First Synthesis of Amphiphilic Octa-Alkylthio Substituted Tetraazaporphyrin Derivatives with Four Terminal Carboxylic Acid Groups

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First Synthesis of Amphiphilic Octa-Alkylthio Substituted Tetraazaporphyrin Derivatives with Four Terminal Carboxylic Acid Groups

By

Elmahdy Abdulhamied

A Thesis
Submitted to the Faculty of Graduate Studies
Through the Department of Chemistry and Biochemistry
in Partial Fulfillment of the Requirements for
the Degree of Master of Science at the

University of Windsor

Windsor, Ontario, Canada

2016

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First Synthesis of Amphiphilic Octa-Alkylthio Substituted Tetraazaporphyrin Derivatives with Four Terminal Carboxylic Acid Groups

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September 20, 2016
Author’s Declaration of Originality

I hereby certify that I am the sole author of this thesis and that no part of this thesis has been published or submitted for publication.

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Abstract

Reported here is the first octaalkylthiosubstituted tetraazaporphyrin (TAP) that contains four terminal carboxylic acid groups to generate an amphiphilic TAP for applications in LB films and self-organizing materials. A key step of the chosen synthesis is the step-wise alkylation of sodium maleonitriledithiolate, with two different alkyl bromides and has not been reported previously. The formation of dialkylthio-maleodinitrile side-products with two identical side-chains could not be avoided when the reactions were conducted in round bottom flasks (batch reactor) but selective monoalkylation and dialkylation was achieved in a flow reactor. However, the three different dialkylthio-maleodinitrile products could be separated by chromatography because of their different numbers of carboxylic ester groups. Conversion of the dialkylthio-maleonitrile derivatives to the TAP macrocyclic was achieved by the established Mg templated cyclization in refluxing propanol as long as the carboxylic acid groups are protected as esters. The obtained tetra-ester TAP was demetallated in acetic acid and hydrolyzed to the tetra-acid in warm potassium hydroxide following procedures previously reported for octa-acid TAPs.
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<tr>
<td>CHCl₃</td>
<td>Chloroform</td>
</tr>
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<td>¹³C NMR</td>
<td>Carbon 13 nuclear magnetic resonance</td>
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<td>DCM</td>
<td>Dichloromethane</td>
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<td>DMF</td>
<td>Dimethyl formamide</td>
</tr>
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1. Introduction

Porphyrrins and their numerous derivatives are materials of remarkable properties and are ubiquitously found in chemistry, materials science, physics, biology and medicine. They are the red color in blood (heme) and the green in leaves (chlorophyll); they are also excellent ligands that can coordinate with almost every metal in the Periodic Table. Grounded in natural systems, porphyrins are incredibly versatile and can be modified in many ways; each new modification yields derivatives, demonstrating new chemistry, physics and biology, with a vast array of medicinal and technical applications. In particular, porphyrins derivatives such as tetraphenylporphyrins (TPPs), tetraazaporphyrins (TAPs), and phthalocyanines (Pcs) (Figure 1) have important functions in natural systems and in technology because of their exceptional chemical, optical and electronic properties as molecules.\textsuperscript{1,2}

\[ \text{MTAP} \quad \text{MPc} \quad \text{MTPP} \]

\[ M = 2H, \text{ or Metal} \]

\textit{Figure 1.} Structure of porphyrin derivatives (MTAP, MTPP, MPc).
1.1 Applications of thin films of porphyrin derivatives (TPP, TAPs, and Pcs)

TPPs, TAPs, and Pcs have been tested for almost any technical application, which required the synthesis of numerous derivatives to optimize their properties for a specific task. For instance, self-assembled films of cobalt porphyrins with amine groups in ortho and para positions in Figure 2 have been formed to coat gold substrates. Both modified gold surfaces completely cover the charge transfer of a Fe(CN)₆³⁻/⁴⁻ redox couple in solution, indicating the layer is highly resistive in behavior, and the porphyrin with amine groups at ortho position displayed a higher charge-transfer resistance with a better protective behavior compared to the porphyrin with amine groups in para position.³

![Diagram of porphyrin molecules](image)

**Figure 2.** (a) 5,10,15,20-tetrakis-(2-aminophenyl) porphyrin-cobalt(II), and (b) 5,10,15,20-tetrakis-(4-amihenyl) porpyrin-cobalt(II), [Co(II)(T(p-NH2)PP)]³

Also, by Y. Feng *et al.*, effective corrosion inhibitor on iron surface have been applied by designing 5,10,15,20-tetraphenylporphyrin (TPP) and 5,10,15,20-tetra-(4chlorophenyl)porphyrin (TCIPP) (Figure 3) and used them to prepare adlayers on iron surface.⁴
Moreover, porphyrins and Pcs have displayed an essential potential photoelectric conversion, storage devices, and photo catalytic molecular devices by accumulating 5,10,15,20-tetrakis(p-N,N,N-trimethylanilinium)porphyrin tetraiodide (TAPPI) and copper sulfophthalocyanine (CuTsPc) (Figure 4) as the co-sensitizers on reduced graphene oxide (RGO)-based composite films. (The assembly and photoelectronic property of reduced graphene oxide/porphyrin/ phthalocyanine composite films). In addition, TAPs and Pcs show high sensitivity to different types of gases such as NH₃, NO₂ and C₂H₅OH vapor. The gas sensitivity responses of the PbTAP(t-Bu)₄ film (Figure 3) to NH₃, NO₂ and C₂H₅OH vapor showed that the responses of the thin films were in the following order: C₂H₅OH>NH₃>NO₂.
Numerous applications of TAPs and Pcs in optics, sensing, and catalysis require processing into thin films and the properties of these thin film materials importantly depend on the electronic interactions and supramolecular arrangements of the porphyrin macrocycles in the films. For various existing processing methods for the preparation of porphyrin thin films, solution processing has the advantage of being compatible with low cost printing methods as well as self-assembly and self-organization processes. Both self-assembly and self-organization may provide structural control at a molecular length that extends over macroscopic length scales because of the co-operative nature of these processes. In this filed, which is generating thin films by depositing the porphyrin derivatives onto substrates, there are various type of techniques widely used such as self-assembly monolayer (SAM), Langmuir-Blodgett (LB) monolayer films, vapour deposition, and spin-coating films. Herein, LB monolayer films techniques will represent because it will be used for generating a monolayer film of Tetraazaporphyrin (TAP) in this study.

1.2. Langmuir-Blodgett method for thin films of Porphyrin derivatives

1.2.1. Langmuir (L) and Langmuir-Blodgett (LB) Monolayer Films of Porphyrin Derivatives (TPP, Pcs, & TAPs)

The L and LB films technique have been made and presented for the first time by Irving Langmuir and Katharine Blodgett. By spreading a water insoluble molecules, usually amphiphilic compound, onto a water immiscible solvent (often CHCl₃) of sufficient vapor pressure, spreading is usually accomplished onto the water surface. The amphiphilic compound remains on water surface after the spreading solvent (CHCl₃) evaporates. Then, the amphiphilic compound condenses together by using movable barriers, and the surface pressure is monitored by a Wilhelmy plate. Initially, after the spreading, the monolayer phase is usually described as a two dimension (2-D) gas phase that will be compressed to 2-D expanded liquid phase. However, continued compression that increases surface pressure will cause a collapse of the monolayer surface and generates a multilayer film or third dimension (3-D).
Then, by transferring the monolayer at the air-water interphase onto a substrate, the LB films are generated. The substrate is usually dipped in and pulled out vertically at a controlled speed but this can also be accomplished at an angle other than 90°. Porphyrin derivatives frequently form rigid layers that are often subject to a horizontal transfer because they are difficult to transfer by a vertical dipping process.\(^7,\,^8\) This is accomplished by either lowering the water level to expose a substrate positioned underneath the air-water interface (submerged in the aqueous phase) or by contacting the monolayer with the substrate from the top and then lifting it up again (Langmuir–Schäfer transfer). Multiple transfers generate multilayers that are classified as X-, Y-, or Z-type structures for conventional amphiphilic compounds.

Porphyrin derivatives have been reported as Langmuir films by Alexander in 1937.\(^9\) After that, LB films of porphyrins and Pcs were studied in 1980s\(^10\) before the field became very large and a lot of work was published in the 1990s.\(^11,\,^12\)

For the preparation of porphyrin and Pc thin films, the LB technique has continued an important method even though more straightforward solution deposition techniques, such as solution casting, printing, and spin-coating, are more frequently applied for the deposition of thin films. Thin films of porphyrins and Pcs are required for many potential applications in organic electronics, non-linear optics, and gas sensing for which the LB technique still provides an unmatched control over structure at the supramolecular level if well-defined Langmuir monolayers are obtained at the air-water interface.

The formation of Langmuir- and LB-films with high structural order usually requires substituted porphyrin and Pc derivatives with a distinct amphiphilic character that form aggregate free solutions in water immiscible solvents. Self-organizing porphyrins and Pcs may show in-plane alignment of the macrocycles by forming, for example, columnar stacks that are oriented perpendicular to the dipping direction or parallel to the dipping direction (Figure 5) at the air-water interface.\(^8\)
Figure 5. Schematic representing of the proposed molecular orientation resulting from horizontal and vertical transfer techniques. Substrate dipping orientations are shown as well as an expanded view of the proposed molecular orientations.\textsuperscript{8}

Strong intermolecular interactions may promote self-organization but are also a constant problem because strongly aggregating and less soluble porphyrins and Pcs are difficult to spread into stable monolayers and transfer of the often rigid films onto substrates can be cumbersome. One way to solve this problem has been to process the compounds as mixtures with typical surfactants and other amphiphilic molecules. Del Cano \textit{et al}\textsuperscript{13} also reported that the stacking has been prevented by using the mixture of TiOPc with fatty acid and shown the face on orientation rather than edge on orientation.

