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A Computational Study of Substituent Effects on the Thioallylic Rearrangement Reaction Pathway

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Abstract

The goal of this study was to use electronic structure calculations to predict the geometries of the reactant and the transition state, as well as to calculate threshold energies of the thioallylic rearrangement mechanism, while observing the effects of different substituents. The initial structure is as follows: R-S-CHRCR=CR_2 (shown in figure 2), where the R groups represent different substituents. The substituents were chosen based upon electron donating (R= —NH_2; —OCH_3), electron withdrawing (R= —CF_3), and steric properties (R= isopropyl; benzene) and were tested in a number of combinations on the possible R positions. The transition state was found to be a short-lived sulfur bridge between the first and third carbon of the structure, resulting in the final state with the sulfur on the third carbon and a shift of the double bond to the first and second carbon (CHR=CRCR_2-S-R). The specific energies found for the original thioallylic structure (R_1=H; R_4=CH_3) were 48.0 kcal mol^{-1} for the trans orientation and 48.4 kcal mol^{-1} for the cis orientation. Oxyallylic structures underwent the same calculations to compare the effect of oxygen versus sulfur in the rearrangement. Oxyallylic threshold energy values were 61.1 kcal mol^{-1} and 61.8 kcal mol^{-1} for the trans and cis isomers, respectively. The computational methods used in this study include Density Functional Theory (DFT) calculations to find transition state energies and geometries, as well as the Quantum Theory of Atoms in Molecules (QTAIM) as a model to visualize electron localization and densities in the described structures. Though this research was purely computational, the results are important to synthetic chemistry and biology. That said, there have been biological and biomedical studies that have found garlic-derived organosulfur compounds to have capabilities to inhibit cell proliferation, and act in metabolic processes to aid in the treatment or management of certain diseases. Providing preliminary results on this system may be a beneficial starting point for the research and synthesis of compounds involving the thioallyl moiety.

1. Introduction

Interest in thioallylic rearrangement reactions began in the late 1960s and throughout the 1970s after extensive research was invested in Claisen and Cope rearrangements, characterized by [3,3]-sigmatropic shifts.[1] A sigmatropic shift can be described as a molecular rearrangement in which a sigma bond is shifted to a new location within a system as a result of the reorganization of π-bonds. The discovery of both the Cope and Claisen rearrangements provided simple mechanisms for the synthesis of larger and more complex molecules and proved to be important reaction pathways for the development of molecules in organic chemistry. More specifically, [3,3]-sigmatropic rearrangements have been applied to the total synthesis of complex natural compounds.[2] Examples include, but are not limited to (±)-Eremopetasidione, (-)-mesembrine, (+)-galanthamine, and (±)-gelsemine. The specific reactions of the Cope and Claisen rearrangements are described as a thermoisomerization of a 1,5-diene to yield a regioisomer of the 1,5-diene compound (Cope rearrangement) and the thermal conversion of an allyl vinyl ether into an unsaturated carbonyl compound (Claisen rearrangement). The Claisen rearrangement is closely related to the Cope rearrangement; the

Claisen can be classified as a variant Cope mechanism including an oxygen atom in the system. Other atoms, such as sulfur, can replace the oxygen in systems that undergo sigmatropic shifts.[3] The number of chemistry-based studies on the thioallylic rearrangement is limited, however. Of the research that has been completed, there is not a concrete proposal as to how the mechanism for thioallylic rearrangement occurs. In a study[4] that observed the many characteristics and isomeric properties of thermal allyl phenyl sulfide rearrangement, there were a few possible mechanisms presented, but none were favored as the definitive pathway. Three mechanisms proposed are given by Kwart and Johnson: a dissociative mechanism, a radical dissociation-recombination mechanism, and a heavy atom isotope effect mechanism. In the discussion of which mechanisms are most possible, the researchers considered the effect of substituent groups, as well as solvent effects. With this being the most extensive research on this compound, the three mechanistic possibilities should be considered as viable pathways for the rearrangement mechanism.

