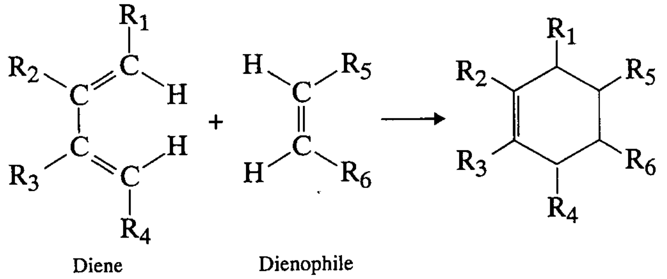
Essay

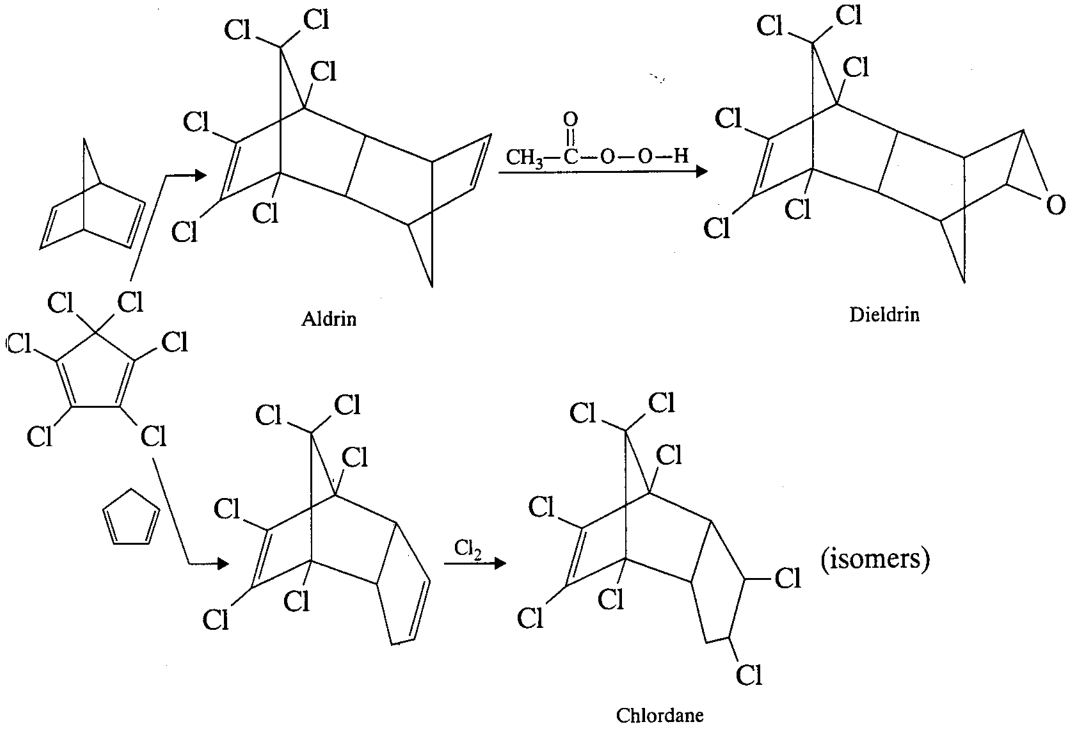
Diels–Alder Reaction and Insecticides

Since the 1930s, it has been known that the addition of an unsaturated molecule across a diene system forms a substituted cyclohexene. The original research dealing with this type of reaction was performed by Otto Diels and Kurt Alder in Germany, and the reaction is known as the **Diels–Alder reaction.** The Diels–Alder reaction is the reaction of a **diene** with a species capable of reacting with the diene, the **dienophile.**

