

THE DIELS-ALDER REACTION

CHM 222

EXPERIMENTAL OBJECTIVES

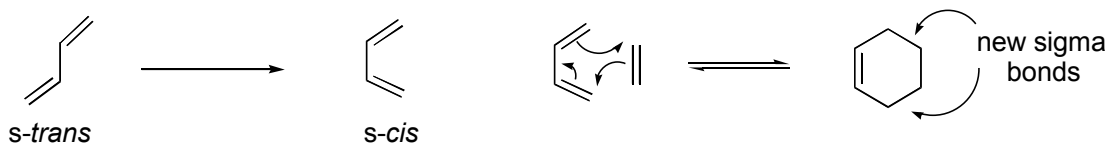
To use the Diels-Alder reaction in a multi-step compound synthesis

LEARNING OBJECTIVES

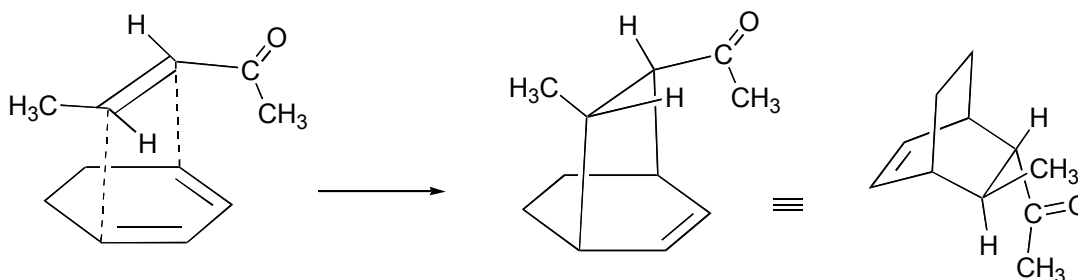
- To carry out a two-step synthesis, isolating the intermediate product and final product

BACKGROUND

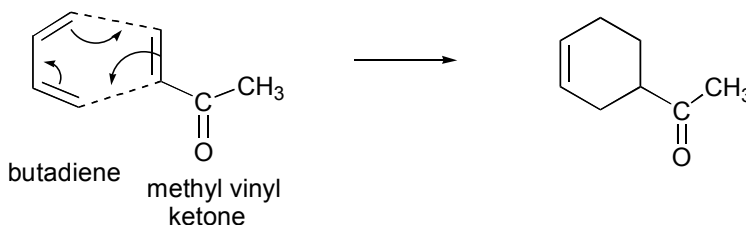
Otto Diels and his pupil Kurt Alder received the Nobel Prize in 1950 for their discovery and work on the reaction that bears their names. Its great usefulness lies in its high yield and high stereospecificity. A cycloaddition reaction, it involves the 1,4-addition of a conjugated diene in the *s-cis*-conformation to an alkene in which two new sigma bonds are formed from two pi bonds.



The adduct is a six-membered ring alkene. The diene can have the two conjugated bonds contained within a ring system as with cyclopentadiene or cyclohexadiene, or the molecule can be an acyclic diene that must be in the *cis* conformation about the single bond before reaction can occur.

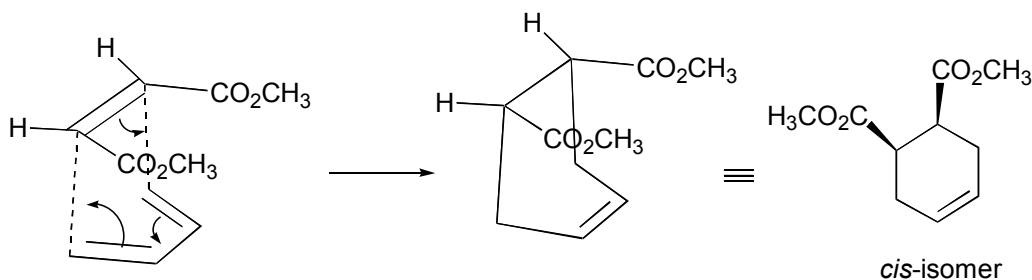


The reaction works best when there is a marked difference between the electron densities in the diene and the alkene with which it reacts, the dienophile. Usually the dienophile has electron-attracting groups attached to it while the diene is electron rich, e.g., as in the reaction of methyl vinyl ketone with 1,3-butadiene.

