The Diels–Alder Reaction of 2,4-Hexadien-1-ol with Maleic Anhydride

A Novel Preparation for the Undergraduate Organic Chemistry Laboratory Course

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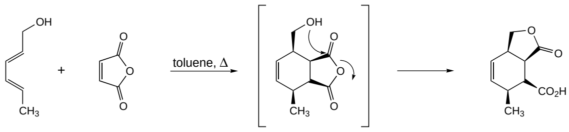
The ideal undergraduate organic chemistry laboratory experiment involves several important components. These components include the examination of one or more interesting and historically important reactions to provide an interesting organic molecule, stimulating yet challenging ^{1}H nuclear magnetic resonance (NMR) and infrared (IR) spectroscopic data analysis, and a straightforward and consistently reproducible experimental procedure that can be completed within a typical laboratory time frame. In addition, an element of the unknown is important, to allow student input into the experiment and avoid the cookbook aspect of many typical undergraduate laboratory experiments. An experiment that has been carried out in our organic laboratory course for the past several years contains each of these components, as it involves both a Diels–Alder reaction and the ring-opening of a cyclic anhydride, ^{1}H NMR data that allow utilization of both 1-D and simple 2-D experiments, and formation and isolation of an analytically pure crystalline product within one hour.

The Diels–Alder reaction clearly is one of the most important organic reactions taught to undergraduate organic chemistry students, and most undergraduate organic textbooks contain sections on the reaction's mechanism, stereochemical outcome, and overall scope and limitations (*1*). The most common Diels–Alder reaction carried out in undergraduate organic chemistry laboratories involves the reaction between cyclopentadiene and maleic anhydride (*2*). Although this reaction works quite well and generates a product that is isolated easily, cracking of the cyclopentadiene dimer is a nuisance, and the product generated by this reaction gives a ^{1}H NMR spectrum that is difficult for students to analyze completely.

Another important topic in all undergraduate organic chemistry textbooks is the addition/elimination reaction of carboxylic acid derivatives (*3*). Nucleophilic attack on anhydrides, acid chlorides, esters and amides typically is examined, and interconversion of these functional groups is presented. Most undergraduate organic chemistry laboratory texts contain simple esterification reactions and often acylation reactions of amines, such as aniline (*4*). An experiment involving the ring opening of a cyclic anhydride, in concert with a Diels–Alder reaction, would be a useful alternative to these reactions.

The reaction of equimolar amounts of *trans*,*trans*-2,4-hexadien-1-ol (**1**) and maleic anhydride (**2**) in refluxing toluene for 5 min generates upon cooling a white crystalline material that can be isolated in yields ranging from 50 to 90% by simple vacuum filtration (*5*). The reaction can be carried out on microscale amounts (50 mg of each reactant) or in gram-scale amounts without significantly diminishing the yields. Analysis of the IR spectrum of this material readily indicates that the anhydride moiety is no longer present, but that two new carbonyl peaks are evident (1766 and 1728 cm^{-1}) along with the expected olefin (1693 cm^{-1}). Careful analysis of the ^{1}H NMR and IR spectral data indicates that the product of the reaction is the isobenzofuranone derivative **4** (eq 1).



1 **2** **3** **4** (1)

This product arises by the expected Diels–Alder reaction, to form intermediate anhydride **3**, followed by intramolecular cleavage of the anhydride by the pendant alcohol to generate the lactone with concomitant formation of the carboxylic acid moiety. The stereochemical outcome of this reaction can be explained by application of the endo rule to give all cis **3**, perfectly positioning the hydroxymethyl group to attack the reactive anhydride moiety.

An extremely valuable exercise involves an in-depth analysis of the ^{1}H NMR spectrum[1] of this material (Fig. 1). Fortuitously, the spectrum contains no overlapping resonances, and all but two of the signals exhibit clearly defined coupling patterns that can be evaluated by students who have a basic understanding of coupling and chemical shift. The spectrum contains four sets of doublets of doublets (δ 4.43, 4.10, 3.44, 3.08), a clear doublet of triplets (δ 5.63), and a beautiful doublet of doublet of doublets (δ 5.81). Each of the individual couplings can be matched in order to assign most of the resonances. Utilization of several simple homonuclear decoupling experiments allows for the assignment of each signal with confidence (Fig. 2). For example, the most obvious assignment involves the signal resulting from the molecule's single methyl group, a doublet (J = 7.3 Hz) at 1.12 ppm. Decoupling of this signal affects only one other resonance in the spectrum, a multiplet at δ 2.65, which must therefore correspond to H_5. Decoupling of this multiplet at δ 2.65 affects four different resonances, at δ 5.81, 5.63, 3.08, and 1.12. This result clearly indicates that the signal at δ 3.08 corresponds to H_4, α to the carboxylic acid moiety, and demonstrates long-range (four-bond) coupling of H_5 through the olefin. Decoupling of the multiplet at δ 3.28 again affects both olefin resonances (δ 5.81 and 5.63), and in this case the three sets of doublet of doublets at δ 4.43, 4.10, and 3.44. This result indicates that the signal at δ 3.28 corresponds to H_{7a} and verifies the assignments of the resonances at 4.43 ($H_{1\beta}$), 4.10 ($H_{1\alpha}$), and 3.44 (H_{3a}).

