Experimental Section

Materials. Spectroscopic grade CCl_4 was stored over molecular sieves. Commercial indan, tetralin, TNB, and DNB were purified by standard procedures. Benzocyclobutene was prepared and purified according to literature methods.[15] The diannelated compounds were a gift from Professor Randolph Thummel.

Measurements. All solutions were prepared by weight. A Varian EM 390 NMR spectrometer was used to obtain the Δ values. The peak positions were measured with a frequency counter and the values of Δ obtained to within ± 0.1 Hz. For most compounds 10–15 solutions covering a range of $[D]_0$ from 0.08 to 0.4 mol/kg of solvent were used except where noted in the Results and Discussion section.

Acknowledgment. We are grateful to Professor Randolph Thummel for the gift of the two diannelated benzene compounds. This work was partially supported by an NSF undergraduate research participation program, Grant No. SMI-76-03971 A03.

Registry No. Tetralin–trinitrobenzene (1:1), 73506-06-6; indan–trinitrobenzene (1:1), 73506-07-7; benzocyclobutene–trinitrobenzene (1:1), 73523-12-3; *o*-xylene–trinitrobenzene (1:1), 2590-50-3; benzo[1,2:4,5]dicyclopentene–trinitrobenzene (1:1), 73512-99-9; 1,2,4,5-tetramethylbenzene–trinitrobenzene (1:1), 1095-52-9; benzo[1,2:3,4]dicyclopentene–trinitrobenzene (1:1), 73506-08-8; 1,2,3,4-tetramethylbenzene–trinitrobenzene (1:1), 2636-28-4; tetralin–dinitrobenzene (1:1), 73506-09-9; indan–dinitrobenzene (1:1), 73506-10-2; benzocyclobutene–dinitrobenzene (1:1), 73506-11-3; *o*-xylene–dinitrobenzene (1:1), 26397-19-3; benzo[1,2:4,5]dicyclopentene–dinitrobenzene (1:1), 73506-12-4; 1,2,4,5-tetramethylbenzene–dinitrobenzene (1:1), 1611-15-0; benzo[1,2:3,4]dicyclopentene–dinitrobenzene (1:1), 73506-13-5; 1,2,3,4-tetramethylbenzene–dinitrobenzene (1:1), 26397-23-9.

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Thermolysis of 6-*endo*-(Carbomethoxy)bicyclo[3.1.0]hex-2-ene: Comparison with the Parent Compound and Effect of Different Thermolysis Techniques

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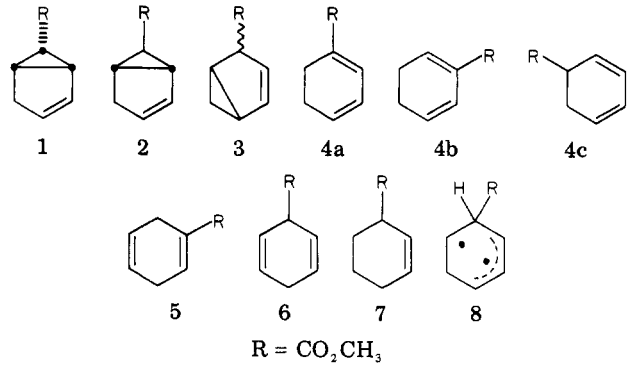
Thermal isomerizations of vinylcyclopropanes have been studied in great depth with regard to concerted vs. stepwise mechanisms.[1,2] Recent interest has focused on the thermal epimerization and rearrangements of bicyclo[3.1.0]hex-2-enes which can occur via exocyclic (C_1–C_6) and endocyclic (C_1–C_5) cyclopropyl bond cleavage.[3] We investigated the thermolysis of 6-*endo*-(carbomethoxy)bicyclo[3.1.0]hex-2-ene (**1**) in order to determine the mode of cleavage. We initially focused our attention on the formation of epimer **2**, using optically active compounds to demonstrate for the first time that both one-center and two-center thermal epimerization can occur competitively.[3] In the course of this investigation, we found that endocyclic bond cleavage



resulted in the formation of 1,3-cyclohexadienes. *No 1,4-cyclohexadienes were observed.* In contrast, bicyclo[3.1.0]hex-2-ene (BCH) is reported to give both 1,3- and 1,4-cyclohexadienes. In view of the relative stabilities of 1,3- vs. 1,4-cyclohexadienes, the apparent absence of the 1,4 isomer prompted us to further investigate the thermolysis of **1**.

