^8	0.0001
6	1.0×10^5	6.2×10^7	0.0016	1.9×10^4	9.1×10^5	0.0206	1.4×10^4	6.2×10^5	0.0222
7	1.6×10^8	2.8×10^5	551.6774	6.8×10^7	2.1×10^3	31988.5816	9.6×10^7	2.8×10^3	33567.1934
8	1.0×10^9	4.5×10^8	2.2387	9.7×10^8	1.9×10^7	52.1614	9.9×10^8	1.3×10^7	77.7632
9	2.9×10^6	2.2×10^7	0.1336	2.0×10^6	2.4×10^4	83.5742	1.8×10^6	1.2×10^4	145.3711
10	9.8×10^4	3.8×10^7	0.0026	2.0×10^6	9.6×10^7	0.0209	3.4×10^4	8.4×10^7	0.0004
11	2.6×10^4	9.1×10^4	0.2854	6.1×10^4	5.7×10^3	10.6831	4.8×10^4	5.5×10^3	8.7060

3.6. Hydrogen Atom Transfer Reactions in Non-polar Solvents

Overall, the effect of solvents on the chain transfer reactions is more pronounced than the one on the propagation step: hydrogen atom transfer reactions respond better to the changes in dielectric constants than propagation reactions, as visualized in Figure 3.9. Hence, in this dissertation, hydrogen atom transfer reactions shown in Table 3.11 are modeled in various solvents and temperatures. The transition state geometries and C-S bond lengths are calculated at M06-2X/6-311+G(3df,2p) // M06-2X/6-31+G(d,p) level of theory in implicit solvent, as displayed in Table 3.12.

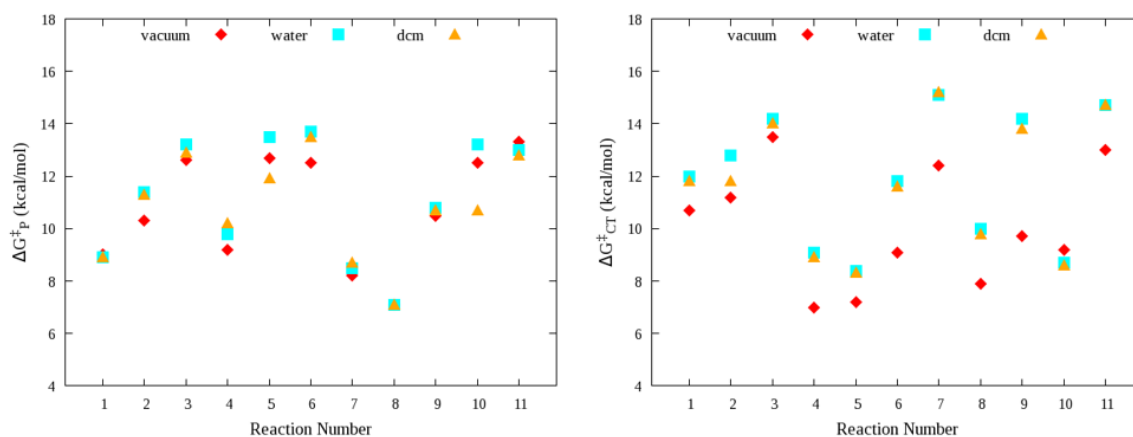


Figure 3.9. Comparison of the activation free energies of propagation and chain transfer steps, in different environments.

Table 3.11. Hydrogen transfer step reactions considered.

Reaction	Thiol	Radical	Solvent	Temperature (K)
12	$\text{C}_6\text{H}_5\text{SH}$	$(\text{CH}_3\text{H}_7)_n\text{CH}_2^\bullet$	Benzene	298
13	$\text{C}_6\text{H}_5\text{SH}$	$(\text{CH}_3)_2\text{CH}_2^\bullet$	Benzene	298
14	$\text{C}_6\text{H}_5\text{SH}$	$(\text{CH}_3)_3\text{C}^\bullet$	Benzene	298
15	$\text{C}_6\text{H}_5\text{SH}$	$(\text{C}_6\text{F}_{13})_n\text{CF}_2^\bullet$	1-Hexene	303
16	$\text{C}_6\text{H}_5\text{SH}$	$\text{HOCH}_2\text{CH}_2^\bullet$	Toluene	353
17	$\text{C}_6\text{H}_5\text{SH}$	$\text{PhCH}_2^\bullet$	Hexane	298
18	$\text{OH}(\text{CH}_2)_2\text{SH}$	$(\text{C}_6\text{H}_{12})\text{CH}_3\text{CO}^\bullet$	Benzene	353
19	$\text{OH}(\text{CH}_2)_2\text{SH}$	$(\text{C}_6\text{H}_{12})\text{CH}_3\text{CO}^\bullet$	Benzene	353

Table 3.12. Hydrogen atom transfer (HAT) transition state geometries and C-S bond distances ($\text{\AA}$) in implicit solvent environments. (For reactions 12-17: M06-2X/6-311+G(3df,2p) // M06-2X/6-31+G(d,p), for reactions 18,19: M06-2X/6-31++G(d,p)).

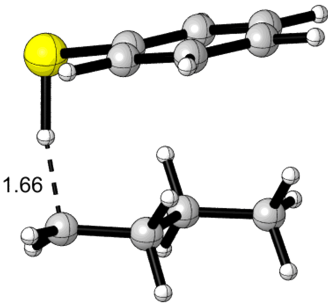
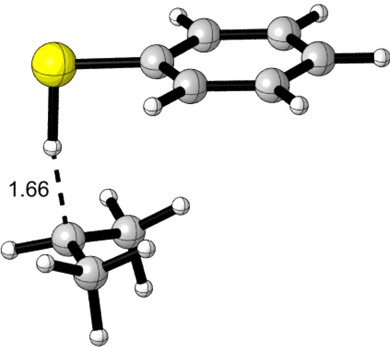
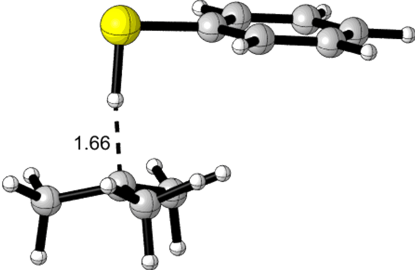
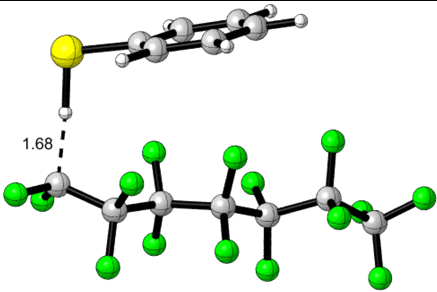
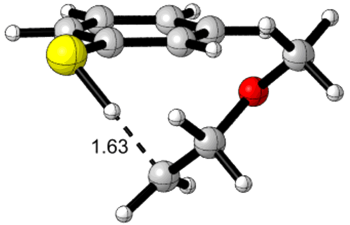
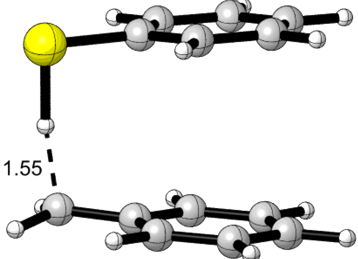
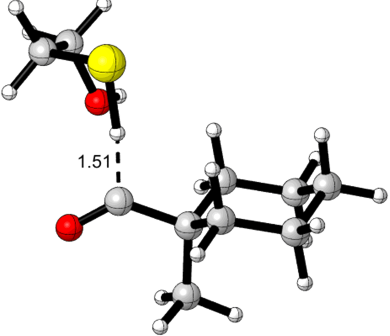
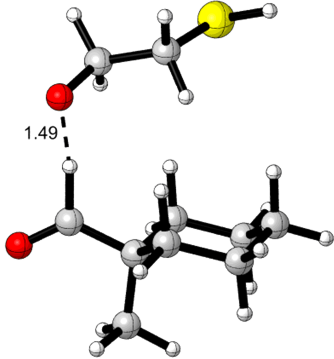
Reaction	Transition State Geometries
12	
13	
14	
15	

Table 3.12 HAT transition state geometries. (cont.)

