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1,3-Dipolar Cycloaddition of 3-Oxidopyrazinium to Methyl Acrylate: An Experimental and Computational Investigation

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Abstract

1,3-Dipolar cycloaddition reaction between 3-oxidopyrazinium and methyl acrylate has been studied both experimentally and theoretically. Structures of the obtained cycloadducts, exo and endo isomers, were characterised based on spectral data namely IR, ^{1}H and ^{13}C NMR. These reactions can be interpreted in terms of the classical 1,3-dipolar cycloaddition reaction of 3-oxidopyridinium. Moreover the observed cycloaddition reaction has been investigated theoretically by means of the Hartree-Fock method using 6-31G as the basis sets in the gas phase in order to have more insight into their reaction profiles. All the geometries on the reaction paths have been optimised and the transition state structures have been ascertained by frequency analysis. Since the synthesis has been carried out in acetonitrile, the optimised structures have been used for single point computationin this solvent using the density functional method with B3LYP as the functional. The computations have allowed the determination of the activation energies and enthalpy changes of the reactions. These have been used for the interpretation of kinetic and thermodynamic stabilities. It is generally found that the addition reactions have lower activation energy and enthalpy changes in acetonitrile compared to the gas phase.

1.0 Introduction

Cycloaddition reactions are important reactions with both synthetic and mechanistic interest in organic chemistry [1]. They have been long and widely used for the synthesis of cyclic and heterocyclic compounds. In recent years, 1,3-dipolar cycloaddition has emerged as a powerful method for the synthesis of five-membered ring with new chiral centres [2]. Many such compounds have pharmaceutical and agricultural importance. For instance, reaction between 3-oxidopyrzinium and methyl acrylate leads to bridged bicyclic system, diazabicyclo[3.2.1]octanes, which are key structural components biologically active natural products such as anticancer quinocarcin [3] and antibiotic lemonomycin [3].

In order to have a better understanding of the mechanistic pathway that these cycloaddition reactions undergo, a detailed charaterisation of transition states is necessary. However this is virtually difficult by experimentation and in this way computational chemistry has proved to be a useful tool for predicting stability and to locate the transition states and hence elucidate the reaction mechanism [4]. Recently, with the explosive growth of computational power and availability of user friendly software, there is an increasing interest in the use of theoretical methods to explore the mechanisms of reactions in terms of energetics and thermodynamic analysis [4]. More interestingly, it is now possible to study the mechanism of reactions theoretically in the medium in which the reactions are actually carried out and hence explore solvent effects.

2.0 Methodology

2.1 Experimental

Synthesis of 5,6-dimethyl-pyrazin-2-one

A solution of glycinamide hydrochloride (1.11 g, 10 mmol) in a mixture of methanol (20 ml) and water (2 ml) was cooled to about -50 ˚C while 2,3 butanedione was added rapidly. The temperature was maintained by constant addition of either dry ice or liquid nitrogen into an insulated container. After the addition of 2,3 butanedione, aqueous sodium hydroxide (12.5 N, 2 ml, 25 mmol) was added dropwise over 5 min. The reaction mixture was maintained below -30 ˚C for 1.5 hr and at room temperature for 3 hr, then treated with concentrated hydrochloric acid (2 ml), followed by solid sodium hydrogencarbonate (2 g). After filtration, the neutral filtrate was concentrated to remove methanol. The tacky concentrate was leached with methanol (20 ml) and filtered to remove salts. The filtrate was evaporated and the residue was leached with chloroform (25 ml) and just enough water added to the dark aqueous phased supernatant. This aqueous phase was extracted with chloroform (3 × 25 ml). The chloroform extracts were evaporated to give crude product (0.76 g, 61.2% yield), orange in colour. Recrystallisation from acetone (50 ml) yields pale pink needle crystals (0.16 g, 12.9%, m.p, 171-173 ˚C).

IR value (cm^{-1}): 3442(ν_{N-H}), 2980(ν_{C-H}), 1690($\nu_{C=O}$), 1624($\nu_{C=C}$), 1612($\nu_{C=N}$); ^{1}H NMR ($CDCl_3$), δ(ppm): 7.89(1H, s), 2.27(3H, s), 2.25(3H, s); ^{13}C NMR ($CDCl_3$), δ(ppm): 158.5, 143.8, 133.7, 131.7, 18.7, 16.5.

Synthesis of 3,4-dihydro-1,5,6-trimethyl-3-oxopyrazin-1-ium iodide

5,6-Dimethyl pyrazin-2-one (700 mg, 5.64 mmol) and iodomethane (1.78 ml, 28.2 mmol, and 5 equiv) were refluxed in acetonitrile (150 ml) under nitrogen atmosphere for 24 hr. The solvent was removed under vacuum. The residue was washed with DCM followed by filtration to give dark brown crystalline solid (0.63 g, 36.1%, m.p>250 ˚C).

IR value (cm^{-1}): 3436(ν_{N-H}), 2918(ν_{C-H}), 1687($\nu_{C=O}$), 1631($\nu_{C=C}$), 1611($\nu_{C=N}$); ^{1}H NMR ($CDCl_3$), δ(ppm): 8.34(1H, s), 5.54(3H, s), 4.30(3H, s), 2.69(3H, s), 2.67(3H, s); ^{13}C NMR ($CDCl_3$), δ(ppm): 160.2, 156.1, 129.4, 21.3, 14.6, 14.0.

