1987

I. Generation and mechanistic study of t-butyl exo-methylene-substituted 2,3-dimethylene-2,3-dihydrofurans and a thiophene analogue; II. Generation and study of the dimerization of alkyl ring-substituted 2,3-dimethylene2,3-dihydrofurans; III. Diels-Alder reaction of 2,3-dimethylene-2,3-dihydrofuran and o-xylylene; IV. Formation of the 2,5-dimethylene-2,5-dihydrothiophene trimer and its synthetic application

Yih-chuan Jason Huang
Iowa State University

Huang, Yih-chuan Jason

I. GENERATION AND MECHANISTIC STUDY OF T-BUTYL EXO-METHYLENE-SUBSTITUTED 2,3-DIMETHYLENE-2,3-DIHYDROFURANS AND A THIOPHENE ANALOGUE. II. GENERATION AND STUDY OF THE DIMERIZATION OF ALKYL RING-SUBSTITUTED 2,3-DIMETHYLENE-2,3-DIHYDROFURANS. III. DIELS-ALDER REACTION OF 2,3-DIMETHYLENE-2,3-DIHYDROFURAN AND O-XYLYLENE. IV. FORMATION OF THE 2,5-DIMETHYLENE-2,5-DIHYDROTHIOPHENE TRIMER AND ITS SYNTHETIC APPLICATION

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by

Yih-chuan Jason Huang

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For the Graduate College

Iowa State University
Ames, Iowa
1987

TABLE OF CONTENTS

GENERAL INTRODUCTION

For the last few years, Professor Trahanovsky's research group has been focusing on the chemistry of the flash vacuum pyrolysis (FVP) of a variety of heterocyclic aromatic systems. The studies led to the most efficient synthesis of 2,3-dimethylene-2,3-dihydrofuran (1) and its derivatives as well as to the discovery of the first evidence of the thiophene analogue of 1 by the isolation of its [4+2] dimer. This dissertation contains four different sections. The first section involves the study of the chemistry of three t-butyl exo-methylene-substituted derivatives of 1 and one of their thiophene analogues. In the second section, we compared the behavior of several alkyl ring-substituted derivatives of 1 in their dimerization. Section three looks into the mechanism of the Diels-Alder reaction of 1 with some dienophiles. And finally, in the fourth section, a convenient synthesis of cyclooctadecane from the thiophene trimer of 2,5-dimethylene-2,5-dihydro-thiophene is presented.

EXPLANATION OF DISSERTATION FORMAT

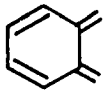
This dissertation has been written using the alternate dissertation format and consists of four sections as complete papers in the style suitable for publication in Journals published by the American Chemical Society. All of the experimental results presented were contributed by the candidate.

SECTION I. GENERATION AND MECHANISTIC STUDY OF t-BUTYL EXO-METHYLENE-SUBSTITUTED 2,3-DIMETHYLENE-2,3-DIHYDROFURANS AND A THIOPHENE ANALOGUE

INTRODUCTION

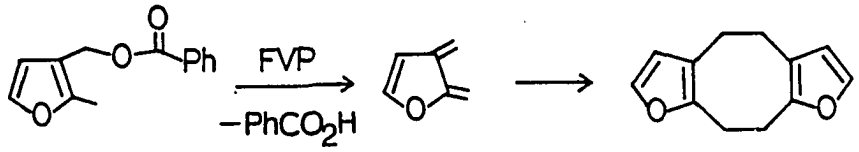
In the past decade, flash vacuum pyrolysis (FVP) has attained recognition as a method in generation of novel intermediates that are useful both synthetically and mechanistically as summarized in recent literature.[1-5]

One area in FVP which has received considerable attention during the past twenty years for its mechanistic significance and synthetic application is the generation and chemistry of o-quinodimethane (1).[6-8]



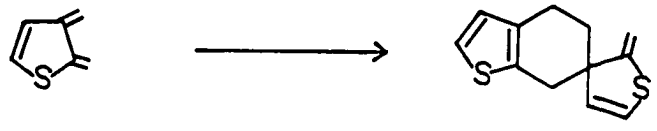
1

During the past few years, our research group has been actively studying the scope of the chemistry of 2,3-dimethylene-2,3-dihydrofuran (2), the furan analogue of 1. Compound 2, conveniently prepared by the flash vacuum pyrolysis of 2-methyl-3-furylmethyl benzoate (3), dimerizes rapidly in solution at temperatures above -30° C to form 4, the head-to-head, [4+4] dimer of 2 in high yield.[9]



3 2 4

The exclusiveness of this 4+4 process is very unique since for most other members of the o-quinodimethanes family, e.g., o-xylylene (1)[1-5] and 2,3-dimethylene-2,3-dihydrothiophene (5);[10] their dimerization predominantly proceeds via the 4+2 process, also known as the Diels-Alder reaction.



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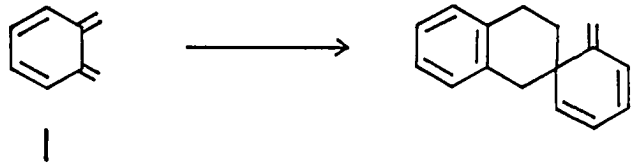
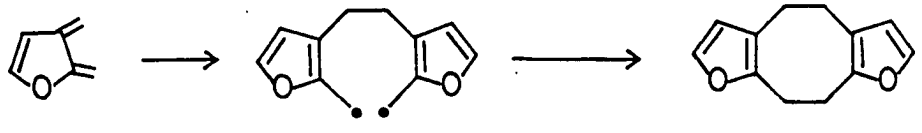


1

On the basis of a secondary deuterium kinetic isotope effect study, this [4+4] dimerization of 2 is rationalized to proceed through diradical 6.[11]

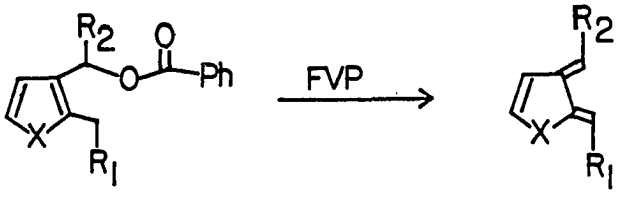


2 6

In this mechanism, it was suggested that only the 3-methylene is directly involved in the rate determining step to form 6, but the 2-methylene is involved in the product forming step.

Substituent effects, which consist of steric and electronic effects, are very useful for studying reaction mechanisms. Substituents that cause steric hindrance at the transition state would retard the reaction. Thus we expected that a t-butyl group on the 2-methylene position of 2 would not affect the rate of dimerization but could affect the type of products formed, and we also anticipated that a t-butyl group on the 3-methylene position would retard the rate of dimerization.

In this research, we like to report the results of a study of a series of t-butyl exo-methylene-substituted 2,3-dimethylene-2,3-dihydrofurans 7a, 7b, 7c and a thiophene analogue of 7a, 8 prepared from the FVP of their corresponding benzoates 9a-c and 10. Their behavior is consistent with our expectations and offers unambiguous evidence for the proposed two-step mechanism.

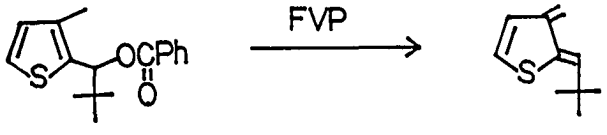


9 7

a. R_1 = t-Bu R_2 = H X = O

b. R_1 = H R_2 = t-Bu X = O

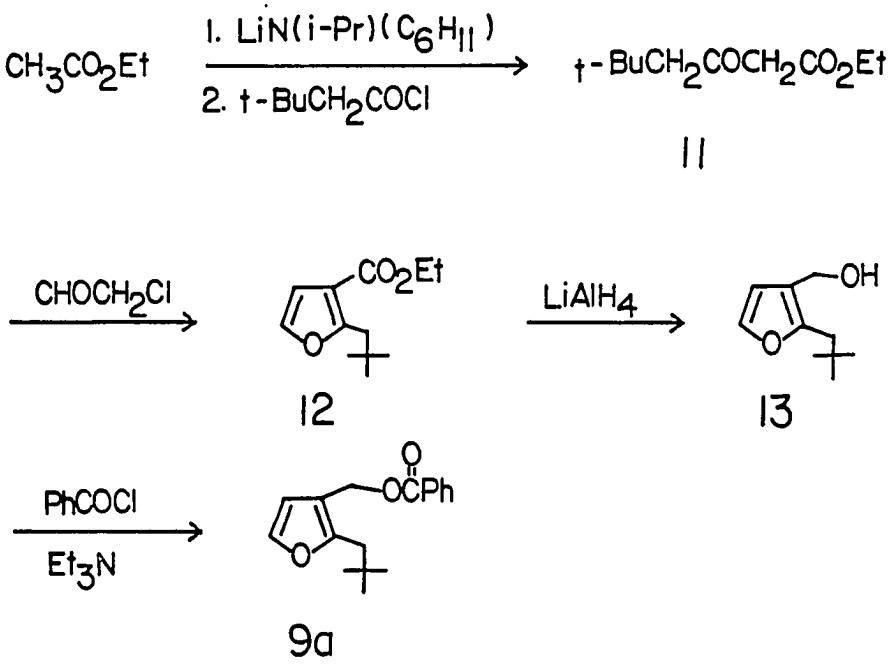
c. R_1 = t-Bu R_2 = t-Bu X = O



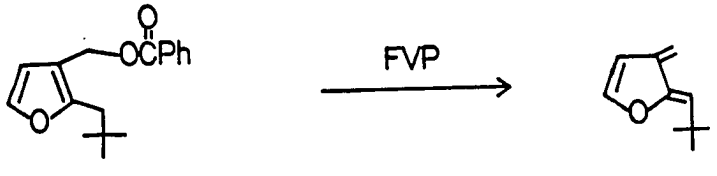
10 8

RESULTS

2-Neopentyl-3-furylmethyl benzoate (9a) was prepared by the cyclization of ethyl t-butylacetoacetate (11) and chloroacetaldehyde to give ethyl 2-neopentyl-3-furoate (12) followed by lithium aluminum hydride reduction and esterification of the resulting 2-neopentyl-3-furylmethyl alcohol (13) with benzoyl chloride. Ethyl t-butylaceto-acetate (11) was prepared by treating ethyl acetate with a base followed by the introduction of t-butylacetyl chloride.[12]



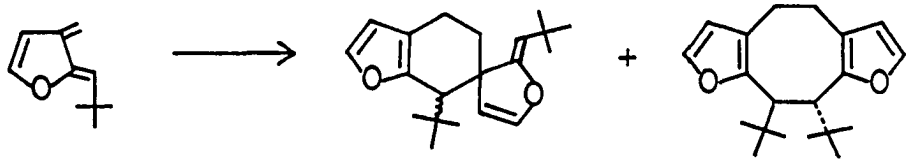
The flash vacuum pyrolysis of 9a was performed using the method previously reported at temperatures from 520-650°C and ca. 10^{-5} Torr.[13] A white band of the product was produced in the cold trap at -196°C. A 1 to 1 mixture of carbon disulfide and deuterochloroform was distilled into the trap through a side arm and the product mixture was allowed to warm slowly to -78°C. The proton NMR spectrum of the pyrolysate were recorded at -60°C (see Appendix, Figure 1) indicating the presence of 3-methylene-2-t-butyl-methylene-2,3-dihydrofuran (7a). Quantitative proton NMR analysis using dibromoethane as an internal standard indicated that the yield of 7a from the FVP of 9a was 50%. The spectrum also revealed that the monomer 7a exists as a single isomer, presumably the less crowded Z form.



9a 7a

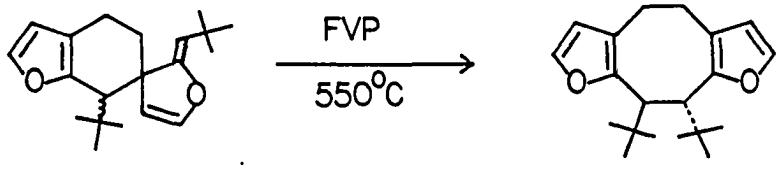
Upon warming to room temperature, 7a dimerized giving two stereoisomeric [4+2] dimers 14a and 14b in approximately equal amount in addition to a small amount of the head to head, [4+4] dimer 15.

A mixture of the [4+2] dimers and the [4+4] dimer was separated by column chromatography. The constitution of the [4+2] dimers was determined by a 2-D proton NMR spectrum (see Appendix, Figure 2) of the mixture and is consistent with the [4+2] dimer obtained from 2,3-dimethylene-2,3-dihydrothiophene (5).[13,14] The [4+4] dimer (15) (see Appendix, Figure 3) is presumed to be the trans isomer. The combined yield of the dimers 14a, 14b, and 15 from the pyrolysis of 9a was 40%.



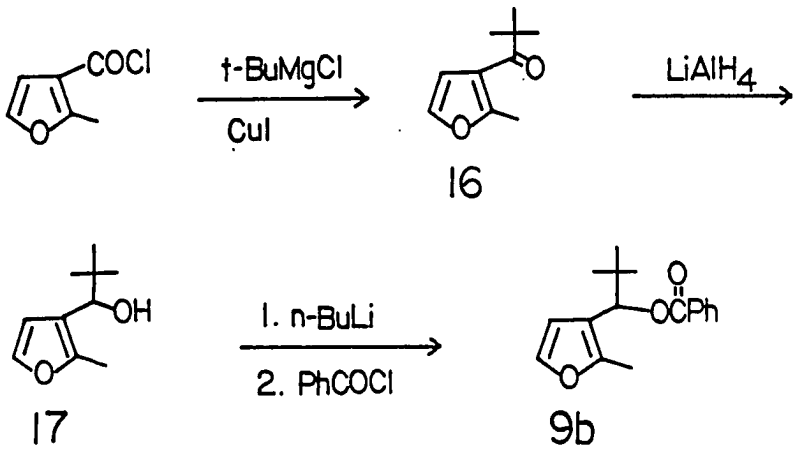
14a 14b 15

It is worth noting that when the mixture of the two [4+2] dimers 14a and 14b was pyrolyzed at 550°C, the major product was the more thermodynamically stable [4+4] dimer 15.

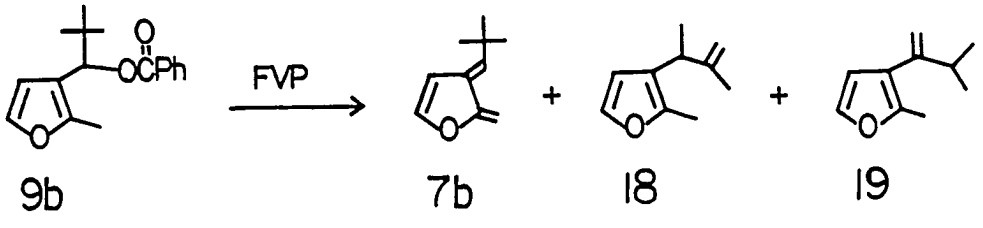


Measurement of the rate of disappearance of 7a (in 1:1 $CS_2/CDCl_3$ at -10°C) by low temperature proton NMR spectroscopy, using the method previously reported,[11] gave an average k = 1.6 x 10^{-3} L mol^{-1} sec^{-1} (see Appendix, Table I), which is comparable to that reported for the dimerization of 2,3-dimethylene-2,3-dihydrofuran (2) (1:1 $CS_2/CDCl_3$, -10°C, k = 2.7 x 10^{-3} L mol^{-1} sec^{-1}).[11]

2-Methyl-3-furyl(t-butyl)methyl benzoate (9b) was prepared by lithium aluminum hydride reduction of 2-methyl-3-furyl t-butyl ketone (16) to alcohol 17 which was then converted to the alkoxide with n-BuLi followed by esterification with benzoyl chloride. 2-methyl-3-furoyl t-butyl ketone (16) was prepared from the Grignard reaction of t-butylmagnesium chloride and 2-methyl-3-furyl chloride under the catalysis of copper iodide.[15,16]

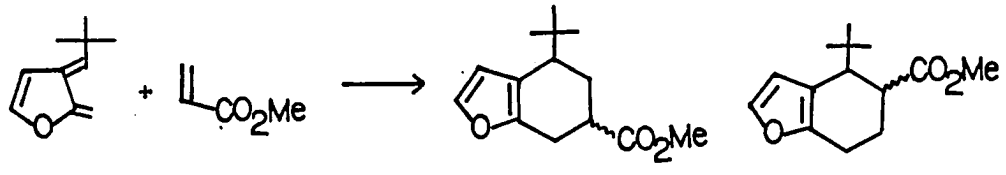


The flash vacuum pyrolysis of 9b was performed using the general method at temperatures from 460 to 510°C and ca. 10^{-5} Torr. The proton NMR spectrum (Appendix, Figure 4) of the pyrolysate showed that 2-methylene-3-t-butylmethylene-2,3-dihydrofuran (7b), presumably the less crowded E isomer as the major product (47%) along with the two isomeric minor products 18 and 19. Compound 7b was so unreactive that we were able to store it in solution for weeks in the refrigerator. Attempts to allow 7b to dimerize were undertaken by letting a solution of 7b in CS_2 (0.1M) stand at room temperature as well as at 35°C under N_2 until all the monomer was decomposed as indicated by GC analysis. In both cases no dimers were detected.

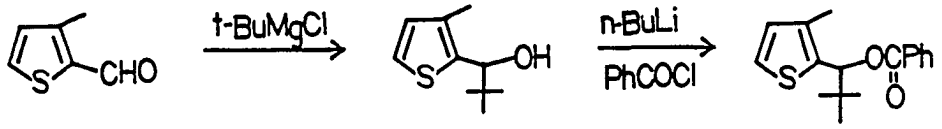


9b 7b 18 19

When a large excess of methyl acrylate was allowed to react with 7b, a mixture of four Diels-Alder adducts in a ratio of 5:3:1.5:1 were obtained. However, the spectrum of the mixture is too complex to assign the adducts individually.



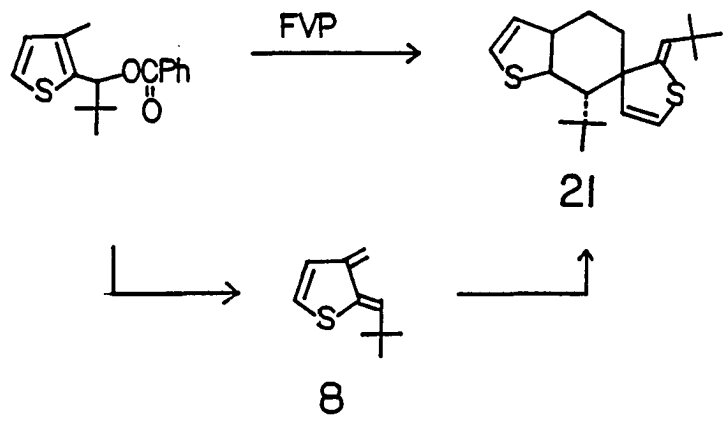
3-Methyl-2-thienyl(t-butyl)methyl benzoate (10) was prepared by the Grignard reaction of 3-methyl-2-thiophenecarboxaldehyde and t-butylmagnesium chloride to give 3-methyl-2-thienyl(t-butyl)methyl alcohol (20) which was converted to the alkoxide with n-BuLi followed by esterification with benzoyl chloride.



20 10

The FVP of 10 performed at 500-520°C afforded one single [4+2] dimer 21 as the major product accompanied by a substantial amount of polymer.

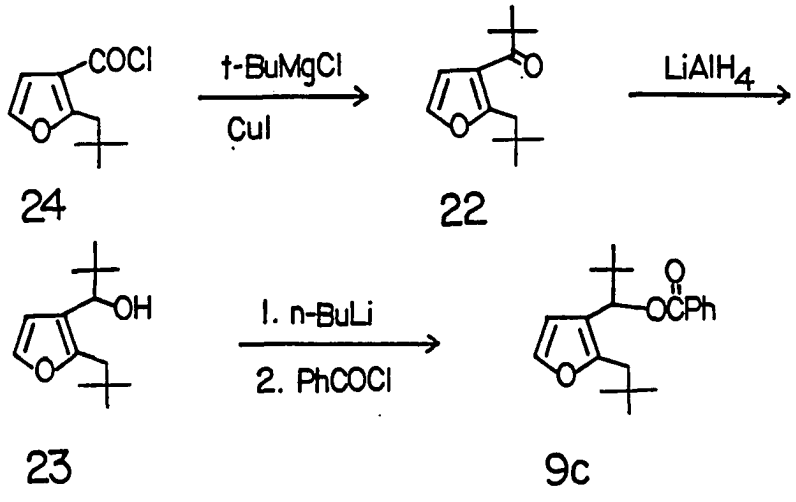
Purification of the crude pyrolysate by column chromatography on silica gel (hexane) gave 21 (^{1}H NMR spectrum see Appendix, Figure 5) in 25.8% yield.



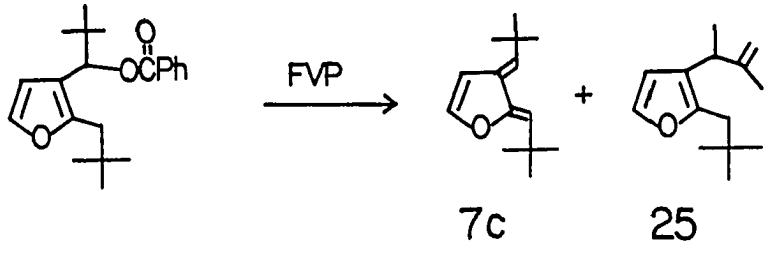
Evidently, dimer 21 was the result of the dimerization of 8 upon warming. In an attempt to observe 8 spectroscopically, a proton NMR spectrum of the crude pyrolysate was recorded at -65°C; signals for dimer and polymers dominated the spectrum. No evidence for the presence of monomer 8 at that temperature was detected.

2-Neopentyl-3-furyl(t-butyl)methyl benzoate (9c) was prepared by lithium aluminum hydride reduction of 2-neopentyl-3-furyl t-butyl ketone (22) to alcohol 23 which was then converted to its alkoxide with n-BuLi followed by esterification with benzoyl chloride.

Ketone 22 was prepared by the reaction of 2-neopentyl-3-furyl chloride (24) with t-butylmagnesium chloride catalyzed by copper iodide.[15,16]

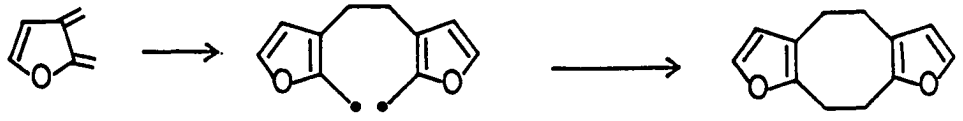


The flash vacuum pyrolysis of 9c was performed under the normal condition at 530°C. GCMS and proton NMR spectrum (see Appendix, Figure 6) of the pyrolysate showed that 2,3-di-t-butylmethylene-2,3-dihydrofuran (7c) was the major product along with the rearranged side product 25 in a 2 to 1 ratio. Compound 7c was found not surprisingly to be even less reactive than 2-methylene-3-t-butylmethylene-2,3-dihydrofuran (17b).



DISCUSSION

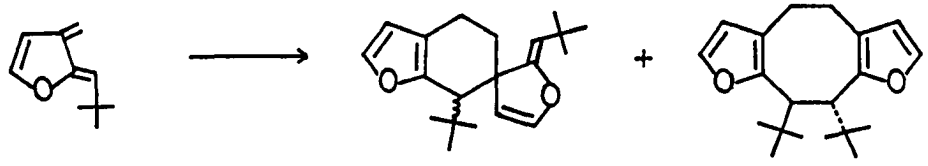
A recent kinetic study of the dimerization of 2,3-dimethylene-2,3-dihydrofuran (2) based on deuterium isotope effects[17] has supported a stepwise mechanism involving 6 as an intermediate.[11] In this mechanism, only the 3-methylene is directly involved in the rate determining step to form 6, but the 2-methylene is involved in the product formation step.



2 6

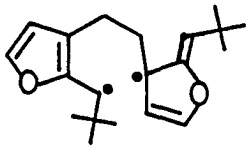
Thus we expected that a t-butyl group on the 2-methylene position would not affect the rate of dimerization but could affect the type of products formed and we expected that a t-butyl group on the 3-methylene position would retard the rate of dimerization.

The dimerization of 7a gave two stereoisomeric [4+2] dimers 14a and 14b in addition to the head to head, [4+4] dimer 15.



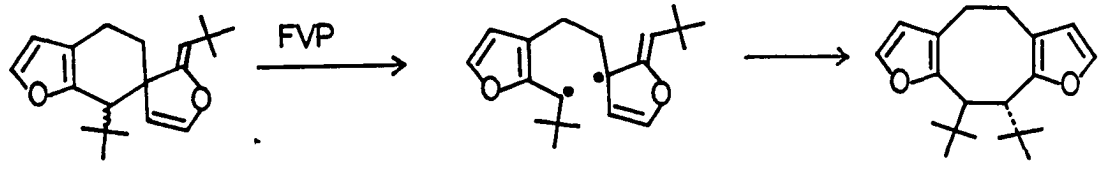
14a 14b 15

This observation is consistent with the two-step mechanism proposed for the dimerization of 2,3-dimethylene-2,3-dihydrofuran (2). Compounds 14a, 14b and 15 can be assumed to originate from the same diradical intermediate 26. The bulky t-butyl groups retard the rate of formation of the [4+4] dimer and consequently the [4+2] dimerization becomes competitive.



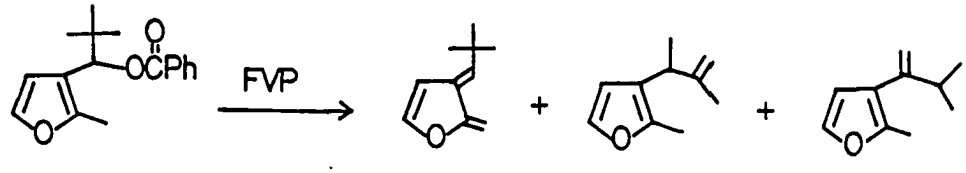
26

Further support of the constitution of the [4+2] dimers was obtained by pyrolyzing a mixture of these dimers; the major product was the more thermodynamically stable [4+4] dimer, formed, evidently, via diradical 26.



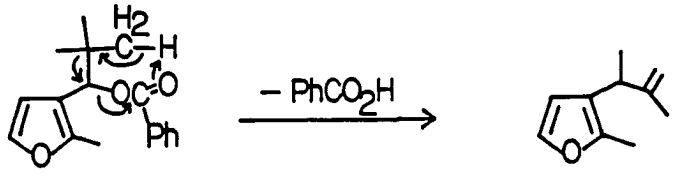
The behavior of 7b was also found to be consistent with the proposed two-step mechanism.[11] The bulky t-butyl group would be expected to significantly retard the rate of dimerization of 7b and indeed, it is stable at room temperature.

In addition to 7b, the FVP of 9b also gave rise to two minor isomers, 18 and 19.



9b 7b 18 19

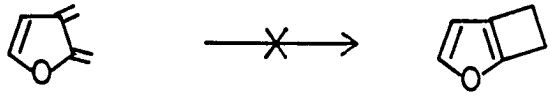
The formation of 18 can be rationalized as the result of a seven-membered cyclic transition state, in which breaking of a C-H bond is synchronous with the migration of C-C bond electrons, and separation of the leaving group, benzoic acid. An excellent precedent for this kind of pyrolytic rearrangement is the formation of camphene (27) from the pyrolysis of isobornyl benzoate 28.[18] At this time it is not clear how 19 is formed.



18

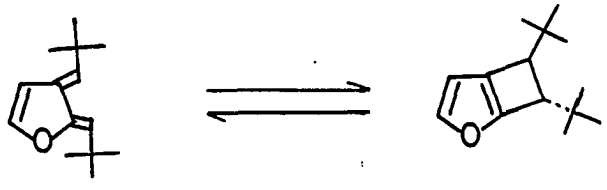
28 27

For all the furan monomers we have studied so far, the open form 2 is always favored over the closed form 29 in contrast to the benzene system.



29

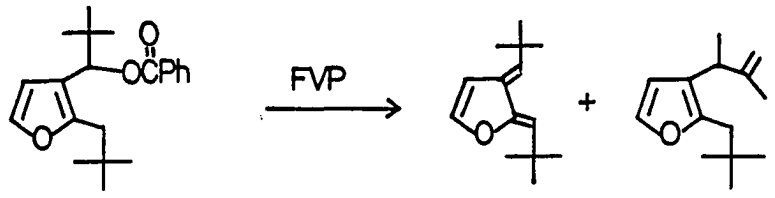
Apparently the resonance energy of the furan ring in 29 is insufficient to compensate for the strain energy of the four membered ring. If we introduce t-butyl groups on both methylenes, as in 2,3-di-t-butylmethylene-2,3-dihy- drofuran (7c), the steric interference between each bulky t-butyl group and the ring might reduce the energy difference between the open form and the closed form to shift the equilibrium toward the closed form.



7c

In the case of o-xylylene (1), bulky substitution favoring ring closure due to non-planar configuration has been reported.[19,20]

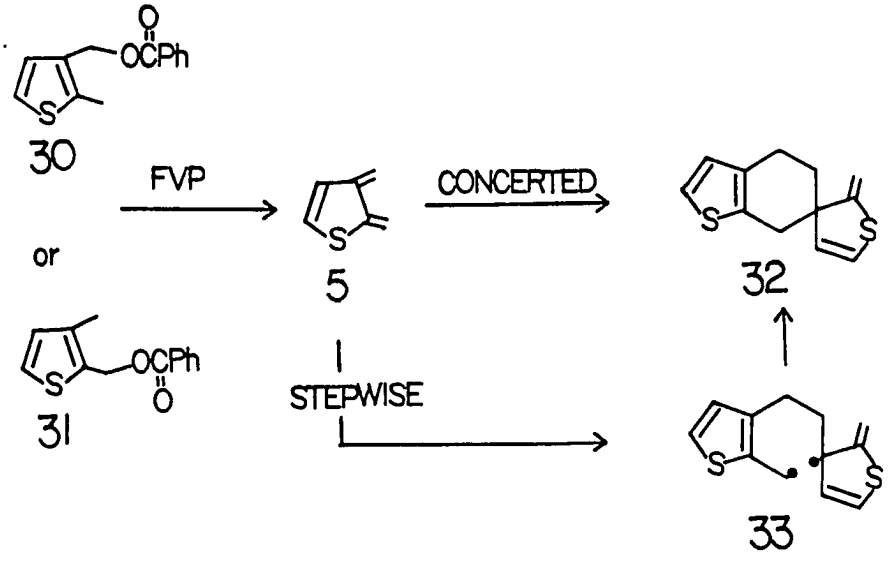
When 2-neopentyl-3-furyl(t-butyl)methyl benzoate (9c) was prepared and pyrolyzed, it gave again the open form 2,3-di-t-butylmethylene-2,3-dihydrofuran (7c) as the major product along with the rearranged product 25 in a 2 to 1 ratio. Molecule 7c is, not surprisingly, even less reactive than 2-methylene-3-t-butylmethylene-2,3-dihydrofuran (7b).



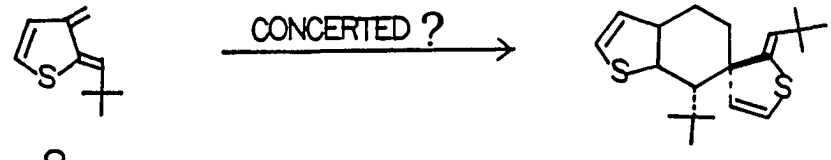
7c 25

We believe that 2-methylene-3-t-butylmethylene-2,3-dihydrofuran (7b) and 7c are the most unreactive o-quinodimethanes reported to date; they are the ideal model systems for further studies of the chemistry of o-quinodimethanes.

A previous study by the author on the FVP of benzoates 30 and 31 has established that the primary product is the [4+2] dimer 32 of the unisolated thiophene monomer 5.[10]



The dimerization of 5 can be rationalized by a stepwise mechanism involving diradical intermediate 33, or alternatively, a concerted [4+2] cycloaddition of two monomers which leads directly to the [4+2] dimer. Since stereospecificity is the logical result of a concerted cycloaddition, 3-methyl-2-thienyl(t-butyl)methyl benzoate (10) was prepared and pyrolyzed. A single isomeric [4+2] dimer 21 (its stereochemistry is assumed via a model study) with the same constitution as 32 was the major product. This result suggests that the dimerization of 8 is a concerted process. Also, no closed form of the monomer was detected. Apparently, the resonance energy of thiophene is still insufficient to compensate for the strain energy of the four-membered ring.



8 21

EXPERIMENTAL

Methods and Equipment

The pyrolysis apparatus has been previously described,[13] and its detailed diagram is presented in the Appendix, Figure 7. ^{1}H and ^{13}C NMR spectra were recorded on JOEL FX-90Q or Nicolet-300 spectrometers. Chemical shifts are recorded in parts per million (δ) from tetramethylsilane (TMS). High resolution mass spectra were measured with an Associated Electronics Industries MS-902 instrument. Gas chromatograph/mass spectroscopy (GC/MS) was performed with a Finnigan 4000 instrument and an INCOS data system. GLC analyses were performed with a Hewlett Packard HP 5840A instrument.

2-Neopentyl-3-furylmethyl Benzoate (9)

A solution of 3.1 g (35 mmole) of ethyl acetate in 4 mL of THF was added dropwise to a stirred solution containing 70 mmole of lithium N-isopropylcyclohexylamide in 60 mL of THF at -78°C. The mixture was allowed to stir for 10 min, followed by the addition of 4.7 g (35 mmole) of t-butyl-acetyl chloride. After stirring for an additional 20 min, 15 mL of 20% HCL was added to quench the reaction. After the mixture reached room temperature the layers were separated. The aqueous layer was extracted with ether (2 x

10ml). The combined organic layers was washed with $NaHCO_3$ and brine. After drying ($MgSO_4$) and removal of the solvent, 5.5 g (30 mmole, 85.7%) of ethyl t-butylacetoacetate (11) was recovered: ^1H NMR ($CDCl_3$) δ 4.15 (q, J = 7.5 Hz, 2H), 3.38 (s, 2H), 2.40 (s, 2H), 1.25 (t, J = 7.5 Hz, 3H), 1.10 (s, 9H).

A quantity of 5.4 g (29 mmole) of ethyl t-butylacetoacetate (11) was converted using the procedure previously described[9] for the synthesis of ethyl 2-methyl-3-furoate to yield 3.3 g (15.7 mmole, 54%) of ethyl 2-neopentyl-3-furoate (12): bp 45-7°C (0.3 mm); IR (thin film) 1720, 1360, 1305, 1275, 1150 cm-1; ^1H NMR ($CDCl_3$) δ 7.20 (d, J = 2 Hz, 1H), 6.61 (d, J = 2 Hz, 1H), 4.20 (q, J = 8.0 Hz, 2H), 2.82 (s, 2H), 1.38 (t, J = 8.0 Hz, 3H), 1.02 (s, 9H).