Reaction	Transition State Geometries
16	
17	
18	
19	

Thiophenols are very efficient hydrogen donors to alkyl radicals due to their low S-H bond dissociation energy [55]. Reactions 12-17 include hydrogen atom transfer reaction between thiophenol and various alkyl radicals, which are butyl radical, iso-

propyl radical, tert-butyl radical, perfluoroheptyl radical, 2-methoxyethyl radical and benzyl radical in non-polar solvents calculated at M06-2X/6-311+G(3df,2p) // M06-2X/6-31+G(d,p) level of theory. Theoretical rate constants are correlated with the experimental results (Table 3.13). It is known that, in the reactions of thiyl radicals, hydrogen atom transfer is favored for electron-rich radicals, however the hydrogen atom exchange is disfavored for electron-poor radicals due to the mismatch philicity characters [55]. Reactions 12-14 are in accordance with this fact, since from primary to second and tertiary alkyl radicals the forward rate constant (k_H) is increased. Reaction 14 is the fastest reaction amongst the others, due to the nucleophilicity of the tert-Butyl radical, while reaction 15 is the slowest because of the electrophilic character of perfluoroheptyl radical. Similarly, in reaction 16, the electron-withdrawing β -alkoxy group decreases the reaction rate in contrast with the alkyl radicals. Reaction 17, which is the hydrogen transfer of benzyl radical from thiophenol, reacts slower than alkyl radicals because the radical is stabilized by the aromatic ring, also the reaction is in equilibrium with the back reaction.

Reactions 18 and 19 occur between 2-mercaptoethanol and 1-methyl cyclohexane-1-carbonyl radical in benzene calculated at M06-2X/6-31++G(d,p) methodology. While reaction 18 is the hydrogen transfer of the thiol (-SH) group, reaction 19 consists of the hydrogen atom abstraction from hydroxyl (-OH) group of 2-mercaptoethanol. The activation Gibbs free energy barrier of hydrogen atom abstraction from thiol group is 12.3 kcal/mol, on the other hand, the activation Gibbs free energy barrier hydrogen abstraction from hydroxyl group is 28.7 kcal/mol. Consequently, reaction 18 has the forward rate constant 7.8×10^6 , while the hydrogen abstraction from hydroxyl is not possible (4.7×10^{-4}) since bond dissociation energy of O-H bond is higher than S-H bond. The bond dissociation energy of S-H bond is 88 kcal/mol, in other respects, the bond dissociation of O-H bond is 102 kcal/mol [84]. On the other hand, the reverse rate constant of reaction 19 is 1.2×10^8 , hence the hydrogen transfer arises from the aldehyde. The reverse reaction of reaction 18 is 3.3×10^7 is in accordance with the expectations of Dénès *et al.* [55] since it is more rapid than the forward reaction.

Table 3.13. Theoretical and experimental rates of hydrogen atom transfer reactions.

Reactions 12-17 are calculated at the M06-2X/6-311+G(3df,2p) // M06-2X/6-31+G(d,p) level in vacuum and solvent. Reactions 18 and 19 are calculated at the M06-2X/6-31++G(d,p) level in solvent environment.

Reaction	Vacuum			Solvent		
	k_H	k_{-H}	k_{Hexp}	k_H	k_{-H}	k_{Hexp}
12	1.7×10^7	3.7×10^{-2}	-	3.4×10^7	7.6×10^{-2}	1.3×10^8
13	1.4×10^8	5.5×10^2	-	1.2×10^8	3.8×10^2	1.0×10^8
14	1.5×10^8	4.6×10^3	-	2.3×10^8	4.2×10^3	1.4×10^8
15	2.9×10^7	3.7×10^{-2}	-	1.7×10^5	1.7×10^{-1}	2.8×10^5
16	1.1×10^7	1.5×10^{-4}	-	1.5×10^7	8.7×10^{-5}	7.6×10^7
17	7.1×10^5	2.6×10^4	-	1.3×10^6	3.2×10^4	3.0×10^5
18	-	-	-	7.8×10^6	3.3×10^7	7×10^6
19	-	-	-	4.7×10^{-4}	1.2×10^8	-

Overall, the hydrogen atom transfer rate depends on the philicity character of radical. The rate of reaction increases as the nucleophilicity of radical increases and the rate of reaction decreases as the electrophilicity of the reaction increases. The electron-withdrawing groups decelerate the transfer reaction by preventing the share of electrons. Moreover, the hydrogen atom reactions are controlled by the bond dissociation energies of hydrogen donor.

3.7. Descriptors

Previous studies on radicals have reported that the relative electrophilicities or nucleophilicities can be easily described with descriptors [67,68]. It has been shown that chemical potential and chemical hardness affect the electrophilicity of radicals [70]. In this study, three different descriptors, local electrophilicity (ω^+_{rc}), global electrophilic-

ity (ω) and nucleophilicity (ω^-) indices are used to understand the characteristics of sulfur and carbon centered radicals in different environments. While the global indices describe the reactivity of the molecule, the local ones identify only the radical atoms that play a part in the reaction.

The local electrophilicity indices and the propagation rate constants are well correlated with each other in different media (Figure 3.10). The positive slopes indicate that the increase in the electrophilicity of radical leads to an increase in the propagation rate constants; a decrease in the nucleophilicity index correlates with an increase in the k_P value as expected, shown in Figure 3.11. This result is in a good agreement with the work by Findik *et al.* [51], where they reported that electrophilic character of the sulfur radical influences tremendously the rate constant of the thiol-ene reaction in the propagation step.

In the chain transfer reactions, the carbon centered radical having high local electrophilicity and high global electrophilicity indices shows less reactivity to hydrogen abstraction (Figure 3.10). When the nucleophilicity index of carbon centered radicals increases, the rate constant of the chain transfer increases (Figure 3.11). Additionally, for all descriptors, the variance of the chain transfer is found to be higher than for propagation. These results explain the higher amount of decrease in the rate constant as well as the activation free energy for chain transfer step in contrast with the propagation step upon solvation. In the light of this knowledge, it can be easily concluded that the ratio of k_P and k_{CT} (k_P/k_{CT}) driving the thiol-ene polymerization can be manipulated in different environment to yield tailor-made polymers.

