Chapter 1

Addition reactions

A general introduction about the mechanistic aspects of various addition reactions is presented. A detailed survey of literature along with the objectives of this thesis is stated in this chapter.

1.1 Introduction

An accurate preview of the mechanistic pathway of any chemical reaction can be made possible through a deep insight into the chemical structures of the reactant, product, transition state and intermediate of that reaction. A precise knowledge of molecular structure can be obtained through quantum mechanical calculations. All such calculations are made possible through efficient computer programs and the credit of the development of such quantum computational packages goes initially to J. A. Pople. However chemical reactions take place at lightning speed. In a fraction of millisecond, electrons jump from one atom to another. It is virtually impossible to experimentally map every little step in a chemical process. Here comes the worth of theoretical study. Today the computer is an important device for chemists. A qualitative interpretation of any reaction mechanism can be bridged with an actual happening or experimental findings through a high-degree of accurate quantification of electronic structure parameters such as electronic energy, charge density, potential energy surface etc. Results of theoretical analysis is found complementary with the information obtained by chemical experiments in most of the cases, even it can in some cases predict hitherto unobserved chemical phenomena. Simulations are so realistic that they predict the outcome of traditional experiments. Even so it can be used to design synthetic pathways to new compounds.

1.2 Addition Reaction: Definition & Types

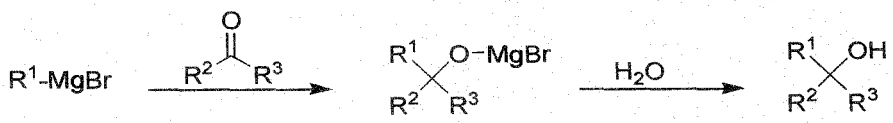
Among a variety of reactions, we choose to study the addition reactions. In an addition reaction two or more molecules combine to form a larger one. There are basically four ways by which addition reaction can take place and on that basis it can be categorized as (A) Electrophilic addition (B) Nucleophilic addition (C) Free radical addition (D) Concerted addition.

In electrophilic addition reaction first step involves the formation of an intermediate cation that arises from the reaction of a positively charged species or positively polarized reagent with a multiple bond and the second step is a combination of the resulting intermediate with a species carrying an electron pair and often bearing a negative charge. In nucleophilic addition reaction a

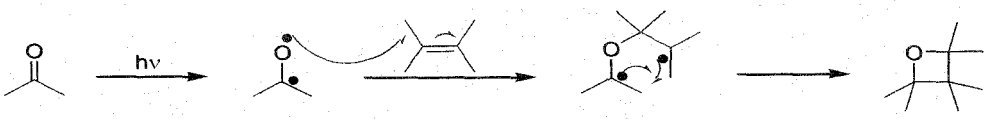
nucleophile brings its pair of electrons to one carbon atom of the double or triple bond, creating a carbanion in the first step and the second step is the combination of this carbanion with a positive species. Radical addition reactions involve the addition of a reactive species with an unpaired electron (radical or free radical) to a multiple bond to give an intermediate that also has an unpaired electron. Radical addition reactions are chain reactions. That feature makes them mechanistically unique from other addition reactions. In case of last one i.e., concerted addition reaction, the mechanism is somewhat different because here the addition of reagents to multiple bonds occur in a single step without ionic or radical intermediates. Representative examples of various addition reactions are given below:

(A) Electrophilic addition: Chlorination reaction

(B) Nucleophilic addition: Addition of Grignard reagent to carbonyl group



(C) Free radical addition: Paterno Buchi reaction



(D) Concerted addition: Diels-Alder reaction

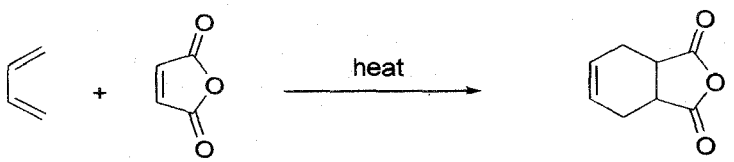


Figure 1.1: (A), (B), (C), (D) are the representative examples of addition reaction.

