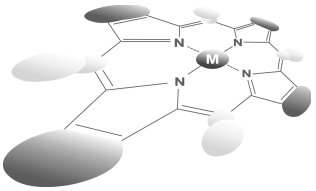
Journal of Porphyrins and Phthalocyanines
J. Porphyrins Phthalocyanines 2023; **27**: 1394–1397
DOI: 10.1142/S1088424623500992

Published at https://www.worldscinet.com/jpp/



Expanding pnictogen-assisted self-assembly of disulfide macrocycles to include heteroarenes

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Received 17 February 2023
Accepted 20 April 2023

Dedicated to Prof. Jonathan L. Sessler on the occasion of his 65th birthday

ABSTRACT: New routes to the formation of macrocyclic molecules are of high interest to the supramolecular chemistry community and the chemistry community at large. Here we describe the incorporation of heterocyclic core units into discrete macrocycles via the utilization of a pnictogen-assisted self-assembly technique. This method allows for the rapid and efficient formation of discreet macrocyclic units from simple dithiol precursors in high yields with good control over macrocycle size. Up to this point, this technique has been reported on primarily benzylic thiol systems with very little incorporation of endohedral heteroatoms in the resulting assemblies. This study demonstrates the effective incorporation of heterocyclic core molecules allowing for the formation of a more functional cavity, resulting in the formation and crystallization of novel furan- and thiophene-based disulfide dimer and trimer macrocycles, respectively, that are isolated from a range of other larger discrete macrocycles that assemble as well. These disulfide macrocycles can be trapped as their more kinetically stable thioether congeners upon sulfur extrusion.

KEYWORDS: self-assembly, dynamic covalent chemistry, dithiol, disulfide, thiophene, furan, pnictogen, antimony, macrocycle.

INTRODUCTION

Macrocyclic molecules are of great continuing interest to the scientific community. Fascination with macrocyclic structures emerged from the synthesis of crown ethers in 1967 by Pederson [1], who went on to be awarded the 1987 Nobel Prize along with Cram and Lehn for their work on synthetic macrocycles and cryptands [2, 3]. These types of molecules have more recently found widespread uses in many fields. For example, in materials design and sensing, a few highlights include macrocycles within stimuli-responsive supramolecular polymers [4], and within "imprint and report" sensing arrays for genetic modifications [5]. The ability to synthesize further functional macrocycles will continue to be of interest as the need for more highly tunable and complex molecular systems and functional materials concomitantly increases along with the expanding diversity of synthetic techniques available to chemistry.

When considering how to design and synthesize more varied types of molecular assemblies, dynamic covalent chemistry (DCvC) is a particularly powerful tool. DCvC utilizes the dynamic nature of reversible reactions, such as thiol-disulfide exchange or aldol exchange, to allow for the formation and breaking of reversible covalent bonds, essentially selecting the most thermodynamically stable product [6]. This methodology, paired with the self-assembly of macrocycles, allows for the synthesis of multiple macrocyclic species in a single reaction, with control of product distribution afforded through the manipulation of variables such as temperature,

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concentration, external stimuli, and/or the presence of templating species [7–10].

