

Unimolecular Reaction in the [1,3] Thioallylic Rearrangement Mechanism

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Abstract

The thioallylic rearrangement is of special importance to organic chemists because it provides a method for creating C-S bonds, which have been proven to have medical properties. Using computational chemistry, the mechanism of the thioallylic rearrangement was shown to be concerted, and the effects of different substituents in the R1-R4 positions on the threshold energies and electron density with electron donating groups decrease the activation barrier. The sulfur atom experiences the most significant change in electron density, as observed in the QTAIM studies, as it carries more electron density in the transition state than in the ground and product state geometries.

1. Introduction

Unimolecular decomposition reactions can be analyzed using both computational and experimental methods. The thioallylic rearrangement mechanism is investigated computationally in order to provide insight into the movement of atomic charge throughout the rearrangement of the transition state.

The Claisen and Cope rearrangements have interested scientists since 1912, when the Claisen rearrangement was first discovered. The mechanisms for the Cope and Claisen rearrangements were proposed in the 1960s. These rearrangements allow for a stereoselective [3,3]-sigmatropic shift, providing a powerful tool for synthetic chemists.¹

The Cope rearrangement follows the general form:

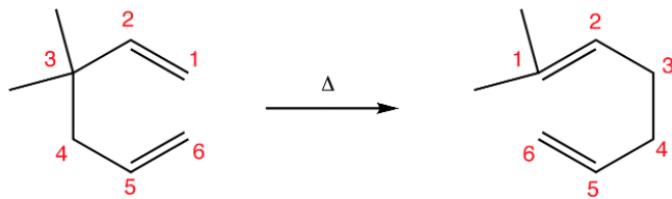


Figure 1. Cope rearrangement¹

Essentially the Cope rearrangement is a thermal isomerization of a 1,5-diene to yield a regioisomer of the 1,5-diene compound. The Claisen Rearrangement, aptly named after Rainer Ludwig Claisen, and discovered in 1912, resembles the following:

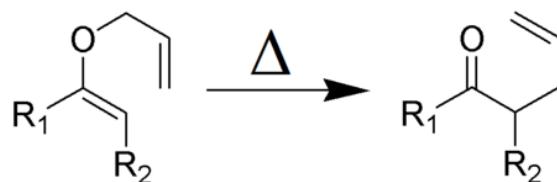


Figure 2. General Claisen Rearrangement ²

The Claisen rearrangement is the thermal conversion of an allyl vinyl ether into an unsaturated carbonyl molecule.

These simple reactions allow synthetic chemists to create complex molecules, and important application to natural compounds². A sulfur can be substituted for an oxygen, allowing for a thio-Claisen rearrangement. An example from mechanism is:

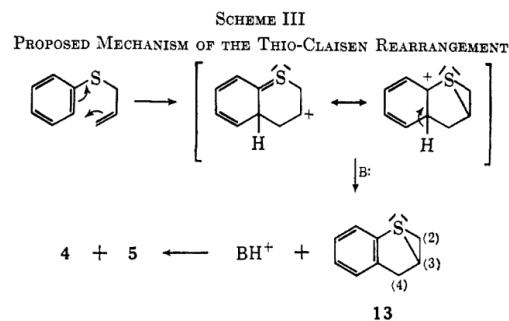


Figure 3. Thio-Claisen rearrangement³

The thio-claisen rearrangement has been studied in detail, with the key results predicting transition state structures and an exothermic mechanism³.

A [1,3] thioallylic rearrangement is similar to a thio claisen rearrangement in that it involves the breaking and forming of new bonds at a sulfur-carbon interface. Research on thioallylic rearrangements is infrequent, but of the research completed, there is not an established mechanism for the transition state of a thioallylic rearrangement. Three mechanisms were proposed by Kwart and Johnson⁴, who tested substituent and solvent effects on the reaction pathway. Understanding substituent effects in a thioallylic rearrangement is beneficial to the understanding and application of these compounds in organic synthesis.

