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Abstract
The reaction of benzenesulfonyl azides with oxabicyclic alkenes to form aziridines, reported by Chen et al. (J. Org. Chem. 2019, 84, 18, 11863-11872), could proceed via initial [3+2] cycloaddition to form triazoline intermediates followed by dinitrogen cleavage or via initial dinitrogen cleavage of the benzenesulfonyl azide to afford a nitrene intermediate followed by insertion of this species into the olefinic bond of the oxabicyclic alkene. Calculations at the DFT M06-2X/6-311G+(d,p) level show that the initial [3+2] cycloaddition has barriers of 17.3 kcal/mol (endo) and 10.2 kcal/mol (exo) while the initial nitrogen extrusion step has a barrier of 38.9 kcal/mol. The rate-determining step along the former pathway is the dinitrogen cleavage from triazoline cycloadducts which has barriers of 32.3 kcal/mol (endo) and 38.6 kcal/mol (exo) and that along the latter pathway is dinitrogen cleavage from benzenesulfonyl azide with an activation of barrier of 38.9 kcal/mol. The [3+2] addition of benzenesulfonyl azide with oxabicyclic alkene to afford endo and exo triazoline intermediates is kinetically favored over the dinitrogen cleavage from benzenesulfonyl azide by 21.6 and 28.1 kcal/mol for endo and exo pathway respectively. Thus, the preferred pathway for the reaction of oxabicyclic alkene with benzenesulfonyl azide is via initial [3+2] addition followed by dinitrogen cleavage, contrary to the proposal by Chen et al. The lower activation barrier for the dinitrogen extrusion step leading to endo aziridine compared to exo isomer means that the endo product will be formed as the major product, confirming the
experimental observation. The position of substituents on the benzene group of the benzenesulfonyl azide greatly affects the endo / exo diastereoselectivity.

Keywords: Aziridines, oxabicyclic alkene, benzenesulfonyl azides, triazoline, dinitrogen extrusion, cycloaddition.

1. Introduction
Aziridines well-known three-membered heterocycles containing a nitrogen atom, and are among the most widely used intermediates in organic synthesis, where they act as precursors for the synthesis of complex molecules due to the strains incorporated in their skeletons. In addition to their importance as reactive intermediates, many biologically-active compounds have been found to possess these three-membered rings1–9. Over 130 biologically active aziridine-containing compounds have been confirmed to have pharmacological activity including antitumor, antibacterial, and antimicrobial effects10. Even though aziridines have been synthesized by the reactions of nitrene precursor N-tosyliminobenzylidinane with olefins, N-tosyliminobenzylidinane has a short shelf-life and poor solubility in common solvents11–14. In 2019, Chen and co-workers successfully reported the synthesis of aziridines by employing a three-component cycloaddition of oxabicyclic alkene with NaN₃ and arylsulfonyl chlorides under metal-free conditions with the aziridine products in good yield up to 82% yield (Scheme 1)15. Also, the endo-cycloadduct was obtained as the predominant product, although the cycloaddition of oxabicyclic alkenes have been known to generally produce the exo-product as the predominant product. Chen and co-workers reported that the group position properties of the monosubstituted arylsulfonyl chlorides had little effect on product yield, but had a large effect on the endo/exo diastereoselectivities of the product; 4-benzenesulfonyl azides gave the endo-cycloadduct as the predominant product whiles 2 or 3-nitrobenzenesulfonyl chloride gave
the exo-cycloadduct as the predominant product. Moreover, electron-withdrawing groups on the oxabicyclic alkene had reduced the product yield but with improved endo-selectively whiles electron-donating groups on the oxabicyclic alkene had slightly higher yields but with decreased endo-selectivity.

**Scheme 1.** Three-component cycloaddition of oxabicyclic alkene in the presence of NaN$_3$ and arylsulfonyl chloride to afford *endo* (**P_Endo**) and *exo* (**P_Exo**) aziridines.$^{15}$

Although the products from Chen and co-workers are known, the mechanistic rationale for the observed diasterioselectivities has not been established. After the arylsulfonyl azide has been generated from the reaction of NaN$_3$ with arylsulfonyl chloride, the plausible mechanism for the reaction of arylsulfonyl azide with oxabicyclic alkene to afford the aziridine products are depicted in **Scheme 2 and 3**. Chen et al. have proposed that the reaction could proceed via an initial dinitrogen cleavage from arylsulfonyl azide to form a nitrene species and subsequent insertion of this species into the olefinic bond of oxabicyclic alkene to afford the aziridine products.$^{15}$ However, the reaction could also proceed via [3+2] cycloaddition to afford triazoline intermediates and subsequent dinitrogen cleavage from this intermediate to form the final aziridine products. Which pathway is preferred? Computational chemistry methods are often employed in the
prediction and rationalization of reactivity trends in order to provide theoretical guidance for correlative experiments.

Herein, density functional theory (DFT) calculations are employed to elucidate the mechanism of the reaction of arylsulfonyl azides with oxabicyclic alkene toward the formation of aziridines. The aim of this study is to provide a detailed mechanistic insight into the reaction of arylsulfonyl azides with oxabicyclic alkene by examining the energetics of the various elementary steps leading to the formation of the observed exo/endo products in the experimental work of Chen et al \(^{15}\). The effect of different substituents on the benzene group of the benzenesulfonyl azide and on the oxabicyclic alkene on the energetics of the reaction is also investigated. In addition, the effect of solvent on the energetics of the reaction is also explored. An in-depth understanding of the mechanism of the reaction will provide chemical insights into the reactivity of the reaction which is crucial for the control and development of better synthetic methods to influence product outcomes.
Scheme 2. Proposed reaction pathway for the reaction of oxabicyclic alkene 1A and arylsulfonyl azide 2A to afford aziridines P_Endo and P_Exo via Path A.