Flash vacuum pyrolysis of **1** at 490 °C gives a pyrolysate mixture composed of ca. 38% epimer **2**, 17% 4-(carbomethoxy)bicyclo[3.1.0]hex-2-ene (**3**), 35% 1,3-cyclohexadienes (**4**), and 10% unreacted starting material, according to GLC analysis. Products were isolated via sequential preparative GLC utilizing both fluorosilicone (QF-1) and FFAP as stationary-phase materials. Proton NMR, GLC analyses, ultraviolet spectra, and comparison with known compounds[4] were used to verify the structures of isolated products. At lower temperature (460 °C), the fractional conversion of **1** is lower with only **2** and **3** appearing in approximately equal amounts (ca. 10% each). The 1,3-cyclohexadienes are not observed until a pyrolysis temperature of 475 °C and they became more significant at higher temperature with a slight decrease in formation of **3**. The rearrangement of **1** to **3** is an example of the well-known vinylcyclopropane rearrangement.[2] **3** appeared to be a mixture of both epimers in approximately equal amounts based on the proton NMR spectrum of the collected material: ($CDCl_3$) δ 0.0 (m, 0.5 H), 0.3 (m, 0.5 H), 1.0 (br m, 1 H), 2.0 (m, 2 H), 3.7 (s, 3 H), 5.4 (m, 1 H), 6.1 (m, 1 H). Since **3** was a mixture of epimers, we attempted to isomerize **3** to the conjugated ester. Treatment of **3** with 0.2 M $NaOCH_3/CH_3OH$ for 1 h at room temperature results in rearrangement to 1-(carbomethoxy)-1,4-cyclohexadiene (**5**), identified by comparison with an authentic sample.[4] This transformation can be followed by NMR by using $NaOCD_3/CD_3OD$. Integration of the peak areas in the spectrum showed the incorporation of deuterium into the methylene region of **5**. GLC analysis of the product showed it to be composed of ca. 90% **5**. Surprised by the absence of significant amounts of the 1,3-cyclohexadienes, we reacted authentic **5** with $NaOCD_3/CD_3OD$ in an NMR tube. A solid precipitated immediately. The addition of a few drops of D_2O brought the material into solution and the NMR spectrum showed H–D exchange at the methylene carbon *with no observable rearrangement to a 1,3-cyclohexadiene.* Recent studies on the comparable stabilities of 1,3- vs. 1,4-cyclohexadienes lend some support to the preferred formation of the 1,4 isomer,[5-7] but its preponderance is surprising and probably

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reflects differences in the rates of protonation at alternate sites.

The pyrolysate from 1 contained all three possible 1,3-cyclohexadienes; the predominant isomer was 1-(carbomethoxy)-1,3-cyclohexadiene (**4a**). If the conjugated 1,3-cyclohexadienes are thermodynamically more stabe than the 1,4 isomers, then **5** and **6** are potential intermediates in the thermolysis of **1**. Furthermore, thermolysis of the parent compound, bicyclo[3.1.0]hex-2-ene (BCH), leads to the formation of 1,3- and 1,4-cyclohexadienes in the ratio of 1.5:1.[8,9] Therefore, we prepared 3-(carbomethoxy)-1,4-cyclohexadiene (**6**) to complete our inventory of the isomeric cyclohexadienes and to study the thermal behavior of **5** and **6**. Under the flash vacuum pyrolysis conditions used for **1**, 10–15% of both **5** and **6** were converted to methyl benzoate as determined by the NMR spectra of their respective pyrolysates. Presumably, hydrogen gas was emitted; no other products were evident from analysis of the NMR spectra. These results are consistent with the reported thermal conversion of 1,4-cyclohexadiene to benzene and hydrogen at 303 °C under conditions where the 1,3 isomer is stable.[8] It is clear from the thermolysis results that **5** and **6** are not formed in the flash vacuum thermolysis of **1**. By contrast, **6** disproportionated in the gas chromatograph (12-ft FFAP column at 170 °C) to give methyl benzoate and the dihydro compound **7**. The percent conversion varied considerably with amounts injected and at least one other compound was present. Disproportionation of **6** in the gas chromatograph (on several different columns) as compared to its behavior under flash vacuum pyrolysis conditions probably reflects the difference in the thermal behavior of **6** in the condensed vs. gas phases. **5** was stable in the gas chromatograph under identical conditions.

