**KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY**

**KUMASI-GHANA**

**COLLEGE OF SCIENCE**

**DEPARTMENT OF CHEMISTRY**

INVESTIGATION OF THE MECHANISM OF FORMATION OF NITRO-SUBSTITUTED NICOTINE ANALOG VIA THE (3 + 2) CYCLOADDITION REACTION OF (E)-SUBSTITUTED NITROETHENE DERIVATIVES AND *C, N*-DISUBSTITUTED PYRIDINYL NITRONES: A DENSITY FUNCTIONAL THEORY STUDY

**BY**

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**SEPTEMBER, 2021**

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A Thesis Submitted to the Department of Chemistry, Kwame Nkrumah University of Science and Technology in Partial Fulfillment of the Requirements for the Degree of BSc. (Hons) in Chemistry

**BY**

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**&**

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# DECLARATION

I, Appiah Oscar, hereby declare that this submission is my own work towards BSc. Degree in Chemistry and that, to the best of my knowledge, it contains neither material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

Appiah Oscar ……………………. …………………….

(Candidate) Signature Date

Certified by:

Richard Tia, PhD ……………………. …………………….

(Supervisor) Signature Date

Certified by:

Evans Adei, PhD ……………………. …………………….

(Supervisor) Signature Date

# DEDICATION

I dedicate my dissertation work to my lovely parents, Mr. Sampson Appiah and Mrs. Comfort Appiah for their unflinching love and support towards my academic carrier. May the good lord continue to bless them in all their endeavors.

# ACKNOWLEDGEMENT

I am grateful to the Almighty God for how far he has brought me by showering his abundant grace, protection, good health and extreme guidance upon me throughout my education. I also express my heartfelt gratitude to my family, both near and afar for their love and support through this phase of my life. I say a very big thank you to them for their immense contribution, encouragement and guidance during the entire period of my research. For my supervisors: Dr. Richard Tia and Prof. Evans Adei, I can’t thank them as much for the great work done on me. I thank them for challenging me to think further, work harder, dream bigger and pushing me to the edge in getting this work done. I don’t think people say thank you to teachers often enough. Thank you for the doors you have opened for me, I am very grateful.

Finally, I would like to appreciate my group mates. I would not have made it this far without their help and encouragement. God richly bless you all.

# ABSTRACT

Nitro-substituted nicotine analogs have important biological activities, and thus several methods have been investigated for their synthesis. The formation of nitro-substituted nicotine analogs via the (3 + 2) cycloaddition (32CA) reaction of (E)-substituted nitroethene derivatives and *C, N*-disubstituted pyridinyl nitrones have been investigated using Density functional theory (DFT) at the B3LYP-D3/6-311G (d, p) level of theory. The results show that the reaction leads to the formation of the 4-nitro substituted *exo* isoxazolidine nicotine analog (**P2A**). The addition of the (E)-substituted nitroethene derivatives to the *C, N*-disubstituted pyridinyl nitrone exhibits a high degree of regio-and stereoselectivity. Electron-withdrawing and -donating groups substitution on both the (E)-substituted nitroethene derivatives (**A1**) and *C, N*-disubstituted pyridinyl nitrone (**A2**) increase the activation barriers relative to the parent reaction but the energetics trend remains the same throughout. Global reactivity indices calculations have shown that the most electrophilic reactant in this reaction is the alkene while the three-atom component is the nucleophile, hence decreasing the electron density on the alkene increases its electrophilicity whereas increasing the electron density on the nitrone increases its nucleophilicity.

**Keywords**: Three-atom component; alkene; nitro substituted nicotine analog; nitroethene; nitrone

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# CHAPTER ONE

# INTRODUCTION AND LITERATURE

## 1.1 Nicotine

Nicotine is a major alkaloid found in the tobacco plant possessing a pyridine group and a pyrollidine group [1]. It has a diverse set of biological and pharmacological activities, making it more attractive for use in medicine [2]. It is used in the treatment of Alzheimer’s and Parkinson’s disease [3,4]. Nicotine is a biodegradable compound, making it an ecologically friendly component of plant protection products [5]. Due to its biological activities, there has been a development of interest in their study. Concerns about the potentially harmful effects of nicotine on biological system brought about the study of nicotine analogs which mimics the effects of nicotine on biological systems but with less harmful effect [6]. There is and have also been several investigations into its analogs in an attempt to reduce its potency or enhance it [7]. Nicotine analogs (derivatives) are primarily synthesized by 32CA reactions [8].



The (3 + 2) cycloaddition (32CA) reaction is a very popular cycloaddition strategy for the synthesis of five-membered heterocycles [9]. 32CA reactions are a classic synthetic organic chemistry reaction that yields regio-and stereochemically specific heterocycles that are essential to both academia and industry. These reactions are electrophilic and nucleophilic in nature, and the reaction route is regulated by dipole and dipolarophile substituent effects [10].

## 1.1.1 (3 + 2) Cycloaddition reactions

Because of their ability to produce regio- and/or stereoselectively cyclic motifs with organic compounds, cycloaddition reactions are among the most valuable organic reactions in the synthetic organic chemist's toolkit [11]. They are reactions in which two π-bonded molecules react to form a new cyclic molecule with the formation of two new σ bonds. The 32CA reaction, a reaction between a 1,3-dipole and a dipolarophile, resulting in the formation of a five-membered ring, is an important member of this class of reactions [12]. The 32CA reaction may produce highly complex heterocycles with numerous stereogenic centers from simple starting materials. As a result, this reaction is frequently utilized as a critical step in the synthesis of numerous natural products and pharmaceuticals. The 32CA reaction may produce highly complex heterocycles with numerous stereogenic centers from simple starting materials. As a result, this reaction is frequently utilized as a critical step in the synthesis of numerous natural products and pharmaceuticals [12]. Because of its powerful ability to effectively produce different five-membered heterocycles such as isoxazolidines, 32CA reactions have grown in popularity and applicability [13,14]. The 32CA reactions do not involve other reagents except for 1,3-dipoles and dipolarophiles.