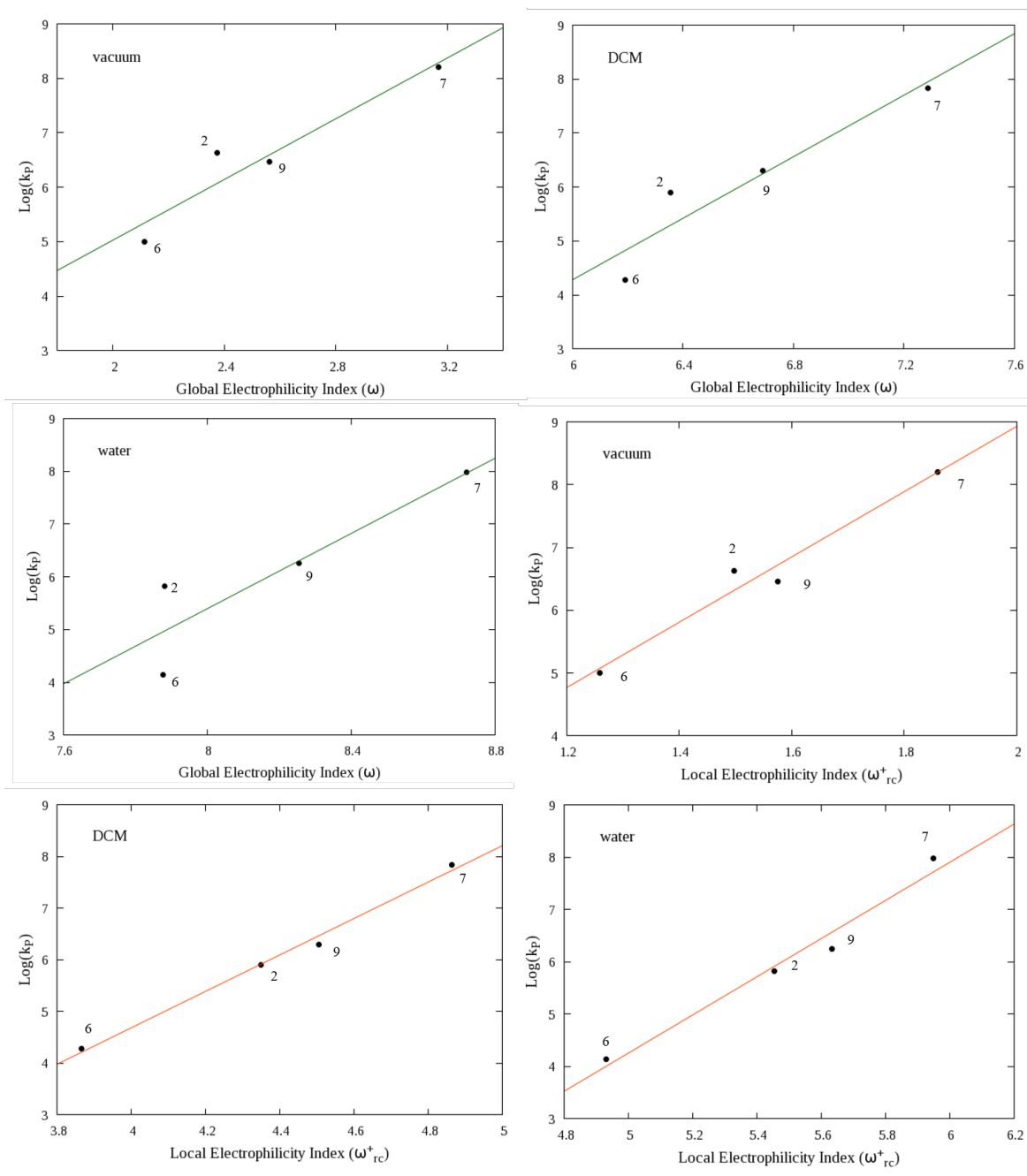


Figure 3.10. Correlation between logarithmic scale of rate constant and local electrophilicity index for propagation step in vacuum ($R^2 = 0.97$) in DCM ($R^2 = 0.99$) in water ($R^2 = 0.97$) and the correlation between logarithmic scale of rate constant for chain transfer step and global electrophilicity index in vacuum ($R^2 = 0.85$) in DCM ($R^2 = 0.85$) and in water ($R^2 = 0.87$).