**Path B**

![Pathway diagram]

Scheme 3. Proposed reaction pathway for the reaction of Oxabicyclic alkene 1A and arylsulfonyl azide 2A to afford aziridines P_Endo and P_Exo via Path B.  

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2. Computational details and methodology

All the quantum chemical calculations were carried out with the Spartan’14 and Gaussian 09 computational chemistry software suites at the M06-2X/6-311+G(d,p) levels of theory. The Minnesota functional M06-2X, developed by Zhao and Truhlar, is a hybrid meta-generalized gradient approximation (meta-GGA) functional that has been shown to be effective at geometry optimizations and computing thermochemical and kinetic parameters of chemical reactions. Using the polarizable continuum model (PCM), 1,4-dioxane was employed to compute solvation effects in the reactions.

The guess geometries of the molecules were constructed with the Spartan’s graphical model builder and minimized interactively using the molecular mechanics force field. Transition state structures were computed by first obtaining guess input structures. This was achieved by constraining specific internal coordinates of the molecules (bond lengths, bond angles, dihedral angles) while fully optimizing the remaining internal coordinates. This procedure gives appropriate guess transition state input geometries which are then submitted for full transition state calculations without any geometry or symmetry constraints.

Full harmonic vibrational frequency calculations were carried out to verify that each transition state structure had a Hessian matrix with only a single negative eigen value, characterized by an imaginary vibrational frequency along the respective reaction coordinates. Intrinsic reaction coordinate calculations were then performed to ensure that each transition state smoothly connects the reactants and products along the reaction coordinate.

The global electrophilicities (ω), and maximum electronic charge (ΔN_{max}) of the various benzenesulfonyl azide derivatives were calculated using equations (1) and (2). The electrophilicity index measures the ability of a reactant to accept electrons and it has been found to be a function of the electronic chemical potential, μ = (EHOMO + ELUMO)/2 and chemical hardness, η = (ELUMO - EHOMO) as defined by Pearson’s acid-base concept. Hence, species with large electrophilicity...
values are more reactive towards nucleophiles. These equations are based on the Koopmans theory
originally established for calculating ionization energies from closed-shell Hartree–Fock
wavefunctions, but have since been adopted as acceptable approximations for computing
electronic chemical potential and chemical hardness.

\[ \omega = \mu^2 / 2\eta \] (1)
\[ \Delta N_{\text{max}} = -\mu / \eta \] (2)

The maximum electronic charge transfer (\(\Delta N_{\text{max}}\)) measures the maximum electronic charge that
the electrophile may accept. Thus, species with large \(\Delta N_{\text{max}}\) index would be best electrophile and
hence poor nucleophile given a series of compounds.

**3.0 Results and discussion**

Based on scheme 2 and 3, the reaction of oxabicyclic alkene 1A with benzenesulfonyl azide have
been studied at the M06-2X/6-311G+(d,p) level of theory. The formation of products P_Endo and
P_Exo was proposed by Chen and co-workers to occur via an initial dinitrogen extrusion from
benzenesulfonfonyl azide 2A to afford intermediate 3A through TS3. Intermediate 3A then inserts
into the olefinic bond of the oxabicyclic alkene through TS4_Endo and TS4_Exo to afford
products P_Endo and P_Exo respectively. Based on some preliminary calculations, we
proposed an alternative pathway for the reaction of oxabicyclic alkene with benzenesulfonyl azide.
We propose that the formation of P_Endo and P_Exo occur also via an initial [3+2] cycloaddition
fashion or 1,3-dipolar cycloaddition reaction between the benzenesulfonyl azide and the
oxabicyclic alkene to afford intermediates A_Endo and A_Exo through TS1_Endo and TS1_Exo
respectively. Intermediates A_Endo and A_Exo then undergo dinitrogen cleavage or extrusion
through TS2_Endo and TS2_Exo to afford products P_Endo and P_Exo as depicted in scheme
2.
The results of the reaction of oxabicyclic alkene with benzenesulfonyl azide in the gas phase and the effect 1,4-dioxane solvent on the energetics of the reaction are discussed in Section 3.1 and 3.2 respectively. The effect of electron-donating groups and electron-withdrawing groups on the benzene moiety of the benzenesulfonyl azide on the reaction of oxabicyclic alkene with benzenesulfonyl azide are discussed in section 3.3. The reaction of 4-nitrobenzenesulfonyl and 4-methoxybenzenesulfonyl azide with several di-substituted oxabicyclic alkenes are discussed in section 3.4. Section 3.5 discusses the change in regioselectivity when 2 or 3-substituted benzenesulfonylazide is employed. Section 3.6 deals with the orbital interactions between benzenesulfonyl azide and oxabicyclic alkene, while the global reactivity indices for the various oxabicyclic alkenes and benzenesulfonyl azides are discussed in Section 3.7. All the energies reported herein are Gibbs free energy with zero-point corrections.

3.1 Reaction of oxabicyclic alkene and benzenesulfonyl azide to afford aziridines P_Endo and P_Exo

The relative energies of the reactants, intermediates, transition states and products as well as optimized geometries of the transition state structures involved in the reaction of oxabicyclic alkene with benzenesulfonyl azide are shown in Figure 1 and Figure 2 respectively. For Path B, in the first step of the reaction, benzenesulfonyl azide undergoes dinitrogen extrusion through TS3 with an activation barrier of 38.9 kcal/mol and reaction energy of 11.8 kcal/mol leading to the formation of intermediate 3A. Intermediate 3A then inserts itself into the olefinic bond of the oxabicyclic alkene as shown in Scheme 2 through TS4_Endo and TS4_Exo with activation barriers of 4.3 and 4.3 kcal/mol respectively leading to the formation of products P_Endo and P_Exo. This pathway is not selective towards any of the products.

