

Experiment 5: Preparation of Trans-cinnamic Acid from Malonic acid and Benzaldehyde with the Knoevenagel reaction.

Ref. CGWW, pp 703

Background:

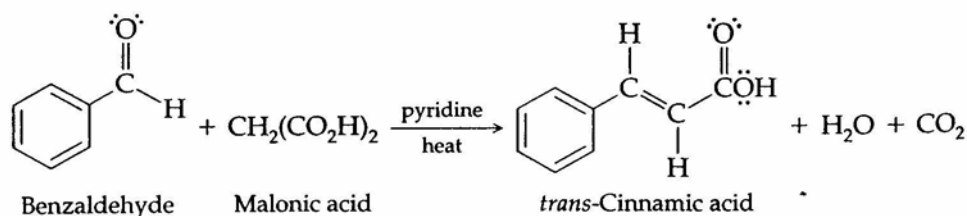
Those reactions that are called aldols derive their name from the early nineteenth-century organic literature. The term was first applied to a self-addition product of acetaldehyde that forms under basic conditions. The product, 3-hydroxybutanal, can form in yields as high as 50% in the presence of sodium hydroxide. This substance eventually became referred to as aldol, because it was both an aldehyde and an alcohol.

The aldol reaction can be defined in the broad sense as a reaction in which a nucleophile-generated alpha to an electron-withdrawing functional group (in the large majority of cases, carbonyl groups are responsible for the α -hydrogen acidity, although they are not required) adds to a carbonyl group (it may be self-condensation as in the example of acetaldehyde, but it may also involve attack on another carbonyl containing species, if it is present). The Knoevenagel reaction is another condensation possessing a mechanism similar to that of the aldol reaction.

Emil Knoevenagel (1865-1921) was born in Hanover, Germany. He was the son of a chemist and started his studies at the Technical Institute at Hanover. Later he studied with both Meyer and Gattermann at Göttingen where he received a Ph.D. in 1889. When Victor Meyer moved to Heidelberg, Knoevenagel accompanied him. In 1896 he was appointed assistant professor of organic chemistry at Heidelberg and, in the same year, published his studies on the reaction that now bears his name. He eventually became professor of organic chemistry in 1900.

Interestingly, although Knoevenagel demonstrated the effectiveness of amine bases in promoting aldol-type reactions and though, as noted above, he was particularly interested in pyridine, he overlooked this material's potential application to aldol condensations. It was left to Verley (1899) and Doebner (1900) to introduce successful modifications of the condensation in which pyridine appears to play a number of roles: as a solvent, as a base, and assisting in the decarboxylation.

The Knoevenagel reaction in its simplest form is the condensation of malonic esters (or their analogues) with aldehydes or ketones in the presence of an amine base catalyst plus a small amount of carboxylic acid (or amino acid) cocatalyst. The condensation products are often α,β -unsaturated carbonyl compounds. For example,



Other substances possessing an acidic methylene group have been incorporated in aldol-type reactions. These materials include ethyl cyanoacetate and ethyl acetoacetate, as well as phenylacetonitrile, benzyl ketones, and aliphatic nitro compounds. The reaction is often run in benzene or toluene solvent, so that the water formed can be continuously removed. Other cocatalysts, besides carboxylic acids, are various ammonium salts, such as ammonium acetate and piperidinium acetate. The Knoevenagel reaction gives highest yields when aldehydes are used as the electrophile, although selected ketones can sometimes give acceptable yields. One of the more important properties of these reactions from a synthetic perspective is that they offer a route to the formation of C-C bonds.

In the formation of the first synthetic intermediate, the very effective Verley-Doebner modification of the fundamental Knoevenagel condensation is used. This modification uses malonic acid in place of the conventional ester to promote enolization. In addition, the heterocyclic amine, pyridine, functions as both the base catalyst and the solvent. A cocatalyst, B-alanine (an amino acid), is also introduced. Mechanistically, the reaction closely resembles the aldol condensation in that in both cases a carbanion is generated by abstraction, by base, of a proton alpha to a carbonyl group to yield a hydrogen-bonded delocalized dianion that is stabilized as an enolate anion.

The enolate anion then acts as a nucleophile and attacks the carbonyl carbon of a second carbonyl-containing molecule in the reaction. The intermediate aldol product, the β -hydroxyacid undergoes rapid dehydration under these conditions, to give the α,β -unsaturated diacid.