Although the thioallyl mechanism is seldom researched theoretically, thioallyl containing compounds have been given some importance in the biochemistry community. Lee⁵ and researchers concluded that thioallyl compounds can hinder malignant cells and inhibit cell proliferation. In a more recent study done by Ogawa et al., S-allylcysteine (SAC) and S-allylmercaptopcysteine (SAMC), two thioallyl proteins, disrupted the buildup of reactive oxygen species (ROS), slowing down the aging process⁶.

The Cope and Claisen rearrangements have been studied in depth and the reaction mechanisms are widely accepted as concerted following a cyclic transition state. However, studies on the mechanism of the thioallylic rearrangement have not led to a concrete understanding of the thioallylic rearrangement pathway. Kwart⁷ proposes three distinct transition state configurations based off of the heavy atom isotope effects the sulfur experiences:

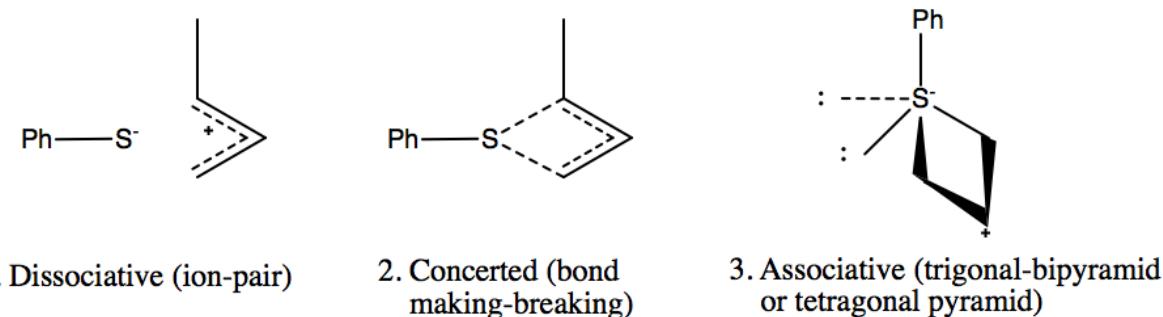


Figure 4. Kwart's transition state configurations

The isotope effect occurs when the rate of the reaction is influenced by the difference in isotope of the studied atom. These three models represent three possible transition state configurations of interest and are the basis of this study.

This research also aims to understand the effects of substituents and their electron density on the reaction coordinate system for a thioallylic pathway. Similar to the Cope and Claisen rearrangements, the thioallylic molecule undergoes a [1,3] π bond migration:

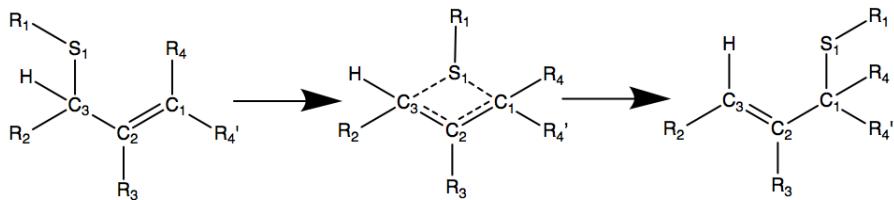


Figure 5. 1,3 π bond migration (thioallylic mechanism)

Shown is the concerted mechanism, and represents a possible transition state structure for the thioallylic rearrangement.

2. Methods

Computational chemistry was used to calculate reaction energies and examine atomic charge distributions for the thioallylic rearrangement. The specific methods used were Density Functional Theory (DFT) and Quantum Theory of Atoms in Molecules (QTAIM). Density functional theory uses a single determinant wave function to describe electrons in a molecule. DFT then generates a density from the square of a wavefunction and then calculates the energy of a molecule based on that density. The DFT methods B3PW91 and M06-2X were used to compare theories as well as predict substituent effects. The M06-2X method is especially useful in calculating the energies of transition state geometries. QTAIM provides information about electron localizations, densities, and atomic charges on each atom. QTAIM and DFT were used in alignment with similar studies⁸⁻¹⁰ observing solvent and substituent effects on the Claisen [3,3]-rearrangement mechanism.

