Purpose

The goal is perform two different Diels-Alder reactions. The products are analyzed by IR, ^{13}C and ^{1} NMR spectroscopy, and X-ray crystallography.

Learning Objectives

Setup a sealed reaction vessel for long-term reaction including correct use of parafilm.

Comparison of kinetic vs. thermodynamic control in reactions.

Perform chemical synthesis at low temperatures and with kinetic control.

Identify dienes and dienophiles and determine if a structure is electron rich or electron poor.

Techniques of recrystallization.

Interpretation of NMR and X-ray structures to determine relative stereochemistry.

Equipment

- 25 mL Erlenmeyer flask
- Filtration setup with Hirsch funnel
- Vials
- Melting point apparatus
- 250 mL Beaker (ice-bath)

Chemicals

- Maleic anhydride
- Furan
- Diethyl ether (anhydrous)
- N-phenylmaleimide
- α-terpinene
- Methanol

New Material –

Vollhardt, P.; Schore, N. E.; Organic Chemistry: Structure and Function Chapter 14.6, 14.8.

References –

Diels, O.; Alder, K.; Ber., 1929, 62, 554

Stockmann, H.; J. Am. Chem. Soc. 1961, 26, 2025

Woodward, R. B.: Baer, H.; J. Am. Chem. Soc. 1948, 70, 1161

Diels, O.; Koch, W.; Rost, H.; Ber. 1938, 73, 1163

Theory and Background

Introduction

The molecular orbitals in pi systems are capable of unique reactions and rearrangements within a single molecule or between the pi systems of several molecules. The Diels-Alder reaction is a 4+2 cycloaddition reaction that uses an electron rich diene and an electron poor dienophile (Figure H.1), when the two molecules contact an electrocyclic mechanism allows for rehybridization of four of the six carbons and formation of a cyclohexene ring with very precise stereochemistry.

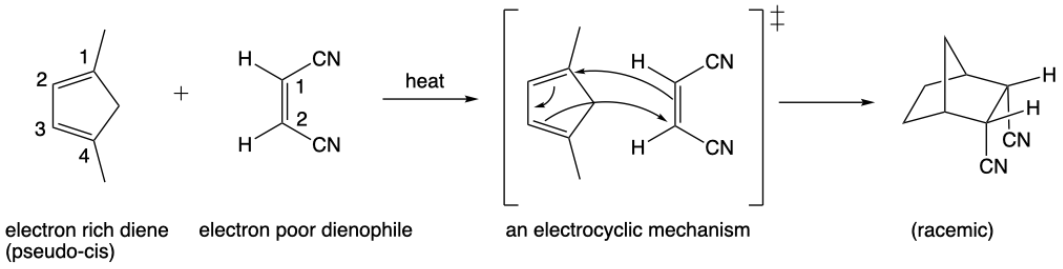


Figure H.1: The Diels-Alder reaction - a 4+2 cycloaddition reaction.

Diels-Alder reactions are synthetically useful in that they produce highly stereospecific rings with four stereo-centers that can be pre-determined by the correct choice of starting materials. Otto Diels and Kurt Alder were awarded the Nobel Prize in Chemistry in 1950 for their discovery of this reaction. However, to date the reaction is not commonly used in many large-scale industrial applications. Diels-Alder reactions are used in the purification of medrogestone and a variation on a Diels-Alder reaction using a nitrile as a dienophile is used in the synthesis of the reverse transcriptase inhibitor Abacavir as shown in Figure H.2.