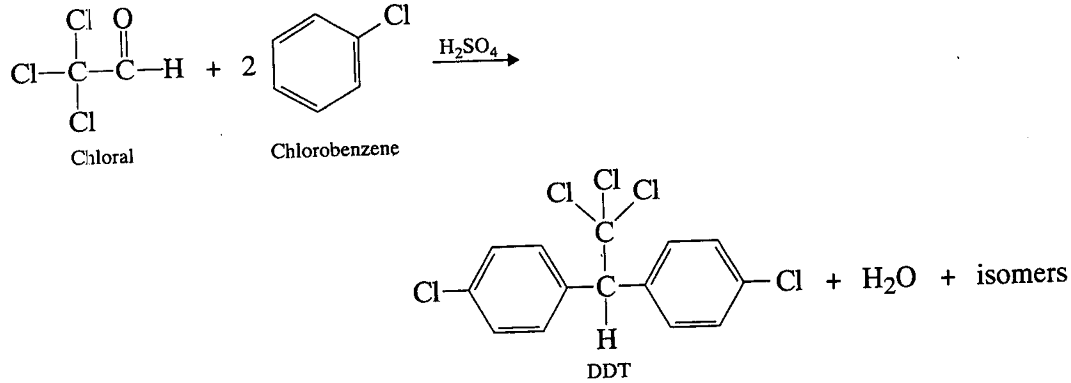


The product of the Diels–Alder reaction is usually a structure that contains a cyclohexene ring system. If the substituents as shown are simply alkyl groups or hydrogen atoms, the reaction proceeds only under extreme conditions of temperature and pressure. With more complex substituents, however, the Diels–Alder reaction may go on at low temperatures and under mild conditions. The reaction of cyclopentadiene with maleic anhydride (Experiment 48) is an example of a Diels–Alder reaction carried out under reasonably mild conditions.

In the past, a commercially important use of the Diels–Alder reaction involved the use of hexachlorocyclopentadiene as the diene. Depending on the dienophile, a variety of chlorine-containing addition products may be synthesized. Nearly all these products were powerful **insecticides.** Three insecticides synthesized by the Diels–Alder reaction are shown here.



Dieldrin and Aldrin are named after Diels and Alder. These insecticides were once used against the insect pests of fruits, vegetables, and cotton; against soil insects, termites, and moths; and in treating seeds. Chlordane was used in veterinary medicine against insect pests of animals, including fleas, ticks, and lice. These insecticides are seldom used today.



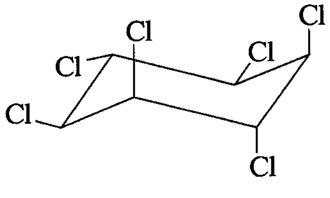
The best known insecticide, DDT, is not prepared by the Diels–Alder reaction but is nevertheless the best illustration of the difficulties that were experienced when chlorinated insecticides were used indiscriminately. DDT was first synthesized in 1874, and its insecticidal properties were first demonstrated in 1939. It is easily synthesized commercially, with inexpensive reagents.

At the time DDT was introduced, it was an important boon to humanity. It was effective in controlling lice, fleas, and malaria-carrying mosquitoes and thus helped control human and animal disease. The use of DDT rapidly spread to the control of hundreds of insects that damage fruit, vegetable, and grain crops.

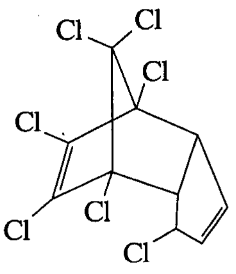
Pesticides that persist in the environment for a long time after application are called **hard pesticides.** Beginning in the 1960s, some of the harmful effects of such hard pesticides as DDT and the other chlorocarbon materials became known. DDT is a fat-soluble material and is therefore likely to collect in the fat, nerve, and brain tissues of animals. The concentration of DDT in tissues increases in animals high in the food chain. Thus, birds that eat poisoned insects accumulate large quantities of DDT. Animals that feed on the birds accumulate even more DDT. In birds at least two undesirable effects of DDT have been recognized. First, birds whose tissues contain large amounts of DDT have been observed to lay eggs having shells too thin to survive until young birds are hatched. Second, large quantities of DDT in the tissues seem to interfere with normal reproductive cycles. The massive destruction of bird populations that sometimes occurred after heavy spraying with DDT became an issue of great concern. The brown pelican and the bald eagle were placed in danger of extinction. The use of chlorocarbon insecticides was identified as the principal reason for the decline in the numbers of these birds.