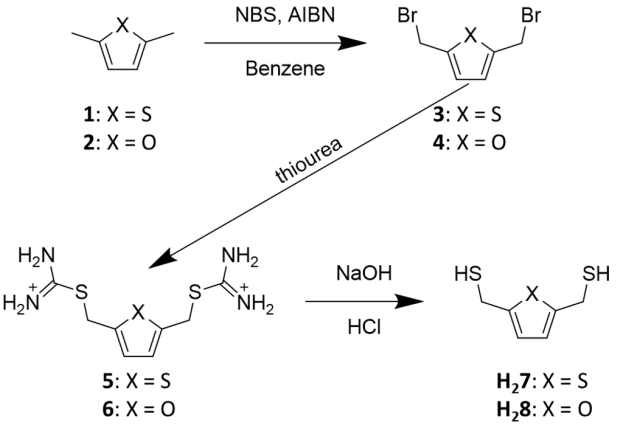
We previously reported a facile method for synthesizing disulfide- and thia-cyclophanes using a pnictogen-directed thiol self-assembly pathway [10]. By using a thiolate-coordinating pnictogen (Pn), generally $SbCl_3$, in a mildly oxidative environment, families of discrete disulfide cyclophanes can be isolated in less than an hour with no presence of disulfide oligomers or polymers, which can predominate in the absence of the pnictogen additive. Further, these disulfide cyclophanes can undergo sulfur extrusion giving thiacyclophanes and fully hydrocarbon cyclophanes [9]. Recently, we have also shown that these methods apply to a wide range of di- and trithiols, including ligands without an aromatic core, longer arm lengths, and core heteroatom incorporation [11]. Notably lacking from our prior investigations on the scope of these self-assembly reactions are dithiols featuring simple heterocyclic cores such as furan and thiophene.

Testing the extent to which these methods function when incorporating heterocyclic aromatic species, this work describes the use of these Pn-directed self-assembly methods to synthesize families of thiophene- and furan-containing disulfide macrocycles. These aromatic, heteroatom-containing motifs have found utility in drug design [12,13], optoelectronics [14–16], and functional polymeric materials [17–19]. These desirable properties can be further exploited when incorporated into structured macrocycles where preorganization and macrocyclization favor the endohedral functionality of the heteroatoms, leading us to explore assembling these structures utilizing Pn-directed self-assembly.

RESULTS AND DISCUSSION

To examine the efficacy of our synthetic methodology on more functional core units, we chose to synthesize dithiols that could serve as analogues to well-known heterocyclic macrocycles upon dynamic covalent self-assembly. Due to their ubiquity and inherent functional utility, we chose thiophene and furan dithiols to form macrocycles with similar endohedral functionality to crown ethers, thia-crown ethers, calixfurans, and calixthiophenes. These analogues also provided the double benefit of having readily available starting materials in the form of 2,5-dimethylthiophene (**1**) and 2,5-dimethylfuran (**2**). These starting molecules could then be transformed into the subsequent dithiol self-assembly building blocks of 2,5-bis(mercaptomethyl)thiophene ($\mathbf{H_27}$) and 2,5-bis(mercaptomethyl)furan ($\mathbf{H_28}$) following a series of steps modified from previously reported syntheses in literature (Scheme 1) [11, 20].

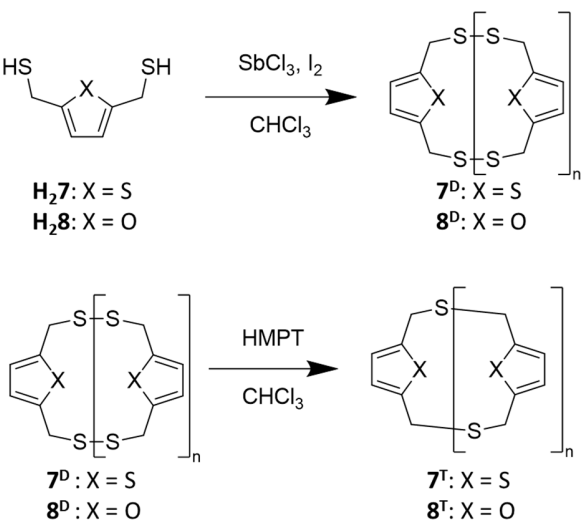
These substrates could then undergo Pn-directed self-assembly to form discrete disulfide macrocycles. The macrocycles are formed ranging from dimer to hexamer



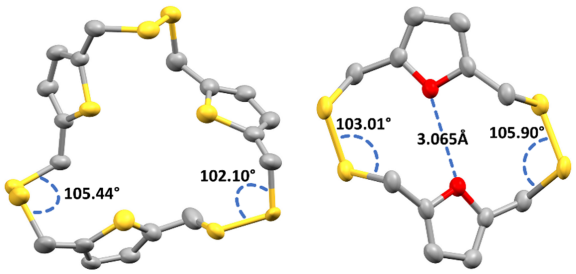
Scheme 1. Synthesis of dithiol macrocyclic precursors $\mathbf{H_27}$ and $\mathbf{H_28}$.