Synthesis of 5,8-dimethyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1] octane-6-carboxylate

A mixture of 3,4-dihydro-1,5,6-trimethyl-3-oxopyrazin-1-ium iodide (0.63 g, 2.4 mmol) with triethylamine (0.68 ml, 4.8 mmol, 2 equiv) and methyl acrylate (0.66 ml, 7.2 mmol, 3 equiv) in dry acetonitrile (100 ml) was refluxed for 2 hr and the mixture turned orange. The solvent and excess methyl acrylate was removed under vacuum. Water (30 ml) was added and the extracted with DCM (3 × 30 ml). All the DCM extract were combined and dried over anhydrous magnesium sulphate before the solvent was removed. The residue (0.27 g, 50.0%) brown oil was purified and separated by chromatography (silica, hexane:ethyl acetate as 1:2) and two products, identified as exo and endo, were obtained as colourless plates (118 mg, 21.6% and 18 mg, 3.3%).

IR value (exo) (cm^{-1}): 3436(ν_{N-H}), 3054(ν_{C-H}), 1721($\nu_{C=O}$ ester), 1665($\nu_{C=O}$ amide), 1637($\nu_{C=C}$); H NMR (exo) ($CDCl_3$), δ(ppm): δ7.68(1H, s), δ4.33(1H, d), δ4.20(1H, d), δ3.73(3H, s), δ3.67(1H, d), δ3.05(1H, q), δ3.64(1H, qui), δ2.31(3H, s), δ2.15(1H, q), δ1.31(3H, s); H NMR (endo) ($CDCl_3$), δ(ppm): δ7.47(1H, s), δ4.32 (1H, d), δ4.09(1H, d), δ3.66(3H, s), δ3.54(1H, d), δ3.06(1H, q), δ2.46(2H, m), δ2.33(1H, s), δ1.55(1H, s); ^{13}C NMR (endo) ($CDCl_3$), δ(ppm): 171.6, 170.9, 142.3, 92.9, 65.9, 64.9, 54.1, 52.1, 31.9, 29.9, 21.1; ^{13}C NMR (exo) ($CDCl_3$), δ(ppm): 173.5, 171.6, 145.8, 91.0, 66.2, 63.7, 53.5, 52.2, 32.4, 29.7, 17.5.

2.2 Computational methods

Geometrical parameters of reactants, transition states and products were fully optimised at the HF level of theory using 6-31G basis sets in gas phase to make a first-level prediction for the system. The Synchronous Transit-Guided Quasi-Newton (STQN) method [5] was used to locate the transition structures. This method consists of QST2 and QST3 options. However, QST2 failed and QST3 was used which proved to be successful in locating the transition structure. The transition states were further confirmed by vibrational analysis and characterised by only one imaginary vibrational mode. As HF theory neglects electron correlation, there could be systematic errors in geometries and hence inaccurate activation energies are obtained. However, DFT is a viable method which is used to include electron-correlation in order to yield reasonable activation energies and appropriate geometries.

In this work the mechanism of the cycloaddition reaction was studied in both the gas phase and the solvent acetonitrile so as to mimic the real experimental condition. The useful form to describe these

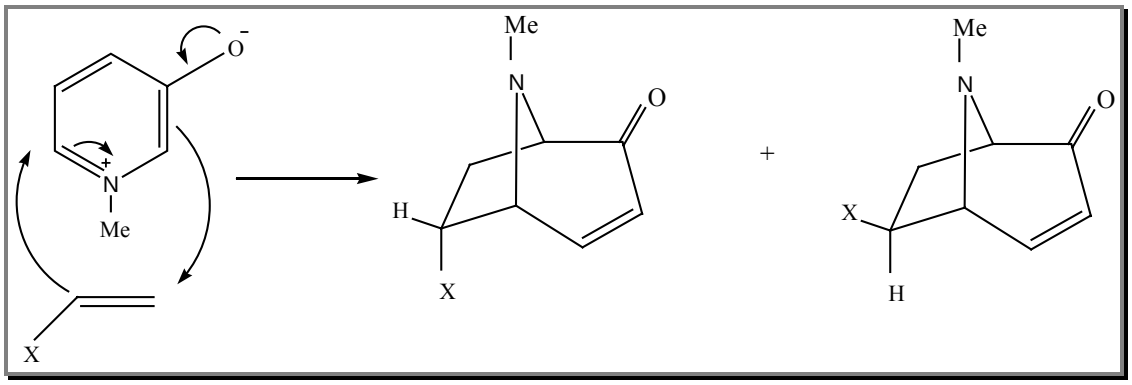
interactions is the continuum models in which the solute is placed into a cavity within the solvent [5]. The electronic distribution of the solute polarises the continuum and generates an electric field inside the cavity, which in turn affects the solute's geometry and electronic structure [6]. The Tomasi's Polarized Continuum Model (PCM) was used. It defines the cavity as the union of a series of interlocking atomic spheres [5]. Full geometry optimisations were done in acetonitrile. However, the structural parameters in the gas phase and acetonitrile as the solvent are similar and the gas phase optimised structures were used for single point energy computation in the solvent.