2. Previous Research

2.1 Studies in Chemistry

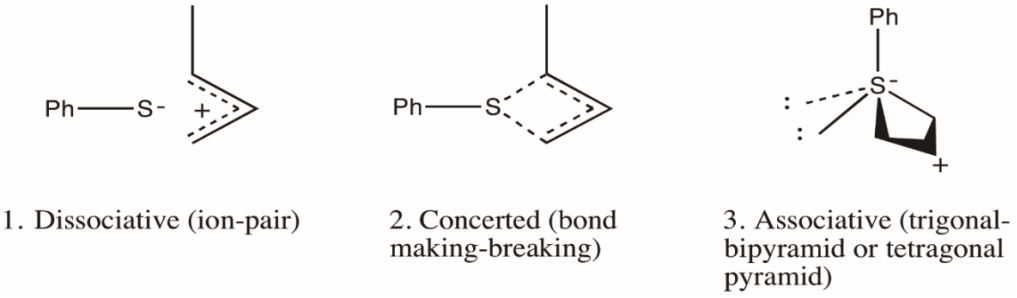
The mechanisms and product formations of aza-, oxy-, and thio-Claisen compound rearrangements have been examined for several years, as studies have continued since the discovery of the Claisen rearrangement in 1912. Finding the mechanism and transition state structure of the thio-Claisen rearrangement, also called the allyl vinyl sulfide rearrangement, has received some attention.[5] Comprehensive computational studies of substituent effects on the allyl vinyl sulfide show transition state structures, and suggest the mechanism to be exothermic.[5] Observing specific factors, including the effects of different substituent groups and solvents on the transition state geometries, and threshold energies of compounds undergoing sigmatropic rearrangement is beneficial to the basic understanding and application of these compounds and their derivatives in organic synthesis.

2.2 Studies in Biology and Biomedicine

Though the number of studies on the chemical properties and mechanisms of thioallylic structures is minimal, there have been studies that focus on the biological implications of thioallylic molecules. These biological perspectives propose an interest in thioallylic molecules and thioallyl derivatives for their potential interactions with cells and the impact of thioallylic structures toward cell reproduction.[6] Lee et al. suggested that thioallylic compounds are inhibitors of cell proliferation. This was concluded from previous information that shows a garlic derivative, S-allylmercatocysteine (SAMC) to inhibit the growth of vascular smooth cells and umbilical endothelial cells. Other research supports these findings, suggesting the same SAMC compound to inhibit cell growth through the induction of apoptosis.[7] Additionally, in a more recent study[8] S-allylcysteine (SAC) and SAMC were observed for their effects in aging. This work proposes that these compounds disrupt the buildup of reactive oxygen species (ROS), which in turn slows aging processes of cells. These biological studies show that the importance of understanding thioallylic compounds may lead to useful development of compounds to interact with cells.

2.3 Significance

There are numerous longstanding studies that have investigated the chemical and biochemical functionalities of Claisen and Cope rearrangements; reports of the mechanisms of these reactions have been widely accepted. However, studies on the mechanism of the thioallylic rearrangement have not led to a concrete understanding of the pathway. Kwart[9] proposes three possible transition state configurations for the thioallyl: the first proposal includes an ion pair interaction between the sulfur and a cationic carbon, the second is a concerted mechanism through a bond making-bond breaking process, and the final suggests the presence of a trigonal bipyramidal structure.



1. Dissociative (ion-pair) 2. Concerted (bond making-breaking) 3. Associative (trigonal-bipyramid or tetragonal pyramid)

Figure 1. Kwart's three proposals for the transition state structure of the thioallylic rearrangement.

In Kwart's study, the proposals were based off of heavy atom isotope effects experienced by the sulfur atom in the thioallyl. The heavy atom isotope effect occurs when the rate of a reaction changes due to the difference in isotope of the present compounds. The three models represent possible transition state geometries calculated using the Bigelesien-Mayer equation that show the different structures of different sulfur isotopes.

2.4 Purpose of this research project

This research project uses Kwart's proposals as a basis for the investigation of the thioallylic rearrangement system. Doing these calculations is beneficial in understanding the mechanism of the reaction and the effect of different substituents on the rearrangement. Threshold energy values provide an approximation of the amount of energy it would take for the reaction to occur. This is crucial information, as it provides an idea of the parameters that would be needed to apply the reaction in a laboratory setting. The goal of the project was to find transition state geometries, the threshold energies of the pathway, and to investigate the effects of different substituents on the system's pathway and threshold energies.