It is interesting to compare the thermolysis of **1** with that of the parent compound BCH. In the substituted case (**1**), the products formed with the lowest activation energies are the epimer **2** and the vinylcyclopropane rearrangement product **3**, products which would not be observed in the thermolysis of unlabeled BCH. Moreover, the formation of **3** must occur via initial rupture of the C_1–C_5 bond while the formation of **2** occurs mainly via C_1–C_6 bond cleavage,[3] suggesting similar free energies of activation for the two modes of cleavage. The thermolyses of BCHs bearing deuterium as positional markers have been reported to lead to automerization through cleavage of the internal cyclopropane bond.[10] The epimerization of deuterium at C-6 in a dideuterio BCH was described in similar mechanistic fashion. Our results and those of Baldwin and Gilbert[11] on the thermal isomerization of **2** (R = vinyl) demonstrate that external cyclopropane bond cleavage of substituted bicyclohexenes is a competitive pathway. The formation of cyclohexadienes must occur via C_1–C_5 bond cleavage to probably give the biradical **8**, followed by H migration which requires a greater activation energy.[9] It appears that the activation energy required for formation of the 1,3 isomer is less than that for the 1,4 isomer (H migration to a localized C radical vs. an allylic C radical). This would lead directly to formation of **4a** which can thermally isomerize to **4b** and **4c**.[12] However, we are surprised at the absence of **5**, most of which would have survived the pyrolysis conditions and the GLC separation conditions we utilized.

One must consider that flash vacuum pyrolysis[13] often gives different products and/or product ratios than pyrolysis in a sealed tube or other conditions resulting in longer contact time. In our experience, the former method provides much cleaner results and better reproducibility. These differences must be considered in comparing results using different techniques. For example, when we thermolyzed **1** by dripping the liquid onto a column of glass helices at 490 °C under slow nitrogen gas flow,[14] we observed the formation of methyl benzoate as an additional major component of the pyrolysate.

Experimental Section

Proton magnetic resonance spectra were recorded with a Varian Associates T-60 spectrometer. GLC analyses were performed with a Varian Aerograph A-90-P3. Helium was used as the carrier gas at a flow rate of ca. 60 mL/min. The following aluminum columns purchased from Varian Associates were used for preparative collection in the temperature range of 150–170 °C: column A, FFAP, 20 ft × $^3/_8$ in., 30% on 45/60 Chromosorb W; column B, QF-1, 20 ft × $^3/_8$ in., 30% on 45/60 Chromosorb W. On column A, **3** appears first followed by **1**, **2**, and **4c** (not cleanly resolved). On column B, **1**, **3**, and **4c** (unresolved) appear first followed by **2**. Thus, the separation technique was chromatography on column A to collect **3** and, as a mixture, **1**, **2**, and **4c**, followed by **4a** and **4b**, a total of four fractions. The mixture fraction was reinjected on column B to separate **1**, **2**, and **4c**. Product ratios are estimated on the basis of peak areas of chromatograms normalized by comparison with peak areas of known mixtures; samples of products and **5** were reinjected to verify that rearrangement does not occur in the gas chromatograph under the conditions employed. A small amount of minor product (<1%), collected via preparative GLC, gave an NMR spectrum consistent with the structure of a cyclopentenylidene: ($CDCl_3$) δ 2.6 (m, 4 H), 3.7 (s, 3 H), 5.6 (m, 1 H), 6.6 (m, 1 H), 7.3 (m, 1 H); but further analysis of this material was not pursued. Cyclopentenylidenes have been observed in the thermolysis of substituted bicyclo[3.1.0]hex-2-enes.[15]

Flash Vacuum Pyrolysis. An 18 in. × $^5/_8$ in. quartz column in a temperature-controlled oven was evacuated to ca. 50 μm. A sample of **1** at room temperature was allowed to vaporize through the column and the pyrolysate was collected in a liquid-nitrogen-cooled trap.

