**Investigating the mechanism of formation of nitro-substituted nicotine analogue via the [3 + 2] Cycloaddition reaction of (E)-substituted nitroethene derivatives and (Z)-C-(3-pirydyl)-N-aryl-nitrones: A Density Functional Theory (DFT) study**

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**Abstract**

Nitro-substituted nicotine analogues have important biological activities, and thus several methods have been investigated for their synthesis. The formation of nitro-substituted nicotine analogues via the [3 + 2] cycloaddition (32CA) reaction of (E)-substituted nitroethene derivatives and (Z)-C-(3-pirydyl)-N-aryl-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 analogue (**P2A**). The addition of the (E)-substituted nitroethene derivatives to the (Z)-C-(3-pirydyl)-N-aryl-nitrone exhibits a high degree of regio-and stereoselectivity. Electron-withdrawing and -donating groups substitution on both the (E)-substituted nitroethene derivatives (**A1**) and (Z)-C-(3-pirydyl)-N-aryl-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; density functional theory; nicotine analogues; nitroethene; nitrone

1. **Introduction**

Cycloaddition reactions are widely acknowledged to be among the most useful organic reactions [1]. They have been recognized as one type of fundamental synthetic methodologies in which cyclic structures and two bonds can be generated in a single manipulation [2]. Classes of organic reactions that have widespread applicability include those that solve the difficulties of regio- and stereo-selectivity [3]. These reactions are however compatible with a wide range of functional groups. [3 + 2] Cycloaddition (32CA) reactions are a good example of cycloaddition reactions. 32CA reaction is a useful method for the synthesis of five-membered heterocycles [4]. It involves the reaction between an ethylene derivative (ED) and a three-atom component (TAC). This reaction theory was initially proposed by Smith in 1938, but then Huisgen generalized it in the 1960s so it can be applied globally [4,5]. These are classic synthetic organic chemistry reactions that yield regio- and stereochemically specified heterocycles that are significant to both academics and industry. The electrophilic and nucleophilic natures of the interacting species are important in these reactions, and the reaction route is regulated by the numerous substituents on both reactants [6].

Nicotine analogues are one of the compounds from which five-membered heterocycles generated by 32CA reactions can be formed [7]. Nicotine is a key alkaloid present in the tobacco plant [8]. Because of its biological activity, it is employed in pharmaceuticals, and as a result, much study is being conducted on it [9].

The (32CA) reaction of nitrones with (E)-substituted nitroethene yields both enantiomeric and stereoisomeric isoxazolidines and furan derivatives (see scheme 2). This reaction is a critical step in the synthesis of heterocycles and natural products such as nicotine analogues. Conjugated nitroalkenes are an intriguing category of possible reactants in such processes. This is because the nitro group on the ethylene derivative improves the biological activity of the heterocyclic compound involved [10–12].

Singh et al [13], reported the development of an efficient route to novel nicotine analogue by reacting α-(3-Pyridyl)-N-phenylnitrone (**1**) with several dipolarophiles (**2**) yielding the products **5**,**6** and **7** (scheme 1). They found out that reacting the nitrone with electron-rich dipolarophiles favors the formation of products **5** and **6**. Regioselectivity is reversed when the nitrone is reacted with an electron-deficient dipolarophile and stereospecifically leads to the formation of product **7** which is an *endo* cycloadduct. They reported that this reversed regioselectivity is mostly observed in reaction of nitrones with highly electron-deficient dipolarophiles such as nitroalkenes.

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



Kuzenkov et al [14], also synthesized a fungicide using this same reaction route where they reacted ethyl acrylate, styrene, and their derivatives with *N*-(pyridin-3-ylmethylidene)-*N-* phenylaminoxidesin toluene at boiling for 15–20 h with monitoring the reaction progress by TLC. They also observed the same results as that of Singh et al.

In 2019, Fryźlewicz et al[15] reported on the [3 + 2] cycloaddition reaction of an electron deficient ethylene derivative, (*E*)-3,3,3-Trichloro-1-nitroprop-1-ene with *N*-aryl(pyridin-3-yl) nitrones under mild conditions. They observed that the reaction is fully regio- and stereoselective and leads to the formation of 4-nitro-substituted nicotine analogue (*exo*). Their result was not in total agreement with that of Singh et al. Even though this reaction provides routes to the stereo- and regio-selective synthesis of pharmaceutically important structures, not much is known of the source of the regio- and stereo-selectivity and the impact of substituent on the reactivity and selectivity in this reaction. For the first time, density functional theory (DFT) calculations have been employed to the study of this reaction to ascertain as to what is controlling the reactivity and selectivity of the reaction between (E)-substituted-nitroethene (**A1**) and (Z)-C-(3-pirydyl)-N-aryl-nitrone, (**A2**). The effect of a wide range of substituent on both reactants with different electronic and steric effects have been investigated in this study. Also the effect of solvent on the reaction has been investigated.