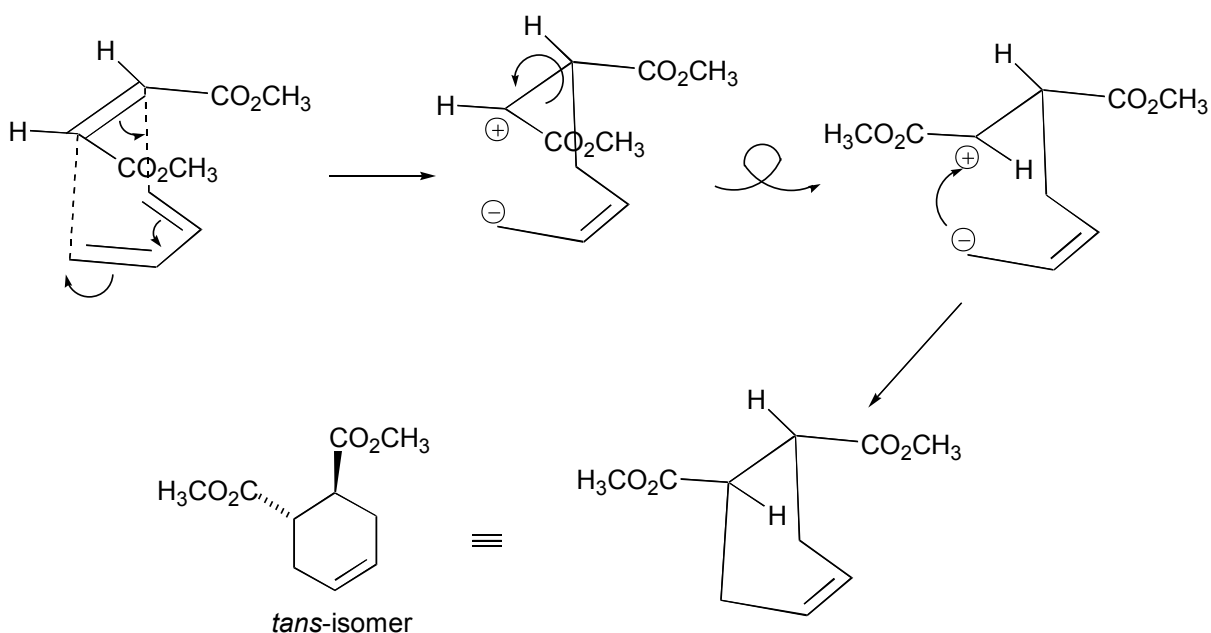


Diels-Alder

Retention of the configurations of the reactants in the products implies that both new sigma bonds are formed almost simultaneously. If not, then the intermediate with a single new bond could rotate about that bond before the second sigma bond is formed, thus destroying the stereospecificity of the reaction.



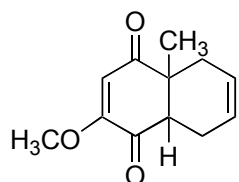
This does not happen:



This reaction is not polar in that no charged intermediates are formed. Neither is it radical because no unpaired electrons are involved. It is instead known as a concerted reaction, or one in which several bonds in the transition state are simultaneously made and broken. When a cyclic diene and a cyclic dienophile react with each other as in the present reaction, more than one stereoisomer may be formed. The isomer that predominates is the one which involves maximum overlap of pi electrons in the transition state. The transition state for the formation of the *endo*-isomer in the present reaction involves a sandwich with the diene directly above the dienophile. To form the *exo*-isomer the diene and dienophile would need to be arranged in a stair-step fashion.