The type, number, and location of peripherally attached side-chains and other substituents mainly control and effect on the properties and structures of Langmuir- and LB-films of porphyrins and Pcs. Only a few examples exist that take advantage of an axial attachment of functional groups to central metals such as Ti and Al\textsuperscript{14} (Figure 6). Porphyrin and Pc derivatives may accept one of two extreme orientations, the edge-on or flat-on orientations of the macrocycle, with regard to the interface. Of the two, the edge-on arrangement is common while a flat-on orientation is rare but most common is a tilted (edge-on) orientation of the macrocycle. Both of the type of orientation and intermolecular interactions between the macrocycle profoundly affect the stability, optical, and electronic properties of these films.
Porphyrans that do not contain longer flexible chains are usually insufficiently amphiphilic to form compressible monolayers at the air-water interface and their high propensity for spontaneous aggregation often generates 3D structures instead of monolayers. 3D structures have likely been generated if the determined lowest limiting area per molecule is significantly smaller than the minimum limiting area per tetraarylporphyrin of about 0.90 nm$^2$ determined for a monolayer with an edge-on orientation of the porphyrin ring. The maximum limiting area per tetraarylporphyrin is approximately 2.25 nm$^2$ for a face-on orientation of the porphyrin ring.

Capan et al$^{16}$ have reported a typical example for the formation of 3D structures at the air-water interface. They reported limiting areas per porphyrin of 0.50 nm$^2$, 0.43 nm$^2$, 1.15 nm$^2$ and 0.15 nm$^2$ for Langmuir films of 2,3,7,8,12,13,17,18-Octaethyl-21H,23H-porphyrine as metal free, iron(III) chloride, magnesium(II), and cobalt(II) derivatives (Figure 7). As have been displayed on AFM images (Figure 8), a transfer of these 3D Langmuir films onto different substrates at surface pressures between 10 and 20 mN m$^{-1}$ still generated rather smooth LB films. Uptake of Volatile Organic Compounds (VOCs) such as benzene, toluene and chloroform of these LB films was measured with using the Quartz Crystal Microbalance (QCM) technique and revealed a dependence of adsorption rates on the type of metal center and the polarity of the organic molecules in the vapor.
Figure 7. Structure of 2,3,7,8,12,1,17,18-Octaethyl-21H,23H-porphyrine as metal free or metallated by Co, Mg, FeCl.

Figure 8. Left: Pressure-Area isotherms of Octaethyl-porphyrin as metal free, iron(III) chloride, magnesium(II), and cobalt(II) derivatives designated as porp1-4 in the graph, respectively. Right: AFM image of metal free Octaethyl-porphyrine.\textsuperscript{17}

The formation of 3D (multilayer) structures frequently used for sensing applications such as the free-base 5,10,15,20-tetraphenylporphyrin especially for the sensing of oxidative gases\textsuperscript{18,19} to make compression of the free-base 5,10,15,20-tetraphenylporphyrin at the air-water interface as has been established by de Sales and Mansur and rationalized with the low amphiphilic character of tetraphenylporphyrin and its propensity to aggregate.\textsuperscript{20}

Without the existing of longer flexible side-chains, the amphiphilic character of tetraphenylporphyrin derivatives have been improved by using the incorporation of polar...
axial groups to the central metal. Langmuir monolayers and LB films of MTPP and their 1:1 molar mixtures with stearic acid have been characterized and investigated by Li et al.\textsuperscript{21} Moreover, in Figure 9, the formation of well-defined Langmuir monolayers has been confirmed for both porphyrin derivatives and their mixtures as displayed via the occupied surface areas per molecule and BAM images. BAM images show the formation of two domains for the mixture of stearic acid with TbOH-porphyrin at surface pressures below 19 mN/m even though the measured surface areas for the 1:1 mixtures of porphyrin with stearic acid agree with the predicted values of surface areas per molecule of the individual porphyrin and stearic acid. In addition, the mixtures of stearic acid with GdOH-porphyrinis not affected by the surfactant because the stronger and spontaneous aggregation between GdOH-porphyrin molecules. By polarized UV–Vis and transmission/reflection IR spectroscopy and by AFM, the transferred LB films were calculated. After doing these calculations, a small increase in average tilt angle of the porphyrin rings from about 50° for the pure porphyrins to about 60° for the mixtures have been suggested as has been shown in figure 9.

**Figure 9.** Left: Surface pressure area isotherms of (a) TbOHP, (a') 1:1 mixture of TbOH and stearic acid (SA), GdOHPand (b') 1:1 mixture of GdOHP and stearic acid. Right: Proposed arrangements of porphyrins and stearic acid in Langmuir and LB films of (a) TbOHP, (b) TbOHP\textbackslash stearic acid, (c) GdOHP, and (d) GdOHP\textbackslash stearic acid.\textsuperscript{21}

The attachment of long flexible side-chains that may also assistance to control over the alignment of the macrocycle are considered as the most common approach for
circumventing spontaneous aggregation and improving amphiphilic behavior of the porphyrin derivatives. An interesting example is 5,10,15,20-tetra-4-oxy (2-stearic acid) phenylporphyrin (TSPP) that has a common surfactant covalently linked to the macrocycle. Langmuir monolayers and LB films of its free base, Cu(II), and Mn(III)Cl derivatives (Figure 10) were studied by Liu et al.\textsuperscript{22} Surface pressure area isotherms and limited areas per molecule (2.71, 2.61 and 2.74 nm\textsuperscript{2}, respectively, Figure 11) are rather similar for all three porphyrins and suggest flat-on orientations of the macrocycle in all three cases. A flat-on orientation of the macrocycle is also in agreement with the expectation that the carboxylic acid groups are in contact with the water surface and the aliphatic side-chains are oriented orthogonally to and way from the water surface. However, BAM images suggest that no condensed monolayer is formed but domains and networks of aggregates with more complex structures. This may be less surprising considering that the attraction between carboxylic acid groups is higher than between carboxylic acid and water and the difficulty of the aliphatic chains to pack closely. Perhaps, more defined monolayers can be obtained at pH values of >10 for the subphase to ensure a complete deprotonation of all carboxylic acid groups.\textsuperscript{22} The formation of more complex molecular aggregates is also confirmed by polarized UV–Vis spectroscopy on transferred LB films as they reveal rather different tilt angles for the macrocycles of the three different compounds [31° for metal free, 0° for Cu(II), and 52° for Mn(III)Cl] although their similar limited surface areas in the Langmuir films. In addition, UV–Vis spectra confirmed differences in the π–π interactions between the three different types of porphyrins and the authors proposed the different packing structures given in Figure 11 for each type of porphyrin based on these measurements. However, packing structures A and C in particular are highly unlikely and the actual films more likely consist of small aggregates that arrange into larger aggregates or networks.
Figure 10. Structure of the free base, Cu(II), and Mn(III)Cl of TSPP.²³

Figure 11. (Left).\(p\pm A\) isotherms of TSPP, TSPPCu(II) and TSPPMn(III)Cl. (Right). Monolayer structures of TSPP (a), TSPPCu(II) (b) and TSPPMn(III)Cl (c).²³

By Choudhury et al, a related but less surfactant-like approach was chosen. Choudhury has attached different spacer chains with carboxylic acid end-groups to the 4-positions of the phenyl rings of a free base tetraphenylporphyrin.²⁴ Unexpectedly, all derivatives appear to prefer tilted edge-on orientations but with largely varying limiting mean surface
areas per molecule from 0.25 nm$^2$ to 0.87 nm$^2$ at a surface pressure of 20 mN m$^{-1}$. Clearly, values well below 0.9 nm$^2$ cannot be consistent with the presence of monolayers but, unfortunately, additional measurements that visualize the uniformity and 2D/3D structure of Langmuir and LB films, such as BAM and AFM images, were not provided. Interestingly, smaller surface areas per porphyrin below 0.6 nm$^2$, were observed for tetraphenylporphyrins with longer and more flexible spacer chains and larger surface areas for TPPs with shorter and inflexible spacer chains, which the authors explained with a restricted orientational flexibility of the porphyrin ring with short spacers that prevent them from acquiring a well-ordered and closed packed monolayer structure. Subsequent studies on related tetraazaporphyrins have shown that strong interactions between carboxylic acid groups may generate more complex 3D structures and nanoaggregates and should be considered for the interpretation of surface pressure area isotherms.$^{17}$

Tetraazaporphyrins (TAPs) have only been reported few times to study their LB properties even though their smaller size provides better solubility and weaker co-facial interactions in comparison to Pcs and TPPs. Both properties should lead to a more straightforward spreading and less spontaneous aggregation at the air-water interface. Also, the facile control of TAPs self-organization properties through the change of their central metal ion is considered as another potential advantage.$^{25-28}$

Most of TAPs that have been investigated are based on the 2,3,7,8,12,13,17,18-octa-thio substituted design except Ding et al$^{29}$ and Valkova et al$^{30}$ who did study the mixture of regioisomers of CuTAPs. Also, by attaching the TAPs with tert-butyl groups, the solubility increases and the spontaneous aggregation between TAP cores decrease. CuTAPs (Figure 12) reveals two separated phases; (1) is 1.11 nm$^2$ area per molecule below a surface pressure of 7mN m$^{-1}$, and (2) is 0.66 nm$^2$ above 10mN m$^{-1}$ (Figure 13). The UV–Vis spectra of solution and LB films shows slight electronic interactions between the macrocycles and a limiting area per molecule of 0.66 nm$^2$ which decides the TAPs are forming an edge-on orientation of the macrocycle in a dense monolayer (Figure 13).
Figure 12. A mixture of regioisomers of copper _II_. tetra-_tert-butyl-_5,10,15,20-tetraazaporphyrin.29

Figure 13. Surface pressure-area isotherm of CuTAP(t-Bu) at the air-water interface at room temperature (left) and its UV–VIS spectra in chloroform solution and as 20-layer LB films deposited at 25 and 7 mN/m.29

In 1993, the mesomorphic copper derivative of 2,3,7,8,12,13,17,18-octakis(octylthio)-5,10,15,20-tetraazaporphyrin was the first LB studies on TAPs that reported via Bonosi et al. (Figure 14). However, a homogeneous monolayers have not been obtained at the air-water interface because of the strong self-aggregation of the TAP into columnar stacks.31 While a stable and reproducible surface films were obtained with mixtures of the TAP and stearic acid that could be transferred onto quartz plates treated with
dimethyldichlorosilane. By UV–Vis and ESR spectroscopies, the LB films has been analyzed and confirmed the presence of columnar stacks in the LB films of mixtures with stearic acid, despite a 20-fold excess of the latter, but no overall orientational order was deduced.

