University of Texas at Austin
College of Natural Sciences
Department of Chemistry
Austin, Texas

Investigating the Influence of $n \rightarrow \pi^*$ Interactions on the Regioselectivity of Diels-Alder Reactions

Theodore L. Jefferson

DECEMBER 2023

Investigating the Influence of $n \rightarrow \pi^*$ Interactions on the Regioselectivity of Diels-Alder Reactions
Theodore L. Jefferson

Table of Contents

I. Background

Abstract This research project seeks to explore the influence of $n \rightarrow \pi^*$ interactions on the regioselectivity of Diels-Alder reactions, a fundamental aspect of organic synthesis. By combining computational modeling and experimental approaches, the aim is to elucidate the specific contributions of $n \rightarrow \pi^*$ interactions to the regioisomeric outcomes of these reactions. The experimental design involves the selection of dienes and dienophiles with varying electron-donating and electron-withdrawing substituents, allowing for the modulation of $n \rightarrow \pi^*$ interactions. Computational methods will predict the impact of these interactions on the transition states of Diels-Alder reactions, providing a theoretical framework for experimental observations. Synthesis under controlled conditions, coupled with comprehensive characterization using NMR spectroscopy, mass spectrometry, and X-ray crystallography, will validate the role of $n \rightarrow \pi^*$ interactions in governing regioselectivity. The expected outcomes include the identification of specific $n \rightarrow \pi^*$ interactions influencing regioselectivity and the correlation between computational predictions and experimental results. This study holds significance in guiding the rational design of Diels-Alder reactions for the synthesis of complex organic molecules, potentially leading to more efficient and selective synthetic methodologies. The proposed research contributes to the broader understanding of the role of $n \rightarrow \pi^*$ interactions in molecular recognition and reactivity. Put simply, this proposal seeks to understand if it is possible to take advantage of the tunable induced stability provided by $n \rightarrow \pi^*$ interactions in the Diels-Alder products to control and modulate the reaction's regioselectivity.

Rationale The regioselectivity of Diels-Alder reactions is a pivotal factor that dictates the feasibility and efficiency of synthetic routes, particularly in the context of complex organic molecule synthesis. Understanding and manipulating regioselectivity can significantly enhance the precision and control over the synthesis of target compounds. While extensive research has been devoted to elucidating the factors that govern regioselectivity in Diels-Alder reactions, the specific contribution of $n \rightarrow \pi^*$ interactions remain an underexplored aspect.

The rationale for investigating $n \rightarrow \pi^*$ interactions in the context of Diels-Alder regioselectivity stems from the increasing recognition of the role these interactions play in molecular recognition and reactivity. $n \rightarrow \pi^*$ interactions involve the interaction between an electron lone pair (n) and the antibonding orbital (π^*) of a nearby double bond. These interactions have been observed to significantly influence the geometric and electronic properties of molecules[1], thereby affecting their behavior in chemical reactions.

In the realm of Diels-Alder reactions, where the alignment of molecular orbitals is crucial for the reaction to proceed, the influence of $n \rightarrow \pi^*$ interactions on regioselectivity becomes a compelling avenue of exploration. The electron-donating or withdrawing nature of substituents in the diene or dienophile can modulate these interactions, potentially directing the reaction towards specific regioisomers. By comprehensively understanding the interplay between $n \rightarrow \pi^*$ interactions and regioselectivity, a new dimension in the design of tailored synthetic methodologies can potentially be unlocked.

Furthermore, the potential impact of this research extends beyond the realm of synthetic organic chemistry. Diels-Alder reactions are widely employed in medicinal chemistry for the construction of bioactive compounds and pharmaceutical intermediates. Therefore, uncovering the role of $n \rightarrow \pi^*$

interactions in these reactions may offer insights into enhancing the efficiency and selectivity of drug synthesis, a critical aspect in the development of therapeutic agents.

In summary, investigating $n \rightarrow \pi^*$ interactions in the regioselectivity of Diels-Alder reactions represents a novel and promising avenue. This research not only addresses a significant gap in our understanding of molecular interactions but also holds the potential to revolutionize synthetic methodologies, with implications for both organic synthesis and medicinal chemistry.

