

Computational Studies of the Explicit Role of the Solvent in Facilitating Transformations in Main Group Chemistry

by

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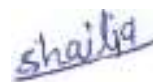
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**Dedicated to
my parents**

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-Shailja Jain

"Live and allow others to live, hurt no one; life is dear to all living beings."

-Lord Mahavira

"It is better to win over self than to win over a million enemies."

-Lord Mahavira

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Abbreviations

AIMD	<i>ab initio</i> Molecular Dynamics
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
COSMO	Conductor-like Screening Model
CH ₂ Cl ₂	Dichloromethane
DFT	Density Functional Theory
dr	Diastereomeric Ratio
GGA	Generalized Gradient Approximation
IRC	Intrinsic Reaction Coordinate
IE	Interaction Energy
KS	Kohn-Sham
LDA	Local Density Approximation
MP2	Second-order Møller–Plesset Perturbation Theory
MARIJ	Multipole Accelerated Resolution of Identity
M06	Minnesota 06
NBO	Natural Bond Orbital
NCI	Non-covalent Interactions
PBE	Perdew, Burke and Ernzerhof
PCM	Polarizable Continuum Model
RI	Resolution of Identity
SCF	Self-consistent Field
TZVP	Triple Zeta Valence plus Polarization
TS	Transition state

TOF

Turn over Frequency

TON

Turn over Number

THF

Tetrahydrofuran

Physical Constants

Avogadro's Constant	$(N_A) = 6.02214129 \times 10^{23} \text{ mol}^{-1}$
Atomic Mass Unit	$(u) = 1.660538921 \times 10^{-27} \text{ kg}$
Boltzmann's Constant	$(k) = 1.3806488 \times 10^{-23} \text{ JK}^{-1}$
Bohr Radius	$(a_0) = 5.291772109 \times 10^{-11} \text{ m}$
Elementary Charge	$(e) = 1.602176565 \times 10^{-19} \text{ C}$
Gas Constant	$(R) = 8.3144621 \text{ JK}^{-1} \text{ mol}^{-1}$
Mass of Electron	$(m_e) = 9.10938291 \times 10^{-31} \text{ kg}$
Mass of Proton	$(m_p) = 1.672621777 \times 10^{-27} \text{ kg}$
Mass of Neutron	$(m_n) = 1.674927351 \times 10^{-27} \text{ kg}$
Rydberg Constant	$(R) = 1.097373157 \times 10^5 \text{ cm}^{-1}$
Speed of Light	$(c) = 2.99792458 \times 10^8 \text{ ms}^{-1}$
Planck's Constant	$(h) = 6.62606957 \times 10^{-34} \text{ Js}$

Chapter 1

A Brief Introduction about Solvent Chemistry and Non-Covalent Interactions in Main Group Transformations

Chapter 1

A Brief Introduction about Solvent Chemistry and Non-Covalent Interactions in Main Group Transformations

Abstract

The chemistry of low valent main group compounds has grown as an alternative to the chemistry of less abundant and toxic transition metals complex. It has been found that low valent compounds such as carbenes, silylenes, and germylenes are efficient for activating small molecules and catalysis. However, in this research area, the reaction mechanism and the factors that affect the rate of reaction are not understood completely. Since most of the reactions occur in the solvent phase, the solvent has been an essential factor that can influence the rate and the selectivity of the reactions. In this chapter, an overview of the solvent's influence in low valent main group chemistry and stereoselectivity has been provided.

1.1 Why Main Group Transformations?

Transition metal complexes have been extensively used in many inorganic and organic reactions, as these compounds show good coordination with the substrate.¹⁻⁵ However, transition metal complexes are expensive, less abundant, and toxic. In contrast, main group complexes are cheap and readily available. Therefore, main group chemistry has become a popular research area over recent years as an alternative to transition metal chemistry. In this regard, frustrated Lewis pairs (FLPs),⁶⁻⁸ compounds with multiple bonds between main group elements,⁹⁻¹⁰ low valent main group compounds,^{11-15a} have explored in homogeneous catalysis and for facile activation of small molecules.

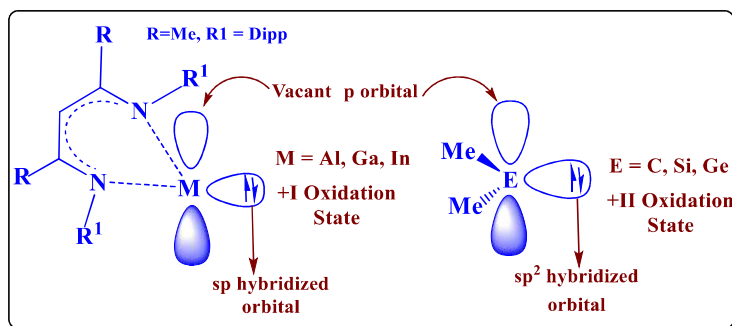
Although small molecule activation and catalysis by low valent main group complexes have been widely studied, mechanistic investigations and factors that affect reaction rates are not explored well.^{15b-15c} This understanding of reactions at a molecular level is essential because it improves the turnover number (TON) and yield of the reaction. Computational chemistry plays a dominant role here, helping to investigate mechanistic pathways and selectivity. Moreover, two important aspects of chemistry: structure and reactivity of the system, can be understood with computational methods.

Furthermore, existing research indicates that the solvent can strongly influence rate, selectivity, and yield of the reactions. However, the effect of solvent in the main group transformations is less explored. The focus of the current thesis work is twofold: a) understanding the *explicit role of the solvent in low-valent main group chemistry* through covalent and non-covalent interactions, b) the *explicit role of the solvent in controlling stereoselectivity* through non-covalent interactions. Density functional theory (DFT)¹⁶⁻¹⁷ has become a powerful tool to study the kinetics and thermodynamics of reactions, as it can handle large chemical systems with high accuracy. Therefore, in this thesis, computational investigations with DFT calculations have been carried out to understand the solvent's role in the main group reactions.

1.2 Low Valent Main Group Compounds

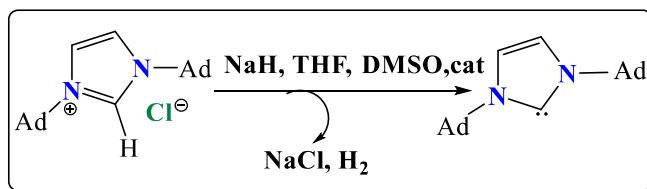
Chemistry of low valent main group compounds has become a field of intense research in recent years as the central atom of these compounds has a lone pair of electrons along with vacant orbitals, thereby having the potential to show both nucleophilic as well as electrophilic character, which leads to interesting chemical properties. The compounds contain the main group elements in lower oxidation states than the normal oxidation states are known as low valent main group compounds. For example, carbenes, silylenes, germynes, borylenes, and NacNacAl(I) compounds are low oxidation state main group compounds because here, carbon, silicon, and germanium are stable in a lower oxidation state (II) than their normal

oxidation state (IV) and boron and aluminum stable in a lower oxidation state (I) than their normal oxidation state (III) (see scheme 1.1 below). Moreover, low valent main group compounds also includes compounds in zero oxidation states, such as carbenes,¹⁸⁻¹⁹ silylenes,²⁰ and germylenes.²¹ The synthesis and stabilization of these complexes (as a monomer) under mild conditions is possible due to the incorporation of bulky ligands, which hinder the compound's oligomerization and polymerization.



Scheme 1.1 Compounds of groups 13 and 14 in their lower oxidation states.

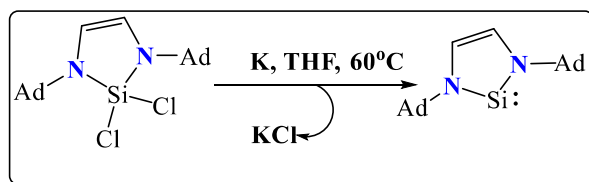
In 1991, Arduengo and coworkers synthesized the first stable N-heterocyclic carbene (NHC) using 1,3-di-adamantyl-imidazolium-chloride and sodium hydride (see Scheme 1.2) in THF solvent.²² Reported that this carbene is kinetically and thermodynamically stable due to the bulky group on the nitrogen atom and electron density transfer from nitrogen to the vacant p orbital of the carbon atom, respectively. Later, N-heterocyclic carbenes (NHCs) have been employed to a large extent as a Lewis base catalyst in the area of organocatalysis.²³ Moreover, many transition metal, and main group complexes, which are difficult to isolate, could be stabilized through employing NHCs as supporting ligands.²⁴⁻²⁶ Braunschweig and coworkers have isolated the first zero-valent beryllium compounds using cyclic alkyl amino carbene (CAAC).²⁷



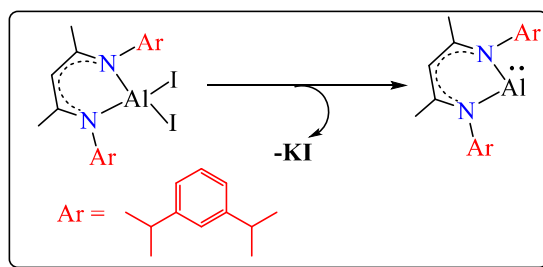
Scheme 1.2 The synthesis of the first stable N-heterocyclic carbene (NHC).

Furthermore, considerable efforts were made to explore this field. Many other low-valent main group compounds such as silylenes, germylenes, borylenes, and NacNacAl(I) were isolated, exhibiting carbene-like behavior. West and coworkers synthesized the first N-heterocyclic silylene²⁸ by reduction of

dichlorosilane in the presence of elemental potassium (Scheme 1.3). Moreover, in 2000, Roesky and coworkers succeeded in synthesizing the first monomeric Al(I) complex with the bulky NacNac ligand (Scheme 1.4).²⁹ These compounds have various applications in many fields of chemistry, like organic synthesis,³⁰⁻³² small-molecule activation,³³⁻³⁵ and catalysis.³⁶⁻⁴¹



Scheme 1.3 The synthesis of the first stable N-heterocyclic silylene.



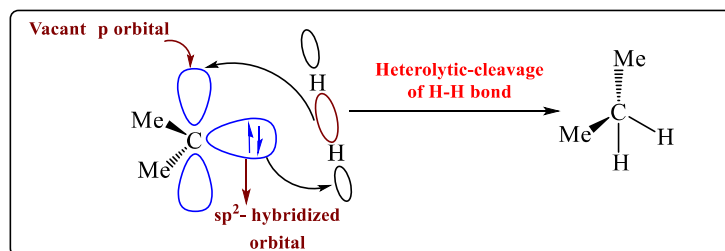
Scheme 1.4 The synthesis of the first stable monomeric NacNac complex.

1.2.1 Low Valent Main Group Compounds as Small Molecule Activators

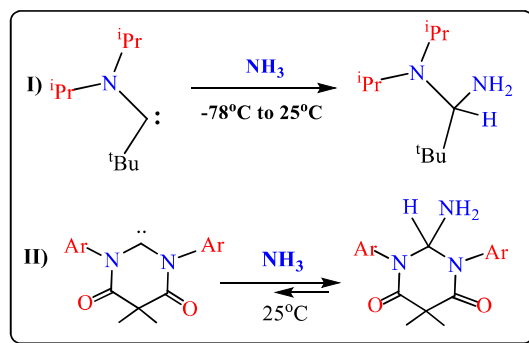
Small molecules (H_2 , CO_2 , CO , and NH_3) are readily available, less expensive, and can be used as a synthon to form different chemicals. However, small molecules are very stable and usually require a catalyst to cleave them. Previous reports indicate that transition metal complexes are widely used for the activation of small molecules.⁴²⁻⁴⁴ In this regard, ammonia (NH_3) activation has been reported with pincer-based (nickel (Ni) and iridium (Ir)) transition metal complexes.⁴⁵ However, it has been found that the activation of NH_3 is challenging by transition metal complexes because it can form a Lewis adduct. In contrast, alkyl-amino carbenes, and diamidocarbenes are found to be capable of activating NH_3 under mild conditions. The carbene's nucleophilic attack on N-H bonds in ammonia leads to N-H bond activation (see Scheme 1.6).⁴⁶⁻⁴⁷ In 2005, Power and coworkers have shown that H_2 activation by alkyne analogue digermynes compound (see scheme 1.6).⁴⁸

Moreover, it has been reported that the activation of small molecules such as H_2 , CO , NH_3 , and CO_2 is also possible by silylene, carbene, and NacNacAl(I) complexes. In this regard, Bertrand and coworkers have reported that the acyclic carbenes $[\text{C}(\text{tBu})\text{NiPr}_2]$ are found capable of activating dihydrogen, and this

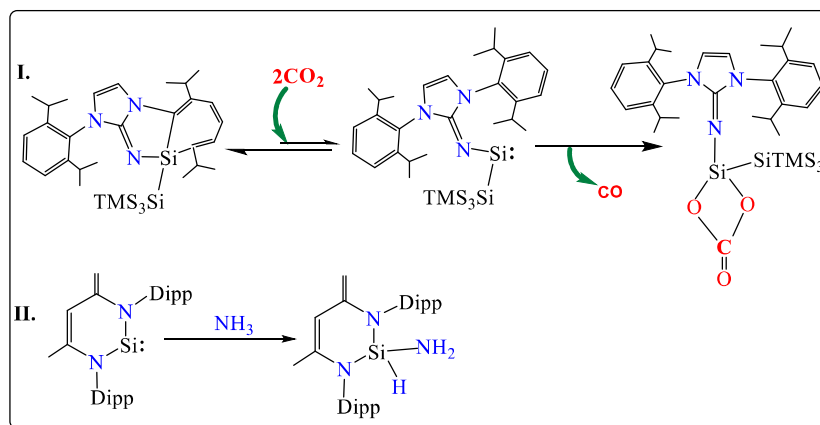
leads to the formation of the $\text{H}_2\text{C}(\text{tBu})\text{NiPr}_2$ product through oxidative addition on the carbon center.⁴⁹ Furthermore, Inoue and coworkers have recently shown that the iminosupersilylsilylene that was in equilibrium with a silepin complex $[\text{Si}(\text{IV})]$ can activate H_2 and CO_2 .⁵⁰ In 2009, Roesky and coworkers have reported the ammonia activation by an N-heterocyclic silylene at room temperature.⁵¹



Scheme 1.5 The activation of H_2 by a carbene compound.



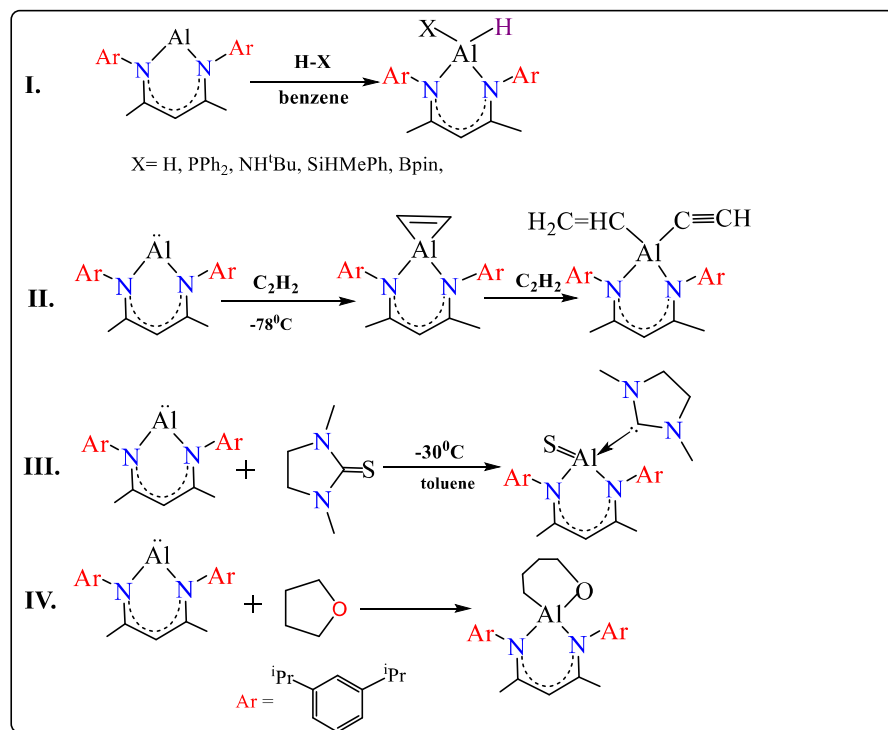
Scheme 1.6 Activation of ammonia by N-heterocyclic carbenes.



Scheme 1.7 Activation of CO_2 by a silepin (which is a dormant form of silylene) complex.

Furthermore, small molecule activation processes have also been explored with group 13 metal's compounds such as aluminum compounds. NacNacAl(I) compound was employed recently by Nikonov and co-workers to activate the H-H, H-P, H-N, H-O, H-Si, H-B, and H-C σ bonds.⁵² The same group also showed that the NacNacAl(I) complex could activate even stronger σ bonds, such as C-F, C-O, P-P, and C-S (Scheme 1.8 below).⁵³

Interestingly, what is notable is that the only aromatic solvents like benzene, toluene, and anisole^{29,53,54-56} have employed in the reactions of the aluminum (I) complex. Moreover, Nikonov and coworkers have reported that experiments of σ -bond (H-N, H-H, H-P, H-C, and H-B) cleavage by a NacNacAl(I) complex in diethyl ether solvent was unsuccessful.⁵² This indicates that unwanted side reactions or decomposition processes might be occurring in aliphatic solvents, rendering them less useful. Nevertheless, the clear preference for aromatic solvents leads to an important question: does the aromatic solvent play any role in σ bond activation by NacNacAl(I) complex? To answer this question, quantum chemical calculations with DFT has been performed, which will be explained in Chapter 3 of this thesis.



Scheme 1.8 σ and π bond activation by the NacNac Al(I) complex.

1.3 Solvent Chemistry

The solvent is an entity that dissolves a solute and exists in excess amount in the solution. The word solvent is derived from Latin and means "loosen." The solvent can be characterized by its properties such as density, vapor pressure, relative permittivity, and surface tension.

Broadly, solvents can be classified into two categories; a) polar solvents (with a dielectric constant usually more than 15.0) and b) non-polar solvents (with a dielectric constant generally less than 15.0). Polar solvents include water, acetone, dimethylformamide (DMF), tetrahydrofuran (THF), and ethyl acetate, whereas benzene, toluene, hexane, cyclohexane, pentane are non-polar solvents.

Moreover, the solvent has been extensively used in many fields of chemistry and biology, such as for chemical and biological reactions,⁵⁷⁻⁶² the rubber industry,⁶³ plastic industry⁶⁴, and the painting industry.⁶⁵ Since all homogeneous reactions happen in a solvent phase, and the solvent is known to take part in many reactions actively, in this thesis, the role of solvents in chemical transformations have been studied. Previous studies show that the presence of the solvent can bring a million-times change in the rate of reactions, yield, chemical equilibria, the stability of the system, and selectivity. Solvent can affect the reaction through polarity,⁶⁶⁻⁶⁸ specific covalent bonding interactions with the substrates,⁶⁹ proton shuttles,⁷⁰⁻⁷¹ and through hydrogen bonding with reactants and transition states.⁷² Even though the solvent plays a vital role in catalysis and selectivity, relatively less attention has been paid to the explicit role of the solvent in computational investigations. Also, the effect of explicit solvent molecules in the main group transformations is not understood completely. Hence, DFT calculations need to be performed in order to develop a deeper understanding of the solvent's impact on reaction mechanisms.

In DFT calculations, three types of models can be employed to study the effect of the solvent in reactions:

- a) An implicit model, where the solvent is considered as a dielectric medium that surrounds the solute molecule. The dielectric medium is defined by its relative permittivity or dielectric constant (ϵ).
- b) An explicit model, which involves several individual solvent molecules, *i.e.*, this model treats solvent molecules explicitly. Quantum chemical calculations with explicit solvent models are orders of magnitude more expensive than implicit solvent models.
- c) Hybrid implicit-explicit solvent model, which involves individual solvent models along with a dielectric medium.

It is essential to consider a solvent model (implicit or explicit solvent method) for the solution phase calculations because the molecular electronic wave function in solution is different from the gas phase molecular electronic wave function. In this thesis, the implicit solvent model calculations and combined

explicit-implicit calculations (which we will refer to as the explicit role of the solvent) in the main group transformations have been studied.

1.3.1 Implicit Solvation Models or Continuum Solvation Models

In implicit solvation models, the solvent is considered as a continuous dielectric medium that surrounds the solute molecule (see figure 1.1 a). In 1920, Born introduced the first dielectric continuum solvation model, and it was modified by Lars Onsager in 1936.⁷³ Since the Onsager model considers the dipole moment within the molecule, this solvation model is not applicable where molecules have a net zero dipole moment.

Currently, the Polarizable Continuum Model (PCM) is the most commonly used implicit solvation model. The PCM⁷⁴ model uses atomic spheres with 1.2 times the van der Waals radii to define the molecular cavity. To consider the solvent effect in quantum chemical calculations, two types of PCM solvent models have been employed in the literature: i) D-PCM, where the continuum is a polarizable dielectric, and ii) C-PCM, where the continuum is conductor-like. The C-PCM model is similar to the Conductor-like Screening Model (COSMO).⁷⁵ The COSMO model treats the solvent as a continuum with a dielectric constant (ϵ) of the solvent. Furthermore, where the charge distribution of a molecule can be determined, the COSMO implicit solvation model is applicable. For example, in DFT, HF, and semiempirical calculations, the COSMO method can be used to study the solvent-solute interactions.

1.3.2 Explicit-Solvation Models

Explicit solvation models involve individual solvent molecules, *i.e.*, this model treats solvent molecules explicitly (see figure 1.1 b). This is a more realistic model than implicit solvation models because the explicit solvation method includes direct, specific solvent-solute interactions. However, primarily due to the fact that explicit solvation models are computationally expensive, the explicit effect of the solvent in chemical reactions has not been explored well. These models are usually found in the application of molecular dynamics (MD) and Monte Carlo (MC) simulations. In order to study the effect of the solvent on chemical reactions, we need to add the solvent molecules explicitly around the substrate.

1.3.3 Hybrid Implicit-Explicit Solvation Models

This model includes both continuous dielectric medium and individual solvent molecules to calculate solvent effects (see figure 1.1 c). Therefore, calculations carried out using this model are accurate. However, this model is computationally expensive; the use of this model is rare. In this thesis, the solvent effect in main group reactions has studied using this method, *i.e.*, hybrid Implicit-Explicit solvation models.

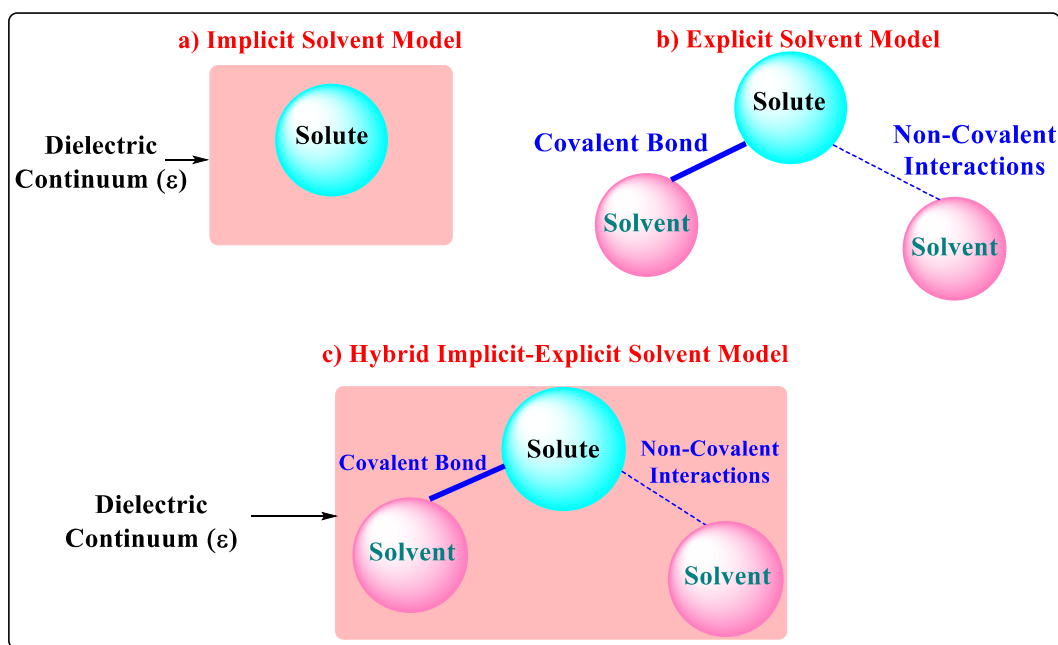


Figure 1.1 A representation of the solvent models.

1.4 Non-Covalent Interactions

Non-covalent interactions are considered weak interactions because the actual sharing of electrons between the interacting atoms, ions, or molecules is not involved in these interactions.⁷⁶ Non-covalent interactions were discovered by van der Waals in the 1870s: he explained that the interactions between atoms or molecules are responsible for the noted discrepancies in the state functions of ideal and real gases.⁷⁷ Furthermore, in 1930, Fritz London employed quantum mechanics. He described the fundamental

behavior of van der Waals interactions.⁷⁸ Later, many different kinds of dispersion effects, such as electrostatic, London dispersion, polarization, and charge transfer interactions, have been explored.

Even though non-covalent interactions are much weaker than covalent interactions, they can influence the physical and chemical properties of substances. However, it has been reported that the effects of these interactions are essential only up to a distance of about 5.0 Å.⁷⁹ Many kinds of non-covalent interactions, such as hydrogen bonds, σ -hole bonds, cation- π interactions, anion- π interactions, π - π stacking, C-H/ π , C-H/O, C-H/F interactions, lone pair interactions, and lone pair-cation- π interactions have been studied, and it has been shown that they can influence chemical and biological reactions.⁸⁰⁻⁸² The non-covalent interactions such as π - π stacking, C-H/ π , cation- π are dispersion dominated interactions. These non-covalent interactions have been illustrated in Figure 1.2 below. In this thesis work, the dispersion-dominated non-covalent interactions have been demonstrated. The C-H/ π , C-H/O, Cl/ π , and π - π non-covalent interactions between solvent and substrate have been studied in the main group transformations. Dispersion corrections to DFT calculations have been included to capture the long-range interactions.^{82b}

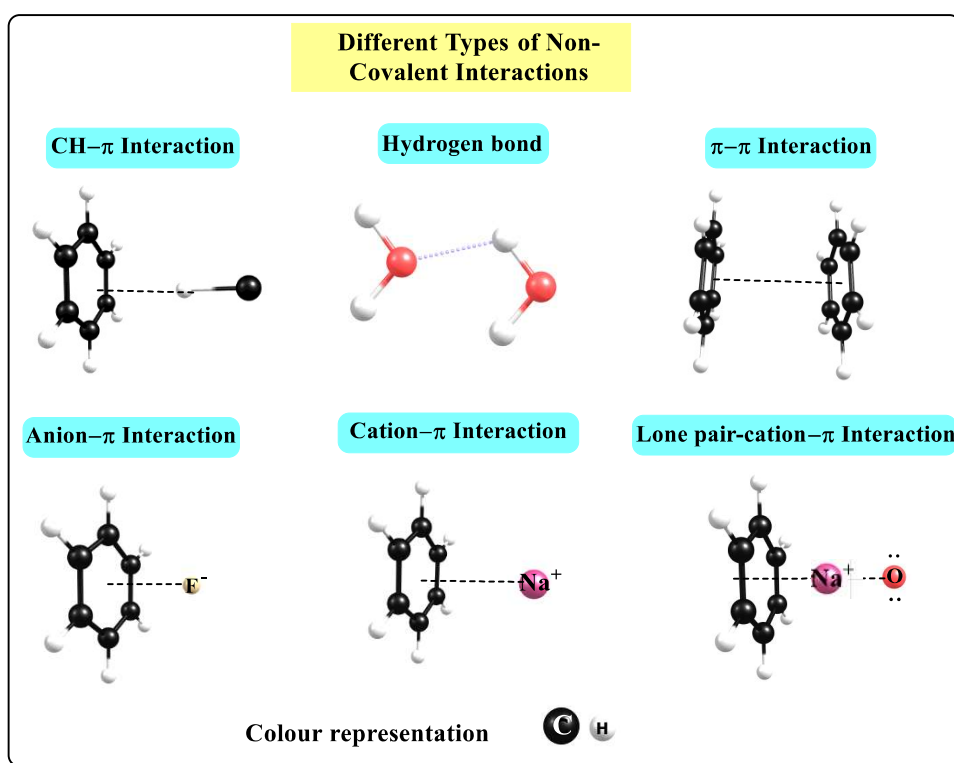
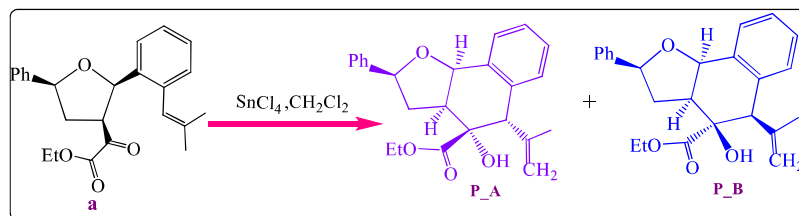


Figure 1.2 Different types of non-covalent interactions.

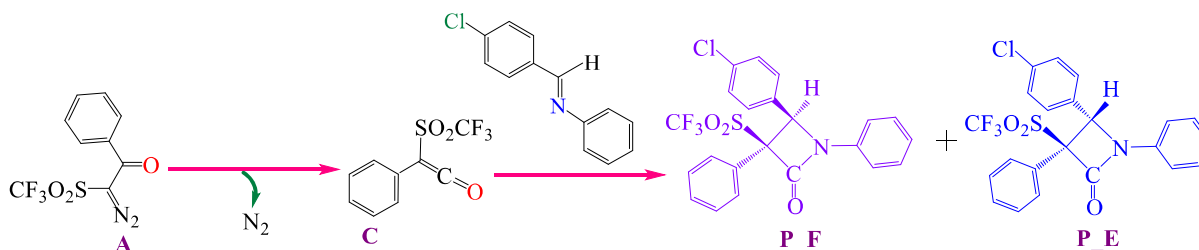
1.5 Stereoselectivity

Since stereoselectivity plays a vital role in many fields of chemistry and biology such as organic synthesis,⁸³⁻⁸⁴ asymmetric synthesis,⁸⁵ drug metabolism,⁸⁶ pharmacology,⁸⁷ and medicinal chemistry,⁸⁸ it is essential to find the origin of stereo-selectivity in organic reactions and asymmetric catalysis. Stereoselectivity depends on the stereo controlling transition states, and this has made DFT a powerful tool to understand the origin of stereoselectivity, as transition states search can be carried out with high accuracy using DFT. In this regard, computational investigations in stereoselectivity of asymmetric catalysis have been reported by Houk,⁸⁹ Schoenebeck,⁹⁰ Wheeler,⁹¹ Thiel,⁹² Wu,⁹³ Liu,⁹⁴ Sakaki,⁹⁵ and many other groups. Previous studies indicate that many factors, such as solvent,⁹⁶ additives,⁹⁷ and temperature⁹⁸ influence the stereoselectivity. Among these factors, the solvent plays the most pivotal role, as most of the organic reactions are carried out in a solvent. The solvent induces stereoselectivity due to the differential stabilization of the two stereo controlling transition states by the interaction of solvent molecules with the substrate in different ways.

Previous reports have discussed the effect of different solvents, and the explicit role of solvent molecules, on stereoselectivity.⁹⁹⁻¹⁰⁰ In addition to these effects, the role of dispersion is important in controlling the stereoselectivity of many reactions, where the role of non-covalent effects such as hydrogen bonding, π - π stacking, as well as C-H/ π , and C-H/O interactions between solvent and substrate have been studied.¹⁰¹⁻¹⁰² Even though the effect of solvent on stereoselectivity has been widely investigated, the number of studies that show non-covalent interactions between solvent and substrate to be the major reason for the stereoselectivity are not studied well. In order to explore the influence of the solvent on the stereoselectivity, we have considered two important, stereoselective organic reactions: the carbonyl-ene reaction,¹⁰³ which is a reaction between the ene and the enophile for selective carbon-carbon bond formation, and b) the Staudinger reaction, which is a [2+2] cycloaddition reaction¹⁰⁴ between a ketene and an imine for the synthesis of triflones. Non-covalent interactions between the solvent and substrate are responsible for the stereoselectivity of these reactions have demonstrated.



Scheme 1.9 (a) The reaction for the formation of the tricyclic tetrahydrofuran diastereomers **P_A** and **P_B** via the intramolecular carbonyl-ene reaction.



Scheme 1.9 (b) The reaction for the formation of the triflones diastereomers **P_F** and **P_E** via the [2+2] cycloaddition Staudinger reaction.

1.6 Objectives of This Thesis

A large amount of the chemical reactions take place in the solvent, and the solvent has been seen to have a distinct influence on the rate of the reaction, selectivity, and molecular association. In biological and organic reactions, it has been reported that the solvent can influence the chemical reaction through polarity, non-covalent interactions, and specific covalent bonding interactions with the substrates. However, the role of the solvent is not understood well even now. In this thesis, we have tried to shed light on those new roles of the solvent.

It has been noted that σ and π bond activation by low valent NacNacAl(I) complex has always been carried out in an aromatic solvent such as benzene, toluene, and anisole. Therefore, the question that has to be asked here is - what role does the aromatic solvent play in Al(I) chemistry? In order to address this issue, DFT calculations have been carried out, and the first example of metal-solvent cooperativity in main group chemistry has been demonstrated.

The next question we have asked is: does the solvent affect silylene chemistry through non-covalent interactions? Hence, DFT calculations, as well as *ab initio* molecular dynamic (AIMD) simulations, have been carried out to find the explicit role of the solvent, where the ability of the solvent to influence the efficiency of chemical processes catalytically through $\text{C-H}/\pi$ interactions in the formation of silepin complex, and in the activation of CO_2 , has been investigated.

A further question that we have asked is: how does the solvent control the stereoselectivity of intramolecular carbonyl-ene and intermolecular Staudinger reactions? We have demonstrated that the non-covalent interactions between the solvent and substrate are the major reason for the high stereoselectivity of these two reactions.

Hence, in this thesis, we have served to illustrate the vital role of the solvent in small molecule activation by low valent main group complexes, as well as its effect on stereo-selectivity. It has been shown that the solvent can influence the rate of the reaction through covalent bonding as well as through non-covalent interactions and enhance the turnover frequency of the reaction.

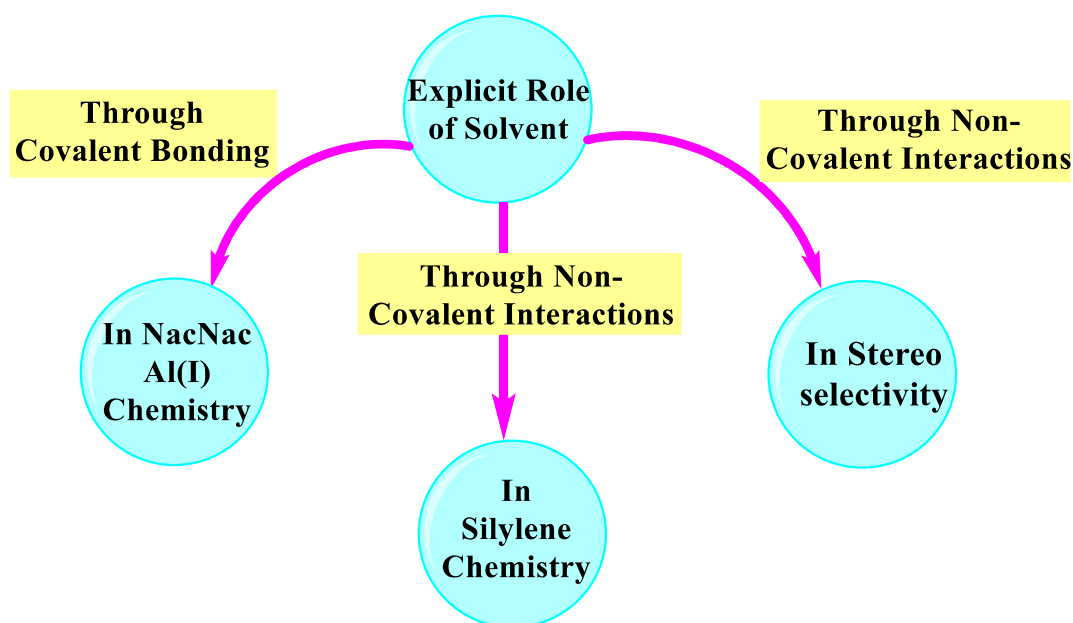


Figure 1.3 Structural representation of the explicit role of the solvent in the main group transformations studied in the current thesis.

1.7 Organization of the Thesis

This thesis is divided into seven chapters.

Chapter-1: Introduction:

This chapter provides a brief introduction about solvent chemistry and non-covalent interactions in low valent main group chemistry and the stereoselectivity of the carbonyl-ene and the Staudinger reaction.

Chapter-2: Fundamentals Computational Chemistry:

In this chapter, the fundamentals of quantum chemical methods such as density functional theory (DFT) have been provided. Also, the NBO analysis, volume correction methods, turnover frequency calculations, and the NCI plot analysis have been described in brief.

Chapter-3: The Unusual Role of the Aromatic Solvent in Single Site Al(I) Chemistry: Insights from Theory:

In this chapter, the explicit role of the aromatic solvent in σ bond activation, such as in H-H, N-H, and P-H activation by NacNacAl(I) complexes, has been discussed. We have shown that Al (I) converts into Al (III) by activating one of the three π bonds of the benzene solvent. It has been observed that the solvent molecule has a positive effect on the turnover frequency of σ bond activation processes (orders of magnitude higher than in the absence of an explicit solvent molecule).

Chapter-4: Can the Solvent Enhance the Rate of Chemical Reactions through C-H/ π Interactions? Insights from Theory:

This chapter describes the rate of chemical reactions that can be influenced by non-covalent C-H/ π interactions between substrates, and the solvent has been studied. The C-H/ π interactions were found to be more dominant than π - π interactions between the solvent (toluene) and the substrate. Calculations suggest that the rate of the silepin formation process is enhanced due to C-H/ π interacting solvent with the substrate.

Chapter-5: CO₂ Activation Assisted by C-H/ π Non-Covalent Interactions between Solvent and Substrate:

In this chapter, how the rate of CO₂ activation by a low valent silicon complex is influenced by C-H/ π interactions between substrates and the solvent have been illustrated. We have observed that the presence of an explicit solvent molecule improves the turnover frequency of the CO₂ activation process. Furthermore, *ab initio* molecular dynamics (AIMD) simulations have been carried out to study the exchange between solvent molecules and their effect on free energy profiles.

Chapter-6: The Effect of Solvent-Substrate Non-covalent Interactions on the Diastereoselectivity in the Intramolecular Carbonyl-Ene and the Staudinger [2+2] Cycloaddition Reactions:

This chapter describes the non-covalent interactions between the solvent and substrate are responsible for the origin of stereoselectivity of the Carbonyl-Ene and the Staudinger [2+2] cycloaddition reaction. Interestingly, in both cases, the calculations suggest that the non-inclusion of explicit solvent molecules lead to only a small difference between the competing transition states. Therefore, explicit solvent molecules are the major cause of high diastereoselectivity in both reactions.

Chapter-7: Conclusion and Future Outlook:

This chapter provides conclusions and the future outlook of this thesis.

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Chapter 2

Fundamentals of Computational Chemistry

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Fundamentals of Computational Chemistry

Abstract

Density functional theory is used as a tool to investigate mechanistic pathways of main group reactions. In this chapter, the fundamental of DFT has been discussed in brief. The DFT methods have allowed us to compute the energy of systems as a functional of electron density. Moreover, DFT has become a powerful tool to study reactivity, structures, transition states, spectra, and other properties of chemical systems with accuracy. After establishing the favorable reaction mechanism (lowest energy), TOF calculations, NBO analysis, interaction energy calculations, volume correction in the entropy, and NCI plot analyses have been carried out in this thesis work. In this chapter, the theoretical background of these methods has been described in brief.

2.1 Introduction

Computational chemistry includes solving chemical problems on a computer using algorithms rather than developing new algorithms or theoretical methods. Douglas Hartree was the first scientist who used external "computers" for theoretical calculations of molecules.¹ Computational method can be employed today for geometry optimizations, determining the energy of molecules, transition state searches, IR, Raman, NMR, and Circular Dichroism spectra analysis, bond and orbitals analysis, the determination of polarizability, electron affinities, population analysis, and to study the effect of dispersion interactions. Single-step and multistep reaction pathways can be represented as energy profile diagrams derived from the corresponding potential energy surfaces.

Computational chemistry involves the following methods to study various problems:

i) Molecular mechanics, which is based on force fields and does not use a wave function. Therefore, molecular mechanics methods cannot be employed to study electronic effects. However, these methods are faster than quantum chemical methods.

ii) *Ab initio* quantum chemistry methods, which are based on the Schrödinger equation. The term *ab initio* means from the beginning or first principles. Examples of *ab initio* quantum chemistry methods are Hartree Fock, post Hartree Fock, and Quantum Monte Carlo methods.

iii) Semi-empirical methods, which use a simpler Hamiltonian than the correct molecular Hamiltonian and use empirical (derived from experimental evidence) information. Hence, semi empirical methods are inexpensive methods.

iv) Density functional theory, based on electron density probability, which can speed up the calculations. Furthermore, DFT methods can handle large chemical systems with accuracy.

v) *Ab initio* molecular dynamics (AIMD), which lead together Newton's and Schrödinger's equations, with the interatomic forces derived from the electronic wave function.

In addition to these approaches, there are *ab initio* quantum chemical methods such as coupled-cluster (CC)² and configuration interaction (CI)³, which are computationally expensive. Quantum chemical calculations with DFT have been performed in work described in this thesis, as it is the best theoretical method to study large systems with accuracy.⁴ In Section 2.3 of this chapter, the fundamentals of DFT have been providing. Also, elementary quantum mechanics has been reviewed in the next section of this chapter to understand the basis of DFT. Moreover, natural bond orbital (NBO) analysis, the volume correction method, turnover frequency calculations with the energetic span model, interaction energy calculations, and the NCI plot analysis have been discussed briefly in this chapter.

2.2 Elementary Quantum Mechanics

2.2.1 The Schrödinger Equation, Hamiltonian Operator, and the Wave Function

In 1926, Erwin Rudolf Josef Alexander Schrödinger proposed the time-dependent non-relativistic Schrödinger equation. Modern quantum mechanics is based upon solving this equation, which allows us to calculate the wave function at any time. However, the objective of quantum chemical approaches is to solve the time-independent Schrödinger equation (TISE), as most of the time-dependent interactions are not significant in chemical problems. The many-body TISE for the system with n number of electrons and m number of nuclei is given by;

$$\hat{H}\Psi(x_1, x_2, x_3, \dots, x_n, r_1, r_2, \dots, r_m) = E\Psi(x_1, x_2, x_3, \dots, x_n, r_1, r_2, \dots, r_m) \quad (2.11)$$

Where, E (eigen value) is the total energy of the system, $\Psi(x_n, r_m)$ (eigen function) is the wave function for the system, which is a function of $3m$ space coordinates of nuclei and the $3n$ space coordinates and n spin coordinates of electrons.

Moreover, a wave function is also known as a state function that contains all possible information about the system. All the information about the system can be extracted from the wave function by employing a suitable operator on it. The wave function ($\Psi(x_n, r_m)$) is not a physical observable but the square of $\Psi(x_n, r_m)$, probability density ($|\Psi(x_1, x_2, x_3, \dots, x_n)|^2$), provides the physical interpretation of the wave function.

Equation 2.12 represents the probability, where the electrons 1, 2,..., n are found in volume $dx_1, dx_2, \dots, dx_n$.

$$\int \dots \int |\Psi(x_1, x_2, x_3, \dots, x_n)|^2 dx_1 dx_2 \dots dx_n \quad (2.12)$$

$\hat{H}(x_n, r_m)$ is a Hamiltonian operator, which is expressed as;

$$\hat{H} = \frac{-\hbar}{2} \sum_{a=1}^m \frac{1}{m_a} \nabla_a^2 - \frac{\hbar}{2m_e} \sum_{i=1}^n \nabla_i^2 + \sum_a \sum_{a>b} \frac{Z_a Z_b e^2}{r_{ab}} - \sum_a \sum_i \frac{Z_a e^2}{r_{ia}} + \sum_j \sum_{i>j} \frac{e^2}{r_{ij}} \quad (2.13)$$

In above equation (2.13), the first two terms represent the kinetic energy of the nuclei and electrons, respectively. The remaining three terms represent the nuclear-nuclear repulsion, nuclear-electron attraction, and electron-electron repulsion respectively, $\hbar = h/2\pi$ and h is the Planck's constant, m_a and m_e are the masses

of the nuclei and electrons respectively, Z_a and Z_b represent the charges of nuclei, r_{ab} is the distance between the nuclei a and b , r_{ia} represents the distance between the i^{th} electron and the a^{th} nuclei and r_{ij} is the distance between the i^{th} and the j^{th} electron.

2.2.2 The Born-Oppenheimer Approximation

To simplify the Schrödinger equation (S.E.), Börn and Oppenheimer proposed an approximation in 1927 that is based on the fact that nuclei move much slower than electrons because nuclei are much heavier than electrons. Hence, we can assume that all electrons exist in the field of fixed nuclei, *i.e.*, the nuclear kinetic energy is zero, and the nuclear potential energy is merely a constant. Therefore, the molecular Hamiltonian operator is shown in equation 2.14 effectively reduces the electronic Hamiltonian.

$$\hat{H}_{\text{el}} = \frac{-\hbar}{2m_e} \sum_{i=1}^n \nabla_i^2 - \sum_a \sum_i \frac{Z_a e^2}{r_{ia}} + \sum_j \sum_{i>j} \frac{e^2}{r_{ij}} \quad (2.14)$$

Hence, the Schrödinger equation with the electronic Hamiltonian would be;

$$\hat{H}_{\text{el}} \Psi_{\text{el}} = E_{\text{el}} \Psi_{\text{el}} \quad (2.15)$$

The total energy of the system can be written as;

$$E_{\text{tot}} = E_{\text{el}} + E_{\text{nn}} \quad (2.16)$$

Where E_{el} is the electronic energy and E_{nn} is the nuclear-nuclear repulsion, which is given by;

$$E_{\text{nn}} = \sum_a \sum_{a>b} \frac{Z_a Z_b e^2}{r_{ab}} \quad (2.17)$$

2.2.3 The Variational Principle

To solve the S.E. for any molecule first, we need to construct a Hamiltonian operator corresponding to that molecule and then find the eigen functions and eigenvalues for the Hamiltonian operator. However, there is no actual process to solve the Schrödinger equation precisely for any system. Therefore, we need a trial wave function to solve this issue. To do this, we take the help of the variational principle, which states

that *"the energy calculated using a trial wave function is always an upper bound to the original ground state energy (E_0) of the system of interest."*

$$E(\Psi) = \frac{\langle \Psi | \hat{H} | \Psi \rangle}{\langle \Psi | \Psi \rangle} \geq E_0 = \frac{\langle \Psi_0 | \hat{H} | \Psi_0 \rangle}{\langle \Psi_0 | \Psi_0 \rangle} \quad (2.18)$$

Where, $\frac{\langle \Psi | \hat{H} | \Psi \rangle}{\langle \Psi | \Psi \rangle}$ is expectation value of energy ($E[\Psi]$), and $\langle \Psi | \hat{H} | \Psi \rangle = \int \Psi^* \hat{H} \Psi d\tau$.

Ψ_0 is the true ground state wave function. The corresponding energy E_0 can be found by the full minimization of the given functional $E(\Psi)$ with respect to all of the allowed n electronic wave functions.

2.3 Density Functional Theory

The quantum chemical methods based on the wave function (Ψ), are found to be more expensive because the wave function is a $4n$ variable, $3n$ for spatial, and n for spin variables for each electron. Also, the complexity of the wave function increases with the number of electrons in the system. To reduce this complexity in the calculations of essential properties of any system, it is necessary to consider an alternative for a wave function. The best choice of wave function dependent methods, in terms of efficiency and accuracy, is density functional theory (DFT). DFT allows us to compute any molecule's energy and other properties by using the electron density as a fundamental parameter. Unlike the wave function, the electron density is an experimental observable and measurable quantity and depends on three spatial coordinates. Therefore, electron density-based methods are more economical than wave function-based methods. Moreover, one can employ DFT for computing all kinds of properties of many different types of systems, including large systems. In the next subsection, functional and electron density have been reviewed in brief.

2.3.1 Functional

A function of another function is known as functional. The functional takes a function as an input and provides an output, whereas a function takes a number as an input to give an output. For example, the variational integral $F[\phi] = \langle \phi | \hat{H} | \phi \rangle / \langle \phi | \phi \rangle$ is a functional of the variation function ϕ . Like a function, one can find the derivative of a functional. The differentiation of a functional $F[g]$ can be expressed as;

$$\partial F[g] = F[(g+\partial x)] - F[g] = \int \frac{\partial F}{\partial g(x)} \partial g(x) \cdot dx \quad (2.19)$$

Different types of functional such as local-density, generalized gradient, meta-generalized gradient, and hybrid approximations can be employed in the DFT method.

2.3.1.1 Local-Density approximation (LDA)

LDA is applicable to the homogeneous gas system, where the electron density $\rho(\vec{r})$ fluctuate slowly with the position. In particular, the electron density can be treated locally as a uniform electron gas in this approximation. Thus, the exchange-correlation energy at each point of the system will be the same. LDA is the uncomplicated approximation to find the exchange-correlation. According to LDA, exchange-correlation power can be represented as

$$E_{XC}^{LDA}[\rho] = \int \rho(\vec{r}) \epsilon_{XC}(\rho(\vec{r})) d\vec{r} \quad (2.20)$$

where ϵ_{XC} is the exchange-correlation energy per particle of a homogeneous electron gas of electron density ρ . The exchange-correlation energy can be written as the summation of exchange and correlation terms. $\epsilon_{XC}(\rho) = \epsilon_X(\rho) + \epsilon_C(\rho)$

LDA approximation is applicable for closed-shell systems, while LSDA (local spin density approximation) is relevant for open-shell system (free radical) calculations.