1.3 Background

Great deals of theoretical works in the investigation of the mechanistic aspects of various addition reactions are available in literature. Brief accounts of theoretical exertion are appended below.

1.3.1 Electrophilic Addition

Electrophilic addition across the olefinic double bond is a fundamental process in organic chemistry that has both theoretical value and far reaching synthetic applications. Oodles theoretical works have been performed on different electrophilic addition reactions.[1] Previously the mechanism of electrophilic addition of H^+, F^+, Cl^+, Br^+, ^+SR, ^+HgX, Ag^+ to ethylene was studied using extended Huckel molecular orbital calculations.[1a] The results correlate well with the experimental data and chemical intuition. Local hardness has been found to be a good selectivity descriptor for Markonikov addition to substituted alkenes.[1b] It is the only density functional descriptor which can predict the orientation of addition of hydrogen halides to mono substituted alkenes.

Control of regio- and stereo-chemistry, particularly in conformationally flexible acyclic systems, is of fundamental concern to rational synthesis design. Khan et.al.,[1c] have studied the regio- and stereo-chemistry of electrophilic attack on different allylic systems. They delineate the factors which control selectivity. The reactivity models have been found to provide a sensitive and unambiguous account of the preferred stereochemistry of electrophilic additions to double bonds. Assignment is based on direct evaluation of the relative affinities of diastereotopic olefin faces toward a test electrophile (H^+). From theoretical analysis it has been found that substitution of olefins with electron- releasing groups, e.g., methyl, not only enhances the overall activation toward electrophilic addition but also results in high regio- and stereo-selectivity. On contrary, electron-withdrawing substituents e.g., cyano deactivates the system and also reduces the selectivity.

The pyrimidine base, Cytosine (Cyt) is found both in DNA and RNA. In eukaryotic genomes, enzymatic methylation of cytosine results 5-methyl cytosine. Cytosine undergoes

protonation at one of the three plausible sites namely N3, O2 and N4 (Figure1.2) respectively. The mechanism for the effects of protonation and methylation of cytosine has been studied by Jin et.al, by means of CBS-QB3 and CBS-QB3/PCM methods.[1d]

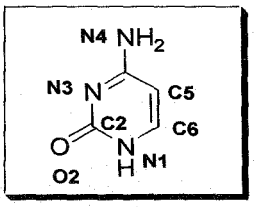


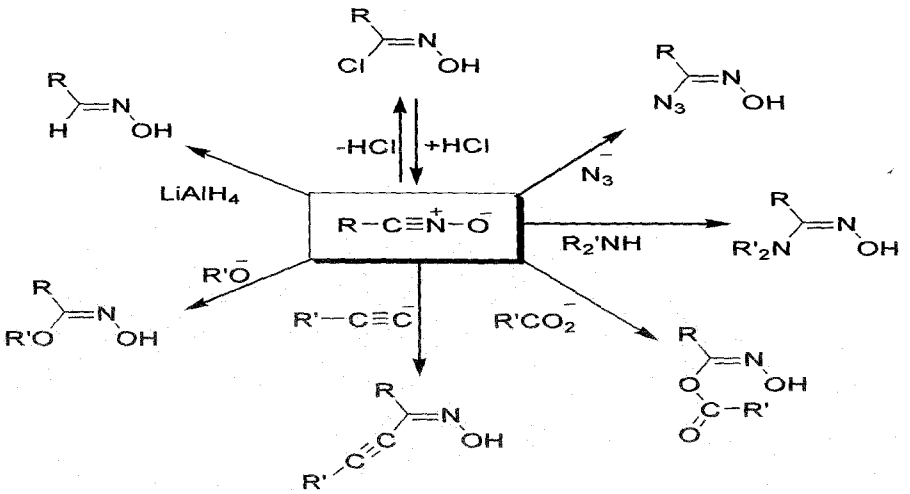
Figure 1.2 Structure of cytosine.