Conjugate addition (1,4 addition) of pyridine and ionization of a carboxylic acid are followed by decarboxylation and concomitant elimination of pyridine to yield the α,β -unsaturated carboxylic acid. An alternative mechanism that involves a simultaneous decarboxylation and dehydration of the diacid alcohol to the α,β -unsaturated diacid via a **six-membered ring transition state** has been proposed. Is this proposal consistent with the trans stereochemistry seen in the product? Account for your choice.

Trans-cinnamic acid:

Reagents and Equipment. In a 10-mL round-bottom flask containing a magnetic stir bar, weigh and place 1.5 g (14.4 mmol) of malonic acid followed by 120 mg of β -alanine. Now, in the hood, add 3 mL of pyridine and 580 μ L of freshly distilled benzaldehyde.

CAUTION: Pyridine is a toxic amine with a strong unpleasant odor. Both reagents should be stored and dispensed in the hood.

Attach the flask to a water-jacketed reflux condenser, and place the assembly in a sand bath on a magnetic stirring hot plate.

Reaction Conditions. Heat the mixture with stirring at a sand bath temperature of about 130 °C for 1.5 h.

Isolation of Product. Allow the reaction mixture to cool to room temperature and, in the hood, remove the flask. Transfer the reaction solution using a Pasteur pipet to a 50 mL Erlenmeyer flask containing 12 mL of ice-cold water. Rinse the round-bottom flask with an additional 3 mL of ice-cold water, and transfer the rinse to the same Erlenmeyer flask in like manner. Now add, in small portions, 6 M HCl (~5 mL). A white precipitate forms. Add the HCl until the solution tests weakly acidic to pH paper. Collect the precipitate of trans-cinnamic acid by vacuum filtration using a Hirsch funnel,. Wash the white crystal with three 2-mL portions of cold water. To partially dry the material, continue the suction for an additional 15 min (remember to cover the Hirsch funnel with filter paper to protect the filter cake from contamination with dust from the laboratory atmosphere during the extended air-drying period). Don't pull the hood sash down completely.

Purification and Characterization. Weigh the crude acid and calculate the percent yield. Determine the melting point. Compare your results with the literature value. If your material melts below the literature value, for characterization recrystallize approximately 30 mg from hot water using the Craig tube. Dry as before and re-determine the melting point. To further characterize the material, obtain IR and ^1H NMR spectra. Compare your spectra with those recorded in The Aldrich Library of IR Spectra and/or The Aldrich Library of NMR

Spectra. Interpret the IR and NMR spectra and specifically account for chemical shifts of the vinylic hydrogens.

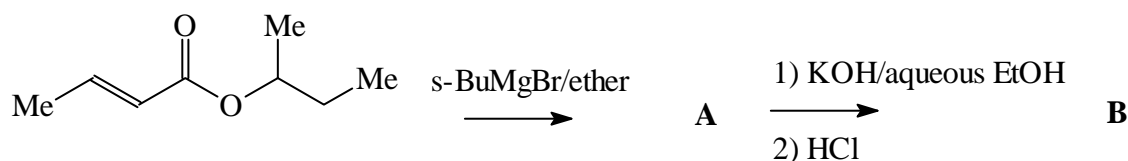
Chemical Tests. Add several crystals (~5 mg) of the trans-cinnamic acid to 1 mL of 5% sodium bicarbonate on a watch glass. Does evolution of CO_2 indicate the presence of a carboxylic acid? Does the material give a positive bromine test for unsaturation?

Questions:

1. Be sure to write the two potential complete step-by-step mechanisms for the formation of trans-cinnamic acid from malonic acid and benzaldehyde. Why is the trans acid formed preferentially?
2. Write a complete mechanism for the addition of diethyl malonate to ethanal in the presence of base to form a β -hydroxy ester.
3. Outline a synthesis that forms at least one C-C bond for each of the following compounds:
 - (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CHCO}_2\text{H}$
 - (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CN})(\text{CO}_2\text{CH}_2\text{CH}_3)$
4. As mentioned in the discussion, ketones generally give poor yields in the Knoevenagel reaction with diethyl malonate. However, the reaction with ketones gives good yields with ethyl cyanoacetate and malononitrile. Explain.
5. Give the structure of the products of the Knoevenagel reaction for the following pair reactants:
 - (a) Cyclopentanone + malononitrile (dicyanomethane)
 - (b) Benzaldehyde + ethyl acetoacetate
 - (c) Propanal + nitromethane

Experiment 6. Addition of a Grignard reagent to *s*-butyl but-2-enoate (*s*-butyl crotonate): hydrolysis of the addition product and identification of the final product.