A solution of 3.0 g (14.3 mmole) of ethyl 2-neopentyl-3-furoate (12) in 10 mL of ether was reduced with $LiAlH_4$ using the procedure described[9] previously for the synthesis of 2-methyl-3-furylmethyl alcohol to give 2.3 g (13.7 mmole, 96%) of 2-neopentyl-3-furylmethyl alcohol (13): ^1H NMR ($CDCl_3$) δ 7.35 (d, J = 2 Hz, 1H), 6.40 (d, J = 2 Hz, 1H), 4.48 (s, 2H), 2.52 (s, 2H), 1.68 (br, 1H), 0.95 (s, 9H). A solution of 2.3 g (13.7 mmole) of 2-neopentyl-3-furylmethyl alcohol (13) and 2.1 g (20.5 mmole) of triethylamine in 40 mL of ether was esterified with benzoyl chloride

using the procedure previously described[9] for the synthesis of 2-methyl-3-furylmethyl benzoate to yield 3.3 g (12.1 mmole, 88%) of 9a: IR (thin film) 1720, 1460, 1365, 1268, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15-7.88 (m, 2H), 7.56-7.32 (m, 3H), 7.28 (d, J = 2 Hz, 1H), 6.38 (d, J = 2 Hz, 1H), 5.18 (s, 2H), 2.58 (s, 2H), 0.99 (s, 9H); high resolution mass spectrum, calcd for $C_{17}H_{20}O_3$ 272.14125, measured 272.14131.

2-Methyl-3-furyl(t-butyl)methyl Benzoate (9b)

A mixture of 50 g (0.36 mole) of methyl 2-methyl furoate in 200 mL of 20% sodium hydroxide was allowed to reflux for 2 h. After the mixture had reached room temperature, it was acidified with 100 mL of concentrated HCl with rapid stirring. A white solid formed which was collected by suction filtration. The solid was dried under vacuum to give 43 g (0.34 mole, 95%) of 2-methyl-3-furoic acid: mp 95-97°C; ^1H NMR ($CDCl_3$) δ 11.52 (br, 1H), 2.30 (d, J = 2 Hz, 1H), 6.71 (d, J = 2 Hz, 1H), 2.62 (s, 3H). A 10.6 g (84 mmole) quantity of 2-methyl-3-furoic acid was added to 49.0 g (410 mmole) of thionyl chloride and the mixture was stirred at 40°C for 24 h. The excess thionyl chloride was removed by simple distillation and the remaining dark oil was distilled under reduced pressure (65-67°C, 20 mm) to yield 10.6 g (73 mmole, 87.3%) of 2-methyl-3-furoyl chloride: IR (thin film) 1760, 1560, 1525, 1270 1210 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 2 Hz, 1H), 6.70 (d, J = 2 Hz, 1H), 2.51 (s, 3H). A quantity of 34.5 mL of t-butylmagnesium chloride (69 mmole, 2M in ether) was added dropwise to a suspension of 9.0 g (62 mmole) of 2-methyl-3-furyl chloride and 17.7 g (93 mmole) of copper iodide in 80 mL of ether at -78°C. The stirring mixture was allowed to reach room temperature overnight. The resulting green suspension was poured into 50 mL of ice-cooled 2N HCl. The layers were separated and the organic layer was washed with 2N HCl, $NaHCO_3$ and brine. After the organic layer was dried and concentrated, 8.5 g (51 mmole, 82.5%) of 2-methyl-3-furyl t-butyl ketone (16) was recovered: ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 2 Hz, 1H), 6.78 (d, J = 2 Hz, 1H), 2.52 (s, 3H), 1.27 (s, 9H).

An 8.5 g (51 mmole) quantity of 2-methyl-3-furyl t-butyl ketone (16) was reduced with $LiAlH_4$ using the procedure described previously[9] to give 7.7 g (46 mmole, 90.2%) of 2-methyl-3-furylmethyl(t-butyl) alcohol (17): IR (thin film) 3400 (br), 1625, 1510, 1425, 1150, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 2 Hz, 1H), 6.43 (d, J = 2 Hz, 1H), 4.35 (br, 1H), 2.28 (s, 3H), 1.85 (br, 1H), 0.95 (s, 9H). To a solution of 4.0 g (24 mmole) of the alcohol in 80 mL of dry THF ($LiAlH_4$), 12.5 mL of n-BuLi (2 M in hexane) was added via a syringe at 0°C. The mixture was stirred for 10

min and 3.7 g (26 mmole) of benzoyl chloride was added dropwise. The resulting red mixture was allowed to sit overnight at room temperature. After the addition of 50 mL of water, the aqueous layer was extracted with ether (50 mL x 2) and the combined organic layers was washed with water, $NaHCO_3$ and brine. Drying ($MgSO_4$) and removal of the solvent followed by purification with column chromatography on silica gel (5% ether in hexane) gave 4.1 g (15 mmole, 62.5%) of 9b: IR (thin film) 1710, 1309, 1260, 1095, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12-7.90 (m, 2H), 7.57-7.35 (m, 3H), 7.21 (d, J = 2 Hz, 1H), 6.32 (d, J = 2 Hz, 1H), 5.76 (s, 1H), 2.37 (s, 3H), 1.08 (s, 9H); high resolution mass spectrum, calcd for $C_{17}H_{20}O_3$ 272.14125, measured 272.14089.

3-Methyl-2-thenyl(t-butyl)methyl Benzoate (10)

A solution of 5.0 g (40 mmole) of 3-methyl-2-thiophenecarboxaldehyde in 30 mL of ether was added dropwise to 22 mL of t-BuMgCl (2 M in ether) with rapid stirring at 0°C. The suspension after being stirred at room temperature overnight was poured into a mixture of 40 mL of 10% HCl and 50 g of ice. The aqueous layer was extracted with ether (25 mL x 2). The combined organic layers was washed with water, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give 6.4 g (34,8 mmole, 86.9%) of 3-methyl-2-thienyl(t-butyl)-methyl alcohol: ^1H NMR ($CDCl_3$) δ 7.12 (d, J = 6 Hz, 1H),

6.70 (d, J = 6 Hz, 1H), 4.68 (s, 1H), 2.18 (s, 3H), 0.98 (s, 9H), 1.16 (br, 1H). Without further purification, a quantity of 4.1 g (2.2 mmole) of the alcohol was esterified with n-BuLi and benzoyl chloride using the procedure described for the synthesis of 2-methyl-3-furyl(t-butyl)-methyl benzoate (9b) to give 2.3 g (8.0 mmole, 36.4% of 3-methyl-2-thienyl(t-butyl)methyl benzoate (10): IR (thin film); ^{1}H NMR ($CDCl_3$) δ 8.20-8.05 (m, 2H), 7.52-7.36 (m, 3H), 7.10 (d, J = 6 Hz, 1H), 6.77 (d, J = 6 Hz, 1H), 6.11 (s, 1H), 2.34 (s, 3H), 1.10 (s, 9H); high resolution mass spectrum, calcd for $C_{17}H_{20}O_2S$ 288.11841, measured 288.11865.

2-Neopentyl-3-furyl(t-butyl)methyl Benzoate (9c)

A quantity of 1.8 g (8.6 mmole) of ethyl 2-neopentyl-3-furoate (12) was converted to 0.8 g (3.6 mmole, 41.9%) of 2-neopentyl-3-furyl t-butyl ketone (22) using the multi-step synthesis previously described for the synthesis of 2-methyl—3-furyl t-butyl ketone (16). For 22: ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 2 Hz, 1H), 6.48 (d, J = 2 Hz, 1H), 3.08 (s, 2H), 1.48 (s, 9H), 1.12 (s, 9H).

A 0.8 g (3.6 mmole) quantity of 2-neopentyl-3-furyl t-butyl ketone (22) was reduced with $LiAlH_4$, using the procedure described for the synthesis of 2-methyl-3-furyl-(t-butyl)methyl alcohol (17) to give 0.65 g (2.9 mmole,

80.6%) of 2-neopentyl-3-furyl(t-butyl)methyl alcohol (23): ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 2 Hz, 1H), 6.38 (d, J = 2 Hz, 1H), 4.31 (s, 1H), 2.48 (s, 2H), 1.52 (br, 1H), 1.00 (s, 9H), 0.96 (s, 9H). A 0.62 g (2.8 mmole) quantity of the alcohol was esterified with n-BuLi and benzoyl chloride using the procedure previously described for the synthesis of 2-methyl-3-furyl(t-butyl)methyl benzoate (9b) to give 0.7 g (2.1 mmole, 75.0%) of 9c: IR (thin film); ^{1}H NMR ($CDCl_3$)δ 8.35-8.10 (m, 2H), 7.64-7.46 (m, 3H), 7.32 (d, J = 2 Hz, 1H), 6.47 (d, J = 2 Hz, 1H), 5.80 (s, 1H), 2.72 (s, 1H), 1.10 (s, 9H), 1.02 (s, 9H); high resolution mass spectrum, calcd for $C_{21}H_{28}O_3$ 328.20385, measured 328.20353.

General Pyrolysis Procedure

The pyrolyses were run at furnace temperatures from 400 to 800°C. The sample chamber was heated to 60-70°C and the system was evacuated to ca. 10^{-5} Torr during the pyrolysis. A condenser cooled to ca. -20°C was inserted between the quartz pyrolysis tube and the liquid nitrogen-cooled trap to collect the unreacted starting material and the benzoic acid formed as a byproduct. The liquid nitrogen-cooled trap was used to collect the products. Upon completion of the pyrolysis, the trap was warmed to -78°C and carbon disulfide or deuterochloroform was distilled into the trap through the

side arm. Also added was a known amount of dibromoethane as an internal standard for quantitative studies.

Pyrolysis of 2-Neopentyl-3-furylmethyl Benzoate (9a)

Pyrolyses were performed with ca. 0.2 g of 9a at 520, 580, and 650°C using the general procedure. The pyrolysate was collected in 3 mL of 1:1 $CS_2/CDCl_3$ from the trap and ^1H NMR spectrum of the product 3-methylene-2-t-butylmethylene-2,3-dihydrofuran (7a) was recorded at -60°C: ^1H NMR ($CDCl_3/CS_2$ 1:1, -60°C) (see Appendix, Figure 1) δ 6.77 (br, 1H), 5.75 (d, J = 3 Hz, 1H), 5.25 (s, 1H), 4.96 (d, J = 1 Hz, 1H), 4.74 (d, J = 1 Hz, 1H), 1.15 (s, 9H). Upon warming, 16 slowly dimerized to give mostly two stereoisomeric [4+2] dimers 14a and 14b (ca. 1:1) in addition to a small amount (5%) of a [4+4] dimer 15. The rate of disappearance of 7a was measured with low temperature proton NMR spectroscop at -10°C using the procedure previously described[11] to give an average of 1.6×10^{-3} L mol^{-1} sec^{-1} (see Appendix, Table I). The mixture of 14a and 14b was purified by column chromatography (silica gel, hexane). Their ^1H NMR signals (see Appendix, Figure 2) were partially separated by a COZY 2-D ^1H NMR analysis. For 14a: ^1H NMR ($CDCl_3$) δ 7.22 (br, 1H), 6.39 (d, J = 3 Hz, 1H), 6.10 (br, 1H), 5.25 (d, J = 3 Hz, 1H), 4.21 (s, 1H), 2.85-2.65 (m, 1H), 2.75 (s, 1H), 2.25-2.12 (m, 1H),

1.83-1.52 (m, 2H), 1.06 (s, 9H), 0.97 (s, 9H); GC/MS (70eV) m/e (% base peak) 300.02 (16.25), 243.96 (10.26), 242.94 (43.00), 200 (11.42), 186.94 (25.04), 172.90 (25.67), 150.96 (11.05), 149.96 (67.45), 148.98 (31.70), 134.92 (61.47), 90.88 (39.33), 56.98 (100.00). For 14b: ^{1}H NMR ($CDCl_3$) δ 7.22 (br, 1H), 6.47 (d, J = 3 Hz, 1H), 6.10 (br. 1H), 5.02 (d, J = 3 Hz, 1H), 4.27 (s, 1H), 2.63 (s, 1H), 2.45-2-38 (m, 1H), 2.25-2.12 (m, 1H), 1.83-1.52 (m, 2H), 1.05 (s, 9H), 1.03 (s, 9H); GC/MS (70eV) m/e (% base peak) 300.02 (23.79), 256.98 (11.16), 243.98 (11.18), 242.94 (48.66), 200.96 (13.75), 186.94 (19.34), 172.92 (12.79), 150.98 (16.03), 149.98 (94.10), 148.98 (45.97), 135.98 (10.62), 134.92 (100.00), 120.96 (19.01), 90.88 (41.14), 46.96 (80.59). Quantitative ^{1}H NMR analysis using dibromoethane as a standard indicated that the pyrolysis of 9a gave 7a in 50% yield and the conversion of 7a to dimers 14a, 14b, and 15 was about 90%.

Pyrolysis of dimers 14a and 14b

A quantity of 50 mg (0.17 mmole) of the mixture of dimers 14a and 14b was pyrolyzed at 550^{o}C in the normal manner except without the condenser. GC and ^{1}H NMR analyses of the pyrolysate showed that the [4+4] dimer (15) was the major product. The crude product was purified by column chromatography (silica gel, hexane) to give 32 mg (0.11

mmole, 62.7%) of 15: ^{1}H NMR ($CDCl_3$) (see Appendix, Figure 3) δ 7.20 (d, J = 1.5 Hz, 1H), 6.15 (d, J = 1.5 Hz, 1H), 3.14 (s, 2H), 2.86 (m, 2H), 2.54 (m, 2H), 0.87 (s, 18H); GC/MS (70 eV) m/e (% base peak) 300.02 (3.13), 242.94 (12.76), 187.94 (7.03), 186.92 (31.79) 172.88 (12.56), 114.90 (3.36). 57.06 (100.00); ^{13}C NMR ($CDCl_3$) δ 153.03, 137.95, 120.22, 115,78, 50.89, 37.60, 29.61, 27.34.

Pyrolysis of 2-Methyl-3-furyl(t-butyl)methyl Benzoate (19b)

A quantity of 300 mg (1.1 mmole) of 9b was pyrolyzed at 510^{o}C under the normal conditions. GC and ^{1}H NMR analyses of the crude pyrolysate at room temperature indicated that the monomer 2-methylene-3-t-butylmethlene-2,3-dihydrofuran (7b) was the major product (85%) along with ca. 15% of two monomeric byproducts 18 and 19. Compound 7b: ^{1}H NMR ($CDCl_3$) δ 6.77 (m, 1H), 6.06 (d, J = 2.7 Hz, 1H), 5.81 (s, 1H), 4.68 (d, J = 2 Hz, 1H), 4.52 (d, J = 2 Hz, 1H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 160.89, 147.92, 130.44, 129.54, 104.86, 81.34, 33.68, 30.73; UV ($CHCl_3$) λmax 318 nm, ϵmax = 2500. A mixture of 18 and 19 was purified by column chromatography (silica gel, hexane). Assignment of their structures was based on the analysis of the ^{1}H NMR spectrum of this mixture. Compound 18: ^{1}H NMR ($CDCl_3$) (see Appendix, Figure 8) δ 7.23 (d, J = 1.8 Hz, 1H), 6.20 (d, J = 1.8 Hz, 1H), 4.80 (d, J = 0.9 Hz, 1H), 4.76 (d, J = 0.9 Hz,

1H), 3.25 (q, J = 7.2 Hz, 1H), 2.24 (s, 3H), 1.66 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H); GC/MS (70 eV) m/e (% base peak) 140.06 (100.00), 135.06 (58.03), 121.06 (19.00), 109.08 (54.36), 107.12 (24.45), 105.10 (13.49), 91.04 (34.90), 81.04 (13.52), 79.04 (28.48), 53.04 (14.54). Compound 19: ^{1}H NMR ($CDCl_3$) (see Appendix, Figure 8) δ 7.25 (d, J = 1.8 Hz, 1H), 6.30 (d, J = 1.8 Hz, 1H), 5.07 (d, J = 1.5 Hz, 1H), 4.90 (d, J = 1.5 Hz, 1H), 2.57 (m, J - 6.6 Hz, 1H), 2.34 (s, 3H), 1.08 (d, J = 6.6 Hz, 6H); GC/MS (70 eV) m/e (% base peak) 150.08 (100.00), 135.06 (32.67), 121.06 (24.44), 107.12 (30.37), 105.10 (20.74), 91.04 (35.15), 79.06 (24.41), 53.04 (12.69). Quantitative ^{1}H NMR analysis using dibromomethane as a standard indicated that the pyrolysis of 9b gave 7b in 43 % yield.

Diels-Alder Reaction of 7b with Methyl Acrylate

A 300 mg (1.1 mmole) quantity of 9b was pyrolyzed at 510°C. Upon completion of the pyrolysis, 10 mL of methyl acrylate was slowly distilled into the trap via the side arm. The pyrolysate was allowed to warm to room temperature. GCMS of the crude mixture indicated the presence of four adducts in a 5:3:1.5:1 ratio. The mixture was purified by column chromatography (silica gel, 5% ether in hexane) to give 92 mg (0.39 mmole; 71%) of four Diels-Alder adducts: IR (thin film) 1735, 1636, 1556, 1170,

900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 1H), 6.30 (m, 1H), 3.78 (s, 0.86H), 3.69 (s, 0.28H), 3,67 (s, 0.43H), 3,65 (s, 1.43H), 3.10-2.00 (m, 6H), 0.96 (s, 9H).

Pyrolysis of 3-Methyl-2-thenyl(t-butyl)methyl Benzoate (10)

A quantity of 100 mg (0.34 mmole) of 10 was pyrolyzed at 500°C in the normal manner. The pyrolysate was collected in CS_2 and concentrated. GC and ^1H NMR analyses of the crude product mixture showed that a single [4+2] dimer 21 was the major product. Purification by column chromatography on silica gel (hexane) yielded 15.0 mg (0.045 mmole, 25.8%) of the [4+2] dimer (21): ^1H NMR ($CDCl_3$) (see Appendix, Figure 5) δ 7.07 (d, J = 5 Hz, 1H), 6.68 (m, 1H), 3.12 (s, 1H), 3.02-2.85 (m, 1H), 2.55-2.42 (m, 1H), 1.83-1.60 (m, 2H), 1.16 (s, 9H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.82, 136.76, 136.70, 136.40 133.27, 126.55, 122.68, 118.27, 61.28, 54.45, 37.24, 24.95, 33.32, 31.51, 29.54, 20.70.

Pyrolysis of 2-Neopentyl-3-furyl(t-butyl)methyl Benzoate (9c)

A quantity of 200 mg (0.61 mmole) of 9c was pyrolyzed at 530°C in the normal fashion. GCMS and ^1H NMR of the pyrolysate indicated that 2,3-di-t-butylmethylene-2,3-dihydrofuran (7c) as the major product along with a rearranged monomeric compound 25 in a 2 to 1 ratio. The combined yield

using dibromomethane as an internal standard was calculated to be 41%. The two compounds were not separated. Their ^1H NMR signals were distinguished and assigned individually (see Appendix, Figure 6). For 7c: ^1H NMR ($CDCl_3$) δ 6.75 (m, 1H), 6.08 (d, J = 2.6 Hz, 1H), 5.61 (s, 1H), 5.12 (s, 1H), 1.17 (s, 9H), 1.15 (s, 9h); GC/MS (70 eV) m/e (% base peak) 206.00 (36.37), 191.00 (19.56), 163.00 (11.24), 150.00 (24.16), 149.00 (100.00), 135.00 (19.56), 126.00 (25.13), 121.00 (21.15), 107.00 (13.36), 91.00 (18.67), 69.00 (11.50), 57.00 (29.03). For 25: ^1H NMR ($CDCl_3$) δ 7.22 (m, 1H), 6.17 (d, J = 2 Hz, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 3.22 (q, J = 7.1 Hz, 1H), 2.45 (s, 2H), 1.62 (s, 3H), 1.35 (d, J = 7.1 Hz, 3H), 1.03 (s, 9H); GC/MS (70 eV) m/e (relative intensity) 206.10 (46.24), 191.10 (12.51), 150.08 (62.73), 149.08 (100.00), 135.06 (41.23), 131.08 (17.12), 121.06 (24.61), 107.06 (22.70), 105.08 (16.73), 93.08 (15.08), 91.06 (24.71), 79.06 (16.78), 77.04 (14.46), 57.08 (72.65).

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APPENDIX

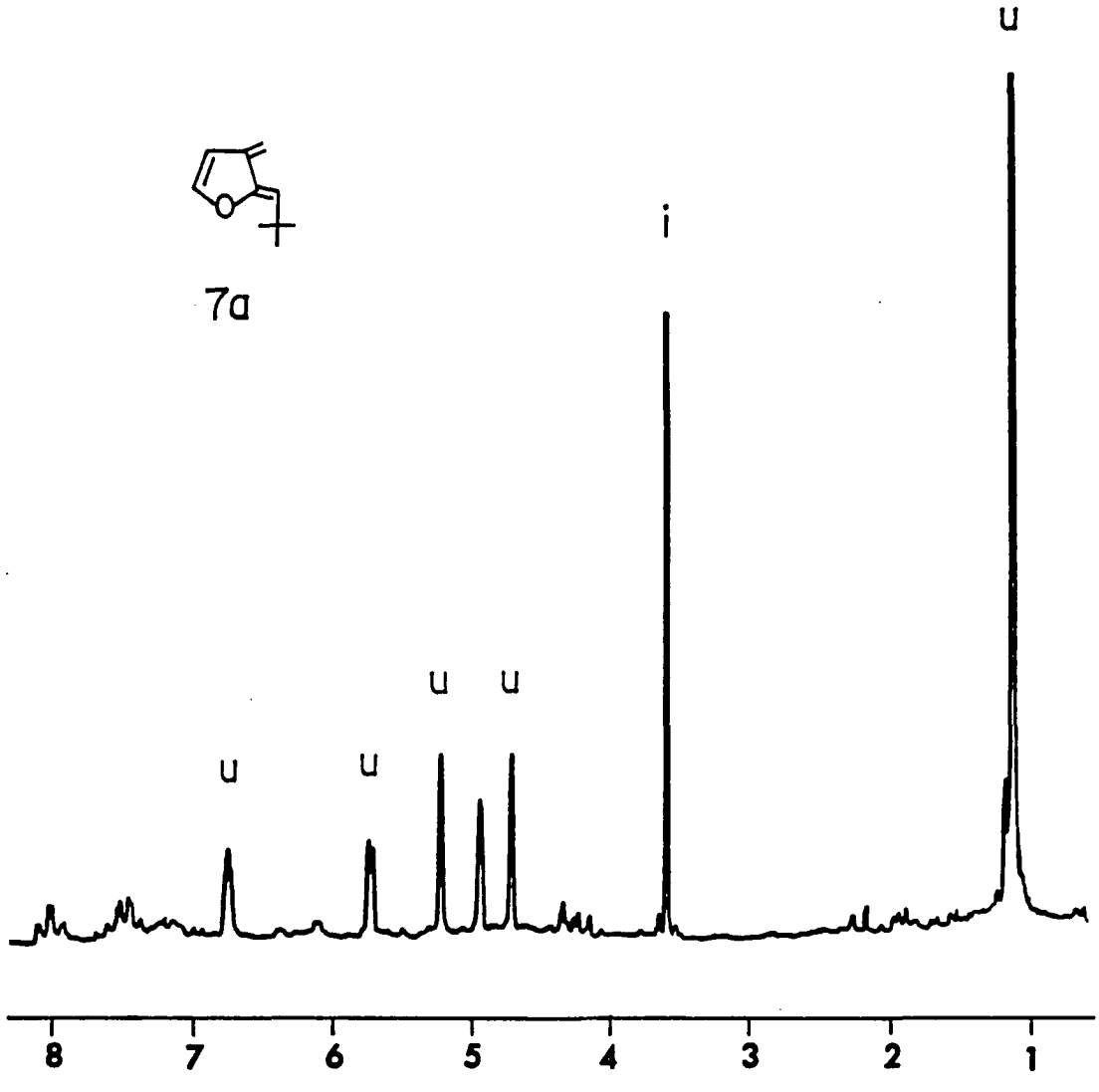


Figure 1. Proton NMR spectrum of 3-methylene-2-t-butylmethylene-2,3-dihydrofuran (7a) recorded at -60°C in 1:1 $CS_2/CDCl_3$ (u = 7a, i = dibromoethane)

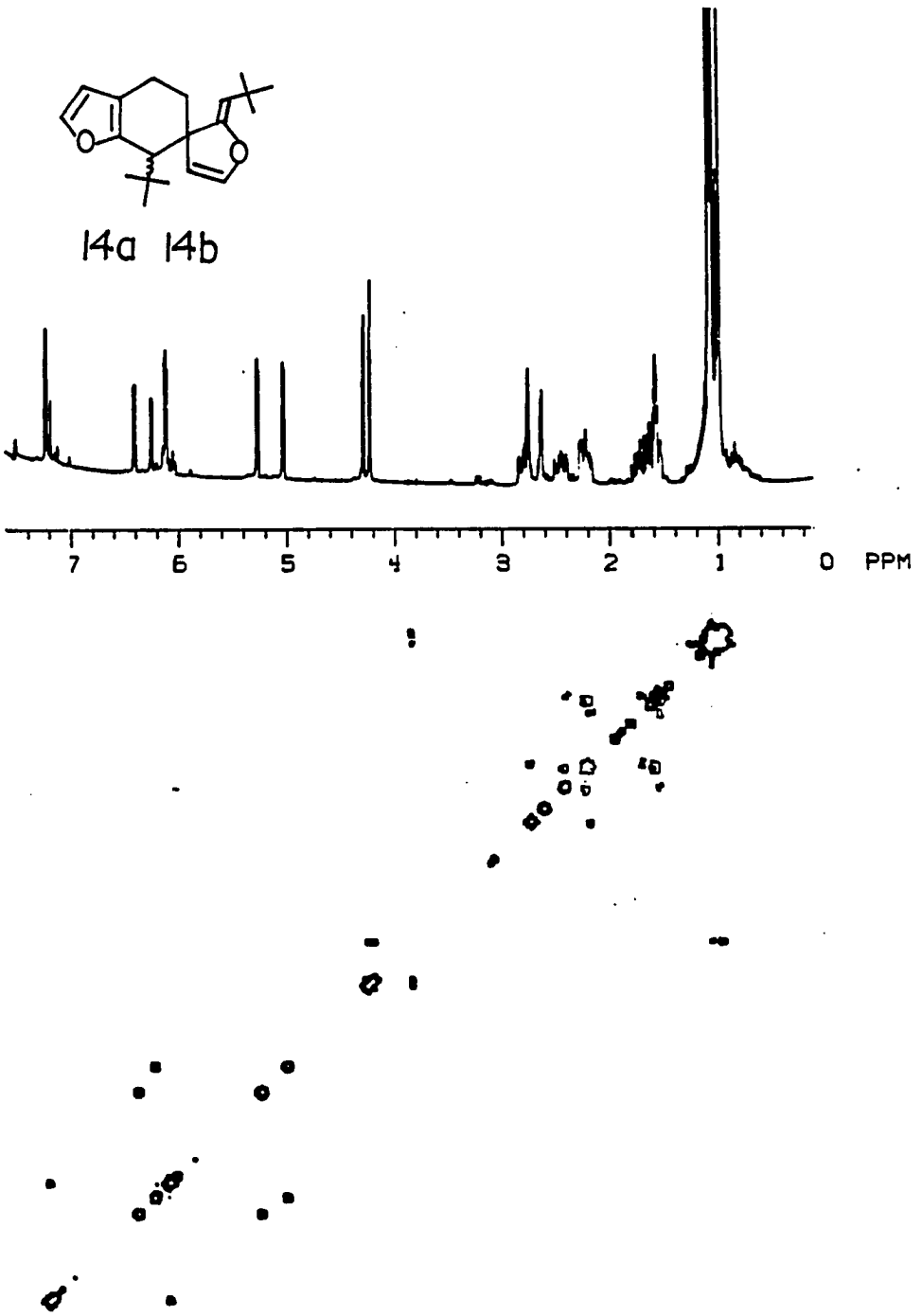
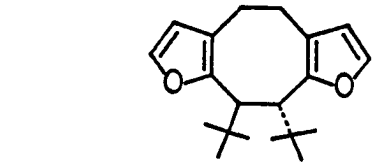


Figure 2. 2-D proton NMR spectrum of two isomeric [4+2] dimers 14a and 14b of 3-methylene-2-t-butyl-methylene-2,3-dihydrofuran (7a) in $CDCl_3$



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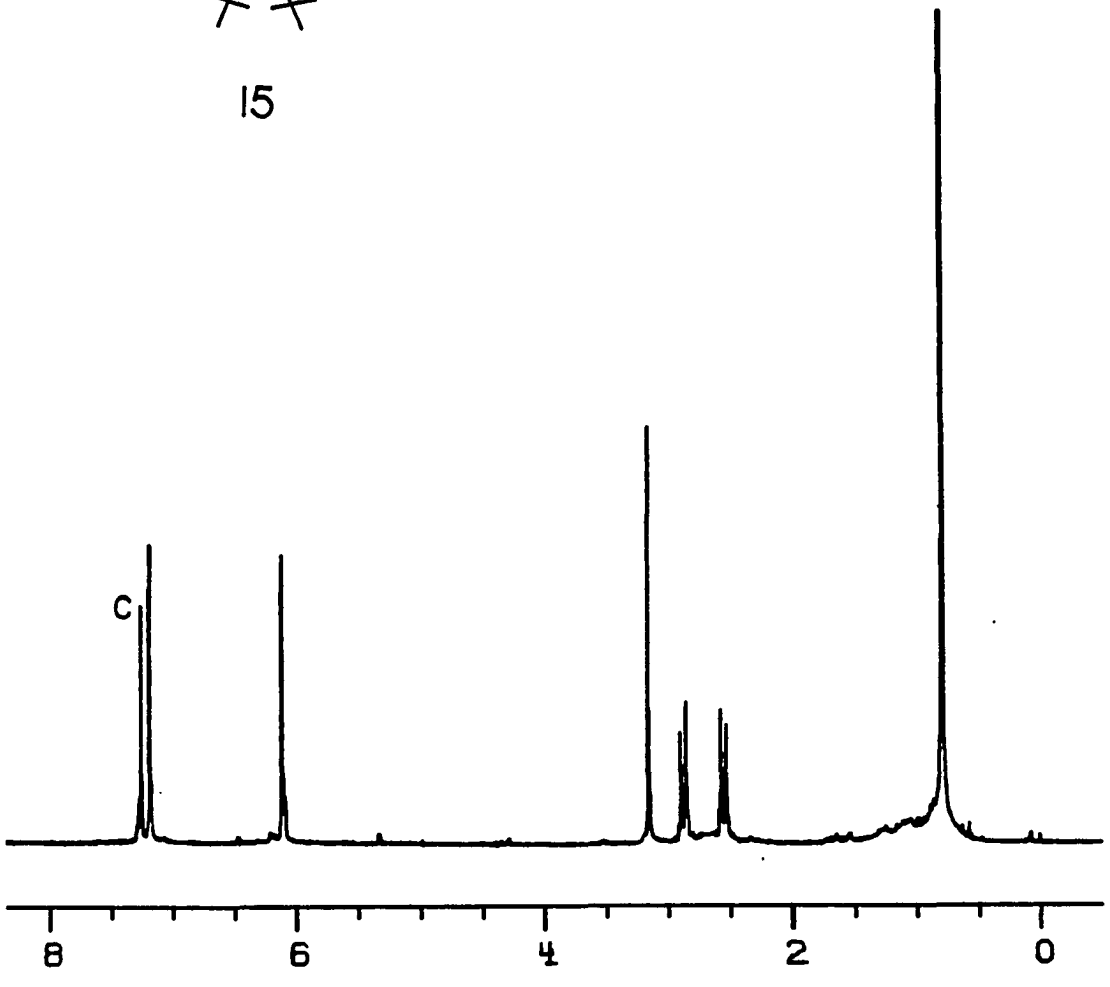


Figure 3. Proton NMR spectrum of the [4+4] dimer 15 of 3-methylene-2-t-butylmethylene-2,3-dihydrofuran (7a) in $CDCl_3$ (C = $CHCl_3$)

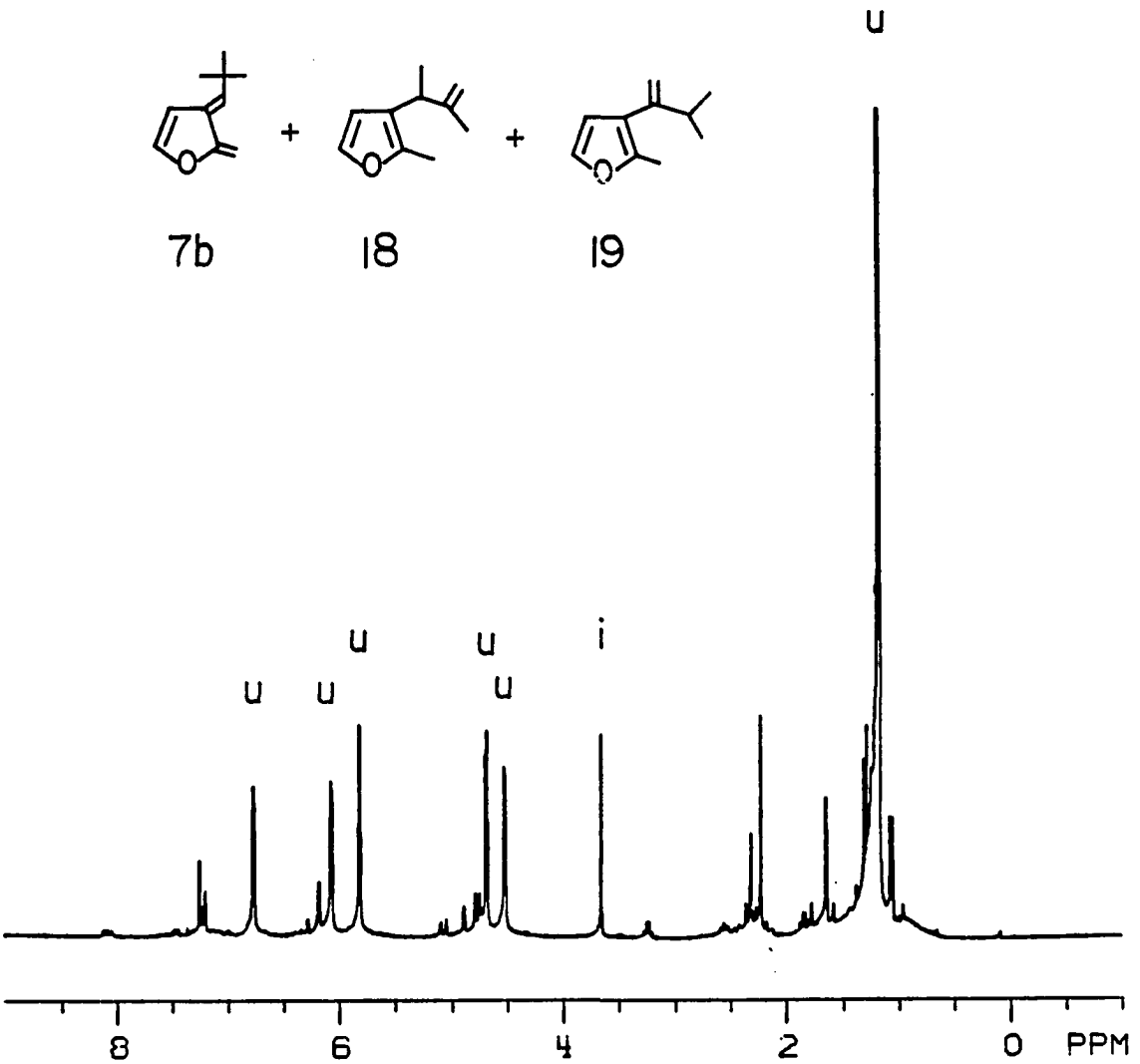


Figure 4. Proton NMR spectrum of 2-methylene-3-t-butyl-methylene-2,3-dihydrofuran (7b), 18 and 19 in $CDCl_3$ (i = dibromoethane, u = 7b, 18 and 19, see Figure 8)