1.3.2 Nucleophilic Addition

Nucleophilic addition to carbonyl group is an elementary reaction in organic chemistry and biochemistry. Common examples include ester and amide hydrolysis, aldol condensation and numerous reactions of organometallic reagents and ylides. Plethora of theoretical investigations on various nucleophilic addition reactions are available in literature.[2] Among the earlier studies, important one is the exploration of the energy profiles for the nucleophilic addition of hydroxide ion to formaldehyde both in the in the gas and solution phase. The calculations were performed using ab initio method with the 6-31G* basis function and subsequently by Monte Carlo simulation.[2a] Later on, the effect of solvation was studied by integral equation theory.[2b]

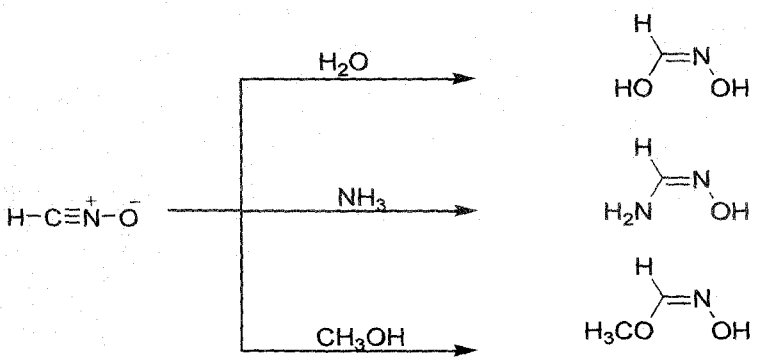
Nitrile oxides are versatile reagents used in organic synthesis. These can undergo a series of reactions with nucleophilic agents as shown in (scheme 1.1).

Scheme 1.1



Nguyen et.al, made an attempt to rationalize the stereospecificity of addition of neutral nucleophiles to nitrile oxides using ab initio method.[2e] They used the simple model reactions of water with the formonitrile oxide (HCNO) and with acetonitrile oxide (CH_3NO). From simulations they concluded that the reactions are concerted but highly asynchronous in nature. Subsequent mechanistic studies on the addition reactions of fulminic acid (HCNO) to water, ammonia, and methanol (Scheme 1.2) also confirm the one step mechanism of these reactions.[2d]

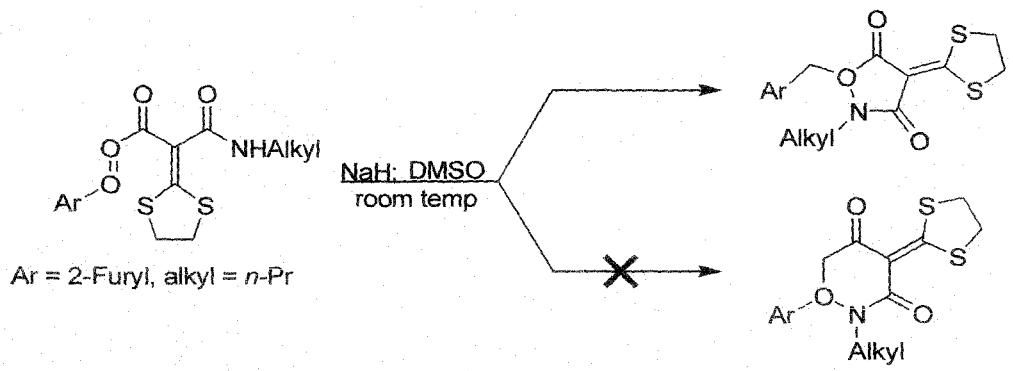
Scheme 1.2



The mechanism of the intramolecular nucleophilic addition of N-alkylfurylacryl acetamide has been investigated in the DFT based approach.[2g] Three possible reaction channels have been considered based on the possible conformations of the reactant, which endures in three

stages hydrogen elimination, followed by the nucleophilic addition via an anti-Michael (Michael) mechanism and then proton transfer. The calculations show that the pathway corresponding to the reactant with the most stable conformation is the most favorable one and accordingly anti-Michael addition is more favorable than the Michael addition pathway (Scheme 1.3), considering the solvent effect.