Literature Review The understanding of $n \rightarrow \pi^*$ interactions, non-covalent interactions between a lone pair of electrons (n) and an antibonding π^* orbital in a neighboring molecule, has evolved through a combination of empirical observations, theoretical developments, and experimental validations. In the mid-20th century, initial observations of these interactions were largely empirical, driven by the need to explain unusual molecular conformations and reactivity patterns.

Theoretical advancements in quantum chemistry and molecular orbital theory during the 1960s, particularly the work of Roald Hoffmann and Robert B. Woodward laid the groundwork for a more systematic understanding of orbital interactions[2-5]. Hoffmann and Woodward's papers are foundational as they provided a theoretical framework for understanding orbital interactions, including those involved in $n \rightarrow \pi^*$ interactions. Their work laid the groundwork for the application of molecular orbital theory to explain the conformational preferences of six-membered rings. This paper marked a crucial step in elucidating the fundamental principles governing molecular structure and reactivity.

In 1996, Anthony Stone introduced the π-hole concept, emphasizing the electrostatic component of these interactions[7]. Stone's introduction of the π-hole added a new dimension to the understanding of $n \rightarrow \pi^*$ interactions by emphasizing the electrostatic component. The π-hole concept provided a powerful and intuitive way to explain the directional nature of interactions involving aromatic rings. Stone's work offered a conceptual framework that influenced subsequent theoretical studies and contributed to a more holistic understanding of the forces at play in these non-covalent interactions.

The 2011 review by Murray and Politzer on the electrostatic potential is crucial for its comprehensive overview of the electrostatic aspects of non-covalent interactions. This work delves into the intricacies of electrostatic potential surfaces and their role in governing molecular recognition[8]. Understanding the electrostatic nature of $n \rightarrow \pi^*$ interactions is pivotal for predicting and rationalizing the behavior of molecules in various chemical processes.

Wang and Hobza's 2008 paper on the energy decomposition analysis of π - π interactions, closely related to $n \rightarrow \pi^*$ interactions, contributes valuable insights into the energetics of these interactions. By breaking down the interaction energy into components, the study provides a detailed understanding of the factors influencing the stability of molecular complexes. This work aids in the quantitative assessment of π - π interactions and enhances the predictive power of theoretical models.

The 2000s witnessed the rise of computational studies, employing methods such as density functional theory (DFT) and *ab initio* calculations to quantify $n \rightarrow \pi^*$ interactions[10]. Meanwhile, the 2010s brought

about a synergy of computational and experimental approaches, with advancements in techniques like X-ray crystallography and NMR spectroscopy providing direct evidence of these interactions in crystal structures and solution-phase studies[1].

In summary, seminal papers, such as Hoffmann and Woodward's work in the 1960s and Stone's 1996 contribution, along with more recent studies by researchers like Murray and Politzer (2011) and Wang and Hobza (2008), have contributed to the comprehensive understanding of $n \rightarrow \pi^*$ interactions. The 2010s brought about a synergy of computational and experimental approaches, with advancements in techniques like X-ray crystallography and NMR spectroscopy providing direct evidence of these interactions in crystal structures and solution-phase studies. These computational and experimental approaches, while tangential to what is being explored in this proposal, set a precedent for how to approach and analyze $n \rightarrow \pi^*$ interactions.

As of late, the $n \rightarrow \pi^*$ interaction has garnered significant attention due to its impact on molecular systems. According to modern understanding, this interaction involves the overlap of the lone pair (n) of a nucleophile with the antibonding π^* orbital of a carbonyl group, resulting in a weak yet pervasive force. Computational methods, particularly natural bond orbital (NBO) analysis, have been instrumental in unraveling the nature and energy of these interactions. The energy of an $n \rightarrow \pi^*$ interaction is governed by the degree of orbital overlap and the energy of mixing, with typical energies estimated to be around 0.3-0.7 kcal/mol[13]. Notably, the ubiquity of carbonyl groups across chemistry and biology underscores the broad impact of $n \rightarrow \pi^*$ interactions. These interactions play a crucial role in dictating protein structure, influencing the conformation and activity of biomacromolecules such as proteins, polyesters, and peptoids[1]. Furthermore, the $n \rightarrow \pi^*$ interaction has implications for the reactivity of small molecules, as evidenced by its influence on the quantum yield of fluorogenic probes. Understanding and characterizing the $n \rightarrow \pi^*$ interaction has not only refined our comprehension of molecular interactions but has also led to the identification of new types of hydrogen bonds within peptides and proteins. This emergent interaction continues to inspire new thoughts and discoveries, highlighting its significance in molecular systems.

