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In situ 3D Electrochemical Deposition of Conductive Poly(dopamine) Composites in Living Tissues for Biocompatible Man-Machine Interfaces

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14. ABSTRACT

This report summarizes results obtained over the final year (2020-2021) of this collaborative MSIT-AFOSR research project. Our long term goal has been to create reliable, stable, bioelectronic interfaces between implantable engineered components and living tissue (Martin 2015). These interfaces are critical for a number of current and emerging devices that provide for restoration of function for disabled individuals, and improved human-machine interactions. The focus of our efforts are hybrid conjugated polymer materials that take
advantage of design features required for optimizing their performance. Considerable recent work from our own laboratories and elsewhere has shown that alkoxyfunctionalize polythiophenes such as poly(3,4-ethylene dioxythiophene) (PEDOT) are particularly attractive for biomedical devices because of their low impedance, chemical stability, and ability to have their surface chemistry precisely tailored (Donahue et al. 2020). They have mechanical properties that are intermediate of those of the hard, inorganic engineered devices (typically crystalline metals and semiconductors) and soft, wet, living tissue. Electrochemical deposition is a convenient means for depositing these materials from a precursor solution of monomer and dopant . Typically functional films with low frequency (<1 kHz) impedances 100x to 1000x lower than the bare metal electrode can be achieved with PEDOT films of order 500 nm or so in nominal thickness (Cui et al. 2001; Cui and Martin 2003).
This research project investigated the use of natural products (polymers based on dopamine, a neurotransmitter) and the design and synthesis of new materials that combine together thiophene chemistry and dopamine / phenolamine functionality. Polydopamine (PDA) is an analog to natural melanin, a biopolymer found in skin and hair as well as in certain ionically active organs including the ear and brain. PEDOT and melanin / PDA have several similar molecular design features including a conjugated backbone, pendant oxygens that donate charge, and no primary hydrogens that are often associated with chemical instabilities (Figure 1) (Kim et al. 2007)(Martin et al. 2010). Our collaborators in Prof. Bong Sup Shim's lab at Inha University in Korea are actively investigating methods to deposit and optimize the performance of PDA films that are expected to have particular value in creating more biocompatible materials because they are derived from all-natural starting products. We have recently created new materials that bring together features of both the PEDOT and PDA by designing hybrid monomers that bring together both chemistries on the same molecule (Figure 2) (Nagane et al. 2020).

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Re: Final Report for Project: "In-Situ Electrochemical Deposition of Conductive Poly(dopamine) Composites in Living Tissues for Biocompatible Man-Machine Interfaces"
MSIT-AFOSR Program for Materials and Next Generation

Date: July 21, 2021

To: Tony Kim, Air Force Office of Scientific Research

From: David C. Martin, Associate Dean for Research and Entrepreneurship and Professor of Materials Science and Engineering and Biomedical Engineering, The University of Delaware

Collaborator: Prof. Bong Sup Shim, Chemical Engineering, Inha University, Korea

Overview

This report summarizes results obtained over the final year (2020-2021) of this collaborative MSIT-AFOSR research project. Our long term goal has been to create reliable, stable, bioelectronic interfaces between implantable engineered components and living tissue (Martin 2015). These interfaces are critical for a number of current and emerging devices that provide for restoration of function for disabled individuals, and improved human-machine interactions. The focus of our efforts are hybrid conjugated polymer materials that take advantage of design features required for optimizing their performance.

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natural starting products. We have recently created new materials that bring together features of both the PEDOT and PDA by designing hybrid monomers that bring together both chemistries on the same molecule (Figure 2) (Nagane et al. 2020).

Research Progress

In last year's progress report we described the synthesis and initial characterization of a wide variety of novel functionalized EDOT monomers that we have prepared in our laboratory including EDOT with a carboxylic acid (EDOT-acid), aldehyde (EDOT-aldehyde), maleimide (EDOT-maleimide), dopamide (EDOT-dopamide), and tyramine (EDOT-tyramine). Of these monomers, EDOT-maleimide (EDOT-MA) is particularly interesting to explore because there are a wide variety of reactions that are possible for further tailoring of the structure and properties (Figure 3). Maleimides will efficiently react with furans, thiols, amines, and azides. They can also react with themselves and with the thiophenes as well.

Over the past year we have prepared chirally-controlled versions of the EDOT-MA monomer by starting with a chirally-pure reagent. Figure 4 shows a 1H NMR spectrum of the EDOT-MA monomer in its racemic form with both R and S variants present, while Figure 5 shows the corresponding NMR spectrum for the chirally-pure EDOT-MA in the S configuration. Both of the NMR spectra are similar, since the chirality does not signficantly influence the position of the hydrogen resonances. The hydrogen peaks are all present and in their expected positions, confirming the structure and purity of the EDOT-MA compounds.

Dramatic differences are immediately obvious when characterizing the solid-state structure of EDOT-MA (racemic) and EDOT-MA (chiral), as shown the transmitted, crossed-polarized light optical micrographs in Figure 6. The racemic EDOT-MA shows small, ~1 micron crystals, whereas the chiral EDOT-MA are much larger (~500 microns). DSC experiments show a melting point of ~105 C for the racemic EDOT-MA, whereas the chiral EDOT-MA melts at ~128 C. Both samples melt into isotropic liquids and form apparently amorphous glasses on cooling under typical conditions.

The large crystals of chiral EDOT-MA have made it possible for us to do full single crystal structure in collaboration with the crystal structure facility in the Department of Chemistry, directed by Prof. Glenn Yap. The results of this analysis are shown in Figure 7. The space group of the chirally pure EDOT-MA(S) sample turns out to be trigonal $P3_1$, which is #144 in the International Tables of Crystallogaphy. The unit cell parameters are a=b=0.8959 nm, and c=1.1662 nm, with Z=3 molecules per unit cell organized in stacks of 3-fold symmetric helices pointed along the c-direction. The calculated density of the unit cell is 1.566 gm/cm^3. The experimental powder diffraction patterns of EDOT-MA(S) are essentially identical to the theoretical predictions obtained from this unit cell determination.

Although the EDOT-MA racemic mixtures have much smaller crystals, by careful choice of solvent and solidification conditions we managed to grow them large enough to do single crystal determinations as well. The crystals are monoclinic ($P2_{1/c}$, space group #14), with a=1.2772 nm, b=0.6012 nm, c=1.4715 nm, and unique angle beta = 107.897 degrees. There are

Z=4 molecules per unit cell, with two left handed and two right handed molecules associated in pairs. The calculated density of the EDOT-MA racemic crystals 1.552 gm/cm^3.

Over the past year we have focused additional attention on cholesterol functionalized versions of EDOT. Cholesterol is a membrane-active molecule that has shown particular promise for controllling self-assembly behavior in the solid state (crystallization and liquid crystal formation). We have developed two routes for creating cholesterol-functionalized variants of EDOT, as shown in Figure 8. The first route uses EDOT-acid as the starting product, forming an ester by reacting with the hydroxyl group on the end of the cholesterol moiety. The second route uses the EDOT-MA monomer, which can react with the thiol group on the end of thiol-cholesterol. Like with EDOT-MA, it is also possible to control the chirality of EDOT-MA-cholesterol to a certain extent by using chirally-pure EDOT-MA in this reaction. However in this case the final product is not completely a single enantiomer since the thiol-maleimide reaction does not control the stereochemistry of its reaction product (Figures 9 and 10).

As with our other monomers, we have characterized the chemical structures with proton NMR (Figure 11), DSC (Figure 12), and hot-stage optical microscopy (Figures 13 and 14). The protons can all be identified in the NMR spectrum, and again chirality has no significant impact on the position of the characteristic resonances. The DSC shows clear melting and crystallization transitions (Figure 13 and 14). The monomers show interesting evidence for recrystallization from the melt in the solid-state by optical microscopy, the details of which we have only just begun to investigate by X-ray diffraction.

We have also found that the EDOT-acid-cholesterol monomer can be reacted to form polymers in organic solvents. The UV-vis spectra shown in Figure 15 shows the extended conjugation typical from EDOT polymers. Furthermore, the NMR spectra of the monomer and polymer shown in Figure 16 confirm the formation of high molecular weight products. Specifically, the resonances corresponding to the hydrogens on the thiophene ring (indicated as “a” in Figure 16a) are much weaker if not entirely absent in the polymer (Figure 16b). We have obtained size exclusion chromatography data indicating molecular weights of ~9000 gm/mol (Figure 17). The ability to create variants of PEDOT that are soluble in non-polar solvents is novel, and may lead to interesting processing routes for creating functionalized films and fibers.

Finally, we conclude with an example of the flexiblity that these new materials have now provided us for creating functionalized PEDOT films with controlled electrochemial properties. Shown in Figure 18 are the monomers we have studied (left column) and their corresponding polymers (right column). The well studied PEDOT films formed from PEDOT are electrically active, and can be readily deposited by electrochemical deposition. EDOT-MA can be similarly polymerized to create the corresponding polymer PEDOT-MA, but now with a maleimide functional group at every monomer position. EDOT-MA-cholesterol can be polymerized to form the PEDOT-MA-cholesterol polymer. Alternatively, films of PEDOT-MA can be exposed to thio-cholesterol to create films that have cholesterol functionalized at their external surfaces.

Figure 19 shows the electrical properties of these various films. Depositing either PEDOT or PEDOT-MA on a bare gold electrode significantly reduces the impedance at low frequencies. The PEDOT-MA-cholesterol polymer, on the other hand, does not reduce the

impedance of the electrode (however, nor does it increase much for that matter). Exposing a film of PEDOT-MA to thiol-cholesterol causes a systematic increase of the impedance, eventually plateauing after 60 minutes. The impedance of the cholesterol-functionalized PEDOT-MA still remains low at the lowest frequencies.

The schematic diagram explains what is happening based on these results. The PEDOT and PEDOT-MA films are low impedance (dark blue), whereas the PEDOT-MA-cholesterol does not change the impedance from the bare electrode (green). Adding thiol-cholesterol to a PEDOT-MA film results in a thin layer of PEDOT-MA-cholesterol to be formed on the surface of the PEDOT-MA. Since this layer is molecularly thin, it increases the impedance somwhat but the film remains relatively low impedance at the lowest frequencies since the bulk of the transport is dominated by the underlying PEDOT-MA substrate.

We look forward to further studies on these materials, and in particular we are hoping to implement these chemistries into new generations of biochemical sensors. We are exploring actively exploring collaboration opportunities with investigators at other laboratories (Aberdeen Proving Ground) and in industry (Waters Corporation). We would welcome substantive discussions with others from the Air Force or elsewhere.

