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Observation by flow 1H NMR and dimerization kinetics and products of reactive ortho-quinodimethanes and benzocyclobutadiene

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Observation by flow ^1H NMR and dimerization kinetics and products of reactive *ortho*-quinodimethanes and benzocyclobutadiene

by

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1990

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GENERAL INTRODUCTION

For the past few years, the Trahanovsky research group has focused on the study of various reactive molecules. Of major interest has been the *o*-quinodimethane class of reactive molecules which includes *o*-xylylene, the benzenoid analogue. Work has begun quite recently on another very interesting reactive molecule, benzocyclobutadiene. The four sections of this dissertation cover work involving *o*-xylylene and several of its derivatives, benzocyclobutadiene, and 2,3-dimethylene-2,3-dihydrothiophene.

Section 1 describes the observation of 1,2-dimethylene-1,2-dihydronaphthalene and *o*-xylylene by flow ^{1}H NMR. A detailed description of the flow-NMR apparatus and technique is given. Section 2 involves the flow ^{1}H NMR observation, dimerization kinetics, and product studies of a series of 3-alkyl- and 3,6-dialkyl-1,2-xylylenes. In Section 3, the ^{1}H NMR observation of benzocyclobutadiene by the technique of flow NMR is presented. Synthesis of 2-trimethylsilylbenzocyclobutenyl-1 mesylate, an excellent precursor for the generation of benzocyclobutadiene, is outlined. Finally, Section 4 covers the observation of 2,3-dimethylene-2,3-dihydrothiophene by flow ^{1}H NMR. The dimerization rates for this reactive *o*-quinodimethane were measured and are presented as well.

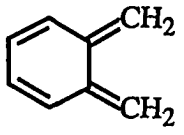
EXPLANATION OF DISSERTATION FORMAT

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. As such, each section has its own numbering system and each section's references follow it. The research described in the results and experimental sections was done by the author unless otherwise indicated.

SECTION 1. OBSERVATION OF 1,2-DIMETHYLENE-1,2-DIHYDRONAPHTHALENE AND *O*-XYLYLENE BY FLOW ^{1}H NMR

INTRODUCTION[1]

The reactive molecule *o*-xylylene (**1**) and its derivatives are part of the larger,



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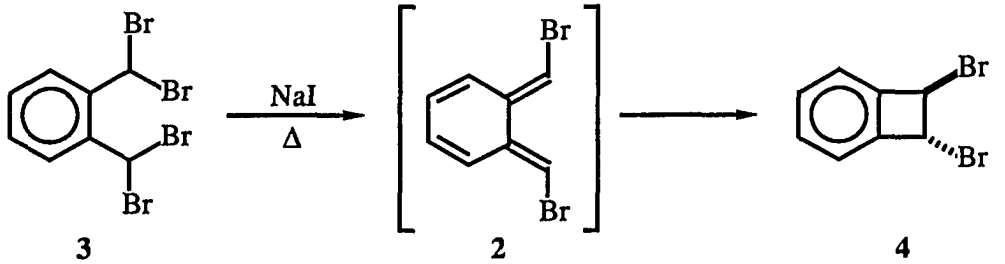
very important class of reactive molecules called *o*-quinodimethanes (*o*-QDM's). In 1957, Cava first proposed an *o*-xylylene (**2**) as an intermediate in the conversion of



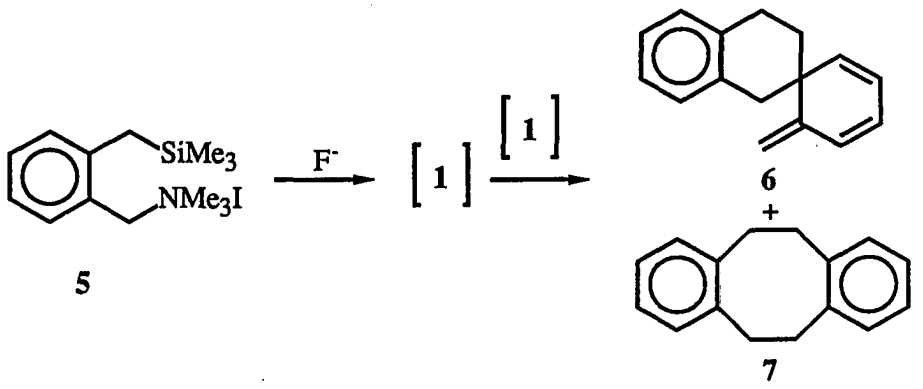
3 **2** **4**

α,α,α′,α′-tetrabromo-*o*-xylene (**3**) to *trans*-1,2-dibromobenzocyclobutene (**4**),[2,3] a reaction reported by Finkelstein in 1910.[4] Since its suggestion, **1** and its derivatives have been the subject of many theoretical[5-8] and experimental[7-11] studies and have been used in numerous organic syntheses.[10,12-14]

Many methods have been used to generate *o*-xylylenes. Some of these include the extrusion of small molecules from cyclic systems[7,8,13,14] and 1,4-elimination processes involving thermal, base induced, reductive, and fluoride ion induced eliminations.[13,14]

It has been shown that the fluoride ion can be used to promote 1,2-eliminations of halosilanes to give acetylene,[15] benzyne,[16] and strained alkenes.[17,18] The fluoride ion induced 1,4-elimination from [*o*-((trimethylsilyl)alkyl)benzyl]-trimethylammonium halides has been an extremely valuable method for the

generation of *o*-quinodimethanes.[10,19-24] A variety of substituted *o*-xylylenes can be generated from their easily prepared precursors using this method.[10,19-22] Generation of *o*-xylylene (**1**) from [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) by this method has been found to be rapid and quantitative,



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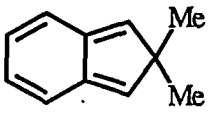
making it particularly suitable for spectroscopic investigations.[20,21] Once formed, **1** dimerizes to give the known, stable [4 + 2] (**6**) and [4 + 4] (**7**) dimers[25] in approximately a 9:1 ratio.[20]

Considerable work has focused on obtaining evidence for various reactive *o*-xylylenes by direct observation using spectroscopic means. This has proven challenging, requiring special techniques due to their high reactivity. Successful techniques have included UV-visible spectroscopy in both solution[26] and a low temperature matrix,[7,8,27] and by IR, Raman, fluorescence, and fluorescence excitation spectroscopy in a low temperature matrix,[27] as well as UV-photoelectron spectroscopy in the gas phase.[28] Several *o*-xylylenes have been observed in solution by UV-visible spectroscopy and their rates of dimerization have been measured.[20,21] The first *o*-xylylene derivative to be observed by ^{1}H NMR is that of the stable 2,2-dimethyl-2H-indene (**8**) reported by Dolbier et al.[29,30]



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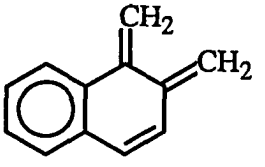
UV-visible spectroscopy has been frequently used to observe transient species and study their kinetics under flow conditions. Since UV-visible spectroscopy is quite sensitive, low concentrations of reagent solutions can be used. This is particularly advantageous in cases where the rate of disappearance of the transient species is a function of its concentration. The nondiagnostic nature of UV-visible spectroscopy is however a drawback.

NMR spectroscopy on the other hand does provide structural information, but suffers in that it is relatively insensitive. Also, the slow time scale of conventional NMR experiments limits its application to observation of reactive molecules having half-lives much greater than the NMR time scale. Stopped-[31-34] and continuous-flow[31,32,35-41] methods coupled with NMR spectroscopy have however been successfully used to observe relatively short-lived species. Flow-NMR spectroscopy involves the continuous flowing of reagent solutions through a mixing chamber to generate a transient species which is subsequently detected by the NMR spectrometer. Flow methods utilizing UV-visible and NMR spectroscopy provide a complimentary set of tools for the study of reactive species.[42]

In this section, the flow-NMR apparatus, technique, and its use in the observation of 1,2-dimethylene-1,2-dihydronaphthalene (**9**) and **1** are described.



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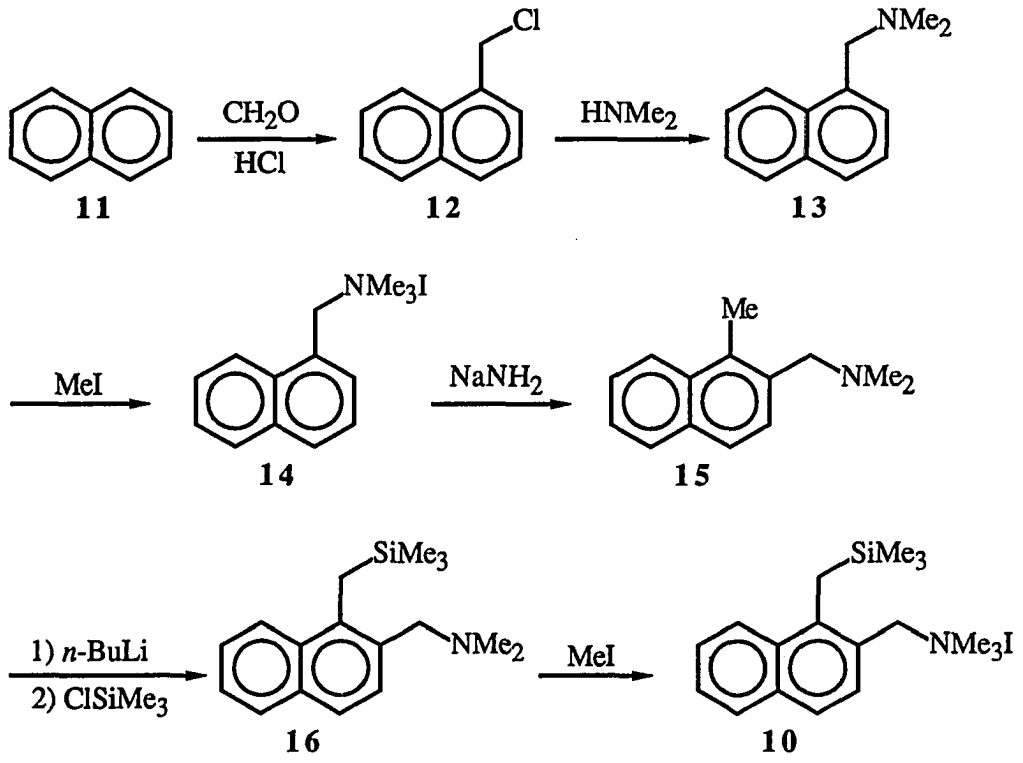
RESULTS

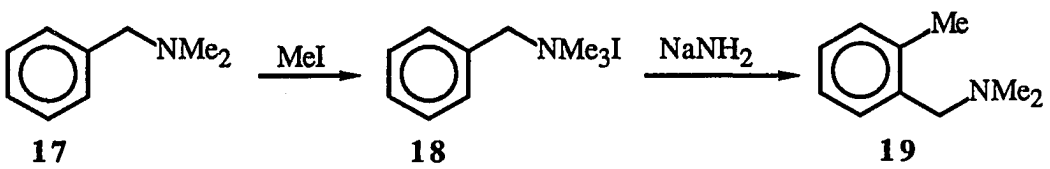
Initial work focused on obtaining the ^{1}H NMR spectrum of 1,2-dimethylene-1,2-dihydronaphthalene (**9**)[43] using the flow-NMR apparatus (see Experimental Section) since this reactive molecule is approximately 200 times less reactive than *o*-xylylene (**1**) itself.[20,22] The precursor of **9**, [1-(trimethylsilylmethyl)]trimethyl(2-naphthylmethyl)ammonium iodide (**10**), was prepared as outlined in Scheme 1. The ^{1}H NMR signals of **9** were detected at 25 °C by mixing an acetonitrile-d_3 (CD_3CN) solution of **10** (0.01 M) and a CD_3CN solution of tetrabutylammonium fluoride (TBAF) (0.166 M) at a total flow rate of 12 mL/min using the flow NMR technique (Figure 1a).

Scheme 1

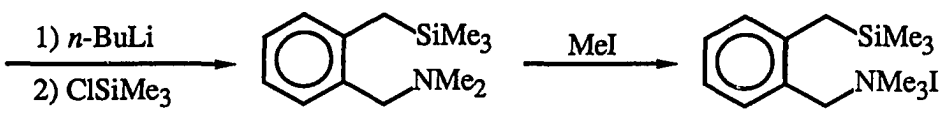


[*o*-((Trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) was prepared by the procedure of Ito et al.[10] starting from N,N-dimethylbenzylamine (**17**) as outlined in Scheme 2.

Scheme 2



17 **18** **19**



20 **5**

Mixing at 25 °C, a 10^{-3} M solution of **5** in CD_3CN and a 6 x 10^{-3} M solution of TBAF in CD_3CN at a total flow rate of 45 mL/min resulted in a ^1H NMR spectrum containing a number of signals in the low-field portion (Figure 1c). The low-field signals of the expected [4 + 2] (**6**) and [4 + 4] (**7**) dimers (~9:1 ratio) of **1**[25] were observed in a spectrum of the recycled product-mixture solution (Figure 1b). It is evident that the spectrum obtained by mixing the two reagent solutions at a total flow rate of 45 mL/min (Figure 1c) exhibits peaks pertaining to the stable dimers, but also exhibits additional peaks in this region as well. Indeed, computer subtraction of the spectrum of the recycled product-mixture solution (Figure 1b) from that obtained by mixing the two reagent solutions at a total flow rate of 45 mL/min (Figure 1c) results in a spectrum showing four signals in the low field portion (Figure 1d) which are attributed to **1**. The spectrum obtained by mixing a 10^{-3} M solution of **5** in CD_3CN

with a 6×10^{-3} M solution of TBAF in CD_3CN at a total flow rate of 3 mL/min shows primarily the signals for **6** and **7** (Appendix, Figure A-1).

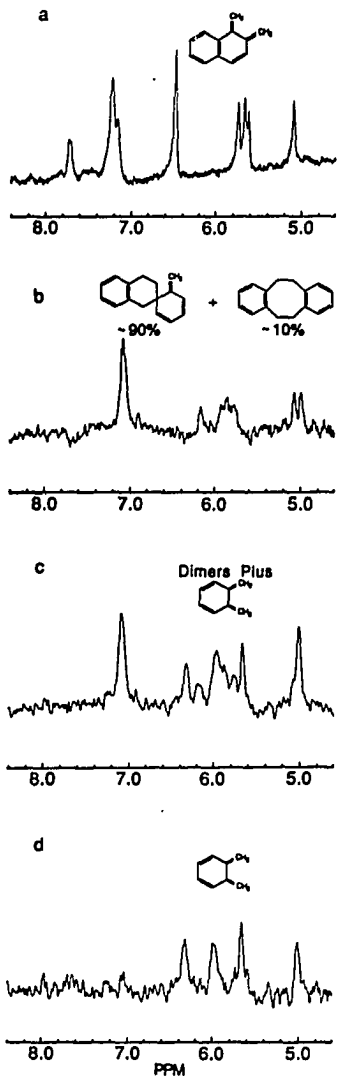


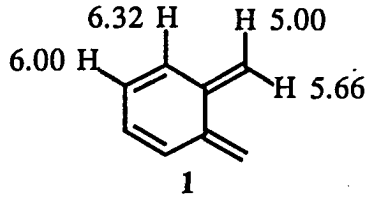
Figure 1. Flow ^{1}H NMR spectra (300 MHz): (a) obtained by mixing 0.01 M [1-(trimethylsilylmethyl)]trimethyl(2-naphthylmethyl)ammonium iodide (**10**) in CD_3CN with 0.166 M TBAF in CD_3CN; flow rate, 12 mL/min; number of scans 500; pulse interval, 1 s; (b) of the recycled product mixture resulting from mixing 10^{-3} M [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate, 45 mL/min; number of scans 831; pulse interval, 0.127 s; (c) obtained by mixing 10^{-3} M [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate, 45 mL/min; number of scans 831; pulse interval, 0.127 s; (d) obtained by computer subtraction of the spectrum in Figure 1b from the spectrum in Figure 1c

DISCUSSION

The ^1H NMR spectrum observed for 1,2-dimethylene-1,2-dihydronaphthalene (**9**) (Figure 1a) is consistent with that expected. The low field portion of the spectrum is similar to that of 2,2-dimethyl-2H-indene (**8**)[29,30] and the region between 6 and 5 ppm shows four exocyclic methylene proton signals, one of which is higher than the others because the corresponding proton is not deshielded by an adjacent π-bond. At faster flow rates, signals for **10** were observed, while at slower flow rates, signals for the dimers of **9** were observed.[22]

Comparison of the spectrum obtained of the recycled product-mixture solution of **1** (Figure 1b) with that obtained by mixing 10^{-3} M **5** in CD_3CN and 6×10^{-3} M TBAF in CD_3CN at a total flow rate of 45 mL/min (Figure 1c) confirms the presence of additional peaks. It is apparent that these additional signals are due to a transient species because gradual slowing of the flow rate results in lower intensity of these signals until they disappear altogether at a flow rate of 3 mL/min (Appendix, Figure A-1). The spectrum of the recycled product-mixture solution of **1** (Figure 1b) and that obtained at 3 mL/min (Appendix, Figure A-1) are very similar in appearance.

The four signals seen in the computer-subtracted spectrum (Figure 1d) can be attributed to the protons of the reactive molecule *o*-xylylene (**1**). The peak positions are in agreement with those observed for **9** and **8**[29,30] and are assigned as follows: δ 6.32 (α), 6.00 (β), 5.66 ((Z)-methylene), and 5.00 ((E)-methylene).



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From the positions of the ^1H NMR signals, it is clear that **1** is a highly reactive polyene not having any aromatic or antiaromatic character. In addition, the observation of **1** by flow NMR confirms the singlet nature of this reactive molecule.[5-8]

Parameters such as flow rate, concentration, and pulse interval must be properly adjusted in order to successfully observe a reactive molecule by flow NMR. The composition of the mixed solution at the detection point depends on the transfer time, which can be easily varied by changing the flow rate (see Experimental Section).[31,32] Thus, to observe short lived species, the transfer time must be minimized by using a fast flow rate.

Since these reactive *o*-xylylenes disappear by dimerization[25] which is a second order process, the rate of disappearance depends on the concentration of the reactive molecule itself.[44] Thus, a lower concentration of precursor reduces the rate of dimerization of the reactive *o*-xylylene once it is formed. The concentration of the precursor solution used must however be within the detection capability of the instrument. In addition, the rate of generation of the reactive *o*-xylylene depends on the ratio of TBAF to precursor. Due to its high reactivity, **1** is generated relatively slowly during the flow-NMR experiment by using only a six-fold excess of TBAF to **5** rather than a 100-fold excess as was used during its kinetic measurements.[20] Slower generation of **1** is necessary in the flow NMR experiment so that dimerization does not occur prior to detection.

The pulse interval, which is the interval between the FT NMR spectrometer's radiofrequency pulses, is the time during which the free induction decay is collected. The length of the pulse interval determines how much data can be collected during each free induction decay. Changes in the solution composition due to dimerization

during collection of the free induction decay are undesirable because they cause line broadening and phase anomalies.[45] Because of this consequence and the short lifetime of the reactive species, it is desirable to keep the pulse interval short. Care must be taken however to ensure that the pulse interval is long enough to permit sufficient nuclear spin relaxation so the signal intensity is not suppressed. Since the solution is continuously flowing, it is constantly being replaced in the detection region and thus the desired pulse interval is a function of the flow rate. Shorter pulse intervals are used for fast flow rates while longer pulse intervals are used for slow flow rates. Optimal pulse intervals were determined by judging the overall quality of spectra obtained of *p*-xylene in carbon tetrachloride at various flow rates. It is critical that factors such as flow rate, concentration, and pulse interval are optimized in order to obtain the highest quality spectrum using the smallest possible volume of reagent solutions.

The usefulness of the of flow-NMR technique has been demonstrated by the successful observation of 1,2-dimethylene-1,2-dihydronaphthalene (**9**) and also *o*-xylylene (**1**) in the presence of its stable dimers. It is clear that fluoride ion induced 1,4-elimination from [1-(trimethylsilylmethyl)]trimethyl(2-naphthylmethyl)-ammonium iodide (**10**) and [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) provide an excellent method for the generation of **9** and **1**, respectively for their flow NMR study.

EXPERIMENTAL SECTION

General Procedures

^1H NMR spectra were recorded on a Varian EM-360 or Nicolet NT-300 spectrometer. Chemical shifts are reported relative to tetramethylsilane.

Capillary gas chromatographic analyses were performed using a Hewlett-Packard HP 5840A gas chromatograph equipped with a 30-m DB-1 capillary column (J & W Scientific) using nitrogen as a carrier gas and a flame ionization detector.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All flow NMR spectra were taken on a Bruker WM-300 spectrometer (300 MHz) using acetonitrile-d_3 (CD_3CN) as solvent and residual $NCCD_2H$ as internal standard (δ 1.93). CD_3CN was purchased from Cambridge Isotope Laboratories.

N,N-Dimethylbenzylamine, naphthalene, *n*-butyllithium in hexanes, and chlorotrimethylsilane were purchased from Aldrich Chemical Co. Methyl iodide was purchased from Fisher Scientific Co. N,N-Dimethylbenzylamine and methyl iodide were used without further purification. Chlorotrimethylsilane was distilled from calcium hydride immediately before use. *n*-Butyllithium was standardized before use by titration.

[1-(Trimethylsilylmethyl)]trimethyl(2-naphthylmethyl)ammonium iodide (10)

Naphthalene (**11**) (128 g, 1 mol) was converted to 1-chloromethylnaphthalene (**12**) in 54% yield by the procedure of Grummitt and Buck.[46] To **12** (95.2 g, 540 mmol) in 400 mL of acetonitrile was added 100 g of dimethylamine (2.67 mol) after which the mixture was stirred for 24 h. Ether was added to the mixture and the mixture was extracted repeatedly with 1 M aqueous HCl solution. The acid extracts were made

basic with 1M aqueous NaOH solution and the resulting solution was extracted with ether. The combined ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the volume reduced leaving 96 g of N,N-dimethylnaphthylamine (**13**) (96 % yield). Methyl iodide (100 g, 704 mmol) was added dropwise to a solution of **13** (96 g, 518 mmol) in 400 mL of absolute ethanol while stirring. After completion of the addition, the solution was heated to reflux for 30 min. Cooling the solution resulted in formation of white crystals which were vacuum filtered and rinsed with ether, then dried under vacuum (10^{-2} mm Hg, 25 °C) for 24 h. The resultant trimethyl-(1-naphthylmethyl)ammonium iodide (**14**) (165 g, 97% yield) was used without further purification. Trimethyl(1-naphthylmethyl)ammonium iodide (**14**) (160 g, 489) was converted to [1-(methyl)](2-naphthylmethyl)dimethylamine (**15**) (35.5 g, 36% yield) in the same manner as used by Brasen and Hauser[47] to convert benzyltrimethyl-ammonium iodide to (*o*-methylbenzyl)dimethylamine. To a stirring solution of **15** (21.0 g, 105 mmol) in 350 mL of anhydrous ether (under nitrogen atmosphere) was added *n*-butyllithium (212 mmol) at 0 °C over 30 min. The solution was then stirred at room temperature for 22 h. A mixture of chlorotrimethylsilane (30 g, 276 mmol) and trimethylamine (6 mL) was added to the solution (0 °C) all at once and the solution was allowed to stir for 24 h. The mixture was quenched with a cold aqueous solution of sodium bicarbonate and extracted with ether. The ethereal solution was washed with brine, dried over anhydrous magnesium sulfate, filtered, and the volume reduced. A 28.2 g quantity (99% yield) of [1-(trimethylsilylmethyl)](2-naphthylmethyl)dimethylamine (**16**) was obtained. Methyl iodide (60 g, 423 mmol) was added dropwise to a solution of **16** (28.2 g, 104 mmol) in 250 mL of CH_3CN while stirring. After completion of the addition, the solution was heated to reflux for 24 h. Cooling the solution and addition of ether resulted in the precipitation of a white

solid, **10**, which was recrystallized from 1:1, ethyl acetate-acetone. ^{1}H NMR ($CDCl_3$) δ 8.10-7.20 (m, 6H), 3.55 (s, 2H), 2.82 (s, 2H), 2.30 (s, 9H), 0.06 (s, 9H); HRMS (obtained by the Fast Atom Bombardment technique) calcd. for the cation ($C_{18}H_{28}NSi^+$) 286.19911 and for the salt and the iodide ion ($C_{18}H_{28}I_2NSi^-$) 540.00806, found 286.19890 and 540.01037, respectively.

[*o*-((Trimethylsilyl)methyl)benzyl]trimethylammonium iodide (5)

A 4.88 g (36.1 mmol) quantity of N,N-dimethylbenzylamine (**17**) was converted to [*o*-((trimethylsilyl)methyl)benzyl]dimethylamine (**20**) in a 32% yield by the three step procedure of Ito et al.[10] A 2.57 (11.6 mmol) quantity of **20** was converted to **5** in 87% yield by the procedure of Ito et al.[10] mp 188-189 °C [lit.[10] 189.5-190.5 °C]; ^{1}H NMR (CD_3CN) δ 7.42-7.18 (m, 4H), 4.41 (s, 2H), 3.02 (s, 9H), 2.33 (s, 2H), -0.04 (s, 9H) [lit.[10] ^{1}H NMR (CD_3CN) δ 7.3-6.6 (m, 4H), 4.36 (s, 2H), 2.85 (s, 9H), 2.07 (s, 2H), -0.32 (s, 9H)]. See Appendix for a detailed description of the preparation of **5**.

General Procedure for Flow NMR

The flow-NMR apparatus (Figure 2), consisting of two 50-mL gastight syringes (Hamilton, Model 1050), a variable speed syringe pump, polyethylene tubing, and the mixing-chamber flow-tube base assembly, was designed for ease of use and versatility over a wide range of reactivity. The apparatus resides on a cart making it easily transportable to and from the spectrometer location. The mixing-chamber flow-tube base assembly (Figure 3) was designed by W. S. Trahanovsky and C.-H. Chou and was built by the Ames Laboratory Engineering Services. It was designed to be easily inserted and removed from the wide-bore probe (5 cm) of the spectrometer magnet.

Teflon was used to construct the mixing chamber and base because of its chemical inertness and ease of machining. The mixing chamber (Figure 3, inset),

patterned after one used by Fyfe and co-workers,[48] provides fast and efficient mixing of the two solutions. The two solutions in the side chambers enter the central chamber through two sets of side arms. The top set of side arms is arranged so that the mixed solution circulates in a clockwise direction. This circulating flow meets that from the lower side arms circulating in the opposite direction, thus resulting in rapid and complete mixing.

The flow tube (Figure 3) consists of a glass capillary tube (1 mm ID, 2 mm OD) mounted inside a 5-mm NMR tube both of whose tops are fused to a glass-to-Teflon union. The top of the glass-to-Teflon union is secured against the bottom of the mixing chamber and a liquid-tight seal is formed using a Kalrez rubber o-ring. Upon mixing, the solution is rapidly transferred by the capillary to the lower portion of the flow tube which is positioned within the detector coil of the NMR spectrometer. The efficiency of the system depends on the time between generation of the reactive molecule and when detection begins. This transfer time[31,32] is primarily a function of the solution flow rate and the distance between the mixing chamber and detection point. With this apparatus, mixing occurs within the magnet of the NMR spectrometer, directly above the point of detection thus giving a minimal transfer time. Fast accumulation of spectra under continuous-flow conditions was possible by use of a Bruker WM-300 pulse FT NMR spectrometer. After detection, the spent solution flows up and out of the flow tube through the side arm and is collected outside of the magnet in a receiving flask.

In order to observe the magnetic resonance phenomenon, a population difference must be established between the two spin states of the protons by allowing the protons to reside in the magnetic field for a period of time.[31,32] To achieve this, the solution containing the precursor of the reactive molecule is flowed through a coil

of polyethylene tubing (not shown) housed in the cavity of the base before entering the mixing chamber (Figure 3). The precursor solution spends 10-12 s in this coil at a flow rate of 45 mL/min.

A typical run is carried out by filling one of the syringes with a 10^{-3} M solution of [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) in CD_3CN and the other syringe with a 6 x 10^{-3} M solution of TBAF in CD_3CN. Just before data collection is begun, the mixing-chamber flow-tube base assembly is lowered into the probe of the magnet. The syringe pump allows controlled, equal delivery of the two solutions to the mixing chamber and thus at a given flow rate, the mixed solution has a constant composition in the detector region. At a total flow rate of 45 mL/min, the fastest possible for this apparatus, the time between when the two solutions are mixed and when the mixed solution reaches the detection point (transfer time) is approximately 0.2 s. The transfer time is increased to approximately 80 s at a total flow rate of 0.1 mL/min. See Appendix for a detailed description of the flow NMR procedure.

Tetrabutylammonium fluoride (TBAF)

TBAF was prepared by the procedure of Macias[22] with the following modification: water was removed under vacuum (10^{-2} mm Hg, 25 °C) over a 24 h period resulting in the formation of a hygroscopic white solid. See Appendix for a detailed description for the preparation of TBAF.

CD_3CN purification

CD_3CN was purified for reuse after each flow NMR experiment by the following procedure: 1) addition of 0.1 mL concentrated sulfuric acid followed by distillation;

2) distillation from calcium hydride; 3) distillation from phosphorus pentoxide. All distillations were performed using a Vigreaux column and Drierite drying tube.