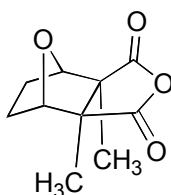
The Diels-Alder reaction has been used extensively in the synthesis of complex natural products because it is possible to exploit the formation of a number of chiral centers in one reaction and also the regioselectivity of the reaction. For example, the first step in R. B. Woodward's synthesis of cortisone was the formation of a Diels-Alder adduct.

Diels-Alder



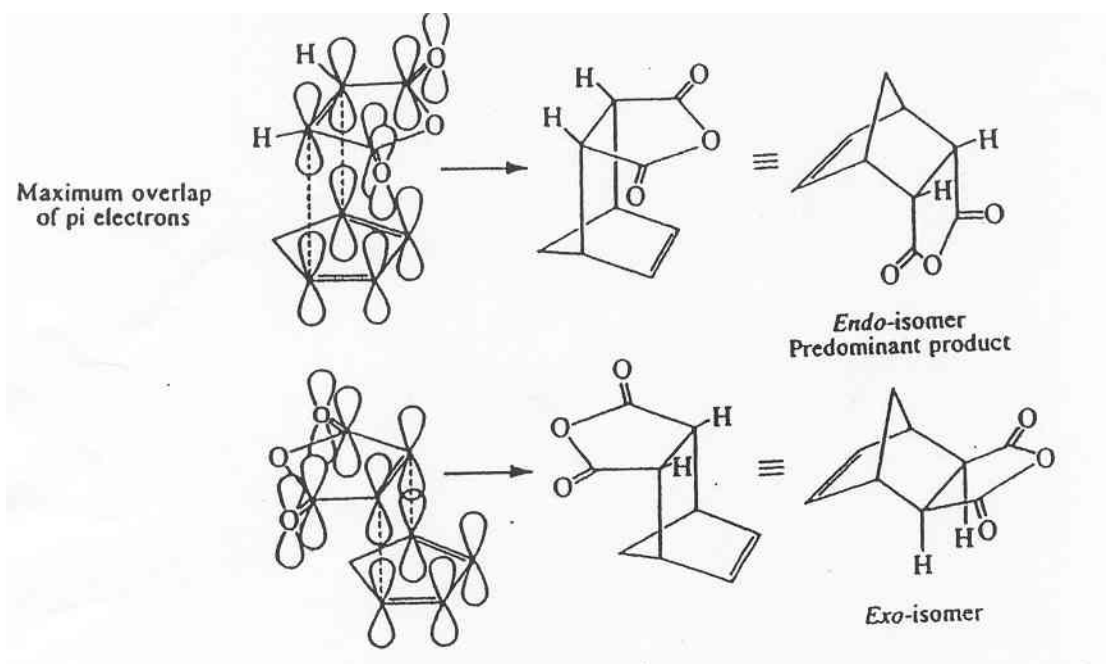
Woodwards diels-Alder adduct

But the reaction is also subject to steric hindrance, especially when the difference between the electron-withdrawing and donating characters of the two reactants is not great. When Woodward tried to synthesize cantharidin, the active ingredient in Spanish fly, by the Diels-Alder condensation of furan with dimethylmaleic anhydride, the reaction did not work. The reaction possesses $-\Delta V^*$ (it proceeds with a net decrease in volume). High pressure should overcome this problem, but this reaction will not proceed even at 600,000 lb/in². Cantharidin is a powerful vesicant (blister-former).

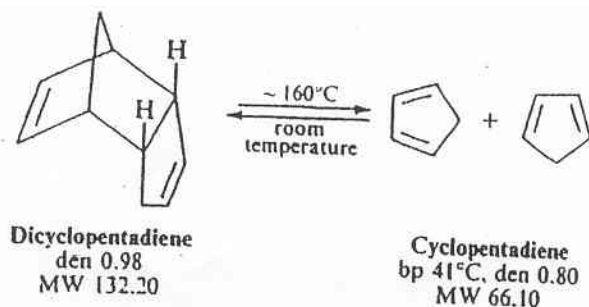


Cantharidin

Woodward and Roald Hoffmann, Nobel prize winners for their work, formulated the theoretical rules involving the correlation of orbital symmetry, which govern the Diels-Alder and other electrocyclic reactions.