The energies of the reactants, products and transition states were used to plot reaction profiles and for a given reaction, the activation energy and enthalpy change were obtained. These parameters can be related to kinetic and thermodynamic stabilities respectively.

3.0 Results and Discussion

3.1 1,3-Dipolar cycloaddition of 3-oxidopyridinium with methyl acrylate

1,3-Dipolar cycloadditions between 3-oxidopyridiniums and a variety of dipolarophiles have been extensively studied experimentally by Dennis *et al*. [7] and they reported that these reactions give a mixture of the endo and exo isomers as shown in Scheme 1.



Scheme 1: Cycloadducts obtained from the reaction of 3-oxidopyridinium with different dipolarophiles.

Using quantum chemical calculations, we attempt to find out the activation energy and enthalpy change for the cycloaddition reaction shown in the scheme and to interpret the results obtained in the terms of kinetics and thermodynamics parameters.

The simplest model system examined consists of an unsubstituted 1,3-dipole, which is free of regiochemical and stereochemical complications. In Figure 1, the computed geometries of the transition state structures and their respective products are shown. The computation done in the gas phase employing HF/6-31G theory level indicates that the activation energies leading to the endo and exo isomers are 121.19 kJ/mol and 104.42 kJ/mol respectively. These results suggest that the path leading to the exo product should be preferentially followed. In addition, the enthalpy change of the reaction also shows that this isomer is favoured as it is more exothermic by 2.04 kJ/mol. According to experimental studies, a mixture of both isomers is obtained [7]. The theoretical computations support this observation as there is a close energy difference between these two products (Figure 2).

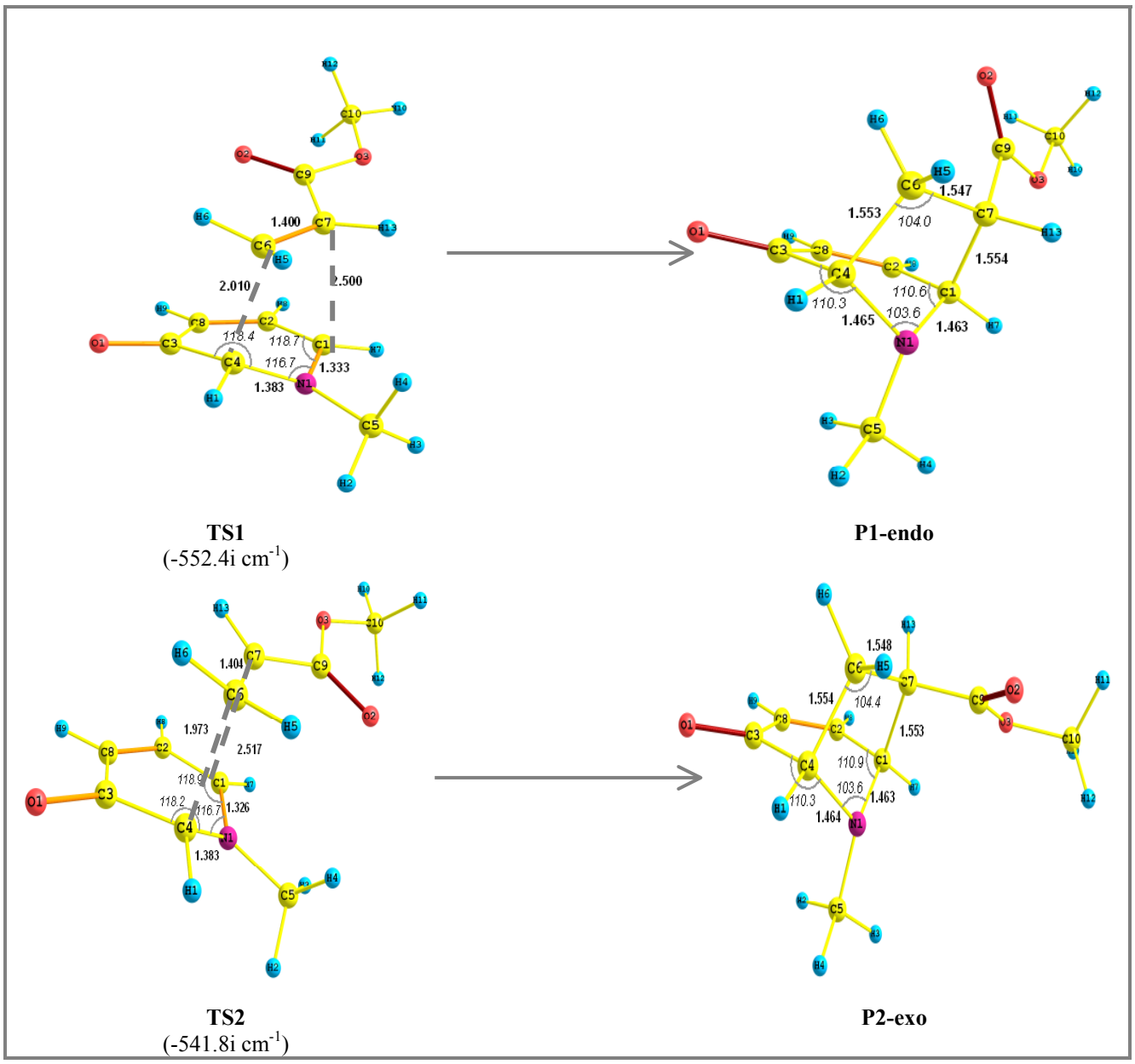


Figure 1: Computed geometries (HF/6-31G (gas phase), imaginary frequency for TSs, selected distances in Å and selected bond angles in º) of TS1, TS2, P1-endo and P2-exo.