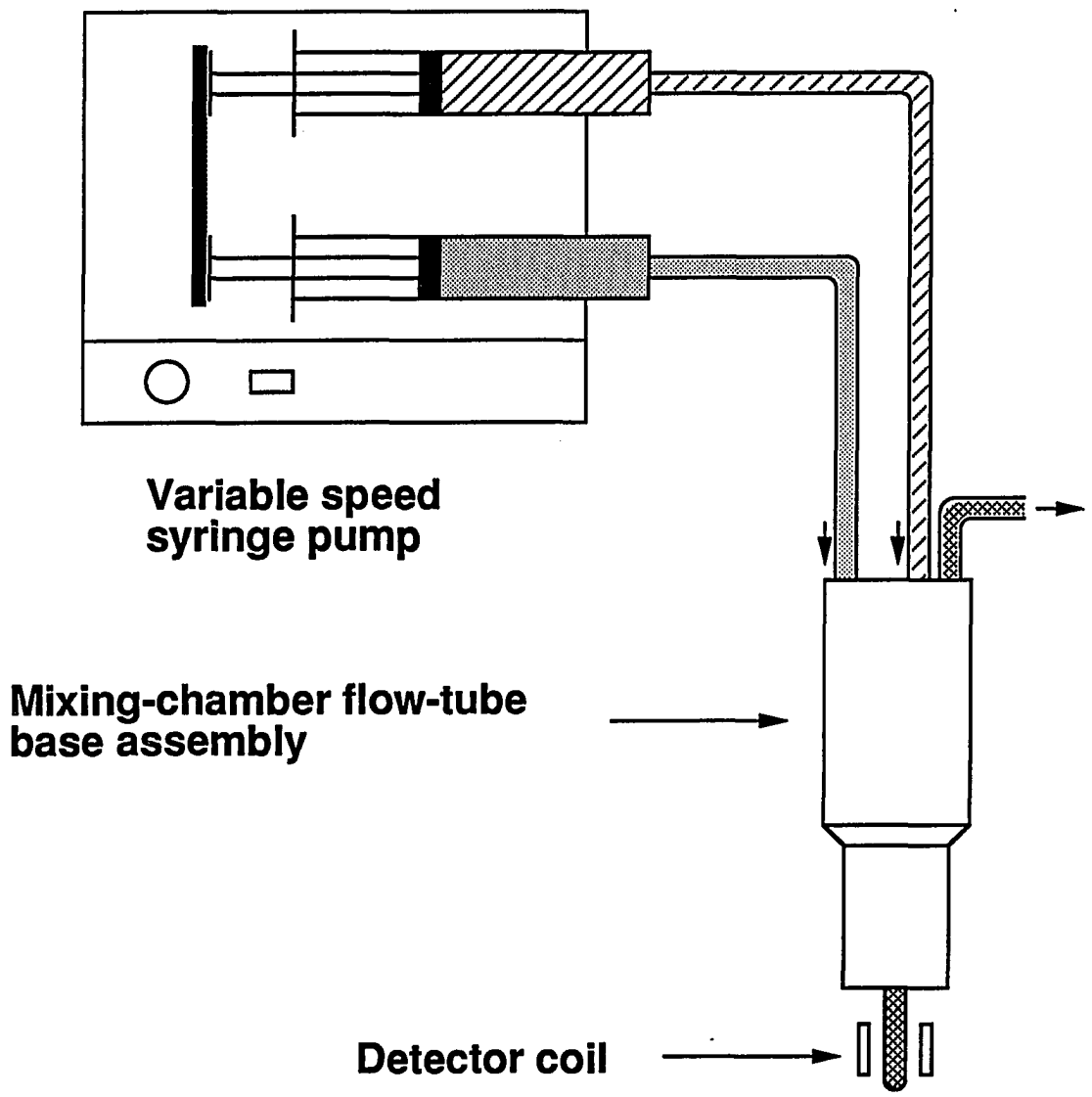

Figure 2. Flow NMR apparatus

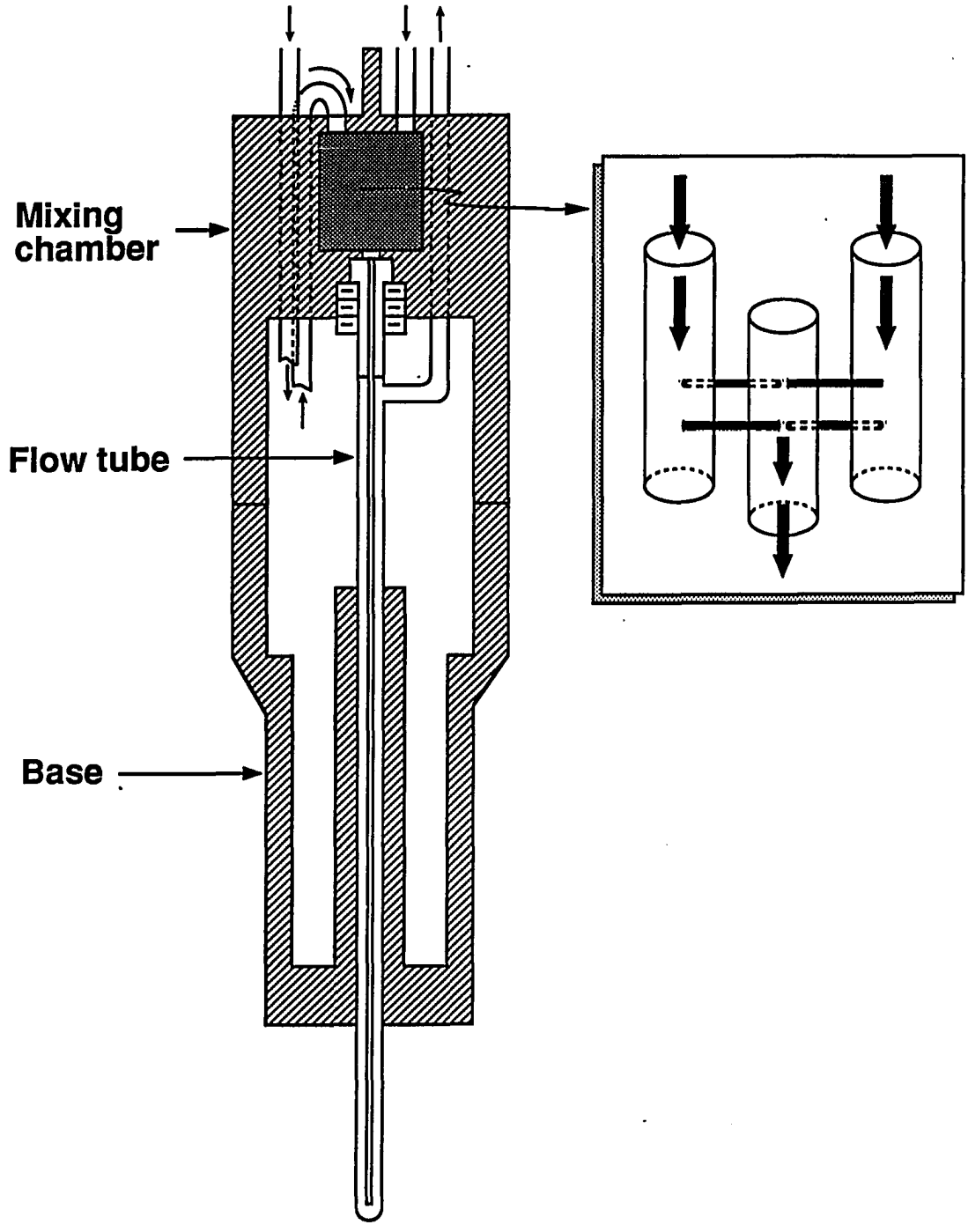

Figure 3. Mixing-chamber flow-tube base assembly

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APPENDIX

Detailed Description for the Preparation of [o-((Trimethylsilyl)methyl)benzyl]trimethylammonium Iodide

Benzyltrimethylammonium iodide (18)[47]

Methyl iodide (21.2 g, 150 mmol) was added dropwise over 15 min to a solution of N,N-dimethylbenzylamine (**17**) (15 g, 111 mmol) in 20 mL of absolute ethanol while stirring. After completion of the addition, the solution was heated to reflux for 30 min. Cooling the solution resulted in formation of white crystals which were vacuum filtered, rinsed twice with ether, then dried under vacuum (10^{-2} mm Hg, 25 °C) for 24 h. The benzyltrimethylammonium iodide (**18**) (30.5 g, 99% yield) was used without further purification.

(*o*-Methylbenzyl)dimethylamine (19)[47]

To 100 mL of liquid ammonia, contained in a 3-neck round bottom flask with a stir bar and fitted with a dry ice condensor (dry ice-acetone), was added small pieces of sodium (2 x 5 mg) until the blue color persisted. Ferric nitrate (24.4 mg) was added, followed by piecewise addition of sodium (1.01 g, 44.1 mmol) while stirring. The solution was allowed to stir for 15 min, then **18** (contained in an Ehrlenmeyer flask attached to the 3-neck round bottom flask with a short piece of large diameter rubber tubing) was added to the blue solution over a 15 min period. The solution was stirred for an additional 2h, after which the excess sodium amide was carefully destroyed by adding 1 g of ammonium chloride. Water (15 mL) was added to the reaction mixture which was then allowed to warm to room temperature. The solution was extracted with ether. The ether extracts were then combined and washed with brine, followed by water. The organic phase was dried over anhydrous potassium carbonate, then

filtered, and the volume reduced leaving 3.5 g (66% yield) of **19**. ^{1}H NMR ($CDCl_3$) δ 7.30-7.05 (m, 4H), 3.37 (s, 2H), 2.38 (s, 3H), 2.27 (s, 6H).

[*o*-((Trimethylsilyl)methyl)benzyl]dimethylamine (20)[10]

To a stirring solution of **19** (3.5 g, 23.4 mmol) in ether (under nitrogen atmosphere) was added *n*-butyllithium (19.8 mL, 47.4 mmol, 2.4 M) at 0 °C over 15 min. The solution was then stirred at room temperature for 24 h. A mixture of chlorotrimethylsilane (6.42 g, 59.1 mmol) and trimethylamine (0.86 mL) was added to the solution (0 °C) all at once and the solution was allowed to stir for 4 h. The mixture was quenched with a cold aqueous solution of sodium bicarbonate and extracted with ether. The ethereal solution was washed with brine, dried over anhydrous magnesium sulfate, filtered, and the volume reduced. A 2.57 g quantity (49% yield) of the clear oil was obtained after vacuum distillation (58 °C, 0.3 mm Hg). ^{1}H NMR ($CDCl_3$) δ 7.20-6.87 (m, 4H), 3.23 (s, 2H), 2.20 (s, 2H), 2.13 (s, 6H), -0.08 (s, 9H).

[*o*-((Trimethylsilyl)methyl)benzyl]trimethylammonium iodide (5)[10]

Methyl iodide (4.1 g, 29 mmol) was added dropwise over 15 min to a solution of **20** (2.57 g, 11.6 mmol) in 3 mL of absolute ethanol while stirring. After completion of the addition, the solution was heated to reflux for 50 min. Cooling the solution resulted in formation of white crystals which were vacuum filtered, rinsed twice with ether, then dried under vacuum (10^{-2} mm Hg, 25 °C) for 24 h (3.77 g, 87% yield).

Detailed Description for the Preparation of TBAF

A 25.1 mL quantity of 40% tetrabutylammonium hydroxide (38.2 mmol) was neutralized with 15.9 g of 4.8% hydrofluoric acid (38.2 mmol). Water was removed

while stirring under vacuum (10^{-2} mm Hg, 25 °C) over a 24 h period resulting in the formation of a hygroscopic white solid.

Detailed Description of the Flow NMR Procedure

Preparation

The clean, oven dried glassware (2 x 250-mL and 1 x 500-mL Ehrlenmeyer flasks) was flushed out with nitrogen gas. Nitrogen gas was bubbled through the CD_3CN. The polyethylene tubing and mixing-chamber flow-tube base assembly were flushed out with nitrogen gas. The precursor and TBAF were weighed out, placed in the 250-mL Ehrlenmeyer flasks, and CD_3CN was added to each via syringe.

Experiment

The solutions were drawn into the 50-mL gastight syringes using the syringe fill tubes and any bubbles present were eliminated from the syringes. The polyethylene tubing of the mixing-chamber flow-tube base assembly was attached to the syringes with the Luer-lock connectors. The tubing that transports the TBAF solution is connected directly to the mixing chamber and is marked with an "F" on the Luer-lock connector. The tubing that transports the precursor solution, labelled "SM", is first directed to the base through one of the openings in the top of the mixing chamber before actually flowing into the mixing chamber.

Both syringes were tightly secured in the clamps of the syringe pump. The end of the tubing that transports the spent solution was placed in the 500-mL Ehrlenmeyer flask (receiving flask). The solution was then slowly pumped through the tubing and into the mixing-chamber flow-tube base assembly (pump setting = 100x, 10-25%). Due to differences in the length of tubing, the two solutions reached the mixing chamber at slightly different times. Proper mixing of the two solutions was assured by the

replacement of bubbles in the narrow glass capillary with a continuous flow of solution.

The mixing-chamber flow-tube base assembly could now be inserted in the magnet of the NMR spectrometer. The lift air was turned on and the mixing-chamber flow-tube base assembly was placed at the opening of the magnet where it was suspended by air. While the NMR operator slowly decreased the lift air, the mixing-chamber flow-tube base assembly was gently lowered into the magnet, using the tubing and fishing line, until it came to rest. The operator gently pushed on the top of the mixing-chamber flow-tube base assembly with a wooden stick to ensure its proper positioning in the magnet.

The lock signal was observed on the display of the NMR spectrometer console and the instrument was shimmed. NMR parameters from a past experiment were read in from the disk, then the desired experiments were run while collaborating with the NMR operator.

After the reagent solutions were used up, a spectrum of the recycled product mixture solution under flowing conditions was desired. The tubing from one of the empty syringes was briefly disconnected. While the syringe was still in the clamp of the syringe pump, the syringe plunger was drawn back filling it with air. The tubing was reconnected and these steps were repeated for the other syringe. The pump was turned on to force out the solution from the tubing and mixing-chamber flow-tube base assembly into the receiving flask, using air. The tubing was disconnected from the syringes and the syringes were removed from the clamps. The syringes, fitted with syringe fill tubes, were then filled with the spent solution from the receiving flask. The syringes were placed in the clamps of the syringe pump and the tubing was reconnected. The tubing and mixing-chamber flow-tube base assembly were slowly

filled with spent solution until the waste tubing line coming up out from the magnet contained a continuous flow of solution. The desired experiment was then run using the spent solution.

The mixing-chamber flow-tube base assembly was removed from the magnet by turning on the lift air and carefully guiding it, using the tubing and fishing line, to the opening where it was retrieved. All of the desired files were saved on the disk when the experiment was completed.

Clean-up

The tubing and mixing-chamber flow-tube base assembly was purged of solution as was done earlier in preparation for obtaining the recycled product-mixture solution spectrum. Additional solution was removed from the bottom of the flow tube by holding the mixing-chamber flow-tube base assembly on its side with the exit port of the flow tube at the lowest point while forcing air through the system using the syringe pump and syringes. Any small amounts of solution remaining in the two 250-mL Ehrlenmeyer flasks and the gastight syringes was transferred to the receiving flask containing the spent solution.

The tubing and mixing-chamber flow-tube base assembly was rinsed with acetone (30 mL in each of two plastic syringes) followed by purging with air using plastic syringes. The tubing and mixing-chamber flow-tube base assembly was then rinsed with pentane (30 mL in each of two plastic syringes) followed by purging with air using plastic syringes until all traces of solvent disappeared.

CD_3CN distillation

The spent solution was poured into a 250-mL round-bottom flask with a stir bar, and approximately 0.1 mL of concentrated H_2SO_4 was added. Distillation was

performed while stirring, using a Vigreaux column and a drying tube. The first fraction (approximately 1 mL) of CD_3CN was collected in a small round-bottom flask. The distillate was then collected with a 250-mL round-bottom flask. The distillate appeared slightly yellow in color at this time, but the color disappeared during the next distillation. The last 2-3 mL's of CD_3CN were collected in the same small round-bottom flask as was used to collect the first fraction.

Approximately 0.5 g of calcium hydride and a stir bar were added to the 250-mL round-bottom flask containing the CD_3CN from the previous distillation. Distillation was performed as before with the yellow color now disappearing from the distillate.

Phosphorus pentoxide (ca. 0.5 g) and a stir bar were then added to the 250-mL round-bottom flask containing the CD_3CN from the previous distillation. Distillation was performed as before. When completed, the 250-mL round-bottom flask containing the purified CD_3CN was stoppered with a glass stopper and sealed with Parafilm (and also the small round-bottom flask containing all of the first and last fractions).

CD_3CN is expensive, so care was exercised during each handling and distillation. In order to conserve CD_3CN, the last remaining portions in the distillation pot were distilled down as far as possible and collected in the small round-bottom flask . At the beginning of this distillation sequence, the first and last fractions from the previous distillation sequence (contained in the small round-bottom flask) were added to the spent solution from the experiment, thus effectively recycling this portion.

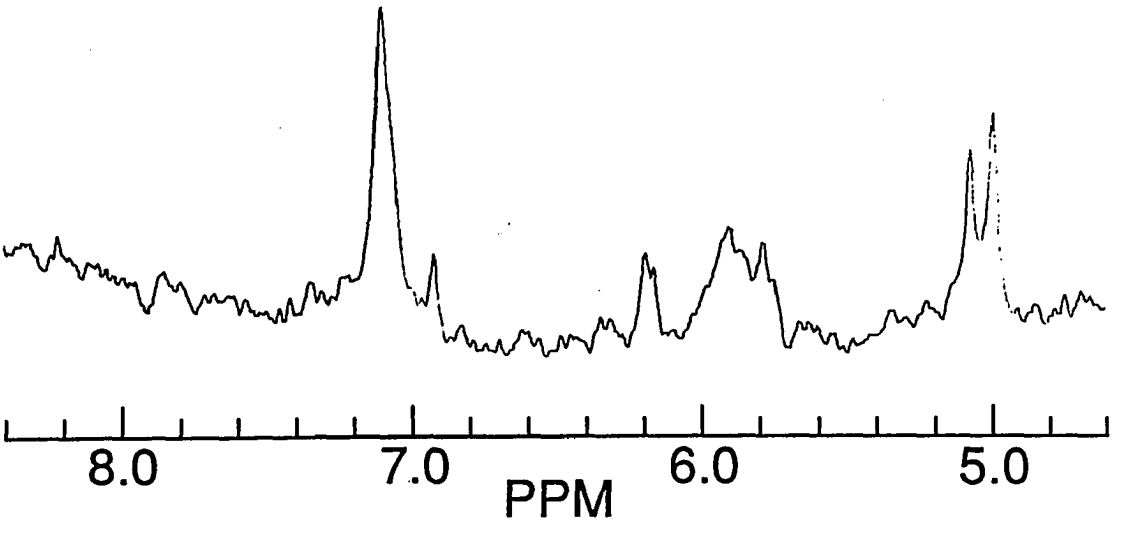
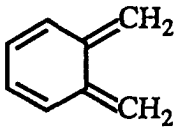


Figure A-1. Flow ^{1}H NMR spectrum (300 MHz) obtained by mixing 10^{-3} M [o-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide (**5**) in CD_3CN with 6×10^{-3} M TBAF in CD_3CN; flow rate, 3 mL/min; number of scans 1206; pulse interval, 0.512 s

SECTION 2. DIMERIZATION KINETICS, PRODUCT STUDIES, AND FLOW ^{1}H NMR OF 3-ALKYL- AND 3,6-DIALKYL-1,2-XYLYLENES

INTRODUCTION[1]

The reactive molecule *o*-xylylene (**1**) and its derivatives have been the subject of



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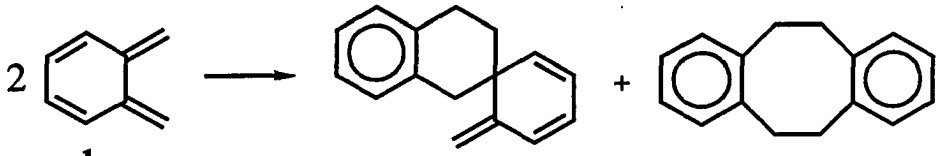
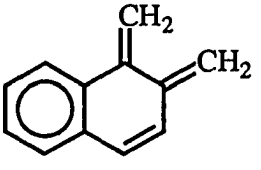
considerable study.[2-11] It has been demonstrated that **1** can be generated in solution by fluoride ion induced 1,4-elimination from [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium halides.[8,12] Using this method, **1** can be formed rapidly enough so that it can be observed by UV-visible spectroscopy[13] and flow ^{1}H NMR.[14] A variety of substituted *o*-xylylenes have been generated from their easily prepared presursors using this method.[13] Upon generation, **1** rapidly dimerizes following second order kinetics to give the stable [4 + 2] (**2**) and [4 + 4] (**3**) dimers[15] in a 9:1 ratio.[13]



1 **2** **3**

The reactivity of these reactive *o*-xylylenes is measured by the rate of their dimerization reaction. Two systems whose dimerization rates have been measured are **1**[13] and 1,2-dimethylene-1,2-dihydronaphthalene (**4**).[16] The naphthalene system



4

4, which has a benzene ring annulated on to the parent *o*-xylylene structure, dimerizes at a rate that is approximately 200 times slower than that of *o*-xylylene (**1**)

itself (Table 1).[17] The enthalpies of activation for the two are similar while the entropy of activation for **4** is lower than that for **1**. These observations raise the question of whether the lower reactivity of **4** is due to a smaller resonance energy gain in the transition state leading to dimerization or due to steric hindrance caused by the annulated benzene ring blocking one of the exocyclic methylenes relative to the other.

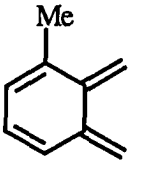
Table 1. Comparison of the second order dimerization rate constants (25 °C) and activation parameters for *o*-xylylene (**1**)[a] and 1,2-dimethylene-1,2-dihydronaphthalene (**4**)[b]

Compound	k, M^{-1} s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	12,500	2.0	-33
4	61	3.0	-40

[a]Reference 17.

[b]Reference 16.

To examine the difference in reactivity between **1** and **4**, 3-methyl-1,2-xylylene (**5**) was studied. The methyl group of **5** models the steric influence of the annulated



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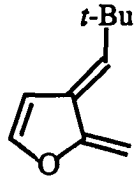
benzene ring on the nearest exocyclic methylene in **4**. However, the transition state resonance energy changes for **5** and **1** are approximately the same.

It is of interest to investigate the effect of bulky groups on the reactivity of

organic molecules. Trahanovsky and Macias concluded that bulky alkyl groups in the 4- or 4,5-positions of 1,2-xylylenes have little effect on the dimerization rate and thus dimerization proceeds by a non-endo approach.[13] It was found that the dimerization rate for 2-methylene-3-*tert*-butylmethylene-2,3-dihydrofuran (**6**) is



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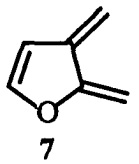
greatly slowed relative to the parent, 2,3-dimethylene-2,3-dihydrofuran (**7**). However,



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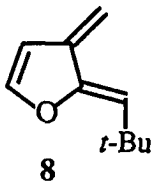
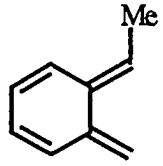
the rate of dimerization for the derivative with a *tert*-butyl group in the 2-exocyclic methylene position (**8**) is not significantly slowed.[18] Initial bond formation during



8

the stepwise dimerization of furan *o*-quinodimethanes is clearly occurring between the two 3-exocyclic methylene groups.[19] In an analogous study, the methyl group in the *o*-xylylene derivative, 5-ethylidene-6-methylene-1,3-cyclohexadiene (**9**), had



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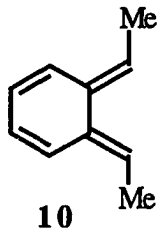
little effect on the dimerization rate. However, with one methyl group on each of the two exocyclic methylenes (**10**), the dimerization rate was greatly slowed.[16] This



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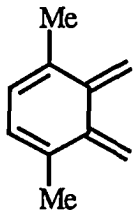
result gives evidence for a stepwise dimerization mechanism in the case of *o*-xylylenes.

Alkyl groups flanking the exocyclic methylenes of *o*-xylylenes should offer steric hindrance during dimerization. These alkyl groups are near, but not directly on the reactive sites as is true for **9** and **10**. It is expected that these alkyl groups will lower the rate of dimerization, possibly giving a very unreactive *o*-xylylene, and also affect the dimer products obtained. To this end, a series of four alkyl substituted *o*-xylylenes (**5**, **11-13**) were studied.



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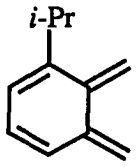

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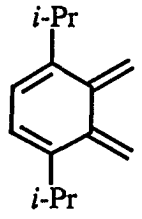

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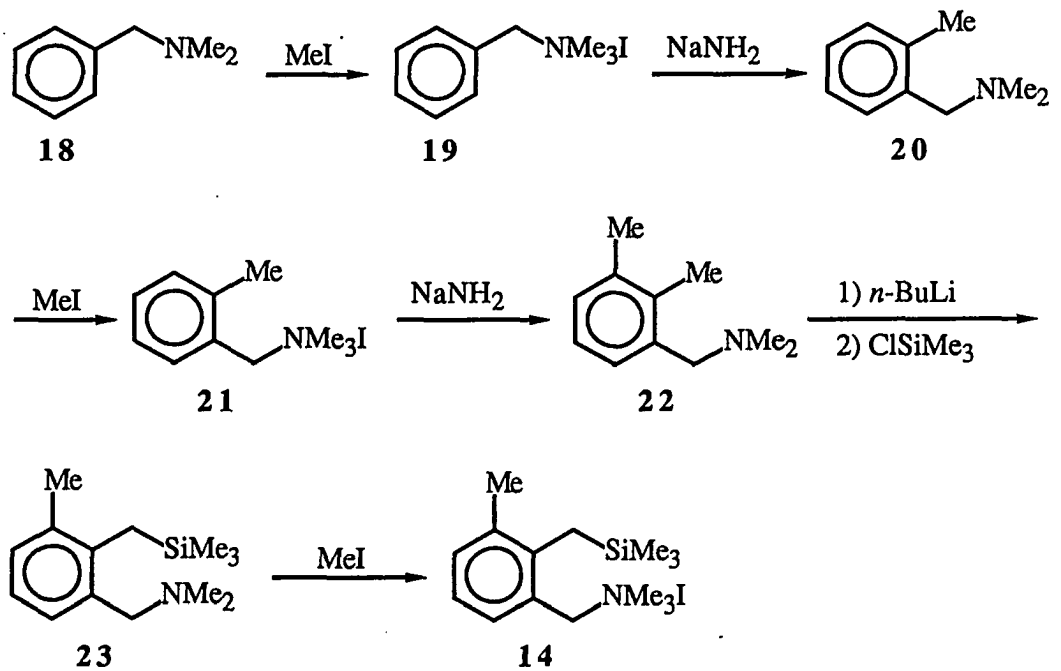
The usefulness of flow NMR in the study of reactive molecules has been demonstrated by the observation of **4** and also **1** in the presence of its stable dimers.[14,20] In this section, the observation of **5** and **11-13** using the flow-NMR technique is described along with the dimerization kinetics and product studies for each.

RESULTS

The precursors (**14-17**) to the series of four alkyl substituted *o*-xylylenes (**5**, **11-13**) containing methyl or isopropyl groups flanking one or both of the exocyclic methylene groups were prepared. Starting from N,N-dimethylbenzylamine (**18**), [2-((trimethylsilyl)methyl)-3-methylbenzyl]trimethylammonium iodide (**14**), the precursor to the first member of the series 3-methyl-1,2-xylylene (**5**) was prepared (Scheme 1). This reaction scheme is analogous to that used for the preparation of [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide, the precursor to **1**,[8,12] but involves an additional Sommelet-Hauser rearrangement.[21]

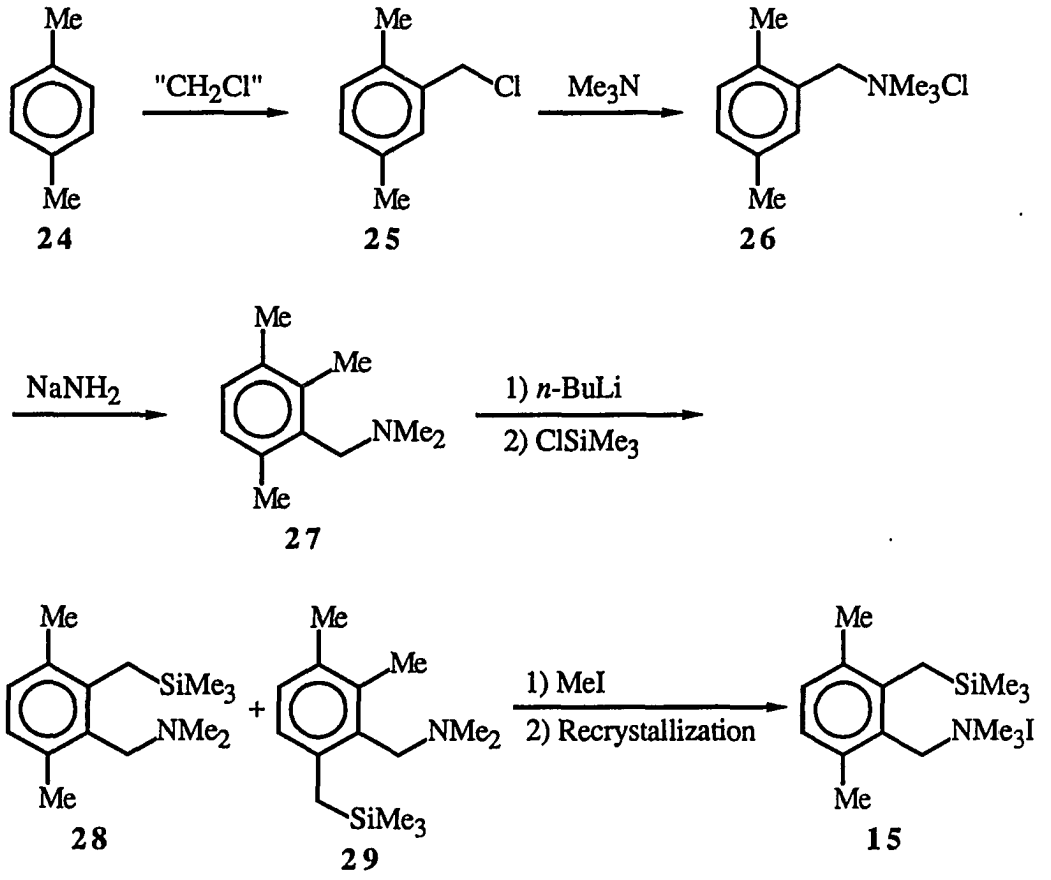
Scheme 1



Starting from *p*-xylene (**24**), [2-((trimethylsilyl)methyl)-3,6-dimethylbenzyl]-trimethylammonium iodide (**15**), the precursor to 3,6-dimethyl-1,2-xylylene (**11**), was

prepared (Scheme 2). The key steps involve chloromethylation[22] of **24** and also lithiation/silylation of 2,3,6-trimethylbenzyldimethylamine (**27**) in which the possibility exists for the formation of two isomers, [2-((trimethylsilyl)methyl)-3,6-dimethylbenzyl]dimethylamine (**28**) and [2-((trimethylsilyl)methyl-5,6-dimethyl-benzyl]dimethylamine (**29**). The desired isomer **28** was formed in a 16:1 ratio and treatment of this mixture with methyl iodide resulted in formation of the corresponding trimethylammonium iodide salts. Recrystallization of the mixture of trimethylammonium iodide salts left only the desired product **15**. The presence of the correct product (**15**) was confirmed by treatment of an acetonitrile (CH_3CN) solution.

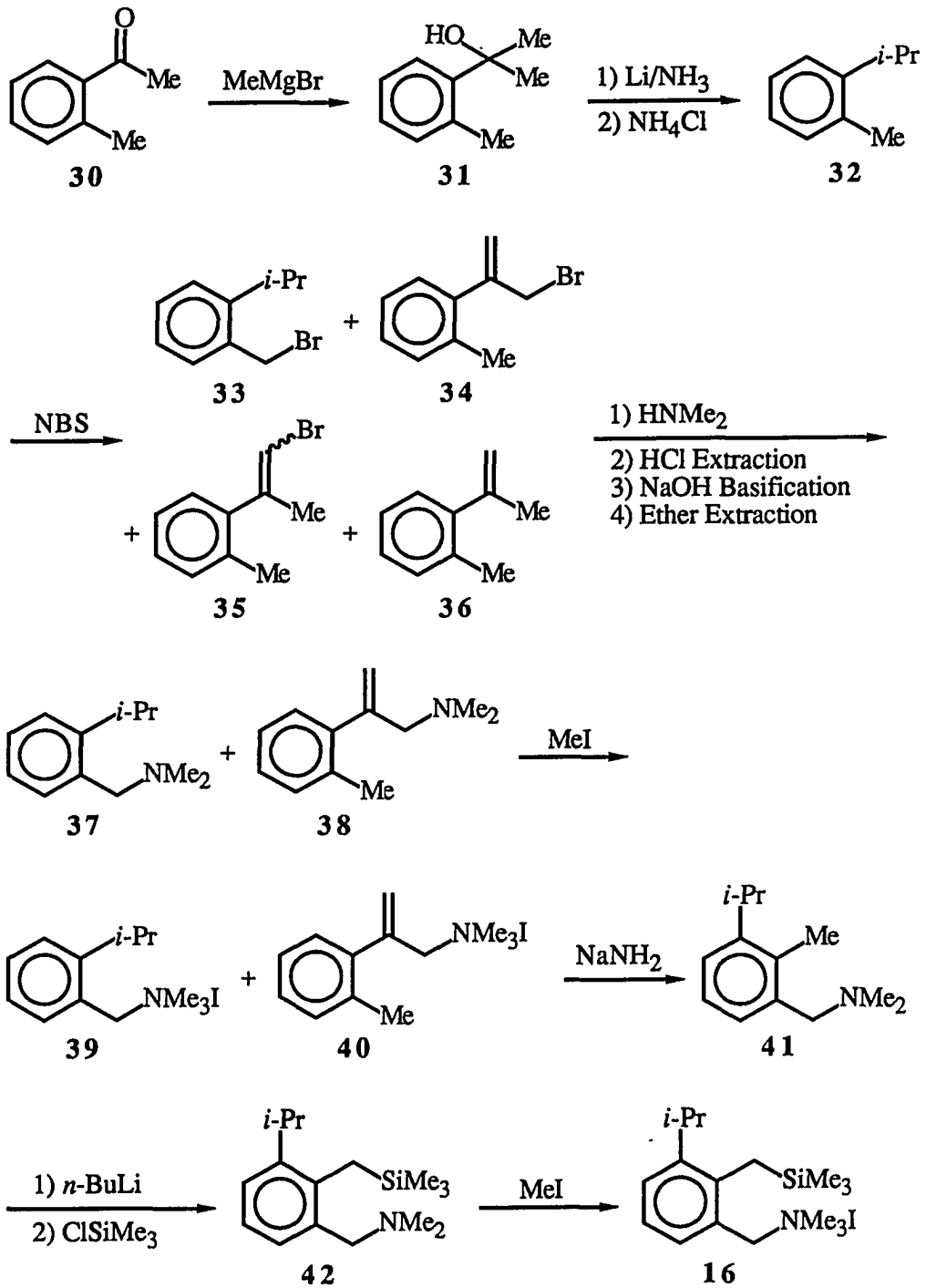
Scheme 2



of this trimethylammonium iodide salt with a solution of tetrabutylammonium fluoride (TBAF) in CH_3CN to give the expected [4 + 2] dimer. Also, the symmetrical **11** was observed by flow NMR. More details of product and flow NMR studies are given later in this section.