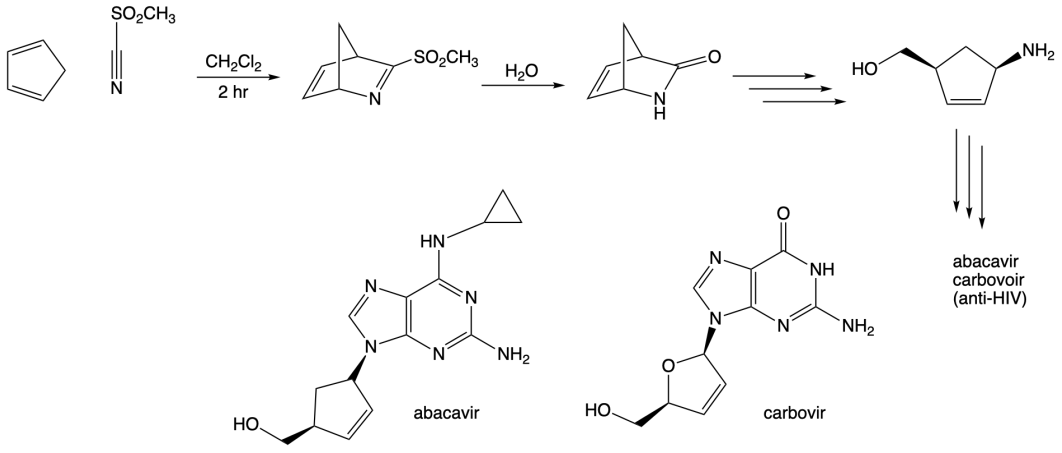


Figure H.2: Partial synthesis of abacavir using a hetero-Diels-Alder reaction

Griffiths, F. E. Previdoli, J. Org. Chem. 1993, 58, 6129

E. D. Pinheiro, O. A. C. Antunes, J. M. D. Fortunak, Antiviral Res. 2008, 79, 143

Kinetic vs. Therodynamic Reactions

Kinetics (rate of a reaction) and thermodynamics (enthalpy, entropy and spontaneity of reaction) are major factors in all chemical reactions. In many cases kinetics and thermodynamics work to form a single product, but in some cases there is a balance between both factors and careful adjustments to reaction conditions can shift product ratios.

Reactions where the rate of reaction is the major factor to determining products are said to be under kinetic control. These reactions follow the path with the lowest activation energy regardless of the ultimate stability of the product. Kinetic control tends to occur at lower temperatures and shorter reaction times where a product that is formed quickly is trapped and unable to reverse reaction. Reactions where the overall enthalpy of reaction is the major factor to determining products are said to be under thermodynamic control. These reactions produce the lowest energy product (most exothermic reaction) regardless of the activation energy. Thermodynamic control tends to occur at high temperatures and long reaction times where there's plenty of energy for molecules to reverse reactions and settle into the lowest possible energy positions.

Mechanism and Stereoselectivity

Diels-Alder reactions are typically under kinetic control. The major product in most Diels-Alder reactions goes through the low energy endo transition state (Figure H.3) to produce the sterically hindered endo product. In the endo transition state, the lone pairs and pi-orbitals on the electron-withdrawing groups of the dienophile interact with the pi-orbitals of the diene and lower the overall transition state energy. However, this results in a product with steric hindrance as the electron-withdrawing groups end up pointed into the 'cup' of the newly formed cyclohexene.

Diels-Alder reactions have high activation energies and the stabilization of the transition state significantly speeds up reaction even at moderate to high temperatures and the fastest formed (kinetic) product predominates. The exo product (Figure H.4)has less steric hindrance in the final product so is thermodynamically more stable, but lacks the pi-orbital interactions in the transition state so is difficult to form. It is only with very high temperatures or long reaction times that the exo (thermodynamic) product tends to form as the major product.

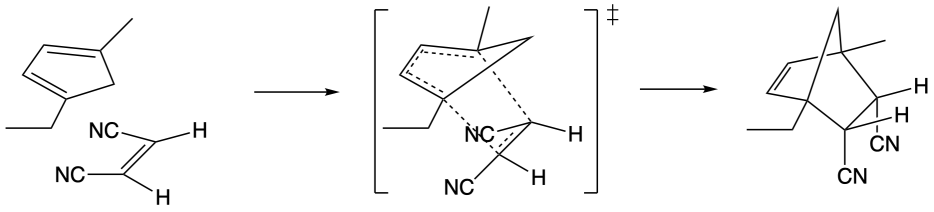


Figure H.3: Endo transition state with the electon-withdrwaing groups towards the diene.