Personnel

University of Delaware personnel that have participated on this project over the last year include:

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Publications

Seunghyeon Lee, Busra Ozlu, Taesik Eom, David C. Martin, and Bong Sup Shim, "Electrically Conducting Polymers for Bio-interfacing Electronics: From Neural and Cardiac Interfaces to Bone and Artificial Tissue Biomaterials", **Biosensors and Bioelectronics**, 170, 112620, (2020).
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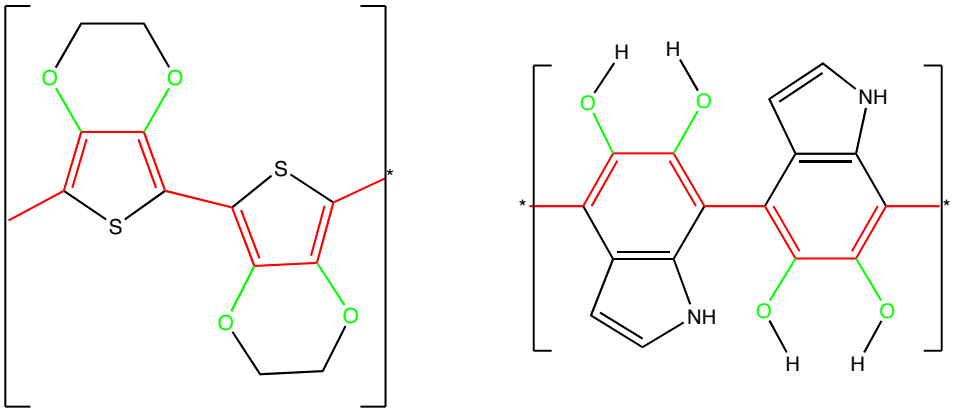


PEDOT PDA / melanin

Figure 1: Chemical repeat structures of PEDOT (left) and poly(dopamine) / melanin (PDA) (right). Both polymers have an extended conjugated backbone (red) with pendant oxygens (green) and no primary hydrogens. These features lead to high electrical activity and chemical stability.

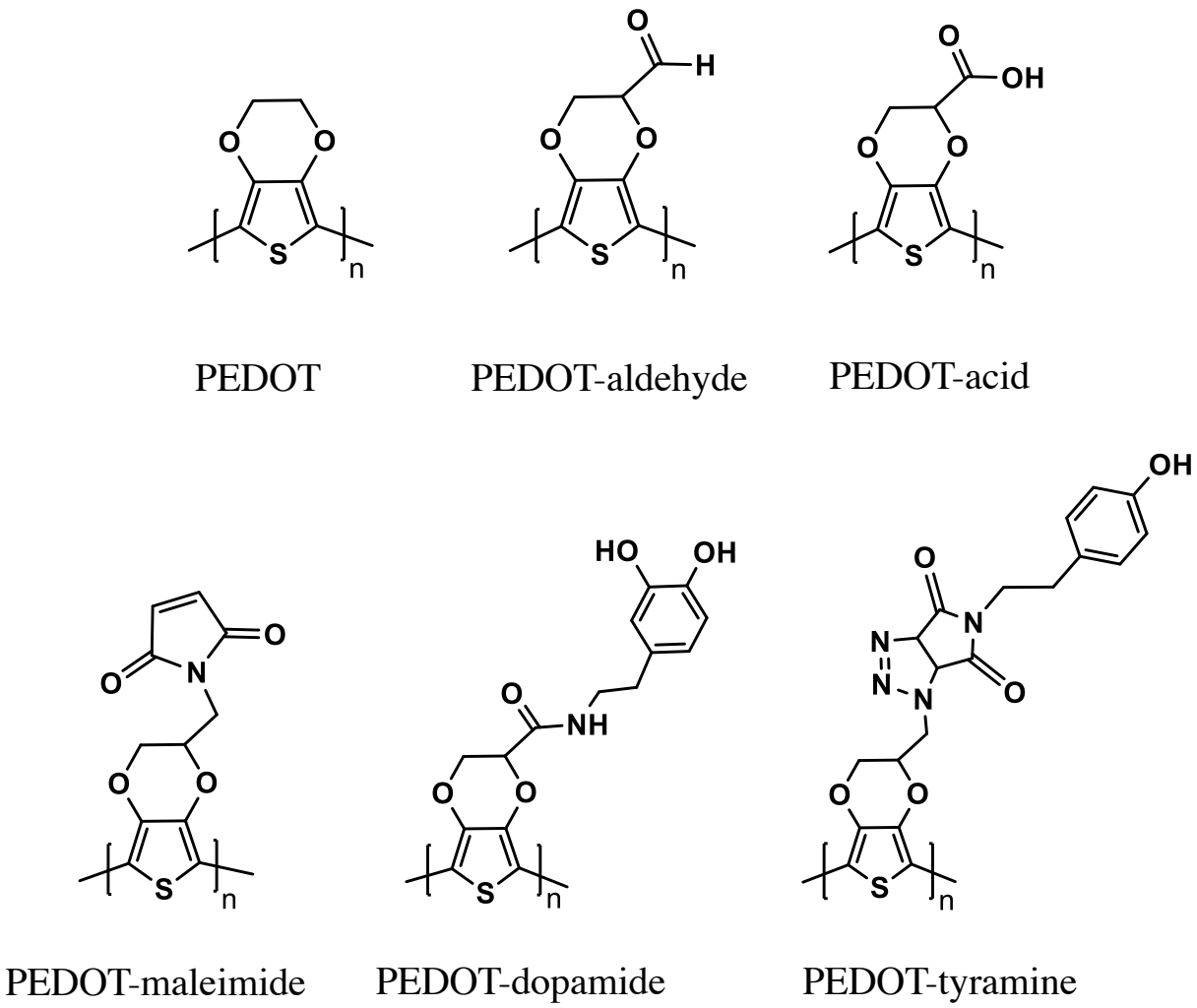


Figure 2: Chemical repeat structures of PEDOT and several functionalized PEDOTs prepared from monomers synthesized in our laboratory including PEDOT-aldehyde, PEDOT-acid, PEDOT-maleimide, PEDOT-dopamide, and PEDOT-tyramine.

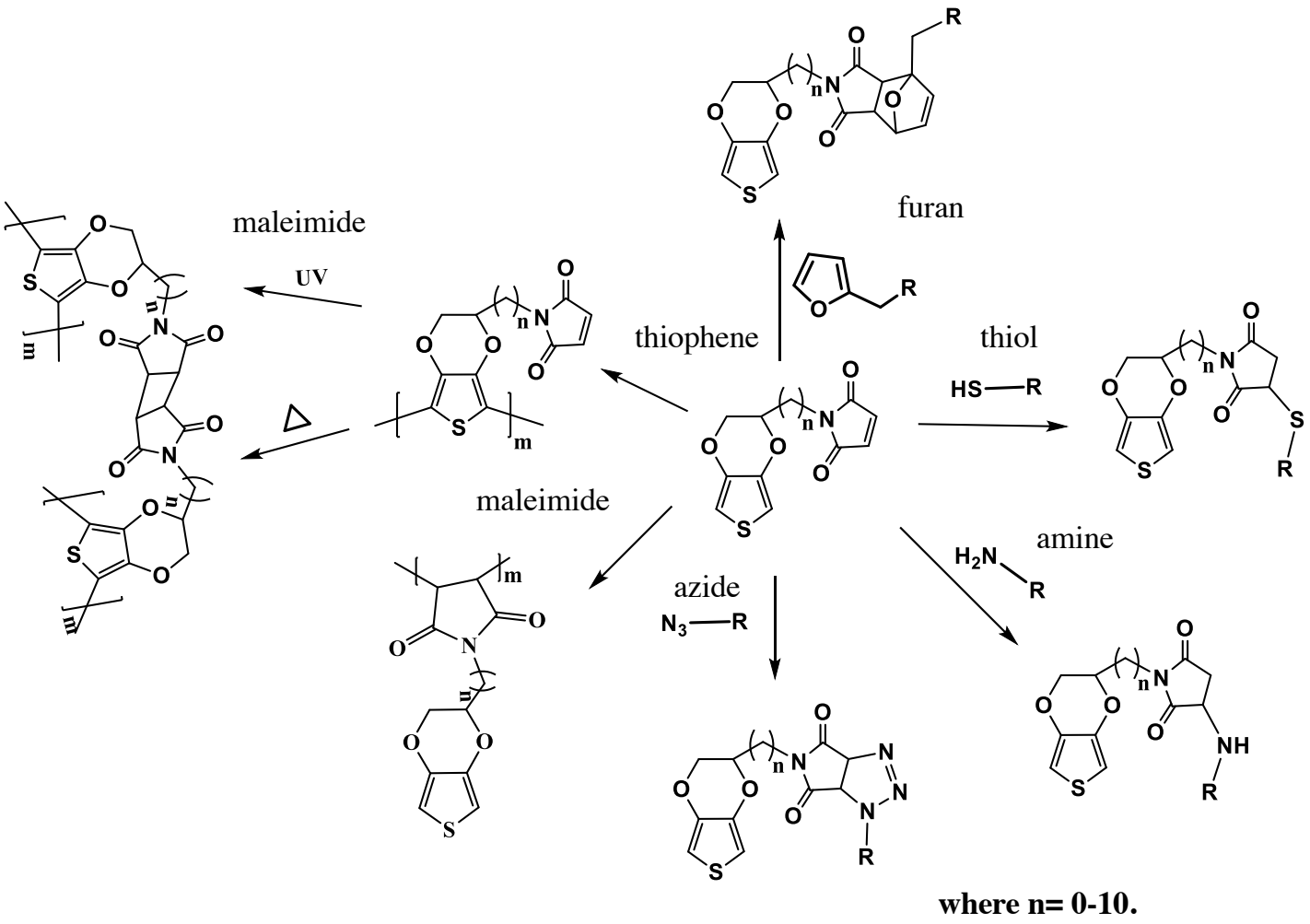


Figure 3: A maleimide functionality on EDOT is particularly powerful because it can be reacted with a wide variety of targets including furans, thiols, amines, azides, as well as other maleimides and thiophenes.