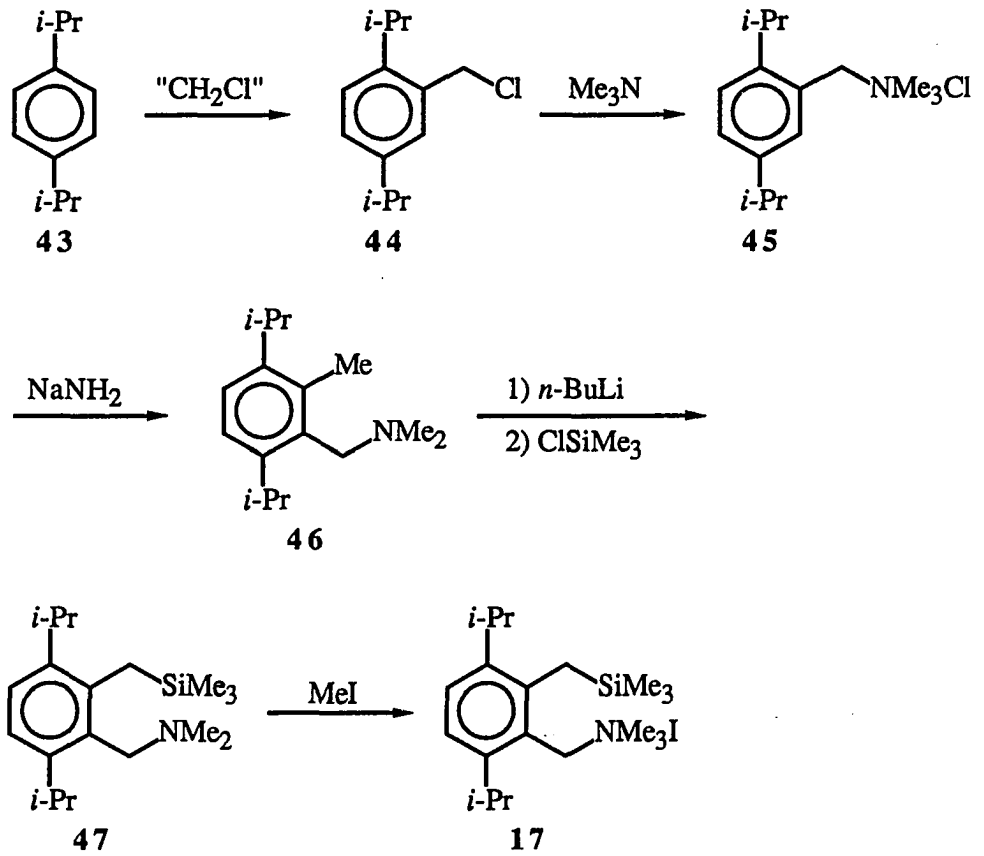
The precursor to 3-isopropyl-1,2-xylylene (**12**), [2-((trimethylsilyl)methyl)-3-isopropylbenzyl]trimethylammonium iodide (**16**), was prepared starting from 2'-methylacetophenone (**30**) (Scheme 3). The ketone (**30**) upon treatment with methyl Grignard gave 2-methyl-α,α-dimethylbenzyl alcohol (**31**), which was reduced to *o*-cymene (**32**) by the procedure used by Hall for the reduction of α-tetralol to tetralin.[23,24] NBS bromination of **32** gave the desired 2-isopropylbenzyl bromide (**33**) in a mixture of unreacted **32** and the side products 2-methyl-α-bromomethylstyrene (**34**), 2-methyl-β-bromo-α-methylstyrene (**35**), and 2-methyl-α-methylstyrene (**36**).[25] This product mixture was allowed to react with dimethylamine in ethanol and was extracted with hexanes following the addition of water. Extraction of this organic phase with 1 M HCl followed by basification with 2 M NaOH and ether extraction gave the desired amine, (2-isopropylbenzyl)dimethylamine (**37**) and also 2-methyl-α-dimethylaminomethylstyrene (**38**) in approximately a 9:1 ratio. The bromide **35** did not react with dimethylamine and was thus removed along with **32** and **36** during the acid extraction step. The mixture of the two amines **37** and **38** was then alkylated with methyl iodide resulting in the formation of the two amine salts, (2-isopropylbenzyl)trimethylammonium iodide (**39**) and [2-(2-methylphenyl)propenyl]trimethylammonium iodide (**40**). Under Sommelet-Hauser rearrangement conditions,[21] only **39** reacted giving 2-methyl-3-isopropyldimethylbenzylamine (**41**) which was carried on to **16**.

Scheme 3


O
Me
Me
MeMgBr
HO
Me
Me
Me
1) Li/NH3
2) NH4Cl
i-Pr
Me
30
31
32
i-Pr
Br
Br
Me
33
34
NBS
Br
Me
Me
Me
Me
35
36
1) HNMe2
2) HCl Extraction
3) NaOH Basification
4) Ether Extraction
i-Pr
NMe2
NMe2
Me
37
38
MeI
i-Pr
NMe3I
NMe3I
Me
39
40
NaNH2
i-Pr
Me
NMe2
41
1) n-BuLi
2) ClSiMe3
i-Pr
SiMe3
NMe2
42
MeI
i-Pr
SiMe3
NMe3I
16

[2-((Trimethylsilyl)methyl)-3,6-diisopropylbenzyl]trimethylammonium iodide (**17**), the precursor to 3,6-diisopropyl-1,2-xylylene (**13**), was prepared starting from 1,4-diisopropylbenzene (**43**) (Scheme 4) in a manner analogous to the preparation of **15**.

Scheme 4



A λ_{max} of 376 nm was determined for 3-methyl-1,2-xylylene (**5**) by mixing a CH_3CN solution of [2-((trimethylsilyl)methyl)-3-methylbenzyl]trimethylammonium iodide (**14**) with a CH_3CN solution of TBAF in the optical path of a diode-array rapid scanning UV-visible spectrophotometer. Upon formation, the reactive species rapidly disappeared following second order kinetics, but fast accumulation of spectra

was possible using the diode-array spectrophotometer. The value of λ_{max} measured for **5** is consistent with that reported for *o*-xylylene (**1**) (λ_{max} = 367 nm).[13]

The molar absorptivity (ε_{max}) for **5** was determined with the use of a stopped-flow kinetic apparatus. This experiment was performed by mixing a 10^{-3} M solution of **14** in CH_3CN with concentrations of TBAF in CH_3CN of 0.01. 0.05, 0.1, 0.25, and 0.5 M and monitoring the absorbance of **5** at 376 nm. As the fluoride ion concentration was increased, the absorbance also increased but then leveled off starting at a concentration of 0.05 M. At this point, a quantitative conversion of **14** to **5** was assumed.[13,16] From this absorbance and the concentration of **14**, a value of ε_{max} = 3167 M^{-1} cm^{-1} was calculated.

The decay of **5** was monitored at 25 °C using the stopped-flow technique[13] by mixing a 10^{-3} M solution of **14** in CH_3CN with a 0.1 M solution of TBAF in CH_3CN. Least-squares fit analysis[26] of a plot of 1/conc. versus time gave a straight line of excellent fit, the slope of which is the second order rate of dimerization for **5** (k = 1.15 ± 0.03 x 10^4 M^{-1} s^{-1}). In this same manner, dimerization rate constants for **5** were determined at 35 and 45 °C as well. Using the Arrhenius relationship,[27] plots of ln k versus 1/T gave the activation enthalpy and entropy[28] for **5** ($\Delta H^{\ddagger}$ = 1.4 ± 0.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -35 ± 1.6 eu).

As with **5**, the λ_{max} and ε_{max} values for **11-13** were determined and are included with those for **1** and **5** in Table 2. Dimerization rates for **11** and **12** were determined at 25, 35, and 45 °C using the stopped-flow technique (Table 3). Due to its lower reactivity, the rates of dimerization for **13** were determined by mixing a 10^{-3} M solution of **17** in CH_3CN with a 0.1 M solution of TBAF in CH_3CN in the optical path of a Cary spectrophotometer at 15, 25, and 35 °C (Table 3). The activation parameters for these reactive o-xylylenes (**11-13**) were calculated[28] and are shown in Table 4.

Table 2. λ_{max} and ε_{max} in CH_3CN for *o*-xylylene (**1**),[a] 3-methyl-1,2-xylylene (**5**), 3,6-dimethyl-1,2-xylylene (**11**), 3-isopropyl-1,2-xylylene (**12**), and 3,6-diisopropyl-1,2-xylylene (**13**)

Compound	λ_{max}, nm	ε_{max}, M^{-1} cm^{-1}
1	367	3015
5	376	3167
11	380	3624
12	373	3604
13	388	2962

[a]Reference 13.

Table 3. Second order rate constants for the dimerization of 3-methyl-1,2-xylylene (**5**), 3,6-dimethyl-1,2-xylylene (**11**), 3-isopropyl-1,2-xylylene (**12**), and 3,6-diisopropyl-1,2-xylylene (**13**) in CH_3CN[a]

Temp, °C	$k_5 \times 10^{-3}$, M^{-1} s^{-1}	$k_{11} \times 10^{-3}$, M^{-1} s^{-1}	$k_{12} \times 10^{-3}$, M^{-1} s^{-1}	$k_{13} \times 10^{-3}$, M^{-1} s^{-1}
15	—	—	—	0.196± 0.005
25	11.5 ± 0.3	5.23 ± 0.16	5.57 ± 0.17	0.244± 0.007
35	13.3 ± 0.3	6.37 ± 0.17	6.81 ± 0.18	0.301± 0.010
45	15.2 ± 0.4	7.66 ± 0.22	8.23 ± 0.25	—

[a]Calculated values. The starting concentrations of **5**, **11**, or **12** and TBAF were 5.00×10^{-4} and 5.00×10^{-2} M, respectively. The starting concentrations of **13** and TBAF were 2.00×10^{-4} and 2.00×10^{-2} M, respectively.

Table 4. Activation parameters for the dimerization of 3-methyl-1,2-xylylene (**5**),[a] 3,6-dimethyl-1,2-xylylene (**11**),[a] 3-isopropyl-1,2-xylylene (**12**),[b] and 3,6-diisopropyl-1,2-xylylene (**13**)[c] in CH_3CN

Compound	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
5	1.4 ± 0.5	-35 ± 1.6
11	2.3 ± 0.3	-33 ± 1.0
12	2.5 ± 0.3	-33 ± 1.0
13	2.6 ± 0.6	-39 ± 1.8

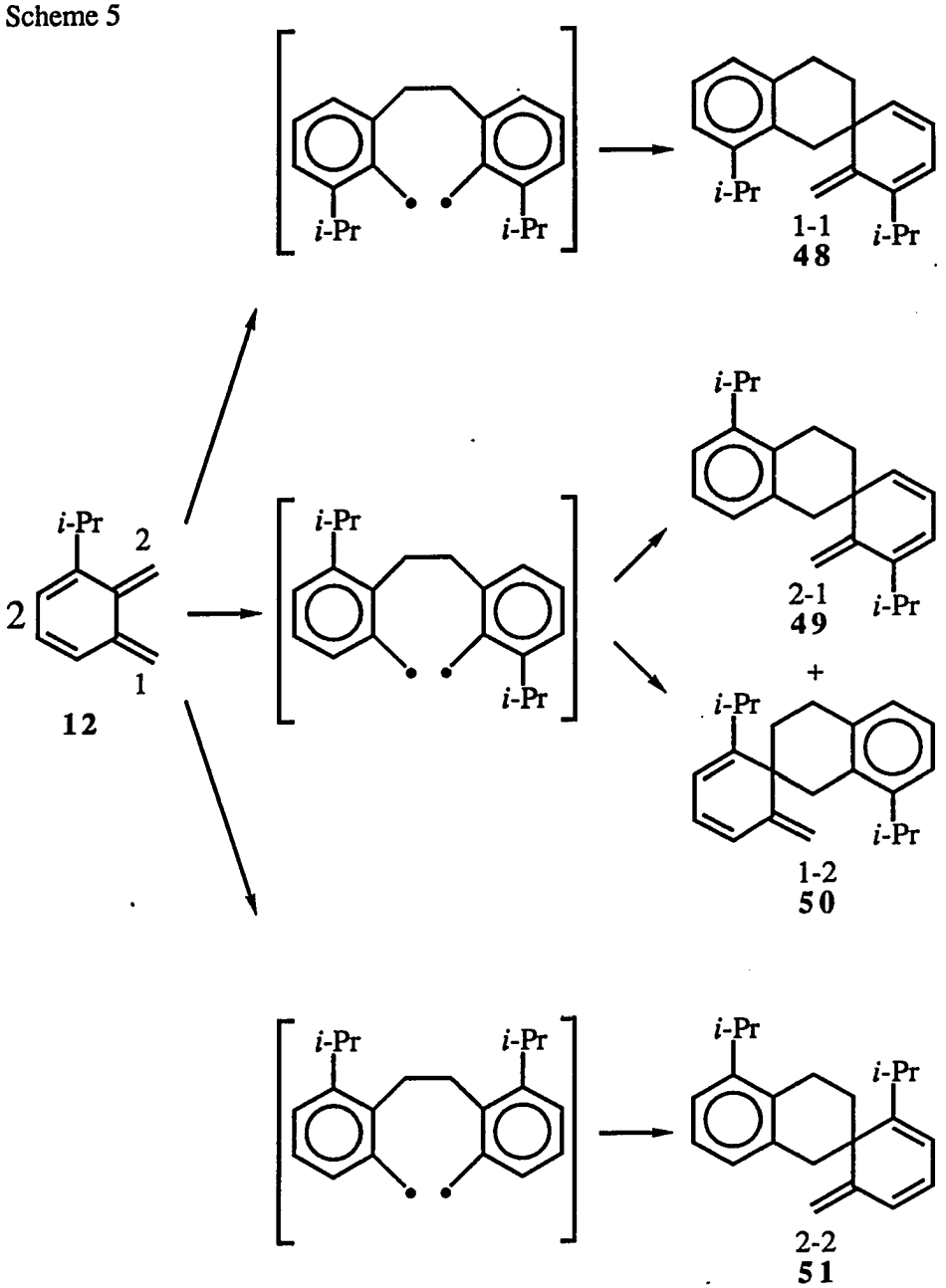
[a] T_{ave} = 34.6 °C.

[b] T_{ave} = 34.8 °C.

[c] T_{ave} = 24.7 °C.

Because 3-methyl-1,2-xylylene (**5**) and 3-isopropyl-1,2-xylylene (**12**) are unsymmetrical, four [4 + 2] and two [4 + 4] dimers are possible for each from dimerization reactions involving only the exocyclic methylene groups. The symmetrical **11** and **13** can each give rise to only one [4 + 2] and one [4 + 4] dimer. Treatment of a solution of [2-((trimethylsilyl)methyl)-3-isopropylbenzyl]trimethylammonium iodide (**16**) in CH_3CN with a solution of TBAF in CH_3CN resulted in the formation of the dimer mixture of **12**. The resulting four dimer products were separated by preparative HPLC and their ^1H NMR spectra were obtained. Based on their spectra, it is evident that these products are the expected four [4 + 2] dimers (Scheme 5, **48-51**). These [4 + 2] dimers are formed by initial joining of the 1-1 (**48**), 2-1 (**49**), 1-2 (**50**), and 2-2 (**51**) methylenes of the two reactive molecules followed by closure. The relative yields of these four [4 + 2] dimers was determined to be 46, 24, 23, and 7% by analytical HPLC.

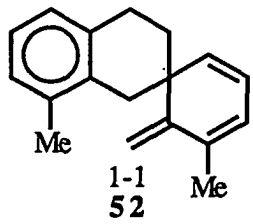
Scheme 5


i-Pr
i-Pr
1-1
48
i-Pr
2
2
1
12
i-Pr
i-Pr
2-1
49
i-Pr
+
i-Pr
i-Pr
1-2
50
i-Pr
i-Pr
i-Pr
i-Pr
2-2
51

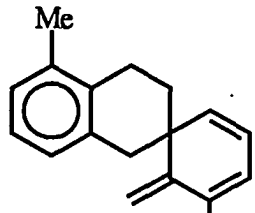
The exocyclic methylene proton signals of two of these [4 + 2] dimers are at relatively low field (5.27-4.99 ppm) in their ^{1}H NMR spectra, while those of the other two [4 + 2] dimers are at relatively high field (4.88-4.47 ppm). In the "low field group", one of the dimer's pair of exocyclic methylene signals are at 5.27 and 4.99 ppm. The other "low field group" dimer's exocyclic methylene protons gives rise to signals at 5.27 and 5.06 ppm. One of the dimers in the "high field group" has its exocyclic methylene signals at 4.87 and 4.47 ppm while those for the other dimer in this group are at 4.88 and 4.58 ppm. By integration of these exocyclic methylene signals in the ^{1}H NMR spectrum of the dimer mixture, the relative yields of these four [4 + 2] dimers was determined as 42 (5.27, 4.99 ppm) and 21% (5.27, 5.06 ppm) for the "low field group" and 28 (4.87, 4.47 ppm) and 9% (4.88, 4.58 ppm) for the "high field group". From the ^{1}H NMR spectrum of the dimer mixture of **12**, it was estimated that only a trace of the two possible [4 + 4] dimers was present.

The mixture of dimer products for 3-methyl-1,2-xylylene (**5**) was obtained in a similar manner as for **12**. The exocyclic methylene region of the ^{1}H NMR spectrum of this dimer mixture is very similar in appearance to that of **12**. By analytical HPLC, the relative yields of the four [4 + 2] dimers (Scheme 6, **52-55**) was found to be 44, 33, 13, and 10%. Calculation of the relative yields, using the integrated exocyclic methylene signals in the ^{1}H NMR spectrum of the dimer mixture, gave 42 (5.22, 5.00 ppm) and 13% (5.22, 5.09 ppm) for the "low field group" and 32 (4.92, 4.58 ppm) and 13% (4.90, 4.66 ppm) for the "high field group". Only a trace of the two possible [4 + 4] dimers in the dimer product mixture was estimated by ^{1}H NMR.

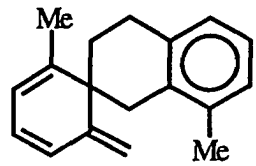
Scheme 6



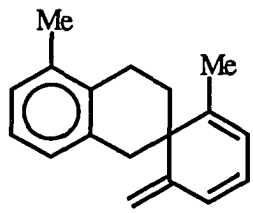
1-1
52



2-1
53



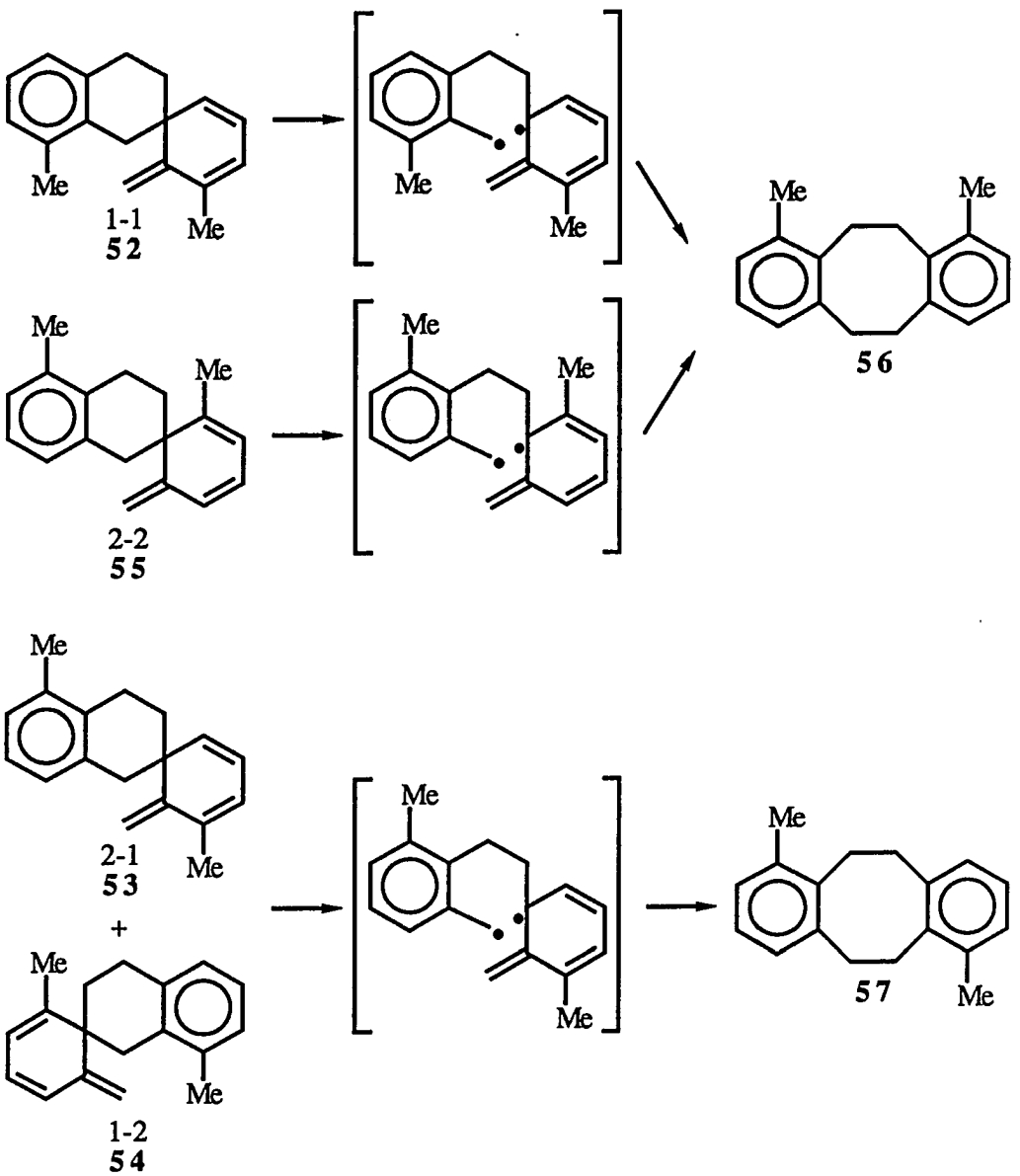
1-2
54



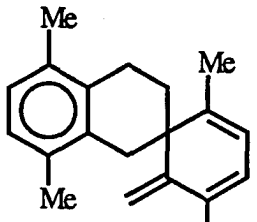
2-2
55

It has been shown that flash vacuum pyrolysis (FVP) of the [4 + 2] dimer (**2**) of *o*-xylylene (**1**) results in formation of the [4 + 4] dimer (**3**) by the cleavage of one bond.[29] When the mixture of [4 + 2] dimer products (**52-55**) of **5** was subjected to FVP conditions,[30] approximately a 1:1 mixture of the two possible [4 + 4] dimers (**56** and **57**) was found (Scheme 7). Similarly, the [4 + 2] dimer products (**48-51**) of **12** were flash vacuum pyrolyzed giving approximately a 1:1 ratio of the two [4 + 4] dimers (**58** and **59**).

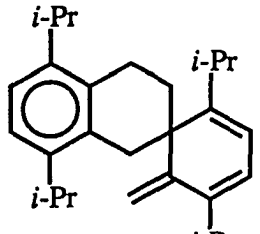
Scheme 7


Me
1-1
52
Me
Me
Me
Me
Me
Me
Me
2-2
55
Me
Me
Me
Me
56
Me
2-1
53
Me
+
Me
Me
1-2
54
Me
Me
Me
Me
57
Me

When a CH_3CN solution of either [2-((trimethylsilyl)methyl)-3,6-dimethylbenzyl]trimethylammonium iodide (**15**) or [2-((trimethylsilyl)methyl)-3,6-diisopropylbenzyl]trimethylammonium iodide (**17**) was treated with a CH_3CN solution of TBAF, the expected [4 + 2] dimer (**60** and **61**, respectively) was formed. In



60



61

either case, no evidence for the corresponding [4 + 4] dimer could be found by ^1H NMR. The exocyclic methylene signals in the ^1H NMR spectrum of the [4 + 2] dimer (**60**) of 3,6-dimethyl-1,2-xylylene (**11**) are at relatively high field (5.07 and 4.61 ppm) as are those of the [4 + 2] dimer (**61**) of 3,6-diisopropyl-1,2-xylylene (**13**) (5.10 and 4.66 ppm).

The ^1H NMR spectra for **5**, **11**, and **12** were all observed using the flow NMR technique in the same manner as was used to observe *o*-xylylene (**1**).[20] When a 10^{-3} M solution of [2-((trimethylsilyl)methyl)-3-methylbenzyl]trimethylammonium iodide (**14**) in acetonitrile-d_3 (CD_3CN) was mixed with a 6 x 10^{-3} M solution of TBAF in CD_3CN at a total flow rate of 45 mL/min, a spectrum showing signals for the reactive **5** in the presence of its stable dimer mixture (**52-55**) is obtained. Computer subtraction of the recycled product mixture solution (containing **52-55**) from that obtained by mixing the two reagent solutions at a combined flow rate of 45 mL/min, results in a spectrum of the reactive molecule **5** alone (Figure 1a). Similarly, ^1H NMR spectra for **11** (Figure 1c) and **12** (Figure 1b) were obtained. The bulk of the isopropyl group in [2-((trimethylsilyl)methyl)-3-isopropylbenzyl]trimethylammonium iodide

(**16**) hinders attack of the fluoride ion resulting in slower formation of **12**. Unreacted starting material (**16**) is thus present in the flow NMR spectrum of **12** (Figure 1b).

Due to the lower reactivity of **13**, its ^{1}H NMR spectrum (Figure 1d) can be obtained directly, using the flow NMR technique, by mixing a 2×10^{-3} M solution of **17** in CD_3CN with a 3.3×10^{-3} M solution of TBAF in CD_3CN at a total flow rate of 45 mL/min or 24 mL/min. The spectrum obtained at 45 mL/min shows a small amount of **17** while that obtained at 24 mL/min shows a small amount of the stable [4 + 2] dimer (**61**).

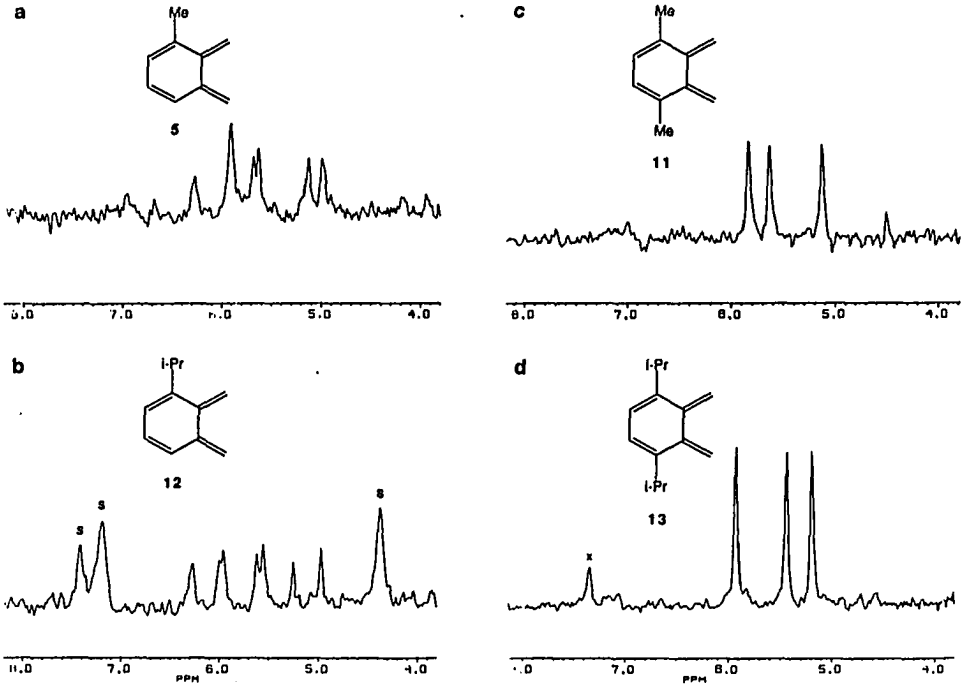


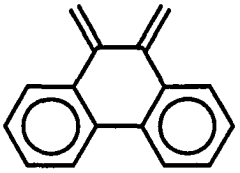
Figure 1. Flow ^{1}H NMR spectra (300 MHz) of: (a) 3-methylene-1,2-xylylene (**5**) obtained by computer subtraction of the spectrum of the recycled product mixture solution from that obtained by mixing 10^{-3} M [2-((trimethylsilyl)-methyl)-3-methylbenzyl]trimethylammonium iodide (**14**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate 45 mL/min; pulse interval 0.127 s; (b) 3-isopropyl-1,2-xylylene (**12**) obtained by computer subtraction of the spectrum of the recycled product mixture solution from that obtained by mixing 10^{-3} M [2-((trimethylsilyl)methyl)-3-isopropylbenzyl]trimethyl-ammonium iodide (**16**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate 45 mL/min; pulse interval 0.127 s; s = starting material; (c) 3,6-dimethyl-1,2-xylylene (**11**) obtained by computer subtraction of the spectrum of the recycled product mixture solution from that obtained by mixing 10^{-3} M [2-((trimethylsilyl)methyl)-3,6-dimethylbenzyl]trimethyl-ammonium iodide (**15**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate 45 mL/min; pulse interval 0.127 s; (d) 3,6-diisopropyl-1,2-xylylene (**13**) obtained by mixing 2 x 10^{-3} M [2-((trimethylsilyl)methyl)-3,6-diisopropylbenzyl]trimethylammonium iodide (**17**) in CD_3CN with 3.3 x 10^{-3} M TBAF in CD_3CN; flow rate 45 mL/min; pulse interval 0.127 s; number of scans, 256; x = solvent impurity

DISCUSSION

It is evident when comparing the second order rate constants for the dimerization of 3-alkyl- and 3,6-dialkyl-1,2-xylylenes (Table 3) with *o*-xylylene (**1**) itself (Table 1), that the rates of dimerization are indeed slowed, but not by a very large amount. The activation enthalpies (Table 4) for these alkyl substituted *o*-xylylenes (**5**, **11-13**) are all low and quite similar (1-3 kcal mol^{-1}). The activation entropy for **13** is very low (-39 eu), indicating greater orientation requirements in its dimerization compared to the other *o*-xylylenes. The activation enthalpies of **5** and **11-13** are similar to those of **1** itself (2.0 kcal mol^{-1}). There is good evidence that 2,3-dimethylene-2,3-dihydrofuran (**7**) dimerizes by a stepwise mechanism involving a diradical intermediate.[18,19] It is believed that all *o*-quinodimethanes as reactive as **7** dimerize by this mechanism. Since **1** is more reactive than **7**, it is also believed to dimerize by a stepwise mechanism involving a diradical intermediate.[16]

The dimerization rate of **5** is approximately 0.9 times that of **1** and 190 times that of 1,2-dimethylene-1,2-dihydronaphthalene (**4**). It is apparent that the methyl group in **5** has little effect on the dimerization rate, so the lower reactivity of **4** is not due to steric hindrance caused by the annulated benzene ring.