2.3.1.2 Generalized Gradient Approximation (GGA)

LDA fails where the density varies rapidly, as in molecules. In order to solve this problem, one has to consider the gradient of the electron density ($\nabla(\rho)$). $E_{XC}^{GGA}[\rho]$ can split into the exchange and correlation parts: $E_{XC}^{GGA}[\rho] = E_X^{GGA}[\rho] + E_C^{GGA}[\rho]$.

In 1988, Becke introduced B88, Bx88, and Becke88 GGA exchange functionals, which improves DFT calculations. The commonly used GGA correlation functionals are Perdew (P86 or Pc86), Perdew-Wang (PW91 or PWc91), and Lee-Yang-Parr (LYP functional such as B88LYP or BLYP). Furthermore, we can combine any exchange functional with the correlation functional in DFT calculations. For example, BLYP

functional represents the combination of the Becke exchange functional and the LYP correlation functional. Currently, both empirical and nonempirical GGA functionals are available for use. Perdew-Burke Ernzerhof (PBE), a commonly used GGA functional, does not involve empirical parameters.

2.3.1.3 Meta-Generalized Gradient Functionals

Meta-GGA functionals are an extension of GGA functionals that depend on the second derivatives of the electron density (kinetic-energy density). In the meta-GGA approximation, the exchange-correlation energy can be expressed as;

$$E_{XC}^{MGGA}[\rho^\alpha, \rho^\beta] = \int f(\rho^\alpha, \rho^\beta, \nabla \rho^\alpha, \nabla \rho^\beta, \nabla^2 \rho^\alpha, \nabla^2 \rho^\beta, \tau_\alpha, \tau_\beta) dr \quad (2.21)$$

where, τ_α, τ_β are the non-interacting kinetic energy density terms that can be defined as

$$\tau_\alpha = \frac{1}{2} \sum_i |\nabla \theta_{i\alpha}^{KS}(r)|^2 \text{ where, the } \theta_{i\alpha}^{KS} \text{ are the Kohn-Sham orbitals for the electrons that have } \alpha \text{ spin.}$$

meta-GGA functionals are more accurate but computationally more expensive than GGA functionals. For example, M06-L is a meta-GGA functional that gives a better performance as it contains 37 optimized parameters. Another example of a meta-GGA functional is TPSS, a nonempirical meta-GGA functional and provides better results than the PBE functional.

2.3.1.4 Hybrid Functionals

Nowadays, mostly employed functionals are hybrid exchange-correlation functionals, which provide accurate results. Because these functional include an exact exchange term from Hartree-Fock theory along with the exchange-correlation energy from other sources such as empirical and *ab initio*. The HF exchange energy is given below, is the exact exchange energy for a system of the non-interacting-electrons with electron density equal to the real system.

$$E_X^{HF} = - \sum_{i=1}^n \sum_{j=1}^n \langle \Psi_i^{KS}(1) \Psi_j^{KS}(2) | \frac{1}{r_{ij}} | \Psi_i^{KS}(2) \Psi_j^{KS}(1) \rangle \quad (2.22)$$

In 1993 Axel Becke introduced a hybrid approach for DFT calculations modified by Stevens *et al.*, in 1994. The most popular hybrid DFT functional is B3LYP or Becke3LYP.

It is challenging to say that which DFT functional is best because the use of functional depends on the type of system and properties are being calculated.

2.3.2 The Electron Density

The electron density is a fundamental component of density functional theory. It is defined as the probability of finding one electron of random spin within a particular volume. The electron density can be expressed by the following integral equation.

$$\rho(\vec{r}) = N \int \dots \int |\Psi(\vec{x}_1, \dots, \vec{x}_n)|^2 d\vec{x}_1 d\vec{x}_2 \dots d\vec{x}_n \quad (2.23)$$

where, $\vec{x} = \vec{r}, s$ and $\rho(\vec{r})$ is the probability of finding any of the N electrons in the volume $d\vec{r}_1$, with arbitrary spin. The remaining $N-1$ electrons will have random positions and spins in the state denoted by Ψ . Furthermore, $\rho(\vec{r})$ (electron density) is a quantum-mechanical observable and can be measured by experimental techniques such as x-ray diffraction, electron diffraction, and scanning tunneling microscope. Also, $\rho(\vec{r})$ is a non-negative function of three spatial coordinates that integrate to the total number of electrons, *i.e.*, $\rho(\vec{r}) \geq 0$ and $\int \rho(\vec{r}) d\vec{r}_1 = N$ where $\rho(\vec{r} \rightarrow \infty) = 0$. In order to quantify and analyze the topology of ρ , the gradient of ρ (first derivative, $\nabla(\rho)$) has to be considered. Since at critical points, the gradient vanishes, the characteristic of critical points is determined by the Hessian of ρ (second derivative, $\nabla^2(\rho)$).

Furthermore, the probability of finding electrons pair with spins σ_1 and σ_2 simultaneously within two different volume elements $d(\vec{r}_1)$ and $d(\vec{r}_2)$ whereas other $N-2$ electrons have arbitrary spins and positions is known as the *pair density* that can be given as

$$\rho(\vec{x}_1, \vec{x}_2) = N(N-1) \int \dots \int |\Psi(\vec{x}_1, \vec{x}_2, \dots, \vec{x}_n)|^2 d\vec{x}_3 \dots d\vec{x}_n \quad (2.24)$$

The pair density is also a positive quantity like electron density, and it contains all the information about electron correlation.

2.3.3 The Hohenberg-Kohn Theorems

Density functional theory was first proposed by Pierre Hohenberg and Walter Kohn in 1964.⁵ They have proved two theorems regarding the electron density on which DFT has been constructed. In other words, these theorems are the basis of Kohn-Sham density functional theory.

The details and proof of the two H.K. theorems have been given below.

Theorem 1:

The external potential $\hat{V}_{\text{ext}}(\vec{r})$ is within a trivial additive constant a unique functional of the electron density $\rho(\vec{r})$. Since $\hat{V}_{\text{ext}}(\vec{r})$ fixes H we see that the full many-particle ground state is a unique functional of $\rho(\vec{r})$.

Proof

Let us assume two external potentials $\hat{V}_{\text{ext}}$ and $\hat{V}'_{\text{ext}}$ (these differ from each other by more than an additive constant), giving the same ground-state electron density $\rho(\vec{r})$. These two different external potentials will definitely correspond to two individual electronic Hamiltonian operators $\hat{H}$ and $\hat{H}'$ respectively, and $\hat{H}$ and $\hat{H}'$ will belong to two different ground state wave functions Ψ , and Ψ' respectively. E_0 and E_0' are the ground state energies corresponding to the two wave functions Ψ , and Ψ' respectively.

i) E_0 and E_0' ii) $\hat{H}$ and $\hat{H}'$ can be expressed as follows;

$$E_0 = \langle \Psi | \hat{H} | \Psi \rangle, E_0' = \langle \Psi' | \hat{H}' | \Psi' \rangle, \text{ where } E_0 \neq E_0' \quad (2.25)$$

$$\hat{H} = \hat{T} + \hat{V}_{\text{ee}} + \hat{V}_{\text{ext}}$$

$$\hat{H}' = \hat{T}' + \hat{V}'_{\text{ee}} \text{ and } \hat{V}'_{\text{ext}}$$

Since both wave function gives rise to the same electron density, overall we can represent as;

$$\hat{V}_{\text{ext}} \Rightarrow \hat{H} \Rightarrow \Psi \Rightarrow \rho(\vec{r}) \Leftarrow \Psi' \Leftarrow \hat{H}' \Leftarrow \hat{V}'_{\text{ext}}$$

Now, if we apply the variational principle, where Ψ' as a trial wave function for $\hat{H}'$;

$$E_0 < \langle \Psi'_0 | \hat{H} | \Psi'_0 \rangle = \langle \Psi'_0 | \hat{H}' | \Psi'_0 \rangle + \langle \Psi'_0 | \hat{H} - \hat{H}' | \Psi'_0 \rangle \quad (2.26)$$

After putting the value of $\hat{H}$ and $\hat{H}'$,

$$E_0 < E'_0 + \langle \Psi'_0 | \hat{T} + \hat{V}_{ee} + \hat{V}_{ext} - \hat{T} - \hat{V}_{ee} - \hat{V}'_{ext} | \Psi'_0 \rangle = E_0 < E'_0 + \int \rho(r) \{ \hat{V}_{ext} - \hat{V}'_{ext} \} dr \quad (2.27)$$

Right-hand side of equation (2.26) can also be write as;

$$E'_0 < E_0 - \int \rho(r) \{ \hat{V}_{ext} - \hat{V}'_{ext} \} dr \quad (2.28)$$

Addition of equations (2.26) and (2.27) leads following results;

$$E_0 + E'_0 < E'_0 + E_0, \text{ or } 0 < 0$$

Therefore, it has been proved that there cannot be two different $\hat{V}_{ext}$ that provides the same ground-state electron density.

The ground state energy is a functional of ground-state electron density that can be represented as;

$$E_v[\rho_0] = T[\rho_0] + V_{ne}[\rho_0] + V_{ee}[\rho_0] \quad (2.29)$$

$$E_v[\rho_0] = \int \rho_0(\vec{r}) v(\vec{r}) d\vec{r} + T[\rho_0] + V_{ee}[\rho_0] \quad (2.30)$$

Where, $\rho_0(\vec{r})v(\vec{r})d\vec{r}$ is the system-dependent part, and $T[\rho_0] + V_{ee}[\rho_0]$ is the system independent part. The later part called the Hohenberg-Kohn functional $F_{HK}[\rho_0]$ (given below).

$$F_{HK}[\rho_0] = T[\rho_0] + V_{ee}[\rho_0] \quad (2.31)$$

F_{HK} is universal functional of electron density, which is independent of external potential (V_{ext})

Up to this extent, we have understood that the ground state electron density alone is sufficient to calculate all properties of the system chosen. However, it does not advise us on how to be assured that the electron density employed to estimate the properties is the true ground-state electron density for the system. In the second Hohenberg-Kohn theorem, the prescription for this has been provided.

Theorem 2:

" $F_{HK}[\rho_0]$, the functional that delivers the ground state energy of the system, delivers the lowest energy, in the case that the input density is true ground state density, ρ_0 ."

This theorem can be represented as

$$E_0 \leq E[\rho] = T[\rho] + E_{ne}[\rho] + E_{ee}[\rho] \quad (2.32)$$

Proof

Let us assume that guess density that will have its own Hamiltonian $\hat{H}'$ and wave function Ψ . This wave function can be used as a guess wave function for the Hamiltonian, which is generated from the external potential V_{ext} . Hence, we can represent;

$$\langle \Psi | \hat{H} | \Psi \rangle = T[\rho] + V_{ee}[\rho] + \int \rho(\vec{r}) \hat{V}_{\text{ext}} d\vec{r} = E[\rho] \geq E_0[\rho_0] = \langle \Psi_0 | \hat{H} | \Psi_0 \rangle \quad (2.33)$$

2.3.4 The Kohn-Sham approach

As discussed in the previous section, the electron density is a fundamental quantity for calculating the ground state properties of any atomic or molecular system. The Hohenberg-Kohn theorem suggests that the ground state energy of an atomic or molecular system can be expressed as

$$E_0 = \min_{\rho \rightarrow N} (F_{\text{H.K.}}[\rho] + \int \rho(\vec{r}) V_{\text{Ne}}(\vec{r}) d\vec{r}) \quad (2.34)$$

Where $F_{\text{H.K.}}[\rho]$ is a universal functional; it contains the kinetic energy, the classical Coulomb, and the non-classical contribution.

$$F[\rho(\vec{r})] = T[\rho(\vec{r})] + J[\rho(\vec{r})] + E_{\text{ncI}}[\rho(\vec{r})] \quad (2.35)$$

Here, $J[\rho]$ is known, but the kinetic energy term (which is a major part of total energy) $T[\rho(\vec{r})]$ is unknown. To calculate the kinetic energy exactly, Kohn and Sham published one paper in 1965, where the concept of the reference system of non-interacting electrons has been mentioned. The non-interacting reference system is constructed from a set of orbitals in the Hohenberg-Kohn formalism such that the kinetic energy can be obtained with adequate accuracy. Hence,

$$T_s = -\frac{1}{2} \sum_i^N \langle \Psi_i | \nabla^2 | \Psi_i \rangle \text{ and } \rho_s(\vec{r}) = \sum_i^N \sum_s |\Psi_i(\vec{r}, s)|^2 = \rho(\vec{r}) \quad (2.36)$$

Where T_s is the kinetic energy, and Ψ_i is the wave function of the reference system. By using this, the kinetic energy term can be calculated. Even if both the systems (interacting, as well as non-interacting) have the same electron density, it is noticeable that $T_s \neq T$. However, the major portion of the kinetic energy $T[\rho(\vec{r})]$ is recouped *via* T_s . To correct this error, Kohn and Sham introduced the partition of the universal functional, where the exchange-correlation energy $E_{xc}[\rho]$ has been added. Therefore, the universal functional can be written as;

$$F[\rho] = T_s[\rho] + J[\rho] + E_{xc}[\rho] \quad (2.37)$$

$$\text{where, } E_{xc}[\rho] = (T[\rho] - T_s[\rho]) + E_{ee}[\rho] - J[\rho] \quad (2.38)$$

The components of energy that are unknown or difficult to obtain from other theoretical methods (such as the contribution of electron exchange and electron correlation, the correction for the self-interaction, the residual portion of the kinetic energy (not included in the term T_s)), are involved in this functional ($E_{xc}[\rho]$).

The next question is how we can find the potential $V_s(\vec{r})$ for the non-interacting reference system, which is associated with the same density as the interacting system? To address this issue, we will rewrite the energy of the system as given below:

$$E[\rho] = T_s[\rho] + J[\rho] + E_{EX}[\rho] + E_{Ne}[\rho] \quad (2.39)$$

The further expansion of terms involved in equation (2.38) will lead to

$$E[\rho] = T_s[\rho] + \frac{1}{2} \iint \frac{\rho(\vec{r}_1) \rho(\vec{r}_2)}{r_{12}} d\vec{r}_1 d\vec{r}_2 + E_{EX}[\rho] + \int V_{Ne} \rho(\vec{r}) d\vec{r} \quad (2.40)$$

$$= -\frac{1}{2} \sum_i^N \langle \Psi_i | \nabla^2 | \Psi_i \rangle + \frac{1}{2} \sum_i^N \sum_j^N \iint |\Psi_i(\vec{r}_1)|^2 \frac{1}{r_{12}} |\Psi_j(\vec{r}_1)|^2 d\vec{r}_1 d\vec{r}_2 + E_{EX}[\rho] -$$

$$\sum_i^N \int \sum_A^M \frac{Z_A}{r_{1A}} |\Psi_i(\vec{r}_1)|^2 d\vec{r}_1 \quad (2.41)$$

In equation (2.39) the only unknown term is $E_{EX}[\rho]$. Now, according to the variational principle, upon minimization of the energy under the constraint $\langle \Psi_i | \Psi_j \rangle = \delta_{ij}$ leads to the *Kohn-Sham equation*.

$$-\frac{1}{2} \nabla^2 + \left[\int \frac{\rho(r_2)}{r_{12}} dr_2 + V_{xc}(r_1) - \sum_A^M \frac{Z_A}{r_{1A}} \right] \Psi_i = \epsilon_i \Psi_i \quad (2.42)$$

Where, $V_{xc}(\vec{r})$ can be defined as;

$$V_{XC}(\vec{r}) = \frac{\partial E_{XC}[\rho(\vec{r})]}{\partial \rho(\vec{r})} \quad (2.43)$$

New, improved potential $V_{eff}(\vec{r})$ can be calculated from these equations, which will eventually provide self-consistency. Furthermore, the theoretical mapping in between the kinetic energy and the density can be done by using Ψ_{is} . However, Ψ_{is} is not equivalent to the real orbitals of the system. Furthermore, the Kohn-Sham wave function is a single determinant approach that fails in the case of multiple determinants.

DFT is therefore employed to find better approximations to these two quantities (V_{XC} and E_{XC}) that will provide functionals and allow the computation of the energy of the systems.

Figure 2.1 below describes the self-consistent cycle for the K.S. iteration.

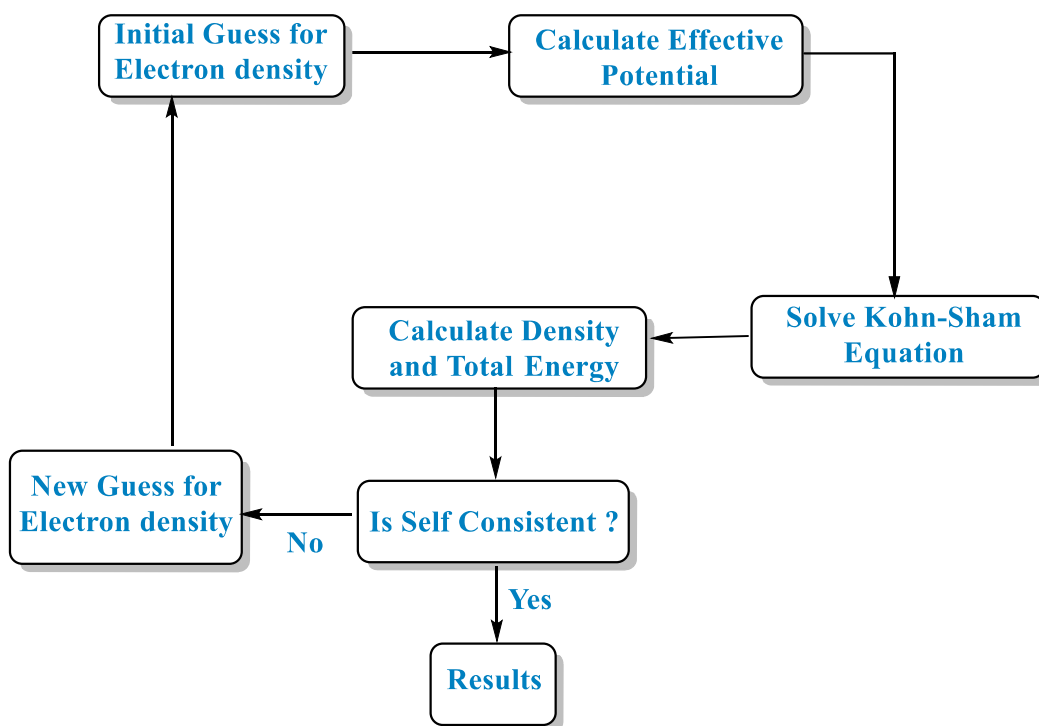


Figure 2.1 The flow chart of the self-consistent cycle for Kohn-Sham iterations for the single-step during optimization.

2.3.5 Dispersion Corrections

The attractive unit of the van der Waals interactions between directly non bonded atoms and molecules dispersion interactions are. Usually, GGA and hybrids, functionals that replace part of the local by nonlocal H.F. exchange, cannot describe long-range (dispersion interactions) interactions.⁸ Since van der Waals (vdW) interactions play a critical role in many chemical systems; it is essential to implement of dispersion effects in the calculations. The development of effective inclusion of dispersion corrections (DFT-D) by Grimme provides a proper explanation for the non-covalent interactions or dispersion interactions.⁹⁻¹² The total energy of the chemical system acquired after inclusion of dispersion correction to the functional can be expressed as;

$$E_{\text{MF-D}} = E_{\text{MF}} + E_{\text{disp}} \quad (2.44)$$

Where E_{MF} is the mean-field energy calculated by H.F. or DFT, and E_{disp} is the dispersion energy, does not have real physical meaning; it is a model-dependent quantity. This can be represented as;

$$E_{\text{disp}} = -S_6 \sum_{i=1}^{N_{\text{at}}-1} \sum_{j=i+1}^{N_{\text{nat}}} \frac{C_6^{ij}}{R_{ij}^6} f_{\text{dmp}}(R_{ij}) \quad (2.45)$$

Where N_{at} is the atoms in the system, C_6^{ij} is the dispersion coefficient for pair ij atom, S_6 is a global scaling factor, R_{ij} is the interatomic distance, and f_{dmp} is damping function, is described by;

$$f_{\text{dmp}}(R) = \frac{1}{1 + e^{-a(\frac{R}{R_0}-1)}} \quad (2.46)$$

Here, R_0 is the sum of atomic van der Waals radii.

2.4 The Volume Corrections Method for Determining the Translational Entropy

To calculate the free energy of any reaction, the calculation of entropy is a fundamental task. It is well known that the total entropy is the sum of translational, vibrational, and electronic components.

$$S_{\text{tot}} = S_{\text{trans}} + S_{\text{rot}} + S_{\text{vib}} + S_{\text{el}} \quad (2.47)$$

The translational entropy can be calculated by using the Sackur-Tetrode equation,¹³ which is given by;

$$S_{\text{trans}} = R \ln \left[\left(\frac{10^{-15/2}}{N_A^4 [X]} \right) \left(\frac{2\pi MRT e^{5/3}}{h^2} \right)^{3/2} \right] \quad (2.48)$$

Where $[X]$ is the concentration of the particle, T is the temperature, M is the mass of the particle, N_A is the Avogadro number, k is the Boltzmann constant, and h is the Planck constant.

However, in liquid or in the solution phase, the Sackur-Tetrode equation overestimates the translational entropy, as it ignores the molecular volume (V_{mol}). To overcome this problem, Mammen *et al.* introduced the *free volume* correction to the translational entropy that calculates the more accurate translational entropy.¹⁴ In this method, it has been presumed that the volume of molecules in solution is smaller than the total volume.

$$V_{\text{free}} = C_{\text{free}} \left(\left(\sqrt[3]{\frac{(10^{27})}{[X]N_0}} \right) - \sqrt[3]{V_{\text{mol}}} \right)^3 \quad (2.49)$$

Where C_{free} is 8 (for cube), N_0 is the Avogadro's number. After free volume correction to Equation 2.18, the translational entropy is expressed by

$$S_{\text{trans}}^{\text{analyte}} = R \ln \left[\left(\frac{10^{-15/2} V_{\text{free}}^{\text{solvent}}}{N_0^4 [\text{analyte}]} \right) \left(\frac{2\pi MRT e^{5/3}}{h^2} \right)^{3/2} \right] = 11.1 + 12.5 \ln(T) + 12.5 \ln(M) + 8.3 \ln V_{\text{free}}^{\text{solvent}} \quad (2.50)$$

Where, T is the temperature, $V_{\text{free}}^{\text{solvent}}$ is the free volume. Therefore, this equation provides the translational entropy in solution.

2.5 Turnover Frequency Calculation with the Energetic Span Model (ESM)

The turnover number per unit time is known as the turnover frequency (TOF). The TOF provides an estimate of the efficiency of a catalyst, thus helps to design better catalysts. In computational chemistry, when we study the reaction mechanism, we calculate the thermodynamics and the kinetics of the reaction (the free energy profile). For the experimentalists, it will be more understandable if we can also calculate the TOF using the theoretical results. Sason Shaik and Sebastian Kozuch developed the energetic span model (ESM) to calculate the catalytic cycle's efficiency.¹⁵⁻¹⁷ This model allows us to calculate the TOF from the computationally obtained free energy profile. ESM creates a bridge between experimental data and theoretical calculations because it approximates only the reactants or products, which are located between the TDI and TDTS (TDI is TOF-determining intermediate, TDTS is TOF determining transition

state) that accelerate or inhibit the reaction. According to ESM, the equation for the TOF calculation is given as;

$$\begin{aligned} TOF &= K_{\beta} T/h e^{-\delta E/RT} \\ \delta E &= T_{TDTS} - T_{TDI} \quad \text{If TDTS appears after TDI} \\ \delta E &= T_{TDTS} - T_{TDI} + \Delta G, \quad \text{If TDTS appears before TDI} \end{aligned} \quad (2.51)$$

Where K_{β} is the Boltzmann's constant, T is the temperature in K, and δE is the energetic span of the cycle. Moreover, the ESM model uses all the kinetic information (rate-determining transition state, potentially rate-influencing transition states, and the intermediates), not just one transition state or intermediate to determine the efficiency of the catalytic cycle. In this thesis, ESM has been applied to find the efficiency of solvent assisted processes.

2.6 Natural Bond Orbital (NBO) Analysis

NBO is a sequence of natural localized orbital sets, which are useful for the calculation of the electron density distribution and charger transfer in molecules. In 1955, Per-Olov Löwdin introduced the concept of ‘natural’ (localized) orbitals, where he described the unique set of orthonormal 1-electron functions that are intrinsic to the n -electron wave function $Y(1,2,\dots,n)$. The NBO analysis is a method that can transform a given wave function, Ψ , into a localized form, corresponding to the lone pairs and bonds components of the Lewis structure.⁷ NBO method based on the second-order perturbation theory that involves all interactions between donor NBOs and acceptor NBOs. The donor-acceptor interaction energy $E(2)$ can be represented as follow;

$$E(2) = \sum_{ij} q_i \frac{F(i,j)^2}{\epsilon_i - \epsilon_j} \quad (2.52)$$

Where q_i is the donor orbital occupancy, and $F(i,j)$ is the NBO Fock matrix element. NBO calculations and results have been reported in this thesis, which has been performed to analyze the bonding interactions in main group complexes.

2.7 Quantification of Stereoselectivity

The stereoselectivity of chemical reactions can be represented either as an enantiomeric ratio (er) or a diastereomeric (dr) ratio. The diastereomeric ratio (dr) (for the diastereoselective reaction) is directly proportional to the relative rates of formation of the diastereomeric products, *i.e.*, the ratio of products depends on the relative free energy barrier ($\Delta\Delta G^\ddagger$). Hence, the selectivity for the kinetically controlled reaction (at a given temperature) can be defined as;

$$\frac{k_{P_A}}{k_{P_B}} = \frac{[P_A]}{[P_B]} = e^{\frac{-\Delta\Delta G^\ddagger}{RT}} \quad (2.53)$$

where, k is the rate constant, and $\Delta\Delta G^\ddagger = \Delta G_2^\ddagger - \Delta G_1^\ddagger$ (see figure 2.2 below).

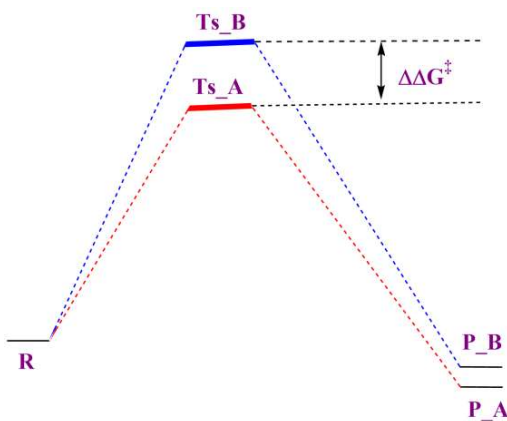


Figure 2.2 The free energy and the relative free energy barrier for two diastereomers, **P_A** and **P_B**.

Therefore, one can quantify the selectivity by computing the relative free energy difference between the two stereo controlling transition states.

2.8 The Non-Covalent Interactions (NCI) Plot

The NCI plot, developed by Yang *et al.*, is useful for analyzing and capturing non-covalent interactions.¹⁸ The NCI plot is a program that shows the graphical representation of inter and intramolecular non-covalent interactions, based on the electron density and its derivatives. Non-covalent interactions were recognized as low density and low reduced gradient regions.

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Chapter 3

The Unusual Role of Aromatic Solvent in Single-Site Aluminum(I) Chemistry: Insights from Theory

Chapter 3

The Unusual Role of Aromatic Solvent in Single-Site Aluminum(I) Chemistry: Insights from Theory

Abstract

The single-site activation of strong σ bonds (such as that of H-H, P-H, and N-H) remains a significant challenge in main-group chemistry, with only a few cases reported to date. In this regard, recent exciting experiments performed with aluminium(I) complexes hold significance because they have been seen to activate a variety of strong σ bonds. Such chemistry is generally seen to occur in aromatic solvents. In this chapter, computational studies with DFT reveal the interesting reason for this: an explicit aromatic solvent molecule acts as a catalyst by converting the aluminium(I) complex into aluminium(III) during the process. Different cases of σ bond activation by aluminium(I) complexes have been investigated and the efficiency of H-X (X=H, NH^tBu, PPh₂) bond activation in the presence of an explicit benzene solvent molecule is orders of magnitude higher than that in its absence. This work therefore reveals the chemistry of aluminium(I) complexes to be richer and more complex than that previously realized, and shows it to be dependent on metal-solvent cooperativity; the first known example of its kind in main-group chemistry.

3.1 Introduction

Small molecule activation by main group compounds has gained much attention in recent years, as an alternative to expensive and potentially more toxic transition metal chemistry.¹⁻³ While carbenes,⁴ silylenes,⁵⁻⁷ and germylenes⁸⁻⁹ have been successfully employed; researchers have also tried to explore activation possibilities with group 13 metal¹⁰ and aluminum compounds. The focus has been on converting Al(I) compounds to Al(III) by the oxidative addition of small molecules such as H₂, NH₂R and HPPPh₂. In 2000, Roesky and coworkers succeeded in synthesizing the first monomeric Al(I) complex with the bulky NacNac ligand¹¹ which exhibits a singlet carbene like behavior.¹²⁻¹⁴ This has been employed recently by Nikonov and co-workers to activate the H-H, H-P, H-N, H-O, H-Si, H-B, and H-C σ bonds.¹⁵ More recently, Nikonov's group has also shown that the NacNacAl(I) complex can activate even stronger σ bonds such as C-F and C-O,¹⁶ P-P, C-S¹⁷ and π bonds such as C=S and P=S.¹⁸ It is believed that the activation proceeds at a single, group 13 metal center.^{15,19-23}

Single site activation of H-H, H-P, H-N, and other such robust σ bonds by main group compounds^{15,19-23} (and by "single-site" frustrated Lewis pairs²⁴) has generally proved to be difficult, with only a few reported instances of the same.²⁵⁻²⁶ Hence, the recent investigations with the NacNacAl(I) complex represent an important advance in the chemistry of main group elements. However, what is notable is that the reactions of aluminum chemistry have always been carried out in aromatic solvents: benzene^{11,15} toluene²⁷⁻³⁰ or anisole.¹⁶ When Nikonov and co-workers attempted to conduct such σ bond cleavage experiments in diethyl ether, they were unsuccessful.¹⁶ It is possible that unwanted side reactions or decomposition processes might be occurring in aliphatic solvents, rendering them less useful. However, the clear preference for aromatic solvents does give rise to an important question: *does the aromatic solvent employed play an explicit role in the σ bond activation by Al(I) complexes? If so, what role does it play?*

The current computational study with density functional theory (DFT) addresses this issue, by the investigation of the Al(I) mediated activation of the H-X (X= H-H, H-N, and H-P) bond. What is proposed is that the Al(I) complex is first converted to Al(III) by the activation of one of the three π bonds of the aromatic solvent (benzene –employed experimentally in all the cases studied).¹⁵ Figure 3.1 below shows the optimized structure of the complex "A" that would be formed during this process. This is a 1,4 coordinated structure (the corresponding 1,2 coordination of the benzene NacNacAl(III) complex was seen to be considerably less favorable, by 20.5 kcal/mol (ΔE)). It is this complex A that can activate the σ bond in the substrate employed: the explicit solvent molecule acting as a ligand to the aluminum center and

activating the σ bond through metal-solvent cooperativity. This proposed reaction is illustrated in Scheme 3.1 below, for the case of H-H bond activation.

The advantage of the solvent molecule cooperating in this fashion is that it would lead to a reduction in steric strain in the transition state, *i.e.*, it would convert a strained three-membered transition state to a more stable structure, thereby making the process more facile. As will be shown in the Results and Discussion section, not only do the calculations indicate the formation of complex **A** to be likely, the σ bond activation of a range of different robust bonds is also seen to be considerably facilitated by the cooperativity between the aluminum center and the aromatic solvent molecule. Furthermore, we have also elaborated upon why this crucial role of the solvent has been missed by previous X-Ray and NMR investigations, as well as from previous experiments done in C_6D_6 .¹⁵

There have been previous computational studies that have investigated the energetics of σ and π bond activation by the $NacNacAl(I)$ complex by direct oxidative addition.^{17,20-23} However, the current work is the first to shed light on the explicit role of the aromatic solvent molecule and show how it is able to considerably enhance the potency of the $NacNacAl(I)$ system.

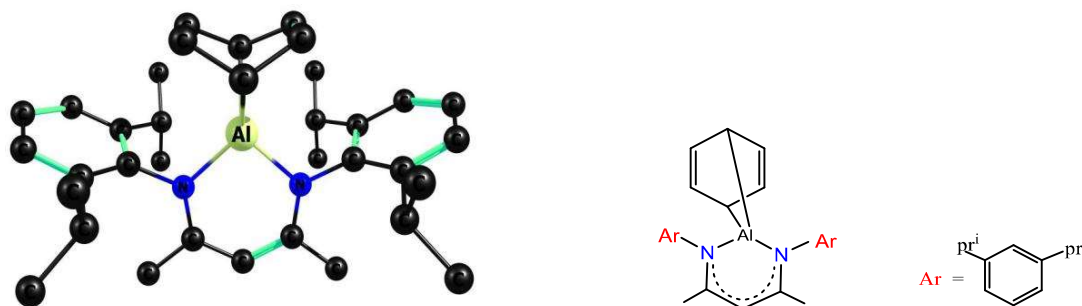
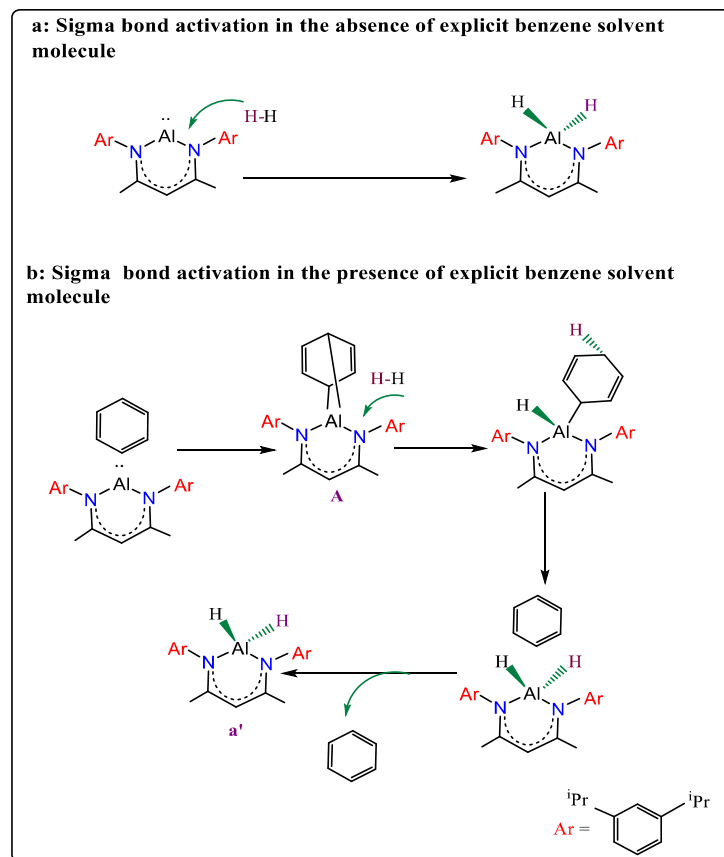


Figure 3.1 The optimized geometry of the complex “A” formed by reaction of the $Al(I)$ complex with benzene. All hydrogen atoms have been removed for the purpose of clarity.



Scheme 3.1 The proposed σ bond activation reaction for the H-H bond by the NacnacAl(I) complex (a) in the absence and (b) in the presence of an explicit benzene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model).

3.2 Computational Details

All the DFT calculations were carried out using the Turbomole 7.0 suite of programs.³¹ Geometry optimizations were performed using the Perdew, Burke, and Erzenhof density functional(PBE)³² functional, the electronic configuration of the atoms was described by a triple- ζ basis set augmented by a polarization function (Turbomole basis set TZVP).³³ The resolution of identity (ri)³⁴ along with the multipole accelerated resolution of identity (marij)³⁵ approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. The real (not model) system has been employed for all the calculations. Care was taken to ensure that the obtained transition state structures possessed only one imaginary frequency corresponding to the correct normal mode, in order to obtain more

reliable energy values for the investigated potential energy surface. In addition, intrinsic reaction coordinate (IRC)³⁶ calculations were done with all the transition states in order to further confirm that they were the correct transition state, yielding the correct reactant and product structures. Solvent effects were introduced by using the COSMO model³⁷ with the dielectric constant $\epsilon = 2.27$ for benzene. The option “disp” provided in the Turbomole package (DFT-D3) was used for dispersion-corrected DFT calculations for all the calculations with Turbomole.³⁸ The values reported are ΔG values, with zero point energy, internal energy, and entropic contributions, with the temperature taken to be 298.15K. The translational entropy term in the calculated structures was corrected through a free volume correction introduced by Mammen *et al.*³⁹ This volume correction is to account for the unreasonable enhancement in translational entropy that is generally observed in computational softwares. Then, in order to find the efficiency of the catalytic cycle in our mechanism, we have calculated the relative efficiency with the AUTOF program by employing the “Energetic Span Model” (ESM), developed by Shaik and coworkers⁴⁰⁻⁴² on all the free energy profiles discussed in the chapter. The turnover frequency (TOF) calculations take into account the principal rate-determining transition state, potentially rate-influencing transition states and intermediates during the catalysis process.

3.3 Results and Discussion

3.3.1 Formation of Complex A and H-H bond activation

Figure 3.2 below shows the free energy profile for the conversion of the NacNacAl(I) complex to NacNacAl(III), experimentally observed by Nikonov and co-workers,¹⁵ in the presence of an explicit benzene solvent molecule. Complex A is formed after the surmounting of a barrier of 21.7 kcal/mol, and lies 4.8 kcal/mol higher in energy in comparison to the reactants. NBO analysis shows that the charge on the aluminum in the original NacNacAl(I) complex is +0.7, while it is +1.8 in the Al(III) complex A. Furthermore, inspection of the donor-acceptor orbital interactions in A through NBO analysis^{43,44} shows that there is considerable interaction between the π bonding orbitals of benzene and the aluminum (see Figure 3.2 below). Hence, the evidence suggests that the benzene solvent molecule is able to successfully coordinate and interact with the aluminum center and increase its oxidation state, leading to the complex A. Also, the fact that the formation of this complex is slightly endergonic implies that a dynamic equilibrium would exist between its formation and dissociation back to the reactants: NacNacAl(I) and benzene. This

may explain why the formation of this benzene complex aluminum compound has not been detected at the NMR timescale employed in the experiments.¹⁵ This also helps explain why the structure of complex **A** escaped detection by X-ray diffraction studies: the crystallization procedure involved treatment under vacuum and washing with hexane, which would have removed the benzene molecule from the vicinity of the NacNacAl(I).¹⁵ Nevertheless, in solution, the ubiquitous presence of a solvent molecule in the vicinity of NacNacAl(I) makes the reaction between NacNacAl(I) and benzene, and therefore, the formation of complex **A**, an inevitability. Hence, **A** is likely to be the predominant complex present in a solution of benzene, or, by extension, other aromatic solvents.

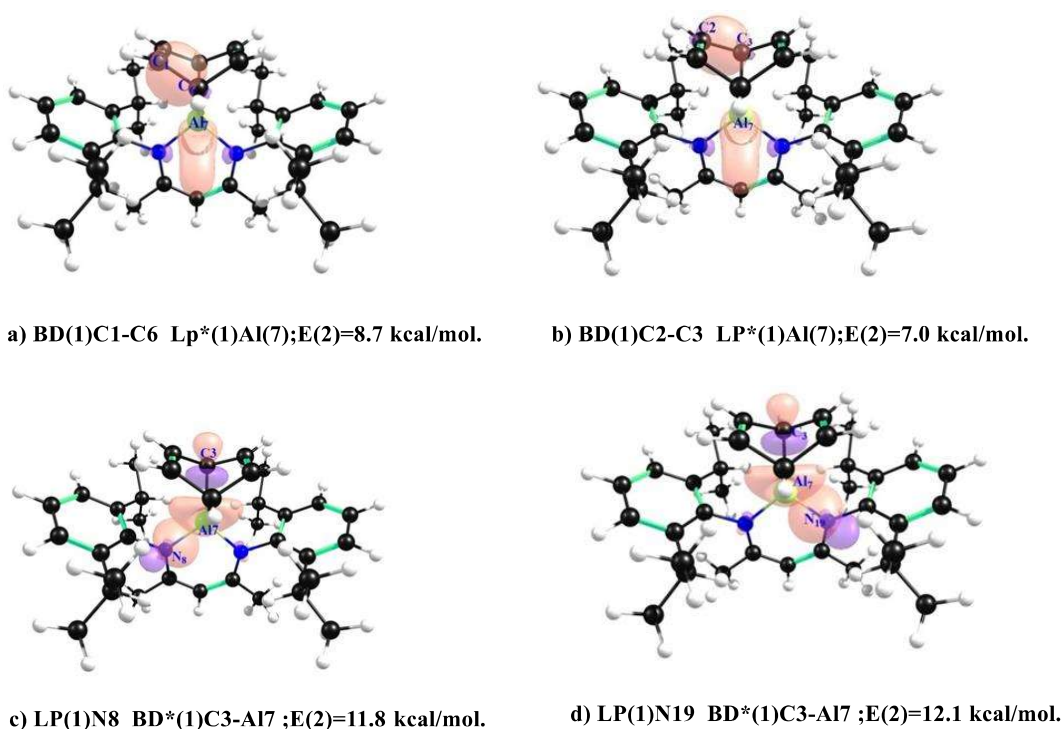


Figure 3.2 NBO analysis for complex **A**, which suggests that the bonding between benzene solvent and NacNac Al(I) complex.

Calculations further show that the approach of the substrate H₂ to **A**, and the subsequent activation of the H-H bond, would occur through the cooperation between the aluminum and the *para* carbon of the coordinated benzene, leading to the formation of the intermediate **int1_a**. The barrier for this is 34.6 kcal/mol from the reactant complex (see Figure 3.3). Subsequent to this, the additional hydrogen at the *para* carbon is transferred to the aluminum, leading to the ejection of benzene from the complex and the

formation of the final, observed product, **2_a**. Therefore, the explicit benzene solvent molecule acts as a catalyst during this process.

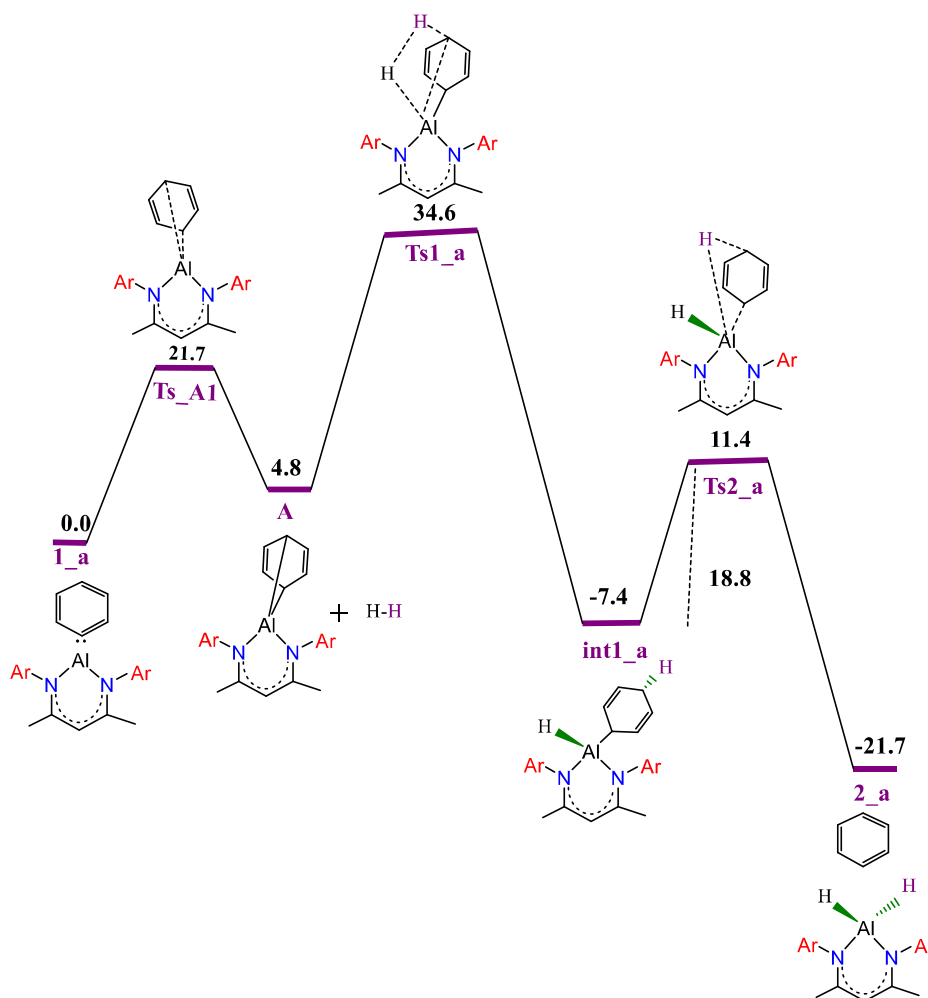


Figure 3.3 The free energy profile (ΔG in kcal/mol) for H-H bond activation by complex **A**.

There is a further important experimental observation that relates to experiments done in C₆D₆ by Nikonov and coworkers: they did not observe any deuterium scrambled product when they undertook H-H activation experiments in C₆D₆ with the NaCnacAl(I) complex. Since the reaction outlined in our proposed mechanism invokes the explicit role of the solvent, why was no deuterium scrambling observed? The interesting reason for this is understood when one looks carefully at the structure of **int1_a** (see Figure 3.4 below).

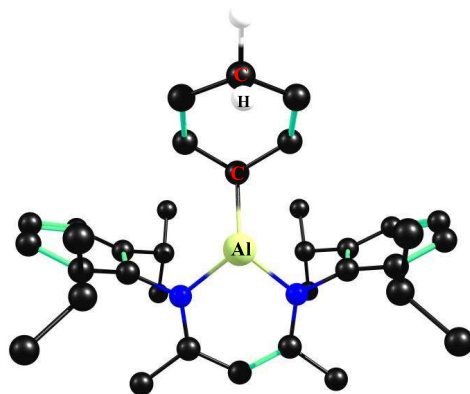


Figure 3.4 The optimized geometry of the complex **int1_a** suggests that deuterium scrambling is not possible. All hydrogen atoms have been removed for the purpose of clarity.

In this intermediate, the Al---C (phenyl) bond might be able to rotate, but that would still lead back to the hydrogen on the *para* carbon facing the aluminum, *i.e.*, to no deuterium scrambling. The only way the scrambling could occur would be if the $[C_6H_7]^+$ species were to dissociate from the aluminum center entirely and then rotate and come back to coordinate with the aluminum, with the deuterium now on the *para* carbon facing the aluminum center. Such a process would be highly unfavorable energetically, and thus, very unlikely. Thus, only H can transfer to aluminum and not D, which excludes the possibility of the deuterium scrambled product.

The next obvious question at this point would be to enquire how the process detailed in Figure 3.3 and explained above compares to the direct oxidative addition of H_2 to the $NacNacAl(I)$ complex. Shown in Figure 3.5 is the reaction profile for this process. This is seen to have a barrier of 36.6 kcal/mol, which is 2.0 kcal/mol higher than the slowest step of the benzene assisted process (Figure 3.3). Hence, the direct addition would be less efficient. In order to provide a more quantitative estimate of how much this direct process suffers in comparison to the benzene assisted one, we have determined the efficiency for the free energy profiles shown in Figure 3.3 and Figure 3.5, by both the AUTOF excel version⁴⁵ and AUTOF old text-style⁴⁶ program, by employing the “Energetic Span Model” (ESM) developed by Shaik and Kozuch.³⁸⁻⁴⁰ For details regarding the ESM method, please see the Computational Details section. The relative efficiency values (see Table 3.1) indicate that the activation of the H-H bond by assistance of the explicit benzene molecule is 30 times more efficient than the corresponding direct oxidative addition without the explicit assistance of the solvent.

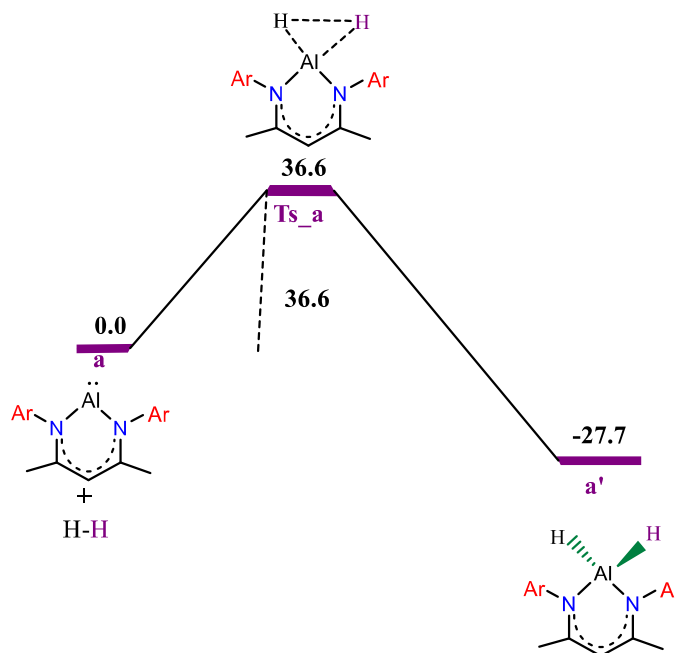
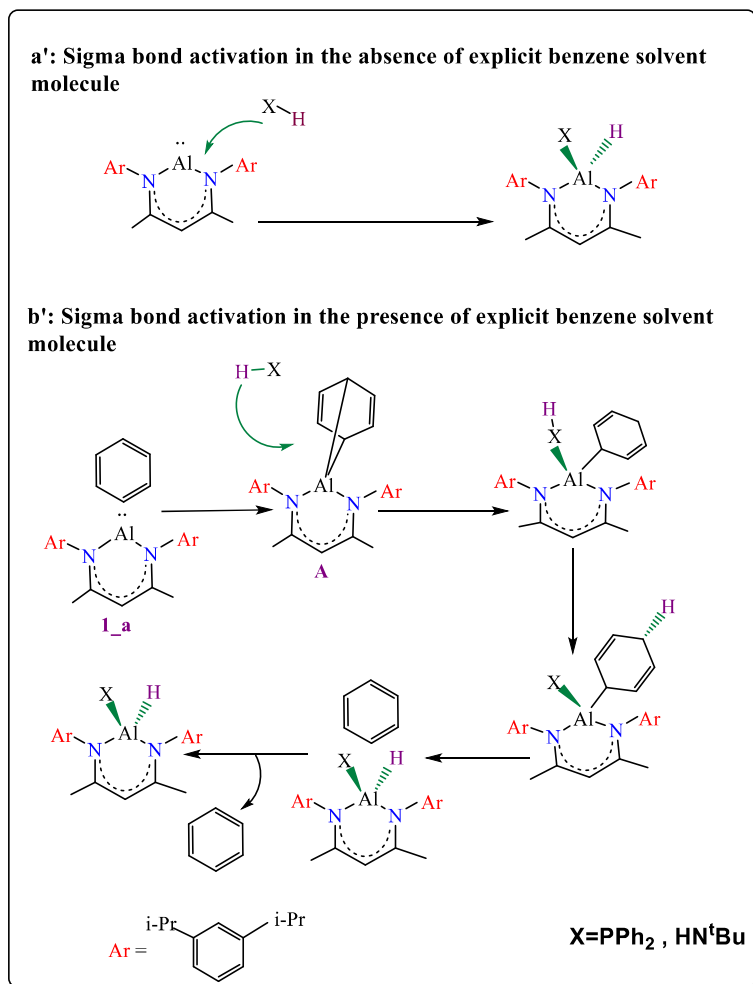


Figure 3.5 The free energy profile (ΔG in kcal/mol) for H-H bond activation without the explicit assistance of the solvent.