Equally instructive is the demonstration that a simple two-dimensional NMR experiment can be used to help make proton assignments. The COSY spectrum for the molecule (Fig. 3) again allows determination of the connectivity of the molecule. For example, again starting with the methyl doublet at δ 1.12, a large cross peak demonstrating connectivity to the H_5 methine at δ 2.65 is present. The other cross peaks for the resonance at δ 2.65 demonstrate that H_5 also is coupled to resonances at δ 3.08 (H_4), δ 5.63 (H_6), and δ 5.81 (H_7). Each resonance shows the expected

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cross peaks. Comparison of the COSY results to the homonuclear decoupling experiments serves as a strong learning tool for students who have difficulty understanding the basis for either of these experiments.

Application of NOE difference spectroscopy to compound **4** also allows for a simple demonstration of an important technique. Assignment of the $H_{1\alpha}$ and $H_{1\beta}$ protons can be made by carrying out an NOE difference experiment with irradiation of the signal corresponding to H_{7a}. In addition to significant enhancement of the signals corresponding to H_{3a}, H_4, and H_5, enhancement of the resonance at δ 4.43 is observed, allowing the assignment of that resonance as $H_{1\alpha}$.

This experiment also allows much latitude for student input into the reaction procedure and determination of the product structure. Most importantly, when this experiment is presented to our students, the structure of the final product is not provided. Instead, the students are expected to determine the outcome of the reaction after a careful inspection of the analytical data. The infrared spectrum of the product is extremely useful in this regard, as the previously noted absence of characteristic absorptions for both the alcohol and the anhydride functional groups indicates that more than just a simple Diels–Alder reaction has occurred. Considering the importance of the ^1H nuclear magnetic resonance spectral data to the characterization of the product, it is also appropriate to require students to determine the ideal NMR solvent through simple solubility studies. Solubility studies using potentially suitable solvents such as chloroform, acetone, acetonitrile, and dimethylsulfoxide help students relate the physical properties of the product to the presence (or absence) of particular functional groups. We have also experimented with allowing students to determine the proper amount of time required for completion of the reaction, utilizing thin layer chromatography experiments after 1, 3, 5, 10, and even 30 minutes of heating. Such an approach ensures that the reaction will succeed in high yield, as students who do not heat or mix the reaction mixture thoroughly will discover from their TLC analysis that unreacted starting material remains.

This reaction therefore provides a useful experimental and pedagogical tool for undergraduate organic students. Even if comprehensive ^1H NMR analysis is beyond the scope of the class, the reaction still presents the opportunity for examination of a simple Diels–Alder reaction accompanied by an addition/elimination reaction of an anhydride. The reaction is extremely straightforward to carry out, and high yields of crystalline analytically pure material can be isolated readily in a 1–2-hour laboratory class period.

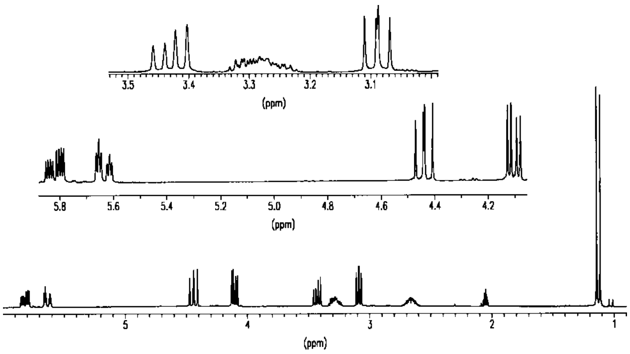
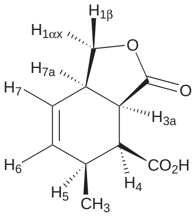


Figure 1. ^1H NMR spectrum of compound **4** in acetone-d_6.



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5.81 (ddd, J = 10.1, 4.4, 2,2 Hz, 1 H, H_6)
5.63 (dt, J = 10.0, 2.3 Hz, 1 H, H_7)
4.43 (dd, J = 8.5, 7.4 Hz, 1 H, $H_{1\alpha}$)
4.10 (dd, J = 8.5, 3.5 Hz, 1 H, $H_{1\beta}$)
3.38 (dd, J = 9.2, 4.8 Hz, 1 H, H_{3a})
3.28 (m, 1 H, H_{7a})
3.08 (dd, J = 5.6, 4.8 Hz, 1 H, H_4)
2.65 (m, 1 H, H_5)
1.12 (d, J = 7.3 Hz, 3 H, $-CH_3$)

Figure 2. ^1H NMR data for compound **4** in acetone-d_6.