α,β -Unsaturated carbonyl compounds can either undergo direct nucleophilic attack at the carbonyl group (often called *1,2-addition*) or conjugate addition at the β -carbon (often called *Michael* or *1,4-addition*). The site of attack is dependent on the nature of the α,β -unsaturated carbonyl compound and on the attacking nucleophile. When Grignard reagents are used as nucleophiles, the site of addition is not always easy to predict, and both 1,2- and 1,4-addition products can be formed.



This experiment illustrates the addition of 2-butylmagnesium bromide to the α,β -unsaturated ester *s*-butyl but-2-enoate. In a second step, the addition product **A** is reacted with aqueous KOH to yield the final product **B**. By analysing the spectra you obtain for the addition and final products – you identify them – you will ascertain whether the addition occurs 1,2 or 1,4 in this case

Materials

1. Preparation of *s*-butyl 3-methylheptanoate

magnesium turnings (FW 24.3)	1.88g (77mmol)	flammable
2-bromobutane (FW 137.0)	10.5mL (98mmol)	flammable, irritant
<i>s</i> -butyl but-2-enoate (FW 142.2)	4.27g (30mmol)	irritant
(Experiment 2)		
diethyl ether		flammable, irritant
hydrochloric acid (conc.)		corrosive
sodium bicarbonate solution		
(saturated)		

2. Preparation of 3-methylheptanoic acid

ethanol		flammable, toxic
potassium hydroxide (FW 56.1)	0.93 (17mmol)	corrosive
sodium chloride solution (saturated)		

Procedure

All apparatus must be thoroughly dried in a hot ($>120^{\circ}\text{C}$) oven before use. **CARRY OUT THE REACTION ON $\frac{3}{4}$ SCALE.**

1. Preparation and addition of 2-butyilmagnesium bromide

Place the magnesium turnings in a 250 mL two- or three-neck flask fitted with a reflux condenser carrying a calcium chloride guard tube, a 50 mL addition funnel, and a stirrer bar. Stopper the third neck, and place the flask in a water bath on a magnetic stirrer/hotplate. Place a solution of the 2-bromobutane in 25 mL *dry* diethyl ether in the addition funnel. Add 2 mL of the 2-bromobutane solution to the flask, heat the reaction mixture to reflux for a few minutes in a hot water bath, and start the stirrer. The formation of the Grignard reagent should start almost immediately. Add the remainder of the bromobutane solution at such rate as to maintain the diethyl ether at gentle reflux. After the addition has been complete, heat the solution under reflux for a further 10 min, and then cool the flask in an ice bath for 10 min. In the meantime, place a solution of the *s*-butyl but-2-enoate in 30 mL diethyl ether in the addition funnel; add this dropwise to the stirred ice-cooled reaction mixture. After the addition of the ester is complete, stir the mixture for a further 10 min in the ice bath, and then at room temperature for 30 min. Place 8 mL concentrated hydrochloric acid, 10 mL diethyl ether and 50 g crushed ice in a 250 mL beaker. Stir the mixture vigorously, and slowly pour the Grignard reaction mixture into the beaker, adding more ice if necessary to keep the temperature at about 0°C . Transfer the mixture to a separatory funnel and separate the layers. Retain the ether layer, and extract the aqueous layer with 3 x 10 mL diethyl ether. Combine all the ether layers and wash them with 10 mL saturated sodium bicarbonate solution, then with 10 mL water, and dry them over MgSO_4 . Filter off the drying agent with suction, evaporate the filtrate on the rotary evaporator, and distil the residue from a 10 mL flask under reduced pressure (*ca.* 9 mm Hg) using a vacuum pump, collecting the product at *ca.* 90°C . Record the exact bp, yield, and the IR and NMR (CDCl_3) spectra of your product.