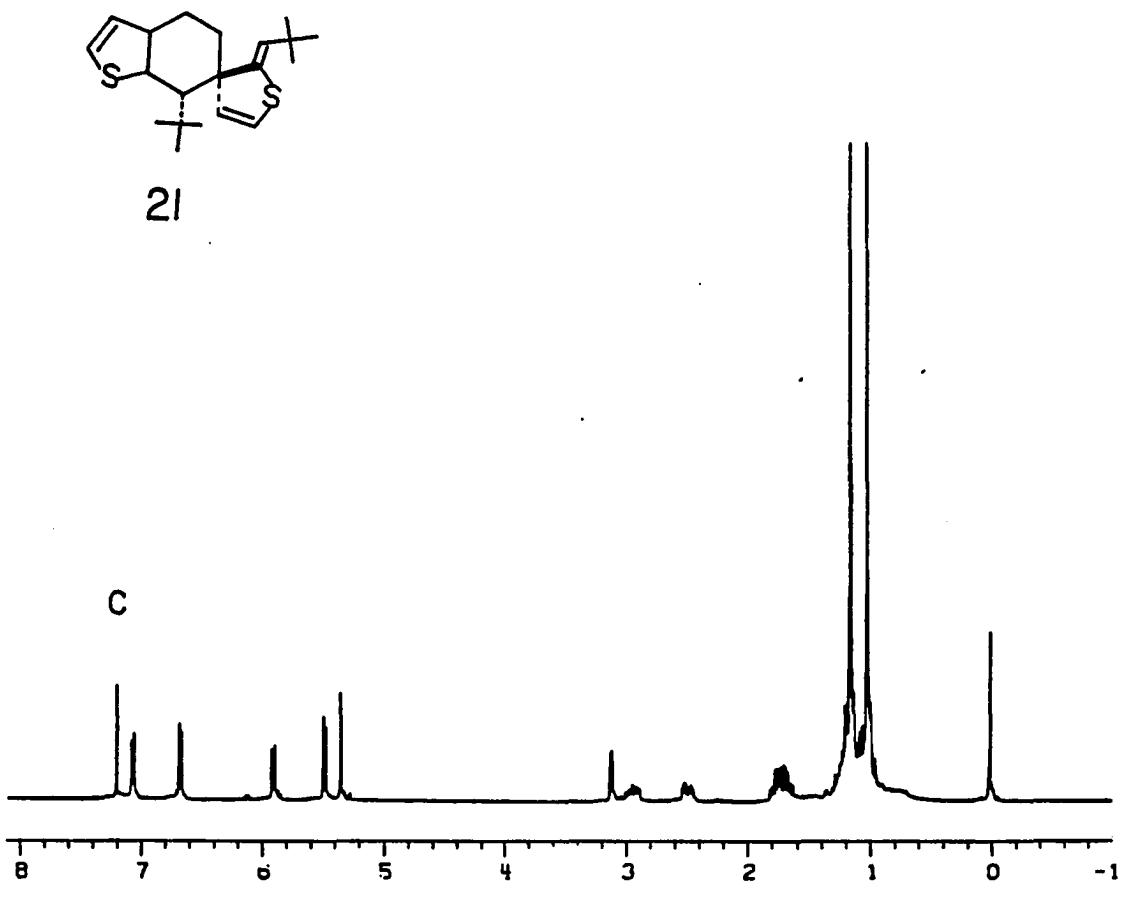


Figure 5. Proton NMR spectrum of the [4+2] dimer 21 of 3-methylene-2-t-butylmethylene-2,3-dihydrothiophene (8) in $CDCl_3$ (C = $CHCl_3$)

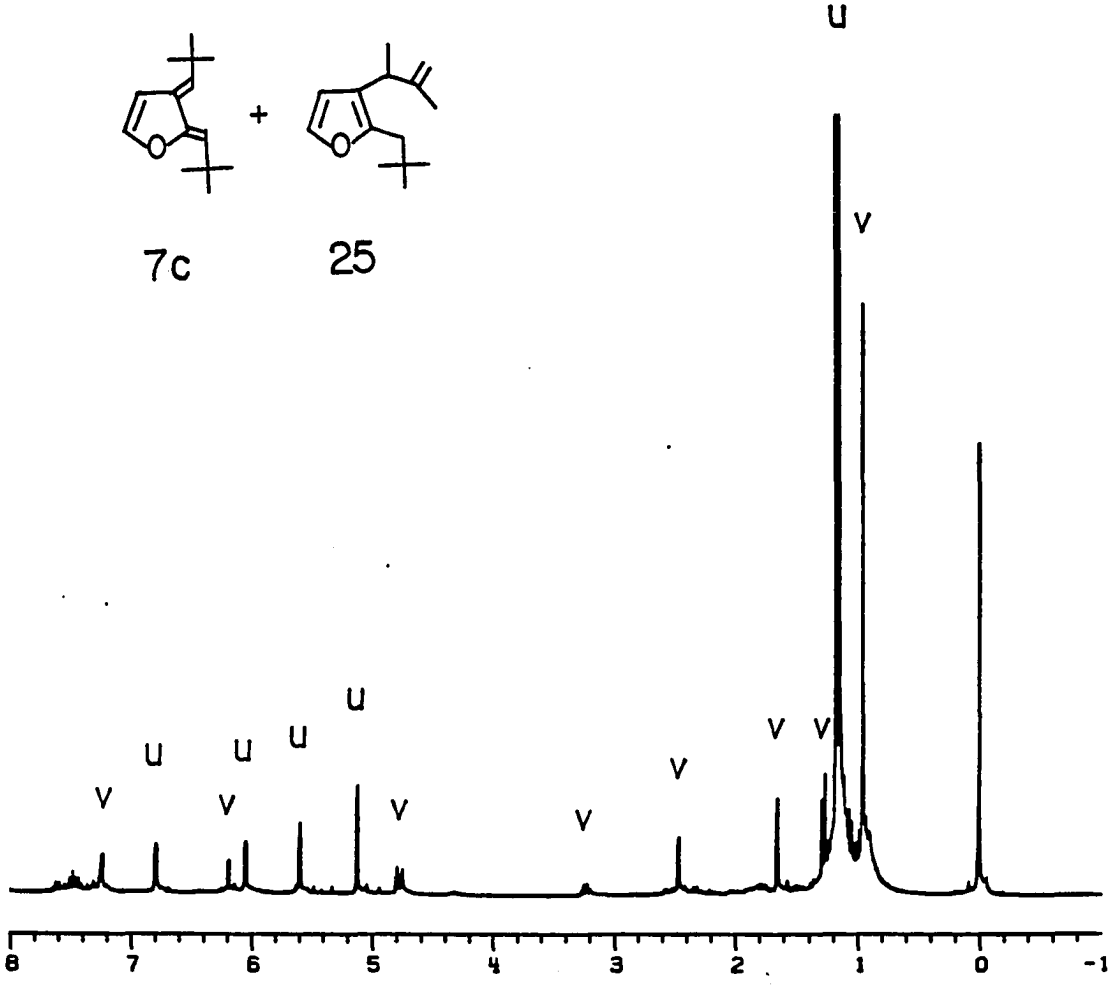


Figure 6. Proton NMR spectrum of 2,3-di-t-butylmethylene-2,3-dihydrofuran (7c) and 25 in $CDCl_3$ (u = 7c, v = 25)

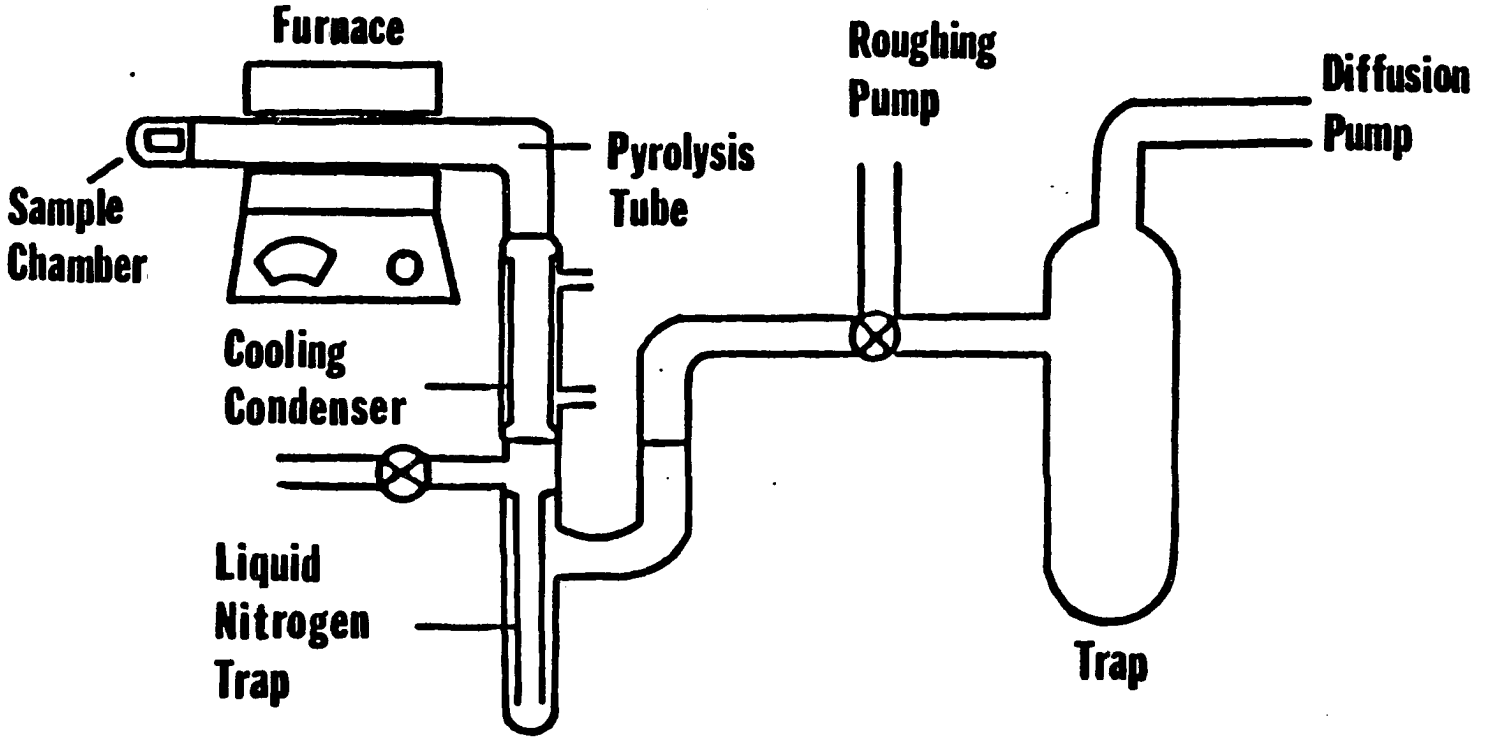


Figure 7. Schematic diagram of the pyrolysis apparatus

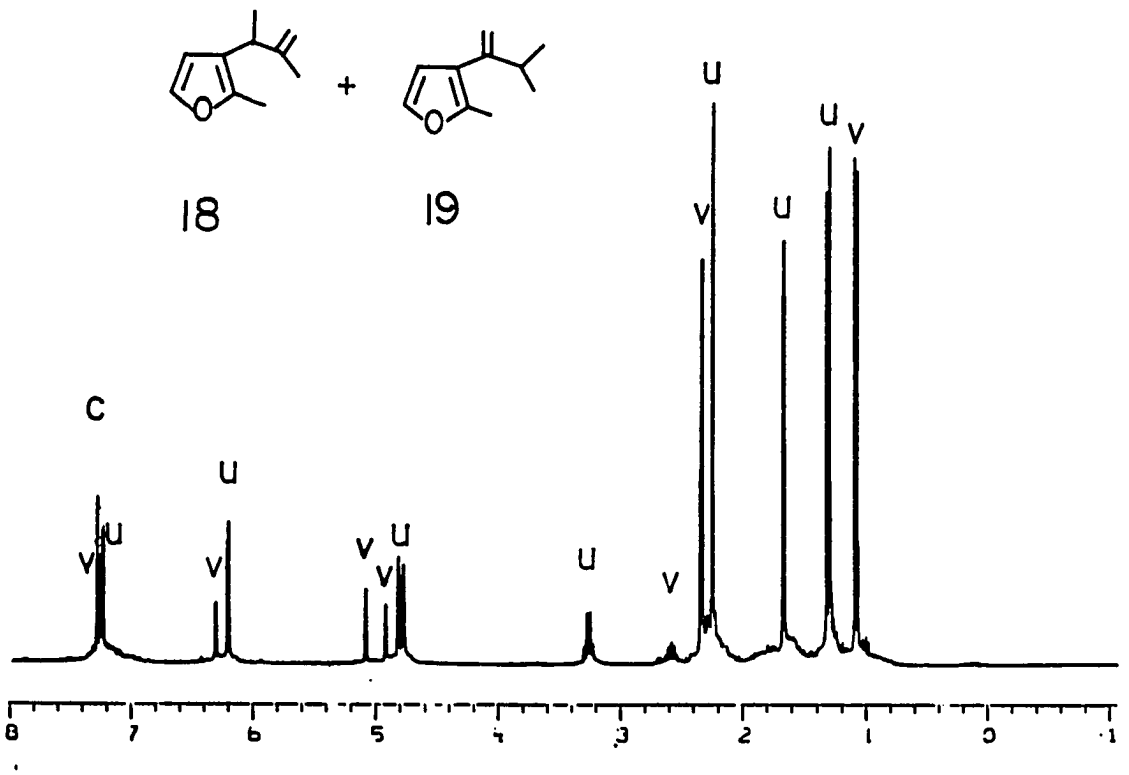


Figure 8. Proton NMR spectrum of 18 and 19 in $CDCl_3$ (c = $CHCl_3$, u = 18, v = 19)

Table I. Rate of disappearance of 2-t-butylmethylene-3-methylene-2,3-dihydrofuran (7a) measured by low temperature proton NMR spectroscopy at -10°C in 1:1 $CS_2/CDCl_3$ using dibromoethane as an internal standard

Time, min	[7a], mol L^{-1}	$[7a]^{-1}$, L mol^{-1}
0	0.025	40.0
20	0.024	41.2
40	0.022	43.7
70	0.021	46.0
85	0.021	47.5
100	0.020	49.2
ka = 1.53×10^{-3} L mol^{-1} sec^{-1} [a]		
0	0.026	38.0
20	0.025	39.8
50	0.023	43.1
75	0.022	45.6
90	0.021	47.0
105	0.021	48.6
ka = 1.68×10^{-3} L mol^{-1} sec^{-1} [a]		

[a]The rate constants are the slopes of the best straight lines (x axis = time, y axis = L mol^{-1}) derived by linear regression using a Hewlett Packard calculator (HP 15C).

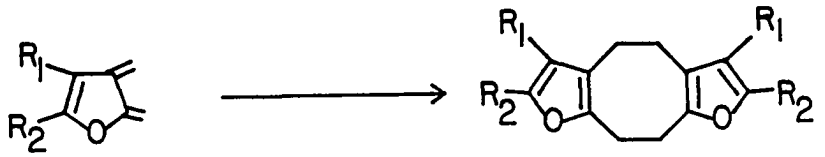
SECTION II. GENERATION AND STUDY OF THE DIMERIZATION OF ALKYL RING-SUBSTITUTED 2,3-DIMETHYLENE-2,3-DIHYDROFURANS

INTRODUCTION

We have thus far investigated the substituent effect on the dimerization of 2,3-dimethylene-2,3-dihydrofuran (1a). Several t-butyl exo-methylene-substituted furan monomers were generated from the flash vacuum pyrolysis (FVP)1-5 of the corresponding benzoates and their reactivity studied.[6] The results are in good agreement with the proposed stepwise dimerization mechanism in which only the 3-methylene is directly involved in the rate determining step to form the diradical intermediate. The 2-methylene, on the other hand, has a determining effect on the dimer formation.

We were also interested in finding out if any kind of effect on the dimerization would be present when substituents were introduced on the less reactive ring carbons of the furan monomer.

Previous studies on some 4 or 5 mono-alkyl substituted furan monomers 1b, 1c and 1d have shown virtually no changes in their behavior from the parent system.[7,8] They all dimerized to give primarily the head to head, [4+4] dimers at comparable, but not identical, rates. The fact that the bulky t-butyl group on the 5 position did not retard the rate suggested that the dimerization probably prefers a non-endo approach.[7]



1

a $R_1 = R_2 = H$

b $R_1 = H \quad R_2 = Me$

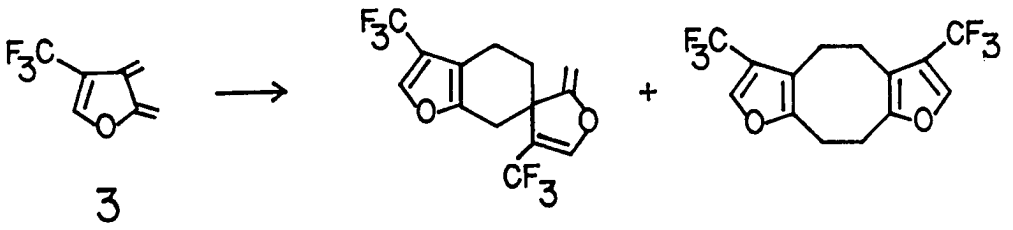
c $R_1 = Me \quad R_2 = H$

d $R_1 = H \quad R_2 = t\text{-}Bu$

In another study, when a 4-carbomethoxy-5-methyl disubstituted furan monomer 2 was generated and allowed to dimerize, a drastic change was observed. Compound 2 dimerized to give a mixture of not fully characterized [4+2] dimers as the main products in addition to the normal head to head [4+4] dimer.[9]

2

Similar observation was made with the 4-trifluoromethyl monomer 3 and the benzo[b] furan monomer 4.[10,11]



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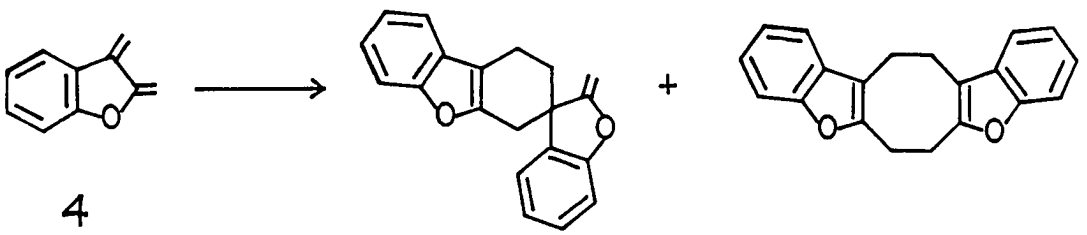
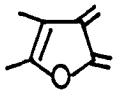


4

There is one thing which monomers 2, 3 and 4 have in common. They all have substituents on the 4 position. Also among them, 2 and 4 are both 4,5-disubstituted, and 2 and 3 have strong electron withdrawing substituents. In an attempt to determine which factor favors the [4+2] dimer, two 4,5 dialkyl disubstituted monomers 5 and 6 and one 5-carbomethoxy substituted monomer 7 were generated and studied.



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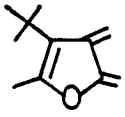

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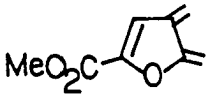
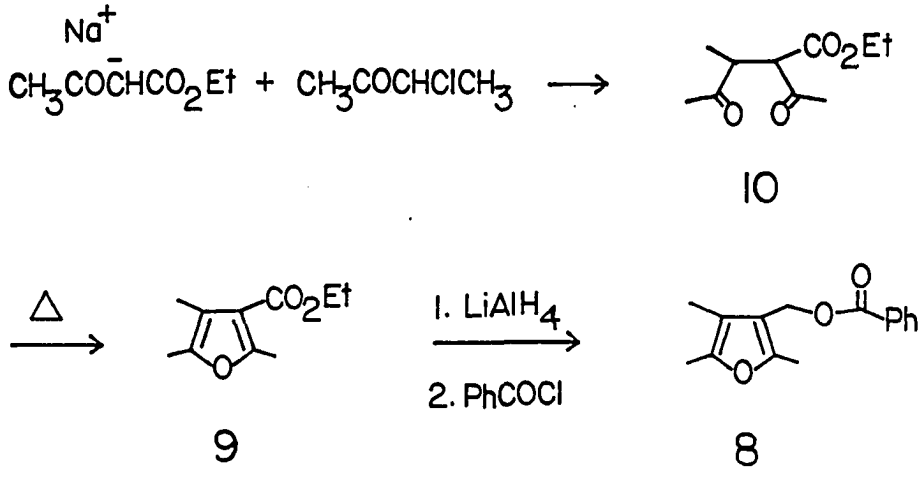


7

Also, a copyrolysis of two different benzoates was performed to allow us to look into the feasibility of the synthesis of mixed dimers that have synthetic potentials.

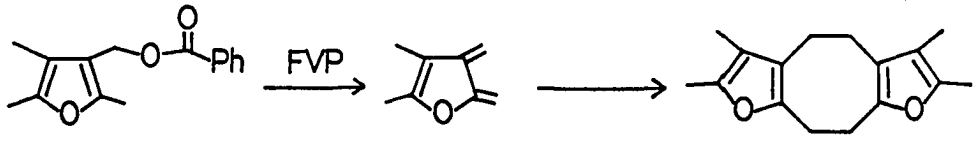
RESULTS

2,4,5-Trimethyl-3-furylmethyl benzoate (8) was synthesized by reduction of 9 followed by esterification of the alcohol. Ethyl 2,4,5-trimethyl-3-furoate (9) was prepared by the condensation of sodium ethyl acetoacetate and 3-chloro-2-butanone to give diketone ester 10, followed by its cyclization with the elimination of a molecule of water.[12]



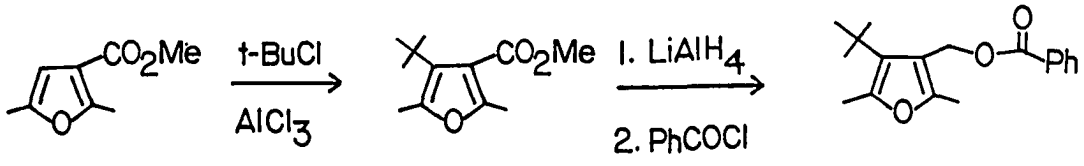
The FVP of 8 was performed at 600°C under the normal conditions. The pyrolysate was collected in 10 mL of carbon disulfide and was allowed to warm gradually to room temperature. GC and proton NMR spectra (see Appendix, Figure 1) of the crude pyrolysate showed that the head to head, [4+4] dimer (11) was the major product. Purifica-

tion of the crude product by column chromatography on silica gel (hexane) afforded dimer 11 in 43.5% yield.



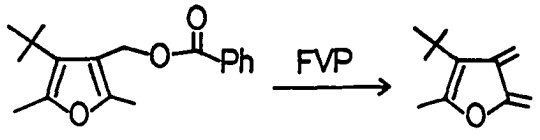
11

2,5-Dimethyl-4-t-butyl-3-furylmethyl benzoate (12) was synthesized by the reduction of methyl 2,5-dimethyl-4-t-butyl-3-furoate to the corresponding alcohol which was then converted to the alkoxide with n-butyl lithium followed by esterification with benzoyl chloride. Methyl 2,5-dimethyl-4-t-butyl-3-furoate was prepared by a Friedel-Crafts alkylation of methyl 2,5-dimethyl-3-furoate with t-butyl chloride in the presence of aluminum chloride.[13]



12

FVP of 12 was performed at 520°C in the normal fashion. Low temperature proton NMR at -60°C (see Appendix, Figure 2) supported the presence of 5-methyl-4-t-butyl-2,3-dimethylene-2,3-dihydrofuran (6).



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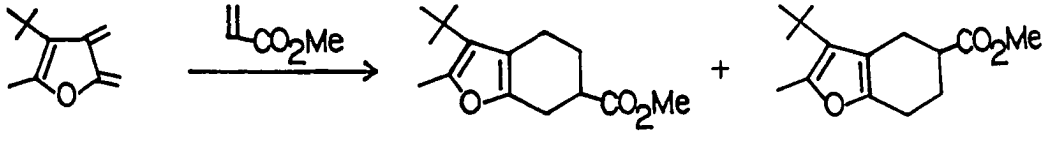
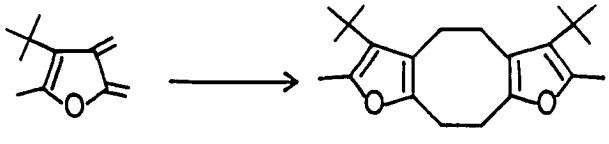


13 14

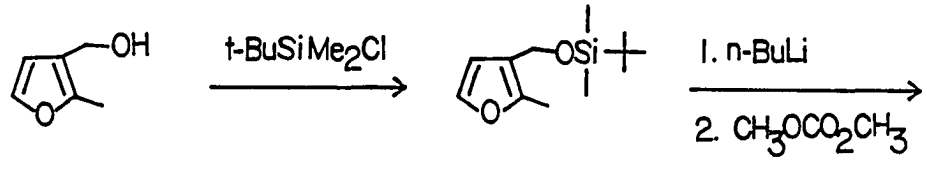
When a large excess of methyl acrylate was added to the pyrolysis trap prior to warming, a mixture of the Diels-Alder adducts 13 and 14 (8:1) was obtained in 37.7% yield.

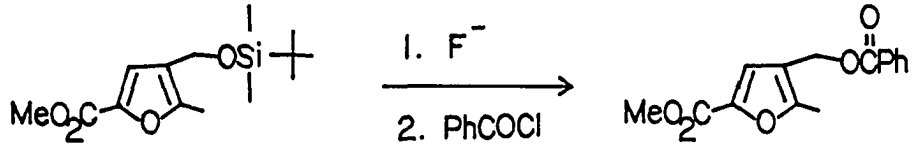
GCMS analysis of the crude pyrolysate solution upon warming to room temperature indicated the formation of a major dimer. Concentration and purification by column chromatography on silica gel (hexane) gave the head to head, [4+4] dimer (15) in 13.7% yield (see Appendix, Figure 3).



15

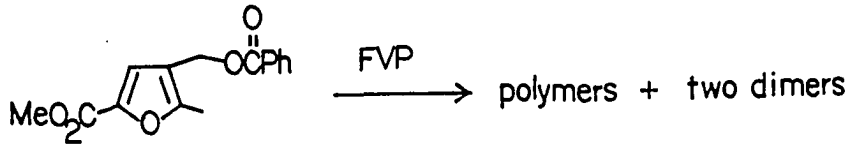
5-Carbomethoxy-2-methyl-3-furylmethyl benzoate (16) was prepared as follows: 2-methyl-3-furylmethyl alcohol was first protected with a t-butyldimethyl silyl group; metallation and condensation of the silyl ether with dimethyl carbonate gave compound 17. Deprotection of 17 and esterification of the resulting alcohol with benzoyl chloride gave 16.[14]



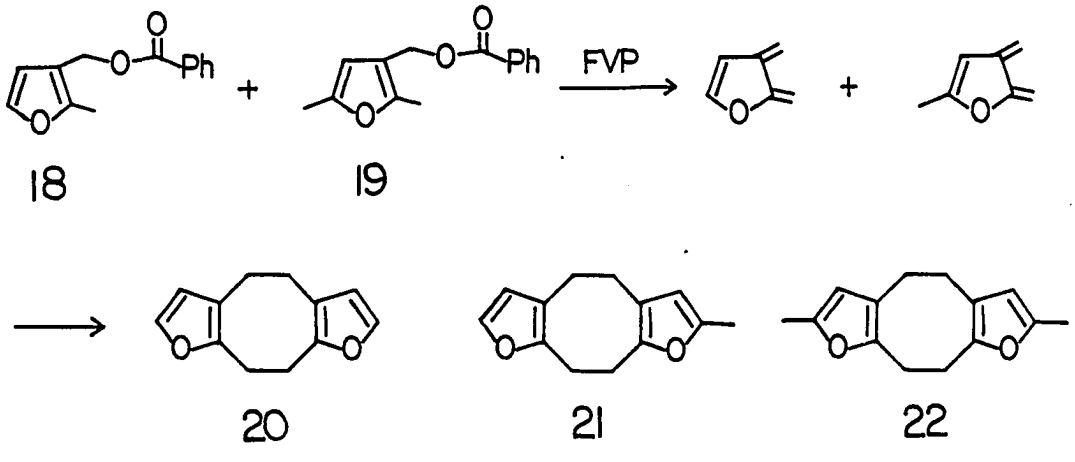


17 16

Numerous pyrolyses at various temperatures all resulted in polymer formation. Only GCMS analysis of a very concentrated sample was able to detect a very small amount of two dimeric products.

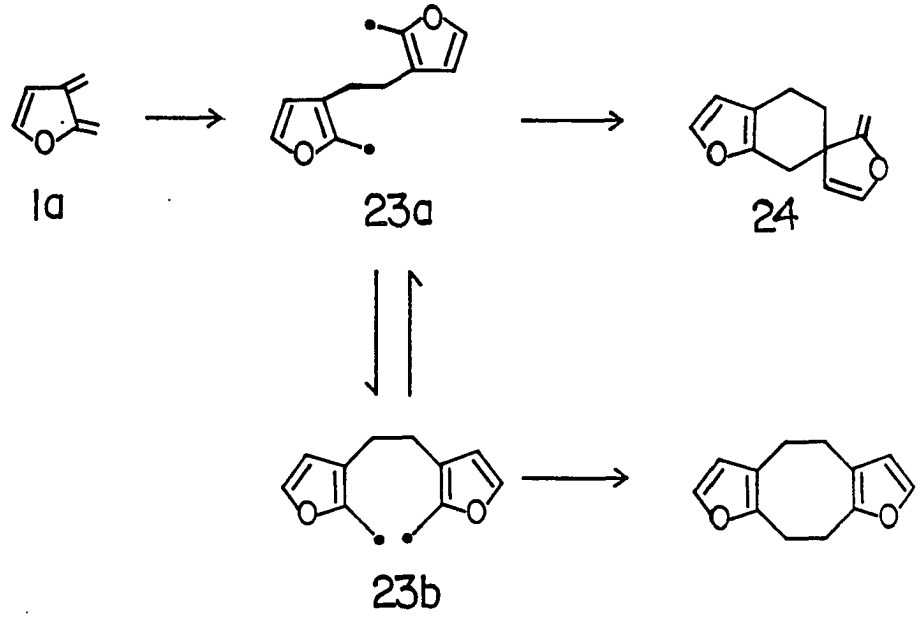


An equal molar quantity of 2-methyl-3-furylmethyl benzoate (18) and 2,5-dimethyl-3-furylmethyl benzoate (19) was placed in the sample head and pyrolyzed in the normal fashion. The pyrolysate was collected in 15 mL of carbon disulfide and was allowed to warm slowly to room temperature. GCMS and proton NMR of the crude pyrolysate showed the presence of three dimers 20, 21 and 22 as the major products in a 1:2:1 ratio.[8] An analytical sample of 21 was collected by preparative GC and its proton NMR spectrum shows three different furan protons (see Appendix, Figure 4).



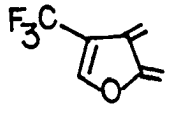
DISCUSSION

On the basis of a secondary deuteurium kinetic isotope effect study,[15] the dimerization of 2,3-dimethylene-2,3-dihydrofuran (1a) was proposed to proceed through diradical 23 which could exist in either conformation 23a or 23b.



It is reasonable to assume that the relative orientation of the two furan moieties in 23 is important in determining the final products. Rotation of the initially formed 23a to 23b followed by fast coupling of two radicals would give the [4+4] dimer. If, for some reason, e.g., steric hindrance, free rotation between 23a to 23b was retarded, then dimerization to give the [4+2] dimer 24 would become competitive. Since all three previously studied substituted

monomers 2, 3 and 4 gave [4+2] dimers as the main products, and all of them bear relatively bulky ring substituents, we decided to investigate more systems to determine the validity of this concept.



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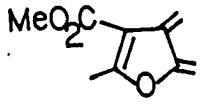

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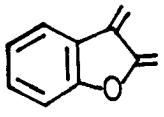
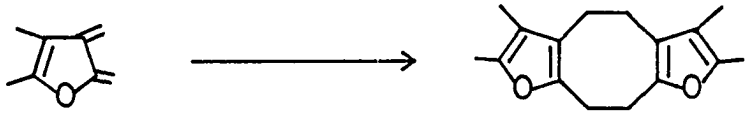


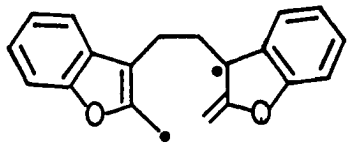
4

A sterically comparable model of 4, 4,5-dimethyl-substituted furan monomer 5, was prepared. Upon warming, only the head to head, [4+4] dimer 11 was formed. This suggests, at least for monomer 4, that steric hindrance is not what causes the [4+2] dimer to come in.