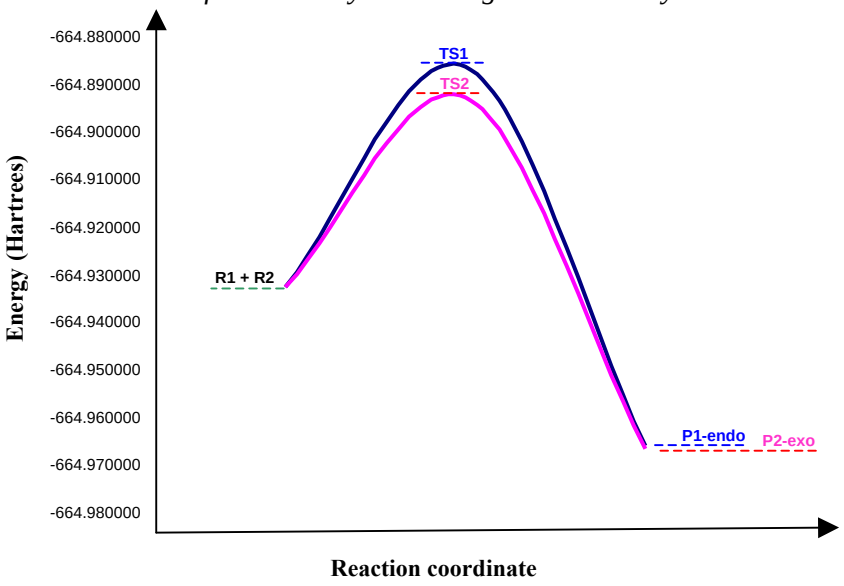
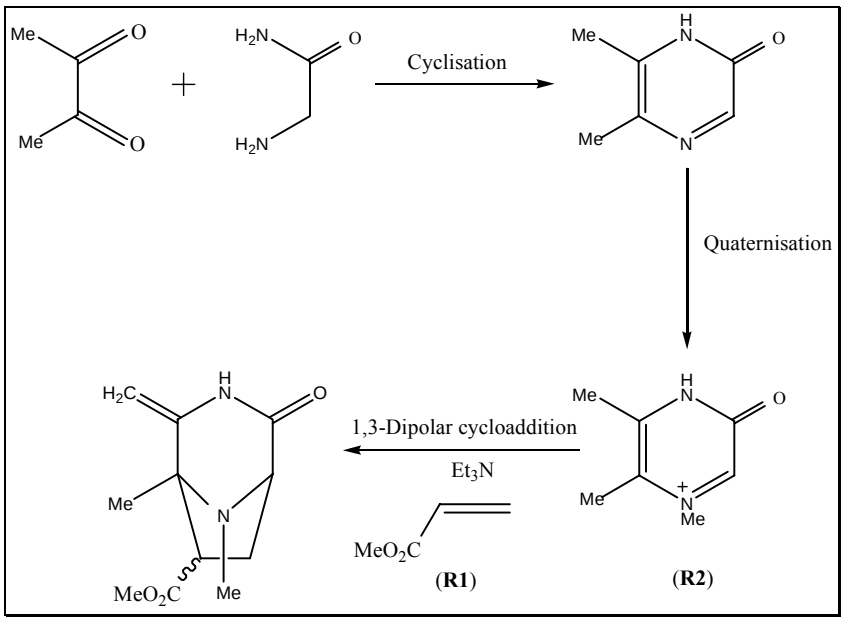


Figure 2: The energy profile for the cycloaddition reaction between 3-oxidopyridinium and methyl acrylate in the gas phase.

3.2 1,3-Dipolar cycloaddition of 3-oxidopyrazinium with methyl acrylate

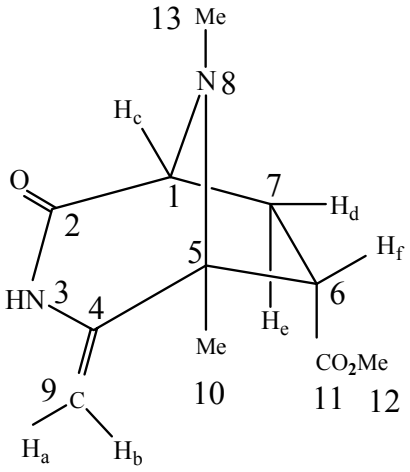
3.2.1 Synthesis

Based on this simple system, the cycloaddition reactions between 3-oxidopyrazinium and methyl acrylate has been studied. The aims of this work were to synthesise the cycloadducts formed between the reaction of 1,5,6-trimethyl-3-oxidopyrazinium with methyl acrylate followed by characterisation. Afterwards, the cycloaddition process was studied theoretically.