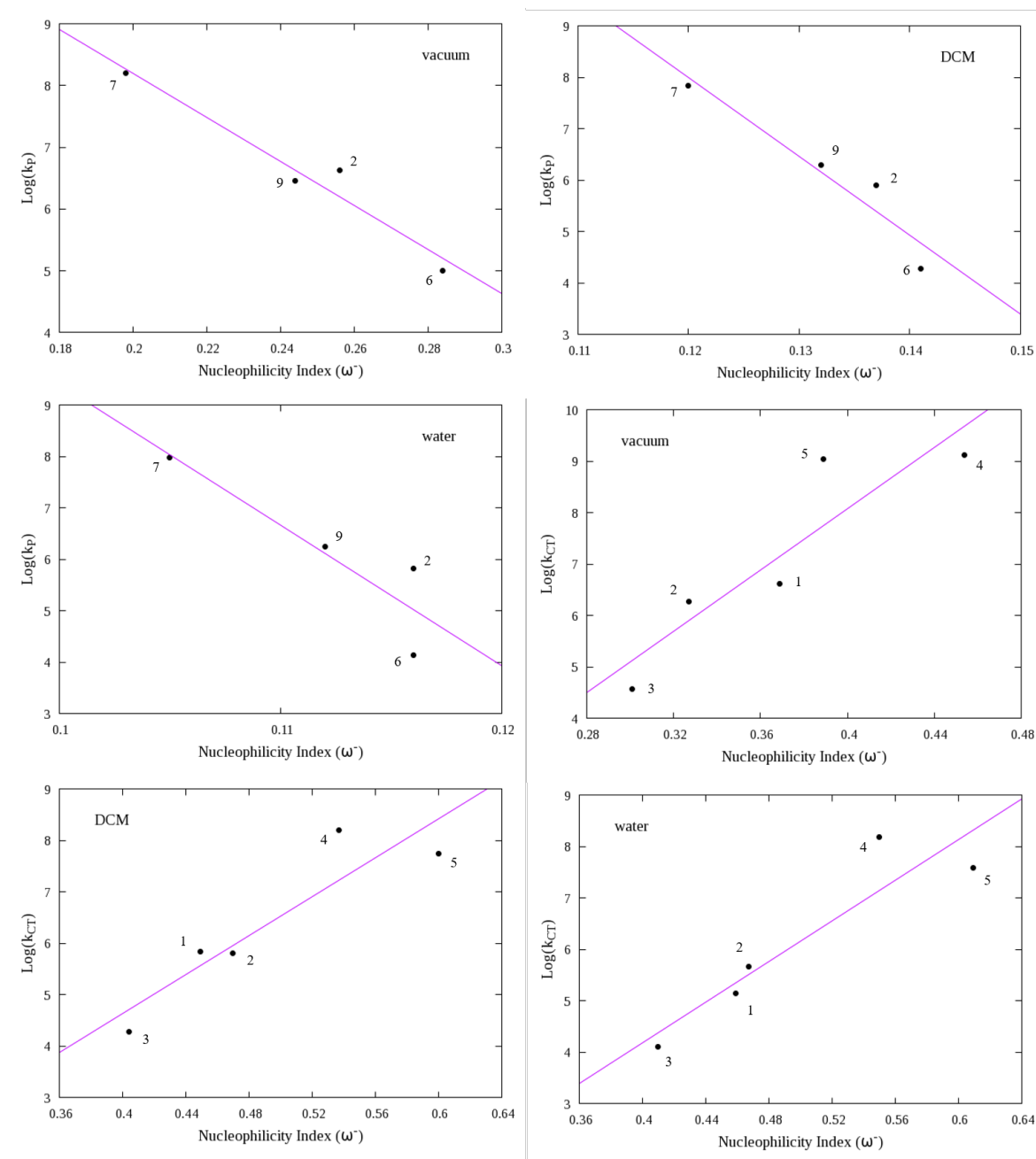


Figure 3.11. Correlation between logarithmic scale of rate constant for propagation step and nucleophilicity index in vacuum ($R^2 = 0.95$) in DCM ($R^2 = 0.90$) in water ($R^2 = 0.82$) and the correlation between logarithmic scale of rate constant for chain transfer step and nucleophilicity index in vacuum ($R^2 = 0.82$) in DCM ($R^2 = 0.84$) in water ($R^2 = 0.85$).

In summary, the reactions of a variety of thiols with different alkenes are examined in order to enlighten the role of solvents on propagation and chain transfer reactions. Based on the potential energy surface diagram, the kinetic and thermodynamic pathways have been determined and the k_P/k_{CT} ratio was calculated both in the non-polar solvent, DCM and the polar solvent, water. While the solvent polarity affects slightly the propagation rate constant, the chain transfer rate constant depends more on the environment. Alteration of the media allows the k_P/k_{CT} ratio to be manipulated to obtain tailor-made polymers.

Furthermore, three different descriptors such as the global electrophilicity index, the local electrophilicity and nucleophilicity indices have been used to shed light on the philicity features of the carbon and sulfur radicals. The descriptors are found to be well correlated with k_P , k_{CT} and the k_P/k_{CT} ratio in all media. The propagation rate constant k_P is found to be best correlated with the local and global electrophilicity indices whereas the chain transfer rate constant k_{CT} correlates well with the global electrophilicity index. Overall, usage of conceptual density functional theory would be appropriate in the prediction of the rates of the thiol-ene reactions in all media.

4. SOLVENT EFFECT ON CaO BOND STRENGTH WITHIN HYDRATED CALCIUM CLUSTERS

4.1. Background

The knowledge regarding the behavior of calcium ion in water environment has utmost importance to enlighten the binding mechanism of drugs and biological materials to hydroxyapatite (HAP), as well their presence in extracellular fluids have roles on biochemical functions. The conformational changes of calcium clusters enable the control of biochemical processes of cell [17].

The studies regarding the coordination numbers (CNs) of hydrated calcium clusters are controversial due to the flexibility of the first hydration shell and the low atomic number of the species involved [17]. Bai *et al.* have stated that CNs of the first hydration shell calcium clusters are not constant when temperature changes, compared with hydrated magnesium clusters [85]. The CNs of hydrated calcium clusters are determined as eight by molecular dynamics (MD) simulations and crystal structures in aqueous solution with the Ca-O bond distance as 2.46 Å [17]. Infrared multiple photon dissociation (IRMPD) spectroscopy analysis has reported the hydrated calcium clusters to have CN of eight for large clusters and CN of six for smaller clusters [86]. Density functional theory (DFT) calculations, performed in vacuum with BLYP/6-311+G(d,p) level of theory have revealed the first hydration shell of bivalent calcium ion to be fully occupied with six water molecules (Figure 4.1) [2].

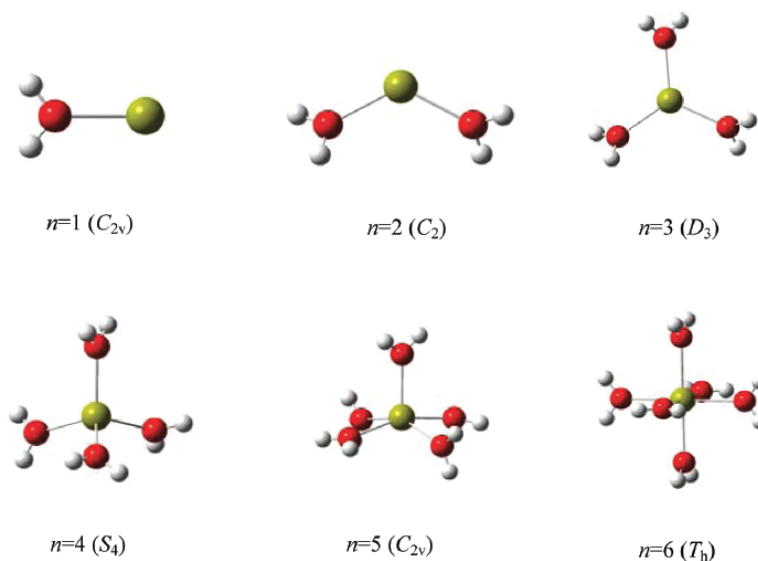


Figure 4.1. Ground state geometries of first hydration shell calcium structures and their point group in vacuum (BLYP/6-311+G(d,p)) [2].

Hydrated calcium structures are in equilibrium with ion-water interactions and hydrogen bonds of solvent molecules. Small hydrated calcium clusters can give information about ion-solvent interactions and large clusters can inform about the structures and reactivities of ions in solvent media [86]. The second shell structures are shown in Figure 4.2. In this study, only the first hydration shell structures are taken into account to investigate the interaction of calcium ion form with water molecules and the solvent effect on the stability of clusters.

Lei and Pan have stated that Ca-O bond distances are directly correlated with the cluster size. The bond distances of $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ complexes increase as the number of water molecules bonded to bivalent calcium ion (n) increase due to the shielding effect of first hydration shell molecules. The effect of Ca^{+2} ion becomes weaker as the shell number of complex increases [2]. Similar correlation is observed by natural bond orbital (NBO) analysis as the effect of Ca^{+2} ion on water molecules decreases with the increasing number of hydration shells [85]. First hydration shell consists

of electrostatic interactions between water molecules and bivalent calcium ion, water molecules are bonded each other with hydrogen bonds (H-bonds) forming multishells (4.2) [86].