5 11

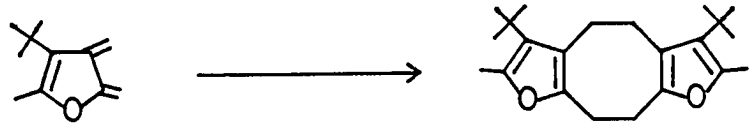
The fact that 4 gave predominantly the [4+2] dimer can be rationalized by a higher contribution of resonance form 25 in the diradical intermediate.



⟶ [4 + 2] dimer

25

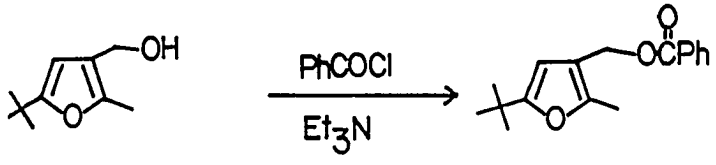
Another 4,5-disubstituted furan monomer,4-t-butyl-5-methyl-2,3-dimethylene-2,3-dihydrofuran (6) from the FVP of 2,5-dimethyl-4-butyl-3-furylmethyl benzoate (12) also gave the [4+4] dimer 15 as the major product, but with a much lower yield (13.7%).

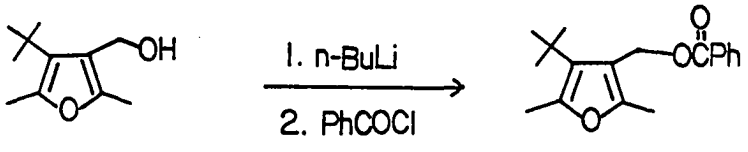


6 15

The abnormally low yield of 15 can be explained by the fact that for monomer 6 the t-butyl at the C-4 position is much closer to the rate determining center, 3-methylene, than in the case of 5-t-butyl-2,3-dimethylene-2,3-dihydrofuran (1d), where the t-butyl at C-5 is located relatively far away from the reacting center for it to have any significant retarding effect on the dimerization process. This assumption was supported by the fact that during the

esterification of 2,5-dimethyl-4-t-butyl-3-furylmethyl alcohol, the alkoxide had to be made by treating the alcohol with n-BuLi followed by the addition of benzoyl chloride to give the benzoate 12. This is a standard way to prepare benzoate from sterically hindered alcohols.[16] In contrast, 2-methyl-5-t-butyl-3-furylmethyl benzoate, the precursor of 1d, can simply be prepared by treating the alcohol with benzoyl chloride in the presence of triethylamine.





12

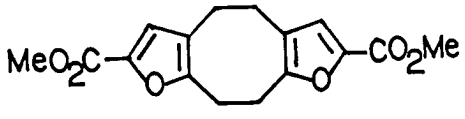
This observation further complements the stepwise dimerization mechanism in which only the 3-methylene is involved in the rate-determining step.

Based on our results, a bulky alkyl substituent on the 4 position plus a methyl group on the 5 position of furan monomer 6 failed to produce any [4+2] dimer; whereas previous studies indicated that less bulky electron withdrawing substituents on the 4 position alone gave [4+2]

dimers as the major products. This observation apparently does not favor our original assumption that [4+2] dimerization becomes competitive if the free rotation of the diradical intermediate is sterically hindered.

An electronic effect seems to be the only remaining logical explanation. However, when benzoate 16 was pyrolyzed, GCMS analysis was able to detect only a very small amount of two dimeric products among the polymeric substance.

We can only postulate that one is the [4+4] dimer 26. The other is the [4+2] dimer 27.



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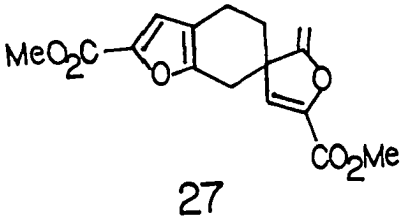
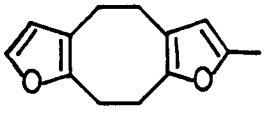


27

A strong electron withdrawing substituent on the 5 position of the furan monomer evidently has a strong adverse effect on its stability.

Even though the mixed dimer 21 we obtained from the co-pyrolysis of two benzoates is still a very simple system, this success does open up possibilities for the synthesis of

more complex compounds. After all, the dimerization of furan monomers is a very convenient way to generate an eight-membered ring which is know to exist in some natural products.



21

EXPERIMENTAL

Methods and Equipment

The pyrolysis apparatus has been previously described.[17] NMR spectra were recorded on Varian E 360, JOEL FX-90Q or Nicolet-300 spectrometers. High resolution mass spectra were measured with an Associated Electronics Industries MS-902 instrument at 70eV. Gas chromatography/ mass spectroscopy (GC/MS) was performed with a Finnigan 4000 instrument and an INCOS data system. GLC analyses were performed with a Hewlett Packard HP 5840A instrument with a 25 meter, SP 2100 thin film (methylsilicone-coated) capillary column.

2,4,5-Trimethyl-3-furylmethyl Benzoate (8)

Ethyl 2,4,5-trimethyl-3-furoate (9) was prepared with modification of the sequence by Dann and coworkers for their synthesis of ethyl 2,5-dimethyl-3-furoate.[12]

Ethyl 2,4,5-trimethyl-3-furoate (9): IR (thin film) 1720, 1625, 1600, 1245, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (q, J = 7 Hz, 2H), 2.48 (s, 3H), 2.17 (s, 3H), 2.05 (s, 3H), 1.35 (t, J = 7 Hz, 3H).

A quantity of 1.8 g (10 mmole) of ethyl 2,4,5-trimethyl-3-furoate (9) was reduced with lithium aluminum

hydride using the procedure described previously[8] for the synthesis of 2,5-dimethyl-3-furylmethyl alcohol to give 1.2 g (8.6 mmole, 86%) of 2,4,5-trimethyl-3-furylmethyl alcohol: IR (thin film) 3380, 1650, 1600, 1205, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.39 (s, 2H), 2.21 (s, 3H), 2.06 (s, 3H), 1.90 (s, 3H) 1.68 (br, 1H). Without further purification, the alcohol was converted to 2,4,5-trimethyl-3-furylmethyl benzoate (8) with benzoyl chloride using the procedure described previously for the synthesis of 2,5-dimethyl-3-furylmethyl benzoate. Purification by column chromatography on silica gel (5% ether in hexane) yielded 1.8 g (7.4 mmole, 87%) of 8: IR (thin film) 1718, 1650, 1605, 1570, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25-7.95 (m, 2H),7.65-7.40 (m, 3H), 4.62 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.98 (s, 3H); high resolution mass spectrum, calcd for $C_{15}H_{16}O_3$ 244.10995, measured 244.11038.

2,5-Dimethyl-4-t-butyl-3-furylmethyl Benzoate (12)

To a suspension of 13.3 g (0.1 mole) of aluminum chloride in 100 mL of carbon disulfide which was being stirred was added dropwise a solution of 7.7 g (0.05 mole) of methyl 2,5-dimethyl-3-furoate and 4.6 g (0.05 mmole) of t-butyl chloride. After the addition, the dark mixture was stirred overnight at room temperature. The resulting mixture was poured onto 200 g of ice with rapid stirring to

form a milky suspension. The aqueous layer was separated and extracted with ether (50 mL x 2). The combined organic layers was washed with sodium bicarbonate and brine, dried and concentrated. The crude product was purified by column chromatography on silica gel (5% ether in hexane) gave 4.5 g (0.021 mole, 42%) of methyl 2,5-dimethyl-4-t-butyl-3-furoate: IR (thin film) 1718, 1620, 1580, 1445, 1250, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s,3H), 2.48 (s, 3H), 2.23 (s, 3H), 1.31 (s, 9H).

A quantity of 3.0 g (14.3 mmole) of methyl 2,5-dimethyl-4-t-butyl-3-furoate was reduced with lithium aluminum hydride using the procedure previously described for the synthesis of 2,5-dimethyl-3-furylmethyl alcohol to give 2.2 g (12.1 mmole, 86.7%) of 2,5-dimethyl-4-t-butyl-3-furylmethyl alcohol: ^1H NMR ($CDCl_3$) δ 4.40 (br, 2H), 2.21 (s, 3H), 2.09 (s, 3H), 1.50 (br, 1H), 1.28 (s, 9H). A quantity of 5.9 mL of n-BuLi (2.15 M) was added via a syringe to a solution of 2.2 g (12.1 mmole) of the alcohol in 30 mL of dry THF. The mixture was stirred for 10 min and a solution of 1.87 g (13.3 mmole) of benzoyl chloride in 10 mL of THF was added. The resulting red mixture was stirred overnight under nitrogen. After the addition of 30 mL of water, the aqueous layer was extracted with ether (30 mL x 2) and the combined organic layers was washed with water, sodium

bicarbonate and brine, dried and concentrated, the crude product was purified by column chromatography on silica gel (5% ether in hexane) to give 2.6 g (9.0 mmole, 74.4%) of 12: ^{1}H NMR ($CDCl_3$) δ 8.20-7.85 (m, 2H), 7.58-7.25 (m, 3H), 5.10 (s, 2H), 2.25 (s, 3H), 2.05 (s, 3H), 1.26 (s, 9H); high resolution mass spectrum, calcd for $C_{18}H_{22}O_3$ 286.15690, measured 286.15671.

5-Carbomethoxy-2-methyl-3-furylmethyl Benzoate (16)

To a solution of 6.0 g (53.5 mmole) of 2-methyl-3-furylmethyl alcohol in 12 mL DMF which was being stirred was added 9.7 g (64.2 mmole) of t-butyldimethylsilyl chloride and 9.1 g (133.8 mmole) of imidazole. The mixture was stirred overnight at room temperature. After the addition of 100 mL of ether, the mixture was washed with ammonium chloride(aq) and brine, dried and concentrated to give 10.6 g (49.5 mmole, 92.5%) of 2-methyl-3-furylmethyl t-butyldimethylsilyl ether: b.p. 47-48°C (0.2 mm); ^{1}H NMR ($CDCl_3$)δ 7.18 (d, J = 2 Hz, 1H), 6.22 (d, J = 2 Hz, 1H), 4.47 (s, 2H), 2.30 (s, 3H), 0.94 (s, 9H), 0.21 (s, 6H). To a solution of 5.0 g (23.4 mmole) of the silyl ether in 40 mL of ether which was being stirred rapidly was added 18.7 mL (1.5 M in hexane) of n-BuLi via a syringe. After the mixture was stirred for 1 h at room temperature, the resulting deep red solution was added dropwise to 4.2 g (46.7 mmole)

of dimethyl carbonate in 5 mL of ether at -60°C. The mixture was then stirred for 4 h from -60°C to room temperature. After the addition of water, the layers were separated and the organic layer was washed with water and brine, dried and concentrated. The crude product was purified by vacuum distillation (110°-112°C, 0.25 mm) to give 2.7 g (9.9 mmole, 42.3%) of 5-carbomethoxy-2-methyl-3-furylmethyl t-butyldimethylsilyl ether (17): ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 1H), 4.42 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 0.89 (s, 9H), 0.10 (s, 6H). To 2.67 g (9.8 mmole) of the ether was added 19.6 mL of tetrabutylammonium fluoride (1 M in THF) with stirring. The mixture was then diluted with 20 mL of ether and washed with brine. After separation, the organic layer was dried and concentrated. Vacuum distillation (109-111°C, 0.4 mm) of the crude product gave 1.35 g (7.9 mmole, 81%) of 5-carbomethoxy-2-methyl-3-furylmethyl alcohol: ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 1H), 4.32 (s, 2H), 3.71 (s, 3H), 2.62 (br, 1H), 2.33 (s, 3H). A quantity of 0.6 g (3.53 mmole) of 17 was esterified with benzoyl chloride using the procedure described previously for the synthesis of 2,5-dimethyl-3- furylmethyl benzoate to give 0.8 g (2.9 mmole, 82.2%) of 5-carbomethoxy-2-methyl-3-furylmethyl benzoate (16): m.p. 54-56°C; IR (thin film) 1720, 1600, 1532, 1450, 1275, 1090

cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28-7.90 (m, 2H), 7.67-7.35 (m, 3H), 7.15 (s, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.45 (s, 3H); high resolution mass spectrum, calcd for $C_{15}H_{14}O_5$ 274.08413, measured 274.08429.

General Pyrolysis Procedure

The pyrolyses were run at furnace temperatures from 400 to 800°C. The sample chamber was heated to 60-70°C and the system was evacuated to ca. 10^{-5} Torr during the pyrolysis. A condenser was inserted between the quartz pyrolysis tube and the liquid nitrogen-cooled trap to collect the unreacted starting material and the benzoic acid formed as a byproduct. The liquid nitrogen-cooled trap was used to collect the products. Upon completion of the pyrolysis, carbon disulfide or deuterochloroform was distilled into the trap through the side arm. The trap was then warmed to -78°C. Also added was a known amount of dibromoethane as an internal standard for quantitative studies.

Pyrolysis of 2,4,5-Trimethyl-3-furylmethyl Benzoate (8)

A quantity of 100 mg ((0.35 mmole) of 8 was pyrolyzed at 600°C in the normal manner. The pyrolysate was colleted in 10 mL of carbon disulfide and was allowed to warm gradually to room temperature. GC and proton NMR spectra of the crude pyrolysate showed that the [4+4] dimer 11 was the

only major product. Purification of the crude product by column chromatography on silica gel (hexane) yielded 18.5 mg (0.076 mmole, 43.4%) of 11: ^{1}H NMR (see Appendix, Figure 1) ($CDCl_3$) δ 2.98 (s, 2H), 2.60 (s, 2H), 2.05 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.20, 148.94, 120.95, 118.26, 26.05, 22.58, 13.74, 7.98; GC/MS (70 eV) m/e (relative intensity) 244.05 (15.02), 219.08 (27.52), 204.12 (18.53), 189.06 (12.11), 173.98 (9.24), 122.01 (100), 106.96 (21.01).

Pyrolysis of 2,5-dimethyl-4-t-butyl-3-furylmethyl Benzoate (12)

A quantity of 150 mg (0.52 mmole) of 12 was pyrolyzed at 520°C under the normal condition. The pyrolysate was collected in 10 mL of 1:1 $CS_2/CDCl_3$ from the liquid nitrogen-cooled trap and proton NMR spectrum recorded at -60°C showed evidence for the presence of 5-methyl-4-t-butyl-2,3-dimethylene-2,3-dihydrofuran (6): ^{1}H NMR (see Appendix, Figure 2) ($CDCl_3/CS_2$) δ 5.17 (s, 1H), 4.78 (m, 1H), 4.70 (s, 1H), 4.55 (m, 1H), 1.82 (s, 3H), 1.25 (s, 9H). Upon warming, polymers were found to be the major products. Concentration and purification of the crude pyrolysate solution by column chromatography on silica gel (hexane) yielded 6.3 mg (0.0192 mmole, 13.7%) of the [4+4] dimer 15: ^{1}H NMR (see Appendix, Figure 3) (C_6D_6) 3.02 (s, 4H), 2.30 (s, 4H), 1.85 (s, 6H), 1.36 (s, 18H); ^{13}C NMR (C_6D_6) δ

154.02, 146.35, 119.55, 112.98, 33.69, 29.87, 26.44, 22.91, 9.41; GC/MS (70 eV) m/e (relative intensity) 328.18 (16.41), 313.16 (30.18), 271.12 (12.01), 164.12 (64.20), 149.18 (100.00), 121.06 (18.45), 91.04 (13.56), 57.06 (19.53).

Diels-Alder Reaction of 5-Methyl-4-t-butyl-2,3-dimethylene-2,3-dihydrofuran (6) with Methyl Acrylate

A 113 mg (0.69 mmole) quantity of 2,5-dimethyl-4-t-butylfurylmethyl benzoate (12) was pyrolyzed at 530°C under the normal conditions. Upon completion, a solution of 10 mL of methyl acrylate was deposited into the trap through a side arm. After warming of the trap, the mixture of the crude adducts was purified by column chromatography (silica gel, 5% ether in hexane) to give 65 mg (0.26 mmole, 37.7%) of the Diels-Alder adducts 13 and 14 (8:1) based on GCMS analysis. For 13: ^{1}H NMR (C_6D_6) δ 3.36 (s, 3H), 3.05-1.72 (m, 7H), 1.80 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (C_6D_6) δ 174.46, 155.30, 144.86, 111.43, 109.23, 51.19, 40.35, 33.98, 29.91, 26.31, 26.09, 19.91, 9.36; high resolution mass spectrum, calcd for $C_{15}H_{22}O_3$ 250.15690, measured 250.15579. The concentration of 14 was too low to be detected by either proton NMR or ^{13}C NMR spectroscopy.

Copyrolysis of 2-methyl-3-furylmethyl Benzoate (18) and 2,5-dimetheyl-3-furylmethyl Benzoate (19)

A mixture of 0.28 g (1.3 mmole) of 18 and 0.30 g (1.3 mmole) of 19 was copyrolyzed at 610°C under the normal conditions. The pyrolysate was collected in 15 mL of carbon disulfide from the trap and was allowed to warm slowly to room temperature. GCMS and proton NMR of the pyrolysate showed a total amount of 54 mg (0.27 mmole, 41%) of dimers 20, 21 and 22 as the major products in a 1:2:1 ratio. An analytical sample of 21 was collected by preparative GC: ^{1}H NMR (see Appendix, Figure 4) ($CDCl_3$) δ 7.15 (d, J = 2 Hz, 1H), 6.05 (d, J = 2 Hz, 1H), 5.64 (s, 1H), 2.96 (s, 4H), 2.68 (s, 4H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 150.06, 149.09, 147,84, 139.72, 118.59, 117.99, 113.44, 109.38, 26.00, 25.73, 24.97, 24.87; high resolution mass spectrum, calcd for $C_{13}H_{14}O_2$ 202.09938, measured 202.09852.

Pyrolysis of 5-carbomethoxy-2-methyl-3-furylmethyl Benzoate (16)

Pyrolyses were performed with ca. 100 mg of 16 at 640, 680, and 720°C using the general procedure. A quantity of 10 mL of carbon disulfide was deposited into the trap through a side arm and the trap was warmed up to -78°C and then slowly to room temperature. GC and proton NMR spectrum of the crude pyrolysate indicated the absence of any significant amount of volatile products. Polymers were the

major products in all occasions. However, GCMS did give evidence for two dimers **26** and **27** in about 1% yield each. GC/MS (70 eV) m/e (relative intensity) for **26** and **27**: 304.00 (4.62), 245.00 (7.09), 152.00 (100), 128.00 (8.30), 109.00 (6.21), 93.00 (9.46), 92.00 (11.14), 65.00 (17.61), 59.00 (11.51); 304.00 (9.19), 245.00 (8.57), 152.00 (100), 128.00 (6.94), 109.00 (2.32), 93.00 (11.24), 92.00 (11.98), 65.00 (17.94), 59.00 (11.12).

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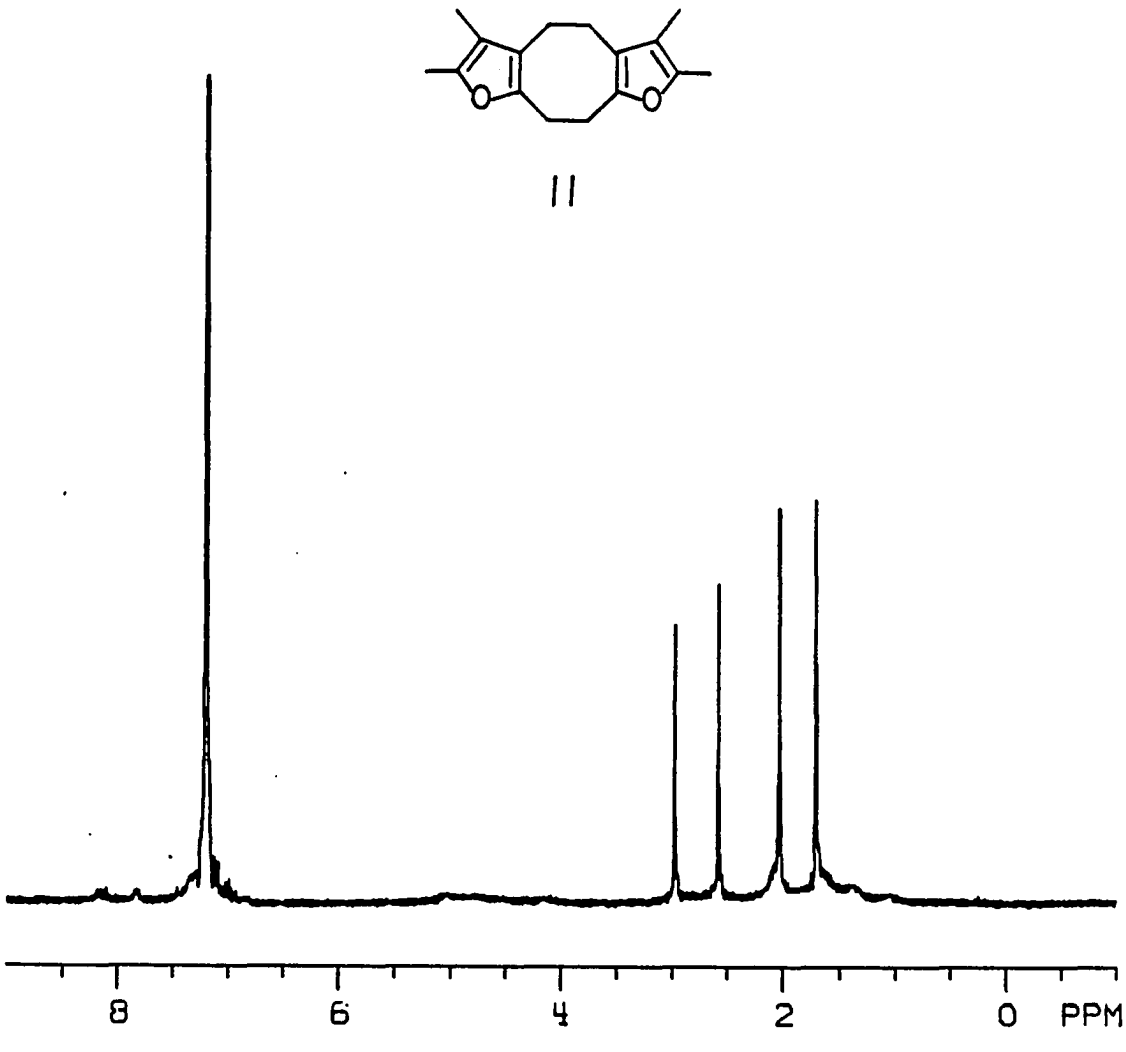
APPENDIX



11

Figure 1. Proton NMR spectrum of the [4+4] dimer 11 of 4,5-dimethyl-2,3-dimethylene-2,3-dihydrofuran (5) recorded in C_6D_6

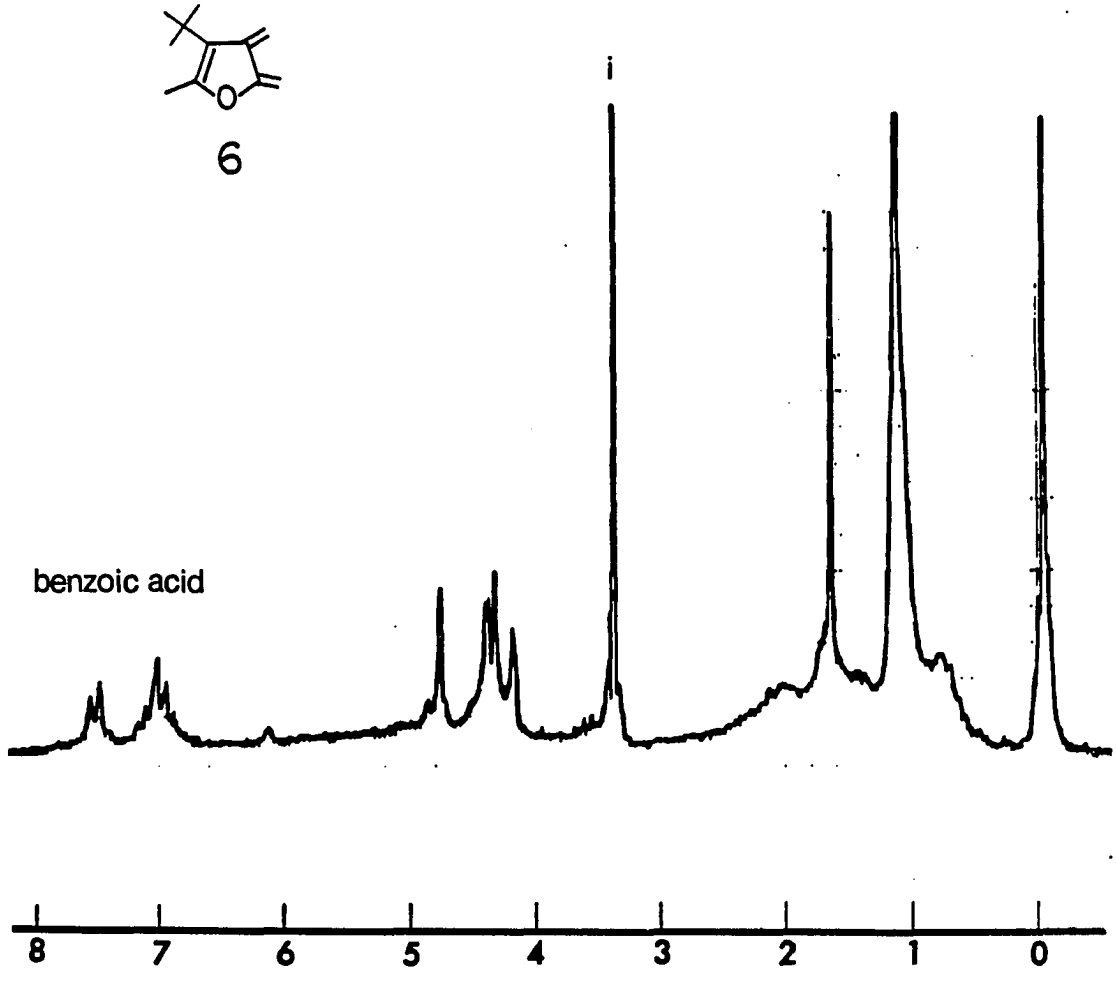


Figure 2. Proton NMR spectrum of 5-methyl-4-t-butyl-2,3-dimethylene-2,3-dihydrofuran (6) recorded at -60°C in $CDCl_3/CS_2$ (i = dibromoethane, broad signals between 0.5 - 2.5 ppm are presumed to be caused by polymers)

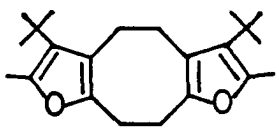


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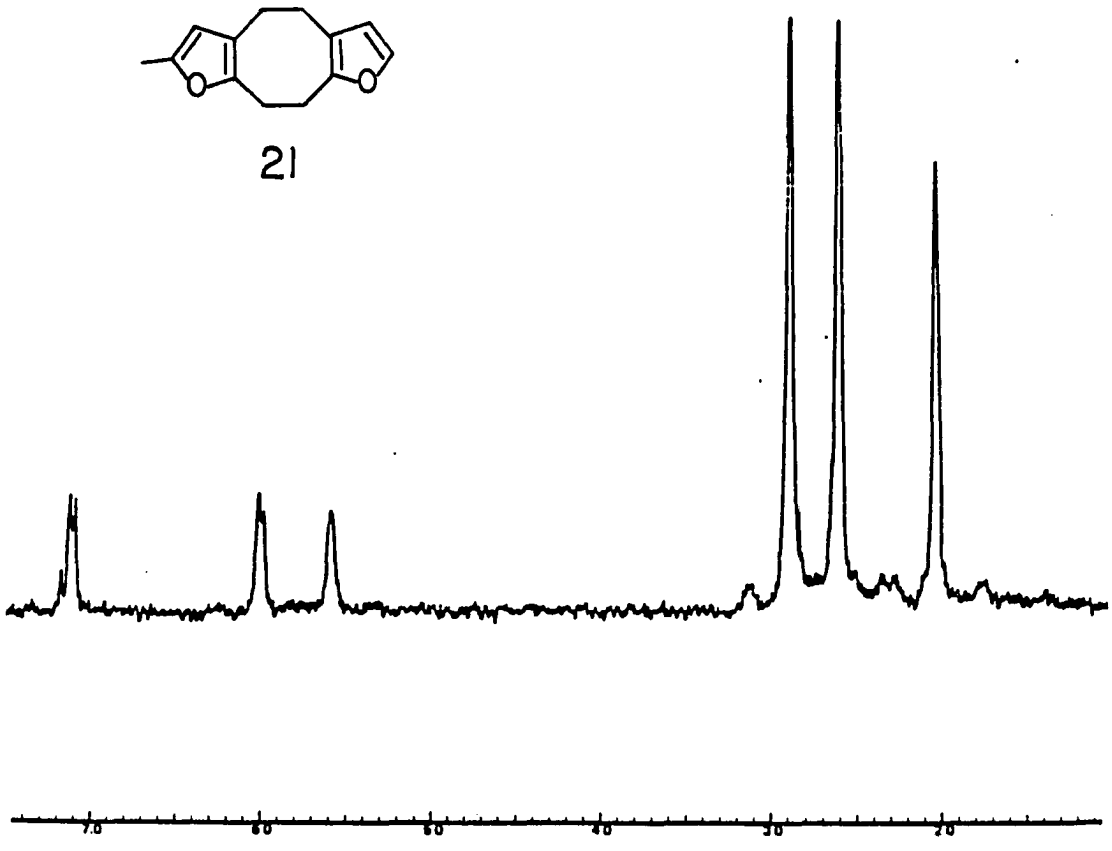
Figure 3. Proton NMR spectrum of the [4+4] dimer 15 of 5-methyl-4-t-butyl-2,3-dimethylene-2,3-dihyarofuran (6) recorded in C_6D_6



21

Figure 4. Proton NMR spectrum of the mixed dimer 21 of 2,3-dimethylene-2,3-dihydrofuran (1a) and 5-methyl-2,3-dimethylene-2,3-dihydrofuran 16 recorded in C_6D_6

SECTION III. DIELS-ALDER REACTION OF 2,3-DIMETHYLENE-2,3-DIHYDROFURAN AND o-XYLYLENE

INTRODUCTION

Despite numerous investigations over the past fifty years, the detailed mechanism for the Diels-Alder reaction[1] is still uncertain.[2-9] Opinion has swayed from one extreme where this type of [4+2] reaction is regarded as completely synchronous to the other extreme where a stepwise process involving a diradical intermediate is suggested. The former view has been gaining ground for the last decade or two, partly due to the strong influence exerted by the Woodward-Hoffmann rules[3] and the secondary deuterium isotope effect studies by Taagepera and Thornton.[10]

The stepwise mechanism, on the other hand, is still not lacking strong proponents. In 1974,[11] Dewar et al. published a preliminary account of a detailed theoretical study of the Diels-Alder reaction between 1,3-butadiene and ethylene to give cyclohexene. They were able to locate a transition state which proved to be very unsymmetric, one of the CC bonds being essentially completely formed while the other was still very weak. As expected, the opposite was proposed by Caramella et al. shortly after.[12] In 1978,[13] a theoretical study of the retro-Diels-Alder reaction of cyclohexene by Dewar again predicted the transition state to be very unsymmetric. In an attempt to determine the reaction mechanism of the Diels-Alder cycloaddition of ben-

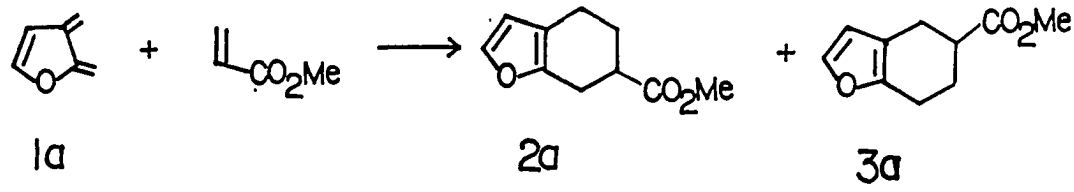
zocyclobutene with dienophiles, the stabilities for the assumed intermediate structures were examined by Kametani and coworkers[7] using MINDO/3, STO-3G and 4-31G methods. Their results also concluded that the reaction is stepwise and involves a diradical intermediate. A most recent theoretical study by Dewar et al.[8] further concluded that the Diels-Alder reaction in general proceeds via very unsymmetrical transition states, close to diradicals structurally and energetically. The regioselectivities and rates of various Diels-Alder reactions are successfully predicted on this basis.

However, a recent publication by Houk et al.[9] dealing with the Diels-Alder reaction of 1,1,4,4-tetradeuterio-1,3-butadiene with cis- or trans-1,2-dideuterioethylene has provided both experimental and theoretical evidence that are consistent with a synchronous concerted mechanism.

The reaction of butadiene with ethylene to form cyclohexene is the proto type of the Diels-Alder reaction and therefore is undoubtedly of fundamental interest. However, due to the high degree of symmetry of each reactant as well as the small HOMO-LUMO gap,[4] butadiene and ethylene are poor representatives of most other substituted systems.

We have been studying the chemistry of 2,3-dimethylene-2,3-dihydrofurans, generated by the flash vacuum pyrolysis

(FVP) of the corresponding benzoates, for many years.[14,15] Trapping of 2,3-dimethylene-2,3-dihydrofuran (1a) with methyl acrylate consistently resulted in the formation of two regioisomeric adducts 2a and 3a.

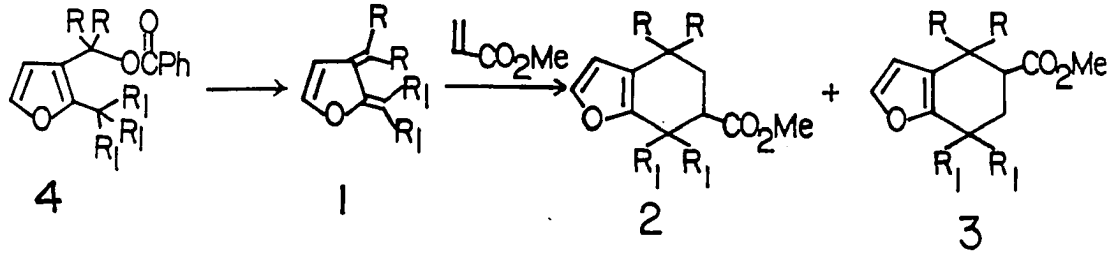


1a 2a 3a

In order to determine whether this is a concerted or a stepwise reaction, a variety of dienophiles were selected to react with 1a. The stereochemistry of the resulting adducts should give some clue concerning the reaction mechanism. In addition, two deuterated 2,3-dimethylene-2,3-dihydrofurans were prepared and trapped with methyl acrylate, and the ratios of each set of isomeric adducts were measured and compared to the parent system to determine if there is a secondary deuterium kinetic isotope effect that would support a stepwise mechanism.