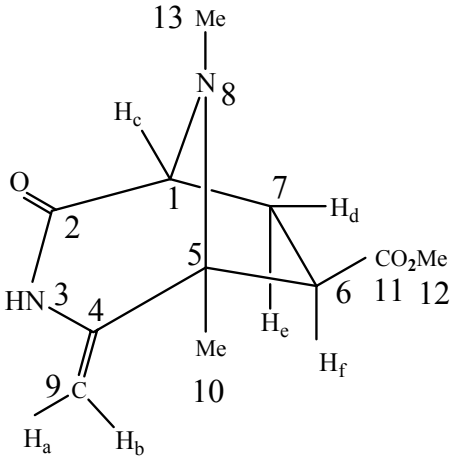


Scheme 2: Synthetic pathway for the reaction between 3-oxidppyrazinium and methyl l acrylate.

The first step is the reaction between glycinamide hydrochloride and 2,3-butanedione to yield 5,6-dimethylpyrazin-2-one followed by the conversion of pyrazinone into its pyrazinium salt. The next step is the deprotonation of the quarternary nitrogen by using triethylamine followed by the addition of methyl acrylate to form the cycloadducts namely the endo and exo isomers (Scheme 2) which were characterised by IR and NMR (Figure 3 and Figure 4).



endo



exo

The IR spectrum of both isomers show peaks at 3436 cm^{-1} indicating the N-H stretching, 3054 cm^{-1} for the C=C stretching and 2963 cm^{-1} for the C-H stretching. Two C=O stretching peaks are observed at 1721 cm^{-1} and 1665 cm^{-1} corresponding to ester and amide group respectively. This confirms that the cycloaddition reaction has taken place.

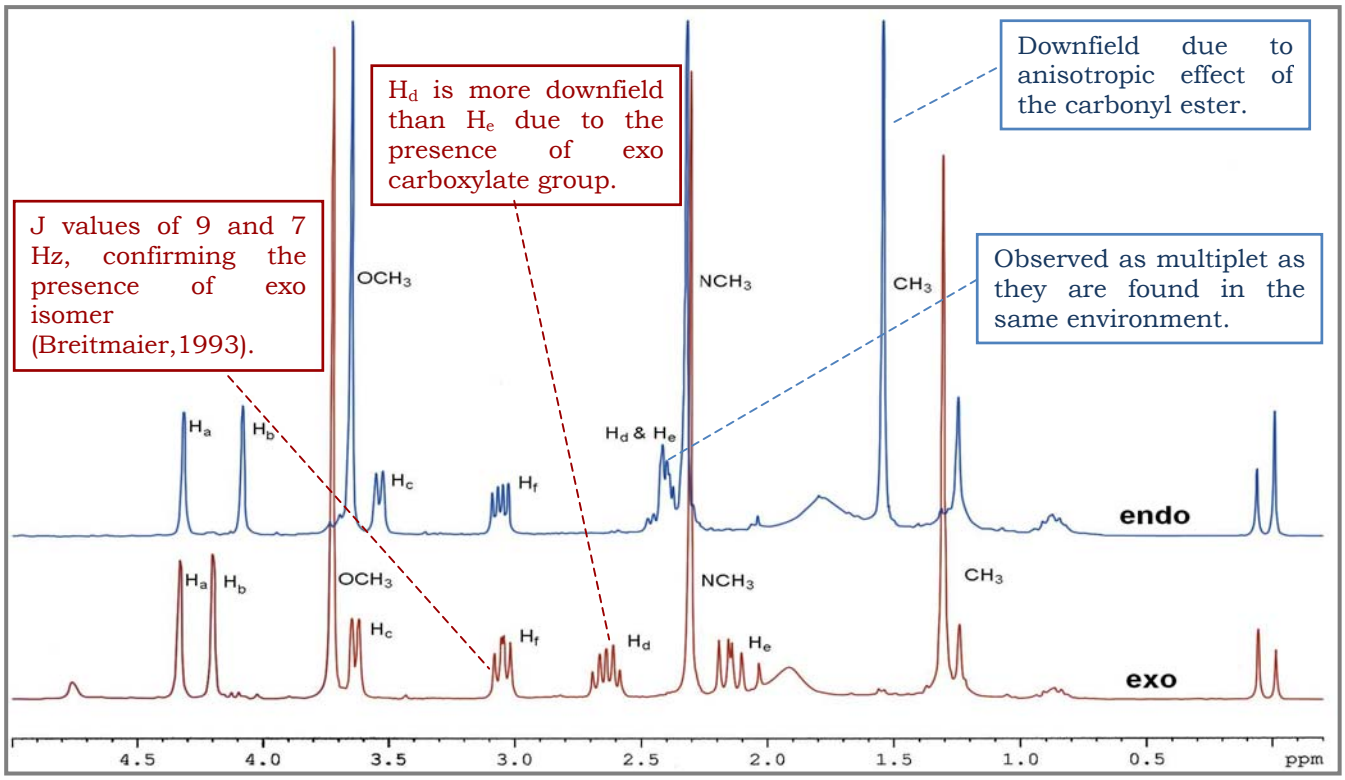


Figure 3: ^{1}H NMR spectrum of endo and exo isomers in $CDCl_3$.