Cyclopentadiene is obtained from the light oil from coal tar distillation but exists as the stable dimer, dicyclopentadiene, which is the Diels-Alder adduct from two molecules of the diene. Thus, generation of cyclopentadiene by pyrolysis of the dimer represents a reverse Diels-Alder reaction. In the Diels-Alder addition of cyclopentadiene and maleic anhydride the two molecules approach each other in the orientation shown in the drawing above, as this orientation provides maximal overlap of π -bonds of the two reactants and favors formation of an initial π -complex and then the final *endo*-product. Dicyclopentadiene also has the *endo*-configuration.



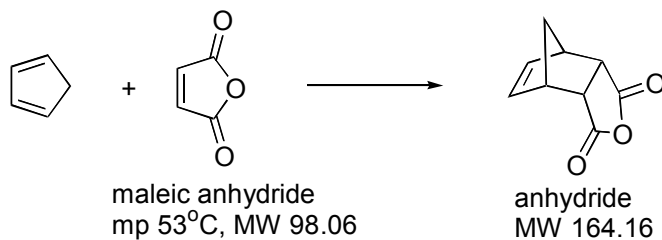
EXPERIMENT

Gas chromatography reveals that cyclopentadiene is 8% dimerized in 4 hours and 50% dimerized in 24 hours when stored at room temperature. Therefore, it should be kept on ice and used as soon as possible.

1. CRACKING OF DICYCLOPENTADIENE

We'll do this for you.

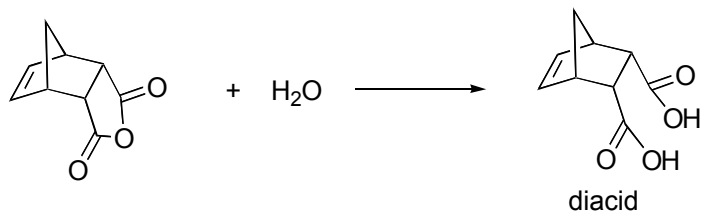
2. *CIS*-NORBORNENE-5,6-*ENDO*-DICARBOXYLIC ANHYDRIDE



Place 3 g (? moles) of maleic anhydride in a 125 mL Erlenmeyer flask and dissolve the anhydride in 10 mL of ethyl acetate by gentle heating on a hot plate. Add 10 mL of ligroin (bp 60-90°C), cool the solution to 0°C in an ice bath, and leave it in the bath (some material may crystallize).

Measure 3 mL of cyclopentadiene (? moles), and add it to the ice-cold solution of maleic anhydride. Swirl the solution in the ice bath for a few minutes until the exothermic reaction is over and the adduct separates as a white solid. Then, carefully (gently) heat the mixture on a hot plate until the solid is all dissolved. Do not boil off all of your solvent. If moisture has gotten into your reaction, a little of the corresponding, insoluble, diacid will need to be removed by filtration of the hot solution. Place the flask on a cork ring and allow to cool slowly. If you let the solution stand undisturbed, you may be rewarded with a beautiful display of crystal formation. mp ~165°C; typical yield is ~4.1 g.

Dispose of your crystallization solvent in the waste container provided.

3. *CIS-NORBORNENE-5,6-ENDO-DICARBOXYLIC ACID*

For the preparation of the *endo*, *cis*-diacid, place 2 g (? moles) of the anhydride from part 2 in 25 mL of deionized water. Heat the mixture with swirling, until the contents boil. Continue to heat the boiling mixture until all of the material dissolves (an oil substance may initially form, but will eventually completely dissolve). Allow the solution to cool slowly. Since the diacid has a tendency to remain in a supersaturated solution, let the solution cool to room temperature and, if needed, gently scratch the flask at the water/air interface inside the flask. Let crystallization proceed spontaneously to give large needles, then cool the solution on ice, and filter to isolate the product. mp $\sim 180^{\circ}\text{C}$, typical yield is ~ 2 g.

Dispose of your aqueous solution by flushing down the drain.