Base-Catalyzed Rearrangement of 3 to 5. **3** (50 mg) in CD_3OD was placed in an NMR tube and the proton NMR spectrum recorded. $NaOCD_3/CD_3OD$ (2 N, 50 μL) was added to the NMR tube. After 1 h, the proton NMR spectrum showed that rearrangement had occurred. D_2O was added and the solution was extracted with $CDCl_3$. The chloroform extract gave a proton NMR spectrum similar to that of **5** (without the OCH_3 signal) but with a reduced methylene region (proton count of 1.4 instead of 4). GLC analysis showed the presence of mainly one compound (ca. 90%) which had a retention time indentical with **5**.

Reaction of 5 with $NaOCD_3/CD_3OD$. A solution of 2 N $NaOCD_3/CD_3OD$ was placed in an NMR tube. **5** (100 mg) was added, resulting in the immediate formation of a precipitate. A few drops of D_2O was added to dissolve the precipitate and the proton NMR spectrum was immediately recorded. The spectrum showed a methylene region with a proton count identical with that of the upfield olefinic protons, suggesting the incorporation of two deuteriums at methylene positions. The spectrum showed no signals other than those expected for **5** and solvent.

Rearrangement of 6 in the Gas Chromatograph and via Flash Vacuum Pyrolysis. The injection of **6** onto an aluminum 12 ft × 0.25 in. FFAP column (10% free fatty-acid polymer on 60/80 Chromosorb P purchased from Varian Associates) at 170 °C resulted in a chromatogram giving a well-separated first peak and poorly resolved second peak (at least two components).

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Samples of both peaks were collected. The proton NMR spectrum of the first peak gave δ 2.0 (m, 6 H), 3.1 (m, 1 H), 3.6 (s, 3 H), 5.8 (s, 2 H), and the compound was assigned structure **7**. The second peak was shown to be a mixture containing methyl benzoate, starting material (**6**), and at least one other compound which was not identified. Qualitatively similar results were obtained on an Alltech CS-8 6 ft × $^1/_8$ in. stainless-steel column (10% cyanosilicone on Chromosorb W-AW, 100/120 mesh).

The flash vacuum pyrolysis of **6** gave a pyrolysate whose proton NMR spectrum could be accommodated solely by the proton signals of methyl benzoate and starting material (**6**).

Acknowledgment. We thank the Research Committee, UMSL, for financial support.

Registry No. 1, 22664-28-4; 2, 29569-87-7; 3, epimer 1, 73378-49-1; 3, epimer 2, 73378-50-4; 4a, 30810-15-2; 4b, 40002-24-2; 4c, 54162-19-5; 5, 50983-21-6; 6, 30889-20-4; 7, 25662-37-7.

Methyl Acetyl Phosphate. A Small Anionic Acetylating Agent

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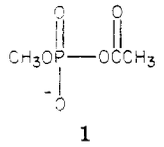
Alkyl monoesters of acetyl phosphate ($ROPO_2(COCH_3)O^-$) are of significant interest for mechanistic studies on the reactivity of carboxylic–phosphoric acid anhydride derivatives. For example, aminoacyl adenylates, the activated derivatives of amino acids which are transient intermediates in the biosynthesis of aminoacyl tRNAs, are elaborate members of this functional classification.[1] On the basis of the known reactivity patterns of such compounds,[2,3] another important potential use would be the acetylation of a nucleophile that is adjacent to a cation in an enzyme. However, to our knowledge, no acceptable synthesis of a simple monoalkyl compound has been reported. Studies of this class of compound, therefore, have invariably involved the easily accessible derivative phenyl acetyl phosphate, prepared from phenyl phosphate and acetic anhydride.[2-6] Extension of this method to the use of ethyl phosphate or methyl phosphate in place of phenyl phosphate gives impure, uncharacterized products.[2,7] Therefore, any preparation of an alkyl monoester of acetyl phosphate requires a different synthetic strategy.