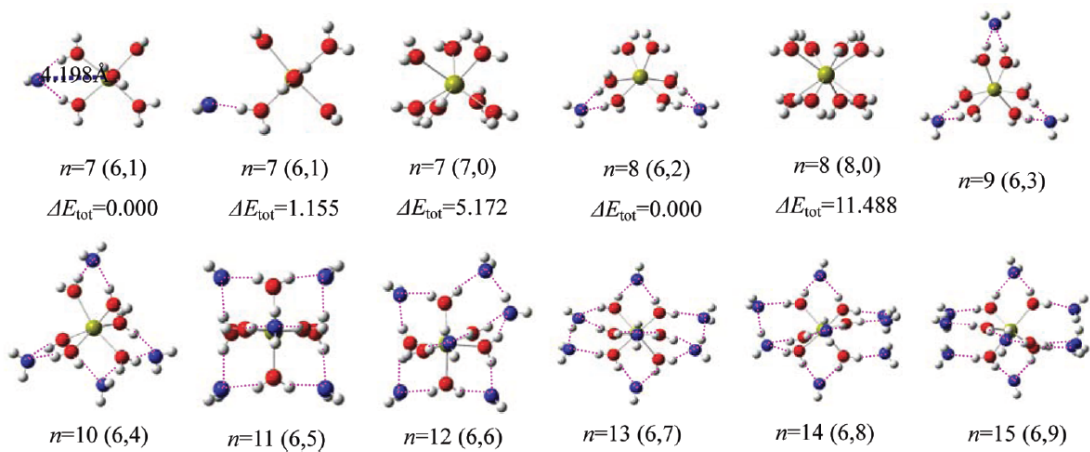


Figure 4.2. Ground state geometries of first and second hydration shell calcium structures, where $n = 7$ -15. Geometries are represented as (n_1, n_2) where n_1 is the first shell water molecules, n_2 is the second shell water molecules in vacuum (BLYP/6-311+G(d,p)) [2].

It is known that cations behave differently in vacuum and aqueous solutions. The study about calcium phosphate clusters reported that the $\text{Ca}_9(\text{PO}_4)_6$ clusters packed in vacuum, however the calcium ions are tended to migrate on surface in water causing the increase in number of possible configurations [87]. Similarly, the CN of $\text{K}^+(\text{H}_2\text{O})_m$ clusters is smaller in gas phase, while the CN of cation is equal in water and 1,4-difluorobenzene solutions [88]. The solvent effect may change the stability of $\text{Ca}(\text{H}_2\text{O})_n$ complexes. Determining the clusters' structures is crucial for understanding since the hydrated calcium ions play critical role in biological processes [2]. To the best of our knowledge, the stability of clusters in water has not been elaborated yet computationally. Density functional theory (DFT) is used for optimization and frequency calculations and by utilizing local mode analysis an intrinsic measurement for

evaluation of Ca-O bond strength is derived.

4.2. Computational Procedure

Density functional theory (DFT) is used to obtain optimized structures and frequency calculations using Gaussian16 [89]. $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ complexes are generated by binding $n = 1-8$ water molecules with bivalent calcium ion explicitly. Geometries are optimized at vacuum (1.0 atm, 298 K) and the structures with highest point groups are obtained. The clusters are optimized in vacuum with high point symmetry and are also optimized in an implicit solvent environment using the polarizable continuum solvation model (C-PCM). Water ($\epsilon=78.36$) [59] is selected as solvent because of its importance in biological systems.

All calculations are performed with the ωB97XD functional and the Pople's 6-311++G(d,p) basis set. The $\omega\text{B97XD}/6-311++\text{G(d,p)}$ methodology is selected due to its success on noncovalent interactions [90]. The method is suitable for short-range interactions, as well as for long-range interactions by including dispersion and long-range corrections [29,91].

Vibrational spectroscopy is utilized to obtain a quantitative measurement for Ca-O bonds of the hydrated calcium clusters. Normal modes of molecules are delocalized due to electronic and mass coupling, therefore normal vibrational modes in a molecule cannot be used directly to measure the bond strength [92]. It is known that electronic coupling is related with potential energy and mass coupling is engaged with the kinetic energy of a vibrational mode [93]. The electronic coupling is eliminated by solving the Wilson equation and Konkoli and Cramer reported that mass coupling can be suppressed by solving mass-decoupled equivalent of the Wilson equation, generating local vibrational modes [94]. Contrary to normal modes, local mode force constants are related with internal coordinates such as bond length, bond angle and dihedral angle. Zou and Cremer demonstrated that local stretching force constant k^a of a bond is associated with its intrinsic strength [95]. Therefore, local vibrational force

constants are utilized to provide information about the strength of covalent bonds and non-covalent interactions quantitatively. In this work, local mode analysis (LMA) is applied to quantify the strength of Ca-O bonds in hydrated calcium clusters. The local mode analysis is carried out with the program package COLOGNE2017 [96]. The average values of Ca-O bonds within $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ clusters are taken into account.

In order to compare the local mode force constants, k^a are converted to relative bond strengths via the following power relationship:

$$BSO\ n = A(k^a)^B \quad (4.1)$$

where, k^a is the local mode force constants of Ca-O bonds within hydrated calcium clusters. The coefficients A and B are derived from the reference molecules CaH_2 and CaO in vacuum and water. CaH_2 has the $BSO\ n$ of 1.0 and k^a of 0.97 [$\text{mDyn}/\text{\AA}$] in vacuum with $D_{\infty h}$ point group symmetry. CaO has the $BSO\ n$ of 2.0 and k^a of 4.12 [$\text{mDyn}/\text{\AA}$] in vacuum with $C_{\infty v}$ point group symmetry, leading the constants A and B of 1.0137 and 0.4779, deriving Equation 4.2.

$$BSO\ n(\text{Ca} - \text{O})_{\text{vacuum}} = 1.0137(k^a)^{0.4799} \quad (4.2)$$

CaH_2 has the $BSO\ n$ of 1.0 and k^a of 0.46 [$\text{mDyn}/\text{\AA}$] in water with C_{2v} point group symmetry. CaO has the $BSO\ n$ of 2.0 and k^a of 1.83 [$\text{mDyn}/\text{\AA}$] in water with $C_{\infty v}$ point group symmetry, leading the constants A and B of 1.4729 and 0.5057 deriving Equation 4.3.

$$BSO\ n(\text{Ca} - \text{O})_{\text{water}} = 1.4729(k^a)^{0.5057} \quad (4.3)$$

4.3. Hydrated Calcium Clusters

Hydrated calcium clusters are optimized in vacuum and aqueous media. The compact structures of $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ clusters are generated with high group symmetries such as D_3 , S_4 and T_h . The complexes are also optimized in aqueous media and the orientation of water molecules have changed to form less compact and low-symmetry structures shown in Table 4.1.

Table 4.1. Geometries of hydrated calcium clusters, Ca-O bond distances (Å) and point group symmetries (ω B97XD/6-311++G(d,p)) in vacuum and water.