RESULTS

When an excess of methyl acrylate was added to the pyrolysis product trap that contains 2,3-dimethylene-2,3-dihydrofuran (1a), 2-methylene-3-dideuteriomethylene-2,3-dihydrofuran (1b) or 2-dideuteriomethylene-3-methylene-2,3-dihydrofuran (1c), each generated from the FVP of its corresponding benzoates 4a, 4b and 4c, three pairs of isomeric adducts were obtained. The ratio of each pair of adducts can be determined by integrating the two distinctive methoxy signals in the proton NMR spectrum (see Appendix, Figures 1, 2, 3).



a. $R = R_1 = H$

b. $R = D \quad R_1 = H$

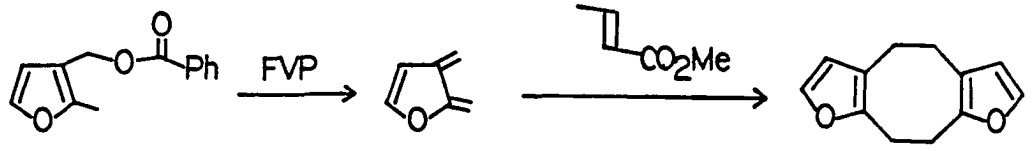
c. $R = H \quad R_1 = D$

By comparing the ratios of the three adducts, an average deuterium isotope effect[16] (k_D/k_H) of 1.06 ± 0.469 was observed (Table I).

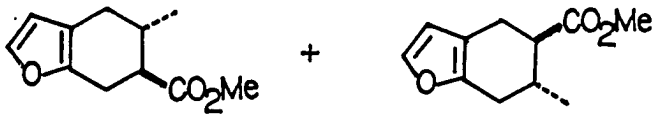
Table I. Calculation of the secondary deuterium isotope effect on the Diels-Alder reaction of 1a, 1b and 1c with methyl acrylate

	$\frac{2a}{3a}$	$\frac{2b}{3b}$	$\frac{3a}{2a}$	$\frac{3c}{2c}$	$\sqrt{\frac{2b}{3b}/\frac{2a}{3a}}$	$\sqrt{\frac{3c}{2c}/\frac{3a}{2a}}$
Run 1	3.5	4.4	0.31	0.34	1.12	1.05
Run 2	3.2	4.2	0.28	0.32	1.14	1.07

Methyl crotonate and methyl isocrotonate were used as a pair of cis-trans dienophiles in our probe into the mechanism of the [4+2] addition of 2,3-dimethylene-2,3-dihydrofuran (1a) with dienophiles. The reaction of 1a generated from the FVP of 2-methyl-3-furylmethyl benzoate (4a) with methyl crotonate gave the [4+4] dimer 5 as the major product (40%) along with 18.8% of a pair of trans adducts 6 and 7 in a 3 to 1 ratio. Apparently the reactivity of methyl crotonate toward 2,3-dimethylene-2,3-dihydrofuran (1a) is substantially lower than that of methyl acrylate. As a result the [4+4] dimerization becomes competitive despite the presence of a large excess of dienophile. The mixture of 6 and 7 was separated from 5 by column chromatography. Their structures were confirmed by NMR spectra (see Appendix, Figures 4, 5).



5

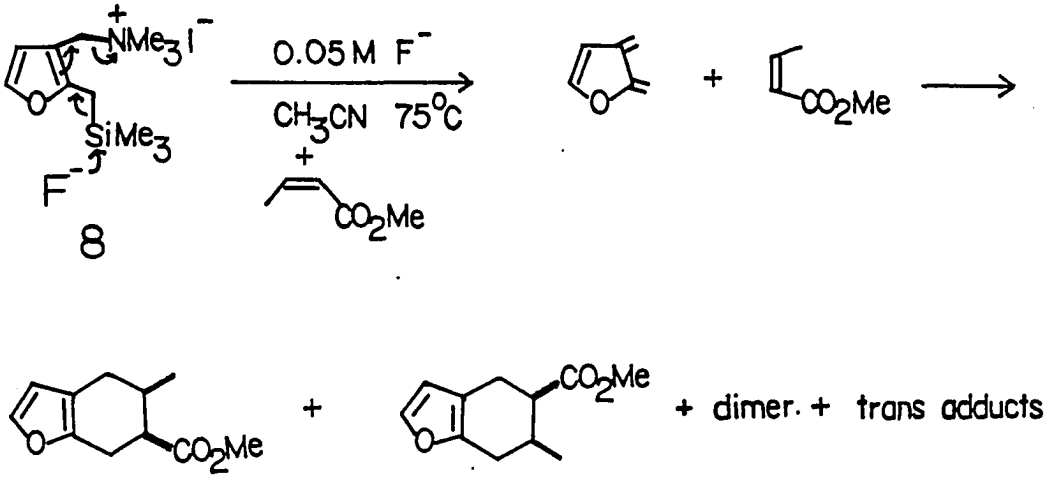


6 7

Repeated attempts to trap 1a generated pyrolytically with a large excess of methyl isocrotonate all resulted in the formation of the [4+4] dimer 5 as the only product.

We decided to generate 1a via fluoride induced 1,4-elimination from 2-methyl(trimethylsilyl)-3-furylmethyltrimethylammonium iodide (8).[17] The immediate advantage of this approach is that we can elevate the reaction temperature to allow the [4+2] cycloaddition of 1a and methyl isocrotonate to become more competitive. At the refluxing temperature of the solvent (acetonitrile), 1a was generated in the presence of methyl isocrotonate to afford again dimer 5 as the major product; however, a small amount

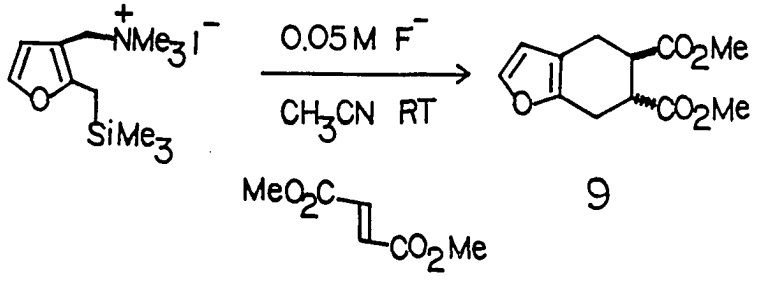
of adducts (17%) was also isolated. Proton NMR and GC analysis showed that among the mixture of adducts, 90% was the two cis adducts 6a and 7a in a 10:1 ratio, the remaining 10% was the two trans adducts.

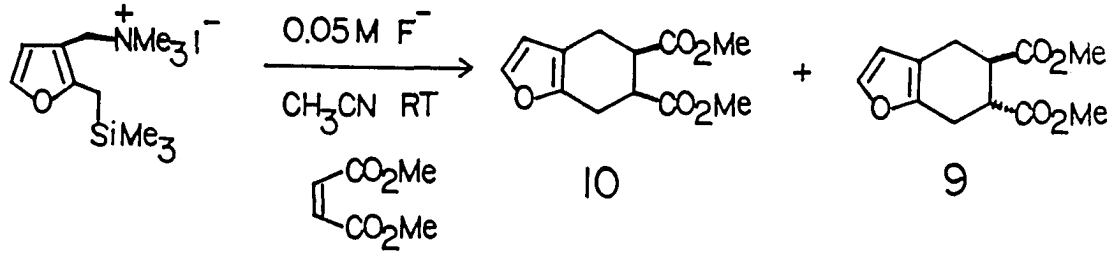


These results are inconclusive due to the contamination of methyl isocrotonate by about 5% of its trans isomer. We decided to use another pair of cis-trans dienophiles, dimethyl fumarate and dimethyl maleate, for our study because they can be acquired commercially in high purity. Due to the high melting points of these two dienophiles, the possibility of generating 1a through pyrolytic means was

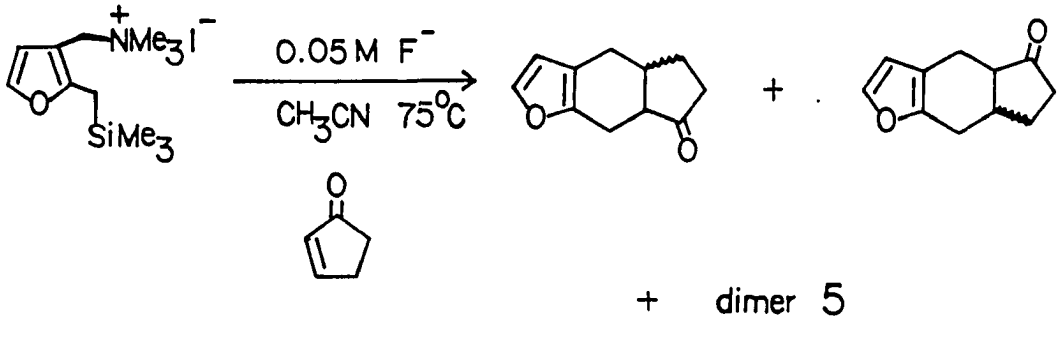
ruled out. Again, 1a was generated by the fluoride induced 1,4-elimination from iodide 8 in the presence of dienophiles.

Reaction of 1a with dimethyl fumarate gave the trans adduct 9 as the only product indicated by its NMR spectra (see Appendix, Figures 6, 7). However, reaction of 1a with dimethyl maleate afforded both 9 and its cis isomer 10 in a 4 to 1 ratio (see Appendix, Figures 6, 7) in addition to a small amount of the [4+4] dimer 5. No isomerization of the dienophile took place based on a GC analysis of the reaction mixture. The cis adduct was separated from the trans by column chromatography (see Appendix, Figures 10, 11)

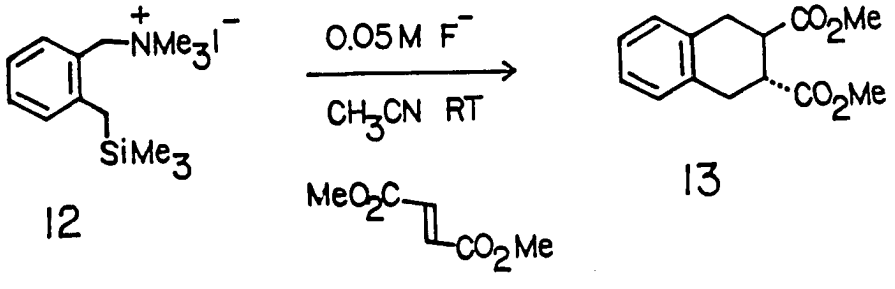




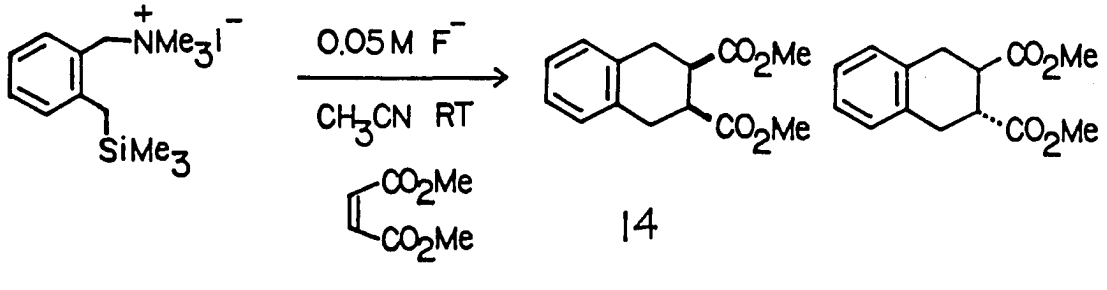
Further evidence for the non-stereospecific and non-regiospecific nature of this type of [4+2] cycloaddition was obtained from the reaction of 1a with cyclopentenone. GCMS analysis of the product mixture showed the presence of three adducts and the [4+4] dimer 5 in a 3.7:1.5:1:3.1 ratio (see Appendix, Figure 12). The mixture of adducts was separated from 5 by column chromatography to give a total yield of 21.7%. Their retention times are so close that two of them are virtually on top of one another. It is quite possible that two of the four possible adducts were not resolved. This is not unusual since GC was never able to resolve the two adducts of 1a and methyl acrylate or methyl crotonate. The proton NMR spectrum of the mixture of adducts shows evidence for at least three isomers (see Appendix, Figure 13).



We also investigated the Diels-Alder reactions of o-xylylene (11) with dienophiles. o-Xylylene could be conveniently generated at room temperature using the same fluoride induced 1,4-elimination from [o-(trimethylsilyl) methyl]benzyltrimethylammonium iodide 12.[18] Reaction of o-xylylene with dimethyl fumarate gave, as anticipated, only the trans adduct 13. However, when o-xylylene was generated in the presence of dimethyl maleate. GC analysis (see Appendix, Figure 14) and proton NMR spectroscopy (see Appendix, Figure 15) of the product mixture shows the trans adduct (NMR spectra, see Appendix, Figures 16, 17) was the major product over its cis isomer in a 2:1 ratio. The cis isomer 14 was separated from its trans isomer by column chromatography (see Appendix, Figures 18, 19).



12 13



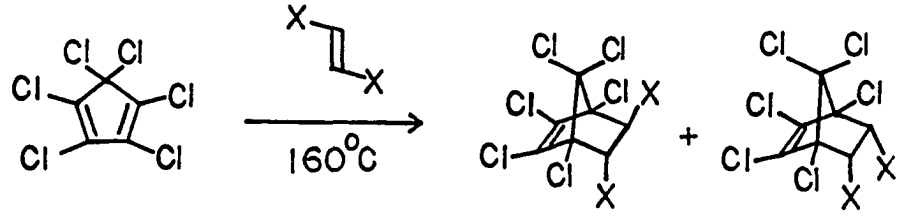
14

DISCUSSION

A statement on Diels-Alder reactions was made recently by Ciganek[5] that "there is almost unanimous agreement that the Diels-Alder reaction is a concerted [4+2] process". This is quite surprising since even Houk, one of the most prominent proponents of the concerted mechanism for the Diels-Alder reaction, admits that "Diels-Alder reactions of substituted dienes and dienophiles have been found to occur by both concerted and stepwise mechanisms."[9]

A more sensible middle ground on the controversy seems to be that the stereospecific [4+2] cycloaddition in Diels-Alder reactions represents the rule, and the non-stereospecific ones are the exception. In fact, in addition to numerous theoretical studies that conclude a stepwise mechansim involving diradical intermediates for the Diels-Alder reaction,[8] there do exist experimental results to support the stepwise process. According to Sauer amd Sustmann's rationalization,[4] one can expect the stepwise mechanism, thus perhaps a non-stereospecific reaction when the HOMO-LUMO separation is large. Also, substituents such as electron withdrawing groups capable of stabilizing diradical intermediates will favor the stepwise mechanism. Houk also gave similar arguments.[19] The experimental

evidence reported in the literature does confirm these considerations. The Diels-Alder reaction of hexachlorocyclopentadiene (15) with different dienophiles described by Mark[20] gave results that can only be explained on the basis of diradical intermediates.

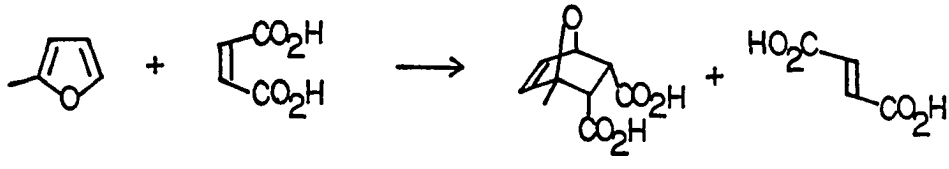


a. X = Cl	5	:	95
b. X = CN	57	:	43
c. X = Ph	71	:	29
d. X = CO_2Me	73	:	27
e. X = Me	100	:	0

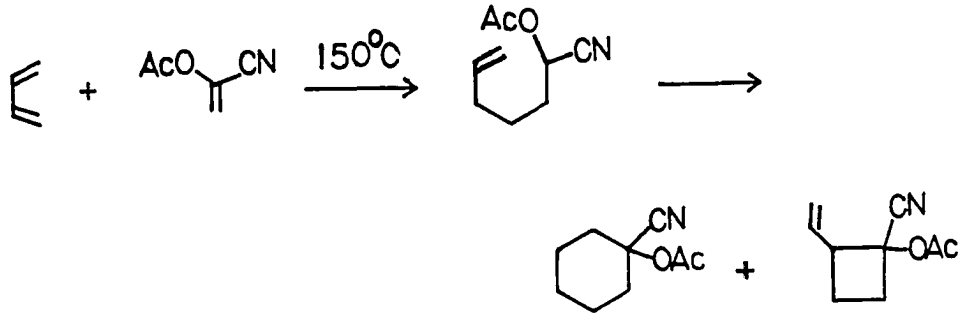
Huybrechts and van Mele[21] also reported that the [4+2] addition of 1,3-cyclohexadiene to cis- and trans- butene to be non-stereospecific.

Another example of a non-concerted cycloaddition can be seen from the reactions of furans with maleic acid.[22] When 2-methylfuran was allowed to react with maleic acid, up to 17% of fumaric acid was recovered. No fumaric acid was

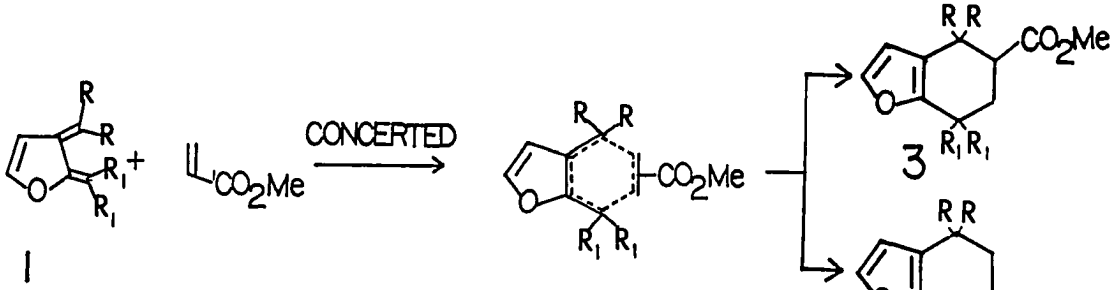
found when furan and 2,5-dimethylfuran were subjected to the same reaction conditions. The observation was explained in terms of a reversible formation of a zwitterionic intermediate.



Further evidence for a stepwise Diels-Alder reaction was reported by Little[23] on the reaction of butadiene and 1-cyanovinyl acetate. When butadiene was allowed to react with 1-cyanovinyl acetate in benzene at 150°C, the cyclohexane adduct and the vinylcyclobutane were recovered in a 7:1 ratio. A common diradical intermediate was proposed. Similar results were reported by Banks et al.[24]



The Diels-Alder reaction of 2,3-dimethylene-2,3-dihydrofuran (1a) and its two deuterated analogues 1b and 1c with methyl acrylate gave a pair of isomeric adducts in each case. If this follows a concerted mechanism, the deuterium isotope effect would enhance the rate of the formation of adducts 2b, 3b, 2c and 3c by an equal factor. In other words, the ratios 2b/3b and 2c/3c should remain unchanged from 2a/3a.



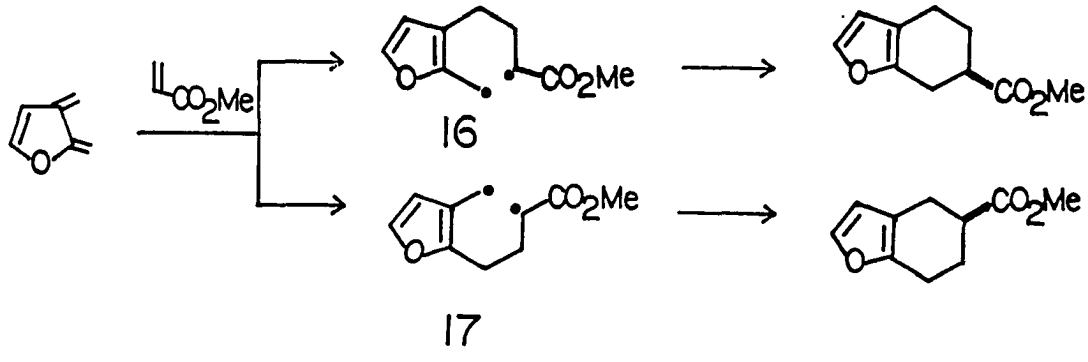
1

a. $R = R_1 = H$

b. $R = D \quad R_1 = H$

c. $R = H \quad R_1 = D$

In our study, a secondary deuterium isotope effect of 1.1 was detected by comparing the ratios of three adduct pairs. This can best be explained by a stepwise mechanism that involves diradical intermediates 16 and 17, and the rate-determining step involves bonding at either exomethylene position with the unsubstituted end of methyl acrylate.

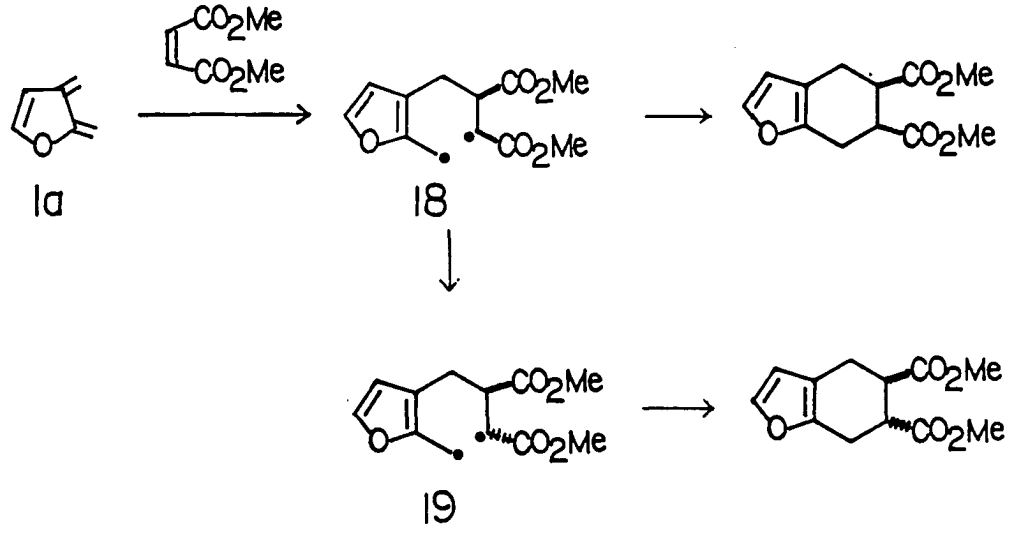


16

17

Stereospecificity is a necessary result of a concerted cycloaddition. In stepwise cycloadditions, the stereochemical course depends largely on the relative rates of the ring closure and the bond rotation within the intermediate. A stepwise mechanism with a diradical intermediate would lead to a non-stereospecific reaction if rotations about single bonds in the intermediate are faster than ring closure to the cycloadduct; if, however, rotations are slower than the normally fast ring closure reaction, a stepwise reaction can also take place stereospecifically. Therefore, the observation of stereospecificity does not guarantee a concerted mechanism, but a non-stereospecific cycloaddition reaction is always a good indication of a stepwise mechanism.

When 2,3-dimethylene-2,3-dihydrofuran (1a) was allowed to react with dimethyl maleate; both the trans and the cis adducts were formed in a 4:1 ratio. This result strongly suggests that a stepwise mechanism was involved in this [4+2] cycloaddition. The life time of the intermediate diradical 18 is long enough to allow the bond rotation to place in favor of the transoid intermediate 19. This also explains why no cis adduct was found in the reaction of 1a with dimethyl fumarate since the intermediate was already in the favored transoid form.



Similar argument can be used to explain the Diels-Alder reaction of o-xylylene with dimethyl maleate that gives both trans and cis adducts in a 2:1 ratio. This result is

especially pertinent since it offers experimental evidence for a previous theoretical study by Kametani et al. that favors a stepwise mechanism for the Diels-Alder cycloaddition of o-xylylene with dienophiles.[7]

The best evidence for a stepwise Diels-Alder mechanism would be the detection of a true intermediate. Nevertheless, our results do provide unambiguous evidence that the Diels-Alder reactions of 2,3-dimethylene-2,3-dihydrofuran (2) with methyl acrylate, methyl isocrotonate, dimethyl maleate, and cyclopentenone and o-xylylene with dimethyl maleate are non-stereospecific and therefore, stepwise.

EXPERIMENTAL

Methods and Equipment

The pyrolysis apparatus has been previously described.[25] NMR spectra were recorded on Varian E 360, JOEL FX-90Q or Nicolet-300 spectrometers. High resolution mass spectra were measured with an Associated Electronics Industries MS-902 instrument at 70eV. Gas chromatography/ mass spectroscopy (GC/MS) was performed with a Finnigan 4000 instrument and an INCOS data system. GLC analyses were performed with a Hewlett Packard HP 5840A instrument with a 25 meter, SP 2100 thin film (methylsilicone-coated) capillary column.

2-Methyl-3-furylmethyl Benzoate (4a)

2-Methyl-3-furylmethyl benzoate (4a) was prepared with modifications of the procedure by Trahanovsky et al.[15]

Purification by vacuum distillation yielded 8.76 g (40.5 mmole, 90%) of 4a: IR (thin film) 1720, 1605, 1450, 1320, 1250, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.2-7.9 (m, 2H), 7.5-7.3 (m, 3H), 7.25 (d, J = 2 Hz, 1H), 6.40 (d, J = 2 Hz, 1H), 5.14 (s, 2H), 2.36 (s, 3H).

2-Methyl-3-furylmethyl-α,α-d_2 Benzoate (4b)

2-Methyl-3-furylmethyl-α,α-d_2 benzoate (4b) was prepared with modifications of the procedure by Trahanovsky et al.[15]

Purification of the crude product by vacuum distillation yielded 8.5 g (39.0 mmole, 89.4%) of 4b: IR (thin film) 1720, 1600, 1520, 1275, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22-7.25 (m, 5H), 7.20 (d, J = 2 Hz, 1H), 6.34 (d, J = 2 Hz, 1H), 2.35 (s, 3H).

2-Trideuteriomethyl-3-furylmethyl Benzoate (4c)

2-Trideuteriomethyl-3-furylmethyl benzoate (4c) was kindly provided by C. H. Chou.

Isocrotonic Acid

A quantity of 9.0 g (0.1 mole, 50%) of isocrotonic acid was prepared from 1,3-dibromo-2-butanone by the procedure of Rappe.[26]

For isocrotonic acid: ^1H NMR ($CDCl_3$) δ 8.12 (br, 1H), 6.73-6.18 (m, 1H), 6.08-5.64 (m, 1H), 2.15 (dd, J = 8 Hz, 1.5 Hz, 3H).

Methyl Isocrotonate

Methyl isocrotonate was prepared from isocrotonic acid by the procedure of Bowden.[27]

Purification of the crude product by vacuum distillation gave 6.5 g (0.07 mole, 58.3%) of methyl isocrotonate (95% cis, 5% trans): ^1H NMR ($CDCl_3$) δ 6.52-6.08 (m, 1H), 5.85-5.70 (m, 1H), 3.72 (s, 3H), 2.10 (dd, J = 8 Hz, 1.5 Hz).

2-Methyl(trimethylsilyl)-3-furylmethyltrimethylammonium Iodide (8)

2-Methyl(trimethylsilyl)-3-furylmethyltrimethylammonium iodide (8) was prepared by the suggestion of Wiseman.[17]

A solution of 8.0 g (55.4 mmole) of 2-methyl-3-furoyl chloride in 40 mL of dimethylamine (30% in H_2O) was stirred overnight at room temperature. The solution was extracted with ether; the organic layer was washed with brine, dried and concentrated to give 6.8 g (44.4 mole, 80.1%) of N,N-dimethyl-2-methyl-3-furamide: ^1H NMR ($CDCl_3$) δ 7.28 (d, J = 2 Hz, 1H), 6.47 (d, J = 2 Hz, 1H), 3.10 (s, 6H), 2.35 (s, 3H). To a solution of LDA (43.0 mmole) in THF at -78°C which was being stirred was added 6.0 g (39.2 mmole) of the amide. The resulting deep red mixture was stirred for 20 min, 4.9 g (43.0 mmole) of chlorotrimethylsilane was then added rapidly to minimize disilylation. The mixture turned light orange and was allowed to stand overnight. After the addition of water, the mixture was extracted with ether.

The organic layer was separated and washed with $NaHCO_3$ and brine. The crude product was dried and concentrated to give 7.7 g (34.2 mmole, 87.2%) of N,N-dimethyl-2-(trimethylsilyl)methyl-3-furamide: ^1H NMR ($CDCl_3$) δ 7.12 (s, 1H), 6.29 (s, 1H), 2.92 (s, 6H), 2.26 (s, 3H), -0.18 (s, 9H). To a slurry of 1.2 g (31 mmole) of LAH in 40 mL of ether was added 7.0 g (31 mmole) of the amide at 0°C. The suspension was stirred overnight and a standard workup[28] yielded 4.9 g (23.2 mmole) of N,N-dimethyl-2-(trimethylsilyl)methyl-3-furyl-methylamine. A solution of 4.9 g (23.2 mmole) of the amine and 16.5 g (116 mmole) of methyl iodide in 50 mL of acetonitrile was stirred overnight. After the addition of ether to the reaction mixture, iodide 8 precipitated out as a yellowish solid. Recrystallized from ethyl acetate/acetone (1:1) yielded 7.2 g (20.4 mmole, 88.2%) of 8 as a white solid: mp 214-216°C; ^1H NMR (CD_3CN) δ 7.40 (d, J = 2 Hz, 1H), 6.45 (d, J = 2 Hz, 1H), 4.32 (s, 2H), 3.05 (s, 9H), 2.25 (s, 2H), 0.05 (s, 9H).

General Pyrolysis Procedure

The pyrolyses were run at furnace temperatures from 400 to 800°C. The sample chamber was heated to 60-70°C and the system was evacuated to ca. 10^{-5} Torr during the pyrolysis. A condenser was inserted between the quartz pyrolysis tube

and the liquid nitrogen-cooled trap to collect the unreacted starting material and the benzoic acid formed as a byproduct. The liquid nitrogen-cooled trap was used to collect the products. Upon completion of the pyrolysis, dienophiles were introduced through the side arm, and the trap was warmed to -78°C for several hours and then slowly to room temperature.

Diels-Alder Reaction of 2,3-Dimethylene-2,3-dihyrofuran (1a) with Methyl Acrylate

A 335 mg (1.55 mmole) quantity of 2-methyl-3-furyl-methyl benzoate (4a) was pyrolyzed at 620°C. A solution of 10 mL of methyl acrylate and 10 mL of carbon disulfide was deposited into the trap when the pyrolysis was completed. The trap was warmed to -78°C and then slowly to room temperature. The mixture was concentrated to give the crude product which was purified by column chromatography (silica gel, 5% ether in hexane) to give 122 mg (0.68 mmole, 44%) of the Diels-Alder adducts 2a and 3a (3.5:1): ^{1}H NMR (C_6D_6) δ 7.15 (d, J = 2 Hz, 1H), 6.05 (d, J = 2 Hz, 1H), 3.37 (s, 0.67H), 3.34 (s, 2.33H), 2.90-1.58 (m, 7H).

Diels-Alder Reaction of 2-Methylene-3-dideuteriomethylene-2,3-dihydrofuran (1b) with Methyl Acrylate

A 285 mg (1.3 mmole) quantity of 2-methyl-3-furyl-methyl-α,α-d2 benzoate (4b) was pyrolyzed at 627°C using the

procedure described for the reaction 2,3-dimethylene-2,3-dihydrofuran (1a) with methyl acrylate. Purification of the crude product by column chromatography gave 98 mg (0.53 mmole, 41%) of the Diels-Alder adducts 2b and 2c (4.4:1): ^{1}H NMR (C_6D_6) δ 7.18 (d, J = 2 Hz, 1H), 6.05 (d, J = 2 Hz, 1H), 3.38 (s, 0.56H), 3.35 (s, 2.44H), 2.0-1.62 (m, 5H); high resolution mass spectrum, calcd for $C_{10}H_{10}D_2O_3$ 182.09129, measured 182.09113.

Diels-Alder Reaction of 2-Dideuteriomethylene-3-methylene-2,3-dihydrofuran (1c) with Methyl Acrylate

A 277 mg (1.26 mmole) quantity of 2-trideuteriomethyl-3-furylmethyl benzoate (4c) was pyrolyzed at 620°C using the procedure described for the reaction of 2,3-dimethylene-2,3-dihydrofuran (1a) with methyl acrylate. Purification of the crude product by column chromatography gave 103 mg (0.567 mmole, 45%) of the Diels-Alder adducts 2c and 3c (2.9:1): ^{1}H NMR (C_6D_6) δ 7.18 (d, J = 2 Hz, 1H), 6.04 (d, J = 2 Hz, 1H), 3.39 (s, 0.76H), 3.36 (s, 2.23H), 2.78-1.70 (m, 5H); high resolution mass spectrum, calcd for $C_{10}H_{10}D_2O_3$ 182.09129, measured 182.09098.

Diels-Alder Reaction of 2,3-Dimethylene-2,3-dihydrofuran (1a) with Methyl Crotonate

A 0.5 g (2.3 mmole) quantity of 2-methyl-3-furylmethyl benzoate (4a) was pyrolyzed at 590°C. A solution of 20 mL

of methyl crotonate in 20 mL of carbon disulfide was deposited into the trap during the pyrolysis. Upon completion, the trap was warmed to -78°C and then slowly to room temperature. GCMS analysis of the crude product mixture showed that the [4+4] dimer and the adducts were present in a 2:1 ratio. A quantity of 84 mg (0.43 mmole, 18.8%) of the adducts was separated from the dimer by column chromatography on silica gel (2% ether in hexane). Proton NMR analysis indicated adducts 6 and 7 were obtained in a 3:1 ratio: ^{1}H NMR (C_6D_6) δ 7.18 (d, J = 1.5 Hz, 1H), 6.05 (d, J = 1.5 Hz, 1H), 3.39 (s, 0.75H), 3.35 (s, 2.25H), 2.05-1.84 (m, 6H), 0.91 (d, J = 6 Hz, 2.25H), 0.84 (d, J = 6 Hz, 0.75H); ^{13}C NMR (C_6D_6) δ for 6: 125.23, 148.11, 140.90, 115.86, 110.00, 51.51, 47.40, 31.97, 29.71. 26.02, 19.24; for 7: 175.61, 149.22, 140.74, 114.6, 109.91, 51.45, 47.50, 31.83, 30.50, 25.24, 19.60; GC/MS (70eV) m/e (% base peak) 194.16 (15.48), 163.14 (4.65), 135.16 (35.41), 134.14 (90.31), 119.12 (46.50), 117.14 (8.30), 108.16 (35.71), 105.14 (17.61), 95.04 (9.12), 94.06 (100.00, 91.10 (37.51), 81.10 (12.55), 65.08 (15.61).