All geometries were optimized using a 6-311+G basis set with a Gaussian 09 Revision D.01¹¹. Transition states were found by Amina using a QST3 input method in the B3PW91 theory. This research used the M06-2X method to find the optimum transition state geometries. Transition states are characterized by 1 imaginary frequency, but some transition states are harder to find computationally than others. Intrinsic reaction coordinate¹² (IRC) calculations were run on some transition states in order to confirm the optimized structures. Threshold energies were obtained using the sum of the zero-point and electronic energies for the optimized ground state and transition state structures. Transition state input structures were estimated using previous research that suggested a concerted mechanism for the thioallylic rearrangement⁴.

Electron localizations, densities, and atomic charges for atoms in the mechanism were completed using the Quantum Theory of Atoms in Molecules¹³ (QTAIM). The atomic charges were compared in the ground state, transition state, and final geometries for the S1 sulfur and the C1-C3 carbons.

GaussView¹⁴ was used to visualize the geometries for the optimized ground state, transition state, and end state structures for energy calculations. AimStudio¹⁵ was used to visualize the shift in electron density on the atoms in the thioallyl from ground state-end geometry in addition to providing a geometric interpretation for those shifts in electron density as the sulfur atom moved through the transition state.

3. Results and Discussion

3.1. Energy Calculations

Electron withdrawing and electron donating groups were placed at positions R₁, R₄, R_{4'}, and R₃ on the thioallylic backbone. The calculated transition states suggested a concerted mechanism was followed⁷, indicating a bridge-like transition of S₁ from C₃ to C₁ (see figure 5). This is in agreement with Kwart, who hypothesized that the thioallylic rearrangement would occur in a similar mechanism to the Claisen and Thio-Claisen rearrangements.

M06-2X and B3PW91 Calculations

Threshold energy is the computationally predicted, minimum amount of energy required for a system to go from reactant to product. A lower threshold energy indicates a more favorable reaction. The effect of adding an electron withdrawing or donating group to the R1 and R4 positions and of adding bulkier side chains, are two factors impacting the threshold energies. Another important factor to consider is the effect on threshold energy of an E or Z configuration.

Table 1. Threshold Energies

| TEST # | M06-2x | | Threshold Energies | | PW91 (Amina) | |
|----------|----------|------------------|--------------------|-----------|--------------|-----------|
| | R1 | R4 | Cis (Z) | Trans (E) | Cis (Z) | Trans (E) |
| 1 | H | CH3 | 52.8 | 51.4 | 48.4 | 48 |
| 2 | H | NH2 | 43 | 40.1 | 37 | 35 |
| 3 | COCH3 | H | 52.3 | - | - | - |
| 4 | BENZENE | CH3 | 48.2 | 47 | 42.6 | 41.4 |
| 5 | H | OCH3 | 45.2 | 43 | 42 | 39.3 |
| 6 | SCH3 | H | 41.2 | - | - | - |
| 7 | H | BENZENE | 53.8 | 49.2 | - | - |
| 8 | H | SCH3 | 52.9 | 46.5 | - | - |
| 9 | H | OH | 49.4 | 45.8 | - | - |
| 10 | H | SH | 53 | 49.8 | - | - |
| 11 | H | NHCH3 | 37.9 | 36.7 | - | - |
| 12 | H | N(CH3)2 | 34.5 | 34.7 | - | - |
| 13 | H | N(CH2CH3)2 | 36.3 | 34.2 | - | - |
| 14 | H | CH3* | 50.7 | - | 44.7 | - |
| 15 | H | C2H5 | 50.7 | - | - | - |
| 16 | SCH3 | CH3 | 40.8 | 40 | - | - |
| 17 | H | CF3 | 57.5 | 57.1 | 49.8 | 49 |
| 18 | BENZENE | CF3 | 50.6 | 50.7 | 44.7 | 44.4 |
| 19 | CH3 | CH3 | 53 | 51.8 | 48.3 | 46.3 |
| 20 | CF3 | CH3 | 50.2 | 48.7 | 44.4 | 43 |
| 21 | CH2CH3 | CH3 | 52.6 | 51.3 | 47.3 | 46.8 |
| 22 | ISOBUTYL | CH3 | 52.4 | 52.4 | 48 | 46.4 |
| 23 | T-BUTYL | CH3 | 53 | - | 47.3 | 45.8 |
| 24 | BENZENE | OCH3 | 42 | 39.9 | 37.9 | 34.6 |
| 25 | H | F | 54.8 | 52.1 | 48.2 | 45.1 |
| 26 | H | CH3** | 52.3 | 50.1 | 45.1 | 42 |
| 27 | H | OCH3* | 33.3 | - | 31.2 | - |
| 28 | H | OCH3=R4, NH2=R4' | 26.4 | 34.7 | - | - |
| *=R4&R4' | | | | | | |
| **=R3&R4 | | | | | | |