The activation enthalpies for **4** and **5** (3.0 and 1.4 kcal mol^{-1}, respectively) are both lower than that of **7** (9.8 kcal mol^{-1})[16] and 9,10-dimethylene-9,10-dihydrophenanthrene (**62**) (10.2 kcal mol^{-1}).[16] The activation enthalpies for all of these



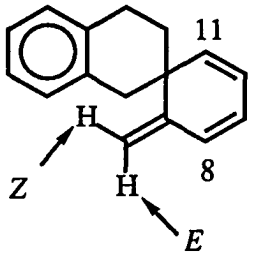
62

reactive *o*-quinodimethanes reflect the aromatic resonance energy difference between the starting *o*-quinodimethane and its diradical intermediate. Thus, the diradical intermediate derived from **5** (no RE to benzene RE) is more stable than that of **4** (benzene RE to naphthalene RE) which is more stable than either **7** (no RE to furan RE) or **62** (the RE of two benzenes to phenanthrene RE).[31] The low activation entropy of **4** indicates stricter orientation requirements in the formation of its diradical intermediate than for **5**. The difference in reactivity between **1** and **4** is thus due to the fact that **4** has a lower gain in resonance energy in its transition state leading to dimerization than **1** does.

When either **5** or **12** is allowed to dimerize, all four possible [4 + 2] dimers are observed. This is consistent with the fact that these alkyl groups don't affect the rate of dimerization a great deal.

Analysis of the exocyclic methylene region in the ^{1}H NMR spectrum of the [4 + 2] dimers (Scheme 6, **52-55**) of **5** reveals that the "low field group" signals (5.22-5.00 ppm) result from two of the four dimers present in 42 and 13%, while the "high field group" signals (4.92-4.58 ppm) result from the other two dimers present in 32 and 13%. HPLC analysis gave relative yields of the four [4 + 2] dimers in this mixture of 44, 33, 13, and 10%. The two methods of analysis are in agreement. Similar analysis of the ^{1}H NMR spectrum of the dimers of **12** (Scheme 5) reveals that the two dimers in the "low field group" (5.27-4.99 ppm) are present in 42 and 21% while those in the "high field group" (4.88-4.47 ppm) are present in 28 and 9%. Again, these results are in agreement with the HPLC relative yields (46, 24, 23, and 7%). The fact that all four possible [4 + 2] dimers are present, demonstrates that initial attack is occurring at both the 1- and the 2-methylene positions (Scheme 5), however it is slightly preferred at one of the methylenes compared to the other.

For the four [4 + 2] dimers of **5** (Scheme 6), it is believed that **52** and **53** are in the "low field group" while **54** and **55** are in the "high field group". In the case of the [4 + 2] dimers of **12** (Scheme 5), the "low field group" contains **48** and **49** while the "high field group" contains **50** and **51**. The upfield shift of the exocyclic methylenes in the ^{1}H NMR spectra of these spiro dimers is due to the presence of an alkyl group in the 11 position. This is evident by comparison of two [4 + 2] dimers (**60** and **61**) having an



alkyl group in the 11 position with a [4 + 2] dimer (**2**) not having an alkyl group in the 11 position. The chemical shift of the exocyclic methylene protons for **2** is 4.93 ppm[15] while the chemical shifts for those of **60** and **61** are 5.07, 4.61 ppm and 5.10, 4.66 ppm, respectively. The bulk of the alkyl group in the 11 position causes tilting of the spiro ring resulting in the (*Z*)-methylene proton residing over the aromatic ring. This increases the shielding of the (*Z*)-methylene proton shifting it upfield[31] as seen for both **60** and **61**. For both the [4 + 2] dimer mixtures of **5** and **12**, the "high field group" dimers are assigned as such because of the presence of an alkyl group in the 11 position (**54, 55** and **50, 51**, respectively). It is reasonable that dimers **52, 53** and **48, 49** are in the "low field group" because they have no alkyl group in the 11 position, but have an alkyl group in the 8 position which is directly adjacent to the exocyclic methylene protons. Unfortunately, for either dimer mixture (**52-55**; **48-51**), it is impossible to distinguish the two dimers in the "low field group" (**52** and **53**; **48** and **49**) or the two dimers in the "high field group" (**54** and **55**; **50** and **51**) by their ^{1}H NMR

spectra. Table 5 summarizes the relative yield data (determined by ^1H NMR integration) for the [4 + 2] dimer products of 3-methyl-1,2-xylylene (**5**) and 3-isopropyl-1,2-xylylene (**12**). It is probable that analogous dimers from each dimer mixture are formed in approximately the same relative yield.

Table 5. Relative yields (determined by ^1H NMR integration) of the [4 + 2] dimer products from 3-methyl-1,2-xylylene (**5**) and 3-isopropyl-1,2-xylylene (**12**)

Dimer	Structure[a]	Relative Yield 1	Relative Yield 2	Relative Yield 3	Relative Yield 4
52	1-1	42	42	13	13
53	2-1	13	13	42	42
54	1-2	32	13	32	13
55	2-2	13	32	13	32
48	1-1	42	42	21	21
49	2-1	21	21	42	42
50	1-2	28	9	28	9
51	2-2	9	21	9	21

[a]Designation of which two exocyclic methylene groups are initially joined during dimerization.

The unequal formation of the dimer products (**52-55**; **48-51**) in the dimerization of either **5** or **12** is due to partial blocking of the methylene group nearest the alkyl group, relative to the other methylene group. The product distribution observed is consistent with that predicted by a stepwise mechanism involving a diradical

intermediate. However, since the individual [4 + 2] dimers cannot be identified, the concerted mechanism utilizing an exo approach cannot be ruled out. It is not clear why little or no [4 + 4] dimer was formed for each of **5, 11-13** when a significant amount (~10%) is formed in the dimerization of *o*-xylylene (**1**).[15,13]

Pyrolysis of the dimer product mixture of either **5** or **12** gave approximately a 1:1 ratio of the two possible [4 + 4] dimers **56, 57** and **58, 59**, respectively. Upon pyrolysis, one [4 + 2] dimer from the "low field group" and one from the "high field group" form the same [4 + 4] dimer. For the case of the dimers of **5**, [4 + 2] dimers **52** and **55** form [4 + 4] dimer **56** while [4 + 2] dimers **53** and **54** form [4 + 4] dimer **57** (Scheme 7). Using the relative yields (from HPLC analysis) of the four [4 + 2] dimers of **5**, two [4 + 2] dimers in 44 and 10% would give one [4 + 4] dimer in 54% while the other two [4 + 2] dimers (33 and 13%) would give the second [4 + 4] dimer in 46%. This is consistent with that obtained experimentally via pyrolysis and is true in the case of **12** as well (53 and 47% yield of the two [4 + 4] dimers predicted from the [4 + 2] dimer relative yields determined by HPLC analysis). The fact that comparable amounts of the two [4 + 4] dimers are formed upon pyrolysis confirms the fact that approximately one half of the initial bond forming reactions during dimerization of **5** and **12** are occurring at the more hindered 2-methylene position (Scheme 5).

The flow NMR spectra for all of these alkyl substituted *o*-xylylenes (**5, 11-13**) are normal (Figure 1) and the peak positions for each are similar to that of *o*-xylylene (**1**).[14,20] The alkyl groups do not appear to distort the ring in any great manner, since the chemical shifts aren't affected in a large measure. As in the case of **1**, these reactive molecules are ordinary olefins with nc special aromatic or antiaromatic character.

The observation by flow NMR of these substituted *o*-xylylenes (**5, 11-13**) of varied reactivity shows that flow NMR is indeed flexible and useful over a range of reactivities. By varying the concentrations of the precursor and TBAF solutions, and changing the flow rates and spectral acquisition parameters, the flow-NMR spectra for species of differing reactivities can be observed.

From these results, it can be concluded that alkyl groups flanking the exocyclic methylene groups in *o*-xylylenes don't affect the dimerization rate or products a great deal. Somewhat surprisingly, the two isopropyl groups in 3,6-diisopropyl-1,2-xylylene (**13**) don't provide enough steric hindrance to give a stable *o*-xylylene. In addition, the lower reactivity of 1,2-dimethylene-1,2-dihydronaphthalene (**4**) compared to *o*-xylylene (**1**) is due to a larger gain in resonance energy for the dimerization of **1** and is not due to steric hindrance caused by the annulated benzene ring in **4**.

EXPERIMENTAL SECTION

General Procedures

^1H NMR spectra were recorded on a Nicolet NT-300 spectrometer. Chemical shifts are reported relative to tetramethylsilane.

Capillary gas chromatographic analyses were performed using a Hewlett-Packard HP 5840A gas chromatograph equipped with a 30-m DB-1 capillary column (J & W Scientific) using nitrogen as a carrier gas and a flame ionization detector.

Analytical HPLC analyses were performed on an ISCO Model 2350 instrument with a Model 2360 Gradient Programmer, and a Spectra-Physics SP4270 integrator, using a C_{18} reverse phase column (25 cm, 4.6 mm diameter, 5 μm particle size). The preparative HPLC analysis was performed with a Beckman 110B Solvent Delivery System, a 421A Controller, and a 163 Variable Wavelength Detector, using a C_{18} reverse phase column (25 cm, 10 mm diameter, 5 μm particle size).

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

All flow NMR spectra were taken on a Bruker WM-300 spectrometer (300 MHz) using acetonitrile-d_3 (CD_3CN) as solvent and residual $NCCD_2H$ as internal standard (δ 1.93). CD_3CN was purchased from Cambridge Isotope Laboratories.

N,N-Dimethylbenzylamine, *p*-xylene, 2′-methylacetophenone, 1,4-isopropylbenzene, *n*-butyllithium in hexanes, and chlorotrimethylsilane were purchased from Aldrich Chemical Co. Methyl iodide was purchased from Fisher Scientific Co. N,N-Dimethylbenzylamine, *p*-xylene, 2′-methylacetophenone, 1,4-diisopropylbenzene, and methyl iodide were used without further purification. Chlorotrimethyl-

silane was distilled from calcium hydride immediately before use. *n*-Butyllithium was standardized before use by titration.

[2-((Trimethylsilyl)methyl)-3-methylbenzyl]trimethylammonium iodide (14)

A 15.0 g (111 mmol) quantity of N,N-dimethylbenzylamine (**18**) was converted to 2-methylbenzyldimethylamine (**20**) utilizing the procedure of Brasen and Hauser[21] and further converted to 2,3-dimethylbenzyldimethylamine (**22**) in the same manner (35% overall yield). A 707 mg (4.3 mmol) quantity of this amine (**22**) was converted to [2-((trimethylsilyl)methyl)-3-methylbenzyl]dimethylamine (**23**) in 90% yield using a similar procedure as used by Ito et al. for the preparation of [*o*-((trimethylsilyl)-methyl)benzyl]dimethylamine.[8] Finally, **23** was converted to **14** in >90% yield by standard techniques. mp 188-189 °C (dec.); IR (KBr) 3005, 2957, 1491, 1472, 1246, 1144, 841 cm^{-1}; ^1H NMR (CD_3CN) δ 7.32-7.26 (m, 2H), 7.12-7.07 (m, 1H), 4.43 (s, 2H), 3.01 (s, 9H), 2.40 (s, 2H), 2.28 (s, 3H), -0.04 (s, 9H); ^{13}C NMR (CD_3CN) δ 142.48, 137.88, 133.56, 132.67, 125.01, 124.72, 67.29, 53.26, 21.80, 21.21, -1.13; Anal. calcd. for $C_{15}H_{28}INSi$: C, 47.74; H, 7.48; N, 3.71. Found: C, 47.92; H, 7.18; N, 3.75.

[2-((Trimethylsilyl)methyl)-3,6-dimethylbenzyl]trimethylammonium iodide (15)

p-Xylene (**24**) (8.7 g, 81.6 mmol) was converted to 2,5-dimethylbenzyl chloride (**25**) in 39% yield in a manner similar to that used by Grummitt and Bush for the preparation of 1-chloromethylnaphthalene.[22] A 3.6 g (23.5 mmol) quantity of **25** was dissolved in 39 mL of a 3 M solution of trimethylamine in methanol and the mixture was heated to reflux for 17 h. After cooling to room temperature the reaction mixture was triturated with ether and the white solid, 2,5-dimethylbenzyltrimethyl-ammonium chloride (**26**) was isolated in 90% yield. A 3.1 g (14.5 mmol) quantity of **26** was converted to 2,3,6-trimethylbenzyldimethylamine (**27**) (38% yield) by the

procedure used by Brasen and Hauser[21] for the preparation of 2-methylbenzyldimethylamine. The amine **27** (0.98 g, 5.5 mmol) was converted to [2-((trimethylsilyl)methyl)-3,6-dimethylbenzyl]dimethylamine (**28**) in 72% yield in a manner similar to that used by Ito et al.[8] for the preparation of [*o*-((trimethylsilyl)methyl)-benzyl]dimethylamine. A small quantity of the undesired isomer [2-((trimethylsilyl)methyl)-5,6-dimethylbenzyl]dimethylamine (**29**) was also formed (16:1 ratio of **28** to **29**). The trimethylammonium iodide salt was prepared in the usual manner (>90% yield), and the desired **15** was selectively recrystallized (1:1 ethyl acetate-acetone). mp 176-177 °C (dec.); IR (KBr) 2993, 2951, 1491, 1464, 1246, 1148, 847 cm^{-1}; ^1H NMR (CD_3CN) δ 7.19 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 4.54 (m, AB type, 2H), 3.01 (s, 9H), 2.44 (s, 2H), 2.40 (s, 3H), 2.24 (s, 3H), -0.08 (s, 9H); ^{13}C NMR (CD_3CN) δ 143.12, 139.01, 135.17, 133.14, 128.04, 123.71, 63.97, 53.41, 22.40 (2C), 21.84, -1.26; Anal. calcd. for $C_{16}H_{30}INSi$: C, 48.72; H, 7.67; N, 3.55. Found: C, 49.15; H, 8.04; N, 3.56.

[2-((Trimethylsilyl)methyl)-3-isopropylbenzyl]trimethylammonium iodide (16)

A 35.6 g (265 mmol) quantity of 2'-methylacetophenone (**30**) was treated with methyl Grignard (398 mmol) in ether to give 2-methyl-α,α-dimethylbenzyl alcohol (**31**) in 83% yield. The alcohol **31** was reduced to *o*-cymene (**32**) in 93% yield by the procedure described by Hall for the reduction of α-tetralol to tetralin.[24] *o*-Cymene (**32**) (15 g, 112 mmol), N-bromosuccinimide (19.9 g, 112 mmol), and benzoyl peroxide (54.6 mg) were combined in 400 mL of CCl_4 and the mixture was heated to reflux for 2 h after which it was cooled in an ice bath. The succinimide crystals were removed by filtration and then the solvent was removed under reduced pressure leaving 23.8 g of an oil. The desired 2-isopropylbenzyl bromide (**33**) (29%) was obtained as part of a

mixture of **32** (35%) and the side products, 2-methyl-α-bromomethylstyrene (**34**) (18%), 2-methyl-ß-bromo-α-methylstyrene (**35**) (9%), and 2-methyl-α-methylstyrene (**36**) (9%).[25] This mixture (23.8 g in 200 mL ethanol) was combined with 9.0 ml of a 11.16 M solution of dimethylamine in ethanol and refluxed 12 h. To the cooled reaction mixture was added 50 mL of water followed by extraction with hexanes (3 x 50 mL). This organic phase was extracted with 1 M HCl (3 x 50 mL). Basification of the combined acid extracts with 2 M NaOH followed by extraction of this with ether (3 x 50 mL), drying over anhydrous magnesium sulfate, and finally evaporation of the ether gave 2.96 g of a yellow oil. This oil was approximately a 9:1 ratio of 2-isopropyl-dimethylbenzylamine (**37**) and 2-methyl-α-dimethylaminomethylstyrene (**38**). Alkylation of the mixture of two amines (2.96 g) with methyl iodide followed by a Sommelet-Hauser rearrangement, using the procedure outlined by Brasen and Hauser,[21] gave the desired 2-methyl-3-isopropyldimethylbenzylamine (**41**) in 40% yield (the isomeric amine salt [2-(2-methylphenyl)propenyl]trimethylammonium iodide (**40**) did not react and was thus eliminated). The amine **41** (1.2 g, 6.29 mmol) was carried on to **16** in two steps (66%) in a manner similar to that used by Ito et al for the preparation of [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium iodide.[8] mp 210-211 °C (dec.); IR (KBr) 3005, 2964, 1493, 1456, 1252, 1238, 1130, 841 cm^{-1}; ^1H NMR (CD_3CN) δ 7.44 (d, J = 0.8 Hz, 1H), 7.41 (d, J = 0.9 Hz, 1H), 7.18 (m, 1H), 4.45 (s, 2H), 3.14 (m, 1H), 3.01 (s, 9H), 2.44 (s, 2H), 1.19 (d, J = 6.76 Hz, 6H), -0.05 (s, 9H); ^{13}C NMR (CD_3CN) δ 148.49, 140.67, 132.51, 128.26, 125.31, 125.17, 67.45, 53.26, 30.44, 23.50, 20.28, -1.39; Anal. calcd. for $C_{17}H_{32}INSi$: C, 50.36; H, 7.96; N, 3.45. Found: C, 50.25; H, 8.08; N, 3.41.

[2-((Trimethylsilyl)methyl)-3,6-diisopropylbenzyl]trimethylammonium iodide (17)

1,4-Diisopropylbenzene (**43**) (10 g, 62 mmol) was converted to 2,5-diisopropylbenzyl chloride in a 14% yield in a manner analogous to that used to prepare **25**. This chloride (**44**) (1.8 g, 4.6 mmol) was carried on to **17** in 25% yield in a manner analogous to that described for the preparation of **15** from **25**. mp 196-197 °C (dec.); IR (KBr) 3007, 2993, 1491, 1472, 1236, 1130, 862 cm^{-1}; ^1H NMR (CD_3CN) δ 7.32 (d, J = 8.25 Hz, 1H), 7.21 (d, J = 8.23 Hz, 1H), 4.72 (d, J = 14.1 Hz, 1H), 4.55 (d, J = 14.1 Hz, 1H), 3.31 (m, 1H), 3.11 (m, 1H), 2.99 (s, 9H), 2.60 (d, J = 14.5 Hz, 1H), 2.45 (d, J = 14.6 Hz, 1H), 1.32 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz; 3H), -0.10 (s, 9H); ^{13}C NMR (CD_3CN) δ 149.47,145.44, 141.29, 128.33, 123.09, 121.96, 62.35, 53.20, 30.88, 30.42, 27.19, 25.29, 21.72, -1.58; Anal. calcd. for $C_{20}H_{38}INSi$: C, 53.68; H, 8.56; N, 3.13. Found: C, 53.86; H, 8.35; N, 3.12.

Dimers of 5

To a solution of **14** (340 mg, 0.9 mmol) in 5 mL of CH_3CN was added dropwise a solution of TBAF (353 mg, 1.35 mmol) in 5 mL of CH_3CN, while stirring and under nitrogen. The reaction mixture was allowed to stir at room temperature for 1 h after which it was concentrated, triturated with ether, and then cooled resulting in the precipitation of a white solid. The solid was removed by filtration and the solvent was evaporated resulting in a 66% yield of the dimer mixture (**52-55**). Only a trace of the [4 + 4] dimers (**56** and **57**) was detected by analysis of the ^1H NMR spectrum.

Flash vacuum pyrolysis of the dimer mixture 52-55

The dimer mixture **52-55** (70.5 mg, 0.3 mmol) was pyrolyzed at 575 °C in a FVP system (10^{-5} mm Hg).[30] The pyrolysis was complete after 8 h. A colorless oil was rinsed with $CDCl_3$ from the liquid nitrogen trap after warming, yielding essentially a

1:1 mixture of **56** and **57** as determined by GC and ^{1}H NMR analysis. ^{1}H NMR ($CDCl_3$) δ 6.91-6.73 (m, 12H), 3.13-3.09 (m, 16H), 2.33 (s, 6H), 2.31 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.69, 140.26, 138.95, 138.11, 135.40, 135.30, 127.98, 127.86, 127.64, 127.40, 125.49 (2C), 35.25, 33.88, 28.98, 28.38, 20.29, 19.66.

Dimer of 11

A 39.0 mg (0.1 mmol) quantity of **15** was converted to **60** (11.1 mg, 0.04 mmol, 84%) in a manner analogous to that used for the preparation of the dimers of **5**. None of the [4 + 4] dimer was observed in the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$) δ 6.93-6.87 (m, AB type, 2H), 5.73 (s, 2H), 5.07 (s, 1H), 4.61 (s, 1H), 3.10 (d, J = 18 Hz, 1H), 2.76 (d, J = 17 Hz, 1H), 2.68-2.39 (m, 2H), 2.25 (s, 3H), 2.17 (s, 3H), 1.92 (s, 3H), 1.87 (s, 3H), 1.79-1.17 (m, 2H).

Dimers of 12

A 324 mg (0.8 mmol) quantity of **16** was converted to the mixture of [4 + 2] dimers, **48-51** (107 mg, 0.38 mmol, 92%) in a manner analogous to that used for the preparation of the dimers of **5**. Only a trace of the [4 + 4] dimers (**58** and **59**) was detected by analysis of the ^{1}H NMR spectrum.

Flash vacuum pyrolysis of the dimer mixture 48-51

The dimer mixture **48-51** was flash vacuum pyrolyzed (570 °C, 7 x 10^{-6} mm Hg) in a manner analogous to that used to convert **52-55** to **56** and **57**, to give the two [4 + 4] dimers (**58** and **59**) in approximately a 1:1 ratio as determined by GC and ^{1}H NMR analysis. ^{1}H NMR ($CDCl_3$) δ 7.06-6.90 (m, 12 H), 3.28-3.05 (m, 20 H), 1.24 (d, J = 7.7 Hz, 12 H), 1.21 (d, J = 7.0 Hz, 12 H).

Separation of dimers 48-51 by preparative HPLC

The dimer mixture (**48-51**) of **12** was prepared as described earlier. The dimers (**48-51**) were separated by monitoring the chart recorder and collecting fractions in tubes when each individual dimer exited the detector outlet. Each dimer was then isolated by reducing the volume of the solvent (9:1 MeOH-H_2O) and adding approximately 1 mL of $CDCl_3$ to the residue. This was washed with a small amount of H_2O then separated. The organic phase was dried over anhydrous $MgSO_4$ and filtered. ^1H NMR spectra were obtained for each of the four (**48-51**) dimers.

Dimers of 13

A 11.2 mg (0.02 mmol) quantity of **17** was converted to **61** (4 mg, 0.01 mmol, 85%) in a manner analogous to that used for the preparation of the dimers of **5**. None of the [4 + 4] dimer was observed in the ^1H NMR spectrum. ^1H NMR ($CDCl_3$) δ 7.13-7.05 (m, AB type, 2H), 5.86 (d, J = 6 Hz, 1H), 5.78 (d, J = 6 Hz, 1H), 5.09 (s, 1H), 4.66 (s, 1H), 3.29 (d, J = 15 Hz, 1H), 3.24-3.06 (m, 2H), 2.94 (d, J = 17 Hz, 1H), 2.77-2.67 (m, 2H), 2.62-2.48 (m, 2H), 1.26-1.08 (m, 26H).

General Procedures for Kinetic Measurements

Determination of λ_{max} for 5

A 2-cm path length UV-visible cell was charged with 3 mL of CH_3CN and 0.1 mL of a 0.1 M TBAF solution. To this was rapidly added 1.0 mL of 10^{-3} M **14** in CH_3CN, the cell shaken once, then quickly placed in the optical path of a Perkin-Elmer 7000 Lambda-Array UV-visible Spectrophotometer. Spectra were recorded every 0.3 s in the spectral range 350-410 nm. From a plot of absorbance versus wavelength, the λ_{max} was determined. Determination of the λ_{max} values for **11-13** was performed in a similar manner.

Determination of ε_{max} for 5, 11-13

Values of ε_{max} for **5** and **11-13** were determined in a similar manner to that used by Trahanovsky and Macias.[13,16] The concentrations of TBAF in CH_3CN were 0.01, 0.05, 0.1, 0.25, and 0.5 M while the concentration of **14**, **15**, **16**, or **17** in CH_3CN was 10^{-3} M.

Measurement of the rate constant for the dimerization of 5 using the stopped-flow method

Kinetic experiments involving **5** were monitored with use of a Canterbury SF3A stopped-flow UV-visible spectrophotometer.[13,16] A typical run was carried out by filling one of the syringes with a TBAF solution in CH_3CN (0.1 M) and the other syringe with a solution of **14** in CH_3CN (10^{-3} M). The drive piston was pushed forward manually propelling the reactants from the syringes through the mixing chamber and into the observation cell. With the monochromator set at 376 nm, the λ_{max} for **5**, the absorbance curve for the formation and decay of the reactive molecule was recorded. Rate constants for the dimerization of **5** were determined by analyzing the plot of 1/conc. versus time by a least-squares method.[26] Rate constants for **11** and **12** were measured in the same manner as for **5**. By using a thermostatted water bath to maintain the temperature, rate constants for **5**, **11**, and **12** could be determined at 25, 35, and 45 °C.

Measurement of the rate constant for the dimerization of 13

A 2-cm path length UV-visible cell was charged with 3.0 mL of CH_3CN and 1.0 mL of a solution of **17** in CH_3CN (10^{-3} M). To the solution of **17** in the cell was rapidly added 1.0 mL of a 0.1 M solution of TBAF in CH_3CN, the cell shaken once, then quickly placed in the optical path of a Cary 219 UV-visible spectrophotometer.[16]

With the monochromator set at 388 nm, the absorbance decay of **13** versus time was recorded. The temperature of the UV-visible cell within the spectrophotometer was maintained at 15, 25, or 35 °C using a circulating water bath. Rate constants for the dimerization of **13** were then calculated at the three temperatures in a manner similar to that of **5**, **11**, and **12**.