**Scheme 1.1**: (3 + 2) cycloaddition reaction

## 1.1.2 1,3 dipoles and nitrone as 1,3 dipole

A 1,3-dipole is a system of three atoms over which are distributed four π electrons. Nitrogen, carbon, oxygen, and sulfur are the most frequent atoms found in 1,3-dipoles. The 1,3 dipoles are generally classified into two; the allyl anion and allenyl anion type. The allyl anion type has four electrons in three parallel Pz orbitals perpendicular to the plane of the dipole and it is bent. The allenyl anion type has an extra π orbital located in the plane orthogonal to the allenyl anion type molecular orbital (MO) and it is linear [15]



**Figure 1****.1: Classification of 1,3-dipoles**

1,3-dipoles containing various combinations of carbon and hetero atoms are theoretically possible and Huisgen classified eighteen possibilities of 1,3-dipoles into allyl and propargyl type as shown below.



**Figure 1.2****: Various possible forms of 1,3 - Dipoles**

Nitrones, which are basically organic molecules consisting of an N-oxide of an amine, are synthetically effective 1,3-dipoles. They can exist as either a cyclic or an acyclic molecule. Among the rationale behind the successful synthetic utilization of nitrones is that, unlike other 1,3-dipoles, nitrones are stable compounds that do not need to be prepared in situ, readily available and easy to handle. Nitrone cycloaddition to olefins is one of the most functional conventions for the construction of isoxazolidine where the dipolarophiles are usually alkenes, whereas dipoles are represented by suitable nitrones [14] as shown in figure 1.3.



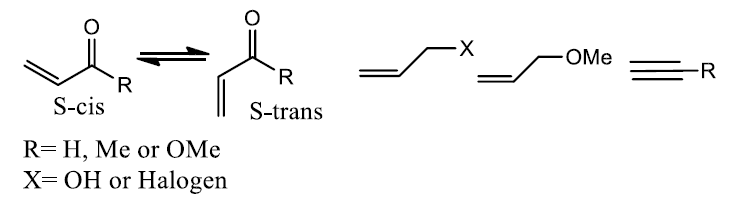
**Figure 1.3****: Nitrone cycloaddition reaction**

The reaction presents three types of selectivity: regioselectivity, diastereoselectivity and enantioselectivity and their prediction, is realized through an analysis of steric and electronic factors, but most importantly through the frontier molecular orbital (FMO) theory [14]. The regioselectivity is controlled by both steric and electronic effects and, generally, in the cycloadditions of electron-rich or electron-neutral alkenes with nitrones, the 5-substituted isomer is obtained with respect to the 4-sustituted isomer. The nitrone can also approach in an endo or an exo mode to yield two different diastereomers. The endo/exo selectivity in the 32CA reaction is primarily controlled by the structure of the substrates or by a catalyst. However, in reaction in which the nitrone can undergo Z/E interconversion, the endo/exo assignment of the products is opened to more than one interpretation and as such, the definition of cis or trans is used. The use of a chiral catalyst is employed as a factor for the control of the enantioselectivity.

## 1.1.3 The dipolarophile and nitroethenes as a dipolarophile

Dipolarophile like a dienophile in Diels Alder reaction is a reactive alkene or alkyne containing 2π electrons. Therefore, α, β-unsaturated aldehydes, ketones, esters, allylic alcohols, allylic halides, vinylic ethers, and alkynes readily act as good dipolarophiles (Fig.1.4). The alkene moiety may

contain mono-, di-, tri- or even tetra-substituents but due to steric factors, tri- and tetra-substituted alkenes often display very low reactivity in reactions with dipoles.



**Figure 1.4****: Representation of some dipolarophiles**

Alkenes activated by a powerful electron withdrawing group such as the nitro group are versatile substrates and intermediates in a variety of transformations in organic synthesis [16]. The use of nitroethenes as dipolarophiles in these reactions permits the synthesis of nitro-substituted isoxazolidines [17,18]. These can easily be further functionalized because of their unique tendency to convert the NO2 group into other functional groups [18].

In literature [19–21], 32CA reaction of pyridine substituted nitrone with (E)-substituted nitroethene yields very useful isoxazolidines analogs of nicotine, with complete regio-, enatio- and stereoselectivities.

Singh et al, 2005 [8] reported the development of an efficient route to a novel nicotine analog by reacting α-(3-pyridyl)-N-phenylnitrone (**1**) with several substituted alkenes (**2**) yielding the products **5**, **6** and **7** (scheme 1.2). Their results showed that reacting the nitrone with electron-rich alkenes favor the formation of the regio- and diastereomeric products **5** and **6** whereas withelectron-deficient alkenes the **7** is formed. They reported that this reversed regioselectivity is mostly observed in reaction of nitrones with highly electron-deficient alkenes such as nitroalkenes, however, the basis for this observation was not outlined [22].

**Scheme 1.2:** Reaction of α-(3-pyridyl)-N-phenylnitrone (**1**) with several dipolarophiles (**2**).



In 2019, Fryźlewicz et al [23] reported on the 32CA reaction of an electron-deficient alkene, (*E*)-3,3,3-trichloro-1-nitroprop-1-ene **(A)** with *N*-aryl(pyridin-3-yl) nitrones **(B)** under mild conditions (see scheme 1.3). They observed that the reaction was completely regio- and stereoselective leading to the formation of 4-nitro-substituted nicotine analog (**D**). As established, though this reaction provides a facile approach to a highly selective and efficient product outcome (nicotine analog) a systematic study to understand this unique reactivity is lacking.

**Scheme 1.3:** Reaction between (*E*)-3, 3, 3-trichloro-1-nitroprop-1-ene and *N*-aryl (pyridin-3-yl) nitrones



## 1.2 Problem Statement

This reaction provides routes to the regio- and stereo-selective synthesis of several synthetically and pharmaceutically important structures in organic and natural product chemistry. However, the factors controlling the regio- and stereo-selectivities and the impact of substituents on the reactivity and selectivities of the reactions have not been systematically studied.

