Synthetic Functionalities for Ion and Electron Conductive Polymers

Applications in Organic Electronics
and Biological Interfaces

Tobias Abrahamsson

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**Applications in Organic Electronics
and
Biological Interfaces**

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Description of the cover:

The illustration represents a branching polymer network.

**Synthetic Functionalities for Ion and Electron Conductive Polymers:
Applications in Organic Electronics and Biological Interfaces**

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During the course of the research underlying this thesis, Tobias Abrahamsson was enrolled in Forum Scientium, a multidisciplinary graduate school at Linköping University, Sweden.

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“If a cognition is to have objective reality, i.e., if it refer to an object and have in that object its signification and meaning, then the object must be capable of being given in some way. For otherwise the concepts are empty; and though we have thought by means of them, we have in fact cognized nothing through this thinking, but have merely played with presentations.”

Immanuel Kant

Critique of Pure Reason
On the Supreme Principle of All Synthetic Judgments

A 156-157, B 195-196

Immanuel Kant, Critique of Pure Reason – Unified Edition (1781 and 1787 editions) Translated by Werber S. Pluhar. (1996 by Hackett Publishing Company Inc.)

Abstract

In the search for understanding and communicating with all biological systems, in humans, animals, plants, and even microorganisms, we find a common language of all communicating via electrons, ions and molecules. Since the discovery of organic electronics, the ability to bridge the gap and communicate between modern technology and biology has emerged. Organic chemistry provides us with tools for understanding and a material platform of polymer electronics for communication. Such insights give us not only the ability to observe fundamental phenomenon but to actively design and construct materials with chemical functionalities towards better interfaces and applications. Organic electronic materials and devices have found their way to be implemented in the field of medicine for diagnostic and therapeutic purposes, but also in water purification and to help tackle the monumental task in creating the next generation of sustainable energy production and storage. Ultimately it's safe to say that organic electronics are not going to replace our traditional technology based on inorganic materials but rather the two fields can find a way to complement each other for various purposes and applications. Compared to conventional silicon based technology, production of carbon-based organic electronic polymer materials are extremely cheap and devices can even be made flexible and soft with great compatibility towards biology.

The main focus of this thesis has been developing and synthesizing new types of organic electronic and ionic conductive polymeric materials. Rational chemical design and modifications of the materials have been utilized to introduce specific functionalities to the materials. The functionalities serving the purpose to facilitate ion and electron conductive charge transport for organic electronics and with biological interface implementation of the polymer materials.

Multi-functional ionic conductive hyperbranched polyglycerol polyelectrolytes (dendrolytes) were developed comprising both ionically charged groups and cross-linkable groups. The hyperbranched polyglycerol core structure of the material possesses a hydrophilic solvating platform for both ions and maintenance of solvent molecules, while being a biocompatible structure. Coupled with the peripheral charged ionic functionalities of the polymer, the dendrolyte materials are highly ionic conductive and selective towards cationic and anionic charged atoms and large molecules when implemented as ion-exchange membranes. Homogenous ion-exchange membrane casting has been achieved by the implementation of cross-linkable functionalities in the dendrolytes, utilizing robust click-chemistry for efficient micro and macro fabrication processing of the ion-exchange membranes for organic electronic devices. The ion-exchange membrane material was implemented in electrophoretic drug delivery devices (organic electronic ion pumps), which are used for delivery of ions and neurotransmitters

with spatiotemporal resolution and are able to communicate and be used for therapeutic drug delivery purposes in biological interfaces. The dendrolyte materials were also able to form free-standing membranes, making it possible for implementation in fuel cell and desalination purposes.

Trimeric conjugated thiophene pre-polymer structures were also developed in the thesis and synthesized for the purpose of implementation of the material *in vivo* to form electrically conductive polymer structures, and in such manner to be able to create electrodes and ultimately to connect with the central nervous system. The conjugated pre-polymers being both water soluble and enzymatically polymerizable serve as a platform to realize such a concept. Also, modifying the trimeric structure with cross-linkable functionality created the capability to form better interfaces and stability towards biological environments.

Populärvetenskaplig Sammanfattning

I sökandet efter förståelse och att kommunicera med alla biologiska system, människor, djur, växter och till och med mikroorganismer hittar vi ett gemensamt språk för all kommunikation via elektroner, joner och molekyler. Sedan upptäckten av organisk elektronik har förmågan att kommunicera och överbrygga klyftan mellan modern teknik och biologi vuxit fram. Där organisk kemi ger oss verktyg till förståelse och en materiellplattform av polymerelektronik till att kunna skapa denna kommunikation. Sådana insikter ger oss inte bara möjligheten att observera grundläggande fenomen utan till att aktivt utforma och konstruera material med kemiska funktioner för att uppnå bättre gränssnitt inom applikationer. Organiska elektroniska material och enheter har hittat sätt att bli implementerade inom medicin för diagnostiska och terapeutiska ändamål, men även inom vattenrening och för att hjälpa med att ta itu med den enorma uppgiften att skapa nästa generation av hållbar energiproduktion och lagring. I slutändan är det med säkerhet att säga att organisk elektronik inte kommer att ersätta vår traditionella teknik baserad på oorganiska material utan att båda fälten strävar efter att hitta sätt att komplettera varandra för olika ändamål och applikationer. Jämfört med konventionell kiselbaserad teknik är produktionen av kolbaserade organiska elektroniska polymermaterial extremt billigt och enheter kan till och med göras flexibla och mjuka med god kompatibilitet emot biologi.

Det huvudsakliga ändamålet för denna avhandling har varit att utveckla och syntetisera nya typer av organiska elektron- och jonledande polymermaterial. Där rationell kemisk design och modifieringar av materialen har använts för att introducera specifika funktioner hos materialen. Funktioner vars ändamål varit till underlätta jonisk och elektronisk laddningstransport hos organisk elektronik samt biologiska gränssnittsimplementering av polymermaterialen.

Multifunktionella hypergrenade polyglycerol polyelektrolyter (dendrolyter) har utvecklats, bestående av både joniskt laddade samt tvärbidningsbara funktionella grupper. Den hypergrenade polyglycerolens kärnstrukturen hos materialen bidrar med hydrofiliska egenskaper för både joner och bevarande av lösningsmedelmolekyler i sin struktur, som samtidigt är biokompatibel. Tillsammans med polymerens yttre kringliggande laddade joniska funktioner bidrar till att göra materialen oerhört joniskt ledande, selektiva gentemot katjoner och anjoner samt erhålla transport möjligheter för stora molekyler vid implementering som jonbytesmembran. Homogena jonbytarmembran har uppnåtts vid gjutning med hjälp av implementeringen av de tvärbidningsbara egenskaperna hos dendrolyterna, som utnyttjar robust klick-kemi för effektiv mikro- och makrotillverk-

ning av jonbytarmembranen för organiska elektroniska enheter. Jonbytarmembranmaterialen kan implementeras för elektrofores baserade läkemedelsleverans i den organiska elektroniska jonpumpen (OEIP), som används vid leverans av joner och signalsubstanser med spatiotemporal upplösning. Som i sin tur kan kommunicera med biologiska gränssnitt för terapeutiska ändamål. Dendrolytmaterialen kunde även bilda fristående membranstrukturer, vilket möjliggör implementering för bränsleceller och för vattenavsaltningsändamål.

Trimer konjugerade tiofen pre-polymerstrukturer har också utvecklats i tesen och syntetiserades i syfte med att implementera materialen *in vivo* för att bilda elektriska ledande polymerstrukturer. På ett sådant sätt kunna skapa elektroder och slutligen anslutas till det centrala nervsystemet. De konjugerade pre-polymererna var både vattenlösliga och enzymatiskt polymeriserbara fungerar som en plattform för att förverkliga ett sådant koncept. Genom att modifiera den trimeriska strukturen med tvärbindningsbar funktionalitet och på sådant sätt skapa förmågan att bilda bättre gränssnitt och stabilitet emot biologiska miljöer.

Acknowledgement

“If I have seen the future it is by standing on the shoulders of giants”

Isaac Newton letter to Robert Hooke, 1675

The famous metaphor that generally refers to building on the understanding gained by those gone before us, applies as much to those in the past to those whom we share our presence with. I'd like to extend a thanks for this outlook for the future, as not only in regards to scientific knowledge but to all the people I share and have shared my life with on a daily basis in every possible way, making life enjoyable with an optimistic outlook of what yet to come.

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Tack så mycket!

List of Included Publications

Paper I

Formation of monolithic ion-selective transport media based on “click” cross-linked hyperbranched polyglycerol

Tobias Abrahamsson, David J. Poxson, Erik O. Gabrielsson, Mats Sandberg, Daniel T. Simon, Magnus Berggren

Frontiers in Chemistry, **2019**, 7, 484

Contributions: Synthesis, chemical characterization, manuscript writing

Paper II

Capillary-fiber based electrophoretic delivery device

David J. Poxson, Erik O. Gabrielsson, Alberto Bonisoli, Ulrika Linderhed, Tobias Abrahamsson, Isabella Matthiesen, Klas Tybrandt, Magnus Berggren, Daniel T. Simon

ACS Appl. Mater. Interfaces, **2019**, 11, 14200-14207

Contributions: Material development, synthesis & characterization, manuscript writing

Paper III

Investigating the role of polymer size on ionic conductivity in free-standing hyperbranched polyelectrolyte membranes

Tobias Abrahamsson, Mikhail Vagin, Maria Seitanidou, Arghyamalya Roy, Jaywant Phopase, Ioannis Petsagkourakis, Nathalie Moro, Klas Tybrandt, Xavier Crispin, Magnus Berggren, Daniel T. Simon

Polymer, **2021**, 223, 123664

Contributions: Material synthesis, fabrication, chemical and electrical characterization, analysis, conception and writing manuscript

Paper IV

Seamless integration of bioelectronic interface in an animal model via in-vivo polymerization of conjugated oligomers

Giuseppina Tommasini, Gwennaël Dufil, Federica Fardella, Xenofon Strakosas, Eugenio Fergola, Tobias Abrahamsson, David Bliman, Roger Olsson, Magnus Berggren, Angela Tino, Eleni Stavrinidou, Claudia Tortiglione

Bioactive Materials, **2021**

Contributions: Material synthesis and characterization

Paper V

In vivo formation of organic bioelectronic hydrogel devices

Xenofon Strakosas, Hanne Biesmans, Tobias Abrahamsson, Karin Hellman, Malin Silverå Ejneby, Mary J. Donahue, Peter Ekström, Fredrik Ek, Marios Savvakis, Martin Hjort, David Bliman, Mathieu Linares, Daniel T. Simon, Roger Olsson, Magnus Berggren

Manuscript in preparation

Contributions: Synthesis, chemical characterization, material-device interface conceptualization, manuscript writing

Related Publications Not Included in the Thesis

Paper I

A biomimetic evolvable organic electrochemical transistor

Jennifer Y. Gerasimov, Dan Zhao, Ayesha Sultana, Tobias Abrahamsson, Shaobo Han, David Bliman, Deyu Tu, Daniel T. Simon, Roger Olsson, Xavier Crispin, Magnus Berggren, Simone Fabiano

Adv. Electron. Mater. **2021**, 2001126

Paper II

Soft iontronic delivery devices based on an intrinsically stretchable ion selective membrane

Dennis Cherian, Samuel Lienemann, Tobias Abrahamsson, Nara Kim, Magnus Berggren, Daniel T. Simon, Klas Tybrandt

Flexible and Printed Electronics, **2021**

Paper III

Flexible organic electronic ion pump fabricated using inkjet printing and microfabrication for in-vitro high precision delivery of bupivacaine

Dennis Cherian, Arghyamalya Roy, Alex Bersellini Farinotti, Tobias Abrahamsson, Theresia Arbring Sjöström, Klas Tybrandt, Magnus Berggren, Camilla I. Svensson, David Nilsson, David J. Poxson, Daniel T. Simon

Manuscript in preparation

Paper IV

Minding the gap: Rational design of materials for evolvable organic electrochemical transistors

Jennifer Y. Gerasimov, Arnab Halder, Padinhare Cholakkal Harikesh, Sarbani Ghosh, Abdelrazek Mousa, Tobias Abrahamsson, Diana Priyadarshini, David Bliman, Roger Olsson, Igor Zozoulenko, Daniel T. Simon, Magnus Berggren, Simone Fabiano

Manuscript in preparation

Paper V

Proton-coupled electron transfers of 9-fluorenone: towards organic electrochemical hydrogen storage

Hamid Ghorbani Shiraz, Mikhail Vagin, Tero-Petri Ruoko¹, Krzysztof Karoń, Mieczysław Łapkowski, Tobias Abrahamsson, Viktor Gueskine, Thomas Ederth, Magnus Berggren, Xavier Crispin

Manuscript in preparation

Paper VI

Enzymatically formed Organic Electrochemical Transistor materials with stable bio interfaces

Marios Savvakis, Xenofon Strakosas, Tobias Abrahamsson, David Bliman, Roger Olsson, Daniel Simon, Magnus Berggren

Manuscript in preparation

Table of Contents

Abstract	vii
Populärvetenskaplig Sammanfattning	ix
Acknowledgement	xi
List of Included Publications	xv
Related Publications Not Included in the Thesis	xvii

I Background and Theory

1. Introduction	1
1.1 Organic Electronics	1
1.2 Organic Bioelectronic	2
1.3 Aim of the Thesis	2
1.4 Thesis Outline	3
2. Organic Chemistry and Electronics	5
2.1 Atomic Orbitals	5
2.2 Molecular Orbitals	7
2.3 Orbital Hybridization	9
2.4 Band Gap Theory	11
2.4.1 Organic Semi-Conductors and Doping	13
3. Polymers	15
3.1 Polymer Synthesis - Polymerization	15
3.1.1 Linear Hyperbranched and Dendritic Polymers	17
3.1.2 Hyperbranched Polyglycerol	19
3.2 Synthesis & Polymerization of Conjugated Polymers	19
3.2.1 Chemical Polymerization - Cross-Coupling Reaction	20
3.2.1.1 Palladium Catalyst	21
3.2.1.2 Suzuki-Miyaura Coupling	22
3.2.2 Enzymatic Polymerization	24
3.3 Synthetic Functionalities	25
3.3.1 Polyelectrolyte Functionality	26
3.3.1.1 Self-Doping in Conjugated Polymers	26
3.3.2 Cross-Linking Functionalities	27
3.3.2.1 Thiol-ene Cross-Linking	28
3.3.2.2 Amide Cross-Linking for Biological Interfaces	29

4. Ionic Transport and Ion Selective Membranes.....	31
4.1 Electrolytes and Ionic Conductivity.....	31
4.1.1 Ionic Transport	32
4.1.2 Diffusion Coefficient Ion Transport and Diffusion Potential ...	33
4.2 Ion-Exchange Membranes	35
4.2.1 Donnan Potential	36
4.2.2 Fixed Ionic Charges in Ion-Exchange Membranes	37
4.2.3 Ion-Exchange Capacity.....	39
4.2.4 Swelling and Water Content.....	39
5. Organic Bioelectronics and Iontronics	41
5.1 Iontronics Devices.....	42
5.1.1 Organic Electrochemical Transistor	42
5.1.2 Organic Electronic Ion Pump	43
5.1.2.1 Planar OEIP	44
5.1.2.2 Capillary OEIP	45
5.2 Electrochemical Cells – Large Ion-Exchange Membranes	46
5.2.1 Fuel Cell	46

II Experimental and Results

6. Material Synthesis and Structural Characterizaiton	51
6.1 Synthesis of Hyperbranched Polyglycerol	51
6.2 Dialysis	52
6.3 Gel Permeation Chromatography.....	53
6.4 Nuclear Magnetic Resonance Spectroscopy	54
6.4.1 Polymer NMR	57
6.4.2 Polymer Molecular Weight Analysis by ¹ H-NMR	58
6.4.3 Degree of Branching – Inverse Gated ¹³ C-NMR.....	58
6.5 Multi-Functionalization	60
6.5.1 Polymer Degree of Functionalization ¹ H-NMR	60
6.5.2 A-HPG Synthesis	61
6.5.3 C-HPG Synthesis.....	63
6.6 Conjugated Triemer Synthesis	65
6.6.1 ETE-S Synthesis	65
6.6.2 ETE-Carboxylate Synthesis	67
6.6.3 High Performance Liquid Chromatography–Mass Spectroscopy	69

7. Device Fabrication.....	71
7.1 Ion-Exchange Membrane Ink Formulation and Casting	71
7.2 OEIP Capillary Device Fabrication.....	74
7.2.1 MIMIC OEIP	75
7.3 Free-Standing IEM and E-Cell Device	77
7.4 ETE-NHS Activation with PolyLysine Gels.....	78
8. Overview of the Publications	79
9. Concluding Remarks and Outlook	83
Bibliography	87
Publications	97
Paper I - Formation of Monolithic Ion-Selective Transport Media Based on “Click” Cross-Linked Hyperbranched Polyglycerol	
Paper II - Capillary-Fiber Based	
Paper III - Investigating the Role of Polymer Size on Ionic Conductivity in Free- Standing Hyperbranched Polyelectrolyte Membranes	
Paper IV - Seamless Integration of Bioelectronic Interface in an Animal Model via <i>In Vivo</i> Polymerization of Conjugated Oligomers	
Paper V - <i>In Vivo</i> Formation of Organic Bioelectronic Hydrogel Devices	

Part I

Background and Theory

1 Introduction

1.1 Organic Electronics

It is common when hearing the word ‘electronics’ for our minds to wander off to the world of physics, technology and engineering based on the phenomena of electricity, with the control and flow of electrons in inorganic material devices. With the construction of such devices based on electrical metal conductors and semiconductors take the shape of immobile networks of connected crystalline structures, where electrons can move freely and be conducted. Organic materials on the other hand deal with carbon-based molecules, and more specifically in the category of organic polymers, consist of repeating molecular units based on carbons connected with each other into large unifying networks. However, organic polymers were long believed to only be electrically insulating materials (plastics) and it wasn’t until the discovery of doped polyacetylene in the 1970s that showcased that organic polymeric materials could indeed be electrically conductive.¹ The discovery marks the birth of the field of organic electronics which instead of relying on inorganic materials such as metals, can construct electrically conductive devices entirely based on carbon materials.

Since the initial discovery, the field has expanded outside of the laboratory environment and found many applications in the society. Organic light-emitting diodes (OLEDs) which emits light upon applying an electrical current are a common feature today found in displays in smartphones, television screens and other types of displays. Organic solar cells that use organic polymers and molecules to produce electricity from the sunlight and organic field-effect transistors (OFETs) comprising organic semiconductor materials, can be utilized for large-scale manufacturing of electronic products, to name a few. The great benefits of organic electronics is that the organic molecules and polymers used can be synthesized at a low-cost compared to traditional inorganic electronics and large scale production of organic electronic devices can be realized via simple screen-printing² and ink-jet methods.³ Other major benefits with organic electronic materials that set them apart from inorganic materials (such as silicon), are the inherent ‘soft’ (mechanical) characteristics to the materials, along with the capability for low-temperature processing and not being oxidized in aqueous electrolytes.⁴ These are significant factors for realizing the possibility of biological interfacing of the materials.

1.2 Organic Bioelectronics

Unlike in electronics, biological systems' mode of communicating is not only conducted by the movements of electrical charges (electrons), but also utilizes a wide variety of ions and different kinds of molecules as signaling carriers. The central nervous system fires electrical action potentials through the neuronal axons which in turn are translated into different biological signals at the synapses of target cells found throughout the body. Signaling substances range from small ionic species such as calcium (Ca^{2+}) regulating muscle contractions to neurotransmitters (adrenaline, dopamine, serotonin GABA etc.) and hormones with long-lasting effects on the physiological conditions. Even the propagation of the electrical action potential along the axons in nerve cells themselves are mediated and regulated by various ionic fluxes causing depolarization in the cell's membrane.

Organic bioelectronic devices interact with biological systems by working as translator and communicator with our senses and functions and pose requirements of the materials used in such devices, with the capabilities of conducting both electronic and ionic signals. Synthesis of organic molecules and polymers enables various desired physical and chemical properties, enabling integration, stability and biocompatibility.⁵ Also, the materials' ability to demonstrate flexibility, elasticity and compatible morphologies all play important roles for the possibility of integrating the bioelectronic devices and materials into biology. Organic electronic and ionic materials help us realize this construction of organic bioelectronic tools, to make the connection with biological systems to be able to record and regulate, finding its way into life science and biomedical applications.

1.3 Aim of the Thesis

The aim of this thesis has been to synthesize a new generation of ionic and electronic conductive materials. The properties of the materials have been tailored for manufacturing and implementation in organic electronic devices and for biological interfaces. Hyperbranched polyelectrolytes (dendrolytes) materials were developed with multiple functionalities, combining ion conductive properties with cross-linking capabilities to construct homogenous membrane networks, allowing greater control of ionic currents for both small and large ionic species, in turn widening the possibility for available therapeutic drugs that can be delivered and implemented with electrophoretic devices for medical purposes. The dendrolyte materials capabilities also shows promises to be utilized in other application areas such as in water desalination and energy production (fuel cell) purposes.

Organic electronic conductive pre-polymer materials have also been developed and synthesized to realize implementation with biological interfaces, utilizing *in vivo* polymerization strategies with biologically available metabolites and catalysts to convert the materials into electronic conductors. These materials and resulting electrodes open up the possibility of creating synapse-like constructions.