Objectives Building upon the comprehensive literature review that delineates the historical evolution of our understanding of $n \rightarrow \pi^*$ interactions, this research project aims to investigate the influence of these interactions on the regioselectivity of Diels-Alder reactions. The objectives of this experimental endeavor are guided by the gaps and insights highlighted in the reviewed literature.

Elucidate Specific Contributions of $n \rightarrow \pi^*$ Interactions. Leveraging insights from seminal works, such as Hoffmann and Woodward's foundational paper and Stone's π-hole concept, our primary objective is to unravel the specific contributions of $n \rightarrow \pi^*$ interactions to the regioisomeric outcomes in Diels-Alder reactions. By employing a combination of syntheses *in vitro* and computational modeling *in silico*, we seek to predict the influence of these interactions on the transition states of the reactions, providing a theoretical framework for subsequent experimental observations.

Modulate $n \rightarrow \pi^*$ Interactions Through Substituent Variation. Drawing inspiration from Wang and Hobza's energy decomposition analysis and the broader computational studies on π - π interactions, the

experimental design involves the judicious selection of dienes and dienophiles with varying electron-donating and electron-withdrawing substituents. This strategic substitution aims to modulate the strength and orientation of $n \rightarrow \pi^*$ interactions, allowing for the systematic exploration of their impact on regioselectivity.

Validate Computational Predictions through Synthesis and Characterization. Addressing the need for a combination between theoretical and experimental approaches emphasized in the literature, our experimental design incorporates the synthesis of Diels-Alder reactions under controlled conditions. Comprehensive characterization techniques, including NMR spectroscopy, mass spectrometry, and X-ray crystallography, will be employed to validate the role of $n \rightarrow \pi^*$ interactions in governing regioselectivity. This approach ensures a robust correlation between computational predictions and experimental results.

Identify Specific $n \rightarrow \pi^*$ Interactions Influencing Regioselectivity: Building on the conceptual framework provided by the literature, we aim to identify specific $n \rightarrow \pi^*$ interactions that play a pivotal role in determining regioselectivity. This objective aligns with the overarching goal of unraveling the molecular factors that govern the outcome of Diels-Alder reactions and contributes to a deeper understanding of the nuanced interactions at play.

Contribute to Rational Design of Diels-Alder Reactions. The ultimate objective of this research is to contribute to the rational design of Diels-Alder reactions for the synthesis of complex organic molecules. By elucidating the role of $n \rightarrow \pi^*$ interactions in molecular recognition and reactivity, more efficient and selective synthetic methodologies can potentially be unlocked. The expected outcomes hold significance in the broader context of organic synthesis and have the potential to guide advancements in the field.

In summary, this research project seeks to bridge theoretical insights from the literature with experimental observations, aiming to advance our understanding of $n \rightarrow \pi^*$ interactions and their impact on the regioselectivity of Diels-Alder reactions. Through a multidisciplinary approach, the study endeavors to contribute valuable knowledge for the rational design of organic synthesis processes.

II. Experimental Plan

Reaction Design The Diels-Alder reaction, a cornerstone in organic synthesis, offers a versatile platform for constructing complex molecular architectures. Central to the success of this reaction is the regioselectivity, which governs the specific positions of bond formation, directly impacting the diversity and efficiency of the synthesized compounds. In this experimental design, the aim is to deploy a strategic exploration of the regioselectivity in Diels-Alder reactions while keeping the oft-neglected $n \rightarrow \pi^*$ interactions in mind. Recognizing the influence of these interactions on molecular recognition and reactivity, the primary approach involves the meticulous selection of dienes and dienophiles known not only to produce regioisomerism, but also to participate in $n \rightarrow \pi^*$ interactions. By introducing a spectrum of electron-donating and electron-withdrawing substituents, the aim is to modulate $n \rightarrow \pi^*$ interactions systematically. This nuanced and deliberate reaction design seeks to unravel the intricate interplay between substituent effects, molecular geometry, and the resulting regioselectivity, laying the foundation for a comprehensive understanding of the role played by $n \rightarrow \pi^*$ interactions in Diels-Alder reactions.