Scheme 1.3



1.3.3 Radical Addition

The mechanism of radical addition to alkenes is a subject of great interest. In basic chemistry it represents a fundamental bond forming process and in applied chemistry it is interesting as many polymerization reactions go via radical mechanism. Carbon-centered radicals are nucleophilic or electrophilic species, depending upon the substituent at the radical center. Electron-donating substituents like alkyl or alkoxy groups increase the nucleophilicity whereas electron-withdrawing substituents like ester or nitrile groups swell their electrophilic behavior.[3,4] Investigations for a variety of cases have shown that nucleophilic radicals approach the olefinic carbon atoms at angles between 104° and 108 °. Geometry of transition states for the addition of the methyl radical to ethylene at the UHF/6-31G* level is shown in Figure 1.3.[5]

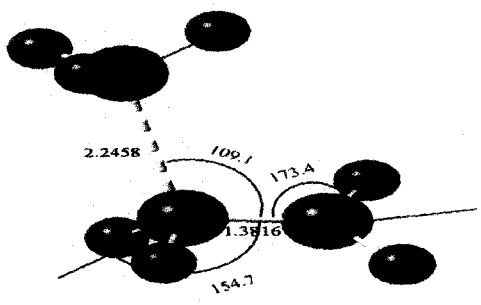
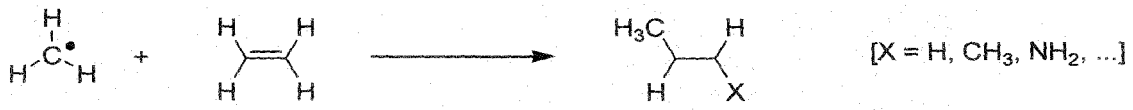


Figure 1.3 Geometry of transition state for the addition of the methyl radical to ethylene.

The rate of additions of radicals to alkenes is governed by a complex interplay of polar, enthalpy and steric effects.[6] However, establishing the relative importance of these factors in specific case is quite difficult.[7,8] Wong et.al., have performed theoretical investigation on the addition reactions of methyl radical with a series of substituted alkenes (Scheme 1.4).[9]

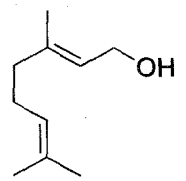
Scheme 1.4



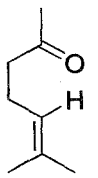
They reach the imperative conclusion that polar contributions to the reactivity of the methyl radical toward alkenes are insignificant and the reaction exothermicity is the foremost influencing factor. From the ab initio study (QCISD/6-311G*+ZPVE) on the addition of different radicals ($CH_3^{\cdot}$, $CH_2OH^{\cdot}$, $CH_2CN^{\cdot}$ and $(CH_3)_3C^{\cdot}$) to the substituted alkenes CH_2=CHX (X=H, NH_2, F, Cl, CHO, and CN) followed by curve crossing model analysis, it has been concluded that unlike the methyl radical, both polar and enthalpy effects are important for the latter three radicals.[10] The polar factor leads to tert-butyl radical displaying strong nucleophilic character which stabilizes the transition states by 20-25 KJ mol^{-1} compared with those for the relatively non polar reactions of methyl radical.

Natural emission of volatile organic compounds (VOCS) plays a major role in the atmospheric chemistry particularly in rural and remote areas. Vegetation is the most important source of these compounds. Terpenoids represent the most profuse VOCS emitted by plants.

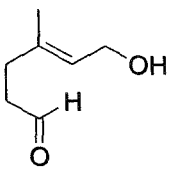
Trans-geraniol (1), 6-methyl-5-hepten-2-one (2), and 6-hydroxy-4-methyl-4-hexenal (3) (Figure 1.4) are such worth mentioning terpenoids.