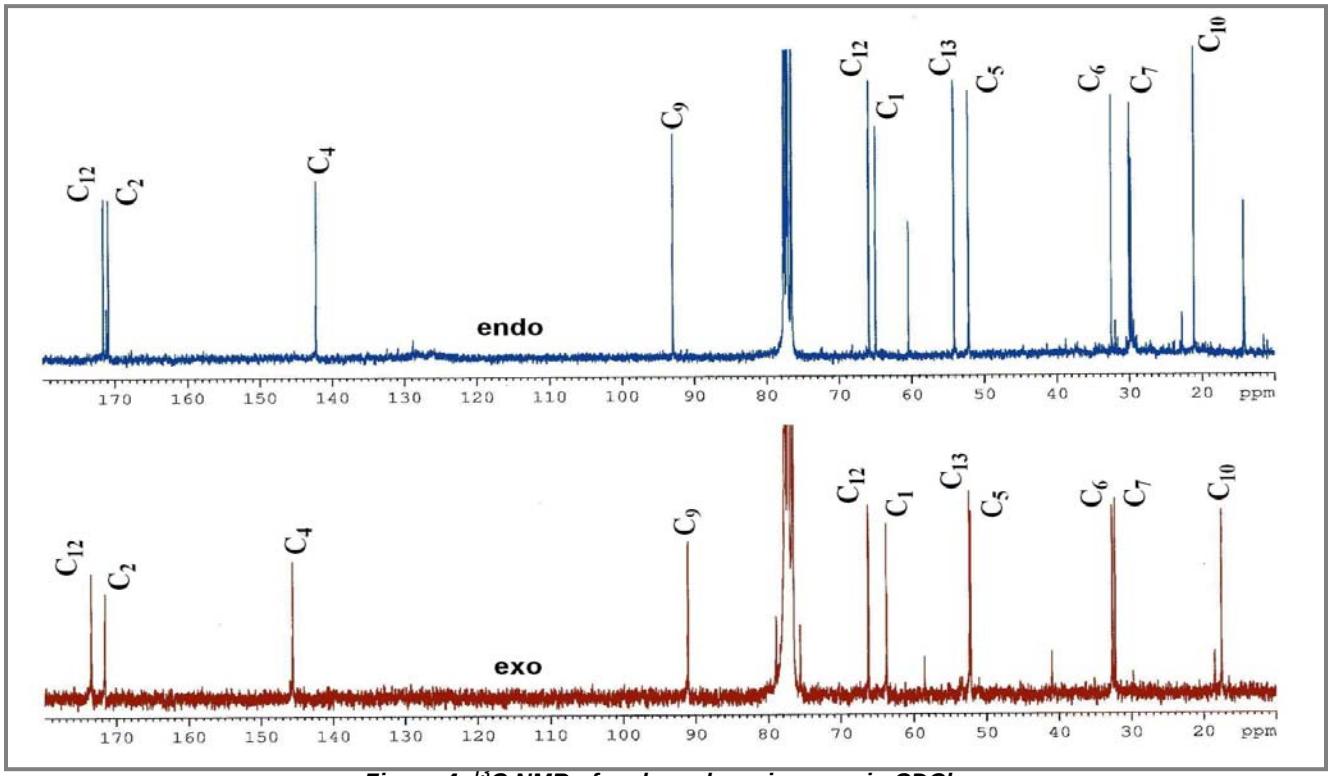
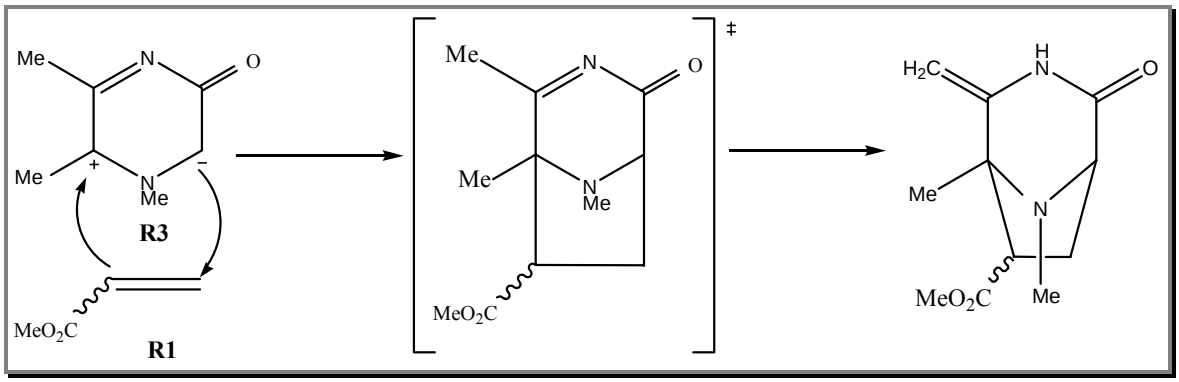


Figure 4: ^{13}C NMR of endo and exo isomers in $CDCl_3$.

3.2.2 Computational studies

In order to unravel the mechanistic details of cycloaddition, the reaction has also been studied theoretically (Scheme 3).



Scheme 3: 1,3-Dipolar cycloaddition between R1 and R3.

Geometrical parameters of reactants, transition states and products were fully optimised at the HF level using 6-31G as basis sets. The optimised structures including bond lengths and bond angles are presented in Figure 5 for the TSs and the cycloadducts. One negative imaginary frequency was observed for each transition state while the others do not present any imaginary frequencies.