Tetrabutylammonium fluoride (TBAF)

The preparation of TBAF has been described in detail.[20]

General Procedure for Flow NMR

The flow-NMR experiment has been described in detail.[20]

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APPENDIX

Table A-1. Kinetic data for 3-methyl-1,2-xylylene (**5**) measured at 24.6 °C in CH_3CN

Time, s	Absorbance	[**5**], M	$[\mathbf{5}]^{-1}$, M^{-1}
0.30	0.1909	3.01E-04	3.32E+03
0.35	0.1700	2.68E-04	3.73E+03
0.40	0.1534	2.42E-04	4.13E+03
0.45	0.1390	2.19E-04	4.56E+03
0.50	0.1265	2.00E-04	5.01E+03
0.55	0.1157	1.83E-04	5.47E+03
0.60	0.1077	1.70E-04	5.88E+03
0.65	0.0997	1.57E-04	6.35E+03
0.70	0.0926	1.46E-04	6.84E+03
0.75	0.0870	1.37E-04	7.28E+03
0.80	0.0817	1.29E-04	7.75E+03
0.85	0.0771	1.22E-04	8.22E+03
0.90	0.0720	1.14E-04	8.80E+03
0.95	0.0688	1.09E-04	9.21E+03
1.00	0.0644	1.02E-04	9.84E+03
1.05	0.0619	9.77E-05	1.02E+04
1.10	0.0587	9.27E-05	1.08E+04
1.15	0.0563	8.89E-05	1.13E+04
1.20	0.0541	8.54E-05	1.17E+04
1.25	0.0514	8.11E-05	1.23E+04
1.30	0.0498	7.86E-05	1.27E+04
1.35	0.0477	7.53E-05	1.33E+04
1.40	0.0456	7.20E-05	1.39E+04
1.45	0.0441	6.96E-05	1.44E+04
1.50	0.0417	6.58E-05	1.52E+04
1.55	0.0411	6.49E-05	1.54E+04
1.60	0.0396	6.25E-05	1.60E+04
1.65	0.0378	5.97E-05	1.68E+04
1.70	0.0369	5.83E-05	1.72E+04
1.75	0.0358	5.65E-05	1.77E+04
1.80	0.0346	5.46E-05	1.83E+04
1.85	0.0334	5.27E-05	1.90E+04
1.90	0.0325	5.13E-05	1.95E+04
1.95	0.0314	4.96E-05	2.02E+04
2.00	0.0305	4.82E-05	2.08E+04
2.05	0.0296	4.67E-05	2.14E+04
2.10	0.0288	4.55E-05	2.20E+04
2.15	0.0285	4.50E-05	2.22E+04
2.20	0.0276	4.36E-05	2.29E+04

Table A-1 (continued)

Time, s	Absorbance	[5], M	$[5]^{-1}$, M^{-1}
2.25	0.0262	4.14E-05	2.42E+04
2.30	0.0262	4.14E-05	2.42E+04
2.35	0.0256	4.04E-05	2.47E+04
2.40	0.0244	3.85E-05	2.60E+04
2.45	0.0239	3.77E-05	2.65E+04

Table A-2. Kinetic data for 3-methyl-1,2-xylylene (**5**) measured at 35.4 °C in CH_3CN

Time, s	Absorbance	[**5**], M	$[\mathbf{5}]^{-1}$, M^{-1}
0.20	0.1931	3.05E-04	3.28E+03
0.25	0.1655	2.61E-04	3.83E+03
0.30	0.1455	2.30E-04	4.35E+03
0.35	0.1284	2.03E-04	4.93E+03
0.40	0.1151	1.82E-04	5.50E+03
0.45	0.1042	1.65E-04	6.08E+03
0.50	0.0956	1.51E-04	6.63E+03
0.55	0.0874	1.38E-04	7.25E+03
0.60	0.0813	1.28E-04	7.79E+03
0.65	0.0759	1.20E-04	8.35E+03
0.70	0.0709	1.12E-04	8.93E+03
0.75	0.0666	1.05E-04	9.51E+03
0.80	0.0620	9.79E-05	1.02E+04
0.85	0.0592	9.35E-05	1.07E+04
0.90	0.0565	8.92E-05	1.12E+04
0.95	0.0532	8.40E-05	1.19E+04
1.00	0.0496	7.83E-05	1.28E+04
1.05	0.0478	7.55E-05	1.33E+04
1.10	0.0458	7.23E-05	1.38E+04
1.15	0.0434	6.85E-05	1.46E+04
1.20	0.0414	6.54E-05	1.53E+04
1.25	0.0399	6.30E-05	1.59E+04
1.30	0.0382	6.03E-05	1.66E+04
1.35	0.0368	5.81E-05	1.72E+04
1.40	0.0353	5.57E-05	1.79E+04
1.45	0.0348	5.49E-05	1.82E+04
1.50	0.0330	5.21E-05	1.92E+04
1.55	0.0322	5.08E-05	1.97E+04
1.60	0.0305	4.82E-05	2.08E+04
1.65	0.0293	4.63E-05	2.16E+04
1.70	0.0285	4.50E-05	2.22E+04
1.75	0.0285	4.50E-05	2.22E+04
1.80	0.0268	4.23E-05	2.36E+04
1.85	0.0271	4.28E-05	2.34E+04
1.90	0.0257	4.06E-05	2.46E+04
1.95	0.0254	4.01E-05	2.49E+04
2.00	0.0237	3.74E-05	2.67E+04

Table A-3. Kinetic data for 3-methyl-1,2-xylylene (**5**) measured at 44.9 °C in CH_3CN

Time, s	Absorbance	[**5**], M	$[\mathbf{5}]^{-1}$, M^{-1}
0.15	0.1906	3.01E-04	3.32E+03
0.20	0.1582	2.50E-04	4.00E+03
0.25	0.1363	2.15E-04	4.65E+03
0.30	0.1197	1.89E-04	5.29E+03
0.35	0.1058	1.67E-04	5.99E+03
0.40	0.0950	1.50E-04	6.67E+03
0.45	0.0857	1.35E-04	7.39E+03
0.50	0.0783	1.24E-04	8.09E+03
0.55	0.0722	1.14E-04	8.77E+03
0.60	0.0669	1.06E-04	9.47E+03
0.65	0.0622	9.82E-05	1.02E+04
0.70	0.0570	9.00E-05	1.11E+04
0.75	0.0548	8.65E-05	1.16E+04
0.80	0.0515	8.13E-05	1.23E+04
0.85	0.0479	7.56E-05	1.32E+04
0.90	0.0449	7.09E-05	1.41E+04
0.95	0.0431	6.80E-05	1.47E+04
1.00	0.0413	6.52E-05	1.53E+04
1.05	0.0390	6.16E-05	1.62E+04
1.10	0.0372	5.87E-05	1.70E+04
1.15	0.0355	5.60E-05	1.78E+04
1.20	0.0337	5.32E-05	1.88E+04
1.25	0.0317	5.00E-05	2.00E+04
1.30	0.0311	4.91E-05	2.04E+04
1.35	0.0302	4.77E-05	2.10E+04
1.40	0.0291	4.59E-05	2.18E+04
1.45	0.0279	4.40E-05	2.27E+04
1.50	0.0265	4.18E-05	2.39E+04
1.55	0.0262	4.14E-05	2.42E+04
1.60	0.0245	3.87E-05	2.59E+04
1.65	0.0245	3.87E-05	2.59E+04
1.70	0.0231	3.65E-05	2.74E+04

Table A-4. Kinetic data for 3,6-dimethyl-1,2-xylylene (**11**) measured at 24.0 °C in CH_3CN

Time, s	Absorbance	[11], M	$[11]^{-1}$, M^{-1}
0.4	0.2371	3.27E-04	3.06E+03
0.5	0.2108	2.91E-04	3.44E+03
0.6	0.1892	2.61E-04	3.83E+03
0.7	0.1704	2.35E-04	4.25E+03
0.8	0.1557	2.15E-04	4.66E+03
0.9	0.1425	1.97E-04	5.09E+03
1.0	0.1317	1.82E-04	5.50E+03
1.1	0.1226	1.69E-04	5.91E+03
1.2	0.1139	1.57E-04	6.36E+03
1.3	0.1061	1.46E-04	6.83E+03
1.4	0.1009	1.39E-04	7.18E+03
1.5	0.0943	1.30E-04	7.69E+03
1.6	0.0896	1.24E-04	8.09E+03
1.7	0.0856	1.18E-04	8.47E+03
1.8	0.0822	1.13E-04	8.82E+03
1.9	0.0779	1.07E-04	9.30E+03
2.0	0.0737	1.02E-04	9.83E+03
2.1	0.0713	9.84E-05	1.02E+04
2.2	0.0681	9.40E-05	1.06E+04
2.3	0.0648	8.94E-05	1.12E+04
2.4	0.0622	8.58E-05	1.17E+04
2.5	0.0601	8.29E-05	1.21E+04
2.6	0.0572	7.89E-05	1.27E+04
2.7	0.0555	7.66E-05	1.31E+04
2.8	0.0544	7.51E-05	1.33E+04
2.9	0.0524	7.23E-05	1.38E+04
3.0	0.0512	7.06E-05	1.42E+04
3.1	0.0487	6.72E-05	1.49E+04
3.2	0.0472	6.51E-05	1.54E+04
3.3	0.0467	6.44E-05	1.55E+04
3.4	0.0447	6.17E-05	1.62E+04
3.5	0.0439	6.06E-05	1.65E+04
3.6	0.0428	5.91E-05	1.69E+04
3.7	0.0414	5.71E-05	1.75E+04
3.8	0.0402	5.55E-05	1.80E+04
3.9	0.0394	5.44E-05	1.84E+04
4.0	0.0378	5.22E-05	1.92E+04
4.1	0.0372	5.13E-05	1.95E+04
4.2	0.0361	4.98E-05	2.01E+04
4.3	0.0355	4.90E-05	2.04E+04
4.4	0.0347	4.79E-05	2.09E+04
4.5	0.0339	4.68E-05	2.14E+04

Table A-4 (continued)

Time, s	Absorbance	[11], M	$[11]^{-1}$, M^{-1}
4.6	0.0328	4.53E-05	2.21E+04
4.7	0.0323	4.46E-05	2.24E+04
4.8	0.0314	4.33E-05	2.31E+04
4.9	0.0309	4.26E-05	2.35E+04
5.0	0.0304	4.19E-05	2.38E+04
5.1	0.0293	4.04E-05	2.47E+04
5.2	0.0295	4.07E-05	2.46E+04

Table A-5. Kinetic data for 3,6-dimethyl-1,2-xylylene (**11**) measured at 35.3 °C in CH_3CN

Time, s	Absorbance	[**11**], M	$[\mathbf{11}]^{-1}$, M^{-1}
0.3	0.2267	3.13E-04	3.20E+03
0.4	0.1946	2.68E-04	3.72E+03
0.5	0.1698	2.34E-04	4.27E+03
0.6	0.1511	2.08E-04	4.80E+03
0.7	0.1361	1.88E-04	5.33E+03
0.8	0.1237	1.71E-04	5.86E+03
0.9	0.1120	1.55E-04	6.47E+03
1.0	0.1042	1.44E-04	6.96E+03
1.1	0.0966	1.33E-04	7.50E+03
1.2	0.0888	1.23E-04	8.16E+03
1.3	0.0830	1.15E-04	8.73E+03
1.4	0.0776	1.07E-04	9.34E+03
1.5	0.0738	1.02E-04	9.82E+03
1.6	0.0692	9.55E-05	1.05E+04
1.7	0.0655	9.04E-05	1.11E+04
1.8	0.0615	8.49E-05	1.18E+04
1.9	0.0597	8.24E-05	1.21E+04
2.0	0.0558	7.70E-05	1.30E+04
2.1	0.0534	7.37E-05	1.36E+04
2.2	0.0505	6.97E-05	1.44E+04
2.3	0.0496	6.84E-05	1.46E+04
2.4	0.0472	6.51E-05	1.54E+04
2.5	0.0458	6.32E-05	1.58E+04
2.6	0.0437	6.03E-05	1.66E+04
2.7	0.0423	5.84E-05	1.71E+04
2.8	0.0408	5.63E-05	1.78E+04
2.9	0.0391	5.39E-05	1.85E+04
3.0	0.0377	5.20E-05	1.92E+04
3.1	0.0359	4.95E-05	2.02E+04
3.2	0.0351	4.84E-05	2.06E+04
3.3	0.0339	4.68E-05	2.14E+04
3.4	0.0331	4.57E-05	2.19E+04
3.5	0.0317	4.37E-05	2.29E+04
3.6	0.0311	4.29E-05	2.33E+04
3.7	0.0300	4.14E-05	2.42E+04
3.8	0.0297	4.10E-05	2.44E+04
3.9	0.0280	3.86E-05	2.59E+04

Table A-6. Kinetic data for 3,6-dimethyl-1,2-xylylene (**11**) measured at 44.8 °C in CH_3CN

Time, s	Absorbance	[**11**], M	$[\mathbf{11}]^{-1}$, M^{-1}
0.3	0.2011	2.77E-04	3.60E+03
0.4	0.1698	2.34E-04	4.27E+03
0.5	0.1484	2.05E-04	4.88E+03
0.6	0.1304	1.80E-04	5.56E+03
0.7	0.1165	1.61E-04	6.22E+03
0.8	0.1056	1.46E-04	6.86E+03
0.9	0.0966	1.33E-04	7.50E+03
1.0	0.0890	1.23E-04	8.14E+03
1.1	0.0812	1.12E-04	8.93E+03
1.2	0.0757	1.04E-04	9.57E+03
1.3	0.0711	9.81E-05	1.02E+04
1.4	0.0669	9.23E-05	1.08E+04
1.5	0.0631	8.71E-05	1.15E+04
1.6	0.0587	8.10E-05	1.23E+04
1.7	0.0552	7.62E-05	1.31E+04
1.8	0.0529	7.30E-05	1.37E+04
1.9	0.0503	6.94E-05	1.44E+04
2.0	0.0483	6.66E-05	1.50E+04
2.1	0.0451	6.22E-05	1.61E+04
2.2	0.0440	6.07E-05	1.65E+04
2.3	0.0415	5.73E-05	1.75E+04
2.4	0.0403	5.56E-05	1.80E+04
2.5	0.0384	5.30E-05	1.89E+04
2.6	0.0367	5.06E-05	1.97E+04
2.7	0.0359	4.95E-05	2.02E+04
2.8	0.0348	4.80E-05	2.08E+04
2.9	0.0331	4.57E-05	2.19E+04
3.0	0.0325	4.48E-05	2.23E+04
3.1	0.0312	4.30E-05	2.32E+04
3.2	0.0295	4.07E-05	2.46E+04
3.3	0.0293	4.04E-05	2.47E+04
3.4	0.0276	3.81E-05	2.63E+04
3.5	0.0273	3.77E-05	2.65E+04
3.6	0.0260	3.59E-05	2.79E+04
3.7	0.0257	3.55E-05	2.82E+04
3.8	0.0252	3.48E-05	2.88E+04
3.9	0.0241	3.33E-05	3.01E+04

Table A-7. Kinetic data for 3-*t*-propyl-1,2-xylylene (**12**) measured at 24.1 °C in CH_3CN

Time, s	Absorbance	[12], M	$[12]^{-1}$, M^{-1}
0.4	0.2379	3.30E-04	3.03E+03
0.5	0.2122	2.94E-04	3.40E+03
0.6	0.1898	2.63E-04	3.80E+03
0.7	0.1712	2.38E-04	4.21E+03
0.8	0.1549	2.15E-04	4.65E+03
0.9	0.1409	1.95E-04	5.12E+03
1.0	0.1293	1.79E-04	5.57E+03
1.1	0.1195	1.66E-04	6.03E+03
1.2	0.1108	1.54E-04	6.51E+03
1.3	0.1030	1.43E-04	7.00E+03
1.4	0.0959	1.33E-04	7.52E+03
1.5	0.0905	1.26E-04	7.96E+03
1.6	0.0846	1.17E-04	8.52E+03
1.7	0.0799	1.11E-04	9.02E+03
1.8	0.0759	1.05E-04	9.50E+03
1.9	0.0723	1.00E-04	9.97E+03
2.0	0.0693	9.61E-05	1.04E+04
2.1	0.0657	9.11E-05	1.10E+04
2.2	0.0625	8.67E-05	1.15E+04
2.3	0.0601	8.34E-05	1.20E+04
2.4	0.0578	8.02E-05	1.25E+04
2.5	0.0554	7.69E-05	1.30E+04
2.6	0.0531	7.37E-05	1.36E+04
2.7	0.0508	7.05E-05	1.42E+04
2.8	0.0488	6.77E-05	1.48E+04
2.9	0.0468	6.49E-05	1.54E+04
3.0	0.0451	6.26E-05	1.60E+04
3.1	0.0440	6.10E-05	1.64E+04
3.2	0.0423	5.87E-05	1.70E+04
3.3	0.0409	5.67E-05	1.76E+04
3.4	0.0395	5.48E-05	1.82E+04
3.5	0.0383	5.31E-05	1.88E+04
3.6	0.0375	5.20E-05	1.92E+04
3.7	0.0358	4.97E-05	2.01E+04
3.8	0.0356	4.94E-05	2.02E+04
3.9	0.0342	4.74E-05	2.11E+04
4.0	0.0331	4.59E-05	2.18E+04
4.1	0.0322	4.47E-05	2.24E+04
4.2	0.0311	4.31E-05	2.32E+04
4.3	0.0300	4.16E-05	2.40E+04
4.4	0.0298	4.13E-05	2.42E+04
4.5	0.0287	3.98E-05	2.51E+04

Table A-8. Kinetic data for 3-*t*-propyl-1,2-xylylene (**12**) measured at 35.4 °C in CH_3CN

Time, s	Absorbance	[12], M	$[12]^{-1}$, M^{-1}
0.3	0.2223	3.08E-04	3.24E+03
0.4	0.1880	2.61E-04	3.83E+03
0.5	0.1635	2.27E-04	4.41E+03
0.6	0.1440	2.00E-04	5.01E+03
0.7	0.1288	1.79E-04	5.60E+03
0.8	0.1162	1.61E-04	6.20E+03
0.9	0.1053	1.46E-04	6.85E+03
1.0	0.0973	1.35E-04	7.41E+03
1.1	0.0897	1.24E-04	8.04E+03
1.2	0.0827	1.15E-04	8.72E+03
1.3	0.0769	1.07E-04	9.37E+03
1.4	0.0726	1.01E-04	9.93E+03
1.5	0.0685	9.50E-05	1.05E+04
1.6	0.0642	8.91E-05	1.12E+04
1.7	0.0609	8.45E-05	1.18E+04
1.8	0.0575	7.98E-05	1.25E+04
1.9	0.0551	7.64E-05	1.31E+04
2.0	0.0515	7.14E-05	1.40E+04
2.1	0.0492	6.83E-05	1.47E+04
2.2	0.0468	6.49E-05	1.54E+04
2.3	0.0453	6.28E-05	1.59E+04
2.4	0.0430	5.97E-05	1.68E+04
2.5	0.0407	5.65E-05	1.77E+04
2.6	0.0404	5.60E-05	1.78E+04
2.7	0.0387	5.37E-05	1.86E+04
2.8	0.0369	5.12E-05	1.95E+04
2.9	0.0355	4.93E-05	2.03E+04
3.0	0.0349	4.84E-05	2.07E+04
3.1	0.0332	4.61E-05	2.17E+04
3.2	0.0323	4.48E-05	2.23E+04
3.3	0.0315	4.37E-05	2.29E+04
3.4	0.0304	4.22E-05	2.37E+04
3.5	0.0292	4.05E-05	2.47E+04
3.6	0.0287	3.98E-05	2.51E+04
3.7	0.0275	3.82E-05	2.62E+04

Table A-9. Kinetic data for 3-*t*-propyl-1,2-xylylene (**12**) measured at 45.1 °C in CH_3CN

Time, s	Absorbance	[12], M	$[12]^{-1}$, M^{-1}
0.3	0.1944	2.70E-04	3.71E+03
0.4	0.1632	2.26E-04	4.42E+03
0.5	0.1407	1.95E-04	5.12E+03
0.6	0.1218	1.69E-04	5.92E+03
0.7	0.1092	1.51E-04	6.60E+03
0.8	0.0976	1.35E-04	7.39E+03
0.9	0.0889	1.23E-04	8.11E+03
1.0	0.0814	1.13E-04	8.86E+03
1.1	0.0744	1.03E-04	9.69E+03
1.2	0.0686	9.52E-05	1.05E+04
1.3	0.0649	9.00E-05	1.11E+04
1.4	0.0602	8.35E-05	1.20E+04
1.5	0.0559	7.76E-05	1.29E+04
1.6	0.0535	7.42E-05	1.35E+04
1.7	0.0508	7.05E-05	1.42E+04
1.8	0.0469	6.51E-05	1.54E+04
1.9	0.0451	6.26E-05	1.60E+04
2.0	0.0424	5.88E-05	1.70E+04
2.1	0.0409	5.67E-05	1.76E+04
2.2	0.0389	5.40E-05	1.85E+04
2.3	0.0371	5.15E-05	1.94E+04
2.4	0.0351	4.87E-05	2.05E+04
2.5	0.0345	4.79E-05	2.09E+04
2.6	0.0327	4.54E-05	2.20E+04
2.7	0.0307	4.26E-05	2.35E+04
2.8	0.0301	4.18E-05	2.39E+04
2.9	0.0287	3.98E-05	2.51E+04
3.0	0.0278	3.86E-05	2.59E+04
3.1	0.0278	3.86E-05	2.59E+04
3.2	0.0261	3.62E-05	2.76E+04
3.3	0.0253	3.51E-05	2.85E+04
3.4	0.0253	3.51E-05	2.85E+04
3.5	0.0241	3.34E-05	2.99E+04

Table A-10. Kinetic data for 3,6-di-*i*-propyl-1,2-xylylene (**13**) measured at 15.4 °C in CH_3CN

Time, s	Absorbance	[**13**], M	$[\mathbf{13}]^{-1}$, M^{-1}
0	2.5287	4.27E-04	2.34E+03
3	1.7678	2.98E-04	3.35E+03
6	1.4648	2.47E-04	4.04E+03
9	1.2414	2.10E-04	4.77E+03
12	1.1179	1.89E-04	5.30E+03
15	0.9873	1.67E-04	6.00E+03
18	0.8781	1.48E-04	6.75E+03
21	0.8309	1.40E-04	7.13E+03
24	0.7567	1.28E-04	7.83E+03
27	0.7091	1.20E-04	8.35E+03
30	0.6604	1.11E-04	8.97E+03
33	0.6162	1.04E-04	9.61E+03
36	0.5796	9.78E-05	1.02E+04
39	0.5502	9.29E-05	1.08E+04
42	0.5247	8.86E-05	1.13E+04
45	0.5000	8.44E-05	1.18E+04
48	0.4744	8.01E-05	1.25E+04
51	0.4584	7.74E-05	1.29E+04
54	0.4330	7.31E-05	1.37E+04
57	0.4219	7.12E-05	1.40E+04
60	0.4005	6.76E-05	1.48E+04
63	0.3899	6.58E-05	1.52E+04
66	0.3736	6.31E-05	1.59E+04
69	0.3576	6.04E-05	1.66E+04
72	0.3438	5.80E-05	1.72E+04
75	0.3351	5.66E-05	1.77E+04
78	0.3272	5.52E-05	1.81E+04
81	0.3148	5.31E-05	1.88E+04

Table A-11. Kinetic data for 3,6-di-*i*-propyl-1,2-xylylene (**13**) measured at 25.3 °C in CH_3CN

Time, s	Absorbance	[**13**], M	$[\mathbf{13}]^{-1}$, M^{-1}
0	2.0157	3.40E-04	2.94E+03
3	1.5151	2.56E-04	3.91E+03
6	1.2630	2.13E-04	4.69E+03
9	1.0573	1.78E-04	5.60E+03
12	0.9213	1.56E-04	6.43E+03
15	0.8158	1.38E-04	7.26E+03
18	0.7430	1.25E-04	7.97E+03
21	0.6690	1.13E-04	8.86E+03
24	0.6200	1.05E-04	9.55E+03
27	0.5794	9.78E-05	1.02E+04
30	0.5354	9.04E-05	1.11E+04
33	0.5036	8.50E-05	1.18E+04
36	0.4712	7.95E-05	1.26E+04
39	0.4437	7.49E-05	1.34E+04
42	0.4208	7.10E-05	1.41E+04
45	0.4019	6.78E-05	1.47E+04
48	0.3833	6.47E-05	1.55E+04
51	0.3629	6.13E-05	1.63E+04
54	0.3463	5.85E-05	1.71E+04
57	0.3354	5.66E-05	1.77E+04
60	0.3156	5.33E-05	1.88E+04
63	0.3083	5.20E-05	1.92E+04
66	0.2995	5.06E-05	1.98E+04
69	0.2881	4.86E-05	2.06E+04
72	0.2796	4.72E-05	2.12E+04
75	0.2755	4.65E-05	2.15E+04
78	0.2621	4.42E-05	2.26E+04
81	0.2536	4.28E-05	2.34E+04
84	0.2487	4.20E-05	2.38E+04

Table A-12. Kinetic data for 3,6-di-*t*-propyl-1,2-xylylene (**13**) measured at 34.8 °C in CH_3CN

Time, s	Absorbance	[**13**], M	$[\mathbf{13}]^{-1}$, M^{-1}
0	1.8712	3.16E-04	3.17E+03
3	1.3596	2.30E-04	4.36E+03
6	1.0917	1.84E-04	5.43E+03
9	0.9167	1.55E-04	6.46E+03
12	0.7906	1.33E-04	7.49E+03
15	0.7132	1.20E-04	8.31E+03
18	0.6354	1.07E-04	9.32E+03
21	0.5749	9.70E-05	1.03E+04
24	0.5342	9.02E-05	1.11E+04
27	0.4927	8.32E-05	1.20E+04
30	0.4553	7.69E-05	1.30E+04
33	0.4255	7.18E-05	1.39E+04
36	0.4009	6.77E-05	1.48E+04
39	0.3799	6.41E-05	1.56E+04
42	0.3595	6.07E-05	1.65E+04
45	0.3427	5.78E-05	1.73E+04
48	0.3236	5.46E-05	1.83E+04
51	0.3123	5.27E-05	1.90E+04
54	0.3009	5.08E-05	1.97E+04
57	0.2918	4.93E-05	2.03E+04
60	0.2793	4.71E-05	2.12E+04
63	0.2710	4.57E-05	2.19E+04
66	0.2629	4.44E-05	2.25E+04
69	0.2483	4.19E-05	2.39E+04
72	0.2408	4.06E-05	2.46E+04
75	0.2340	3.95E-05	2.53E+04
78	0.2269	3.83E-05	2.61E+04

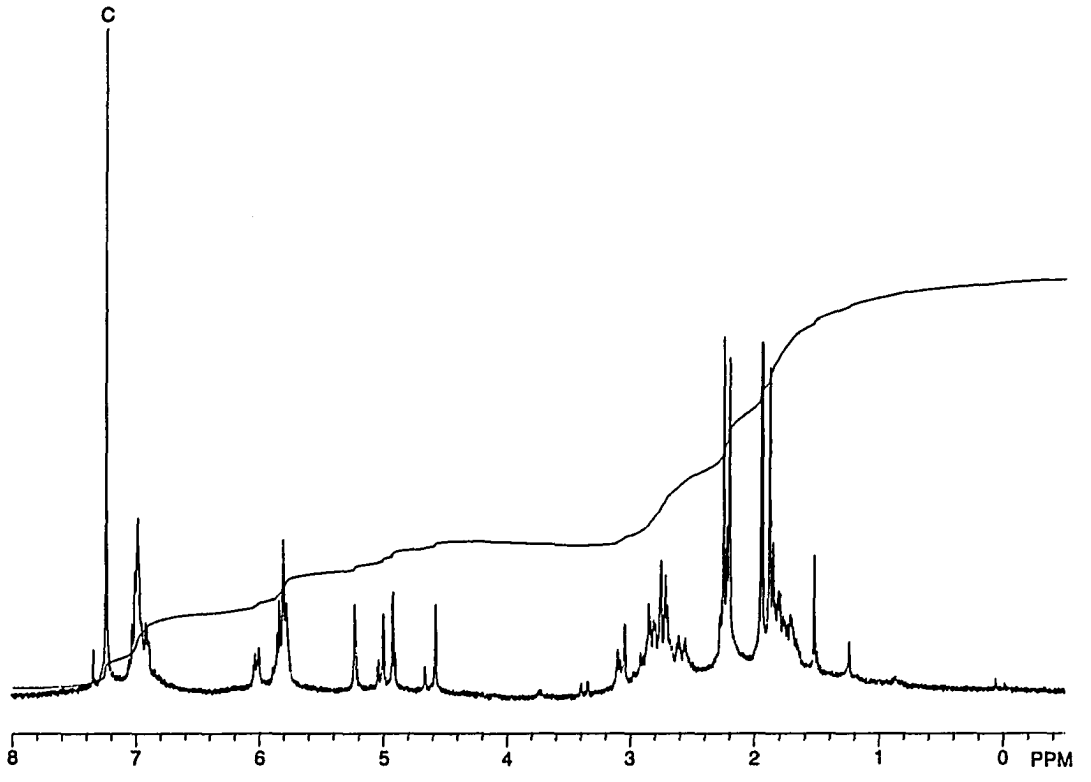


Figure A-1. ^1H NMR spectrum (300 MHz, $CDCl_3$) of the dimer products of 3-methyl-1,2-xylylene (**5**) (C = $CHCl_3$)

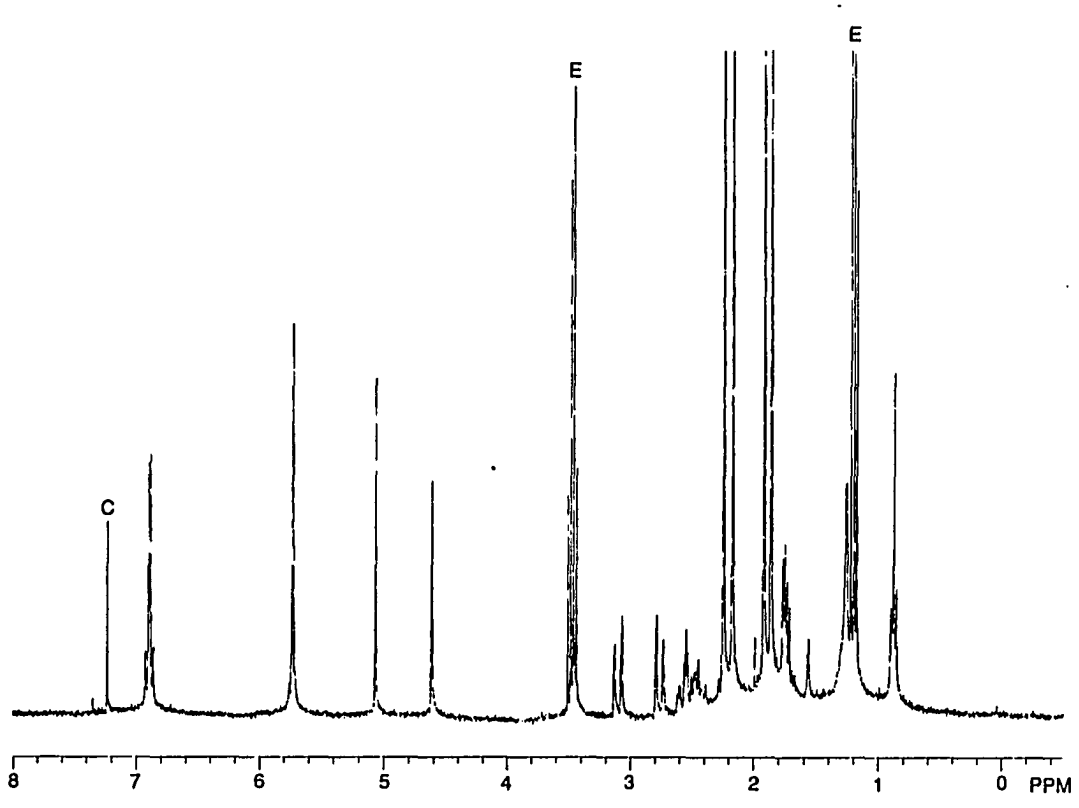


Figure A-2. ^1H NMR spectrum (300 MHz, $CDCl_3$) of the dimer product of 3,6-dimethyl-1,2-xylylene (**11**) (C = $CHCl_3$, E = ET_2O)

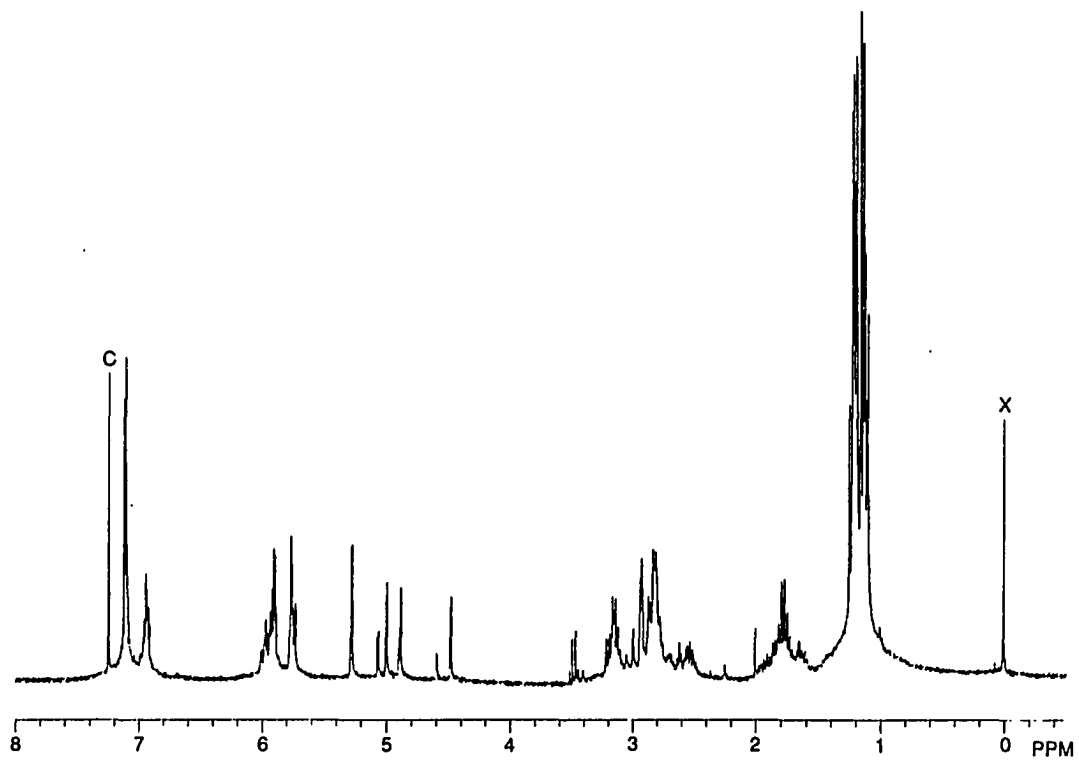


Figure A-3. ^1H NMR spectrum (300 MHz, $CDCl_3$) of the dimer products of 3-isopropyl-1,2-xylylene (**12**) (C = $CHCl_3$, X = impurity)