3.3.2 N-H Bond Activation

Next, we investigated the mechanism for N-H σ bond activation by the NacNacAl(I) complex with the assistance of the explicit benzene solvent molecule (this experiment had also been done in benzene¹⁵). This mechanism was seen to be slightly different. As shown in Scheme 3.2, an additional step occurs in this process before the *para* coordinated H complex is formed. In this step, there is prior coordination of the H-X (where X is the nitrogen-containing group: ^tBuNH, in the case studied) to the aluminum center. The free energy profile for the N-H bond activation in the experimentally studied ^tBuNH₂ complex is shown in Figure 3.6. The slowest step is seen to have a barrier of 28.5 kcal/mol and involves the interaction of the nitrogen with the aluminum center, with a corresponding loss of coordination of the *para* carbon in the benzene with aluminum. The barrier for the direct σ bond activation, in the absence of explicit solvent assistance, was seen to be much higher: 37.0 kcal/mol (See Figure 3.7).



Scheme 3.2 The σ bond activation reaction for the H-N and H-P bond cases by the Al(I) complex (**a'**) in the absence of explicit solvent and (**b'**) in the presence of an explicit benzene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model).

It is to be noted that the $\Delta E^\ddagger$ that has been previously reported for this direct N-H activation is 18.5 kcal/mol, at the BP86-D3/def2-SVP level of theory, for the case of NH₃ activation.²⁰ This is the $\Delta E^\ddagger$, and not the $\Delta G^\ddagger$, value, and the corresponding $\Delta E^\ddagger$ for our NH₂^tBu case is 22.5 kcal/mol. Furthermore, in order to see how our calculations compare to the previous results, we have also calculated the $\Delta E^\ddagger$ for the case of NH₃ activation. This ΔE value has been found to be 19.8 kcal/mol, which compares well with the previously reported value (18.5 kcal/mol). These results, therefore, indicate the reliability and robustness of the current calculations. It is also to be noted that this process occurs experimentally at room temperature, and therefore, a barrier of 37.0 kcal/mol would be difficult to overcome for the system (the temperature for the H-H activation, discussed earlier, was 70°C, consistent with the higher solvent assisted barrier obtained for

that case). This suggests that the benzene assisted process would be operational for the N-H σ bond activation reaction, while the barrier would be too high for the reaction to occur in the absence of the explicit solvent molecule. A further interesting fact is that the efficiency for this process is *six orders of magnitude* greater for the benzene assisted process in comparison to the direct oxidative addition (See Table 3.1)! These results showcase the importance of taking the role of the explicit solvent molecule into account in this chemistry.

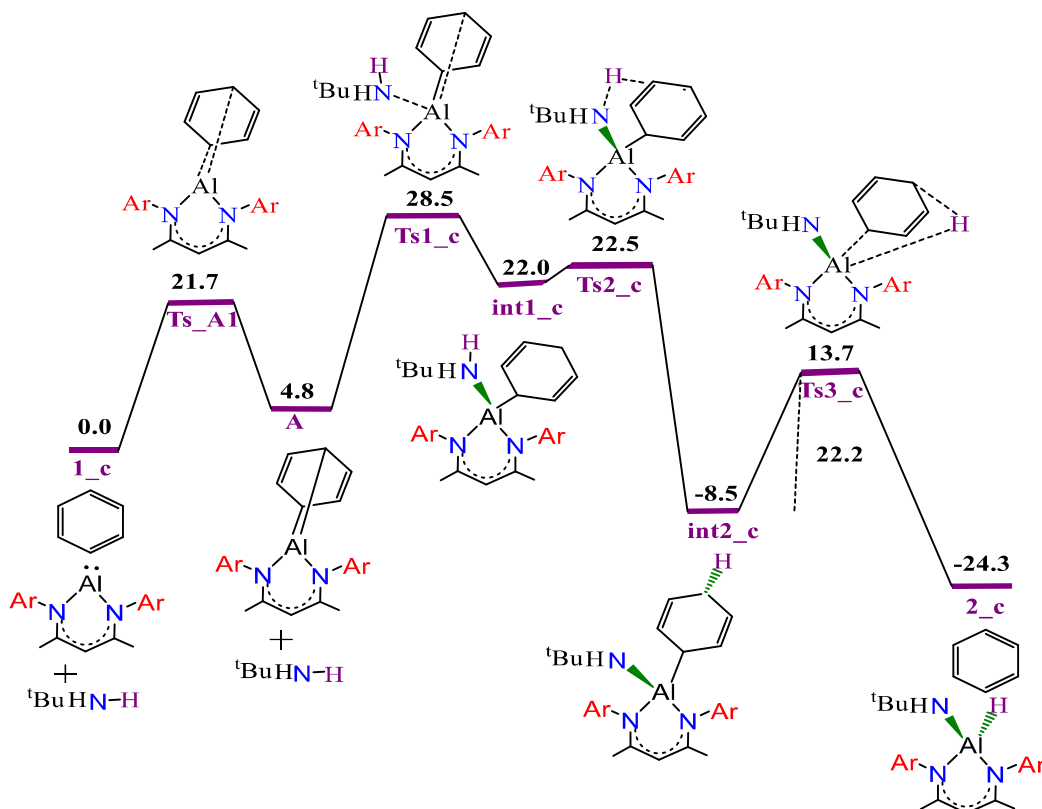


Figure 3.6 The free energy profile (ΔG in kcal/mol) for N-H bond activation by complex A.

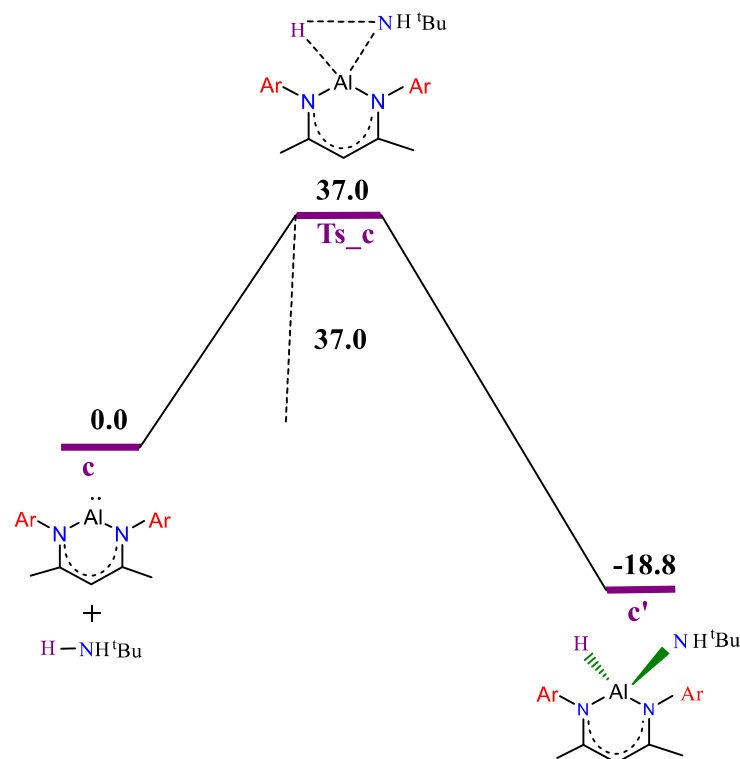


Figure 3.7 The free energy profile (ΔG in kcal/mol) for N-H bond activation without the explicit assistance of the solvent.

3.3.3 P-H Bond Activation

Studied next was the mechanism for P-H bond activation, which is the same as the mechanism for N-H bond activation (see Scheme 3.2). The obtained free energy profile for the experimentally studied substrate (HPPH₂) is shown in Figure 3.8 below, while the corresponding free energy surface in the absence of explicit solvent assistance is shown in Figure 3.9. The barrier for the slowest step in the benzene assisted case (24.9 kcal/mol) is 5.1 kcal/mol lower than the slowest step barrier without the assistance of the solvent. This reaction, too, is seen to occur experimentally at room temperature, which suggests strongly that solvent assistance is a necessity to make the σ bond activation process possible. Furthermore, ESM calculations show that in this case as well, the efficiency of the process is increased considerably, by four orders of magnitude, by the explicit assistance of the solvent (see Table 3.1).

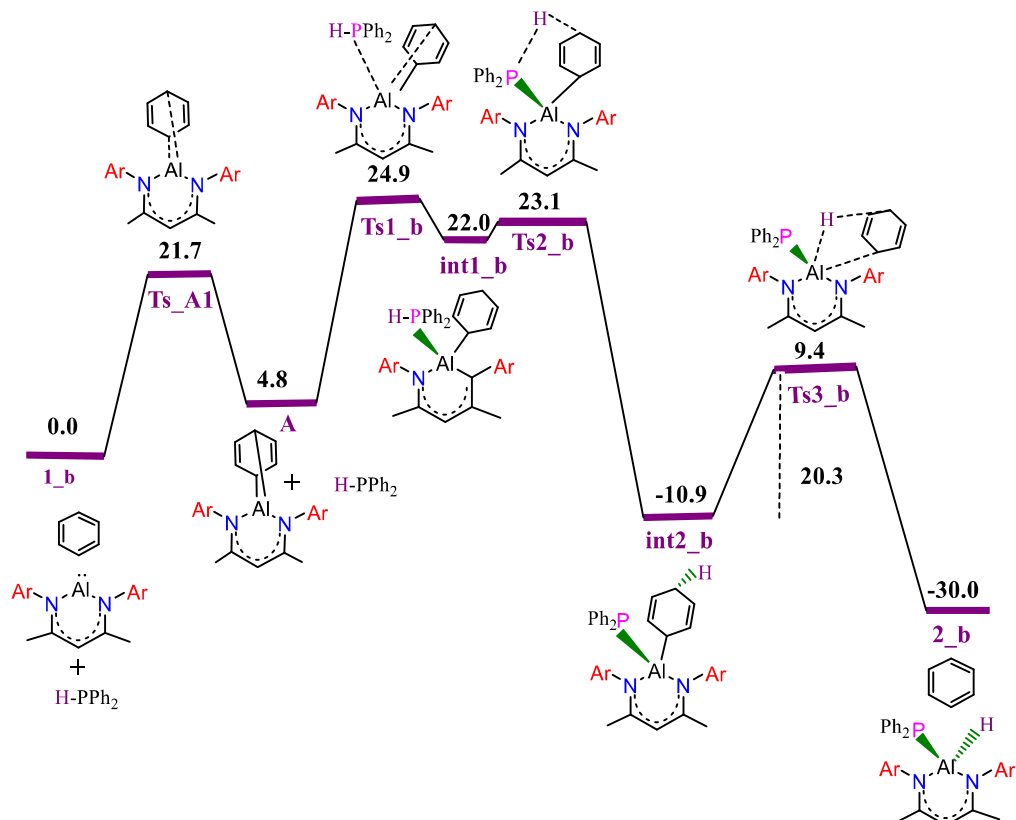


Figure 3.8 The free energy profile (ΔG in kcal/mol) for P-H bond activation by complex A.

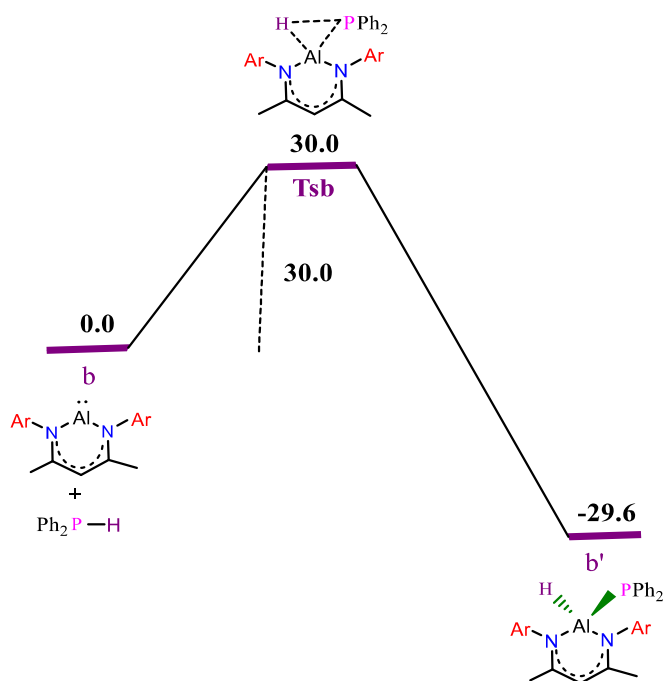


Figure 3.9 The free energy profile (ΔG in kcal/mol) for P-H bond activation without the explicit assistance of the solvent.

Table 3.1 The values for the relative efficiency obtained for both our mechanism as well as oxidative addition without the explicit assistance of the solvent.

H-X Bond Activation	Relative Efficiency
H-H	0.29×10^2
H-N	1.7×10^6
H-P	0.5×10^4

3.3.4 Investigating the possibility of NacNacAl(I)–aliphatic solvent cooperativity

Previous sections have focused on the explicit role of the aromatic solvent, benzene, in substantially increasing the efficiency of the σ -bond activation process by the NacNacAl(I) complex for the cases studied. This section endeavors to show why aliphatic solvents, such as hexane, would not be able to function in a similar cooperative fashion. The free energy profiles for the activation of different σ bonds (terminal C–H and three different C–C bonds) in hexane by the NacNacAl(I) complex are shown in Figures 3.10-3.13. A perusal of the values ($\Delta G^\ddagger=53.7, 82.9, 97.8$, and 83.3 kcal/mol, respectively) makes it clear that the σ -bond activation process would be kinetically unfeasible at the temperatures employed in the experiments. This indicates that there is no explicit role of the hexane solvent in the activation of the H–X bond. Moreover, this also suggests that cleavage of the C–C, C–H, or other σ bonds in other aliphatic solvents would also be unlikely, thereby indicating that cooperativity would

be likely to occur only through dearomatization–aromatization in aromatic solvents such as benzene, toluene, and anisole. Activation of H-X by NacNacAl(I) in hexane, and other aliphatic solvents, would thus occur as direct activation without the explicit involvement of the solvent. It should, however, be noted that σ -bond activation of substrates by the Al(I) complex is not precluded in aliphatic solvents, it is just that the efficiency of the chemistry would be (sometimes markedly) decreased in the aliphatic solvents, at least for the cases discussed herein.

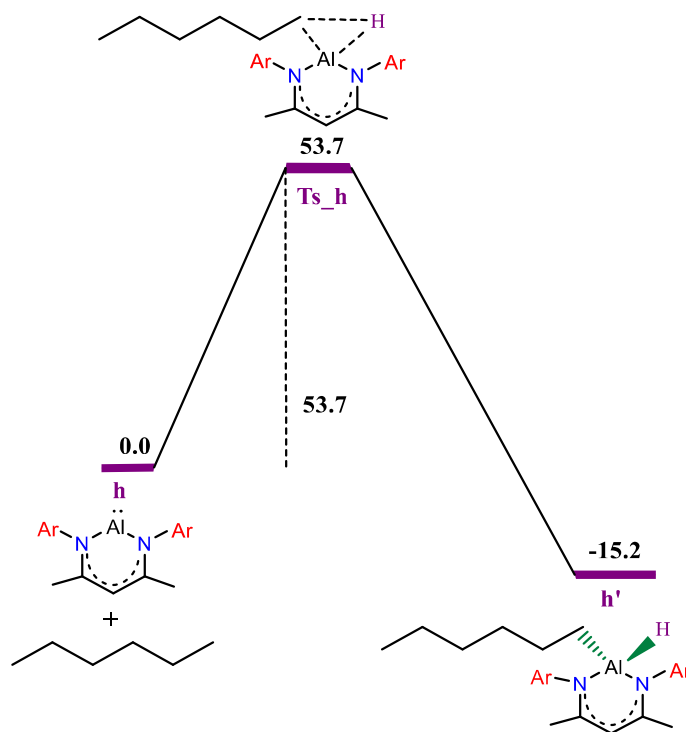


Figure 3.10 The free energy profile (ΔG in kcal/mol) for the formation of h' (hexane NacNacAl(III) complex) by activation of the terminal C-H bond. The high barrier suggests that the reaction would be kinetically unfavorable.

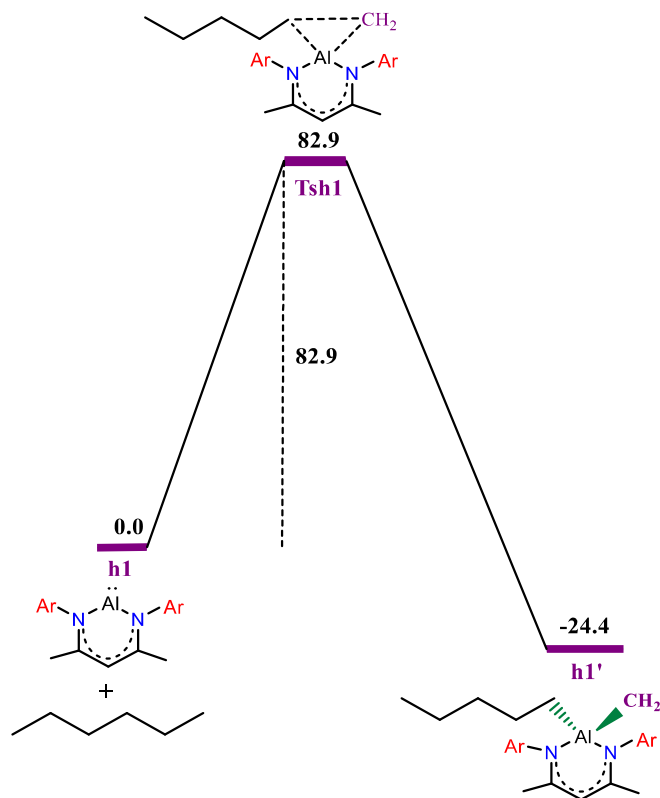


Figure 3.11 The free energy profile (ΔG in kcal/mol) for the formation of **h1'** (hexane–NacNacAl(III) complex) by activation of the 1, 2 C-C bond. The high barrier suggests that the reaction would be kinetically unfavorable.

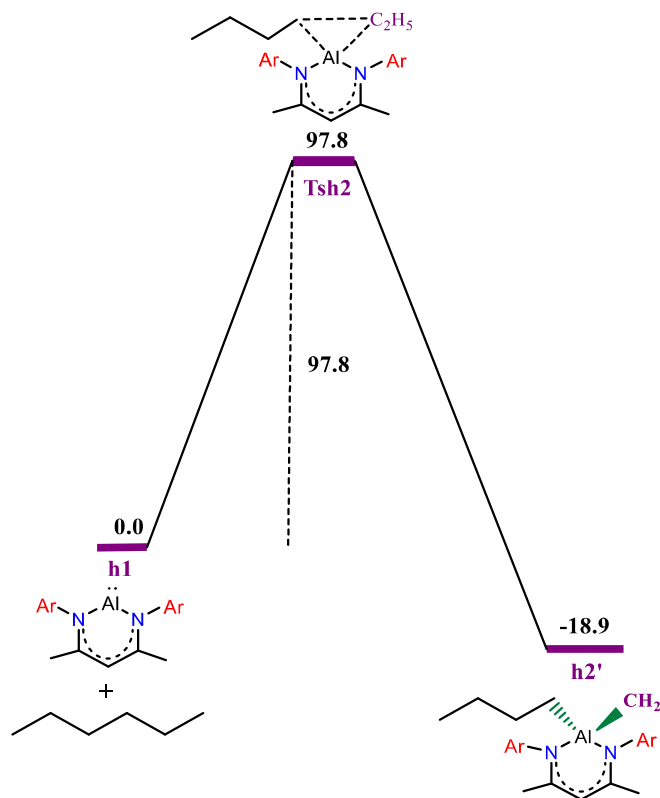


Figure 3.12 The free energy profile (ΔG in kcal/mol) for the formation of **h2'** (hexane–NacNacAl(III) complex) by activation of the 2,3 C–C bond. The high barrier suggests that the reaction would be kinetically unfavorable.

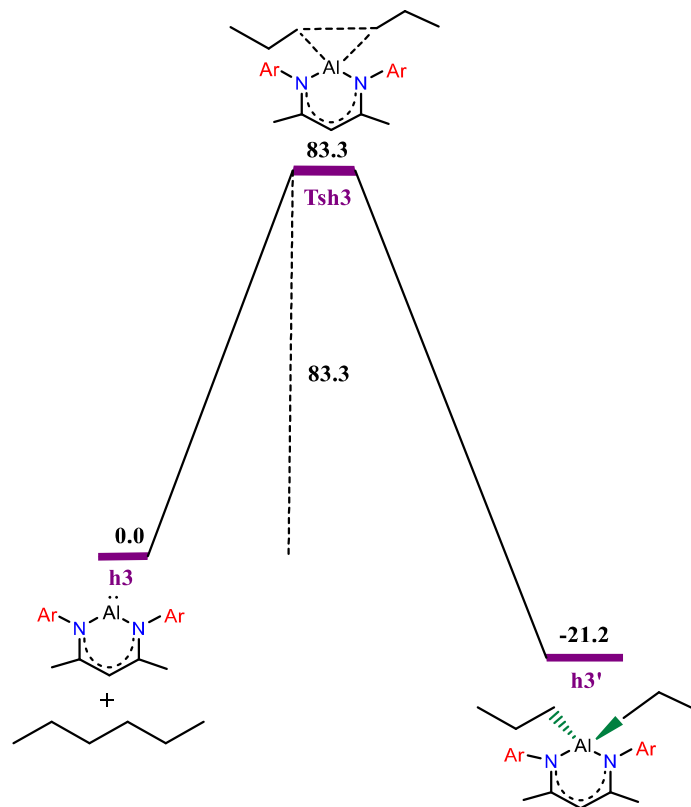


Figure 3.13 The free energy profile (ΔG in kcal/mol) for the formation of **h3'** (hexane–NacNacAl(III) complex) by activation of the 3,4-C-C bond. The high barrier suggests that the reaction would be kinetically unfavorable.

3.4 Conclusion

The mechanism for σ -bond activation of the H-H, H-N and H-P bonds by the NacNacAl(I) complex, as experimentally reported,¹⁵ was carefully investigated with DFT. It was observed that the solvent was far from spectator in this chemistry: it actively and explicitly participated in the σ -bond activation process and had a significant effect on the efficiency. The current work therefore reveals that aluminium(I) chemistry, for the cases studied, is richer and more complex than had been realized, and is actually an example of metal–solvent cooperativity. Although there are examples of solvent binding as a ligand in transition-metal complexes,^{46,47} to the best of our knowledge, this is the first example of its kind in main-group chemistry, not only of solvent binding as a ligand, but also of metal–solvent cooperativity. Indeed, as shown in Figure 3.14, the log plot of the relative efficiencies have taken, with and without the explicit

assistance of the solvent, to fit the relative efficiency values for different cases of σ -bond activation by the aluminium (I) complex into a single graph. This plot suggests that solvent's effect on the efficiency of σ -bond activation is $\text{N-H} > \text{P-H} > \text{H-H}$.

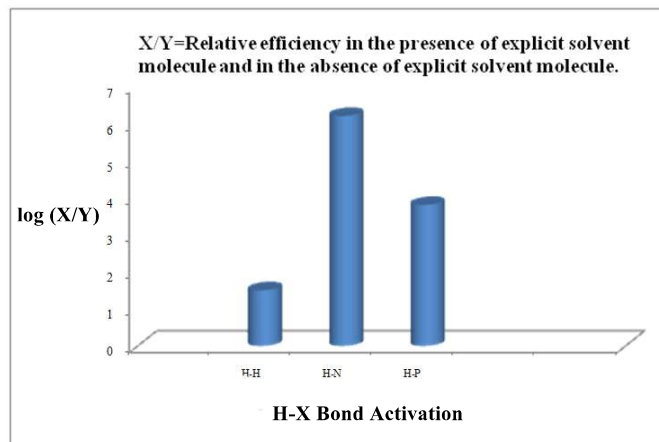


Figure 3.14 The log plot of the relative efficiencies for the activation of different H-X bonds, with and without the explicit assistance of the solvent.

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Chapter 4

Can the Solvent Enhance the Rate of Chemical Reactions through C-H/ π Interactions? Insights from Theory

Chapter 4

Can the Solvent Enhance the Rate of Chemical Reactions through C-H/ π Interactions? Insights from Theory

Abstract

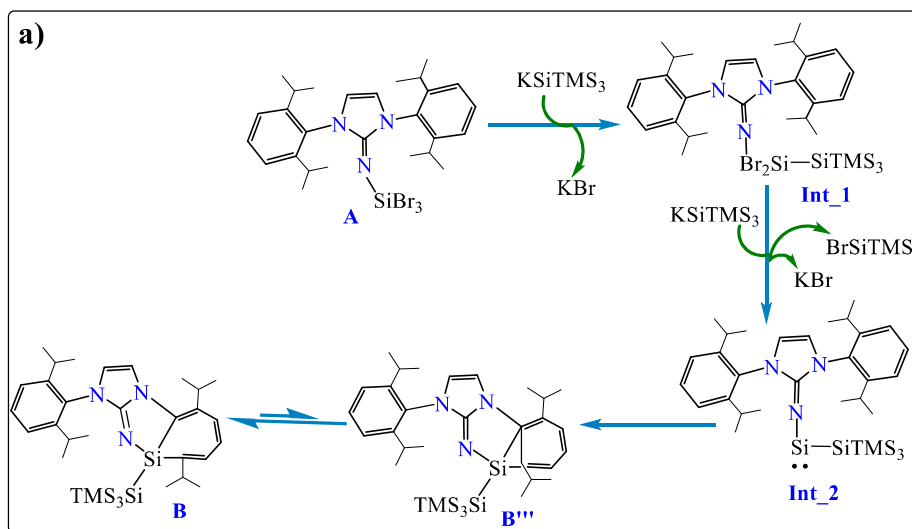
The current computational study with density functional theory (DFT), shows that the rate of silepin formation can be influenced through non-covalent C-H/ π interactions between substrates and the solvent. It is shown that intramolecular carbon-carbon, by a low valent silicon complex is favourably affected by the explicit presence of the solvent toluene. Furthermore, non-covalent interactions between solvent and substrate have confirmed with *ab initio* molecular dynamics (AIMD) simulations. AIMD simulation demonstrated that the C-H/ π non-covalent interaction is distinctly preferred over other non-covalent interactions. Hence, this chapter focuses on C-H/ π interactions between solvent and substrate can enhance the rate of the reaction and turn over frequency.

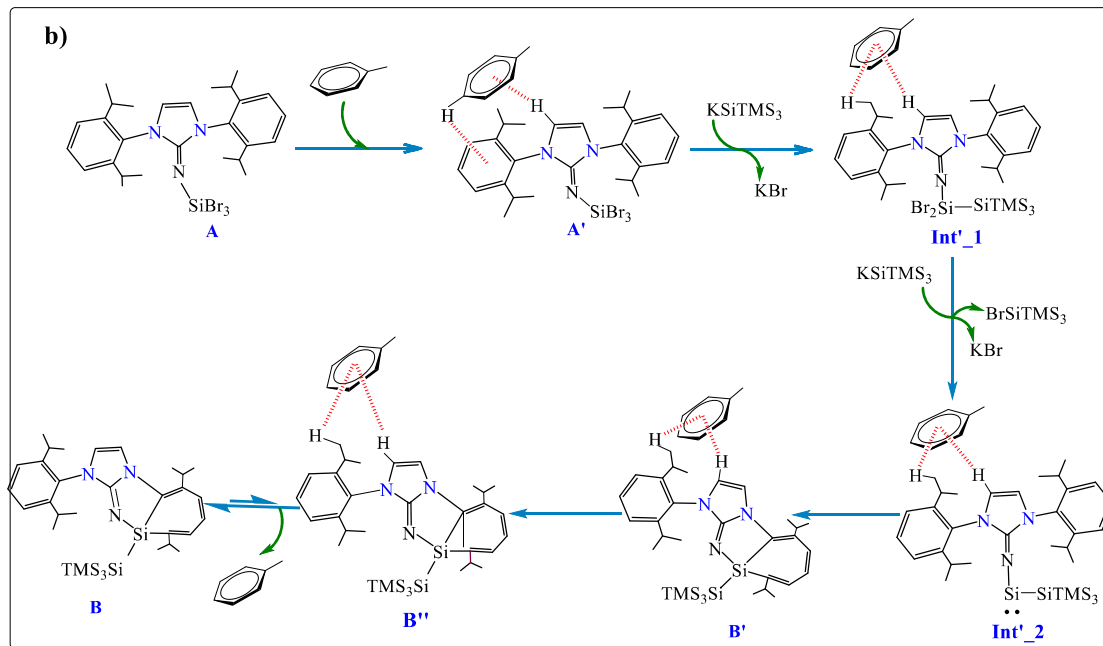
4.1 Introduction

The role of the solvent in chemical reactions automatically assumes importance, because a significant amount of chemistry takes place in the solvent phase. A large body of research exists indicating that the solvent can influence chemical reactions through polarity^{1,3} or through specific covalent bonding interactions with the substrates.^{4,5} Solvent water molecules are known to act as proton shuttles in several reactions of biological significance.^{6,8} Furthermore, it is also known that the solvent can interact in a hydrogen bonded fashion with reactants and transition states and have an effect on the rates as well as on the selectivity of reactions.^{9,10} All of this leads to an interesting question: would it also be possible for the solvent to influence chemistry through other non-covalent interactions, such as C-H/ π and π - π stacking? How significant would such an effect be? Would the solvent serve to catalytically accelerate reactions by such interactions, and if so, what would be the effect of this mediation on the turnover frequency (TOF)? A computational study is ideally suited to address these questions. Such studies would, however, have been hampered in the past, because of the need to properly and accurately take care of dispersion effects, which are important in C-H/ π and π - π stacking interactions. Methods such as CCSD(T)¹¹ or MP2¹² that could do so are too expensive for a comprehensive study of mechanistic cycles of real (not model) systems, while more efficient approaches such as density functional theory (DFT) suffered from a lack of proper representation of dispersion effects. However, this lack in DFT has been resolved recently by the development of very effective implementations of dispersion corrections. Indeed, certain dispersion (D3)¹³ corrected functionals such as TPSS¹⁴ and B3-LYP¹⁵ are seen to provide estimations for non-covalent interactions such as for π - π stacking, which compare excellently with experiment.¹⁶ Therefore, the time is now ripe for a careful and complete computational investigation, with dispersion corrected DFT-D3 methods, of mechanistic cycles that include C-H/ π and/or π - π stacking interactions with the solvent.

The reason it is important to investigate this is because it is known that C-H/ π and π - π stacking interactions play a significant role in various fields of biology and chemistry,¹⁷ such as in proteins and biomolecules,¹⁸⁻²² supramolecular chemistry²³⁻²⁶ crystal packing,²⁷⁻³¹ and drug design,³² or through intramolecular or intermolecular substrate-substrate interactions. This wide-ranging impact provides a reason to believe that C-H/ π and π - π stacking interactions *between substrate and solvent*, which have propose to study, might also have significant consequences in different areas of chemistry. The area that have chosen to focus upon is the important, emerging new field of main group chemistry. Low valent main group compounds have been known to play a key role in various σ , π bond activations³³⁻³⁶ of small molecules, as well as in catalysis,³⁷⁻⁴¹ supplanting traditionally employed transition metal-based systems

for these processes. There have also been several computational studies analyzing the influence of low valent main group compounds on small molecule activation.³³ Silylenes constitute one of the most important low valent main group compounds for small molecule activation,⁴²⁻⁴⁵ because of their small HOMO-LUMO gap ($\sim 2-3\text{eV}$), but low valent germanium and tin compounds have also shown promise. There are now some reports of oxidative addition and reductive elimination by Ge(II) ⁴⁶ Sn(II) ⁴⁷ and Si(II) ⁴⁸ complexes. Interestingly, in 2017, Rieger, Inoue and co-workers reported a process involving the reversible conversion of Si(II) to Si(IV) , through successive oxidative addition and reductive elimination steps.⁴⁹ Employing toluene as the solvent, the silicon based complex, **A** (see Scheme 4.1a), was converted into a highly reactive acyclic iminosilylsilylene Si(II) intermediate, which underwent intramolecular insertion into the carbon-carbon double bond of a coordinated di-isopropyl phenyl (dipp) group to form a silacycloheptatriene (silepin) complex (see Scheme 4.1a) where the formal oxidation state of silicon was +4. The silepin complex was readily reconverted to Si(II) , and this ease of change of oxidation state allowed for the activation of small molecules such as carbon dioxide, hydrogen and ethylene.⁴⁹ Given the relevance and importance of this system, it is an ideal candidate for investigating the possibility of non-covalent interactions between the silicon complexes involved and a toluene solvent molecule (see Scheme 4.1b). The results obtained indicate that $\text{C-H}/\pi$ interactions are more significant over π/π interactions, and lead to the presence of $\text{C-H}/\pi$ interacting solvent molecules in the vicinity of the substrate. This result is further supported by *ab initio* molecular dynamics (AIMD) simulations, which have been employed previously in homogeneous catalysis by Vidossich and Ujaque.⁵⁰ Hence, $\text{C-H}/\pi$ interactions between solvent and substrate do indeed turn out to be relevant, and, as will be shown in the Results and Discussion section, it has been found that this important effect leads to increased efficiency for silepin formation, as well as for the subsequent small molecule activation reactions.





Scheme 4.1 The proposed mechanism for the formation of the silepin complex: a) in the absence and b) in the presence of an explicit toluene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model).

4.2 Computational Methods

The calculations were carried out using the Turbomole 7.0 and 7.1 suite of programs.⁵¹ Geometry optimizations were performed using the TPSS density functional,¹⁴ the electronic configuration of the atoms was described by a diffuse def2-triple ζ basis set augmented by a polarization function (Turbomole basis set def2-TZVP).⁵² The resolution of identity (ri)⁵³ along with the multipole accelerated resolution of identity (marij)⁵⁴ approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. The real (not model) system has been employed for all the calculations. The transition states were confirmed to have only one imaginary frequency, corresponding to the correct normal mode. In addition, intrinsic reaction coordinate (IRC)⁵⁵ calculations were done with all the transition states, in order to further confirm that they were the correct transition states, yielding the correct reactant and product structures. Solvent effects were introduced by using the COSMO model⁵⁶ with the dielectric constant $\epsilon = 2.38$ for toluene. The option “disp” provided in the Turbomole package (DFT-D3) was used for dispersion-corrected DFT calculations for all the calculations.¹³ This is an option that is

often not turned on by users of quantum chemical codes, though it is present today in most such codes. The current results serve to emphasize the importance of turning on this correction when doing quantum chemical calculations. The computation of the Hessian matrix and calculation of zero-point energy has been performed at the same level of theory as for the electronic energy calculations, *i.e.*, at the TPSS/def2-TZVP level of theory. Unless otherwise specified, the values reported in the chapter are ΔG values, with zero point energy, internal energy, and entropic contributions included, with the temperature taken to be 298.15K. It is to be noted that the ΔG values are calculated with the reactant species considered to be separated and not complexed together (so as to get a proper estimate of the free energy required to bring the reactants together to form more ordered complexes). However, the solvent molecules associated with the reactant have been considered as a complex with the reactant when calculating the ΔG . This is because solvent molecules will be ubiquitously present in the vicinity of reactant molecules and do not have to be brought in the sphere of the reactants, to begin with. The translational entropy term in the calculated structures was corrected through a free volume correction method introduced by Mammen *et al.*⁵⁷. This is to account for the unreasonable enhancement in translational entropy that is generally observed in computational software. Furthermore, in order to check the reliability of the calculations, single-point calculations were done at the B3-LYP-D3/TZVP/COSMO ($\epsilon=2.38$, where ϵ represents the dielectric constant) and M06-2x/TZVP/COSMO ($\epsilon=2.38$) levels of theory. The free energy profiles have been given in the SI (see Figures S7-S10). The trends of all of the energy profiles were seen to be the same as at the TPSS-D3/def2-TZVP level of theory. In order to find the efficiency of the catalytic cycle in our mechanism, the relative efficiency with the AUTOF⁵⁸ program, employing the “Energetic Span Model” (ESM), developed by Shaik and coworkers,⁵⁹⁻⁶⁰ have calculated on all the free energy profiles discussed in this chapter.

Moreover, analysis with NBO 3.1 has been done by using the Gaussian 09 software,⁶¹ at the B3-LYP/6-31g** level of theory.

4.2.1 The interaction energy due to C-H/ π non-covalent interactions

In order to quantify C-H/ π non-covalent interactions in the presence of toluene, the interaction energy (EI)⁶² between the two non-covalently bonded fragments has been calculated by employing the following formula:

$$EI = E_{\text{complex}} - (E_{\text{part1}} + E_{\text{part2}}), \quad (4.1)$$

Where, E_{complex} is the single point energy of the non-covalently bonded complex, E_{part1} and E_{part2} are the single point energies of the two fragments separated from an optimized geometry of the non-covalently bonded complex, at the TPSS-D3/def-2TZVP and the B3-LYP-D3/TZVP levels of theory.

4.2.2 *Ab Initio* Molecular Dynamics (AIMD)

AIMD simulations have been performed with the TeraChem 1.9 quantum chemistry software package,⁶³ using the B3-LYP functional and the 6-31g* basis set,⁶⁴ to calculate the Born Oppenheimer potential energy surface. Dispersion effects have been included with the DFT-D3 correction. Solvent effects have been introduced by the conductor-like screening model, COSMO, with $\epsilon=2.38$ employed to model the solvent toluene. Simulations have been run at room temperature (298.0 K). The speed of the calculations was enhanced because of the efficiency of TeraChem, which accelerates the simulations by evaluating the two electron integrals on GPUs. The ADIIS (augmented direct inversion in the iterative subspace) algorithm⁶⁵ available in TeraChem has been employed as an alternative tool for self consistent field calculations at each AIMD step, when the default DIIS algorithm failed to converge. The time step employed was 0.5 femtoseconds. Spherical boundary conditions (with a radius of 15.0 angstroms) have been applied. This has been done in order to ensure that the solvent molecules included in the AIMD simulations would not fly away significantly from the substrate. Furthermore, this also allows the modeling of the natural pressure that would exist in solution because of the bulk presence of solvent molecules around the substrate and the explicitly considered solvent molecules.

4.3 Results and Discussion

4.3.1 The Silepin System: Significance of C-H/ π Interactions between Substrate and Solvent

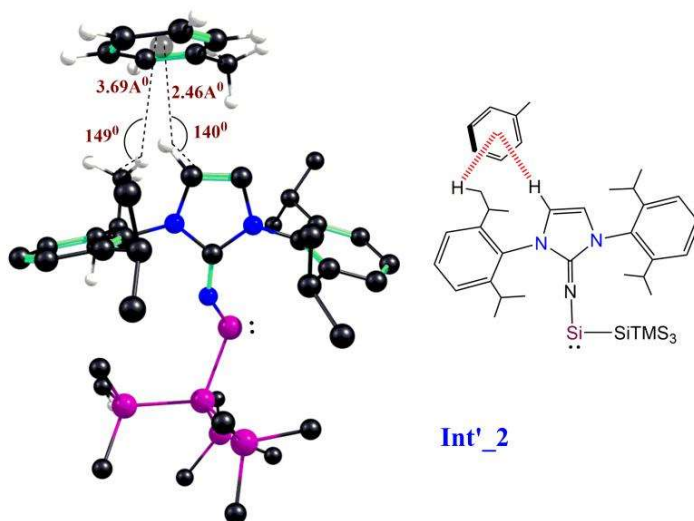
As mentioned in the Introduction, the Si(IV) silepin system reported by Rieger, Inoue and co-workers⁴⁹ has been studied with density functional theory (DFT), keeping in mind the possible effect, through non-covalent interactions, of the aromatic solvent toluene. All the reactant, intermediate and

product species shown in Scheme 4.1 were optimized with and without an explicit toluene molecule. The first calculations investigating the possibility of non-covalent interactions were done with the important intermediate species **Int_2**. Toluene was added at several different positions: (i) above the diisopropylphenyl (dipp) rings, for possible π - π stacking interactions, (ii) at the silicon center, for lone pair- π interactions, as well as (iii) above the C-H of the methyl group of dipp, for C-H/ π interactions. Interestingly, for (i) and (iii), it was observed that the toluene shifted during the optimization to a position where there were two C-H/ π interactions between the C-H of one of the carbons of the imidazole ring and the π ring of the toluene, as well as the C-H of the toluene and the π ring of the dipp ring, a structure referred to as **Int_2'** (see Figure 4.1). Calculations indicate that the solvent prefers C-H/ π interactions with **Int_2'** in place of π - π stacking. The presence of a CH₃ group on the toluene may provide steric inhibitions to effective π - π stacking. The fact that the final structure (**Int_2'**) does indeed show C-H/ π interactions has been ascertained by looking at the interaction energy through additional single point energy calculations at the TPSS-D3/def2-TZVP and B3-LYP-D3/TZVP levels of theory (for more details, please see the Computational Details section) between the two non-covalently bonded fragments. As Table 4.1, shown below, indicates, the interaction energy between toluene and **Int_2** was favorable by 7.7 kcal/mol at the TPSS-D3/def2-TZVP and by 7.9 kcal/mol at the B3-LYP-D3/TZVP levels of theory, respectively. Furthermore, as Figure 4.1 shows, the distances of the hydrogen atoms of C-H and the center of the π ring were seen to be 2.46 Å and 3.69 Å for the two C-H/ π interactions. Therefore, they fall in the accepted range for C-H/ π interactions.⁶⁶

Furthermore, the angles between the center of the toluene ring, the hydrogen, and the carbon were found to be 140° and 149° for the two C-H/ π interactions, which, too, fall within the accepted range of C-H/ π interactions. The other optimized structure for the other solvent-substrate interactions, (ii), mentioned above, was found to be less stable by 2.6 kcal/mol (ΔE) than **Int_2'**, indicating, therefore, that lone-pair/ π and other C-H/ π interactions were not as favorable. They have, therefore, not been considered further in this study.

Subsequent to this, all the other reactant, intermediate, and product structures, **A'**, **Int'_1**, and **B'** were also optimized with the explicit toluene molecule moiety attached and also showed the same C-H/ π interactions. The corresponding interaction energy values have been compiled in Table 4.1 and are seen to be favorable for all the cases. Furthermore, the bond lengths and angles for all the cases fall in the range 2.4-3.8 Å and 120-150°, respectively, indicating the presence of C-H/ π interactions.

Figure 4.1 The optimized geometry of the complex **Int'_2** where C-H/ π non-covalent interactions have



been shown. Hydrogen atoms (except for toluene) have been removed for the purpose of clarity.

Table 4.1 The interaction energies due to C-H/ π interactions. The values are provided in kcal/mol. The structures of the non-covalently bonded systems are provided in Figures 4.3 and 4.4 below.

Non-covalently bonded Systems	ΔE at TPSS-D3/def2-TZVP	ΔE at B3-LYP-D3/TZVP
A'	-8.1	-8.4
Ts'_1	-8.2	-8.4
Int'_1	-7.4	-7.8

Ts'_2	-8.4	-8.9
Int'_2	-7.7	-7.9
Ts'_3	-7.6	-7.8
B'	-7.1	-7.5

To further validate this result, *ab initio* molecular dynamics (AIMD) at room temperature have employed. It has been noted here that the use of AIMD in the context of the current work is primarily to provide support to the static DFT calculations. The ideal way to employ AIMD would be to have a large number of solvent molecules in various solvent shells around the substrates. This, however, is too expensive, computationally and outside the scope of the current work. Nevertheless, AIMD, as used here, with three toluene molecules placed in positions around the substrate in order to maximize non-covalent interactions, does provide interesting corroboration to the static DFT calculations by showing that the C-H/ π non-covalent interaction is distinctly preferred over other interactions.

We began by placing three toluene solvent molecules randomly around **Int_2**, at different positions around the substrate. In other words, there was a significant difference in distance between the three toluene molecules, with no solvent-solvent interactions present. It has been observed that after 6182 steps {corresponding to about 3.0 picoseconds (ps)}, only one interaction remained. This structure possessed the same C-H/ π non-covalent interaction that had been found to be the most favorable {structure (i), discussed above} in the static DFT calculations. Moreover, once the interaction was formed, it remained for the duration of the AIMD simulation, up to 17,182 steps. The snapshots obtained from the simulations have been shown in Figure 4.2 below. This provides further indication that the C-H/ π non-covalent interaction between solvent and substrate indeed predominates over other non-covalent interactions in this system.

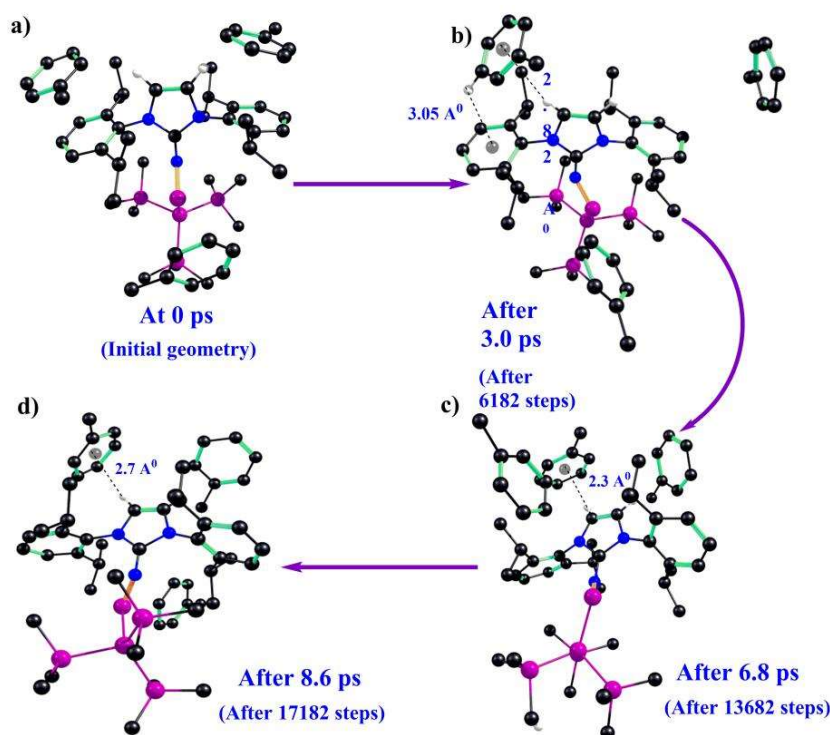


Figure 4.2 The different snapshots for observed C-H/ π interactions in the room temperature ab initio molecular dynamics simulations. a) Initial geometry (starting point of the simulation) at 0.0 ps, b) after 3.0 ps, when the bond distance for two different C-H/ π interactions between the hydrogen atoms of C-H and the center of the π ring are 2.82 Å and 3.05 Å, c) after 6.8 ps, when the bond distance for the C-H/ π interaction is 2.3 Å, and d) after 8.6 ps, when the bond distance for the C-H/ π interaction is 2.7 Å.

4.3.2 The Efficiency of the Silepin Formation, with and without the Explicit Presence of the Solvent

Figure 4.3 below shows the free energy profile for the formation of the silepin complex in the presence of C-H/ π non-covalent interactions with toluene. The intermediate **Int'_1** is formed after surmounting a barrier of 16.4 kcal/mol and lies 37.2 kcal/mol lower in energy in comparison to the reactants. The approach of one more equivalent of KSiTMS₃ to **Int'_1** and elimination of BrSiTMS₃ and KBr leads to the formation of **Int'_2**. Subsequent to this, intramolecular insertion of the silicon into the

carbon-carbon double bond of di-isopropyl phenyl (dipp) ring of **Int'_2** leads to the formation of the final observed product, **B'**.