In our proposed pathway (Path A), we observed that the [3+2] addition reaction of benzenesulfonyl azide with the oxabicyclic alkene through TS1_Endo and TS1_Exo is kinetically favored with an activation barrier of 17.3 and 10.8 kcal/mol leading to the formation of
intermediate $A_{\text{Endo}}$ and $A_{\text{Exo}}$ respectively. Moreover, formation of intermediates $A_{\text{Endo}}$ and $A_{\text{Exo}}$ is exergonic and thermodynamically favored by -42 and -43.5 kcal/mol respectively. The stability of $A_{\text{Endo}}$ and $A_{\text{Exo}}$ reveal that intermediates $A_{\text{Endo}}$ and $A_{\text{Exo}}$ should be observed in the reaction. Intermediates $A_{\text{Endo}}$ and $A_{\text{Exo}}$ then undergo dinitrogen extrusion through $\text{TS2}_{\text{Endo}}$ and $\text{TS2}_{\text{Exo}}$ with activation energies of 32.3 and 38.6 kcal/mol. Formation of products $P_{\text{Endo}}$ through $\text{TS2}_{\text{Endo}}$ is kinetically favored over formation of $P_{\text{Exo}}$ via $\text{TS2}_{\text{Exo}}$ by 6.6 kcal/mol. From the results, the rate-determining step for the formation of products $P_{\text{Endo}}$ and $P_{\text{Exo}}$ is the dinitrogen extrusion from intermediates A as depicted in Scheme 2. Although the formation of intermediate $A_{\text{Exo}}$ is kinetically favored over the formation of intermediate $A_{\text{Endo}}$, the overall formation of products $P_{\text{Endo}}$ and $P_{\text{Exo}}$ is controlled by the dinitrogen cleavage step which is the rate-determining step of this reaction hence $P_{\text{Endo}}$ will be formed in greater yield than $P_{\text{Exo}}$. This accounts for observations made by Chen and co-workers in their experimental work where $P_{\text{Endo}}$ was isolated as the major product and $P_{\text{Exo}}$, the minor product. Our results indicate that the most feasible pathway for the formation of products $P_{\text{Endo}}$ and $P_{\text{Exo}}$ is through Path A and not Path B, looking at the energetics of the reaction.

It should be noted that [3+2] addition of benzenesulfonyl azide with oxabicyclic alkene to afford intermediates $A_{\text{Endo}}$ and $A_{\text{Exo}}$ is kinetically feasible over the dinitrogen cleavage from benzenesulfonyl azide by 21.6 and 28.1 kcal/mol for endo and exo pathway respectively. Also, formation of intermediates $A_{\text{Endo}}$ and $A_{\text{Exo}}$ is thermodynamically favoured over the formation of intermediate 3A by 54.3 and 55.3 kcal/mol respectively. Although the subsequent insertion of intermediate 3A into the olefinic bond of the oxabicyclic alkene is kinetically and thermodynamically feasible, the energetics show that intermediates $A_{\text{Endo}}$ and $A_{\text{Exo}}$ would be formed quickly over intermediate 3A rendering the formation of intermediate 3A less likely to occur. Moreover, the products distribution of $P_{\text{Endo}}$ and $P_{\text{Exo}}$ would be even if the reaction
is to go through **Path B** since the activation barrier for reaction of intermediate **3A** with oxabicyclic alkene is 4.3 and 4.3 kcal/mol for **TS4_Endo** and **TS4_Exo** respectively but an even product distribution is not observed, hence the most feasible pathway for the formation of aziridines **P_Endo** and **P_Exo** for the reaction of oxabicyclic alkene with benzenesulfonyl azides is through **Path A** and not **Path B**.
Figure 1 Zero-point energy corrected Gibbs free energy profile for the reaction of Oxabicyclic alkene and benzenesulfonyl azide to afford Aziridines P_Endo and P_Exo. All stationary points are optimized at the M06-2X/6-311G+(d,p) level of theory at 85 °C in gas phase. Relative energies in kcal/mol.
Figure 2. Gas phase optimized geometries of possible transition state structures involved in reaction of oxabicyclic alkene with benzenesulfonyl azide as calculated by M06-2X/6-311+G(d,p) at 85 °C. Bond lengths are in Å.
3.2.1 Effects of solvent 1,4-dioxane on the energetics of the reaction

Using the polarizable continuum model (PCM), the effect of solvent 1,4-dioxane on the energetics of the reaction of oxabicyclic alkene with benzenesulfonyl azide was investigated. There appears to be a minimal solvent effect on Path B. 1,4-dioxane marginally reduces the activation barrier of the dinitrogen cleavage from benzenesulfonyl azide through TS3 by 1.2 kcal/mol. Also the activation barrier for the insertion of the nitrone species (intermediate 3A) into the olefinic bond of oxabicyclic alkene is 4.2 (endo) and 4.0 kcal/mol (exo) in 1,4-dioxane. With these results, we can still infer that the product distribution of P_Endo and P_Exo should be even if the reaction is to proceed via Path B.

Along Path A, 1,4-dioxane marginally increase the activation barrier of the [3+2] addition step through TS1_Endo and TS1_Exo by 0.4 and 0.6 kcal/mol respectively. Moreover, 1,4-dioxane slightly reduces the activation barrier for the dinitrogen extrusion step through TS2_Endo and TS2_Exo by 2.0 and 2.3 kcal/mol respectively. The activation barrier of the dinitrogen extrusion step via TS2_Endo and TS2_Exo is 29.8 and 36.0 kcal/mol respectively. In 1,4-dioxide, formation of products P_Endo through TS2_Endo is kinetically favored over formation of P_Exo via TS2_Exo by 6.2 kcal/mol compared to 6.3 kcal/mol in the gas phase. Although there are slight variations in the activation barriers, the energetic trends remain unchanged hence gas phase calculations are deemed adequate for the reactions studied.

| Medium     | TS1_Endo | TS1_Exo | TS2_Endo | TS2_Exo | TS3   | TS4_Endo | TS4_Exo |
|------------|----------|---------|----------|---------|-------|----------|---------|
| Gas Phase  | 17.3     | 10.8    | 32.3 (31.9) | 38.6 (38.3) | 38.9  | 4.3      | 4.3     |
| 1,4-Dioxane| 17.7     | 11.5    | 30.3 (29.8) | - (36.0) | 37.3  | 4.2      | 4.0     |