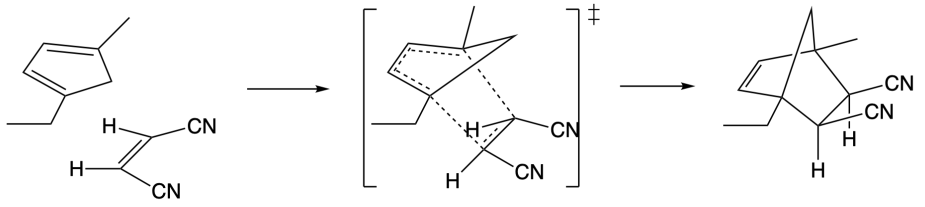


Figure H.4: Exo transition state with the electon-withdrwaing groups away from the diene.

Recrystallization and X-Ray Crystallography

Crystallization or recrystallization is a method for purifying a solid substance away from small amounts of other solid or non-solid impurities. Crystallization takes advantage of differing solubilities for substances to form a solution that is saturated or super-saturated in the desired substance and unsaturated in undesired substances. Most substances are soluble in solvents with similar properties, and less soluble in solvents with dissimilar properties. Also, most solids are more soluble when the solution is heated as heat helps disrupt the lattice energy in the solid.

Crystallization may occur spontaneously as the product is less soluble in the reaction solvent than the starting material so as it forms, the intermolecular forces of the pure solid solute are stronger than the intermolecular forces between the solute and the solvent. The product can then be collected by filtration with a high degree of purity. If the product stays soluble in the reaction solvent and is collected as a mixture with remaining starting material or crystallizes as a mixture of compounds the sample may be recrystallized.

To recrystallize a substance we dissolve the mixture in the minimum amount of hot solvent. This maximizes the solubility of all substances in the mixture and makes a solution that is just minimally unsaturated in the target substance. The solution is then allowed to cool. Cooling the solution decreases the solubility of all solutes, but the target solute, which was barely soluble initially, is now supersaturated and precipitates (aka crashes out) from solution. The impurities, which are in much lower concentrations, stay unsaturated even in the cold solvent and stay in solution. Recrystallization works well with small amounts of soluble impurities, but poorly when there is a large percentage of impurity or if impurities are poorly soluble in the recrystallization solvent.

Like many purification techniques crystallization takes advantage of the equilibrium between two phases, in this case the solid crystal and the liquid solution. Solids will tend to crystallize as pure compounds and even a mixture with substances of similar rates of crystallization the substances will tend to form into separate crystals. Separating those crystals later is still problematic but the molecules will be separate on a microscopic scale. As a consequence, the slower the process of crystallization is, the longer the equilibration process will be and the more exchanges between phases a molecule will have allowing it to find the minimum energy position, and the higher the purity and more consistent the crystal structure of individual crystals will be.

If crystals are formed of sufficient purity and with minimal flaws (cracks, blending of multiple crystals, empty spaces in the crystal lattice etc.) it is possible to exactly image the positions of individual atoms in the structure. X-ray diffraction or X-ray crystallography uses the diffraction of a beam of X-rays off of the molecules in the crystal to exactly image places of high/low electron density, which can be mapped into three-dimensional structures that show: bond lengths, bond angles, relative position, and if heavy atoms are present even the absolute stereochemistry. Obtaining crystals suitable crystals is not a trivial, as many organic molecules form amorphous solids (glasses) or the crystals are too small or too flawed for good diffraction, but if a crystal is obtainable highly detailed information is possible for a small organic molecules and large biological structures such as proteins.

118B Exp H Procedure

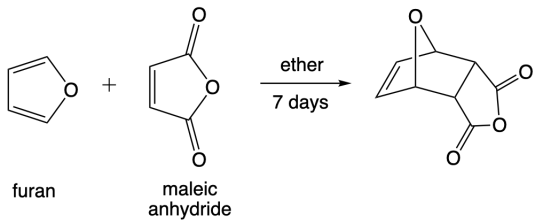
This experiment will be done in INDIVIDUALLY.

Safety Precautions

1. Maleic anhydride and N-phenylmaleimide are strong irritants. Wear gloves at all times when handling these materials.
2. Maleic anhydride will react with water, so keep the sample dry and all bottles tightly capped.
3. Furan, a-terpinene, ether, and methanol are all highly flammable and minor irritants.
4. Ether is highly volatile. Keep the bottle tightly capped not in use and in the fume hood at all times. Cork your flask with ether in it at all times.