Now, the pertinent question is what the profile would look like in the absence of the explicit toluene solvent molecule. Figure 4.4 below shows the results obtained for this. The barrier for the formation of **Int_2** is 16.4 kcal/mol, which is 2.7 kcal/mol higher than the toluene assisted process. Hence, the formation of the silepin complex without the involvement of explicit solvent would be less efficient. In order to provide a more quantitative estimate of how much the process is aided by toluene, efficiency for the free energy profiles shown in Figures 4.3 and 4.4 by employing the “Energetic Span Model” (ESM) developed by Shaik and Kozuch⁵⁹⁻⁶⁰ have determined. By the ESM, it has been found that the intermediates **Int'_1** and **Int_1** are the TDI, and the transition states **Ts'_3** and **Ts_3** are the TDTS for the respective cases with and without the C-H/ π interaction with the toluene (see Figures 4.3 and 4.4). These calculations suggest that the barriers (TDTS – TDI) for the toluene assisted and the toluene unassisted processes are 25.9 kcal/mol and 26.6 kcal/mol, respectively. For details regarding the ESM method, please see the Computational Details section. The relative efficiency values (shown in Table 4.2 below) indicate that the formation of the silepin complex with the assistance of the explicit toluene molecule is 3.7 times more favourable. Hence, the solvent serves to accelerate the reaction rate via C-H/ π interactions. The reason why this is so has been studied by looking at donor acceptor orbital interactions through analysis with NBO 3.1⁶⁷⁻⁶⁹ with the Gaussian 09 software at the B3-LYP/6-31g**/D2 level of theory. (The Gaussian software was employed instead of Turbomole for the specific investigations because the study of donor-acceptor orbital interactions with NBO is not possible with Turbomole). The interaction energies for the principal donor-acceptor interactions between the atoms involved in the respective transition states in **Ts'_2** and **Ts_2** were seen to be more favorable in the presence of toluene than in its absence (see Figure 4.5 below). This serves to stabilize **Ts'_2** over **Ts_2** and explains why the barrier for this step is lowered significantly, by 2.7 kcal/mol, for the toluene bonded case (see Figures 4.3 and 4.4). Hence, even though the toluene molecule is not directly a part of the transition state, its presence is seen to have a distal effect on the donor-acceptor interactions. For the other two transition state cases, **Ts'_1** and **Ts_1** and **Ts'_3** and **Ts_3**, the NBO analysis does not show significant differences in the donor-acceptor interactions, but differences do exist in the barriers, favouring the toluene included process, stemming from changes in the enthalpy rather than in the electronic energies.

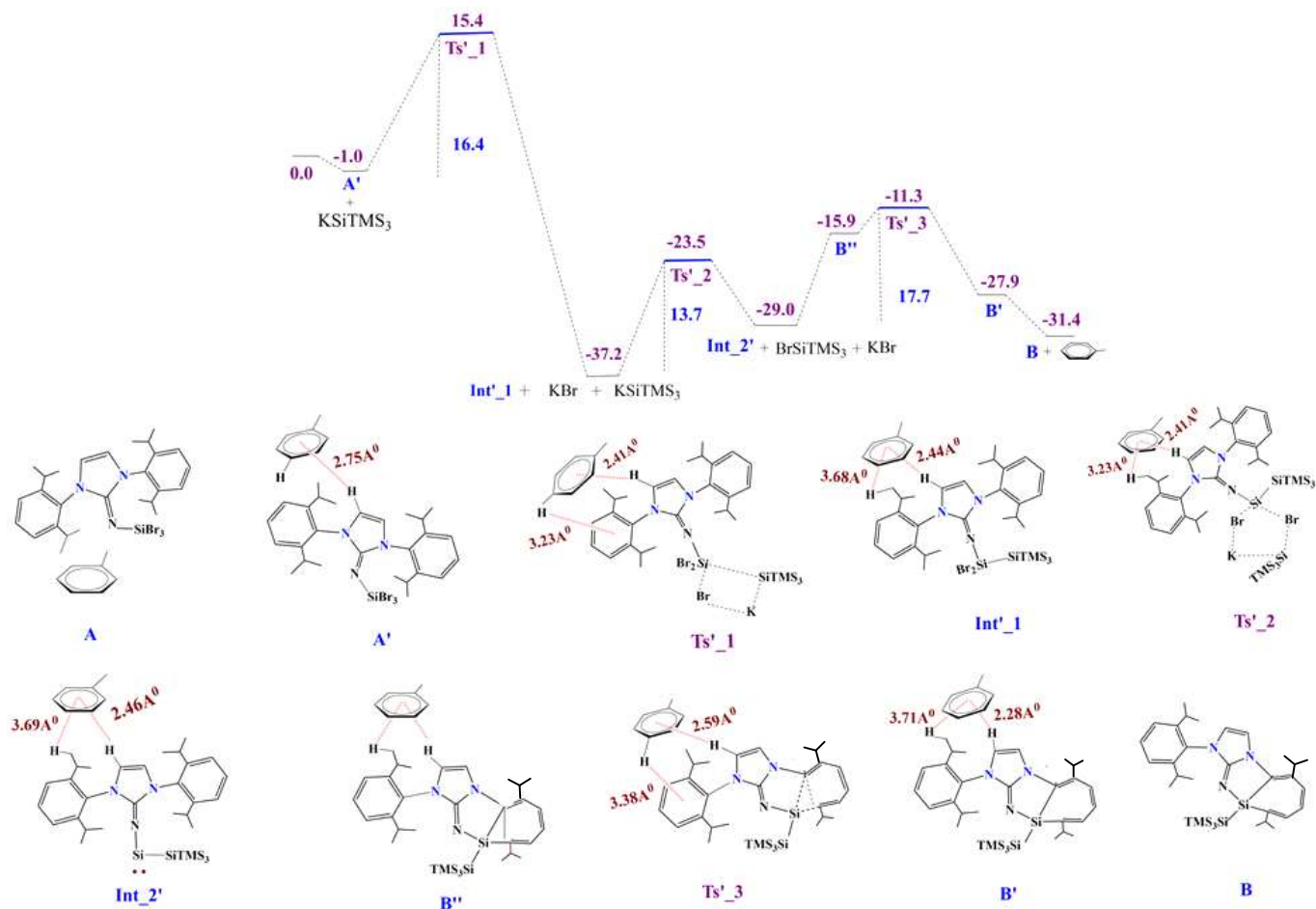


Figure 4.3 The free energy profile (ΔG in kcal/mol) for the formation of the silepin complex **B'** in the presence of an explicit toluene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model).

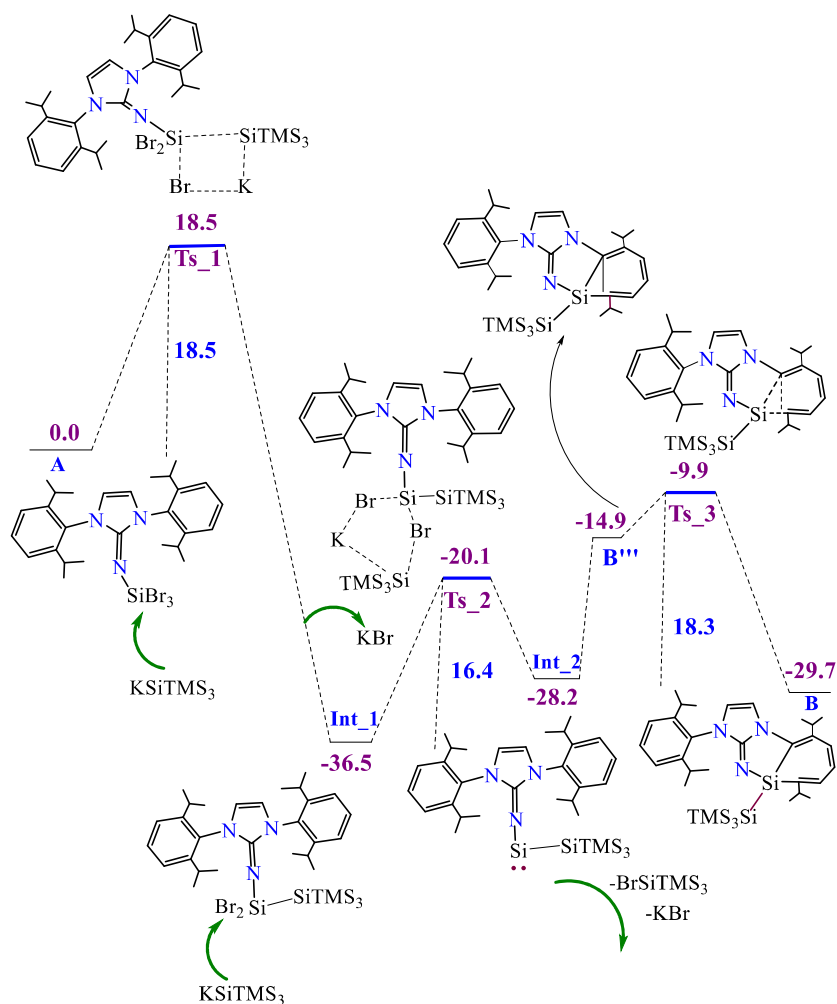


Figure 4.4 The free energy profile (ΔG in kcal/mol) for the formation of the silepin complex **B** in the absence of an explicit toluene molecule.

Table 4.2 The relative efficiencies obtained for the silepin complex formation and activation processes, due to the explicit assistance of the solvent.

Process	Relative Efficiency
Formation of the silepin complex	3.7×10^0

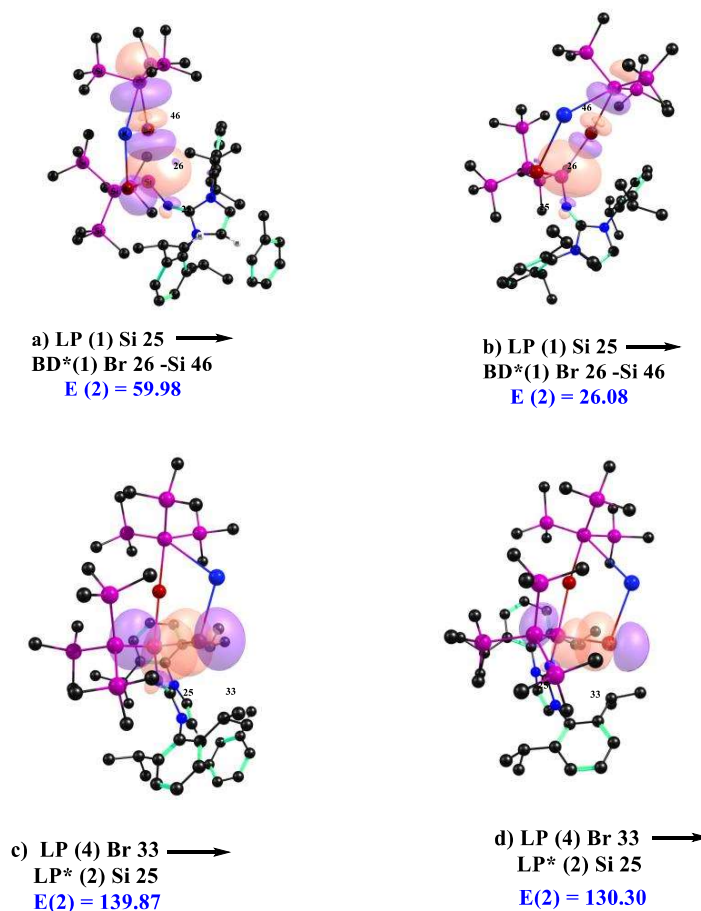


Figure 4.5 The interactions between orbitals in the transition states: a) and c) in the presence of toluene (**Ts'_2**), b) and d) in the absence of toluene (**Ts_2**). Hydrogen atoms have been removed for the purpose of clarity.

4.3.3 Does π - π Stacking between Toluene Molecules Affect the C-H/ π Interaction between Solvent and Substrate?

The previous section makes it clear that non-covalent C-H/ π interactions between substrate and solvent lead to rate enhancement for the silepin formation process. However, it could be argued that the model employed is insufficient, in that a second toluene solvent molecule could undergo π - π stacking with the C-H/ π interacting toluene, and thereby reduce the C-H/ π interaction in the actual system. In order to

explore whether this is possible, further calculations with an expanded model, containing a second toluene molecule, arranged to π stack with the first (see Figure 4.6) have been done. The orientation of the two toluene molecules avoided a staggered conformation, in order to minimize the repulsion between the CH_3 groups. The same energy profile as shown in Figure 4.3 earlier was then calculated with this model. The electronic energies (ΔE and $\Delta E^\ddagger$ values) were determined, because, if π - π stacking between the toluenes affects the potential energy surface, it would reveal this effect in the ΔE calculations. Table 4.3 below shows that, in fact, the inclusion of the second toluene actually reduces the barriers for the conversion. NBO analysis for **Ts_d** (**TS_2** in the presence of two explicit toluene molecules) at the B3-LYP/6-31g**/D2 level of theory provides an explanation for this. The interaction energies for the donor-acceptor interactions between the atoms involved in the transition state in **Ts_d** were seen to be more favourable in the presence of two toluenes, than in one toluene (see Figure 4.7 below and Table 4.4 below). The electron density at the silicon centre does get further drawn towards the toluene when it also π stacks with another toluene, but the presence of the second silicon atom provides stabilization to the silicon, thereby allowing the five membered transition state to be stabilized.

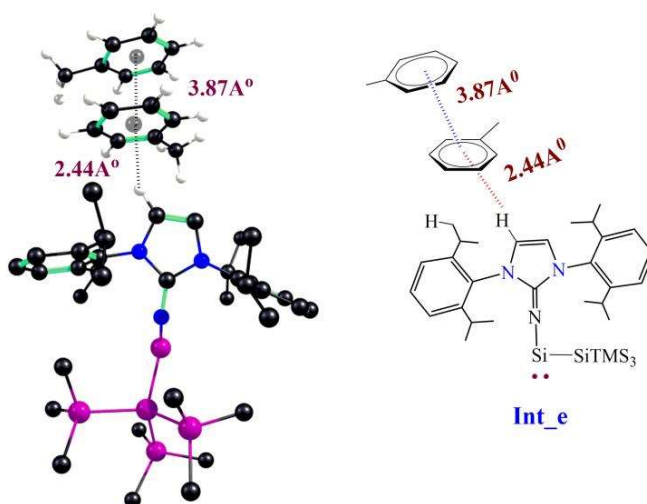


Figure 4.6 The optimized geometry of the iminosilylsilylene complex with two explicit toluene molecules (**Int_e**), where C-H/ π (between substrate and solvent) and π - π (between solvent and solvent) non-covalent interactions have been shown. Hydrogen atoms (except for toluene) have been removed for the purpose of clarity.

Table 4.3 The energy barriers a) in the presence of two explicit toluene b) in the presence of one explicit toluene, and c) in the absence of explicit toluene molecules. $\Delta E_1^\ddagger$, $\Delta E_2^\ddagger$ and $\Delta E_3^\ddagger$ represent the barriers for the first, second and third steps for the silepin formation.

	a) $\Delta E^\ddagger$ (in kcal/mol) in the presence of two explicit toluenes	b) $\Delta E^\ddagger$ (in kcal/mol) in the presence of one explicit toluene	c) $\Delta E^\ddagger$ (in kcal/mol) in the absence of explicit toluenes
$\Delta E_1^\ddagger$	2.8	3.7	4.4
$\Delta E_2^\ddagger$	1.0	2.1	5.0
$\Delta E_3^\ddagger$	14.4	14.6	15.0

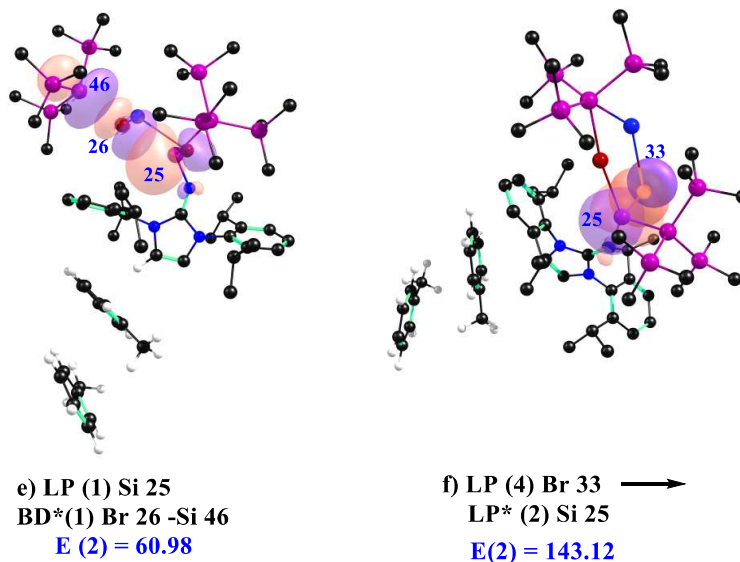


Figure 4.7 The interactions between orbitals in the transition state in the presence of two toluene molecules. Hydrogen atoms have been removed for the purpose of clarity.

Table 4.4 NBO results (second order perturbation energy E(2) in kcal/mol) for **Ts_d**.

Donor		Acceptor		E (2) in the presence of two toluene
Occupancy		Occupancy		
LP (1)	1.2439	BD*(1)	0.52361	60.98
Si 25		Br 26		
		-Si 46		
LP (4)	1.65142	LP* (2)Si	0.50131	143.12
Br 33		25		

4.4 Conclusion

This chapter reveals an important, previously uninvestigated, role of the solvent: its ability to influence the efficiency of chemical processes in a catalytic fashion through C-H/ π interactions. A recently developed silepin complex,⁴⁹ has been investigated with full quantum chemical calculations with density functional theory (DFT). The C-H/ π interactions were seen to be more dominant than π - π interactions between the solvent toluene and the substrate in this case. This was further confirmed by *ab initio* molecular dynamics (AIMD) simulations done at room temperature, which revealed that randomly placed toluene molecules would orient such that C-H/ π interactions predominated over other non-covalent interactions. Having thus established the need to consider solvent-substrate C-H/ π interactions, we have then demonstrated that the explicit presence of the C-H/ π interacting solvent molecule improves the facility of the silepin formation reaction. The work therefore shows that the solvent can enhance the rate of chemical reactions through non-covalent C-H/ π interactions.

Furthermore, the current investigation throws up the question: are there other non-covalent interactions possible between solvent and substrate that could have a possible beneficial role on the reactivity of the substrate? For instance, geometry optimizations that have done considering tetrahydrofuran (THF) as an explicit solvent molecule and the silylene complex as the substrate yielded evidence of non-covalent C-H/O interactions between the two moieties. This suggests that there are likely to be several other systems where there is a hidden role of the solvent that is affecting the activity of the systems.

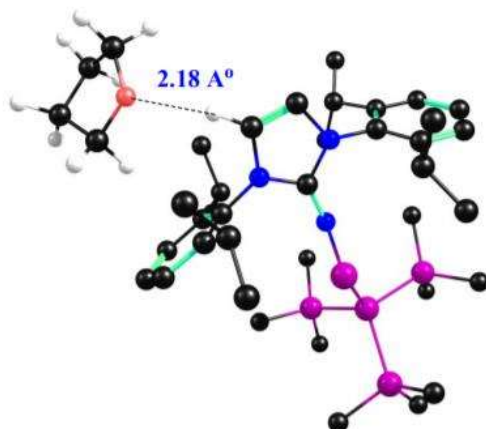


Figure 4.8 The optimized geometry of a structure that demonstrates the presence of C-H/O interactions between a silylene molecule and an explicit tetrahydrofuran (THF) solvent molecule.

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Chapter 5

CO₂ Activation Assisted by C-H/ π Non-Covalent Interactions between Solvent and Substrate

Chapter 5

CO₂ Activation Assisted by C-H/ π Non-Covalent Interactions between Solvent and Substrate

Abstract

A current computational study has been performed to understand the influence of C-H/ π interactions between substrates and the solvent on the rate of CO₂ activation by a low valent silicon complex. It has been seen that CO₂ activation by a silepin complex is favorably affected by the explicit presence of the solvent toluene due to C-H/ π interactions between toluene and the substrate. Furthermore, ab initio molecular dynamics (AIMD) simulations have been performed to understand the exchange between solvent, which demonstrates that even if the C-H/ π interacting solvent molecule is displaced from the complex, another could quickly take its place, thus maintaining the interaction. Hence, this work shows how non-covalent interactions between the solvent and substrate can enhance the rate of the reaction and expand our understanding of the role and influence of the solvent in effecting important chemical reactions.

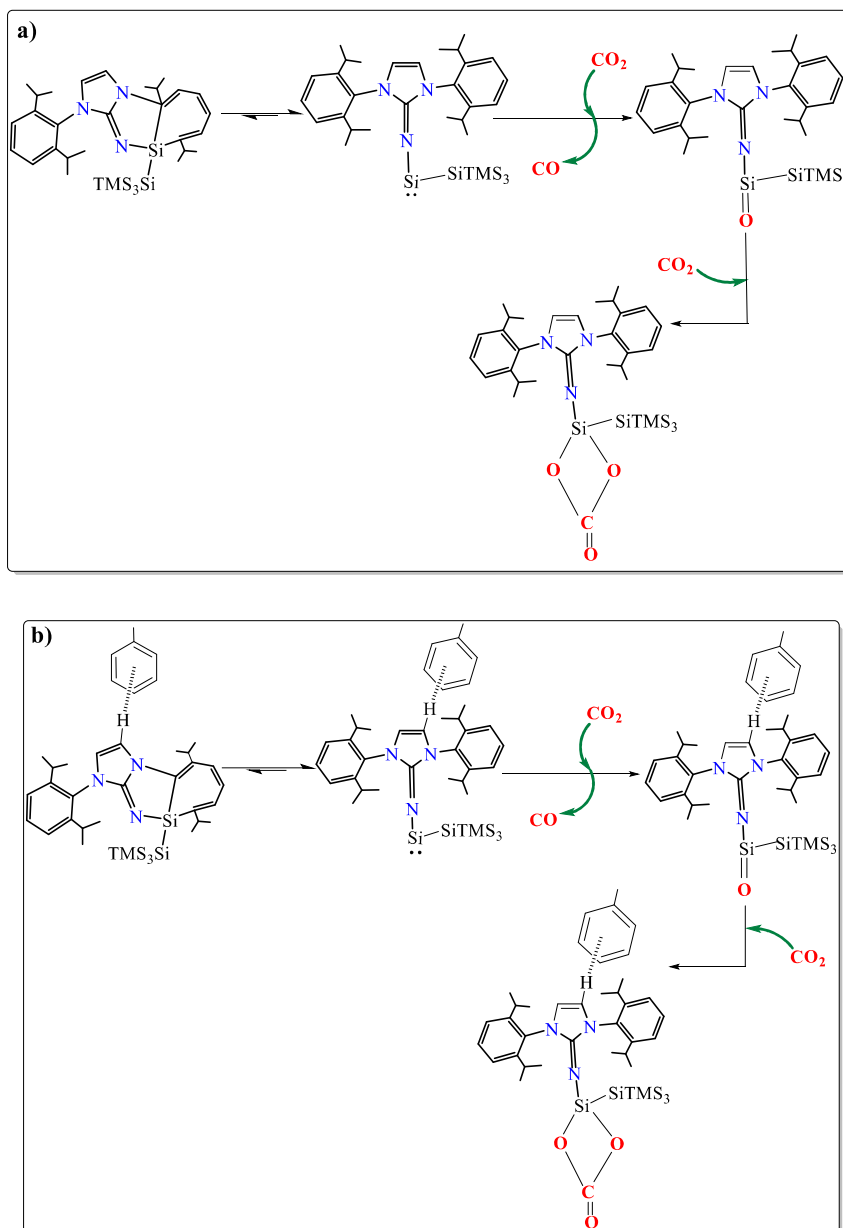
5.1 Introduction

Since CO₂ is a small molecule, readily available and its increasing concentration in the atmosphere is responsible for global warming, the utilization of CO₂ has gained much attention in recent years. Reduction and activation reactions of CO₂ are seen to play a vital role in the conversion of CO₂ into valuable chemicals.¹⁻³ CO₂ is a kinetically and thermodynamically stable molecule; the reduction and activation process of CO₂ required a suitable catalyst. In this regard, the transition metal catalyst has been applied in the various activation, hydrogenation, and electrochemical and photochemical reduction reactions of CO₂.⁴⁻⁸ However, transition metal complexes are expensive and toxic; an alternative of transition metal complex catalyzed CO₂ activation and reduction reactions should be explored. Recently low valent main group complex such as carbene, germylene, silylene, and phosphine shows good reactivity with CO₂ and leads to the stable activated product.⁹⁻¹² Furthermore, it has been seen that these low valent complexes react with CO₂ differently; such as N-heterocyclic carbenes forms adduct with CO₂,¹³ the reaction between silylene and CO₂ proceed through the oxygen transfer from CO₂ to the silylene,¹⁴ germylene-hydrides react with CO₂ *via* carbonyl insertion into the Ge(II)-H bond,¹⁵ and in the reaction of CO₂ and phosphine insertion of CO₂ into the P-H bond takes place.¹⁶

Silylenes are one of the interesting low valent main group compounds because these compounds have strongly donating behavior and flexibility in coordination.¹⁷ Thus, silylenes have been widely used in catalysis,¹⁸ and as supporting ligands for transition metal complexes,¹⁹⁻²⁰ Furthermore, existing reports indicate that both acyclic and cyclic silylenes are efficient for small molecule activation.²¹⁻²³ Moreover, Robin Walsh and coworkers have studied the reaction of silylene and CO₂, where they reported that CO₂ could behave as an oxidant.²⁴ Driess and coworkers have reported the reduction of CO₂ with the siloxysilylene.²⁵ According to these studies of activation of CO₂ by the silylene, it has been observed that mostly silylene complexes yield the dimeric CO₂ activated product.

However, the activation of CO₂ by the silepin complex (isolated by the Rieger, Inoue, and coworkers, which is a dormant form of iminosilylene) was interesting because it yielded CO₂ activated product was monomeric in nature.²⁶ Therefore, this chapter focuses on the activation of CO₂ by the Silepin complex. Computational investigations of the previous chapter suggest that an explicit solvent molecule catalytically accelerates the reactions and enhances the silepin formation reaction's turnover frequency. It has been seen that the C-H/ π interactions were more dominant than π - π interactions between the solvent toluene and the substrate. The influence of C-H/ π interaction in the reaction rate arises the question; Does the C-H/ π non-covalently interacting solvent molecule also affect the rate of the CO₂ activation by the silepin complex? Hence, in the current chapter, the explicit solvent molecule's role in the activation of CO₂

reaction by the C-H/ π non-covalent interaction has been investigated. Furthermore, in the previous chapter, the position of solvent with respect to the substrate have already found by AIMD simulation as well as static DFT calculations. Hence, in this computational study, the C-H/ π non-covalently interacting explicit solvent molecule at the same position (as silylene (**Int_1**) in the previous chapter) have included in the reactant, transition states, intermediates, and product of the CO₂ activation process. Scheme 5.1 below shows the activation of CO₂ by the silepin complex in the absence and presence of an explicit solvent molecule.



Scheme 5.1 The proposed mechanism for the activation of CO₂ by the silepin complex: a) in the absence an explicit toluene solvent molecule, and b) in the presence of an explicit toluene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model).

5.2 Computational Methods

The calculations were performed using the Turbomole 7.0 and 7.1 suite of programs.²⁷ Geometry optimizations were done using the TPSS functional (meta-GGA),²⁸ the atoms' electronic configuration was described by a diffuse def2-triple ζ basis set augmented by a polarization function (Turbomole basis set def2-TZVP).²⁹ The resolution of identity (ri)³⁰ and the multipole accelerated resolution of identity (marij)³¹ approximations have used for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. The real (not model) system has been taken for all the calculations. The structures of transition state were confirmed to have only one imaginary frequency, corresponding to the correct normal mode. Also, intrinsic reaction coordinate (IRC)³² calculations were done with all the transition states in order to confirm further that they were the correct transition states, yielding the correct reactant and product structures. Solvent effects were introduced by using the COSMO model³³ with the dielectric constant $\epsilon = 2.38$ for toluene. The option “disp” provided in the Turbomole package (DFT-D3) was used for dispersion-corrected DFT calculations for all the calculations.³⁴ The computation of the Hessian matrix and calculation of zero-point energy has been performed at the same level of theory as for the electronic energy calculations, *i.e.*, at the TPSS/def2-TZVP level of theory. Unless otherwise specified, the values reported are ΔG values, with zero-point energy, internal energy, and entropic contributions included, with the temperature taken to be 298.15K. It is to be noted that the ΔG values are calculated with the reactant species considered to be separated and not complied together (to get a proper estimate of the free energy required to bring the reactants together to form more ordered complexes). However, the solvent molecules associated with the reactant have been considered as a complex with the reactant when calculating the ΔG . This is because solvent molecules will be ubiquitously present in the vicinity of reactant molecules and do not have to be brought in the sphere of the reactants, to begin with, reaction. The translational entropy term in the calculated structures was corrected through a free volume correction method introduced by Mammen *et al.*³⁵ This is to account for the unreasonable enhancement in translational entropy that is generally observed in computational software. Furthermore, the efficiency of the catalytic cycle in our mechanism has been calculated by employing the “Energetic Span Model” (ESM).³⁶⁻³⁸

5.2.1 *Ab Initio* Molecular Dynamics (AIMD)

AIMD simulations have been carried out with the TeraChem 1.9 quantum chemistry software,³⁹ using the B3-LYP functional and the 6-31g* basis set,⁴⁰ to calculate the Born Oppenheimer potential energy surface. Dispersion effects have been included with the DFT-D3 correction. Solvent effects have been introduced by the conductor-like screening model, COSMO, with $\epsilon = 2.38$ employed to model the solvent (toluene). AIMD simulations have been run at 1000.0 K temperature (the reason for this high temperature has been explained in the Results and Discussion section). The speed of the calculations was enhanced because of the efficiency of TeraChem, which accelerates the simulations by evaluating the two electron integrals on GPUs. The ADIIS (augmented direct inversion in the iterative subspace) algorithm⁴¹ available in TeraChem has been employed as an alternative tool for self consistent field calculations at each AIMD step, when the default DIIS algorithm failed to converge. The time step employed was 0.5 femtoseconds. Spherical boundary conditions (with a radius of 15.0 angstroms) have been applied. This has been done in order to ensure that the solvent molecules included in the AIMD simulations would not fly away significantly from the substrate. Furthermore, this also allows the modeling of the natural pressure that would exist in solution because of the bulk presence of solvent molecules around the substrate and the explicitly considered solvent molecules.

5.3 Results and Discussion

5.3.1 The Efficiency of the Activation of CO₂ by the Silepin complex, with and without the Explicit Presence of the Solvent

Our calculations detailing the role of toluene in this reaction are shown in Figure 5.1 below. Before the approach of CO₂, the silepin complex (**B'**) is converted to **Int'_2** after surmounting a barrier of 16.6 kcal/mol. The subsequent steps involve the approach of CO₂ and the elimination of CO, as well as the approach of a second CO₂, leading eventually to the formation of the CO₂ activated product **C'**; a monomeric silicon structure having silicon bridging with CO₂ (see Figure 5.1). Moreover, calculations

suggest that the slowest step in this process is the conversion of **Int'_2** to **Int'_3**, having a barrier of 22.8 kcal/mol.

Interestingly, when the mechanism for the CO₂ activation by the silepin complex (**B**) in the absence of an explicit molecule of toluene have investigated, it has been found that the barrier for the slowest step (25.3 kcal/mol) was higher by 2.5 kcal/mol (see Figure 5.2). In order to find the relative efficiency of both the CO₂ activation process (in the presence and the absence of toluene solvent molecule), turn over frequency calculations with the ESM approach have been performed. Calculations indicate that this translates to the efficiency for this process is as much as sixty times greater for the toluene assisted process (see Table 5.1 below). The reason for the difference in the barrier is seen to be the difference in the electronic energies (ΔE) for **Ts'_3** and **Ts_3** and **Ts'_5** and **Ts_5** and the difference in enthalpy (ΔH) in the case of **Ts'_6** and **Ts_6**.

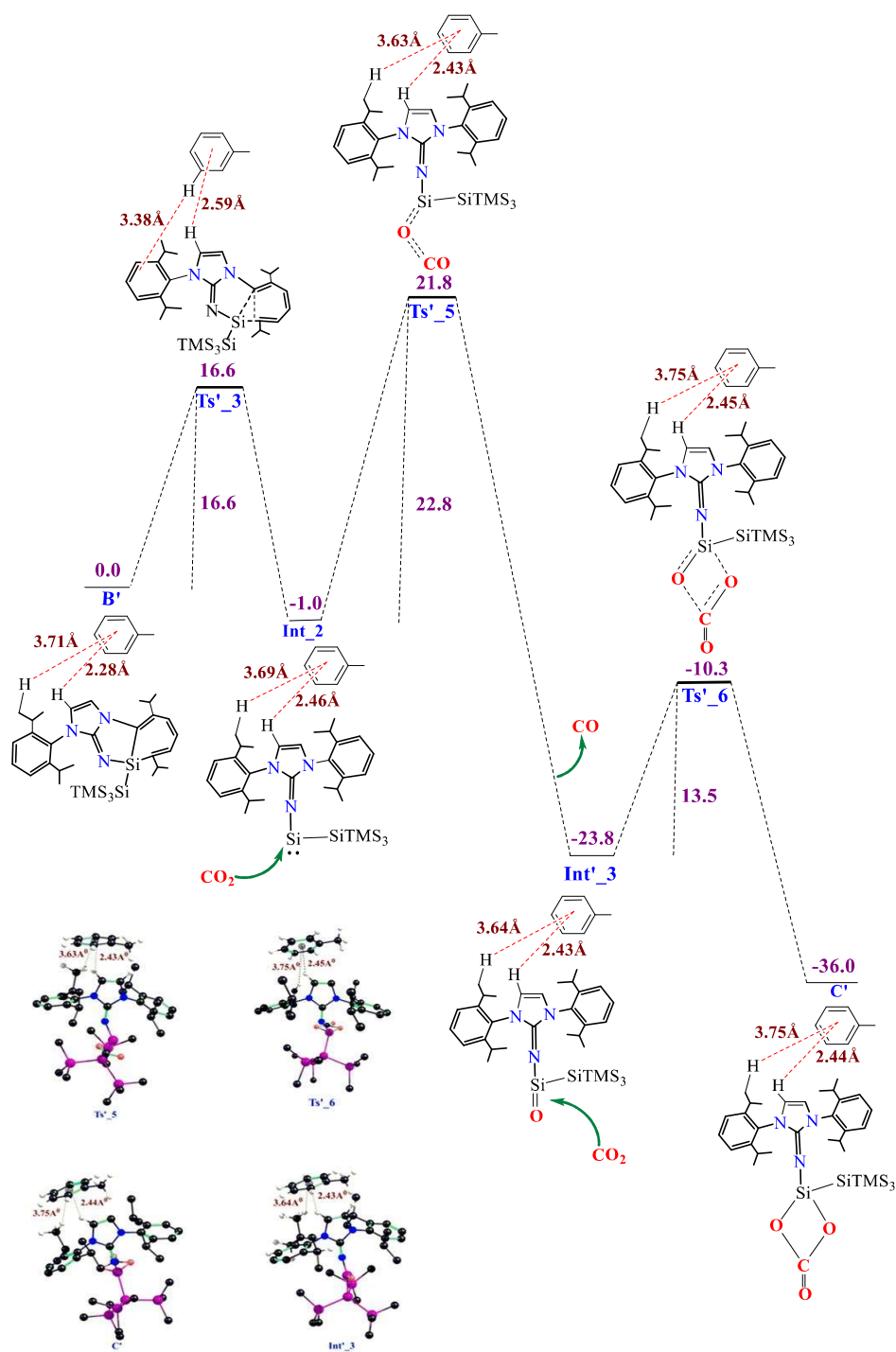


Figure 5.1 The free energy profile (ΔG in kcal/mol) for the activation of CO₂ by the silepin complex (**B'**) in the explicit presence of a toluene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model). The optimized structures obtained for the transition states and intermediates are also shown below the profile.

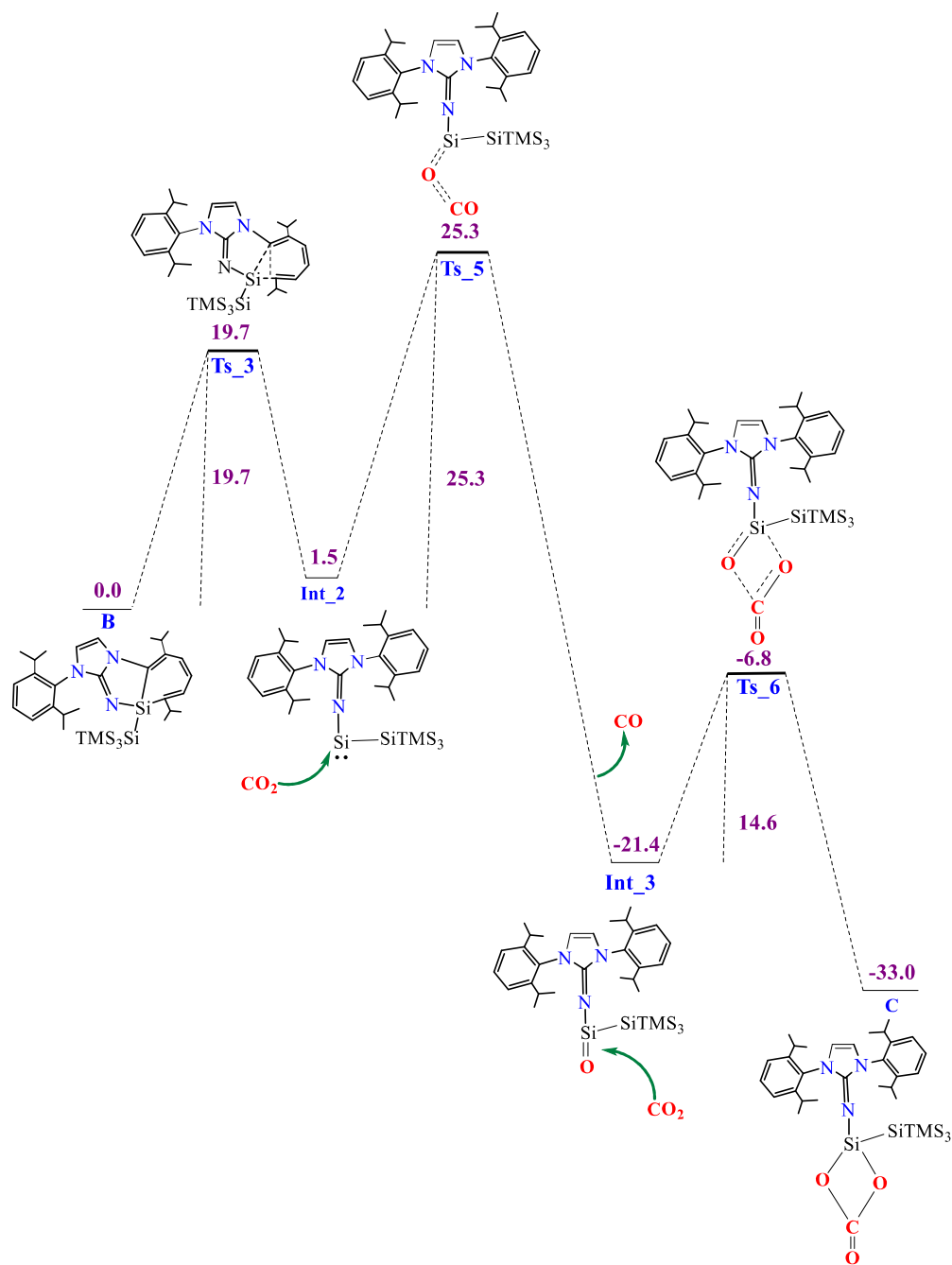


Figure 5.2 The free energy profile (ΔG in kcal/mol) for the activation of CO₂ by the silepin complex (**B**) in the absence of an explicit toluene molecule.

Table 5.1 The relative efficiencies obtained for the CO₂ activation by the silepin complex due to the explicit assistance of the solvent.

Process	Relative Efficiency
Activation of CO ₂ by the silepin complex	0.6*10 ²

Hence, what these calculations show is that, even though there are only two C-H/ π interactions involved between the solvent molecule and the silicon system in each of the intermediates and the transition states, and C-H/ π interactions are considered to be weak, they are still influential enough to create an order of magnitude of difference in the efficiency of the CO₂ activation process.

Furthermore, in order to quantify non-covalent interactions, the interaction energy between solvent and substrate have been calculated, which suggest the interaction energy between toluene and **Ts_5** (rate-determining Ts) was favorable by 7.2 kcal/mol at the TPSS-D3/def2-TZVP and by 7.1 kcal/mol and B3-lyp/TZVP level of theory (see table 5.2 below).

Table 5.2 The interaction energies due to C-H/ π interactions. The values are provided in kcal/mol.

Non-covalently bonded Systems	ΔE at TPSS-D3/def2- TZVP	ΔE at B3- LYP-
Ts'_5	-7.2	-7.1
Ts_'6	-6.8	-7.0
C'	-6.9	-7.1

5.3.2 Exchange between Solvent Molecules and their Effect on Potential Energy Surface: AIMD simulation

Now, there is another important point that should also be taken into account. Since C-H/ π is a non-covalent interaction, it is possible that after some period of time, the toluene would be displaced from the

silicon center, thus eliminating this interaction. However, because the silicon complex in solution would, at any instant in time, be surrounded by several solvent molecules, it is quite likely that even if one toluene molecule were to be displaced, another would take its place. In order to investigate this, AIMD simulations have been done at 1000.0 K temperature. This is because the exchange process was not observed in the AIMD simulations done at room temperature (as studied in the previous chapter); once one toluene formed a C-H/ π interaction with the substrate, this interaction was consistently present until the end of the simulation, with the other two toluene molecules randomly oriented around the complex. It is due to the fact that the total number of steps that were considered for the simulation at room temperature (17,182 steps) may not have been adequate to observe the exchange process between one toluene and the other. Therefore, we decided to "accelerate" the process by doing the simulations at an elevated temperature. The results obtained are shown through five snapshots in Figure 5.3 below.

It has been observed that, after 1.7 ps, the coordinating toluene was displaced from the C-H/ π interaction, and there was no interaction of any of the three toluenes considered with the substrate for 3400 steps. However, after that, another toluene molecule approached the silicon complex and formed a C-H/ π interaction with the substrate. Now, considering the total time for this simulation and calculating the amount of time when there is no C-H/ π interaction, we see that 63.0% of the time there was C-H/ π interaction, and the remaining 37.0% of the time, there was no C-H/ π interaction during the simulation. However, this was when there were only three solvent molecules considered.

In the real system, with dozens of solvent molecules likely to be present around the substrate, it is evident that there would be solvent-substrate interaction for a more significant majority of the time. Hence, the calculations indicate that the determination of the potential energy surface for the Si(II) to Si(IV) conversion, as well as the CO₂ activation by the Si(IV) complex, should include an explicit toluene molecule with a C-H/ π interaction with the substrate. This C-H/ π interaction should be considered in the reactants, intermediates, and products formed in all the potential energy surfaces calculated. One could argue that this, too, could influence the nature of the potential energy surfaces. The exchange of one toluene solvent molecule with another could lead to entropic changes: there would be a favorable entropic effect on the potential energy surface upon the exit of toluene from the silicon complex and an unfavorable entropic penalty for the subsequent gain of another C-H/ π interacting toluene molecule.

Here why this should not matter for the potential energy surface. Figure 5.4 below shows a scenario where the exchange of one toluene solvent molecule with another takes place between the reactant and transition state species, in the specific case where the reactant is the silylene complex and the transition state involves

CO₂ activation, *i.e.*, for the slowest step of the CO₂ activation process. It is clear from the figure that the favorable and unfavorable entropic effects would cancel each other out. In this figure, the C-H/ π interaction between solvent and substrate remains in the reactant and transition state, and hence the calculation of the barrier (*i.e.*, the difference in energy between the reactant and transition state) is unaffected by the exchange process. Now, if the solvent exchange were to happen at the point where the transition state was formed, then we would have a situation where there would be a C-H/ π interacting toluene molecule in the reactant but no C-H/ π interacting toluene molecule in the transition state and that would affect the barrier, and thus, the potential energy surface. However, since it has been discussed earlier that the C-H/ π interacting solvent would be present for a significant majority of the time, and the loss of solvent from the substrate would occur for only a brief period, the probability that this would occur at the transition state is very low. Therefore, such situations represent only minor possibilities during the reaction. Nevertheless, it has been decided to check the effect of these minor possibilities on the potential energy surface. To this end, some additional calculations have been done for the slowest step of the CO₂ activation case, where (I) we have considered the case where no toluene was coordinated with the substrate, while a C-H/ π interacting toluene was present in the transition state and in the product, (II) toluene was coordinated in the substrate and the product, but no C-H/ π interacting toluene was present in the transition state, and (III) toluene was coordinated in the substrate and the transition state, but no C-H/ π interacting toluene was present in the product. The free energy profiles corresponding to these three cases are shown in Figures 5.5-5.7 below.

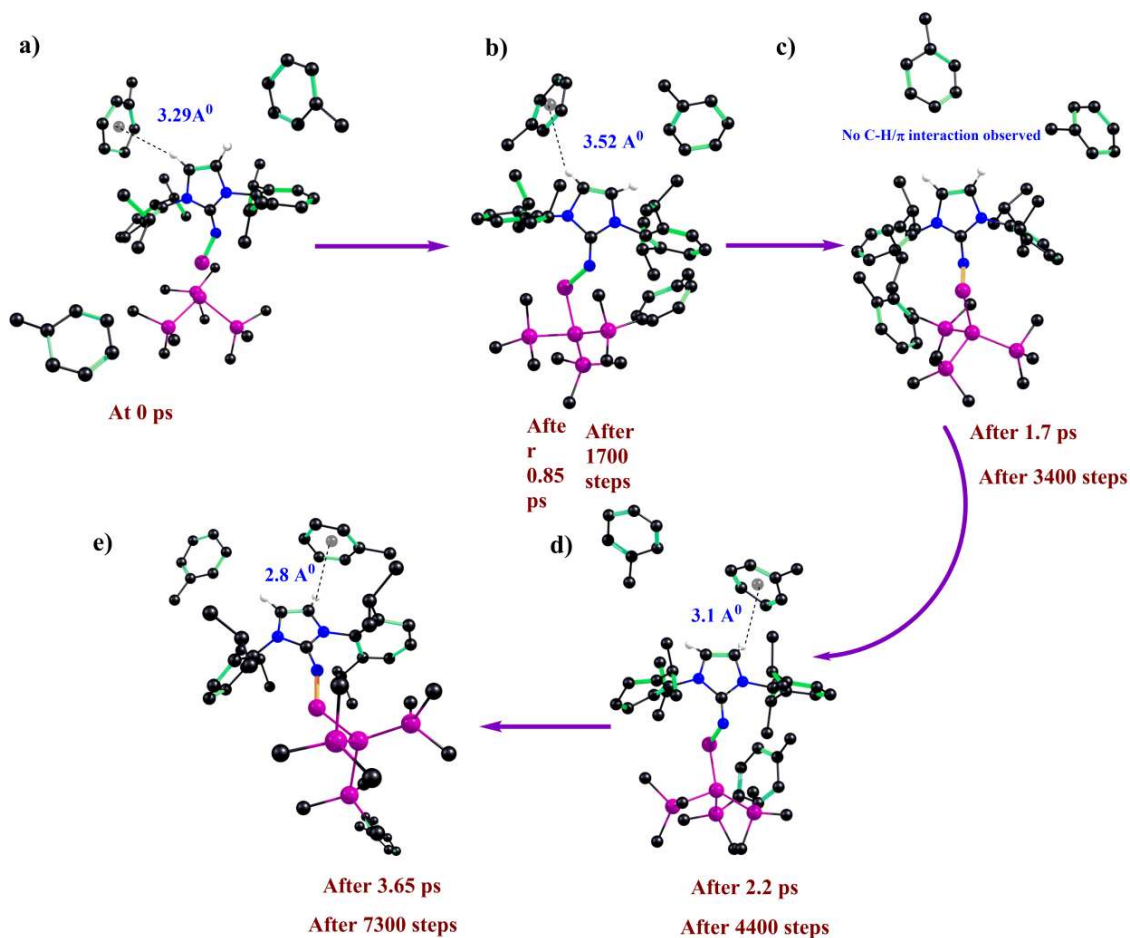


Figure 5.3 The different snapshots for observed C-H/ π interactions in ab initio molecular dynamics simulations done at a temperature of 1000.0 K. a) Geometry at 0.0 ps, where the bond distance for C-H/ π interaction between the hydrogen atoms of C-H and the center of the π ring is $3.29 \text{ \AA}$ b) after 0.85 ps, when the bond distance for C-H/ π interactions is $3.52 \text{ \AA}$ c) after 1.7 ps, when C-H/ π interaction is not observed d) after 2.2 ps, when the bond distance for the C-H/ π interaction is $3.10 \text{ \AA}$, and e) after 3.65 ps when the bond distance for the C-H/ π interaction is $2.8 \text{ \AA}$.

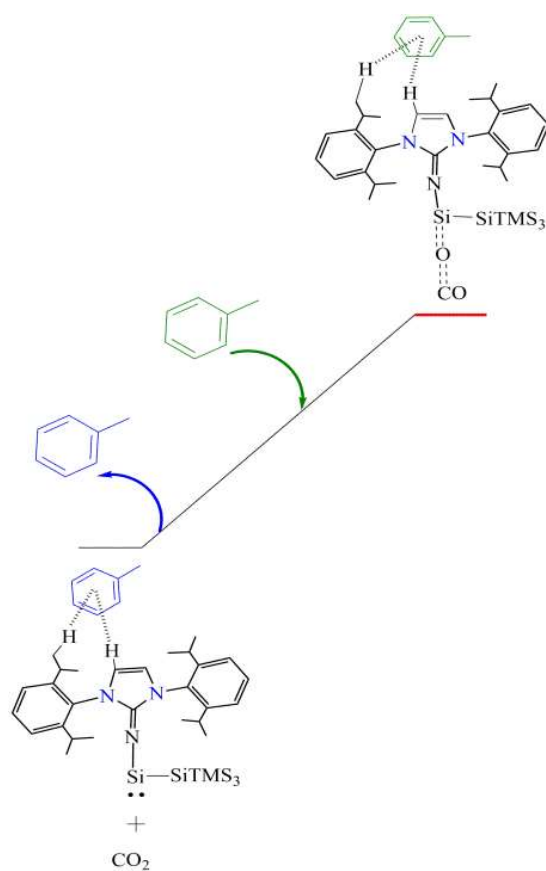


Figure 5.4 The exchange of one toluene solvent molecule with another toluene, which shows that C-H/ π interaction between substrate and solvent would be present in the reactants well as in the transition state.