1H NMR of EDOT-MA

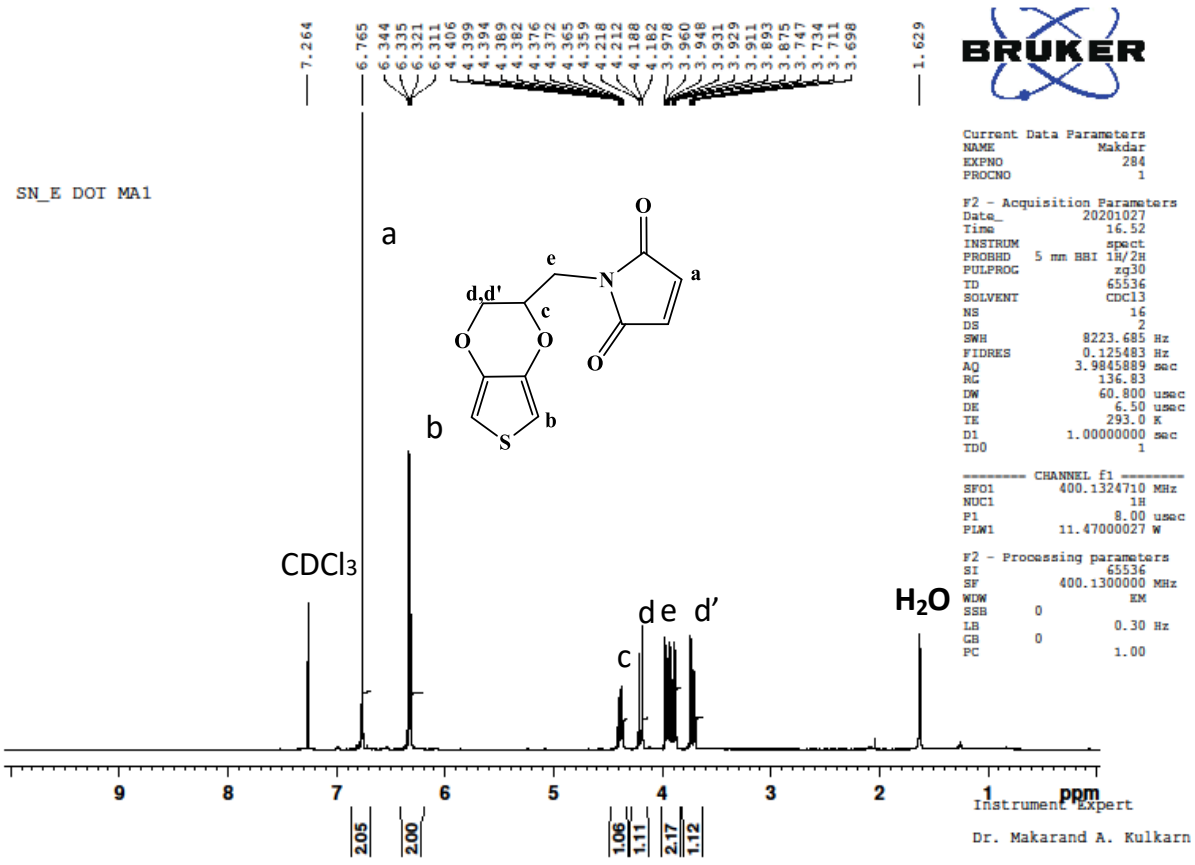


Figure 4: Proton NMR spectrum of racemic EDOT-MA showing the expected positions of the hydrogen resonances, individually labeled a-e.

Bruker ^{1}H NMR

1H NMR of (S)EDOT-MA

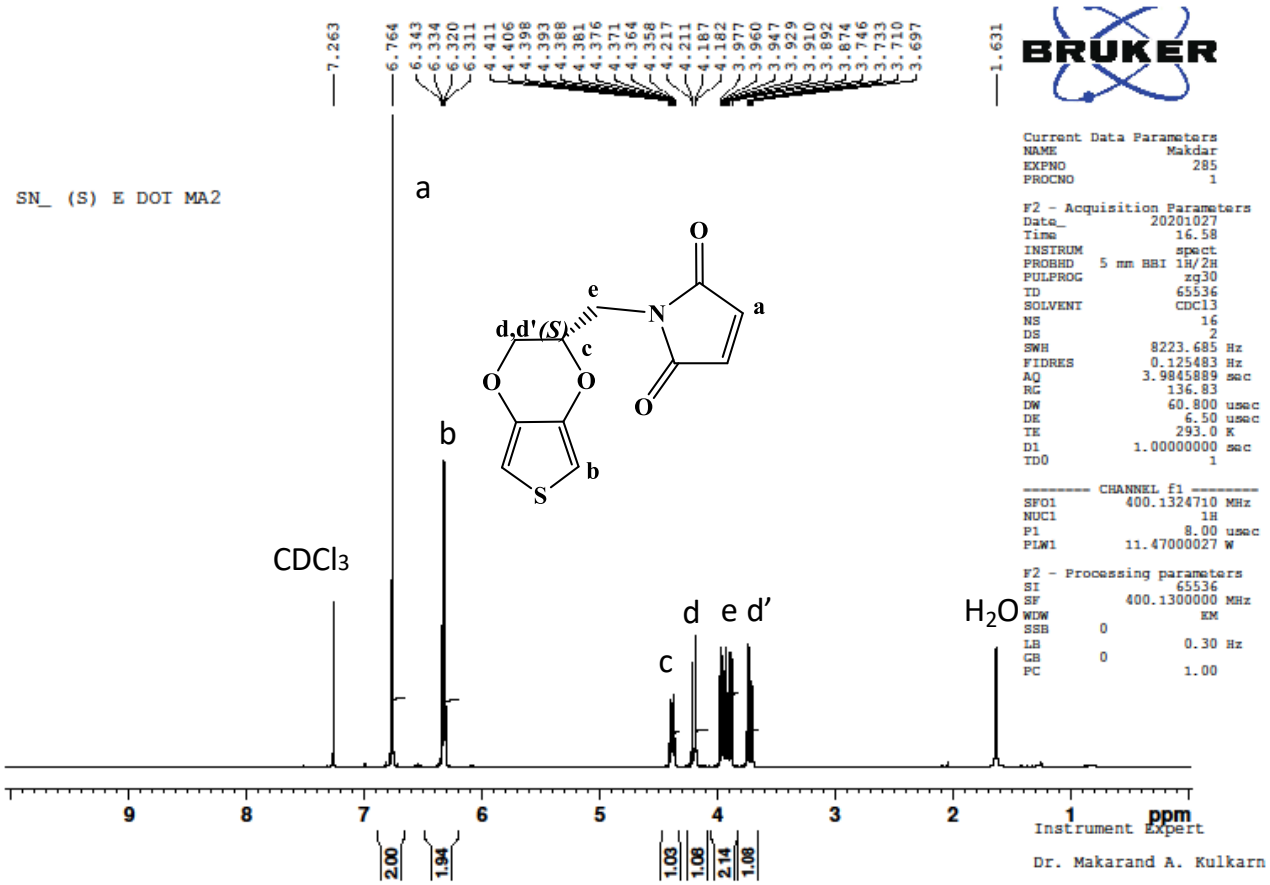
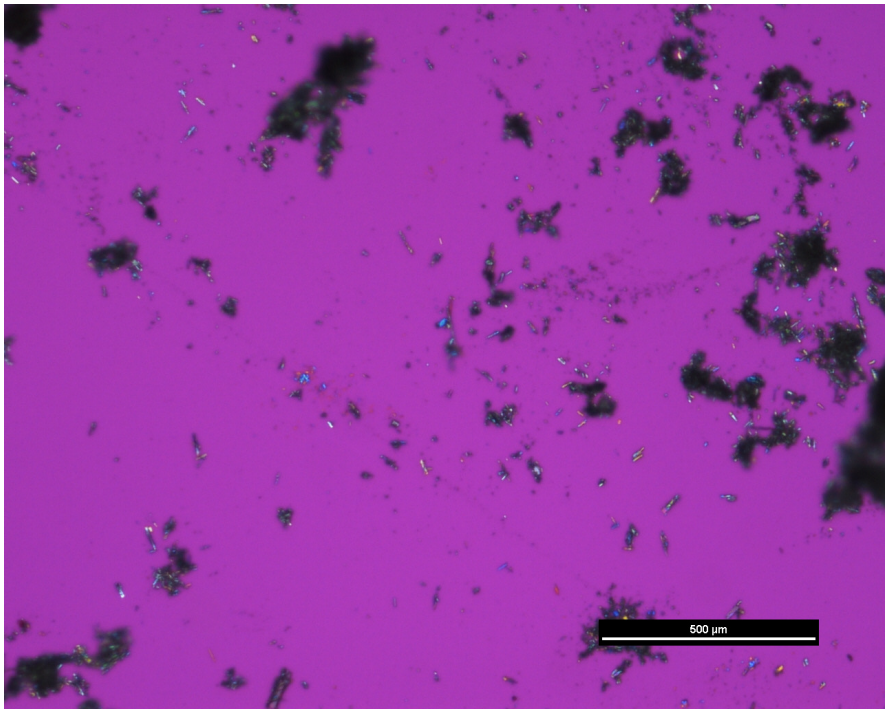
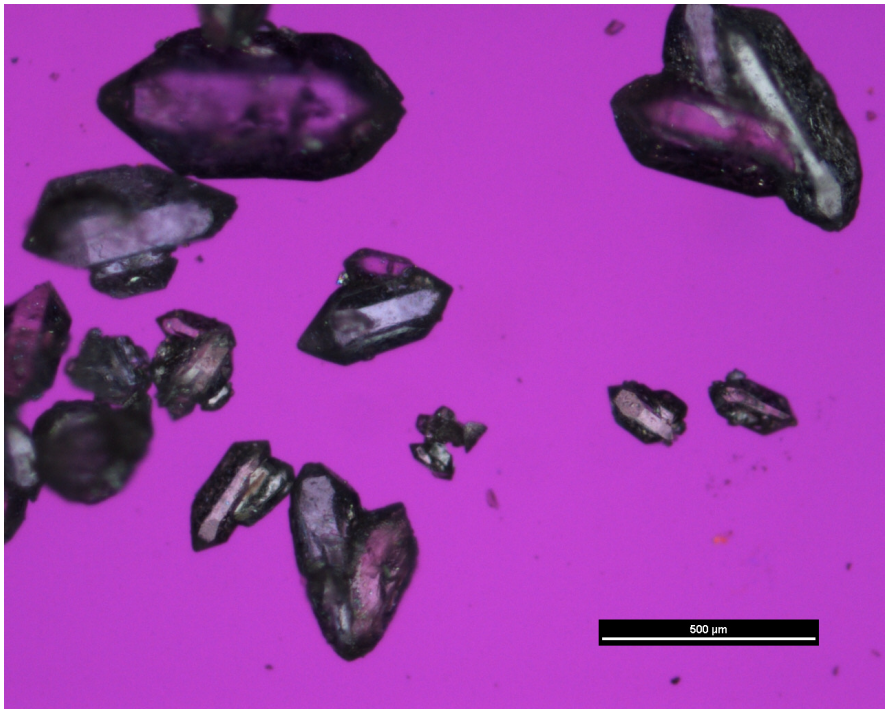


Figure 5: Proton NMR spectrum of chirally pure EDOT-MA (S configuration) showing the expected positions of the hydrogen resonances, individually labeled a-e. The spectrum is indistinguishable from the racemic mixture in Figure 4.