Week 1: Furan and Maleic Anhydride

This reaction uses the aromatic compound furan (isolated via several steps from corncobs) and maleic anhydride. Which is the diene and which is the dienophile?



1. In a 25 mL Erlenmeyer flask dissolve 0.5 g of maleic anhydride in 5.0 mL diethyl ether (anhydrous).

2. Add 0.75 mL of furan.

3. Tightly cork the flask and wrap the cork with parafilm.

   Parafilm is a wax sheet that provides a seal around the cork to help prevent evaporation, but needs to be stretched tightly to form the seal. Your TA will demonstrate the proper use of parafilm to prevent evaporation of the volatile ether solvent.

4. Store the sealed flask in your locker until the following lab period.

Week 2 – Furan and Maleic Anhydride

5. Remove the sealed flask from your locker. You should see white crystals of the Diels-Alder adduct.

6. Filter the crystals with a Hirsch funnel and a small piece of filter paper.

7. Allow the crystals to dry by pulling air through the Hirsch funnel then on a piece of weigh paper.

8. Tare a vial and obtain the mass of the furan-maleic anhydride adduct by difference.

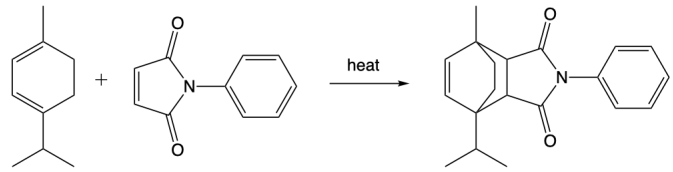
9. Obtain a melting point of the adduct.

10. Label the vial with 118B – furan-maleic anhydride adduct and your name and turn in to your TA.

11. The filtrate containing diethyl ether can be disposed of in the diethyl ether waste bottle. The cork can be disposed of in the trash.

Week 2 - alpha-Terpinene and N-Phenylmaleimide

This reaction uses α-terpinene, a terpene isolated from marjoram essential oil (*Organum marjorana L.*), and N-phenylmaleimide. Which is the diene and the dienophile?



12. In a 25 mL Erlenmeyer flask mix 0.1 g of N-phenylmaleimide in 0.25 mL α-terpinene.

> N-Phenylmaleimide is very expensive. Use care in weighing out the sample so as to avoid waste.

13. Carefully heat the flask gently on a hot plate to dissolve the N-phenylmaleimide and create a yellow oil.

14. Heat for an additional 15 minutes or until the yellow color had disappeared and the N-phenylmaleimide is completely reacted.

15. Cool the reaction flask to room temperature and add 3.0 mL of methanol.

16. Place the reaction flask in an ice bath made of a 250 mL beaker, ice, and water for about 20 minutes for crystallization.