Like the double bonded compounds that undergo Claisen and Cope rearrangements, the thioallylic compound (initial geometry: R-S-CHRCR=CR_2) observed in this study undergoes a pi bond migration between the first carbon and the third carbon. The thioallyl contains one double bond rather than the two double bonds seen in 1,5-dienes, allyl vinyl oxide and allyl vinyl oxide derivatives. Since sulfur is known to be a reactive agent and is prevalent in various naturally-occurring compounds, understanding the mechanism of thioallylic structures is valuable for the advancement of synthetic and biochemical development, specifically in laboratories. Additionally, studying this system with theoretical methods allows the molecules to be observed at an atomic level. Using computational methods provides visualizations of atoms in three-dimensional space and allows the examination of electron localization in a given molecule. Understanding where the electrons are located in a molecule helps with predicting how a molecule will interact with other atoms and molecules and can provide deeper insight into the reasons a molecule behaves in such a way obtained by the results of a calculation. Furthermore, from a practical viewpoint, computational studies can be more efficient than testing procedures in a laboratory experiment.

3. Methods

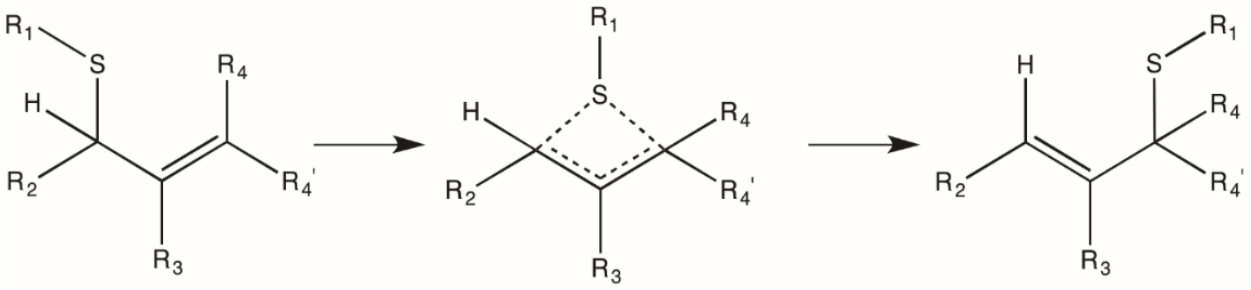
Substituents were chosen based on three properties: electron withdrawing characteristics, electron donating characteristics, and steric hindrance. These groups have the potential to change the behavior of compounds, depending on the intramolecular interactions and specifics of the mechanism. Electron withdrawing groups remove electrons from pi bonding systems, which create more electrophilic compounds. Electron donating groups have the opposite effect by giving electron density to the pi bond system, which in turn gives the compound more nucleophilic properties. Substituents with high steric properties can have intramolecular effects by interfering with the movement of other atoms in a molecule. In conjunction with testing the substituents, both cis (Z) and trans (E) isomers of the allylic structures were tested for differences in energy and behavior. Additional calculations observing electron localizations and densities were completed using the Quantum Theory of Atoms in Molecules (QTAIM). Many of the computational methods used in this project were the same or similar to methods used in successful computational studies observing the Claisen mechanism completed by other researchers.[10-12] In one study conducted by Debnath and Mondal, substituent and solvent effects were observed using density functional theory. Similarly, this project used density functional theory calculations to find transition state geometries and the effects of electron donating groups, electron

withdrawing groups and substituents with heavy steric hindrance on the single pi bond system. Along with this, an oxyallylic rearrangement pathway was observed under the same conditions as the thioallyl to compare the behavior of an oxygen shift to a sulfur shift.

Calculations were completed with a density functional theory method using the B3PW91 level of theory. All geometries were optimized using a 6-311+G (2d,p) basis set with Gaussian 09 Revision D.01[13] and the transition states were found using the QST3 input method. The rearrangement pathway for each successfully optimized structure was confirmed via intrinsic reaction coordinate (IRC) calculations. Threshold energies were obtained using the sum of electronic and zero point energies of the optimized ground state and transition state geometries. Estimations of the transition state geometries were based on previous proposals suggesting a concerted structure for the sulfur allyl.[9] Electron densities and atomic charges were run with the AIMQB application and visualized with AIMAll software.[14]

4. Results and Discussion

Electron withdrawing groups and electron donating groups were used as substituents at different locations (R_1, R_2, R_3, R_4, R_4') on the thioallylic and oxyallylic molecules. The transition state found for both the thioallyl and oxyallyl correlates to the concerted mechanism discussed in previous studies.[9] This is a short-lived intermediate where the sulfur atom forms a bridge between the first and third carbon of the structure (see Figure 2).