Bruker ^{1}H NMR

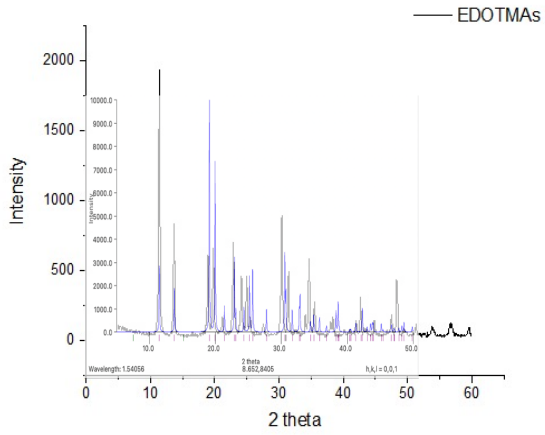


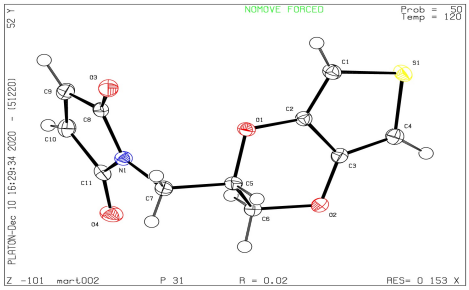
Racemic EDOT-maleimide

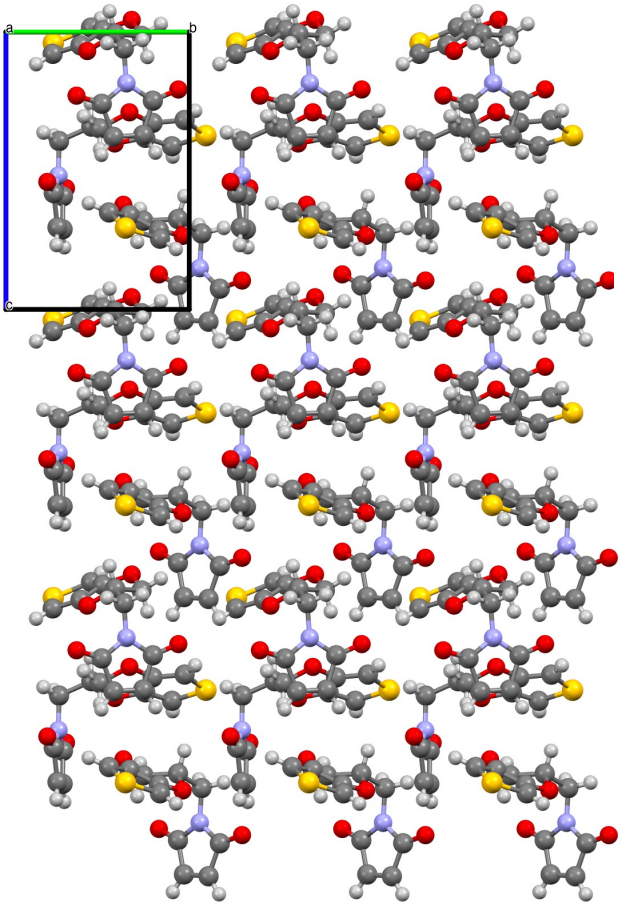


Chiral EDOT-maleimide

Figure 6: Transmitted light optical microscopy of EDOT-MA (racemic) (top) and EDOT-MA (chiral) (bottom). The chiral EDOT-MA shows large, highly faceted crystals (~500 micron) with characteristic angles. The EDOT-MA (racemic) is also crystalline but they are much smaller in size (~1 micron).







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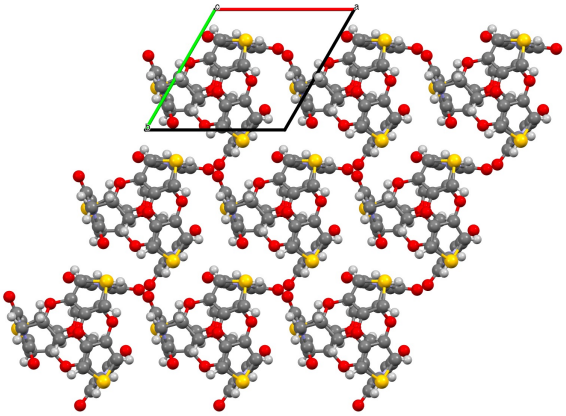


[001] projection

Space group #144
trigonal P 3_1
a=b=0.8959 nm
c=1.1662 nm
Z=3
density = 1.566 gm/cm^3

Figure 7: Unit cell structure of chirally pure EDOT-MA(S) determined by the University of Delaware crystallographic laboratory from a single crystal. The simulated powder diffraction pattern is essentially identical to that seen experimentally.

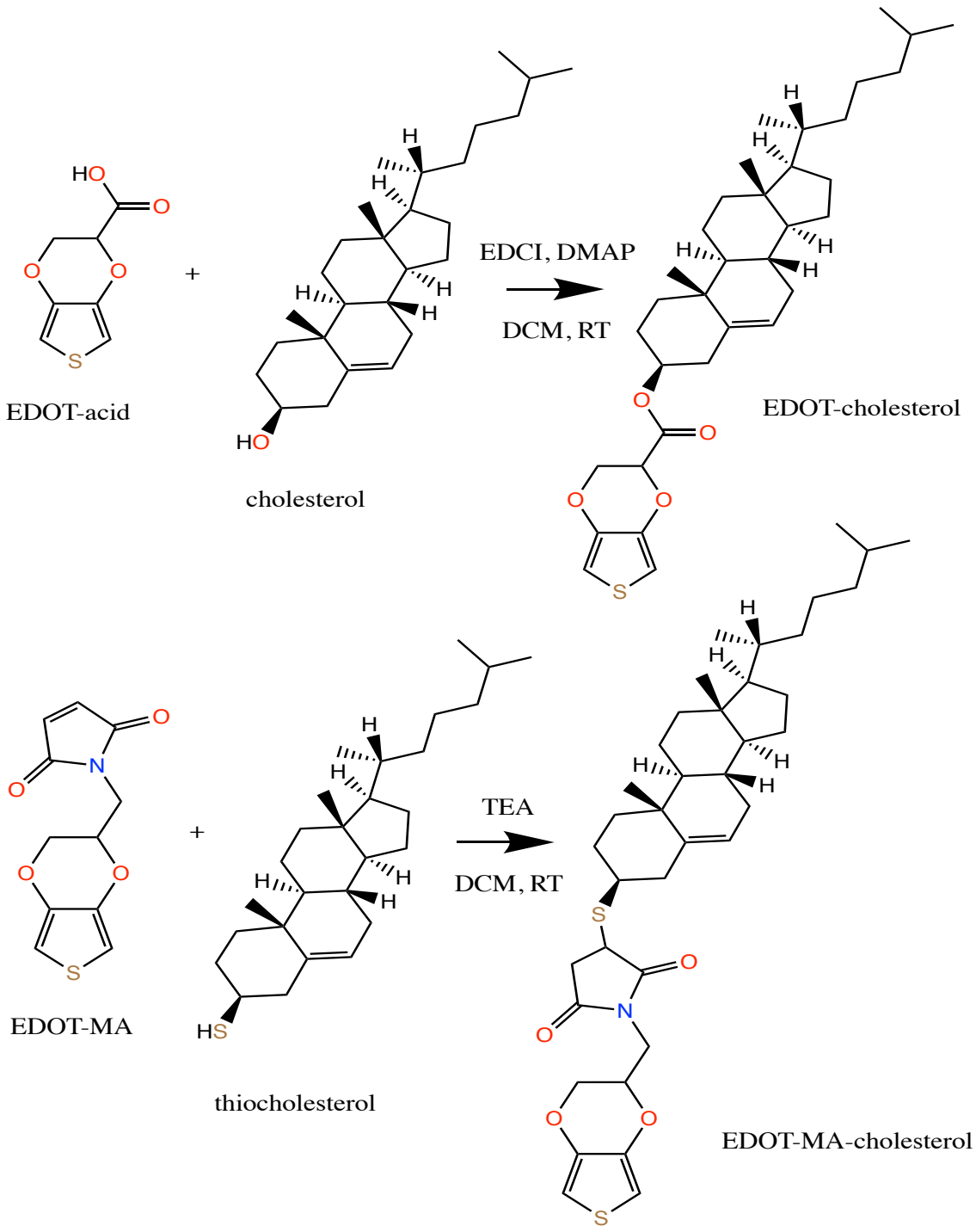


Figure 8: Chemical structures of 3,4-ethylene dioxythiophene–carboxylic acid (EDOT-acid) cholesterol, and the EDOT-cholesterol monomer prepared by esterification with N-(3-dimethyl-aminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane (DCM) solvent at room temperature (Nagane, 2020). Chemical structures of 3,4-ethylenedioxythiophene-maleimide (EDOT-MA), thiocholesterol, and the EDOT-MA-cholesterol monomer prepared by maleimide-thiol click reaction with tetraethylamine (TEA), also in DCM at room temperature.