Because DDT is chemically inert, it persists in the environment without decomposing to harmless materials. It can decompose very slowly, but the decomposition products are every bit as harmful as DDT itself. Consequently, each application of DDT means that still more DDT will pass from species to species, from food source to predator, until it concentrates in the higher animals, possibly endangering their existence. Even humans may be threatened. As a result of evidence of the harmful effects of DDT, the Environmental Protection Agency banned general use of DDT in the early 1970s; it may still be used for certain purposes, although permission of the Environmental Protection Agency is required. In 1974, the EPA granted permission to use DDT against the tussock moth in the forests of Washington and Oregon.

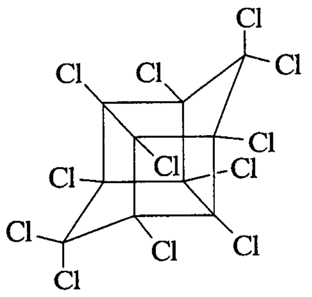
Because the life cycles of insects are short, they can evolve an immunity to insecticides within a short period. As early as 1948, several strains of DDT-resistant insects were identified. Today, the malaria-bearing mosquitoes are almost completely resistant to DDT, an ironic development. Other chlorocarbon insecticides were developed to use as alternatives to DDT against resistant insects. Examples of these chlorocarbon materials include Dieldrin, Aldrin, Chlordane, and the substances whose structures are shown here. Heptachlor and Mirex are prepared using Diels–Alder reactions.



Lindane



Heptachlor

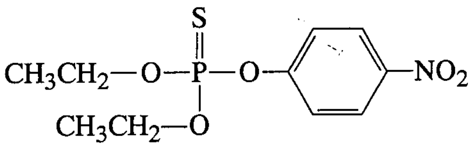


Mirex

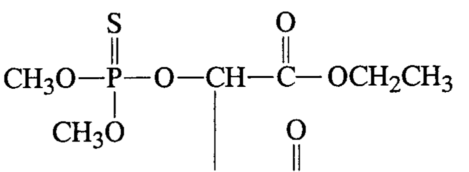
In spite of structural similarity, Chlordane and Heptachlor behave differently than DDT, Dieldrin, and Aldrin. Chlordane, for instance, is short-lived and less toxic to mammals. Nevertheless, all the chlorocarbon insecticides have been the objects of much suspicion. A ban on the use of Dieldrin and Aldrin has also been ordered by the Environmental Protection Agency. In addition, strains of insects resistant to Dieldrin, Aldrin, and other materials have been observed. Some insects become addicted to a chlorocarbon insecticide and thrive on it!

The problems associated with chlorocarbon materials have led to the development of "soft" insecticides. These usually are organophosphorus or carbamate derivatives, and they are characterized by a short lifetime before they are decomposed to harmless materials in the environment.

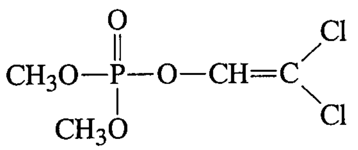
The organic structures of some organophosphorus insecticides are shown here.



Parathion



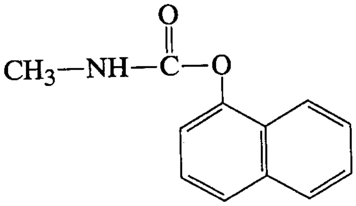
Malathion



DDVP or Dichlorvos

Parathion and Malathion are used widely for agriculture. DDVP is used in "pest strips," which are used for combating household insect pests. The organophosphorus materials do not persist in the environment, so they are not passed between species up the food chain, as the chlorocarbon compounds are. However, the organophosphorus compounds are highly toxic to humans. Some migrant and other agricultural workers have lost their lives because of accidents involving these materials. Stringent safety precautions must be applied when organophosphorus insecticides are being used.

The carbamate derivatives, including Carbaryl, tend to be less toxic than the organophosphorus compounds. They are also readily degraded to harmless materials. Nevertheless, insects resistant to soft insecticides have also been observed. Furthermore, the organophosphorus and carbamate derivatives destroy many more nontarget pests than the chlorocarbon compounds do. The danger to earthworms, mammals, and birds is very high.