R_1=H; Ph; CH_3; CF_3; ethyl; isopropyl; T-butyl
R_3= H; CH_3 R_2= H R_4= H; CH_3; CF_3; NH_2; OCH_3; F
R_4'= H; CH_3; CF_3; NH_2; OCH_3; F

Figure 2: Thioallylic reaction pathway with a concerted transition state structure

The threshold energy for the thioallyl when R_1 = H and R_4 = CH_3 was found to be 48.4 kcal mol^{-1} for cis (Z) orientation and 48.0 kcal mol^{-1} for trans (E) orientation. The oxyallylic activation energies were consistently higher by approximately 15 kcal mol^{-1}; oxyallylic energy for cis (Z) where R_1 = H and R_4 = CH_3 was 61.8 kcal mol^{-1} and 61.1 kcal mol^{-1} for trans (E). Generally, for both the sulfur allyl and oxygen allyl, cis orientation caused slightly higher threshold energies, however not by a significant amount (see Tables 1 and 2).

Table 1. Threshold energies for thioallylic structures with respective substituents

R_1	R_4	Threshold Energies (kcal/mol)	
		Cis (Z)	Trans (E)
H	**CH_3**	48.4	48.0
H	**CF_3**	49.8	49.0
benzene	**CH_3**	42.6	41.4
benzene	**CF_3**	44.7	44.4
H	**NH_2**	37.0	35.0
CH_3	**CH_3**	48.3	46.3
CF_3	**CH_3**	44.4	43.0
ethyl	**CH_3**	47.3	46.0
isopropyl	**CH_3**	48.0	46.4
T-butyl	**CH_3**	47.3	45.8
H	**OCH_3**	42.0	39.3
benzene	**OCH_3**	37.9	34.6
H	**F**	48.2	45.1
H	**CH_3***	45.1	42.0
H	**CH_3****	44.7 (cis/trans does not apply)	
H	**OCH_3****	31.2 (cis/trans does not apply)	

*Substituent was located on R_3 and R_4
**Substituents located on R_4 and R_4'

Table 2. Threshold energies for oxyallylic structures with respective substituents

R_1	R_4	Threshold Energies (kcal/mol)	
		Cis (Z)	Trans (E)
H	**CH_3**	61.8	61.1
H	**CF_3**	64.6	66.9
benzene	**CH_3**	45.8	44.7
benzene	**CF_3**	50.8	48.2
H	**NH_2**	49.4	48.2
CH_3	**CH_3**	60.5	60.3
CF_3	**CH_3**	45.1	45.6
ethyl	**CH_3**	58.4	58.5
isopropyl	**CH_3**	59.3	57.8
T-butyl	**CH_3**	55.6	55.3
H	**OCH_3**	58.6	54.1
benzene	**OCH_3**	45.2	41.2
H	**F**	63.4	59.5
H	**CH_3***	56.4	60.1
H	**CH_3****	60.4 (cis/trans does not apply)	
H	**OCH_3****	45.98 (cis/trans does not apply)	

5. Discussion

5.1 Importance of Threshold Energies

Transition state theory describes the reaction rates of a specific reaction, assuming its mechanism has a quasi-equilibrium state. Chemical equilibrium describes the state of a reaction when the reactants and products are present at concentrations where the forward and reverse reactions occur at a rate that does not change with time. Quasi-equilibrium describes systems that differ only slightly from the equilibrium of the reaction. Reactions that exhibit this type of equilibrium usually proceed at a slow and steady rate. These reactions involve an intermediate structure, which serves as the transition state geometry between the reactants and the products. Since the transition state is related to the threshold energy of the compound, obtaining both the geometries and energies of the thioallyl is helpful in gaining more insight on the rearrangement. The threshold energy of a formed compound describes the minimum amount of kinetic energy it takes for colliding particles to form a new, combined molecule. The numerical value of the threshold energy is important when attempting to synthesize molecules because it provides a guideline for how much energy will be needed to form the desired product.