17. Filter the crystals with a Hirsch funnel and a small piece of filter paper.

18. Allow the crystals to dry by pulling air through the Hirsch funnel then on a piece of weigh paper.

19. Tare a vial and obtain the mass of the α-terpinene-N-phenylmaleimide adduct by difference.

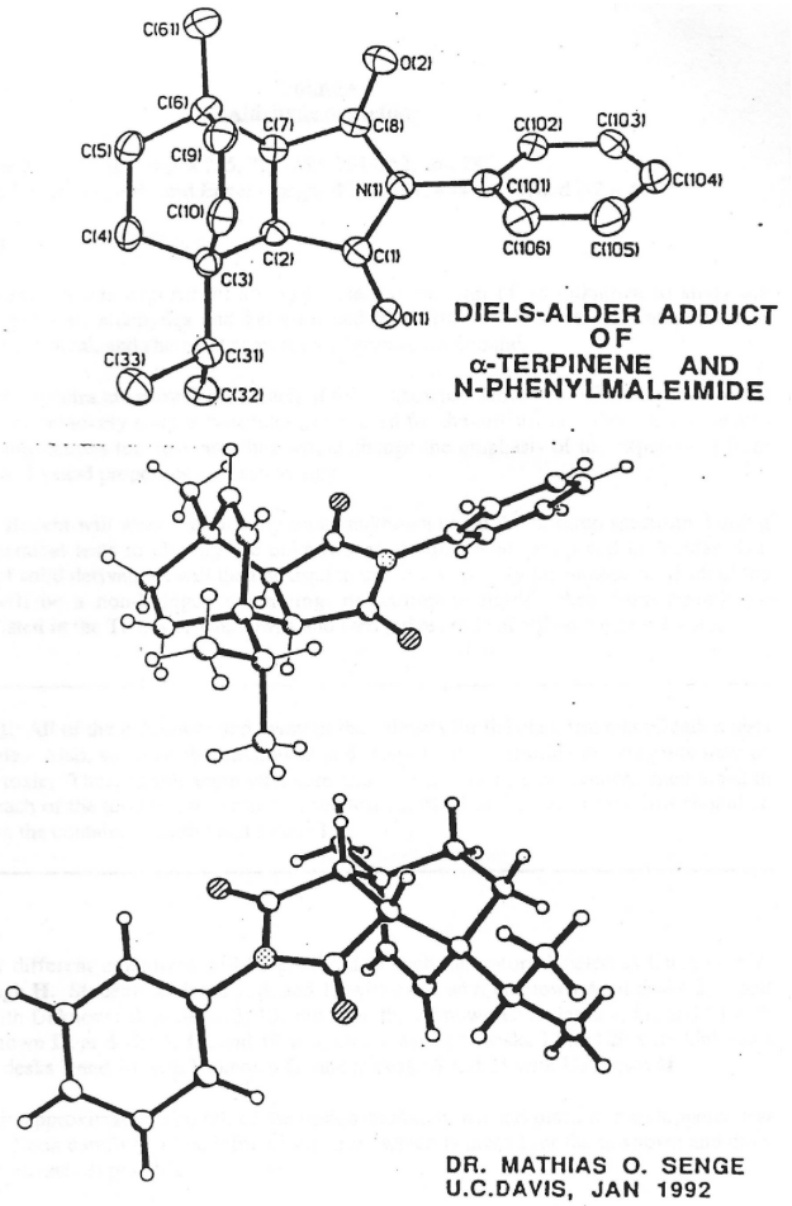
20. Obtain a melting point of the adduct.