1
(*E*)-3,7-dimethylocta-2,6-dien-1-ol



2
6-methylhept-5-en-2-one



3
(*E*)-6-hydroxy-4-methylhex-4-enal

Figure 1.4 Structures of different terpenoids.

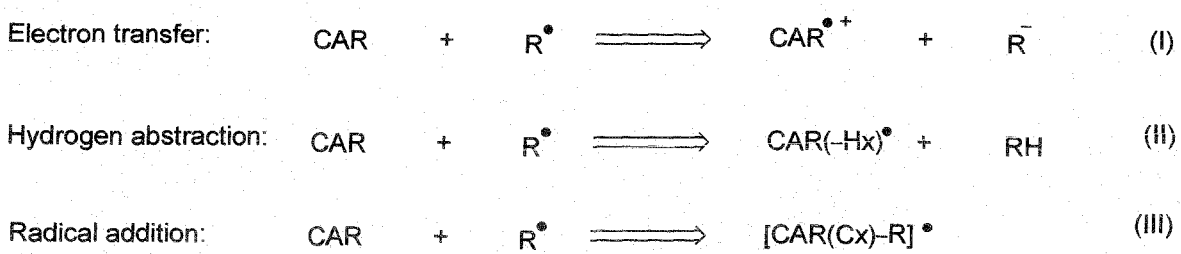
The primary degradation pathways of these terpenoids (1, 2 & 3) involve reaction with OH radicals, NO_3 radicals and ozone. A combined density functional and transition state theory approach has been employed to investigate the gas phase addition reaction of OH radical to trans geraniol (**1**), 6-methyl-5-hepten-2-one (**2**), and 6-hydroxy-4-methyl-4-hexenal (**3**).[11] All different possibilities for the addition of the OH radical to the C-C double bonds have been considered. The rate coefficients obtained from theoretical investigation are in good agreement with the available experimental data.

The addition reaction of alkyl radicals to multiple bonds is of fundamental importance as a carbon-carbon bond forming reaction. High level ab initio calculations have been performed for the addition of methyl radical to ethyne, propyne, ethane and propene.[12] These calculations confirm that these reactions are contra thermodynamic in nature, with addition to the alkenes being favored despite the alkyne addition having the greater exothermicity. It has been concluded that the greater barrier for addition to alkynes is primarily the result of larger singlet-triplet gap in the substrate. The barrier raising effect dominates the barrier lowering effect of the reaction exothermicity.

In recent years, epidemiological evidence has been reported which supports a protective effect of carotenoids in the development of chronic diseases, especially cardiovascular ones and in cancer. These diseases seem to have their origin in the oxidative damage of biological tissues

due to the action of free radicals. For this reason it has been suggested that antioxidant like β-carotene may play an important role in their prevention. A theoretical study of the reaction of β-carotene with nitrogen dioxide radical in solution was carried out using DFT method at the B3LYP/6-31G(D) level and polarizable continuum model (PCM) to account for the solvent effect.[13] Three feasible reaction mechanisms (Scheme 1.5) electron transfer, hydrogen abstraction and radical addition were considered. From these calculations it is apparent that in

Scheme 1.5



non polar solvents like heptanes, the reaction takes place simultaneously through hydrogen abstraction mechanism. This therefore supports on theoretical grounds the experimental observation of 4-nitro-β-carotene as an oxidation product of degradation of β-carotene by cigarette smoke in non polar environments.