![Structure of new discotic metallomesogens](image)

**Figure 14.** Structure of new discotic metallomesogens of 2,3,7,8,12,13,17,18-octakis(alkylthio)-5,10,15,20-tetraazaporphyrin (TAP).\(^{31}\)

Ricciardi *et al.* have investigated Langmuir and LB films by attachment of only methyl groups in 2,3,7,8,12,13,17,18-Octakis(methylthio)-5,10,15,20-21H,23H-tetraazaporphyrin.\(^{32}\) The compound forms floating islands of randomly oriented three-dimensional aggregates at the air-water interface but, surprisingly, shows some preferential edge-on alignment when transferred onto hydrophobized quartz and glass substrates by the Langmuir-Shäfer technique according to polarized UV–Vis spectroscopy and ellipsometry. Rather than monolayers, both sets of results approve the ordered deposition of three-dimensional aggregates and the presence of floating islands was confirmed by BAM (Figure 15) and UV–Vis reflection spectroscopy (Figure 16) from the floating film on the water surface at different fixed surface pressures after equilibrium.
Low surface pressures = (0.5, 2, and 5 mN\textpermm, respectively)

High surface pressures = (15, 30, and 40 mN\textpermm, respectively)

Figure 15. BAM images of floating islands of three-dimensional aggregates generated by HO\textsubscript{2}TAP at low and high surface pressures.$^{32}$

Figure 16. Absolute reflection spectra (Left) and normalized reflection spectra (Right) from the floating film on the water surface at different fixed surface pressures after equilibrium.$^{32}$
Designing of TAP molecules that form stable monolayers with face-on orientation of the macrocycle by the attachment of polar and amphiphilic side-chains have been attempted by Eichhorn et al.\textsuperscript{33} Attachment of ethylene glycol chains produces compounds 3,6-dioxahexylthio and 3,6,9 trioxadecylthio chains and their metal complexes (Co(II), Ni(II), Cu(II), Zn(II)) that likely orient flat-on at the air-water interface with the ethylene glycol chains being submerged in the water layer. However, according to grazing incidence XRD, an edge-on orientation has shown in the transferred LB films (Figure 17). On the other hand, the strong dependence of the surface pressure-area isotherms on the metal ion complexed by the macrocycle (2H, Co, Ni, Cu, Zn) and the chain length of the ethylene glycol (Figure 17) was unexpected. Both of these factors also altered the self-organization of these compounds into columnar mesophases, which certainly also affects their behavior at the air-water interface.

![Figure 17](image.png)

**Figure 17.** (Left) Pressure–area isotherms of Langmuir films with defined collapse pressure (Cu73), ill-defined collapse pressure (Co52), and no obvious collapse pressure (H73) and (Right) Change from the face-on to the edge-on orientation of Cu52 during the transfer from the L film to the LB film.\textsuperscript{33}

The attachment of eight aliphatic side-chains with terminal carboxylic acid groups in compounds octa-acid and -hydroxyl tetraazaporphyrins[H\textsubscript{2}TAP(CH\textsubscript{2})\textsubscript{n}COOH or H\textsubscript{2}TAP(CH\textsubscript{2})\textsubscript{n}OH] was more successful to generate more amphiphilic free metal TAPs.\textsuperscript{17} A C10 spacer chain provided sufficient amphiphilic character for stabilizing a flat-on orientation at surface pressures up to 40mN/m while shorter aliphatic spacer chains and
terminal hydroxyl groups were not sufficient. The conformation of the TAP is proposed to be spider-like based on the calculated limited area per molecule and film thickness measured by ellipsometry (Figure 18).

![Brewster angle microscopy images of the Langmuir film of H2TAP(CH2)10COOH at different surface pressures and film thicknesses (determined by ellipsometry) and proposed changes in idealized conformations depending on surface pressure.](image)

Kayal et al. reported the first formation of cross-linked Langmuir films by azide/acetylene click chemistry. Compounds H$_2$TAP with eight terminal azide and acetylene groups were reacted at the air-water interface with copper (II) acetate and sodium ascorbate as catalyst system dissolved in the subphase. Cross linking was rather efficient but, unfortunately, the TAP molecules preferentially formed three-dimensional structures rather than a monolayer because of their low amphiphilicity. Surprisingly, some of these compounds with shorter spacer chains displayed columnar mesophases and could be thermally cross-linked in their mesophases.

1.2.2. The L and LB Characterization Methods
Since the 1990s the LB technique, like many others, has enormously benefited from easier accessible characterization methods. Earlier LB work often solely relied on pressure-area isotherms for the characterization of compressibility and structures of Langmuir films while contemporary routine use of Brewster angle microscopy (BAM)
and ellipsometry provides pivotal information on film uniformity and thickness, respectively. Grazing incidence XRD and IR measurements at the air-water interface have also become more common but cannot yet be considered routine investigations. The same characterization techniques are also applied to the LB-film after transfer onto a substrate but, in addition, LB films may be studied by typical surface characterization methods such as atomic force microscopy (AFM), scanning tunneling microscopy (STM), and X-ray diffraction (XRD).

1.3. Synthesis of Tetraazaporphyrins

In 1937, tetraazaporphyrins (TAPs) were synthesized for the first time by Linstead and Cook by reacting diphenylmaleodinitrile and magnesium powder at 275 °C for 10 minutes. The yield of magnesium octaphenyl TAP was 92%. They also synthesized the first metal-free TAP by boiling the magnesium octaphenyl TAP for 2 hours in 85% formic acid (Figure 19).

Today’s most common synthetic approach was also developed by Linstead and Whalley. They reported the cyclization of different maleodinitriles to TAPs by reacting them with magnesium n-propoxide in n-propyl alcohol to give the magnesium tetraazaporphyrins at room temperature after 2 days under the exclusion of light. The
metal-free TAP was obtained as a dark purple powder after treatment with acetic acid in 74%.

Surprisingly, reactions of maleodinitriles with other metal cations and alcohols have failed to generate the metallated TAP but the reason for the specificity towards Mg and n-propanol is not fully understood. The following mechanism for the tetraazaporphyrin formation in magnesium n-propoxide/n-propanol mixtures has been proposed by Linstead et al (Figure 20).

![Figure 20. The mechanism of the substituted tetraazaporphyrins formation.](image)

While the formation of the magnesium TAP has been achieved by only one method, its demetalation to the metal-free TAP has been achieved with a range of different conditions but all of them rely on a Bronsted acid. Cook and Linstead used formic acid for 2 hours whereas Linstead and Whalley used acetic acid for 1-5 hrs. Ricciardi et al used concentrated trifluoroacetic acid (CF₃COOH) and ice water while Eichhorn et
al\textsuperscript{38} demetallated a MgTAP by using hot acetic acid (80°C) for about 1 hour. More recently, Ahmida et al\textsuperscript{17} obtained the metal free TAP with hot acetic acid within 1-2 hours year and Kayal et al\textsuperscript{34} also used hot acetic acid but it was a 5:1 mixture with THF and required for 8 hours at 80 °C.

The differences between metal-free and metallated TAPs are easily recognized by their characteristic UV/VIS spectra, which is used for monitoring demetalation and metalation processes. The metallated TAPs have a higher symmetry than the metal-free derivatives which is why they show only two intense absorptions at ~670 nm (Q-Bands). In contrast, the metal-free derivative has a lower symmetry due to a splitting of the Q bands into peaks at ~710 nm and ~690 nm. However, both of the metallated and free-metal TAPs have one Soret band at 370 nm (Figure 21).\textsuperscript{39, 40}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{uv_vis_absorption.png}
\caption{UV/VIS absorption spectra of metallated and demetallated TAPC5COOCH3 (THF, 2.0 x 10^{-5}M and 2.25 x 10^{-5}M).\textsuperscript{39}}
\end{figure}
1.4. The Objective of Thesis

The objective of this thesis is to develop more amphiphilic TAPs that can be easily processed by the LB technique and give a face-on orientation at the air-water interfaces. To accomplish this, the preparation of more amphiphilic TAPs is necessary that requires the attachment of at least two different types of substituents, one of hydrophilic and one of hydrophobic character.

Herein, the synthesis of the first type of low-symmetry TAP containing four hydrophobic alkyl chains and four alkyl chains terminated with polar carboxylic acid groups is reported. The footprint of a flat-on TAP macrocycle and the four carboxylic acid groups is about equal and the proposed arrangement of the TAP at the air-water interface is shown in Figure 19.

![Figure 19. The proposed arrangement of the TAP at the air-water interface.](image)

**Figure 22.** The structure and proposed conformation at the air-water interface of the first type of low-symmetry TAP containing four hydrophobic alkyl chains and four alkyl chains terminated with polar carboxylic acid groups.

It is expected that the 4 alkyl-carboxylic acid groups (hydrophilic) are sufficient to pin down the TAP core at the water surface, especially if the carboxylic acid groups are deprotonated at high pH. The 4 alkyl groups (hydrophobic) are expected to increase the solubility in less polar organic solvents such as CHCl₃ and to promote the face-on
orientation in Langmuir and LB films. An increase in solubility of in the spreading solvent (CHCl₃) should also minimize aggregation that causes the formation of 3D structures.