1.4 Thesis Outline

The thesis consists of two major parts, divided up as part I consisting of background and theory. While Part II presents the pragmatic section of experimental and results in conjunction with the published research in the thesis. Chapter 2 deals with the theory behind organic chemistry and organic electronics, such as bond formation and conductivity in organic molecules and polymers. Chapter 3 covers the chemistry of polymers, the synthesis and their functionalities which can be modified for various applications and interfaces. Ionic transport and ion-exchange membrane fundamentals are presented in chapter 4 and in chapter 5 covers the applications of organic electronic materials in iontronics devices.

In part II presents chapter 6 the synthesis and characterization methods for the materials developed in the thesis and in chapter 7 is the ink formulation of ion-exchange membrane casting and device fabrications covered. Chapter 8 gives an overview of the included publications and chapter 9 for the conclusion and future outlook. Finally, the scientific results developed in this thesis are provided in the form of included publications.

In paper I was the synthesis and characterization of multi-functionalized hyperbranched polyglycerol developed (dendrolyte). Cationic functional groups together with cross-linking groups were introduced to the polymer material and the thiol-ene “click” cross-linking capability of the dendrolyte was investigated. The dendrolyte was able to form free-standing ion-exchange membrane (IEM) structures which can be employed for efficient micro and macro fabrication in the presence of aqueous solution and oxygen environment. The IEM was implemented in an organic electronic ion pump (OEIP) device and demonstrated ion transport capabilities for small monovalent ion (Cl^-) and large ionic species (methyl blue $^{2-}$, ~ 800 g/mol).

With paper *II* was a new anionic dendrolyte synthesized and was implemented in a capillary based OEIP. The capillary template enabled device miniaturization, providing both substrate and encapsulation of the IEM. The micro device enables implementation of the OEIP for e.g. *in vitro* studies on cell level and the device template provided a means for efficient characterization the IEMs fixed charge concentration.

In paper *III* was a fundamental study on the effect of the polymer size on the ionic conductivity in the dendrolyte materials developed in paper *I* & *II* as IEMs. With the hyperbranched polyglycerol core functionality's increasing size, an increase in ionic conductivity was observed, which was not linked to an increase in swelling/electrolyte uptake in the membrane.

With paper *IV* and *V* were water soluble conjugated thiophene-based trimer (pre-polymer) structures synthesized and applied in biological interfaces. The materials were able to polymerize *in vivo* and form conductive networks catalyzed by enzymatic activities. The side chain functionality of the trimer was modified in paper *V* to introduce cross-linking capability in order to form stable amide bonds for the conductive structures with the biological interfaces.

2 Organic Chemistry and Electronics

When discussing organic chemistry and electronics, our understanding of atomic and molecular orbital theory forms the foundation of our knowledge. Either if it's about electronic conductivity of an organic semiconductor material or regarding the chemical reactivity of a molecule, we turn to the atomic orbital model and associated energetics to form a basis for our explanations and theory.

2.1. Atomic Orbitals

The early measurement of the absorption spectrum of hydrogen, performed by Johann Balmer in 1885, displayed discrete lines in the visible spectrum with specific wavelengths. This indicates for the hydrogen atom - consisting of one proton and one electron (zero net charge) - that the electron only can occupy specific energy levels when excited by light (energy), therefore being quantized. The planetary model with the particle nucleus in the center and with the electron(s) orbiting round the nucleus provides a good illustration of this concept of how matter is build up (Figure 2.1). The quantized energy levels can be viewed as different shells with specific distances (1, 2, 3, 4 etc.) to the nucleus where the electrons are orbiting but there's nothing that tells us why this would be the case and why the electrons would adopt these specific sites with corresponding shells. However quantum-mechanics teaches us the so-called wave-particle duality, which states that photons and electrons adopt the dual characteristics of a particle and a wave, and both views are needed to form a coherent explanation.

Figure 2.1. (Left) Illustration of Lyman ($n > 1$ to $n = 1$) and Balmer ($n > 2$ to $n = 2$) electron transition series wavelengths for hydrogen. (Right) visible spectrum and Balmer absorption lines.

Heisenberg's Uncertainty Principle tells us that we can never know both the particles position and the momentum at the same time.⁶ With the energy levels of an electron being quantized, therefore the momentum is known, the exact position of an electron can no longer be exactly determined. If we instead view the electron as a standing wave, the quantized levels can be seen as specific frequencies of vibrational movement that the electrons adopt. Just like a string is vibrating at specific frequencies, the electron is constantly displacing or 'vibrating' in three-dimensions in space, distributing its probability of presence in space (like an electron cloud) at specific frequency levels. This gives rise to the characteristics of the atomic orbital.

The first orbital is the 1s-orbital and is located closest to the nucleus, therefore in the first electron shell. The electron carries a fundamental polarization property in the form of an intrinsic angular momentum, termed the electron spin. S-orbitals have a spherical shape and can contain a maximum of two electrons and the electrons spin properties are paired up against each other. When we reach the element Lithium, which contains three electrons the second 2s orbital host an electron. Because 2s is located further away from the nucleus (second shell) it has a higher energy state. When we get to boron (5 electrons) the 1s and 2s orbitals are completely filled with electrons and the last electron will start to fill another kind of orbitals, the 2p orbitals (Figure 2.2). The p-orbital has a lobe shape (like a dumbbell) and can adopt three directional orientations p_x , p_y and p_z , each able to contain two electrons (six in total) and are energetically located at slightly higher energy level than the 2s-orbital. When we get to the transition metals in the periodic table the electrons will also start to fill the d-orbital (located between s and p) and has even five directional orientations of space.

Electrons located at the outermost shell is termed the valence electrons and plays a fundamental role in the chemistry of atoms and molecules. Elements such as He, Ne, Ar etc. are noble gases, with atomic orbitals completely filled with electrons making them typically utterly unreactive. Other elements forms bonds with each other via interactions of the valence electrons to adopt completely filled electron orbital formations (noble gas structure). The carbon atom is unique due to its midway location in the second period, making the carbon atom neither electropositive nor electronegative. The result of this is that the carbon tends to share its four valence electrons and are able to create four bonds, rather than to gain or lose one electron in its pursuit to achieve noble gas configuration. As a result the carbon atom has not only the ability to form bonds with other elements but has the unique ability to extensively bond with other carbon atoms to form organic molecules. In particular, organic chemistry are mostly concerned with combining the s- and p-orbitals of the carbon atom to form bonds and create organic molecules. Those bonds are of great importance to form the electronic structure of the active materials of organic electronics.

Figure 2.2. Atomic orbital with spherical 1s (small sphere) and 2s (bigger sphere) (left) stacked upon each other. The 2s orbital is higher in energy and located further away from the nucleus. The three 2p orbitals are aligned along their directional axes.

2.2 Molecular Orbitals

When atoms bond to each other in order to form molecules, the formation of such bonds are generated by the overlapping of the valence orbitals which makes sharing of electrons possible. In the simplest case, two hydrogen atoms 1s orbitals will combine in phase (constructive wave function overlap) and generate an σ -orbital. The energy level of the formed σ -orbital provides a lower energy level for the electrons to reside in, by the electrons being paired up to achieve a noble gas configuration, like in the case of H_2 (Figure 2.3). The electrons are therefore being shared and resides mainly in between both nucleuses. In turn, a σ^* -orbital will also be formed at a higher energy state. This is the anti-bonding orbital formation when the orbital wave function is being combined out of phase (destructive wave function overlap), thus destabilizing the bond. In the case of two helium atoms consisting of four electrons in total, two of the electrons will have to go into the anti-bonding σ^* -orbital thus disrupting the bond formation. A He_2 molecule will not be formed because of the bonding and anti-bonding molecular orbitals combined energy level will not be lower than that of the individual helium atoms with filled 1s orbital states. The 2s-2s orbital bonding is just like the 1s bonding orbital but forms the bonding and anti-bonding orbitals at a higher energy state, being located further away from the nucleuses. The σ -bond overlap is characterized by a cylindrical shape and the bond is symmetrical.⁷

Figure 2.3. Two hydrogen atoms contributing with one electron from their respective 1s orbitals, combines to form a bonding σ -orbital.

Things become a bit more complicated when dealing with the p-orbitals. Since the p-orbitals have three possible orientations in space of the atomic orbital, giving rise to three possible bonding combinations (Figure 2.4). The $p_x - p_x$ overlap results in forming an end-on symmetrical overlap, a σ -bond with the electrons being located mainly in between the nucleuses. This will not be the case for the remaining two $p_y - p_y$ and $p_z - p_z$ overlap. Instead, the overlaps occur perpendicularly and the electron density is not located directly between the two nucleuses but rather on the sides. This is the π -bond and it's not symmetrical. Unlike the σ -bond, the side-on interaction of the p-orbitals is weaker and will in turn receive a higher energy state for the π -bond. Just like the s-orbitals, the p-orbitals will in turn form antibonding orbitals but since the overlap of the π -bond is weaker, the anti-bonding π^* will therefore be lower in energy than the antibonding σ^* .

Figure 2.4. P-orbital overlap. The side on overlapping in p_y and p_z forms weaker π -bonds, where the electron density is located on the sides instead of between the nucleis.

A more general important factor for the bond strength is that the overlapping orbitals have the same size, a 2p-2p orbital overlap will be more extensive than a 2p-3p overlap. Lastly, symmetry is also important. The s-orbital can overlap with a p-orbital head-on to form a σ -bond, but in another configuration it will start to overlap with anti-bonding (destructive) region to cancel the interaction. Simply from geometrical reasons, different oriented p-orbitals are not able to form a bond since they're either perpendicular to each other or the overlap is canceled out with bonding and anti-bonding characters. Stable molecular bonds are therefore only formed if the resulting orbital overlap is lower in energy than the initial states of the atomic orbitals. The formed bonding orbital is called the highest occupied molecular orbital (HOMO) and the anti-bonding is called the lowest unoccupied molecular orbital (LUMO). The energy levels of the HOMO and LUMO dictates if reactions occur between atoms (or molecules) to form new bonds and products.

2.3 Orbital Hybridization

In valence bond theory, the development of the orbital hybridization performed by Linus Pauling (1931)⁸ can be considered *the* fundamental axiom of modern organic chemistry. The optimal geometrical orientation of the included atoms in the methane (CH_4) molecule adopt a tetrahedral orientation in space with a central carbon atom, which maximizes the distance to each hydrogen. Therefore, all four hydrogen-carbon bonds would be identical and the bond angles will be 109.5° (Figure 2.5). This angle is what we also see in the crystal structure of diamond, tetrahedrally coordinated with identical bond angles between all the carbon atoms. But, if all the bonding hydrogens are identical, it would imply that all the bonds are of identical orbital overlap character. This is explained by describing the orbitals of the bonding carbon's one 2s and three 2p orbitals to be hybridized into four identical sp_3 -bonds (Figure 2.5). In turn, the four formed bonds of the carbon, each consists of $\frac{1}{4}$ s and $\frac{3}{4}$ p character. If the orbitals otherwise would be said to consist of one s-s and three s-p, the bonding angle between the three s-p would be 90° . But since the carbon's 2s orbital can interact with the four hydrogens 1s orbitals in any direction, the hybridization into four sp^3 bonds distributes the part s- and part p-orbital characters to identical σ -bonds with the hydrogens and thus explains the tetrahedral formation.⁹

In the case of multiple bonds e.g. carbon-carbon double bonds form sp^2 and the triple bonds form sp -hybridization. The ethene ($\text{H}_2\text{C}=\text{CH}_2$) molecule is a planar molecule with approximately 120° bond angles, where $\frac{1}{3}$ s and $\frac{2}{3}$ p will hybridize to form three sp^2 orbitals. These three sp^2 -orbitals will σ -bond two hydrogens and one to the other carbon molecule. The planarity arises from the π -bond formed with the remaining perpendicular p-orbital overlap between the

two carbon atoms to give the double bond (Figure 2.5). Ethyne ($\text{HC}\equiv\text{CH}$) in turn hybridizes two sp orbitals ($\frac{1}{2}$ - s and $\frac{1}{2}$ - p each) to form one σ -bond with hydrogen and another with the other carbon. Remaining two $2p$ -orbitals on each carbon overlap and forms two π -bonds. To optimize the distances between the nucleuses and to satisfy the orientation of the p -orbitals overlap, the molecule will adopt a completely linear $\text{H}-\text{C}\equiv\text{C}-\text{H}$ structure with an 180° bond angle.

Figure 2.5. Orbital hybridization into sp^3 , sp^2 and sp for a carbon atom with displayed bonds. In methane are the four σ -bonds identical via the sp^3 bonds overlap with the $1s$ orbitals of the hydrogens. Ethene is a planar molecule where the carbons form three σ -bond with the sp^2 -orbitals with a 120° angle. The planarity arises from the perpendicular p -orbital overlap forming the π -bond. In turn ethyne is a linear molecule with the two sp -orbitals being 180° in order to form the two π -bonds.

The orbital hybridization is not limited to carbons but also applies to other elements with p -orbitals as well (N, O, Cl, S, P etc.). Here, we are able to start to build molecules in chemistry and the bonds will dictate the reactivity and the stability of molecules. An important concept is the difference in electronegativity in atoms. In formaldehyde the double bond between carbon and oxygen, $\text{H}_2\text{C}=\text{O}$ (sp^2 and p -orbital overlap) will satisfy the noble gas configuration of electrons in oxygen and the carbon also after forming two more bonds with hydrogen (sp^2). But because the oxygen nucleus contains more protons than the carbon, it will in turn attract the shared negative electrons in closer proximity towards to the oxygen atom. This causes in turn the carbon atom to become

more electropositive, therefore becoming more reactive towards electron donating atoms to form a new bond – the carbon is now considered electrophilic. In combination with the low energy π^* -orbital with the double bond, makes the anti-bonding orbital readily available to accept electrons and disrupt the bond. The electron donating group is in turn nucleophilic, since it desires to donate electrons to form bonds. These interactions are driven by the combination of LUMO and HOMO interactions in chemistry. Of course there's much more to be said about bonding and reactions in organic chemistry⁷ but this fundamental axiom bridges our understanding of modern organic chemistry with quantum theory.

2.4 Band Gap Theory

In organic electronics, the conjugation of organic molecules is very important to explain the behavior of their semiconducting characteristics. What makes an organic molecule conjugated is the alternation of single and double bonds along its structure. As seen in the ethene molecule the π double bond arises from the perpendicular p-orbitals overlapping to the sp^2 orbitals between the two carbons causing planarity (Figure 2.5). If in turn one of the carbons is single bonded (σ) to another carbon of an ethene (instead of hydrogens) butadiene is formed (Figure 2.6). The planarity will remain for the new molecule and the phenomenon of conjugation occurs, which causes the π -electrons to be distributed between all the carbon bonds. The electron distribution arises from all the carbon p-orbitals being aligned and a chain of orbital overlaps is thus formed. These four p-orbitals can arrange themselves into two constructive π bonding and two π^* antibonding energy states. The two new energy states of bonding and anti-bonding, respectively, will both be lower and higher than the previous states of ethene (Figure 2.6). If we continue to add ethene molecules in this fashion to form a longer and longer chain, the energy levels of the orbitals will continue to split up and to form bands. In turn, the bonding (HOMO) and anti-bonding (LUMO) will be separated by a band gap (E_g), which decreases as the chain turns longer.

Figure 2.6. Increasing the conjugated chain length introduces new energy states of the π -bonds orbital conformations and in turn decreases the band gap. In a hypothetical infinitely long polyacetylene chain, these levels will start to blend and form seamless bands. By doping the material can extra energy levels of electron and holes be introduced into the material, making it more conductive.

In a pure (metallic) conductor the HOMO band and LUMO band will be overlapping, meaning the electrons can flow interchangeably between the atoms through the empty conduction band (LUMO) and being electron conductive. If the band gap is large, the energy level between the conduction band (LUMO) and the binding valence band (HOMO) will be separated so much that it will consume much energy to excite an electron into the conduction band. The resulting material will then appear as an insulator. Polyacetylene is an organic semiconductor, where the bands are not overlapping but the band gap energy level is low enough for electrons to be readily excited into the conductive band.

2.4.1 Organic Semi-Conductors and Doping

Silicon is one of the most explored inorganic material and is crucial as the semi-conductor in electronic circuits such as those used in computers. The research done by Alan J Heeger, Alan G. MacDiarmid and Hideki Shirakawa in developing Polyacetylene¹⁰ was awarded the Nobel Prize in Chemistry in 2000.¹¹ It marks the discovery of electrically conductive conjugated organic polymers. Polyacetylene itself is a semi-conductor and like most conjugated polymers requires doping to be made conductive. A dopant introduces additional HOMO and LUMO levels that are either higher or lower respectively than that of the pristine conjugated polymer itself and it donate or accept charges (Figure 2.6). A chemical dopant causes an oxidation or reduction reaction to occur to the conjugated polymer and introduces charge carriers in the material, as holes or electrons. If the dopant *i.e.* donates electrons to the polymer, reduction occurs and the process is termed n-doping. On the other hand, if electrons are transferred from the polymer to the dopant, oxidation occurs and p-doping occurs. Electrochemical doping can be introduced by submerging a conjugated polymer electrode in an electrolyte and by applying a potential between it and a working electrode.¹² Ions from the electrolyte will be able to charge-compensate the introduced electrochemical oxidation or reduction occurring in the conjugated polymer. Although polyacetylene doesn't have any commercial applications, it sparked the work on developing new generations of conductive organic polymer materials and the following development of organic electronic devices.

3 Polymers

Polymers is a category of substances comprised of large macromolecular structures. These structures are constituted by many small repeating molecular sub-units forming the poly- (many) -mers (parts) connected to each other through covalent bonds. The category polymer is very broad and can refer both to natural polymers such as DNA, proteins, cellulose, hair, sugars, and synthetic 'man made' polymers which are generally referred to as plastics, typically insulators, but can also be the semi-conductive conjugated polymers (polyacetylene). Natural and synthetic polymers are not mutually exclusive to each other since we also find a grey zone of semi-synthetic polymers, which can be natural derived polymers that have been synthetically modified (cellulose, lignin, vulcanized rubber).

In either case polymers are created through the process of polymerization, where a small monomer (mono-, "one") molecule reacts and covalently bind together with another monomer, followed by a reaction with another monomer, the process can continue to propagate and ultimately form macromolecules such as long chains and three-dimensional structures. Polymers are not restricted of being constituted of one type of monomer units but often can be comprised of two or more of different types of monomers. DNA which is comprised of four different nucleotide monomers and proteins in mammals comprises of more than twenty different types of amino acids monomers, joining together thousands and thousands of these monomers to create incredibly complex polymeric structures. By having several different types of monomers, the complexity of the polymer composition increase significantly, since the monomers can be connected in a vast array of different combination sequences and amounts of the monomer. This thesis will focus mainly on synthetic ionic and electron conductive polymers.

3.1 Polymer Synthesis - Polymerization

The earliest types of man-made polymers were typically semi synthetic (cellulose) types of polymers - in as - naturally derived polymeric structures that were chemically modified in different ways. Polymers were initially thought of as congregates of small molecules (as colloids) held together by an unknown force. It wasn't until 1920 that Hermann Staudinger first proposed that polymers were actually consisting of small repeating molecules, held together by covalent bonds in long chains – macromolecules.¹³ The understanding of their bonding structures expanded our knowledge on how to synthesize polymers – polymerization - and chemists like Wallace Carothers, went on to revolutionize society by developing and synthesizing materials such Nylon and synthetic rubber (Neoprene) by polymerization reactions from small monomer units.

In figure 3.1 is shown an anionic polymerization example of ethylene oxide forming the polymer polyethylene glycol (PEG). Polymerization reactions can be initiated in several different ways by the presence of an initiator, heating, UV,¹⁴ acidic and alkaline conditions,^{15,16} radicals¹⁷ and electropolymerization¹⁸ etc. In the example is a hydroxyl bearing molecule deprotonated by base, forming an alkoxide which is acting as an initiator and reacts with the monomer ethylene oxide (epoxide). The ring-opening mechanism with the epoxide monomer generates in turn a new available reactive group (alkoxide group), which in turn can continue to react with the addition of more epoxide monomer creating a larger and larger polymeric structure. As can be seen from the reaction, it only takes one initiator molecule to start the chain reaction in the presence of one type of monomer, forming a polymer structure, in this case a *homopolymer*. A *heteropolymer* on the other hand is in turn derived from two (or more) types of monomers through co-polymerization.

The chain reaction in ‘theory’ can continue indefinitely by continuously addition of monomer but will eventually reach termination at some point. There are several reasons why termination occurs in polymerization depending on the conditions and the type of reaction (radical, anionic polymerization etc.) employed, but termination typically can be attributed to limitation of diffusion and mass transfer of the involved reactants. With the continuous growth of the polymer the sheer mass of the polymer particle increases, eventually precipitation occurs due to the polymer no longer being soluble in solution. Simply, the kinetics of the reaction will no longer be favorable to continue the growth of the polymer.

Figure 3.1. Anionic polymerization of ethylene oxide. The polymer chain reaction is initiated/catalyzed under alkaline conditions. The ring-opening reaction can also occur with elevated temperature.

One of the greatest challenges in polymer synthesis is controlling the homogeneity of the formed polymers. A polymer can consist of thousands of monomers, the polymerization in turn can create a large distribution of differently formed polymer sizes through the reaction, caused by different points of termination in

the polymers growth. The polymer size distribution in a mixture can be measured by its dispersity, which is a measurement of the heterogeneity of the different particle sizes. The dispersity (D_M) can be calculated by the fraction of the mass-average molar mass (M_w) with the number-average molar mass (M_n):

$$D_M = \frac{M_w}{M_n} \quad (3.1)$$

These parameters can be measured by techniques such as GPC (Gel Permeation Chromatography) and $^1\text{H-NMR}$ (Nuclear Magnetic Resonance). M_n is derived by measuring the number average molecular mass, meaning the average total number of molecules (monomers) per polymer in a polymer mixture. But M_n doesn't take into account the polymer size or shape. M_w on the other hand takes this into account, which is a measurement of the mass-average molar mass of a sample, since a large polymer molecule will have a larger contribution to the sample than a small polymer.