The “base” geometry contained a methyl in the R₄ position as follows:

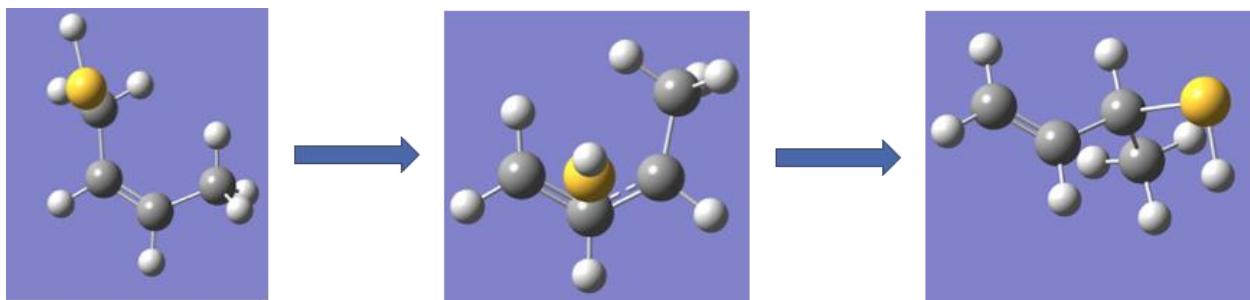


Figure 6. Methyl in the R₄ position

-CH₃ contains electron donating character, and acts by slightly increasing the electron density in a conjugated system through induction. The -CH₃ in the R₄ position represents a “base” structure where the substituent has little inductive or resonance effects on the threshold energy. In the next example, NH₂ was added as an inductively withdrawing and resonance donating group. Electron donating groups activate the conjugated system through a resonance effect, lowering the amount of energy needed to go from the ground state to the transition state. In trials 2, 5, 8, 9, 11, 12, and 13, the effects of adding different inductively donating and resonance withdrawing groups are similar.

In trials 2, 11, 12, and 13, the effect of adding an electron-donating group with varying carbon chains attached was investigated. By adding a methyl and a hydrogen to the original NH₂ structure from trial 2, the threshold energy was reduced. When the R₄ substituent was an -N(CH₃)₂ group, the threshold energy was lowered even further, perhaps due to the slightly electron donating character of the methyl groups. However, when R₄ was changed to -N(CH₂CH₃)₂, there was little change in the threshold energy, indicating that steric hindrance is not a very significant factor when considering substituent effects.

When inductively and resonance withdrawing groups were added to the R₄ position, with R₁ staying a hydrogen, the threshold energies increased. Electron withdrawing groups withdraw electron density from a pi system, causing an increase in the energy required to get the ground state into the transition state. When R₄ was a strong electron withdrawing group, a -CF₃ group, the threshold energy was nearly double the energy of having R₄ be an electron donating group:

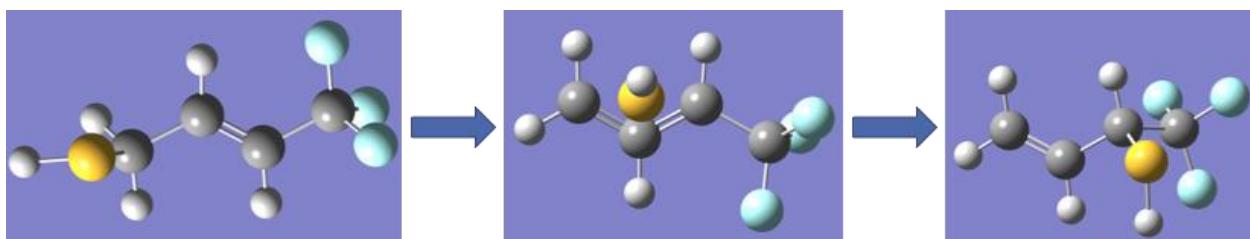


Figure 7. E configuration for R₄= -CF₃

However, when an electron donating group like benzene is added in the R₁ position, the threshold energy is slightly decreased (as seen in trials 17 and 18), which follows the general trend that electron-donating groups lower the activation energy for this rearrangement.

The effects of different substituents in the R₁ position are similar to the substituent effects in the R₄ position. When an electron withdrawing group, -COCH₃, was put on R₁ (reference trials 3 and 6 in figure 3), the threshold energy was relatively high. Another electron withdrawing group, -CF₃, was placed in the R₁ position, and as previously asserted, it caused an increase in the threshold energy.

If the R₄ position were instead filled with an electron donating group like benzene, SCH₃, or a carbon chain, the threshold energies tend to decrease. Interestingly, trial 6 contains a disulfide bridge between the sulfur of the original molecule and the R₁ group:

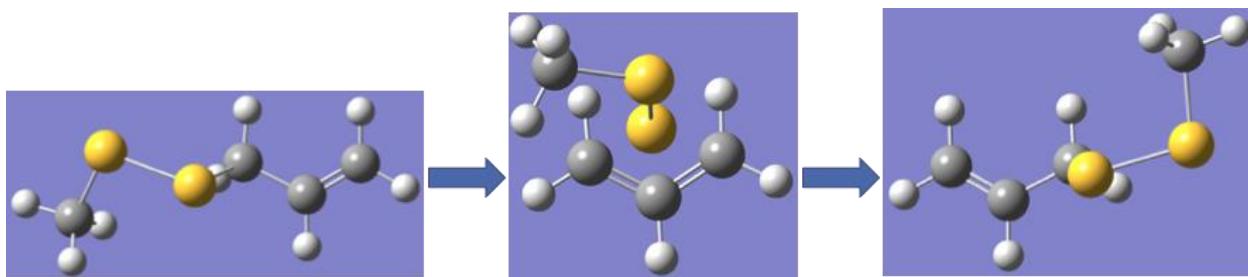


Figure 8. Disulfide Bridge

which consequently lowers the threshold energy significantly compared to the $-\text{COCH}_3$ group on R_1 , as indicated in trial 3. When the system is given a slightly electron donating group in the R_4 position as in trial 16, the energy is lowered even further. The disulfide link seems to stabilize the sulfur as it moves through the transition state, perhaps by lowering the electron density on the $\text{S}1$ sulfur in the transition state. When a phenyl, a weakly electron donating group, is added in the R_1 position, the energy is relatively high, as an aromatic ring does not have enough electron donating character to significantly lower the threshold energy of the system. Carbon chains of various lengths were also placed in the R_1 position, with the R_4 position consistently being a methyl group. The chain length of the R_1 substituent does not significantly affect threshold energy.

When a $-\text{CH}_3$ group is placed in the R_3 and R_4 positions the threshold energy is slightly lowered from the “base” structure. If an even stronger electron donating group, $-\text{OCH}_3$, is placed at the R_4 and R_4' positions, the threshold energy is lowered even further than by adding an $-\text{N}(\text{CH}_3)_2$ substituent in trial 12. When both R_4 and R_4' are electron donating groups (reference trial 28) the threshold energy is significantly lower, especially in the “Z” structure, where the sulfur group was Z to the NH_2 group. The significant change in threshold energy in the Z and E geometries indicates some possible steric effects caused the $-\text{OCH}_3$ group interfering with the movement of the sulfur group across the pi bond.