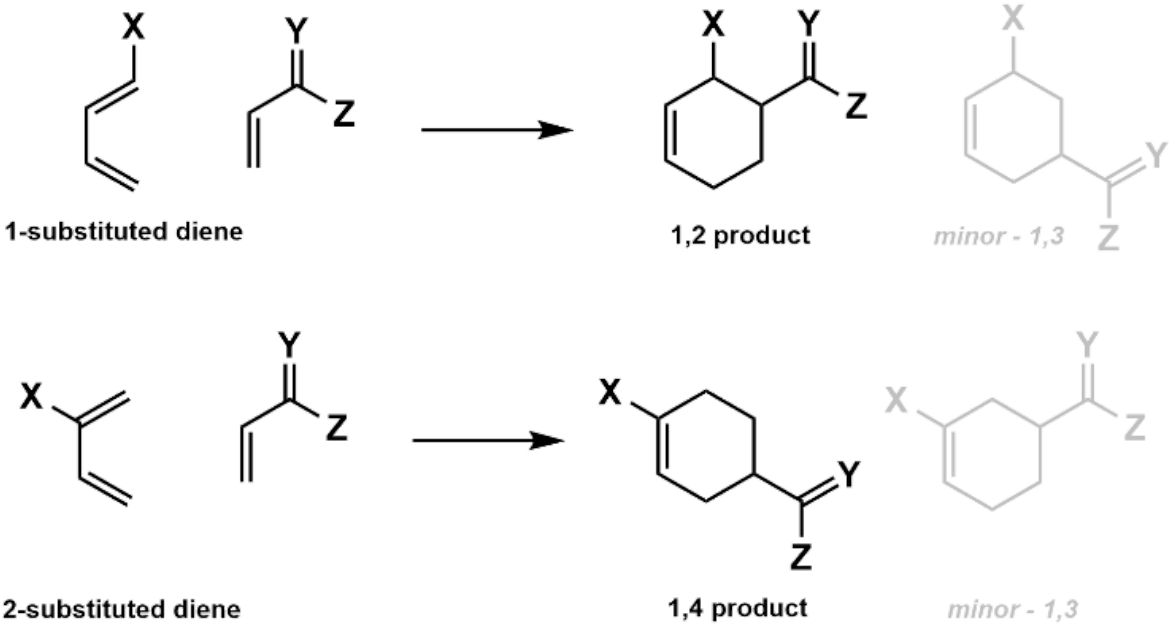
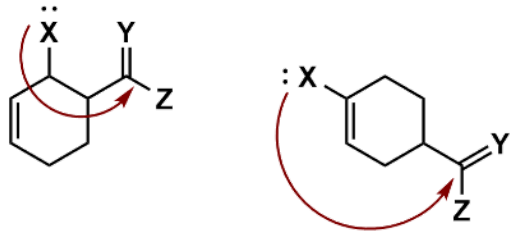


Figure 1: General regioselective outcomes of asymmetric dienes in Diels-Alder reactions, where 1-substituted dienes yield 1,2 products and 2-substituted dienes yield 1,4 products. 1,3 products only are made in minor yields, begging the question of the possibility of modulating regioselectivity.

Selection of Dienes and Dienophiles. To probe the influence of $n \rightarrow \pi^*$ interactions on Diels-Alder regioselectivity, a carefully chosen set of dienes and dienophiles will be employed. The selection will encompass a range of substrates known for 1) exhibiting regioisomerism in Diels-Alder reactions by using asymmetric dienes, and 2) substrates known for having a tunable $n \rightarrow \pi^*$ interaction[1]. This diversity ensures a robust examination of the role of $n \rightarrow \pi^*$ interactions across different molecular contexts.



Can we take advantage of the tunable induced stability provided by $n \rightarrow \pi^*$ interactions to modulate regioselectivity?

Position	Source	Derivatives
X	Diene	amine[a1,a2], ketone[b1,b2], thioketone[c1,c2]
Y	Dienophile	oxygen[a], sulfur[b]
Z	Dienophile	OMe[a1,b1], NMe_2[a2,b2]

Figure 2: Selected dienes and dienophiles for initial screening, explicitly chosen to tune the $n \rightarrow \pi^*$ interaction, and subsequently, probe the influence of it on the Diels-Alder regioselectivity.