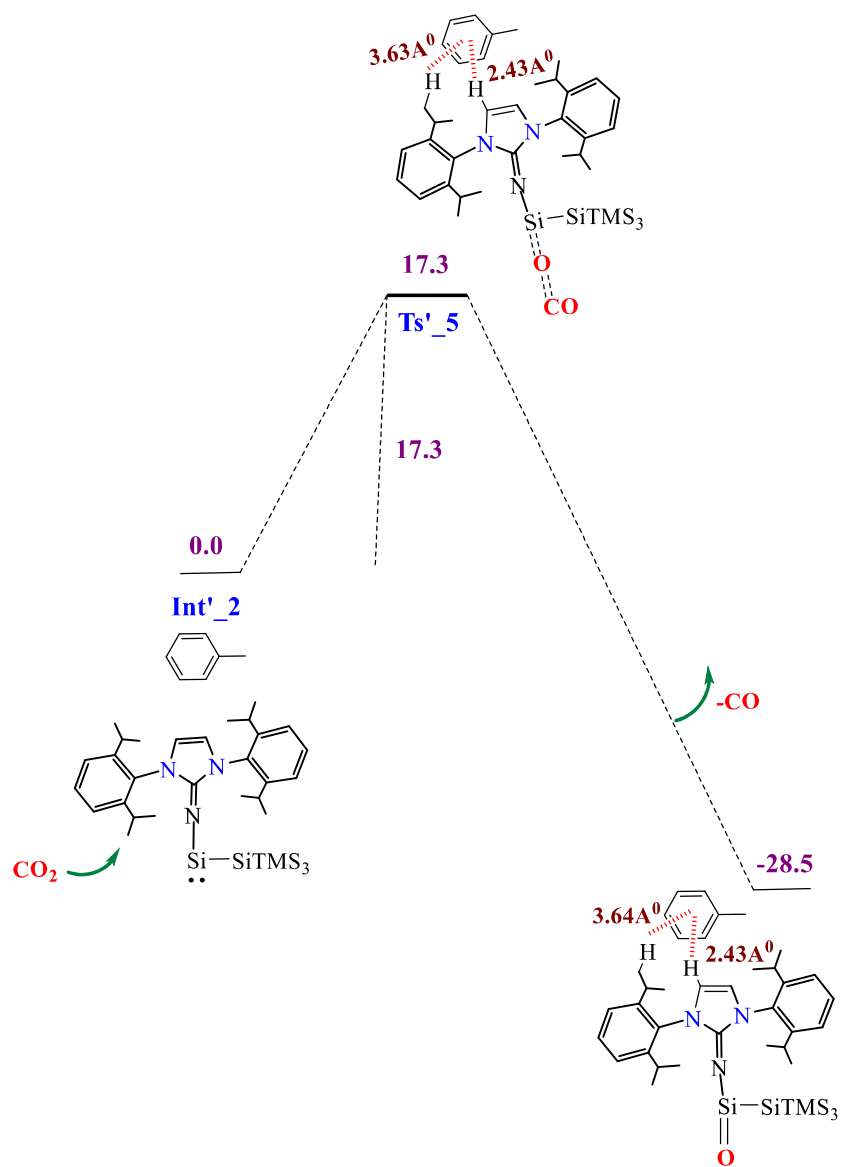


Figure 5.5 The free energy profile for the case where toluene is not involved in C-H/ π interaction with the substrate (**Int'_2**) for the slowest step of the CO₂ activation process by the silepin complex.

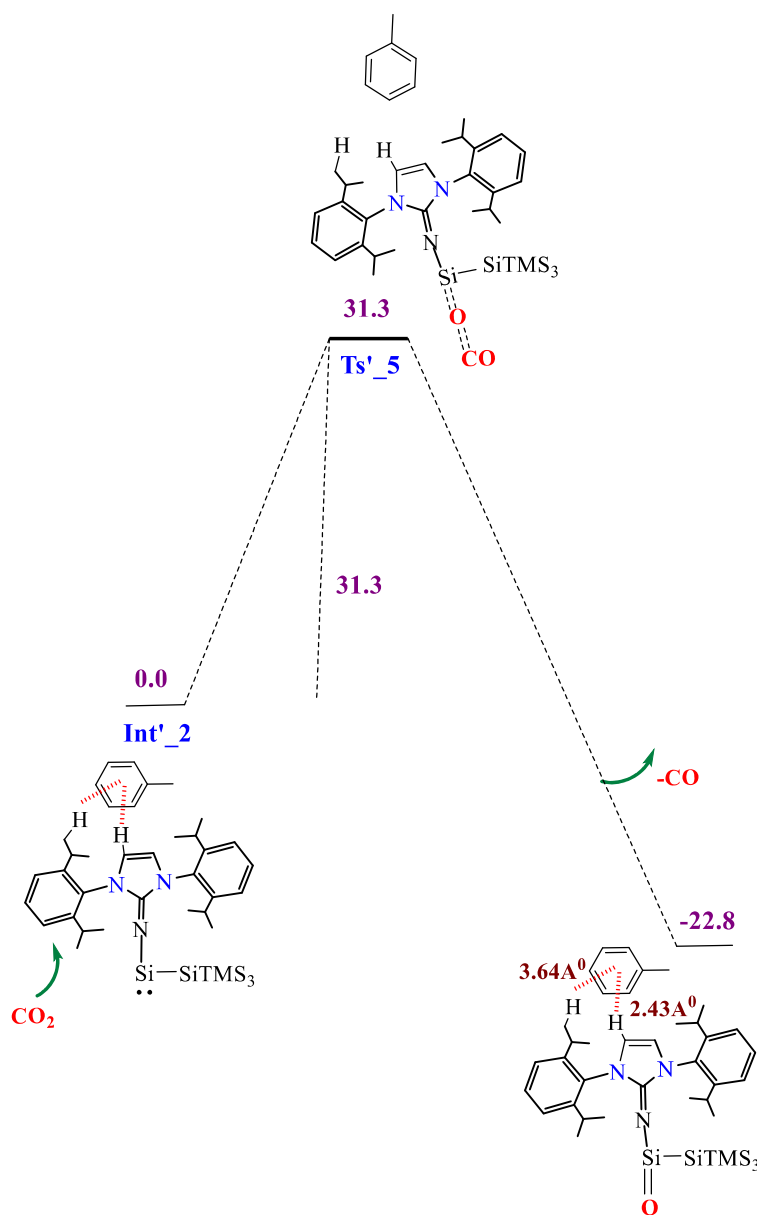


Figure 5.6 The free energy profile for the case where toluene is not involved in C-H/ π interaction with the transition state (**Ts'_5**) for the slowest step of the CO₂ activation process by the silepin complex.

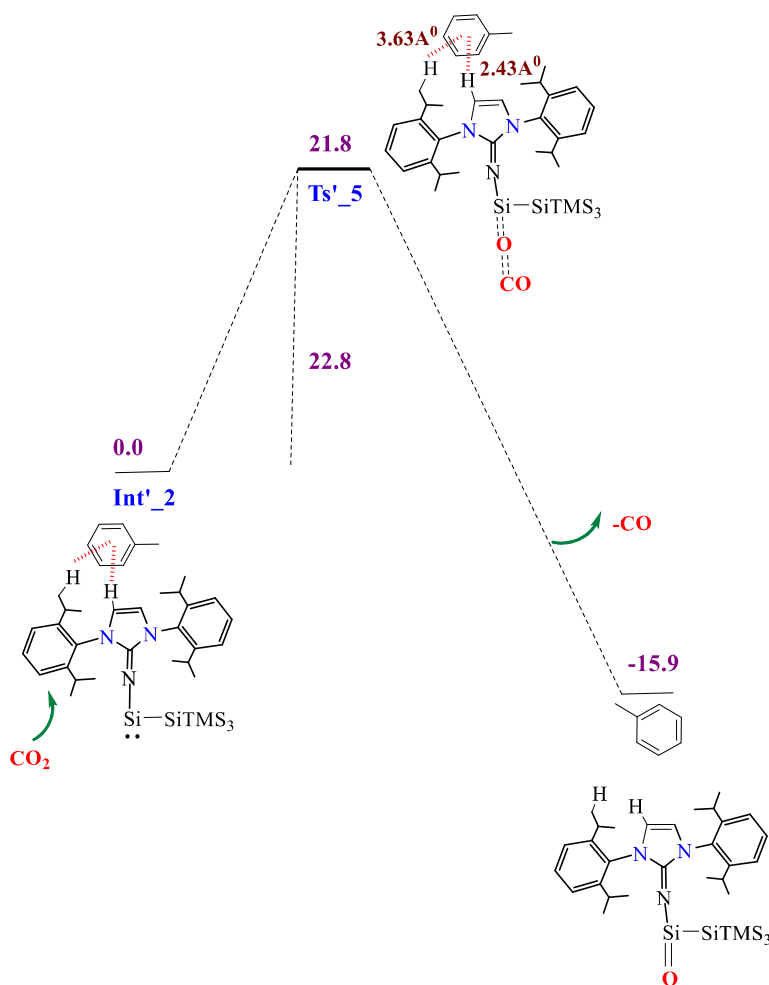


Figure 5.7 The free energy profile for the case where toluene is not involved in C-H/ π interaction with the product (IV) for the slowest step of the CO₂ activation process by the silepin complex.

Furthermore, TOFs have also been calculated for these cases and based on the values obtained, the efficiencies of the CO₂ activation process for these cases relative to the TOF for the same process when the toluene was present in all of the reactant, transition state, and the product. As Table 5.3 values indicate, in two out of the three cases, the CO₂ activation would actually become significantly more facile if the exchange occurred during the reaction. In only one of the three cases, would the CO₂ activation process become significantly less favorable. Hence, for the overwhelmingly significant majority of the time, the inclusion of the C-H/ π interacting solvent molecule would have a salutary effect on the CO₂ activation process.

Table 5.3 The efficiency values for cases where the possibility that exchange of one toluene for another would be occurring while the CO₂ activation was taking place, relative to the case where toluene was attached in the reactant, transition state, and the product, for the slowest step of the CO₂ activation reaction.

Different Cases	Relative Efficiency
I	1.0×10^4
II	5.8×10^{-7}
III	1.0×10^0

5.4 Conclusions

The current computational investigation with DFT calculations provides novel insight into the small molecule activation by low valent silicon complex (silylene). Calculations indicate that the explicit solvent molecule (Toluene) influences the reaction barriers of the CO₂ activation process through C-H/ π interaction. Furthermore, ab initio molecular dynamics (AIMD) revealed that exchange would occur in a facile manner between solvent molecules so that for a significant portion of time, C-H/ π interactions would exist between solvent and the silicon complex. Next, the efficiency of the CO₂ activation by silepin was improved by as much as sixty times due to the toluene's presence have demonstrated.

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Chapter 6

The Effect of Solvent-Substrate Non-covalent Interactions on the Diastereoselectivity in the Intramolecular Carbonyl-Ene and the Staudinger [2+2] Cycloaddition Reactions

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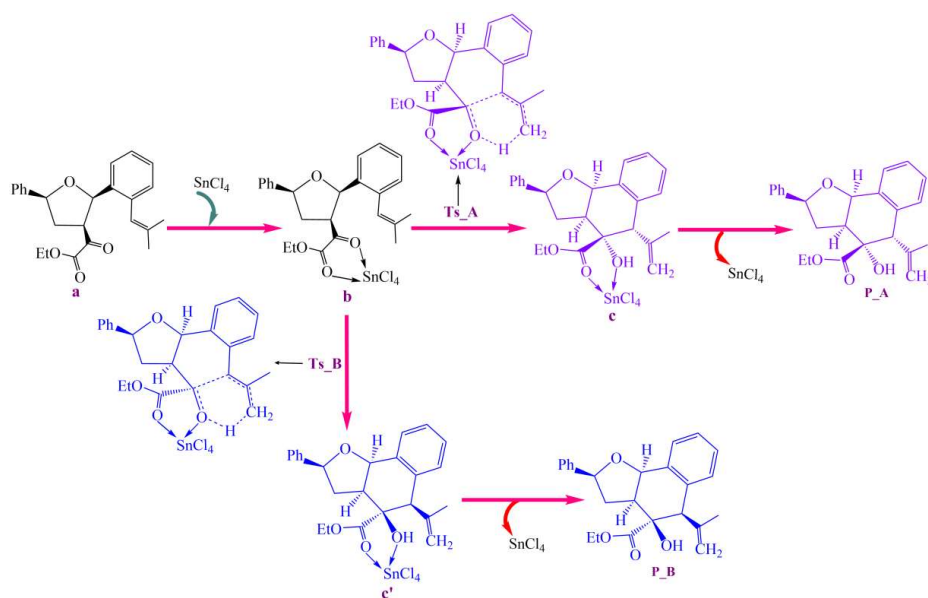
Abstract

Non-covalent interactions have been identified as important contributing factors in determining selectivity in organic transformations. However, cases where non-covalent interactions between solvent and substrate are responsible for a major extent for determining selectivity, are rare. The current computational study with density functional theory (DFT) identifies two important transformations where this is the case: the intramolecular carbonyl-ene reaction and the Staudinger [2+2] cycloaddition reaction. In both cases, the role of explicit solvent molecules interacting non-covalently with the substrate has been taken into account. Calculations indicate that the diastereomeric ratio (dr) would be 95.0:5.0 for the formation of tricyclic tetrahydrofuran diastereomers *via the* intramolecular carbonyl-ene reaction, and 94.0:6.0 for the formation of the triflones diastereomers *via the* Staudinger [2+2] cycloaddition reaction, which corroborates with the experiment. Interestingly, in both the cases, the calculations indicate that the non-inclusion of explicit solvent molecules would lead to only a small difference between the competing transition states, which leads to the conclusion that solvent-substrate non-covalent interactions are the major cause for diastereoselectivity in both the cases considered.

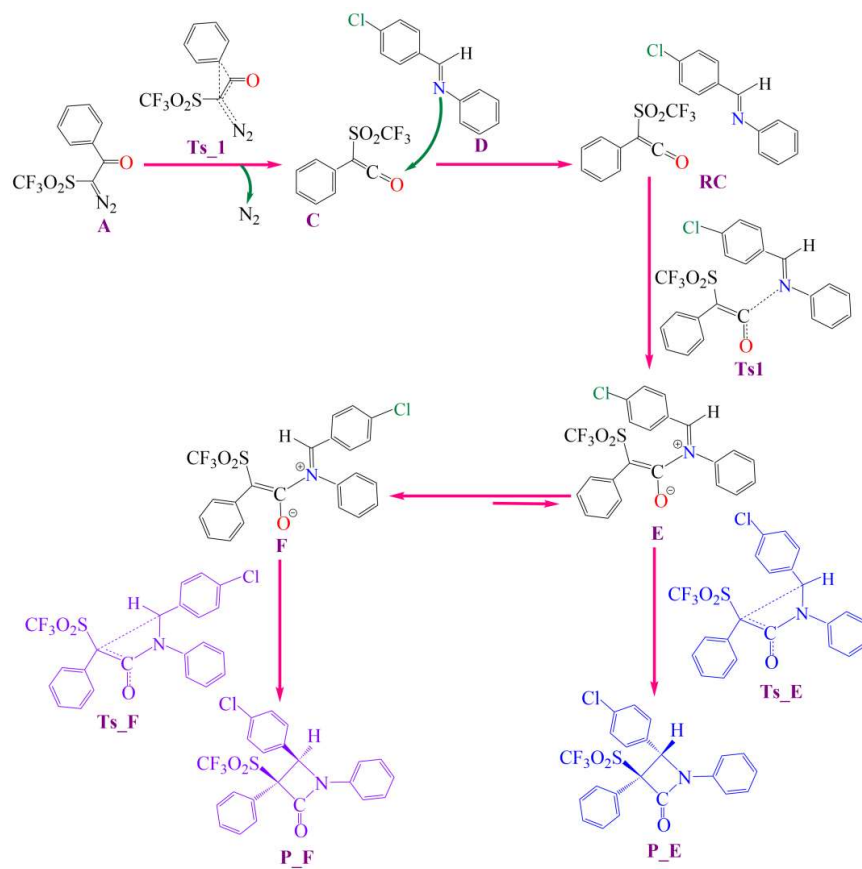
6.1 Introduction

Stereoselectivity plays a central role in various fields of chemistry and biology, such as organic synthesis,¹⁻⁵ asymmetric synthesis,⁶⁻⁸ drug metabolism,⁹⁻¹⁰ pharmacology,¹¹ and medicinal chemistry.¹² Therefore, understanding the origin of stereoselectivity in organic reactions is essential. It has been found that many factors influence the stereoselectivity,¹³⁻¹⁵ including the solvent,¹⁶⁻²⁰ additives^{16, 21-22} and temperature.²³ Also, the solvent is seen to play the most pivotal role in different chemical reactions.²⁴⁻²⁹ There are several reports investigating the effect of different solvents,²⁶⁻²⁹ including reports of the explicit role of solvent molecules, on stereoselectivity. In addition to these effects, the role of non-covalent effects such as hydrogen bonding, π - π stacking, as well as C-H/ π , and C-H/O interactions has also been investigated, and non-covalent interactions between explicit solvent molecules and the substrate have been seen to be important.^{16,30-33} It is, however, rare to find reports that show non-covalent interactions between solvent and substrate to be the major reason for the observed stereoselectivity.³⁴⁻³⁵ The reason could be because this is a rare phenomenon, but an interesting hypothesis that we propose and explore here is that this is a widespread occurrence that has not received adequate attention because of a lack of inclusion of explicit solvent effects in computational investigations. In order to give credence to this hypothesis, two important highly stereoselective organic reactions have considered: a) the carbonyl-ene reaction, which is a reaction between the ene and the enophile for selective carbon-carbon bond formation,³⁶⁻³⁹ and b) the Staudinger [2+2] cycloaddition reaction between a ketene and an imine⁴⁰⁻⁴² for the synthesis of β -lactamstriflones. The current computational study investigates whether a) and b) represent two cases where non-covalent interactions between explicit solvent molecules and the substrate were the major reason for the stereoselectivity.

The choice of these two reactions stems from the fact that they represent two diverse examples of highly stereoselective reactions. The carbonyl-ene reaction is single-step and intramolecular (see Scheme 6.1), whereas the Staudinger reaction is a multi-step and intermolecular reaction (see Scheme 6.2). Moreover, the carbonyl-ene reaction is organocatalyzed⁴³ and the Staudinger reaction is a catalyst-free reaction. Furthermore, the solvent employed in the carbonyl-ene reaction is aliphatic (dichloromethane),⁴⁴ while the solvent used in the Staudinger reaction is aromatic (toluene).⁴⁵ Hence, these two systems represent ideal test cases for our hypothesis. If solvent-substrate non-covalent interactions are seen to be the major cause for stereoselectivity in these two very diverse systems, this would provide credible support to our argument that selectivity arising largely from such interactions is a more widespread phenomenon than previously considered.



Scheme 6.1 The reaction mechanism for the formation of the tricyclic tetrahydrofuran diastereomers **P_A** and **P_B** via the intramolecular carbonyl-ene reaction.



Scheme 6.2 The reaction mechanism for the formation of the β -lactams triflones diastereomers **P_F** and **P_E** via the [2+2] cycloaddition Staudinger reaction.

The calculations have been done using density functional theory (DFT). The effect of the solvent in the stereoselectivity of the two reactions has been explored through hybrid explicit-implicit solvation calculations. Two cases of explicit solvent inclusion have been considered for the intramolecular carbonyl-ene reaction: (i) one and (ii) four non-covalently interacting explicit solvent dichloromethane molecules have been incorporated in the calculations. Also, for the Staudinger [2+2] cycloaddition reaction two cases have been considered: (i) the explicit inclusion of one explicit toluene solvent molecule and ii) two non-covalently interacting explicit solvent toluene molecules. The reasons for choosing these specific cases of explicit solvent inclusion have been discussed in the Results and Discussion section. Non-covalent interactions have been captured with dispersion corrected⁴⁶⁻⁴⁷ DFT calculations. Moreover, as will be shown in the next section, the results from the calculations indicate that non-covalent interactions play the central determining role in giving rise to the observed diastereoselectivity in these two chemical systems. Our calculations reveal that non-covalent interactions such as Cl/ π and π/π are significant up to a distance of 4.8 Å. A perusal of the literature indicates that the effects of long-range interactions such as C-H/ π and anion/ π -HB are significant up to a distance of more than 5 Å.⁴⁸⁻⁵⁰

6.2 Computational Details

The calculations were carried out using the Turbomole⁵¹ 7.0 and 7.1 suite of programs. Geometry optimizations were performed using the TPSSH⁵² functional; the electronic configuration of the atoms was described by a triple ζ (Turbomole basis set TZVP⁵³) basis set. For the Sn atom, the diffuse def2-triple ζ basis set augmented by a polarization function (Turbomole basis set def2-TZVP⁵⁴) has been employed. The resolution of identity (ri)⁵⁵ along with the multipole accelerated resolution of identity (marij)⁵⁶ approximations have been used for an accurate treatment of the electronic Coulomb term in the density functional calculations. The real (not model) system has been employed for all the calculations. The structures of transition states were confirmed to have only one imaginary frequency, corresponding to the correct normal mode. In addition, intrinsic reaction coordinate (IRC)⁵⁷ calculations were done with all the transition states, in order to further confirm that they were the correct transition states, yielding the correct reactant and product structures. The option “disp” given in the Turbomole package (DFT-D3)⁴⁶⁻⁴⁷ was employed for dispersion-corrected DFT calculations for all the calculations. The computation of the Hessian matrix and the calculation of zero-point energy have been also carried out at the same level of theory as for the electronic energy calculations, *i.e.*, at the TPSSH/TZVP, def2-TZVP (Sn) level of theory. The values provided are ΔG values (unless otherwise specified), with zero-point energy, internal energy, and entropic

contributions included, with the temperature taken to be 298.15 K. Furthermore, solvent effects were introduced by using the COSMO model⁵⁸ with the dielectric constant $\epsilon = 8.93$ for dichloromethane and $\epsilon = 2.38$ for toluene.

6.2.1 Diastereomeric Ratio (dr) Calculations

Stereoselectivity of chemical reactions can be represented as an enantiomeric (er) or diastereomeric (dr) ratio. The diastereomeric ratio (dr) (for the diastereoselective reaction) is directly proportional to the relative rates of formation of the diastereomeric products, *i.e.*, the ratio of products depends on the relative free energy barrier ($\Delta\Delta G^\ddagger$). Hence, selectivity for the kinetically controlled reaction can be defined as (see equation (6.1) and (6.2) below);

$$\frac{k_{P_A}}{k_{P_B}} = \frac{[P_A]}{[P_B]} = e^{\frac{-\Delta\Delta G^\ddagger}{RT}} \quad (6.1)$$

$$de = \frac{1 - e^{\frac{-\Delta\Delta G^\ddagger}{RT}}}{1 - e^{\frac{-\Delta\Delta G^\ddagger}{RT}}} \times 100 \quad (6.2)$$

Here, k is the rate constant, and $\Delta\Delta G^\ddagger = \Delta G_2^\ddagger - \Delta G_1^\ddagger$ (see figure 6.1 below), de is diastereomeric excess.

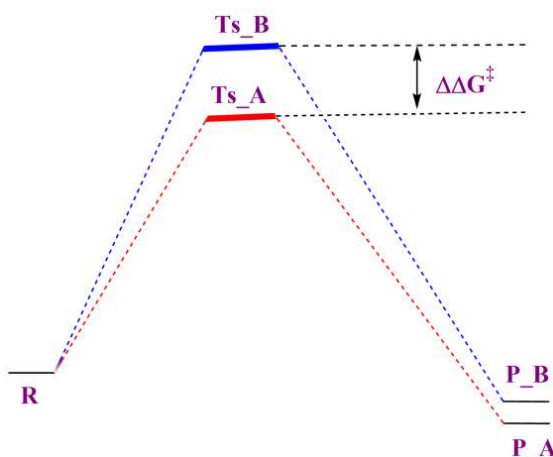


Figure 6.1 The free energy and the relative free energy barrier for two diastereomers **P_A** and **P_B**.

6.2.2 Non-Covalent Interaction (NCI) Plot

Analysis of non-covalent interactions in the stereo-controlling transition states has been carried out by employing the non-covalent interaction (NCI) plot developed by Yang *et al.*⁵⁹⁻⁶⁰ The NCI plot is a program that shows the graphical representation of inter and intramolecular non-covalent interactions based on the electron density and its derivatives.

6.3 Results and Discussions

6.3.1 Achieving Diastereoselectivity in the Intramolecular Carbonyl-Ene Reaction

As mentioned in the Introduction, full quantum chemical calculations have been performed with density functional theory (DFT), in order to understand the origin of stereoselectivity in the intramolecular carbonyl-ene reaction, reported by Schneider and coworkers.⁴⁴ This group has discussed the stereoselective synthesis of tetrahydrofuran and its use in an intramolecular carbonyl-ene reaction in the presence of the Lewis acid SnCl₄. Intermolecular and intramolecular carbonyl-ene reactions have been reported with Lewis acids such as AlMe₃ and SnCl₄,⁶¹ because Lewis acid coordinated dienophiles influence the rate and the diastereoselectivity of the carbonyl-ene reaction.⁶²⁻⁶³

Scheme 6.1, shown earlier in the Introduction, indicates that the SnCl₄ molecule binds with the reactant **a**, which leads to the formation of the intermediate **b**. Next, two stereo controlling transition states **Ts_A** and **Ts_B** lead to the formation of the intermediates **c** and **c'** respectively. The diastereomer products **P_A** and **P_B** are formed after the elimination of the SnCl₄ molecule. Now, since the diastereomeric ratio (dr) is directly proportional to the relative rates of formation of the diastereomers,¹⁴ the relative energy barriers ($\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$; electronic and free energy difference between the two stereo controlling transition states) for the formation of diastereomers (**P_A** and **P_B**) have been calculated. The $\Delta\Delta E^\ddagger$ is 1.2 kcal/mol and the $\Delta\Delta G^\ddagger$ is 1.3 kcal/mol for the stereo controlling transition states **Ts_A** and **Ts_B** (see Figure 6.2 below). Since energy values within a range of +/- 1.0 kcal/mol are subject to systematic errors in DFT calculations, the small values of $\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$ may suggest low diastereoselectivity for this reaction. However, the experimentally reported dr is 95.0:5.0 for **P_A** and **P_B** formation.⁴⁴ This seeming contradiction between calculation and experiment suggests that the solvent employed, dichloromethane,

could be having a non-negligible, explicit effect on the stereoselectivity of the reaction. Therefore, our computational studies then focused on the role of explicit dichloromethane molecules in influencing the diastereoselectivity.

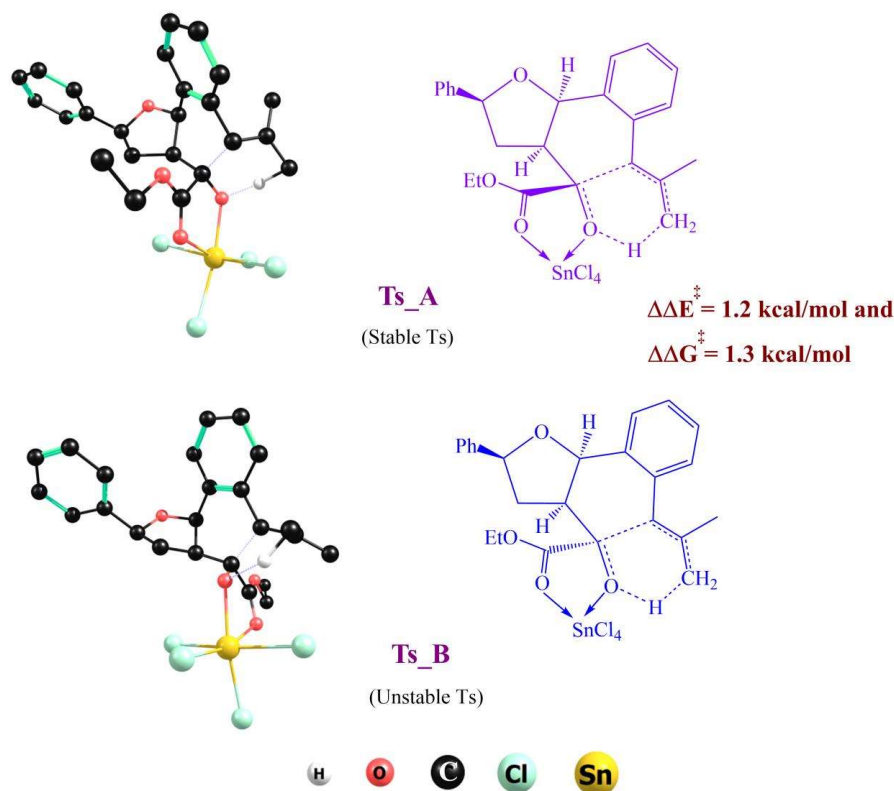


Figure 6.2 Stereo-controlling transition states **Ts_A** and **Ts_B** for the formation of the diastereomers **P_A** and **P_B**, respectively, in the absence of explicit dichloromethane solvent molecules (*i.e.* with the implicit solvent model). Hydrogen atoms have been removed for the purpose of clarity.

We began by investigating the possibility of non-covalent interactions between the solvent and the reactant (**b**). In order to find the orientation of the solvent dichloromethane with respect to the substrate, a dichloromethane molecule was added at several different positions near reactant **b** (i) at the oxygen of the ring (the furan oxygen), for possible C-H/O and Cl/ π non-covalent interactions, (ii) at the oxygen of the ethoxy group, (iii) at the carbonyl oxygen, for different possible C-H/O non-covalent interactions, and (iv) at the phenyl ring, for possible C-H/ π interactions. Calculations show that optimization of the case (ii) input structure gave rise to the most stable geometry, followed by case (iii) {0.5 kcal/mol higher than case (ii)}, case (i) {0.6 kcal/mol higher than case (ii)}, and case (iv) {1.1 kcal/mol higher than case (ii)} (ΔE values reported in all cases). However, since the energy differences are quite small, and, as mentioned earlier, fall within the range of systematic error in DFT calculations, we have decided to consider two cases: (a) where

a lone dichloromethane molecule was added near the oxygen of the ethoxy group {case (ii)}, and (b) where four dichloromethane molecules were added, one at each of the positions considered in the cases (i)-(iv). The two stereo-controlling transition states were then determined for these two cases (a) and (b), and the $\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$ values were calculated for each case.

Case (a). The $\Delta\Delta E^\ddagger$ and the $\Delta\Delta G^\ddagger$ values were found to be 3.3 kcal/mol and 2.3 kcal/mol respectively. This indicates that the gap between the stereo-controlling transition states (and, therefore, the diastereoselectivity) is increased to a significant extent upon the addition of an explicit solvent molecule of dichloromethane near the oxygen of the ethoxy group. The reason for this are the additional C-H/O and C-H/ π non-covalent interactions that are present in the transition state **Ts'_A**, which stabilize this transition state, whereas only C-H/O non-covalent interactions are present in the transition state **Ts'_B**. Figure 6.3 shown below illustrates the non-covalent interactions between the solvent and the stereo controlling transition states, and the relative energy difference between them.

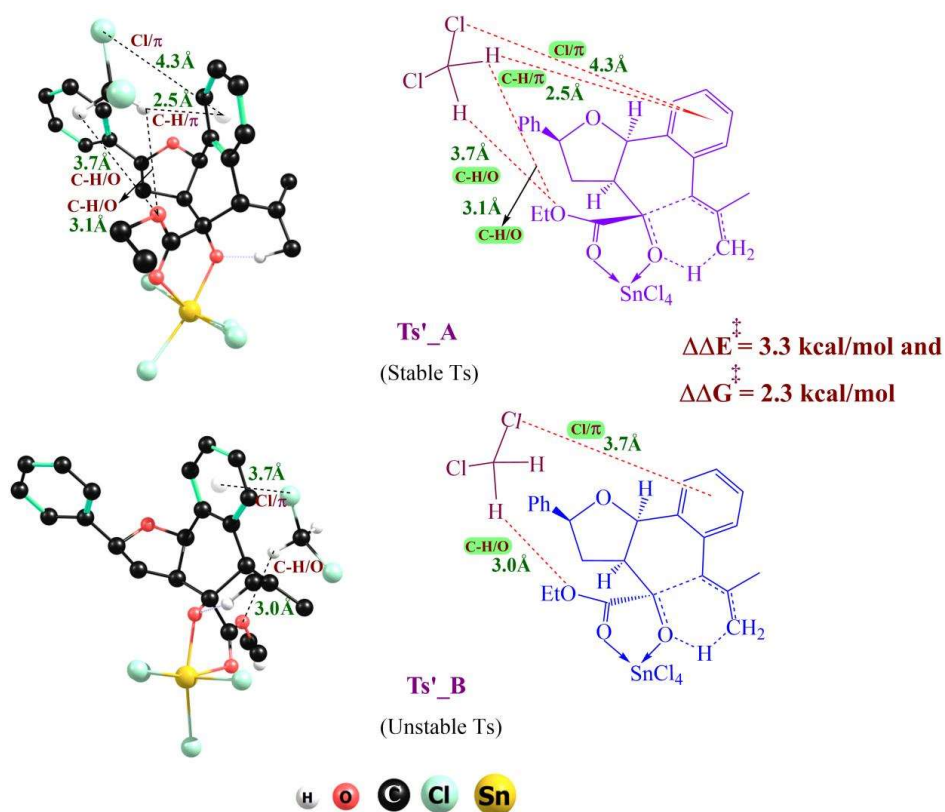


Figure 6.3 Stereo-controlling transition states **Ts'_A** and **Ts'_B** for the formation of the diastereomers **P_A** and **P_B** respectively in the presence of one explicit dichloromethane solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model). Hydrogen atoms (except for moiety involved in non-covalent interactions) have been removed for the purpose of clarity.

Case (b). Since, as mentioned above, only minor differences were seen in the stability of the optimized geometries when dichloromethane was added at different positions in the reactant **b**, four explicit dichloromethane solvent molecules (at all four positions discussed above) were added in the stereo-controlling transition states. The relative energy barrier ($\Delta\Delta G^\ddagger$) was found to be 4.1 kcal/mol for this case. This indicates that with the increase in the number of non-covalent interactions, the transition states are preferentially stabilized (see Figure 6.4 below), which gives rise to the experimentally observed diastereoselectivity.

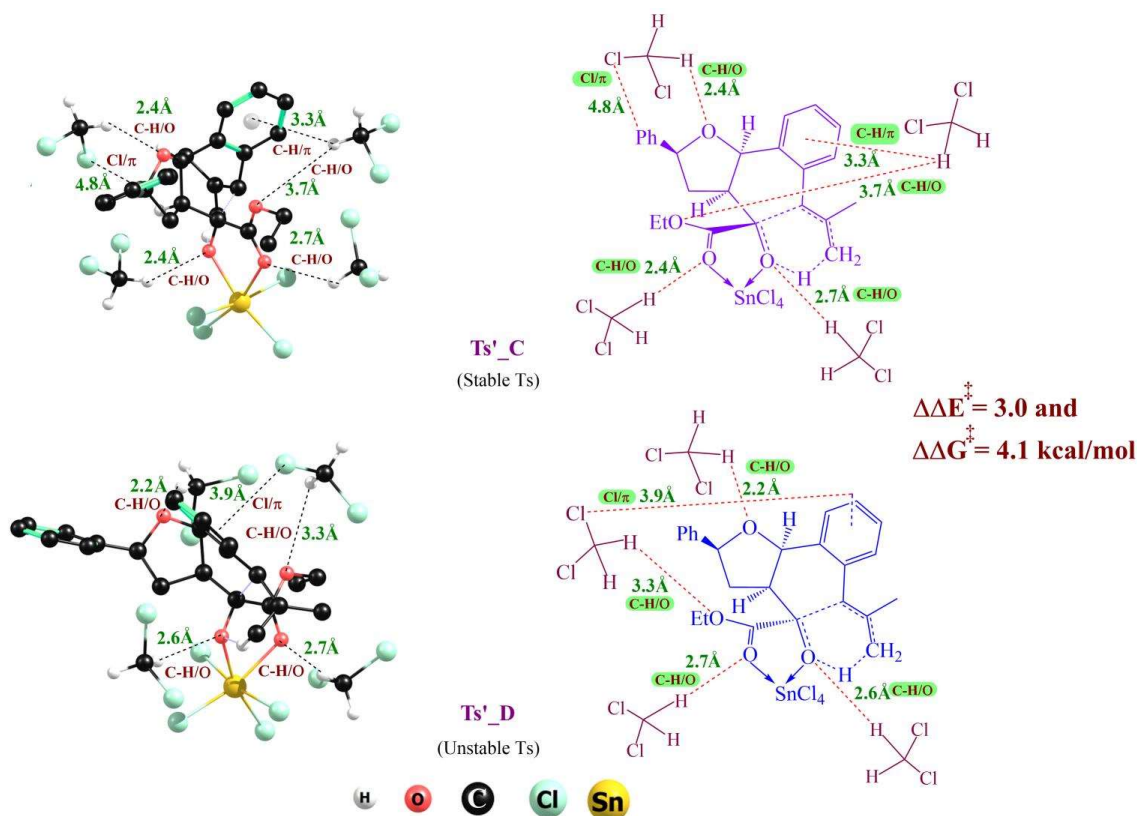


Figure 6.4 Stereo-controlling transition states **Ts'_C** and **Ts'_D** for the formation of the products **P_A** and **P_B** respectively in the presence of four explicit dichloromethane solvent molecules (*i.e.*, with the hybrid implicit-explicit solvent model). Hydrogen atoms (except for the dichloromethane moiety) have been removed for the purpose of clarity.

In order to quantify the non-covalent interactions, the non-covalent interaction (NCI) plot analysis was performed, which indicates that both **Ts'_A** and **Ts'_B** are stabilized by C-H/O and Cl/ π non-covalent interactions, but **Ts'_A** benefits from an additional C-H/ π interaction (see Figure 6.5).

The NCI plot analysis was also performed for the stereo-controlling transition states that had been obtained in the presence of explicit dichloromethane solvent molecules, and the results indicate that **Ts'_A** and **Ts'_C** are stabilized by additional C-H/ π and Cl/ π non-covalent interactions (Figure 6.5 below). In other words, there is greater stabilization through non-covalent interactions when explicit solvent molecules are present, and this explains the increased gap in the $\Delta\Delta E^\ddagger$ and the $\Delta\Delta G^\ddagger$ values, and thus, the experimentally observed diastereoselectivity. This analysis suggests that transition states with more number of non-covalent interactions are more stable (**Ts'_A** and **Ts'_C**) than the transition states with fewer number of non-covalent interactions (**Ts'_B** and **Ts'_D**).

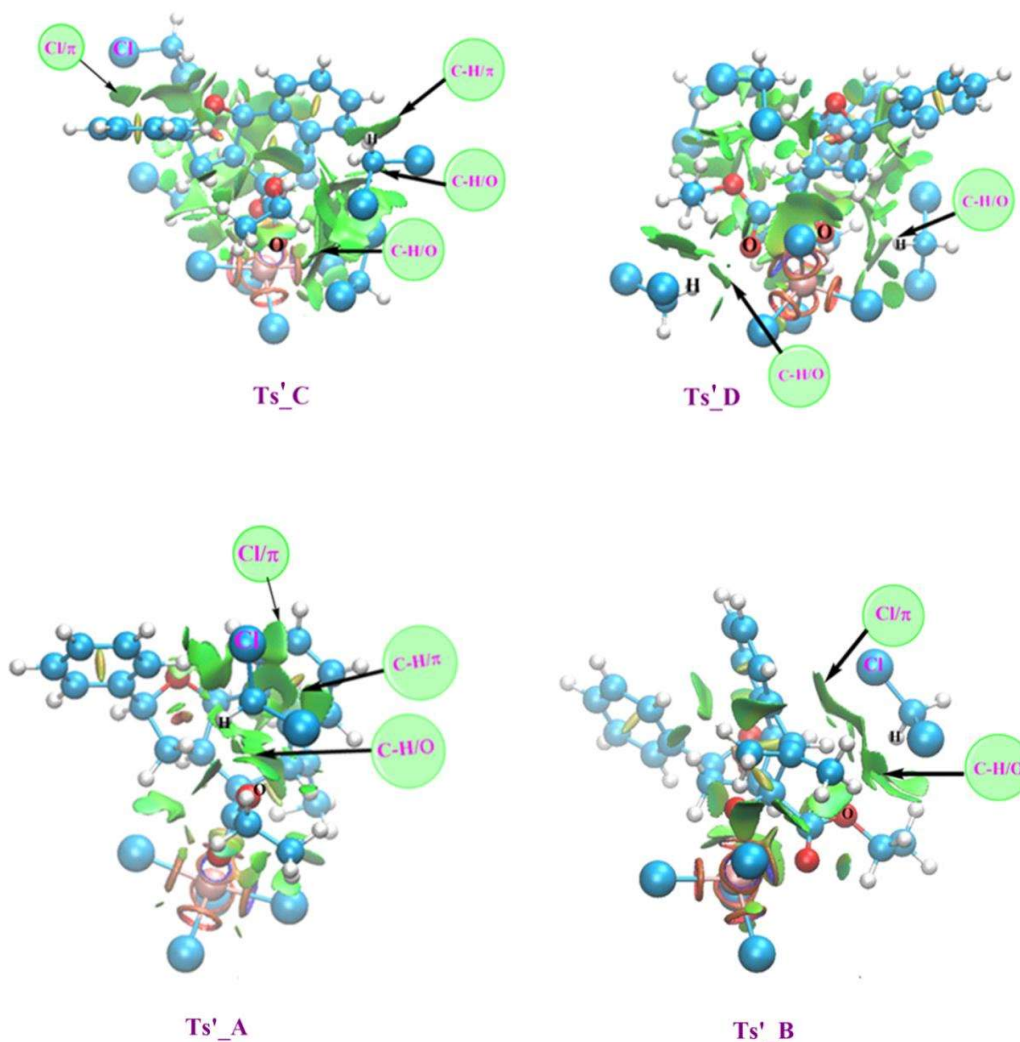


Figure 6.5 The NCI plots for stereo-controlling transition states that show the non-covalent interactions between solvent and substrate. Images **Ts'_A** and **Ts'_B** are in the presence of one explicit dichloromethane solvent molecule and images **Ts'_C** and **Ts'_D** are in the presence of four explicit dichloromethane solvent molecules.

6.3.2 Diastereoselectivity in the [2+2] Cycloaddition Staudinger Reaction

In the previous section, how the stereoselectivity of the intramolecular carbonyl-ene reaction is controlled by non-covalent interactions between the reactant and explicit aliphatic dichloromethane solvent molecules has demonstrated. In this section, the possibility that such non-covalent interactions can likewise play an exclusive role in determining the diastereoselectivity of the Staudinger [2+2] cycloaddition reaction has investigated. As noted in the Introduction, this reaction is significantly different from the carbonyl-ene reaction in its nature, and takes place in the aromatic solvent toluene. Shibata and *coworkers* have reported the stereoselective synthesis of β -Lactam-triflone, where the heterocyclic frameworks containing triflones were synthesized in catalyst-free conditions.⁴⁵ Triflones are useful in pharmaceutical applications, and β -lactams (heterocycles triflones) have shown antibiotic properties and thus found applications in biology, being employed in antibacterial treatments.

Figure 6.6 below shows the free energy profile of the stereoselective Staudinger reaction in the absence of explicit solvent molecules. Calculations indicate that the free energy barrier for ketene formation (**C**) is 29.6 kcal/mol. Next, the reactant complex (**RC**) leads to the formation of intermediate **E** via **Ts1**, which is exergonic by -41.5 kcal/mol. Due to steric hindrance, this intermediate (**E**) isomerizes into intermediate **F**. Subsequent to this, the free energy barriers for the formation of **P_E** and **P_F** are 20.0 kcal/mol and 19.3 kcal/mol via the stereo-controlling transition states **Ts_E** and **Ts_F** respectively, where **P_F** is the major diastereomer and **P_E** is the minor diastereomer. Since the dr depends on the relative energy barrier ($\Delta\Delta G^\ddagger$) of the stereo-controlling transition states, the $\Delta\Delta G^\ddagger$ has been calculated. This was seen to be 0.7 kcal/mol for the diastereoselective transition states **Ts_E** and **Ts_F**. In other words, the difference is small, and clearly does not account for the experimentally reported significant dr for these two diastereomers, 94.0:6.0. Thus, the inclusion of an explicit solvent molecule in the calculations was seen to be warranted.

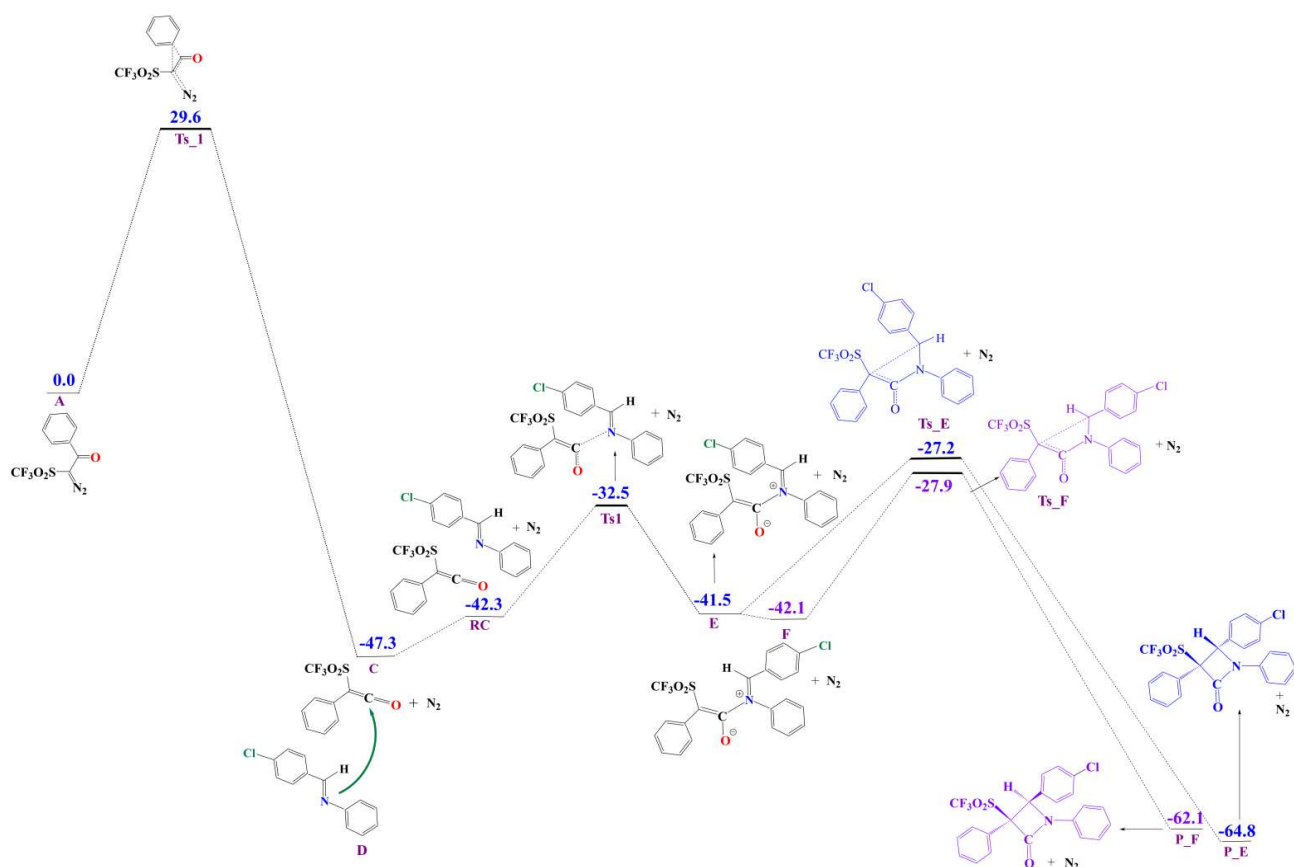


Figure 6.6 The free energy profile for the formation of the β -lactams triflones diastereomers **P_E** and **P_F**, in the absence of an explicit toluene solvent molecule (*i.e.*, with the implicit solvent model).

Case I. Achieving Diastereoselectivity in the Staudinger [2+2] Cycloaddition Reaction in the Presence of One Explicit Solvent Molecule (Toluene)

We began by investigating the possibility of non-covalent interactions between the solvent and the intermediate **E**. This intermediate was considered because the free energy profile in Figure 6.6 shows that this is the important intermediate in the reaction, occurring just prior to the formation of the stereocontrolling transition states **Ts_E** and **Ts_F**, which determine the stereoselectivity. In order to find the orientation of the aromatic solvent toluene with respect to intermediate **E**, one toluene molecule was added at several different positions of intermediate **E**: i) near the phenyl ring for possible π/π , and C-H/O non-covalent interactions, (ii) near the chlorophenyl ring for possible C-H/ π , $\pi-\pi$, and Cl/ π non-covalent interactions and (iii) near another phenyl ring for possible π/π and C-H/ π non-covalent

interactions. The calculations reveal that the optimized structure with C-H/ π , π/π and C-H/O non-covalent interactions {case (iii)} is the most stable: by 4.9 kcal/mol in comparison to the optimized case (ii) structure, and 3.3 kcal/mol in comparison to the optimized case (i) structure. Therefore, it becomes clear that case (iii) would represent the orientation of choice for a toluene molecule when it came in the vicinity of the intermediate. Therefore, an explicit solvent molecule of toluene was added in the diastereoselective transition states (**Ts'_F** and **Ts'_E**) near the phenyl ring, for possible C-H/ π and π/π non-covalent interactions (see Figure 6.7 below). The relative energy barrier ($\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$) was then determined, and the values, $\Delta\Delta E^\ddagger = 2.5$ kcal/mol and $\Delta\Delta G^\ddagger = 2.4$ kcal/mol, showed that the presence of the explicit solvent molecule created the important difference at this rate controlling step, thereby leading to the experimentally observed diastereoselectivity.