3.1.1 Linear Hyperbranched and Dendritic Polymers

There are vast arrays of terms in regards to different types of polymeric structural arrangements but the simplest structure is the linear polymer. In a linear polymer, the monomers are joined together as a single chain (as seen previously with PEG, Figure 3.1) commonly referred to as the 'backbone'. Hyperbranched and dendritic polymers on the other hand consists of a branched polymer backbone structure. The branching arises from polymerization with a monomer unit that allows the polymer growth in more than one direction, therefore covalently branching, creates an intrinsic three-dimensional structure to the polymer (Figure 3.2). Also typically in the synthesis of branched polymers is the utilization of a core initiator molecule with multiple 'arms', allowing an initial branching starting point for the polymer to grow from (Figure 3.2).

Hyperbranched and dendrimer polymers differs in the sense that a dendrimer polymer structure is perfectly branched, meaning that at every point of monomer branching (generation) propagation occurs (dendritic subunits). Meanwhile a hyperbranched polymer is not perfectly branched and consists of a mix of linear and dendritic subunits for each generation (typically ~0.4 - 0.7 degree of branching) In terms of synthesis and applications are hyperbranched polymers much easier and cheaper to synthesize and can be made in a "one pot synthesis". In contrast, to be able to ensure a perfectly branched structure in a dendrimer requires separation and purification steps between each generation of the polymer

growth. Therefore to synthesize a high molecular weight dendrimer (several generations) is a lengthy process and limits their applications. Even though all polymers can form three-dimensional structures, a linear polymer chain can be coiled and folded in several different ways but the hyperbranched and dendrimer polymers will be much more limited in their possible structural arrangements. This is because the connected covalent bonds are limiting the branches distance to each other, hyperbranched and dendrimers will instead adopt more of a spherical topology and rheology properties. In turn the end groups (-OH, Figure 3.2) in a dendritic polymer will only be located at the periphery of the structure. Highly branched structures therefore limits the phenomena of intermolecular chain entanglements, lowers their viscosity, allows for good solubility and can be readily functionalized.¹⁹

Figure 3.2 Top Linear Polyglycerol structure, bottom hyperbranched and dendritic polyglycerol. Linear polymer chains are able to adopt numerous different structural conformations, while hyperbranched and dendritic polymers are much more limited in their arrangements due to the covalent bonding branches. Dendritic polymers have a perfect branched structure (blue), while hyperbranched consist of parts of linear subunits as well. The hyperbranched and dendritic polymers consists of a core molecule with three available branching 'arms'.

3.1.2 Hyperbranched Polyglycerol

Hyperbranched polyglycerol (HPG) comprises of a hydrophilic branching polyether polyol structure (Figure 3.2). The structure have been widely studied in biomedical applications due to its great biocompatibility and low toxicity.²⁰ The polyether structure is also chemically stable and with its many available hydroxyl group, making it a good platform to introduce various of chemical functionalities. HPGs have been implemented as drug delivery vehicles, where the hyperbranched globular core with micelle-like properties serve as a great nano-encapsulation platform for guest molecules which can be utilized for delivery and release of compounds.^{21–24} Compared with linear (PEG) analogues, the hyperbranched structure allows for hard-sphere like topology formation, which enables the encapsulation capabilities not seen with the linear counterparts.²⁵

3.2 Synthesis & Polymerization of Conjugated Polymers

Conjugated polymers consist of repeating monomer units with alternating single and double bonds causing planarity through sp^2 -hybridization (see Orbital section 2.3). In general the majority of conjugated polymers seen today are linear chains (Figure 3.3) and in comparison to most sp^3 -hybridized (non-conjugated) polymers, the conjugated polymers have much lower solubility which presents challenges in their synthesis and implementation with biological interfaces which may require water solubility. In turn the molecular weight of synthesized conjugated polymers are in general lower than that of non-conjugated polymers, but high molecular weights is not always a necessity to achieve desired electrical conductive properties. Different aromatic conjugated polymer chains have the ability π - π stack on top of each other, which is a non-covalent inter-molecular interaction between the π -electrons of the two aromatic system.²⁶ The stacking holds them together and in turn can facilitate the charge transfer between the chains. To synthesize conjugated polymers, chemical and/or electrochemical polymerization methods are employed to polymerize the monomers.

Figure 3.3. Commonly used conjugated polymers.

With *electrochemical polymerization*, a conductive polymer film can be obtained directly on an electrode surface by applying a fixed potential. The polymerization rate can be controlled by the applied potential and the time but the applied potential must be high enough to initiate the oxidation of the monomer subunits (Figure 3.4). As the polymer chain length increases in turn the solubility decreases, forming a precipitate on top of the electrode.³ For the polymerization to continue to propagate, the oxidation step with electron transport needs to occur through the bulk of the film on the electrode, limiting the possibility of polymerization propagation, therefore are only thin films of conjugated polymers formed. In comparison, a challenge with *chemical polymerization* is the control of the degree of polymerization, which can cause a wide range of distribution of the length of the formed polymer product.

Figure 3.4. Electrochemical polymerization of thiophene.

3.2.1 Chemical Polymerization - Cross-Coupling Reaction

Cross-coupling reactions catalysed by metals are one of the most important type of reactions in modern organic synthesis. Two molecular fragments, an organo-metallic with an organic halide are joined together, forming new carbon-carbon sigma-bond (Figure 3.5). More specifically, for the significance of the development of the palladium-catalyzed cross-coupling reaction were Richard F. Heck, Ei-ichi Negishi and Akira Suzuki awarded the Nobel Prize in Chemistry 2010 for developing “palladium-catalyzed cross couplings in organic synthesis”.²⁷ The reactions have found applications in both industrial and laboratory synthesis since and in organic electronics have the reaction been proven to be a powerful tool for the synthesis of conjugated polymers.

Figure 3.5. Suzuki cross-coupling reaction. The palladium catalyst will coordinate the thiophenebromide and thiopheneboronic molecules to form new σ -bonds.

3.2.1.1 Palladium catalyst

The oxidation state of the transition metal plays a fundamental role in the cross-coupling reaction catalytic cycle. What makes up a palladium catalyst depends on what atoms and ligands are bonded to the metal. There are commercially available catalysts such as Pd(II) pre-catalyst complexes in order to maintain the activity upon storage. The oxidative state of the palladium is +2 and must therefore be reduced to the active Pd(0) state before it can start a cross-coupling cycle with oxidative addition.²⁸ This can be done *in situ* by the presence of a transmetalating agent e.g. the organoboronic reagent such as in the Suzuki-Miyaura reaction (Figure 3.5).

It is assumed that all of the ten valence electrons in Pd(0) are occupying the d-orbital, thus receiving a $4d^{10}$ configuration and completely fills the d-orbital level instead of adopting a $4d^85s^2$ configuration (Figure 3.6) and Pd(II) in turn preferably adopts a $4d^8$ configuration instead of $4d^65s^2$.²⁸ The chemistry between these two stable oxidation states are the driving force in the catalytic cycle and each oxidative state has its set of characteristic reactions. Since palladium in general (not always) prefers to bind in four ligands, with each ligand contributing with two electrons respectively, Pd(0) favours forming saturated 18 electrons $4d^{10}$ tetrahedral complexes and Pd(II) is forming unsaturated 16 electrons $4d^8$ square planar complexes. It's more energetically favourable with the d^8 electron pairing in the square planar formation (leaving one orbital empty) for Pd(II) complex, then adopting a tetrahedral formation with unpaired electrons (Figure 3.6). The Pd(0) d^{10} is electron rich and nucleophilic, prone to oxidative reactions, while Pd(II) d^8 is electrophilic and prone to reduction reactions.²⁹ By switching between the two oxidative states, Pd(0) and Pd(II) in turn can complete the general catalytic cycle of *oxidative addition*, *transmetalation* and *reductive elimination* in the coupling reaction.

Figure 3.6. Common Palladium bonding geometries for Pd(0) and Pd(II) with four ligands (providing eight electrons) complexes. The Pd(0) provides with ten electrons and adopt a tetrahedral formation by completely filling its 4d orbital. Pd(II) provides with eight electrons and adopts a square planar geometry leaving the high energy $d_{x^2-y^2}$ orbital unoccupied in the complex.

3.2.1.2. Suzuki-Miyaura coupling

There are several different types of Palladium-catalyzed cross-coupling reactions, but for cross-coupling thiophenes is the Suzuki-Miyaura reaction an excellent and versatile synthesis (Figure 3.7).³⁰ The reaction utilizes boron as a transmetalation reagent and have a wide range of functional group tolerance.

Organoboron (vinyl, alkyn or aryl) species forms a new carbon-carbon bond together with an organohalide (vinyl or aryl) in the Suzuki cross-coupling. The catalytic cycle is initiated with oxidative addition of the organohalide to the Pd(0) forming an organo-Pd(II)-halide complex (Figure 3.7). It is generally held that the presence of base (sodium or potassium carbonate, hydroxide or alkoxide) in aqueous solution is crucial for the reaction.³¹ Before transmetalation the palladium may be activated via hydroxypalladation forming organo-Pd(II)-OR by displacing the halide. More significant is the formation of organoboron-ate with base, increasing the nucleophilicity of the organic group, facilitating the transmetalation with the palladium-complex. In the final step, the two organic

groups are joined together by reductive elimination, forming a new carbon-carbon σ -bond while regenerating the Pd(II) to its initial active Pd(0) oxidation state for another cycle.

Even though the Suzuki-Miyaura coupling may appear to be involved, the application of the reaction is today common for large-scale synthesis. A primary advantage is the relatively low toxicity of the prepared compounds and handling of side products.³ E.g. the tin based organostannane reagents used in Stille coupling can be highly toxic.

Figure 3.7. Catalytic cycle of palladium in the Suzuki-Miyaura cross-coupling reaction. The reaction is initiated by oxidative addition of the organohalide ($\text{R}_1\text{-X}$) to the palladium catalyst, forming a Pd(II)square planar complex. Before undergoing transmetalation is the complex further activated by hydroxypalladation and replaces the bound halide (X). The formed organoboronate ($\text{R}_2\text{-B-(OR)}_3^-$) due to the presence of base facilitates the transmetalation by making it more nucleophilic, in turn the organo-fragment (R_2) can complex bind to the Pd(II). Finally reductive elimination occurs, joining both organo-fragments together ($\text{R}_1\text{-R}_2$) by forming a new σ -bond and in turn regenerating the palladium catalyst to its initial Pd(0) oxidative state, being able to undergo another catalytic cycle.

3.2.2 Enzymatic Polymerization

For applications and interfacing conjugated polymers with biological system *in vivo*, available reagents and enzymes can be utilized to catalyze the polymerization process to form the conjugated polymers (Figure 3.8).^{32,33} The major advantage in utilizing enzymes to catalyze the polymerization is that it doesn't involve biologically hazardous compounds and can be considered as 'green' environmental friendly chemistry.³⁴ Just like in electrochemical and chemical metal-catalyzed polymerization does it involve oxidation and reduction (redox) but instead the redox-reaction is mediated by the enzymes. Enzymes such as Glucose and Lactate Oxidase can be utilized to generate peroxide from glucose and lactose respectively together with oxygen and water, which can induce the polymerization to occur directly. But high concentration levels of peroxide can be harmful *in vivo*, thus the reaction may be coupled with a peroxidase enzyme such as HRP (Horseradish Peroxidase), which can utilize small amounts of peroxide to facilitate the polymerization of the monomers (Figure 3.8).^{35,36}

Figure 3.8. Enzymatic polymerization of thiophene. Glucose oxidase enzyme catalyze together with glucose, oxygen and water to generate peroxide. Peroxide can decomposed by itself to generate radicals to be used for the polymerization, but coupling the peroxide with a peroxidase enzyme (such as Horseradish Peroxidase) can be utilized to catalyze the polymerization reaction.

3.3 Synthetic Functionalities

Depending on the type of monomer used, the polymer backbone may have different types of (side chain) functional groups attached. The functional groups can be modified synthetically and these groups give certain chemical characteristics to the polymers but are not part of forming the covalent backbone of the polymer (Figure 3.9). Functional groups can be e.g. hydroxyl, halogen, amine, ionic, saturated and unsaturated groups etc. The functional groups in hyperbranched and dendrimer polymers will be located at the periphery at the terminal end units of the polymers (and also at the linear segments in hyperbranched polymers). In the case of linear polymers, the functional groups will be located along the backbone chain (Figure 3.9). Even though these functional groups are not involved in forming the intramolecular covalent backbone bonds of an individual polymer, these are instead free to form other intra- and intermolecular bonds and interactions with the surrounding. Modifying monomers and polymers with different types of synthetic functionalities gives us a toolbox to utilize for different purposes, to achieve more efficient ion and electron transport in the materials and by introducing cross-linking functionalities, the ability to form stable interfaces of the polymeric materials in various systems. With the introduction of multiple functional groups, multi-functionalization, several different chemical characteristics can be introduced to a polymeric structure at the same time.

Figure 3.9. Schematic of linear, hyperbranched and dendritic polymeric structures with available chemical modifiable side group functionalities (light blue). In a linear polymer are the functional side groups located along the polymer chain while dendritic side group functionalities are located at the periphery of the polymer structure. Hyperbranched polymers consist of a mix of both linear and dendritic components.

3.3.1 Polyelectrolyte Functionality

Polyelectrolytes are a group of polymers which bears fixed electrolyte functional groups. Polycationic polymers bearing positively charged groups and polyanionic polymers having negatively charged groups. When placed in a polar or aqueous solution, these groups can dissociate with their counter ions and become ionically charged. Ionizable groups in polyelectrolytes can be classified either as strong or weak (for their acid respectively base from, which depends on their ability to dissociate with H^+ at certain pH's). A typically strong ionizable electrolyte group is the sulfonate ($-SO_3^-$) group, while a carboxylate ($-COO^-$) is weaker in comparison. This plays an important role when designing polyelectrolytes and ultimately in their applied purposes. Strong electrolyte groups such as (anionic) sulfonate provides with great cationic solubility, in turn making them ideal in ionic conductive materials. But sulfonate groups can act as surfactants, therefore will only form poor ionic interfaces and such materials can be difficult to immobilize on e.g. surfaces. Ionic groups plays an important part in polymers for organic electronics, not only to facilitate ion and electron conductivity but on the other hand also helps increasing the solubility of the monomers and polymers by making them process able from aqueous solutions, which is useful e.g. to be able to apply conjugated polymers *in vivo*.

3.3.1.1 Self-doping in Conjugated Polymers

Ionically charged side chain functionalities can be introduced in conjugated polymers to give them polyelectrolyte characteristics. The fixed ionic charged groups can act as electrolytes in the conjugated polymer, increasing the conjugated polymers water-solubility but can also act as counter ions in the case of doping. With oxidation of the polymer by introducing polarons and bipolarons (Figure 3.10) states, the ionic groups can intra-molecularly arrange themselves to charge compensate the polaronic states via ejection of the charged group's mobile counter ions. This is called self-doping.³⁷ However, in the case of conjugated polymers the presence of side chain functional groups can also affect the planarity of the main conjugated chain, by inducing steric hindrance and in turn decrease the π -orbitals overlap and lower the conductivity.

Figure 3.10. Formation of a bipolaron from oxidation with ionic side chain functionalities charge compensating by self-doping.

3.3.2 Cross-Linking Functionalities

With chemical cross-linking we generally refer to the process of joining different polymer molecules together via covalent bonds. Unlike polymerization, the covalent bonds created through cross-linking are only very short segments/local but proceeds by binding together the bulk of different polymer particles with each other and/or at interfaces, creating larger unifying networks. Example of the utilization of cross-linking is by forming a solid ion-exchange membrane structure, by UV-light exposure of a polyelectrolyte in solution to form the solid network structure. Depending on the degree of cross-linking, the resulting mechanical properties can be adjusted, ranging from soft flexible to rigid brittle materials by increasing the amount of cross-linking.

Typically, chemical cross-linking are initiated by heat, UV-irradiation, pH or by pressure and different types of reactions can e.g. be esterification and free-radical reactions.³⁸ Another type of cross-linking is physical cross-linking, which unlike chemical cross-linking are only formed by weaker interactions, such as ionic, hydrogen bonding and van der Waals. Thus physical cross-linking, unlike chemical, are usually unstable and reversible, and exposure to solvents, heat, pH can upheave the cross-linking. Introducing chemically cross-linkable functionalities in monomers and polymers enables the ability to later process such structures in solution and upon cross-linking form stable solid material networks (Figure 3.11).

Figure 3.11. Hyperbranched polyglycerol (grey ball, left) with allyl functionalities (orange) chemically cross-linked via UV-exposure together with a thiol (orange) bearing cross-linker (yellow ball) forming a solid gel network (right).

3.3.2.1 Thiol-ene Cross-linking

The reaction seen in figure 3.11 occurs between a thiol and an alkene (e.g. allyl, vinyl and acrylate) functionality via a free-radical mechanism forming thioether bonds. Thiol-ene reactions are typically initiated by heating or UV-exposure and is aided by an initiator (photo- or thermal-initiator) which decomposes resulting in the formation of free radicals (Figure 3.12). A formed free radical attacks the thiol group via radical hydrogen abstraction, forming a thiyl radical which can proceed to attack and add onto an alkene double bond.³⁹ The final step involves a chain transfer of the formed carbon radical to another thiol, generating a new thiyl radical along with the formed anti-Markovnikov thioether product. The thiol-ene reaction is considered as “click” chemistry which signifies that the reaction can be performed with mild reaction conditions, in a broad range of solvents as well as with the presence of water and oxygen⁴⁰ and has a large thermodynamic driving force.⁴¹ Thiol-ene cross-linking is suitable for processing in both micro- and macroscale since the radical “click” cross-linking reaction is not sensitive to oxygen and usage of aqueous solvent, making it a readily available and applicable for general manufacturing processes.

Figure 3.12. Thiol-ene radical reaction mechanism, initiated by an UV-initiator.

3.3.2.2 Amide Cross-linking for Biological Interfaces

N-Hydroxysuccinimide (NHS) is one of the most commonly used activation agent used for chemical cross-linking in chemistry and biochemistry to form amide bonds.⁴² The cross-linking reaction requires carboxyl ($-\text{COOH}$) and amine ($-\text{NH}_2$) functionalities. The carboxyl groups together with NHS (or the water soluble sulfo-NHS analogue) can form activated NHS ester compounds in the presence of carbodiimides such as ethyl(dimethylaminopropyl) carbodiimide (EDC) (Figure 3.13). The EDC acts as an initial coupling reagent with the carboxylate to form an unstable O-acylisourea ester intermediate. Even though EDC activation of carboxylates can be used directly to couple with primary amines, the instability of the O-acylisourea ester intermediate is readily hydrolyzed in aqueous solution (creating an urea byproduct of the EDC) if it doesn't couple quickly enough with the amine and requires acidic conditions (pH 4.5) for efficient cross-linking. To increase the cross-coupling efficiency at pH closer to physiological conditions are MES buffer (4-morpholinoethanesulfonic acid) or PBS buffer (phosphate-buffered saline) often used in combination with increasing the amount of EDC reagent used to compensate for the low efficiency.

To improve the cross-coupling efficiency is NHS (or sulfo-NHS) used in combination with EDC. In turn the NHS couples to the EDC activated carboxyl group to form the less labile succinate (NHS) ester and forming the urea byproduct from the carbodiimide in the process (Figure 3.13). Succinate ester (NHS activated) compounds are stable enough to be isolated and are less readily hydrolyzed in the presence of water at physiological pH. EDC and NHS activated ester reagents are both very reactive towards primary amine groups which are ubiquitously found in biological systems to form stable amide bonds, making the activation of carboxylates a great way to cross-link to proteins. By combining the reagents *in situ*, mixtures of carboxylate bearing molecules/polymers with EDC/NHS activation can therefore be prepared and applied directly to form cross-links with amine group bearing bio interfaces.

Figure 3.13. EDC/sulfo-NHS activated cross-linking mechanism of carboxylic acid bearing group ($-R$) together with amine bearing polymer or biomolecule, forming a stable amide bond. The O-acylisourea ester intermediate is also reactive towards amine groups and couples into stable amide bonds but is easily hydrolyzed. A combination with sulfo-NHS is therefore used in order to amide couple more efficiently in the presence of water and physiological pH.

4 Ionic Transport and Ion Selective Membranes

4.1 Electrolytes and Ionic Conductivity

Electrolytes are conductive due to consisting of dissolved mobile ionic atoms and/or ionic molecules of cationic and anionic charges in a solution. Typical small cations can be simple metal ions such as K^+ , Na^+ and Mg^{2+} and anions from halogens such as Cl^- and Br^- but an electrolyte can also consist of more complex charge bearing biomolecules (neurotransmitters, DNA and polypeptides) and synthetic polyelectrolytes consisting of multiple repeating charged functional groups. An electrolyte can be categorized as either a strong or a weak electrolyte. In the case of a strong electrolyte such as $NaCl$, the salt is completely dissolved in solution and the Na^+ and Cl^- ions fully disassociate. While in the case of a weak electrolyte, the ions only partially disassociate. Regardless, the number of positive and negative charges must be equal in order to maintain electroneutrality in the solution.