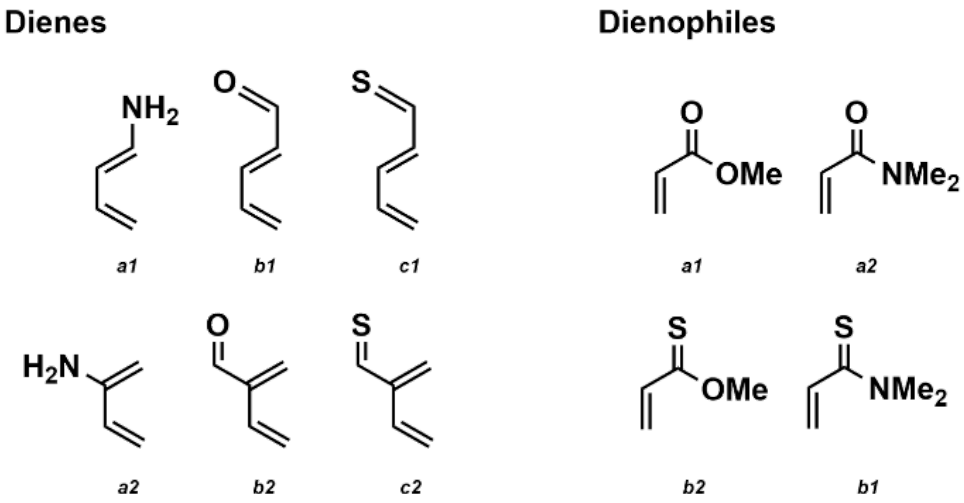


Figure 3: Dienes are labeled alphabetically based on their unique X substituent and numerically based on the position of that substituent, whereas dienophiles are labeled alphabetically based on their unique Y substituent, and numerically based on the Z substituent. For example, a 1-substituted amine diene is labeled a1, while a 2-substituted amine diene is a2.

Introduction of Electron-Donating and Electron-Withdrawing Substituents. To systematically modulate $n \rightarrow \pi^*$ interactions, the chosen diene series *a* - *c* and dienophile series *a* - *b* will be functionalized with electron-donating and electron-withdrawing substituents. The substitution patterns will be strategically designed to alter the electronic properties of the molecules, thereby influencing the strength and orientation of $n \rightarrow \pi^*$ interactions. This modification will create a spectrum of molecular environments, allowing for a nuanced exploration of how these interactions impact regioselectivity.

For dienes, substituents such as 1) alkyl groups, 2) methoxy groups, and 3) amino groups will be incorporated as electron-donating moieties, while 4) nitro groups, 5) cyano groups, and 6) halogens will serve as electron-withdrawing substituents. Similarly, electron-donating and withdrawing groups will be introduced in the dienophiles, ensuring a comprehensive analysis of the interplay between $n \rightarrow \pi^*$ interactions and regioselectivity. The specific substituents chosen for each diene and dienophile would be done through a combination of reaction and computational screening of the regioselectivity for each combination.

Because each diene will be paired with each additional diene substituent (36 possible pairings), and each dienophile will be paired with each additional dienophile substituent (24 possible pairings), only a select few representative reactions would be screened through actual *in vitro* synthesis, as synthesizing every single combination would require 864 trials total, which is non-efficient and non-economical to do with physical chemicals. Therefore, it is most efficient to do ~95% of the combinations *in silico*, which can handle this demanding amount rapidly. Afterward, any suspicious results can be affirmed or rejected based on *in vitro* synthesis.

This deliberate design of the reaction substrates is incredibly thorough to properly elucidate the correlation between the nature of substituents, the strength of $n \rightarrow \pi^*$ interactions, and the resulting 1,2 or 1,4 product to 1,3 product regioisomeric distribution in the Diels-Alder products. The systematic variation of substituents will provide valuable insights into how the admittedly subtle changes in molecular structure can orchestrate regioselective outcomes through the modulation of $n \rightarrow \pi^*$ interactions.

Computational Modeling Computational modeling of $n \rightarrow \pi^*$ interactions involves the use of advanced methods to understand the nature and energy of these interactions. Natural bond orbital (NBO) analysis has been particularly instrumental in providing insights into the energy and characteristics of $n \rightarrow \pi^*$ interactions[1]. This approach partitions electron density from diffuse molecular orbitals into localized Lewis-type orbitals, allowing for the computation of the energy of mixing, which is crucial in understanding the strength of $n \rightarrow \pi^*$ interactions[9]. Additionally, computational methods such as density functional theory (DFT) and *ab initio* calculations have been employed to study the geometry and energetics of $n \rightarrow \pi^*$ interactions in molecular systems[10].