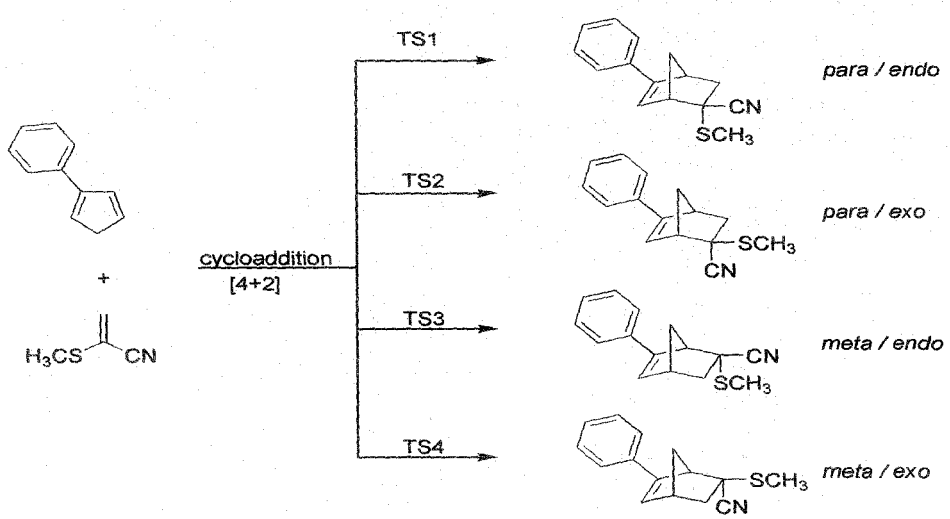
1.3.4 Concerted Addition

Concerted addition is a class of chemical reaction where all bond breaking and bond making processes occur in a single step without any radical or ionic intermediate. Cycloaddition, a variety of pericyclic reaction is an important example of concerted addition. It is an excellent technique for the carbon-carbon bond forming process in synthetic organic chemistry. The reaction proceeds through cyclic transition state. The energy necessary to attain the transition state is usually provided externally either thermal or photochemical activation of the reactants. Theoretical explorations of these reactions are avowed categorically as follows:

1.3.4.1 (4+2) Cycloaddition

The Diels-Alder reaction remains one of the most useful approaches to cyclic organic compounds in terms of regio control and simplicity. Furthermore, the introduction of hetero atoms in the dienophile or diene or in both of them presents a powerful tool for the preparation of a wide variety of heterocyclic compounds. Extensive theoretical investigations have been performed on Diels-Alder reaction.[14] Ab initio calculations for the Diels-Alder reaction between 2-phenylcyclopentadiene and α-(methylthio)acrylonitrile (Scheme 1.6), show the existence of four transition structures on the potential energy surface corresponding to the formation of para/endo, para/exo, meta/endo and meta/exo adducts.[14d] The formation of the para adducts takes place with smaller energy barriers than the formation of the meta products. However the theoretical prediction correlates well with the observed experimental data.

Scheme 1.6



The Diels-Alder reaction of cyclopentadiene and acrolein in a model room temperature ionic liquid ([mmim][PF_6]) has been investigated with the help of KS-DFT/3D-RISM-KH theory.[14c] It has been calculated that the ionic liquid can distort noticeably the transition state geometry, inverting the order of frontier orbitals and leading to an enhancement of the asynchronicity of the reaction. This method of calculation has been found to be able to reproduce the experimental features, concerning the reaction rate and endo selectivity enhancement in ionic

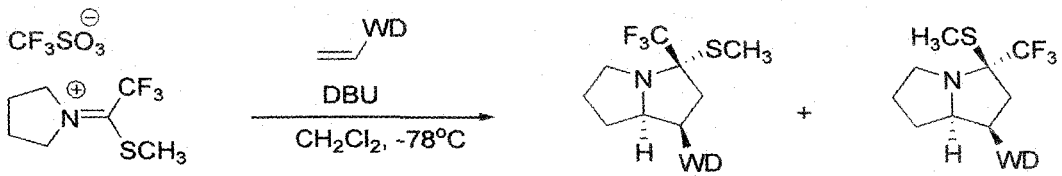
liquids. The rate acceleration is attributed to the free energy of solvation, which promotes aggregation of non ionic molecules in solutions. On the other hand, the endo selectivity enhancement is ascribed to the most favourable π–π interaction between the reactants in presence of ionic liquid.