2. Experimental Methods

Chemicals: All reagents and solvents were purchased from Sigma-Aldrich and Fluka Chemical Companies and used as received unless otherwise stated. 1-Propanol and methanol were dried over 4 Å and 3 Å molecular sieves, respectively, whereas dry and air-free dichloromethane, tetrahydrofuran, and diethyl ether were obtained from a solvent purification system (Innovative Technology Inc. MA, USA, Pure-Solv 400). Silica gel 60 (35-70 mesh ASTM, from EM Science, Germany) was used for column chromatography and Silica Gel 60 aluminum backed sheets (EM Science, Germany) for thin layer chromatography.

Instrumentation: 1H-NMR and 13C-NMR spectra were obtained on Bruker NMR spectrometers (DRX 500 MHz and DPX 300 MHz). The residual proton signal of the deuterated solvent (usually chloroform (CDCl₃)) was used as a reference signal and multiplicities of the peaks are given as s = singlet, d = doublet, t = triplet, and m = multiplet. Coupling constants are given in Hz and only calculated for 1st-order systems. Data are presented in the following order: integration, multiplicity, and coupling constant. Fourier Transform Infrared spectra (FT-IR) were obtained on a Bruker Vector 22 as KBr pellets or thin films on KBr windows. Relative peak intensities and shapes in IR are abbreviated as vs = very strong, s = strong, m= medium, w = weak, and br = broad. Mass spectrometry measurements were performed by Kirk Green at the Regional Center for Mass Spectrometry (McMaster University) and by Janeen Auld at the departmental MS facility on a Waters XEVO G2-XS TOF (University of Windsor). UV/VIS absorption spectra were run on a Varian Cary 50 Conc UV-visible spectrophotometer. Elemental analysis was performed on a Perkin Elmer 2400 combustion CHNS analyser at the Centre for Catalysis and Materials Research at the University of Windsor.
Scheme 1: List of all conversions of MDN to MDN derivatives reported in this thesis.

2.1. Synthesis of disodium 1,2-dicyanoethylene-1,2-dithiolate (MDN)

Scheme 2: Reaction of carbon disulfide with sodium cyanide to disodium 1,2-dicyanoethylene-1,2-dithiolate.
By following the literature procedure by Davidson and Holm\textsuperscript{41}, \(\text{CS}_2\) (24.5 mL, 0.41 mol) was added drop wise to NaCN (20 g, 0.4 mol) in 125mL of DMF at 0\(^\circ\)C under an inert atmosphere. The reaction was left stirring for 3 hours until all NaCN had dissolved and a red-brownish precipitate was obtained. Reagent grade isobutyl alcohol (300 mL) was added to the mixture and heated to dissolve the brownish solid. The hot solution was filtered to remove insoluble impurities; the red-brown filtrate was collected and cooled in an ice bath for 24 h to yield a brownish crystalline precipitate. The precipitate was washed with dry diethyl ether (130 mL) to remove dark colored impurities and then dissolved in DI water (800 mL) and stored in the fridge (2 \(^\circ\)C and dark) for 24 hours. All precipitated sulphur and impurities were filtered off and the brownish to yellow filtrate was concentrated until brownish to red crystals precipitated. The red crystals were dried in vacuum for 3 hours and then dissolved in anhydrous boiling ethanol (100 mL). The hot solution was filtered immediately to remove insoluble impurities and the filtrate was cooled to room temperature. Addition of dry diethyl ether (250 mL) precipitated the product as small yellow-brown crystals that were washed with diethyl ether. The filtrate was left in the freezer overnight and checked for more precipitate of product. This recrystallization procedure was repeated another 3 times until the obtained crystals of MDN were bright yellow. A high purity of the MDN and the absence of any solvents are important for increasing the shelf life of this intermediate.

Yield: 11.82 g (52\%) of MDN as bright yellow crystals.

\(\text{IR (cm}^{-1})\): 2262, 2185 (\(\nu(\text{C}≡\text{N})\)), 1639, 1617 (m, \(\nu(\text{C}≡\text{C})\)), 1446, 1428, 1119 (s, \(\nu(\text{C-S})\)), 1057 (s, \(\nu(\text{S-Na}+)\)).

\(\text{\(^{13}\text{C NMR, (DSMO)}\)}\ \delta\): (C=S, 126.54ppm), (C=C, 124.15ppm).

\(^{13}\text{C NMR, (DSMO)}\)\: (C=S, 126.54ppm), (C=C, 124.15ppm).
Figure 23. IR spectrum of disodium 1,2-dicyanoethylene-1,2-dithiolate (MDN).

Figure 24. $^{13}$C NMR of the disodium 1,2-dicyanoethylene-1,2-dithiolate (MDN).
2.2. Synthesis of (Z)-4,5-diisocyno-2,2,7,7-tetramethyl-3,6-dithia-2,7-disilaoct-4-ene (MDN-1)

![Reaction Scheme](image)

**Scheme 3:** Reaction of trimethylchlorosilane with MDN.

Trimethylchlorosilane (3 mL, 22mmol) was added to a yellow solution of MDN (2g, 10.7mmol) in THF (100 mL) under nitrogen. The color of the mixture immediately changed to red but remained unchanged when stirred for 24h. Precipitated NaCl was filtered off and the filtrate was concentrated to half the volume before hexanes (50 mL) were added to precipitate the product. Precipitation was completed in the fridge overnight and the precipitate was filtered off. The precipitate was again dissolved in a minimum of THF and precipitated by the addition of hexanes before dried in vacuum. The obtained red-brown solid was barely soluble in chloroform but sufficiently soluble in DMSO for NMR measurements. Unfortunately, neither proton nor carbon NMR spectra showed any of the characteristic peaks of the MDN and silane.

![Figure 25. $^{13}$C NMR of reaction mixture.](image)
2.3. Synthesis of (Z)-5,6-diisocyano-3,3,8,8-tetraisopropyl-2,9-dimethyl-4,7-dithia-3,8-disiladec-5-ene (MDN-2)

\[
\text{MDN-2} \quad \xrightarrow{\text{THF/24h}} \quad \text{NC} \quad \text{S} \quad \text{Si} \quad \text{NC} 
\]

**Scheme 4**: Reacting of Triisopropylchlorosilane with MDN.

Triisopropylchlorosilane (3.3 mL, 15 mmol, 2.2 eq) were added to a yellow solution of MDN (2 g, 10.7 mmol) in THF (100 mL) under nitrogen. The mixture slowly turned red while it was stirred for 24 h. Reduction of the volume to 50% aided the precipitation of NaCl that was filtered off before hexanes (50 mL) were added to the filtrate for the precipitation of the product. Precipitation was completed by keeping the mixture in a freezer for 4-5 hours to give a yellow-orange solid. Again, the obtained solid required DMSO as solvent for NMR measurements but neither \(^1\text{H}\) nor \(^{13}\text{C}\) NMR contained characteristic peaks of the expected product.

![Figure 26. \(^{13}\text{C}\) NMR of reaction mixture.](image)
2.4. Synthesis of (Z)-S,S'-1,2-diisocyanoethene-1,2-diyl diethanethioate (MDN-3)

**Reaction 1**

\[
\begin{align*}
\text{NC}_2\text{S} & \quad \text{SNa} \quad + \quad 2 \quad \text{O} \\
\text{NC} & \quad \text{SNa} \quad \xrightarrow{\text{THF, 2h, 0-25°C}} \quad \text{NC} \quad \text{SO} \\
\text{MDN-3} & \quad + \quad 2 \quad \text{NaCl}
\end{align*}
\]

**Scheme 5:** Reacting of acetic acid chloride with MDN.

Acetic acid chloride (3.6 g, 64 mmol, 2.2 eq) was added drop-wise to a solution of MDN (4.0 g, 21 mmol) in THF (115 mL) at 0 °C. The yellow mixture immediately turned from yellow to dark orange, then to red-brown, and eventually to dark brown when warmed to room temperature after one hour. Ethyl acetate was added and this mixture was extracted with water three times. The ethyl acetate layer was dried over sodium sulfate, filtered, and finally evaporated to give a dark brown solid, which was recrystallized from DCM by the addition of hexanes.

TLC studies confirmed the presence of at least 3 compounds that were all stable as confirmed by 2D TLC. IR and \(^1\text{H}\) NMR confirmed the presence of expected peaks (e.g. the C≡N, C=C, and CO stretching modes in IR at 2234, 1629, and 1716 wavenumbers, respectively, and an intense singlet at 1.97 ppm for the methyl groups in \(^1\text{H}\) NMR). However, \(^{13}\text{C}\) NMR and the mass spectra were not consistent with the expected product structure.
**Figure 27.** IR spectrum of reaction mixture.

**Figure 28.** $^{13}$C NMR of reaction mixture.
Figure 29. Mass spectrum of reaction mixture.

Reaction 2

\[
\text{N=SNa} + 2 \text{ tert-Butanol} \rightarrow 35 ^\circ \text{C, 2 mL THF} \rightarrow \text{MDN-3} \rightarrow \begin{cases} \text{NaO} & \text{o} \\ \text{O} & \text{N} \end{cases} + \begin{cases} \text{C-ONa} \\ \text{CH}_2\text{Na} \end{cases}
\]

Scheme 6: Reaction of MDN with isopropenyl acetate.