Electronic conductivity is given by Ohm's law which can be applied as well for ionic conductivity. The major difference is in charge transport of ions, as they involve a significant amount of mass being moved compared to an electron, causing ionic conductivity to generally be several orders of magnitude lower than electronic conductivity. Since ions also come in different masses, charges and shapes, electrolyte solutions have different conductivities. The ionic conductivity also depends on the amount of dissolved ions, the ionic concentration, which in turn affects the conductivity of the electrolyte solution, with higher concentrations resulting in higher conductivity. The sum conductivity (σ) of an electrolyte is given by:

$$\sigma = \sum_i z_i \mu_i v_i c F \quad (4.1)$$

where z_i is the charge number, μ_i mobility and v_i stoichiometric coefficient of given ion (i), c is the concentration of the electrolyte and F is the Faraday constant ($96\,485\text{ C mol}^{-1}$).

4.1.1 Ionic Transport

Ionic transport is the directional movement of ions in an electrolyte solution. The process is dictated by three major categories: *diffusion*, *migration* and *convection* (Figure 4.1). Diffusion occurs passively by the movements of ions from a more concentrated region to a region of lower concentration in solution, called a concentration gradient. Migration is the process of ionic movements in the presence of an electric field. Finally, convection is when the ions move because of the movement of the fluid. Such movements can arise by stirring of the electrolyte solution and density gradients by e.g. temperature variations in the electrolyte solution.

Figure 4.1. The modes of ion transport in an electrolyte. Ionic movement by diffusion occurs by moving from a more concentrated to a less concentrated region. Migration by applying an electrical field, separating the ions by charge towards the cathode and anode. Convection by the movements of the solvent liquid.

With ionic diffusion being dictated by the concentration gradient between a higher to a lower concentration, the transport is described by Fick's first law:⁴³

$$J = -D_i \nabla C_i \quad (4.2)$$

where J ($\text{mol m}^{-2} \text{s}^{-1}$) describes the diffusion flux of ions in the gradient, which is the amount of substance that flows in an area of direction over a time interval. D_i ($\text{m}^2 \text{s}^{-1}$) describes the diffusion coefficient of the ionic species or diffusivity, meaning the ion's ability to move in solution and C_i is the concentration (mol).

In migration, the ionic species are transported under an electrical field potential. The potential induces a force upon the ions, causing cations to be transported towards the negative electrode and anions towards the positive electrode. The ion's ability to move and be transported under a potential is given by their mobility (μ) which is in relation to the diffusion coefficient (D_i) and is given by Einstein's equation:

$$\mu = \frac{D_i}{k_B T} \quad (4.3)$$

where k_B corresponds to the Boltzmann constant ($1.38 \times 10^{-23} \text{ m}^2 \text{ kg s}^{-2} \text{ K}^{-1}$) and T is the temperature in Kelvin. The diffusion and migration components are linked with each other due to the transport of the ions when applying a potential. The flux of ions due to migration creates a concentration gradient resulting in a diffusive movement of the involved ions. In turn, the separation of oppositely charged ionic species induces the electrical field with the migration.

To describe the flux of ions under an electrical potential thus needs to take both components into account and the Nernst-Planck equation couples both phenomena:

$$J = -D_i \nabla c_i + \frac{z_i F}{RT} D_i C_i \Delta \varphi \quad (4.4)$$

Where z_i is the ion charge number, F the Faraday constant ($96\,485 \text{ C mol}^{-1}$), R is the ideal gas constant ($8.3144 \text{ J mol}^{-1}$), T is the absolute temperature (Kelvin), D_i the ionic diffusion coefficient and φ the electrical potential. The first part of the equation describes the ionic diffusional flux (from eq. 4.2) and the second part the migrational ionic flux.

4.1.2 Diffusion coefficient, ion transport number and diffusion potential

An electrolyte consists of two or more ionic species which contribute differently to the conductivity. The reason for this is related to the different diffusion coefficient exhibited by the ions in the electrolyte. The Stokes-Einstein equation (4.5) describes spherical particles undergoing Brownian motion in a uniform liquid, linking the diffusion coefficient (D_i) with respect to the particle radius (r):

$$D_i = \frac{RT}{N_A \eta 6 \pi r} \quad (4.5)$$

where R is the ideal gas constant, T absolute temperature, N_A is Avogadro's constant and η is the viscosity of the homogenous liquid. A list of some common ion diffusion coefficients can be seen in Table 4.1. In general, the diffusion coefficient tends to scale with the particle size, where smaller ions and molecules diffuse more efficiently than larger ones. However, this may hold true for most

monovalent anions but isn't always the case and the diffusion coefficient for $K^+ > Na^+ > Li^+$ can be seen as reverse in terms of ionic size. This is because the diffusion coefficient is dependent on the solvents ability to solvate the ionic species, therefore is the hydration radius of the ion better correlated to the diffusion coefficient (D_i) rather than the bare radius of the ion.

Table 4.1. List of diffusion coefficient of common cations and anions.

<i>Ion</i>	<i>Diffusion coefficient ($m^2 s^{-1}$)</i>
H^+	9.31×10^{-9}
Li^+	1.03×10^{-9}
Na^+	1.33×10^{-9}
K^+	1.96×10^{-9}
OH^-	5.27×10^{-9}
Cl^-	2.03×10^{-9}
Br^-	2.01×10^{-9}

The transport number (t) defines the fraction of the total ionic flux for a specific ion in an electrolyte (eq. 4.6) when a current is applied. As seen with the diffusion coefficient Table 4.1 a small ion such as H^+ has a much higher diffusion coefficient than Cl^- and in turn will contribute significantly more to the ionic current of an HCl (aq.) electrolyte (eq. 4.6). It's also worth mentioning here the special cases of H^+ and OH^- for which ionic transport in aqueous solution is not solely attributed to solvated ionic movement. Rather, the Grotthuss mechanism describes how H^+ and OH^- transport occurs through H-bonding network propagation through the water molecules in solution.⁴⁴ In turn the ions don't need to move but are rather created by donation and withdrawal of hydrogens between the water molecules in a long chain series of events.

$$t_{H^+} = \frac{D_{H^+}}{D_{H^+} + D_{Cl^-}} \approx 0.8 \quad t_{Cl^-} = \frac{D_{Cl^-}}{D_{H^+} + D_{Cl^-}} \approx 0.2 \quad (4.6)$$

In the case of two electrolytes with different concentrations being in contact with each other, by diffusional force the more concentrated electrolyte's ions will diffuse to the lower concentrated electrolyte to even out the concentration gradient. But as seen with the transfer numbers, the anionic and cationic species exhibit different mobilities and in turn the ion with higher mobility may move more rapidly than the counterion with lower mobility. This will result in an initial charge imbalance at non-equilibrium and create an electrical double layer at the junction of the two electrolytes. The effect is referred to as the diffusion potential (or liquid junction potential) and the magnitude of the diffusion potential is governed by the differences of the ionic mobilities, which acts by compensating the low mobility ion's diffusion to even out the charge imbalance.⁴⁵ The diffusion potential (ϕ_{diff}) can be calculated by eq 4.7:

$$\phi_{diff} = (t_+ - t_-) \frac{RT}{F} \ln\left(\frac{c_1}{c_2}\right) \quad (4.7)$$

where c_1 and c_2 are the respective electrolytes concentrations, R is the ideal gas constant, F is Faraday's constant and T is the absolute temperature (Kelvin).

4.2 Ion Exchange Membranes

An ion exchange membrane (IEM) is a semi-permeable membrane that allows the transport of specific ions through its structure, while at the same time blocking the passage of other ions and neutral molecules. Organic IEMs are typically constructed out of cross-linked polyelectrolytes, containing high amounts of fixed ionic charges with a hydrophobic polymer backbone. Cation-exchange membranes (CEM) have fixed negative charges and have selective permeability towards positive cations, while an anion-exchange membrane (AEM) contains fixed positive charges and in turn has selectivity towards anions (Figure 4.2). In turn, neutral membranes and membranes consisting of both positive and negative charges don't display any particular selectivity for cations and anions. Free mobile ions with the opposite charge of the fixed ionic charges in an IEM are referred to as counter ions and mobile ions with the same charge as the fixed charges are called co-ions. The fixed ionic charges in the IEM in turn can be compensated by an equal amounts of mobile counter ions in an electrolyte to maintain local electroneutrality (ion-exchange), while repelling co-ions from entering the IEM structure which creates an unequal distribution of the mobile ions.

Figure 4.2. Ion transport by migration through a) an anion exchange membrane (AEM) b) a cation exchange membrane (CEM) and c) a neutral membrane. Ion-exchange membranes repel and block the passage of ions with the same charge as the membranes fixed ionic charges, while allowing counter ions to pass through. Neutral membranes show no selectivity towards anions or cations.

4.2.1 Donnan Potential

When an IEM with a high amount of fixed ionic charge concentration is submerged in an electrolyte with relative lower concentration to the IEM, a concentration gradient for the counter ions and co-ions will be created between the IEM and the electrolyte. The mobile counter ions, which have higher concentration inside the membrane, will strive to diffuse outwards from the membrane. While mobile co-ions, with a concentration higher in the electrolyte, will strive to move in towards the membrane.⁴⁶ This will create a charged interface at the membrane, an electrical field gradient which opposes the diffusion gradient of the ions and keeps the counter-ions inside the membranes while excluding the co-ions from entering and thus remaining in the electrolyte.

In the case of a CEM, a net positive charge will be created outside of the membrane interface and a net negative charge inside of the membrane interface. The potential across the membrane is referred to as the Donnan Potential and is given by:

$$\varphi_D = \frac{RT}{zF} \ln\left(\frac{c_{electrolyte}}{c_{fix}}\right) \quad (4.7)$$

where z is the charge, $c_{electrolyte}$ the electrolyte concentration of the counter ions and c_{fix} is the concentration of the membranes fixed charges. IEMs with higher amount of fixed ionic charges will have a stronger pronounced effect of the inclusion and exclusion of the counter ions and co-ions respectively. The Donnan exclusion is in turn only effective if the fixed charge concentration of the membrane is higher than the electrolyte concentration.

4.2.2 Fixed Ionic Charges in Ion Exchange Membranes

As discussed briefly in the previous section on electrolytes (4.1), depending on the ionic composition, an electrolyte can either be strong or weak. The same principle applies to the fixed ionic charges in the polyelectrolytes of IEMs. A typical strong fixed electrolyte group employed in CEMs is the sulfonate group while a carboxylate is weaker (Figure 4.3). This is because of the charged anionic group's ability to disassociate with the counter ions in solution and stabilize the charge. The sulfonate group has the ability to stabilize the negative ionic charge by dispersal of the charge over the three oxygen atoms. In comparison the carboxylate has only two resonance structures and the dispersal of the negative charge can only occur over the two oxygens.

Figure 4.3. Resonance structure of negatively charged groups commonly found in ion-exchange membranes.

In the case of the fixed cationic charges in AEMs, commonly found charged groups are different quaternary ammonium and phosphonium functionalities (Figure 4.4). The effect on the cationic charge with only different heteroatoms possess some difficulties to elucidate. Nitrogen and phosphorus belongs to the same group in the periodic table but the sizes of the atoms are different with nitrogen being smaller than phosphorus, which in turn would lead to having a higher charge density. On the other hand, the charged nitrogen atom would be able to attract electron density from the bonding carbon substituents (R_x) more efficiently, therefore being more capable to ‘neutralize’ some of the charge but at the same time being able to create stronger bonds with bonding carbon atoms. Some studies on ionic liquids^{47–49} have shown that cations with a central phosphonium have a stronger positive charge than the ammonium equivalents. But it’s important to take into consideration which functional groups (R_x) are attached and which counterions are involved to determine if either is more efficient and conductive than the other.

Figure 4.4. Cationic quaternary ammonium (left) and phosphonium charged groups.

Depending on the application, it’s be important that the IEM exhibits good stability for the fixed ionic charges. In the case of AEMs which may encounter strong alkaline conditions, e.g. *Hoffmann elimination* may occur (Figure 4.5). An alkoxide (or hydroxyl) can attack the β -hydrogens of the cationic charge resulting in an elimination reaction, with the charged group acting as leaving group and in turn forming an alkene. Another possible degradation mechanism can be a straight forward nucleophilic substitution (S_N2) reaction.⁵⁰

Figure 4.5. (Top) Hoffmann elimination mechanism. (Bottom) Nucleophilic substitution (S_N2) degradation.

4.2.3 Ion-exchange capacity

The ion exchange capacity (IEC) is an important physical parameter for an IEM. The parameter is linked with the type and amount of fixed ionic charged groups in the IEM, which affects the ionic transport capabilities. Typically, the IEC is measured by simple acid-base titration and the values of the IEC are usually given as milliequivalents (ion-exchanged) per gram of dry membrane material (meq/g). It's important to take into consideration what type of counterion is being used with the titration, since it'll affect the outcome of the IEC value. This is because the type of fixed charged group will affect its ability to associate with the specific counterion. High IEC typically corresponds to high permselectivity (selective transport towards specific type of ion) and water content parameters.

4.2.4 Swelling and water content

Synthesizing an IEM based on a polyelectrolyte with a lot of ionic charges is great in regards to forming a membrane with high ionic conductivity and good ionic selectivity. But introducing a lot of charges in the membrane structure can produce some major challenges. With increasing ionic charges, membrane swelling plays an increasingly important role when placed in a solution. Significant swelling can occur by solvent molecules being able to enter the membrane

to solvate the fixed ionic charges with their free counterions and also by penetrating micro pores in the IEM's structure. The swelling causes gel microphase separation between the hydrophilic domains (e.g. fixed charges) and the hydrophobic domains (e.g. polymer backbone and cross-linker regions). Too much swelling in turn can decrease the ion selectivity of the membrane by allowing co-ions to penetrate the membrane as well.

The hydrophobic domains provide mechanical stability for the IEM structure and to compensate significant swelling, the degree of cross-linking can be increased in the IEM so as to decrease the solvent content. Another approach is to utilize encapsulation of the IEM which is commonly employed in micro fabricated devices or incorporating other material components that provide mechanical structural stability, limiting the degree of swelling. There's a tradeoff here as well since some degree of swelling is necessary for an IEM to be able to solvate ions and efficiently conduct ionic movement through the membrane structure.

5 Organic Bioelectronics and Iontronics

Biological systems' way of communicating and regulating bodily functions are rarely done solely by electricity as in electronics. When a neuron fires an action potential to travel down the axon reaching the axon terminal, the electrical signal is converted to various ionic and molecular signals (Figure 5.1). The moving action potential causes depolarization in the cell membrane, where small voltage-gated ion-channel proteins are located. This affects the opening and closing of the ion-channels and affects the influx and out flux of ions such as Na^+ , K^+ , Ca^{2+} and Cl^- in the cell. At the end of the axon, the action potential affects the ionic concentration and membrane depolarization at the synaptic cleft. The synaptic cleft interfaces the neuron with other cells via electrical and chemical synapses. For electrical synapses, the gap junction between the cells is usually very small and ions can flow efficiently between the cells, causing the post-synaptic cell to be depolarized quickly and efficiently. With chemical synapses, the synaptic gap is much larger and instead signalling between the cells is performed by the release of molecular neurotransmitters such as GABA, adrenaline, dopamine, serotonin etc. These molecules are much larger (>150 g/mol) compared to a Na^+ ion (23 g/mol) but can regulate a wide variety of functions in the body.

Figure 5.1. Nerve cells communicating which each other by a mix of electrical and chemical signals. A stimulated nerve cell generates an electrical signal that travels down its axon and reaches the axon terminals. The electrical signal causes depolarization in the axon terminal in turn generating the release of ionic/chemical signals in the synaptic cleft that can propagate the signal to other cells. In the case of e.g. an electrical synapse, causes depolarization through the flux of ions and generation of a new electrical signal in the other nerve cell to travel down its axon.

Organic Bioelectronics explores the field of interface between biology and organic electronics. With the different ways of communication via electrons, ions and molecules, organic electronics can be used in several of applications such as therapeutic purposes,^{51–54} bridging the gap between technology and biology. Compared to metals which are stiff, components based of organic electronics can be made soft to interface better with soft tissue etc.⁵⁵ Being organic, the various (polymer) material in the organic electronic devices can be made non-toxic and biocompatible. Organic Bioelectronics can also be applied in non-mammalian systems as in plants forming electronic plants.^{56,57}

5.1 Iontronics Devices

Iontronics focuses on the property of ionic motion as the signal carriers in organic electronics. With precise and spatiotemporal control, ionic transport can be regulated and ions delivered.⁵⁸ Iontronic components couple the electrical and ionic signals in organic conductive polymers. Devices such the organic electrochemical transistor (OECT)^{59–61}, electrolyte gated organic field-effect transistor (EGOFET)⁶² and ionic delivery devices all rely on the fluxes of ions of ionic conductors. Ionic conductors form iontronic resistors for devices such as the organic electronic ion pump (OEIP)⁶³ and diodes.⁶⁴ A key component in such a device is the ion-exchange membrane (IEM), as a semi-permeable “channel” that can transport a certain type of ions.

5.1.1 Organic Electrochemical Transistor

The organic electrochemical transistor (OECT) is a transistor operating by the injection of ions from an electrolyte to an organic semi-conductive material.⁶⁵ Injection of ions are controlled by applying a gate voltage between an electrolyte and the organic semiconductor (Figure 5.2). Hence by regulating the gate voltage, the electrical conductivity of the organic conjugated polymer channel drain-source can be controlled by electrochemical doping and de-doping with ions from the gate electrolyte. Therefore, the OECT can be switched on/off and the current can be amplified. The major advantage of OECTs is their ability to operate in aqueous environment and at low voltages, which is crucial for biological interfacing.⁶⁶ The specific organic semiconductors used in OECTs are ion-permeable (e.g. PEDOT:PSS)⁶⁷ allowing ions to penetrate within their film structure and bulk (de)dope. It's also possible to replace the liquid electrolyte with solid-gel electrolytes,⁶⁸ however at the same time OECT's relies on the movement of ionic charges which can make the operational response time slower.

Organic semiconductors molecular structure can be tailored via organic synthesis to enhance sensitivity and selectivity towards specific ions interacting with the OECT. Therefore chemical and biological sensing is a particular application of interest for OECTs.⁶⁹ Specific analytes and biological markers can be monitored by e.g. incorporation of enzymes with the OECT,^{70,71} where the enzymatic activities of analytes in turn can regulate the OECT in real-time.

Figure 5.2. Schematic of an Organic Electrochemical Transistor (OECT) (a) in its off state (gate voltage = 0V). By applying a gate voltage (b) charge carriers can be introduced into the organic semiconductor channel as holes or electrons, which are charge compensated by injection of mobile ions from the electrolyte.

5.1.2 Organic Electronic Ion Pump

The organic electronic ion pump is one of the simplest iontronic components. The device consists of a source and a target electrolyte reservoir each containing an electrode and an ion-exchange membrane to form a circuit between the reservoirs. Operating as an iontronic resistor, the flux of ions delivered from the source to the target reservoir can be controlled by the ionic current (Figure 5.3).

The ionic current between the two reservoirs can take the form of small ionic atom species (H^+ , Na^+ , K^+ , Cl^- etc.) but also as larger ionizable molecules such as neurotransmitters. These ions travel between the reservoirs connected by the ion-exchange membrane (IEM) channel when a potential is applied between the two electrodes. In the IEM (CEM or AEM) fixed ionic charges can solubilize the oppositely charged freely moving ionic species in the electrolyte reservoirs. A perfectly semi-permeable membrane is ideal when the fixed charge concentration in the IEM is higher than the electrolytes in the reservoirs (Donnan exclusion, see section 4.2.1). When a potential is applied between the source and target reservoir, in the ideal case one charge is compensated by moving one

counter ion through the IEM, while co-ions (with the same ionic charge as the fixed charges in the membrane) will be blocked from co-migrating in the opposite direction, from the target to the source.

In this fashion, ions of interest can be transported and “pumped” to a desired target location. Since the dosage delivered can be controlled by the ionic current, precise delivery can be achieved and be applied in *in vivo* interfaces.⁷² Neurotransmitters, chemotherapy, anaesthesia and various molecules can be administered locally and selectively for therapeutic purposes.⁷³ Analogous systems such as micro-fluidics operates by delivering substances through liquid flow, which can cause significant changes in pressure and the target electrolytes concentration of other ions and molecules present in the biological interface. In the OEIP the delivery is achieved through electrophoresis of ions and the liquid flow is negligible from the osmotic drag of water molecules effect.

Figure 5.3. (a) Schematic of an Organic Electronic Ion Pump with selective charge delivery of ions (b) depending on the ion-exchange membrane (IEM) used.

5.1.21 Planar OEIP

OEIPs can be fabricated in planar format through classical development techniques such as photolithography. Via thin film processing the IEM channels can be developed and patterned into devices. High resolution down to micro meter

scale can be patterned on planar substrates and with well-defined dimensions of the IEM the intrinsic ionic resistance can be tailored for the setup (Figure 5.4). Planar OEIPs have been implemented in various biological interfaces, for spinal nerve-stimulation with GABA in mice,⁵⁴ in plants,⁷⁴ in mammalian sensory organs⁵¹ etc. Even though great resolutions can be achieved, the planar geometry processing and dimensions can sometimes be limiting. Fabrication of small narrow IEM channels with rigid encapsulation can limit the IEM water uptake capabilities by swelling, inducing high resistance in the channel. The solvation of ions becomes more limited in the IEM, decreasing the ionic transport capabilities and making it difficult to deliver large ionic species.

Figure 5.4 IEM channel patterns developed via photolithography on a planar glass substrate down to 2.5-10 μm resolution.

