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The chemistry of thiophene-based bis-(*p*-quinodimethanes): an approach to macrocycles

ABSTRACT

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Introduction

p-Quinodimethanes are an important class of organic reactive intermediates, first proposed by Szwarc in a report describing the pyrolysis of *p*-xylene.¹ Based on the observed pyrolysis products, the parent *p*-quinodimethane (*p*-xylylene, **1**) was suggested as the key reactive intermediate. *p*-Xylylene (**1**) and various derivatives have been studied extensively since Szwarc's initial report, in part due to the commercial importance of poly-*p*-xylylene macromolecules.^{2,3} Their unique electronic properties have also been the subject of many theoretical investigations.⁴ A variety of methods have been used to generate *p*-xylylene (**1**)⁵ and it has also been characterized by spectroscopic methods.⁶



Both compounds **2** and **3** are well known heterocycle-based pquinodimethanes. These heterocyclic systems have been generated by a variety of methods⁷ and both the furan- and thiophene-based p-quinodimethanes (**2** and **3**) have been characterized by spectroscopic methods. Like the p-xylylene (**1**), compounds **2** and **3** are reactive intermediates shown to form oligomers and polymers in solution. The heterocycle-based *p*-quinodimethanes are conveniently generated by flash vacuum pyrolysis of the corresponding heterocyclic ester. For example, the thiophene-based *p*-quinodimethane (**3**) is formed by elimination of benzoic acid from ester **4** (Scheme 1).^{7b} The observation of cyclophane products (i.e., **5** and **6**) is consistent with the formation of diradical intermediates. Some time ago, we described the generation of bis(furan-based) *p*-quinodimethanes (**8**) by the pyrolysis of diester substrates (**7**).⁸ The bis(furan-based) *p*-quinodimethanes were found to give products consistent with diradical chemistry, including products from disproportionation, cleavage, and coupling reactions. The chemistry also gives macrocyclic products from 15 to 22 carbons in fair yields (23–58%) from the bis(furan-based) *p*-quinodimethanes.

Bis-2,5-dimethylene-2,5-dihydrothiophenes have been generated in the gas-phase by flash vacuum

pyrolysis (FVP) of diester precursors. These thiophene-based bis-(p-quinodimethanes) are shown to

undergo reactions leading to macrocycles. The conversions are consistent with a mechanism involving

cyclic diradical intermediates followed by disproportionation of the radical centers.



Based on these results, we have sought to extend the chemistry to bis(thiophene-based) *p*-quinodimethanes. As described below, convenient methods have been developed for the synthesis of the precursor thiophene diesters. Flash vacuum pyrolysis of the thiophene diesters has provided macrocycles in fair yields. These pyrolysis products have been further transformed to cyclopentadecane and trace quantities, the natural product *pL*-muscone.



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Scheme 1. Chemistry of the thiophene-based para-quinodimethane (3).

Results

Our initial goal was the preparation of a thiophene diester having a saturated hydrocarbon chain. This was accomplished readily through the well-known nucleophilic chemistry of the 2-thienyl anion (Scheme 2).⁹ Thus, thiophene provides the bis-(2-thienyl) pentane (**8**) from 1,5-dibromopentane in 52% isolated yield. Subsequent formylation gives the dialdehyde (**9**, 93% yield). Reduction and acylation (97%, two steps) then provides the desired thiophene diester (**10**).

In addition to the saturated carbon tether of **10**, thiophene diesters were prepared with a carbonyl and hydroxyl groups in the bridging chain. Starting from the readily prepared dienone (**11**),¹⁰ both the ketone (**13**) and alcohol (**14**) are prepared. The syntheses first involve catalytic hydrogenation of the olefinic bonds to give the 3-pentanone derivative (**12**, Eq. 1). Derivative **13** is prepared by protection of the carbonyl group of **12** as the 1,3-dioxolane and subsequent formylation/reduction/acylation with a deprotection step (see Supporting information). Alcohol **14** is prepared by initial reduction of the carbonyl group of **12** and protection as the *tert*-butyldimethylsilyl ether and subsequent formylation/reduction/acylation/



Scheme 2. Synthesis of pyrolysis substrate.



The pyrolysis experiments were done using previously described methods.^{6a} Briefly, the thiophene substrate (100–500 mg) is placed in a sample chamber and sublimed (ca. 10^{-5} Torr vacuum) through a hot quartz (640 °C) containing quartz chips. The resulting products exit the pyrolysis tube and deposit in a liquid nitrogen cooled trap. When all of the substrate has been sublimed, chloroform is distilled into the trap and the products are isolated. The pyrolysis gives two equivalents of acetic acid, so anhydrous sodium carbonate is added to the trap. The solution is then filtered and the product mixture is subjected to analysis and product purification.

When compound **10** is subject to FVP, three products are observed. Like the analogous furan-based system, the thiophene diester (10) provides a 15-carbon macrocycle (15) as the major product in 45% yield (Scheme 3). NMR analysis indicates that the olefin is formed with cis stereochemistry. Another significant product is the acyclic aldehyde 16, isolated in 21% yield. The yield of this product (16) varies somewhat between experiments, however. Analysis of the crude pyrolysate also shows the presence of a minor amount of the thiophene-based p-quinodimethane (3). Within 24 h, the presence of **3** is negligible. A good NMR spectrum of **3** is obtained by spectral subtraction of the crude product mixture NMR spectrum from immediately after pyrolysis and the spectrum from 24 h later. With ¹H NMR peaks at δ 6.5, 5.3, and 5.0, there is a good match with the published spectrum of the thiophene-based p-quinodimethane (3).¹¹ Presumably, this reactive thiophenebased *p*-quinodimethane undergoes its known oligomerization reactions. None of the expected products from 3 could be isolated, however.