Isopropenyl acetate (0.15 mL, 1.16 mmol, 2.2 eq) was added to a solution of MDN (100 mg, 0.53 mmol) in dry tert-butanol (10 mL) and THF (3 mL) at 35 °C under nitrogen.
The colour of the mixture immediately changed from yellow to dark orange and finally to red after 10 hours of stirring. TLC tests on silica and RP-18 stationary phase were inconclusive but IR spectra of a dried portion revealed characteristic peaks for the stretching vibrations of $\text{C=N}$ (2217), $\text{C=O}$ (1711), and $\text{CH}$ (2970) (Figure 30). The mixture was evaporated to dryness, dissolved in EtAc, and salts were precipitated out by the addition of twice the volume of hexanes. The filtrate was concentrated to give another precipitate, filtered, and finally evaporated for a chromatographic purification. Chromatographic separation of these compound mixtures on silica with DCM and EtAc gave several fractions with different $R_f$ values but the anticipated product structure was not confirmed by IR and NMR analysis (Figs. 31-35). IR spectra confirm the presence of $\text{C=N}$ and $\text{C=O}$ and NMR the presence of the methyl group but the $\text{S-C=O}$ carbon is expected at around 190 ppm in $^{13}$C NMR but no signal is observed in this range. It is possible, that $\text{C=O}$ peak observed in the IR spectrum is caused by remaining EtAc.

Figure 30. IR spectrum of crude product mixture.
Figure 31. IR spectrum of fraction A.

Figure 32. $^{13}$C NMR of fraction A.
Figure 33. $^1$H NMR of fraction A.

Figure 34. IR spectrum of fraction B.
Reaction 3

The reaction was repeated with a larger amount of MDN (500 mg, 2.68 mmole) but otherwise identical conditions. Analysis of the crude product mixture confirmed the presence of stretching absorptions of C≡N, C=O, and C-H in the IR spectra (Figure 36) but signals for the thioester and cyano groups were missing in the $^{13}$C NMR spectrum (Figure 37). For this reason a separation of the product mixture was not attempted.

Figure 35. $^{13}$C NMR of fraction B.
Figure 36. IR spectrum for crude mixture of reaction 3.

Figure 37. $^{13}$C NMR for crude mixture of reaction 3.
2.5. Synthesis of (Z)-S,S'-1,2-diisocyanoethene-1,2-diyl dihexanethioate (MDN-4)

Scheme 7: Reacting Hexanoic acid chloride with MDN.

Hexanoic acid chloride (2 mL, 1.8 mmol, 2.2 eq) was added to a solution of MDN (100 mg, 0.53 mmol) and triethylamine (2 mL) in THF (10 mL) at 0 °C under nitrogen. The reaction mixture immediately changed colour from yellow to dark orange and finally dark green (Figure 38).

After 24 hrs of stirring the colour of the mixture was red. The mixture was filtered to remove precipitated NaCl and concentrated to 10% of the original volume. TLC tests of this mixture revealed only one yellow spot at R_f = 0.52 (silica, EtAc/hexanes) that was stable according to 2D TLC. The mixture was purified by column chromatography (silica, EtAc/hexanes 1:7) to give two fractions with R_f values of 0.6 and 0.5, respectively. Both fractions lacked the signal of the cyano group but showed a peak for the ester group (C=O stretch) in the IR spectra (Figures 39&40). $^{13}$C NMR confirmed the absence of the desired product.
2.6. Synthesis of (Z)-1,2-bis-pentylthio-1,2-ethene-dicarbonitrile (MDN-5)

Reaction 1

![Chemical Reaction Diagram]

**Scheme 8:** Reaction of MDN with 1-bromopentane in methanol.
Bromopentane (2 mL, 11.9 mmol, 2.2 eq) was added to a solution of MDN (1.0 g, 5.3 mmol) in dry methanol (50 mL, filtered through activated aluminum oxide) and stirred at room temperature for 24 hours. The colour of the reaction mixture changed from yellow to red and some precipitate occurred (likely NaBr). TLC analysis (silica, EtAc) revealed 3 spots with $R_f$ values of 0.13, 0.4, and 1.0. The mixture was filtered, the filtrate was evaporated to remove all the MeOH, and the residue was purified by column chromatography on silica with EtAc as mobile phase. The first collected fraction ($R_f = 0.4$) contained the product a reddish-brown oil after evaporation of the solvent.

Yield: 0.7 g (46%)

$^1$H-NMR (CDCl$_3$): 3.082 (4H, t, 7.5 Hz), 1.695, (4H, p, 16.5 Hz), 1.358 (8H, m, 6.6 Hz), 0.883 (6H, t, 6.9 Hz).

$^{13}$C-NMR (CDCl$_3$): (C=C, 120.90), (C≡N, 112.05), (SCH$_2$, 34.99), (CH$_2$ for b,c,d, 30.48, 29.52, 22.04), and (CH$_3$ (e), 13.82).

IR (cm$^{-1}$): (C≡N, 2209.71), and (CH aliphatic, around 2929.14).

Figure 41. IR spectrum of MDN-5 (Fr. 1).
Figure 42. $^1$H NMR spectrum of MDN-5 (Fr1).

Figure 43. $^{13}$C NMR spectrum of MDN-5 (Fr1).
Reaction 2

Scheme 9: Reaction of MDN with 1-bromopentane in THF.

Bromopentane (2.2 mL, 18.0 mmol, 2.2 eq) was added to a solution of MDN (1.5 g, 8.0 mmol) in dry THF (60 mL) and stirred at room temperature for 24 hours. The colour of the reaction mixture changed from yellow to red and some precipitate occurred (likely NaBr). TLC analysis (silica, EtAc) revealed 3 spots with R_f values of 0.13, 0.4, and 1.0. The mixture was filtered, the filtrate was evaporated to remove all the THF, and the residue was purified by column chromatography on silica with EtAc as mobile phase as described above.

Yield: 0.3 g (22%) of reddish-brown oil

^{13}C-NMR (CDCl3): (C=C, 120.94), (C≡N, 111.95), (SCH2, 34.91), (CH2 for b,c,d, 30.38, 29.40, 21.92), and (CH3 (e), 13.67).
Figure 44. $^{13}$C NMR of MDN-5 (fractions 1 and 2).

2.7. Synthesis of (Z)-S-1,2-dicyano-2-(pentylthio)vinyl ethanethioate (MDN-6)

Scheme 10: Reaction of MDN with one equivalent of isopropenylacetate to sodium (Z)-2-(acetylthio)-1,2-dicyanoethenethiolate and subsequent reaction with one equivalent of bromopentane to MDN-6.

Isopropenylacetate (0.39 mL, 3.12 mmol, 1.2 eq) was added drop-wise to a solution of MDN (500 mg, 2.6 mmol) in tert-butanol (20 mL) and THF (2 mL) and stirred for 24 hours at 40 °C under nitrogen. The colour of the mixture changed from yellow to light red but a larger amount of MDN appeared to be unreacted (yellow solid). The reaction temperature was increased to 50 °C and then bromopentane (0.37 mL, 3.0 mmol, 1.2 eq) was added. The mixture was stirred for another 24 hours to give a red solution, which was filtered and
evaporated. The residue was dissolved in a mixture of EtAc/hexanes 1:2, filtered to remove insoluble salts, and evaporated again (IR is given in Figure 45). A brown oil remained that gave two spots on TLC (silica, EtAc/hexanes 1:2) with R<sub>f</sub> values of 0.9 and 0.6. The mixture was separated by column chromatography (silica, EtAc/hexanes 1:5) to give 4 fractions of which only fraction 1 had the colour of the product. IR, <sup>1</sup>H and <sup>13</sup>C NMR of fraction 1 (Figures 46 to 48) confirmed the product to be the dipentane substituted MDN while the product with one thioacetate group was not obtained.

<sup>13</sup>C NMR (CDCl<sub>3</sub>)δ: C=C (121.70), C≡N (111.78), a, b, c, d, e (34.74, 30.91, 29.31, 21.81, 13.58)

![Figure 45. IR spectrum of reaction mixture](image-url)
Figure 46. IR spectrum of fraction 1 (is MDN-5).

Figure 47. $^1$H NMR of fraction 1 (is MDN-5).
2.8. Synthesis of (Z)-5,5′-(1,2-dicyanoethene-1,2-diyl)bis(sulfanediyl)bis(pentane-5,1-diyl) diacetate (MDN-7)

**Reaction 1**

![Chemical structure](image)

Scheme 11: Reaction of MDN with 5-bromopentyl acetate in methanol.

5-Bromopentylacetate (0.18 mL, 1.05 mmol, 2.2 eq) was added to a solution of MDN (100 mg, 0.53 mmol) in MeOH (10 mL) and stirred for 24 hours at room temperature under nitrogen. The dark orange reaction mixture was filtered and evaporated to give dark red oil. IR, $^1$H and $^{13}$C NMRs of this crude product confirmed the structure of the expected product, although no peak of the C=C
stretching vibration and only a tiny peak for the C≡N stretching vibration are visible in the IR (Figures 49-51).

Yield: 130 mg (60%) of red oil.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\): 3.962 (4H, \(t\), 6.3 Hz), 3.036 (4H, \(t\), 7.2 Hz), 1.945 (6H, \(s\)), 1.670 (4H, \(p\), 7.5 Hz), 1.620 (4H, \(p\), 6.6 Hz), 1.441 (4H, \(p\), 6.6 Hz)

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\): C≡N (111.5 ppm), C=C (121.5 ppm), C=O (170.11 ppm), e (63.42 ppm), a(34.23), and d,b,c,f (32.84, 27.44, 24.28, 20.19 ppm)

IR (m\(^{-1}\)): C=C (1454.77), C=O (1733.64), CH (2940.47)

![Figure 49. IR spectrum of MDN-7.](image)
Figure 50. $^{13}$C NMR of MDN-7

Figure 51. $^1$H NMR of MDN-7.
Reaction 2

![Reaction 2 Scheme](image)

**Scheme 12:** Reaction of MDN with 5-bromopentyl acetate in THF.

Reaction amounts and conditions were identical to the previous reaction but THF (15 mL) was used as solvent. The workup was also identical to procedure described above and the obtained IR,$^1$H, and $^{13}$C NMR spectra (Figures 52-54) of the crude product were similar to the spectra reported above and confirmed the structure of the expected product.