5.1.2.2 Capillary OEIP

To overcome the limitations in planar devices such as with large ion delivery or microscopic “delivery tip” geometries, a capillary based OEIP can be utilized. Instead of being deposited on a flat surface with extra steps of chemical photolithography development processes, which may affect the IEM’s composition and ionic transport, the ion channels can be formed in capillary channels via capillary force. The capillary channels act both as substrate and encapsulation for the IEM in the device. Polyelectrolyte solutions can therefore fill up the capillary and be cross-linked inside into an IEM. By being dissolved in a water-

based solution, the polyelectrolytes can form hydrated IEM channels already encapsulated. An advantage to the capillary OEIP is that the IEM material can be made with good reproducibility, since it'll be immediately encapsulated in the device. This overcomes problems in processing with photolithography, which necessitate dehydration and rehydration of the IEM in the various device development steps, which can cause delamination of the IEM. Capillary devices can readily be implemented in close approximation to cells and tissues, and the ionic transport capabilities serve as a great template for large ionic molecular delivery for biological stimulation (Figure 5.5).^{52,53}

Figure 5.5 Schematic of a capillary organic electronic ion pump. The small capillary works as both substrate and encapsulation of the ion-exchange membrane (IEM) which enables easy fabrication miniaturization of the channel.

5.2 Electrochemical Cells – Large Ion-Exchange Membranes

The applications of organic ion-exchange membranes are not limited to small components in organic electronics and for bioelectronics applications. IEMs can be used in technologies such as fuel cells and electrolyzers, desalination, water purification and in energy storage devices.^{75–77} This also calls for upscaling of the membrane dimensions in these applications and often requires free-standing membrane configurations or assembly. The ionic current is usually from small atomic and molecular ions in such devices. For desalination alternating stacks of CEM and AEM are used, creating multiple electrodialysis cells that are used in the separation of salts (e.g. sodium and chloride ions) from water.

5.2.1 Fuel Cell

A fuel cells continuously produce electricity by the supply of a fuel and oxygen (air). The most basic fuel cell operates via a proton-exchange membrane (PEM) with hydrogen gas as a fuel (Figure 5.6). When the hydrogen gas reaches the

anode catalyst electrode, causing the hydrogen to oxidize and split up into positively charged H^+ ions and negatively charged electrons. The hydrogen ions will in turn be transported through the PEM (fixed anionic charges in the membrane) and when reaching the cathode on the other side of the membrane, oxygen molecules can be catalysed with the protons (traveling through the PEM) to form water molecules. The electrons will in conjunction be conducted through the external circuit.

An alternative setup is the alkaline fuel cell which utilizes an AEM. In contrast to the PEMFC the anion exchange membrane fuel cell (AEMFC) uses an ionic current from negatively charged hydroxide ions. Also other types of fuels than hydrogen gas can be used such as methanol, ethanol, ammonia, and glycerol but also alternatives fuels such as lignin can be used (which is an abundant biopolymer by-product from the paper industry).⁷⁸

Figure 5.6. (Left) Schematic of proton exchange membrane fuel cell (PEMFC). Fuel enters the system e.g hydrogen gas and upon reaching the anode electrode interface gets split up into protons and electrons which generates a current. The electrons travels through the external circuit while the positively charged protons gets transported through the PEM and at the cathode electrode on the other side of the membrane, can the protons be catalysed with oxygen to generate water as product. (Right) proton-exchange membrane (based on dendrolyte material) sandwich between two carbon/platinum clothes used as catalysts for the electrodes. The porous cloths allows gases to readily pass into material were e.g. hydrogen gas can be split up into protons and electrons at the electrode PEM interface.

There are various advantages and disadvantages with PEMFC and AEMFC cells (including other types of fuel cells such as the phosphoric acid fuel cells etc.). Hydrogen ions (H^+) by being smaller than hydroxide (OH^-) has a higher diffusion co-efficiency and therefore higher conductivity, facilitating fast ionic

transport. To compensate for this in AEMFC, higher concentrations of hydroxide is required but challenges arise when designing AEM's that are chemically stable in alkaline environments. *Hoffman elimination* stands as the main mechanism for degradation in AEM⁷⁹ but can be eliminated by the removal of β -hydrogens from the cationic charges. On the other hand alkaline fuel cells utilize cheaper catalyst materials such as non-noble metal at their cathode and can be operated more efficiently at lower temperatures due to the alkaline chemistry facilitating the oxygen reduction reaction at the cathode.⁸⁰ PEMFC on the other hand faces the challenge of requiring scarce catalyst material and traditionally platinum needs to be employed as catalyst. Increasing the operating temperatures can facilitate oxidation/reduction reactions and ionic transport in fuel cell but can also affect the water maintenance. In order for the IEM to efficiently be able to conduct ions, hydration of the membrane serves as an important factor. Elevated temperatures cause the water to evaporate and in turn can increase the membrane resistance by drying out. In opposite, water flooding at the cathode catalyst will inhibit the oxygen transport and thus hinder the efficiency, so proper water maintenance is important for the fuel cell and the IEM.

Fuel cell technology puts heavy demands on the IEM's composition and an important aspect is regarding the construction of such devices is the membrane electrode assembly (MEA). The IEM is sandwiched between two electrodes with an embedded catalyst. It's crucial for the polyelectrolyte membrane to have a good interface with the catalyst and electrode, allowing efficient oxidation, transport and reduction to occur. In the case with hydrogen gas for a PEMFC, the electrodes can consist of gas diffusion electrodes, consisting of platinum loaded onto a carbon cloth to get an efficient surface area for the catalyst and allowing the hydrogen gas to be able to pass through the carbon cloth (Figure 5.6). Loading the platinum on a carbon cloth allows efficient surface area for the catalyst. A free-standing IEM is used in the MEA but depending on mechanical properties such as membranes stiffness, poor interface integration can occur with the electrode catalyst interface. To overcome the poor interface heat pressing is commonly employed. An alternative method for better surface integration would be to cast a polyelectrolyte solution directly on top of the catalyst, allowing the polyelectrolyte liquid to penetrate into the carbon cloth structure to form an efficient integration. This of course demands that the IEM can be cast and cross-linked directly in such a manner and avoidance of post cross-linking treatment is preferable, which is not always the case. Finally it's important for the membrane not to be too porous or too thin, otherwise the gaseous reagent will be able to crossover without being catalysed, reducing the efficiency of the device.

Part II

Experimental and Results

6 Material Synthesis and Structural Characterization

6.1 Synthesis of Hyperbranched Polyglycerol

Hyperbranched polyglycerol (HPG) was used as the base material in the synthesis of the different hyperbranched polyelectrolytes (dendrolytes) and to create the ion-exchange membranes used in paper *I*, *II* and *III*. To synthesize HPGs (Scheme 6.1), ring opening multi-branching (ROMB) polymerization of the monomer glycidol was utilized.^{81,82} The glycidol monomer contains two functional groups - an epoxide and a hydroxyl group. During the polymerization, because of the ring-opening mechanism of the epoxide, a new additional hydroxylate group is generated from the glycidol. Thus from each glycidol epoxide reacted in the ring-opening process, two hydroxyl (alkoxide) groups will be available to react further with epoxide groups from other glycidol monomers, resulting in a multi-branching structure.

Scheme 6.1. Schematic representation of Hyperbranched Polyglycerol synthesis. By partial deprotonation of the multi-armed initiator molecule tris(hydroxymethyl)propane (TMP) and slow monomer addition of glycidol, the polymerization can be controlled to minimize linear growth with the polymerization. Hyperbranched polyglycerol synthesis is done in a one pot reaction and the final polymer consists of a central initiator molecule (TMP) with dendritic (D_s), linear (L_{s13} and L_{s14}) and terminal (T_s) subunits.

All glassware was pre-dried at 120 °C before use to ensure water exclusion which otherwise can interfere with the anionic polymerization method. Further, after the glassware assembly consisting of a three-necked round bottom flask equipped with a mechanical stirrer and a distillation setup, the flask was heated to 140 °C with an applied vacuum for 2h as an extra drying step of the equipment. Using the starting molecule 1,1,1-tris(hydroxymethyl)propane (TMP)

which has three available hydroxyl groups enables initial branching growth from the molecule core. The TMP was melted at 65 °C under vacuum and after liquefying, the vacuum was removed and continuous flow of N₂-gas was applied instead. Potassium tert-butoxide in tetrahydrofuran (THF) was added via a syringe to perform partial deprotonation (0.3 eq.) of the TMP's hydroxyl groups together with slow stirring, resulting in a salt precipitating. The precipitated salt was dissolved by adding 1-methyl-2-pyrrolidinone which is a high boiling point (202 °C) solvent and acts as an emulsifying agent in the polymerization. THF and formed side-product tert-butanol were distilled off by raising the temperature to 120 °C.

ROMB polymerization is postulated on fast proton exchange between the formed alkoxide species. Assuming delocalization of the alkoxide charge over the whole system regardless of forming polymer size and between the primary and secondary hydroxyl groups, the partial deprotonation coupled with slow monomer addition is in turn used to minimize side-reactions such as cyclization and to ensure uniform spherical growth.^{81,83} The glycidol monomer, with a target of 10 000 Da for the final polymer product (degree of polymerization = 135) was diluted in dry THF (1/2.5 v/v) and was in turn added with a precision dosing pump over 48h while the reaction was kept heated to 120 °C to continuously distill off the added THF solvent. The reaction was quenched by dissolving the viscous polymer liquid with methanol and dilution with water. The HPG product was dialyzed in water and freeze dried to yield a clear transparent viscous polymer. Before proceeding with further synthetic steps, the HPG polymer needs to be characterized in some way to ensure its branching structure, uniform and 'high' molecular weight.

6.2 Dialysis

Dialysis was employed to achieve 'pure' polymer materials separated from low molecular species and reactants. Conventional purification method used in organic chemistry such as liquid chromatography is not a viable option for macromolecular structures such as polymers, because polymer samples will typically get stuck on silica gels and are difficult to eluate. With dialysis we utilize the separation of molecules e.g. by size through a semi-permeable membrane. In general is the sample to be purified dissolved in a solvent and placed inside a dialysis tubing membrane, which contains small pores. When placed inside a buffer solution (dialysate), small molecules and ions will be able to pass through the membrane pores via diffusion, by moving from the high concentration solu-

tion in the interior of the membrane to the exterior dialysate with low concentration. Large macromolecules such as polymers will not be able to diffuse through the semipermeable membrane due to its large size. The size separation in a dialysis membrane is usually referred to as the molecular weight cut-off (MWCO). In practice this is not a definitive molecular weight cut-off separation, but molecules with molecular weights above the MWCO will diffuse slow enough to allow for an efficient separation.

An alternative and more efficient way of performing dialysis is by utilizing cross-flow filtration. Dialysis by passive diffusion through a dialysis membrane is time consuming and requires several dialysate solution exchanges for efficient purification. In cross-flow filtration, a pump is feeding the dialysis solution through a line by pressure. The feed flow travels tangentially across a semipermeable membrane surface, allowing the small molecules and salts to pass through membrane and gets filtered away while the rest of the dialysis solution gets circulated back and allows it to be able to pass by the membrane surface once again. This continuous circulating process technique of dialysis has the major advantages being much faster and that the filtering membrane continuously get washed during the process which also increase the operational time of the membrane.

6.3 Gel Permeation Chromatography

Gel Permeation Chromatography (GPC) also known as Size Exclusion Chromatography (SEC) is a separation technique based on molecular size. It's commonly applied for characterization of polymers for parameters such as relative molecular weight (M_n and M_w) and polydispersity but can also be used in conjunction as polymer purification. GPC separation technique works by applying a (polymer) solution sample on to a column with a stationary phase consisting of packed porous beads. Compared to other conventional chromatography techniques where the analytes are separated based on the chemical and physical binding interactions with the stationary phase material, the separation of the analytes in GPC are dependent on the size or hydrodynamic volume of the analyte particles. Smaller particles of the analyte will be able to penetrate into the beads pores of the stationary phase and this will in turn increase their retention time of eluate with the mobile phase. While larger sized particles of the analyte on the other hand will not be able to penetrate into the pores so easily and will therefore be able to pass by outside of the beads through the column more efficiently and receive a quicker retention time. The separation of a polymer analyte mixture will therefore be based on the molecular size and it's therefore crucial to choose

the column's particle pores to be in accordance with analyzed sample sizes for efficient separation.

Molecular weight estimation requires appropriate calibration standards. Most commonly used standards consist of linear polymers with well-defined polydispersities (< 1.2) with different molecular weights. However a linear standards macromolecular particle composition and arrangements is significant different than that of a hyperbranched or dendritic polymer, which can cause under or overestimation of the molecular weight if compared to each other due to having different interactions with the stationary phase beads.⁸¹ Even though in theory, the separation is based on the polymers particle sizes, but the chemical composition needs to be taken into account. A polyelectrolytes interaction based on the stationary phase and mobile phase used can be significantly different than that of a neutral hydrophobic polymer.

6.4 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is a technique which is especially used in modern organic chemistry for molecular structure characterization by studying the magnetic fields exhibited by atoms. Quantum mechanics teaches us that in the nuclei, the nucleons, protons and neutrons can be illustrated by having their own intrinsic axes and spin (angular momentum). The result of a nucleon spinning is that it generates a magnetic field and the strength is measured as the magnetic moment (μ). The individual spin of a proton and neutron are quantized and each contribute with a net spin of $\frac{1}{2}$, which in turn can be summarized to give the total nuclei spin (I). Summarizing the total spin of a nuclei is a complex task and not straightforward, where the spins also can get paired against each other. But atoms exhibit either no spin ($I = 0$, such as ^{12}C and ^{16}O 'unfortunately'), half integer-spin ($I = \frac{1}{2}, \frac{3}{2}, \frac{5}{2}$ etc.) and integer spin ($I = 1, 2, 3 \dots$).

With NMR for organic molecules we generally only consider the isotopes ^1H , ^{13}C , ^{15}N , ^{19}F and ^{31}P , which are naturally abundant enough to be practical to study and exhibits a net spin of $\frac{1}{2}$. When placed under a strong external magnetic field (B_0), the spin state of such an atom will exist in either two states, $+\frac{1}{2}$ or $-\frac{1}{2}$ (Figure 6.1). The lower energy spin state ($+\frac{1}{2}$) will be aligned with the external magnetic field and the high energy spin state ($-\frac{1}{2}$) will be in the opposite direction. Thus by employing an external magnetic field strong enough, will the energy spin states of the atoms be large enough to be separated and the atoms can be aligned with the magnetic field in the low energetic spin state.⁷

Figure 6.1. When a sample is placed under magnetic field, the atoms magnetic movement (μ) with half-interger spin (I , eg. ^1H & ^{13}C) in a molecule can be aligned with ($+\frac{1}{2}$) or against ($-\frac{1}{2}$) the magnetic field. NMR utilizes a very strong magnetic field (B_0) to ensure (almost) all of the nucleuses are aligned with the field and by separating the high and low spin states energy levels (ΔE) enough. By sending a short radio frequency pulse to excite and change the direction of the nucleuses to the high energy state, the subsequent relaxation back to the low energy spin state of the atoms can be measured and analyzed.

By sending a short radio-frequency pulse the nuclei is excited to the high energy spin state, followed by relaxation – release of energy – back to the lower energy state. This relaxation is measured in nuclear magnetic resonances as free induction decay (FID). When measuring NMR specific intervals of radio-frequencies are used as excitation pulses (depending on the type of nucleus, ^1H , ^{13}C etc.) and in a molecule because of different atom compositions, types of chemical bonds etc. results in the electron distribution is not homogenous in a molecule. This in turn affects the nuclei spin energy levels (resonance frequencies) of each nucleus. Therefore when measuring a type of nucleus e.g. ^1H , depending on the local chemical environment variations (due to neighboring bonded atoms) of each and every proton, will in turn exhibit specific resonance frequencies. The combined excitation frequencies of a molecule generated by the magnetic pulse are shown in the FID, which can be analyzed and transformed by Fourier Transformation to generate a spectrum (Figure 6.2). Since each nucleus has a specific resonance frequency, these will be displayed as specific frequency signals, called chemical shifts.

By analyzing the spectrum of a molecules different signals chemical shift, coupling pattern and intensity (NMR can be used both qualitative and quantitative), precise molecular structural elucidation can be achieved. Therefore NMR is one of the most powerful analytical techniques available in modern organic chemistry today.

Figure 6.2. (Top) Free Induction Decay (FID) of a small molecule (ETE-S) by ^1H -NMR. Applying a magnetic pulse will excite the nucleuses of a molecule to a higher energy spin state (in opposite direction of the NMR's magnetic field) and relax back into the initial low energy spin state. Depending on a specific nucleus chemical environment (by the bonding neighboring atoms in the molecule) will affect the excitation frequencies of the nucleus to the high energy spin state. (Bottom) With Fourier transformation is the FID converted into a NMR spectrum, exhibiting chemical shift on the x-axis. The individual signals and their coupling pattern corresponds to the specific protons (in ^1H -NMR) of a molecule and depends on their chemical environment (bonded neighboring atoms). The signal integral is in proportion to the number of protons for each corresponding signal. With all this information the molecular structure can be elucidated.

6.4.1 Polymer NMR

Since each individual nuclei give rise to its own signal, 'identical' signals (e.g. hydrogens on a $-\text{CH}_3$ group) will in turn stack and the overall intensity of the signal will scale accordingly to the number of nuclei giving rise to the signal. With polymers which consists of many repeating monomer units, where the chemical environment (bonded neighboring atoms) are almost identical for each of the monomers. The changes are so subtle for each monomer unit of the polymer which results in giving rise to very broad NMR-signals (Figure 6.3). This is because of limitation in the spectral resolution and not being able to distinguish the individual repeating monomer signals, often causing overlaps between different structural groups. Regardless, much information can be extracted and be used in characterization of polymers, polymer molecular weight analysis, degree of functionalization, degree of branching (in hyperbranched polymers) and reaction kinetics to name a few.

Figure 6.3. a) Schematic representation of hyperbranched polyglycerol (HPG) and b) ^1H -NMR of HPG 2500, 5000 and 10 000 Da polymers. The blue and red regions corresponds to the methyl ($-\text{CH}_3$) and methylene ($-\text{CH}_2-$) groups of the central core while the polymer bulk area corresponds to the repeating monomeric subunits.

6.4.2 Polymer Molecular Weight Analysis by ¹H-NMR

The average number molecular weight (M_n) of a polymer can readily be estimated with ¹H-NMR.⁸⁴ A specific chemical unit's signal's area of intensity, will reflect on how many times the unit is repeated in the average polymer and with the amount of polymer in analyzed sample (Figure 6.3).

$$M_n = \frac{\sum N_i M_i}{\sum N_i} = \frac{\sum A_i}{\sum N_i} \quad (6.1)$$

Meaning, the area of signals (A_i) of polymer species (i) will correspond to the number of molecules (N_i) with the molecular weight (M_i). Therefore the average number of repeating monomer (n_x) units can be derived. This can be done by comparing a repeating monomer signal with another signal with a known amount of units in the polymer, e.g. end groups in linear polymers. In the case of a linear polymer, the structure of each polymer will consist of only two end groups in the linear chain. With a branching polymer utilizing a core molecule for initiation, only one will be found in the center per polymer.

$$n_x = \frac{a_x p_y n_y}{a_y p_x} \quad (6.2)$$

Where p = chemical group number of protons, n = number of chemical groups, a = integral area of x = monomer unit and y = reference end group(s).

$$M_n = n_x M_x + n_y M_y \quad (6.3)$$

M_x is the monomer units molecular weight, M_y corresponds to the core group/end group molecular weight, n_x and n_y is the number of repeating units of the monomer (x) and core/end group (y).

6.4.3 Degree of Branching (Inverse Gated ¹³C-NMR)

The degree of branching is a crucial structural parameter when it comes to hyperbranched polymers. Unlike purely dendritical polymers, a hyperbranched polymer contains to some degree of linear parts as well. This structural param-

eter can be measured and estimated with inverse-gated ^{13}C -NMR. What distinguishes inverse gated ^{13}C -NMR from “normal” ^{13}C -NMR is that quantitative integration of the carbon signals will be possible. While running a ^{13}C -NMR, a feature called proton decoupling will usually be active during the entire time of a scan experimental cycle. In short this will eliminate all the carbon signals splitting patterns that would normally be observed in the spectrum. The reason for this is to simplify the spectrum and also to be able to enhance the carbon signals (due to Nuclear Overhauser Effect), making them easier to detect and to reduce the experimental run time. However depending on the carbon, the signal enhancing effect will occur disproportionately and in turn making the spectra non-integrable. HPG’s carbon structure has previously been elucidated (Figure 6.4) and the fraction of the degree of branching (DB) can be calculated via:⁸⁵

$$DB = \frac{2D_s}{2D_s + L_{S13} + L_{S14}} \quad (6.4)$$

Figure. 6.4 ^{13}C -NMR spectra of HPG with assigned subunits to their signals.

D_s represent carbon integral signal from dendritic subunit, while L_{s13} and L_{s14} signals are the integrals from the different possible occurring linear structural subunits.