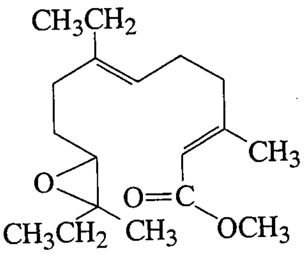


Carbaryl

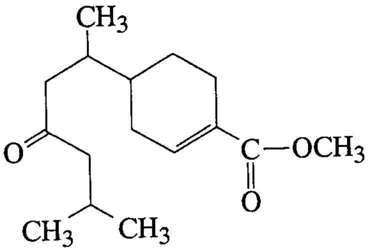
ALTERNATIVES TO INSECTICIDES

Several alternatives to the massive application of insecticides have recently been explored. Insect attractants, including the pheromones (see the essay preceding Experiment 45), have been used in localized traps. Such methods have been effective against the gypsy moth. A "confusion technique," whereby a pheromone is sprayed into the air in such high concentrations that male insects are no longer able to locate females, has been studied. These methods are specific to the target pest and do not cause repercussions in the general environment.

Recent research has been focused on using an insect's own biochemical processes to control pests. Experiments with **juvenile hormone** have shown promise. Juvenile hormone is one of three internal secretions used by insects to regulate growth and metamorphosis from larva to pupa and thence to the adult. At certain stages in the metamorphosis from larva to pupa, juvenile hormone must be secreted; at other stages it must be absent, or the insect will either develop abnormally or fail to mature. Juvenile hormone is important in maintaining the juvenile, or larval, stage of the growing insect. The male cecropia moth, which is the mature form of the silkworm, has been used as a source of juvenile hormone. The structure of the cecropia juvenile hormone is shown next. This material has been found to prevent the maturation of yellow-fever mosquitoes and human body lice. Because insects are not expected to develop a resistance to their own hormones, it is hoped that insects will be unlikely to develop a resistance to juvenile hormone.



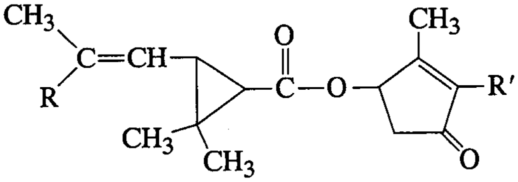
Cecropea juvenile hormone



Paper factor

Although it is very difficult to get enough of the natural substance for use in agriculture, synthetic analogues have been prepared, and they have been shown to be similar in properties and effectiveness to the natural substance. Williams, Sláma, and Bowers (see References) have identified and characterized a substance found in the American balsam fir (*Abies balsamea*), known as **paper factor**, which is active against the linden bug, *Pyrrhocoris apterus,* a European cotton pest. This substance is merely one of thousands of terpenoid materials synthesized by the fir tree. Other terpenoid substances are being investigated as potential juvenile hormone analogues.

Certain plants are capable of synthesizing substances that protect them against insects. Included among these natural insecticides are the **pyrethrins** and derivatives of **nicotine.**



Pyrethrin

R = CH_3 or $COOCH_3$
R' = $CH_2CH{=}CHCH{=}CH_2$ or $CH_2CH{=}CHCH_3$
or $CH_2CH{=}CHCH_2CH_3$

The search for environmentally suitable means of controlling agricultural pests continues with a great sense of urgency. Insects cause billions of dollars of damage to food crops each year. With food becoming increasingly scarce and with the world's population growing at an exponential rate, preventing such losses to food crops becomes absolutely essential.

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Williams, C. M. "Third-Generation Pesticides." *Scientific America, 217* (July 1967): 13.

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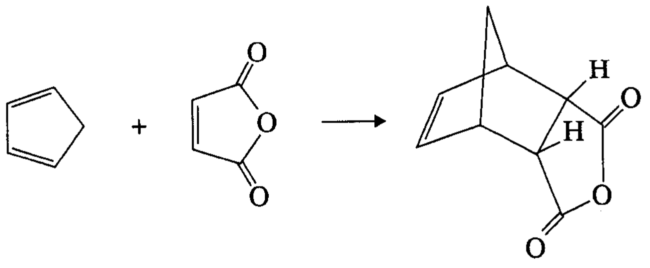
Experiment 48