1.3.4.2 (3+2) Cycloaddition

The cycloaddition of a 1, 3-dipolar species with dienophile for the synthesis of five membered rings is a classic reaction in organic chemistry. 1,3-dipolar cycloadditon (DC) is an important technique for the construction of five membered ring. This protocol is often used for the easy accesses of five membered heterocyclic compounds, complex natural products and bioactive molecules. Wide-ranging theoretical exertions have been performed on 1, 3-DC reactions. [15]

1, 3-DC reaction between trifluoromethyl thiomethyl azomethine ylide and acronitrile (Scheme 1.7) has been studied theoretically to explore the actual mechanistic pathway in DFT based approach.[15a] Relative rates, regioselectivity and endo stereoselectivity have been analyzed and discussed as a function of the substituents on dipole and dipolarophile fragments. Theoretical analysis shows that these reactions are single step processes having dissymmetric transition structures. Transition state energies are in full agreement with the stereochemical outcome.

Scheme 1.7

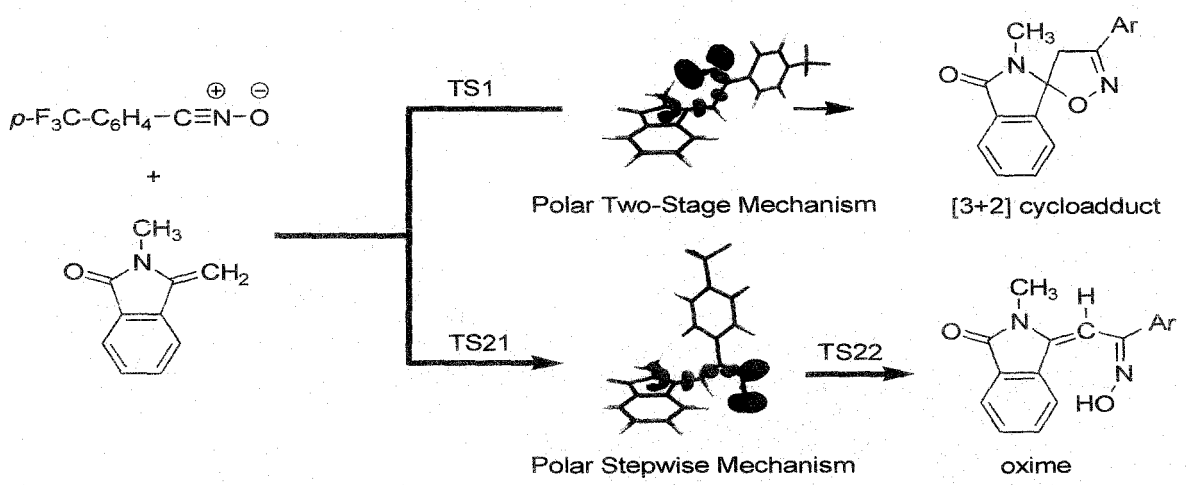


WD = -CN	96 : 4
$-CO_2CH_3$	95 : 5

DFT based study on the mechanism of electrophilically activated nitrile N-oxides with C-C double bonds show the existence of two competitive pathways (Scheme 1.8), one leading to

(3+2) cyclo-adducts and another to two isomeric (E)- and (Z)-oximes.[15c] The 1,3-dipolar cycloadditions take place through a concerted but highly asynchronous transition state, while the formation of the oximes is achieved through stepwise manner with the formation of zwitterionic intermediate. Both the 1, 3-DC reaction and oxime formation have effect through the nucleophilic attack of electron affluent C-C double bond of the dipolarophile to the electrophilically activated nitrile N-oxides. The electrophilicy index has been found to be an important tool in predicting the polar nature of the reactions.