Table 1. Activation energies of the elementary steps involved in the reaction of benzenesulfonyl azide and oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol. Energies in bracket were computed at M06-2X/6-311G(d,p) level.
Table 2. Relative energies of intermediates and products involved in the reaction benzenesulfonyl azide and oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol.

| Medium          | 1A + 2A | A_Endo | A_Exo | 3A + N₂ | P_Endo+N₂ | P_Exo+N₂ |
|-----------------|---------|--------|-------|---------|-----------|----------|
| Gas Phase       | 0.0     | -42.0  | -43.5 | 11.8    | -67.8     | -71.7    |
| 1,4-Dioxane     | 0.0     | -41.6  | -43.5 | 13.4    | -67.8     | -71.9    |

3.2.2 Product distribution in the reaction of oxabicyclic alkene with benzenesulfonyl azide

The Boltzmann distribution has been applied to rationalize the amount of P_Exo and P_Endo that will be formed in the reaction of benzenesulfonyl azide with oxabicyclic alkene using the energetics obtained. Here, the activation barrier for the rate-determining step is employed. The ratio of endo to exo products can be written as:

\[
\frac{P_{\text{endo}}}{P_{\text{exo}}} = \exp \left( \frac{E_{\text{exo}} - E_{\text{endo}}}{kT} \right)
\]

Since \( \text{TS2_Exo} - \text{TS2_Endo} = 6.3 \text{ kcal/mol} \), \( T = 358.15 \text{ K} \), and \( k = 18(0.0019872014) \text{ kcal/mol.K} \)

\[
\frac{P_{\text{endo}}}{P_{\text{exo}}} = \exp \left( \frac{6.3 \text{ kcal/mol}}{18(0.0019872014)\text{kcal/molK} * 358.15\text{K}} \right)
\]

\[
\frac{P_{\text{endo}}}{P_{\text{exo}}} = \exp(0.492)
\]

\[
\frac{P_{\text{endo}}}{P_{\text{exo}}} = 1.64 = \frac{62.1}{37.9} \approx 62 : 38
\]

The experimentally-observed product distribution from the work of Chen et al \(^{15}\) in the reaction of benzenesulfonyl azide with oxabicyclic alkene for endo: exo is 67:33, and this is in excellent agreement with our computed results.
3.3 Substituent effects on the reaction of oxabicyclic alkene with benzenesulfonyl azide
To investigate the effects of substituents on the energetics of the reaction and products outcomes, electron-donating groups and electron-withdrawing groups are introduced at the position R1 of the benzene group on the benzenesulfonyl azide. The aim of this section of the study is to predict the type of substituents that the benzenesulfonyl azide substrate must contain to influence products yield. The results obtained under this section of the study are reported in Table 3 to 7.

3.3.1 Effect of electron-donating groups on the reaction
To establish the effects of electron-donating groups (EDGs) on the energetics of the reaction, we employed Ph, CH₃, OCH₃, OH, and NH₂ substituted benzenesulfonyl azide. In all cases a marginal decrease in activation barriers for the initial [3+2] addition step through TS₁_EN compared to the parent reaction is observed, with Ph and CH₃ having the least activation barrier of 17.1 kcal/mol indicating a decrease by 0.2 kcal/mol, and OCH₃, OH, and NH₂ having activation barriers of 17.2 each. With the exception of NH₂, a marginal increase in activation barriers is also observed for the initial [3+2] cycloaddition addition leading to the formation of intermediates A_Exo through TS₁_Exo. OH has the least activation barrier of 10.5 kcal/mol for the cycloaddition step through TS₁_Ex indicating a marginal increase of 0.3 kcal/mol. The observed trend for TS₁_Ex is OH < Ph < OCH₃ < CH₃ < NH₂. A general increase in activation barrier for dinitrogen extrusion step through TS₂_Endo and TS₂_Exo, the rate-determining step for the formation of products P_Endo and P_Exo, is observed in all cases. The trend for TS₂_Endo is Ph < OH < CH₃ < OCH₃ < NH₂ with Ph having an activation barrier of 32.4 kcal/mol indicating an increase by 0.1 kcal/mol and NH₂ having an activation barrier of 33.3 kcal/mol, an increase by 1.0 kcal/mol. The observed trend for TS₂_Exo leading to the less favored product is also Ph < OH < CH₃ < OCH₃ < NH₂ with Ph and NH₂ having activation barriers of 38.6 and 39.5 kcal/mol indicating a marginal increase by 0.1 and 0.9 kcal/mol respectively.
Also, the effect of OH and OCH$_3$ on the reaction via Path B was also investigated. A marginal decrease in activation barrier for initial dinitrogen extrusion is observed for both OH and OCH$_3$ with OH and OCH$_3$ having activation barriers of 37.1 kcal/mol and 37.0 kcal/mol respectively. Also the activation barriers for the nitrene insertion into the olefinic bond for OH and OCH$_3$ substituents are 3.1 kcal/mol (endo and exo) and 3.2 kcal/mol (endo and exo). With these results, distribution of endo and exo products is expected to be even if the reaction is to proceed via Path B but an even product distribution is not observed in experiment.