Yield: 50 mg (23%) of red oil.

$^1$H NMR (CDCl$_3$) $\delta$: 3.727 (4H, t, 3 Hz), 3.109 (4H, t, 6.6 Hz), 1.778 (6H, s), 1.686 (4H, p, 15.3 Hz), 1.476 (4H, p, 6.6 Hz), 1.349 (4H, p, 6.6 Hz)

$^{13}$CNMR (CDCl$_3$) $\delta$: C≡N (111.21 ppm), C=C (120.24 ppm), and C=O (169.51 ppm) e (63.72 ppm), a(34.61), and d,b,c,f (29.29, 27.77, 24.66, 20.72 ppm)

IR (m$^{-1}$): C=C (1498.51), C=O (1733.56), CH (2942.50)
Figure 52. IR spectrum of MDN-7.

Figure 53. $^1$H NMR of MDN-7
2.9. Synthesis of sodium (Z)-1,2-dicyano-2-(pentylthio)ethenethiolate (MDN-8)

Scheme 13: Reaction of MDN with one equivalent of 1-bromopentane.

Bromopentane (0.12 mL, 0.54 mmol, 1 eq) was added to a solution of MDN (100 mg, 0.53 mmol) in acetonitrile (10 mL) and stirred at room temperature for 10 hours. The solvent of the orange reaction mixture was evaporated and the residue was tested by TLC (silica, EtAc/hexanes 1:5) to reveal 3 different spots at Rf values of 0.40, 0.75, and 0.90. The spot at Rf = 0.9 was identified as the disubstituted side-product we had as reference, which could be removed by extracting the product mixture with a mixture of CH2Cl2/hexanes 1:2 until the extract was colourless. The orange residue was dried in vacuum to yield 60 mg
(48%) and used for the following substitution without further purification and characterization.

2.10. Synthesis of (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate (MDN-10)

**Reaction 1**

\[
\begin{align*}
\text{NC} & \quad \text{SNa} + \text{Br(CH}_2\text{)}_3\text{COOC}_2\text{H}_5 \quad \text{CH}_3\text{CN} & \quad \text{SNC} & \quad \text{S(CH}_2\text{)}_3\text{COOC}_2\text{H}_5 \\
\text{NC} & \quad \text{SNa} & \quad \text{Br(CH}_2\text{)}_3\text{COOC}_2\text{H}_5 & \quad \text{CH}_3\text{CN} & \quad 12 \text{ hrs, rt} & \quad \text{SNC} & \quad \text{S(CH}_2\text{)}_3\text{COOC}_2\text{H}_5 & \quad \text{NaBr} \\
\text{MDN-10} & \quad \text{not observed} & \quad \text{MDN-9} & \quad \text{only product}
\end{align*}
\]

**Scheme 14:** Reaction of sodium (Z)-1,2-dicyano-2-(pentylthio)ethenethiolate (MDN-8) with ethyl-6-bromohexanoate.

Sodium (Z)-1,2-dicyano-2-(pentylthio)ethenethiolate (60 mg, 2.8 mmol) was dissolved in acetonitrile (10 mL) to which 1 eq of ethyl-6-bromohexanoate was added drop-wise at room temperature. The mixture was stirred for 12 hours under nitrogen, filtered, and the solvent was evaporated. IR, $^1$H NMR and $^{13}$C NMR of this crude product mixture (Figures 55-57) agreed with (Z)-diethyl 6,6’-(1,2-dicyanoethene-1,2-diyl)bis(sulfanediyl)dihexanoate as the exclusive product. No measureable amount of (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate was formed which brings us to the conclusion that the starting material contained only MDN and no sodium (Z)-1,2-dicyano-2-(pentylthio)ethenethiolate.

Yield: 72 mg (80%) of orange oil.

$^1$H NMR (CDCl$_3$) $\delta$: 3.813 (4H, q, 6.6 Hz), 3.127 (4H, t, 6.6 Hz), 2.011 (4H, t, 6.9 Hz), 1.581 (4H, p, 5.4 Hz), 1.329 (4H, p, 6.6 Hz), 1.180 (4H, p, 4.2 Hz), 0.963 (6H, t, 2.2 Hz)

$^{13}$C NMR (CDCl$_3$) $\delta$: C≡N (111.91), C=C (120.33), C=O (172.12), f (59.29), a (33.21), e (32.71), d (28.95), b (26.93), c (23.38), g (13.56)

IR (m$^{-1}$): C=O (1730.42) and C-H (2937.99), but with without C≡N
Figure 55. IR spectrum of MDN-9.

Figure 56. $^1$H NMR of MDN-9.
Figure 57. $^{13}$C NMR of MDN-9.

**Reaction 2**

The two-step reaction was repeated by adding 1-bromopentane (0.14 mL, 0.63 mmole, 1.2 eq) to a solution of MDN (100 mg, 0.53 mmole) acetonitrile (10 mL). The reaction was stirred for 24 hours at room temperature under nitrogen and then directly evaporated without filtration. An orange solid was obtained that was extracted with hexanes until the hexanes extract became colourless. TLC confirmed that the red extract exclusively contained the disubstituted product (50 mg after evaporation of hexanes). The remaining solid was dried in vacuum and amounted to 149 mg (MDN, monosubstituted product, and salts). This mixture was dissolved in acetonitrile (10 mL) and ethyl-6-bromohexanoate (0.18 mL, 0.64 mmol, 1.2 eq) was added dropwise to the solution that was then stirred at room temperature under nitrogen overnight. The reaction mixture was filtered and concentrated before tested by TLC. TLC (silica, EtAc/hexanes 1:7)
revealed two spots at Rf values of 0.3 and 0.5. Separation by column chromatography gave one main fraction that was identified as (Z)-diethyl 6,6’-(1,2-dicyanoethene-1,2-diyl)bis(sulfanediyl)dihexanoate by NMR and MS (Figures 58-60). No (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate was found.

Yield: 36 mg (20%) of an orange liquid

\(^1\)H NMR (CDCl\(_3\)) \(\delta\): 4.130 (4H, q, 7.2 Hz), 3.126 (4H, t, 7.2 Hz), 2.321 (4H, t, 7.5 Hz), 1.732 (4H, p, 7.5 Hz), 1.626 (4H, p, 7.5 Hz ), 1.500 (4H, p, 4.5 Hz), 1.264 (6H, t, 7.2 Hz)

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\): C≡N (112.10), C=C (121.16), C=O (173.44), f (60.49), a (34.96), e (34.13), d (29.70), b (28.05), c (24.42), g (14.39)

HR-MS (m/z): [M]\(^+\) = 426.1660, [M+H]\(^+\) = 427.1721

Figure 58. \(^1\)H NMR of MDN-9
Figure 59. $^{13}$C NMR of MDN-9
2.11. Purification of MDN

Clearly, the methods tested above for the preparation of MDN derivatives with two different side-chains did not work well and we hypothesize that one possible impediment is a higher reactivity of the mono-substituted MDN when compared to MDN. Structurally, one would expect similar or even a lower reactivity for the mono-substituted MDN but its much higher solubility in the used organic solvents may be the decisive factor here.

However, the apparent absence of any mono-substituted MDN intermediates let us question the purity of our MDN starting material that has a shelf life of only a few months and is affected by many environmental factors such as chemical impurities, light, and air. Dark yellow MDN (2.3 g) was recrystallized from anhydrous ethanol solution (10 mL) by the addition of diethyl ether (60 mL) at room temperature. Crystallization was completed in the freezer for at least 1 hour. The yellow precipitate was filtered off and the yellow filtrate was concentrated to generate a second fraction of precipitate. This procedure was repeated two more times until the product became a bright yellow powder after drying in vacuum. The amount of 1.3 g of pure MDN was obtained and IR spectrum of the pure MDN samples is provided in Fig. 61.
2.12. Synthesis of (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinyllthio)hexanoate (MDN-10)

Scheme 15: Reaction of MDN with 1-bromopentane to sodium (Z)-1,2-dicyano-2-(pentylthio)ethenethiolate and its conversion with ethyl-6-bromohexanoate.

1-Bromopentane (0.55 mL, 3.3 mmol) was added to a solution of purified MDN (500 mg, 2.7 mmol) in acetonitrile (40 mL) at 0 ºC under argon and the mixture was stirred for 4 hours. The mixture was filtered and evaporated to give an orange solid that was washed with hexanes until the hexanes phase became colourless. The remaining orange solid was dried in vacuum to give 350 mg
(58%) of what was assumed to be mainly sodium (Z)-1,2-dicyano-2- (pentylthio)ethenethiolate. Evaporation of the hexanes phase gave 52 mg of the disubstituted product as a red oil.