Diels-Alder Reaction of 2,3-Dimethylene-2,3-dihydrofuran (1a) with Methyl Isocronate

A solution of 0.44 g (1.68 mmole) of tetrabutylammonium fluoride (0.05 M in acetonitrile) was added dropwise to a

refluxing solution of 0.5 g (1.40 mmole) of 2-methyl(trimethylsilyl)-3-furylmethyltrimethylammonium iodide (8) and 1.4 g (14.0 mmole) of methyl isocronate (95% cis, 5% trans) in 20 ml of acetonitrile. After the addition, the solvent was removed under vacuum, and the residue was extracted with ether (20 mL x 3). The organic layer was washed with sodium bicarbonate and brine. GC analysis of the crude product mixture showed the presence of the [4+4] dimer as the major product accompanied by some adducts. The adducts (46 mg, 17%) were separated from the dimer by column chromatography on silica gel (2% ether in hexane). The proton NMR spectrum indicated that 90% were the two cis adducts in a 10:1 ratio. In addition, 10% of the trans adducts were also found in the mixture. For the major adduct: ^{1}H NMR ($CDCl_3$) δ 7.07 (d, J = 1 Hz, 1H), 5.97 (d, J = 1 Hz, 1H), 3.25 (s, 3H), 3.02-2.05 (m, 6H), 0.83 (d, J = 7.0 Hz, 3H) (see Appendix, Figure 20); ^{13}C NMR ($CDCl_3$) δ 174.21, 147.95, 141.01, 114.90, 110.61, 51.63, 44.16, 30.02, 28.99, 22.24, 14.91 (see Appendix, Figure 21); GC/MS (70eV) m/e (% base peak) 194.04 (26.49), 163.04 (5.94), 135.06 (33.14), 134.06 (100.00), 119.02 (51.77), 117.04 (6.34), 108.04 (38.46), 105.04 (15.58), 94.04 (61.69), 91.04 (35.20), 81.02 (11.70), 65.04 (14.13).

Diels-Alder Reaction of 2,3-Dimethylene-2,3-dihydrofuran (1a) with Dimethyl Fumarate

A quantity of 0.2 g (0.55 mmole) of iodide 8 was allowed to react with dimethyl fumarate using the procedure described for the reaction of 2,3-dimethylene-2,3-dihydrofuran (1a) and methyl isocrotonate with the exception that This reaction was performed at room temperature.

Purification of the crude mixture by column chromatography on silica gel (30% ether in hexane) afforded 83.3 mg (0.35 mmole, 63.6%) of one single adduct, presumably trans 9: ^{1}H NMR (C_6D_6) δ 7.05 (d, J = 1.5 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 3.18-2.42 (m, 6H); ^{13}C NMR (C_6D_6) δ 174.03, 173.64, 147.65, 141.29, 114.95, 109.03, 51.29, 42.12, 41.95, 25.39, 24.49; high resolution mass spectrum, calcd for $C_{12}H_{14}O_5$ 238.08413, measured 238.08465.

Diels-Alder Reaction of 2,3-Dimethylene-2,3-dihydrofuran (1a) with Dimethyl Maleate

The procedure used in the reaction of 2,3-dimethylene-2,3-dihydrofuran and methyl isocrotonate was followed here with the exception that this reaction was performed at room temperature.

GCMS analysis and proton NMR spectroscopy of the crude product showed the presence of two adducts 9 and 10 (70.8 mg, 0.29 mmole, 52.7%) in a 4 to 1 ratio (see Appendix,

Figures 8 and 9). GC analysis also showed that dimethyl maleate did not isomerize. The cis adduct **10** was separated from 9 by column chromatography on silica gel (30% ether in hexane): ^{1}H NMR (C_6D_6) δ 7.03 (d, J = 1Hz, 1H), 5.97 (d, J = 1Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 3.20-2.52 (m, 6H); ^{13}C NMR (C_6D_6) δ 172.68, 172.15, 148.47, 141.29, 115.28, 110.09, 51.18, 51.12, 40.96, 24.20, 23.03 (see Appendix, Figures 10 and 11); high resolution mass spectrum, calcd for $C_{12}H_{14}O_5$ 238.08413, measured 238.08408.

Diels-Alder Reaction of o-Xylylene (11) with Dimethyl Fumarate

A solution of 0.19 g (0.76 mmole) of tetrabutylammonium fluoride (0.05 M in CH_3CN) was added dropwise to a solution of 0.25 g (0.69 mmole) of [o-methyl(trimethylsilyl)benzyl]-trimethylammonium iodide (12) and 1.98 g (13.7 mmole) of dimethyl fumarate in 20 mL of acetonitrile at room temperature. After the addition, the solvent was removed under vacuum and the residue was extracted with ether (20 mL x 3). The ether layer was washed with sodium bicarbonate and brine. GCMS analysis of the crude product mixture indicated that only one adduct, presumably the trans isomer **13**, was formed. Purification by column chromatography on silica gel (30% ether in hexane) gave 102 mg (0.41 mmole, 59.6%) of the trans adduct **13**: ^{1}H NMR (C_6D_6) δ 7.12-6.82

(m, 4H), 3.45 (s, 3H), 3.18-2.70 (m, 4H); ^{13}C NMR (C_6D_6) δ 174.16, 133.97, 128.51, 126.18, 51.18, 42.16, 31.68 (see Appendix, Figures 16, 17); high resolution mass spectrum, calcd for $C_{14}H_{16}O_4$ 248.10486, measured 248.10470.

Diels-Alder Reaction of o-Xylylene (11) with Dimethyl Maleate

The procedure used in the reaction of o-xylylene with dimethyl fumarate was followed here.

GCMS analysis and proton NMR spectroscopy (see Appendix, Figures 14, 15) of the product mixture showed the presence of two adducts in 2:1 ratio (crude weight 97 mg, 0.39 mmole, 56.6%). Also, a trace amount (<1%) of the dimers was detected. Cis adduct 14 was separated from 13 by column chromatography on silica gel (30% ether in hexane): ^1H NMR (C_6D_6) δ 7.09-6.85 (m, 4H), 3.37 (s, 3H), 3.02-2.80 (m, 4H); ^{13}C NMR (C_6D_6) δ 173.85, 134.04, 128.96, 126.05, 51.05, 40.51, 29.80 (see Appendix, Figures 18 and 19); high resolution mass spectrum, calcd for $C_{14}H_{16}O_4$ 248.10486, measured 248.10501.

Diels-Alder Reaction of 2,3-Dimethylene-2,3-dihydrofuran (1a) with Cyclopentenone (15)

The procedure used in the reaction of 1a with isocrotonate was followed here.

GCMS analysis of the crude product showed the presence of three adducts and the [4+4] dimer 5 in a 3.7:1.5:1:3.1 ratio (see Appendix, Figure 12). Separation of the mixture of adducts from 5 by column chromatography gave 42 mg (0.24 mmole, 21.7%) of the adducts: ^{1}H NMR (C_6D_6) δ 7.22 (br, 1H), 7.19 (m, 1H), 6.12 (shoulder), 6.11 (d, J = 1.8 Hz, 1H), 6.05 (d, J = 1.8 Hz, 1H), 3.45-1.02 (m, 20H) (see Appendix, Figure 13); GC/MS (70eV) m/e (% base peak) A: 176.10 (100.00), 161.10 (12.27), 148.08 (17.86), 147.06 (25.68), 133.06 (24.85), 132.06 (53.30), 131.06 (41.31), 119.06 (30.10), 94.04 (80.68), 91.06 (81.55), 65.06 (34.37); B: 176.00 (58.40), 161.00 (7.02), 148.00 (13.66), 147.00 (12.21), 133.00 (12.37), 131.00 (14.98), 119.00 (14.06), 94.00 (100.00), 91.00 (42.76), 81.00 (26.85); C: 176.10 (100.00), 161.10 (12.27), 148.08 (17.86), 147.06 (25.68), 133.06 (24.85), 132.06 (53.10), 131.06 (41.31), 119.06 (30.10), 94.04 (80.68), 91.06 (81.55), 81.02 (20.51).

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APPENDIX

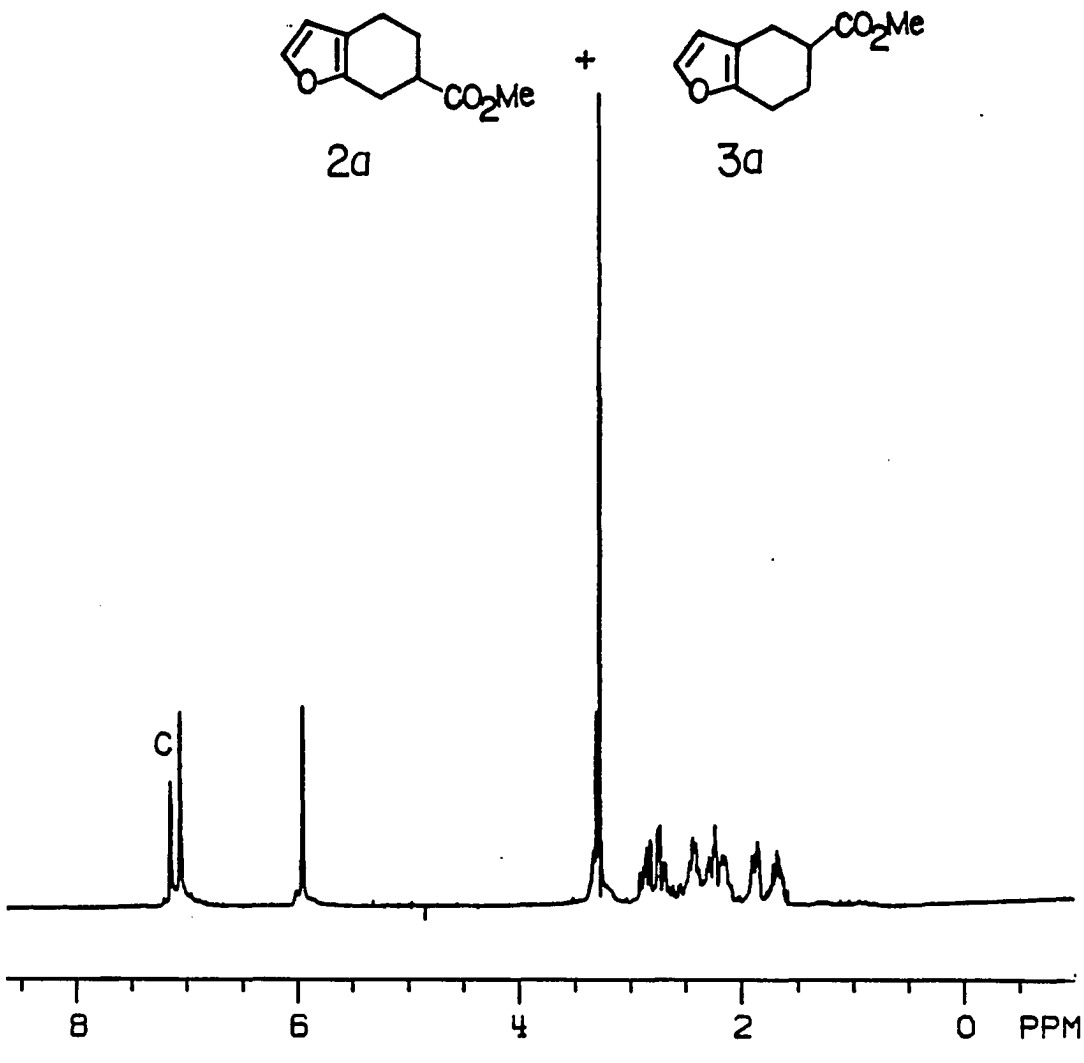


Figure 1. Proton NMR spectrum of the Diels-Alder adducts 2a and 3a in $CDCl_3$ (c = $CHCl_3$)

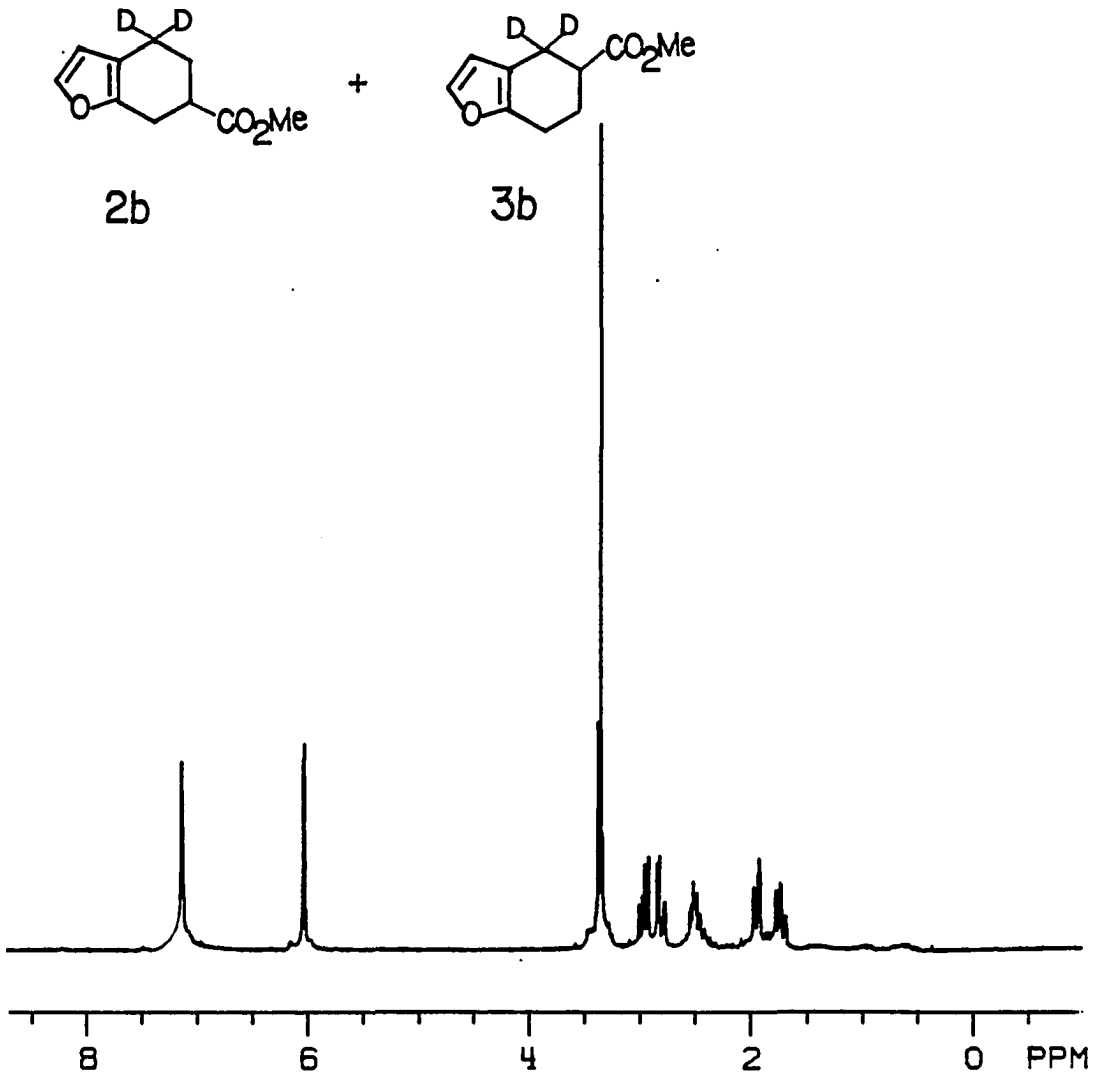


Figure 2. Proton NMR spectrum of the Diels-Alder adducts 2b and 3b in $CDCl_3$

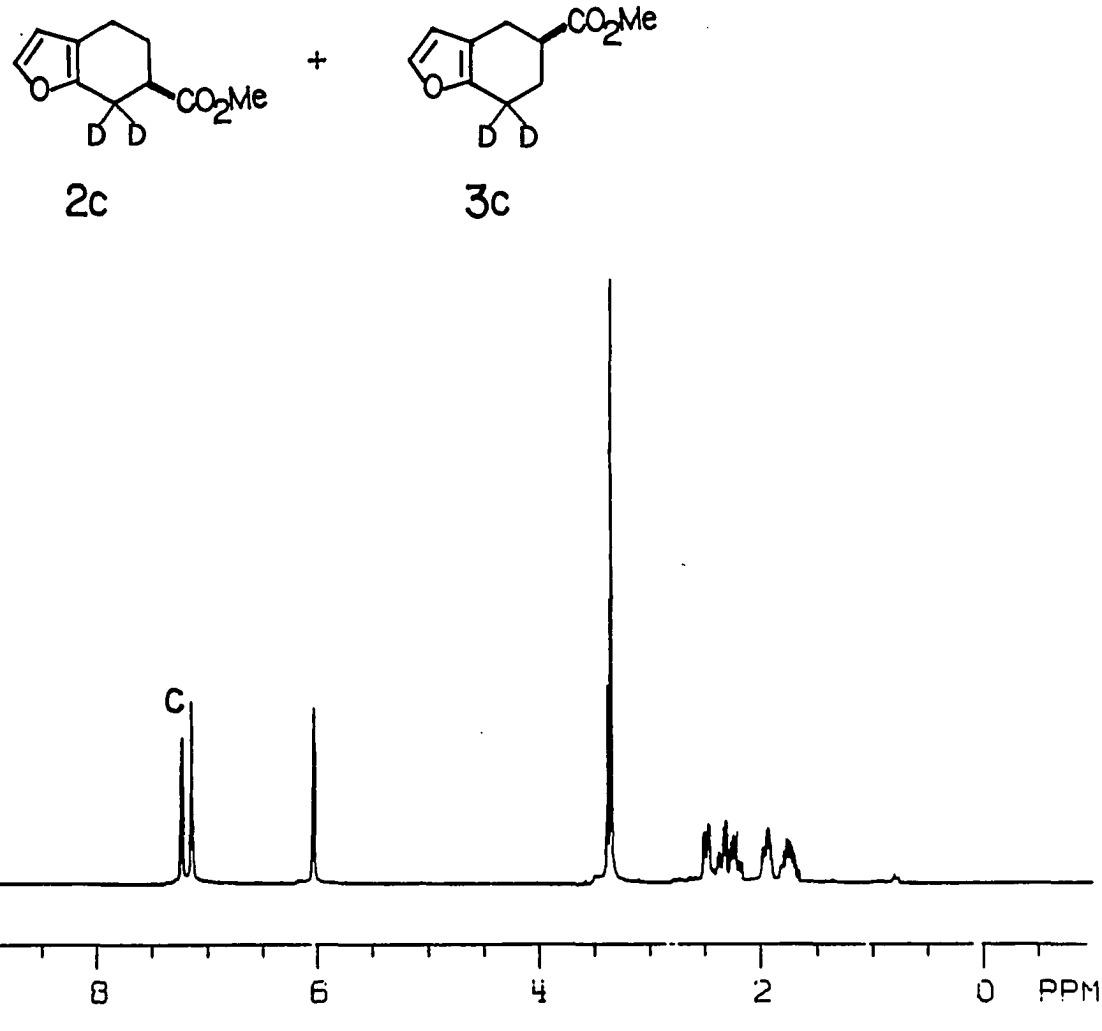


Figure 3. Proton NMR spectrum of the Diels-Alder adducts 2c and 3c in $CDCl_3$ (c = chloroform)

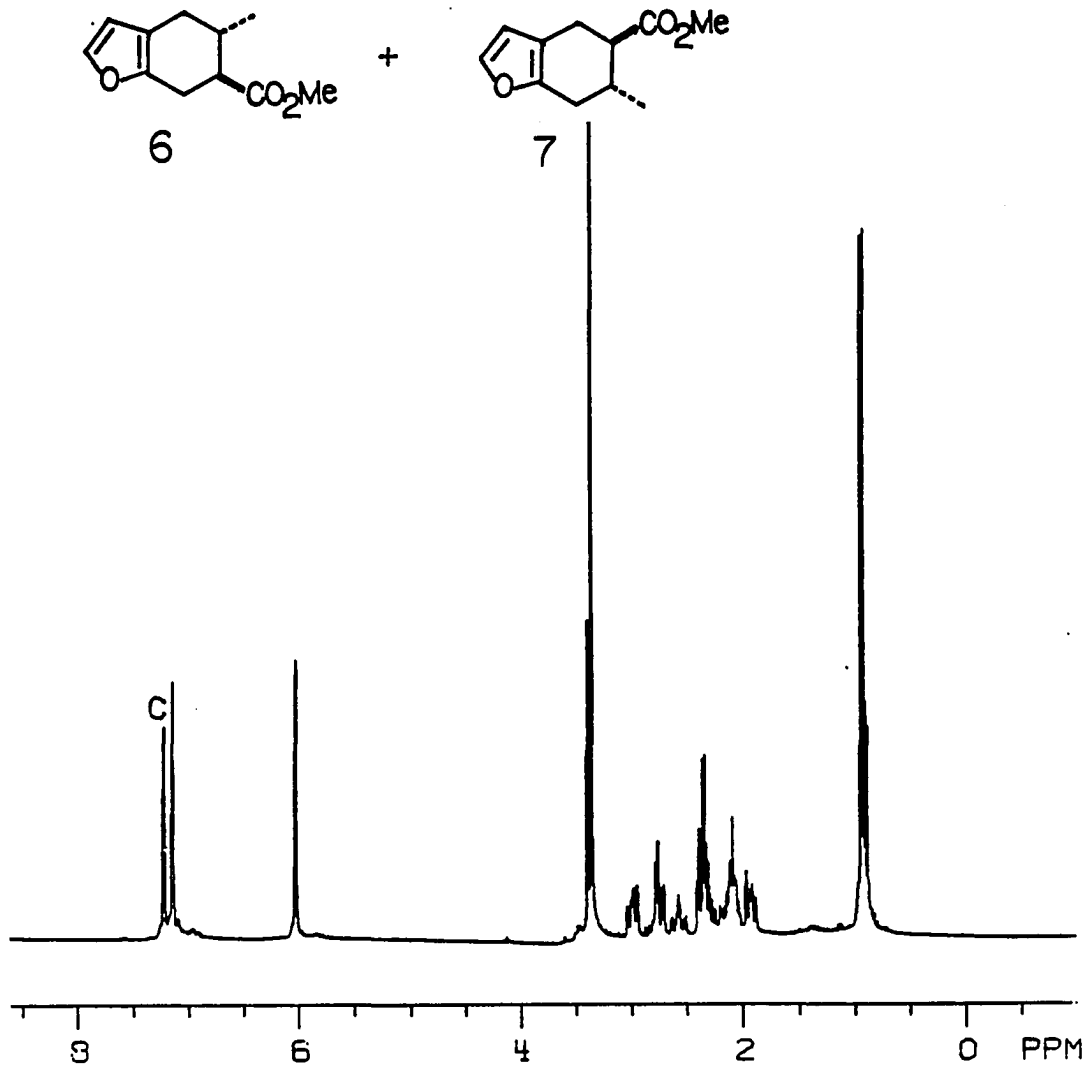
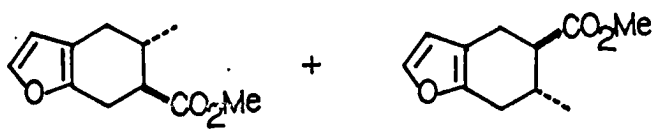


Figure 4. Proton NMR spectrum of the Diels-Alder adducts 6 and 7 recorded in $CDCl_3$ (c = chloroform)



6 7

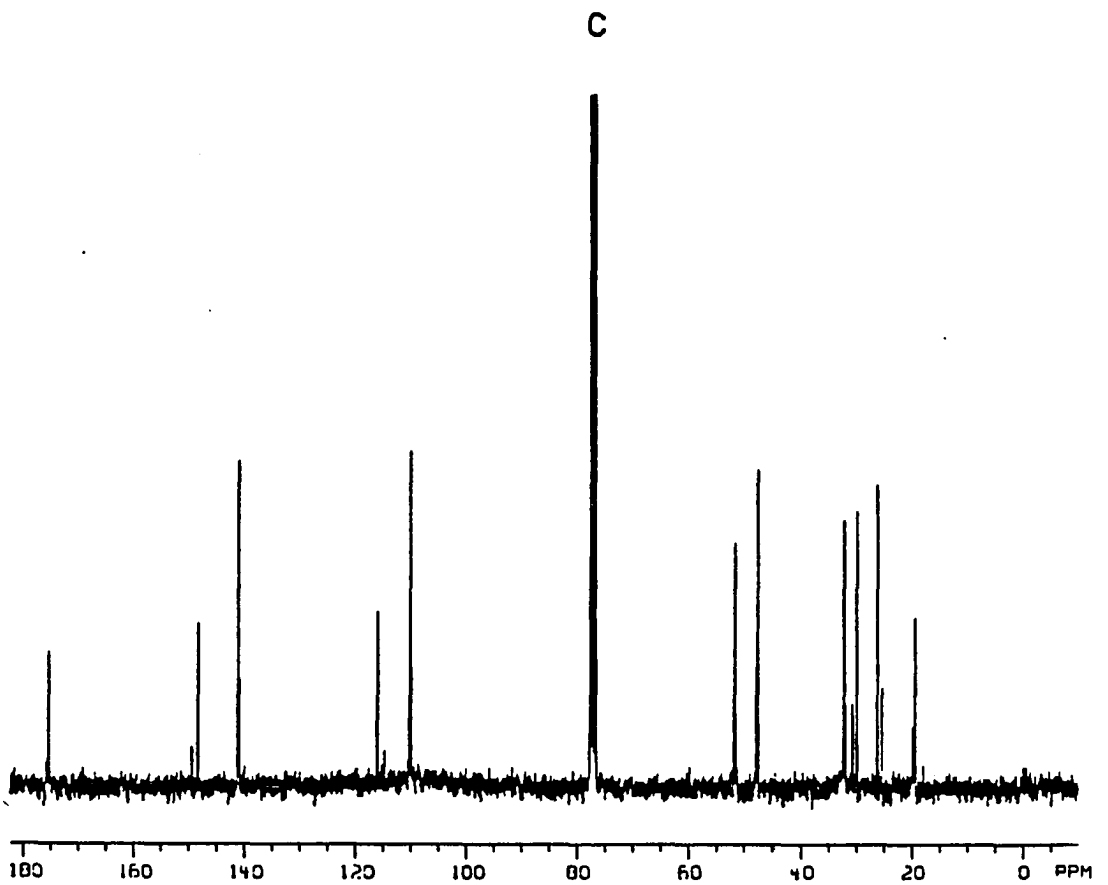


Figure 5. ^{13}C NMR spectrum of Diels-Alder adducts 6 and 7 in $CDCl_3$ (c = chloroform)

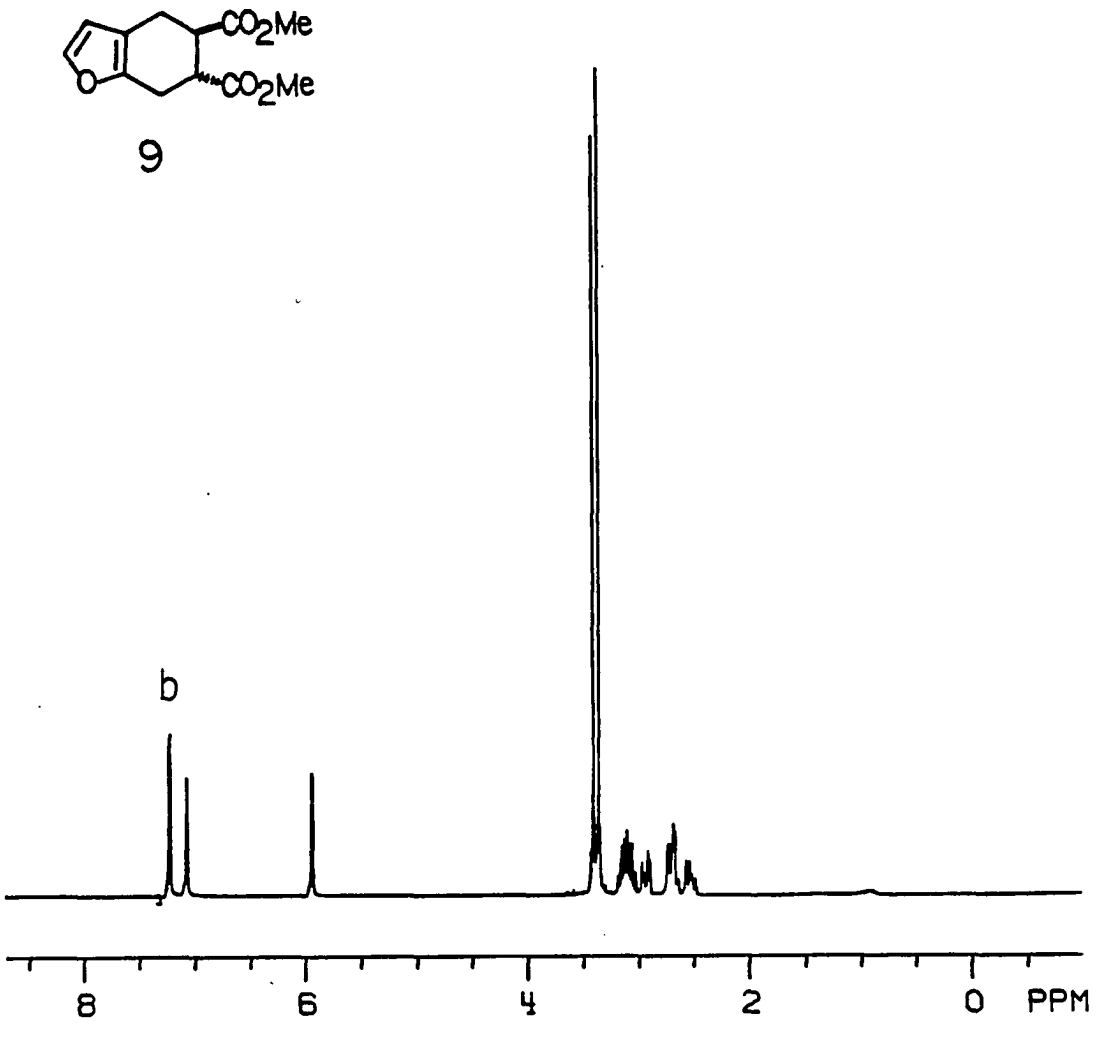


Figure 6. Proton NMR spectrum of the Diels-Alder adduct 9 in C_6D_6 (b = benzene)

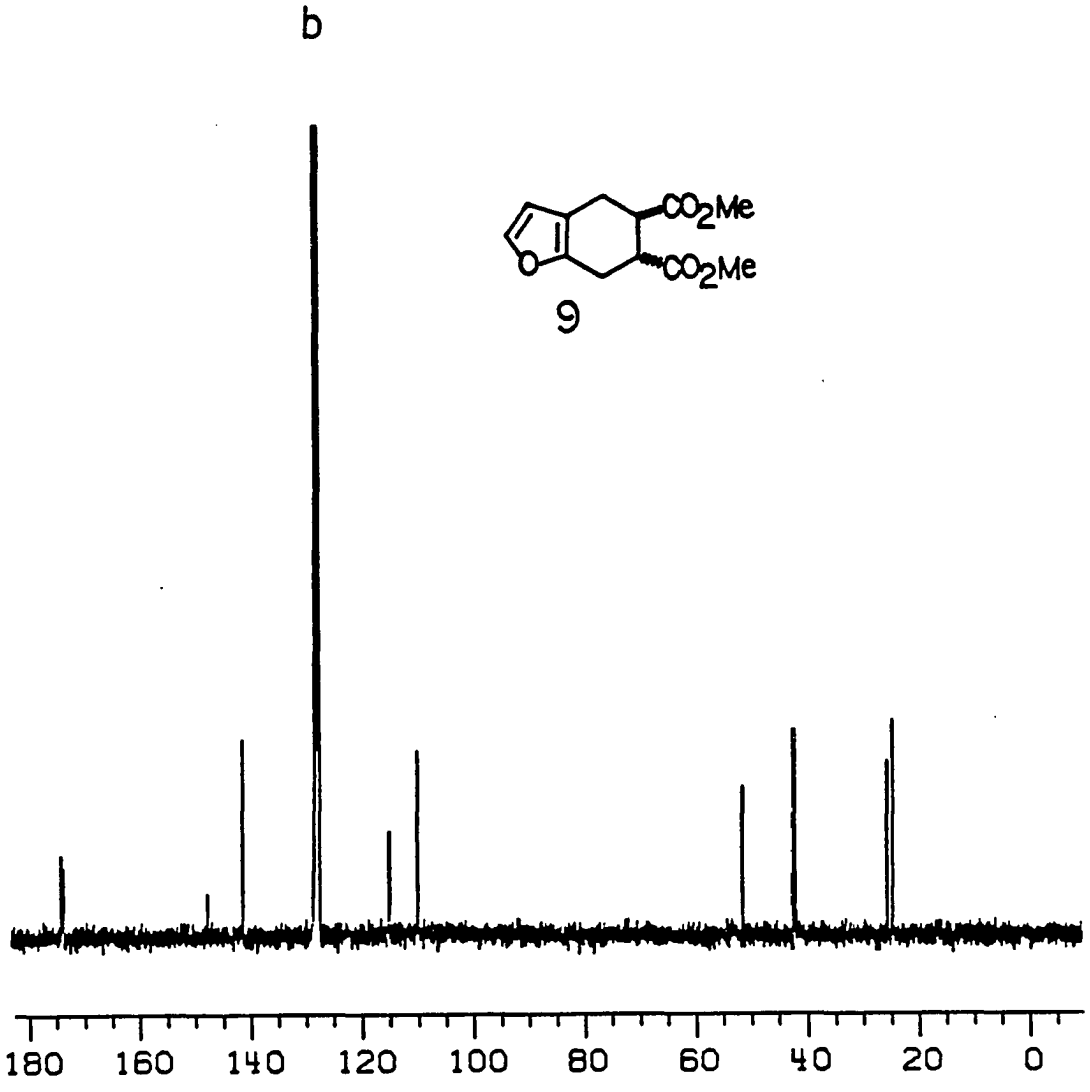


Figure 7. ^{13}C NMR spectrum of Diels-Alder adduct 9 in C_6D_6 (b = benzene)