In the context of this proposal, computational modeling can play a pivotal role. By employing DFT calculations, the geometry and energy of $n \rightarrow \pi^*$ interactions between the dienophile and the diene in the Diels-Alder reaction can be elucidated[10,11]. This modeling can provide insights into how the strength of the $n \rightarrow \pi^*$ interaction influences the regioselectivity of the reaction. Furthermore, NBO analysis can be utilized to quantify the energy of mixing[12] and understand the nature of the $n \rightarrow \pi^*$ interactions in the Diels-Alder products, as employed in previous studies[13]. By systematically varying the molecular structure and electronic properties of the reactants *in silico*, the impact of $n \rightarrow \pi^*$ interactions on the regioselectivity of the Diels-Alder reaction can be elucidated, providing valuable guidance for experimental design and optimization.

Synthesis The synthesis for this experimental project is carefully designed to explore the influence of $n \rightarrow \pi^*$ interactions on the regioselectivity of Diels-Alder reactions. The key objective is to judiciously select dienes and dienophiles with varying electron-donating and electron-withdrawing substituents, allowing for the modulation of $n \rightarrow \pi^*$ interactions in the reaction products. Therefore, the synthetic approach must involve a step-by-step process to ensure control over reaction conditions and to facilitate comprehensive characterization.

Reaction Conditions. The Diels-Alder reactions will be conducted under carefully controlled conditions to ensure reproducibility and minimize side reactions. Reaction parameters such as temperature, solvent, and catalysts will be optimized within an inert atmosphere to achieve high yields of the desired products, and a multitude of sources are available to turn to when deciding these parameters[14]. The goal is to maintain a balance between reaction efficiency and selectivity, with an emphasis on controlling the $n \rightarrow \pi^*$ interactions.

Isolation and Purification. Following the completion of the Diels-Alder reactions, the reaction mixtures will be subjected to isolation and purification steps. Techniques such as column chromatography or recrystallization will be employed to separate and purify the products. The purification process is crucial for obtaining analytically pure compounds for subsequent characterization.

Analysis The analysis phase of this research project is pivotal for deciphering the intricacies of $n \rightarrow \pi^*$ interactions and their impact on the regioselectivity of Diels-Alder reactions. A multi-faceted approach incorporating advanced analytical techniques is employed to characterize reaction products, confirm regioselectivity, and facilitate a rigorous comparison between experimental observations and computational predictions.

Characterization Techniques. Nuclear magnetic resonance (NMR) spectroscopy serves as a powerful tool for elucidating the structural details of the synthesized compounds. The spectra obtained will provide information about the connectivity of atoms, stereochemistry, and the presence of any unexpected side products. In particular, the distinct shifts and splitting patterns in the spectra will be crucial for confirming the regioselectivity of the Diels-Alder reactions.

Mass spectrometry offers a precise determination of molecular weights and provides insight into the composition and purity of reaction products. The technique is instrumental in identifying different regioisomers and assessing the success of the reaction. Mass spectrometric analysis will complement NMR data, ensuring a comprehensive understanding of the synthesized compounds.

For select compounds, X-ray crystallography will be also employed to obtain high-resolution structural information. This technique provides a three-dimensional visualization of molecular arrangements in the crystal lattice, offering unparalleled insights into the spatial arrangement of atoms. X-ray crystallography will be particularly valuable for validating the regioselectivity and confirming the presence of specific $n \rightarrow \pi^*$ interactions in the synthesized products.

Comparative Analysis. The experimental results obtained from NMR spectroscopy, mass spectrometry, and X-ray crystallography will be systematically compared with the computational predictions generated in the modeling section. This comparative analysis aims to validate the accuracy of the computational models and establish a direct correlation between the predicted impact of $n \rightarrow \pi^*$ interactions and the experimentally observed regioselectivity.

Any discrepancies between experimental findings and computational predictions will be carefully examined. This iterative process allows for the identification of potential limitations in the computational models and provides valuable insights for refining the theoretical approach. Adjustments to the models may be made based on experimental observations, ensuring a dynamic and adaptive research methodology.

The degree of agreement between experimental and computational results will be quantitatively assessed, providing a robust measure of the reliability of the computational models. This quantitative comparison enhances the predictive power of the theoretical framework and establishes confidence in the extrapolation of findings to broader reaction contexts.