## 1.3 Aims and Objectives

This work, therefore, aims at the detailed investigation of the reaction pathways for the reaction of *C, N*-disubstituted pyridinyl nitrones and (E)-substituted nitroethenes to address the particular concerns mentioned above using density functional theory (DFT). The study is based on Scheme 1.4 which illustrate the various regio-and stereo-selectivities explored.

## 1.4 Justification

This will help rationalize this unique reactivity pattern seen with the reaction of electron-deficient alkenes with nitrones for the formation of nicotine analogs. This study will also provide a rationalization to the experimental result that was obtained.

**Scheme 1.4**: Proposed scheme for the reaction of (E)-substituted nitroethene derivative (A1) with *C, N*-disubstituted pyridinyl nitrone (A2)



# CHAPTER TWO

## 2.0 COMPUTATIONAL DETAILS AND METHOD

All computations were carried out with the Spartan'14 [24] and Gaussian 09[25] Molecular Modelling programs, employing density functional theory (DFT) at the B3LYP-D3/6-311G(d, p) level of theory. The B3LYP is a gradient-corrected functional of Becke, Lee, Yang, and Parr for exchange and correlation. The B3LYP functional is a Hartree-Fock DFT hybrid functional which has been the bedrock of quantum chemical studies on organic molecules over the years [26]. The B3LYP functional studies the organic reactions which proceed with low energy barriers [27] best, as it avoids the problems of records of near-negative activation barriers such as hybrid gradient approximation functionality M06-2X [28]. The D3 dispersion correction energy term added retains the features of B3LYP/6-311G(d, p), a well-known hybrid density functional approximation combined but at the same time it seeks to avert the challenges of missing London dispersion effects and basis set superposition error as compared to B3LYP without the dispersion correction term which does not take those challenges into consideration [29].

Molecules (input structures) were built and minimized interactively using a suitable molecular mechanics force field utilizing Spartan's graphical user interface. The geometries were then fully optimized without any restrictions. Toluene, benzene, and nitromethane were utilized in computing for solvation effects in the reaction using the polarizable continuum model (PCM) [30].

Transition state structures were computed by first obtaining guess input structures. This was accomplished by constraining the molecules' internal coordinates (bond lengths, bond angles, dihedral angles) while fully optimizing the remaining internal coordinates. This technique generates suitable guess transition state input geometries, which are subsequently submitted for complete transition state computations without any geometry or symmetry constraints.

Full harmonic vibrational frequency calculations were performed to ensure that each transition state structure had a Hessian matrix with just one negative eigenvalue, defined by an imaginary vibrational frequency along the relevant reaction coordinates. Within the Gaussian 09 molecular modeling package, the default self-consistent field (SCF) convergence conditions (SCF=Tight) were utilized [31]. Intrinsic reaction coordinate calculations [32,33] were then performed to ensure that each transition state smoothly connects the reactants and products along the reaction coordinate [34–37]. CYLview was used to display the optimized structures [38].

The rate constants of the reaction at a 25ºC [k(T)] were calculated using equation (1) [39]:

(1)

where kB = 1.380662 × 10-23 J/K, T **=** 298.15 K, h **=** 6.62617 × 10-34 Js, R **=** 1.987 cal/mol, c **=** 1.ΔǂG∘ is Gibbs free energy of activation.

The global reactivity indices of the various transition states were calculated using equations (2) and (3) and the results are shown in Table 3.6 and 3.7. The electrophilicity index has been used as a parameter for the analysis of the chemical reactivity of molecules. It is a measure of the ability of a reaction substrate to accept electrons [40] and is a function of the electronic chemical potential, μ, and chemical hardness, η, as defined by Pearson’s acid-base concept [41]. Species with large electrophilicity values are more reactive towards nucleophiles. The nucleophilicity index [42] of the various reagents is calculated using Eq. (3). The scale of nucleophilicity is made in reference to tetracyanoethylene (TCE) [43]. It is important to note that these equations are based on Koopmans theory [44] which was originally developed for calculating ionization energies from closed-shell Hartree–Fock wave functions, but have since been adopted as acceptable approximations for computing electronic chemical potential and chemical hardness.

ω = μ2/2η (2)

N= EHOMO(Nuc) – E HOMO(TCE) (3)

where µ = (EHOMO + ELUMO)/2 and η = (EHOMO - ELUMO).

EHOMO(TCE) = -9.120689505 eV

The N parameter measures the nucleophilicity whiles ωparameter measures the electrophilicity. Thus, species with large ω values would be excellent electrophiles and species with high values of N would be excellent nucleophiles.

# CHAPTER THREE

## 3.0 RESULTS AND DISCUSSION

From scheme 1.4, two regioisomeric paths are possible. Path A arises from the addition of the C-N-O bond of the nitrone **A2** across the olefinic bond of the alkene **A1** to afford the diastereomers **P1A** and **P2A** through transition states **TS1A** and **TS2A** respectively where the nitro-substituted carbon of **A1** bonds to the pyridine-substituted carbon of **A2**. The pyridine group of the three-atom component can be *anti* to the nitro group of the alkene as seen in **P1A** or *syn* as seen in **P2A**. Path B arises from a preferential addition of oxygen of the nitrone **A2** to the nitro-substituted carbon of **A1** leading to the formation of the diastereomeric cycloadducts **P1B** and **P2B** through transition states **TS1B** and **TS2B** respectively. **P1A** and **P2A**, and **P1B** and **P2B** are regioisomers respectively.

All the energies reported herein are Gibbs free energy with zero-point energy correction.

## 3.1 Analysis of the parent reaction between (E)-substituted-nitroethene (A1) and *C, N*-Disubstituted-pyridinyl nitrone, (A2, R2 = Phenyl and R3 = H).