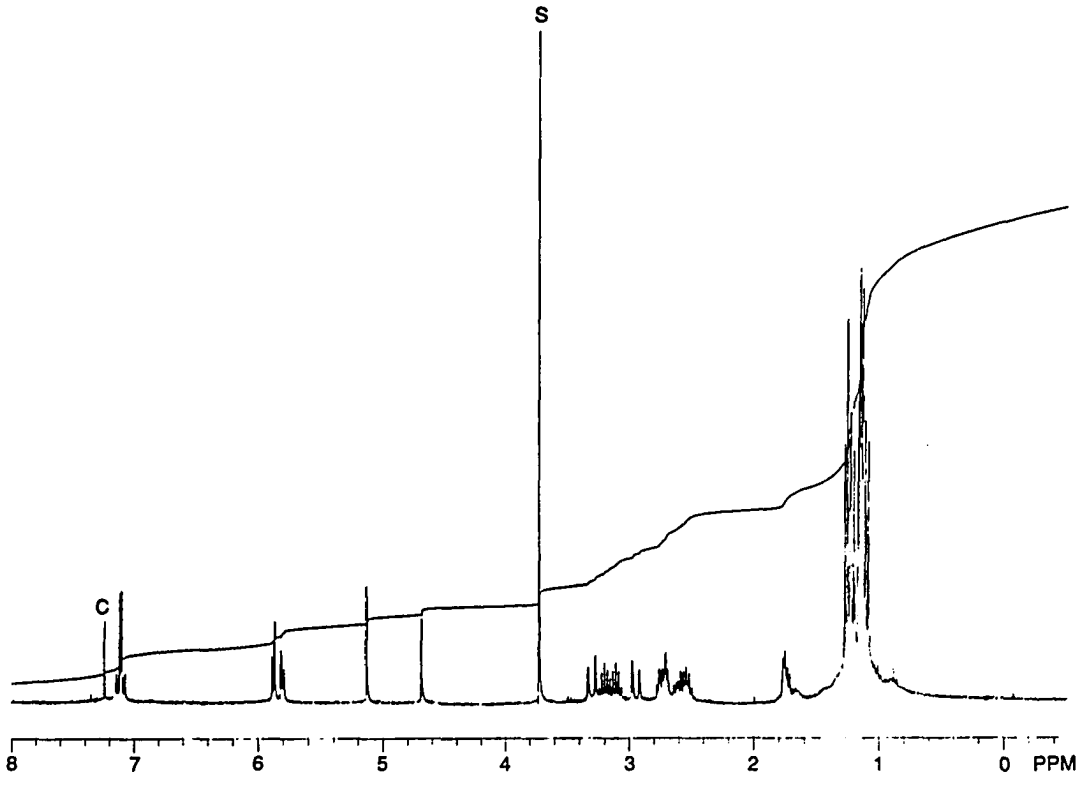


Figure A-4. ^1H NMR spectrum (300 MHz, $CDCl_3$) of the dimer product of 3,6-diisopropyl-1,2-xylylene (**13**) (C = $CHCl_3$, S = 1,2-dichloroethane)

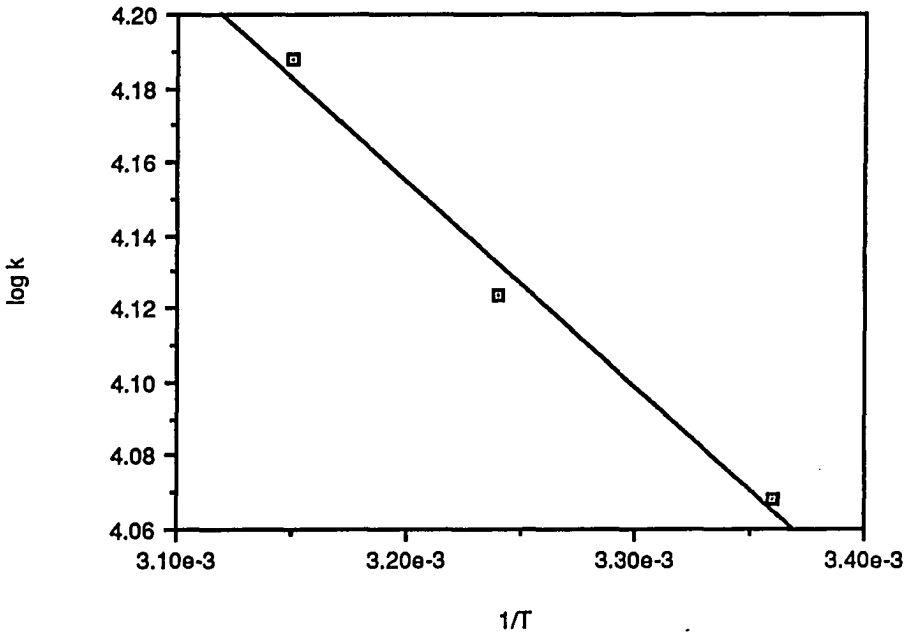


Figure A-5. Plot of log k versus 1/T for 3-methyl-1,2-xylylene (**5**)

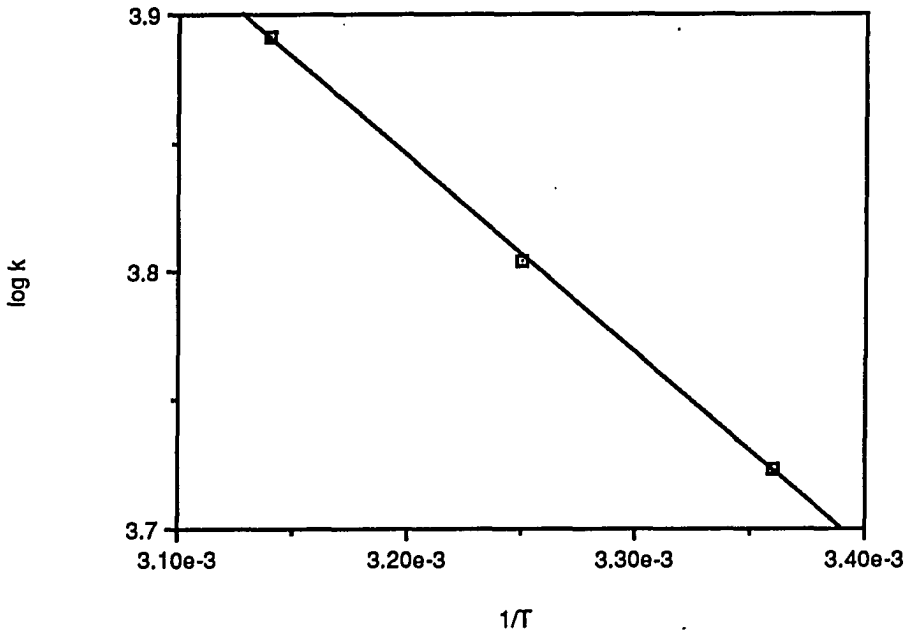


Figure A-6. Plot of log k versus 1/T for 3,6-dimethyl-1,2-xylylene (**11**)

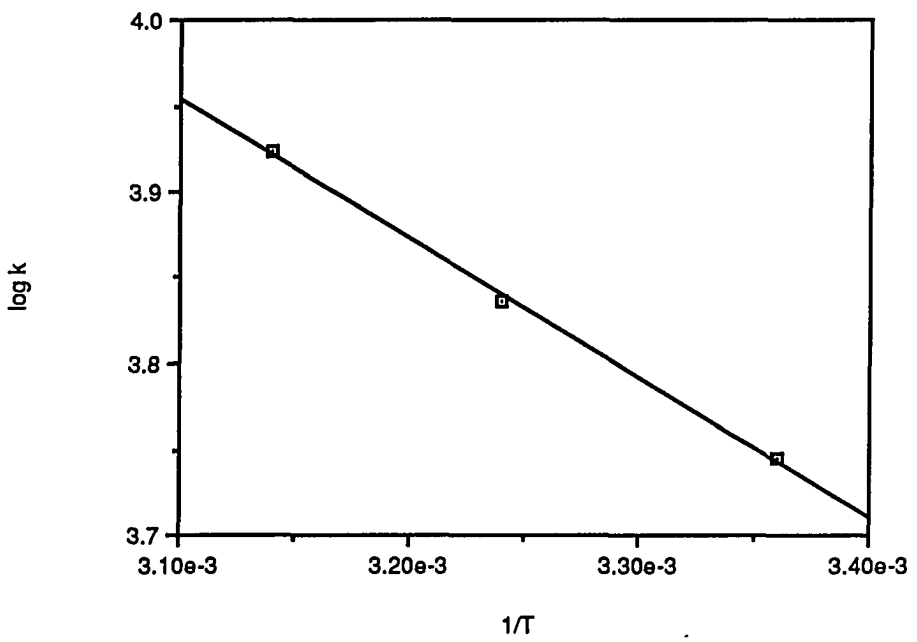


Figure A-7. Plot of log k versus 1/T for 3-isopropyl-1,2-xylylene (**12**)

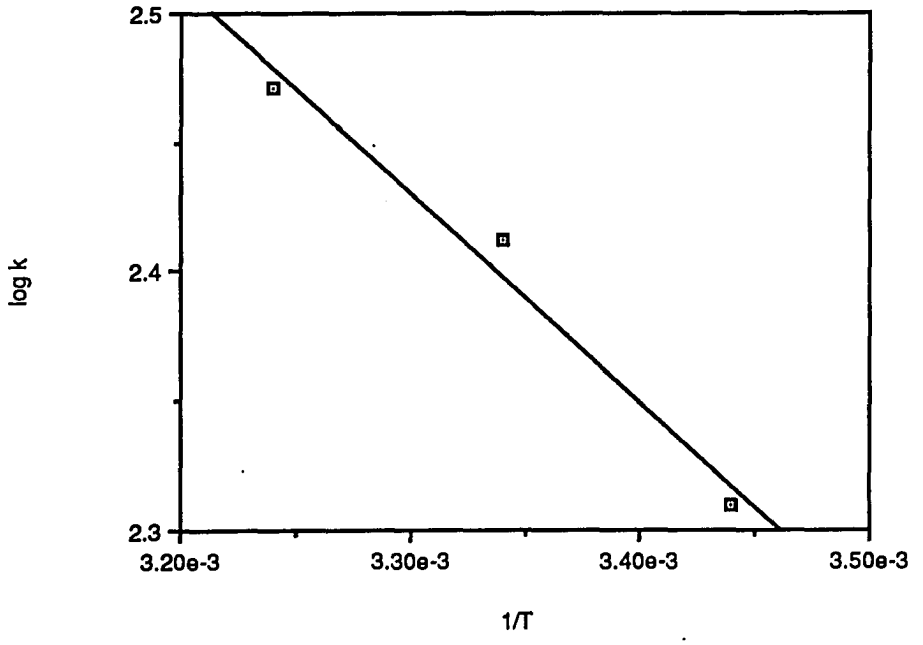


Figure A-8. Plot of log k versus 1/T for 3,6-diisopropyl-1,2-xylylene (**13**)

SECTION 3. OBSERVATION OF BENZOCYCLOBUTADIENE BY FLOW ^{1}H NMR

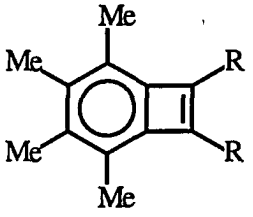
INTRODUCTION[1]

Benzocyclobutadiene (**1**),[2,3] the monobenzo annulated analogue of cyclobutadiene (**2**), is a reactive molecule of considerable experimental[4] and theoretical

1 **2**

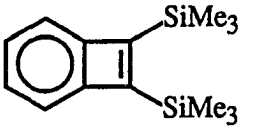
interest,[5-13] but its transient nature has made its study difficult. Cyclobutadiene (**2**) and benzocyclobutadiene (**1**) are important molecules in the understanding of the electronic structure and chemical behavior of cyclic 4n π-electron systems. The high reactivity of **1** is consistent with the destabilizing effect of a 4n system (cyclobutadiene) on a 4n + 2 system (benzene).[14]

Due to the high reactivity of benzocyclobutadiene itself, a number of stable substituted benzocyclobutadienes have been studied. Straub has prepared two highly substituted benzocyclobutadienes (**3** and **4**) which are stable at room temp-



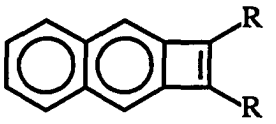
3, R = Ph
4, R = *t*-Bu

erature.[15-18] 1,2-Bis(trimethylsilyl)benzocyclobutadiene (**5**), the least substituted



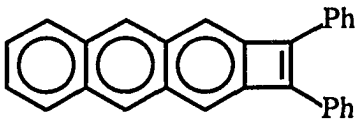
5

stable benzocyclobutadiene prepared thus far, was reported by Vollhardt and Yee.[19] Cava has used aromatic moieties combined with bulky groups in some cases to stabilize benzocyclobutadiene. Naphtho[*b*]cyclobutadiene (**6**)[20] is reactive, although



6, R = H
7, R = Ph

less so than **1**, while 1,2-diphenylnaphtho[*b*]cyclobutadiene (**7**)[21-23] is a stable crystalline material. 1,2-Diphenylanthra[*b*]cyclobutadiene (**8**)[24] is also stable, but



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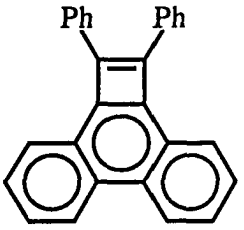

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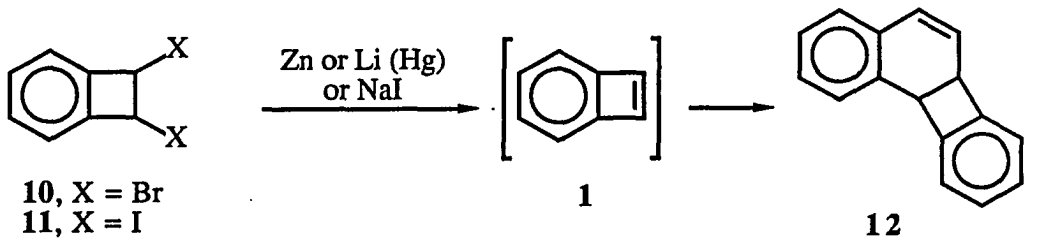
interestingly 1,2-diphenylphenanthro[*b*]cyclobutadiene (**9**)[25] is a reactive species which can be trapped but not isolated. Toda[26,27] has also provided examples of highly substituted benzocyclobutadienes and naphtho[*b*]cyclobutadienes. Stable metal complexes of benzocyclobutadiene have been isolated as well.[28-31]

Because of its high reactivity, methods to generate **1** must have a large driving force. The most widely used methods for its generation have included dehalogenation of 1,2-dihalobenzocyclobutenes and dehydrohalogenation of 1-halobenzocyclobutenes.[3] The dehalogenation of 1,2-dibromobenzocyclobutene (**10**) by Zn, lithium

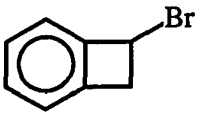


10, X = Br
11, X = I

1

12

amalgam, or sodium iodide results in formation of **1** which rapidly dimerizes forming its stable angular dimer (**12**).[32] Dehalogenation of 1,2-diiodobenzocyclobutene (**11**) occurs even more rapidly than for **10**. In the same manner, **1** is generated by dehydrohalogenation of 1-bromobenzocyclobutene (**13**) using potassium



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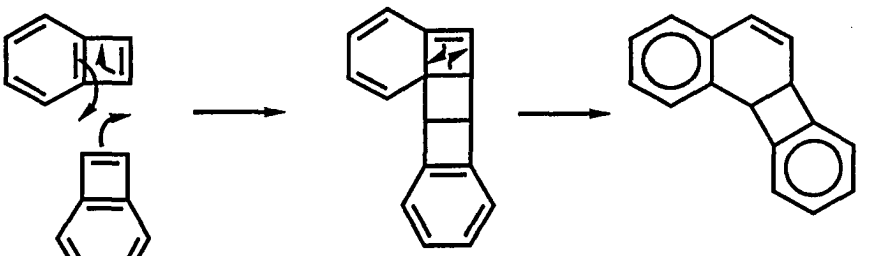
t-butoxide, also resulting in formation of **12**.

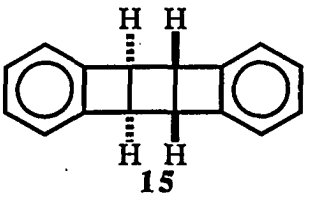
Cava proposed that the angular dimer (**12**) arises by the intramolecular rearrangement of an unstable dimer (**14**) that is formed by a [4 + 2] cycloaddition



14 **12**

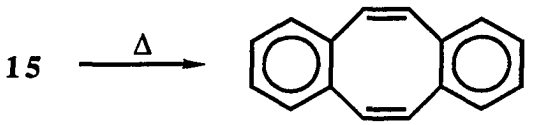
reaction between two benzocyclobutadiene molecules.[32] He suggested that this [4 + 2] cycloaddition involves one molecule of **1** acting as a dienophile and the other as a diene.

The linear dimer **15** is formed when **1** is generated by the debromination of **10**



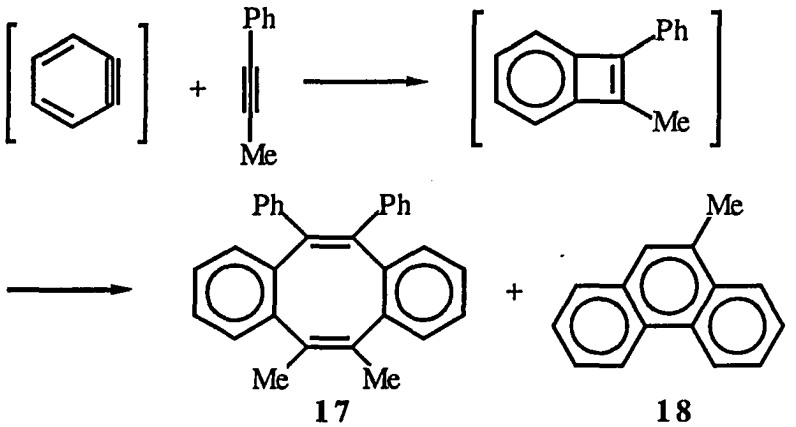
15

(using lithium or sodium amalgam) in the presence of nickel tetracarbonyl.[33,34] This dimer probably arises from an unstable nickel complex in which the two benzocyclobutadiene units are properly oriented to facilitate linear cycloaddition. The *cis, trans, cis* arrangement of **15** was demonstrated by its ozonolysis to give *cis, trans, cis*-1,2,3,4-cyclobutanetetracarboxylic acid.[35] Heating of **15** to its melting point or above results in rearrangement to dibenzo[*a,e*]cyclooctatetraene (**16**).



16

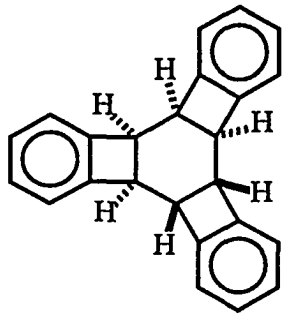
Cycloadditions between benzyne and acetylenes have been used to form substituted benzocyclobutadienes.[3] Generation of benzyne from benzenediazonium-2-carboxylate and reaction with methylphenylacetylene results in formation of 5,6-dimethyl-11,12-diphenyldibenzo[*a,e*]cyclooctatetraene (**17**) presumably via



17 **18**

isomerization of the cooresponding linear dimer. Also found was 9-methylphenanthrene (**18**) which was probably formed by a [4 + 2] cycloaddition reaction between benzyne and methylphenylacetylene. Debromination of 1,2-dibromo-1-methyl-2-phenylbenzocyclobutene with zinc results in the formation of only **17**.

It was recently reported that two trimers of benzocyclobutadiene can be formed in the reaction of 1,2-dibromobenzocyclobutene and $Ni(PPh_3)_4$.[36] When using tetrahydrofuran as a solvent, mainly the *cis, trans, cis* (**15**) and *cis, cis, cis* (**19**) linear dimers were formed with small amounts of both the *cis, cis, cis, trans, cis* (**20**) and all



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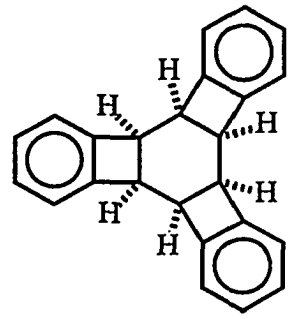

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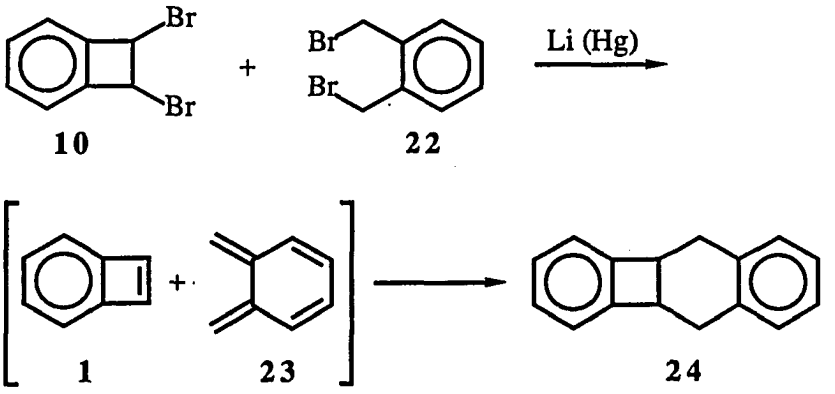
cis (**21**) trimers present as well. In dimethylformamide the major product was the *cis, cis, cis, trans, cis* trimer (**20**), but also present were small amounts of the all *cis* trimer (**21**) and the *cis, trans, cis* (**15**) and *cis, cis, cis* (**19**) linear dimers. Interestingly, there are no examples in the literature of where the angular (**12**) and linear (**15** and/or **19**) dimers of benzocyclobutadiene are formed under the same reaction conditions.

Benzocyclobutadiene (**1**) is a good dienophile in [4 + 2] cycloaddition reactions with dienes. Trapping with furan,[3] dimethylfulvene,[3] spiroheptadiene,[3] 1,3-diphenylisobenzofuran,[3] and various cyclopentadienes[3,37] and cyclopentadienones[38] have all been described. Reaction of **1** with *o*-xylylene (**23**) and 2,3-dihydronaph-



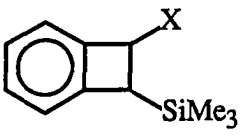
thalene has also been reported.[39-42] Benzocyclobutadiene's reaction as a diene with other dienophiles is however very limited.[3] No adduct was formed when either dimethyl maleate or dimethyl acetylenedicarboxylate was used as the dienophile. In the presence of N-phenylmaleimide, a small amount of the trapped adduct was formed, but the major product was the stable angular dimer (**12**).

Numerous examples of dimer isolation and cycloaddition product formation all provide evidence for the existence of **1**. Direct spectroscopic observation of this reactive species itself has been difficult due to its high reactivity. Benzocyclobutadiene (**1**) has been isolated in a low temperature matrix and its IR,[43,44] UV-visible,[43,44] and photoelectron[45] spectra have been obtained. ^{1}H NMR spectra have been obtained of several substituted benzocyclobutadienes which are stable at room temperature.[17-19,21]

^{1}H NMR spectroscopy provides a good probe of the electronic structure of organic molecules. The high reactivity of **1** however precludes its ^{1}H NMR observation by conventional means. We have successfully used the technique of flow ^{1}H NMR to observe several reactive *o*-quinodimethanes.[46-49] In this section, the preparation of a suitable precursor of **1** and the observation of **1** by flow ^{1}H NMR are presented and discussed.

RESULTS

We have found that reactive *o*-xylylenes can be generated rapidly enough from their easily prepared [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium halide precursors by fluoride ion induced 1,4-elimination,[50,51] that spectroscopic observation is possible.[46-48,52] Fast, quantitative generation of the transient species is necessary for its flow-NMR observation. Synthesis of 2-trimethylsilylbenzocyclobutenyl-1 trimethylammonium iodide (**25**), the analogous precursor of

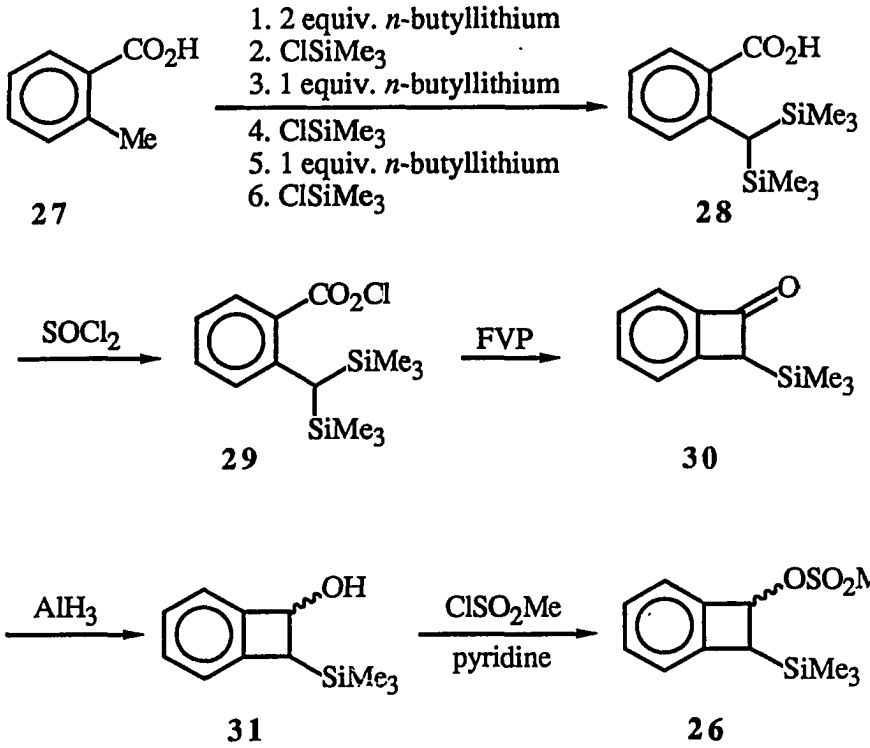


25, X = NMe_3I
26, X = OSO_2Me

benzocyclobutadiene, was unsuccessful. Preparation of 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) was however possible and has proven to be an excellent source of benzocyclobutadiene (**1**).

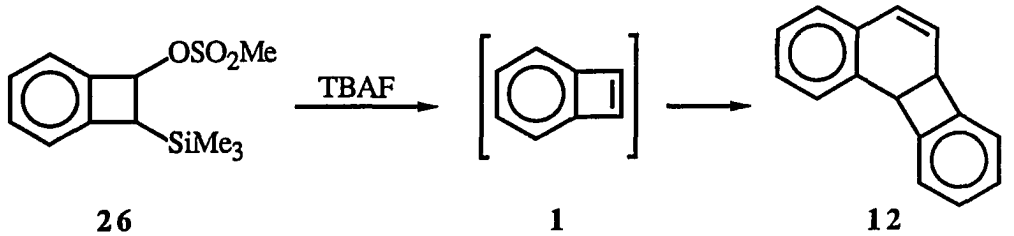
Starting from *o*-toluic acid (**27**), **26** was prepared as a 5:1 mixture of the *cis* and *trans* isomers (Scheme 1). The acid **27** was converted to 2-trimethylsilylbenzocyclobutenone (**30**) in a manner similar to that used by Chenard et al.[53] and Spangler.[54] This involved flash vacuum pyrolysis (FVP) of 2-(bis(trimethylsilyl)-methyl)benzoyl chloride (**29**) to give the desired **30**. Aluminum hydride reduction[55,56] of **30** gave a 5:1 mixture of the *cis* and *trans* isomers of 2-trimethylsilylbenzocyclobutenol (**31**) which was converted to the mesylate (**26**) by standard techniques.

Scheme 1



27 28 29 30 31 26

The stable angular dimer (**12**) of **1** was formed in high yield by treatment of an acetonitrile (CH_3CN) solution of **26** with a CH_3CN solution of tetrabutylammonium fluoride (TBAF). The presence of **12** demonstrates that **1** is generated by fluoride ion



26 **1** **12**

induced 1,2-elimination from the mesylate presursor (**26**).

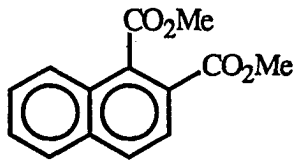
The ^1H NMR spectrum obtained by mixing 10^{-3} M **26** in acetonitrile-d_3 (CD_3CN) with 5 x 10^{-2} M TBAF in CD_3CN in the mixing chamber of the flow NMR apparatus[47] at a total flow rate of 45 mL/min exhibits three major peaks (6.36, 6.26, and 5.78 ppm)

(Figure 1a). These peaks are assigned to **1**. The spectrum in Figure 1b, obtained by mixing the two reagent solutions at a total flow rate of 3 mL/min, is an expanded view (plotted with narrower line broadening than the spectrum in Figure 1a) showing coupling between the six-membered ring protons (6.26 and 5.78 ppm; AA'BB' system). The flow NMR spectrum of the recycled product-mixture solution (Figure 2) shows the expected angular dimer (**12**). The spectra shown in Figures 1a, 1b, and 2 were all obtained with a Bruker WM-300 spectrometer.

A small singlet (7.35 ppm) appears in the aromatic region of the flow NMR spectrum obtained by mixing 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 5 x 10^{-3} M TBAF in CD_3CN at a total flow rate of 45 mL/min (Figure 1a; observed with a Bruker WM-300 spectrometer). Down to a flow rate of 3 mL/min, the intensity of this singlet increases (Appendix, Figures A-1 and A-2). At very slow flow rates (0.3-0.1 mL/min) however, this region resembles that of the recycled product-mixture solution spectrum (Figure 2). When a 3.3 x 10^{-3} M solution of **26** in CD_3CN is mixed with a 0.17 M TBAF solution in CD_3CN at total flow rates of 1-2 mL/min (observed with a Bruker MSL-300 spectrometer), a broad multiplet (7.4-7.0 ppm) is observed in the aromatic region along with several broad signals between 4.8-4.3 ppm (Appendix, Figures A-3, A-4, and A-5).

Slowly treating a CH_3CN solution of **26** and dimethyl acetylenedicarboxylate with a dilute CH_3CN solution of TBAF resulted in formation of the angular dimer (**12**) (67% relative yield) and also a major (31% relative yield) and minor (2% relative yield) adduct in low overall yield. The major adduct was isolated and assigned as

dimethyl-1,2-naphthalene dicarboxylate (**32**) by its ^1H NMR spectrum. The minor



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adduct was identified as such by GCMS, but was not isolated.