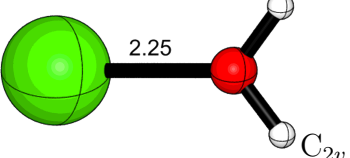
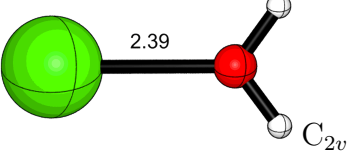
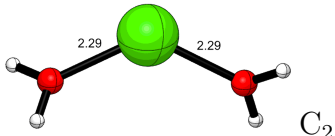
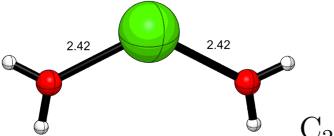
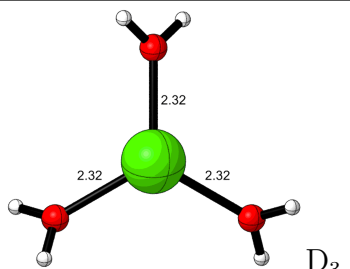
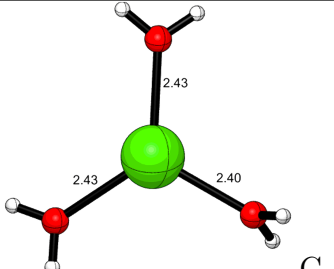
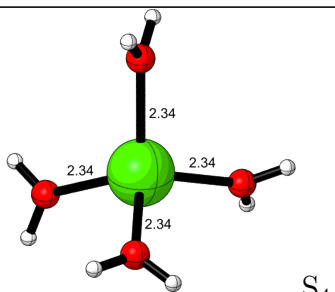
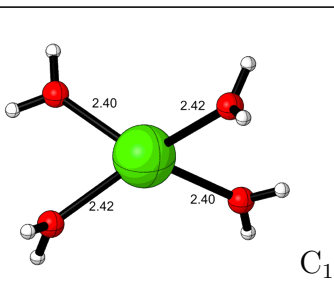
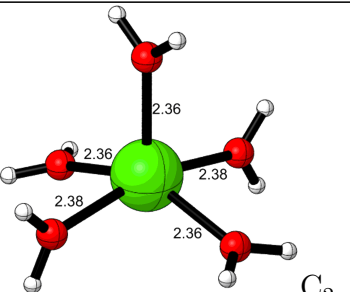
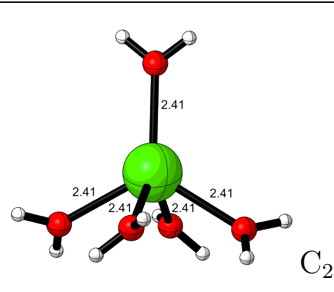
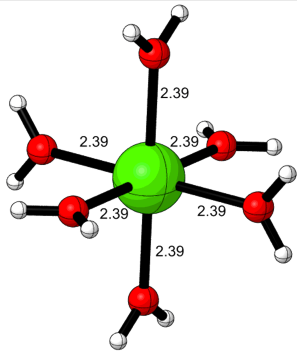
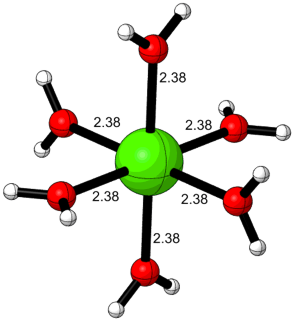
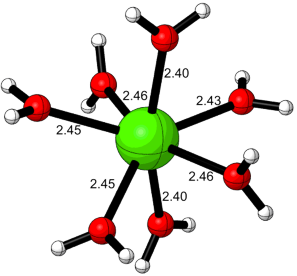
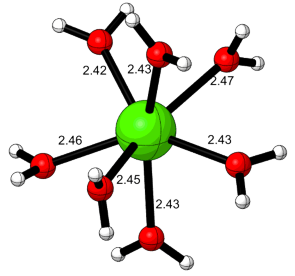
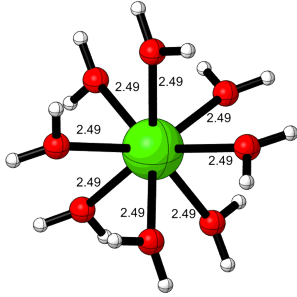
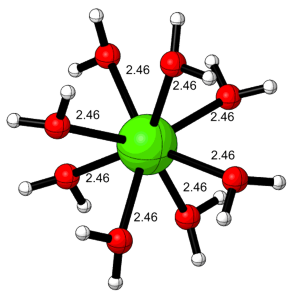
Complex	Vacuum	Water
$[\text{Ca}(\text{H}_2\text{O})]^{+2}$		
$[\text{Ca}(\text{H}_2\text{O})_2]^{+2}$		
$[\text{Ca}(\text{H}_2\text{O})_3]^{+2}$		
$[\text{Ca}(\text{H}_2\text{O})_4]^{+2}$		
$[\text{Ca}(\text{H}_2\text{O})_5]^{+2}$		

Table 4.1 Geometries of hydrated calcium clusters (cont.)

Complex	Vacuum	Water
$[\text{Ca}(\text{H}_2\text{O})_6]^{+2}$	 T_h	 T_h
$[\text{Ca}(\text{H}_2\text{O})_7]^{+2}$	 C_2	 C_1
$[\text{Ca}(\text{H}_2\text{O})_8]^{+2}$	 C_2	 D_4

4.4. Bond Strength Order (BSO)

The BSO values of Ca-O bonds in complexes $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ are compared in vacuum and water. They cover a range of 0.46 to 1.08 in vacuum and 0.91 to 1.26 in water environment, where $[\text{Ca}(\text{H}_2\text{O})_8]^{+2}$ complexes have lowest BSO, whereas $[\text{Ca}(\text{H}_2\text{O})_1]^{+2}$ complex has highest BSO in vacuum and $[\text{Ca}(\text{H}_2\text{O})_6]^{+2}$ has the highest BSO in water.

It is observed that the BSO and local stretching force constant (k^a) of complexes linearly decrease in vacuum as the number of water molecules increases (Figure 4.3, Table 4.2). Similarly, the Ca-O bond distances increases, which indicates the complex that has shortest Ca-O bond distance (2.25 Å) has the highest stretching force constant of 1.08 mDyn/Å, thus has the highest BSO (Figure 4.4, Table 4.2). $[\text{Ca}(\text{H}_2\text{O})_1]^{+2}$ complex is the most stable structure, meanwhile $[\text{Ca}(\text{H}_2\text{O})_8]^{+2}$ is the least stable structure in vacuum and the stability decreases as the cluster size increases.

On the other hand, $[\text{Ca}(\text{H}_2\text{O})_6]^{+2}$ complex is found to be the most stable structure in water with T_h point group symmetry. The cluster has the highest BSO and local stretching force constant (k^a) of 0.73 mDyn/Å, shortest Ca-O bond distance of 2.38 Å. In similar manner with gas phase optimizations, $[\text{Ca}(\text{H}_2\text{O})_7]^{+2}$ and $[\text{Ca}(\text{H}_2\text{O})_8]^{+2}$ are located as the least stable complexes with longest Ca-O bonds and lowest local stretching force constants (Figure 4.3, Figure 4.4, Table 4.2).