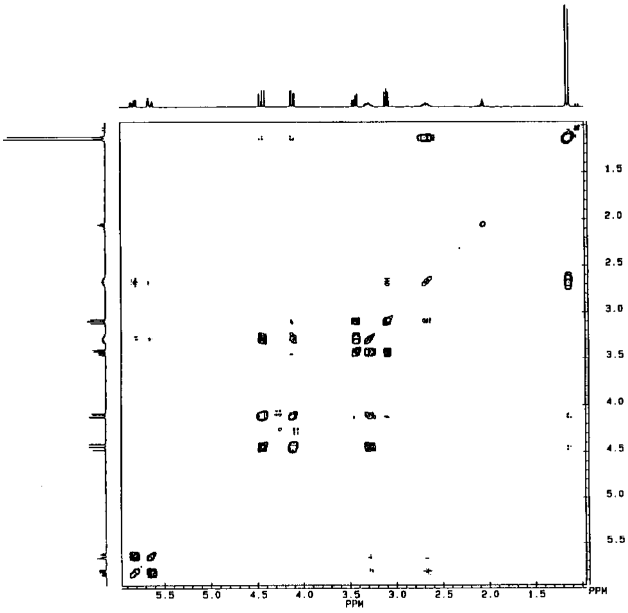

Figure 3. COSY spectrum of compound **4**.

Experimental Procedure

Microscale Preparation of All cis-*1,3,3a,4,5,7a-Hexahydro-5-methyl-3-oxo-4-isobenzofuran-carboxylic Acid*

A mixture of 0.060 g of maleic anhydride and 0.060 g of *E*,*E*-2,4-hexadien-1-ol in 1 mL of toluene in a test tube is heated in a sand bath for 5 min. The rate of heating should be sufficient to maintain the reflux ring approximately half-way up the test tube. Use of a wooden stick to limit bumping is recommended. Thin layer chromatography (developing with ethyl acetate) at this point indicates that no starting material remains. The solution is then allowed to cool slowly to room temperature, during which time a white crystalline material deposits on the sides of the test tube. The reaction mixture is cooled in an ice/water bath for 10 min to ensure complete crystallization of the product. The product is isolated by vacuum filtration, rinsed once with a small amount of cold toluene, and allowed to air dry, leaving 0.075 g (63% yield) of product as a white crystalline solid; mp 159–161 °C (lit. mp 161 °C [5]). Careful recrystallization of this material from toluene gives analytically pure material. IR (KBr) 3294 (broad), 1764, 1729, 1692, 1402, 1376, 1216, 1153, 1046, 994, 811, 716, 667 cm^{-1}.

Macroscale Preparation of All cis-*1,3,3a,4,5,7a-Hexahydro-5-methyl-3-oxo-4-isobenzofuran-carboxylic Acid*

A mixture of 0.40 g of maleic anhydride and 0.40 g of *E*,*E*-2,4-hexadien-1-ol in 5 mL of toluene in a test tube containing a wooden boiling stick is heated under reflux for 5 min. Thin layer chromatography (developing with ethyl acetate) at this point indicates that no starting material remains. The solution is then allowed to cool slowly to room temperature, during which time a white crystalline material deposits on the sides of the test tube and on the wooden stick. The reaction mixture is cooled in an ice/water bath for 10 min to ensure complete crystallization of the product. The product is isolated by vacuum filtration, rinsed several times with small amounts of cold toluene, and air dried, leaving 0.65 g (81% yield) of product as a white crystalline solid (mp 156–159 °C, lit. 161 °C [*5*]). Careful recrystallization of this material from toluene gives analytically pure material.

Note

1. The ^{1}H NMR spectrum of compound **4** is most easily obtained using acetone-d_6 as the solvent, owing to the solubility of **4** in acetone. On the other hand, deuterated chloroform is also an acceptable solvent, although compound **4** is only slightly soluble in chloroform. Observed chemical shifts in the two solvents are similar, although the separation of signals is slightly better in acetone-d_6.

Literature Cited

1. An excellent discussion of the Diels–Alder reaction in an undergraduate text is given in Ege, S. N. *Organic Chemistry: Structure and Reactivity*; D. C. Heath: Lexington, MA, 1994; Chapter 17, pp 733–746.
2. See for example, Williamson, K. L. *Macroscale and Microscale Organic Experiments*, 2nd ed; D. C. Heath: Lexington, MA, 1994; Chapter 25.
3. A typical discussion of addition/elimination reactions in an undergraduate text is given in Solomons, T. W. G. *Organic Chemistry*, 6th ed; Wiley: New York, 1996; Chapter 18.
4. See for example, Roberts, R. M.; Gilbert, J. C.; Martin, S. F. *Experimental Organic Chemistry*; Saunders: Fort Worth, TX, 1994; Chapter 20.
5. The literature reference for this reaction utilizes refluxing benzene as the solvent with a 48-hour reaction time (56% yield): Brettle, R.; Cummings, D. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2385.