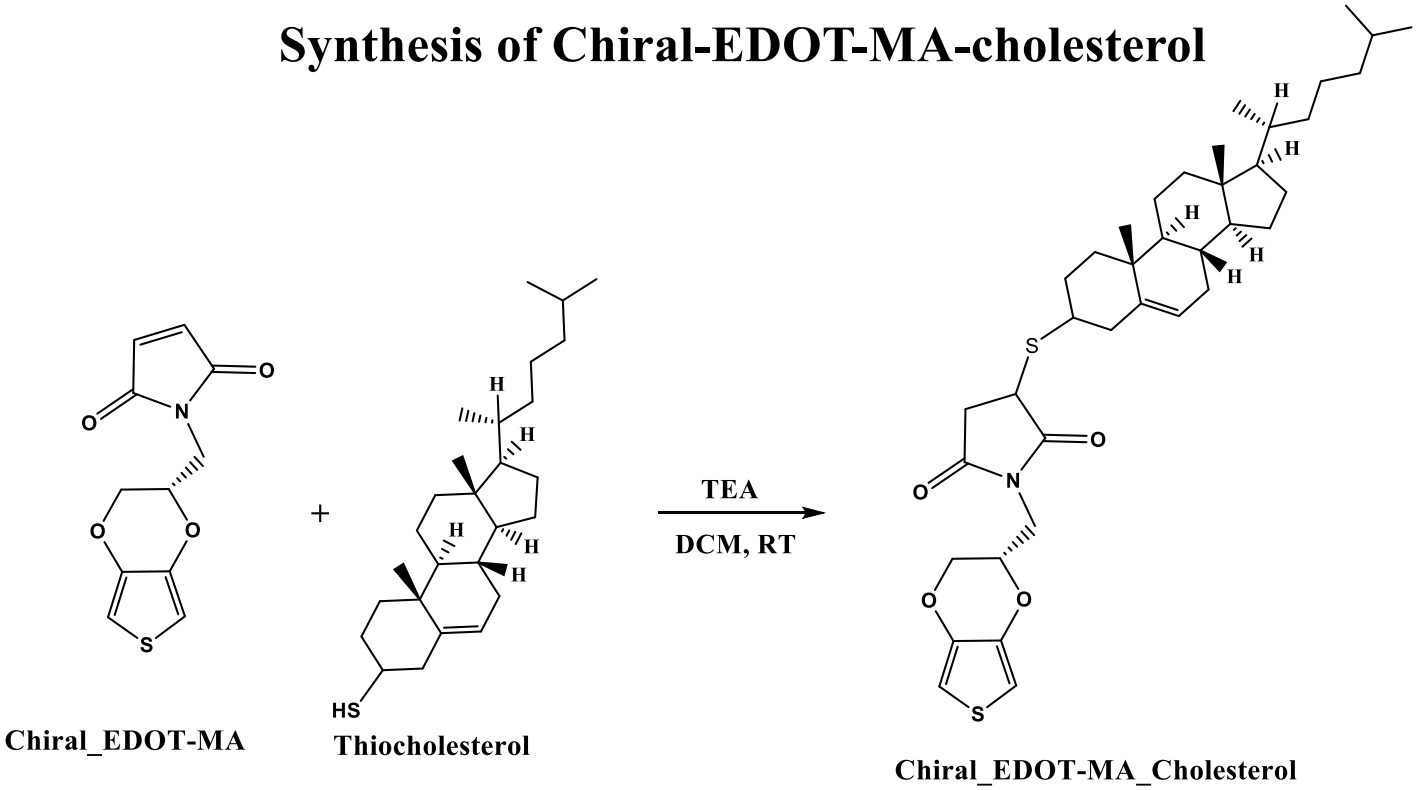
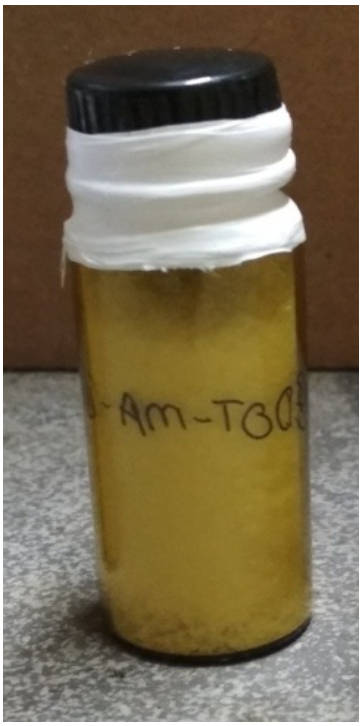
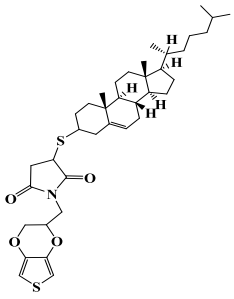


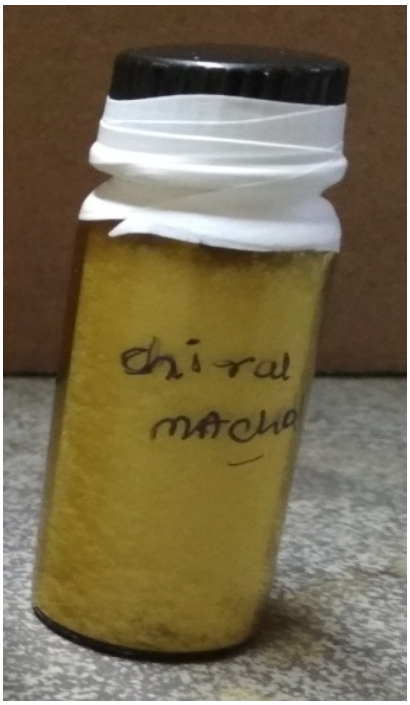
Figure 9: Chemical structures of a 3,4-ethylenedioxythiophene-maleimide (EDOT-MA-cholesterol) with limited control of chirality obtained by using a chirally pure version of EDOT-MA. Although the chirality at the EDOT is controlled, the thiol-maleimide reaction does not control the chirality and so this molecule is racemic mixture of the corresponding products so obtained.

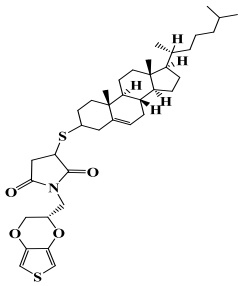




Name: 1-((2,3-dihydrothieno[3,4-*b*][1,4]dioxin-2-yl)methyl)-3-(((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)thio)pyrrolidine-2,5-dione [EDOT-MA-Cholestrol]
Mol. Formula: $C_{38}H_{55}NO_4S_2$
Mol. Weight: 653.98
Quantity: 1.6 gm

Racemic EDOT-MA-cholesterol





Name:1-(((*S*)-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-2-yl)methyl)-3-(((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)thio)pyrrolidine-2,5-dione [(s)EDOT-MA-Cholestrol]
Mol. Formula: $C_{38}H_{55}NO_4S_2$
Mol. Weight: 653.98
Quantity: 1.4 gm

Chiral EDOT-MA-cholesterol

Figure 10: Chemical structures and images of the vials of racemic EDOT-MA-cholesterol (top) and chirally-controlled EDOT-MA-cholesterol (bottom).

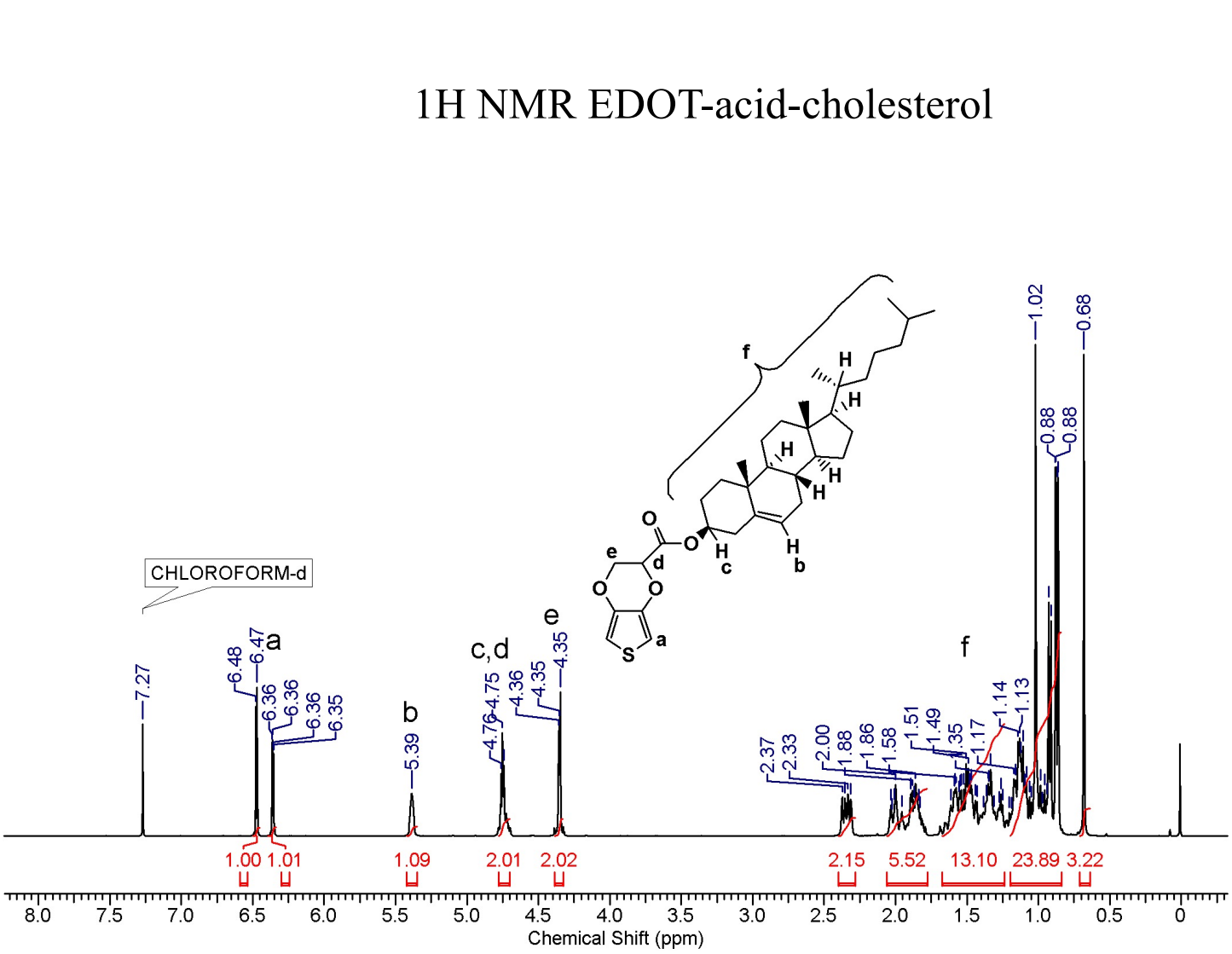
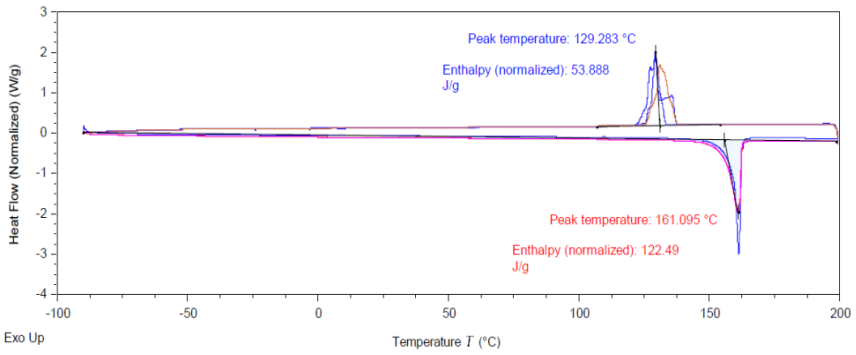
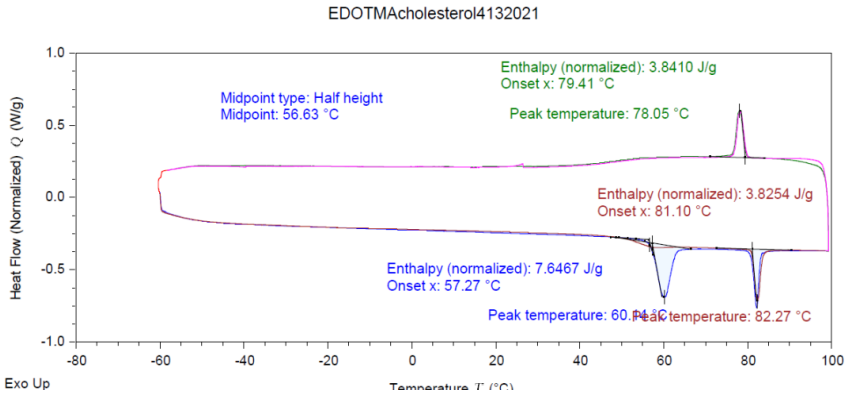


Figure 11: Proton NMR of EDOT-acid-cholesterol (racemic mixture).