21. Label the vial with 118B – α-terpinene-N-phenylmaleimide adduct and your name and turn in to your TA.

22. The filtrate containing methanol can be disposed of in the methanol waste bottle.

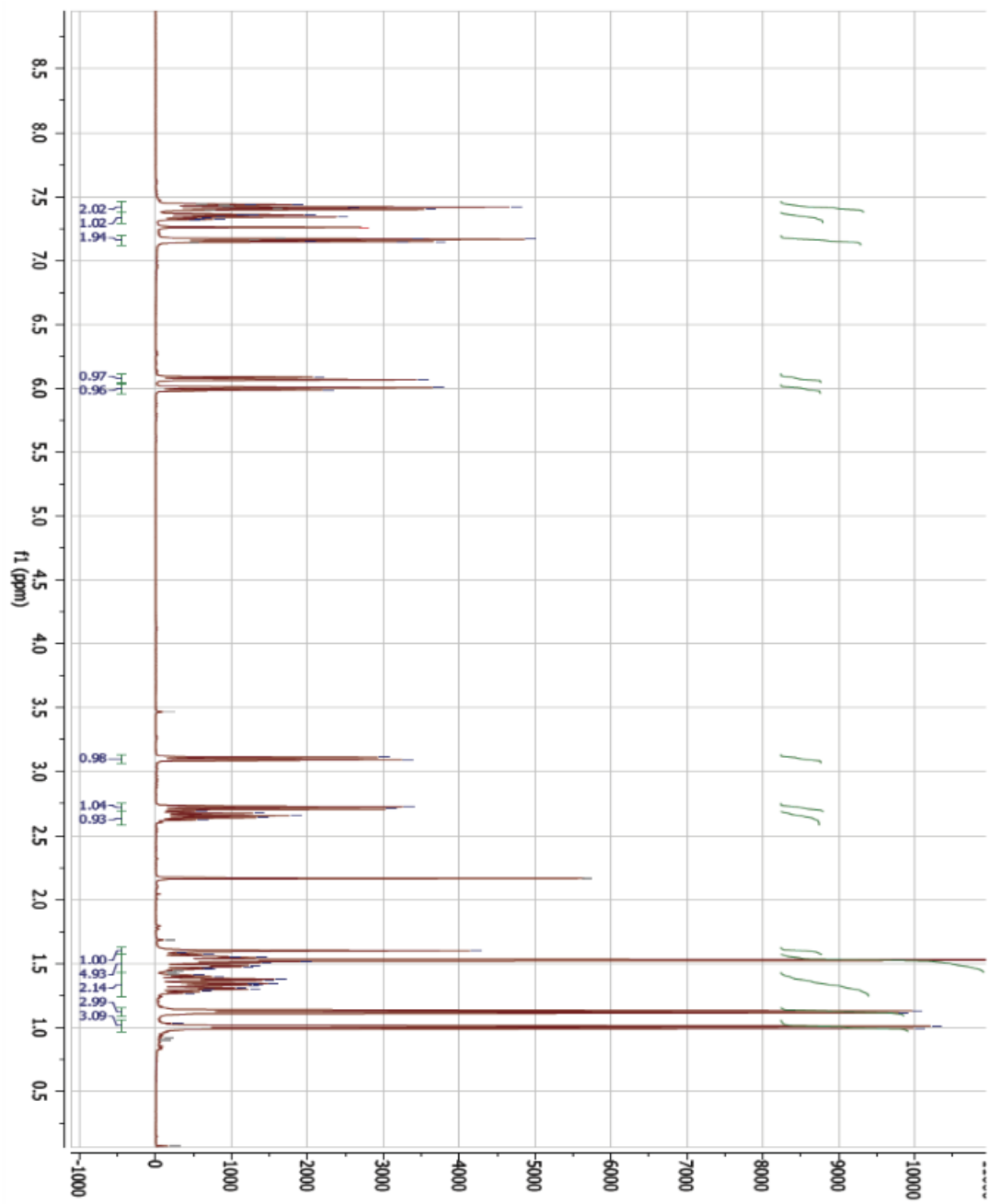
Data

X-ray Crystallography of α-terpinene-N-phenylmaleimide adduct



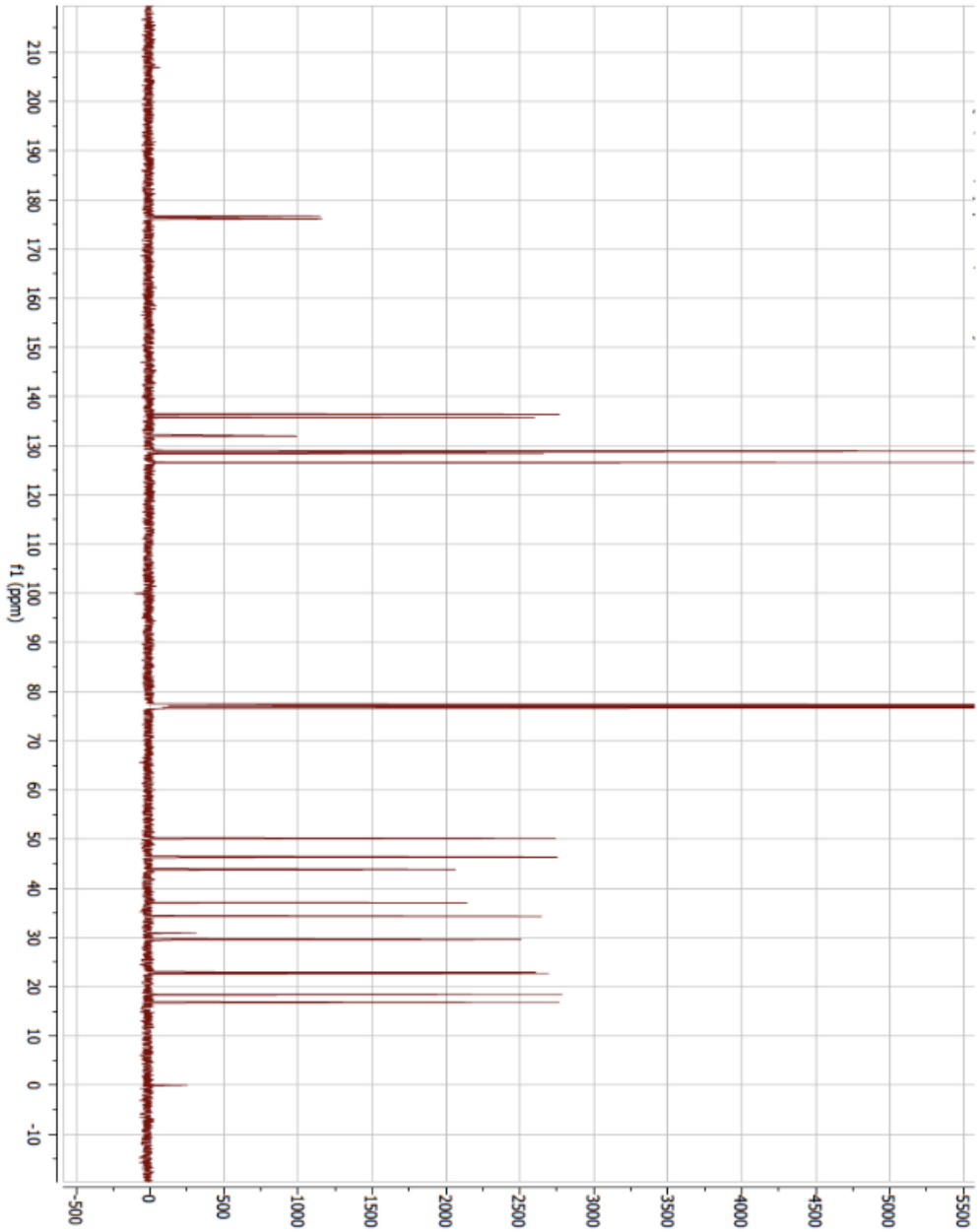
^{1}H NMR of α-terpinene-N-phenylmaleimide adduct

Solvent = $CDCl_3$ (7.26 ppm); Bruker 300 MHz; Run By J. Emerson



^{13}C NMR of α-terpinene-N-phenylmaleimide adduct

Solvent = $CDCl_3$(77.00 ppm); Bruker 75 MHz; Run By J. Emerson



Starting Materials: Maleic Anhyride-Furan Reaction

Complete Report Table H.1.

Report Table H.1: Physical Quantities Table

Reagent/Catalyst	Quantity used, mL	Quantity used, g	Quantity used, moles
Maleic anhydride	NA	_____	_____
Furan	_____	_____	_____

Limiting Reagent: _____(g/mol)

Furan-Maleic Anhydride Adduct

Mass: _____g

Melting Point: _____°C

Description of Product: _____

Data Analysis:

Calculate the Theoretical Yield (show calculation):

Theoretical yield: _____(g)

Theoretical yield: _____(mol)

Calculate the Percent Yield (show calculation):

Actual yield: _____(g)

Actual yield: _____(mol)

Peercent yield: _____%

Observations

Describe any special conditions, errors or deviations from the stated procedure on the back of this page. You may attach additional pages if needed.

Starting Materials: N-Phenylmaleimide and α-terpinene Reaction

Complete Report Table H.2.

Report Table H.2: Physical Quantities Table

Reagent/Catalyst	Quantity used, mL	Quantity used, g	Quantity used, moles
N-Phenylmaleimide	NA	_____	_____
α-Terpinene	_____	_____	_____

Limiting Reagent: _____(g/mol)

N-Phenylmaleimide -α-terpinene Adduct

Mass: _____g

Melting Point: _____°C

Description of Product: _____

Data Analysis:

Calculate the Theoretical Yield (show calculation):

Theoretical yield: _____(g)

Theoretical yield: _____(mol)

Calculate the Percent Yield (show calculation):

Actual yield: _____(g)

Actual yield: _____(mol)

Peercent yield: _____%

Observations

Describe any special conditions, errors or deviations from the stated procedure on the back of this page. You may attach additional pages if needed.