When the ketone **13** and alcohol **14** derivatives are subject to pyrolysis, the expected macrocyclic products are formed. In the case of substrate **13**, the enone **17** is formed as the major product, but the vinyl-substituted product **18** is also formed in considerable amount. Both products are consistent with the formation of the thiophene-based bis-(*p*-quinodimethanes), vide infra. The alcohol **14** likewise gives the macrocyclic alcohol (**19**) from pyrolysis (Scheme 4).

The observed products are consistent with the formation of bis (thiophene-based) *p*-quinodimethanes. Thus, compounds **10** and **14** undergo pyrolysis to give the bis(thiophene-based) *p*-quinodimethanes **19–20** and two equivalents of acetic acid (Scheme 5). As described previously, these elimination reactions occur through a series of steps.^{7b} The acetate group migrates across the thiophene ring by two symmetry allowed [3,3] sigmatropic bond migrations. This places the acetate in position to undergo the β -elimination of acetic acid—generating the thiophene-based *p*-quinodimethane unit. Alternatively, pseudopericyclic rearrangements and ester eliminations have been suggested for similar reactions.¹² With formation of the bis(thiophene-based) *p*-quinodimethanes (**20**), cyclization leads to diradical intermediates **21–22**. This



Scheme 3. Pyrolysis products from diester 10.



Scheme 4. Pyrolysis products from diesters 13 and 14.

intramolecular reaction is similar to the proposed dimerization of the thiophene-based *p*-quinodimethane **3** and formation of the diradical (Scheme 1). The cyclic diradicals **21–22** then undergo hydrogen atom transfer to provide the final olefin products **15** and **18**. In these systems, the ring-fused [2,2]-cyclophanes—radical coupling products from **21** and **22**—were not detected. In total, the transformation of the thiophene diesters to the macrocycle products requires eight independent reaction steps. NMR analysis of the crude product mixtures did not show the presence of any of the bis(thiophene-based) *p*-quinodimethanes—suggesting the entire cyclization occurs in the gas-phase during pyrolysis.

In the pyrolysis of thiophene diester **10**, two acyclic products were observed. The acyclic aldehyde (**16**) was isolated and a low concentration of the thiophene-based *p*-quinodimethane **3** was detected by NMR. It is unlikely that these products are formed from the bis(thiophene-based) *p*-quinodimethane **19**. It is proposed these by-products are formed by bond homolysis and subsequent reaction steps (Scheme 6). Thus, cleavage of the C–O bond gives radical **23** and an acetoxy radical (or methyl radical and CO₂). Radical **23** can provide a route to both minor products: benzylic C–C bond cleavage gives intermediate **3** and compound **16** is formed by hydrogen atom shift and cleavage of the acetate group.

In the pyrolysis of diester **13**, products **17** and **18** are formed and both compounds may explained by the involvement of a bis (thiophene-based) *p*-quinodimethane and subsequent diradical intermediate (Scheme 7). Elimination of the acetic acid provides the bis(thiophene-based) *p*-quinodimethane (**25**) and ring-closure



Scheme 5. Proposed mechanism for the formation of macrocycles 15 and 18.



Scheme 6. Proposed mechanism for the formation of side-products 3 and 16.



Scheme 7. Proposed mechanism for the formation of side-products 17 and 18.

leads to the diradical **26**. The observed products are thought to arise from two competing reaction paths. As in the previous systems, hydrogen atom migration (route a) gives macrocyclic enone (**17**). Extrusion of carbon monoxide (route b) from the 1,5-diradical leads to formation of the two vinyl groups in product **18**. Unfortunately, this latter process is somewhat favorable at the high temperatures of pyrolysis and it limits the yield of the enone product (**17**, 35% yield).

The above pyrolysis reactions provide novel thiophene-containing 15-carbon macrocycles. Thiophene rings may be removed by treatment with Raney-nickel,¹³ providing a potential route to saturated macrocycles. Thus, compound **15** is treated with Raneynickel in ethanol and cyclopentadecane (**27**) is formed in good yield (Scheme 8). Enone **17** reacts with methyl cuprate to provide compound **28**. Subsequent reduction with Raney-nickel gives *dl*muscone (**29**).¹⁴ However only trace quantities of the natural product could be prepared—identified by GCMS spectral match—due to the low recovery of the previous steps.

Conclusions

In summary, we have prepared macrocyclic products in fair yields by flash vacuum pyrolysis of thiophene diesters. A



Scheme 8. Conversion to cyclopentadecane (27) and DL-muscone 29.

mechanism is proposed involving formation of bis(thiophenebased) *p*-quinodimethanes in the gas-phase and cyclization to diradical intermediates. A disproportionation of the radical centers provides the observed macrocycles. In combination with nickelcatalyzed reduction, the chemistry represents a novel method for preparing large, saturated carbocycles.

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Supplementary data

Supplementary data (experimental procedures and characterization data for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet-let.2016.04.062.

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