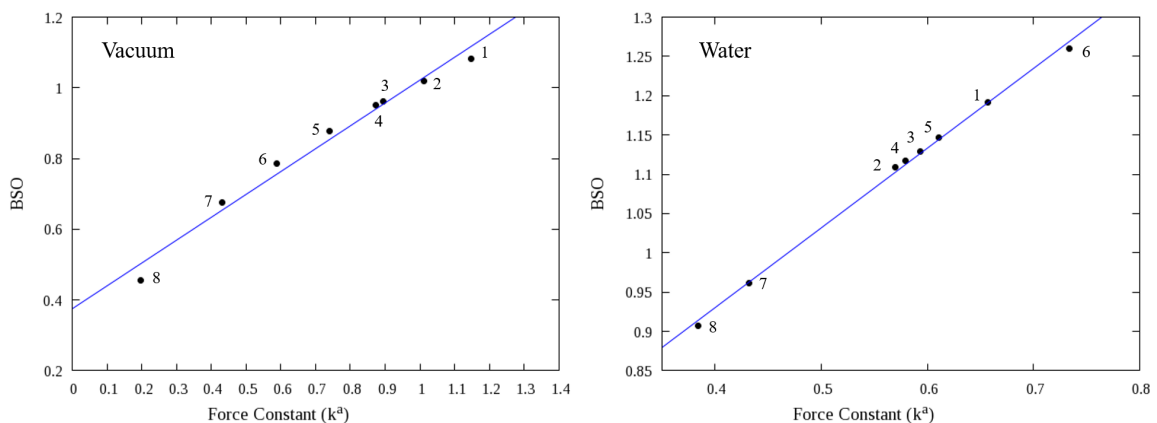


Figure 4.3. Relationship between bond strength order (BSO) and local stretching force constants (k^a) [mDyn/Å] of Ca-O bonds within hydrated calcium clusters $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$, $n=1-8$ in vacuum ($R^2=0.98$) and in water ($R^2=0.99$).

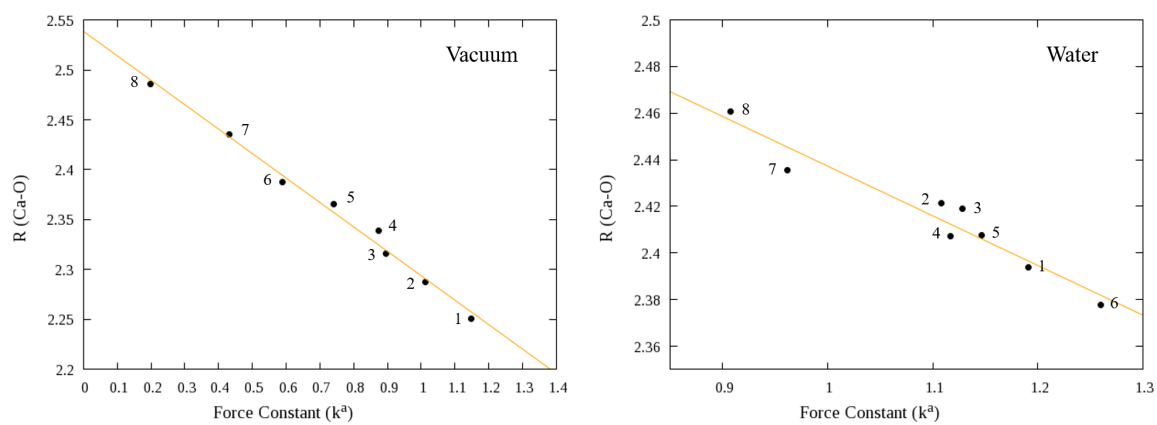


Figure 4.4. Relationship between bond length ($\text{\AA}$) and local stretching force constants (k^a) [mDyn/ $\text{\AA}$] of Ca-O bonds within hydrated calcium clusters $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$, $n=1-8$ in vacuum ment for evaluation of Ca-O bond strength is derived. ($R^2=0.99$) and in water ($R^2=0.93$).

Table 4.2. Bond distance [$\text{\AA}$], local stretching force constant (k^a) [mDyn/ $\text{\AA}$], bond strength order (BSO), electron density ($\rho(r)$) [$e^-/\text{\AA}^3$] and energy density (H) [$e^-/\text{\AA}^3$] of Ca-O bonds within hydrated calcium clusters $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$, $n=1-8$ in vacuum and water ($\omega\text{B97XD}/6-311++\text{G}(\text{d,p})$).

Complex	Vacuum					Water				
	R (Ca-O)	k^a	BSO	$\rho(r)$	H(r)	R (Ca-O)	k^a	BSO	$\rho(r)$	H(r)
$[\text{Ca}(\text{H}_2\text{O})]^{+2}$	2.25	1.15	1.08	0.31	0.04	2.39	0.65	1.19	0.21	0.04
$[\text{Ca}(\text{H}_2\text{O})_2]^{+2}$	2.29	1.01	1.02	0.28	0.04	2.42	0.57	1.11	0.20	0.04
$[\text{Ca}(\text{H}_2\text{O})_3]^{+2}$	2.32	0.90	0.96	0.26	0.04	2.42	0.59	1.13	0.19	0.04
$[\text{Ca}(\text{H}_2\text{O})_4]^{+2}$	2.34	0.87	0.95	0.25	0.04	2.41	0.58	1.12	0.20	0.04
$[\text{Ca}(\text{H}_2\text{O})_5]^{+2}$	2.37	0.74	0.88	0.23	0.04	2.41	0.61	1.15	0.20	0.04
$[\text{Ca}(\text{H}_2\text{O})_6]^{+2}$	2.39	0.59	0.79	0.22	0.04	2.38	0.73	1.26	0.22	0.04
$[\text{Ca}(\text{H}_2\text{O})_7]^{+2}$	2.44	0.43	0.68	0.19	0.04	2.44	0.43	0.96	0.20	0.04
$[\text{Ca}(\text{H}_2\text{O})_8]^{+2}$	2.49	0.20	0.46	0.17	0.04	2.46	0.38	0.91	0.18	0.04

4.5. Electron Density and Energy Density

The electron density ($\rho(r)$) values are linearly correlated with local stretching force constants (k^a) of $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ clusters in vacuum and water environments. According to BSO and k^a results, $[\text{Ca}(\text{H}_2\text{O})_1]^{+2}$ is determined as the most stable complex in gas phase, which is supported by electron density ($\rho(r)$) of $0.31 \text{ e}^-/\text{\AA}^3$. According to Table 4.2, $\rho(r)$ values decrease as the cluster size increases, which indicates the weakening of Ca-O bonds. In aqueous media, $[\text{Ca}(\text{H}_2\text{O})_6]^{+2}$ is defined as the most stable complex with the highest k^a value. Similarly, in water, the most stable cluster has the highest electron density of $0.22 \text{ e}^-/\text{\AA}^3$ indicating the strongest Ca-O bond. On the other hand, the least stable cluster $[\text{Ca}(\text{H}_2\text{O})_8]^{+2}$ has the lowest electron density of $0.18 \text{ e}^-/\text{\AA}^3$, where the Ca-O bond weakens (Table 4.2, Figure 4.5).

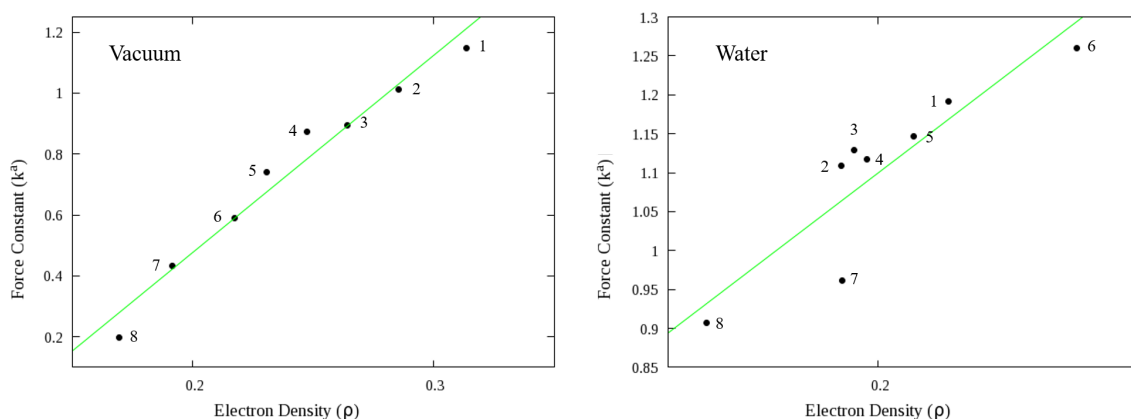


Figure 4.5. Relationship between local stretching force constants (k^a) [$\text{mDyn}/\text{\AA}$] and electron density ($\rho(r)$) [$\text{e}^-/\text{\AA}^3$] of Ca-O bonds within hydrated calcium clusters $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$, $n=1-8$ in vacuum ($R^2=0.96$) and in water ($R^2=0.80$).