The mechanism and selectivities of the 32CA reaction involving (E)-substituted-nitroethene (**A1**, R1= CCl3) and *C, N*-disubstituted-pyridinyl nitrone (**A2**, R2= phenyl and R3 = H) are discussed in this section. **Figure** **3.1** depicts the Gibbs free energy profile for the 32CA reaction of (E)-substituted-nitroethene (**A1**, R1= CCl3) with *C, N*-disubstituted-pyridinyl nitrone (**A2**, R2 = phenyl and R3 = H) in the gas phase and in the solvent phase (benzene). Gas phase results are shown in parenthesis in figure 1. **Table** **3.1** shows the rate constants for the formation of the cycloadducts as shown in scheme 1.4 for the 32CA reaction involving (E)-substituted-nitroethene (**A1**, R1= CCl3) and *C, N*-disubstituted-pyridinyl Nitrone (**A2**, R2= Phenyl and R3 = H) in both gas phase and solvent phase (benzene)

From figure 3.1, for the solvent phase, the reaction pathway that proceeds to generate the *exo*-cycloadduct **P2A** has the lowest activation energy of 0.3 kcal/mol via transition state **TS2A**, hence emerging as the preferred route. The closest competing path is the formation of **P1B** through **TS1B** with an activation barrier of 3.3 kcal/mol. The reaction of (E)-substituted-nitroethene (**A1**, R1= CCl3) with *C, N*-disubstituted-pyridinyl nitrone (**A2**, R2= Phenyl and R3 = H) through transition state **TS2A** yields **P2A** with a rate constant of 2.21 x 1010 s-1, which is about 1.66 x 102 faster than the competing pathway through **TS1B** yielding product **P1B**.

For **Path B**, the reaction through transition state **TS2B** leading to the formation of product **P2B** having an activation energy of 8.22 kcal/mol and a rate constant value of 5.85 x 106 in the solvent phase is the least kinetically favored route. Gas-phase calculation also follows the same trend. Comparing the activation barrier and rate constant value of **P2B** to the other cycloadduct, it could be seen that it has an activation barrier which is higher than all the other transition states and a rate constant which is the lowest of them all i.e. making it the least kinetically favored reaction route. **P1A** has an activation energy of 4.2 kcal/mol higher than its diastereomer of **P2A**. The activation energies for the addition of the C-N-O bond of the three-atom component to the olefinic bond of the alkene along Path **B** are very high in contrast to the activation energies of the **Path A** reaction route. The highly exergonic nature of the various cycloadducts makes them thermodynamically stable, hence making the reaction between **A1** and **A2** an irreversible reaction.

**Table 3.1**: Rate constants of the reaction (E)-substituted-nitroethene with N-Phenyl-C-pyridinyl-nitrone for the formation of the various cycloadducts computed in both gas phase and solvent phase (benzene) at room temperature. **R1** = CCl3, **R2 =** Phenyland **R3 =** H

|  |  |  |
| --- | --- | --- |
| **Products** | **Rate constants[k(T)]/s-1**  **Gas phase** | **Rate constants[k(T)]/s-1**  **Solvent phase (benzene)** |
| **P1A** | 3.07 x 109 | 7.43 x 108 |
| **P2A** | 3.87 x 1012 | 1.81 x 1012 |
| **P1B** | 2.21 x 1010 | 4.23 x 109 |
| **P2B** | - | 5.85 x 106 |

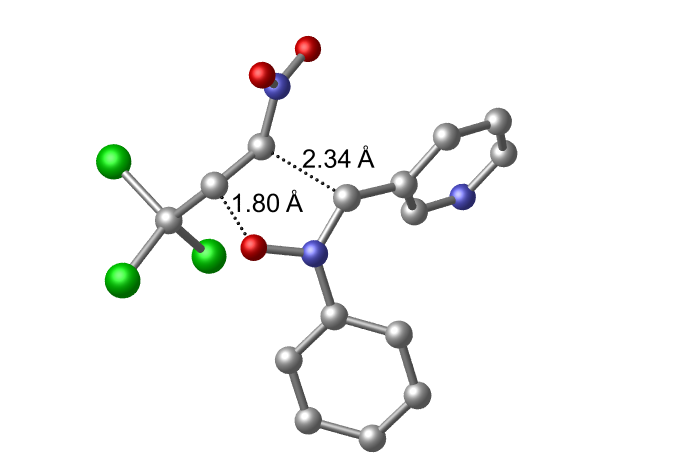
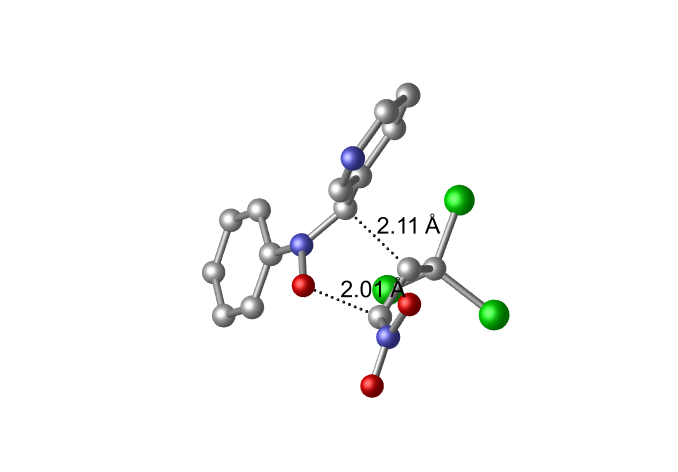
The barriers computed in the gas phase are slightly lower than those in the solution phase. From **Table 3.1**, for the solvent phase, it is seen that the formation of product **P2A** through transition state **TS2A** has the highest rate constant value of 1.81 x 1012. Comparing the rate constant of **P2A** to its competing cycloadduct **P1B** which is 4.23 x 109, it can be seen that the formation of P**2A** is faster than **P1B** by a factor of 2.42 x 103 s-1, showing that P**2A** is highly favored kinetically. The formation of P**2B** has the least rate constant of 5.85 x 106 s-1.