The motivation for our synthesis of methyl acetyl phosphate (**1**) resulted from our work with D-3-hydroxy-



1

butyrate dehydrogenase.[8] This enzyme catalyzes the reduction of acetoacetate and **1** is a functional analogue of this substrate. We believed that **1** would be a good candidate to be an active-site directed acetylating agent of a potentially nucleophilic functional group we proposed to exist on the enzyme[8] adjacent to a cationic binding site. The phenyl ester has an inappropriate functional group for these purposes.

We have developed a simple procedure for the synthesis of **1** based on the conversion of dimethyl acetyl phosphate which itself is readily prepared in an analytically pure condition.[9]

Experimental Section

Dimethyl acetyl phosphate was prepared from a solution of 30 g of acetyl chloride and 70 g of trimethyl phosphate that was refluxed for 12 h.[9,10] Unreacted acetyl chloride was removed under aspirator vacuum. The residue was distilled at 0.01 torr. Fractions boiling between 40 and 55 °C were collected and redistilled on a 10-cm column three times, with the product distilling at 50 °C (lit.[9] bp 51–52 °C (0.05 torr)) to yield 7.5 g of dimethyl acetyl phosphate.

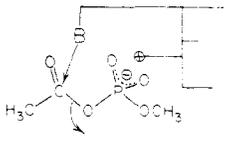
Methyl Acetyl Phosphate (1) Sodium Salt. Dimethyl acetyl phosphate (58 g) was dissolved in 50 mL of acetone which had been dried over magnesium sulfate. To this was added 5.7 g of sodium iodide in 50 mL of dry acetone. The solution was stirred at room temperature in a condenser-equipped flask with a magnetic stirrer. "Drierite" was used to exclude moisture. If heat is used, the reaction causes the product to decompose.[7] After 5 h a large amount of white precipitate had formed. This was collected by filtration and washed with dry acetone. Additional product precipitated from the solution after several hours. The sodium salt of methyl acetyl phosphate was recrystallized from methanol and ether in 70% yield: ^{1}H NMR (D_2O, relative to internal DSS) δ 2.18 (d, $^4J_{PH}$ = 1.4 Hz, 3 H, $CH_3C(O)$), 3.67 (d, $^3J_{PH}$ = 11.6 Hz, 3 H, CH_3O). Anal. (Galbraith Laboratories) $C_3H_6O_5PNa$ (C, H, P).

Kinetics. The rate of hydrolysis of **1** was followed by ^{1}H NMR with 0.05 M substrate and 0.1 M potassium phosphate, pH 7.0 buffer. Cleavage of the anhydride bond produces acetate and methyl phosphate. The concentration of **1** is proportional to the integral of its acetyl proton signal at δ 2.18, whereas the concentration of acetate is proportional to the integral of its proton signal at δ 1.89 (s). The reaction was plotted by first-order methods, yielding a rate constant at pH 7.0, 25 °C, of 1.2×10^{-6} s^{-1}, corresponding to a half-life of 160 h.

Results and Discussion

Methyl acetyl phosphate is relatively stable in solution. The rate of its hydrolysis can be compared to that reported for the phenyl ester by DiSabato and Jencks.[3] Extrapolaring their data at 73, 60, 50, and 37 °C to 25 °C yields a rate constant of 8.2×10^{-7} s^{-1}, which is only slightly less than the rate constant we observe for the hydrolysis of **1**. This suggests that the mechanism involving C–O cleavage of the anhydride found for phenyl acetyl phosphate[2,3] applies to the methyl ester as well.

The stability of methyl acetyl phosphate assures that if it is used as an active-site directed reagent with an enzyme, it will be stable in the absence of nonenzymic nucleophiles. In other words, competing spontaneous reactions are not a problem and acetylation of an enzymic nucleophile may occur specifically if the anionic phosphate group first associates with a cationic binding site. Our



preliminary studies reveal that lactate dehydrogenase, malate dehydrogenase, and alcohol dehydrogenase are all slowly ($t_{1/2}$ ~30 min, 25 mM reagent) inactivated by

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