6.5 Multi-Functionalization

The many available peripheral hydroxyl groups on the HPG polymer were used as a scaffold to introduce different types of functionalities to the polymer. By performing partial functionalization, multiple functional groups could be introduced to the HPG by step wise synthesis. Two major functionalities were introduced to the polymers: polymerizable/cross-linking groups and charged ionic groups. To obtain controllable amounts of multi-functionalization in different ratios makes the choice of solvent very crucial. Since converting the many hydroxyl groups into the new functionalities may render the polymer insoluble at a certain degree of functionalization in the chosen solvent and start to precipitate, thus resulting in obtaining a lesser degree of functionalization than desired. In general, simple and reliable reactions (e.g S_N2) with straightforward reaction mechanisms and introduction of 'simple' functional group are preferred for controllable functionalization of the HPG macromolecule. The reason for this is because there will be numerous reacting groups available at the same time in the polymer, in turn running the risk of causing intra- and intermolecular reactions which can cause e.g. cyclization and polymerization to occur especially if extreme conditions such as very high temperature and strong reactive reagents are used as reaction conditions.

HPG functionalization possess another challenge found in macromolecule synthesis in general which is purification of the products. The amphiphilic nature of multi-functionalized HPG polymers, consisting of both hydrophobic and hydrophilic domains, results in conventional purification method such as extraction and precipitation techniques being difficult to perform due to intermediate solubility in different solvents, prohibiting solvent phase separation. In many cases, the purification thus can be limited to dialysis to be able to separate the polymer product with side products.

6.5.1 Polymer Degree of Functionalization $^1\text{H-NMR}$

When modifying a polymer with new functionalities, such as ionic charge, cross-linking groups etc., the ability to estimate the degree of functionalization (DF, with up to $\pm 1-5$ % accuracy) is an important parameter for structural elucidation of polymers (Figure 6.5). This can be measured with $^1\text{H-NMR}$ by comparing the signal intensity of the introduced chemical groups with the signal intensity reference of the modified groups (monomers).

$$DF = \left(\frac{a_{func}}{a_{ref}} / \frac{p_{func}}{p_{ref}} \right) \quad (6.5)$$

a_{func} is the introduced functionality integral signal, a_{ref} corresponds the modified polymer groups signal and p_{func} & p_{ref} represents the chemical groups number of proton.

Figure 6.5 Schematic illustration of Hyperbranched Polyglycerol functionalized with 20% allyl and corresponding ^1H -NMR spectrum. The black region corresponds to the repeating monomer subunits area (each 5H) and the red regions to the allyl functionalities protons ($1H_a$, $2H_b$ and $2H_c$).

6.5.2 A-HPG Synthesis

The anionic dendrolyte A-HPG in paper *II* and *III* (scheme 6.2) was synthesized by partial deprotonation of HPG with NaH (0.2 eq. to HPG hydroxyl groups) in DMSO, followed by a $\text{S}_{\text{N}}2$ reaction via addition of allyl bromide (0.2 eq. to hydroxyl groups). It was found that by using DMSO as solvent for the allylation reaction, the degree of functionalization would almost directly correspond ($\pm 3\%$) to the amounts of added reactant equivalents. Resulting in compound **1**

(allyl(20)-HPG) with ~20 % allyl degree of functionalization (DF) after stirring overnight at room temperature. Occurrence of variations of the DF was mainly attributed to practical, instrumental and chemical reagent “freshness” errors. The synthesis of allyl(20)-HPG (**1**) was repeated several times and the DF for both the crude and purified products (by dialysis) were compared with negligible differences. Therefore was no further purification necessary for the subsequent step (only NaBr as side product formed in solution), thus a one-pot synthesis strategy could be utilized.

Scheme 6.2. Schematic representation for synthesis of A-HPG (2). a) NaH (0.2 eq.) in DMSO for 1h then allyl bromide (0.2 eq.), r.t. 16h, b) NaH (1 eq.) in DMSO for 1h, r.t., then 1,4-butanedisulfone (1 eq.), 60 °C, 16h, total yield 90%.

In the second synthetic step, the remaining HPG hydroxyl groups (80%) were deprotonated using NaH (1 eq. to -OH). When up-scaling the reaction and performing the synthesis (5-15 g HPG), precautions for heat evolution were especially taken since large quantities of the strong base were added (NaH in DMSO).⁸⁶ By adding the NaH in aliquots and cooling the reaction solution with an ice bath, though on these batch scales (5-15 g HPG) the heat evolution from this step were in general not significantly pronounced. More important at this stage is preventing pressure build up by using an open reaction vessel and allowing the formation of hydrogen gas to escape throughout the reaction.

In the following step with the addition of the alkylating agent 1,4-butanedisulfone (1 eq. to -OH) to the alkoxide-HPG reaction mixture, significant heat evolution could occur if precautions were not taken during the addition such as cooling and slow reagent addition. The alkoxides (R-O⁻) will proceed via a ring-opening

nucleophilic attack on the 1,4 butane sultone, in turn generating anionic butyl-sulfonate groups. The mixture was heated to 60 °C overnight to speed up and ensure complete functionalization (80% sulfonate). The reaction mixture was quenched by addition ice chips and the majority of DMSO solvent was reduced via a lengthy processes of rotary evaporation. The crude A-HPG product dissolved in water was washed with ethyl acetate and the polyelectrolyte was purified with dialysis in water. Even with the dialysis the occurrence of DMSO solvent traces were still prevalent which required additional removal by performing freeze drying which yielded a yellow-whitish solid salt of A-HPG (**2**).

Other polar aprotic solvents (DMF, sulfolane) were investigated for the synthesis of A-HPG, but could only achieve lower degrees of sulfonate functionalization (< 40%). This was attributed to the solvents lower polarity compared to DMSO, therefore not being capable to stabilize the introduction of such high amounts of ionic charges to the hyperbranched macromolecule.

6.5.3 C-HPG Synthesis

Cationic dendrolyte, C-HPG in paper *I* and *III* (scheme 6.3) was also synthesized by initial functionalization with allyl but instead DMF was used as the solvent. Partial deprotonation with NaH (0.2 eq to -OH) of the HPG was performed, followed by addition of allyl bromide (0.2 eq. to -OH). Compared with DMSO, using DMF resulted in partially lower degree of allyl functionalization (~15%) when using the same amount of equivalents (with expected 20%). Higher degrees of allyl functionalization (100%) could be achieved in DMF but didn't react neatly in a 1:1 reagent equivalent to the functionalization degree outcome. No further purification was necessary for allyl(15)HPG (**3**) and the crude product in DMF was used for the next step.

By adding excess of chloroacetate chloride (1.5 eq to -OH), the remaining hydroxyl groups of allyl(15)-HPG were converted into chloroacetate functionalities via esterification. Triethylamine (1 eq. to -OH) base was added to facilitate the process and handle the HCl byproduct. The resulting polymer product (**4**) (85% chloroacetate, 15 % allyl) was easy to purify with conventional extraction method due to its highly hydrophobic solubility (in chloroform/DCM).

In the final step by performing the synthesis in either chloroform or DCM, the substitution reaction with triphenylphosphine resulted in considerable different amounts of cationic triphenylphosphonium functionalization of either ~55% (**5****) or ~85 % (**5***) respectively. In both cases the crude C-HPG (**5**) product would eventually crash out of solution after stirring overnight (with 60 °C heating) but using DCM as the solvent the full functionalization would occur (85%). The final C-HPG products were purified by trituration by dissolving the product in small amounts of methanol and pouring cold diethyl ether on top to precipitate

the polyelectrolyte, followed by decantation of the diethyl ether and thus removing excess triphenylphosphine. The trituration was repeated three times and the semi-pure products were finally purified via dialysis in water/methanol solution to remove remaining triphenylphosphine oxide and other salt side products and leftover reagents. Solvents were evaporation and after drying under vacuum yielded an orange solid polyelectrolyte salt product (**5**).

*Scheme 6.3. Schematic representation for synthesis of C-HPG (**5**). a) NaH (0.2 eq.) in DMF for 1h then allyl bromide (0.2 eq.), r.t. 16h, b) chloroacetate chloride (1.5 eq.) with triethylamine (1 eq.) in DMF, r.t., 16h c) 1.5 eq. PPh₃ in DCM* or CHCl₃**, 60 °C for 16h.*

6.6 Conjugated Trimer Synthesis

Functionalized trimeric thiophenes were synthesized in paper IV and V. The conjugated molecules were used as water soluble pre-polymeric structures to be applied *in vivo* to form electron conductive polymers.

6.6.1 ETE-S Synthesis

Scheme 6.4. Synthesis of ETE-S (**9**). a) NBS (2.16 eq.) in dry DMF, r.t., 24 h, 94% b) NaH (1.3 eq.) 30 min r.t. then 1,4-butanedisulfonate (1.2 eq.) in THF, 60 °C, 16h, 57% c) -84 °C in THF then *n*-BuLi (2M in hexane, 1.07 eq.), stir for 20 min at 0 °C, cooled to -84 °C again followed by isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.05 eq.), r.t., 16 h, 69 % d) EDOT-borolane (**8**, 2.3 eq.), PEPPSI-*i*Pr (5 mol %), KF (6 eq.) in water/DMF, 90 °C, 24h, 50%.

Thiophene building block (**6**) was prepared by dibromination of 3-thiopheneethanol with N-bromosuccinimide (NBS) in DMF (Scheme 6.4) according to previous published literature.⁸⁷ NBS works as a mild source of bromine for the bromination and the reaction occurs selectively at 2 and 5 ortho position for electrophilic substitution on the thiophene-ring, generating 2,5-dibromothiopheneethanol (**6**) and the product was isolated by pouring the reaction solution into ice cold NaHCO₃ (aq.), followed by extraction with diethyl ether and subsequent washing step of the organic phase, drying with MgSO₄ and evaporation of the solvent.

In the next synthesis step, butylsulfonate functionalization was performed by NaH deprotonation of the hydroxyl group followed by addition of 1,4-butanediol in THF to generate the functionality. The product (**7**) formed a precipitate in the reaction solution after being refluxed for several hours which was centrifuged and the supernatant was removed. Additional washing step was performed with cold acetone, centrifugation and removal of the supernatant and the procedure was repeated twice followed by vacuum drying to yield a beige solid of 4-(2-(2,5-dibromothiophen-3-yl)ethoxy)-1-butanesulfonic acid (**7**).

EDOT-2-boronic acid pinacol ester⁸⁸ (**8**) was prepared by treating EDOT with the organolithium reagent BuLi, which is a strong enough base to deprotonate EDOT's ortho position. Dry and inert conditions are very important when handling BuLi due to its high reactivity and ability to spontaneously combust in air. Addition of BuLi to the EDOT solution was performed with a liquid nitrogen/ethyl acetate slushy bath to cool the reaction solution down to -84 °C and under nitrogen atmosphere, to prevent unwanted hydrolysis of BuLi and other side-reactions. The reaction mixture was allowed to reach 0 °C to make sure the deprotonation occurred and the reaction was cooled again to -84 °C followed by addition of isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane reagent. The cooling bath was allowed to thaw and the reaction mixture was stirred overnight at r.t. The work-up performed was done by pouring the solution into ice cold saturated NH₄Cl (aq.), extraction with diethyl ether, subsequent washing and drying of the organic phase and evaporation of the solvent to yield the EDOT-2-boronic acid pinacol ester (**8**) product, resulting in a clear oil with approximately 70-85% purity. Remaining impurities came from unreacted EDOT which didn't affect the next step and could be compensated for by adding more equivalents of the material. A pure product could otherwise be isolated via recrystallization in pentane or hexane, yielding white fluffy crystals.

Finally was Sodium 4-(2-(2,5-bis(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)thiophen-3-yl)ethoxy)butane-1-sulfonate (**9**, ETE-S) synthesized according to literature³² but with modifications in the procedure. The synthesis utilized Suzuki-Miyaura cross-coupling reaction by coupling the dibrominated thiophene reagent (**7**) twice in Pd-catalytic cycle with the EDOT-borolane reagent (>2 eq.) (**8**). This was done by mixing both the dibromothiophene and EDOT-borolane building blocks together with the palladium catalyst PEPPSI-iPr (5 mol %), with KF as a base in DMF/water and heating the reaction to 90 °C overnight under nitrogen atmosphere. After reaching r.t., the reaction mixture was filtered through celite, which was done in order to remove the metal catalyst and other formed insoluble side-products. The crude product was then purified with reverse-phase chromatography (silica C18 column) with an acetonitrile/water mobile phase gradient. The product was dissolved in minimal amount of hot meth-

anol and precipitated in ice cold diethyl ether. The crystallized product was collected via centrifugation and the ether was decanted. Drying under vacuum yielded (**9**, *ETE-S*) as an off white solid.

6.6.2 ETE-Carboxylate

*Scheme 6.5. Synthesis of ETE-Carboxylate (**12**) and ETE-NHS (**13**). a) NaH (1.40 eq.) then *t*Bu-bromoacetate (1.20 eq.) in dry THF, r.t., 16 h, 25% (b) EDOT-2-boronic acid pinacol ester (**8**, 2.61 eq.), PEPPSI-*i*Pr (0.10 eq.), Na₂CO₃ (2.09 eq.) in water/THF (0.14 : 0.86), 80 °C, 16 h, 59% (c) NaOH (10.21 eq.) in water/THF (1:1), 50 °C, 16 h, 37 % (d) EDC (1.50 eq.) sulfo-NHS (2.00 eq.) in DMF, r.t., 16 h, 42%.*

Synthesized 2,5-dibromothiopheneethanol (**6**) hydroxyl group was deprotonated by NaH and functionalized via nucleophilic substitution with *tert*-butyl-bromoacetate. The reaction proved to be unfavorable with lower yields (~25%, **10**), where addition of extra equivalents of reagents and heating didn't improve the yield. The crude product was purified via extraction with dichloromethane and subsequent washing with water, brine, drying of the organic phase with MgSO₄ and filtering. Further purification and isolation of pure product was done via silica column chromatography with a heptane/ethyl acetate mobile phase gradient. Product fractions were collected and the solvent evaporated and dried under vacuum to yield a clear yellow oil of 2-[2-(2,5-dibromothiophen-3-yl)ethoxy]*tert*-butyl ethanoate (**10**). An alternative substitution reaction with methyl-bromoacetate was also performed with similar results. Even though the substitution reaction seemed to work better by analyzing the consumption of the starting material (**6**) and formed product by TLC and HPLC-MS. But similar low yields of the ester product (~25%) was attributed to the occurrence of hydrolysis of the ester (to carboxylate form) during the work-up and purification process, making the product difficult to isolate in high yield.

Suzuki-Miyaura cross-coupling reaction was performed between dibromothiophene building (**10**) and EDOT-borolane reagent (**8**, > 2 eq.) with PEPPSI-iPR (10 mol %) catalyst and Na₂CO₃ (aq.) as base source in THF/water at 80 °C overnight under nitrogen atmosphere. The reaction mixture formed solvent phase separation but vigorous stirring was applied to ensure mixing between the phases. After allowing the reaction mixture to cool down to room temperature, the work-up was done by filtering the solution through Celite and the solvents were removed via rotary evaporation. The crude was dissolved in small amounts of dichloromethane, loaded onto silica and the product was isolated on a silica column with n-heptane/ethyl acetate mobile phase gradient. After drying under high vacuum, ETE-COObu (**11**) was obtained as a brown viscous oil (yield 59 %).

ETE-COObu (**11**) was dissolved in THF and ester hydrolysis was performed by stirring vigorously as a two phase solvent system together with a 1M NaOH aqueous solution while being heated to 50 °C overnight. The hydrolysis of ETE-COOtert-butyl ester was much slower and with considerably less carboxylate conversion than the alternatively synthesized (not reported) ETE-COO-methyl ester (which was completely hydrolyzed in a few hours at room temperature). Also in general are the trimeric ETE structures sensitive to polymerization and elevated temperature with aqueous base or acid conditions have the potential to lead to undesired polymerization side reactions. The crude hydrolyzed product in the aqueous phase was washed with ethyl acetate. The water phase was made acidic with HCl and the product was extracted with ethyl acetate, followed by subsequent washing step with water. Ethyl acetate solvent was evaporated and the pure ETE-COOH oil product was stirred together with 1 eq. of NaOH (aq., 0.01M) overnight until being completely dissolved and converted to its carboxylate form. The water was evaporated and the remaining salt was dissolved in minimal amount of hot methanol and precipitated in cold diethyl ether to yield fluffy white crystals, which was collected by centrifugation and the ether was decanted. Drying under high vacuum yielded a pure off white solid of Sodium 4-(2-(2,5-bis(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)thiophen-3-yl)ethoxy)ethanoate, ETE-COONa (**12**, 42 % yield).

Sulfo-NHS activated ETE-carboxylate (ETE-NHS (**13**)) was synthesized but proved to be difficult to isolate the pure product. The reaction was performed in anhydrous DMF with the coupling reagent ethyl(dimethylaminopropyl) carbodiimide (EDC) to increase the formation of the sulfo-NHS activated product. NHS activated compounds are semi-stable but can be hydrolyzed back into the carboxylic form with the presence of water. When isolating the sulfo-NHS product (**13**) (from excess salt reagents etc.), difficulties occurred to elute the product when performing (reverse-phase) chromatography due to the product being highly hydrophilic, requiring water in the mobile-phase in order to eluate. In

turn facing the risk of hydrolysis before the water solvent was being removed. With HPLC-MS analysis a purity of 60-75% of ETE-NHS was estimated and the rest attributed to ETE-carboxyl (**12**) and sulfo-NHS starting materials. The synthesis and isolation of ETE-NHS (**13**) was only used as a proof of concept, verifying the ETE-carboxylic trimer could be activated with ECD and sulfo-NHS.

6.6.3 High Performance Liquid Chromatography–Mass Spectroscopy

High-performance liquid chromatography-mass spectrometry (HPLC-MS) is a common analytical technique utilized in chemistry, which combines the separation of compounds in a sample with liquid chromatography with mass analysis spectroscopy (MS). Like any other chromatography, molecules are separated by their interaction with a stationary phase and elution with a mobile phase. In the work presented in this thesis was a reverse phase setup used, which uses a hydrophobic stationary phase (C18 silica) and a mobile phase gradient solution going from hydrophilic to more hydrophobic (water/acetonitrile mixture gradient). In turn is hydrophilic molecules such as salt eluted first and subsequently will more organic and hydrophobic molecules come thereafter. The separated ions, neutral compounds from the chromatography are subsequently transferred into the MS system which ionizes the compounds into charged particles with an ion source e.g. electron beam, photon beams and lasers beams etc. In turn, the charged particles can be measured with a mass analyzer which measures the mass-to-charge ratio (m/z) of the ionized compounds and the mass can be detected. In general the use of this technique is limited to smaller organic molecules such as the trimers (not polymers) which is dependent on the capability of efficient separation and ionization of the compounds. However the technique offers an incredibly precise way to attain the precise mass of the molecules and the purity of a sample.

7 Device Fabrication

7.1 Ion-Exchange Membrane Ink Formulation and Casting

To prepare the dendrolyte based ion-exchange membranes for various devices and free-standing membranes setups required membrane ink formulation development. With the polyelectrolyte materials C-HPG and A-HPG (dendrolytes) developed in paper *I*, *II* and *III*, which were partially functionalized with allyl groups and therefore could thiol-ene click cross-linking be utilized (see section 3.3.2.1). For the ion-exchange membrane (IEM) formation required except the dendrolyte materials the essential ink components of a radical initiator, thiol-bearing cross-linker molecule and solvent(s). The radical initiator used was either the photo-initiator 2-Hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959) or the thermal-initiator 2,2'-Azobis(2-methylpropionitrile) (AIBN). As cross-linker was ethoxylated trimethylolpropane tri(3-mercaptopropionate) (Thiocure ETTMP 1300, M_w : 1300, Brunobock) used. The cross-linker polymer (Figure 7.1) consist just like the dendrolyte material of a 1,1,1-tris(hydroxymethyl)propane (TMP) core molecule, providing with three available hydroxyl groups which have been ethoxylated by allowing them to linearly polymerize with ethylene oxide monomer, forming three long PEG chains. The three chain ends have in turn been functionalized with 3-mercaptopropionate, thus bearing thiol end groups. Unlike hyperbranched polyglycerols is the Thiocure 1300 cross-linker insoluble in water or has very poor solubility, therefore setting the minimum requisite for the membrane ink formulation solution to consist of parts of methanol solvent (alt. ethanol, propanol and DMSO). However dendrolyte A-HPG in sodium salt form has very poor solubility in alcohols, therefore was the ink developed for A-HPG consisting of water/methanol mixtures to provide homogenous solubility for all the included ink components (dendrolyte, cross-linker and initiator). Another way to circumvent solubility issues for polyelectrolyte ink formulations is by providing alternative counter ions for the polyelectrolytes. A-HPG in its protonated acid form (PA-HPG) has in fact great solubility even in 1-propanol. C-HPG on the other hand bearing bulky hydrophobic triphenyl group functionalities on its phosphonium charges was readily soluble in both pure methanol and water.

Thiol-ene cross-linking into the IEMs were performed provided with a source of radical initiation by either UV (254-365 nm) or heating (≥ 70 °C) depending on the type of radical initiator used. The sol-gel process (colloidal solution to solid gel network formation) is dependent on the components concentration in solution and too diluted solutions will prohibit the onset of gel formation until the minimum gel concentration is reached.⁸⁹ IEMs casted from highly diluted

solutions can eventually proceed to gelification when cross-linked, which may typically be attributed to solvents evaporating during fabrication processes.

In paper *I* we demonstrated the sol-gel cross-linking proof of concept for multifunctionalized dendrolyte with C-HPG5 (HPG core $M_w \sim 5\text{kDa}$). The dendrolyte, bearing cationic charges and allyl functionalities, has the ability to gelify together with the three-armed thiol bearing PEG cross-linker (Thiocure) via thiol-ene cross-linking. One of the experiments conducted was by thermo-initiated (AIBN) cross-linking at 70°C in DMSO (boiling point 189°C) monitored in 'real-time' with $^1\text{H-NMR}$ (probed scan every minute). With the onset of the radical thiol-ene cross-linking, the sol-gel curing process proceeded extremely rapidly with the loss of signal ($< 1\text{ min}$) due to solid gel formation from the liquid solution.