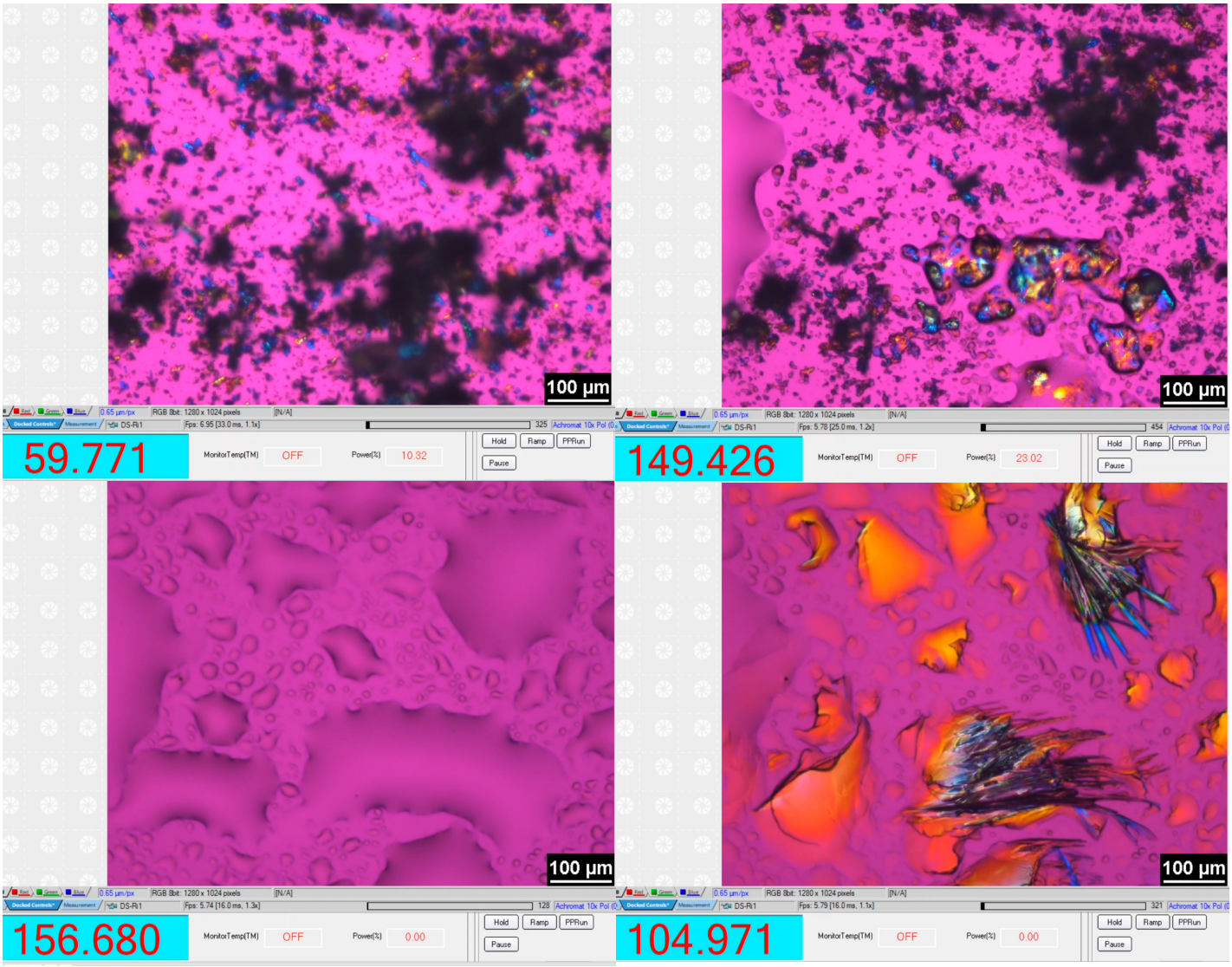


EDOT-acid-cholesterol



EDOT-MA-cholesterol racemic

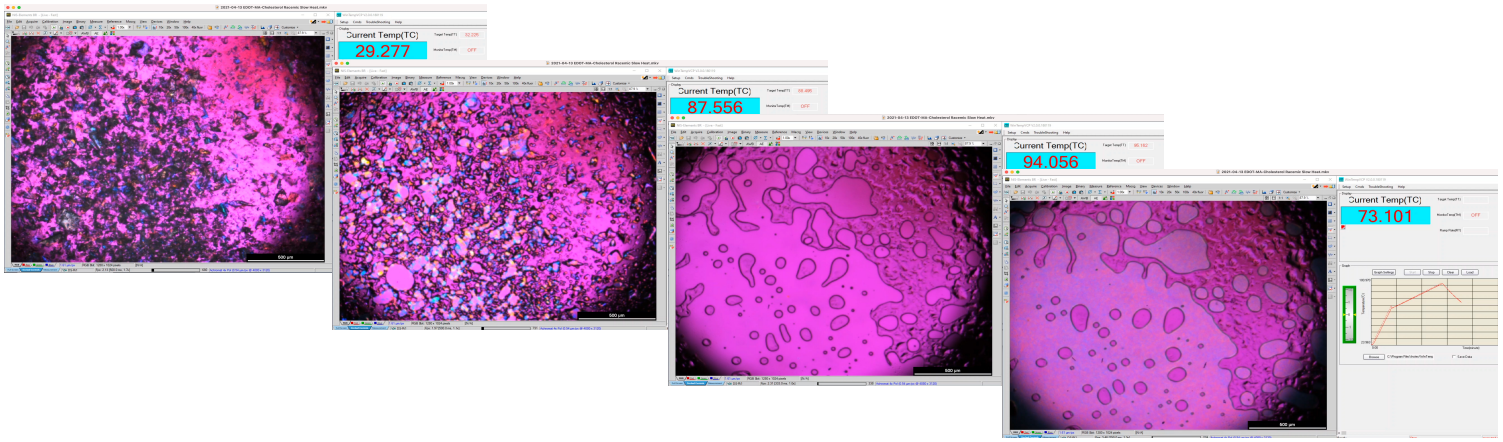
Figure 12: Differential scanning calorimetry (DSC) of EDOT-acid-cholesterol and EDOT-MA-cholesterol.



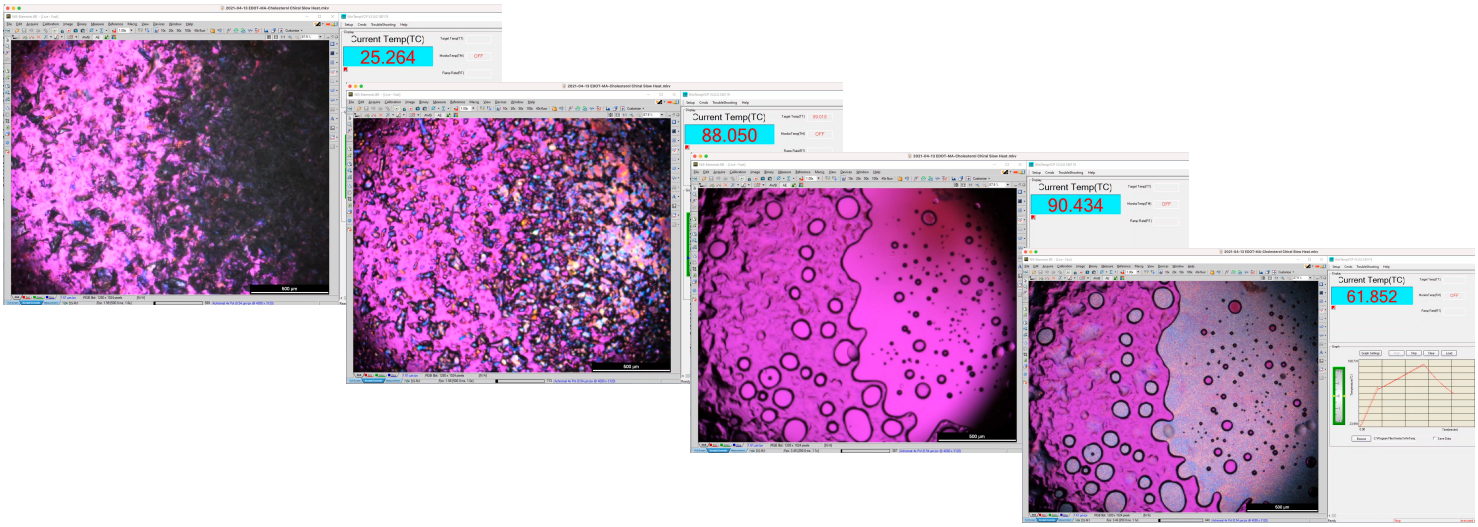
Hot stage optical microscopy of
EDOT-acid-cholesterol

Melting at ~150 C
and recrystallization at ~120 C

Figure 13: Hot-stage optical microscopy of EDOT-acid-cholesterol confirming melting to an isotropic phase at ~150 C, followed by recrystallization at ~120 C during cooling



Racemic EDOT-MA-cholesterol
Tm ~ 82 C Tx~77 C



Chiral EDOT-MA-cholesterol
Tm~86 C Tx~76 C

Figure 14: Hot-stage optical microscopy of racemic EDOT-MA-cholesterol (top) and chirally-controlled EDOT-MA-cholesterol (bottom). The chirally-controlled EDOT-MA-cholesterol melts at a slightly higher temperature. Both samples show evidence for solid-state recrystallization on cooling.