The Diels–Alder Reaction of Cyclopentadiene with Maleic Anhydride

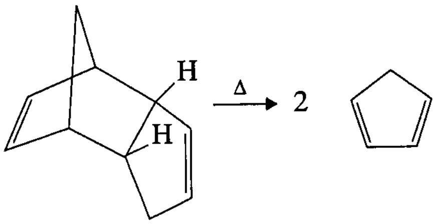
Diels–Alder reaction
Fractional distillation

Cyclopentadiene and maleic anhydride react readily in a Diels–Alder reaction to form the adduct, *cis*-norbornene-5,6-*endo*-dicarboxylic anhydride:



Cyclopentadiene Maleic anhydride *cis*-Norbornene-5,6-*endo*-dicarboxylic anhydride

Because two molecules of cyclopentadiene can also undergo a Diels–Alder reaction to form dicyclopentadiene, it is not possible to store cyclopentadiene in the monomeric form. Therefore, it is necessary to first "crack" dicyclopentadiene to produce cyclopentadiene for use in this experiment. This will be accomplished by heating the dicyclopentadiene to a boil and collecting the cyclopentadiene as it is formed by fractional distillation. To keep it from dimerizing, the cyclopentadiene must be kept cold and used fairly soon.



Dicyclopentadiene Cyclopentadiene

REQUIRED READING

Review:	Technique 5	Section 5.4
New:	Essay:	Diels–Alder Reaction and Insecticides

SPECIAL INSTRUCTIONS

The cracking of dicyclopentadiene should be performed by the instructor or laboratory assistant. If a flame is used for this, be sure that there are no leaks in the system, because both cyclopentadiene and the dimer are highly flammable. The procedure provides enough cyclopentadiene for about 50 students.

WASTE DISPOSAL

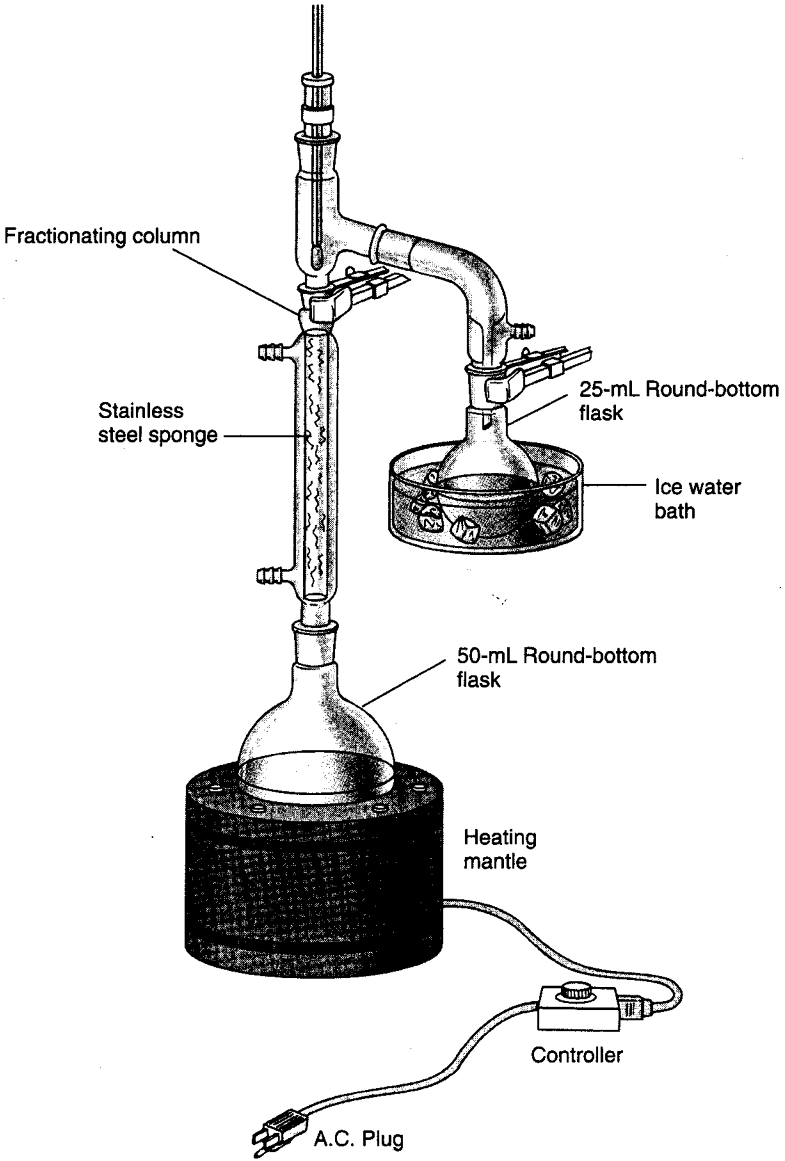
Dispose of the mother liquor from the crystallization in the container designated for nonhalogenated organic solvents.