According to the Cramer-Kraka criterion, the negative value of energy density ($H(r)$) identifies the chemical bond as covalent [93]. The energy density values of Ca-O bonds of $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$ clusters are $0.04 \text{ e}^-/\text{\AA}^3$, which indicates the non-covalent character of Ca-O bonds within first shell hydration clusters (Table 4.2). The relation

between the k^a and $H(r)$ are in agreement with bond strength order and electron density values, since all the complexes have approximately same value, the strongest bond leads to be the most stable cluster: $[Ca(H_2O)_1]^{+2}$ is most stable in vacuum and $[Ca(H_2O)_6]^{+2}$ is most stable in aqueous media.

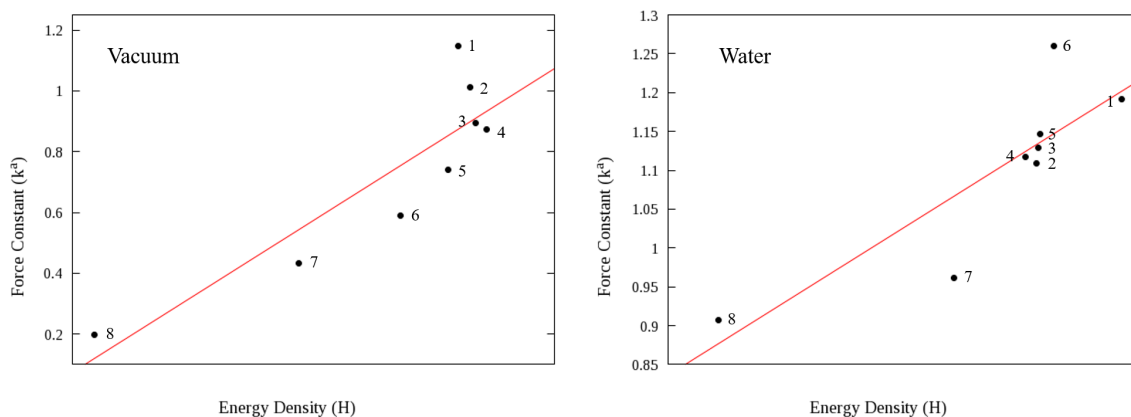


Figure 4.6. Relationship between local stretching force constant (k^a) [mDyn/Å] and energy density ($H(r)$) [$e^-/\text{\AA}^3$] of Ca-O bonds within hydrated calcium clusters $[Ca(H_2O)_n]^{+2}$, $n=1-8$ in vacuum ($R^2=0.78$) and in water ($R^2=0.73$).

In summary, the solvent effect on ground state structures of hydrated calcium clusters are evaluated in this study. Due to the importance in biological processes, it is crucial to determine the stability of $[Ca(H_2O)_n]^{+2}$ complexes in aqueous environment. For this purpose, local stretching force constant (k^a), bond length, electron density ($\rho(r)$) and energy density ($H(r)$) values of Ca-O bonds within hydrated calcium clusters are determined by using local mode analysis (LMA). The bond strength order (BSO) of Ca-O bonds are calculated by using k^a values and utilized in order to compare the stabilities of clusters with different coordination numbers in different media. In the gas phase, the strength of Ca-O bonds linearly decreases as the size of the clusters increases. On the other hand, in aqueous media, clusters show a different behavior as $[Ca(H_2O)_6]^{+2}$ having the strongest Ca-O bond, it forms the most stable form in water. It can be concluded that the CN of 6 is preferred in aqueous media and the

larger clusters (CN= 7 and 8) do not coordinate on the first hydration shell. The result is supported by various experimental and computational studies. Lei and Pan reported that the first hydration shell of calcium ion is fully occupied with six water molecules [2]. Bai *et al.* have reported that CN value may vary in the range of 6 to 8 water molecules and the preference depends on the water molecule activity. At the low molecule activity, where the solution is concentrated, the CN value of six may be preferred, however at high temperature and dilute solutions, seven or eight CN may be favored [85].

This study has enabled us to understand the behavior of hydrated calcium clusters in gas and aqueous phase. Moreover, the solvent effect on the coordination numbers of the clusters is elucidated. Overall, this study may be the first step in the prediction of drug binding to HAP and bone matrix.

4.6. Future Work

Even though the first hydration shell is fully occupied with six water molecules, the growth of the cluster size may change the CN of second hydration shell. Six water molecules coordinate directly to Ca^{+2} ion, however the seventh and more water molecules prefer to bind to the second solvation shell by hydrogen bonding [97]. It is suggested that clusters having the same number of water molecules in the second/third hydration shell form lower-energy structures [2]. The second solvation shell of water will be applied to first solvation shell via hydrogen bonds and the strength of bonds and stability of complexes are going to be evaluated by local mode analysis.

5. CONCLUSIONS

In the first part of the thesis, solvent effect on thiol-ene reactions are investigated by modeling various propagation and chain transfer reactions in solvents with polarity differences. It is concluded that, hydrogen atom transfer reactions depend more on the reaction environment than the propagation step. Therefore, by the manipulation of k_P/k_{CT} ratio, it is possible to synthesize tailor-made polymers. Moreover, the search over the best correlated index among the descriptors: global electrophilicity, local electrophilicity and nucleophilicity indices has revealed that the electrophilicity indices are suitable to use as descriptor on the philicity of carbon and sulfur radicals.

Second part of the thesis consists of the optimizations of hydrated calcium clusters, $[\text{Ca}(\text{H}_2\text{O})_n]^{+2}$, where $n= 1-8$, indicating the number of water molecules that interacted with calcium cation. Local mode analysis (LMA) is utilized in order to obtain the force constants (k^a) of Ca-O bonds within clusters. Bond strength orders are calculated based on the force constants, which revealed the strengths of bonds. The most strongest bond is considered as the most stable structure, which resulted as $[\text{Ca}(\text{H}_2\text{O})_1]^{+2}$ in vacuum and $[\text{Ca}(\text{H}_2\text{O})_6]^{+2}$ in water. It can be concluded that solvent environment effects the stability of structures and CN of the clusters are determined accordingly.

Overall, computational study over the solvent effect on different subjects may enlighten the characteristics of the reactions, as well as the complexes. By solvent alteration, tailor-made polymers can be obtained and the stable forms of different CN of clusters can be generated. We expect this study to contribute as a tool for theoretical and experimental studies in future.

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