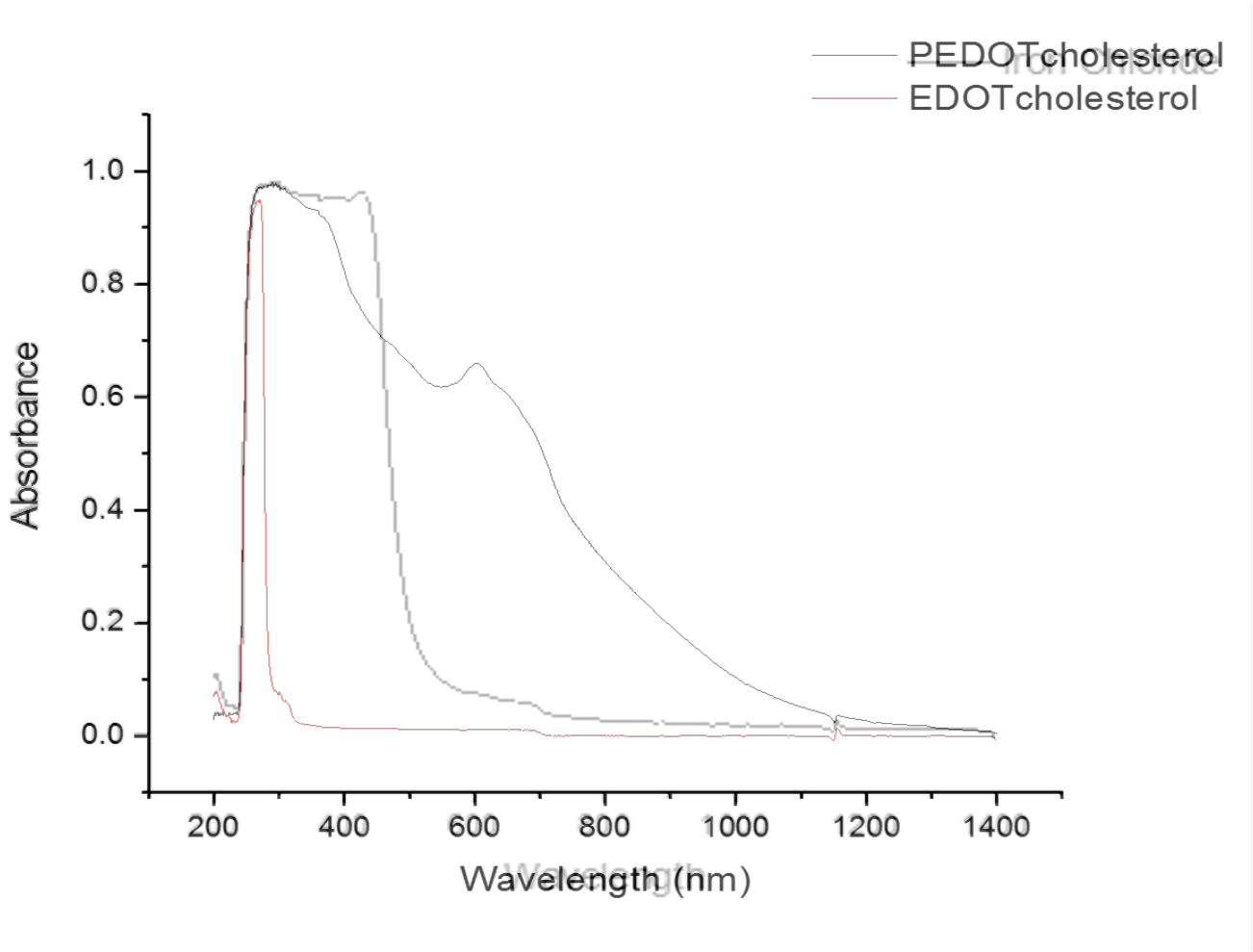
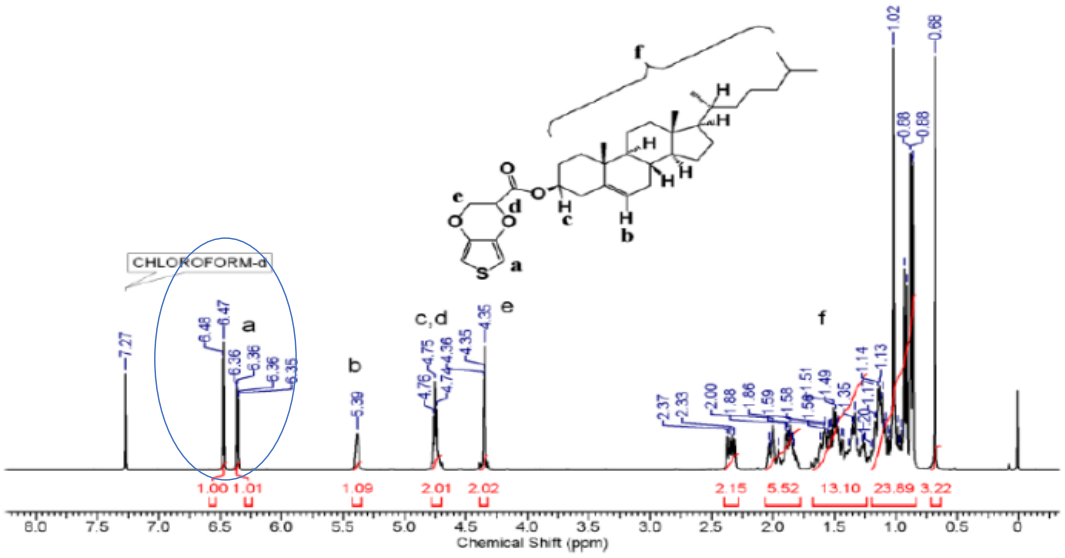
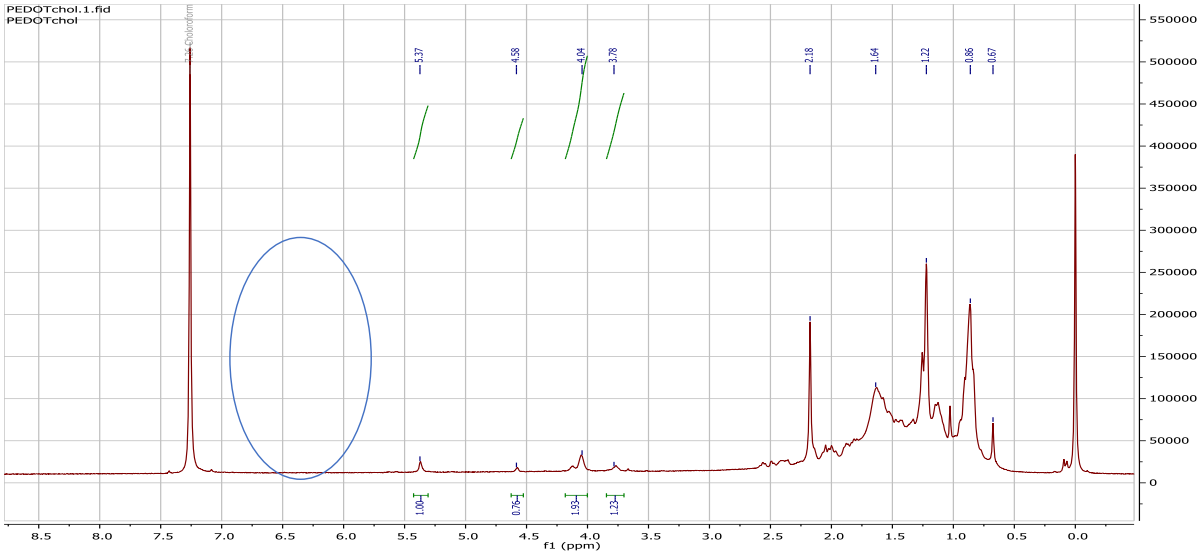


Figure 15: UV-vis spectroscopy of EDOT-acid-cholesterol monomer, PEDOT-acid-cholesterol and the FeCl3 polymerization catalyst. The PEDOT-acid-cholesterol shows the extended absorption associated with polymerization. The PEDOT-acid-cholesterol forms a uniform, dark solution, with evidence for precipitation when held for extended periods of time (several days).

Monomer 1H NMR: expt'l



Polymer 1H NMR: expt'l



Loss of H-thiophene peaks = high molecular weights

Figure 16: Proton NMR of the EDOT-acid-cholesterol monomer (top) and polymer (bottom) shows the loss of the hydrogens on the thiophene ring, consistent with the formation of high molecular weights