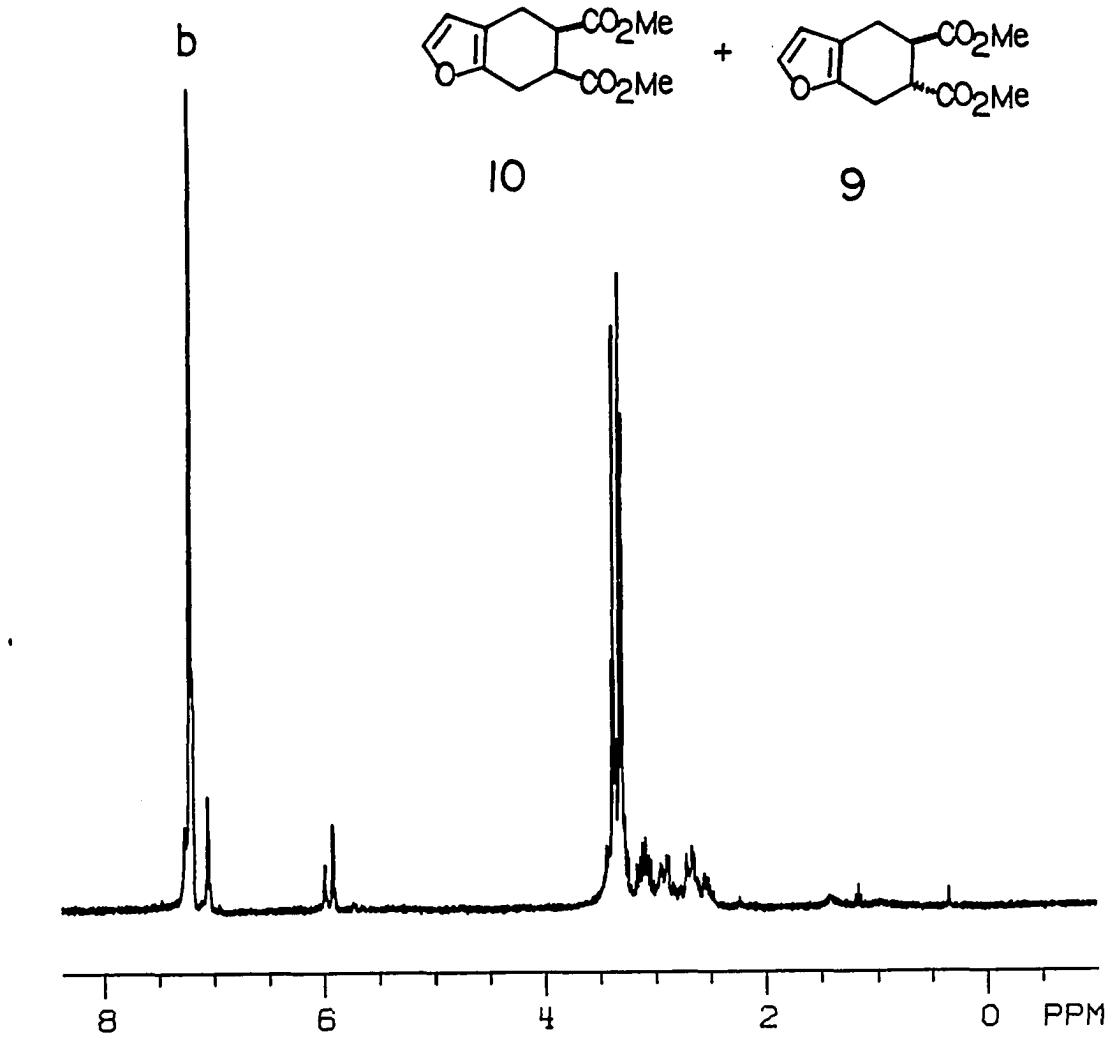
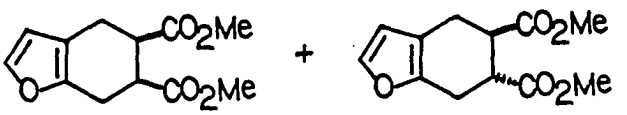
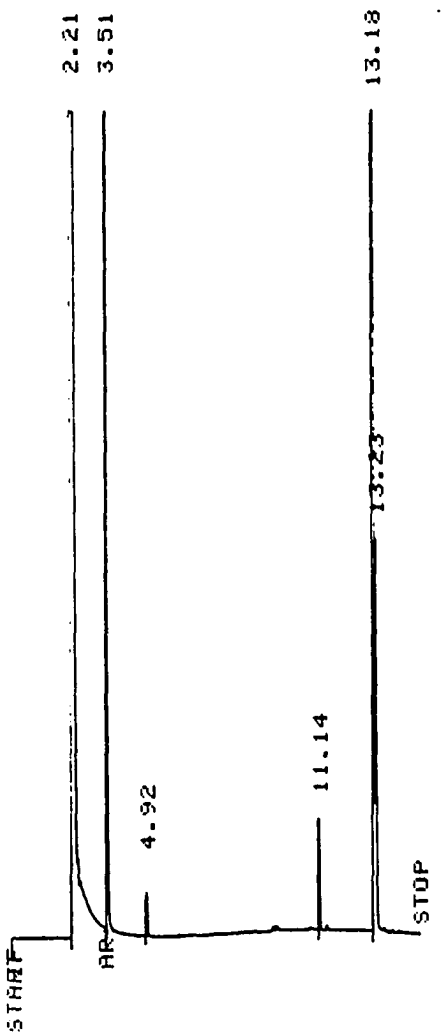


Figure 8. Proton NMR spectrum of the Diels-Alder adducts 9 and 10 (4:1) in C_6D_6 (b = benzene)



10 9



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SLP SENS	0.10		
AREA REJ	1000000000		
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FLOW B	0.0	15.6	

Figure 9. GC trace of the Diels-Alder adducts 9 (13.18) and 10 (13.23) (4:1)

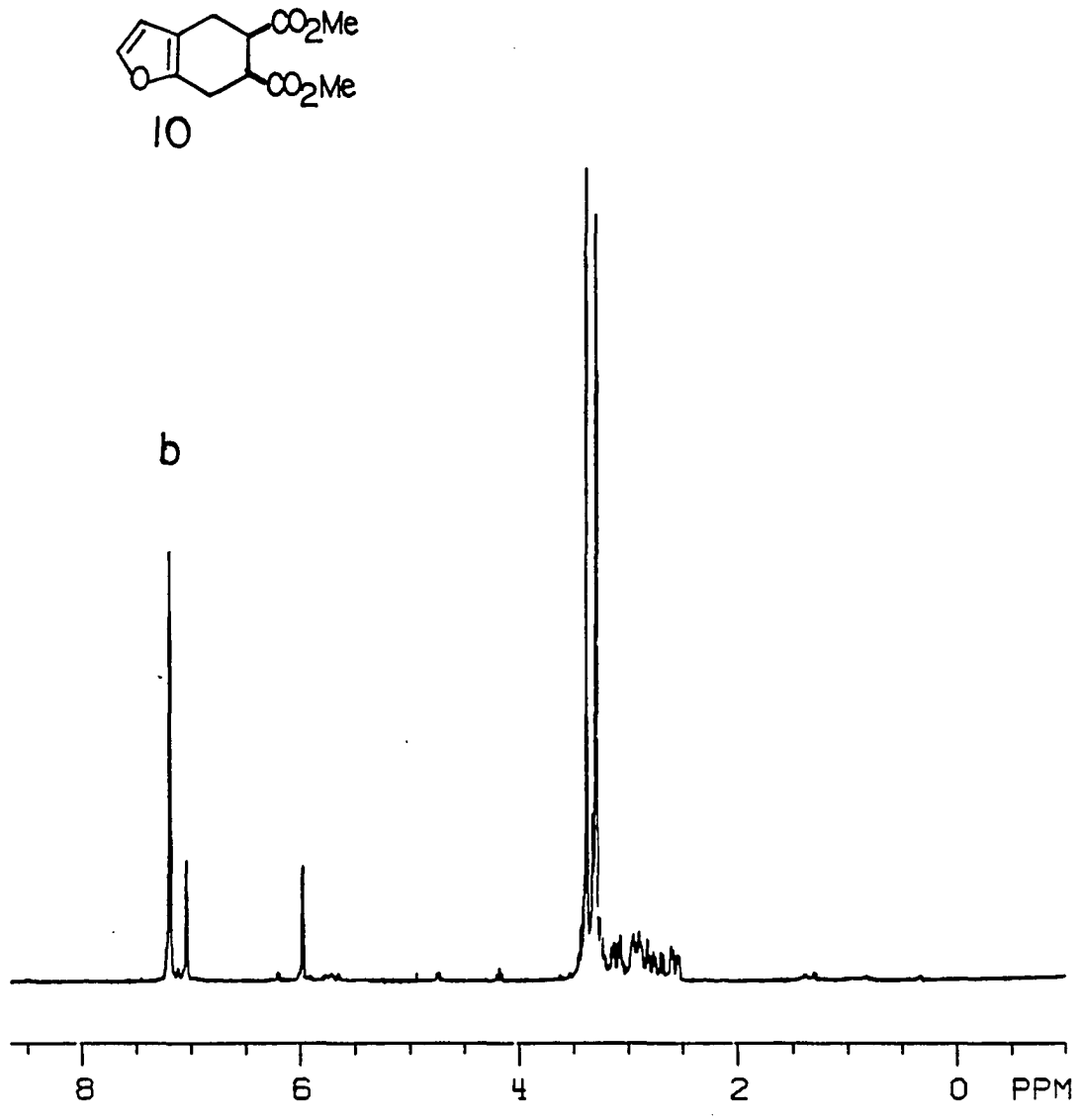


Figure 10. Proton NMR spectrum of the Diels-Alder adduct 10 (4:1) in C_6D_6 (b = benzene)

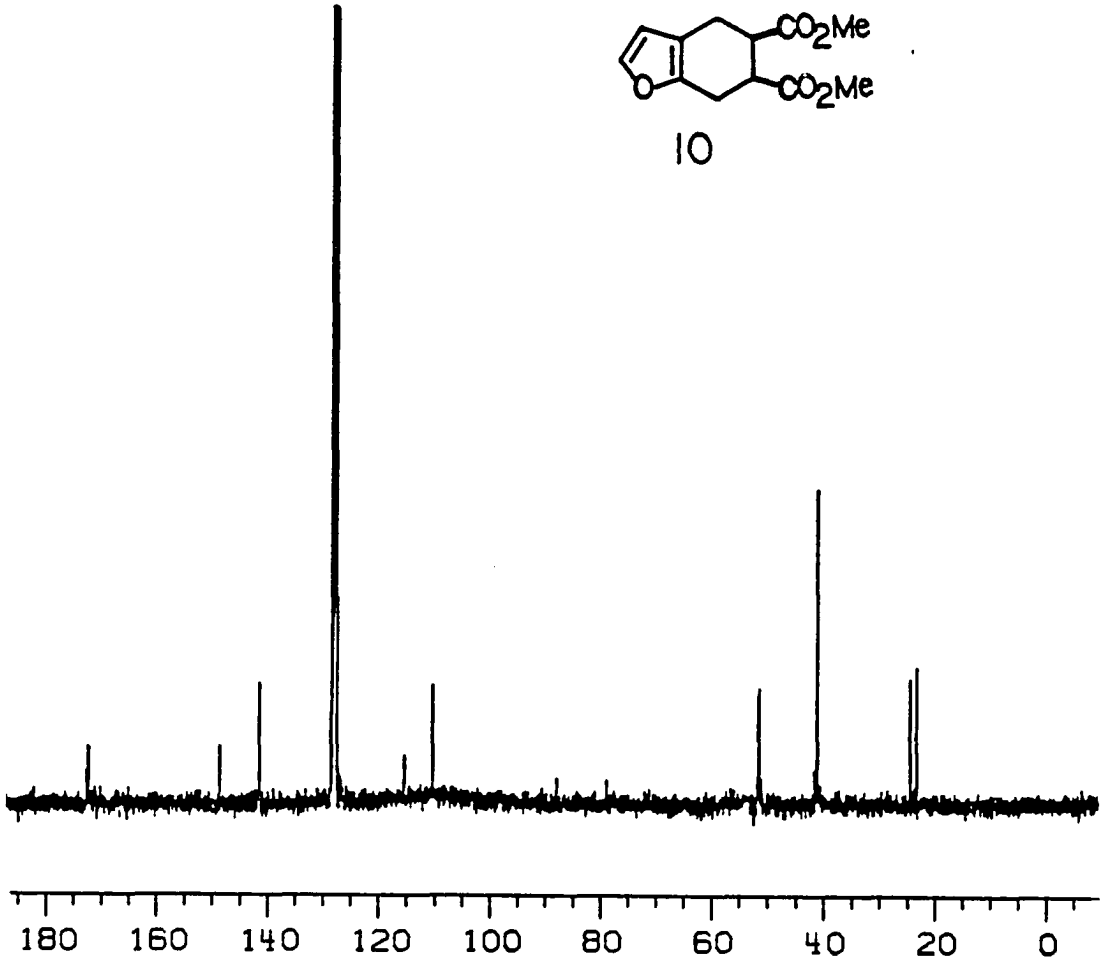
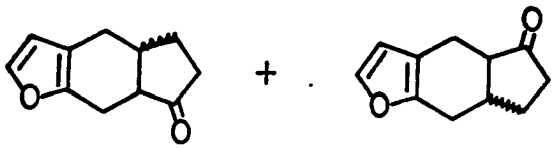
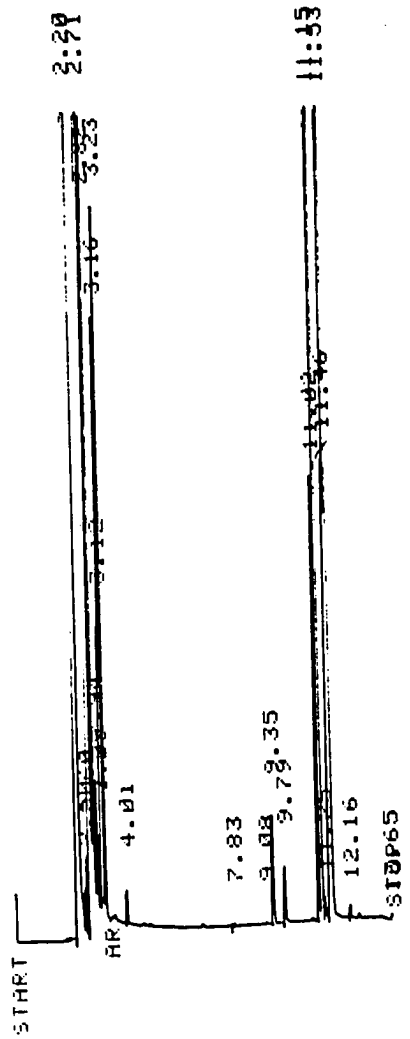


Figure 11. ^{13}C NMR spectrum of the Diels-Alder adduct 10 in C_6D_6 (b = benzene)



+ dimer



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RATE	10.00		
TEMP2	400	200	
TIME2	30.00		
INJ TEMP	400	200	200
FID TEMP	400	250	250
CHT SPD	0.50		
ZERO	10.0		
ATTN 2T	2		
FID SGNL	A		
SLP SENS	0.10		
AREA REJ	100000000		
FLOW A	24.0	26.3	
FLOW B	0.0	15.6	

Figure 12. GC trace of the product mixture of the Diels-Alder reaction of 2,3-dimethyl-2,3-dihydrofuran (1a) with cyclopentenone (11.15 = [4+4] dimer)

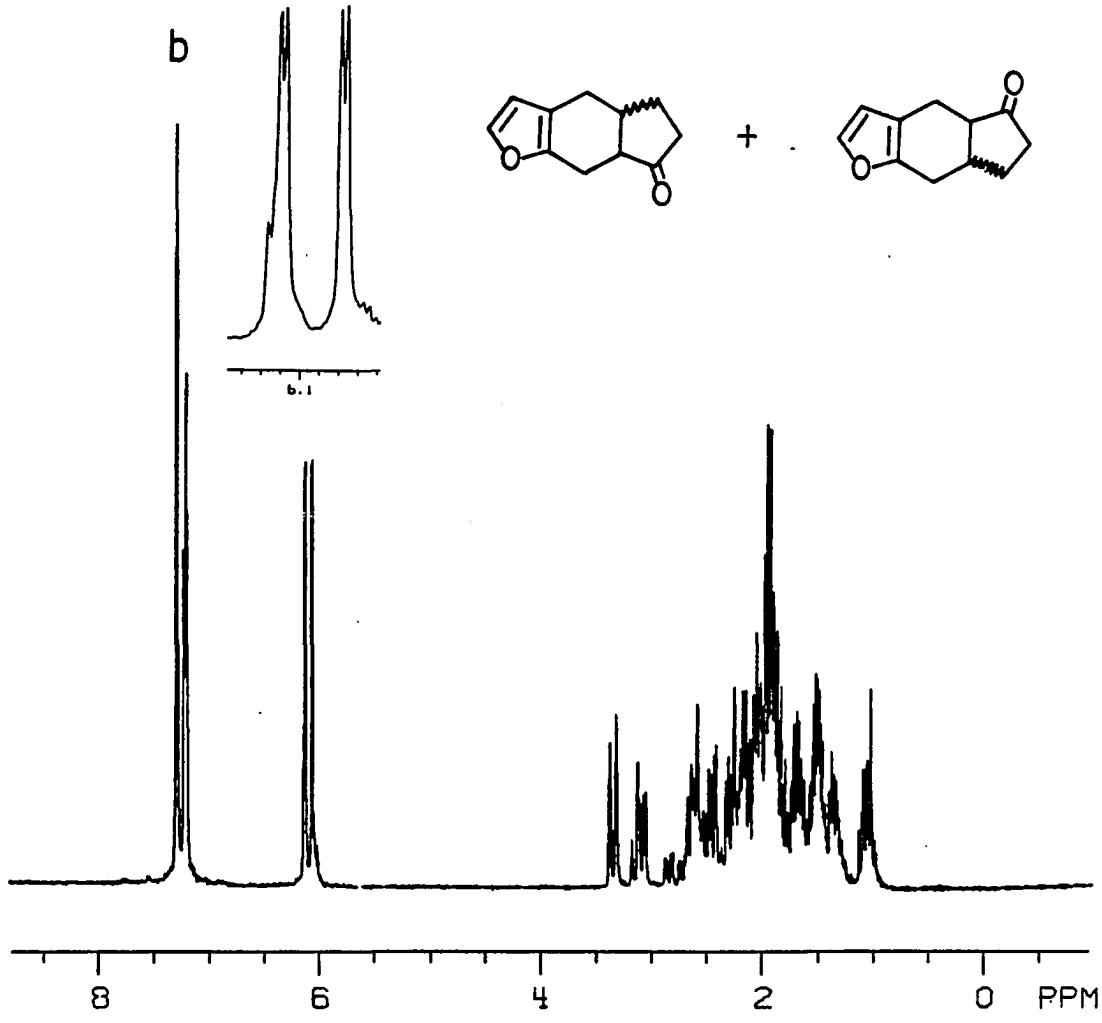
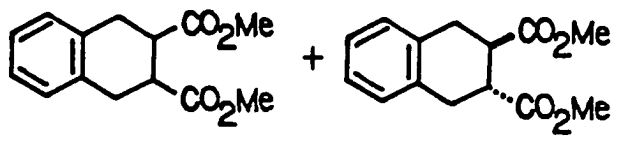
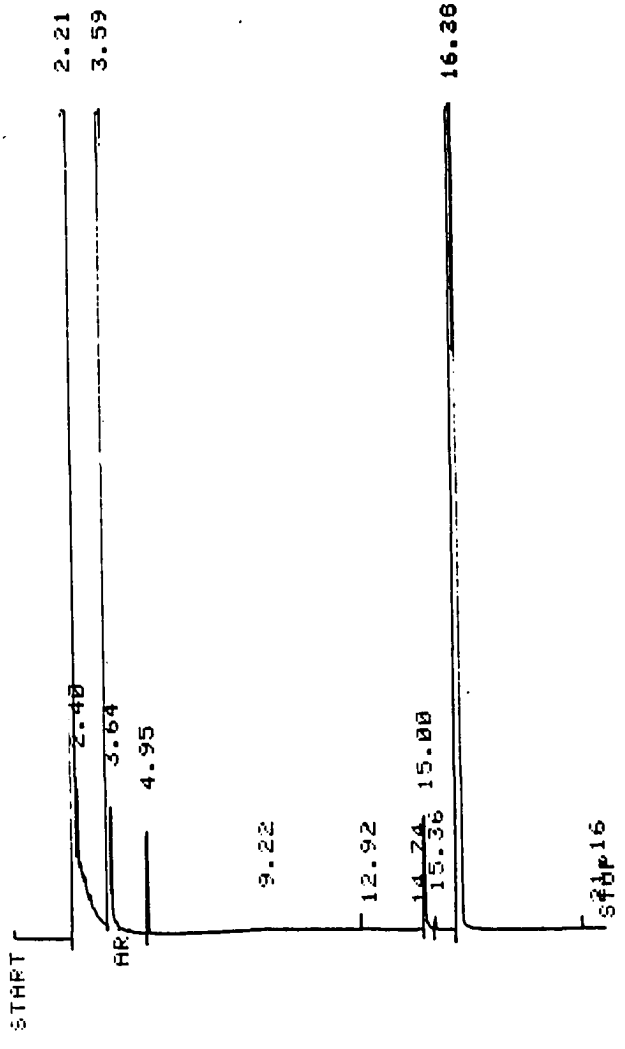


Figure 13. Proton NMR spectrum of the mixture of adducts of 2,3-dimethylene-2,3-dihydrofuran (1a) and cyclopentenone in C_6D_6 (b = benzene)



14 13



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TIME1	5.00		
RATE	10.00		
TEMP2	400	200	
TIME2	30.00		
INJ TEMP	400	200	200
FID TEMP	400	250	250
CHT SPD	0.50		
ZERO	10.0		
ATTN 2^	2		
FID SGNL	A		
SLP SENS	0.10		
AREA REJ	100000000		
FLOW A	24.0	26.3	
FLOW B	0.0	15.6	

Figure 14. GC trace of the Diels-Alder adducts 13 (16.18) and 14 (16.36) (2:1)

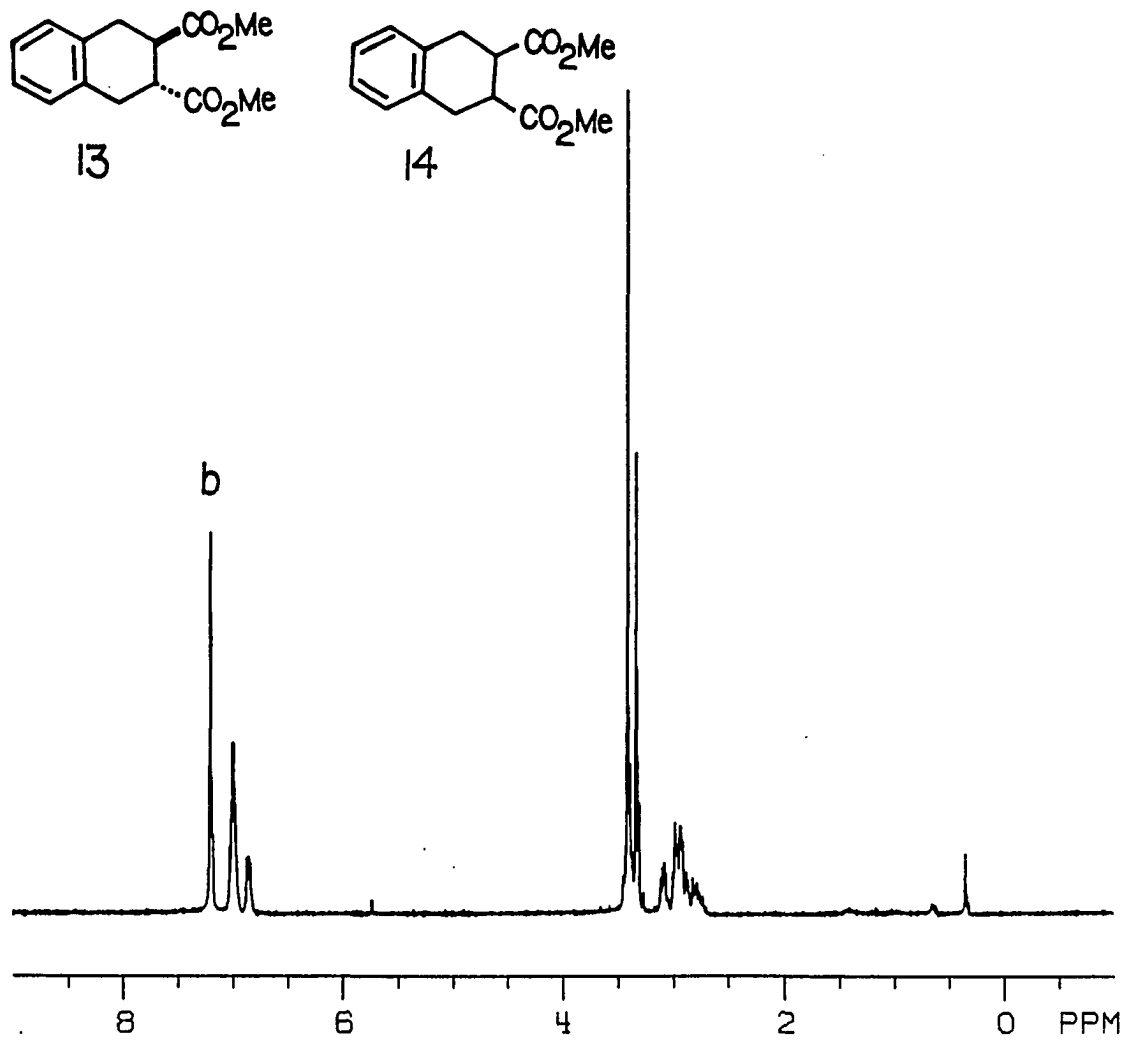


Figure 15. Proton NMR Spectrum of the Diels-Alder adducts 13 and 14 (2:1) in C_6D_6 (b = benzene)

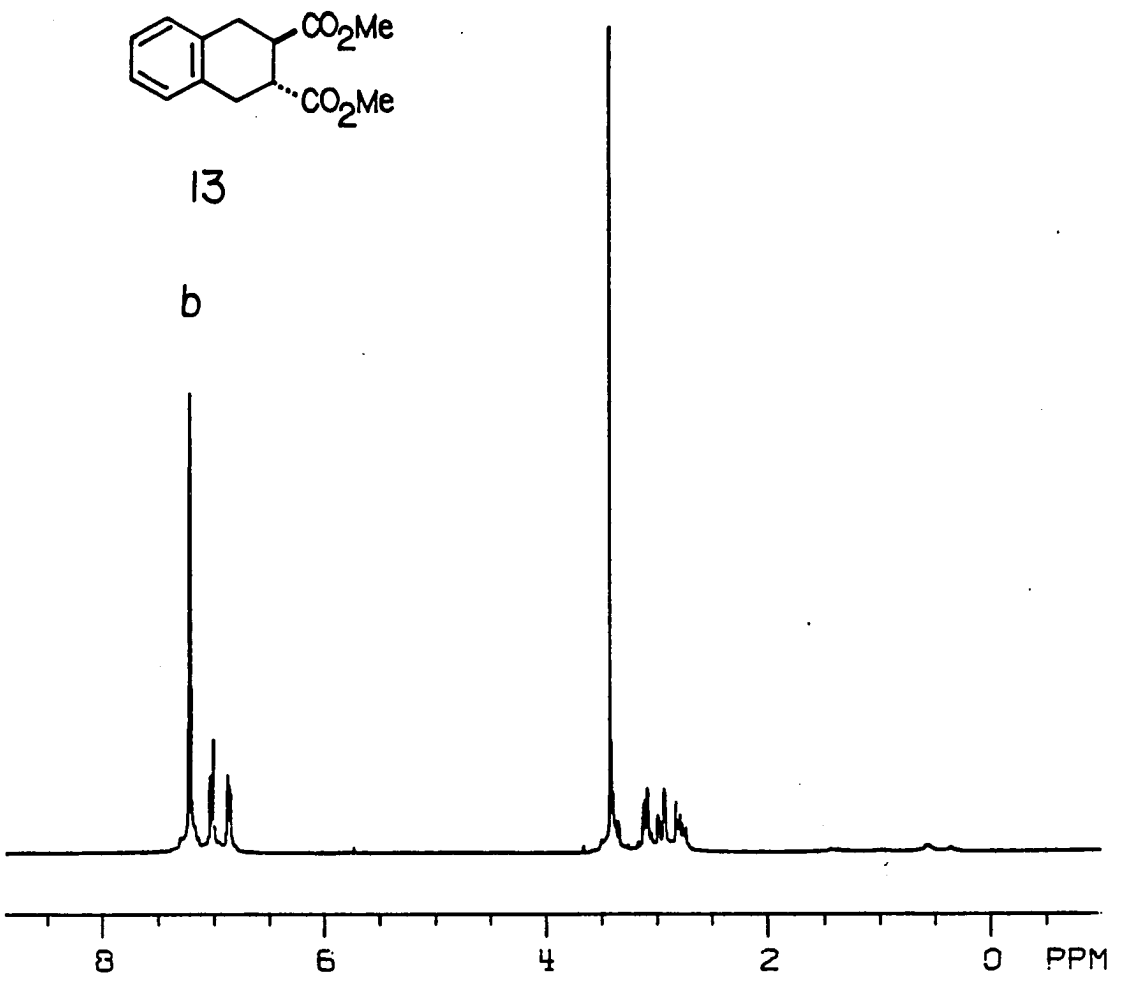


Figure 16. Proton NMR Spectrum of the Diels-Alder adduct 13 in C_6D_6 (b = benzene)

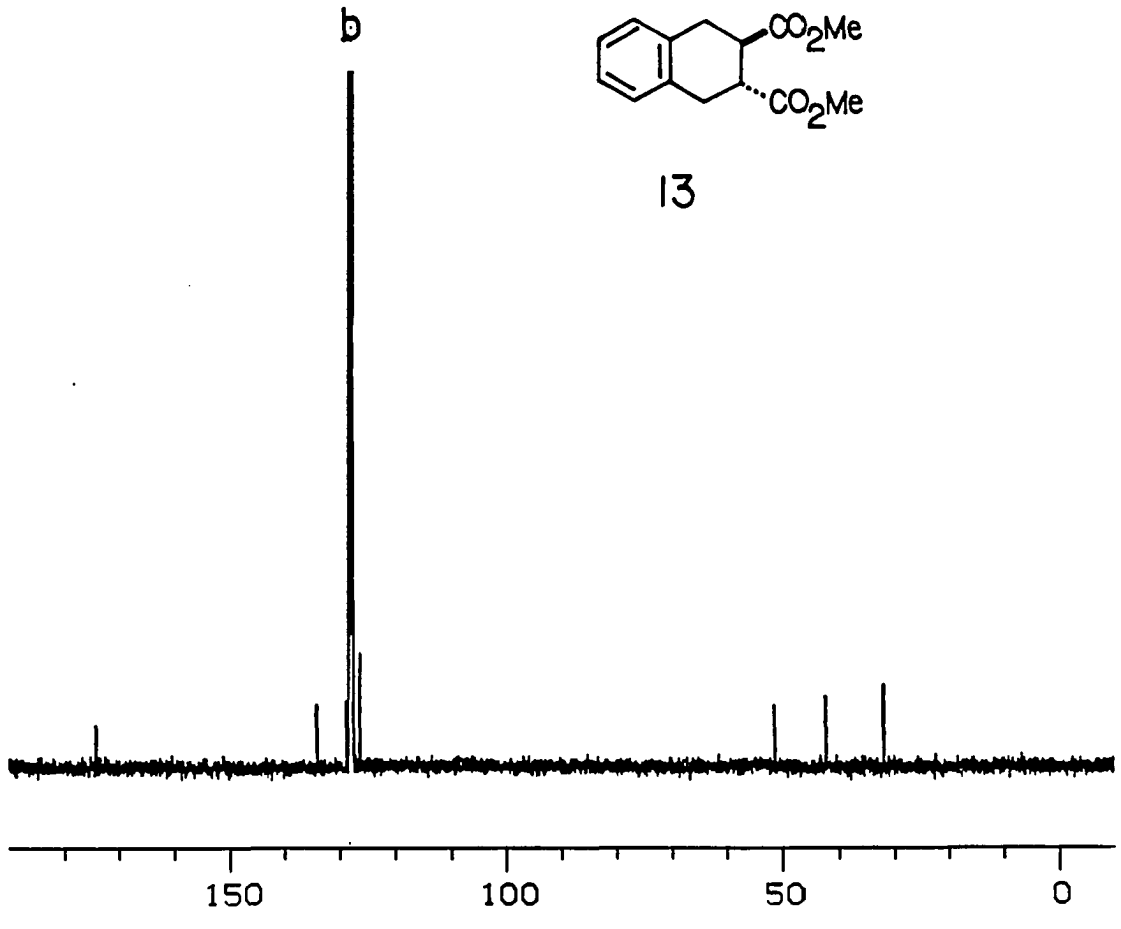


Figure 17. ^{13}C NMR spectrum of the Diels-Alder adduct 13 in C_6D_6 (b = benzene)