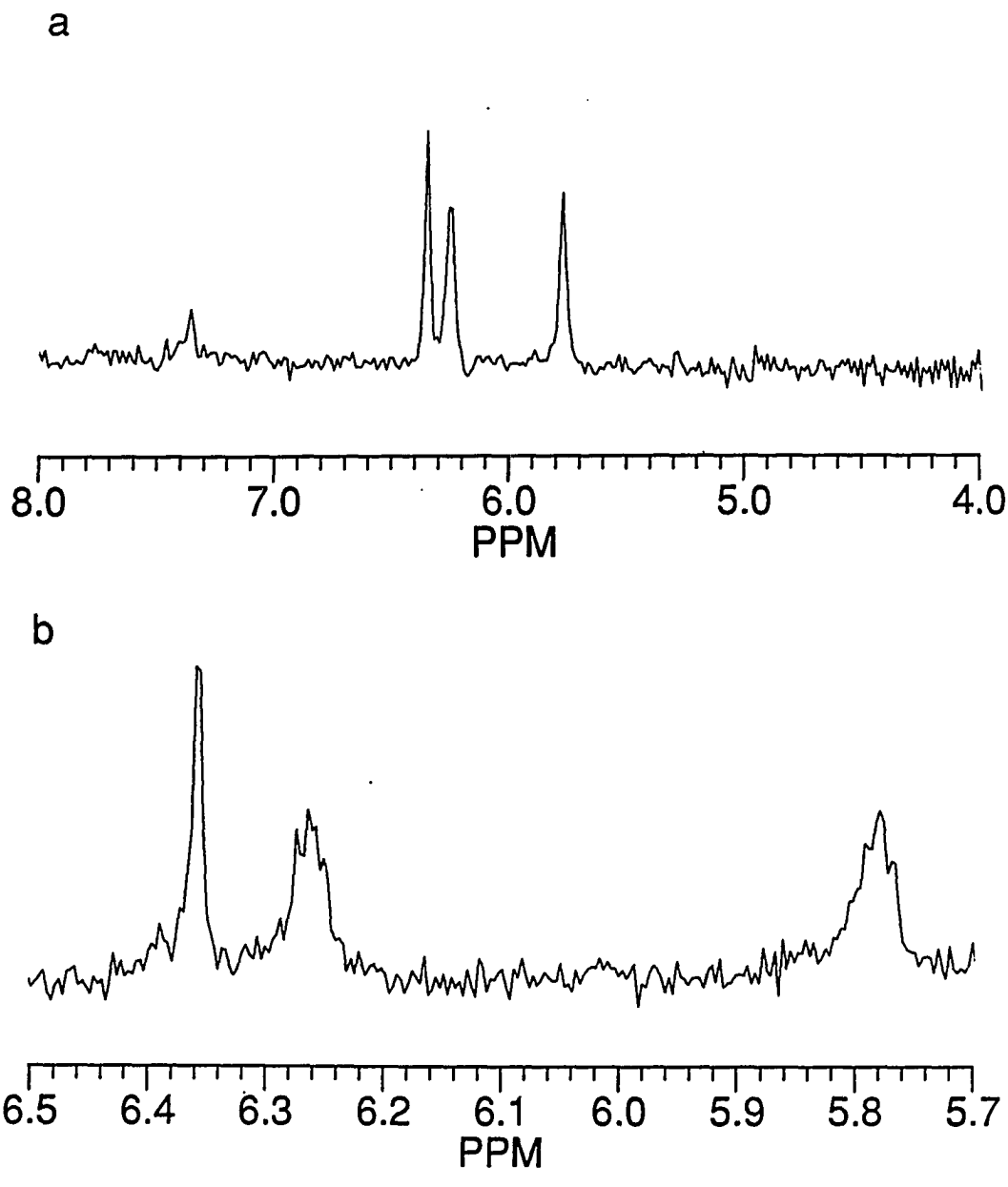


Figure 1. Flow ^{1}H NMR spectra (300 MHz, observed with a Bruker WM-300 spectrometer): (a) obtained by mixing 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 5 x 10^{-2} M TBAF in CD_3CN; flow rate, 45 mL/min; number of scans, 512; pulse interval, 0.127 s; (b) obtained by mixing 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 5 x 10^{-2} M TBAF in CD_3CN; flow rate, 3 mL/min; number of scans, 1105; pulse interval, 1.016 s

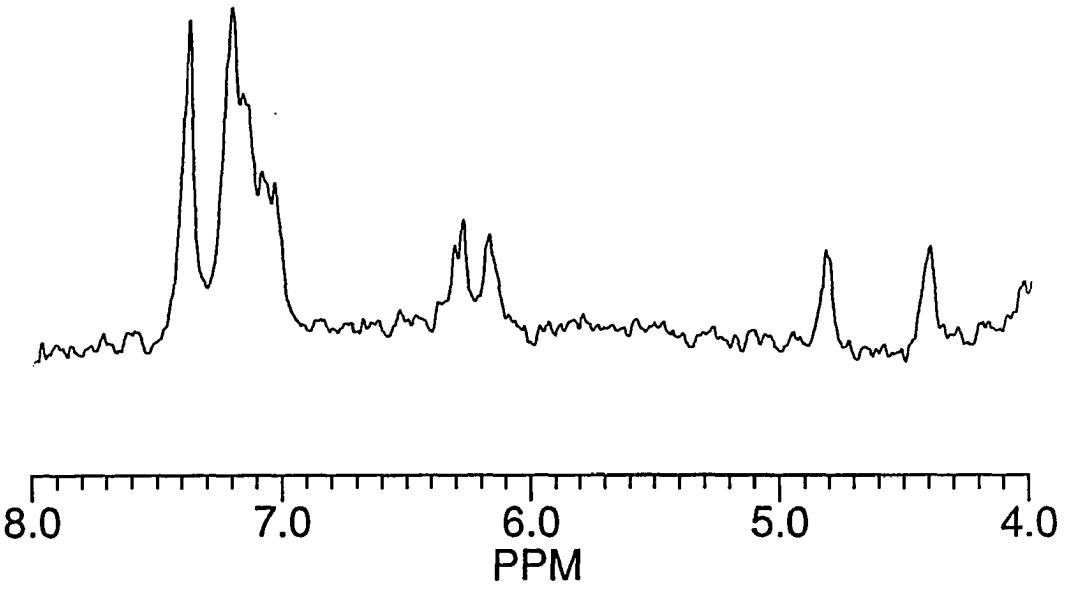


Figure 2. Flow ^{1}H NMR spectrum (300 MHz, observed with a Bruker WM-300 spectrometer) of the recycled product mixture resulting from mixing 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 5×10^{-3} M TBAF in CD_3CN; flow rate, 3 mL/min; number of scans, 1332; pulse interval, 1.016 s

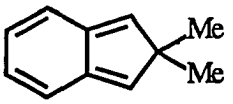
DISCUSSION

It is apparent that the three major peaks present (6.36, 6.26, and 5.78 ppm) in the flow NMR spectrum shown in Figures 1a and 1b, are due to the reactive molecule benzocyclobutadiene (**1**). At much slower flow rates (0.3 to 0.1 mL/min), these three peaks are greatly reduced and peaks due to the stable angular dimer (**12**) are evident (especially in the aromatic region). The flow NMR spectrum of the recycled product mixture solution (Figure 2) exhibits only **12** and none of the benzocyclobutadiene signals. It is evident from these results that **1** can be observed by flow NMR prior to its dimerization.

The singlet (7.35 ppm) observed in the flow-NMR spectra obtained at 45 to 3 mL/min with the Bruker WM-300 spectrometer, and the broad aromatic multiplet (7.4-7.0 ppm) and broad upfield signals (4.8-4.3 ppm) observed with the Bruker MSL-300 spectrometer are consistent with the formation of at least two unstable dimers. Because **1** decays by a second order process, the higher concentration of 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) (3.3×10^{-3}M) and TBAF (0.17 M) was used in an attempt to "build up" a significant amount of the unstable dimers before their rearrangement to **12**. Unfortunately, the quality of all of these spectra is not high enough to make definitive judgements as to the unstable dimers' structure.

The six-membered ring protons of 1,2-bis(trimethylsilyl)benzocyclobutadiene (**5**) are at 6.20 and 5.63 ppm in its ^{1}H NMR spectrum.[19] For the stable 1,2-diphenylnaphthocyclobutadiene (**7**), the two protons in the 3- and 10-positions give rise to a singlet at 6.5 ppm in its ^{1}H NMR spectrum.[21] The six-membered ring proton signals of **1** itself (6.26 and 5.78 ppm) are thus similar to that of these two substituted benzocyclobutadienes as well as that of *o*-xylylene (**23**) (6.3 and 6.0 ppm)[46,47],

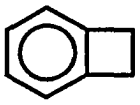
2,2-dimethylisoindene (**33**) (6.08 ppm),[57] and the olefinic protons of 1,3-cyclohexa-



33

34

diene (**34**) (5.80 ppm).[58] The six-membered ring protons of **1** are however significantly upfield of the benzene ring protons of benzocyclobutene (**35**)[2,59] (6.96 ppm) and biphenylene (**36**) (6.72 and 6.62 ppm).[60]



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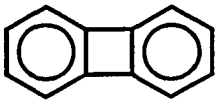

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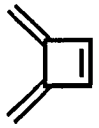
The position of the four-membered ring proton signal (6.36 ppm) is very close to the olefinic ring protons of cyclobutene (**37**) (6.00 ppm)[61] and 3,4-dimethylenecyclo-

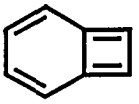
37



38

butene (**38**) (6.70 ppm)[62] and to the five-membered ring proton signals of **33** (6.55 ppm).[57]

From these comparisons, it is reasonable that the structure of benzocyclobutadiene (**1**) is neither antiaromatic or aromatic, but rather a nonaromatic polyene shown as **39**. This is consistent because of the similarity of the spectra of **1**, **23**, and **33**.



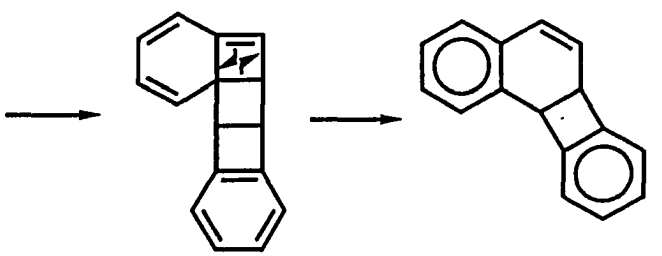
39

The X-ray structure of the highly substituted 1,2-di-*tert*-butyl-3,4,5,6-tetramethylbenzocyclobutadiene (**4**),[15] indicates that the structure of benzocyclobutadiene be represented as **1**. However, these bulky groups could be distorting the benzocyclobutadiene structure.

Although kinetic studies have not been performed on **1**, it is evident from these flow-NMR studies that **1** is just slightly less reactive than *o*-xylylene (**23**). Mixing the precursor and TBAF solutions at a total flow rate of 45 mL/min resulted in a spectrum of **23** in the presence of its stable dimers,[46,47] while at the same flow rate, benzocyclobutadiene could be seen primarily alone.

It has been proposed that benzocyclobutadiene dimerizes by a [4 + 2] cycloaddition reaction involving the aromatic π-bond of one of the benzocyclobutadiene molecules.[32] It is believed that **23** dimerizes by a stepwise mechanism involving a diradical intermediate.[48,63] Because the structure of **39** is analogous to **23**, it is possible that dimerization could be occurring in this manner as well. Coupling of two benzocyclobutadiene molecules would give the diradical intermediate (**40**) which upon closing would give the unstable dimer (**14**). Intramolecular rearrangement of **14**

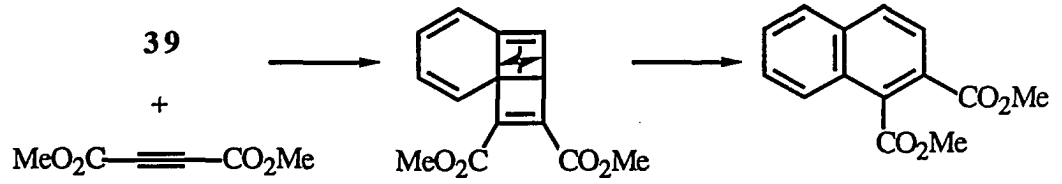
39 **39** **40**



14 **12**

would result in formation of the stable angular dimer (**12**).

Past workers were unsuccessful at trapping **1** with dimethyl acetylene-dicarboxylate.[3] We were successful in this endeavor however, even though the overall yield was low and the major product formed was the dimer **12**. In this case, **1** was generated very slowly by the slow addition of a dilute TBAF solution. At any given time, the concentration of **1** was very low, thus slowing dimerization and enhancing trapping with the large excess of dienophile to give the adduct **32**. Formation of **32** probably arises by an intramolecular rearrangement of the unstable adduct **41**. It is not clear how this unstable adduct (**41**) is formed however.



41 **32**

It is apparent that 2-trimethylsilybenzocyclobutenyl-1 mesylate (**26**) is an excellent precursor for the generation of **1** for its flow NMR study. Fluoride ion induced 1,2-elimination from **26** provides rapid and quantitative formation of **1**.

The usefulness of flow NMR has again been demonstrated by the observation of a species too reactive to be observed by usual NMR methods. The ^{1}H NMR spectrum of **1** provides valuable insight into the structure of this reactive molecule.

EXPERIMENTAL SECTION

General Procedures

^{1}H NMR spectra were recorded on a Nicolet NT-300 spectrometer. Chemical shifts are reported relative to tetramethylsilane.

Capillary gas chromatographic analyses were performed using a Hewlett-Packard HP 5890A Series II gas chromatograph equipped with a 30-m DB-1 capillary column (J & W Scientific) using helium as a carrier gas and a flame ionization detector.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Flow NMR spectra were taken on a Bruker WM-300 (300 MHz) or Bruker MSL-300 (300 MHz) spectrometer using acetonitrile-d_3 (CD_3CN) as solvent and residual $NCCD_2H$ as internal standard (1.93 ppm). CD_3CN was purchased from Cambridge Isotope Laboratories or Isotec Inc.

o-Toluic acid, *n*-butyllithium in hexanes, hexamethylphosphoramide (HMPA), chlorotrimethylsilane, and methanesulfonyl chloride were purchased from Aldrich Chemical Co. Chlorotrimethylsilane was distilled from calcium hydride immediately before use. *n*-Butyllithium was standardized before use by titration.

2-(Bis(trimethylsilyl)methyl)benzoic acid (28).

Preparation of **28** was performed in a manner similar to that used by Chenard et al.[53] and Spangler.[54] To a cooled solution (-78 °C) of *o*-toluic acid (**27**) (5 g, 36.7 mmol) in tetrahydrofuran (40 mL) and HMPA (12 mL) was added 38 mL of *n*-butyllithium (2.0 M, 76 mmol). After stirring for 10 min, 5.9 mL of chlorotrimethylsilane (5.0 g, 46.5 mmol) was added. The solution was allowed to warm to

0 °C over 20 min, then was recooled to -78 °C and 4 mL of HMPA was added. *n*-Butyllithium (20 mL, 2.0 M, 40 mmol) was again added, followed by stirring (10 min) and addition of 5.9 mL of chlorotrimethylsilane (5.0 g, 46 mmol). After warming to 0 °C over 20 min and recooling to -78 °C, the above sequence was repeated adding 4 mL of HMPA, 20 mL of *n*-butyllithium (2.0 M, 40 mmol), and finally 8.0 mL of chlorotrimethylsilane (6.8 g, 63 mmol). The reaction mixture was allowed to warm to room temperature and then stir for 12 h.

To dissolve the salts, 25 mL of water was added and then the mixture was cooled to 0 °C and acidified to pH 2 with 1 M aqueous HCl solution. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were extracted with 1 M aqueous NaOH solution. These extracts were cooled to 0 °C, acidified to pH 3 with 1 M aqueous HCl solution, and then extracted with ether. The ether extracts were combined and dried over anhydrous magnesium sulfate. Removal of the solvent yielded 7.2 g of the white solid (**28**) (70% yield). ^{1}H NMR ($CDCl_3$) δ 7.98-7.95 (m, 1H), 7.42-7.37 (m, 1H), 7.14-7.07 (m, 2H), 3.31 (s, 1H), 0.02 (s, 18H) [lit.[54] ^{1}H NMR (CCl_4) δ 8.15-7.9 (m, 1H), 7.5-6.9 (m, 3H), 3.38 (s, 1H), 0.02 (s, 18H)].

2-(Bis(trimethylsilyl)methyl)benzoyl chloride (29)

Preparation of **29** was performed in a manner similar to that used by Chenard et al.[53] and Spangler.[54] 2-(Bistrimethylsilylmethyl)benzoic acid (**28**) (3g, 11 mmol), thionyl chloride (12.7 g, 10.7 mmol), and 1 drop of dimethylformamide were refluxed for 12 h after which the volume was reduced leaving 3.18 g of the acid chloride (**29**) (99% yield). ^{1}H NMR ($CDCl_3$) δ 8.06-8.03 (m, 1H), 7.44-7.38 (m, 1H), 7.16-7.06 (m, 2H), 2.82 (s, 1H), 0.01 (s, 18 H).

2-Trimethylsilylbenzocyclobutenone (30)

The crude acid chloride (**29**) (2.1 g, 7.0 mmol) was flash vacuum pyrolyzed (595 °C, 1 mm Hg) to give **30** in 50% yield. IR (NaCl plates-neat liquid) 3064, 2957, 1784, 1761, 1580, 1252, 1086, 957, 847 cm^{-1} [lit.[54] IR (neat) 2950, 1760, 1578, 1458, 1435, 1272, 1245, 1147, 1134, 1080, 950, 840, 765, 745, 728, 688, 614 cm^{-1}]; ^1H NMR ($CDCl_3$) δ 7.42-7.22 (m, 4H), 3.85 (s, 1H), 0.07 (s, 9H) [lit.[54] ^1H NMR (CCl_4) δ 7.35-7.04 (m, 4H), 3.76 (s, 1H), 0.05 (s, 9H)]; GCMS (70 eV) m/e (% base peak) 190.0 (36.38), 175.0 (55.09), 147.0 (37.05), 145.0 (35.54), 73.0 (100.00).

2-Trimethylsilylbenzocyclobutenol (31)

Aluminum hydride[55,56] was prepared by the addition of aluminum chloride (35 mg, 0.26 mmol) to lithium aluminum hydride (31 mg, 0.81 mmol) in 25 mL of ether at 0 °C. After warming to room temperature, the solution of aluminum hydride (0.81 mmol) was added to a solution of **30** (0.2 g, 1.0 mmol) in 25 mL of ether and stirring was continued for 5 h. Excess aluminum hydride was quenched with cold saturated aqueous sodium bicarbonate solution and the aqueous phase was extracted with ether. The organic phase was dried over anhydrous magnesium sulfate, filtered, and the volume reduced giving 0.18 g (0.92 mmol) of the alcohol (81% yield; 5:1 mixture of *cis* and *trans* isomers). The alcohol (**31**) decomposed readily, so was stored at -5 °C. IR (NaCl plates-neat liquid) 3389, 3065, 2953, 2897, 1452, 1248, 1150, 1043, 843 cm^{-1}; ^1H NMR (major isomer) ($CDCl_3$) δ 7.25-6.88 (m, 4H), 5.37 (m, 1H), 3.25 (d, J = 4.73 Hz, 1H), 1.98 (d, J = 3.94 Hz, 1H), 0.05 (s, 9H); GCMS (major isomer) (70 eV) m/e (% base peak) 192.1 (15.38), 177.0 (54.88), 73.0 (100.00).

2-Trimethylsilylbenzocyclobutenyl-1 mesylate (26)

To a solution of methanesulfonyl chloride (2.1 g, 18 mmol) in 10 mL of pyridine was added **31** (0.18 g, 0.92 mmol) in 5 mL of pyridine. This mixture was stirred for 7 h after which 10 mL of cold water was added. Extraction with ether, was followed by combination of the organic extracts, washing with cold 1 M aqueous HCl solution, and then cold saturated aqueous sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate and the volume was reduced. Flash column chromatography (the column, containing silica gel, was flushed with 5% triethylamine in ether followed by ether prior to sample loading) using ether as an eluting solvent gave 0.21 g (85% yield) of **26** (5:1 mixture of *cis* and *trans* isomers). This mesylate was stored at -5 °C. mp 38-47 °C; IR (KBr) 3024, 1362, 1173, 843 cm^{-1}; ^1H NMR (major isomer) ($CDCl_3$) δ 7.31-7.01 (m, 4H), 5.94 (d, J = 5.1 Hz, 1H), 3.41 (d, J = 5.1 Hz, 1H), 3.07 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (major isomer) ($CDCl_3$) δ 144.55, 141.52, 130.66, 126.43, 123.40, 121.44, 76.79, 42.26, 38.57, -2.02; HRMS calcd. for $C_{12}H_{18}O_3SSi$ 270.0746, found 270.0743.

Dimerization of benzocyclobutadiene (1)

The stable angular dimer **12** has been previously prepared.[32] A solution of 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) (5 mg, 0.02 mmol) in 0.3 mL of CH_3CN was treated with a solution of TBAF (8.1 mg, 0.03 mmol) in 0.3 mL of CH_3CN and was then allowed to stir for 2 h. The volume was reduced, 0.1 mL of water was added, and this was extracted with hexanes. The organic extracts were combined, dried over anhydrous magnesium sulfate, and the volume reduced giving the dimer (**12**) in 85% yield. ^1H NMR ($CDCl_3$) δ 7.38-6.98 (m, 8H), 6.29 (d, J = 10.21 Hz, 1H), 6.13

(dd, 1H), 4.83 (d, J = 6.09 Hz, 1H), 4.43 (m, 1H); GCMS (70 eV) m/e (% base peak) 204.2 (89.30), 203.2 (100.00), 202.1 (72.41), 101.1 (50.25).

Trapping of benzocyclobutadiene (1) with dimethyl acetylenedicarboxylate

TBAF (40 mg, 0.15 mmol) in 50 mL of CH_3CN was added dropwise to 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) (21 mg, 0.08 mmol) and dimethylacetylene dicarboxylate (1.05 g, 7.4 mmol) in 4 mL CH_3CN while rapidly stirring. Total addition time was 1.25 h after which the mixture was allowed to stir an additional 3.5 h. The volume of the reaction mixture was reduced, dissolved in ether, washed with water, and the organic layers separated. The organic phase was dried over anhydrous magnesium sulfate and then the volume was reduced. The dimer (**12**), major (**32**), and minor adducts were obtained in 67, 31, and 2% relative yield respectively as determined by GC analysis. The major adduct (**32**) was isolated by flash column chromatography (75% hexanes, 25% ether) and identified by ^1H NMR. ^1H NMR (**32**) ($CDCl_3$) δ 8.01 (d, J = 8.66 Hz, 1H), 7.92 (d, J = 8.73 Hz, 1H), 7.91-7.84 (m, 2H), 7.61-7.58 (m, 2H), 4.06 (s, 3H), 3.95 (s, 3H) [lit.[64] ^1H NMR ($CDCl_3$) δ 8.0-7.3 (m, 6H), 4.05 (s, 3H), 3.90 (s, 3H)]; GCMS (**32**) (70 eV) m/e (%base peak) 244.03 (40.78), 213.00 (100.00), 170.00 (12.54), 127.05 (16.90), 126.04 (13.72), 114.02 (12.61).

General Procedure for Flow NMR

The flow NMR experiment has been described in detail.[47]

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APPENDIX

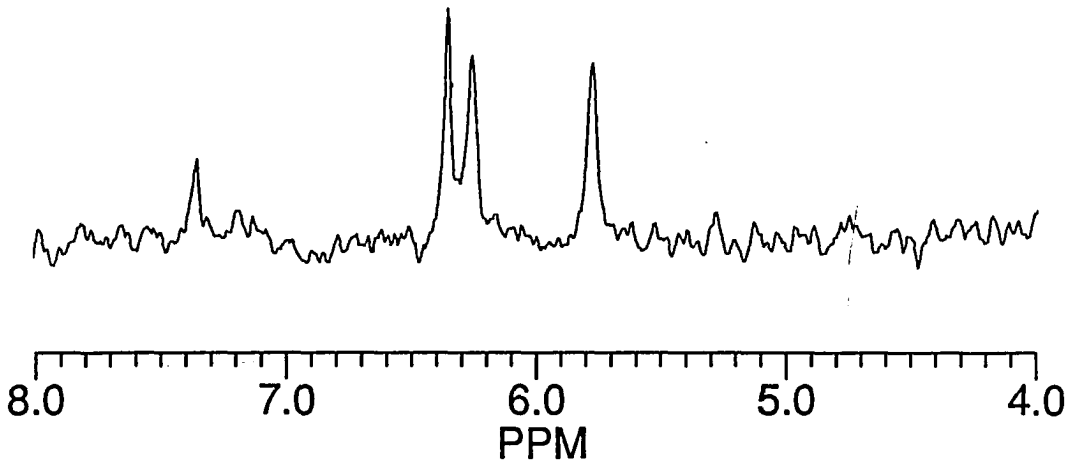


Figure A-1. Flow ^{1}H NMR spectrum (300 MHz, observed with a Bruker WM-300 spectrometer) obtained by mixing 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 5 x 10^{-2} M TBAF in CD_3CN; flow rate, 6 mL/min; number of scans, 512; pulse interval, 0.256 s

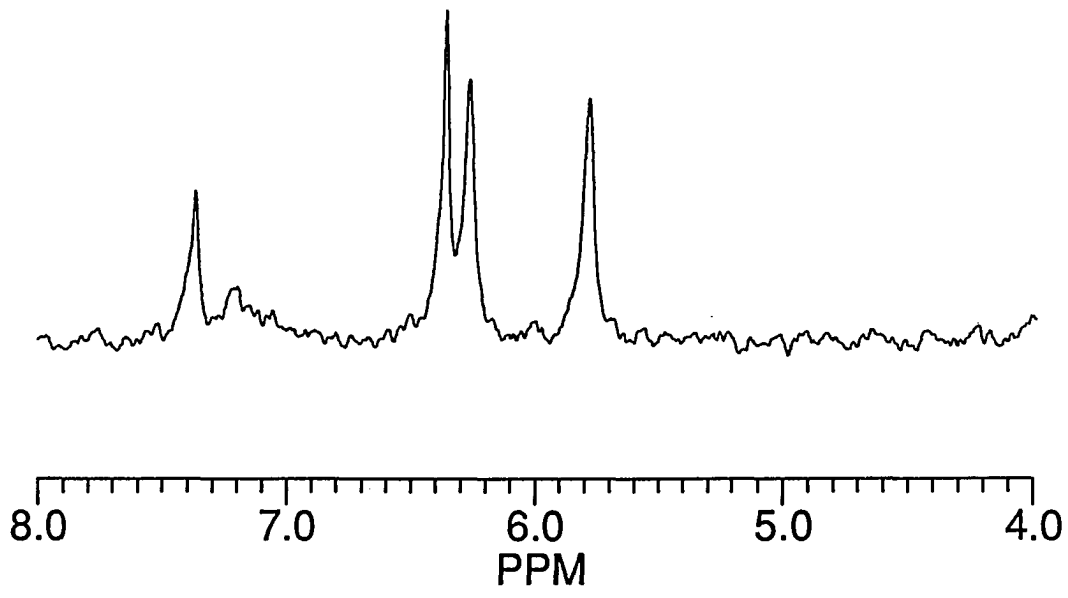


Figure A-2. Flow ^{1}H NMR spectrum (300 MHz, observed with a Bruker WM-300 spectrometer) obtained by mixing 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 5 x 10^{-2} M TBAF in CD_3CN; flow rate, 3 mL/min; number of scans, 1105; pulse interval, 1.016 s

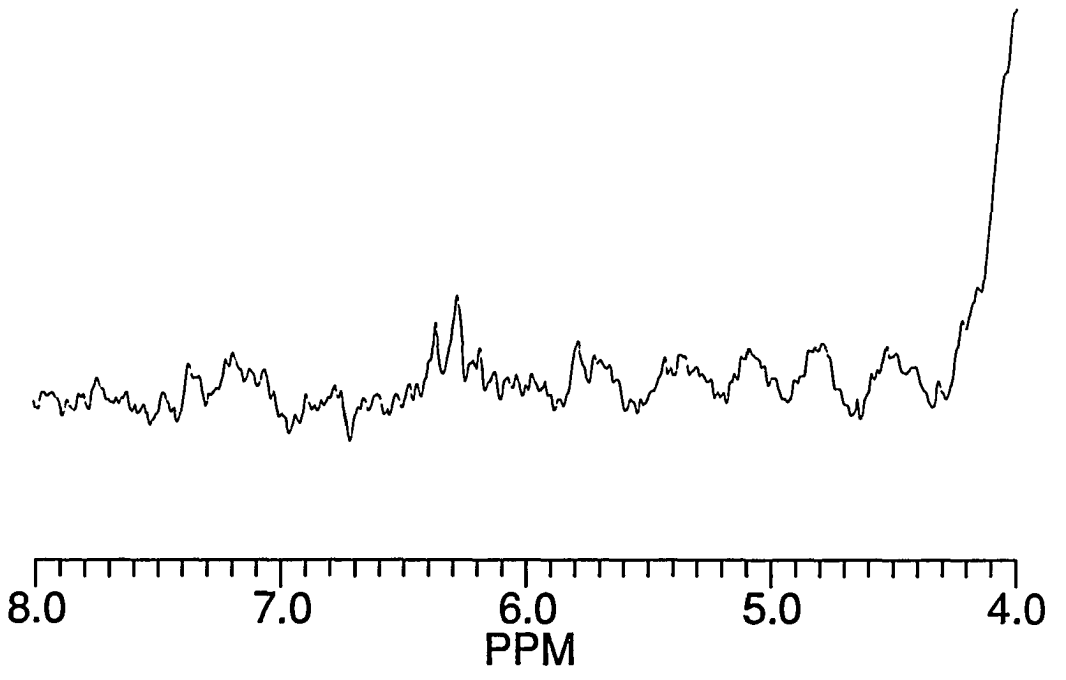


Figure A-3. Flow ^{1}H NMR spectrum (300 MHz, observed with a Bruker MSL-300 spectrometer) obtained by mixing 3.3×10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 0.17 M TBAF in CD_3CN; flow rate, 2 mL/min; number of scans, 64; pulse interval, 0.41 s

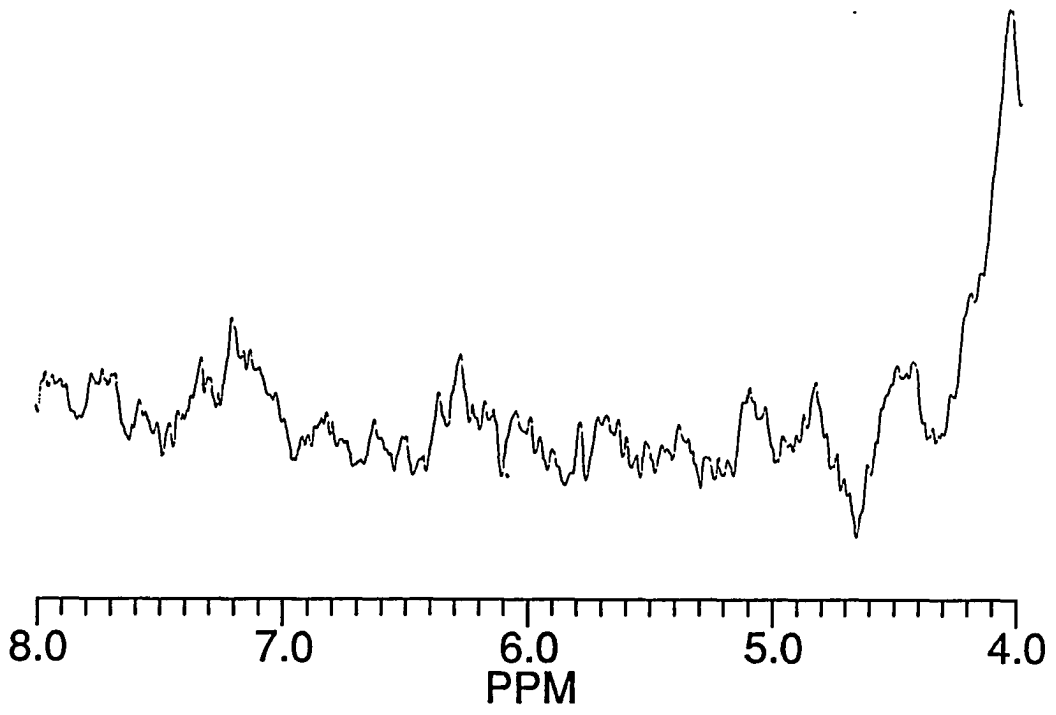


Figure A-4. Flow ^{1}H NMR spectrum (300 MHz, observed with a Bruker MSL-300 spectrometer) obtained by mixing 3.3 x 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 0.17 M TBAF in CD_3CN; flow rate, 1 mL/min; number of scans, 64; pulse interval, 0.41 s

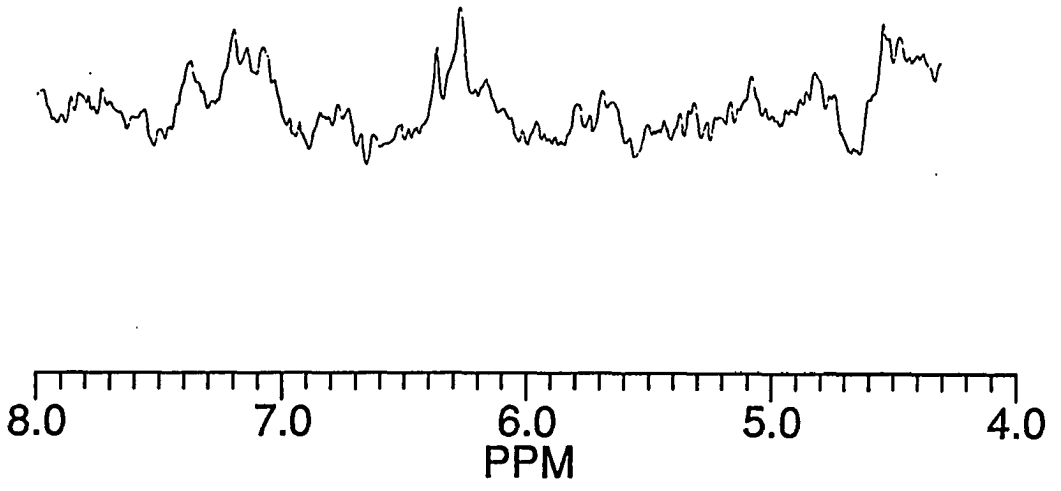
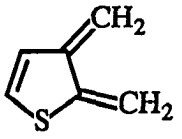


Figure A-5. Flow ^{1}H NMR spectrum (300 MHz, observed with a Bruker MSL-300 spectrometer) obtained by mixing 3.3 x 10^{-3} M 2-trimethylsilylbenzocyclobutenyl-1 mesylate (**26**) in CD_3CN with 0.17 M TBAF in CD_3CN; flow rate, 1 mL/min; number of scans, 64; pulse interval, 0.825 s

SECTION 4. OBSERVATION BY FLOW ^{1}H NMR AND DIMERIZATION KINETICS OF 2,3-DIMETHYLENE-2,3-DIHYDROTHIOPHENE

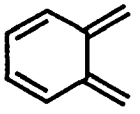
INTRODUCTION

An interesting although seldom studied member of the *o*-quinodimethane (*o*-QDM) family of reactive molecules is 2,3-dimethylene-2,3-dihydrothiophene (**1**).