and isolated in 53% and 89% combined yields for the thiophene and furan cores, respectively (Scheme 2). These crude mixtures were then purified by gel permeation chromatography to identify and isolate the individual oligomeric macrocycles present. After separation, the thiophene product mixture was found to contain 39% dimer, 26% trimer, 9% tetramer, 3% pentamer and 2% hexamer ($\mathbf{7^D_2}$-$\mathbf{7^D_6}$). The furan product mixture was found to contain 47% dimer, 17% trimer, 8% tetramer, 7% pentamer, and 6% hexamer ($\mathbf{8^D_2}$-$\mathbf{8^D_6}$). From these distributions of oligomers, the dimer and trimer of each were further examined.

X-ray quality single crystals of the 2,5-thiophenedimethanethiol trimer ($\mathbf{7^D_3}$) and 2,5-furandimethanethiol dimer ($\mathbf{8^D_2}$) were grown from vapor diffusion of hexanes into chloroform revealing the macrocycles crystallize in



Scheme 2. Synthesis of disulfide macrocycles from dithiol precursors and further sulfur extrusion to thioether macrocycles; "D" denotes disulfide linker, "T" denotes thioether. $\mathbf{7^D}$ is formed in a 53% overall yield (39% $\mathbf{7^D_2}$, 26% $\mathbf{7^D_3}$, 9% $\mathbf{7^D_4}$, 3% $\mathbf{7^D_5}$, and 2% $\mathbf{7^D_6}$). $\mathbf{8^D}$ is formed in an 89% overall yield (47% $\mathbf{8^D_2}$, 17% $\mathbf{8^D_3}$, 8% $\mathbf{8^D_4}$, 7% $\mathbf{8^D_5}$, and 6% $\mathbf{8^D_6}$).



(a) (b)

Fig. 1. X-ray crystal structures of disulfide thiophene trimer macrocycle $\mathbf{7^D_3}$ (a) and disulfide furan dimer macrocycle $\mathbf{8^D_2}$ (b).

the $P2_12_12_1$ (thiophene) and *Pbcn* (furan) space groups (Figs. 1a and 1b).

The C-S-S-C dihedral angles of the thiophene trimer ($\mathbf{7^D_3}$) adopt a slightly strained conformation with dihedral angles between 102.10° and 105.44° (90° disulfide dihedral angle preferred) [21]. The furan dithiol dimer ($\mathbf{8^D_2}$) also exhibits a similar level of strain in its disulfide bonds with C-S-S-C dihedral angles of 103.01° and 105.90°. The furan disulfide macrocycle exhibits a high degree of organization in the solid state, packing into well-defined rows oriented along alternating furan rings with 3.947Å between the faces of the furan rings. This could indicate the presence of weak π-stacking in the solid state between furans of adjacent macrocycles.

These structures can be sulfur extruded to form thioethers using hexamethylphosphorous triamide HMPT, (aka Tris(dimethylamino)phosphine, Scheme 2).

This not only increases the persistence of the macrocycle by removing the labile disulfide bonds, but it also increases the rigidity of these molecules. The furan disulfide trimer ($\mathbf{8^D_3}$) and thiophene disulfide dimer and trimer macrocycles ($\mathbf{7^D_2}$, $\mathbf{7^D_3}$) were subjected to these conditions to form their respective thioether macrocycles ($\mathbf{7^T_3}$, $\mathbf{8^T_2}$, $\mathbf{8^T_3}$, see supporting information for all synthetic details and characterization information). The formation of these species was verified utilizing mass spectrometry (see ESI) and ^{1}H NMR spectroscopy (Fig. 2).