3.3.2 Effect of electron-withdrawing groups on the reaction
In order to establish the effect of electron-withdrawing groups (EWGs) on the energetics of the reaction, we employed F, Cl, CF$_3$, CN, and NO$_2$ substituted benzenesulfonyl azide. In all cases, a marginal decrease in activation barrier is observed for TS$_{1\text{Endo}}$ and TS$_{1\text{Exo}}$ (see table 3), with NO$_2$ having the least activation barrier of 16.8 and 9.3 kcal/mol for TS$_{1\text{Endo}}$ and TS$_{1\text{Exo}}$ respectively. The observed trend for TS$_{1\text{Endo}}$ is NO$_2$ < CN < CF$_3$ < Cl < F. The same trend is also observed for TS$_{1\text{Exo}}$. Also the activation barrier for the di-nitrogen extrusion step through TS$_{2\text{Exo}}$ and TS$_{2\text{Endo}}$ is reduced owing to the presence of these EWGs, with NO$_2$ having the least activation barrier of 30.2 and 35.8 kcal/mol for TS$_{2\text{Exo}}$ and TS$_{2\text{Endo}}$ indicating a decrease by 2.1 and 2.8 kcal/mol respectively. In all cases for both electron-donating and electron-withdrawing groups, at the para-position or position 3 of the benzene group on the benzenesulfonyl azide, dinitrogen-extrusion via TS$_{2\text{Endo}}$ is more favored than dinitrogen extrusion via TS$_{2\text{Exo}}$.

The effect of Cl, F, CN, and NO$_2$ on the energetics of the reaction via Path B was also investigated. For CN and NO$_2$, a marginal increase in activation barrier is observed for the initial nitrogen extrusion via TS$_3$ with CN and NO$_2$ having activation barriers of 39.1 and 39.4 kcal/mol respectively and a marginal decrease is observed for CN and NO$_2$ with activation barriers of 38.0
and 38.3 kcal/mol respectively. In all cases the activation barrier for dinitrogen extrusion via TS3 which is the rate-determining step via Path B is higher than the barrier for dinitrogen extrusion via TS2_Endo and TS2_Exo which the rate-determining step via Path A. This results also indicate that, the most feasible pathway for the reaction of oxabicyclic alkene with arylsulfonyl azides is via Path A and not Path B.
### Table 3. Activation energies of the elementary steps involved in the reaction of Ph-, CH$_3$-, OCH$_3$-, OH-, and NH$_2$-substituted benzenesulfonyl azide and oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol.

| Substituents | TS1_Endo | TS1_Exo | TS2_Endo | TS2_Exo |
|--------------|----------|---------|----------|---------|
| Ph           | 17.1     | 10.6    | 32.4     | 38.7    |
| CH$_3$       | 17.1     | 10.8    | 32.6     | 38.9    |
| OCH$_3$      | 17.2     | 10.7    | 32.9     | 39.1    |
| OH           | 17.2     | 10.5    | 32.6     | 38.8    |
| NH$_2$       | 17.2     | 11.0    | 33.3     | 39.5    |

### Table 4. Relative energies of intermediates and products involved in the reaction of Ph-, CH$_3$-, OCH$_3$-, OH-, and NH$_2$-substituted benzenesulfonyl azide and oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol.

| Substituents | 1A + 2A | A_Endo | A_Exo | P_Endo | P_Exo |
|--------------|---------|--------|-------|--------|-------|
| Ph           | 0.0     | -42.1  | -43.7 | -68.0  | -71.8 |
| CH$_3$       | 0.0     | -41.9  | -43.5 | -67.5  | -71.6 |
| OCH$_3$      | 0.0     | -41.9  | -43.6 | -67.8  | -71.6 |
| OH           | 0.0     | -42.0  | -43.7 | -68.0  | -71.8 |
| NH$_2$       | 0.0     | -41.7  | -43.1 | -67.3  | -71.3 |

### Table 5. Activation energies of the elementary steps involved in the reaction of F-, Cl-, CF$_3$-, CN-, and NO$_2$-substituted benzenesulfonyl azide and oxabicyclic alkene at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol.

| Substituents | TS1_Endo | TS1_Exo | TS2_Endo | TS2_Exo |
|--------------|----------|---------|----------|---------|
| F            | 17.1     | 10.2    | 31.9     | 38.0    |
| Cl           | 17.1     | 10.2    | 31.7     | 37.8    |
| CF$_3$       | 16.9     | 9.7     | 30.9     | 37.1    |
| CN           | 16.9     | 9.6     | 30.6     | 36.1    |
| NO$_2$       | 16.8     | 9.3     | 30.2     | 35.8    |

### Table 6. Relative energies of intermediates and products involved in the reaction of F-, Cl-, CF$_3$-, CN-, and NO$_2$-substituted benzenesulfonyl azide and oxabicyclic alkene at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol.

| Substituents | 1A + 2A | A_Endo | A_Exo | P_Endo | P_Exo |
|--------------|---------|--------|-------|--------|-------|
| F            | 0.0     | -42.4  | -44.1 | -68.5  | -72.4 |
| Cl           | 0.0     | -42.4  | -44.2 | -65.6  | -72.3 |
| CF$_3$       | 0.0     | -42.8  | -44.6 | -69.0  | -72.8 |
| CN           | 0.0     | -42.8  | -44.7 | -69.3  | -72.9 |
| NO$_2$       | 0.0     | -43.0  | -45.0 | -69.6  | -73.1 |
Table 7. Activation energies of the elementary steps involved in the reaction of OH-, OCH₃, F-, Cl-, CN-, and NO₂-substituted benzenesulfonyl azide and oxabicyclic alkene via Path B at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol.

| Substituents | TS3 | TS4_Endo | TS4_Exo |
|--------------|-----|----------|---------|
| H            | 38.9| 4.3      | 4.3     |
| OH           | 37.1| 3.1      | 3.1     |
| OCH₃         | 37.0| 3.2      | 3.2     |
| F            | 38.0| 3.4      | 3.6     |
| Cl           | 38.3| 3.3      | 3.7     |
| CN           | 39.1| 3.0      | 3.4     |
| NO₂          | 39.4| 2.7      | 3.4     |

3.4 Reaction of di-substituted oxabicyclic alkenes with benzenesulfonyl azides

This section of the study investigates how substituents on the oxabicyclic alkene affect the reactivity of oxabicyclic alkenes with benzenesulfonyl azides. 4-nitrobenzenesulfonyl azide and 4-methoxybenzenesulfonyl azide which have very strong electron-withdrawing and electron-donating groups were employed, and substituents were varied on the oxabicyclic alkene. The results of this section of the study are tabulated in tables 8 to 11 and discussed below.