Observation made during cycloaddition process:

- Loss of planarity of the pyrazinium ring.
- C_4-C_6 and C_1-C_7 bond lengths are longer in TSs than in products.
- C_1-C_7 bond is longer than C_4-C_6 in both TSs due to the presence of bulky ester group.
- $\angle C_3C_4N_1$, $\angle C_4N_1C_1$ and $\angle N_1C_1C_2$ angles from TSs to products.
- Lengthening of the C_6-C_7 bond as the double bond is changing to a single bond.

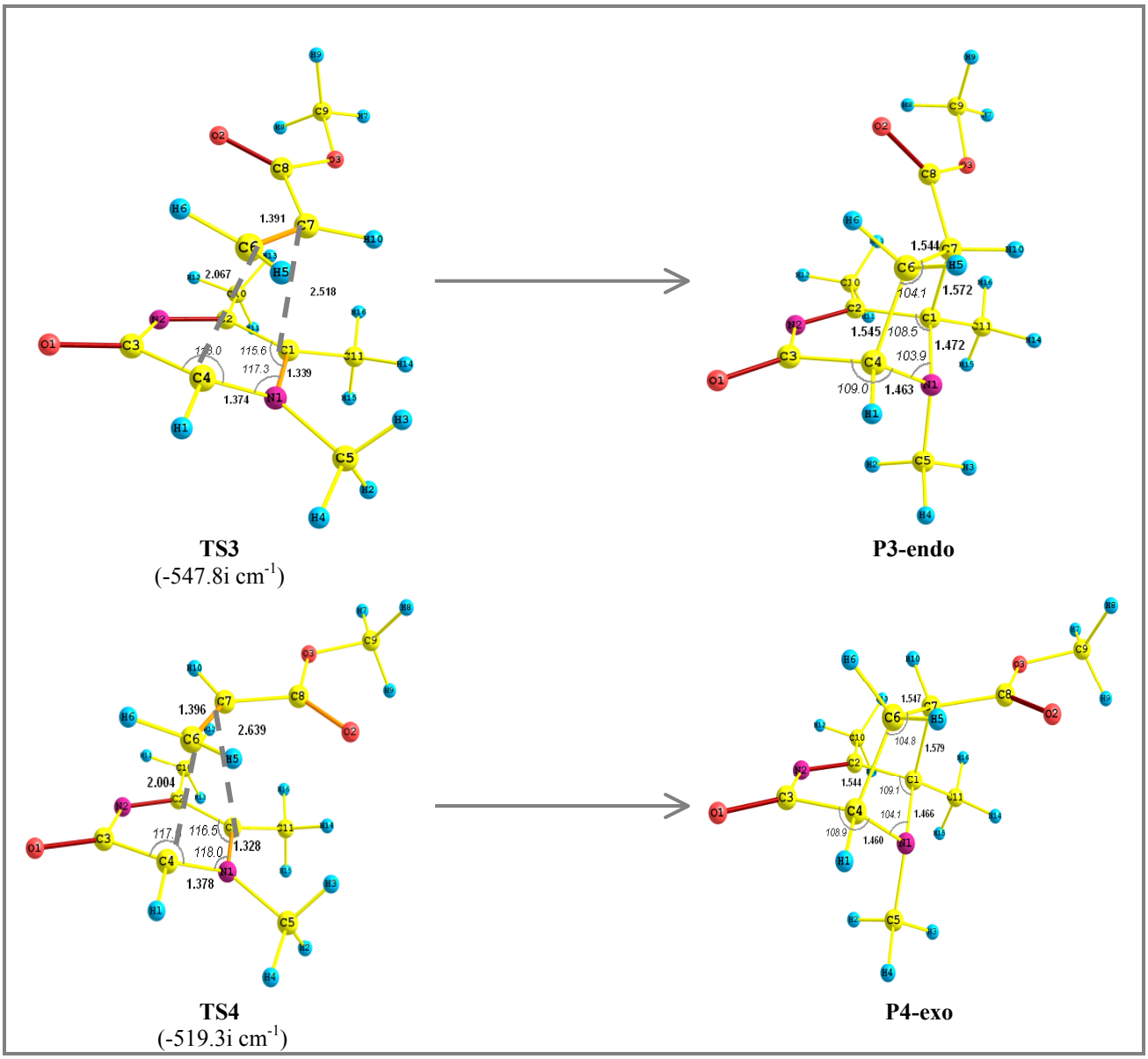


Figure 5: Computed geometries (HF/6-31G (gas phase), imaginary frequency for TSs, selected distances in Å and selected bond angles in º) of TS3, TS4, P3-endo and P4-exo.

So far, emphasis has been laid only on the gas phase cycloaddition which is considered as a crude model. Therefore, solvent effect has also been taken into account by studying the reaction in the medium the reaction is actually carried out that is, acetonitrile. Additionally, DFT calculation has been employed at the B3LYP/6-31G level of theory so as to include the effects of electronic correlations. In this way, the results can be compared with those obtained from the gas phase. It is found that acetonitrile does not affect the optimised structures of these species largely. Hence full geometry optimisations have been done for the species in the gaseous phase and the optimised structures obtained

have been used for single point computations in acetonitrile. The energies obtained by these methods are summarised below.