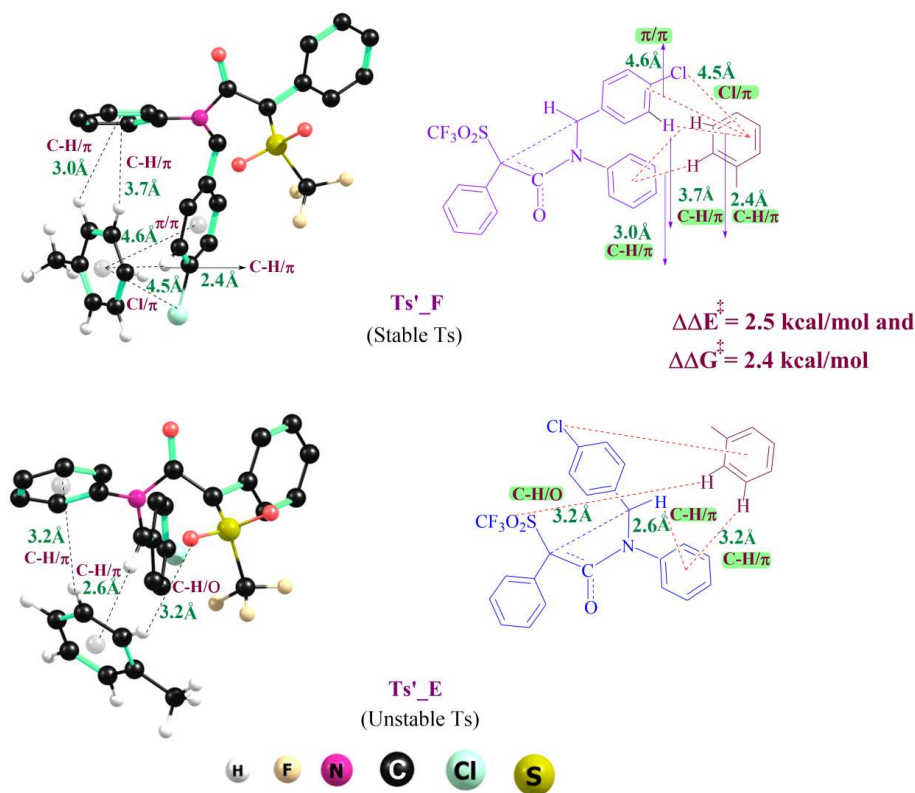


Figure 6.7 The stereo-controlling transition states for the formation of β -lactams triflones *via* the Staudinger reaction in the presence of an explicit toluene solvent molecule (*i.e.*, with the hybrid implicit-explicit solvent model). Hydrogen atoms (except for the moiety involved in non-covalent interactions) have been removed for the purpose of clarity.

The reason for this preferential difference in the transition states was determined, as in the earlier section, through the NCI plot analysis, which showed that C-H/ π , Cl/ π , and π - π non-covalent interactions were present in the transition state **Ts'_F**, which caused the preferential formation of the major diastereomer (see Figure 6.8 below). In contrast, only C-H/ π , and C-H/O non-covalent interactions were seen to be present in the transition state **Ts'_E**, and this caused it to become the minor diastereomer.

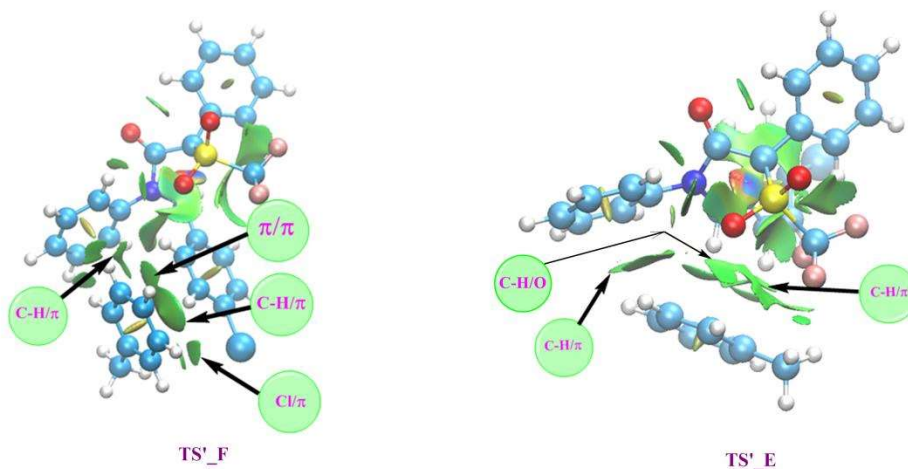


Figure 6.8 The NCI plot for diastereoselective transition states **Ts'_F** and **Ts'_E**, where non-covalent interactions between toluene and the substrate have been shown.

Case (II). Achieving Diastereoselectivity of the Staudinger [2+2] Cycloaddition Reaction in the Presence of Two Explicit Solvent Molecules (Toluene).

To see the effect of solvent-solvent interactions on the stereoselectivity of the Staudinger reaction, we have included another toluene molecule that would interact through π - π stacking with the first toluene molecule in the stereo-controlling transition states. To minimize the repulsion between the CH₃ groups, the orientation of the two toluene molecules has been kept such that the CH₃ groups are at a maximum distance. Calculations reveal that the relative electronic energy barrier ($\Delta\Delta E^\ddagger$) is increased in this case to 3.3 kcal/mol

from 2.5 kcal/mol in the presence of one explicit toluene molecule. Since we have not obtained a single negative frequency in both the competing transition states in the frequency calculations, the relative free energy barrier ($\Delta\Delta G^\ddagger$ value) has not been calculated. It is to be noted that the additional negative frequencies are quite small: in the range of -5.0 cm^{-1} to -42.0 cm^{-1} , and are the result of numerical inaccuracies. In other words, the obtained transition states are correct, and the $\Delta\Delta E^\ddagger$ value is reliable. Nevertheless, since the presence of the additional negative frequencies could affect the $\Delta\Delta G^\ddagger$ value, the $\Delta\Delta G^\ddagger$ value has not been reported. The determined $\Delta\Delta E^\ddagger$ value indicates that solvent-solvent interactions do not reduce the effect of C-H/ π interactions between the solvent and substrate in the Staudinger reaction.

We note that the calculations discussed here do not include a large number of explicit solvent molecules, creating a solvent shell around each species. The reasons for this are two-fold: (i) determining the transition states for such enlarged systems is prohibitively expensive and thus beyond the scope of the current work, and (ii) it is likely that the addition of only a few molecules (or only a single solvent molecule) would suffice to take fully into account explicit non-covalent interactions with the substrate. This is based on the fact that previous computational investigations have reported that calculations in the presence of a few explicit solvent molecules corroborate well with experiment.^{34,35,43} Moreover, calculations with the hybrid explicit-implicit solvent model have been considered more accurate than the implicit model. Truhlar and coworkers, for instance, have reported that the inclusion of a single explicit water molecule in the calculations of pKa values shows good agreement with experiment.⁶⁴ Also, Riveros and coworkers have demonstrated that the addition of explicit solvent molecules improves the calculations of pKa values.⁶⁵

6.4 Conclusions

The current computational study attempts to explore the following idea: that non-covalent interactions between explicit solvent molecules and substrates being the major cause of stereoselectivity is a more general phenomenon than previously considered. This has been investigated by considering two important, diverse organic reactions: the intramolecular carbonyl-ene and the Staudinger reaction, respectively. Calculations reveal that the inclusion of explicit solvent molecule(s) leads to the experimentally observed diastereoselectivity in both the cases. It has been demonstrated that in both the reactions, C-H/ π , Cl/ π , C-H/O, and π - π non-covalent interactions between solvent and substrate are the major reason for the high diastereoselectivity. Furthermore, the NCI plot analysis suggests that the stability of the transition states depends on the number of non-covalent interactions present in the system, *i.e.*,

transition states that lead to the formation of the major diastereomer are more stable because of additional non-covalent interactions, in comparison to transition states corresponding to the formation of the minor diastereomers. The results, therefore, suggest that there are likely to be several other stereoselective reactions where there is a vital, explicit role of the solvent in controlling the stereoselectivity.

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Chapter 7

Summary and Future Outlook

Chapter 7

Summary and Future Outlook

7.1 Focus of this Thesis

Since all homogenous reactions occur in the solvent, the solvent is considered an essential factor in chemical reactions, where it can influence the rate, selectivity, and yield of the reaction.¹⁻³ Considerable experimental and computational studies have been carried out to understand the effect of solvents on various organic and inorganic reactions.⁴⁻⁵ In this thesis work, quantum chemical calculations with DFT have been carried out to explore the solvent's influence in main group transformations. We have chosen main group transformations not only because of the various issues of transition metal chemistry but also because the role of solvents in main group chemistry has not been completely explored. Hence, in this thesis, the two critical aspects of main group transformations: a) small molecule activation by low valent main group complexes,⁶⁻⁷ and b) stereoselectivity of organic reactions, have been demonstrated, where solvent actively and explicitly participates.⁸ Deeper insight into covalent bonding between solvent and substrate and noncovalent interactions between solvent and substrate has been provided. Furthermore, NBO analysis, NCI plot, and interaction energy calculations have been carried out to quantify the interactions/bonding between solvent and substrate. Quantum chemical calculations with DFT for the explicit role of solvent in main group chemistry can be summarized as follows:

(I) DFT calculations have been performed to shed light on the solvent's explicit role in low valent chemistry; Al(I) chemistry. To study the effect of the solvent, the NacNacAl(I) complex has been chosen because it has been noted that aluminum (I) chemistry has always been carried out in aromatic solvents such as benzene, toluene, or anisole. Our calculations suggest that the Al(I) complex is first converted to Al(III) (1,4 coordinated Al-NacNac benzene complex) by the activation of one of the three π bonds of the solvent benzene. It has been shown that an explicit benzene solvent molecule undergoes a dearomatization/aromatization process while acting as a catalyst in σ -activation, such as in H-H, H-N, and H-P reactions. This showcases the ability of the solvent to find exciting and unusual ways to influence

chemical reactions. Therefore, through these investigations, the first example of metal-solvent cooperativity in main group chemistry has been demonstrated.

(ii) Next, we have studied the influence of the aromatic solvent in silylene chemistry *through noncovalent interactions*. Quantum chemical calculations with DFT and AIMD simulations have been performed to explore the role of noncovalent interactions between the solvent (toluene) and substrate. Our calculations reveal that the C-H/ π interactions are more dominant than π - π interactions between the solvent and the substrate in the formation of the silepin complex. Furthermore, *ab initio* molecular dynamics (AIMD) simulations have been carried out at room temperature to confirm the C-H/ π interactions between solvent and substrate. Turn over frequency (TOF) calculations suggest that the explicit presence of the solvent molecule improves the efficiency of the silepin formation reaction through C-H/ π interactions.

(iii) Furthermore, the influence of the solvent in the activation of CO₂ by the silepin complex has been investigated. It has been demonstrated that the C-H/ π interacting solvent molecule affects the rate of the CO₂ activation reaction. Investigations suggest that the presence of C-H/ π interacting toluene solvent improves the turn over frequency by a factor of sixty. Furthermore, *ab initio* molecular dynamics (AIMD) simulations have been carried out to understand the exchange between solvent molecules and their effect on the free energy profile of the CO₂ activation process. This indicates that C-H/ π interactions would exist for a significant amount of time.

(iv) Next, after looking into the solvent's role in low valent main group chemistry, quantum chemical calculations with DFT have been employed to study the explicit role of the solvent in stereoselectivity. Since stereoselectivity plays a vital role in various fields such as organic synthesis, asymmetric synthesis and medicinal chemistry, understanding the origin of stereoselectivity is essential. In Chapter 6 of this thesis, we have shown that noncovalent interactions such as C-H/O, C-H/ π , π / π , and Cl/ π interactions between solvent and substrate are responsible for the stereoselectivity of the carbonyl-ene (in the aliphatic solvent: dichloromethane) and the Staudinger reaction (in the aromatic solvent: toluene). Interestingly, in both cases, it has been found that the non-inclusion of explicit solvent molecules leads to only a small difference in the relative energy barrier, which leads to low selectivity. However, the inclusion of the explicit solvent leads to high selectivity. Furthermore, the NCI plot analysis suggests that the stability of transition states depends on the number of noncovalent interactions present in the system, *i.e.*, transition states that lead to the formation of the major diastereomer are more stable because of additional noncovalent interactions, in comparison to transition states corresponding to the formation of the minor diastereomers.

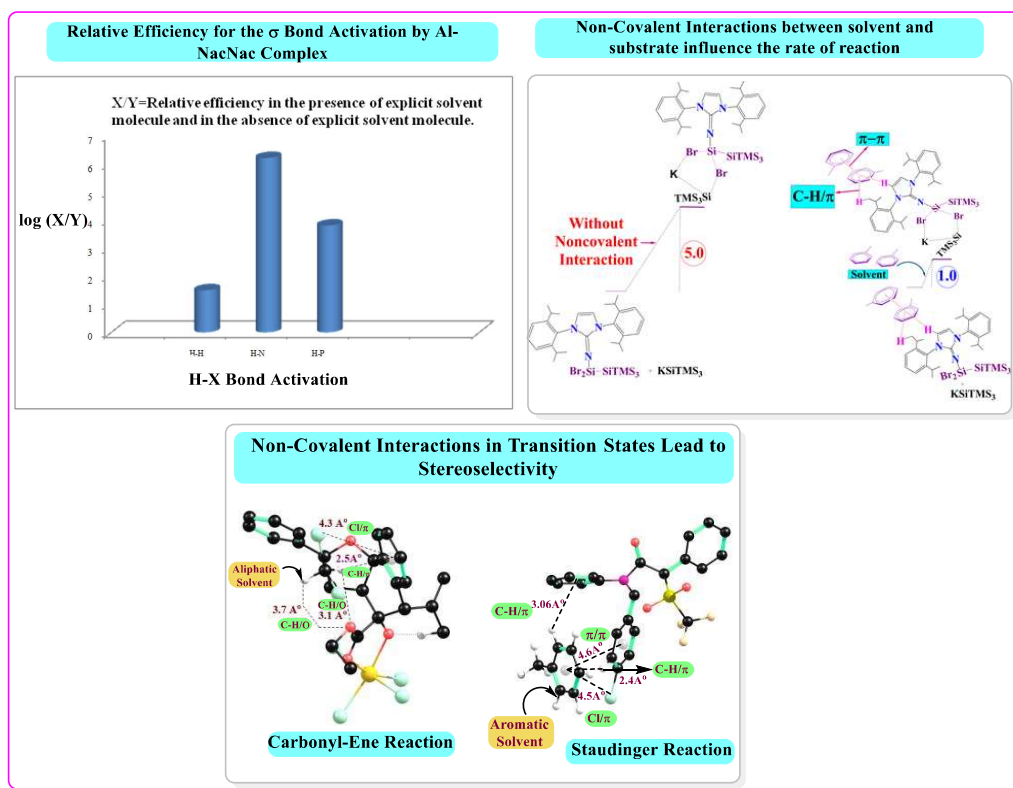


Figure 7.1 Representation of the research work presented in the thesis.

7.2 Computational Methods

The calculations with DFT have been performed using the Turbomole 7.0 and Turbomole 7.1 suites of programs.⁹ The geometry optimizations have been done with the Perdew, Burke, and Erzenhof density functional (PBE)¹⁰ in the case of Al (I) chemistry, TPSS¹¹ in silylene chemistry, and TPSSH¹² in stereoselectivity. A triple- ζ basis set augmented by a polarization function (Turbomole basis set TZVP) and the diffuse basis set (Def2-TZVP) have been employed to describe the electronic configuration of the atoms.¹³ The resolution of identity (ri),¹⁴ along with the multipole accelerated resolution of identity (marij)¹⁵ approximations were used for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. To obtain more reliable energy values for the investigated potential energy profile, single point calculations have been done with hybrid functionals with M06-2x¹⁶ and B3-LYP¹⁷ on the initially optimized geometries. Solvent effects using the COSMO model¹⁸ and dispersion corrections (DFT-D3)¹⁹ have been incorporated. Internal energy and entropy contributions were obtained from

frequency calculations done on the DFT structures at 298.15 K; thus, the energies reported are the ΔG values in this thesis work.

Furthermore, NBO analysis²⁰ has been carried out to analyze the bonding interactions between the solvent and the substrate. Also, interaction energy calculations and the NCI plot analysis²¹ have been performed to quantify the noncovalent interactions. Furthermore, in the low valent silicon chemistry (Chapters 4 and 5), AIMD simulations have been carried out with the TeraChem 1.9 quantum chemistry package,²² using the B3-LYP functional and the 6-31g* basis set.

7.3 Future Outlook

Insights gained from work presented in this thesis shed light on critical areas of research and are also likely to help experimentalists to design systems in which the influence of the *solvent* can be kept in mind to improve the efficiency of the main group systems considerably. In this thesis work, C-H/ π , C-H/O, Cl/ π , and π/π noncovalent interactions have been demonstrated to be useful. This suggests that new systems could be designed where such solvent-substrate interactions would be strengthened, leading to a higher efficiency of the activation reactions and controlling the stereoselectivity of the reactions. Therefore, this work is an interesting forward step in the area of low valent main group chemistry, small molecule activation, catalysis, noncovalent interactions, and stereoselectivity. Several main group catalyzed stereoselective reactions and small molecule activations are reported, where the role(s) of the solvent were previously unexplored.

The consideration of the solvent and noncovalent interactions would have useful implications to obtain deeper insights into the effect of solvent in critical chemical reactions. For example, carbene catalyzed stereoselective reactions²³⁻²⁴ and small molecule activation is an active research area, where solvent and noncovalent interactions need to be studied. This is because the presence of electron-withdrawing substituents on carbenes can play a dominant role in strengthening the noncovalent interactions, and the lone pair on the carbon atom can lead to lone-pair/ π interaction with the aromatic solvents. Furthermore, organic reactions need optimization for the selection of the proper solvent for the reaction. Hence, this thesis work would help choose a solvent based on solvent-substrate interactions. Therefore, in order to improve the turnover number, yield, and selectivity of chemical reactions, the study of the effect of solvent and noncovalent interactions is critical.

The work presented in this thesis would thus not only help experimentalists but also help researchers working in the field of computational chemistry. Lastly, one of the most critical insights from this thesis

work is choosing a solvent model to carry out the calculations to include solvent-solute interactions. The work indicates that among three solvent models: i) implicit, ii) explicit, and iii) hybrid model, the hybrid solvent model, which is a combination of implicit and explicit models, is more accurate, *i.e.*, corroborates better with experiment."

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ABSTRACT

Name of the Student: Shailja Jain**Registration No.:** 10CC15A26024**Faculty of Study:** Chemical Science**Year of Submission:** December 2020**AcSIR academic centre/CSIR Lab:** CSIR-National Chemical Laboratory Pune**Name of the Supervisor:** Dr. Kumar Vanka**Title of the thesis:** Computational Studies of the Explicit Role of the Solvent in Facilitating Transformations in Main Group Chemistry

In all homogeneous chemical reactions, the solvent has been considered a vital component because of its ability to alter the reaction rate, selectivity, and yield. Numerous studies suggest that the solvent can affect the reaction in different ways, such as by acting as a proton shuttle, through its polarity, and through H-bond interactions. However, the explicit role of the solvent in computational investigations has gained relatively less attention. Density functional theory (DFT) as a tool can be employed to provide more in-depth insight into the solvent's effect on a chemical reaction. To investigate this, two types of models can be employed in DFT calculations: (a) an implicit solvent model and (b) an explicit solvent model. To the solution phase calculations, it is essential to employ a solvent model because it is closer to chemical reality and leads to more accurate results.

The aim of this Ph.D. thesis is to explore the implicit and explicit effect of the solvent in main group reactions. Main group reactions have been chosen in order to study the solvent's role because transition metal complexes are toxic, less abundant, and expensive. Also, the role of solvents in main group chemistry has not been explored. In this thesis, the explicit role of the solvent in low valent NacNacAl(I) chemistry, silylene chemistry, as well as the stereoselectivity of organic reactions has been investigated.

It has been shown that the benzene solvent enhances the rate of σ bond (H-H, H-N, and H-P activation) activation by the Al(I) complex. Our work shows the first example of metal-solvent cooperativity in main group chemistry. Moreover, the effect of aromatic solvent (toluene) has been studied in order to understand the rate of formation of the silepin complex (C-C bond activation) as well as CO_2 activation by the silepin complex. In this case, we have demonstrated that the solvent increases the rate of the reaction through C-H/ π noncovalent interactions between the solvent and substrate. Not only the rate of the reaction but also

the stereoselectivity of the reaction can be controlled by the solvent. Our calculations indicate that noncovalent interactions between solvent and substrate are responsible for the stereoselectivity of the carbonyl-ene (aliphatic solvent: dichloromethane) and the Staudinger reaction (aromatic solvent: toluene). Furthermore, TOF calculations, NBO analysis, interaction energy calculations, volume correction in the entropy, and NCI plot analyses have been employed to investigate the solvent effect on the reaction rate and stereoselectivity.

Details of the publications emanating from the thesis work

1) List of publication(s) in SCI Journal(s) (published & accepted) emanating from the thesis work

- (i). **S. Jain** and K. Vanka, The Unusual Role of Aromatic Solvent in Single-Site Aluminum^I Chemistry: Insights from Theory *Chem. Eur. J.* **2017**, *23*, 13957.
- (ii). **S. Jain** and K. Vanka, Can the solvent enhance the rate of chemical reactions through C–H/ π interactions? insights from theory. *Physical Chemistry Chemical Physics*, **2019**, *21*, 14821.
- (iii). **S. Jain** and K. Vanka, *J. Phys. Chem. A* **2020**, 10.1021/acs.jpca.0c05738.

2) List of Papers with abstract presented (oral/poster) at national/international conferences/seminars with complete details.

i) Presented a poster entitled "Why does Small Molecule Activation by Al(I) Compounds Occur Only in Aromatic Solvents? Insights from Theory" at Science day, CSIR NCL Pune, 26-27 Feb 2018 (Recieved a Best Poster Award).

Abstract

The single site activation of strong σ bonds (such as that of H-H, P-H and N-H) remains a significant challenge in main group chemistry, with only a few cases reported to date. In this regard, recent exciting experiments done with Al(I) complexes hold significance, because they, too, have been seen to activate a variety of strong σ bonds. Such chemistry is generally seen to occur in aromatic solvents. The current computational studies with density functional theory (DFT) reveal the interesting reason for this: it is seen that an explicit aromatic solvent molecule acts as a catalyst by converting the Al(I) complex to Al(III) during the process. Different cases of σ bond activation by Al(I) complexes have been investigated and the efficiency for the H-X (X=H, NH^tBu, PPh₂) bond activation in the presence of an explicit benzene solvent molecule has been seen to be orders of magnitude higher than in its absence. The current work, therefore reveals the chemistry of Al(I) complexes to be richer and more complex than realized to date, and shows it to be dependent on metal-solvent cooperativity, the first known example of its kind in main group chemistry.

(ii) Presented a poster entitled, "Can The Solvent Act As a Catalyst In Main Group Transformations? Insights From Theory," at the International Conference Structural and Inorganic Chemistry (ICSIC-II) IISER Pune, 18-19, March 2019 (Recieved Best Poster Award).

Abstract

Since a significant amount of chemistry takes place in the solvent phase, the role of the solvent in chemical reactions is very important. Even though the effect of the solvent in the transition states previously

reported, but the catalytic role of the solvent through non-covalent interaction have not reported yet. However, the current computational study, with density functional theory (DFT), reveals that an explicit aromatic solvent molecule acts as a catalyst through covalently and non-covalently in the small molecule activation by Al-NacNac (Al(I)) and silacycloheptatriene (silepin) complex respectively.

The Al(I) chemistry is generally seen to occur in aromatic solvents which give rise to an important question: does the aromatic solvent employed play an explicit role in the small molecules activation by Al(I) complexes? DFT calculations suggest that an explicit aromatic solvent (benzene) molecule acts as a catalyst by converting the Al(I) complex to Al (III) in the σ bond activation. The efficiency for the σ bond activation in the presence of an explicit benzene solvent molecule has observed orders of magnitude higher than in its absence.

Next, the current computational study with static quantum chemical calculations, as well as with ab initio molecular dynamics (AIMD) simulations with density functional theory (DFT) has been performed in the intramolecular carbon-carbon and CO₂ activation. It has been shown that the toluene solvent molecule is acting as a catalyst and influencing the rate of reaction through C-H/ π non-covalent interaction. The efficiency of the CO₂ activation by silepin was seen to be improved by sixty times due to the presence of the C-H/ π interacting toluene.

(iii) Presented a poster entitled, “Can The Solvent Act As a Catalyst In Main Group Transformations? Insights From Theory,” at the Conference on Recent Trends in Catalysis (RTC 2020), NIT Calicut, 26-29 Feb 2020 **(Recieved Best Poster Award)**.

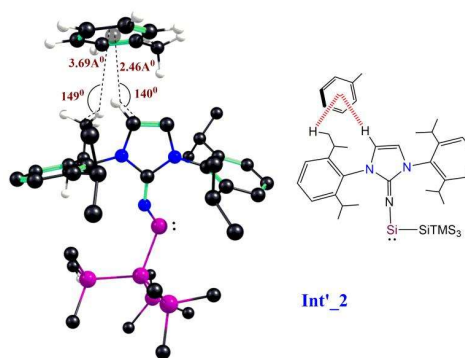
Abstract

Since a significant amount of chemistry takes place in the solvent phase, the role of the solvent in chemical reactions is very important. Even though the effect of the solvent in the transition states previously reported, but the catalytic role of the solvent through non-covalent interaction have not reported yet. However, the computational study, with density functional theory (DFT), reveals that an explicit aromatic solvent molecule acts as a catalyst through covalently and non-covalently in the small molecule activation by Al-NacNac (Al(I)) and silacycloheptatriene (silepin) complex respectively. The Al(I) chemistry is generally seen to occur in aromatic solvents which give rise to an important question: does the aromatic solvent employed play an explicit role in the small molecules activation by Al(I) complexes? DFT calculations suggest that an explicit aromatic solvent (benzene) molecule acts as a catalyst by converting the Al(I) complex to Al (III) in the σ bond activation. Next, the computational study with static quantum

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The optimized geometry of benzene Al-NacNac complex



The optimized geometry of toluene-silylene complex

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3) A copy of all SCI publication(s), emanating from the thesis, to be bound at the end of the thesis.

Density Functional Calculations

The Unusual Role of Aromatic Solvent in Single-Site Aluminum^I Chemistry: Insights from TheoryShailja Jain^[a, b] and Kumar Vanka^{*[a, b]}

Abstract: The single-site activation of strong σ bonds (such as that of H–H, P–H, and N–H) remains a significant challenge in main-group chemistry, with only a few cases reported to date. In this regard, recent exciting experiments performed with aluminum^I complexes hold significance because they have been seen to activate a variety of strong σ bonds. Such chemistry is generally seen to occur in aromatic solvents. Current computational studies with DFT reveal the interesting reason for this: an explicit aromatic solvent molecule acts as a catalyst by converting the aluminum^I complex

into aluminum^{III} during the process. Different cases of σ -bond activation by aluminum^I complexes have been investigated and the efficiency of H–X (X = H, NHtBu, PPh₂) bond activation in the presence of an explicit benzene solvent molecule is orders of magnitude higher than that in its absence. The current work therefore reveals the chemistry of aluminum^I complexes to be richer and more complex than that previously realized, and shows it to be dependent on metal–solvent cooperativity; the first known example of its kind in main-group chemistry.

Introduction

Small-molecule activation by main-group compounds has attracted much attention in recent years as an alternative to expensive and potentially more toxic transition-metal chemistry.^[1–3] Although carbenes,^[4] silylenes,^[5–7] and germynes^[8,9] have been successfully employed, researchers have also tried to explore activation possibilities with group 13 metal^I^[10] and aluminum compounds. The focus has been on converting Al^I compounds to Al^{III} through the oxidative addition of small molecules, such as H₂, NH₂R, and HPPH₂. In 2000, Roesky and co-workers succeeded in synthesizing the first monomeric Al^I complex with the bulky NacNac ligand (HC(CMeNAr)[–]; Ar = 2,6-*i*Pr₂C₆H₃),^[11] which exhibited singlet carbene-like behavior.^[12–14] This was employed recently by Nikonov and co-workers to activate the H–H, H–P, H–N, H–O, H–Si, H–B, and H–C σ bonds.^[15] More recently, the group of Nikonov also showed that the NacNacAl^I complex could activate even stronger σ bonds, such as C–F, C–O,^[16] P–P, and C–S,^[17] and π bonds, such as C=S and P=S.^[18] It is believed that activation proceeds at a single group 13 metal center.^[15,19–23]

Single-site activation of H–H, H–P, H–N, and other such robust σ bonds by main-group compounds (and by “single-

site” frustrated Lewis pairs^[24]) has generally proved to be difficult, with only a few reported instances.^[15,19–26] Hence, recent investigations into the NacNacAl^I complex represent an important advance in the chemistry of main-group elements. However, what is notable is that the reactions of aluminum chemistry have always been carried out in aromatic solvents: benzene^[11,15] toluene,^[27–30] or anisole.^[16] When Nikonov and co-workers attempted to conduct such σ -bond cleavage experiments in diethyl ether, they were unsuccessful.^[16] It is possible that unwanted side reactions or decomposition processes might be occurring in aliphatic solvents, rendering them less useful. However, the clear preference for aromatic solvents does give rise to an important question: does the aromatic solvent employed play an explicit role in σ -bond activation by aluminum^I complexes? If so, what role does it play?

The current computational study with DFT addresses this issue, through the investigation of the Al^I-mediated activation of the H–X (X = H–H, H–N, and H–P) bond. What is proposed is that the Al^I complex is first converted into Al^{III} through the activation of one of the three π bonds of the aromatic solvent (benzene was employed experimentally in all cases studied).^[15] Figure 1 shows the optimized structure of complex **A**, which would be formed during this process. This is a 1,4-coordinated structure (the corresponding 1,2-coordination of the benzene NacNac Al^{III} complex (**B**) was seen to be considerably less favorable, by 20.5 kcal mol^{–1} (ΔE); see Figure S5 in the Supporting Information). Complex **A** can activate the σ bond in the substrate employed: the explicit solvent molecule acts as a ligand for the aluminum center and activates the σ bond through metal–solvent cooperativity. This proposed reaction is illustrated in Scheme 1, for the case of H–H bond activation. The advantage of the solvent molecule cooperating in this fashion is that it leads to a reduction in steric strain in the tran-

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Supporting information for this article can be found under:
<https://doi.org/10.1002/chem.201701642>.

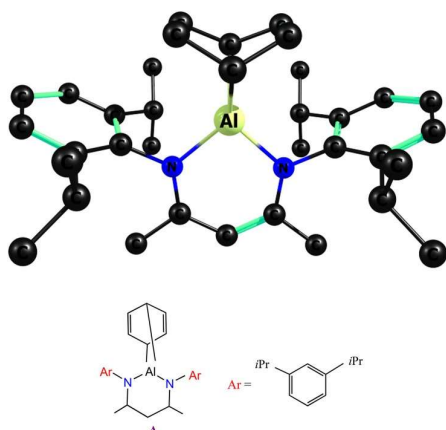
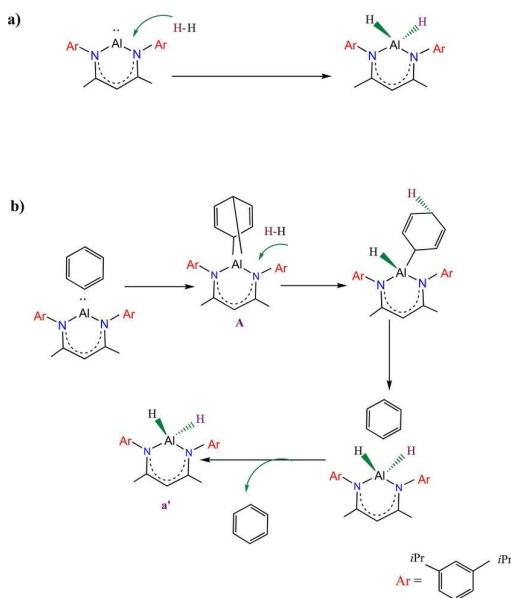


Figure 1. Optimized geometry of complex **A** formed by reaction of the Al^I complex with benzene. All hydrogen atoms have been removed for clarity.



Scheme 1. The proposed σ -bond activation reaction for the H–H bond by the NacNacAl^I complex: a) in the absence and b) in the presence of an explicit benzene solvent molecule.

sition state, that is, it can convert a strained three-membered transition state into a more stable structure, thereby making the process more facile. As shown in the Results and Discussion, not only do the calculations indicate that the formation of complex **A** is likely, but the σ -bond activation of a range of different robust bonds is also seen to be considerably facilitated by the cooperativity between the aluminum center and aromatic solvent molecule. Furthermore, we have also elaborated upon why this crucial role of the solvent has been missed by previous X-ray and NMR spectroscopy investigations, as well as from previous experiments performed in C₆D₆.^[15]

There have been previous computational studies that have investigated the energetics of σ - and π -bond activation by the

NacNacAl^I complex through direct oxidative addition.^[17,20–23] However, this work is the first to shed light on the explicit role of the aromatic solvent molecule, and show how it is able to considerably enhance the potency of the NacNacAl^I system.

Computational Details

All DFT calculations were carried out by using the Turbomole 7.0 suite of programs.^[31] Geometry optimizations were performed by using the Perdew, Burke, and Erzenhof (PBE) density functional,^[32] the electronic configuration of the atoms was described by a triple- ζ basis set augmented by a polarization function (Turbomole basis set TZVP).^[33] The resolution of identity (ri),^[34] along with the multipole accelerated resolution of identity (marij),^[35] approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. The real (not model) system has been employed for all calculations. Care was taken to ensure that the obtained transition-state structures possessed only one imaginary frequency corresponding to the correct normal mode to obtain more reliable energy values for the investigated potential energy surface. In addition, intrinsic reaction coordinate (IRC)^[36] calculations were performed with all transition states to further confirm that they were the correct transition state, yielding the correct reactant and product structures. Solvent effects were introduced by using the COSMO model^[37] with the dielectric constant $\epsilon = 2.27$ for benzene. The option “disp” provided in the Turbomole package (DFT-D3) was used for dispersion-corrected DFT calculations for all calculations with Turbomole.^[38] The values reported herein are ΔG values, with zero-point energy, internal energy, and entropic contributions; the temperature is taken to be 298.15 K. The translational entropy term in the calculated structures was corrected through a free volume correction introduced by Mammen et al.^[39] This volume correction accounts for the unreasonable enhancement in translational entropy generally observed in computational software. To find the efficiency of the catalytic cycle in our mechanism, we calculated the relative efficiency with the AUTOF program by employing the energetic span model (ESM), developed by Shaik and Kozuch^[40–42], on all free energy profiles discussed herein. The turnover frequency (TOF) calculations take into account the principal rate-determining transition state, potentially rate-influencing transition states, and intermediates during the catalysis process. TOF is calculated by using Equation (1):

$$\text{TOF} = \frac{KBT}{h} e^{-\Delta E/RT}$$
$$\Delta E = T_{\text{TDS}} - T_{\text{TDI}} \text{ If TDS appears after TDI}$$
$$\Delta E = T_{\text{TDS}} - T_{\text{TDI}} + \Delta G, \text{ If TDS appears before TDI}$$
(1)

where TDI and TDS are TOF-controlling species (TDI is TOF-determining intermediate, and TDS is TOF-determining transition state). For example, TDI is **Int1 a** and TDS is **TS1 a** in the free energy profile for the H–H bond activation by complex **A** (Figure 2).

This model has been employed to calculate the TOFs for the free energy profiles obtained for the different mechanisms discussed herein. This model can also be employed for stoichiometric reactions, in which the TOF would correspond to the efficiency of the reaction.

Results and Discussion

Figure 2 shows the free energy profile for the conversion of the $\text{NacNacAl}^{\text{I}}$ complex into $\text{NacNacAl}^{\text{III}}$, as experimentally observed by Nikonov and co-workers,^[15] in the presence of an ex-

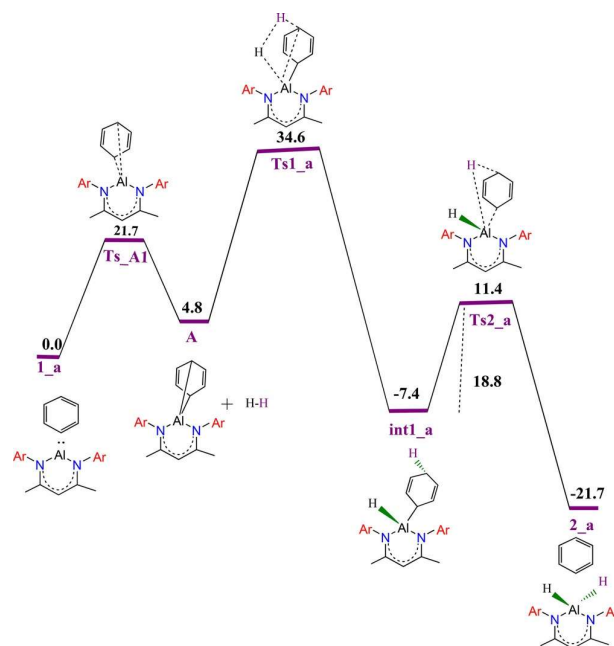


Figure 2. The free energy profile (ΔG in kcal mol^{-1}) for H–H bond activation by complex **A**.

licit benzene solvent molecule. Complex **A** is formed after the surmounting of a barrier of $21.7 \text{ kcal mol}^{-1}$, and lies $4.8 \text{ kcal mol}^{-1}$ higher in energy than the reactants. Natural bond orbital (NBO) analysis shows that the charge on aluminum in the original $\text{NacNacAl}^{\text{I}}$ complex is $+0.7$, whereas it is $+1.8$ in Al^{III} complex **A**. Furthermore, inspection of the donor–acceptor orbital interactions in **A** through NBO analysis^[43,44] shows that there is considerable interaction between the π -bonding orbital of benzene and aluminum (see Table S1 and Figures S1–S4 in the Supporting Information). Hence, evidence suggests that the benzene solvent molecule is able to successfully coordinate and interact with the aluminum center and increase its oxidation state, leading to complex **A**. Also, the fact that the formation of this complex is slightly endergonic implies that a dynamic equilibrium exists between its formation and dissociation back to the reactants: $\text{NacNacAl}^{\text{I}}$ and benzene. This may explain why the formation of this benzene complex aluminum compound has not been detected on the NMR spectroscopy timescale employed in the experiments.^[15] This also helps explains to why the structure of complex **A** has escaped detection in XRD studies: the crystallization procedure involved treatment under vacuum and washing with hexane, which would have removed the benzene molecule from the vicinity of $\text{NacNacAl}^{\text{I}}$.^[15] Nevertheless, in solution, the ubiquitous presence of a solvent molecule in the vicinity of $\text{NacNacAl}^{\text{I}}$ makes

the reaction between $\text{NacNacAl}^{\text{I}}$ and benzene, and therefore, the formation of complex **A**, an inevitability. Hence, complex **A** is likely to be the predominant complex present in a solution of benzene, or, by extension, other aromatic solvents.

Calculations further show that the approach of the substrate H_2 to **A**, and subsequent activation of the H–H bond, would occur through cooperation between aluminum and the *para*-carbon of coordinated benzene, leading to the formation of intermediate **int1_a**. The barrier for this is $34.6 \text{ kcal mol}^{-1}$ from the reactant complex (see Figure 2). Subsequently, additional hydrogen at the *para*-carbon is transferred to aluminum, leading to the ejection of benzene from the complex and the formation of the final, observed product, **2_a**. Therefore, the explicit benzene solvent molecule acts as a catalyst during this process.

There is a further important experimental observation that relates to experiments performed in C_6D_6 by Nikonov and co-workers: they did not observe any deuterium scrambled product when they undertook H–H activation experiments in C_6D_6 with the $\text{NacNacAl}^{\text{I}}$ complex. Because the reaction outlined in our proposed mechanism invokes the explicit role of the solvent, why was no deuterium scrambling observed? An interesting reason for this can be understood by carefully examining the structure of **int1_a** (Figure 3). In this intermediate, the

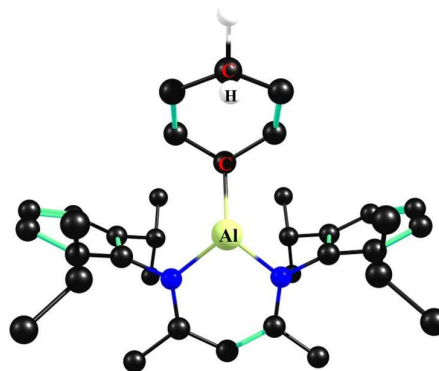


Figure 3. The optimized geometry of complex **int1_a** suggests that deuterium scrambling is not possible. All hydrogen atoms have been removed for clarity.

Al–C (phenyl) bond might be able to rotate, but that would still lead back to hydrogen on the *para*-carbon facing aluminum, that is, no deuterium scrambling would occur. The only way that scrambling could occur would be if the $[\text{C}_6\text{H}_7]^+$ species were to dissociate from the aluminum center entirely, and then rotate and come back to coordinate to aluminum, with the deuterium now on the *para*-carbon facing the aluminum center. Such a process would be highly unfavorable energetically, and thus, very unlikely. Thus, only hydrogen can transfer to aluminum and not deuterium, which excludes the possibility of the deuterium scrambled product.

The next question at this point would be to enquire how the process detailed in Figure 2 and explained above compares with the direct oxidative addition of H_2 to the $\text{NacNacAl}^{\text{I}}$ complex. The reaction profile for this process is shown in Figure 4.

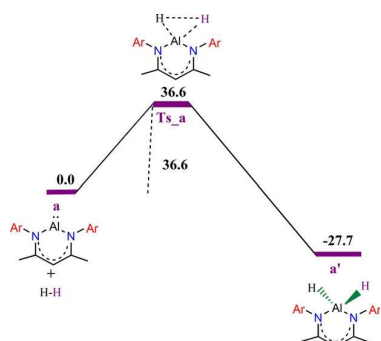


Figure 4. The free energy profile (ΔG in kcal mol^{-1}) for H–H bond activation without the explicit assistance of the solvent.

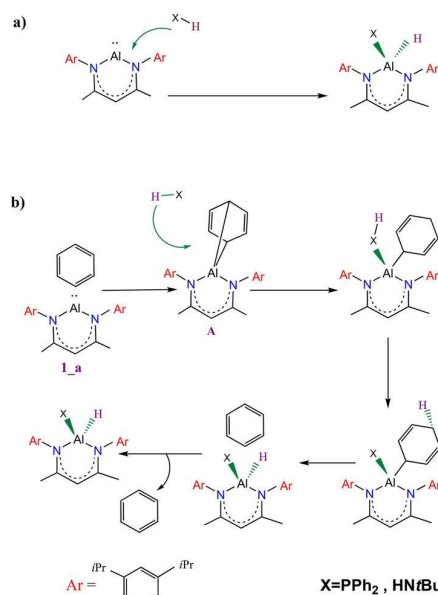
This is seen to have a barrier of $36.6 \text{ kcal mol}^{-1}$, which is $2.0 \text{ kcal mol}^{-1}$ higher than that of the slowest step of the benzene-assisted process (Figure 2). Hence, direct addition would be less efficient. To provide a more quantitative estimate of how much this direct process suffers in comparison to the benzene-assisted one, we have determined the efficiency for the free energy profiles shown in the Figures 2 and 4, by using both the AUTOExcel version^[45] and AUTO old text-style^[46] program, by employing the energetic span model (ESM) developed by Shaik and Kozuch.^[40–42] For details regarding the ESM method, please see the Computational Details section. The relative efficiency values (Table 1) indicate that activation of the H–H bond with assistance from the explicit benzene molecule is 30 times more efficient than the corresponding direct oxidative addition without the explicit assistance of the solvent.

Table 1. Values for the relative efficiency obtained for our mechanism and oxidative addition without the explicit assistance of the solvent.

H–X bond activation	Relative efficiency
H–H	0.29×10^2
H–N	1.7×10^6
H–P	0.5×10^4

N–H bond activation

Next, we investigated the mechanism for N–H σ -bond activation by the NaCNacAl^I complex with the assistance of the explicit benzene solvent molecule (this experiment was also performed in benzene^[15]). This mechanism was seen to be slightly different. As shown in Scheme 2, an additional step occurs in this process before the *para*-coordinated H complex is formed. In this step, there is prior coordination of H–X (X = nitrogen-containing group, which is *t*BuNH herein) to the aluminum center (Scheme 2). The free energy profile for N–H bond activation in the experimentally studied *t*BuNH₂ complex is shown in Figure 5. The slowest step is seen to have a barrier of $28.5 \text{ kcal mol}^{-1}$ and involves the interaction of nitrogen with the aluminum center, with the corresponding loss of coordination of the *para*-carbon in benzene with aluminum. The barrier for direct σ -bond activation, in the absence of explicit solvent



Scheme 2. The σ -bond activation reaction for the H–N and H–P bonds by the Al^I complex a) in the absence and b) in the presence of an explicit benzene solvent molecule.

assistance, was seen to be much higher: $37.0 \text{ kcal mol}^{-1}$ (Figure 6). Notably, the $\Delta E^\ddagger$ value previously reported for this direct N–H activation was $18.5 \text{ kcal mol}^{-1}$, at the BP86-D3/def2-

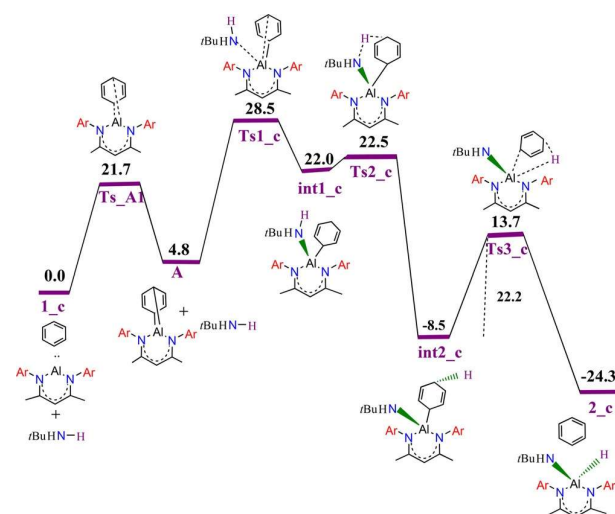


Figure 5. The free energy profile (ΔG in kcal mol^{-1}) for N–H bond activation by complex A.

SVP level of theory, for the case of NH_3 activation.^[20] This is the value of $\Delta E^\ddagger$ and not that of $\Delta G^\ddagger$. The corresponding $\Delta E^\ddagger$ for our NH_2tBu case is $22.5 \text{ kcal mol}^{-1}$. Furthermore, to see how our calculations compared with previous results, we also calculated $\Delta E^\ddagger$ for the case of NH_3 activation. This ΔE value was $19.8 \text{ kcal mol}^{-1}$, which compared well with the previously re-

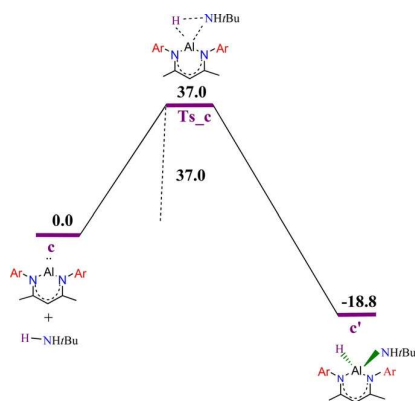


Figure 6. The free energy profile (ΔG in kcal mol^{-1}) for N–H bond activation without the explicit assistance of the solvent.

ported value ($18.5 \text{ kcal mol}^{-1}$). These results therefore indicate the reliability and robustness of the current calculations. It should also be noted that this process occurs experimentally at room temperature, and therefore, a barrier of $37.0 \text{ kcal mol}^{-1}$ would be difficult to overcome for the system (the temperature for H–H activation, discussed earlier, was 70°C ; this is consistent with the higher solvent-assisted barrier obtained for that case). This suggests that the benzene-assisted process would be operational for the N–H σ -bond activation reaction, whereas the barrier would be too high for the reaction to occur in the absence of the explicit solvent molecule. A further interesting fact is that the efficiency for this process is six orders of magnitude greater for the benzene-assisted process than that of direct oxidative addition (Table 1). These results showcase the importance of taking the role of the explicit solvent molecule into account in this chemistry.

P–H bond activation

We next studied the mechanism for P–H bond activation, which was the same as the mechanism for N–H bond activation (see Scheme 2). The obtained free energy profile for the experimentally studied substrate (HPPH_2) is shown in Figure 7, whereas the corresponding free energy surface in the absence of explicit solvent assistance is shown in Figure 8. The barrier for the slowest step in the benzene assisted case ($24.9 \text{ kcal mol}^{-1}$) is $5.1 \text{ kcal mol}^{-1}$ lower than the slowest step barrier without the assistance of the solvent. This reaction, too, is seen to occur experimentally at room temperature, which suggests strongly that solvent assistance is a necessity to make the σ -bond activation process possible. Furthermore, ESM calculations show that, also in this case, the efficiency of the process is increased considerably, by four orders of magnitude, by the explicit assistance of the solvent (Table 1).

Investigating the possibility of $\text{NacNacAl}^{\text{I}}$ –aliphatic solvent cooperativity

Previous sections have focused on the explicit role of the aromatic solvent, benzene, in substantially increasing the efficien-

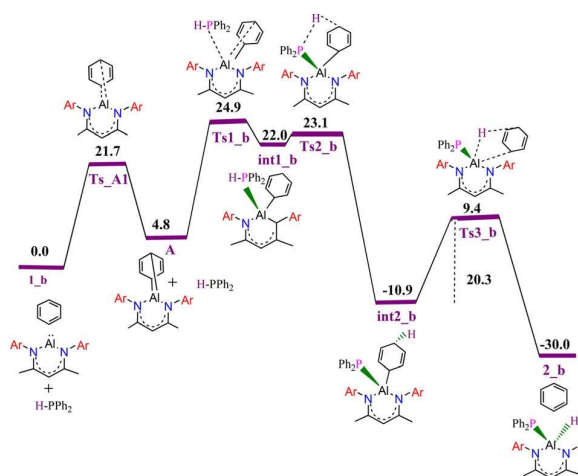


Figure 7. The free energy profile (ΔG in kcal mol^{-1}) for P–H bond activation by complex A.