Finally, Z and E geometries have an effect on the threshold energy for a specific system. In every trial except trial 28, which defined Z as the $-\text{NH}_2$ group being Z to the sulfur group, the E geometry had a lower threshold energy than the Z . This goes along with the widely accepted observation that E molecules are often more stable than Z molecules, whether that be due to sterics or another effect. It is clear, however, that sterics do play a role in the threshold energy, as previously discussed and indicated by the ~ 9 kcal/mol difference between the Z and E geometries.

3.2. QTAIM Calculations

QTAIM software was used to acquire atomic charge data on the atoms of the specific structure at the ground state molecule moved through the transition state and into the final geometry. Electron density data was calculated for all 28 trials, with the $\text{S}1$, $\text{C}1$, and $\text{C}3$ carbons showing the most significant electron density changes.

Table 2. QTAIM results for sulfur

| QTAIM | Electron Density on Sulfur | | | | |
|--------|----------------------------|--------|----------|----------|--------------|
| TEST # | GS Cis | TS Cis | GS trans | TS trans | End geometry |
| 1 | 0.02 | | 0.02 | -0.26 | 0.02 |
| 2 | 0.01 | -0.46 | 0 | -0.46 | 0.01 |
| 3 | 0.05 | -0.15 | - | - | 0.05 |
| 4 | 0.04 | -0.13 | 0.03 | -0.15 | 0.03 |
| 5 | 0.01 | -0.39 | 0.01 | -0.38 | 0.02 |
| 6 | -0.02 | -0.09 | - | - | -0.02 |
| 7 | 0.02 | -0.25 | - | -0.27 | 0.02 |
| 8 | | | | | |
| 9 | 0.02 | -0.34 | 0.02 | -0.36 | 0 |
| 10 | 0.03 | -0.29 | 0.03 | -0.31 | 0.03 |
| 11 | -0.01 | | 0 | -0.47 | 0.02 |
| 12 | 0.01 | -0.51 | 0 | -0.48 | 0.02 |
| 13 | 0 | -0.51 | -0.01 | -0.51 | 0.01 |
| 14 | 0.02 | -0.29 | 0.02 | -0.29 | 0 |
| 15 | 0.01 | -0.3 | - | - | -0.01 |
| 16 | | | | | |
| 17 | 0.05 | -0.12 | 0.05 | -0.14 | 0.08 |
| 18 | 0.06 | -0.02 | 0.05 | -0.05 | 0.08 |
| 19 | 0.02 | -0.18 | 0.01 | -0.19 | 0 |
| 20 | 0.13 | -0.11 | 0.13 | -0.12 | 0.11 |
| 21 | -0.01 | -0.19 | -0.01 | -0.21 | -0.02 |
| 22 | -0.02 | -0.21 | -0.02 | -0.22 | -0.04 |
| 23 | -0.03 | -0.21 | -0.03 | | -0.05 |
| 24 | 0.03 | | 0.03 | -0.25 | 0.06 |
| 25 | 0.03 | -0.23 | 0.03 | -0.25 | 0.08 |
| 26 | 0.02 | -0.26 | 0.01 | -0.27 | 0.01 |
| 27 | 0.01 | -0.49 | - | - | 0.02 |
| 28 | | | | | |