**Scheme 2:** Reaction between (*E*)-3,3,3-Trichloro-1-nitroprop-1-ene (**A**) and *N*-aryl(pyridin-3-yl) nitrones (**B**).



1. **Computational Details and Method**

All computations were carried out with the Spartan'14 [16] and Gaussian 09 [17] 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 [18]. The B3LYP functional studies the organic reactions which proceed with low energy barriers [19] best, as it avoids the problems of records of near-negative activation barriers such as hybrid gradient approximation functionality M06-2X [20]. 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 [21].

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) [22].

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 [23]. Intrinsic reaction coordinate calculations [24,25] were then performed to ensure that each transition state smoothly connects the reactants and products along the reaction coordinate [26–29]. CYLview software was used to display the optimized structures [30].

The rate constants of the reaction at a 25ºC [k(T)] were calculated using equation (1) [31]:

(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 7 and 8. 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 [32] and is a function of the electronic chemical potential, μ, and chemical hardness, η, as defined by Pearson’s acid-base concept [33]. Species with large electrophilicity values are more reactive towards nucleophiles. The nucleophilicity index [34] of the various reagents is calculated using Eq. (3). The scale of nucleophilicity is made in reference to tetracyanoethylene (TCE) [35]. It is important to note that these equations are based on Koopmans theory [36] 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) = -9.12 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.

1. **Results and Discussion**

From scheme 3, 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.

**Scheme 3**: Proposed scheme for the 32CA reaction of (E)-substituted nitroethene derivative (**A1**) with (Z)-C-(3-pirydyl)-N-aryl-nitrone **(A2)** in benzene at the B3LYP-D3/6-311G (d, p) level of theory.



* 1. **Analysis of the parent reaction between (E)-substituted-nitroethene (A1) and (Z)-C-(3-pirydyl)-N-aryl-nitrone, (A2, R2 = Phenyl and R3 = H)**.

The mechanism and selectivities of the 32CA reaction involving (E)-substituted-nitroethene (**A1**, R1= CCl3) and (Z)-C-(3-pirydyl)-N-aryl-nitrone (**A2**, R2= phenyl and R3 = H) are discussed in this section. **Figure** **1** depicts the Gibbs free energy profile for the 32CA reaction of (E)-substituted-nitroethene (**A1**, R1= CCl3) with (Z)-C-(3-pirydyl)-N-aryl-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** **1** shows the rate constants for the formation of the cycloadducts as shown in scheme 3 for the 32CA reaction involving (E)-substituted-nitroethene (**A1**, R1= CCl3) and (Z)-C-(3-pirydyl)-N-aryl-nitrone (**A2**, R2= Phenyl and R3 = H) in both gas phase and solvent phase (benzene)

From figure 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 (Z)-C-(3-pirydyl)-N-aryl-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 1**: Rate constants of the reaction of (E)-substituted-nitroethene (A1) with (Z)-C-(3-pirydyl)-N-aryl-nitrone (A2) for the formation of the various cycloadducts computed in benzene at room temperature. **R1** = CCl3, **R2 =** Phenyland **R3 =** H