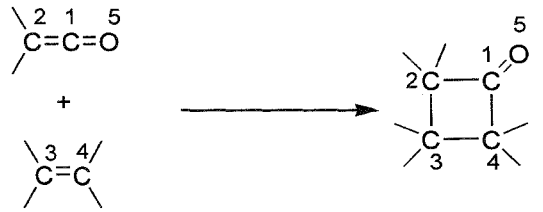
Scheme 1.8



1.3.4.3 (2+2) Cycloaddition

The cycloaddition reaction between ketenes and olefins leading to cyclobutanones (Scheme 1.9) has been studied by means of both the semiemperical and ab initio methodologies.[16] The reaction is found to be concerted in all but in few cases, it takes place through twisted transition states with small charge transfer from the olefin to the ketene. Theoretical analysis shows that the reaction is of the 2+2+2 type rather than $[\pi 2_s + \pi 2_a]$ one. Effects of both ketene and olefin substituents on the energetic, regioselective and stereoselective aspects of the reaction have been studied thoroughly.

Scheme 1.9



1.3.4.4 (1+2) Cycloaddition

Carbenes are mechanistically important as well as synthetically useful intermediates. They react with olefins to form cyclopropane. Theoretical analysis of the mechanistic aspects of (1+2) cycloaddition reactions have been performed in ab initio methodology.[17] The reaction between singlet and triplet methylene with benzene and related aromatic compounds has been investigated by kinetic isotope effects, solvent effects and product studies.[17c] Mechanistic study shows the existence of two distinct reaction pathways for the singlet and the triplet species. For the triplet reaction the proposed intermediate (Figure 1.5) has been detected by ab initio UMP2/6-31G*//UHF/6-31G* calculations, however no stable singlet intermediate has been found. These surveillances are consistent with other carbene addition reactions.

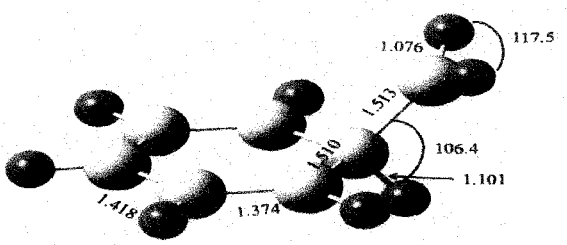


Figure 1.5 Intermediate calculated for the triplet reaction.

Careful investigation on the reaction pathway and transition state geometries of unsaturated carbene-olefin reactions [addition of unsymmetrical alkylidenecarbenes $R(CH_3)C{=}C{:}$, where R=Et, i-pr, t-Bu, to two unsymmetrical olefins, isobutylene and tert-butylethylene] reveals an interesting fact that in all cases, E adduct predominates over the Z

adduct, with increasing stereo-selectivity being observed upon going from R=Et to R=t-Bu in the carbene.[17b]

1.4 Objectives of the Thesis

Theoretical calculations are very helpful tools in understanding the chemistry of reactions. Careful use of computer modeling can help in predicting or optimizing various physical and chemical parameters which determine reaction conditions. Simulations are not a replacement for conventional experiments but it can be used to prop up the experimental results. However the most important role of computer simulations is their use as a predictive tool in a chemical reaction. The ability to predict the outcome of a reaction provides large savings in time and economy. Keeping these factors in mind, the present thesis is aimed to cultivate the objectives, which are affirmed as follows:

(1) We investigate the mechanistic pathway of diprotonation and dimethylation of benzene and predict the stability of the possible isomers (Chapter 3 On Protonation and Methylation of Benzene: A B3LYP DFT Based Study).

(2) We also investigate the mechanistic pathway of an unexpected reaction and correlate the results well with the reported experimental findings (Chapter 4 DFT Based Study on the Mechanism of an Unexpected Reaction of Aldehydes with 1, 3- Dicarbonyl Compounds).

(3) We explore the accuracy and reliability of different Minnesota density functionals for the prediction of heat of formations and ionization potential values of various benchmarked transition metal complexes formed by addition reaction (Chapter 5 Performance of the widely used Minnesota density functionals for the prediction of heat of formations, ionization potentials of some benchmarked first row transition metal complexes).

(4) We investigate the regioselective addition of nitronium ion to 4-quinolones using DFT based reactivity descriptors and validate the results by experimental surveillance (Chapter 6 Regio-

selective/Regio-controlled nitration of 4-quinolones: Convergence of theoretical and experimental findings).

1.1 References and notes

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