Table 3. QTAIM results for carbon 1 (C1)

| QTAIM | Electron Density on C1 | | | | |
|--------|------------------------|--------|----------|----------|--------------|
| TEST # | GS Cis | TS Cis | GS trans | TS trans | End geometry |
| 1 | -0.04 | | -0.09 | 0 | -0.05 |
| 2 | 0.36 | 0.56 | 0.33 | 0.54 | 0.24 |
| 3 | -0.07 | -0.05 | - | - | -0.11 |
| 4 | -0.04 | -0.01 | -0.04 | -0.01 | -0.05 |
| 5 | 0.48 | 0.44 | 0.49 | 0.66 | 0.47 |
| 6 | -0.08 | -0.08 | - | - | -0.1 |
| 7 | -0.04 | 0 | | 0 | -0.06 |
| 8 | | | | | |
| 9 | 0.47 | 0.64 | 0.48 | 0.63 | 0.47 |
| 10 | -0.19 | -0.16 | -0.19 | -0.16 | -0.16 |
| 11 | 0.34 | | 0.33 | 0.54 | 0.24 |
| 12 | 0.3 | 0.57 | 0.33 | 0.55 | 0.24 |
| 13 | 0.37 | 0.57 | 0.37 | 0.56 | 0.25 |
| 14 | 0 | 0.04 | 0 | -0.04 | -0.03 |
| 15 | -0.02 | 0.03 | - | - | -0.04 |
| 16 | | | | | |
| 17 | -0.03 | 0 | -0.03 | 0 | -0.05 |
| 18 | -0.03 | -0.02 | -0.03 | -0.02 | -0.05 |
| 19 | -0.04 | -0.01 | -0.04 | -0.01 | -0.06 |
| 20 | -0.03 | 0.01 | -0.03 | 0.01 | -0.06 |
| 21 | -0.04 | 0 | -0.04 | -0.01 | -0.06 |
| 22 | -0.04 | 0 | -0.04 | -0.01 | -0.06 |
| 23 | -0.04 | 0 | -0.04 | | -0.06 |
| 24 | 0.48 | | 0.49 | 0.63 | 0.43 |
| 25 | 0.48 | 0.61 | 0.49 | 0.61 | 0.46 |
| 26 | -0.04 | 0 | -0.05 | 0 | -0.05 |
| 27 | 1.05 | 1.38 | - | - | 0.97 |
| 28 | | | | | |

Table 4. QTAIM results for carbon 3 (C3)

| QTAIM | Electron Density on C3 | | | | |
|--------|------------------------|--------|----------|----------|--------------|
| TEST # | GS Cis | TS Cis | GS trans | TS trans | End geometry |
| 1 | -0.09 | | -0.04 | -0.04 | -0.08 |
| 2 | -0.09 | -0.03 | -0.07 | -0.02 | -0.08 |
| 3 | -0.11 | -0.04 | - | - | -0.08 |
| 4 | -0.09 | -0.06 | -0.09 | -0.06 | -0.08 |
| 5 | -0.08 | 0 | -0.07 | -0.02 | -0.06 |
| 6 | -0.1 | -0.08 | - | - | -0.08 |
| 7 | -0.1 | -0.04 | | -0.04 | -0.08 |
| 8 | | | | | |
| 9 | -0.08 | -0.02 | -0.07 | -0.02 | -0.08 |
| 10 | -0.09 | -0.04 | -0.08 | -0.03 | -0.07 |
| 11 | -0.09 | | -0.07 | -0.01 | -0.09 |
| 12 | -0.09 | -0.02 | -0.07 | -0.01 | -0.09 |
| 13 | -0.08 | -0.02 | -0.06 | -0.01 | -0.09 |
| 14 | -0.09 | -0.04 | -0.09 | -0.04 | -0.09 |
| 15 | -0.09 | -0.04 | - | - | -0.04 |
| 16 | | | | | |
| 17 | -0.1 | -0.04 | 0.09 | -0.04 | -0.05 |
| 18 | -0.1 | -0.06 | -0.09 | -0.06 | -0.06 |
| 19 | -0.1 | -0.06 | -0.1 | -0.05 | -0.08 |
| 20 | -0.1 | -0.04 | -0.09 | -0.04 | -0.08 |
| 21 | -0.1 | -0.06 | -0.1 | -0.05 | -0.08 |
| 22 | -0.11 | -0.05 | -0.1 | -0.05 | -0.09 |
| 23 | -0.11 | -0.05 | -0.1 | | -0.09 |
| 24 | -0.08 | | -0.07 | -0.04 | -0.08 |
| 25 | -0.08 | -0.03 | -0.08 | -0.03 | 0.06 |
| 26 | -0.1 | -0.05 | -0.09 | -0.04 | -0.09 |
| 27 | -0.07 | 0 | - | - | -0.06 |
| 28 | | | | | |