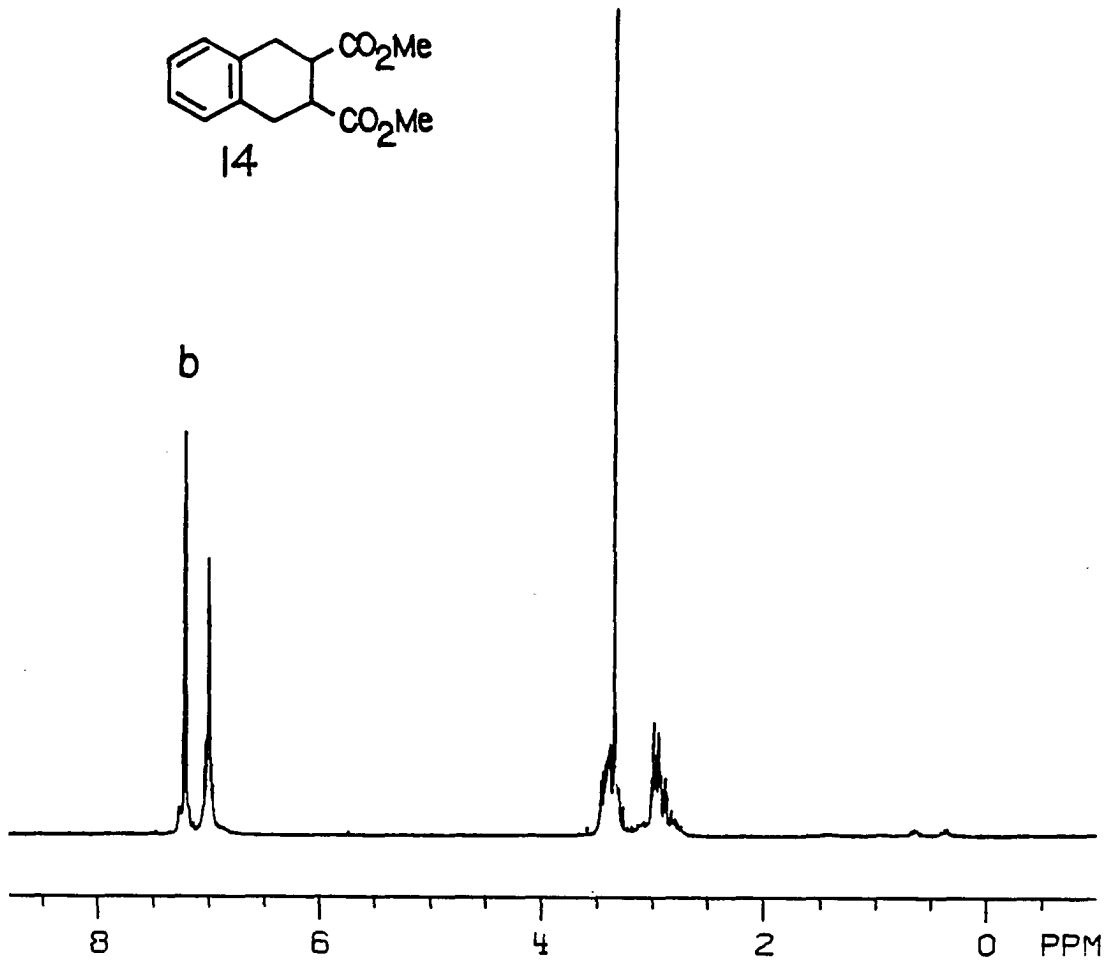


Figure 18. Proton NMR Spectrum of the Diels-Alder adduct 14 in C_6D_6 (b = benzene)

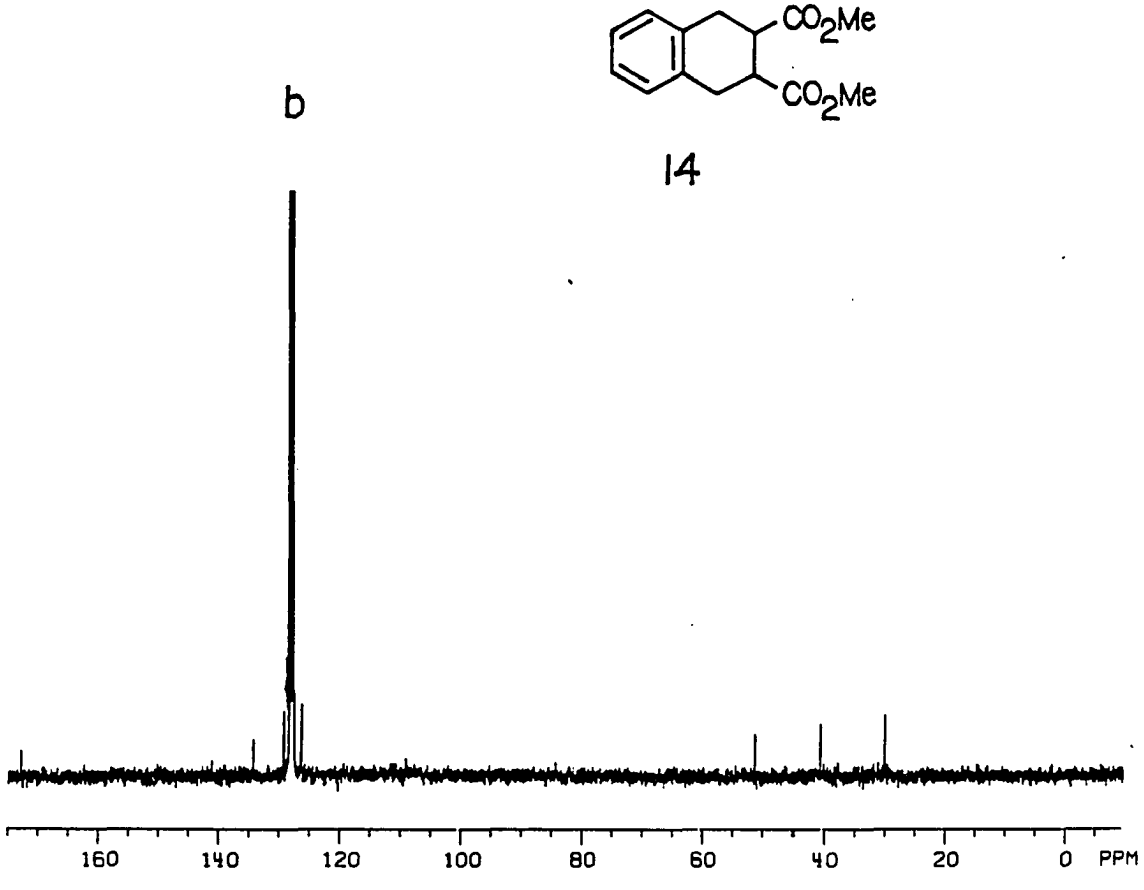


Figure 19. ^{13}C NMR spectrum of the Diels-Alder adduct 14 in C_6D_6 (b = benzene)

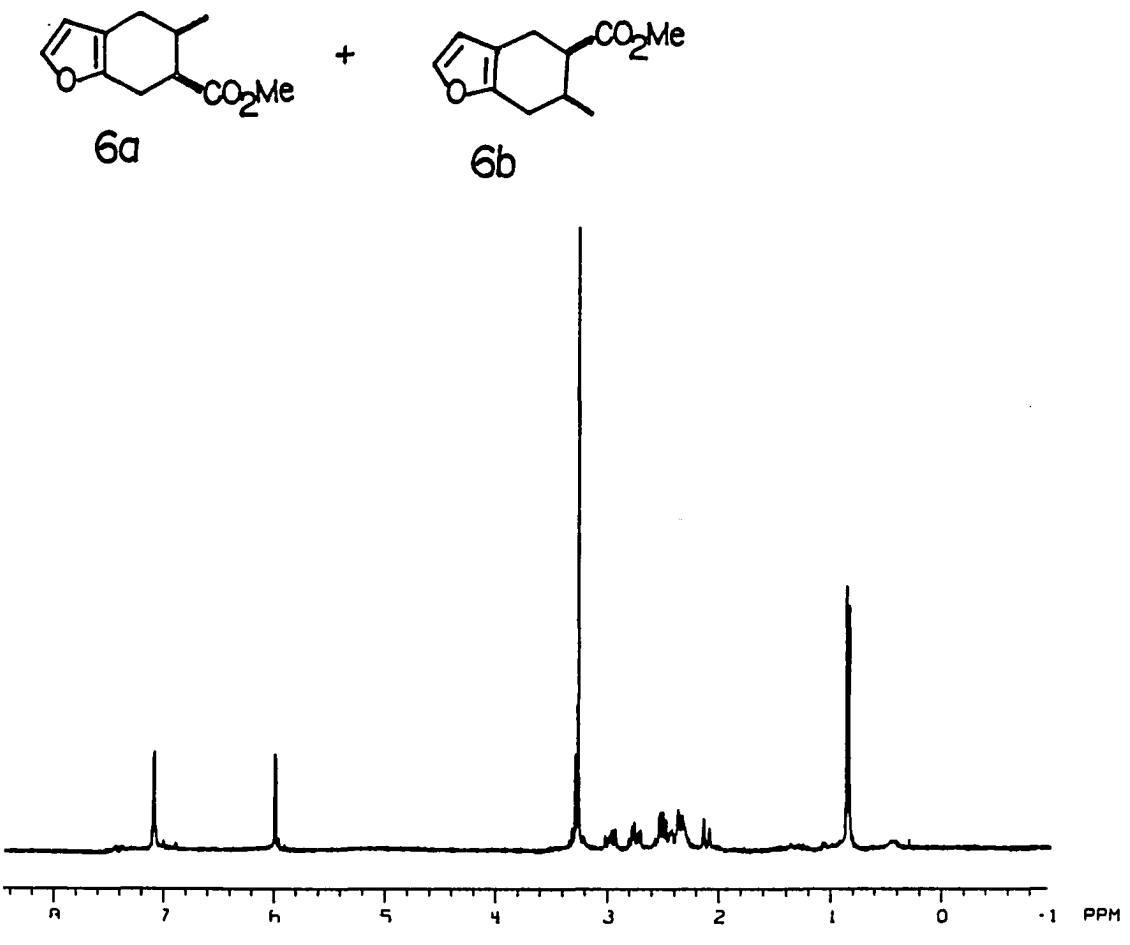


Figure 20. Proton NMR spectrum of the Diels-Alder adducts 6a and 6b in $CDCl_3$ (10:1)

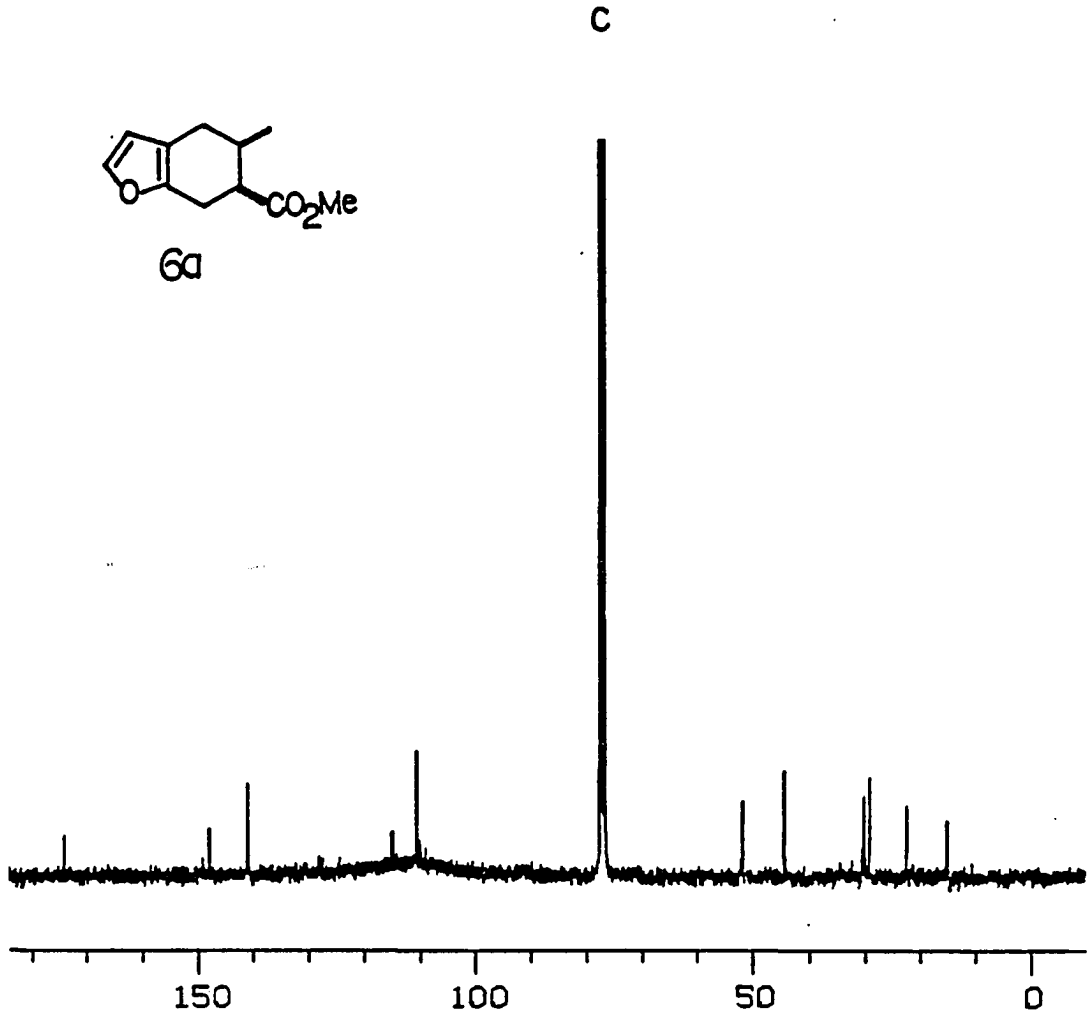
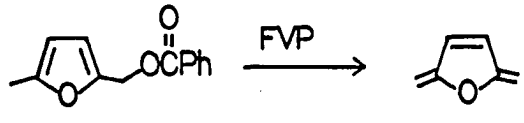


Figure 21. ^{13}C NMR spectrum of the Diels-Alder adduct 6a $CDCl_3$ (c = chloroform)

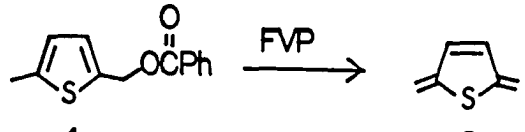
SECTION IV. FORMATION OF THE 2,5-DIMETHYLENE-2,5-DIHYDRO-THIOPHENE TRIMER AND ITS SYNTHETIC APPLICATION

INTRODUCTION

Our research group has been actively pursuing the generation of reactive molecules by flash vacuum pyrolysis (FVP)[1] for the last decade. We were able to generate 2,5-dimethylene-2,5-dihydrofuran (1)[2] or 2,5-dimethylene-2,5-dihydrothiophene (2)[3] by the FVP of 5-methyl-2-furylmethyl benzoate (3) or 5-methyl-2-thenyl benzoate (4) in excellent yields. Our route is superior to others'[4-7] because the products are free from the contamination of other reactants, therefore allowing us to be the first to fully characterize monomers 1 and 2 spectroscopically.

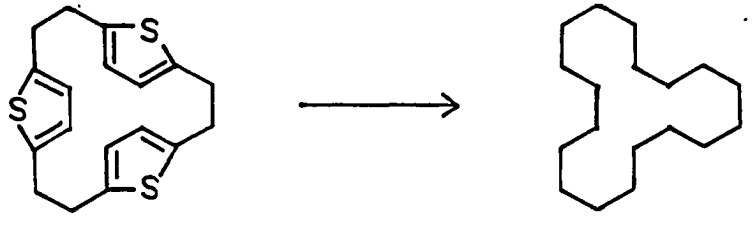


3 1



4 2

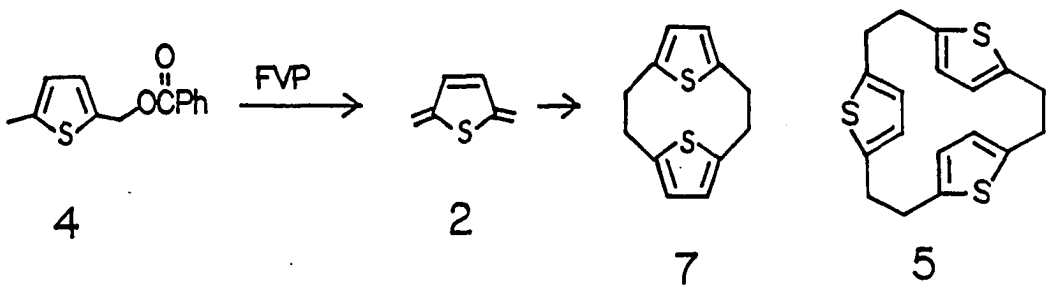
We are also interested in the synthetic applications of the trimer 5 of 2 since it is a potential source of a variety of 18-membered species that have been highly sought after for their synthetic as well as mechanistic implications.[8-16] In this study, we wish to report a convenient synthesis of cyclooctadecane (6) from 5.



5 6

RESULTS AND DISCUSSION

Pyrolysis of 5-methyl-2-thenyl benzoate (4) at ca. 700°C gave thiophene monomer 2 in 75% yield as a yellow substance. Upon standing at room temperature, dimer 7 and trimer 5 were produced in a 1:2 ratio.[3]



4 2 7 5

In order to optimize the formation of the trimer versus the dimer, nine sample tubes of the monomer were prepared and allowed to oligomerize under different concentrations and temperatures. The disappearance of monomer 2 and the emergence of dimer 7 and trimer 11 were monitored by GC using diphenyl as an internal standard. The results are presented in Table I.

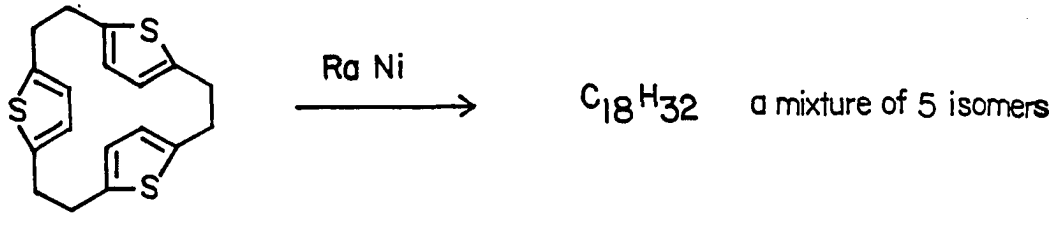
Table I. Oligomerization study of 2,5-dimethylene-2,5-dihydrothiophene (2) monitored by GC using diphenyl as an internal standard

Temp. °C	Conc. M	Tube	Monomer (%) 24h	Monomer (%) 48h	Dimer (%) 24h	Dimer (%) 48h	Trimer (%) 24h	Trimer (%) 48h
-10	0.1	A	60	/	/	/	/	/
-10	0.05	B	60	/	/	/	/	/
-10	0.03	C	61	/	/	/	/	/
20	0.1	D	/	/	9	6	47	34
20	0.05	E	8	/	8	8	29	30
20	0.03	F	10	/	/	/	14	13
35	0.1	G	/	/	11	9	46	49
35	0.05	H	/	/	11	11	29	32
35	0.03	I	/	/	14	10	16	17

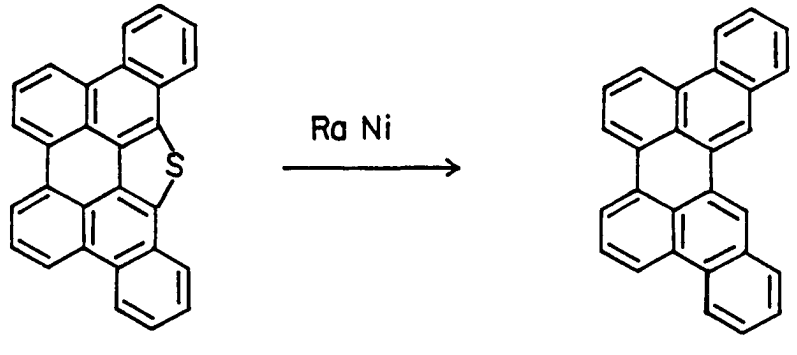
Unexpectedly, low temperature (-10°C) resulted in extensive polymerization. Slightly elevated temperature (35°C) at 0.1 M of monomer concentration was the optimal condition for the trimer formation.

Repeated attempts to desulfurize trimer 5 by an excess amount of Raney nickel[17-19] all resulted in the formation of a mixture of 5 isomers of $C_{18}H_{32}$ based on GCMS analysis. They are all apparently very closely related since all the GC signals literally fall on top of one another (see Appendix, Figure 1). The proton NMR spectrum (see Appendix, Figure 2) of this mixture shows three broad

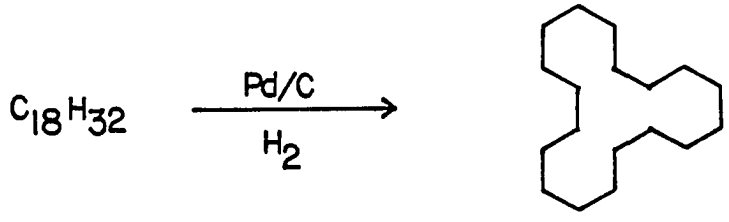
signals at 5.3 ppm (4H), 2.2 ppm (8H) and 1.3 ppm (20H). Evidently, the isomers contain non-conjugated double bonds. The exact location and stereochemistry of the double bonds cannot be determined.



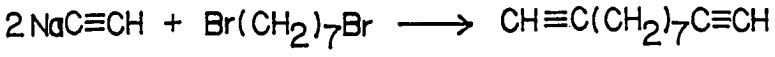
This observation is rather unique since as early as 1960 Raney nickel desulfurization of approximately 190 thiophenes had been described.[19] As far as we know, most products are fully saturated unless the thiophene is incorporated in a multi-nuclei aromatic system such as flavophene 8.[20]

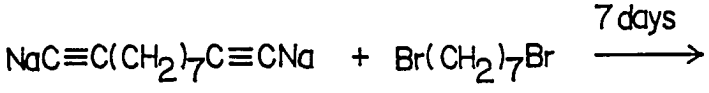


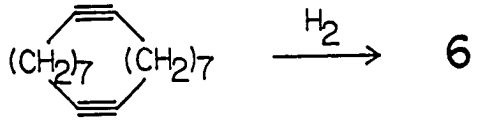
When this mixture of $C_{18}H_{32}$ was allowed to stir in hexane and Pd/C (5%) under a hydrogen balloon for five hours, cyclooctadecane 6 was isolated as the single product in 90% yield. The overall yield is around 40% starting from the benzoate.



Several lengthy, multi-step syntheses of cyclooctadecane (14) in low yield were reported previously. A synthesis of 6 starting from acetylene is outlined below.[21,22]







Our method is very attractive due to the limited number of steps and ease of reactions.

EXPERIMENTAL

Methods and Equipment

The pyrolysis apparatus has been previously described.[23] NMR spectra were recorded on Varian E 360, JOEL FX-90Q or Nicolet-300 spectrometers. Chemical shifts are recorded in parts per million (δ) from tetramethylsilane (TMS). Gas chromatography/mass spectroscopy (GC/MS) was performed with a Finnigan 4000 instrument and an INCOS data system. GLC analyses were performed with a Hewlett Packard HP 5840A instrument with a 25 meter, SP 2100 thin film (methylsilicone-coated) capillary column. Raney Nickel was purchased from Aldrich.

5-Methyl-2-thenyl Benzoate (4)

A solution of 18.0 g (143 mmole) of 5-methyl-2-thiophenecarboxaldehyde in 50 mL of ether was reduced and esterified by the procedure of Miller[3] to yield 26.6 g (115 mmole, 80.4%) of 5-methyl-2-thenyl benzoate (4): bp 87-89°C (0.05 mm) [lit bp 124°C, (0.45 mm)]; ^{1}H NMR ($CDCl_3$) δ 8.15-8.02 (m, 2H), 7.55-7.38 (m, 3H), 6.95 (m, 1H), 6.50 (m, 1H), 5.40 (s, 2H), 2.38 (s, 3H).

Desulfurization of Trimer 5 with Raney Nickel

A solution of 12 mg (0.036 mmole) of thiophene trimer 5 in 20 mL of benzene and ethanol (1:1) was stirred under

nitrogen at 50°C with 2.5 g of Raney nickel overnight. The nickel was filtered off, the solvent was evaporated to afford 8 mg of oil. GC analysis of the crude product mixture showed the presence of 5 isomers (10:8:2.5:1.6:1) (see Appendix, Figure 1). GCMS only resolved four signals bearing the molecular weight of 248. GC/MS (70eV) m/e relative intensity) A: 248.04 (6/01), 149.02 (3.44), 135.02 (11.27), 121.02 (14.78), 95.00 (36.36), 67.02. (100.00); B: 248.04 (6.27), 135.02 (9.15), 121.00 (11.52), 94.02 (38.62), 80.02 (75.41), 55.04 (100.00); C: 248.04 (6.27), 135.02 (9.15), 121.00 (11.52), 94.02 (38.62), 80.02 (75.41), 55.04 (100.00); D: 248.08 (2.26), 121.02 (8.20), 96.02 (33.17), 81.02 (50.39), 67.02 (79.98), 55.04 (100.00). Proton NMR spectrum ($CDCl_3$) δ 5.3 (br, 4H), 2.2 (br, 8H), 1.3 (br, 20H) (see Appendix, Figure 2).

Without purification, the mixture of isomers obtained from desulfurization of thiphene trimer 5 was dissolved in 5 mL of hexane and 4 mg of Pd/C (5%). The mixture was stirred under a hydrogen balloon until all of the starting materials were consumed as indicated by TLC analysis. This process took five h. The resulting suspension was filtered with a glass funnel. After removing of the solvent, 8 mg (0.032 mmole, 88.8%) of cyclooctadecane (6) was recovered: mp 70-74°C (lit.[22] mp 72-73°C); ^1H NMR ($CDCl_3$) δ 1.30 (s, 36H);

^{13}C NMR ($CDCl_3$) δ 27.50; high resolution mass spectrum, calcd for $C_{18}H_{36}$ 252.28171, measured 252.28179.

General Pyrolysis Procedure

The pyrolyses were run at furnace temperatures from 400 to 800°C. The sample chamber was heated to 60-70°C and the system was evacuated to ca. 10^{-5} Torr during the pyrolysis. A condenser was inserted between the quartz pyrolysis tube and the liquid nitrogen-cooled trap to collect the unreacted starting material and the benzoic acid formed as a byproduct. The liquid nitrogen-cooled trap was used to collect the products. Upon completion of the pyrolysis, carbon disulfide or deuterochloroform was distilled into the trap through the side arm. Also added was a known amount of dibromoethane as an internal standard for quantitative studies.

Pyrolysis of 5-Methyl-2-thenyl Benzoate (4)

A 0.5 g (2.1 mmole) quantity of 5-methyl-2-thenyl benzoate (4) was pyrolyzed at 700°C in the normal manner. Upon completion, 18 mL of carbon disulfide was distilled into the trap. The trap was warmed up slowly to -78°C. A quantitative low temperature proton NMR analysis of 3 mL of the pyrolysate using dibromethane was a standard showed the presence of 2,5-dimethylene-2,5-dihydrothiophene (2) in 80%

yield. The remaining 15 mL was divided equally into ten test tubes after 80 mg of biphenyl was added as an internal standard. Nine portions (tubes A to I) were taken and divided into three groups. Group 1: tubes A, D, G (0.1 M monomer) were stored at -10°C, 20°C and 35°C respectives. Group 2; tubes B, E, H were diluted with 1.5 mL carbon disulfide each (0.05 M monomer) and were stored at -10°C, 20°C and 35°C respectively. Group C; tubes C, F, I were diluted with 30 mL carbon disulfide each (0.03 M monomer) and were stored at -10°C, 20°C and 35°C respectively. GC analysis of the nine samples after all the monomers were consumed indicated that tube G (0.1 M monomer at 35°C) afforded the trimer 5 in the highest yield (49%). The overall result is shown in Table I.

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APPENDIX

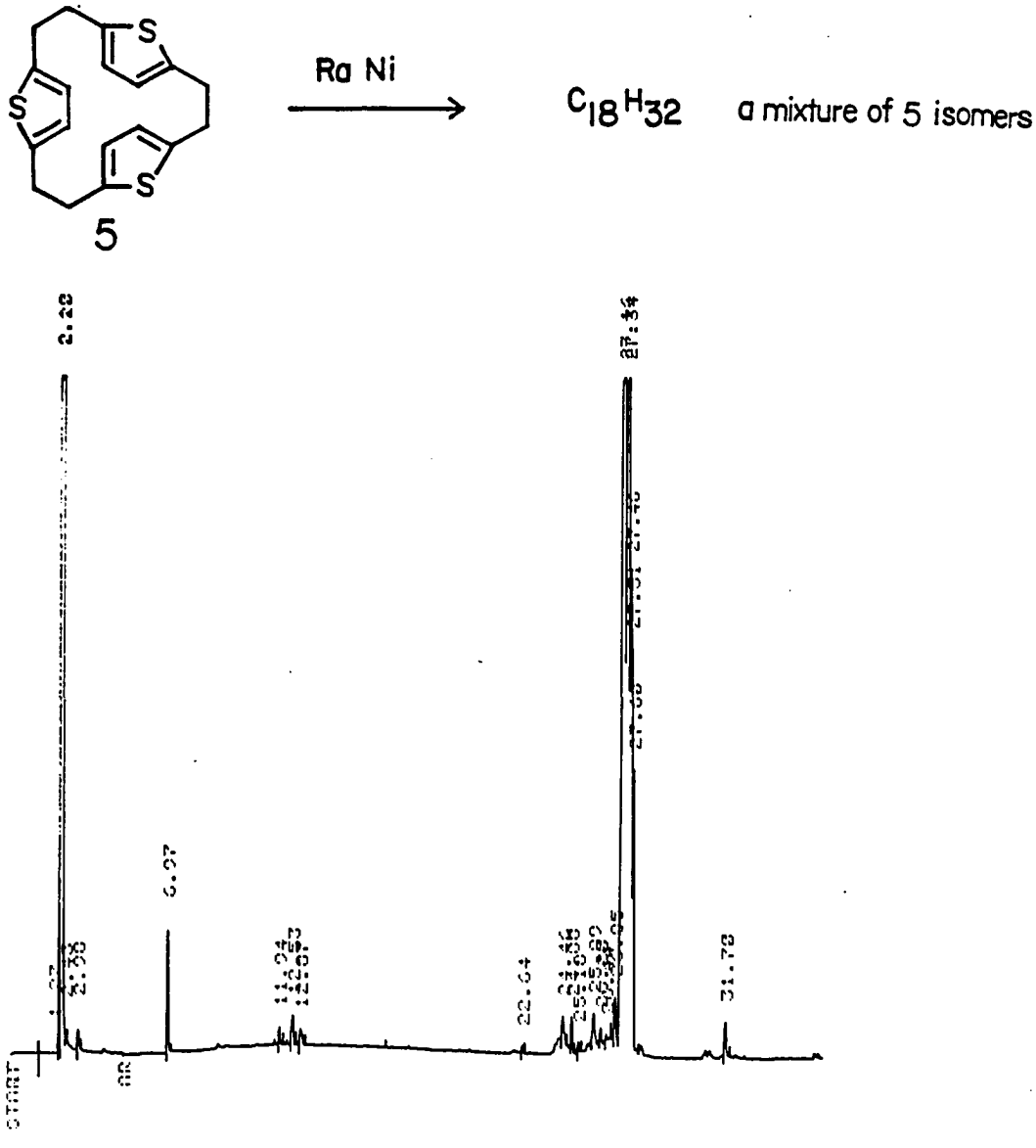
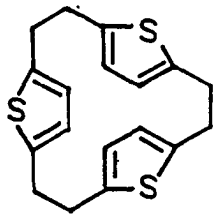


Figure 1. GC trace of the mixture of products after 5 was desulfurized with Ra Ni



5

Ra Ni

$C_{18}H_{32}$ a mixture of 5 isomers

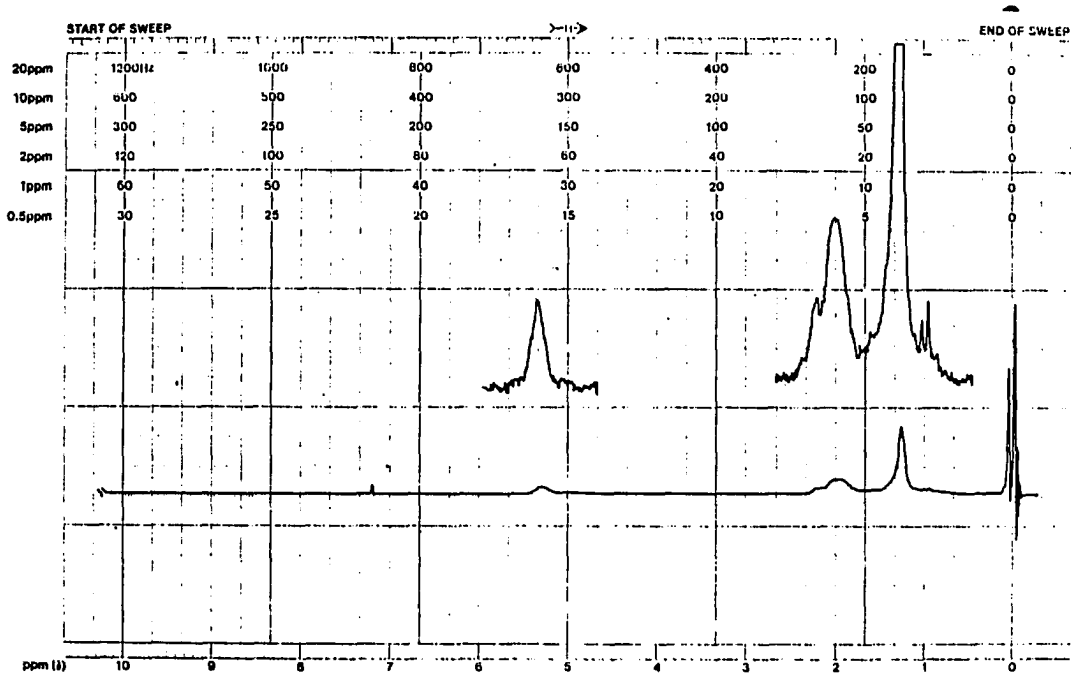


Figure 2. Proton NMR spectrum of the mixture of products after 5 was desulfurized with Ra Ni

GENERAL SUMMARY

In Section I, we report the generation and a mechanistic study of t-butyl exo-methylene-substituted 2,3-dimethylene-2,3-dihydrofurans and a thiophene analogue. The results not only unambiguously support the previous proposed two-step mechanism for the dimerization of 2,3-dimethylene-2,3-dihydrofuran (1), they also provide two of the most unreactive o-quinodimethanes, namely, 2-methylene-3-t-butylmethylene-2,3-dihydrofuran (2) and 2,3-di-t-butylmethylene-2,3-dihydrofuran.

In Section II, the preparation and the dimerization of a series of alkyl ring-substituted and carbomethoxy ring-substituted derivatives of 1 are presented. This study concludes that bulky alkyl substituents on the ring of furan monomers do not promote the [4+2] dimerization process.

In Section III, a Diels-Alder reaction of 1 and its two deuterated analogues with methyl acrylate reveals the presence of a secondary deuterium isotope effect which strongly suppports a stepwise mechanism. This conclusion is further strengthened by the fact that the Diels-Alder reaction of 1 with cis dienophiles proceeds non-stereospecifically. A comparison study of o-xylylene with dienophiles reaches the same conclusion.

In Section IV, we present a convenient synthesis of cyclooctadecane from the thiophene trimer of 2,5-dimethylene-2,5-dihdrothiophene. This route is more efficient than existing routes.

ACKNOWLEDGEMENTS

I am most grateful to Professor Walter S. Trahanovsky for his great patience and intellectual guidance.

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