Our results indicate that when electron-donating groups are substituted at the position 6 and 7 of the oxabicyclic alkene, rendering it electron-rich, the activation barrier for the initial cycloaddition step through TS1_Exo and TS1_Endo is reduced. Electron-donating groups employed in this section of the study are CH₃, OH, and NH₂. A significant decrease in activation barrier for TS1_Endo is observed with OH having the least activation barrier of 12.0 kcal/mol indicating a decrease by 4.8 kcal/mol, followed by NH₂ and CH₃ with activation barriers of 12.1 and 16.3 kcal/mol respectively. It is important to note that electron-donating groups also decrease the activation barrier for the cycloaddition step through TS1_Exo, hence favoring the formation of the exo product too. There appears to be no significant effect on the activation barriers of the dinitrogen extrusion step via TS2_Endo and TS2_Exo since the change in activation barriers are within the range of 0 to 0.9 kcal/mol. The decrease in activation barrier of TS1_Exo and
**TS1_Endo** may correspond to slight increase in product yield but with decreased selectivity since the exo-product is also favoured.

On the other hand, electron-withdrawing groups at the position 6 and 7 of the oxabicyclic alkene significantly decrease the activation barrier of the cycloaddition addition through **TS1_Endo** and increase the activation barrier for **TS1_Exo**, with NO$_2$ having an activation barrier of 13.7 kcal/mol and 11.6 kcal/mol for **TS1_Endo** and **TS1_Exo** respectively. This corresponds to a decrease by 3.1 kcal for **TS1_Endo** and an increase by 1.0 kcal/mol for **TS1_Exo**. The observed trend for **TS1_Endo** is NO$_2$ < Br < CN, with Br and CN having an activation barrier of 14.4 and 14.6 kcal/mol indicating a decrease by 2.4 and 2.2 kcal/mol respectively. The increase in activation barrier for **TS1_Exo** follows this trend: Br < CN < NO with Br, CN, and NO$_2$ having activation barriers of 10.3, 11.5 and 11.6 kcal/mol, an increase by 1.0, 2.2, and 2.3 kcal/mol respectively.

Also, there is significant increase in activation barrier for the dinitrogen extrusion via **TS2_Endo** and **TS2_Exo** with Br having the least activation barriers of 31.2 and 37.0 kcal/mol and NO$_2$ having the highest activation barriers of 33.3 and 38.3 kcal/mol for **TS2_Endo** and **TS2_Exo** respectively.

In the experimental work of Chen et al$^{15}$, they observed that, when electron-withdrawing groups were substituted on the oxabicyclic alkene, the products yield decreased but with improved endo/exo selectivities (up to >99:1 endo/exo) and for the reaction of 4-nitrobenzenesulfonyl azide with di-substituted bromooxabicyclic alkene, only the endo product was isolated.

The decrease in product yield when electron-withdrawing groups are substituted at the position 6 and 7 of the oxabicyclic alkene can be attributed to the increase in activation barrier for **TS2** which is the rate-determining step, and the decrease in yield of the *exo* product isolated under the same
conditions can also be attributed to the increase in activation barrier for the cycloaddition step through \(\text{TS1}_\text{Exo}\).

Effects of substituents on the reaction of 4-methoxybenzenesulfonyl azide with di-substituted oxabicyclic alkene was also investigated. From the results, electron-donating groups marginally decrease the activation barriers for \(\text{TS1}_\text{Endo}\) and \(\text{TS1}_\text{Exo}\) whiles electron-withdrawing groups marginally increase the activation barriers for the cycloaddition step through \(\text{TS1}_\text{Endo}\) and \(\text{TS1}_\text{Exo}\). Also a marginal decrease in activation barrier is observed for \(\text{TS2}_\text{Endo}\) and \(\text{TS2}_\text{Exo}\) when electron-donating groups are substituted at the position 6 and 7 of the oxabicyclic alkene. However, electron-withdrawing groups increase the activation barrier for the dinitrogen extrusion step via \(\text{TS2}_\text{Endo}\) and \(\text{TS2}_\text{Exo}\) respectively.

**Table 8.** Activation energies of the elementary steps involved in the reaction of 4-nitrobenzenesulfonyl azide and several disubstituted oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol

| Substituents | \(\text{TS1}_\text{Endo}\) | \(\text{TS1}_\text{Exo}\) | \(\text{TS2}_\text{Endo}\) | \(\text{TS2}_\text{Exo}\) |
|--------------|-----------------|-----------------|-----------------|-----------------|
| H            | 16.8            | 9.3             | 30.2            | 35.8            |
| CH₃          | 16.3            | 8.9             | 30.2            | 36.1            |
| OH           | 12.0            | 4.2             | 30.7            | 36.6            |
| NH₂          | 12.1            | 8.4             | 30.0            | 35.3            |
| Br           | 14.4            | 10.3            | 31.2            | 37.0            |
| CN           | 14.6            | 11.5            | 32.5            | 37.6            |
| NO₂          | 13.7            | 11.6            | 33.3            | 38.3            |