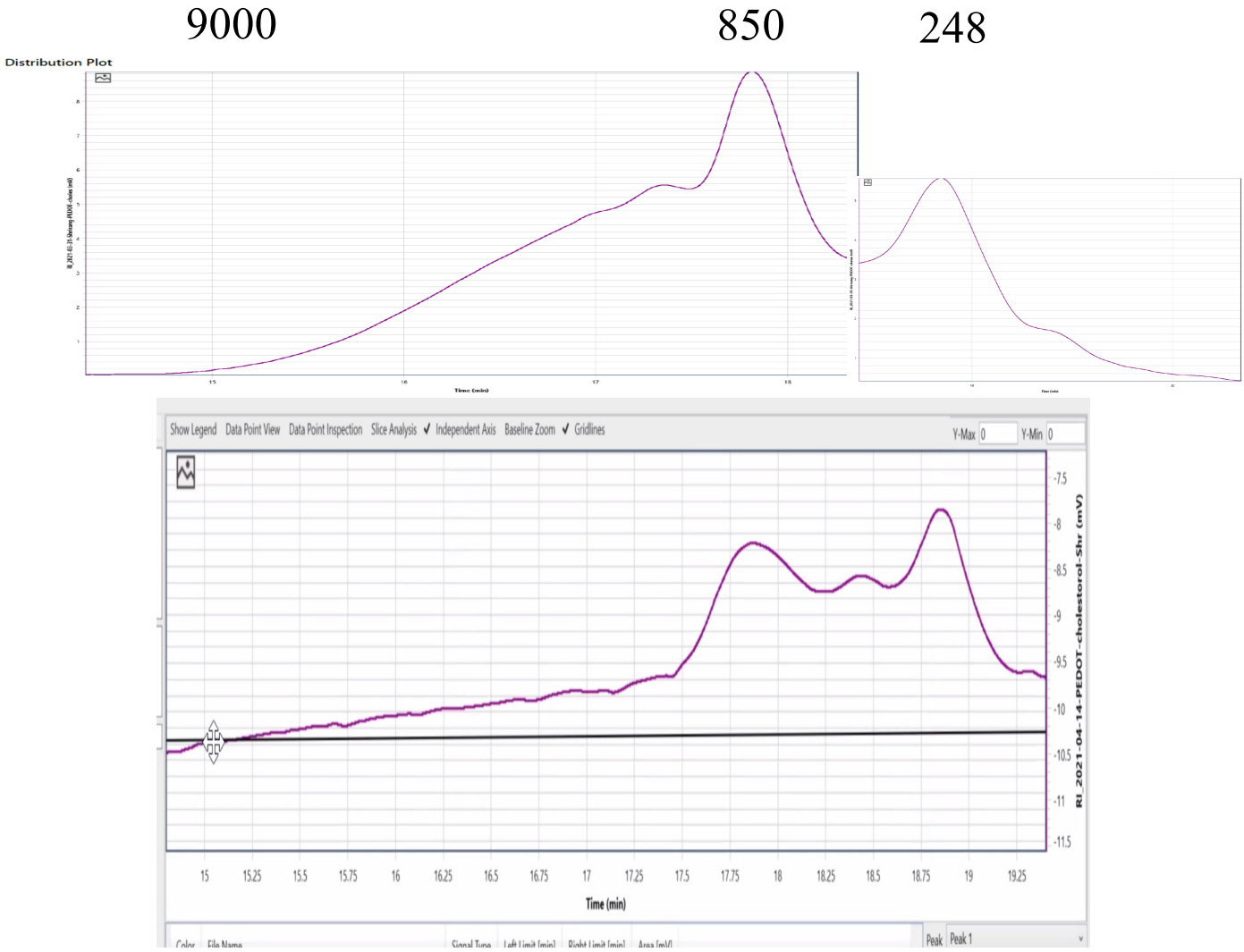


Figure 17: Size-exclusion chromatography (SEC) shows evidence for molecular weight of ~9000 gms/mole for PEDOT-cholesterol. We are hopeful that these organic-soluble samples can be processed into films and fibers. There have been only limited examples of soluble PEDOT variants discussed in the literature, particularly in non-polar solvents.

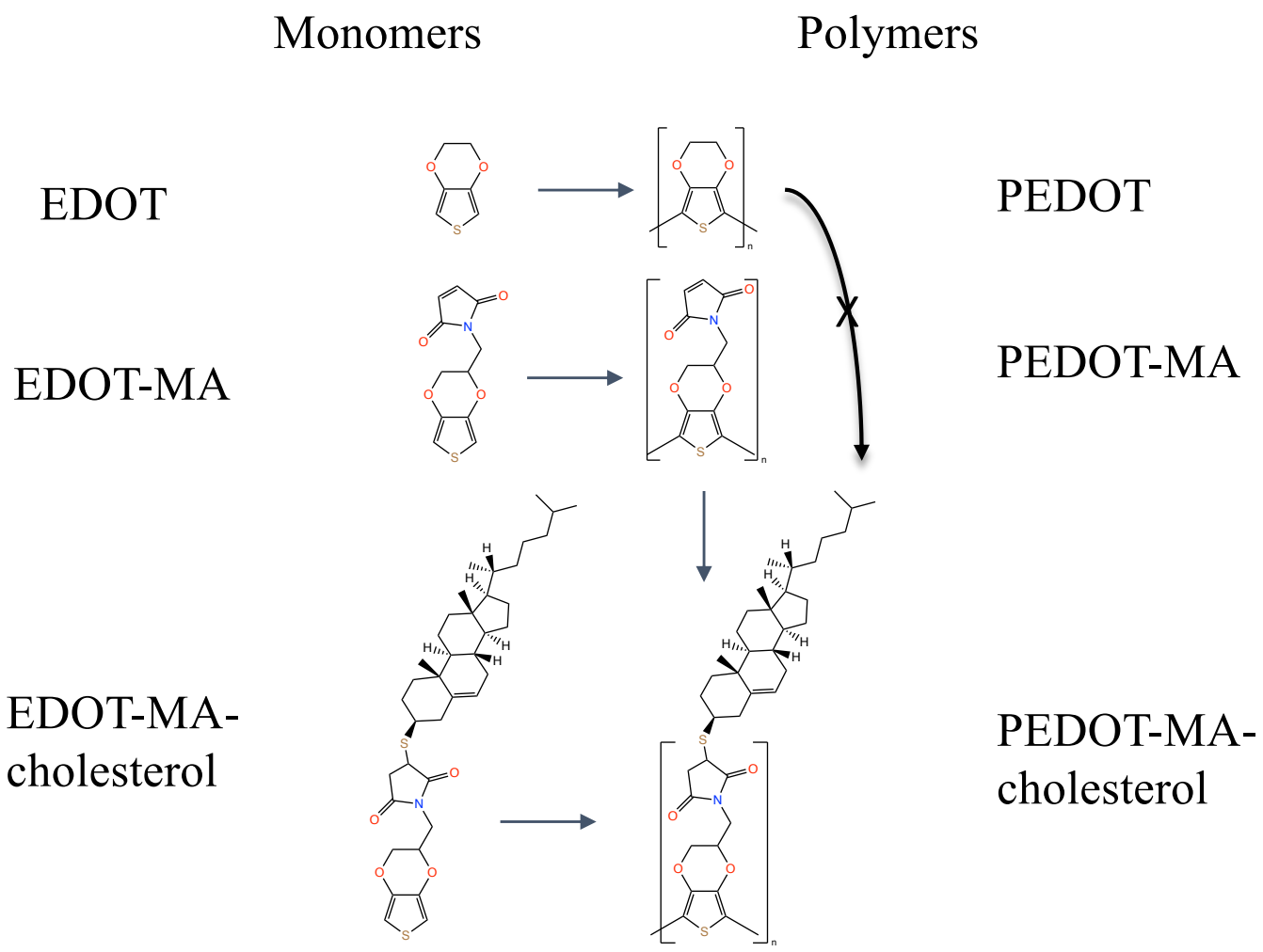
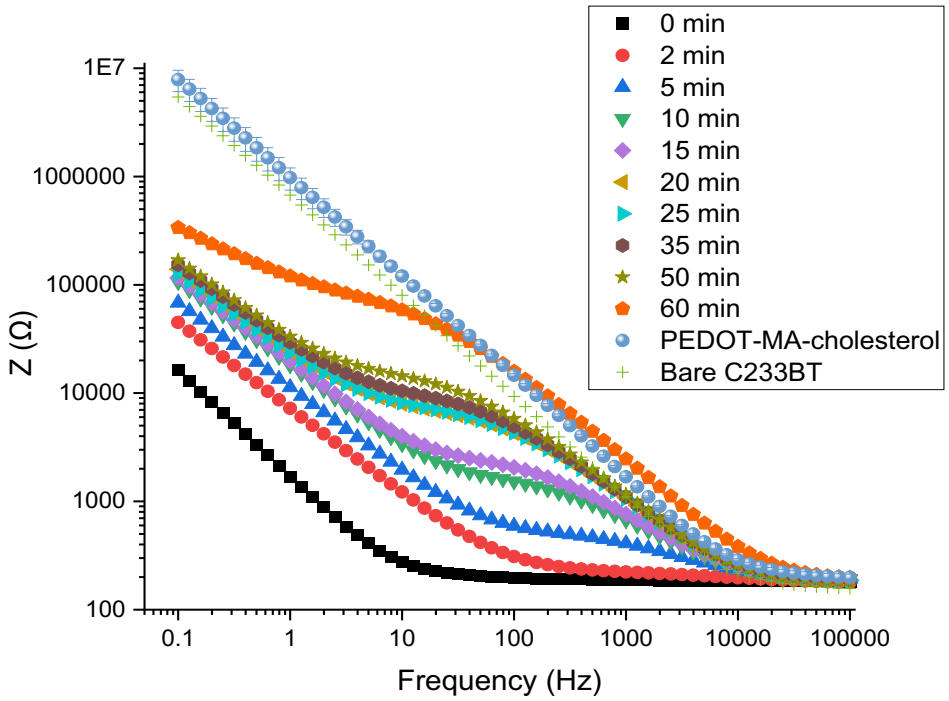


Figure 18: Overview showing the monomers and corresponding polymers that this project has made it possible for us to create and characterization. The usual EDOT monomer reacts to form the polymer PEDOT. The functionalized EDOT-MA monomer forms the corresponding polymer PEDOT-MA. The EDOT-MA-cholesterol can be likewise be polymerized to create PEDOT-MA-cholesterol. Alternatively, the PEDOT-MA polymer can first be polymerized and then functionalized to PEDOT-MA-cholesterol by exposure to thiol-cholesterol. Exposing PEDOT itself to thiol-cholesterol results in no reaction.

Precise Tailoring of Electrode Charge Transport Properties Possible by Post-Polymerization Deposition of Thiocholesterol on PEDOT-MA



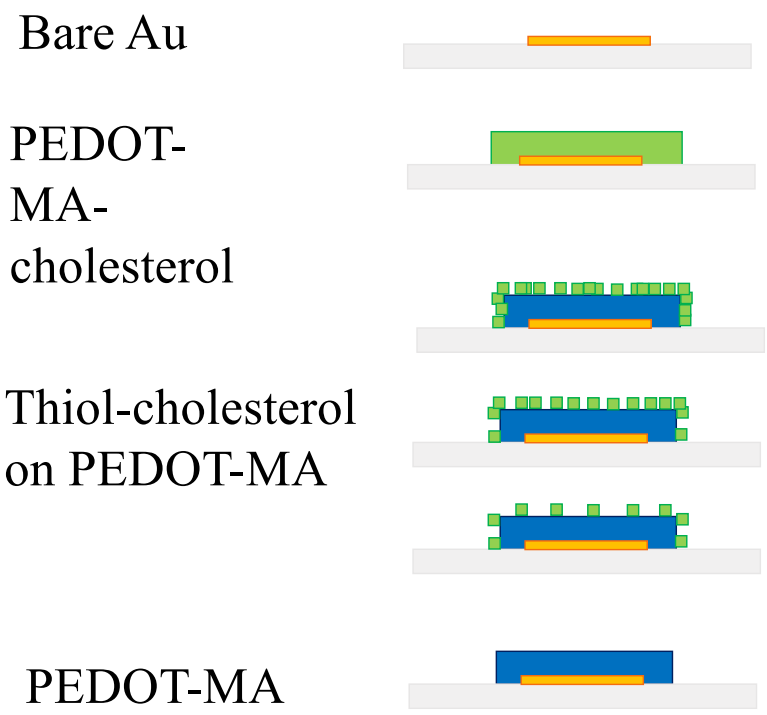


Figure 19: Impedance spectroscopy showing the low impedance of PEDOT-MA (similar to PEDOT). Exposing PEDOT-MA to thiol-cholesterol results in a systematic increase of impedance. The PEDOT-MA-cholesterol polymer prepared directly from the EDOT-MA-cholesterol monomer shows impedance behavior similar to that of the uncoated bare electrode (neither increasing or decreasing impedance).