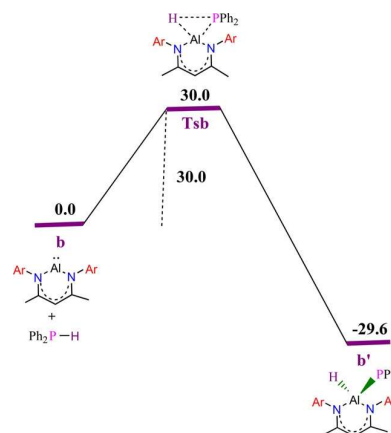


Figure 8. The free energy profile (ΔG in kcal mol^{-1}) for P–H bond activation without the explicit assistance of the solvent.

cy of the σ -bond activation process by the $\text{NacNacAl}^{\text{I}}$ complex, for the cases studied. This section endeavors to show why aliphatic solvents, such as hexane, would not be able to function in a similar cooperative fashion. The free energy profiles for the activation of different σ bonds (terminal C–H and three different C–C bonds) in hexane by the $\text{NacNacAl}^{\text{I}}$ complex are shown in Figures 9–12. A perusal of the values ($\Delta G^\ddagger = 53.7, 82.9, 97.8, \text{ and } 83.3 \text{ kcal mol}^{-1}$, respectively) makes it clear that the σ -bond activation process would be kinetically unfeasible at the temperatures employed in the experiments. This indicates that there is no explicit role of the hexane solvent in the activation of the H–X bond. Moreover, this also suggests that cleavage of the C–C, C–H, or other σ bonds in other aliphatic solvents would also be unlikely, thereby indicating that cooperativity would be likely to occur only through dearomatization–aromatization in aromatic solvents such as benzene, toluene, and anisole. Activation of H–X by $\text{NacNacAl}^{\text{I}}$ in hexane, and other aliphatic solvents, would thus occur as direct activation without the explicit involvement of the solvent. It should, however, be noted that σ -bond activation of substrates by the Al^{I}

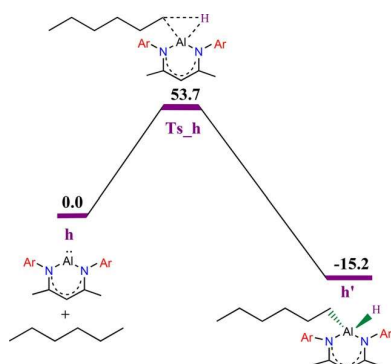


Figure 9. The free energy profile (ΔG in kcal mol⁻¹) for the formation of **h'** (hexane–NacNacAl^{III} complex) by activation of the terminal C–H bond. The high barrier suggests that the reaction would be kinetically unfavorable.

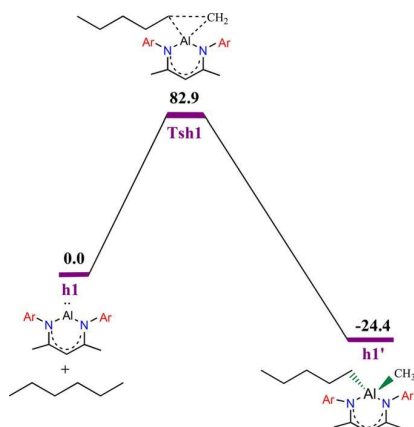


Figure 10. The free energy profile (ΔG in kcal mol⁻¹) for the formation of **h1'** (hexane–NacNacAl^{III} complex) by activation of the 1,2–C–C bond. The high barrier suggests that the reaction would be kinetically unfavorable.

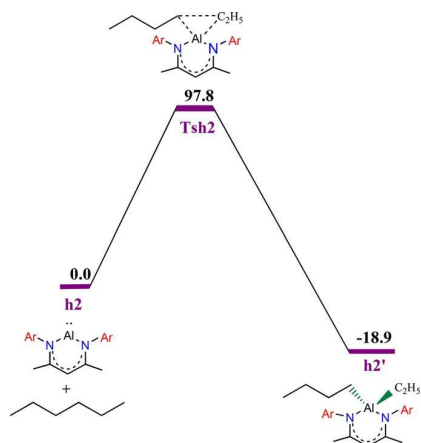


Figure 11. The free energy profile (ΔG in kcal mol⁻¹) for the formation of **h2'** (hexane–NacNacAl^{III} complex) by activation of the 2,3–C–C bond. The high barrier suggests that the reaction would be kinetically unfavorable.

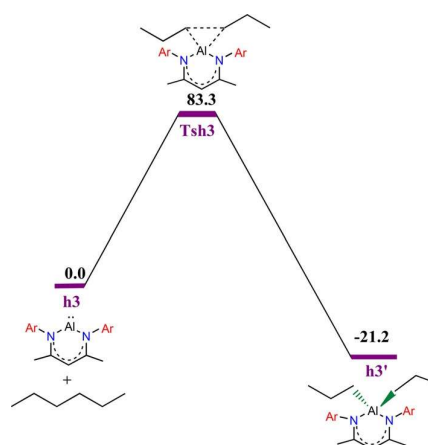


Figure 12. The free energy profile (ΔG in kcal mol⁻¹) for the formation of **h3'** (hexane–NacNacAl^{III} complex) by activation of the 3,4–C–C bond. The high barrier suggests that the reaction would be kinetically unfavorable.

complex is not precluded in aliphatic solvents—it is just that the efficiency of the chemistry would be (sometimes markedly) decreased in the aliphatic solvents, at least for the cases discussed herein.

Conclusion

The mechanism for σ -bond activation of the H–H, H–N and H–P bonds by the NacNacAl^I complex, as experimentally reported,^[15] was carefully investigated with DFT. It was observed that the solvent was far from a spectator in this chemistry: it actively and explicitly participated in the σ -bond activation process and had a significant effect on the efficiency. The current work therefore reveals that aluminum^I chemistry, for the cases studied, is richer and more complex than had been realized, and is actually an example of metal–solvent cooperativity. Although there are examples of solvent binding as a ligand in transition-metal complexes,^[46,47] to the best of our knowledge, this is the first example of its kind in main-group chemistry, not only of solvent binding as a ligand, but also of metal–solvent cooperativity. Indeed, as shown in Figure 13, we had to

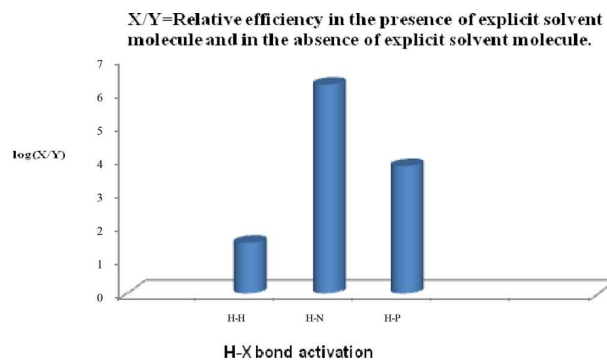


Figure 13. A log plot of the relative efficiencies for the activation of different H–X bonds, with and without the explicit assistance of the solvent.

take the log plot of the relative efficiencies, with and without the explicit assistance of the solvent, to fit the relative efficiency values for different cases of σ -bond activation by the aluminum^I complex into a single graph. Another interesting aspect is that the explicit benzene solvent molecule undergoes a dearomatization/aromatization process, while acting as a catalyst in the σ -activation reactions; this showcases the ability of the solvent to find interesting and unusual ways to influence chemical reactions.

Insights gained from this study therefore not only shed light on this important area of research, but are also likely to help experimentalists design systems in which the role of the solvent can be kept in mind to considerably improve the efficiency of the main-group systems.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aluminum · bond activation · density functional calculations · main group elements · solvent effects

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Can the solvent enhance the rate of chemical reactions through C–H/ π interactions? insights from theory†

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The current computational study with density functional theory (DFT) shows that the rate of chemical reactions can be influenced through non-covalent C–H/ π interactions between substrates and the solvent. It is shown that intramolecular carbon–carbon interaction and CO₂ activation by a low valent silicon complex are both favourably affected by the explicit presence of the solvent toluene, due to C–H/ π interactions between toluene and the silicon complex. Furthermore, *ab initio* molecular dynamics (AIMD) simulations demonstrate that even if the C–H/ π interacting solvent molecule is displaced from the complex, another would quickly take its place, thus maintaining the interaction. Hence, the current work shows how non-covalent interactions between solvent and substrate can enhance the rate of the reaction and expands our understanding of the role and influence of the solvent in effecting important chemical transformations.

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1. Introduction

The role of the solvent in chemical reactions automatically assumes importance, because a significant amount of chemistry takes place in the solvent phase. A large body of research exists indicating that the solvent can influence chemical reactions through polarity^{1–3} or through specific covalent bonding interactions with the substrates.^{4,5} Solvent water molecules are known to act as proton shuttles in several reactions of biological significance.^{6–8} Furthermore, it is also known that the solvent can interact in a hydrogen bonded fashion with reactants and transition states and have an effect on the rates as well as on the selectivity of reactions.^{9,10} All of this leads to an interesting question: would it also be possible for the solvent to influence chemistry through other non-covalent interactions, such as C–H/ π and π – π stacking? How significant would such an effect be? Would the solvent serve to catalytically accelerate reactions by such interactions, and if so, what would be the effect of this mediation on the turnover frequency (TOF)? A computational study is ideally suited to addressing these questions. Such studies would, however, have been hampered in the past, because of the need to properly and accurately take care of dispersion effects,

which are important in C–H/ π and π – π stacking interactions. Methods such as CCSD(T)¹¹ or MP2¹² that could do so are too expensive for a comprehensive study of mechanistic cycles of real (not model) systems, while more efficient approaches such as density functional theory (DFT) suffered from a lack of proper representation of dispersion effects. However, this lack in DFT has been resolved recently by the development of very effective implementations of dispersion corrections. Indeed, certain dispersion (D3)¹³ corrected functionals such as TPSS¹⁴ and B3-LYP¹⁵ provided estimations for non-covalent interactions such as π – π stacking, and were found to compare excellently with experiment.¹⁶ Therefore, the time is now ripe for a careful and complete computational investigation, using dispersion corrected DFT-D3 methods, of mechanistic cycles that include C–H/ π and/or π – π stacking interactions with the solvent.

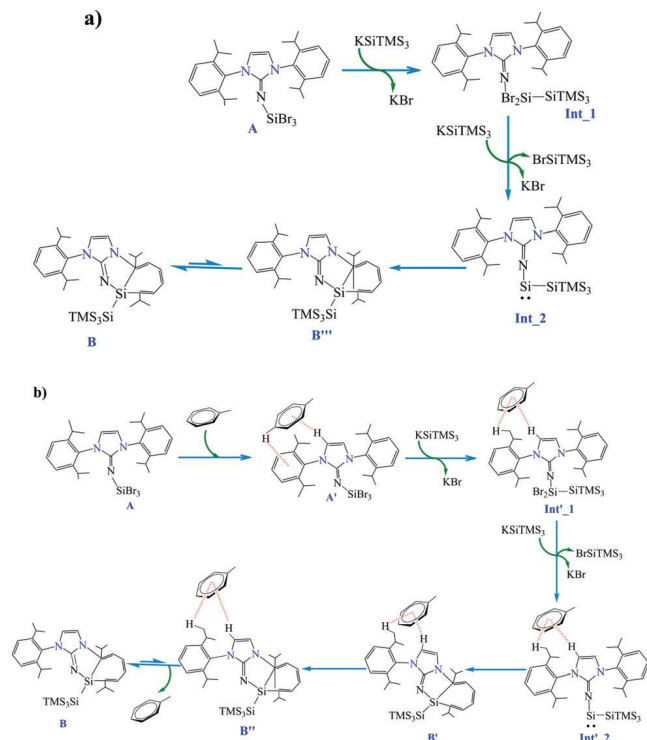
The reason it is important to investigate this is because it is known that C–H/ π and π – π stacking interactions play a significant role in various fields of biology and chemistry,¹⁷ such as in proteins and biomolecules,^{18–22} supramolecular chemistry^{23–26} crystal packing,^{27–31} and drug design,³² or through intramolecular or intermolecular substrate–substrate interactions. This wide-ranging impact provides a reason to believe that C–H/ π and π – π stacking interactions between substrate and solvent, which we propose to study, might also have significant consequences in different areas of chemistry.

The area that we have chosen to focus upon is the important, emerging new field of main group chemistry. Low valent main group compounds have been known to play a key role in various

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† Electronic supplementary information (ESI) available: AIMD simulation results, different free energy profiles and XYZ coordinates of optimized geometries. See DOI: 10.1039/c9cp02646k



Scheme 1 The proposed mechanism for the formation of the silepin complex: (a) in the absence and (b) in the presence of an explicit toluene solvent molecule. The exact 3D orientation of toluene in the complexes shown in (b) has been provided in the ESI† (Scheme S1).

σ , π bond activations^{33–36} of small molecules, as well as in catalysis,^{37–41} supplanting traditionally employed transition metal-based systems for these processes. There have also been several computational studies analyzing the influence of low valent main group compounds on small molecule activation.³³ Silylenes constitute one of the most important set of low valent main group compounds for small molecule activation,^{42–45} because of their small HOMO–LUMO gap (~ 2 – 3 eV), but low valent germanium and tin compounds have also shown promise. There are now some reports of oxidative addition and reductive elimination by Ge(II),⁴⁶ Sn(II)⁴⁷ and Si(II)⁴⁸ complexes. Interestingly, in 2017, Rieger, Inoue and co-workers reported a process involving the reversible conversion of Si(II) to Si(IV), through successive oxidative addition and reductive elimination steps.⁴⁹ Employing toluene as the solvent, the silicon based complex, **A** (see Scheme 1 below), was converted into a highly reactive acyclic iminosilylsilylene Si(II) intermediate, which underwent intramolecular insertion into the carbon–carbon double bond of a coordinated di-isopropyl phenyl (dipp) group to form a silacycloheptatriene (silepin) complex (see Scheme 1a) where the formal oxidation state of silicon was +4. The silepin complex was readily reconverted to Si(II), and this ease of change of oxidation state allowed for the activation of small molecules such as carbon dioxide, hydrogen and ethylene.⁴⁹ Given the relevance and importance of this system, it is an ideal candidate for investigating the possibility of non-covalent interactions between the silicon complexes involved and a toluene solvent molecule

(see Scheme 1b). The results obtained indicate that C–H/ π interactions are more significant over π – π interactions, and lead to the presence of C–H/ π interacting solvent molecules in the vicinity of the substrate. This result is further supported by *ab initio* molecular dynamics (AIMD) simulations, which have been employed previously in homogeneous catalysis by Vidossich and Ujaque.⁵⁰ Hence, C–H/ π interactions between solvent and substrate do indeed turn out to be relevant, and, as will be shown in the Results and Discussion section, we find that this important effect leads to increased efficiency for silepin formation, as well as for the subsequent small molecule activation reactions.

2. Computational methods

The DFT calculations were carried out using the Turbomole 7.0 and 7.1 suite of programs.⁵¹ Geometry optimizations were performed using the TPSS density functional,¹⁴ and the electronic configuration of the atoms was described by a diffuse def2-triple ζ basis set augmented by a polarization function (Turbomole basis set def2-TZVP).⁵² The resolution of identity (ri)⁵³ along with the multipole accelerated resolution of identity (marij)⁵⁴ approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. A real (not model) system was employed for all the calculations. The transition state structures were confirmed to have only one imaginary frequency, corresponding to the correct normal mode. In addition, intrinsic reaction coordinate (IRC)⁵⁵ calculations were done with all the transition states, in order to further confirm that they were the correct transition states, yielding the correct reactant and product structures. Solvent effects were introduced by using the COSMO model⁵⁶ with dielectric constant $\epsilon = 2.38$ for toluene. The option “disp” provided in the Turbomole package (DFT-D3) was used for dispersion-corrected DFT calculations for all the calculations.¹³ This is an option that is often not turned on by users of quantum chemical codes, though it is present today in most such codes. The current results serve to emphasize the importance of turning on this correction when doing quantum chemical calculations. The computation of the Hessian matrix and the calculation of zero-point energy have been performed at the same level of theory as for the electronic energy calculations, *i.e.*, at the TPSS/def2-TZVP level of theory. Unless otherwise specified, the values reported in the manuscript are ΔG values, with zero point energy, internal energy, and entropic contributions included, with the temperature taken to be 298.15 K. It should be noted that the ΔG values are calculated with the reactant species considered as separated and not complexed together (so as to get a proper estimate of the free energy required to bring the reactants together to form more ordered complexes). However, the solvent molecules associated with the reactant have been considered as a complex with the reactant when calculating the ΔG value. This is because solvent molecules will be ubiquitously present in the vicinity of reactant molecules, and do not have to be brought into the sphere of the reactants to begin with. The translational entropy term in the calculated structures was

corrected using a free volume correction method introduced by Mammen *et al.*⁵⁷ This is to account for the unreasonable enhancement in translational entropy that is generally observed in computational software. Furthermore, in order to check the reliability of the calculations, single point calculations were done at the B3-LYP-D3/TZVP/COSMO ($\epsilon = 2.38$, where ϵ represents the dielectric constant) and M06-2X/TZVP/COSMO ($\epsilon = 2.38$) levels of theory. The free energy profiles have been given in the ESI† (see Fig. S7–S10). The trends of all of the energy profiles were seen to be the same as at the TPSS-D3/def2-TZVP level of theory.

2.1 Energetic span model (ESM)

In order to find the efficiency of the catalytic cycle in our mechanism, we have calculated the relative efficiency using the AUTOF⁵⁸ program, employing the “Energetic Span Model” (ESM), developed by Shaik and coworkers,^{59,60} on all the free energy profiles discussed in the manuscript. The turnover frequency (TOF) calculations take into account the principal rate-determining transition state, potentially rate-influencing transition states, and the intermediates during the catalysis process. The TOF is calculated by the following equation:

$$TOF = \frac{K_B T}{h} e^{-\delta E/RT}$$

$$\delta E = T_{TDS} - T_{TDI} \quad \text{If TDS appears after TDI}$$

$$\delta E = T_{TDS} - T_{TDI} + \Delta G \quad \text{If TDS appears after TDI} \quad (1)$$

where K_B is the Boltzmann's constant, T is the temperature in K, TDI: TOF-determining intermediate, and TDS: TOF determining transition state. In order to provide a more quantitative estimate of the TOF, this model has been employed to calculate the TOFs from the free energy profiles obtained for the different mechanisms discussed in the manuscript.

2.2 Interaction energy due to C–H/ π non-covalent interactions

In order to quantify C–H/ π non-covalent interactions in the presence of toluene, the interaction energy (EI)⁶¹ between two non-covalently bonded fragments has been calculated by employing the following formula: $EI = E_{\text{complex}} - (E_{\text{part1}} + E_{\text{part2}})$, where E_{complex} is the single point energy of the non-covalently bonded complex, and E_{part1} and E_{part2} are the single point energies of the two fragments separated from an optimized geometry of the non-covalently bonded complex, at the TPSS-D3/def-2TZVP and the B3-LYP-D3/TZVP levels of theory. Analysis with NBO 3.1 has been done by using the Gaussian 09 software,⁶² at the B3-LYP/6-31g** level of theory.

2.3 Ab Initio molecular dynamics (AIMD)

AIMD simulations have been performed with the TeraChem 1.9 quantum chemistry software package,⁶³ using the B3-LYP functional and the 6-31g* basis set,⁶⁴ to calculate the Born Oppenheimer potential energy surface. Dispersion effects have been included with the DFT-D3 correction. Solvent effects have been introduced by using the conductor-like screening model, COSMO, with $\epsilon = 2.38$ employed to model the solvent toluene.

Simulations have been run at two different temperatures: one at higher temperature (1000.0 K) and the other at room temperature (298.0 K). The reason for doing this has been explained in the Results and discussion section of the manuscript. The speed of the calculations was enhanced because of the efficiency of TeraChem, which accelerates the simulations by evaluating the two electron integrals on GPUs. The ADIIS (augmented direct inversion in the iterative subspace) algorithm⁶⁵ available in TeraChem has been employed as an alternative tool for self consistent field calculations at each AIMD step, when the default DIIS algorithm failed to converge. The time step employed was 0.5 femtoseconds. Spherical boundary conditions (with a radius of 15.0 angstroms) have been applied. This has been done in order to ensure that the solvent molecules included in the AIMD simulations would not fly away significantly from the substrate. Furthermore, this also allows the modeling of the natural pressure that would exist in solution because of the bulk presence of solvent molecules around the substrate and the explicitly considered solvent molecules.

3. Results and discussion

3.1 Silepin system: significance of C–H/ π interactions between substrate and solvent

As mentioned in the Introduction, the Si(IV) silepin system reported by Rieger, Inoue and co-workers⁴⁹ has been carefully studied using density functional theory (DFT), keeping in mind the possible effect, through non-covalent interactions, of the aromatic solvent toluene. All the reactant, intermediate and product species shown in Scheme 1 were optimized with and without an explicit toluene molecule. The first calculations investigating the possibility of non-covalent interactions were done using important intermediate species **Int_2**. Toluene was added at several different positions: (i) above the di-isopropylphenyl (dipp) rings, for possible π – π stacking interactions, (ii) at the silicon center, for lone pair– π interactions, and (iii) above the C–H of the methyl group of dipp, for C–H/ π interactions. Interestingly, for (i) and (iii), it was observed that toluene shifted during the optimization to a position where there were two C–H/ π interactions between the C–H of one of the carbons of the imidazole ring and the π ring of toluene, as well as the C–H of toluene and the π ring of the dipp ring, a structure referred to as **Int_2'** (see Fig. 1 below). The starting (input) geometry submitted and the final optimized structures obtained (for case i, ii and iii) are shown in Fig. S1–S6 in the ESI.† These results indicate that the solvent prefers C–H/ π interactions with **Int_2** in place of π – π stacking. The presence of a CH₃ group on toluene may provide steric inhibitions to effective π – π stacking. The bulkiness of the dipp ring would also discourage π – π stacking between the solvent and the substrate, and lead to a preference for C–H/ π interactions. Furthermore, the same was seen to be true for all of the other intermediate silicon species and the toluene solvent, as well as in the transition states.

The fact that the final structure (**Int_2'**) does indeed show C–H/ π interactions has been ascertained by looking at the

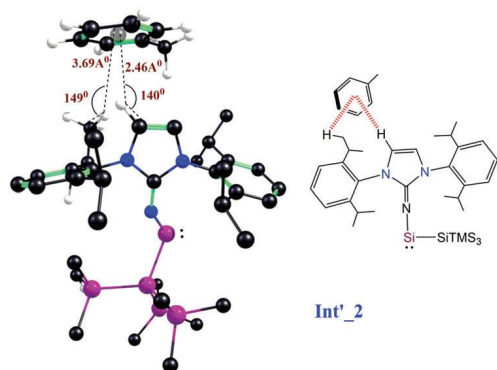


Fig. 1 Optimized geometry of complex **Int'_2** where C–H/ π non-covalent interactions have been shown. Hydrogen atoms (except for toluene) have been removed for the purpose of clarity.

interaction energy through additional single point energy calculations at the TPSS-D3/def2-TZVP and B3-LYP-D3/TZVP levels of theory (for more details, please see the Computational details section) between the two non-covalently bonded fragments. As Table 1, shown below, indicates, the interaction energy between toluene and **Int'_2**, it was favorable by 7.7 kcal mol^{−1} at the TPSS-D3/def2-TZVP and by 7.9 kcal mol^{−1} at the B3-LYP-D3/TZVP levels of theory, respectively. Furthermore, as Fig. 1 shows, the distances of the hydrogen atoms of C–H and the center of the π ring were seen to be 2.46 Å and 3.69 Å for the two C–H/ π interactions. Therefore, they fall in the accepted range for C–H/ π interactions.⁶⁶

Furthermore, the angles between the center of the toluene ring, and hydrogen and carbon were found to be 140° and 149° for the two C–H/ π interactions, which, too, fall within the accepted range of C–H/ π interactions. The other optimized structure for the other solvent–substrate interactions, (ii), mentioned above, was found to be less stable by 2.6 kcal mol^{−1} (ΔE) than **Int'_2**, indicating therefore that lone-pair/ π and other C–H/ π interactions were not as favorable. They have, therefore, not been considered further in this study.

In order to further validate this result, we have employed *ab initio* molecular dynamics (AIMD) simulations at room temperature. We note here that the use of AIMD in the context

of the current work is primarily to provide support to the static DFT calculations. The ideal way to employ AIMD would be to have a large number of solvent molecules in various solvent shells around the substrates. This, however, is too expensive computationally and outside the scope of the current work. Nevertheless, AIMD, as used here, with three toluene molecules placed in positions around the substrate in order to maximise non-covalent interactions, does provide interesting corroboration to the static DFT calculations, by showing that the C–H/ π non-covalent interaction is distinctly preferred over other interactions. Moreover, AIMD has also been employed to provide interesting insights along the same lines later in the manuscript.

We began by placing three toluene solvent molecules randomly around **Int'_2**, at different positions around the substrate. In other words, there was a significant difference in distance between the three toluene molecules, with no solvent–solvent interactions present. We observed that after 6182 steps {corresponding to about 3.0 picoseconds (ps)}, only one interaction remained. This structure possessed the same C–H/ π non-covalent interaction that had been found to be the most favourable {structure (i), discussed above} in the static DFT calculations. Moreover, once the interaction was formed, it remained for the duration of the AIMD simulation, up to 17 182 steps. The snapshots obtained from the simulations have been shown in Fig. S12 in the SI file. This provides further indication that the C–H/ π non-covalent interaction between solvent and substrate indeed predominates over other non-covalent interactions in this system.

Subsequent to this, all the other reactant, intermediate and product structures, **A'**, **Int'_1**, and **B'**, were also optimized with the explicit toluene molecule moiety attached, and they also showed the same C–H/ π interactions. The corresponding interaction energy values have been compiled in Table 1 and are seen to be favourable for all the cases. Furthermore, the bond lengths and angles for all the cases fall in the range of 2.4–3.8 Å and 120–150°, respectively, indicating the presence of C–H/ π interactions.

Now, there is another important point that should also be taken into account. Since C–H/ π is a non-covalent interaction, it is possible that after some period of time, toluene would be displaced from the silicon center, thus eliminating this interaction. However, because the silicon complex in solution would, at any instant in time, be surrounded by several solvent molecules, it is quite likely that even if one toluene molecule were to be displaced, another would take its place. In order to investigate this, further AIMD simulations have been done at an elevated temperature (1000.0 K). This is because the exchange process was not observed in the AIMD simulations done at room temperature: once one toluene formed a C–H/ π interaction with the substrate, this interaction was consistently present until the end of the simulation, with the other two toluene molecules randomly oriented around the complex. This is probably due to the fact that the total number of steps that were considered for the simulation at room temperature (17 182 steps) may not have been adequate to observe the exchange process between one toluene and the other. Therefore, we decided to “accelerate” the process by doing

Table 1 Interaction energies due to C–H/ π interactions. The values are provided in kcal mol^{−1}. The structures of the non-covalently bonded systems are provided in Fig. 2 and 3 below

Non-covalently bonded systems	ΔE at TPSS-D3/def2-TZVP	ΔE at B3-LYP-D3/TZVP
A'	−8.1	−8.4
Ts'_1	−8.2	−8.4
Int'_1	−7.4	−7.8
Ts'_2	−8.4	−8.9
Int'_2	−7.7	−7.9
Ts'_3	−7.6	−7.8
B'	−7.1	−7.5
Int'_3	−6.7	−6.9
Ts'_5	−7.2	−7.1
Ts'_6	−6.8	−7.0
C'	−6.9	−7.1

the simulations at an elevated temperature. The results obtained are shown through five snapshots in Fig. S13 in the ESI.† We did observe that, after 1.7 ps, the coordinating toluene was displaced from the C–H/ π interaction, and there was no interaction of any of the three toluenes considered with the substrate for 3400 steps. However, after that, another toluene molecule approached the silicon complex and formed a C–H/ π interaction with the substrate. Now, considering the total time for this simulation, and calculating the amount of time when there is no C–H/ π interaction, we see that for 63.0% of the time, there was C–H/ π interaction, and during remaining 37.0% of the time, there was no C–H/ π interaction during the simulation. However, this was when there were only three solvent molecules considered. In the real system, with dozens of solvent molecules likely to be present around the substrate, it is evident that there would be solvent–substrate interaction for a more significant amount of the time. Hence, the calculations indicate that the determination of the potential energy surface for the Si(II) to Si(IV) conversion, as well as the CO₂ activation by the Si(IV) complex, should include an explicit toluene molecule undergoing a C–H/ π interaction with the substrate. This C–H/ π interaction should be considered in the reactants, intermediates and products formed in all the potential energy surfaces calculated. The next section will discuss the results obtained by doing this, as well as provide a comparison with the corresponding cases for the system not possessing C–H/ π interactions.

We will see how the efficiency of the reactions is changed as a result.

3.2 Efficiency of Silepin formation, with and without the explicit presence of the solvent

Fig. 2 below shows the free energy profile for the formation of the silepin complex (experimentally observed by Rieger, Inoue and co-workers⁴⁹) in the presence of C–H/ π non-covalent interactions with toluene. The intermediate **Int'_1** is formed after surmounting a barrier of 16.4 kcal mol^{−1}, and lies 37.2 kcal mol^{−1} lower in energy in comparison to the reactants. The approach of one more equivalent of KSiTMS₃ to **Int'_1** and elimination of BrSiTMS₃ and KBr lead to the formation of **Int'_2**. Subsequent to this, intramolecular insertion of silicon into the carbon–carbon double bond of the di-isopropyl phenyl (dipp) ring of **Int'_2** leads to the formation of the final observed product, **B'**.

Now, the pertinent question is what the profile would look like in the absence of the explicit toluene solvent molecule. Fig. 3 below shows the results obtained for this. The barrier for the formation of **Int_2** is 16.4 kcal mol^{−1}, which is 2.7 kcal mol^{−1} higher than that for the toluene assisted process. Hence, the formation of the silepin complex without the involvement of explicit solvent would be less efficient. In order to provide a more quantitative estimate of how much the process is aided by toluene, we have determined the efficiency for the free energy profiles shown in Fig. 2 and 3, by employing the

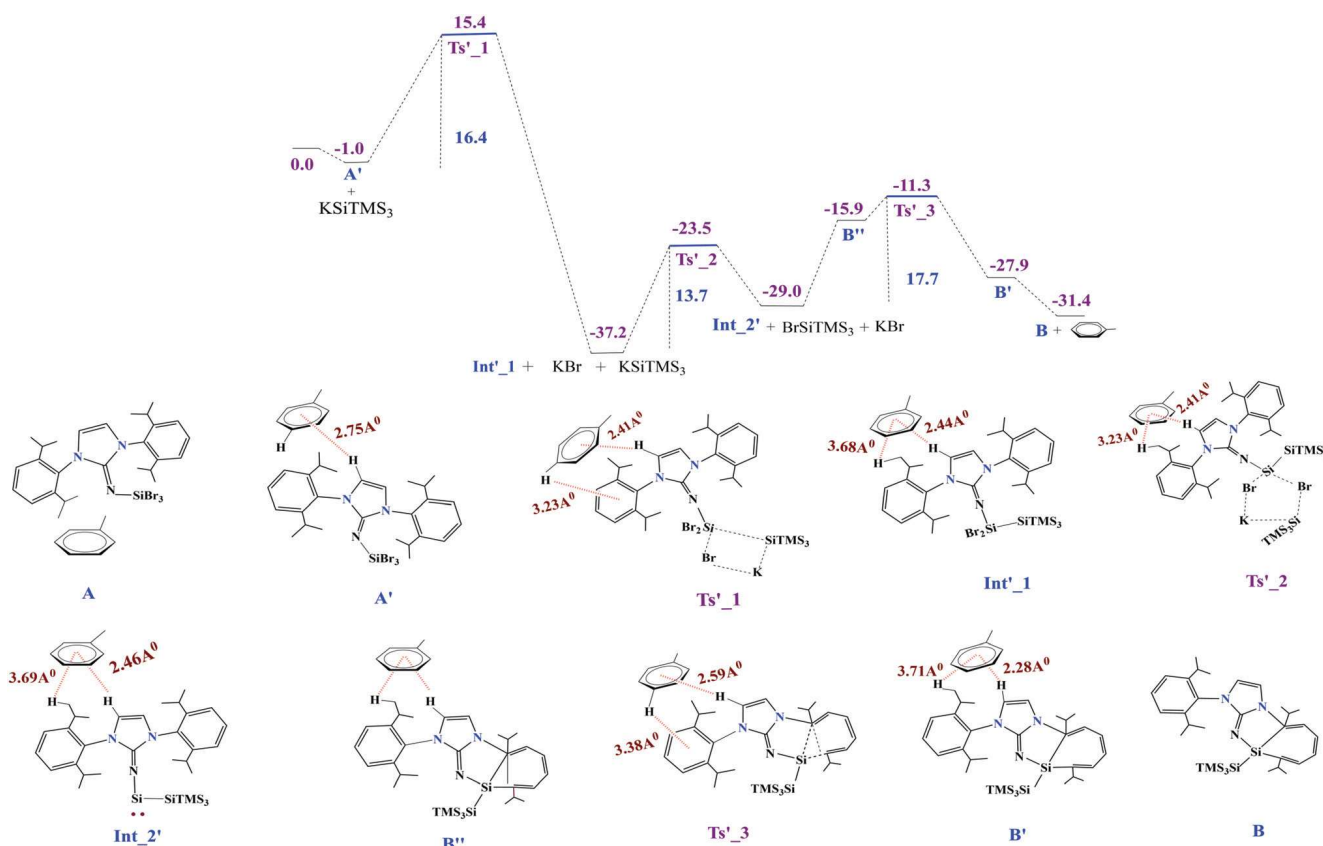


Fig. 2 Free energy profile (ΔG in kcal mol^{−1}) for the formation of silepin complex **B'** in the presence of an explicit toluene solvent molecule. The optimized structures of the intermediates have been shown in the ESI.†

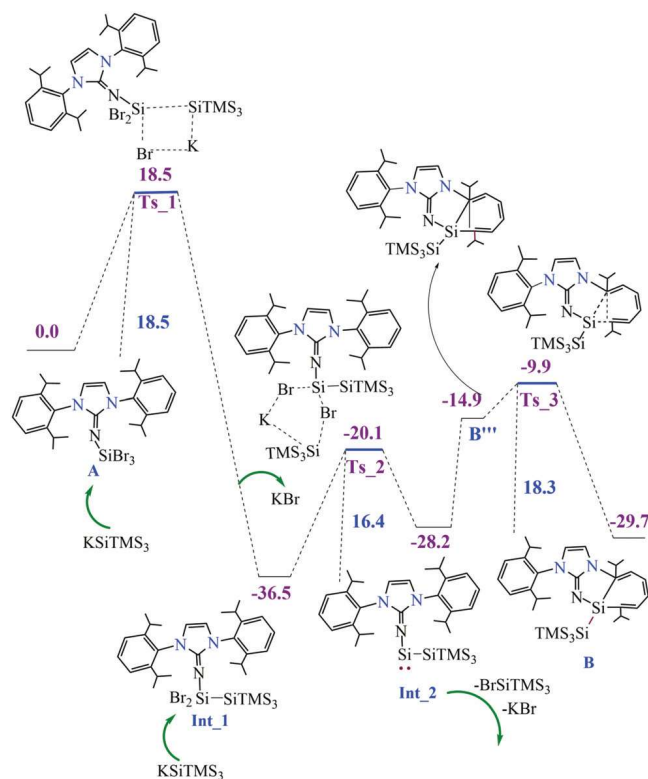


Fig. 3 Free energy profile (ΔG in kcal mol^{-1}) for the formation of silepin complex **B** in the absence of an explicit toluene molecule.

“Energetic Span Model” (ESM) developed by Shaik and Kozuch.^{59,60} By using the ESM, we have found that the intermediates **Int'_1** and **Int_1** are the TDI, and the transition states **Ts'_3** and **Ts_3** are the TDTs for the respective cases with and without the C–H/ π interaction with toluene (see Fig. 2 and 3). These calculations suggest that the barriers (TDTs–TDI) for the toluene assisted and the toluene unassisted processes are $25.9 \text{ kcal mol}^{-1}$ and $26.6 \text{ kcal mol}^{-1}$ respectively. For details regarding the ESM method, please see the Computational details section. The relative efficiency values (shown in Table 3 below) indicate that the formation of the silepin complex with the assistance of the explicit toluene molecule is 3.7 times more favourable. Hence, the solvent serves to accelerate the reaction rate *via* C–H/ π interactions. The reason why this is so has been studied by looking at donor acceptor orbital interactions through analysis with NBO 3.1^{67–69} using the Gaussian 09 software at the B3-LYP/6-31g**/D2 level of theory. (The Gaussian software was employed instead of Turbomole for the specific investigations because the study of donor–acceptor orbital interactions with NBO is not possible with Turbomole.) The interaction energies for the principal donor–acceptor interactions between the atoms involved in the respective transition states in **Ts'_2** and **Ts_2** were seen to be more favourable in the presence of toluene than in its absence (see Fig. 4 below and Table S1 in the ESI†). This serves to stabilize **Ts'_2** over **Ts_2** and explains why the barrier for this step is lowered significantly, by $2.7 \text{ kcal mol}^{-1}$, for the toluene bonded case (see Fig. 2 and 3). Hence, even though the toluene molecule is not directly a part of the transition state, its presence is seen to

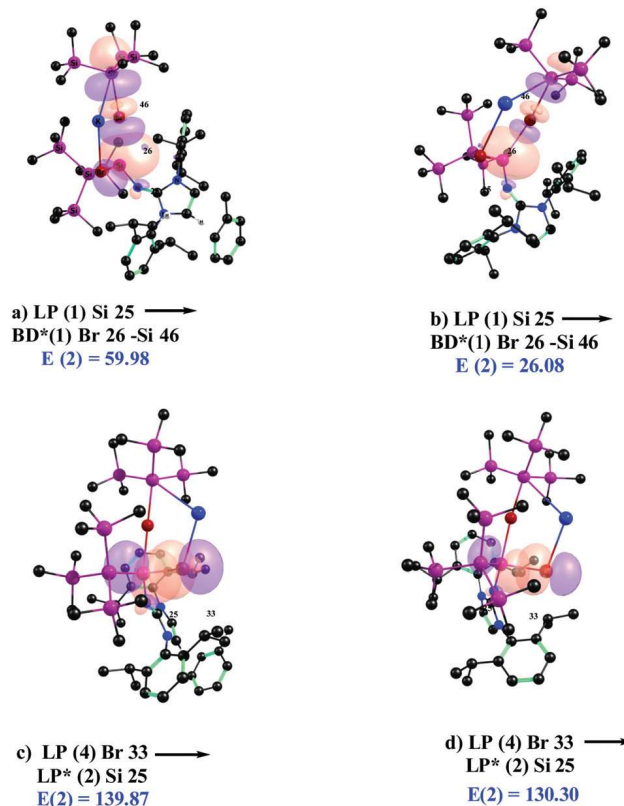


Fig. 4 Interactions between orbitals in the transition states: (a) and (c) in the presence of toluene (**Ts'_2**) and (b) and (d) in the absence of toluene (**Ts_2**). Hydrogen atoms have been removed for the purpose of clarity.

have a distal effect on the donor acceptor interactions. For the other two transition state cases, **Ts'_1** and **Ts_1** and **Ts'_3** and **Ts_3**, the NBO analysis does not show significant differences in the donor–acceptor interactions, but differences do exist in the barriers, favouring the toluene included process, stemming from changes in the enthalpy rather than in the electronic energies.

3.3 Does π – π stacking between toluene molecules affect the C–H/ π interaction between the solvent and the substrate?

The previous section makes it clear that non-covalent C–H/ π interactions between substrate and solvent lead to rate enhancement for the silepin formation process. However, it could be argued that the model employed is insufficient, in that a second toluene solvent molecule could undergo π – π stacking with C–H/ π interacting toluene, and thereby reduce the C–H/ π interaction in the actual system. In order to explore whether this is possible, we have performed further calculations using an expanded model, containing a second toluene molecule, arranged to π stack with the first (see Fig. 5). The orientation of the two toluene molecules avoided a staggered conformation, in order to minimize the repulsion between the CH_3 groups. The same energy profile as shown in Fig. 2 earlier was then calculated using this model. The electronic energies (ΔE and $\Delta E^\ddagger$ values) were determined, because, if π – π stacking between the toluenes affects the potential energy surface, it would reveal this effect in the ΔE calculations. Table 2 below shows that, in fact, the inclusion of the second

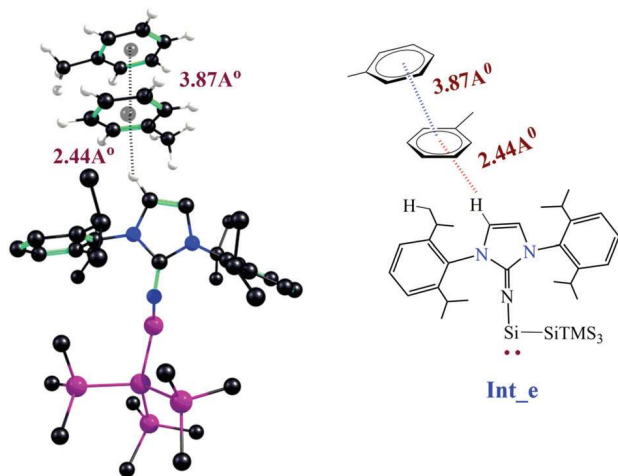


Fig. 5 Optimized geometry of the iminosilylsilylene complex with two explicit toluene molecules (**Int_e**), where C–H/ π (between the substrate and the solvent) and π – π (between solvent and solvent) non-covalent interactions have been shown. Hydrogen atoms (except for toluene) have been removed for the purpose of clarity.

Table 2 Energy barriers (a) in the presence of two explicit toluene molecules (b) in the presence of one explicit toluene, and (c) in the absence of explicit toluene molecules. $\Delta E_1^\ddagger$, $\Delta E_2^\ddagger$ and $\Delta E_3^\ddagger$ represent the barriers for the first, second and third steps for the silepin formation process

	(a) $\Delta E^\ddagger$ (in kcal mol ^{−1}) in the presence of two explicit toluenes	(b) $\Delta E^\ddagger$ (in kcal mol ^{−1}) in the presence of one explicit toluene	(c) $\Delta E^\ddagger$ (in kcal mol ^{−1}) in the absence of explicit toluenes
$\Delta E_1^\ddagger$	2.8	3.7	4.4
$\Delta E_2^\ddagger$	1.0	2.1	5.0
$\Delta E_3^\ddagger$	14.4	14.6	15.0

toluene actually reduces the barriers for the conversion. NBO analysis for **Ts_d** (**TS_2** in the presence of two explicit toluene molecules) at the B3-LYP/6-31g**/D2 level of theory provides an explanation for this. The interaction energies for the donor–acceptor interactions between the atoms involved in the transition state in **Ts_d** were seen to be more favourable in the presence of two toluenes than one toluene (see Fig. 6 below and Table S2 in the ESI†). The electron density at the silicon centre is further drawn towards the toluene when it also π stacks with another toluene, but the presence of the second silicon atom provides stabilization to the silicon, thereby allowing the five membered transition state to be stabilized. Optimized geometries of transition states, intermediates, and product in the presence of two explicit toluene molecules have been provided in the ESI† (Fig. S7). Hence, the inclusion of π – π stacking between toluene solvent molecules reduces the barriers for the Silepin formation of complex.

3.4 Activation of CO₂ by the Silepin complex, with and without the explicit presence of the solvent

Having looked at the formation of the silepin complex in the previous section, the current section focuses on its important application: the activation of CO₂.⁴⁹ CO₂ activation by low

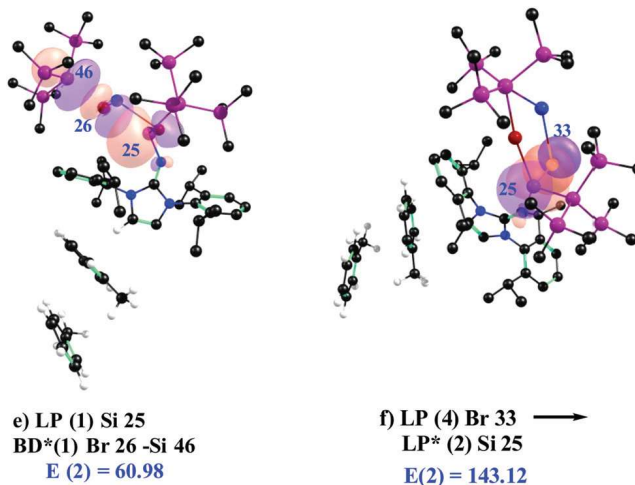


Fig. 6 Interactions between orbitals in the transition state in the presence of two toluene molecules. Hydrogen atoms have been removed for the purpose of clarity.

valent silicon compounds has gained much attention in recent years, but the use of silepin for this purpose was seen to be interesting because the product this yielded was monomeric in nature,⁴⁹ as opposed to the dimeric complexes observed in all of the other reported cases where CO₂ was activated by silylene complexes.⁷⁰ Our calculations detailing the role of toluene in this reaction are shown in Fig. 7 below. Before the approach of CO₂, the silepin complex (**B'**) is converted to **Int'_2** after surmounting a barrier of 16.6 kcal mol^{−1}. The subsequent steps involve the approach of CO₂ and the elimination of CO, as well as the approach of a second CO₂, leading eventually to the formation of the reported product **C'**, a monomeric silicon structure having silicon bridging with CO₂ (see Fig. 7). The slowest step in this process is the conversion of **Int'_2** to **Int'_3**, having a barrier of 22.8 kcal mol^{−1}.

What is interesting is that when we investigated the mechanism for the CO₂ activation by complex **B** in the absence of an explicit molecule of toluene, we found that the barrier for the slowest step (25.3 kcal mol^{−1}) was higher by 2.5 kcal mol^{−1} (see Fig. 8). Calculations using the ESM show that this translates to the efficiency for this process being as much as sixty times greater for the toluene assisted process (see Table 3 below). The reason for the difference in barrier is the difference in the electronic energies (ΔE) for **Ts'_3** and **Ts_3** and **Ts'_5** and **Ts_5** and difference in enthalpy (ΔH) in the case of **Ts'_6** and **Ts_6**.

Hence, what these calculations show is that even though there are only two C–H/ π interactions involved between the solvent molecule and the silicon system in each of the intermediates and the transition states, and C–H/ π interactions are considered to be weak, they are still influential enough to create an order of magnitude of difference in the efficiency of the CO₂ activation process.

Now, we have noted earlier that static DFT, as well as AIMD simulations, indicated the necessity and correctness of including an explicit toluene solvent molecule, but they did also indicate that

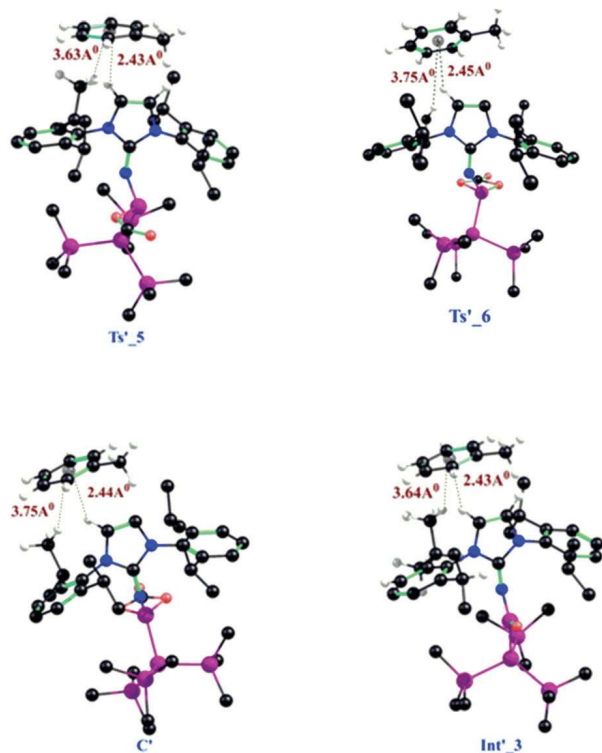
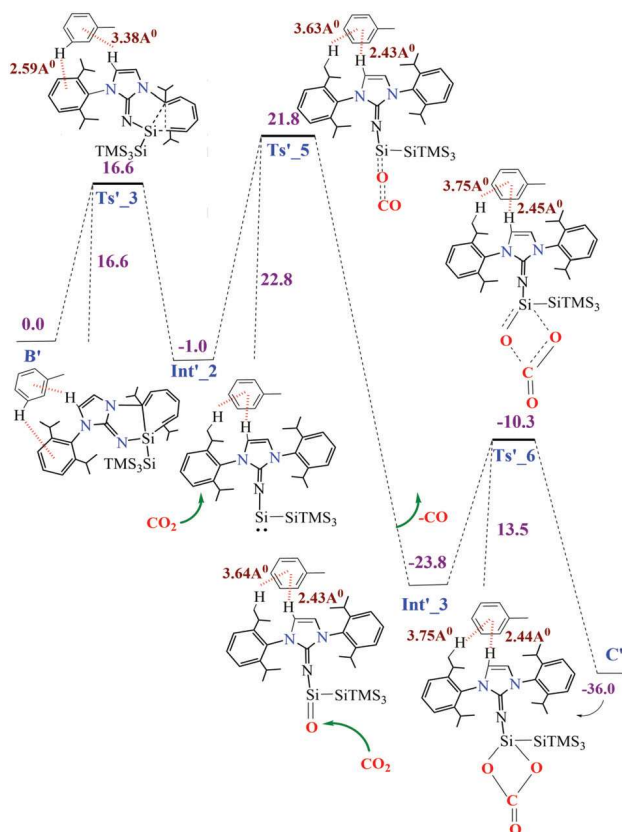


Fig. 7 Free energy profile (ΔG in kcal mol^{-1}) for the activation of CO_2 by the silepin complex (**B'**) in the explicit presence of a toluene solvent molecule. The optimized structures obtained for the transition states and intermediates are also shown below the profile.