NOTES TO THE INSTRUCTOR

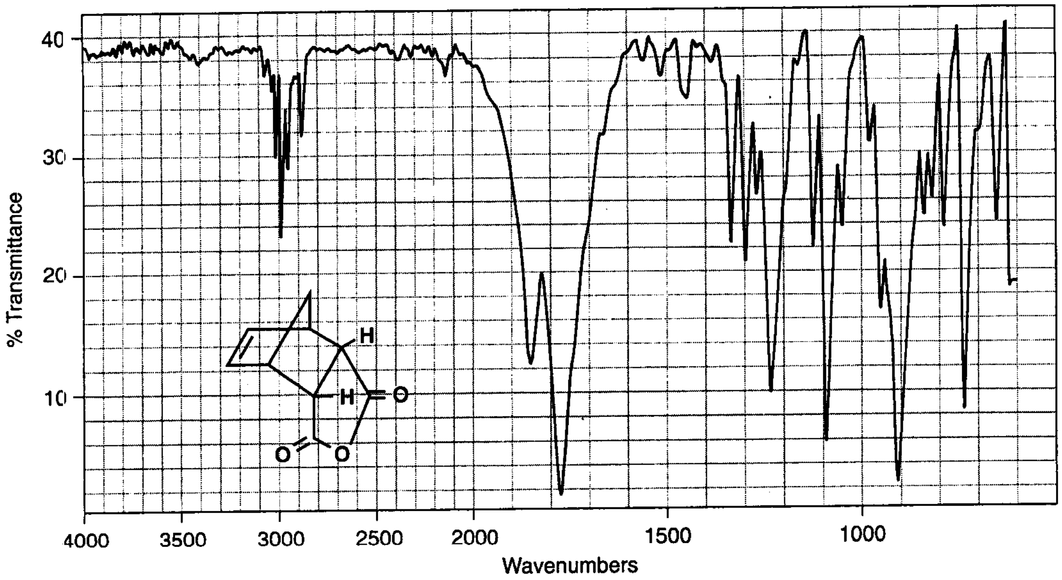
Working in a hood, assemble a fractional distillation apparatus, as shown in the figure. Glassware with a joint size of ₸ 19/22 or larger should be used. If smaller glassware is used, the fractionating column may not be long enough to achieve the necessary separation. Although the required temperature control can best be obtained with a micro burner, using a heating mantle, aluminum block, or sand bath lessens the possibility of a fire occurring. Place several boiling stones and 15 mL of dicyclopentadiene in the 50-mL distilling flask. Control the heat source so that the cyclopentadiene distills at 40–43°C. (If a sand bath is used, the temperature should be 190–200°C, and it may be necessary to cover the sand bath and distilling flask with aluminum foil.) After 30–45 minutes, 6–7 mL of cyclopentadiene should be collected, and the distillation can be stopped. If the cyclopentadiene is cloudy, dry the liquid over granular anhydrous sodium sulfate. Store the product in a sealed container and keep it cooled in an ice-water bath until all students have taken their portions.

PROCEDURE

Preparation of the Adduct. To a Craig tube add 0.100 g of maleic anhydride and 0.40 mL of ethyl acetate. Without inserting the plug, shake the tube gently to dissolve the solid (slight heating in a warm water bath may be necessary). Add 0.40 mL of ligroin (bp 60–90°C), and shake



Fractional distillation apparatus for cracking dicyclopentadiene.



Infrared spectrum of *cis*-norbornene-5, 6-*endo*-dicarboxylic anhydride, KBr.