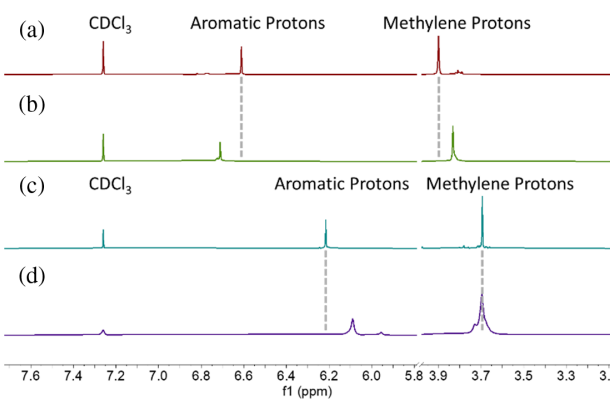


Fig. 2. ^{1}H NMR spectra of the sulfur extrusion of $\mathbf{7^D_2}$ (a) to $\mathbf{7^T_2}$(b), and $\mathbf{8^D_3}$ (c) to $\mathbf{8^T_3}$(d). Key peak shifts corresponding to the aromatic and methylene protons have been indicated.

Future work will explore extruding sulfur from the thioethers to form saturated and unsaturated hydrocarbons, further increasing their functionality and similarity to well-known furan- and thiophene-containing macrocycles. These heterocyclic macrocycles might also provide an excellent test motif for investigating templation and other directed self-assembly techniques by leveraging the endohedral heteroatoms.

CONCLUSION

In conclusion, we were able to successfully synthesize a series of new heteroaromatic macrocycles utilizing Pn-directed self-assembly ($\mathbf{7^D_n}$, $\mathbf{8^D_n}$ where n = 2–6). Of these, we were able to isolate and identify a novel thiophene disulfide dimer and trimer ($\mathbf{7^D_2}$, $\mathbf{7^D_3}$) as well as novel dimeric and trimeric disulfide furan macrocycles ($\mathbf{8^D_2}$, $\mathbf{8^D_3}$). We also saw evidence of larger oligomeric species present in the formation of the disulfides in both the thiophene and furan macrocycles. These novel disulfides were then converted into thioether macrocycles ($\mathbf{7^T_2}$, $\mathbf{8^T_2}$, $\mathbf{8^T_3}$) increasing the persistence of the resulting molecules by "trapping" the labile disulfide linker as a kinetically stable thioether. Two of these macrocycles ($\mathbf{7^D_3}$ and $\mathbf{8^D_2}$) were further characterized by single crystal X-ray diffraction. The synthesis of these species demonstrates the continued substrate scope accessible utilizing Pn-assisted self-assembly methods. The ability to form these macrocycles will allow for future studies on tailor-made macrocycles utilizing the techniques exemplified in this paper as well as the study of templating agents in macrocycle formation. These molecules also hint at desirable solid-state properties as porous crystals, which could potentially be used in the development and formation of new porous materials. These studies add further functionality to this self-assembly technique and may expand the range of applications into host guest sensing systems and complex macrocycle formation utilizing benign reaction conditions as well as the study of porous materials for sensing and remediation.

Acknowledgments

This article is dedicated to Professor Jonathan L. Sessler on the occasion of his birthday. His mentorship and friendship have gone far beyond what one would expect from, originally, an undergraduate research advisor and DWJ hopes to have at least emulated that in some small way in paying it forward in his career. The table of contents image pays homage to Jonathan's love of chemistry, the outdoors, and his "play hard, work harder" mentality; the lead author is an avid outdoorsman and fisherman, and drew inspiration from these passions and his chemistry dissertation project to create the TOC image. This work was supported by US National Science Foundation

(NSF) grant CHE-2003928, and we thank the NSF for support in the form of an instrumentation grant (CHE-1625529). We also thank the NSF for the National Research Traineeship fellowships to LJZ and WAD (NSF DGE-2022168). This work was also supported by the Bradshaw and Holzapfel Research Professorship in Transformational Science and Mathematics to DWJ.

Supporting information

Additional data are given in the supplementary material. This material is available free of charge *via* the Internet at https://www.worldscientific.com/doi/suppl/10.1142/S1088424623500992

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