**Table 9.** Relative energies intermediates and products involved in the reaction of 4-nitrobenzenesulfonyl azide and several disubstituted oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol

| Substituents | \(1\text{A} + 2\text{A}\) | \(\text{A}_\text{Endo}\) | \(\text{A}_\text{Exo}\) | \(\text{P}_\text{Endo}\) | \(\text{P}_\text{Exo}\) |
|--------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| H            | 0.0             | -43.0           | -45.0           | -69.6           | -73.1           |
| CH₃          | 0.0             | -44.2           | -45.8           | -70.6           | -73.7           |
| OH           | 0.0             | -48.4           | -50.4           | -75.3           | -78.4           |
| NH₂          | 0.0             | -45.3           | -46.7           | -70.0           | -74.1           |
| Br           | 0.0             | -42.0           | -43.2           | -70.3           | -71.9           |
| CN           | 0.0             | -40.9           | -41.0           | -67.4           | -70.3           |
| NO₂          | 0.0             | -41.1           | -40.8           | -69.8           | -70.1           |
Table 10. Activation energies of the elementary steps involved in the reaction of 4-methoxybenzenesulfonyl azide and several disubstituted oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol

| Substituents | TS1_Endo | TS1_Exo | TS2_Endo | TS2_Exo |
|--------------|----------|---------|----------|---------|
| H            | 17.2     | 10.7    | 32.9     | 39.1    |
| CH₃          | 16.8     | 10.5    | 33.0     | 38.7    |
| OH           | 16.6     | 10.4    | 33.5     | 39.5    |
| NH₂          | 16.7     | 10.1    | 32.9     | 38.1    |
| Br           | 17.4     | 11.0    | 33.8     | 39.8    |
| CN           | 17.3     | 11.5    | 35.1     | 40.5    |
| NO₂          | 17.1     | 11.6    | 35.8     | 40.7    |

Table 11. Relative energies of intermediates and products involved in the reaction of 4-methoxybenzenesulfonyl azide and several disubstituted oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol

| Substituents | 1A + 2A | A_Endo | A_Exo | P_Endo | P_Exo |
|--------------|---------|--------|-------|--------|-------|
| H            | 0.0     | -41.9  | -43.6 | -67.8  | -71.6 |
| CH₃          | 0.0     | -42.9  | -44.2 | -68.4  | -72.1 |
| OH           | 0.0     | -47.2  | -49.1 | -73.3  | -76.6 |
| NH₂          | 0.0     | -44.0  | -44.9 | -67.2  | -72.5 |
| Br           | 0.0     | -41.3  | -42.4 | -68.3  | -70.9 |
| CN           | 0.0     | -41.0  | -40.8 | -67.5  | -70.0 |
| NO₂          | 0.0     | -41.3  | -40.7 | -68.5  | -69.9 |

3.5 Reaction of oxabicyclic alkene with 2-nitrobenzenesulfonyl azide

Chen and co-workers observed that when 2 or 3-nitrobenzenesulfonyl chloride was used to generate the azide, the exo-cycloadducts were obtained as the predominant products while 4-nitrobenzenesulfonyl chloride gave the endo-cycloadducts as the predominant products. To provide insight into this varying selectivity when position of the substituent is varied, we employed 2-nitrobenzenesulfonyl azide and 2-methoxybenzenesulfonyl azide in our study.

The optimized geometries of the transition state structures as well as the relative energies of the reactants, intermediates, transition states and products involved in the reaction of 2-
nitrobenzenesulfonyl azide with oxabicyclic alkene are shown in Figure 3. In 2-nitrobenzenesulfonyl azide, the nitro group is substituted at the ortho position of the benzene. There appears to be no significant effect on the activation barriers leading to the formation of intermediates A_Endo and A_Exo via TS1_Endo and TS1_Exo respectively. Analysis of transition state structures of TS2_Exo reveal a significant decrease in activation barrier by 6.1 kcal/mol. The activation barrier of the cycloaddition step through TS1_Endo and TS1_Exo are 16.2 and 12.6 kcal/mol respectively. TS1_Exo is kinetically favored over TS1_Endo by 3.6 kcal/mol. Also, the activation barrier for the dinitrogen extrusion via TS2_Endo and TS2_Exo are 29.7 and 29.8 kcal/mol rendering this step less selective. Nevertheless, the overall formation of product P_Exo is kinetically and thermodynamically favoured over the formation of P_Endo. It can be argued that, the reason why the exo-cycloadducts is obtained as the predominant product is the significant decrease in activation barrier of the rate-determining step via TS2_Exo.

A similar observation is observed for the reaction of 2-methoxybenzenesulfonyl azide with benzenesulfonyl azide. A marginal decrease in activation barrier is observed for the cycloaddition step via TS1_Endo and TS1_Exo. The activation barrier for the dinitrogen extrusion via TS2_Endo and TS2_Exo are 35.0 and 37.4 kcal/mol indicating an increase by 2.1 kcal/mol and a decrease by 1.7 kcal/mol respectively. Hence, substituents at the position 2 of the benzenesulfonyl azide favor the formation of the exo-cycloadduct and disfavor the formation of the endo-cycloadducts as observed by Chen et al.\textsuperscript{15}

**Table 12.** Activation energies and relative energies of intermediates and products involved in the reaction of 2-substitutedbenzenesulfonyl azide and oxabicyclic alkene, computed at the M06-2X/6-311+G(d,p) level of theory. Energies in kcal/mol

| Substituent | TS1_Endo | TS1_Exo | TS2_Endo | TS2_Exo | A_Endo | A_Exo | P_Endo | P_Exo |
|-------------|----------|---------|----------|---------|--------|-------|--------|-------|
| NO\textsubscript{2} | 16.2 | 12.6 | 29.7 | 29.8 | -38.9 | -38.1 | 66.2 | -73.1 |
| OCH\textsubscript{3} | 16.7 | 10.3 | 35.0 | 37.4 | -40.7 | -42.1 | -64.4 | -69.8 |
Figure 3. Zero point energy corrected Gibbs free energy profile for the reaction of Oxabicyclic alkene and 2-nitrobenzenesulfonyl azide to afford Aziridines P_Endo and P_Exo. All stationary points are optimized at the M06-2X/6-311G+(d,p) level of theory at 85 °C in gas phase. Relative energies in kcal/mol.
3.6 Normal versus inverse electron demand cycloaddition

Orbital interactions are important factors in determining the reactivity of 1,3-dipolar cycloaddition reactions. In this section, the frontier molecular orbital theory is applied to rationalize the reactivity of the 1,3-dipolar cycloaddition of reactants 1A and 2A. The possible orbital interactions are depicted in Figure 4.