2. Hydrolysis of the addition product.

Place a mixture of 2.0 g of the product, 0.93 g potassium hydroxide, 5 mL ethanol and 1 mL water in a 25 mL round-bottomed flask. Fit a reflux condenser, and heat the mixture under reflux for 30 min. Cool the mixture to room temperature, dilute it with 10 mL water, and acidify it by the addition of 3 mL concentrated hydrochloric acid. Transfer the mixture to a separatory funnel, and extract the product with 3 x 5 mL diethyl ether. Combine the ether layers, wash them with 5 mL saturated sodium chloride solution, and dry them over MgSO_4 . Filter off the drying agent

with suction, evaporate the filtrate on the rotary evaporator, and distil the residue under reduced pressure in the short path distillation apparatus (*ca.* 10 mm Hg) using a vacuum pump, collecting the product at *ca.* 115°C. Record the exact bp, yield and the IR and NMR (CHCl₃) spectra of your product. Also submit this final product for mass spectrometric analysis.

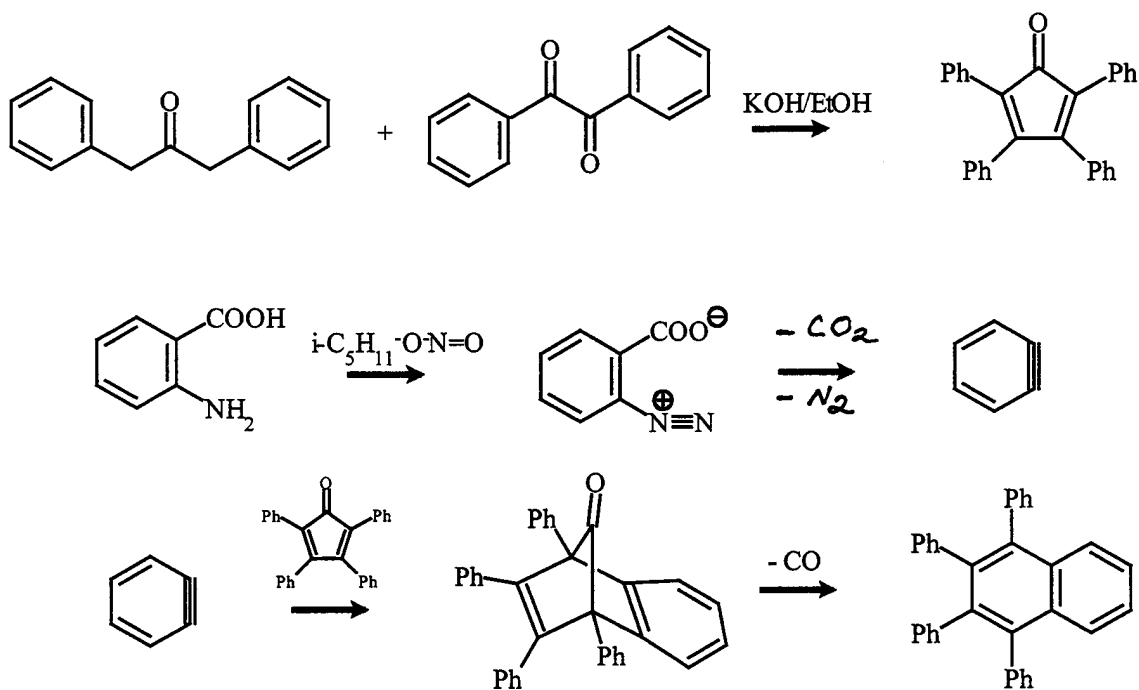
Questions:

1. In the interpretation of the NMR spectra of your products, pay particular attention to the spin-spin splitting patterns.
2. Discuss in detail the factors affecting the 1,2- or 1,4-addition of nucleophiles to α,β -unsaturated carbonyl compounds and account for the regiochemistry seen in this case. What product would you expect if butyllithium is used in place of 2-butyilmagnesium bromide?
3. Suggest an alternative synthesis of the final product.