In figure 5, shown here for reference:

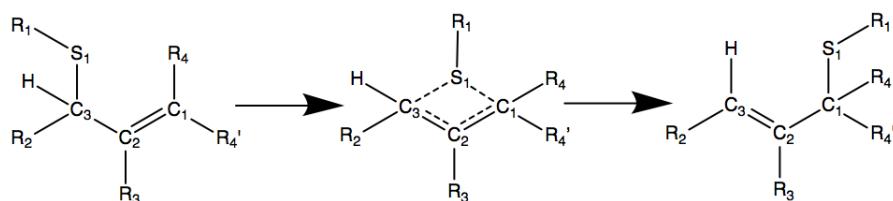


Figure 5. Thioallyl concerted mechanism

the ground state sulfur atom has an approximate atomic charge near zero. Throughout the E and Z transition states, the sulfur atom assumes a more negative atomic charge, indicating that sulfur is carrying electron density more in the transition state than the ground state, which makes sense due to the movement of electrons from the C3 carbon to the

C1 carbon. When R₁ is slightly electron donating, as in trials 21-23, the sulfur ground state has a slightly negative atomic charge, due to the donation of electron density from the R₁ substituent.

The C1 carbon also experiences a charge shift as the molecule moves through the transition state. Most of the ground state C1 atoms have an atomic charge of zero, with the exception being when there is a strong electron donating substituent at the R₄ position. The examples where the C1 carbon experiences the most positive atomic charge coincide with the trials in which the electron donating group on R₄ lowers the threshold energy for the reaction. The partial positive charge on the C1 carbon seems to indicate a reaction pathway that will occur more easily. The transition state atomic charges on the C1 carbon change depending on the substituents. When an electron donating group is attached at R₄, the transition state C1 carbon appears to assume a more positive partial charge, coinciding with a more negative partial charge on the transition state sulfur atom. Any other substituent, however, seems to have a less significant effect on the atomic charge at C1 as it moves through the reaction coordinate.

The C3 carbon does not experience a significant amount of change in its atomic charge as the sulfur moves from C3 to C1 which contains substituents R₄ and R_{4'}. The transition state C3 carbons tend to take on a slightly more negative partial charge than in the ground state, most likely due to the electrons it shares with the partial sulfur/partial double bond.

4. Conclusion

This study supports the concerted mechanism proposed by Kwart⁷. The thioallylic rearrangement could prove invaluable in the creation of organosulfur compounds, which have the potential to be biologically active. In order to lower the threshold energy, inductively electron withdrawing and resonance electron donating groups added at the R₄ and R_{4'} position lowered the threshold energy. When a combination of electron withdrawing and electron donating groups are added as substituents, the effects could potentially counteract one another and not actually decrease the reaction energy. The E/Z conformation of the end products for the thioallylic rearrangement do not have a significant effect on the activation energy for the reaction. Steric effects also appear to not have a significant effect on the threshold energy. Depending on the practical effects of the different substituents, adding a resonance electron donating group would make this reaction more efficient.

5. Future Steps

As -OCH₃ in the R₄ and R_{4'} positions lowered the threshold energy most significantly, a -F substituent should lower the energy even more. Fluorine is a stronger inductively withdrawing group, and contains 3 lone pairs it could donate electrons to the thioallyl through resonance. In addition, the ability of R₂ to cause a decrease/increase in threshold energy was not investigated, but should be examined. The hypothesis is that if R₂ is an inductively donating and resonance withdrawing/non-resonance contributing group, the threshold energy may be lowered even further. Essentially, it is believed that the R₂ substituent should have the opposite properties of the R₄ and R_{4'} substituents in order to lower the activation energy.

6. Works Referenced

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