The analysis phase is key for the successful interpretation of this research proposal, therefore, a comprehensive suite of analytical techniques has been proposed to characterize reaction products, confirm regioselectivity, and validate computational predictions. This integration of experimental and theoretical approaches ensures a holistic understanding of the role of $n \rightarrow \pi^*$ interactions in Diels-Alder reactions, paving the way for nuanced insights into physical organic-based molecular recognition and reactivity.

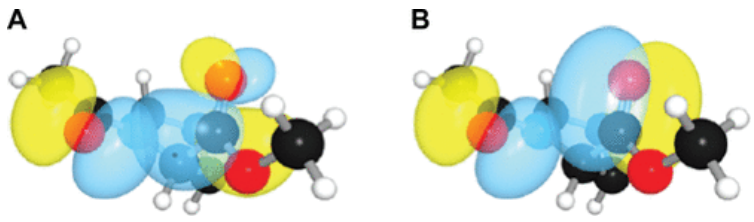


Figure 4: An example of NBO calculations of the $n \rightarrow \pi^*$ interaction found in N-acetylproline methyl ester. Overlap is shown between the *n* donor orbital and both (A) the π^* orbital and (B) the π orbital[1,15].

III. Anticipated Results

Outcomes One of the primary anticipated outcomes of this research project is the identification of specific $n \rightarrow \pi^*$ interactions that exert a discernible influence on the regioselectivity of Diels-Alder reactions. Through the integration of computational modeling and experimental synthesis, the primary aim is to pinpoint the key interactions between lone pair electrons (n) and antibonding π^* orbitals that significantly contribute to the observed regioisomeric outcomes, if any. This outcome is fundamental to advancing our understanding of the molecular factors governing the selectivity of Diels-Alder reactions and contributes to the broader knowledge of non-covalent interactions in chemical reactivity.

The successful correlation between computational predictions and experimental observations represents a pivotal outcome of this research. The validation or dismissal of the role of $n \rightarrow \pi^*$ interactions in the regioselectivity of Diels-Alder reactions through a meticulous comparative analysis is anticipated. Achieving a high degree of agreement between the two sets of data not only strengthens the reliability of our theoretical models but also underscores the predictive power of computational approaches in understanding complex reaction mechanisms. Conversely, any discrepancies between computational and experimental outcomes will guide iterative refinements to enhance the accuracy and applicability of our models.

Challenges Synthesizing regioisomers with a high level of reproducibility and reliability poses a significant challenge in this research. The systematic modulation of $n \rightarrow \pi^*$ interactions require precise control over reaction conditions, substrate concentrations, and reactant purity. Ensuring that the observed regioselectivity is consistent across multiple experimental runs is crucial for drawing robust conclusions. Rigorous optimization of reaction parameters and validation through repeated experiments will be employed to address this challenge and enhance the reliability of the synthetic outcomes.

The inherent complexity of chemical reactions introduces the challenge of potential side reactions or competing pathways that could obscure the regioselectivity arising from $n \rightarrow \pi^*$ interactions. Unwanted reactions may lead to the formation of byproducts, making the isolation and characterization of the desired regioisomers challenging. To address this, reaction conditions will be meticulously optimized, and purification techniques will be tailored to selectively isolate the target products. Careful analysis of reaction byproducts and intermediates will provide insights into potential competing pathways, enabling strategies to mitigate their impact and enhance the overall selectivity of the Diels-Alder reactions.

While insights into $n \rightarrow \pi^*$ interactions and regioselectivity are expected, reproducibility in synthesis and the intricate nature of competing reaction pathways could provide challenges. In addition, the relative lack of strength in the interaction could yield negligible results. Regardless, this proposal is still in a position to advance the understanding of an underexplored molecular interaction in the context of an extremely ubiquitous chemical reaction.

IV. Conclusion

In conclusion, this proposed research project aims to contribute to the ongoing evolution of the understanding of $n \rightarrow \pi^*$ interactions and their influence on the regioselectivity of Diels-Alder reactions. The historical context, as illuminated by seminal works such as those by Hoffmann, Woodward, Stone, Wang, and Hobza, underscores the intricate nature of non-covalent interactions and their pivotal role in shaping molecular reactivity. Building upon this foundation, this proposal's objectives are rooted in addressing key gaps identified in the literature, combining computational modeling with experimental methodologies to provide a comprehensive exploration of these interactions in the context of Diels-Alder reactions.