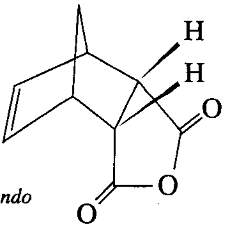
the tube gently to mix the solvents and reactant thoroughly. Add 0.10 mL of cyclopentadiene, and mix thoroughly by shaking until no visible layers of liquid are present. Because this reaction is exothermic, the temperature of the mixture will likely become high enough to keep the product in solution. However, if a solid does form at this point, it will be necessary to heat the mixture gently in a warm water bath to dissolve any solids present. If necessary, add a drop of ethyl acetate to help dissolve the solid, and, again, heat the mixture gently.

Crystallization of Product. Allow the mixture to cool slowly to room temperature by placing the Craig tube in a 10-mL Erlenmeyer flask that has been filled with about 8 mL of water at 50–60°C. The inner plug of the Craig tube should be inserted to prevent evaporation of the solvent. Better crystal formation can be achieved by seeding the solution before it cools to room temperature. To seed the solution, dip a spatula or glass stirring rod into the solution after it has cooled for about 5 minutes. Allow the solvent to evaporate so that a small amount of solid forms on the surface of the spatula or glass rod. Place the spatula or stirring rod back into the solution for a few seconds to induce crystallization. When crystallization is complete at room temperature, cool the mixture in an ice bath for several minutes.

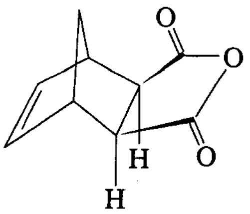
Isolate the crystals from the Craig tube by centrifugation (see Technique 4, Section 4.7, p. 556, and Fig. 4.11, p. 557), and allow the crystals to air-dry. Determine the weight and the melting point (164°C). At the instructor's option, determine the infrared spectrum of the adduct in potassium bromide. Calculate the percentage yield, and submit the product to the instructor in a labeled vial. Compare your infrared spectrum to the one reproduced here.

MOLECULAR MODELING (optional)

In the reaction of cyclopentadiene with maleic anhydride, two products are possible: the *endo* product and the *exo* product.



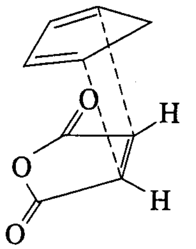
endo

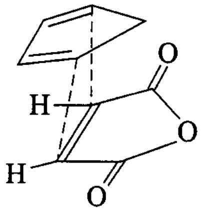


exo

Calculate the heats of formation for both of these products to determine which is the expected **thermodynamic product** (product of lowest energy). Perform the calculations at the AM1 level with a geometry optimization. The actual product of the Diels–Alder reaction is the *endo* product; is this the thermodynamic product? Display a space-filling model for each structure. Which one appears most crowded?

Woodward and Hoffmann have pointed out that the diene is the electron donor and the dienophile the electron acceptor in this reaction. In accordance with this idea, dienes that have electron-donating groups are more reactive than those without, and dienophiles with electron-withdrawing groups are most reactive. Using the reasoning of frontier molecular orbital theory (see the essay "Computational Chemistry" on page 174), the electrons in the HOMO of the diene will be placed into the LUMO of the dienophile when reaction occurs. Using the AM1 level, calculate the HOMO surface for the diene (cyclopentadiene) and the LUMO surface for the dienophile (maleic anhydride). Display the two simultaneously on the screen in the orientations that will lead to the *endo* and *exo* products.





Woodward and Hoffmann suggested that the orientation that leads to the largest degree of constructive overlap between the two orbitals (HOMO and LUMO) is the orientation that would lead to the product. Do you agree?

Depending on the capability of your software, it may be possible to determine the geometrics (and energies) of the transition states that lead to each product. Your instructor will have to show you how to do this.

QUESTIONS

1. Draw a structure for the exo product formed by cyclopentadiene and maleic anhydride.
2. Because the exo form is more stable than the endo form, why is the endo product formed almost exclusively in this reaction?
3. In addition to the main product, what are two side reactions that could occur in this experiment?
4. The infrared spectrum of the adduct is given in this experiment. Interpret the principal peaks.