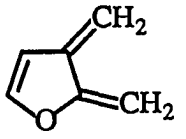
1

Based on resonance energy (RE) differences, it would be expected that **1** (thiophene RE = 29 kcal mol^{-1}) is intermediate in reactivity between *o*-xylylene (**2**) (benzene RE = 36



2

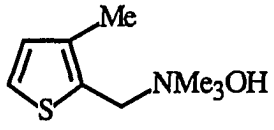
kcal mol^{-1}) and 2,3-dimethylene-2,3-dihydrofuran (**3**) (furan RE = 16 kcal mol^{-1}).[1]



3

Evidence for the existence of **1** has come from dimer product isolation, trapping studies, and also spectroscopic observation.

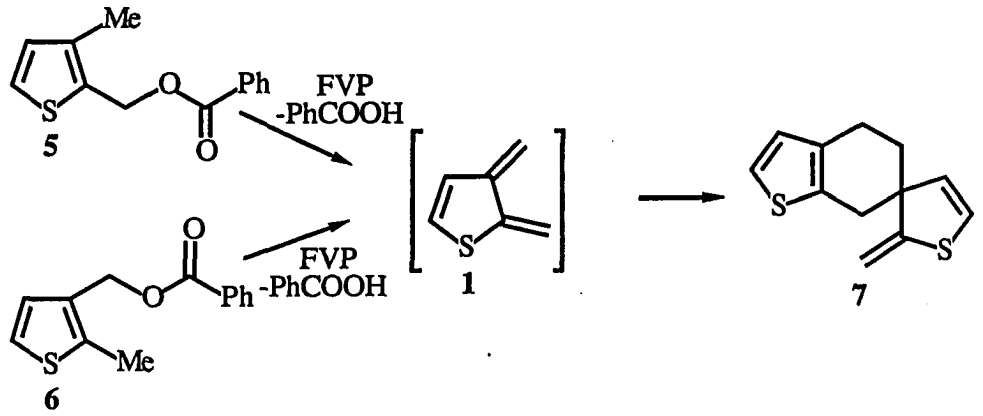
In 1960, Winberg first generated **1** by the pyrolysis of 3-methyl-2-thenyl-trimethylammonium hydroxide (**4**).[2] An intralinear polymer attached through the



4

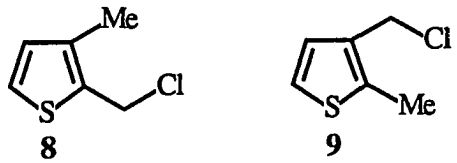
2 and 3 positions of the thiophene ring was obtained in low yield as the sole product.

More recently, **1** was generated by flash vacuum pyrolysis (FVP) of either 3-methyl-2-thenyl benzoate (**5**) or 2-methyl-3-thenyl benzoate (**6**).[3] In both cases, the

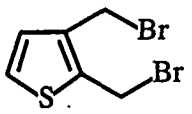


isolated product was a [4 + 2] spiro-dimer (**7**) (20% yield) of **1** accompanied by a substantial amount of white polymer. The structure of **7** was rigorously determined by a deuterium labeling study. No evidence could be found for **1** in a ^{1}H NMR spectrum of the pyrolysate taken at -65 °C. The ^{1}H NMR spectrum of **3** has been observed at low temperatures,[4] while that of **2**[5,6] and several of its derivatives[7] has been observed using the flow NMR technique.

FVP of either 3-methyl-2-thenyl chloride (**8**) or 2-methyl-3-thenyl chloride (**9**)



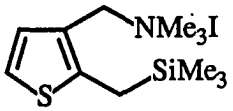
also gave rise to formation of a single dimer product plus polymer.[8] The structure of this dimer was not specifically assigned, but is most likely that of **7**. Trapping of **1** as a [4 + 2] adduct was accomplished in high yield by treatment of 2,3-di(bromomethyl)-thiophene (**10**) with sodium iodide in dimethylformamide at 80 °C in the presence of a



10

dienophile.[9]

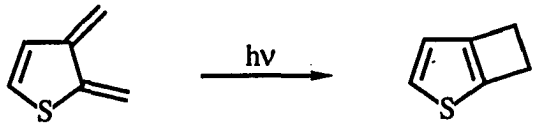
A significant contribution was made by van Leusen in the successful preparation of 3-(trimethylammoniummethyl)-2-(trimethylsilylmethyl)thiophene iodide (**11**).[10,11] In analogy to Ito's approach for the generation of **2** from [2-((tri-



11

methylsilyl)methyl)benzyl]trimethylammonium halides by fluoride ion induced 1,4-elimination,[12,13] **1** can be generated from **11** in solution at room temperature. Upon generation, **1** was trapped by a variety of dienophiles in high yield, but when generated in the absence of dienophiles the spiro-dimer **7** was reported as the major product (80% yield). There are also several examples of where substituted 2,3-dimethylene-2,3-dihydrothiophenes are generated using this general method.[9,14]

The photoelectron spectrum of **1** was observed in the gas phase by pyrolysis of 3-methyl-2-thenyl chloride (**8**).[15] In this same study, the UV-visible spectrum of **1** was obtained in an argon matrix at 16 K. Irradiation of matrix isolated **1** lead to formation of 1,2-dihydrocyclobuta[*b*]thiophene (**12**).[15]



1 **12**

Recent work in the Trahanovsky group has focused on the study of various reactive molecules.[3-7,16,17] The study of several of these reactive molecules has included determination of their rates of dimerization and observation of their ^1H NMR spectra using the flow-NMR technique. In this section, observation of **1** by the flow-NMR technique is described along with the determination of the rate and activation parameters for its dimerization reaction.

RESULTS

All of the experiments described here were performed using 3-(trimethylammoniummethyl)-2-(trimethylsilylmethyl)thiophene iodide (**11**) provided by Professor A. M. van Leusen (Gronigen University, The Netherlands).

A λ_{max} of 350 nm was measured for 2,3-dimethylene-2,3-dihydrothiophene (**1**) by mixing a CH_3CN solution of **11** with a CH_3CN solution of tetrabutylammonium fluoride (TBAF) in the optical path of a Perkin-Elmer UV-visible spectrophotometer at room temperature. A decrease in the absorption at 350 nm was observed during repetitive scanning of the region between 230-400 nm.

The second order decay of **1**, generated by mixing 1 mL of CH_3CN, 0.5 mL of 10^{-3} M **11** in CH_3CN, and 0.5 mL of 0.1 M TBAF in CH_3CN in a UV-visible cell, was monitored at 350 nm using a Cary UV-visible spectrophotometer. A plot of 1/conc. versus time gave a straight line of excellent fit, the slope[18] of which is the second order rate of dimerization. Dimerization rates at 10, 20, 30, and 40 °C were determined in this manner (Table 1). Using the Arrhenius relationship, plots of ln k versus 1/T gave the activation enthalpy and entropy[19] for **1** ($\Delta H^{\ddagger}$ = 7.3 ± 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ = -29.3 ± 1.5 eu).[20] Table 2 lists the activation parameters for **1**, and also *o*-xylylene (**2**)[16] and 2,3-dimethylene-2,3-dihydrofuran (**3**)[4] for comparison.

The ε_{max} for **1** was determined from the average of the maximum absorbance measurements of the three kinetic runs performed at 30 °C. From this average absorbance and the known concentration of **11**, a value of ε_{max} = 7838 M^{-1} cm^{-1} was calculated. The three measurements at 30 °C were used because they were the highest, most consistent maximum absorbance values to be determined at any of the four temperatures.

Table 1. Second order rate constants for the dimerization of 2,3-dimethylene-2,3-dihydrothiophene (**1**) in CH_3CN[a]

T, °C	k, M^{-1} s^{-1}
10	5.04 ± 0.1
20	8.43 ± 0.05
25	10.8 ± 0.04
30	13.6 ± 0.3
40	21.4 ± 0.9

[a]Calculated values. The starting concentrations of **1** and TBAF were 2.5×10^{-4} and 2.5×10^{-2} M, respectively.

Table 2. Activation parameters for the dimerization of 2,3-dimethylene-2,3-dihydrothiophene (**1**),[a,b] *o*-xylylene (**2**),[a,c,d] and 2,3-dimethylene-2,3-dihydrofuran (**3**)[c,e,f]

Compound	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	7.3 ± 0.4	-29.3 ± 1.5
2	3.5 ± 0.13	-29 ± 1.1
3	10.2 ± 0.3	-30.9 ± 1.2

[a]In CH_3CN.

[b]T_{ave} = 25.9 °C.

[c]T_{ave} = 25 °C.

[d]Reference 16.

[e]In 1:1 $CS_2/CDCl_3$.

[f]Reference 4.

Using the flow NMR technique,[6] a 10^{-3} M acetonitrile-d_3 (CD_3CN) solution of **11** was mixed with a 6 x 10^{-3} M TBAF solution in CD_3CN at a total flow rate of 45 mL/min to give the ^1H NMR spectrum shown in Figure 1a. The flow NMR spectrum (obtained at 3 mL/min) of the recycled product-mixture solution shows the signals of a single [4 + 2] dimer along with a small amount of unreacted **1** (Figure 1b). Mixing the two reagent solutions at a total flow rate of 0.1 mL/min results in a spectrum showing primarily the signals for **1**, but also those for the stable dimer (Figure 1c).

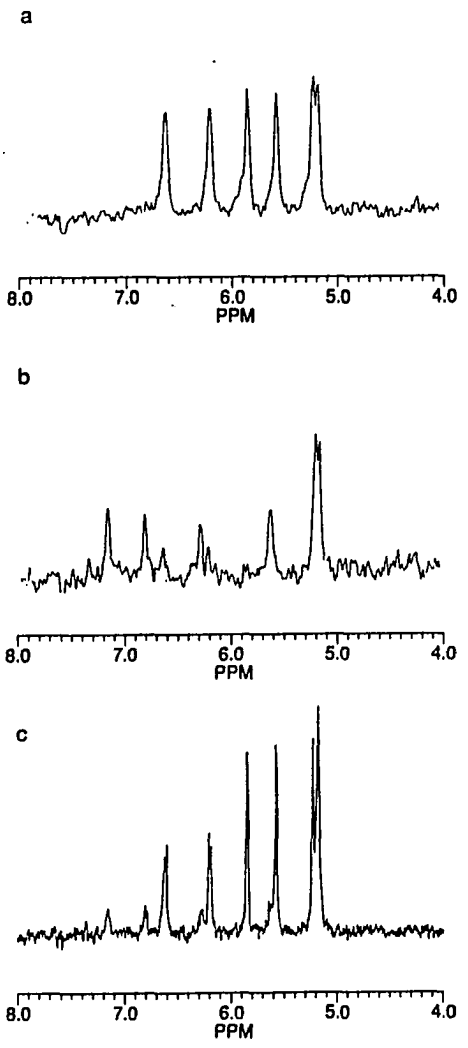


Figure 1. Flow ^{1}H NMR spectra (300 MHz): (a) obtained by mixing 10^{-3} M 3-(trimethylammoniummethyl)-2-(trimethylsilylmethyl)thiophene iodide (**7**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate, 45 mL/min; number of scans, 701; pulse interval, 0.127 s; (b) of the recycled product mixture resulting from mixing 10^{-3} M 3-(trimethylammoniummethyl)-2-(trimethylsilylmethyl)thiophene iodide (**7**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate, 3 mL/min; number of scans, 1400; pulse interval, 0.254 s; (c) obtained by mixing 10^{-3} M 3-(trimethylammoniummethyl)-2-(trimethylsilylmethyl)thiophene iodide (**7**) in CD_3CN with 6 x 10^{-3} M TBAF in CD_3CN; flow rate, 0.1 mL/min; number of scans, 9600; pulse interval, 1.016 s

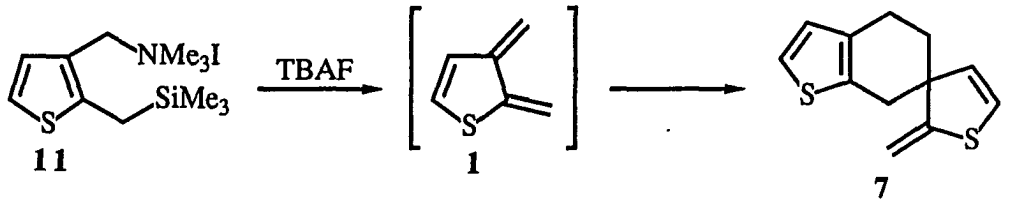
DISCUSSION

The fluoride ion induced 1,4-elimination from 3-(trimethylammonium-methyl)-2-(trimethylsilylmethyl)thiophene iodide (**11**) provides an excellent source of 2,3-dimethylene-2,3-dihydrothiophene (**1**). Rapid and quantitative formation of the reactive species is necessary for its kinetic[16] and flow NMR[5-7,17] studies.

A λ_{max} of 345 nm was reported for **1** in an Ar matrix at 16 K.[15] The λ_{max} value of 350 nm obtained in our studies is thus consistent with that from the matrix isolation study.

The second order rate constant obtained for the dimerization of **1** (k = 10.8 M^{-1} s^{-1} at 25 ° C) places its reactivity between that of o-xylylene (**2**) (k = 9940 M^{-1} s^{-1} at 25 ° C)[16] and 2,3-dimethylene-2,3-dihydrofuran (**3**) (k = 0.036 M^{-1} s^{-1} at 25 ° C).[4] For these three systems, the activation entropies (Table 2) are all similar (~-30 eu) while the activation enthalpies (Table 2) are slightly different, and bear out the differences in reactivity: **2** (3.5 kcal mol^{-1}) is more reactive than **1** (7.3 kcal mol^{-1}) which is more reactive than **3** (10.2 kcal mol^{-1}).

The flow NMR results indicate that **1** is indeed generated by fluoride ion induced 1,4-elimination from **11** and its ^1H NMR spectrum (6.61, 6.20, 5.86, 5.59, 5.24, and 5.19 ppm) can be observed (Figure 1a). Upon formation, **1** dimerizes forming a single [4 + 2] dimer (Figure 1b) which is believed to be **7**. The flow NMR spectrum of this

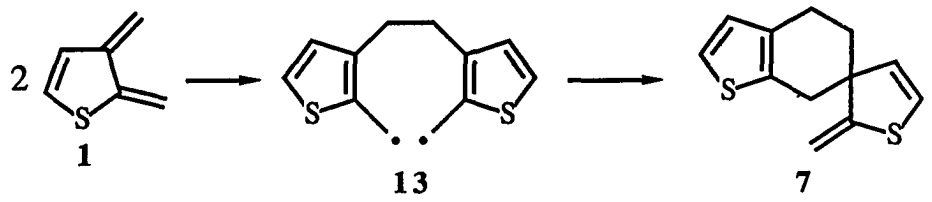


11 **1** **7**

dimer is similar to the spectrum of the dimer obtained by Huang from the preparation of **1** by flash vacuum pyrolysis.

The flow NMR spectrum obtained at a very slow flow rate (0.1 mL/min) (Figure 1c) is of such high quality that coupling between the two protons on the ring of **1** (6.61 and 6.20 ppm) can be observed. The fact that a small amount of the final dimer (**7**) can be seen in this spectrum confirms that **1** is proceeding directly to this dimer.

It is likely that this stable dimer (**7**) arises by a stepwise dimerization of **1** involving a diradical intermediate (**13**). The activation parameters for **1** are similar



1 **13** **7**

to those of **3**, for which good evidence exists for its stepwise dimerization mechanism involving a diradical intermediate.[4,21] The differences in reactivity between **1**, *o*-xylylene (**2**), and 2,3-dimethylene-2,3-dihydrofuran (**3**) are due to differences in the stability of the respective diradicals in the dimerization reaction. The stability of these diradical intermediates is determined by their RE stability (benzene RE > thiophene RE > furan RE).[1]

The dimer product obtained from the dimerization of **3** is its [4 + 4] dimer.[22] However, the dimerization of **1** leads to the formation of its [4 + 2] dimer (**7**) in analogy to **2**, which forms primarily its [4 + 2] dimer (9:1 ratio of [4 + 2] to [4 + 4] dimers).[16,23] Perhaps very slight differences in the approach of the two monomer units or in the geometry of the diradical intermediate have profound effects on the outcome of the final product in the dimerization reactions of these reactive *o*-quinodimethanes.

EXPERIMENTAL SECTION

General Procedures

All flow NMR spectra were taken on a Bruker WM-300 spectrometer (300 MHz) using acetonitrile-d_3 (CD_3CN) as solvent and residual $NCCD_2H$ as internal standard (δ 1.93). CD_3CN was purchased from Cambridge Isotope Laboratories.

3-(Trimethylammoniummethyl)-2-(trimethylsilylmethyl)thiophene iodide (**11**) was provided by Professor A. M. van Leusen.

Tetrabutylammonium fluoride (TBAF)

The preparation of TBAF has been described in detail.[6]

General Procedure for Kinetic Measurements

Determination of λ_{max} for 2,3-dimethylene-2,3-dihydrothiophene (1)

A 1-cm path length UV-visible cell was charged with 2 mL of CH_3CN and 1 mL of 10^{-3} M **11** in CH_3CN. To this was rapidly added 60 μL of 0.1 M TBAF in CH_3CN, the cell shaken once, then quickly placed in the optical path of a Perkin-Elmer 320 UV-visible spectrophotometer. Spectra were recorded every 1 min in the spectral range 230-400 nm. From a plot of absorbance versus wavelength, a λ_{max} of 350 nm was determined.

Measurement of the rate constant for the dimerization of 2,3-dimethylene-2,3-dihydrothiophene (1)

A 1-cm path length UV-visible cell was charged with 1.0 mL of CH_3CN and 0.5 mL of 10^{-3} M **11** in CH_3CN. To this was rapidly added 0.5 mL of 0.1 M TBAF in CH_3CN, the cell shaken once, then quickly placed in the optical path of a Cary 219 spectrophotometer. With the monochromator set at 350 nm, the absorbance decay of

1 versus time was recorded. The experiment was performed at 10, 20, 30, and 40 °C using a circulating water bath to maintain the temperature of the UV-visible cell in the optical path of the spectrophotometer. The rate constants for dimerization were determined at each temperature from the slope of a plot of 1/conc. versus time.[18] The ε_{max} for **1** was calculated using the average of the maximum absorbance from three kinetic runs obtained at 30 °C.

General Procedure for Flow NMR

The flow NMR experiment has been described in detail.[6]

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APPENDIX

Table A-1. Kinetic data for 2,3-dimethylene-2,3-dihydrothiophene (**1**) measured at 10.2 °C in CH_3CN

Time, s	Absorbance	[1], M	$[1]^{-1}$, M^{-1}
60	1.7391	2.22E-04	4.51E+03
210	1.7092	2.18E-04	4.59E+03
360	1.1557	1.47E-04	6.78E+03
510	1.0999	1.40E-04	7.13E+03
660	1.0511	1.34E-04	7.46E+03
810	0.8659	1.10E-04	9.05E+03
960	0.8187	1.04E-04	9.57E+03
1110	0.7442	9.49E-05	1.05E+04
1260	0.7510	9.58E-05	1.04E+04
1410	0.6635	8.47E-05	1.18E+04
1560	0.6081	7.76E-05	1.29E+04
1710	0.5982	7.63E-05	1.31E+04
1860	0.5644	7.20E-05	1.39E+04
2010	0.5651	7.21E-05	1.39E+04
2160	0.5281	6.74E-05	1.48E+04
2310	0.4729	6.03E-05	1.66E+04
2460	0.4716	6.02E-05	1.66E+04
2610	0.4357	5.56E-05	1.80E+04
2760	0.4307	5.50E-05	1.82E+04
2910	0.4229	5.40E-05	1.85E+04
3060	0.4017	5.13E-05	1.95E+04
3210	0.3870	4.94E-05	2.03E+04
3360	0.3632	4.63E-05	2.16E+04
3510	0.4032	5.14E-05	1.94E+04
3660	0.3586	4.58E-05	2.19E+04
3810	0.3438	4.39E-05	2.28E+04
3960	0.3273	4.18E-05	2.39E+04
4110	0.3297	4.21E-05	2.38E+04
4260	0.3095	3.95E-05	2.53E+04
4410	0.3096	3.95E-05	2.53E+04
4560	0.2888	3.68E-05	2.71E+04
4710	0.2956	3.77E-05	2.65E+04
4860	0.2837	3.62E-05	2.76E+04
5010	0.2771	3.54E-05	2.83E+04
5160	0.2775	3.54E-05	2.82E+04

Table A-1 (continued)

Time, s	Absorbance	[1], M	$[1]^{-1}$, M^{-1}
5310	0.2739	3.49E-05	2.86E+04
5460	0.2543	3.24E-05	3.08E+04
5610	0.2430	3.10E-05	3.23E+04
5760	0.2541	3.24E-05	3.08E+04
5910	0.2605	3.32E-05	3.01E+04

Table A-2. Kinetic data for 2,3-dimethylene-2,3-dihydrothiophene (**1**) measured at 19.1 °C in CH_3CN

Time, s	Absorbance	[1], M	$[1]^{-1}$, M^{-1}
0	1.5797	2.02E-04	4.96E+03
100	1.3276	1.69E-04	5.90E+03
200	1.1419	1.46E-04	6.86E+03
300	1.0144	1.29E-04	7.73E+03
400	0.9155	1.17E-04	8.56E+03
500	0.8420	1.07E-04	9.31E+03
600	0.7584	9.68E-05	1.03E+04
700	0.6936	8.85E-05	1.13E+04
800	0.6525	8.32E-05	1.20E+04
900	0.6055	7.73E-05	1.29E+04
1000	0.5658	7.22E-05	1.39E+04
1100	0.5309	6.77E-05	1.48E+04
1200	0.5044	6.44E-05	1.55E+04
1300	0.4727	6.03E-05	1.66E+04
1400	0.4526	5.77E-05	1.73E+04
1500	0.4285	5.47E-05	1.83E+04
1600	0.4079	5.20E-05	1.92E+04
1700	0.3899	4.97E-05	2.01E+04
1800	0.3714	4.74E-05	2.11E+04
1900	0.3585	4.57E-05	2.19E+04
2000	0.3431	4.38E-05	2.28E+04
2100	0.3320	4.24E-05	2.36E+04
2200	0.3145	4.01E-05	2.49E+04
2300	0.3058	3.90E-05	2.56E+04
2400	0.2976	3.80E-05	2.63E+04
2500	0.2845	3.63E-05	2.76E+04
2600	0.2760	3.52E-05	2.84E+04
2700	0.2707	3.45E-05	2.90E+04
2800	0.2621	3.34E-05	2.99E+04
2900	0.2557	3.26E-05	3.07E+04
3000	0.2488	3.17E-05	3.15E+04
3100	0.2364	3.02E-05	3.32E+04
3200	0.2325	2.97E-05	3.37E+04
3300	0.2264	2.89E-05	3.46E+04
3400	0.2186	2.79E-05	3.59E+04
3500	0.2141	2.73E-05	3.66E+04
3600	0.2089	2.67E-05	3.75E+04
3700	0.2058	2.63E-05	3.81E+04
3800	0.1982	2.53E-05	3.95E+04
3900	0.1978	2.52E-05	3.96E+04
4000	0.1917	2.45E-05	4.09E+04

Table A-3. Kinetic data for 2,3-dimethylene-2,3-dihydrothiophene (**1**) measured at 29.4 °C in CH_3CN

Time, s	Absorbance	[1], M	$[1]^{-1}$, M^{-1}
60	1.7083	2.18E-04	4.59E+03
160	1.0712	1.37E-04	7.32E+03
260	0.9255	1.18E-04	8.47E+03
360	0.7767	9.91E-05	1.01E+04
460	0.6757	8.62E-05	1.16E+04
560	0.6044	7.71E-05	1.30E+04
660	0.5413	6.91E-05	1.45E+04
760	0.4868	6.21E-05	1.61E+04
860	0.4847	6.18E-05	1.62E+04
960	0.4231	5.40E-05	1.85E+04
1060	0.4044	5.16E-05	1.94E+04
1160	0.3954	5.04E-05	1.98E+04
1260	0.3704	4.73E-05	2.12E+04
1360	0.3254	4.15E-05	2.41E+04
1460	0.3075	3.92E-05	2.55E+04
1560	0.3059	3.90E-05	2.56E+04
1660	0.2916	3.72E-05	2.69E+04
1760	0.2854	3.64E-05	2.75E+04
1860	0.2577	3.29E-05	3.04E+04
1960	0.2663	3.40E-05	2.94E+04
2060	0.2268	2.89E-05	3.46E+04
2160	0.2246	2.87E-05	3.49E+04
2260	0.2241	2.86E-05	3.50E+04
2360	0.2159	2.75E-05	3.63E+04

Table A-4. Kinetic data for 2,3-dimethylene-2,3-dihydrothiophene (**1**) measured at 40.7 °C in CH_3CN

Time, s	Absorbance	[**1**], M	$[\mathbf{1}]^{-1}$, M^{-1}
60	1.3963	1.78E-04	5613.4
160	0.9224	1.18E-04	8497.4
260	0.7116	9.08E-05	11014.6
360	0.6108	7.79E-05	12832.4
460	0.5265	6.72E-05	14887.0
560	0.4791	6.11E-05	16359.8
660	0.3835	4.89E-05	20438.1
760	0.3987	5.09E-05	19658.9
860	0.3302	4.21E-05	23737.1
960	0.3039	3.88E-05	25791.4
1060	0.2756	3.52E-05	28439.8
1160	0.2552	3.26E-05	30713.2
1260	0.2340	2.99E-05	33495.7
1360	0.2241	2.86E-05	34975.5
1460	0.2253	2.87E-05	34789.2
1560	0.2078	2.65E-05	37719.0
1660	0.2015	2.57E-05	38898.3
1760	0.1831	2.34E-05	42807.2
1860	0.1626	2.07E-05	48204.2

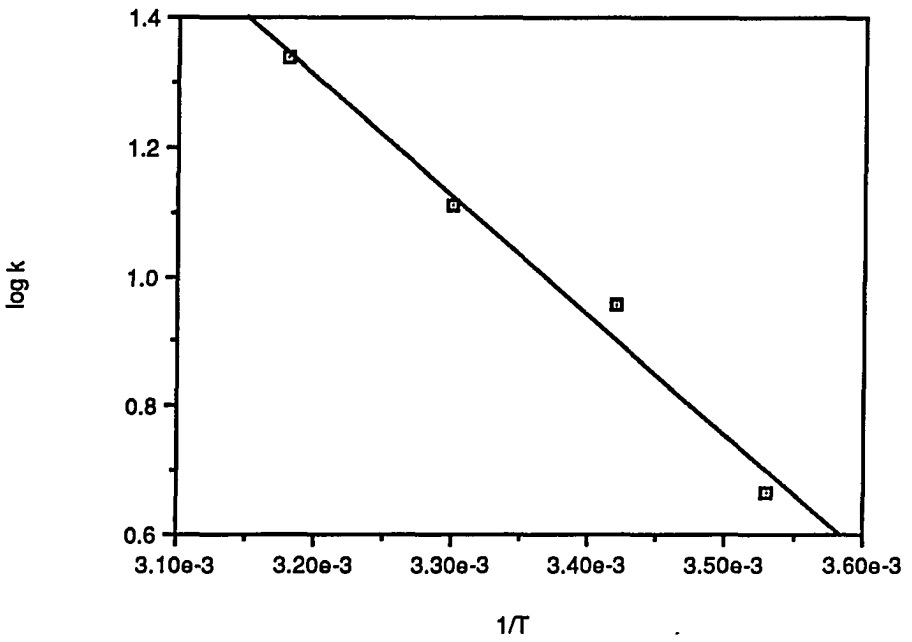

Figure A-1. Plot of log k versus 1/T for 2,3-dimethylene-2,3-dihydrothiophene (**1**)

GENERAL SUMMARY

Section 1 describes the successful flow ^{1}H NMR observation of 1,2-dimethylene-1,2-dihydronaphthalene, and also *o*-xylylene in the presence of its stable [4 + 2] and [4 + 4] dimers. These reactive *o*-xylylenes were generated by fluoride ion induced 1,4-elimination from the appropriate precursors. This study establishes the usefulness of flow NMR in the study of species too reactive to be observed by conventional NMR methods. The flow-NMR apparatus and technique are described in detail in this section.

In Section 2, a series of alkyl substituted *o*-xylylenes is studied to investigate the steric effect of alkyl groups adjacent to the exocyclic methylenes. It is found that methyl or *i*-propyl groups in the 3 and/or 6 position of 1,2-xylylenes have only a small effect on the dimerization rate and dimer products obtained. The ^{1}H NMR spectra were obtained for each of these substituted *o*-xylylenes by flow NMR.

Section 3 describes the use of the flow NMR technique in the first successful ^{1}H NMR observation of benzocyclobutadiene. From this ^{1}H NMR spectrum, it is concluded that benzocyclobutadiene is a very reactive, nonaromatic polyene whose structure is best described as being like that of an *o*-quinodimethane. Fluoride ion induced 1,2-elimination from 2-trimethylsilylbenzocyclobutenyl-1 mesylate provides an excellent source of benzocyclobutadiene in this study. Synthesis of this precursor is presented in this section as well.

The ^{1}H NMR spectrum, obtained by flow NMR, and dimerization rates of 1,2-dimethylene-1,2-dihydrothiophene are presented in Section 4. The rate of dimerization obtained for this reactive *o*-quinodimethane places its reactivity

between the highly reactive *o*-xylylene and the less reactive 1,2-dimethylene-1,2-dihydrofuran.

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