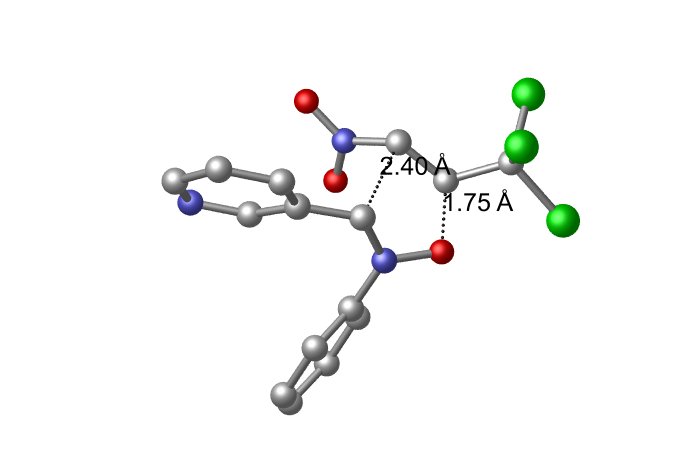
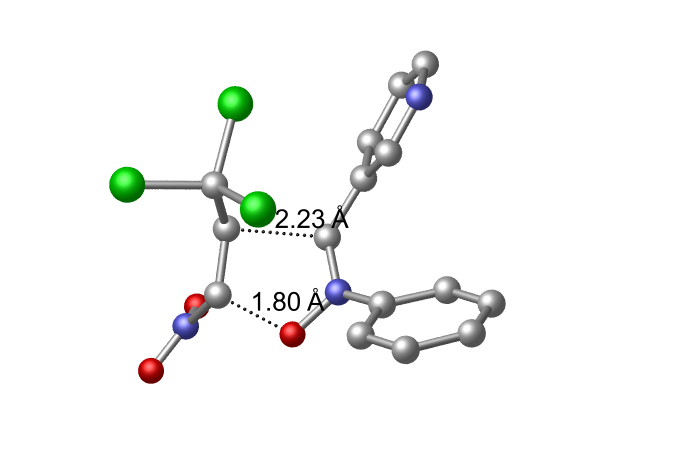
**Figures 3.2** shows the structures of the stationary points (minima and first-order saddle points) for the 32CA reaction between (E)-substituted-nitroethene (**A1**, R1= CCl3) and *C, N*-Disubstituted-pyridinyl Nitrone (**A2**, R2= Phenyl and R3 = H) (**Scheme 1.4**). From figure 3, it can be seen that the three-atom component (**A2**) adds across the alkene (**A1**) in an asynchronous concerted manner, as illustrated by the bond lengths of the transition state structures.

****

**Figure** **3.1:** Gibbs free energy profile for the reaction of (E)-substituted-nitroethene with C, N-Disubstituted pyridinyl nitrone in both gas phase and solvent phase (benzene).

**Figure 3.2:** Graphical representation of optimized structures for TS1A to TS2B for the reaction between (E)-substituted-nitroethene (A1, R1= CCl3) and C, N-Disubstituted pyridinyl Nitrone (A2, R2= Phenyl and R3 = H).

**TS1A TS1B**

**TS2ATS2B**

## 3.3 Analysis of the (3 + 2) cycloaddition reaction between (E)-substituted-nitroethene (A1, R2 = CCl3) and *C, N*-Disubstituted-pyridinyl nitrone, (A2, R2=Phenyl and R3 = H) at different level of theories under experimental conditions

To investigate the possibility of the B3LYP-D3/6-311G(d, p) level of theory underestimating the activation barriers, the reaction between (E)-substituted-nitroethene (**A1,** R1= CCl3) and *C, N*-disubstituted-pyridinyl nitrone, (**A2,** R2=phenyl and R3 = H) was recomputed (full optimization) with the B3LYP/6-311G(d, p), M06/6-311G(d, p) and M06-2X/6-311G(d, p) functionals, and the results are as shown in **Table 3.2**. The barriers at the B3LYP/6-311G(d, p) level are far above the other three, implying the B3LYP/6-311G(d, p) functional might be overestimating the barriers. The M06-2X/ 6-311G(d, p) and M06/6-311G(d, p) barriers are closer but are slightly lower than those at the B3LYP-D3/6-311G(d, p) level, with some marginally negative barriers, implying that these two functionals might be slightly underestimating the barriers compared to the B3LYP-D3/6-311G(d, p) level. Thus, the B3LYP-D3/6-311G(d, p) level is the best for the system under study.

**Table 3.2:** Activation energies and reaction energies of the various elementary steps in the reaction between (E)-substituted-nitroethene derivatives with C, N-disubstituted pyridinyl nitrone at different level of theories. **R1 =** CCl3**, R2 =** Phenyl and **R3 = H**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Level of theory** | **TS1A** | **TS2A** | **TS1B** | **TS2B** | **P1A** | **P2A** | **P1B** | **P2B** |
| **B3LYP** | 18.6 | 14.2 | - | 22.5 | -11.4 | -9.8 | -13.1 | -6.7 |
| **B3LYP-D3** | 5.4 | 0.7 | 4.3 | 8.2 | -23.1 | -21.4 | -25.8 | -20.9 |
| **M06** | -5.7 | -5.8 | 5.6 | 9.9 | -29.3 | -27.5 | -32.7 | -21.0 |
| **M06-2X** | 3.5 | -2.5 | 2.9 | 5.7 | -35.4 | -34.7 | -38.3 | -33.4 |

## 3.4 Effect of solvent on the energetics of the reaction

Using the polarizable continuum model (PCM), the effect of solvent on the energetics of the reaction of (E)-substituted-nitroethene (**A1**, R1 = CCl3) with *C, N*-disubstituted pyridinyl nitrone, (**A2**, R2 =Phenyl and R3 = H) was investigated (see table 3.3). From **Table 3.3**, there appears to be a minimal solvent effect on **Path A** and **Path B**. All three solvents very slightly increase the barriers of the reactions but the differences are well within the margin of error of the method. Also, even with the slight increases the activation barrier trends are still the same. Thus the effect of solvents in the calculations do not affect the selectivity of the reactions.