The orange solid was dissolved in acetonitrile (15 mL) and reacted with the dropwise added ethyl-6-bromohexanoate (0.35 mL, 1.5 mmol). The reaction was stirred for 24 hours at 0 °C under nitrogen, filtered, and the solvent was evaporated in vacuum. TLC analysis (silica, CH$_2$Cl$_2$/hexanes 1:1) of the product mixture confirmed the absence of any (Z)-1,2-bis-pentylthio-1,2-ethenedicarbonitrile (R$_f$ = 0.6) and the presence of some (Z)-diethyl 6,6’-(1,2-dicyanoethene-1,2-diyl)bis(sulfanediyl)dihexanoate (R$_f$ = 0.2) as well as a second yellow spot at R$_f$ = 0.4, which was assumed to be the desired product (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate. The two products were separated by column chromatography (silica, EtAc/hexanes 1:8) to yield 250 mg (33%) of (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate as an orange oil. The structure was confirmed by $^1$H and $^{13}$C NMR as well as HRMS (Figures 62-64)

R$_f$(silica, 1:8 EtAc/hexanes) = 0.4

$^1$H NMR (CDCl$_3$) δ: 4.120 (2H, t, 7.2 Hz), 3.113 (4H, t, 7.5 Hz), 2.311 (2H, t, 7.2 Hz), 1.772 (2H, m, 7.5 Hz), 1.747 (4H, m, 7.5 Hz), 1.466 (4H, m, 7.2 Hz), 1.410 (2H, m, 7.2 Hz) 1.230 (3H, t, 7.2 Hz), 0.911 (3H, t, 6.9 Hz)

$^{13}$C NMR (CDCl$_3$): C≡N (112.10, 112.24), C=C (120.80, 121.46), and C=O (173.24) ppm

HR-MS (m/z): [M]$^+$ = 354.1461, [M+H]$^+$ = 355.1506
Figure 62. $^1$H NMR of MDN-10 (Fr. 2)

Figure 63. $^{13}$C NMR of MDN-10 (Fr. 2)
Figure 64. Experimental (top) and calculated (bottom) MS spectra of MDN-10 (Fr. 2)
2.13. Synthesis of (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate (MDN-10) and (Z)-methyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate (MDN-10’)

Scheme 16: Reaction of MDN with 1-bromopentane to sodium (Z)-1,2-dicyano-2-(pentylthio)ethenethiolate in a flow reactor and its conversion with ethyl-6-bromohexanoate.

A flow reactor was chosen to optimize the yield for the monosubstituted MDN-8 intermediate as these conditions are much less affected by differences in solubility. MDN (50 mg, 2.6 mmol) and one equivalent of 1-bromopentane (0.030 mL, 0.24 mmol) were each dissolved in methanol (10 mL) and transferred into 10 mL gas tide syringes. The flow reactor of 10 mL volume was cooled to 0 ºC in an ice bath and the two components were injected via a syringe pump at a rate of 1.25 mL/h, which is equivalent to a reaction time of 8 hours. The reaction mixture was released directly into a reaction flask that contained a stirred solution of ethyl-6-bromohexanoate (0.045 mL, 0.4 mmol) in methanol (2 mL).

The reaction was stopped 8 hours after all the flow reaction mixture was added to the reaction flask with ethyl-6-bromohexanoate. The final reaction mixture was filtered and the solvent was evaporated to give an orange oil that contained the desired product (R<sub>f</sub> = 0.4) and another product, which could have been (Z)-diethyl 6,6’-(1,2-dicyanoethene-1,2-diyl)bis(sulfanediyl)dihexanoate (R<sub>f</sub> = 0.2) based on TLC analysis (silica, EtAc/hexanes 1:8) but was identified as (Z)-methyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate (MDN-10’) based on
$^1$H and $^{13}$C NMR analysis (Figures 65 and 66). The molar ratio of **MDN-10** and **MDN-10’** was 52% to 48%, respectively.

Yield: 69 mg (80%).

R$_f$ (1:8 ethyl acetate/hexane): 0.4

$^1$H NMR (CDCl$_3$) $\delta$: 4.030 (2H, t, 7.2 Hz), 3.58 (3H, s), 3.040 (4H, t, 7.2 Hz), 2.247 (2H, t, 7.2 Hz), 1.668 (2H, p, 6.6 Hz), 1.584 (4H, m, 7.5 Hz), 1.352 (4H, m, 5.1 Hz), 1.299 (2H, m, 4 Hz), 1.193 (3H, t, 7.2 Hz), 0.855 (3H, t, 6.9 Hz).

$^{13}$C NMR (CDCl$_3$): C=O (173.47, 173.04), C≡N (111.99, 111.95), C=C (121.28, 120.65), CH$_3$ of C5 (21.93), and CH$_3$ of the C$_5$COO[Et,Me] (14.14, 13.72). 6 (60.11), X (51.35).

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**Figure 65.** $^1$H NMR of fraction 1 (mixture of **MDN-10** and **MDN-10’**)

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2.14. Synthesis of isomer mixture of the metal free TAP with 4 pentylthio and four 6-ethoxy-6-oxohexylthio groups (TAP-1)

Scheme 17: Reaction of (Z)-ethyl 6-(1,2-dicyano-2-(pentythio)vinylthio)hexanoate (MDN-10) with magnesium propanolate in propanol.
Following a procedure previously reported by our group, magnesium turnings (100 mg, 4.11 mmol) were reacted with anhydrous 1-propanol (30 mL) at 80 °C under argon until all magnesium was converted (about 24 hours). (Z)-ethyl 6-(1,2-dicyano-2-(pentylthio)vinylthio)hexanoate (MDN-10) (100 mg, 0.28 mmol) was added to a dry flask under argon and 3 mL of the magnesium propanolate mixture were added. This mixture turned blue after 1.5 hours, which indicates the formation of TAP, and was stirred under reflux for a total of 24 hours. THF (10 mL) was added to the reaction mixture at room temperature. The removal of Mg²⁺ was accomplished by the addition of 1M HCl (10 mL). Immediately, the mixture’s color changed from dark blue to dark purple, which is the colour of a metal-free TAP, and the demetalation process was monitored by UV-vis spectroscopy (Figure 67). The metal-free TAP was precipitated by the addition of DI water (20 mL) and one drop of concentrated HCl. The precipitated dark solid was filtered off and subject to TLC analysis (silica, EtAc/hexanes 1:6). Two spots with Rₖ values of 0.09 and 0.45 were observed and the spot at 0.45 was identified as the desired product after separation of the reaction mixture by column chromatography. The structure was confirmed by IR, ¹H and ¹³C NMR, and HR-MS analysis (Figures 68-71).

FW (g/mol): 1474.6525

Yield: 100 mg (25%).

¹H NMR (CDCl₃) δ: 4.030 (8H, t, 7.5 Hz), 3.279 (16H, t, 7.5 Hz), 2.3 (8H, t, 4.8 Hz), 1.881 (16H, m, 6.9 Hz), 1.604 (16H, m, 6.6 Hz), 1.352 (16H, m, 7.5 Hz) 0.932 (12H, t, 4.4 Hz) overlapping with 0.894 (12H, t, 4.2 Hz).

¹³C NMR= C=O (173.51 ppm), C=N (152.18 ppm), aromatic system peak (140.89 ppm), CH₃ of C₅H₁₁ (14 ppm), and CH₃ of the C₅COOC₃H₇ (10 ppm).

IR (Figure 62) for H₂TAP-(C₅H₁₁)₄ (C₅H₁₀COOC₃H₇)₄ = C=O (1734.62), CH (2927.16), and NH (3281.82).

MS (m/z): [M]⁺(1474.6525), [M+H]⁺ (theoretical=1475.6604), [M+H]⁺ (measured=1475.6613).
UV-vis (THF, λ max in nm): MTAP-P19 (373, 510, 670), and HTAP-P19 (380, 525, 630, 720).

**Figure 67.** UV-vis spectra for TAP-1 that shows metallated MTAP-(C₅)₄(C₅COOC₃)₄ and metal free H₂TAP-(C₅)₄(C₅COOC₃)₄.

**Figure 68.** IR spectrum for TAP-1.
Figure 69. $^1$H NMR for TAP-1.

Figure 70. $^{13}$C NMR for TAP-1.
2.15. Synthesis of the tetra-carboxylic acid of TAP-1 (TAP-2)

Scheme 18: Saponification of TAP-1 with sodium hydroxide.

70 mg (0.047mmole) of $\text{H}_2\text{TAP(C}_3\text{H}_{11})_4\text{(C}_3\text{H}_{10}\text{COOC}_3\text{H}_7)_4$ was dissolved in 10 mL of THF and 2 mL of MeOH, and then the reaction was heated up till 55 °C.
Then, around 5 mL of 1 M NaOH was wisely dropped in the mixture at a rate of 1 mL every 20 min. The solution mixture color immediately did change from dark purple to be dark green, which means a TAP sodium carboxylate has formed, and then the reaction was left stirring and refluxing for 24 hours. During the refluxing, about 1 or 2 drops were taken from the solution and acidifying, and then TLC was run for checking the TAP if it completely converted to acid or not. After 24 hours, all the tetra-ester groups of the TAP were converted to carboxylic acid groups, and that have been checked by acidifying the solution by using 1M HCl. The mixture’s color did change to be dark violet which was precipitated out by adding 50 ml DI water, and then the water was extracted with using ethyl acetate to isolate the entire TAP from the aqueous face. During the hydrolysis process, some drops of buffer solution (NH₄Cl) was added to the mixture to control the pH values and range it between 4 to 6 which is the best pH values to have free-base TAP fully protonated (H₂TAPs). Due to the low solubility of the TAP in most of organic solvents especially if it contains carboxylic acid groups as side chains, recrystallization method was processed to purify the tetra-acid TAP rather than using column chromatography. The compound was dissolved in small amount of mixture THF-EtAc, and then large amount of solvent mixture 1:5 (CHCl₃\Hexane) was added onto the solution and left in fridge 2 ℃ for 24 hours. The mixture was filtered and collected in a round bottom flask. Then, the dark violet TAP was washed by pure CHCl₃ to remove any impurity which may stuck in, and the CHCl₃ phase was evaporated and kept in a vial. Moreover, the tetra-acid TAP was left on high vacuum to dry it, and also it was heated up to 70 ℃ and exposed by N₂ gas on it to make it super dry. The product weight was around 65 mg (25%). Also, ¹³C NMR was done for TAP-2 (Figure 73) with promising results with using DMSO for running sample, but the solubility was low, so it has been heated up till 50 ℃ before run the sample. All the peaks showed in the spectrum with low intensity (low solubility). Moreover, IR (Figure 72) was run for TAP-2 and gave all aimed stretches. In addition, mass spectrum was run for P20 to make the final
discussion about the product, and the result was great by having the exact mass for the TAP-2 [M+H]+ by using HR-MS analysis (Figure 74).