Experiment 7: 1,2,3,4-Tetraphenylnaphthalene

Ref.: CGWW, pp 903-927

In this experiment you will synthesize 1,2,3,4-tetraphenylnaphthalene by preparing tetraphenylcyclopentadienone and using it as a diene in a Diels-Alder reaction with benzyne. It is interesting to note that cyclopentadiene itself is highly reactive and cannot be isolated in the condensed phase at ambient temperature. The same thing holds for benzyne, a bonafide transient, and 1,2,3,4-tetraphenylbenzonorbornadien-7-one. **You are concluding your 3D03 laboratory by preparing several exotic transient species.**



Waste Disposal

The ethanolic KOH solution, which is left as a filtrate after collecting the dark purple tetraphenylcyclopentadienone by vacuum filtration, should be neutralized with dilute hydrochloric acid, diluted with water and disposed of in the proper manner. The recrystallization solvents or the filtrate solutions should be placed in the container designated for nonhalogenated organic liquids.

PROCEDURE

Add 0.100 g of benzil, 0.100 g of dibenzyl ketone (1,3-diphenyl-2-propanone, 1,3-diphenylacetone), and 0.80 mL of absolute ethanol to a 3-mL conical vial. Place a spin vane in the vial and attach a water-cooled condenser. Using a sand bath on a heater/stirrer that is adjusted to about 80°C, heat the mixture with stirring until the solids dissolve.

Raise the temperature of the hotplate until the mixture is just below its boiling point. Continue to stir the mixture. Using a 9-inch Pasteur pipet, carefully add dropwise 0.15 mL of ethanolic potassium hydroxide solution downward through the condenser into the vial.

Caution: Foaming may occur

The mixture will immediately turn deep purple. Once you add the potassium hydroxide, increase the temperature of the hotplate until the mixture is boiling gently. Heat the mixture, while stirring, at a gentle boil for 15 minutes. (**The stirring may become problematic.**)

At the end of the heating period, remove the vial from the sand bath and allow the mixture to cool to room temperature. Then place the vial in an ice-water bath for 5 minutes to complete crystallization of the product. Collect the deep purple crystals on a Hirsch funnel. Hold the spin vane with a forceps and scrape off as much solid as possible. Wash the crystals with three 0.5 mL portions of cold 95% ethanol. The rinse solvent can also be used to aid in transferring crystals from the conical vial to the Hirsch funnel and in removing the remainder of the crystals from the spin vane. Dry the tetraphenylcyclopentadienone in an oven for 30 minutes or in air overnight.

The crude product is pure enough (mp 218-220°C) for the preparation of 1,2,3,4-tetraphenylnaphthalene. Weigh the product and calculate the percentage yield. Determine the melting point. A small portion may be crystallized, if desired, from a 1:1 mixture of 95% ethanol and toluene (12 mL/0.5 g; mp 219-220°C). Use a Craig tube for the crystallization. At the instructor's option, determine the infrared spectrum of tetraphenylcyclopentadienone in potassium bromide.

SPECIAL INSTRUCTIONS

It will be dispensed by your teaching assistant. **Special care should be taken to avoid breathing isopentyl nitrite (isoamyl nitrite) as it is a powerful heart stimulant.** The isopentyl nitrite must be stored in a refrigerator when not in use. Restopper the bottle after the liquid has been removed to minimize contact with air.

A small amount of carbon monoxide is produced in this reaction. It is advisable to run the reaction in a hood.

The 1,2-dimethoxyethane (also known as ethylene glycol dimethyl ether and monoglyme) is toxic and although it is used in small quantities as a solvent, it should be handled with care. Dispense 1,2-dimethoxyethane in a hood. Use polyethylene gloves, if available. Do not inhale this substance. Rinse your hands immediately if this solvent comes in contact with your skin.

WASTE DISPOSAL

The methanol and isopropyl alcohol filtrates should be placed in the waste containers designated for disposal of nonhalogenated wastes. Any residual 1,2-dimethoxyethane waste should also be placed in the same waste container.

PROCEDURE

Carry out this reaction in pairs in a hood.

Reaction Mixture. Place 0.100 g of tetraphenylcyclopentadienone (MW 384.5), 0.045 g of anthranilic acid (MW = 137.1), and 1.2 mL of 1,2-dimethoxyethane in a 5-mL conical vial. Add a magnetic spin vane and attach a water-jacked condenser. In a hood, transfer 0.06 mL of isopentyl nitrite (isoamyl nitrite, MW = 117.2, d = 0.875 g/mL) to a 3-mL conical vial.

Cap the vial to prevent loss by evaporation. Replace the lid on the reagent bottle as soon as possible to minimize exposure to air.¹ Dissolve the isopentyl nitrite in 0.50 mL of 1,2-dimethoxyethane.