**Table 3.3**: Activation energies and reaction energies of the various elementary steps in the reaction between (E)-substituted-nitroethene derivatives with *N****-***Substituted-*C-*pyridinyl-nitrones in different solvents. R1 = CCl3, R2 = phenyl and R3 = H

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Solvent** | **TS1A** | **TS1B** | **TS2A** | **TS2B** | **P1A** | **P1B** | **P2A** | **P2B** |
| **Benzene** | 5.4 | 4.3 | 0.7 | 8.2 | -23.1 | -25.8 | -21.4 | -20.9 |
| **Toluene** | 5.4 | 4.4 | 0.8 | 8.3 | -23.0 | -25.7 | -21.3 | -20.8 |
| **Nitromethane** | 6.0 | 5.1 | 0.9 | 9.4 | -21.1 | -24.3 | -19.9 | -19.3 |

## 3.5 Substituent effect on the reaction between (E)-substituted-nitroethene (A1) and *C, N*-Disubstituted-pyridinyl Nitrone (A2)

This section investigates the effects of substituents i.e. electron-withdrawing group (EWG) or electron-donating group (EDG) on the (E)-substituted-nitroethene (**A1**) and C, N-disubstituted-pyridinyl nitrone (**A2**) on the selectivity of the reaction. The direction of electron flow between any two or more reacting systems is defined by electron donating and electron withdrawing groups. To gain insight into the various factors that control the selectivities of the four reactive channels, the effects of various substituents on the reactivity and selectivities of different derivatives of (E)-substituted-nitroethene (**A1**) and C, N-disubstituted-pyridinyl nitrone (**A2**) have been investigated.

## 3.5.1 Analysis of the reaction of (E)-substituted- nitroethene derivatives and N-Phenyl-C-pyridinyl nitrone.

**Table 3.4** displays the activation energies and reaction energies of the various elementary steps involved in the reaction between (E)-substituted- nitroethene derivatives and *N*-Phenyl-*C*-pyridinyl nitrone. The Gibbs free energy profile for the reaction of cyano-substituted nitroethene (R1 = CN) with the *N*-Phenyl-*C*-pyridinyl nitrone (**A2**) is shown in **Fig. 3.3**.

For the alkene (**A1**), the electron donating substituent used were methyl and amine groups. Hydrogen atom was also used as reference. EDGs substitution on **A1** increase the activation barriers in contrast to that of the parent reaction. There is a slight change in energetic trend compared to the parent reaction when EDGs were substituted. Although the reaction path leading to the formation of product **P2A** is observed to be the most kinetically favored, the competing reaction path is the one leading to the formation its diastereomer, **P1A** as opposed to that of the parent reaction where **P1B** is the competing reaction path. This is observed in both the weak and strong electron group (Methyl and NH2 respectively).

For EWGs substitution, it is observed that there is also an increase in activation energies. Comparing the increase in activation energies in EWGs to that of EDGs, the increase is greater in EDGs than in EWGs. There is a slight change in energetic trend in the EWGs substitution. It is observed that the weak EWG (Br) follows the same energetic trend as that of the EDGs substitution where it contradicts that of the parent reaction. The strong EWG (CN) on the other hand has the same energetic trend as that of the parent reaction.

Similar observation as that of EDGs substitution is seen for bulky group substitution, but this time reaction route leading to the formation of product **P1B** is the least kinetically favored as opposed to **P2B** being the least kinetically favored path in the parent reaction.

**Table 3.4:** Activation energies and reaction energies (in kcal/mol) of the various elementary steps in the reaction of (E)-substituted- nitroethene derivatives and N-Phenyl-C-pyridinyl Nitrones.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **R1** | **TS1A** | **TS2A** | **TS1B** | **TS2B** | **P1A** | **P2A** | **P1B** | **P2B** |
| **H** | 6.3 | 4.1 | 7.5 | 8.3 | -19.2 | -17.5 | -22.4 | -21.8 |
| **EDG** | | | | | | | | | |
| **Methyl** | 8.4 | 4.4 | 11.4 | 12.8 | -17.7 | -17.6 | -19.9 | -17.8 |
| **NH2** | 12.9 | 9.9 | 21.1 | 20.3 | -9.8 | -10.3 | -9.1 | -2.5 |
| **EWG** | | | | | | | | | |
| **CN** | 5.1 | 4.3 | 4.7 | 5.6 | -17.0 | -14.1 | -20.8 | -19.3 |
| **Br** | 6.2 | 3.8 | 7.2 | 9.0 | -24.6 | -23.8 | -23.1 | -22.1 |
| **BG** | | | | | | | | | |
| **Phenyl** | 8.4 | 6.9 | 15.8 | 11.0 | -16.8 | -14.7 | -17.8 | -15.3 |



**Figure** **3.3:** Gibbs free energy profile for the reaction of cyano-substituted nitroethene (R1 = CN) with the C, N-Disubstituted pyridinyl nitrone (A2)

## 3.5.2 Analysis of the reaction between (E)-substituted nitroethene and C, N-Disubstituted pyridinyl nitrone derivatives

The reactivity, selectivity and mechanistic effects of different substituents on the nitrogen and carbon atom of the three-atom component have been investigated and the results of the analysis are displayed in **Table 3.5**. The Gibbs free energy profile for the reaction of bromo-substituted three-atom component (R2 = Br) with the (E)-substituted nitroethene is shown in **Fig. 3.4**.

EDGs substitution on the nitrogen atom of the three-atom component sees an increase in activation energies compared to that of the parent reaction, but there is a slight change in reaction trend. For the weak EDG (methyl), it is observed that although the most kinetically favored pathway is that leading the formation of product **P2A**, the next competing pathway is the one which leads to the formation of product **P1A** as opposed to that which is observed in the parent reaction where **P1B** formation is the next competing step. Strong EDG (NH2) also sees a slight change in reaction trend similar to that of the weak EDG, but this time the least kinetically favored pathway is that which leads to the formation of product **P1B** as opposed to what is obtained in the parent reaction. Also EDG substitution on the carbon atom of the nitrone sees a similar observation as that of weak EDGs substitution on the nitrogen atom of the nitrone.