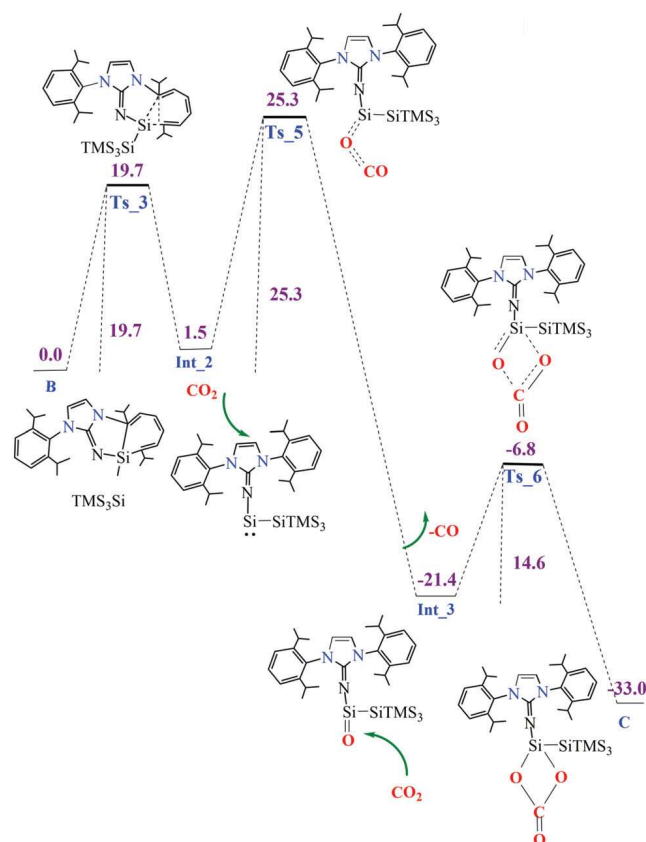


Fig. 8 Free energy profile (ΔG in kcal mol^{-1}) for the activation of CO_2 by the silepin complex (**B**) in the absence of an explicit toluene molecule.

Table 3 Relative efficiencies obtained for the silepin complex formation and activation processes, due to the explicit assistance of the solvent

Process	Relative efficiency
Formation of the silepin complex	3.7×10^0
Activation of CO_2 by the silepin complex	0.6×10^2

the exchange of one C-H/ π interacting toluene with another would occur in solution, although the loss of toluene from the silicon complex would be brief (see Fig. S13 in the ESI[†]). One could argue that this, too, could influence the nature of the potential energy surfaces. The exchange of one toluene solvent molecule with another could lead to entropic changes: there would be a favourable entropic effect on the potential energy surface upon the exit of a toluene molecule from the silicon complex, and an unfavourable entropic penalty for the subsequent gain of another C-H/ π interacting toluene molecule.

We show here why this should not matter for the potential energy surface. Fig. 9 below shows a scenario where the exchange of one toluene solvent molecule with another takes place between the reactant and transition state species, in the specific case where the reactant is the silylene complex and the transition state involves CO_2 activation, *i.e.*, for the slowest step of the CO_2 activation process. It becomes clear from the figure that the favourable and unfavourable entropic effects would cancel each other out. In this figure, the C-H/ π interaction between solvent

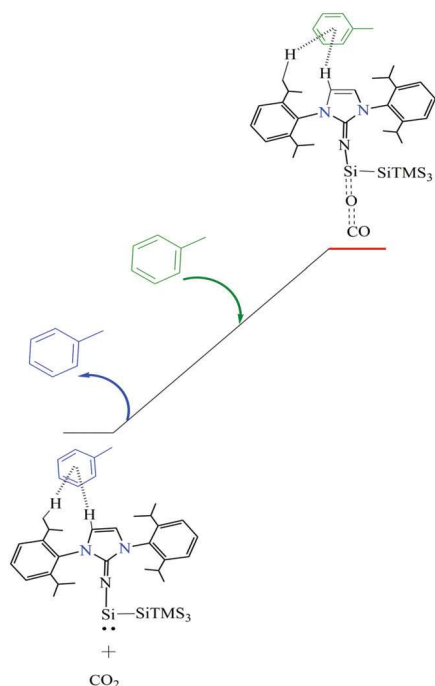


Fig. 9 Exchange of one toluene solvent molecule with another toluene, which shows that C–H/ π interaction between the substrate and the solvent would be present in the reactant as well as in the transition state.

and substrate remains in the reactant and transition state, and hence the calculation of the barrier (*i.e.*, the difference in energy between the reactant and transition state) is unaffected by the exchange process. Now, if the solvent exchange were to happen at the point where the transition state was formed, then we would have a situation where there would be a C–H/ π interacting toluene molecule in the reactant but no C–H/ π interacting toluene molecule in the transition state and this would affect the barrier, and thus, the potential energy surface. However, since we have shown earlier that the C–H/ π interacting solvent would be present for a significant amount of the time, and the loss of solvent from the substrate would occur for only a brief period, the probability that this would occur at the transition state is very low. Therefore, such situations represent only minor possibilities during the reaction. Nevertheless, we have decided to check the effect of these minor possibilities on the potential energy surface. To this end, we have done some additional calculations for the slowest step of CO₂ activation, where (I) we have considered the case where no toluene was coordinated with the substrate, while a C–H/ π interacting toluene was present in the transition state and in the product, (II) toluene was coordinated in the substrate and the product, but no C–H/ π interacting toluene was present in the transition state, and (III) toluene was coordinated in the substrate and the transition state but no C–H/ π interacting toluene was present in the product. The free energy profiles corresponding to these three cases are shown in Fig. S15–S17 in the ESI† TOFs have also been calculated for these cases, and based on the values obtained, the efficiencies of the CO₂ activation process for these cases relative to the TOF for the same process when the toluene was present in all of the reactant, transition state and the product was calculated.

Table 4 Efficiency values for cases where the exchange of one toluene for another would be occurring while the CO₂ activation was taking place, relative to the case where a toluene was attached in the reactant, transition state and the product, for the slowest step of the CO₂ activation reaction

Different cases	Relative efficiency
I	1.0×10^4
II	5.8×10^{-7}
III	1.0×10^0

As the Table 4 values indicate, in two out of the three cases, the CO₂ activation would actually become significantly more facile if the exchange occurred during the reaction. In only one of the three cases would the CO₂ activation process become significantly less favourable. Hence, for the overwhelmingly significant majority of the time, the inclusion of the C–H/ π interacting solvent molecule would have a salutary effect on the CO₂ activation process.

4. Conclusions

The current work reveals an important, previously uninvestigated, role of the solvent: its ability to influence the efficiency of chemical processes in a catalytic fashion through C–H/ π interactions. A recently developed silepin complex,⁴⁹ which had been experimentally observed to activate CO₂ in a facile manner, has been investigated by performing full quantum chemical calculations using density functional theory (DFT). The C–H/ π interactions were seen to be more dominant than π – π interactions between the solvent toluene and the substrate in this case. This was further confirmed by *ab initio* molecular dynamics (AIMD) simulations performed at different temperatures, which revealed that (i) randomly placed toluene molecules would orient such that C–H/ π interactions predominated over other non-covalent interactions and (ii) exchange would occur in a facile manner between solvent molecules, so that for a significant portion of the time, C–H/ π interactions would exist between the solvent and the silicon complex. Having thus established the need to consider solvent–substrate C–H/ π interactions, we have then demonstrated that the explicit presence of the C–H/ π interacting solvent molecule improves the facility of the silepin formation reaction and the activation of CO₂. Indeed, the efficiency of the CO₂ activation by silepin was seen to be improved by as much as sixty times due to the presence of toluene. The work therefore shows that the solvent can enhance the rate of chemical reactions through non-covalent C–H/ π interactions. This can serve as a useful guide to experimentalists working in the field of small molecule activation. This is because, now that having C–H/ π interactions has been seen to be useful, new systems could be designed where such solvent–substrate interactions would be strengthened, which would lead to greater efficiency of the activation processes and thus, to increased yields of the desired products.

Furthermore, the current investigation throws up the question: are there other non-covalent interactions possible between solvent and substrate that could have a possible beneficial effect on the

reactivity of the substrate? For instance, geometry optimizations that we have done considering tetrahydrofuran (THF) as an explicit solvent molecule and the silylene complex **Int_2** as the substrate yielded evidence of non-covalent C–H/O interactions between the two moieties (see the optimized structure shown in Fig. S19 in the ESI†). This suggests that there are likely to be several other systems where there is a hidden role of the solvent that is affecting the activity of the systems.

Therefore, the current findings represent an interesting forward step in the area of small molecule activation research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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The Effect of Solvent–Substrate Noncovalent Interactions on the Diastereoselectivity in the Intramolecular Carbonyl-Ene and the Staudinger [2 + 2] Cycloaddition Reactions

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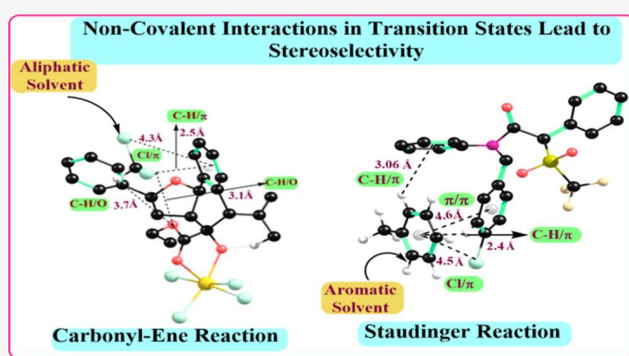


Article Recommendations



Supporting Information

ABSTRACT: Noncovalent interactions (NCIs) have been identified as important contributing factors for determining selectivity in organic transformations. However, cases where NCIs between solvents and substrates are responsible for a major extent for determining selectivity are rare. The current computational study with density functional theory identifies two important transformations where this is the case: the intramolecular carbonyl-ene reaction and the Staudinger [2 + 2] cycloaddition reaction. In both cases, the role of explicit solvent molecules interacting noncovalently with the substrate has been taken into account. Calculations indicate that the diastereomeric ratio would be 95.0:5.0 for the formation of tricyclic tetrahydrofuran diastereomers via the intramolecular carbonyl-ene reaction and 94.0:6.0 for the formation of the triflone diastereomers via the Staudinger [2 + 2] cycloaddition reaction, which corroborates with the experiment. Interestingly, in both the cases, the calculations indicate that noninclusion of explicit solvent molecules would lead to only a small difference between the competing transition states, which leads to the conclusion that solvent–substrate NCIs are the major cause for diastereoselectivity in both the cases considered.



1. INTRODUCTION

Stereoselectivity plays a central role in various fields of chemistry and biology, such as organic synthesis,^{1–5} asymmetric synthesis,^{6–8} drug metabolism,^{9,10} pharmacology,¹¹ and medicinal chemistry.¹² Therefore, understanding the origin of stereoselectivity in organic reactions is essential. It has been found that many factors influence stereoselectivity,^{13–15} including solvents,^{16–20} additives,^{16,21,22} and temperature.²³ Furthermore, a solvent is seen to play the most pivotal role in different chemical reactions.^{24,25} There are several reports investigating the effect of different solvents,^{26–29} including reports of the explicit role of solvent molecules, on stereoselectivity. In addition to these effects, the role of noncovalent effects such as hydrogen bonding, π – π stacking, and C–H/ π and C–H/O interactions has also been investigated, and noncovalent interactions (NCIs) between explicit solvent molecules and the substrate have been seen to be important.^{16,30–33} It is, however, rare to find reports that show NCIs between solvents and substrates to be the major reason for the observed stereoselectivity.^{34,35} The reason could be because this is a rare phenomenon, but an interesting hypothesis that we propose and explore here is that this is a widespread occurrence that has not received adequate attention because of a lack of inclusion of explicit solvent effects in computational investigations. In order to give

credence to this hypothesis, we have considered two important, highly stereoselective organic reactions: (a) the carbonyl-ene reaction, which is a reaction between the ene and the enophile for selective carbon–carbon bond formation^{36–39} and (b) the Staudinger [2 + 2] cycloaddition reaction between a ketene and an imine^{40–42} for the synthesis of β -lactam triflones. The current computational study investigates whether (a) and (b) represent two cases where NCIs between explicit solvent molecules and the substrate were the major reason for the stereoselectivity.

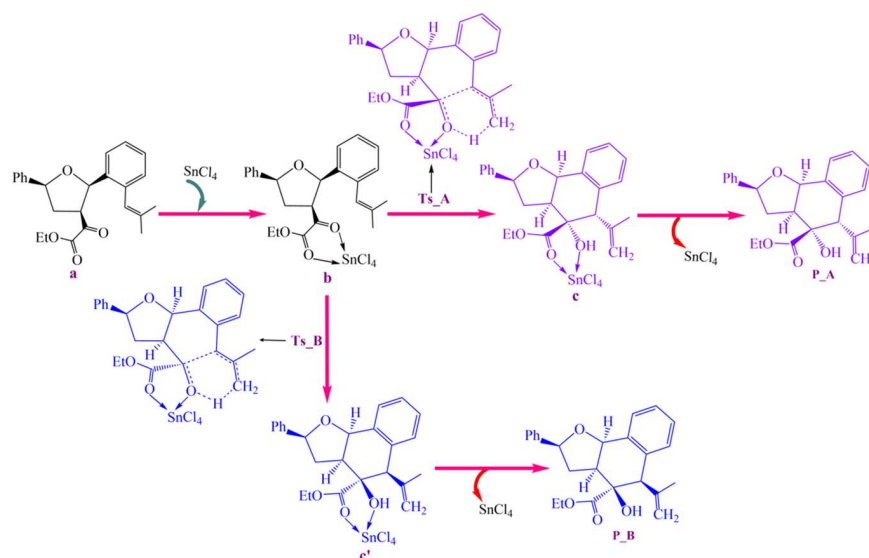
The choice of these two reactions stems from the fact that they represent two diverse examples of highly stereoselective reactions. The carbonyl-ene reaction is single-step and intramolecular (see Scheme 1), whereas the Staudinger reaction is a multistep and intermolecular reaction (see Scheme 2). Moreover, the carbonyl-ene reaction is organo-catalyzed,⁴³ and the Staudinger reaction is a catalyst-free reaction. Furthermore, the solvent employed in the carbonyl-

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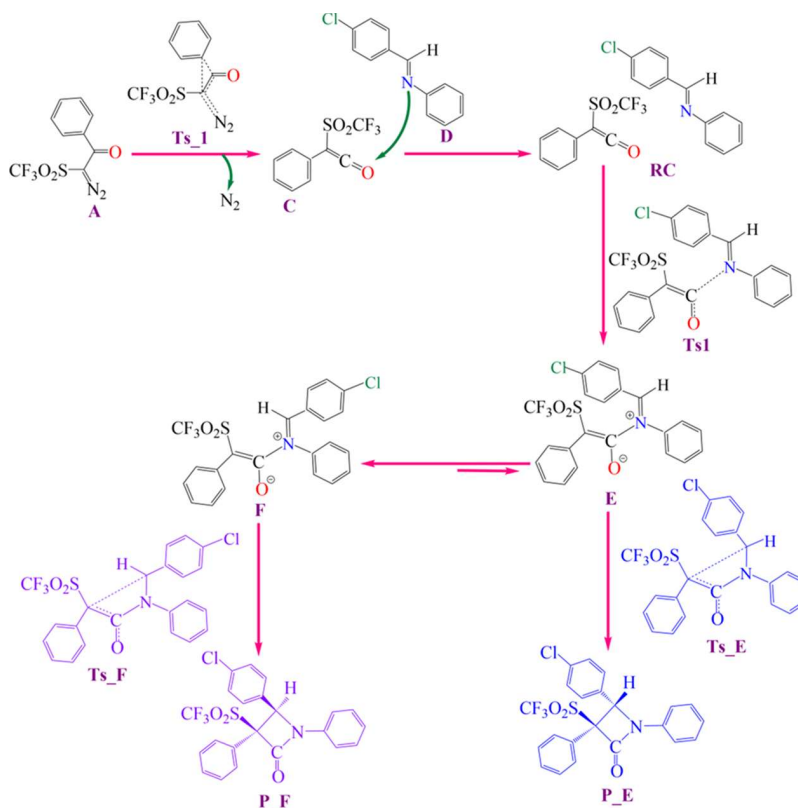
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Scheme 1. Reaction Mechanism for the Formation of the Tricyclic Tetrahydrofuran Diastereomers P_A and P_B via the Intramolecular Carbonyl-ene Reaction



Scheme 2. Reaction Mechanism for the Formation of the β -Lactam Triflone Diastereomers P_F and P_E via the [2 + 2] Cycloaddition Staudinger Reaction



ene reaction is aliphatic (dichloromethane),⁴⁴ while the solvent used in the Staudinger reaction is aromatic (toluene).⁴⁵ Hence, these two systems represent ideal test cases for our hypothesis. If solvent–substrate NCIs are seen to be the major cause for stereoselectivity in these two very diverse systems, this would provide credible support to our argument that selectivity arising largely from such interactions is a more widespread phenomenon than previously considered.

Full quantum chemical calculations with density functional theory (DFT) have been performed, investigating the difference in free energies in the stereoselective transition states for the two separate reaction systems. The effect of the solvent on the stereoselectivity of the two reactions has been explored through hybrid explicit–implicit solvation calculations. Two cases of explicit solvent inclusion have been considered for the intramolecular carbonyl-ene reaction: (i) one and (ii) four noncovalently interacting explicit solvent

dichloromethane molecules have been incorporated in the calculations. Furthermore, for the Staudinger [2 + 2] cycloaddition reaction, two cases have been considered: (I) the explicit inclusion of one explicit toluene solvent molecule and (II) two noncovalently interacting explicit solvent toluene molecules. The reasons for choosing these specific cases of explicit solvent inclusion have been discussed in Section 3. NCIs have been captured with dispersion corrected^{46,47} DFT calculations. Moreover, as will be shown in the next section, the results from the calculations indicate that NCIs play the central determining role in giving rise to the observed diastereoselectivity in these two chemical systems. Our calculations reveal that NCIs such as Cl/ π and π/π are significant up to a distance of 4.8 Å. A perusal of the literature indicates that the effects of long-range interactions such as C–H/ π and anion/ π -HB are significant up to a distance of more than 5 Å.^{48–50}

2. COMPUTATIONAL DETAILS

The DFT calculations were carried out using the Turbomole⁵¹ 7.0 and 7.1 suite of programs. Geometry optimizations were performed using the TPSSH⁵² functional; the electronic configuration of the atoms was described by a triple ζ (Turbomole basis set TZVP⁵³) basis set. For the Sn atom, the diffuse def2-triple ζ basis set augmented by a polarization function (Turbomole basis set def2-TZVP⁵⁴) has been employed. The resolution of identity (ri)⁵⁵ along with the multipole accelerated resolution of identity (marij)⁵⁶ approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the density functional calculations. The real (not model) system has been employed for all the calculations. The transition state structures were confirmed to have only one imaginary frequency, corresponding to the correct normal mode. In addition, intrinsic reaction coordinate⁵⁷ calculations were performed with all the transition states, in order to further confirm that they were the correct transition states, yielding the correct reactant and product structures. The option “disp” given in the Turbomole package (DFT-D3)^{46,47} was employed for dispersion-corrected DFT calculations for all the calculations. The computation of the Hessian matrix and the calculation of zero-point energy have been performed at the same level of theory as for the electronic energy calculations, that is, at the TPSSH/TZVP,def2-TZVP(Sn) level of theory. The values provided in the manuscript are ΔG values (unless otherwise specified), with zero-point energy, internal energy, and entropic contributions included, with the temperature taken to be 298.15 K. Furthermore, solvent effects were introduced using the COSMO model⁵⁸ with the dielectric constant $\epsilon = 8.93$ for dichloromethane and $\epsilon = 2.38$ for toluene.

2.1. Diastereomeric Ratio (dr) Calculations. Stereoselectivity of chemical reactions can be represented as an enantiomeric ratio or dr. The dr (for the diastereoselective reaction) is directly proportional to the relative rates of formation of the diastereomeric products; that is, the ratio of products depends on the relative free energy barrier ($\Delta\Delta G^\ddagger$). Hence, selectivity for the kinetically controlled reaction can be defined as (see eqs 1 and 2 below)

$$\frac{k_{P_A}}{k_{P_B}} = \frac{[P_A]}{[P_B]} = e^{-\Delta\Delta G^\ddagger/RT} \quad (1)$$

$$de = \frac{1 - e^{-\Delta\Delta G^\ddagger/RT}}{1 - e^{-\Delta\Delta G^\ddagger/RT}} \times 100 \quad (2)$$

Here, k is the rate constant, and $\Delta\Delta G^\ddagger = \Delta G_2^\ddagger - \Delta G_1^\ddagger$ (see Figure 1); de is diastereomeric excess.

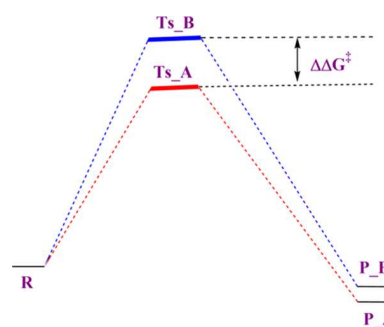


Figure 1. Free energy and the relative free energy barrier for two diastereomers P_A and P_B.

2.2. NCI Plot. Analysis of NCIs in the stereo-controlling transition states has been carried out by employing the NCI plot developed by Yang et al.^{59,60} The NCI plot is a program that shows the graphical representation of inter and intra-molecular NCIs based on the electron density and its derivatives.

3. RESULTS AND DISCUSSION

3.1. Achieving Diastereoselectivity in the Intramolecular Carbonyl-Ene Reaction. As mentioned in the Introduction, full quantum chemical calculations have been performed with DFT, in order to understand the origin of stereoselectivity in the intramolecular carbonyl-ene reaction, reported by Schneider and coworkers.⁴⁴ This group has discussed the stereoselective synthesis of tetrahydrofuran and its use in an intramolecular carbonyl-ene reaction in the presence of the Lewis acid SnCl₄. Intermolecular and intramolecular carbonyl-ene reactions have been reported with Lewis acids such as AlMe₃ and SnCl₄⁶¹ because Lewis acid-coordinated dienophiles influence the rate and the diastereoselectivity of the carbonyl-ene reaction.^{62,63}

Scheme 1, shown earlier in the Introduction, indicates that the SnCl₄ molecule binds with the reactant **a**, which leads to the formation of the intermediate **b**. Next, two stereo-controlling transition states Ts_A and Ts_B lead to the formation of the intermediates **c** and **c'**, respectively. The diastereomer products P_A and P_B are formed after the elimination of the SnCl₄ molecule. Now, because the dr is directly proportional to the relative rates of formation of the diastereomers,¹⁴ the relative energy barriers ($\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$; electronic and free energy difference between the two stereo-controlling transition states) for the formation of diastereomers (P_A and P_B) have been calculated. The $\Delta\Delta E^\ddagger$ is 1.2 kcal/mol, and the $\Delta\Delta G^\ddagger$ is 1.3 kcal/mol for the stereo-controlling transition states Ts_A and Ts_B (see Figure 2). Because energy values within a range of ± 1.0 kcal/mol are subject to systematic errors in DFT calculations, the small values of $\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$ may suggest low diastereoselectivity for this reaction. However, the experimentally reported dr is 95.0:5.0 for P_A and P_B formation.⁴⁴ This seeming contradiction between the calculation and experiment suggests that the solvent employed, dichloromethane, could be having a

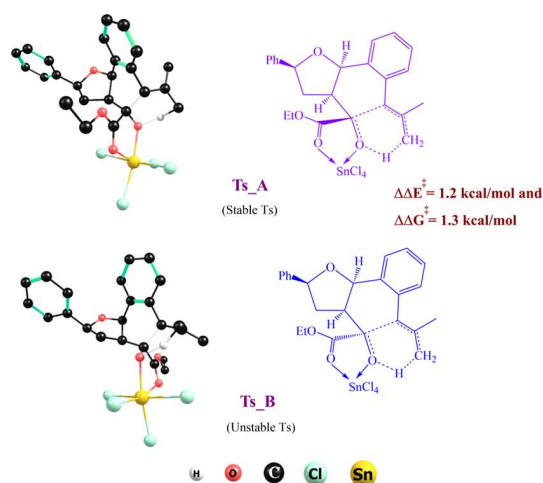


Figure 2. Stereo-controlling transition states **Ts_A** and **Ts_B** for the formation of the diastereomers **P_A** and **P_B**, respectively, in the absence of explicit dichloromethane solvent molecules (i.e., with the implicit solvent model). Hydrogen atoms have been removed for the purpose of clarity.

non-negligible, explicit effect on the stereoselectivity of the reaction. Therefore, our computational studies then focused on the role of explicit dichloromethane molecules in influencing the diastereoselectivity.

We began by investigating the possibility of NCIs between the solvent and the reactant (**b**). In order to find the orientation of the solvent dichloromethane with respect to the substrate, a dichloromethane molecule was added at several different positions near reactant **b** (i) at the oxygen of the ring (the furan oxygen), for possible C–H/O and Cl/π NCIs, (ii) at the oxygen of the ethoxy group, (iii) at the carbonyl oxygen, for different possible C–H/O NCIs, and (iv) at the phenyl ring, for possible C–H/π interactions. Calculations show that optimization of the case (ii) input structure gave rise to the most stable geometry followed by case (iii) {0.5 kcal/mol higher than case (ii)}, case (i) {0.6 kcal/mol higher than case (ii)}, and case (iv) {1.1 kcal/mol higher than case (ii)} (ΔE values reported in all cases). The input geometry, as well as the optimized geometry obtained for cases (i), (ii), (iii), and (iv), has been provided in the Supporting Information (SI) (Figures S1–S8). However, because the energy differences are quite small, and, as mentioned earlier, fall within the range of systematic error in DFT calculations, we have decided to consider two cases: (a) where a lone dichloromethane molecule was added near the oxygen of the ethoxy group {case (ii)}, and (b) where four dichloromethane molecules were added, one at each of the positions considered in the cases (i)–(iv). The two stereo-controlling transition states were then determined for these two cases (a) and (b), and the $\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$ values were calculated for each case.

Case (i). The $\Delta\Delta E^\ddagger$ and the $\Delta\Delta G^\ddagger$ values were found to be 3.3 and 2.3 kcal/mol, respectively. This indicates that the gap between the stereo-controlling transition states (and, therefore, the diastereoselectivity) is increased to a significant extent upon the addition of an explicit solvent molecule of dichloromethane near the oxygen of the ethoxy group. The reason for this is the additional C–H/O and C–H/π NCIs that are present in the transition state **Ts'_A**, which stabilize this transition state, whereas only C–H/O NCIs are present in the transition state **Ts'_B**. Figure 3 illustrates the NCIs

between the solvent and the stereo-controlling transition states and the relative energy difference between them.

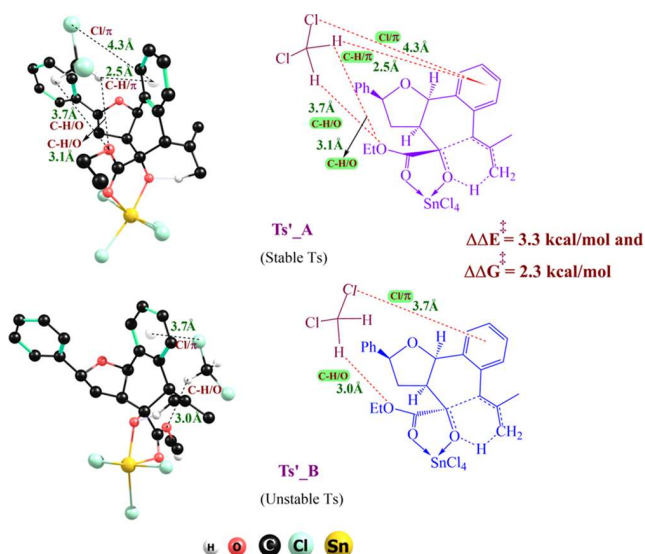


Figure 3. Stereo-controlling transition states **Ts'_A** and **Ts'_B** for the formation of the diastereomers **P_A** and **P_B**, respectively, in the presence of one explicit dichloromethane solvent molecule (i.e., with the hybrid implicit–explicit solvent model). Hydrogen atoms (except for the moiety involved in NCIs) have been removed for the purpose of clarity.

Case (ii). Because, as mentioned above, only minor differences were seen in the stability of the optimized geometries when dichloromethane was added at different positions in the reactant **b**, four explicit dichloromethane solvent molecules (at all four positions discussed above) were added in the stereo-controlling transition states. The relative energy barrier ($\Delta\Delta G^\ddagger$) was found to be 4.1 kcal/mol for this case. This indicates that with the increase in the number of NCIs, the transition states are preferentially stabilized (see Figure 4), which gives rise to the experimentally observed diastereoselectivity.

In order to quantify the NCIs, the NCI plot analysis was performed, which indicates that both **Ts'_A** and **Ts'_B** are stabilized by C–H/O and Cl/π NCIs, but **Ts'_A** benefits from an additional C–H/π interaction (see Figure 5).

The NCI plot analysis was also performed for the stereo-controlling transition states that had been obtained in the presence of explicit dichloromethane solvent molecules, and the results indicate that **Ts'_A** and **Ts'_C** are stabilized by additional C–H/π and Cl/π NCIs (Figure 5). In other words, there is greater stabilization through NCIs when explicit solvent molecules are present, and this explains the increased gap in the $\Delta\Delta E^\ddagger$ and the $\Delta\Delta G^\ddagger$ values and thus the experimentally observed diastereoselectivity.

3.2. Diastereoselectivity in the [2 + 2] Cycloaddition Staudinger Reaction. In the previous section, we demonstrated how the stereoselectivity of the intramolecular carbonyl-ene reaction is controlled by NCIs between the reactant and explicit aliphatic dichloromethane solvent molecules. In this section, we investigate the possibility that such NCIs can likewise play an exclusive role in determining the diastereoselectivity of the Staudinger [2 + 2] cycloaddition reaction. As noted in the Introduction, this reaction is

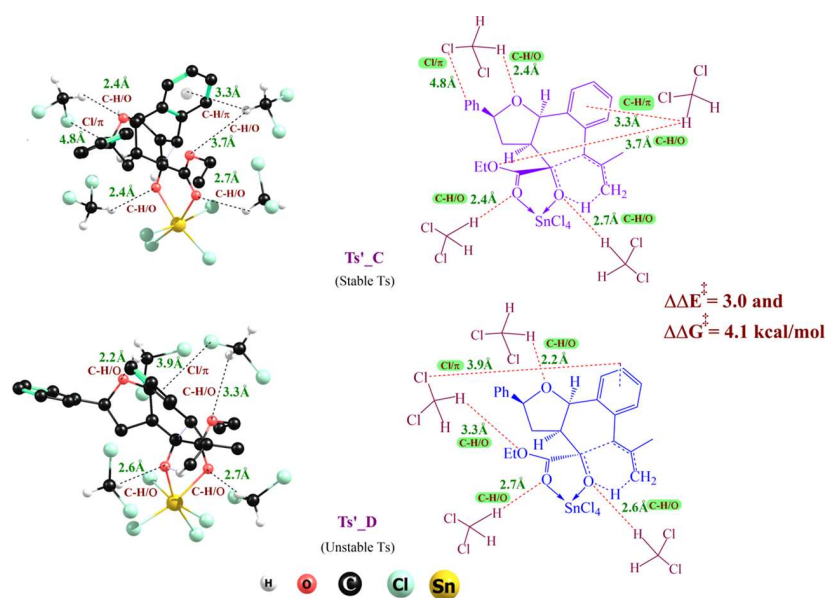


Figure 4. Stereo-controlling transition states Ts'_C and Ts'_D for the formation of the products P_A and P_B , respectively, in the presence of four explicit dichloromethane solvent molecules (i.e., with the hybrid implicit–explicit solvent model). Hydrogen atoms (except for the dichloromethane moiety) have been removed for the purpose of clarity.

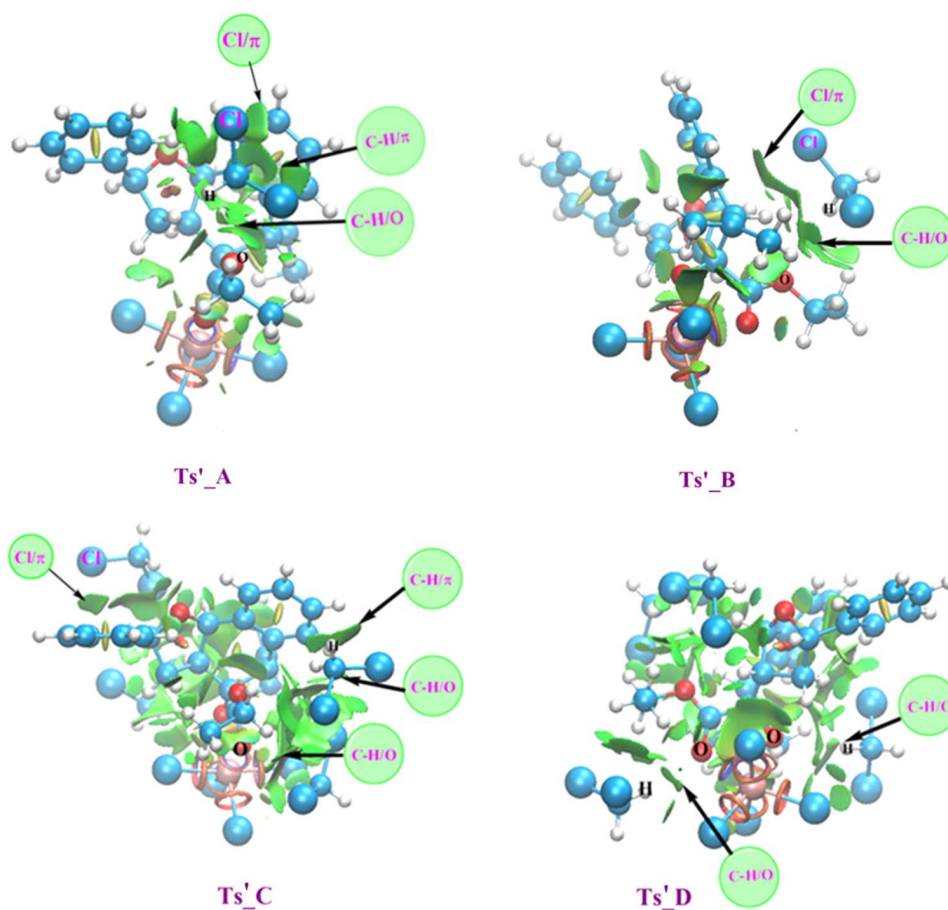


Figure 5. NCI plots for stereo-controlling transition states that show the NCIs between the solvent and substrate. Images Ts'_A and Ts'_B are in the presence of one explicit dichloromethane solvent molecule, and images Ts'_C and Ts'_D are in the presence of four explicit dichloromethane solvent molecules. This analysis suggests that transition states with more NCIs are more stable (Ts'_A and Ts'_C) than the transition states with fewer NCIs (Ts'_B and Ts'_D).

significantly different from the carbonyl-ene reaction in its nature and takes place in the aromatic solvent toluene. Shibata

and coworkers have reported the stereoselective synthesis of β -lactam triflones, where the heterocyclic frameworks containing

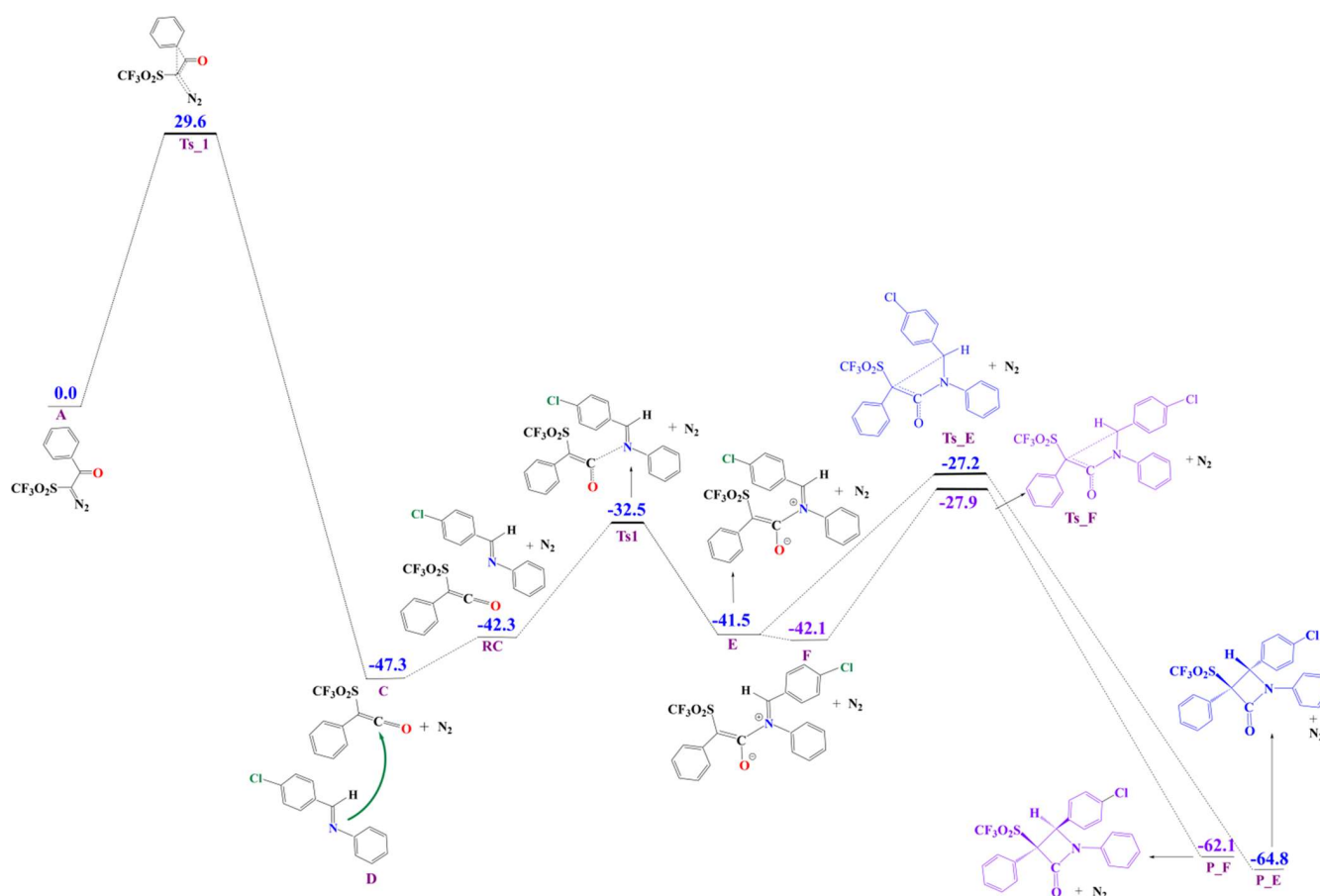


Figure 6. Free energy profile for the formation of the β -lactam triflone diastereomers **P_E** and **P_F**, in the absence of an explicit toluene solvent molecule (i.e., with the implicit solvent model).

triflones were synthesized under catalyst-free conditions.⁴⁵ Triflones are useful in pharmaceutical applications, and β -lactams (heterocycles triflones) have shown antibiotic properties and thus found applications in biology, being employed in antibacterial treatments.

Figure 6 shows the free energy profile of the stereoselective Staudinger reaction in the absence of explicit solvent molecules. Calculations indicate that the free energy barrier for ketene formation (**C**) is 29.6 kcal/mol. Next, the reactant complex (**RC**) leads to the formation of intermediate **E** via **Ts_I**, which is exergonic by -41.5 kcal/mol. Because of steric hindrance, this intermediate (**E**) isomerizes into intermediate **F**. Transition state calculations for the formation of **F** from **E** have been provided in the Supporting Information (Table S2 and Figures S9,S10). Subsequent to this, the free energy barriers for the formation of **P_E** and **P_F** are 20.0 and 19.3 kcal/mol via the stereo-controlling transition states **Ts_E** and **Ts_F**, respectively, where **P_F** is the major diastereomer and **P_E** is the minor diastereomer. Because the dr depends on the relative energy barrier ($\Delta\Delta G^\ddagger$) of the stereo-controlling transition states, the $\Delta\Delta G^\ddagger$ has been calculated. This was seen to be 0.7 kcal/mol for the diastereoselective transition states **Ts_E** and **Ts_F**. In other words, the difference is small and clearly does not account for the experimentally reported significant dr for these two diastereomers, 94.0:6.0. Thus, the inclusion of an explicit solvent molecule in the calculations was seen to be warranted.

3.2.1. Case I. Achieving Diastereoselectivity in the Staudinger [2 + 2] Cycloaddition Reaction in the Presence of One Explicit Solvent Molecule (Toluene). We began by investigating the possibility of NCIs between the solvent and the intermediate **E**. This intermediate was considered because the free energy profile in Figure 6 shows that this is the important intermediate in the reaction, occurring just prior to the formation of the stereo-controlling transition states **Ts_E** and **Ts_F**, which determine the stereoselectivity. In order to find the orientation of the aromatic solvent toluene was added at several different positions of intermediate **E**: (i) near the phenyl ring for possible π/π and C–H/O NCIs, (ii) near the chlorophenyl ring for possible C–H/ π , $\pi-\pi$, and Cl/ π NCIs, and (iii) near another phenyl ring for possible π/π and C–H/ π NCIs. The initial geometries submitted, as well as the final optimized structures obtained, are provided in the supporting information (Figures S11 to S16). The calculations reveal that the optimized structure with C–H/ π , π/π , and C–H/O NCIs {case (iii)} is the most stable by 4.9 kcal/mol in comparison to the optimized case (ii) structure, and 3.3 kcal/mol in comparison to the optimized case (i) structure. Therefore, it becomes clear that case (iii) would represent the orientation of choice for a toluene molecule when it came in the vicinity of the intermediate. Therefore, an explicit solvent molecule of toluene was added in the diastereoselective transition states (**Ts'_F** and **Ts'_E**) near the phenyl ring, for possible C–H/ π and π/π NCIs (see Figure 7). The relative energy barrier

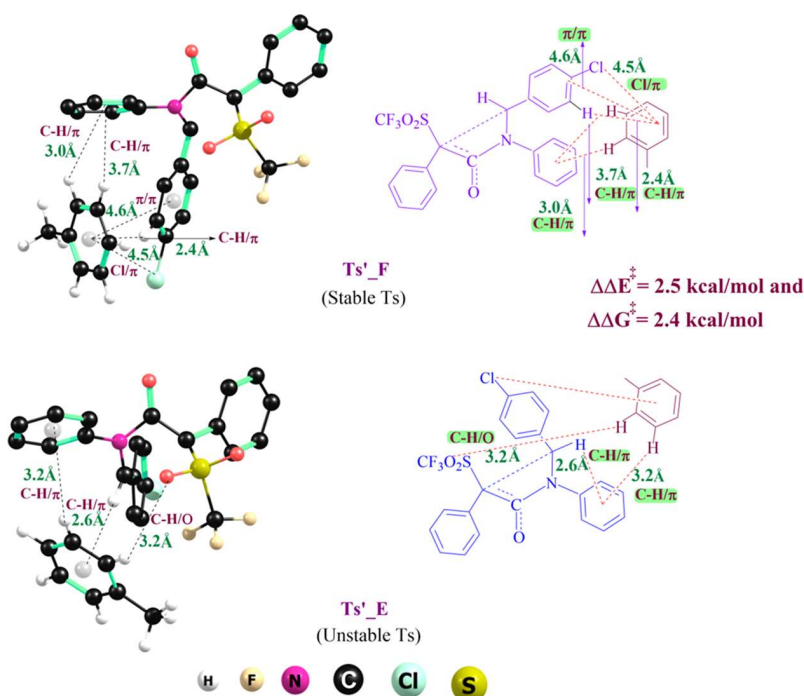


Figure 7. Stereo-controlling transition states for the formation of β -lactam triflones via the Staudinger reaction in the presence of an explicit toluene solvent molecule (i.e., with the hybrid implicit–explicit solvent model). Hydrogen atoms (except for the moiety involved in NCIs) have been removed for the purpose of clarity.

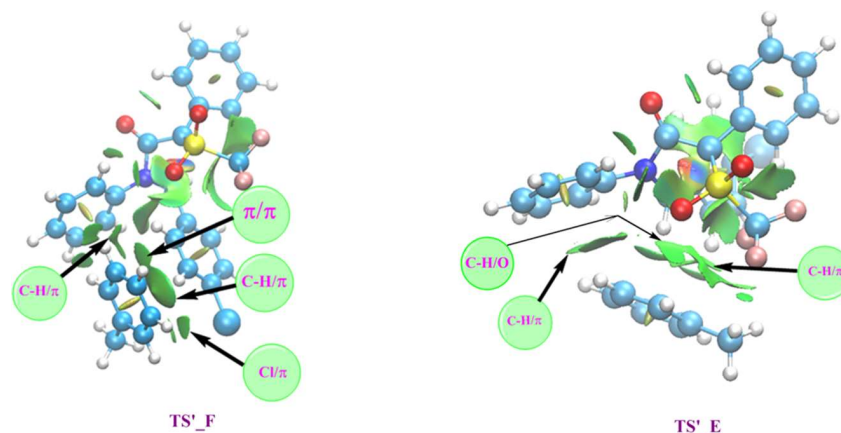


Figure 8. NCI plot for diastereoselective transition states Ts'_F and Ts'_E , where NCIs between toluene and the substrate have been shown.

($\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$) was then determined, and the values, $\Delta\Delta E^\ddagger = 2.5 \text{ kcal/mol}$ and $\Delta\Delta G^\ddagger = 2.4 \text{ kcal/mol}$, showed that the presence of the explicit solvent molecule created an important difference at this rate-controlling step, thereby leading to the experimentally observed diastereoselectivity. The reason for this preferential difference in the transition states was determined, as in the earlier section, through the NCI plot analysis, which showed that C–H/ π , Cl/ π , and π – π NCIs were present in the transition state Ts'_F , which caused the preferential formation of the major diastereomer (see Figure 8). In contrast, only C–H/ π and C–H/O NCIs were seen to be present in the transition state Ts'_E , and this caused it to become the minor diastereomer (Figure 8).

3.2.2. Case (II). Achieving Diastereoselectivity of the Staudinger [2 + 2] Cycloaddition Reaction in the Presence of Two Explicit Solvent Molecules (Toluene). To see the effect of solvent–solvent interactions on the stereoselectivity of the

Staudinger reaction, we have included another toluene molecule that would interact through π – π stacking with the first toluene molecule in the stereo-controlling transition states. To minimize the repulsion between the CH_3 groups, the orientation of the two toluene molecules has been kept such that the CH_3 groups are at a maximum distance (see Figure S17 in the Supporting Information). Calculations reveal that the relative electronic energy barrier ($\Delta\Delta E^\ddagger$) is increased in this case to 3.3 kcal/mol from 2.5 kcal/mol in the presence of one explicit toluene molecule. Because we have not obtained a single negative frequency in both the competing transition states in the frequency calculations, the relative free energy barrier ($\Delta\Delta G^\ddagger$ value) has not been calculated. The obtained negative frequencies corresponding to the correct normal mode, as well as the extra negative frequencies, have been provided in the Theoretical Structures Section in the Supporting Information (see Ts_I and Ts_H). It is to be

noted that the additional negative frequencies are quite small, in the range of -5.0 to -42.0 cm^{-1} , and are the result of numerical inaccuracies. In other words, the obtained transition states are correct, and the $\Delta\Delta E^\ddagger$ value is reliable. Nevertheless, because the presence of the additional negative frequencies could affect the $\Delta\Delta G^\ddagger$ value, the $\Delta\Delta G^\ddagger$ value has not been reported. The determined $\Delta\Delta E^\ddagger$ value indicates that solvent–solvent interactions do not reduce the effect of C–H/ π interactions between the solvent and substrate in the Staudinger reaction.

We note that the calculations discussed here do not include a large number of explicit solvent molecules, creating a solvent shell around each species. The reasons for this are two-fold: (i) determining the transition states for such enlarged systems is prohibitively expensive and thus beyond the scope of the current work and (ii) it is likely that the addition of only a few molecules (or only a single solvent molecule) would suffice to take fully into account explicit NCIs with the substrate. This is based on the fact that previous computational investigations have reported that calculations in the presence of a few explicit solvent molecules corroborate well with the experiment.^{34,35,43} Moreover, calculations with the hybrid explicit–implicit solvent model have been considered to be more accurate than those with the implicit model. Truhlar and coworkers, for instance, have reported that the inclusion of a single explicit water molecule in the calculations of pKa values shows good agreement with the experiment.⁶⁴ Furthermore, Riveros and coworkers have demonstrated that the addition of explicit solvent molecules improves the calculations of pKa values.⁶⁵ We would also like to point out that, in order to validate our results for both cases (a) and (b), we have also performed single-point energy calculations at a different level of theory ($\Delta\Delta E^\ddagger$ at TPSSH-D3/TZVP, def2-TZVP(Sn)//M06-2x-D3/TZVP, def2-TZVP(Sn) and $\Delta\Delta E^\ddagger$ at TPSSH-D3/TZVP, def2-TZVP(Sn)//B3-lyp-D3/TZVP, def2-TZVP(Sn)) and obtained the relative energy barriers of the intramolecular carbonyl-ene and the [2 + 2] cycloaddition Staudinger reactions at these levels of theory. The values are provided in the Supporting Information in Tables S1 and S3, respectively, and show the same trends as those observed and discussed in the two sections above.

4. CONCLUSIONS

The current computational study attempts to explore the following idea: whether NCIs between explicit solvent molecules and substrates being the major cause of stereoselectivity is a more general phenomenon than previously considered. This has been investigated by considering two important, diverse organic reactions: the intramolecular carbonyl-ene and the Staudinger reaction, respectively. Calculations reveal that the inclusion of explicit solvent molecules leads to the experimentally observed diastereoselectivity in both the cases. It has been demonstrated that in both the reactions, C–H/ π , Cl/ π , C–H/O, and π – π NCIs between the solvent and substrate are the major reason for the high diastereoselectivity. Furthermore, the NCI plot analysis suggests that the stability of the transition states depends on the number of NCIs present in the system; that is, transition states that lead to the formation of the major diastereomer are more stable because of additional NCIs, in comparison to transition states corresponding to the formation of the minor diastereomers. The results, therefore, suggest that there are likely to be several other stereoselective reactions where there

is a vital, explicit role of the solvent in controlling the stereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jpca.0c05738>.

The input and output structures, details of linear transit calculations for the E–F isomerization, and the XYZ coordinates of the optimized structures (PDF)

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Notes

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