Running the Reaction. Heat the mixture containing tetraphenylcyclopentadienone and anthranilic acid with a sand bath at about 140°C. When the solution begins to boil, add the solution of isopentyl nitrite through the top of the condenser with a Pasteur pipet over a period of about 30 seconds. (Wear your safety goggles!) Make sure that the pipet is inserted deep into the condenser so that the solution is added directly to the vial. Use a few drops of 1,2-dimethoxyethane to rinse the vial and add this solution to the reaction mixture.

Continue to boil the mixture until the color changes from the deep purple color of the tetraphenylcyclopentadienone to a yellow-orange solution formed after the dienone is consumed (usually less than 10 minutes). If the color has not changed after about 15 minutes, add a drop of pure isopentyl nitrite (no solvent, pipet extended down into the condenser) and continue to boil the solution for an additional 10 minute period. If the color still has not changed to a yellow-orange color after this reflux period, add another drop of isopentyl nitrite and boil the solution for an additional 10 minutes.²

Isolation of Crude Tetraphenylnaphthalene. After the color changes, cool the mixture to room temperature and use a Pasteur pipet to transfer the solution to a beaker containing 5 mL of water and 2 mL of methanol. Stir the mixture well to break up the precipitate. Collect the solid on a Hirsch funnel under vacuum. In some cases, the filtration process may be slow because the solid plugs the filter paper. If this occurs, add a little ice cold methanol to the Hirsch funnel while the mixture is being filtered. Use 10 mL of ice cold methanol to aid the transfer of the solid remaining in the beaker and to wash the solid collected in the Hirsch funnel. Additional product precipitates in the filter flask. Collect this material and add it to the solid in the Hirsch funnel. Rinse the combined solids on the Hirsch funnel with 3 mL of ice cold methanol. Weigh the crude product.

¹ Isopentyl nitrite (isoamyl nitrite) must be stored in a refrigerator. It decomposes in the presence of light and air. This reaction gives the best results if the material has been bought recently. Material from Aldrich Chemical Co. (# 15,049-5) works well.

Crystallization of the Tetraphenylnaphthalene. Purify all the product by crystallization from hot isopropyl alcohol (2-propanol) in order to remove the remaining colored impurities. Place the crude tetraphenylnaphthalene in a 25 mL Erlenmeyer flask and dissolve it in boiling isopropyl alcohol. For the amount of product that you may expect to obtain, it will require approximately 12 mL of boiling isopropyl alcohol to dissolve your crude product (12 mL of solvent/85 mg of product). The 12 mL of isopropyl alcohol is a rough estimate, and you may use more or less than this amount. The solution process is enhanced by breaking up any lumps with a spatula. Once your crude product has dissolved in the boiling solvent, cool the mixture in an ice bath.

When it has cooled somewhat, scratch the side of the flask with a stirring rod. The product slowly crystallizes. Allow the mixture to cool for at least 30 minutes in an ice bath. Collect the product on a Hirsch funnel under vacuum, and wash it with a small amount of ice cold isopropyl alcohol. Allow the solid to dry completely, weigh the product, and calculate the percentage yield.

Determination of Melting Point. When the solid has dried completely, determine the melting point. Pure 1,2,3,4-tetraphenylnaphthalene melts at 196-199°C. When the material has melted, remove the capillary tube from the melting-point apparatus and cool the tube until the material solidifies. Redetermine the melting point (literature 203-205°C)³. The tetraphenylnaphthalene exists in two crystalline forms, each with a different melting point. Submit the sample to the instructor in a labelled vial.

Spectroscopy. At the option of the instructor, obtain the proton NMR spectrum in CDCl_3 .

² If the color has not changed after the additions of the extra isopentyl nitrite, add a small amount (about 0.010 g) of anthranilic acid. Reflux the mixture for another 15 minutes, or until the color changes.

³This compound exhibits a double melting point. The initial melting point varies according to its particle size and is not a reliable index of purity. The remelt melting point is more reproducible and reliable.

Questions:

1. Write a step-by-step mechanism for the formation of tetraphenylcyclopentadienone.
2. Account for the facile extrusion of CO from the D-A adduct.
3. Use MM+ of HYPERCHEM to model 1,2,3,4-tetraphenylnaphthalene, include a printout of your structure in your report, and discuss the results.