FW (g/mol): 1306.4647

Yield: 65 mg (25%).

$^{13}$C NMR (DMSO) $\delta$: C=O (174.20 ppm), C=N (138.69 ppm), C-S (so small peak around 152.00 ppm), CH$_{3}$ of C$_{5}$ (14 ppm).

IR (m$^{-1}$): C=O (1707.80), CH (2923.89), and NH (3286.24).

MS (m/z): [M]$^+$ (1306.4647), [M+H]$^+$ (theoretical=1307.4725), [M+H]$^+$ (measured=1307.4861).

Figure 72. IR spectrum of TAP-2.
Figure 73. $^{13}$C NMR of TAP-2 in d$^6$-DMSO at 50 °C.

Figure 74. HR-MS (+) of TAP-2.
3. Results and Discussion

Our new design for less symmetric TAPs with enhanced amphiphilicity for an improved behavior at interfaces (e.g. processing by the LB technique) necessitates the synthesis of maleodinitrile derivatives containing two different side-chains. At first glance, this appears to be a straightforward undertaking because a stepwise alkylation of the readily prepared disodium 1,2-dicyanoethylene-1,2-dithiolate (MDN) would be sufficient. However, the types of compounds have not been reported, to the best of our knowledge, despite their frequent use for the synthesis of TAPs.

In 2014, Serxho Selmani attempted to synthesize MDN derivatives with two different alkyl chains as part of his 4th-year thesis project and revealed three main problems. 1) The starting material MDN contains significant amounts of impurities unless it was recrystallized not more than 2-3 weeks ago and kept in a freezer. Because of these impurities, the actual amount of MDN was often overestimated and more than 1 equivalent of the alkylating agent was added. 2) The MDN is only slightly soluble in organic solvents, which seems to lower its reactivity while the reactivity of the mono-substituted intermediate is enhanced because of its much higher solubility. 3) Chromatographic separation of a mixture of MDN derivatives with two different and two identical side-chains is difficult because they all have the polar cyano groups in common that dominate the interactions with polar stationary phases (silica and alumina) and polar solvents in case of RP-18 stationary phases.

Our first attempt to circumvent especially problems 2 and 3 was to use protective groups and was based on the assumption that stepwise removal should be much more straightforward because formation of a monothiolate is energetically much more preferred to the formation of a dithiolate. The first choice was to protect the thiolates with silane protective groups also because it seemed feasible that large protective groups such as triisopropylsilane may generate only monoprotected MDN for steric reasons. However, the reactions with trimethylsilyl chloride and triisopropylsilyl chloride did not generate any isolable product or it easily decomposed during work-up. The absence of
signals for CN groups in the NMR spectra suggests that the silane may also attack the N of the cyano group under these conditions. A similar problem may also occur in the second set of reactions that attempted a protection of the thiolate groups with acid chlorides, because the signals for cyano groups were lost. The proposed thioester products MDN-3 and MDN-4 should be significantly more stable than the thiosilanes and, consequently, a decomposition during the work-up procedure is less likely the reason for not observing any product. This statement is supported by the fact that a 2-step, one pot reaction with isopropenyl acetate and bromopentane did not give the mixed substituted MDN-6 but only MDN-5. No MDN-8 was found, which confirms that no thioacetate groups were generated as intermediate products and cleaved off during work-up.

The quality of the MDN starting material was tested by reacting it with bromopentane to give the dialkylated MDN-5 in a moderate yield of about 50%. This reaction was also used to compare methanol and THF as solvents. The reaction occurs in both solvents but yields in methanol were about twice as high as in THF. This was confirmed when MDN was reacted with more polar side-chains for the formation of MDN-7.

Eventually, a statistical approach was chosen once again for the preparation of MDN-10. The first attempts exclusively generated the symmetric MDN-9 but this was attributed to incorrect reagent ratios because of impure MDN. MDN was purified by successive precipitations until a bright yellow crystalline product was obtained. The mono alkylation with bromopentane was now performed at 0 ºC and stopped after 4 hours to give a mixture of mono- and disubstituted MDN products. Fortunately, the disubstituted MDN-5 was sufficiently soluble in hexanes while the monosubstituted MDN-8 was not. So, a simple extraction with hexane allowed us to isolate the pure monosubstituted MDN-8 that appears to be reasonably stable. Overall yields were now at around 80%, which is a more typical value for these conversions and confirms that the lower yields of the previous reactions were mainly caused by impure MDN. MDN-5 was obtained in about 20% yield or 25% of the product mixture.
Conversion of MDN-8 with ethyl-6-bromohexanoate to the desired product MDN-10 worked well but unexpectedly, when this reaction was performed in the highest yielding solvent methanol a partial transesterification was observed. About 50% methyl ester was generated at room temperature and about 15% at 0 ºC. Acetonitrile and THF were tested as alternative solvents to avoid transesterification but yields were again much lower and MDN has a significantly lower solubility in acetonitrile and THF than in methanol. Also, the formation of methyl esters is not a problem for the cyclization to TAPs as those reaction conditions quantitatively generate the propyl esters by transesterification.

The highest yields of MDN-8 and the least amounts of dissubstituted side-products were achieved when the monosubstitution of MDN was conducted under flow conditions. The advantage of flow conditions is a rather accurate control of the local concentrations of reagents, which minimized the amount of formed MDN-5 and other impurities and maximized the amount of formed MDN-8 to about 70-80%. Very careful control of the reaction conditions should generate just MDN-8 and avoid its purification before the second alkylation.

Conversion of MDN-10 to the metal-free TAP was expectedly straightforward and generated the propyl ester derivative. This compound is soluble in many organic solvents and could be purified by column chromatography to give clean and well resolved NMR spectra and MS data. We note that the product is formed as a mixture of 4 regioisomers (Fig. 75). Their separation on conventional columns is not possible and HPLC analysis has not been conducted. TAP-1 is not crystalline at room temperature but is a soft amorphous solid.
Figure 75. The 4 regioisomers of MgTAP-1.

Ester hydrolysis of TAP-1 to TAP-2 was accomplished in a mixture of 1M NaOH and THF at 55 °C for 24 hours and was monitored by TLC and IR spectroscopy. Temperatures above 60 °C decompose the macrocycle over time. Purification of TAP-2 was more of a problem because its low solubility in organic solvents such as CHCl₃, DCM, DMF, and EtAc excluded the use of column chromatography. TAP-2 is more soluble in alcohols but not soluble in water. In fact, even the tetracarboxylate salt of TAP-2 is insoluble in water. Consequently, purification solely relied on repetitive precipitations from alcoholic solutions. The final yield of purified TAP-2 was only 25% but probably 25% was lost by testing different purification methods.

The materials properties of TAP-2 appear to be more interesting than those of TAP-1. TAP-2 forms a soft mesophase at room temperature that clears into and isotropic liquid phase at about 80 °C whereas TAP-1 forms an isotropic amorphous solid. This difference
is mainly attributed to the strong H-bonding interactions between carboxylic acid groups. However, TAP-2 is significantly more soluble and less aggregated in typical spreading solvents used for LB studies (e.g. CHCl$_3$ and CHCl$_3$/THF mixtures) than the previously reported TAPs with eight terminal carboxylic acid groups (Fig. 77).$^{17}$ Clearly, the fewer carboxylic acid groups and extra aliphatic chains increase solubility in aprotic organic solvents and minimizes aggregation according to UV-vis solution studies (Fig. 78).

**Figure 75.** UV-Vis spectra of octa-acid TAP in THF and mixtures of THF and CHCl$_3$ at 1.25 x 10$^{-5}$ molar concentration.$^{17}$

**Figure 76.** UV-vis spectra of the 3 different solutions (5-10% THF/CHCl$_3$, and CHCl$_3$) at 10$^{-4}$ M shows no aggregation of TAP-2.
A sample of TAP-2 has been sent to Christine DeWolf’s group at Concordia University for LB studies in May but, unfortunately, we have not received any results yet.

4. Conclusion

A novel truly amphiphilic TAP derivative has been prepared with four hydrophobic alkyl groups and four alkyl chains terminated with hydrophilic carboxylic acid groups (TAP-2). This TAP is more soluble and aggregates less in spreading solvents such as CHCl₃ than the previously reported TAP with 8 carboxylic acid groups and is expected to give good quality Langmuir and LB film with a face-on orientation of the TAP macrocycle. Also, TAP-2 forms a weakly birefringent soft mesophases while TAP-1 is an amorphous solid at room temperature.

Synthetically, the key step is a step-wise alkylation of sodium maleonitriledithiolate (MDN) that was best achieved by flow chemistry. Particularly advantages for a separation of mono- (MDN-8) and disubstituted MDN (MDN-10) derivatives are their large difference in solubility in hexanes. In fact, MDN-10, TAP-1 and TAP-2 are the first derivatives of their types that contain two different types of side-chains.
5. Future work

The next generation of amphiphilic TAPs with two different types of side-chains will contain four terminal azide or acetylene groups, in addition to four terminal carboxylic acid groups (Figure 79). We have shown in a previous study that TAPs with eight terminal azide or acetylene groups can be cross-linked at the air-water interface by click chemistry but the derivatives did not form Langmuir monolayers because of their lack of amphiphilicity.\(^{34}\)

![Figure 77. The structure of the H\(_2\)TAP-(C\(_5\)H\(_{10}\)N\(_3\))\(_4\)(C\(_5\)H\(_{10}\)COOH)\(_4\) (right) and H\(_2\)TAP-(C\(_5\)H\(_{10}\)C≡CH)\(_4\)(C\(_5\)H\(_{10}\)COOH)\(_4\) that will use for cross-linked chemistry of L monolayer films.](image)
References


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