	Gas phase	Solvent
Method/basis sets	**HF/6-31G**	**B3LYP/6-31G**
Energy of R1/Hartrees	-304.539626	-306.377846
Energy of R3/Hartrees	-454.403182	-457.351710
Energy of R1+R3/Hartrees	-758.942809	-763.729556
Energy of TS3/Hartrees	-758.900890	-763.702072
Energy of TS4/Hartrees	-758.913383	-763.707326
Energy of P3-endo/Hartrees	-758.984085	-763.732021
Energy of P4-exo/Hartrees	-758.983765	-763.731836

Table 1: Energies (Hartrees) of the reactants, transition states and products in both gas phase at HF/6-31G and solvent at B3LYP/6-31G.

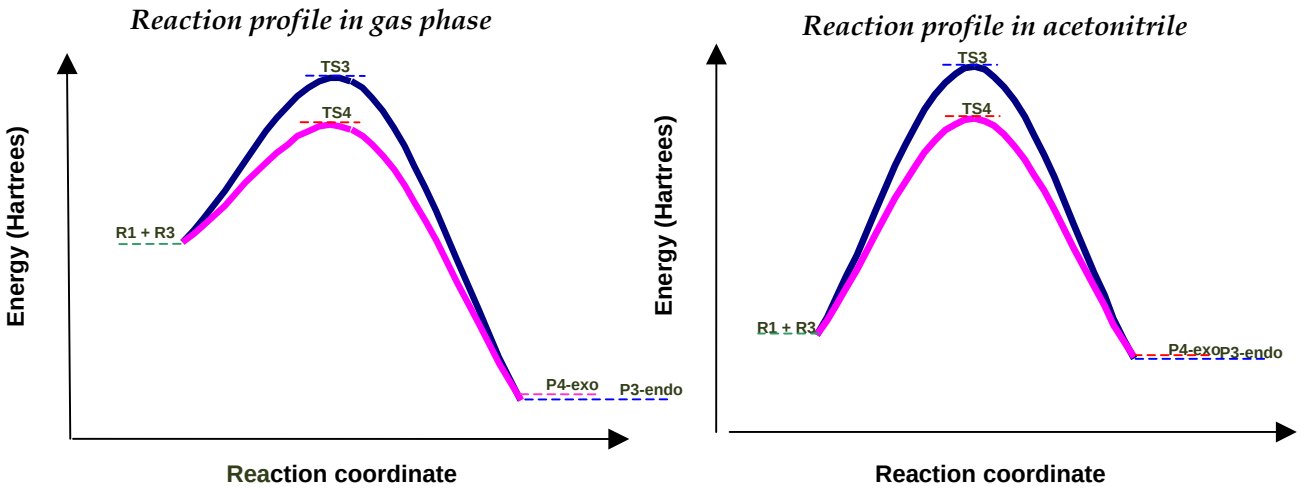


Figure 6: The energy profiles for the cycloaddition reaction between 3-oxidopyrazinium and methyl acrylate in the gas phase and in acetonitrile.

	Gas phase	Solvent
Activation energy E3/kJ/mol	110.1	72.2
Activation energy E4/kJ/mol	77.3	58.4
ΔH3/kJ/mol	-108.4	-6.5
ΔH4/kJ/mol	-107.5	-6.0

Table 2: Activation energies and enthalpy changes of the cycloaddition of 3-oxidopyrazinium with methyl acrylate in both gas phase at HF/6-31G and acetonitrile at B3LYP/6-31G.

Inspection of the data from the Tables 1 and 2 reveals that:

In gas phase:

- **TS4** is more stable than **TS3** by 32.80 kJ/mol,
- **P3** is more stable than **P4** by 0.84 kJ/mol,
- **ΔH3** is more exothermic that **ΔH4** by 0.90 kJ/mol.

In acetonitrile:

- **TS4** is more stable than **TS3** by 13.80 kJ/mol,
- **P3** is more stable than **P4** by 0.49 kJ/mol,
- **ΔH3** is more exothermic that **ΔH4** by 0.5 kJ/mol.

These data indicate that both in the gas phase and acetonitrile, the reaction between **R1** and **R3** via the **TS4** transition state is kinetically preferred with a thermodynamic preference for **P3** as the product. However, this difference is hard to detect experimentally due to close differences.

4.0 Conclusion and Future Work

Present studies showed that the synthesis of the diazabicyclo[3.2.1]octanes occurs as a results of 1,3-dipolar cycloaddition. Spectroscopic methods namely IR, ^{1}H and ^{13}C NMR have been used to elucidate the structures of the intermediates and products formed. These reactions can be interpreted in terms of the classical 1,3-dipolar cycloaddition reaction of 3-oxidopyridinium. It is found that both the endo and exo cycloadducts are obtained. Apart from synthetic studies, the cycloaddition processes have also been studied using quantum chemical calculation in order to shed more light into their reaction profiles. All the geometries of reactants, transition states and products have been fully optimised in the gas phase. The activation barriers for the endo and exo cycloadducts are 110.1 and 77.3 kJ/mol respectively. This computation result shows that the path leading to the exo product is favoured due to the lower energy barrier. Furthermore, this result is in good agreement with experimental data as the exo product is obtained in higher yield compared to the endo product. Additionally, in the presence of polar medium, such as acetonitrile, no significant changes are made except that lower activation energies and enthalpy changes are observed compared to the gas phase.

In continuation with this study, the effect of varying the substitutents on both 1,3-dipoles and dipolarophiles will be investigated as future work.

Acknowledgements

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