Questions

1. Consider the furan – maleic anhydride reaction.

   a. Which compound is the diene? _____

   b. Which compound is the dienophile? _____

   c. Draw the resonance structures of furan below.

   d. Are the pi-bonds on furan electron rich or poor? Explain using the resonance structures you drew above.

   e. Draw the resonance structures of maleic anhydride below.

   f. Are the pi-bonds on maleic anhydride electron rich or poor? Explain using the resonance structures you drew above.

2. Consider the furan – maleic anhydride Diels-Alder adduct.

   a. The melting point for the endo-Diels-Alder adduct of furan and maleic anhydride is reported to be 70 °C. The melting point for the exo-Diels-Alder adduct is reported to be 110 °C. What isomer did you obtain in the synthesis?

   MP of product = _____

   Product is: (circle one) ENDO or EXO

   b. Considering that formation of the endo-adduct is kinetically favored in Diels-Alder reactions, how do you explain your results? What reaction conditions contributed to the formation of this product? (HINT: did you form the kinetic or thermodynamic product?)

3. Look at the X-Ray Crystal structure for the a-terpinene –N-phenylmaleimide adduct.

   a. Product is: (circle one) ENDO or EXO

   b. Considering that formation of the endo-adduct is kinetically favored in Diels-Alder reactions, how do you explain your results? What reaction conditions contributed to the formation of this product? (HINT: did you form the kinetic or thermodynamic product?)

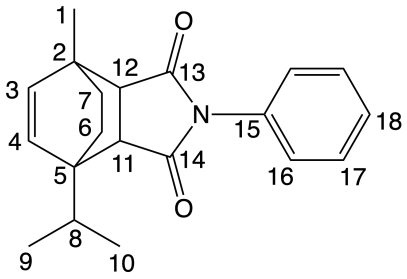
   c. Carefully inspect the bonds between the $C_4 - C_5$, $C_9 - C_{10}$ and $C_{105} - C_{106}$ in the top structure. Use a ruler to measure the relative lengths and estimate the bond angles.

Report Table H.3: Bond Angles and Lengths

Bond	Bond Angle	Bond Length, mm	Hybridization	Functional Group	Predicted Bond Order
$C_4 - C_5$					
$C_9 - C_{10}$					
$C_{105} - C_{106}$					

   d. Explain the difference in bond length and order between the three bonds above.

4. Consider the a-terpinene – N-phenylmaleimide Diels-Alder adduct.



a. Assign which atoms in the molecule give which chemical shifts in the ^{1}H (Report Table H.4)and ^{13}C NMR (Report Table H.5) in the α-terpinene – N-phenylmaleimide adduct, the spectra are provided. (The singlet at 7.26 ppm in the ^{1}H NMR and the triplet at 77.00 ppm in the ^{13}C NMR are due to solvent.)

> In some cases it's not possible to determine the exact assignment, if two or more H or C are nearly chemically equivalent and cannot be distinguished mention this on the blank provided.

Report Table H.4: ^{1}H NMR analysis ($CDCl_3$)

Peak	Shift (ppm	Integration	Multiplicity	Assignment
H_1	0.50	3H	s	the CH_3 on the ring
H_3				
H_4				
H_6				
H_7				
H_8				
H_9				
H_{10}				
H_{11}				
H_{12}				
H_{16}				
H_{17}				
H_{18}				

Report Table H.5: ^{13}C NMR analysis ($CDCl_3$)

Peak	Shift (ppm	Assignment	Peak	Shift (ppm	Assignment
C_1			C_{10}		
C_2			C_{11}		
C_3			C_{12}		
C_4			C_{13}		
C_5			C_{14}		
C_6			C_{15}		
C_7			C_{16}		
C_8			C_{17}		
C_9			C_{18}		

b. Why do the two isopropyl methyl groups have different chemical shifts?

c. Is there any evidence for exo- vs. endo- in the NMR? Explain why/why not.

5. Predict the major organic product(s) of the following reactions.