![Figure 4](image-url)

**Figure 4.** Frontier molecular orbital interactions in the 1,3-dipolar cycloaddition of oxabicyclic alkene and benzenesulfonyl azide at the M06-2X/6-311G+(d,p) level of theory.

The calculated HOMO and LUMO energy for the benzenesulfonyl azide which is the dipole are -9.33 eV and -1.28 eV respectively and that for the dipolarophile are -7.76 and -0.09 eV respectively (Figure 4). The energy gap for the HOMO\textsubscript{dipole} – LUMO\textsubscript{dipolarophile} is 9.25 eV and that of HOMO\textsubscript{dipolarophile} – LUMO\textsubscript{dipole} is 6.48 eV. The dominant pathway is the one which possess the smallest HOMO – LUMO energy gap. The analyses indicate that the dominant interactions occur between the HOMO of the dipolarophile and the LUMO of the dipole, and indication of an inverse
electron demand cycloaddition for the first step of Path A. In this case, the HOMO of the dipolarophile interacts with the low-lying LUMO of the dipole.

3.7 Analysis of the global reactivity indices

The electrophilicity indices is used as a parameter for predicting the chemical reactivity of electrophilic molecules. Molecules with the largest $\omega$ value will be the best nucleophile in a given series of molecules. Also, species with large $\omega$ values will be more reactive towards nucleophiles.

From Table 13, the electrophilicities of the various substituted benzenesulfonyl azide derivatives are in the order NO$_2$ > CN > CF$_3$ > Cl > F > H > Ph > CH$_3$ > OCH$_3$ > OH > NH$_2$ with NO$_2$ being the most electrophilic species and hence more reactive towards the nucleophilic bicyclic alkene.

The trends in activation energies for the initial [3+2] addition are consistent with the $\omega$ electrophilic index value.

Table 13. Global electrophilicities for the various substituted benzenesulfonyl azide. Orbital energies in electron volts (eV)

| Substituent | HOMO | LUMO | $\mu$ | H   | $\Omega$ | $\Delta N_{max}$ |
|-------------|------|------|-------|------|----------|-----------------|
| H           | -9.33| -1.28| -5.31 | 8.01 | 1.75     | 0.66            |
| F           | -9.32| -1.35| -5.34 | 7.98 | 1.78     | 0.67            |
| Cl          | -9.16| -1.47| -5.31 | 7.69 | 1.84     | 0.69            |
| CF$_3$      | -9.81| -1.75| -5.78 | 8.06 | 2.07     | 0.72            |
| CN          | -9.70| -2.09| -5.90 | 7.61 | 2.29     | 0.76            |
| NO$_2$      | -10.03| -2.56| -6.30 | 7.47 | 2.66     | 0.84            |
| Ph          | -8.37| -1.41| -4.89 | 6.96 | 1.72     | 0.70            |
| CH$_3$      | -9.01| -1.18| -5.09 | 7.83 | 1.66     | 0.65            |
| OCH$_3$     | -8.51| -1.07| -4.79 | 7.44 | 1.54     | 0.64            |
| OH          | -8.70| -1.13| -4.91 | 7.56 | 1.60     | 0.65            |
| NH$_2$      | -7.80| -0.96| -4.48 | 7.04 | 1.42     | 0.64            |
Conclusion

Two different pathways for the reaction of benzenesulfonyl azides with oxabicyclic alkenes have been investigated. The results of the study show that the most plausible pathway for the formation of the endo and exo aziridine products is through the initial [3+2] cycloaddition of the benzenesulfonyl azide with oxabicyclic alkene to form triazoline cycloadducts followed by dinitrogen extrusion instead of an initial dinitrogen cleavage from the benzenesulfonyl azide to form a nitrene species and subsequent insertion of this species into the olefinic bond of the oxabicyclic alkene proposed by Chen et al.\textsuperscript{15}

The initial [3+2] addition of benzenesulfonyl azide with oxabicyclic alkene to afford triazoline intermediates is kinetically favored over the dinitrogen cleavage from benzenesulfonyl azide by 21.6 and 28.1 kcal/mol for endo and exo products respectively. Also the formation of intermediate aziridines is thermodynamically favored over the formation of the nitrene species by 54.3 (endo) and 55.3 (exo) kcal/mol. The dinitrogen extrusion step leading to the formation of endo aziridine isomer is kinetically favoured over that of exo isomer by 6.3 and 6.2 kcal/mol in gas phase and 1,4-dioxane respectively. Since the rate-determining step is the dinitrogen extrusion step, product endo aziridine isomer will be formed as the predominant product. Solvent 1,4-dioxane marginally decrease the activation barrier for dinitrogen extrusion step leading to the formation of both endo and exo aziridine product.

The ratio of endo aziridine product to exo product has been calculated using the Boltzmann distribution equation and the results obtained indicate an endo to exo ratio of 62:38 which is in excellent agreement with experiment (endo / exo = 67:33). The position of substituent on the benzenesulfonyl azide affects the endo / exo selectivity of the reaction. Substituents at the para-position of the benzenesulfonyl azide follow the observed diastereoselectivity of endo > exo whiles substituents at the ortho or meta-position would generate the exo cycloadduct as the predominant
product. Electron-donating groups on the oxabicyclic alkene decrease the activation barrier for the rate-determining step while electron-withdrawing groups increase the activation barrier for the rate-determining step. An FMO analysis shows an inverse electron demand nature for the reaction and results obtained are in complete agreement with experimental observation.

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Conflict of Interest
The authors declare that they have no conflict of interest whatsoever regarding the publication of this manuscript.

Supporting Information
The supporting Information file contains Cartesian coordinates of all optimized geometries, and absolute energies of all reactants, intermediates, transition states and products computed in this study.

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