EWGs substitution on the nitrogen atom of the nitrone also sees an increase in activation energies as compared to that of the parent reaction. A slight change in reaction trend is also observed, where the competing pathway to the most kinetically favored path, **P2A** is seen to be **P1A**, contradicting what is obtained in the parent reaction. EWGs substitution on the carbon atom of the nitrone also see similar observation.

Bulky group substitution on the nitrone sees no effect on the reaction trend but rather the activation energies of the various transition states, by increasing them.

**Table 3.5:** Activation energies and reaction energies (in kcal/mol) of the various elementary steps in the reaction of (E)-substituted nitroethene (R1 = CCl3) with C, N-disubstituted pyridinyl nitrones derivatives.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **R2** | **R3** | **TS1A** | **TS2A** | **TS1B** | **TS2B** | **P1A** | **P2A** | **P1B** | **P2B** |
| **Methyl** | **H** | 6.4 | 3.3 | 10.0 | 11.4 | -21.1 | -19.6 | -23.5 | -18.4 |
| **NH2** | **H** | 5.7 | 3.0 | 12.6 | 10.5 | -22.6 | -20.8 | -25.1 | -21.6 |
| **OH** | **H** | 11.6 | 7.7 | 13.1 | 13.7 | -15.6 | -14.3 | -18.2 | -13.8 |
| **CN** | **H** | 4.0 | 1.9 | 7.0 | 6.9 | -29.6 | - | -31.8 | -27.5 |
| **Br** | **H** | 14.2 | 12.2 | 15.2 | 17.6 | -13.5 | -12.1 | -15.2 | -14.0 |
| **4-Me-Ph** | **H** | 6.5 | 1.9 | - | 9.4 | -21.7 | -19.8 | -24.2 | -18.8 |
| **4-F-Ph** | **H** | 5.6 | 0.9 | 4.7 | 8.5 | -21.6 | -19.7 | -24.2 | -18.8 |
| **4-Br-Ph** | **H** | 5.6 | 0.9 | 4.6 | 8.4 | -23.5 | -21.6 | -26.1 | -21.0 |
| **4-Cl-Ph** | **H** | 5.6 | 0.9 | 4.6 | 8.5 | -21.7 | -19.9 | -24.3 | -19.3 |
| **Ph** | **Methyl** | 3.8 | -0.4 | 5.4 | 7.4 | -24.7 | -23.0 | -22.9 | -16.6 |
| **Ph** | **OH** | - | -7.1 | -2.4 | -1.3 | -26.3 | - | -25.6 | -20.0 |
| **Ph** | **CN** | 12.8 | 6.8 | 12.5 | 15.3 | -16.1 | -15.2 | -16.5 | -9.7 |
| **Ph** | **Br** | 8.1 | 3.1 | 7.8 | 11.3 | -31.4 | -30.9 | -26.8 | -30.6 |
| **Ph** | **Phenyl** | 7.6 | -8.8 | 0.8 | 1.2 | -24.8 | -24.3 | -20.4 | -17.7 |



**Figure** **3.4:** Gibbs free energy profile for the (3 + 2) Cycloaddition reaction of (E)-substituted nitroethene and N-bromo pyridinyl nitrone (R2 = Br and R3 = H).

## 3.6 Normal versus inverse electron demand 32CA reaction.

In a chemical reaction, the interaction of frontier molecular orbitals is essential. As reported in literature [23], depending on the pairing up of the frontier molecular orbitals on the three-atom component and the alkene, the 32CA reaction may be classified as a normal electron demand where the HOMO of the **A2** pairs up with LUMO of the **A1**, or inverse electron demand where the LUMO of the **A2** pairs up with the HOMO of the **A1**.

From **Fig. 3.5**, the energy required to promote an electron from the HOMO of the **A2** to LUMO of the **A1** is 4.21 eV while the energy needed to promote an electron from the HOMO of the **A1** to **A2’**s LUMO is 6.40 eV, hence the 32CA reaction of (E)-substituted nitroethene (**A1**) with C-N-Disubstituted pyridinyl nitrone (**A2**) is a normal electron demand cycloaddition due to the relatively smaller energy required to promote electrons from the HOMO of **A2** to the LUMO of the **A1** derivative. However, a competition between normal and inverse electron demand cycloadditions may occur as a result of the low energy difference between the two forms of cycloadditions. The HOMO-LUMO interaction of the reacting species shows that the **A2** reacts as a nucleophile while the **A1** reacts as an electrophile. Consequently, electron-donating groups on the **A2** and electron-withdrawing groups on the **A1** significantly increase the activation barriers as found in the earlier sections.



**Figure** **3.5:** Graphical illustration of the highest occupied molecular orbital (HOMO) – lowest unoccupied molecular orbital (LUMO) interaction between (E)-substituted-nitroethene (A1) and C, N-disubstituted pyridinyl-Nitrone (A2). R1 = CCl3, R2 = Phenyl and R3 = H

## 3.7 Analysis of the reaction with global reactivity indices

This section examines how the inherent reactivity and selectivity of the 32CA reaction of the diverse derivatives of **A1** and **A2** are affected by the nature of the substituents on them. The variation in nucleophilic and electrophilic nature of reacting species due to the electronic nature of the substituents on the reactants are efficiently rationalized by the global reactivity indices. The global electrophilicity index (***ω***) and global nucleophilicity (**N**) are useful descriptors for analyzing the changes in nucleophilicity and electrophilicity of reactants with different substituents. Thus, in a series of reactants, the species with the largest electrophilicity index is the best electrophile while species with the highest nucleophilicity values is the best nucleophile. Since it is now known that the electron density fluxes from the nitrone component to the alkene component in the reactions under study here, **A1** isthe electrophile and **A2** is the nucleophile. Decreasing the electron density of **A1** increases its electrophilicity whiles increasing the electron density on **A2** increases its nucleophilicity. From **Table 3.6**, the electrophilicities of the various derivatives of nitroethene (**A1**) are in the order CN > Br > Ph > H > Me > NH2 and the nucleophilicity of pyridinyl nitrone derivatives (**A2**) are in the order 4-Me-Ph > Me > 4-F- Ph > 4-Br-Ph > 4-Cl-Ph > Br > NH2 > OH > CN in **table** **3.7**.