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

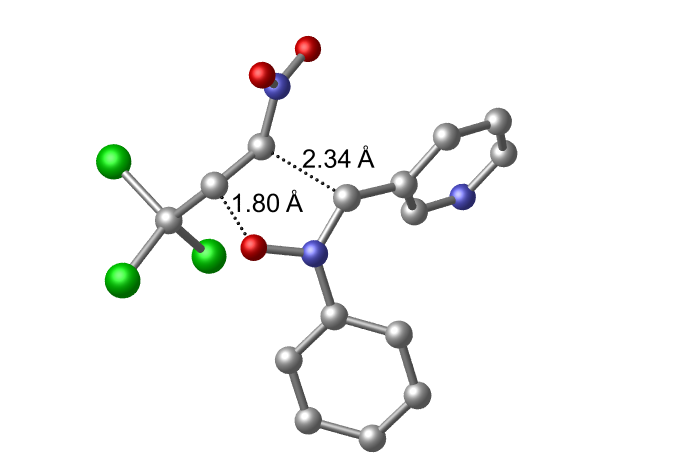
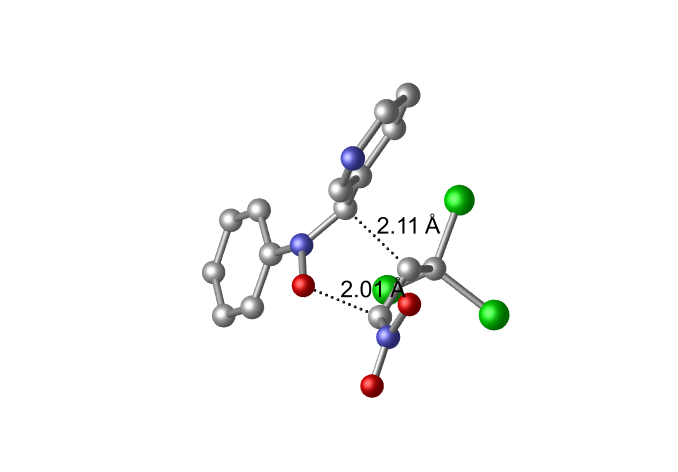
From **Table 1**, for the solvent phase, it is seen that the formation of product **P2A** through transition state **TS2A** has the highest rate constant value of 1.81 x 1012. Comparing the rate constant of **P2A** to its competing cycloadduct **P1B** which is 4.23 x 109, it can be seen that the formation 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.

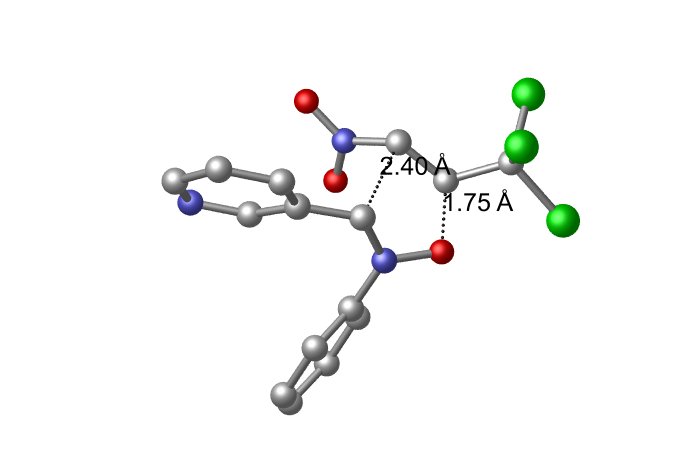
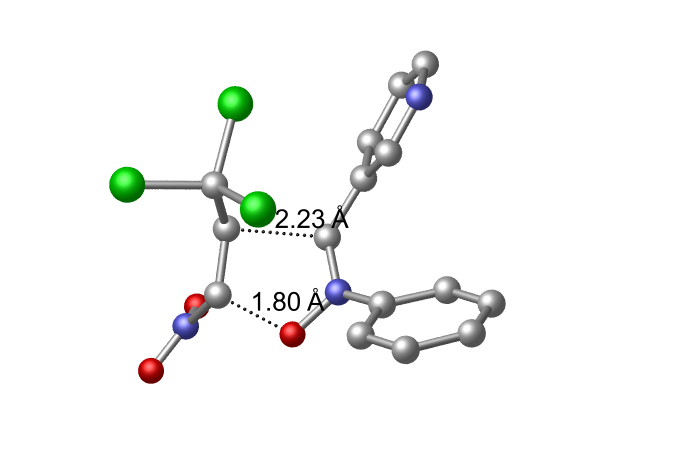
**Figures 2** shows the structures of the stationary points (minima and first-order saddle points) for the 32CA reaction between (E)-substituted-nitroethene (**A1**, R1= CCl3) and (Z)-C-(3-pirydyl)-N-aryl-nitrone (**A2**, R2= Phenyl and R3 = H) (**Scheme 3**). From figure 3, it can be seen that the three-atom component (**A2**) adds across the alkene (**A1**) in an asynchronous concerted manner, as illustrated by the bond lengths of the transition state structures.

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**Figure 1:** Gibbs free energy profile for the reaction of (E)-substituted-nitroethene with (Z)-C-(3-pirydyl)-N-aryl-nitrone in benzene at the B3LYP-D3/6-311G (d, p) level of theory.

**Figure 2:** Graphical representation of optimized structures for **TS1A** to **TS2B** for the reaction between (E)-substituted-nitroethene (**A1**, R1 = CCl3) and (Z)-C-(3-pirydyl)-N-aryl-nitrone (**A2**, R2 = Phenyl R3 = H) in benzene at the B3LYP-D3/6-311G (d, p) level of theory.