Figure 7.1. Schematic representation of a cross-linked network of A-HPG and Thiocure 1300 initiated by the UV-initiator Irgacure 2959.

7.2 OEIP capillary device fabrication

In paper II were glass capillary OEIP devices fabricated (Figure 7.2). The glass capillary fibers (inner diameter of 25 μm , outer diameter 230 μm) coated with an outer protective polyimide coating were cut into 30 cm length pieces with a ceramic cleaving stone. The polyimide coating was stripped from the capillaries (for efficient UV-crosslinking) by heating them to 550 $^{\circ}\text{C}$ for at least 1h and after cooling down to room temperature were the capillaries washed with isopropanol and DI water. One end of the capillaries were fused with a plastic Luer-lock tip (by heat clamping) and assembled with a compatible syringe. The syringe was connected to a nitrogen gas supply, allowing the gas pressure to push liquid solutions introduced in the syringes into the capillaries.

In the first processing step were the capillaries inner surface flushed with 2 M KOH (aq.) for 1h. The step was preformed to etch the inner glass surface and to activate surface hydroxyl(ate) groups of the silica for the next silanization step. Silanization was performed by flushing the capillaries with a 10 % v/v 3-(glycidoxypopyl)trimethoxysilane adhesion promoter in anhydrous toluene for 1h followed by 1h flushing with toluene to remove excess silanization reagent. The solution in the glass capillaries was removed and allowed to dry by nitrogen gas flow. With the last solution treatment step, the capillaries were filled with dendrolyte ink solution (~ 25 % w/w) until the solution was observed to emerge from the capillary outlets. The concentration of dendrolyte in the IEM ink solution was optimized since a too high dendrolyte concentration ($> \sim 30\%$) would result in a too viscous solution and clog the capillary fibers.

The capillaries were subsequently placed under an UV-lamp (254 nm) and the dendrolyte IEM solution was cured for 2h. As the final fabrication step were the glass capillaries cut into 7-15 mm length pieces and the individual fibers were assembled and clamped with heat shrink tubes, to provide an electrolyte reservoir for the inlet and provide ease of handling of the OEIP capillaries (Figure 7.2).

Figure 7.2. Capillary organic electronic ion pump with device dimensions and features.

7.2.1 MIMIC OEIP

In paper *I* and *III* were capillary OEIP devices based on planar substrate fabricated (Figure 7.3). The device fabrication was based on forming capillary structures based on micro molding in capillaries (MIMIC) technique.⁹⁰ A master mold was created by spin-coating SU-8 3050 (MicroChem Corp.) on a silicon wafer (spreading at 500 rpm for 5 sec followed by spinning at 3000 rpm for 30 sec). The wafer was soft baked on a hot plate at 65 °C for 1 min, then increasing the temperature with 10 °C/min until reaching 95 °C and the temperature was held for 15 min. UV exposure of the wafer was done by using a Karl Suss MA/BM 6 mask aligner (300 mJ/cm² at 365 nm) using a I-line pattern filter mask (27 μm wide × 12 μm high lines). The UV-exposed parts were cross-linked with further baking by swift ramping of temperature until reaching 95 °C and the temperature was held for 5 min. The final master mold pattern was then

developed by submerging the wafer for 5 min twice in two separate baths of MR-Dev 600 (Micro resist technology GmbH), rinsed with isopropanol, dried with N₂-gas and the wafer was additional baked for 5 min at 110 °C.

A PDMS mold was created by pouring a solution of Sylgard 184 (Dow Chemical) (10:1 ratio of silicone elastomer base and radical initiator) on top of the fabricated SU8 master mold and was subsequently cured at 120 °C for 1h. The mold was carefully peeled away from the master mold and the PDMS was cut into small pieces, each comprising of two electrolyte reservoirs connected by a 5 mm long capillary line (27 µm wide × 12 µm high). The PDMS pieces and pre-cleaned glass substrates (with Hellamnex) were O₂ plasma treated (100W at 800 mTorr for 5min) and subsequently annealed to each other, forming the capillary channels. The channels were filled with dendrolyte (~ 25 % w/w) ink solution by capillary force and cross-linked with UV (365 nm, 10 mJ/cm²) for 10 min.

Figure 7.3. Fabrication of an OEIP by micro molding in capillary. On top of a silica master mold with defined SU-8 pattern was PDMS poured and cured. The PDMS was peeled away from the master mold and annealed on top of a glass substrate. The capillary channel was filled via capillary force with a dendrolyte solution and subsequently UV-cured to form the IEM.

7.3 Free-standing IEM and E-cell device

In paper *III* were free-standing dendrolyte IEMs fabricated by drop-casting dendrolyte (25–45 % w/w) IEM ink solution in a circular (8 mm Ø) parafilm mold (1 mm thickness) on a Teflon substrate. The solutions were cross-linked into free-standing membranes by 30 min UV-exposure (2 mW/cm² measured at 365 nm) and were subsequently peeled away from the substrate and removed from the molds. The free-standing membranes were mounted in an E-Cell, between two electrolytes (NaCl) reservoirs (7–10 mL volume) connected by a circular opening (0.196 cm²) (Figure 7.4). After the membrane had reached equilibrium with the electrolyte solutions were two large titanium electrodes placed at a fixed distance in close proximity of the membrane interface and electrochemical impedance spectroscopy (EIS) was measured with the ‘indirect method’.⁹¹ With the indirect method was the membrane impedance acquired as the difference between the measured impedance with the membrane in electrolyte solution versus the solution only impedance (without the membrane).

Figure 7.4. E-cell with mounted IEM connecting the two reservoirs with a two-electrode setup.

7.4 ETE-NHS activation with poly lysine gels

Injectable hydrogel mixtures were prepared in paper V by initially preparing component stock solutions. Deionized water solutions of Poly-L-Lysine hydrobromide (M_w 150 000 – 300 000) 10 mg/mL and Polyvinyl alcohol (M_w ~9000-10 000) 20 % aqueous solution (achieved by microwave heating) were prepared. In MES buffer with pH adjusted to 6.9 were Glucose Oxidase (from *Aspergillus niger*) 10 mg/mL, Peroxidase (from horseradish) 10 mg/mL, ETE-Carboxylate 30 mg/mL and EDC/NHS (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide / N-hydroxysulfosuccinimide sodium salt) 50 mM prepared separately. In the following order were the components added from above mentioned stock solutions and mixed into gels with the final concentration: Polyvinyl alcohol (2%), ETE-Carboxylate (1-12 mg/mL), Peroxidase (1-2.5 mg/mL), Glucose Oxidase (1-2.5 mg/mL), EDC/sulfo-NHS (5 mM) and finally Poly-L-Lysine (1 mg/mL).

A run-down of the different components in the gel mixture and their purposes are as following: ETE-carboxylate and the enzymes in combination with EDC/sulfo-NHS can form EDC/NHS activated groups with their carboxylic functionalities. EDC and NHS carboxyl activation facilitates amide bond formation together with the amine groups of the Poly-L-Lysine gel, therefore creating cross-links with the polymer gel. The MES-buffer (2-morpholinoethanesulfonic acid) was used as a compatible solution for the EDC/sulfo-NHS activation to increase the coupling efficiency. The cross-links in combination with the gel matrix helps to limit the diffusion of the trimer and increase the stability of the formed conductive polymer. In conjunction the glucose (added or found *in vivo*), in the presence of the glucose oxidase enzyme with water and oxygen can be catalysed to produce peroxide. The peroxide is used to polymerise the trimer which reaction in turn can be catalysed by the peroxidase enzyme. The Polyvinyl alcohol component was added to increase the solubility properties for the final gel solution which would otherwise result in a cloudy particulate. Aggregation formation without Polyvinyl alcohol were attributed to the ETE-carboxylate (and the sulfo-NHS activated trimer) and sulfo-NHS electrostatic interactions with the Poly-L-Lysine amine groups.

8 Overview of the Publications

Paper I: Formation of Monolithic Ion-Selective Transport Media Based on “Click” Cross-Linked Hyperbranched Polyglycerol

In this project we developed a synthetic strategy to multi-functionalize hyperbranched polyglycerol (HPG, M_w : ~5000) with tunable ionic charges and cross-linkable groups. The polyelectrolyte, capable of micro and macro-fabrication was cross-linked via thiol-ene ‘click’ chemistry into free-standing homogenous IEMs for selective electrophoretic transport of molecules. The HPG polymer being a widely studied material suitable for applications in nano-medicine and biomedical technologies for non-covalent drug encapsulation and delivery with great biocompatibility,⁹² formed a great background platform to be explored for possible implementation as ion-exchange membrane structures.

The hydroxyl end group functionalization of the HPG was developed and the material was characterized via $^1\text{H-NMR}$, resulting in allyl and tri-phenylphosphonium groups with a degree of substitution of ~10 % and ~60% respectively. The multi-functional cationic polyelectrolyte material (C-HPG5) cross-linking capabilities and sol-gel formation parameters were in turn explored. Together with the components of three-armed thiol-bearing PEG polymer (Thiocure 1300), catalytic amounts of the small allyl bearing molecule TATATO (1,3,5-Triallyl-1,3,5-Triazine-2,4,6(1H,3H,5H)-Trione) and a radical initiator, thiol-ene ‘click’ cross-linked free-standing membrane formation was achieved, both thermally and UV-initiated. By monitoring the thermally initiated reaction with NMR in ‘real time’, the fast click cross-linking process could be monitored and displayed, whereas upon initiation proceeded to form the gel very fast (< 1 min). The C-HPG5 material was applied in an organic electronic ion pump (OEIP) device, showcasing the process ability to form membrane micro channels by capillary force and capability of conducting small and large anionic molecules.

Paper II: Capillary-Fiber Based Electrophoretic Delivery Device

In Paper II was the multi-functional anionic charged hyperbranched polyglycerol (A-HPG) developed. Consisting of a HPG (M_w 10 000) core with complete functionalization of the available hydroxyl group, resulting in 20 % allyl and 80% butylsulfonate groups (characterized by $^1\text{H-NMR}$). The A-HPG polyelectrolyte was mixed with the thiol bearing polyglycerol cross-linker (Thiocure 1300) and the photo-initiator 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropio-phenone in a solution mixture of water/methanol. Capillary organic electronic

ion pump (OEIP) devices were fabricated by filling the capillaries (25 μm inner diameter) with the A-HPG solution with subsequent UV cross-linking, forming the membrane material. The high solubility of the hyperbranched polyelectrolytes enabled the possibility of filling the micro-capillaries with high amounts of polyelectrolyte content forming efficient IEMs. With the capillary-OEIP a straightforward method was developed for characterization of the IEM in the devices by performing complete ion-exchange displacement during its operational state, enabling the fixed charge concentration to be measured. The advantage of the capillary device platform was by combining the substrate and encapsulation layer, which enabled overall miniaturization of the device, making the device suitable for studies involving insertion into biological tissue and drug delivery studies down to single cell level.

Paper III: Investigating the role of polymer size on ionic conductivity in free-standing hyperbranched polyelectrolyte membranes

Combining the knowledge obtained throughout the works of Paper *I* and *II* indicated a trend linking the hyperbranched polyelectrolyte polymer size with the conductivity in the formed ion-exchange membranes (IEMs). In Paper *III* we studied the effect on ionic conductivity in the IEMs based on variously sized cationic and anionic hyperbranched polyglycerols (C- & A-HPG), based on series of 2.5, 5 and 10 kDa HPG functionalized polymer core structures. The polyelectrolyte materials were synthesized and thoroughly characterized, to achieve polyelectrolyte materials series with the same amount of charged group functionalities and differences attributed only to the polymer size of the polyelectrolytes. The IEMs were cast, applied and measured in both free-standing membrane E-cell setup and micro fabricated (encapsulated) OEIP devices, with both AC and DC measurements. The increase in ionic conductivity trend was linked to the polyelectrolyte's polymer size used in the IEM. The increase in ionic conductivity was also shown not be in relation with an increased amount swelling by water content in the membrane structure. These findings showcased how a simple chemistry design feature such as employing a larger polyelectrolyte size can increase the performance significantly in IEMs.

Paper IV: Seamless integration of bioelectronic interface in an animal model via *in vivo* polymerization of conjugated oligomers

Paper V: *In vivo* formation of organic bioelectronic hydrogel devices

In paper IV and V were trimeric conjugated thiophenes synthesized. The trimeric (pre-polymer) backbone structure consisting of EDOT (3,4-Ethylenedioxythiophene)-Thiophene-EDOT, was synthesized via a double (Suzuki) cross-coupling reaction to the central thiophene ring and was achieved by synthesizing precursors consisting of dibrominated-thiophene at the 2 and 5 position and mono substituted EDOT with boronic acid pinacol ester group. The central thiophene ring bearing an ethanol group at the 3 position was also functionalized with different side chain functionalities. Initially the trimeric structure ETE-S was synthesized, consisting of a –butylsulfonate sidechain functionality with the purpose of self-doping and importantly inducing water solubility to the conjugated trimer, enabling bio interfacing. In paper IV, the small invertebrate animal model *Hydra vulgaris* was used and incubated together with the water soluble ETE-S trimer. Biocompatibility and self-organized polymerization of the trimer inside of the animal model was demonstrated, driven by the *in vivo* peroxidase enzyme activity. In turn extending the possibility for integration of bioelectronics material into animal tissue which can be used for studying biological and physiological functions and processes, but also the possibility of fabrication of hybrid materials in biological systems.

In Paper V we extended the work with the trimeric structures with animal models, in order to integrate and connect the material with the central and peripheral nervous system. To achieve self-organized, non-invasive and stable neuro-electrodes, injectable trimer containing aqueous ‘gel-cocktail’ solution was developed in order to limit the diffusion of the components and to obtain polymerizable soft electronic conductive materials using non-toxic chemistry and chemicals. The trimeric molecular structure was altered and synthesized to consist of carboxylic side-chain functionality (ETE-carboxylate) which was utilized together with EDC/NHS activation to form stable amide cross-link bonds with a polylysine gel solution. This was further coupled with inclusion of glucose/lactose oxidase and peroxidase enzymes in the mixture in order to catalyze the polymerization of the trimer, driven by the naturally available sugars found in the physiology of the target. In the study we showed broad application areas in various animal models (zebrafish brain, heart and fin, medicinal leeches and in mammalian tissue) for the polymerization strategy, forming stable, biocompatible and conductive materials for *in vivo* application. The developed strategy can presents a paradigm shift for interfacing electronics with biology.

9 Concluding Remarks and Outlook

With the writing of this thesis I've presented rational synthesis design strategies for the development and implementation of new types of organic materials towards the next generation of organic electronic devices and interfaces. As a chemist dealing primarily with synthesis, I believe that we form a fundamental pillar of knowledge for the construction and shaping of the future in the field of organic electronics. But this we can't achieve by ourselves, only by having a constant and close dialogue with physicists, material scientists and other researchers cross-disciplinary is a necessary requirement in order to bridge our understanding and to increase our capabilities to design and synthesis the materials of the future.

Dendrolytes

The ionic conductive dendrolytes based on the hyperbranched polyglycerol (HPG) core structure, provides a great material platform for processing. The high solubility and low viscosity of the hyperbranched polyelectrolytes have allowed us to integrate the materials effectively in ways that was previously not possible with linear commercially available counterparts. HPGs ability to solvate and encapsulate molecules in its structure, resulting in hydrated films being formed and enabling the transport of large ionic molecules. However there's potential for further development yet to be done. First and foremost my intuition tells me, backed up by the research in paper *III* that by employing a higher molecular weight HPG core structure ($> 10\,000$ Da) for the dendrolyte material would most likely be a further improvement, without sacrificing any of the processability or synthesis capabilities of the material. There're already a lot of previously published experimental protocols available for controlled synthesis of HPGs with high molecular weights ($>10\,000$ Da), low polydispersity (<1.5) and high degree of branching ($>60\%$).^{93,94} Such an investigation wouldn't take long to confirm if the resulting dendrolyte material would result in even higher conductivity, improved stability and better swelling characteristics. There is most likely a maximum level to this but I believe there's still a lot of leeway to utilize in here.

To improve the stability of the dendrolyte ion-exchange membranes by increasing the amount of cross-linkable groups ($> 20\%$) and also by replacing the allyl group with other unsaturated cross-linkable group e.g. vinylbenzyl is definitely viable options and preliminary experiments have already been conducted. The introduction of vinylbenzyl (20%) in A-HPG (and 80% anionic charged groups) as cross-linker groups resulted in a more reactive polyelectrolyte which could

form more rigid and mechanically stable IEMs, however the polyelectrolyte was prone to self-polymerization if not stored properly (due to the vinyl groups reactivity). Which isn't necessary a disadvantage for membrane casting efficiency but requires some optimization in storage and handling (freezer, minimize light exposure and addition of radical stabilizer). In general, the A-HPG material as IEMs already displayed high ion conductivity but the stability can be bit lacking as a free-standing IEM structure. Increasing the stability with more cross-linking by sacrificing a bit of the ion conductivity could be of great practical benefit.

Moreover I see some potential improvements with the commercial cross-linker Thiocure ETTMP 1300 used in the thiol-ene cross-linking throughout the thesis. The three thiol groups which are introduced via esterification with 3-mercaptopropionate together with the polymers three linear PEG chains. The reaction is straight forward and probably very efficient (after all they sell the material in oil barrel quantities), but the ester functionalities forms a molecular structural weakness when viewed for the purposes of IEM applications. Ester linkages are prone to hydrolysis, especially if the IEM would be subjugated to harsh acidic and alkaline conditions with e.g. water-splitting induced by electrolysis. Previous published research have addressed this issue and there're available synthesis strategies to circumvent the issue.⁹⁵ Further, it would be interesting to couple thiol functionalities directly with HPG structures and be used as the cross-linker to form IEMs solely based on a hyperbranched matrix.

In conjunction the cationic C-HPG dendrolyte in paper *I* & *III* is not a suitable structure as an AEM exposed to harsh conditions (strong alkaline), since the ionic group functionalities are linked via ester bonds, thus potential hydrolysis. Therefore, I've already almost finished the development of a new synthetic strategy in order to create a new and more stable cationic dendrolyte structure. By linking the cationic functionalization with an alkyl chain directly to the HPG core, similar structural arrangement as the anionic charge in the A-HPG. Creating an efficient and reliable synthetic method to introduce controllable and large amounts of cationic charged functionalities to the HPG have not been a straight-forward and easy task. Even if I could propose numerous of different synthetic strategies, which might be acceptable in the synthesis with small organic molecules, but it's an entirely different story when dealing with macromolecules with hundreds of functional groups, dealing with e.g. solubility and intramolecular cyclization reactions.

In summary, the dendrolyte material has great potential in the field of organic electronics, solving many of the practical issues that comes with fabrication and resulting IEMs ion transport efficiency for both small and large ions. We've come a long way with the development of the dendrolyte ink and are able to utilize ink-jet printing with the material to create well-defined micron resolution

IEM channels for upscale production, capable of being utilized in devices such as the organic electronic ion pump devices for high precision delivery of pain-relief medication (and other medications) for *in vivo* applications. The dendrolyte material has also been developed together with water dispersed polyurethane to form a viscous ink in order to create soft and stretchable IEMs.⁹⁶ Which is important to form conformable and wearable delivery devices.

Organic bioelectronics is not the only application area of interest for the dendrolyte material and I would like to look more into applying the material for energy production and storage purposes. Perfluorinated membrane materials (such as Nafion) have dominated the industry for decades and without a doubt, the chemical composition of such materials provides with exceptional stability as IEMs. However the chemistry involved in perfluorinated polymers and substances are of high concern for both health and environmental reasons.^{97,98} While membranes with very high stability have their applications, but further exploration e.g. with low-temperature Fuel Cells can be a potential application area for the dendrolyte materials (which setup also has it's advantaged and disadvantages with e.g. water-control).

Trimers

To interface conjugated polymers with biology is not a straightforward task. The highly hydrophobic nature of conjugated polymers makes them hard to process and the ability to interface the material with biological systems. The trimeric pre-polymer structure solves some these issues since they can be applied in aqueous solution and be enzymatically polymerized *in vivo*.^{32,33,99} But there're still much to be explored in terms of synthesis design for such structures. The ETE-S trimer has in our laboratory been the standard material to explore for these purposes which also provides with good conductivity for the formed polymeric materials and requires a low applied potential for electrochemical polymerization. However with the sulfonate side chain comes some drawbacks since it gives the trimeric surfactant like capabilities. Being highly soluble makes dispersion of the material an issue and the material tends to spread out easily and not stick to surfaces such as soft biological tissues as easily. The analogue ETE-carboxylic was for this purposes synthesized to address this issue, to be able to form better and more stable interfaces. A high local concentration of the trimer is necessary to efficiently polymerize into larger conductive networks and in this regards was the ETE-carboxylic development successful. The cross-linking capability of ETE-carboxylic was however meet with the drawback of displaying lower conductivity compared to the ETE-S with more efficient self-doping capabilities. To satisfy both needs is a balance and some initial

investigation was undertaken by introducing multiple side-chain functionalities, both carboxylic and sulfonate groups simultaneously to the trimeric structure. But the multiple groups seemed to possibly affect the materials π - π stacking capabilities for the worse. Since we're dealing with self-assembled networks and non-harsh polymerization conditions, in terms of conjugated structure it seems like a simple and as symmetrical as possible structure is the path forward. Increasing the conjugated chain length to tetra- or even pentamer could be a viable option, as long as efficient water solubility is retained. A purely EDOT-based backbone seems also to be useful strategy to improve the conductivity due enhanced planarity.^{99,100} An additional approach could be to introduce a conjugated pre-polymer with branched conjugated moieties in the mixture for possible branched (planar) polymerization propagation.