By elucidating the specific contributions of $n \rightarrow \pi^*$ interactions to regioisomeric outcomes, the aim of this proposal is to provide valuable insights that not only enhance the fundamental understanding of molecular recognition but also offer practical applications for the rational design of synthetic methodologies. The proposed synergy between theoretical predictions and experimental validations, using carefully selected dienes and dienophiles, seeks to establish a robust correlation between computational models and real-world reactions.

The outcomes of this research project hold significance not only for the field of organic synthesis but also for the broader understanding of non-covalent interactions in chemical processes. The identification of specific $n \rightarrow \pi^*$ interactions influencing regioselectivity and the validation of these findings through meticulous experimental characterization represent critical steps toward advancing the precision and predictability of synthetic methodologies.

In summary, this research project stands at the intersection of theoretical and experimental chemistry, and has the potential to unravel the mysteries of $n \rightarrow \pi^*$ interactions and their impact on regioselectivity in Diels-Alder reactions. Through these endeavors, there is an aspiration that this proposal will provide a modest contribution in the field of asymmetric organic synthesis, and inspire further inquiries into the subtle forces that govern chemical reactivity.

V. References

[1] Newberry, R. W.; Raines, R. T. The n→π* Interaction. *Accounts of Chemical Research* **2017**, *50* (8), 1838–1846.

[2] Woodward, R. B.; Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *Journal of the American Chemical Society* **1965**, *87* (2), 395–397.

[3] Hoffmann, R.; Woodward, R. B. Selection Rules for Concerted Cycloaddition Reactions. *Journal of the American Chemical Society* **1965**, *87* (9), 2046–2048.

[4] Woodward, R. B.; Hoffmann, R. Selection Rules for Sigmatropic Reactions. *Journal of the American Chemical Society* **1965**, *87* (11), 2511–2513.

[5] Hoffmann, R.; Woodward, R. B. Orbital Symmetries and Endo-Exo Relationships in Concerted Cycloaddition Reactions. *Journal of the American Chemical Society* **1965**, *87* (19), 4388–4389.

[6] Hoffmann, R.; Woodward, R. B. Orbital Symmetries and Orientational Effects in a Sigmatropic Reaction. *Journal of the American Chemical Society* **1965**, *87* (19), 4389–4390.

[7] Lommerse, J. P. M.; Stone, A. J.; Taylor, R.; Allen, F. H. The Nature and Geometry of Intermolecular Interactions between Halogens and Oxygen or Nitrogen. *Journal of the American Chemical Society* **1996**, *118* (13), 3108–3116.

[8] Murray, J. S.; Politzer, P. The Electrostatic Potential: An Overview. *WIREs Computational Molecular Science* **2011**, *1* (2), 153–163.

[9] Reed, A. E.; Curtiss, L. A.; Weinhold, F. Intermolecular Interactions from a Natural Bond Orbital, Donor-Acceptor Viewpoint. *Chemical Reviews* **1988**, *88* (6), 899–926.

[10] Cho, Y.; Do Hyung Kim; Il Seung Youn; Jae Sung Lee; Singh, N.; Kim, K. S. Density Functional Theory Based Study of Molecular Interactions, Recognition, Engineering, and Quantum Transport in π Molecular Systems. **2014**, *47* (11), 3321–3330.

[11] Bursch, M.; Mewes, J.; Hansen, A.; Grimme, S. Best‐Practice DFT Protocols for Basic Molecular Computational Chemistry**. *Angewandte Chemie International Edition* **2022**, *61* (42).

[12] Bartlett, G. J.; Choudhary, A.; Raines, R. T.; Woolfson, D. N. N→π* Interactions in Proteins. *Nature Chemical Biology* **2010**, *6* (8), 615–620.

[13] Hodges, J. A.; Raines, R. T. Energetics of an N → π* Interaction That Impacts Protein Structure. *Organic Letters* **2006**, *8* (21), 4695–4697.

[14] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels-Alder Reaction in Total Synthesis. *Angewandte Chemie International Edition* **2002**, *41* (10), 1668–1698.

[15] Jakobsche, C. E. et al. N → π* Interaction and N)(π Pauli Repulsion Are Antagonistic for Protein Stability. *Journal of the American Chemical Society* **2010**, *132* (19), 6651–6653.