**TS1ATS1B**

**TS2ATS2B**

* 1. **Analysis of the [3 + 2] cycloaddition reaction between (E)-substituted-nitroethene (A1, R1 = CCl3) and (Z)-C-(3-pirydyl)-N-aryl-nitrone, (A2, R2 = Phenyl R3 = H) at different level of theories under experimental conditions**

To validate the level of theory applied for this work, there was the need to compute the reaction under experimental condition (benzene solvent) against different level of theories. 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 (Z)-C-(3-pirydyl)-N-aryl-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 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 2:** Activation energies and reaction energies of the various elementary steps in the reaction between (E)-substituted-nitroethene derivatives with (Z)-C-(3-pirydyl)-N-aryl-nitrone at

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **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 |

different level of theories. **R1 =** CCl3**, R2 =** Phenyl and **R3 = H**

* 1. **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 (Z)-C-(3-pirydyl)-N-aryl-nitrone, (**A2**, R2 = Phenyl R3 = H) was investigated (see table 3). From **Table 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**: Activation energies and reaction energies of the various elementary steps in the reaction between (E)-substituted-nitroethene derivatives with (Z)-C-(3-pirydyl)-N-aryl-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 |

* 1. **Substituent effect on the reaction between (E)-substituted-nitroethene (A1) and (Z)-C-(3-pirydyl)-N-aryl-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 (Z)-C-(3-pirydyl)-N-aryl-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 (Z)-C-(3-pirydyl)-N-aryl-nitrone (**A2**) have been investigated.

**3.4.1. Analysis of the reaction of (E)-substituted- nitroethene derivatives and (Z)-C-(3-pirydyl)-N-phenyl-nitrone .**

**Table 4** displays the activation energies and reaction energies of the various elementary steps involved in the reaction between (E)-substituted- nitroethene derivatives and (Z)-C-(3-pirydyl)-N-phenyl-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**.

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 4:** Activation energies and reaction energies (in kcal/mol) of the various elementary steps in the reaction of (E)-substituted- nitroethene derivatives and (Z)-C-(3-pirydyl)-N-phenyl-nitrone.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **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**: Gibbs free energy profile for the reaction of cyano-substituted nitroethene (R1 = CN) with the (Z)-C-(3-pirydyl)-N-aryl-nitrone (A2) in benzene at the B3LYP-D3/6-311G (d, p) level of theory.

**3.4.2. Analysis of the reaction between (E)-substituted nitroethene and (Z)-C-(3-pirydyl)-N-aryl-nitrone derivatives**

The reactivity, selectivity and mechanistic effects of different substituents on the nitrogen atom of the three-atom component have been investigated and the results of the analysis are displayed in **Table 5**. The Gibbs free energy profile for the reaction of bromo-substituted three-atom component, **A2** (R2 = Br) with the (E)-substituted nitroethene, **A1** is shown in **Fig. 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 5:** Activation energies and reaction energies (in kcal/mol) of the various elementary steps in the reaction of (E)-substituted nitroethene (R1 = CCl3) with (Z)-C-(3-pirydyl)-N-aryl-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 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) in benzene at the B3LYP-D3/6-311G (d, p) level of theory.

* 1. **Normal versus inverse electron demand 32CA reaction.**

In a chemical reaction, the interaction of frontier molecular orbitals is essential. As reported in literature [10], 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. 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 (Z)-C-(3-pirydyl)-N-aryl-nitrones (**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 5**: Graphical illustration of the highest occupied molecular orbital (HOMO) – lowest unoccupied molecular orbital (LUMO) interaction between **(E)-**substituted-nitroethene (A1) and (Z)-C-(3-pirydyl)-N-aryl-nitrone (A2). R1 = CCl3, R2 = Phenyl and R3 = H in benzene at the B3LYP-D3/6-311G (d, p) level of theory.

* 1. **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 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** **7**.

**Table 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 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 |

1. **Conclusion**

The [3 + 2] cycloaddition reaction between (E)-substituted-nitroethene (**A1**, R1= CCl3) and (Z)-C-(3-pirydyl)-N-aryl-nitrone (**A2**, R2= phenyl and R3 = H) is fully regio- and stereoselective towards the formation of the *exo* 4-nitro substituted nicotine analogue product (**P2A)**. The formation of the *exo* 4-nitro substituted nicotine analogue 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 analogues (**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 analogue. 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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**Conflict of interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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