5.2 Substituent Effects

Electron withdrawing and donating groups can change the chemistry of a reaction by influencing the electron densities and locations in a molecule. When discussing substituent effects, it is the observation of the change in the behavior of the unchanged compound when adding or removing additional atoms. Typically, substituent effects are directly related to induction and resonance that occurs in some compounds. Induction is the effect of substituents on single-bonded molecules, while resonance must involve a single bonded-double bonded molecule. Since the thioallyl is a conjugated system, the substituents would be more likely to cause resonance effects, rather than inductive effects. Resonance is the sharing and delocalizing of electrons in a structure; the substituents can influence how these electrons are shared or moved. However, though the thioallyl is a conjugated system, the rearrangement is influenced more by its concerted mechanism, rather than resonance, and resembles the pericyclic nature of the Cope and Claisen rearrangements.

In this study, substituents were added at different positions of the thioallyl. The "original" structure for the thioallyl consisted of a hydrogen at R_1 and —CH_3 at R_4. As a substituent, —CF_3 was used to observe the effects of electron withdrawing groups on the transition state and threshold energy. With the exception of R_1 remaining a hydrogen with —CF_3 on R_4, when —CF_3 was placed on R_1 or R_4, the threshold energy decreased slightly. Electron withdrawing groups are characterized with the capability of directing electron densities away from a pi system, which may have factored into the lowering of the threshold energy. Electron withdrawing groups are also known to increase the rate of reactions, which supports the findings of lower threshold energies since reactions are typically sped up with lower threshold energies.

Both —NH_2 and —OCH_3 were used as electron donating groups on R_4 and R_4'. Threshold energies decreased more drastically compared to the basic thioallylic arrangement (R_1 = H; R_4 = CH_3) caused by the activating property of the substituents. The electron donating groups effectively decreased the amount of energy needed to transition from the ground state to the final state.

Larger substituents such as t-butyl and benzene did not cause disturbances along the rearrangement pathway likely due to their position on R_1; they were bent in such a way that they did not interact with atoms other than sulfur. Furthermore, the electrons on these groups were positioned so that they did not cause any force interference or interaction between the substituent and the allyl. All IRCs for the reported structures confirmed a reaction pathway showing a 1,3-sulfur shift on the allyl.

5.3 Implications and Applications of Results

Applications of computational chemistry for understanding organic reactions is still a relatively new branch in the overall history of chemistry. However, the methods used are well established. Computationally, the thioallylic rearrangement reaction can occur using a number of substituents to obtain different products. The results suggest that this reaction could also reasonably be applied in a laboratory setting. The threshold energies are low enough and the materials would measure low in danger so that the reaction could theoretically be conducted in a laboratory. One of the disadvantages of conducting the rearrangement step in an experiment would be its likely pungent smell, due to the

sulfur in the reaction. Practically, however, the thioallylic rearrangement could provide a useful step in the synthesis of specific organosulfur compounds.

6. Conclusion

The purpose of this research project was to collect information that could be useful in understanding the mechanism of the thioallylic rearrangement. This study successfully observed the threshold energies and transition state geometries of thioallylic compounds using different substituents. Results support the occurrence of a concerted mechanism of a unimolecular reaction, supporting Kwart's 1976 and 1977 findings. Though there are few chemical studies on this rearrangement reaction, it may prove to be beneficial for the synthesis of organosulfur compounds, including garlic derivatives, which have potential to be beneficial in the treatment of certain diseases. Garlic has been used in different medicinal practices, however has only recently been studied, mainly in biology and biomedicine. With this being said, fully understanding the mechanism of the thioallylic rearrangement would be beneficial to several disciplines of science. Additionally, if the reaction is to be conducted experimentally based on the computational results, it could show the effectiveness of using computational methods in organic studies. Further research on this subject would include experimental studies of the rearrangement, as well as the development of a mechanism for target reactions, especially if the garlic derivatives (like SAC and SAMC) were to be produced. Additionally, studies of the chemical reactivity and bioreactivity of garlic compounds and other organosulfur compounds would help expand the current understanding of the interactions these compounds have in living organisms.

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