**Table 3.6:** Global reactivity indices for (E)-substituted-nitroethene, **A1** (alkene). HOMO, LUMO energies, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω) and global nucleophilicity (N). All in eV.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **R1** | **HOMO** | **LUMO** | **µ** | **ƞ** | **ω** | **N** |
| **CCl3** | -8.70 | -1.85 | -5.27 | 6.84 | 2.03 | 0.43 |
| **H** | -8.36 | -2.80 | -5.58 | 5.56 | 2.80 | 0.76 |
| **Methyl** | -8.17 | -2.57 | -5.37 | 5.60 | 2.57 | 0.95 |
| **NH2** | -6.74 | -1.91 | -4.33 | 4.83 | 1.94 | 2.38 |
| **CN** | -8.90 | -3.74 | -6.32 | 5.16 | 3.87 | 0.22 |
| **Br** | -8.09 | -3.01 | -5.55 | 5.08 | 3.03 | 0.03 |
| **Phenyl** | -7.09 | -2.89 | -4.99 | 4.20 | 2.96 | 2.03 |

**Table 3.7:** Global reactivity indices for N-Substituted-C-pyridinyl-nitrones, **A2** (three-atom components). HOMO, LUMO energies, electronic chemical potential (μ), chemical hardness (η), global electrophilicity (**ω**) and global nucleophilicity (**N**). All in eV.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **R2** | **R3** | **HOMO** | **LUMO** | **µ** | **ƞ** | **ω** | **N** |
| **Methyl** | **H** | -6.09 | -1.85 | -3.97 | 4.24 | 1.86 | 3.03 |
| **NH2** | **H** | -6.25 | -1.93 | -4.09 | 4.32 | 1.94 | 2.87 |
| **OH** | **H** | -6.34 | -1.89 | -4.12 | 4.45 | 1.91 | 2.78 |
| **CN** | **H** | -6.81 | -3.04 | -4.93 | 3.77 | 3.22 | 2.31 |
| **Br** | **H** | -6.21 | -2.16 | -4.19 | 4.05 | 2.17 | 2.91 |
| **Phenyl** | **H** | -6.06 | -2.30 | -4.18 | 3.76 | 2.33 | 3.06 |
| **4-Me-Ph** | **H** | -6.02 | -2.12 | -4.07 | 3.90 | 2.12 | 3.10 |
| **4-Cl-Ph** | **H** | -6.16 | -2.44 | -4.30 | 3.72 | 2.49 | 2.96 |
| **4-F-Ph** | **H** | -6.11 | -2.35 | -4.23 | 3.76 | 2.38 | 3.01 |
| **4-Br-Ph** | **H** | -6.15 | -2.45 | -4.30 | 3.70 | 2.50 | 2.97 |
| **Ph** | **Me** | -5.98 | -1.86 | -3.92 | 4.12 | 1.86 | 3.14 |
| **Ph** | **OH** | -5.85 | -2.03 | -3.94 | 3.82 | 2.03 | 3.27 |
| **Ph** | **CN** | -6.64 | -2.81 | -4.73 | 3.83 | 2.92 | 2.48 |
| **Ph** | **Br** | -6.21 | -2.16 | -4.19 | 4.05 | 2.17 | 2.91 |
| **Ph** | **Ph** | -6.00 | -2.21 | -4.11 | 3.79 | 2.23 | 3.12 |

# CHAPTER FOUR

## 4.0 CONCLUSION

The (3 + 2) cycloaddition reaction between (E)-substituted-nitroethene (**A1**, R1= CCl3) and *C, N*-disubstituted-pyridinyl nitrone (**A2**, R2= phenyl and R3 = H) is fully regio- and stereoselective towards the formation of the *exo* 4-nitro substituted nicotine analog product (**P2A)**. The formation of the *exo* 4-nitro substituted nicotine analog product (**P2A**) isomer is kinetically favored over that of the *endo* isomer (**P1A**) by 4.6 and 4.2 kcal/ mol in benzene solvent and gas phase respectively. The rate constants for the formation of **P2A** through **TS2A** in both gas phase and solvent phase are 3.87 x 1012 and 1.81 x 1012 s-1 respectively, indicating that the formation of **P2A** is kinetically favored over the other cycloadducts.

Irrespective of the electronic nature of substituents on the both reactants (**A1** and **A2**), the reaction channels that regioselectively lead to the formation of the *exo* 4-nitro substituted nicotine analogs (**P2A**) are favored. Electron-donating and withdrawing groups on both **A1** and **A2** increase the activation energies of the reaction relative to the parent reaction but the reaction trend remains the same. The results reveal that the degree of conformational selectivity is controlled by the kinetics of the reaction. In all reactions considered, the channels that selectively lead to the formation of the cis-diastereoisomers proceed with lower activation barriers than the trans-diastereoisomers. As a result of the thermodynamic stability of all the considered isomeric products in all reactions studied, the selectivities observed in the reactions are kinetically controlled.

Irrespective of the polarity of the solvent, this reaction proceeds to the formation *exo* 4-nitro substituted nicotine analog. Polar solvents tend to increase the activation energies while non-polar solvents decrease the activation energies. Global reactivity indices calculated have shown that the most electrophilic reactant in this reaction is the alkene while the three-atom component is the nucleophile, hence electron flow will be from the three-atom component **A2** to the alkene **A1**.

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