There're many synthetic paths left to be explored and what submerges as the appropriate direction to be taken for *in vivo* interfacing of conjugated polymers will be in conjunction with the ink development. The multi-component gel platform serves as a great demonstration of how different components can work together to form supportive networks for efficient interfacing.

Bibliography

- (1) Audenaert, M.; Gusman, G.; Deltour, R. Electrical Conductivity of I₂-Doped Polyacetylene. *Phys. Rev. B* **1977**, *24* (12), 7380–7382. <https://doi.org/10.1103/PhysRevB.24.7380>.
- (2) Cherian, D.; Armgarth, A.; Beni, V.; Linderhed, U.; Tybrandt, K.; Nilsson, D.; Simon, D. T.; Berggren, M. Large-Area Printed Organic Electronic Ion Pumps. *Flex. Print. Electron.* **2019**, *4* (2). <https://doi.org/10.1088/2058-8585/ab17b1>.
- (3) Geoghegan, M.; Hadzioannou, G. *Polymer Electronics*; Oxford University Press, 2013. <https://doi.org/10.1093/acprof:oso/9780199533824.001.0001>.
- (4) Rivnay, J.; Owens, R. M.; Malliaras, G. G. The Rise of Organic Bioelectronics. *Chem. Mater.* **2014**, *26* (1), 679–685. <https://doi.org/10.1021/cm4022003>.
- (5) Simon, D. T.; Gabrielsson, E. O.; Tybrandt, K.; Berggren, M. Organic Bioelectronics: Bridging the Signaling Gap between Biology and Technology. *Chem. Rev.* **2016**, *116* (21), 13009–13041. <https://doi.org/10.1021/acs.chemrev.6b00146>.
- (6) Heisenberg, W. Über Den Anschaulichen Inhalt Der Quantentheoretischen Kinematik Und Mechanik. In *Original Scientific Papers Wissenschaftliche Originalarbeiten*; Blum, W., Rechenberg, H., Dürr, H.-P., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 1985; pp 478–504. https://doi.org/10.1007/978-3-642-61659-4_30.
- (7) Clayden, J.; Greeves, N.; Warren Stuart. *Organic Chemistry - Second Edition*; 2012.
- (8) Chemical, G.; Pauling, B. L. Paramagnetic Susceptibility To the Structure. **1931**, 455 (1927).
- (9) Atkins, P.; Paula, J. de. *Atkins' Physical Chemistry - 9:E Edition*; Oxford University Press, 2009.
- (10) Derivatives, H.; Louis, J.; Macdiarmid, A. G. Synthesis of Electrically Conducting Organic Polymers : **1977**, No. 578, 578–580.
- (11) Heeger, A. J. Nobel Lecture : Semiconducting and Metallic Polymers : Generation of Polymeric Materials *. **2001**, *73* (July), 681–700.
- (12) Heeger, A. J. Electrochemistry of Polyacetylene, (CH)_x; Electrochemical Doping of (CH)_x Films to the Metallic State. **1979**, No. 594, 594–595.
- (13) Staudinger, H. Über Polymerisation. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.* **1920**, *53* (6), 1073–1085. <https://doi.org/10.1002/cber.19200530627>.
- (14) Decker, C. The Use of UV Irradiation in Polymerization. *Polym. Int.* **1998**, *45* (2), 133–141. [https://doi.org/10.1002/\(SICI\)1097-](https://doi.org/10.1002/(SICI)1097-)

- 0126(199802)45:2<133::AID-PI969>3.0.CO;2-F.
- (15) Kim, T.; Assary, R. S.; Marshall, C. L.; Gosztola, D. J.; Curtiss, L. A.; Stair, P. C. Acid-Catalyzed Furfuryl Alcohol Polymerization: Characterizations of Molecular Structure and Thermodynamic Properties. *ChemCatChem* **2011**, *3* (9), 1451–1458. <https://doi.org/10.1002/cctc.201100098>.
 - (16) Wilms, D.; Wurm, F.; Nieberle, J.; Böhm, P.; Kemmer-Jonas, U.; Frey, H. Articles Hyperbranched Polyglycerols with Elevated Molecular Weights: A Facile Two-Step Synthesis Protocol Based on Polyglycerol Macroinitiators. <https://doi.org/10.1021/ma802701g>.
 - (17) Li, Q.; Zhang, L.; Bai, L.; Miao, J.; Cheng, Z.; Zhu, X. Atom Transfer Radical Polymerization. *Prog. Chem.* **2010**, *22* (11), 2079–2088. <https://doi.org/10.1002/9783527809080.catatz01278>.
 - (18) Sadki, S.; Schottland, P.; Brodie, N.; Sabouraud, G. The Mechanisms of Pyrrole Electropolymerization. *Chem. Soc. Rev.* **2000**, *29* (5), 283–293. <https://doi.org/10.1039/a807124a>.
 - (19) Zheng, Y.; Li, S.; Weng, Z.; Gao, C. Hyperbranched Polymers: Advances from Synthesis to Applications. *Chem. Soc. Rev.* **2015**, *44* (12), 4091–4130. <https://doi.org/10.1039/c4cs00528g>.
 - (20) Jafari, M.; Abolmaali, S. S.; Najafi, H.; Tamaddon, A. M. Hyperbranched Polyglycerol Nanostructures for Anti-Biofouling, Multifunctional Drug Delivery, Bioimaging and Theranostic Applications. *Int. J. Pharm.* **2020**, *576* (October 2019). <https://doi.org/10.1016/j.ijpharm.2019.118959>.
 - (21) Wilms, D.; Stiriba, S.-E.; Frey, H. Hyperbranched Polyglycerols: From the Controlled Synthesis of Biocompatible Polyether Polyols to Multipurpose Applications. **2009**. <https://doi.org/10.1021/ar900158p>.
 - (22) Sousa-Herves, A.; Würfel, P.; Wegner, N.; Khandare, J.; Licha, K.; Haag, R.; Welker, P.; Calderón, M. Dendritic Polyglycerol Sulfate as a Novel Platform for Paclitaxel Delivery: Pitfalls of Ester Linkage. *Nanoscale* **2015**, *7* (9), 3923–3932. <https://doi.org/10.1039/c4nr04428b>.
 - (23) Sunder, A.; Krämer, M.; Hanselmann, R.; Mülhaupt, R.; Frey, H. Molecular Nanocapsules Based on Amphiphilic Hyperbranched Polyglycerols. *Angew. Chemie - Int. Ed.* **1999**, *38* (23), 3552–3555. [https://doi.org/10.1002/\(SICI\)1521-3773\(19991203\)38:23<3552::AID-ANIE3552>3.0.CO;2-G](https://doi.org/10.1002/(SICI)1521-3773(19991203)38:23<3552::AID-ANIE3552>3.0.CO;2-G).
 - (24) Krämer, M.; Stumbé, J.-F.; Türk, H.; Krause, S.; Komp, A.; Delineau, L.; Prokhorova, S.; Kautz, H.; Haag, R. PH-Responsive Molecular Nanocarriers Based on Dendritic Core-Shell Architectures. *Angew. Chemie Int. Ed.* **2002**, *41* (22), 4252–4256. [https://doi.org/10.1002/1521-3773\(20021115\)41:22<4252::aid-anie4252>3.0.co;2-f](https://doi.org/10.1002/1521-3773(20021115)41:22<4252::aid-anie4252>3.0.co;2-f).
 - (25) Stiriba, S. E.; Kautz, H.; Frey, H. Hyperbranched Molecular Nanocapsules: Comparison of the Hyperbranched Architecture with the

- Perfect Linear Analogue. *J. Am. Chem. Soc.* **2002**, *124* (33), 9698–9699. <https://doi.org/10.1021/ja026835m>.
- (26) Thakuria, R.; Nath, N. K.; Saha, B. K. The Nature and Applications of π – π Interactions: A Perspective. **2019**. <https://doi.org/10.1021/acs.cgd.8b01630>.
- (27) Li, P. a; Cata, a D. I. U. M.-; Ed, L. Y. Z.; Cou, C.; Ngs, P. L. I. Palladium-Catalyzed Cross Couplings in Organic Synthesis. *Sci. Backgr. Nov. Prize Chem. 2010* **2010**, 50005 (October), 0–12.
- (28) Zweifel, G. S.; Nantz, M. H. *Modern Organic Synthesis: An Introduction*; WILEY, 2017.
- (29) Rydfjord, J. Palladium (II) -Catalyzed Addition Reactions, 2017.
- (30) Bautista, M. V; Carson, M. C.; Varni, A. J.; Ayuso-carrillo, J. Polymer Chemistry Pairing Suzuki – Miyaura Cross-Coupling and Catalyst Transfer Polymerization. **2021**, 1404–1414. <https://doi.org/10.1039/d0py01507e>.
- (31) Lima, C. F. R. A. C.; Rodrigues, A. S. M. C.; Silva, V. L. M.; Silva, A. M. S.; Santos, L. M. N. B. F. Role of the Base and Control of Selectivity in the Suzuki – Miyaura Cross-Coupling Reaction. *ChemCatChem* **2014**, 1291–1302. <https://doi.org/10.1002/cctc.201301080>.
- (32) Stavriniidou, E.; Gabrielsson, R.; Nilsson, K. P. R.; Kumar, S.; Franco-gonzalez, J. F.; Volkov, A. V; Jonsson, M. P.; Grimoldi, A.; Elgland, M.; Zozoulenko, I. V; Simon, D. T. In Vivo Polymerization and Manufacturing of Wires and Supercapacitors in Plants. **2017**, *114* (11), 1–6. <https://doi.org/10.1073/pnas.1616456114>.
- (33) Dufil, G.; Parker, D.; Gerasimov, J. Y.; Nguyen, T. Q.; Berggren, M.; Stavriniidou, E. Enzyme-Assisted in Vivopolymerisation of Conjugated Oligomer Based Conductors. *J. Mater. Chem. B* **2020**, *8* (19), 4221–4227. <https://doi.org/10.1039/d0tb00212g>.
- (34) Krikstolaityte, V.; Kuliesius, J.; Ramanaviciene, A.; Mikoliunaite, L.; Kausaite-Minkstiniene, A.; Oztekin, Y.; Ramanavicius, A. Enzymatic Polymerization of Polythiophene by Immobilized Glucose Oxidase. *Polymer (Guildf)*. **2014**, *55* (7), 1613–1620. <https://doi.org/10.1016/j.polymer.2014.02.003>.
- (35) Åsberg, P.; Inganäs, O. Hydrogels of a Conducting Conjugated Polymer as 3-D Enzyme Electrode. *Biosens. Bioelectron.* **2003**, *19* (3), 199–207. [https://doi.org/10.1016/S0956-5663\(03\)00220-3](https://doi.org/10.1016/S0956-5663(03)00220-3).
- (36) Huang, Y.; Wang, W.; Li, Z.; Qin, X.; Bu, L.; Tang, Z.; Fu, Y.; Ma, M.; Xie, Q.; Yao, S.; Hu, J. Horseradish Peroxidase-Catalyzed Synthesis of Poly(Thiophene-3-Boronic Acid) Biocomposites for Mono-/Bi-Enzyme Immobilization and Amperometric Biosensing. *Biosens. Bioelectron.* **2013**, *44* (1), 41–47. <https://doi.org/10.1016/j.bios.2013.01.001>.
- (37) A. O. Patil, Y. Ikenoue. N. Basescu, N. Colaneri, J. Chen, F. Wudl, A. J. H. Self-Doped Conducting Polymers. *Synth. Met.* **1987**, *20*, 151–159.

- (38) Tillet, G.; Boutevin, B.; Ameduri, B. Chemical Reactions of Polymer Crosslinking and Post-Crosslinking at Room and Medium Temperature. *Prog. Polym. Sci.* **2011**, *36* (2), 191–217. <https://doi.org/10.1016/j.progpolymsci.2010.08.003>.
- (39) Hoyle, C. E.; Bowman, C. N. Thiol-Ene Click Chemistry. *Angew. Chemie - Int. Ed.* **2010**, *49* (9), 1540–1573. <https://doi.org/10.1002/anie.200903924>.
- (40) Killops, K. L.; Campos, L. M.; Hawker, C. J. Robust, Efficient, and Orthogonal Synthesis of Dendrimers via Thiol-Ene “Click” Chemistry. *J. Am. Chem. Soc.* **2008**, *130* (15), 5062–5064. <https://doi.org/10.1021/ja8006325>.
- (41) Lowe, A. B. Thiol-Ene “Click” Reactions and Recent Applications in Polymer and Materials Synthesis. *Polym. Chem.* **2010**, *1* (1), 17–36. <https://doi.org/10.1039/B9PY00216B>.
- (42) Hermanson, G. *Bioconjugate Techniques*, Third Edition; Elsevier, 2013.
- (43) Conlisk, A. T. *Essentials of Micro- and Nanofluidics*; Cambridge University Press: Cambridge, 2012. <https://doi.org/10.1017/CBO9781139025614>.
- (44) Luo, T.; Abdu, S.; Wessling, M. Selectivity of Ion Exchange Membranes: A Review. *J. Memb. Sci.* **2018**, *555* (December 2017), 429–454. <https://doi.org/10.1016/j.memsci.2018.03.051>.
- (45) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods Fundamentals and Applications*; John Wiley & Sons, 2001.
- (46) Strathmann, H. *Ion-Exchange Membrane Separation Processes*; Elsevier, 2004.
- (47) Carvalho, P. J.; Ventura, S. P. M.; Batista, M. L. S.; Schröder, B.; Gonçalves, F.; Esperança, J.; Mutelet, F.; Coutinho, J. A. P. Understanding the Impact of the Central Atom on the Ionic Liquid Behavior: Phosphonium vs Ammonium Cations. *J. Chem. Phys.* **2014**, *140* (6). <https://doi.org/10.1063/1.4864182>.
- (48) Hemp, S. T.; Zhang, M.; Allen, M. H.; Cheng, S.; Moore, R. B.; Long, T. E. Comparing Ammonium and Phosphonium Polymerized Ionic Liquids: Thermal Analysis, Conductivity, and Morphology. *Macromol. Chem. Phys.* **2013**, *214* (18), 2099–2107. <https://doi.org/10.1002/macp.201300322>.
- (49) Tsuchida, Y.; Matsumiya, M.; Tsunashima, K. The Effect of Substituents of Phosphonium-Based Ionic Liquids Evaluated by MP2 Calculation. *J. Mol. Liq.* **2019**, *274*, 455–460. <https://doi.org/10.1016/j.molliq.2018.11.002>.
- (50) Sun, Z.; Lin, B.; Yan, F. Anion-Exchange Membranes for Alkaline Fuel-Cell Applications: The Effects of Cations. *ChemSusChem* **2018**, *11* (1), 58–70. <https://doi.org/10.1002/cssc.201701600>.
- (51) Simon, D. T.; Kurup, S.; Larsson, K. C.; Hori, R.; Tybrandt, K.; Goiny,

- M.; Jager, E. W. H.; Berggren, M.; Canlon, B.; Richter-Dahlfors, A. Organic Electronics for Precise Delivery of Neurotransmitters to Modulate Mammalian Sensory Function. *Nat. Mater.* **2009**, *8* (9), 742–746. <https://doi.org/10.1038/nmat2494>.
- (52) Waldherr, L.; Seitanidou, M.; Jakešová, M.; Handl, V.; Honeder, S.; Nowakowska, M.; Tomin, T.; Karami Rad, M.; Schmidt, T.; Distl, J.; Birner-Gruenberger, R.; von Campe, G.; Schäfer, U.; Berggren, M.; Rinner, B.; Asslaber, M.; Ghaffari-Tabrizi-Wizsy, N.; Patz, S.; Simon, D. T.; Schindl, R. Targeted Chemotherapy of Glioblastoma Spheroids with an Iontronic Pump. *Adv. Mater. Technol.* **2021**, *6* (5), 2001302. <https://doi.org/10.1002/admt.202001302>.
- (53) Seitanidou, M.; Blomgran, R.; Pushpamithran, G.; Berggren, M.; Simon, D. T. Modulating Inflammation in Monocytes Using Capillary Fiber Organic Electronic Ion Pumps. *Adv. Healthc. Mater.* **2019**, *8* (19), 1–7. <https://doi.org/10.1002/adhm.201900813>.
- (54) Jonsson, A.; Song, Z.; Nilsson, D.; Meyerson, B. A.; Simon, D. T.; Linderöth, B.; Berggren, M. Therapy Using Implanted Organic Bioelectronics. *Sci. Adv.* **2015**, *1* (4), e1500039–e1500039. <https://doi.org/10.1126/sciadv.1500039>.
- (55) Feron, K.; Lim, R.; Sherwood, C.; Keynes, A.; Brichta, A.; Dastoor, P. C. Organic Bioelectronics: Materials and Biocompatibility. *Int. J. Mol. Sci.* **2018**, *19* (8). <https://doi.org/10.3390/ijms19082382>.
- (56) Stavriniidou, E.; Gabrielsson, R.; Gomez, E.; Crispin, X.; Nilsson, O.; Simon, D. T.; Berggren, M. Electronic Plants. *Sci. Adv.* **2015**, *1* (10). <https://doi.org/10.1126/sciadv.1501136>.
- (57) Parker, D.; Daguerre, Y.; Dufil, G.; Mantione, D.; Solano, E.; Cloutet, E.; Hadziioannou, G.; Näsholm, T.; Berggren, M.; Pavlopoulou, E.; Stavriniidou, E. Biohybrid Plants with Electronic Roots via in Vivo Polymerization of Conjugated Oligomers. *Mater. Horizons* **2021**. <https://doi.org/10.1039/d1mh01423d>.
- (58) Seitanidou, M.; Tybrandt, K.; Berggren, M.; Simon, D. T. Overcoming Transport Limitations in Miniaturized Electrophoretic Delivery Devices. *Lab Chip* **2019**, *19* (8), 1427–1455. <https://doi.org/10.1039/c9lc00038k>.
- (59) Gerasimov, J. Y.; Zhao, D.; Sultana, A.; Abrahamsson, T.; Han, S.; Bliman, D.; Tu, D.; Simon, D. T.; Olsson, R.; Crispin, X.; Berggren, M.; Fabiano, S. A Biomimetic Evolvable Organic Electrochemical Transistor. *Adv. Electron. Mater.* **2021**, 2001126. <https://doi.org/10.1002/aelm.202001126>.
- (60) Campana, A.; Cramer, T.; Simon, D. T.; Berggren, M.; Biscarini, F. Electrocardiographic Recording with Conformable Organic Electrochemical Transistor Fabricated on Resorbable Bioscaffold. *Adv. Mater.* **2014**, *26* (23), 3874–3878. <https://doi.org/10.1002/adma.201400263>.

- (61) Gkoupidenis, P.; Schaefer, N.; Strakosas, X.; Fairfield, J. A.; Malliaras, G. G. Synaptic Plasticity Functions in an Organic Electrochemical Transistor. *Appl. Phys. Lett.* **2015**, *107* (26). <https://doi.org/10.1063/1.4938553>.
- (62) Berto, M.; Diacci, C.; D'Agata, R.; Pinti, M.; Bianchini, E.; Lauro, M. Di; Casalini, S.; Cossarizza, A.; Berggren, M.; Simon, D.; Spoto, G.; Biscarini, F.; Bortolotti, C. A. EGOFET Peptide Aptasensor for Label-Free Detection of Inflammatory Cytokines in Complex Fluids. *Adv. Biosyst.* **2018**, *2* (2), 1–8. <https://doi.org/10.1002/adbi.201700072>.
- (63) Isaksson, J.; Kjäll, P.; Nilsson, D.; Robinson, N.; Berggren, M.; Richter-Dahlfors, A. Electronic Control of Ca²⁺ Signalling in Neuronal Cells Using an Organic Electronic Ion Pump. *Nat. Mater.* **2007**, *6* (9), 673–679. <https://doi.org/10.1038/nmat1963>.
- (64) Gabriëlsson, E. O.; Tybrandt, K.; Berggren, M. Ion Diode Logics for PH Control. *Lab Chip* **2012**. <https://doi.org/10.1039/c2lc40093f>.
- (65) Bernards, D. A.; Malliaras, G. G. Steady-State and Transient Behavior of Organic Electrochemical Transistors. *Adv. Funct. Mater.* **2007**, *17* (17), 3538–3544. <https://doi.org/10.1002/adfm.200601239>.
- (66) Strakosas, X.; Bongo, M.; Owens, R. M. The Organic Electrochemical Transistor for Biological Applications. *J. Appl. Polym. Sci.* **2015**, *132* (15), 1–14. <https://doi.org/10.1002/app.41735>.
- (67) Andersson Ersman, P.; Nilsson, D.; Kawahara, J.; Gustafsson, G.; Berggren, M. Fast-Switching All-Printed Organic Electrochemical Transistors. *Org. Electron.* **2013**, *14* (5), 1276–1280. <https://doi.org/10.1016/j.orgel.2013.02.027>.
- (68) Lee, H.; Lee, S.; Lee, W.; Yokota, T.; Fukuda, K.; Someya, T. Ultrathin Organic Electrochemical Transistor with Nonvolatile and Thin Gel Electrolyte for Long-Term Electrophysiological Monitoring. *Adv. Funct. Mater.* **2019**, *29* (48). <https://doi.org/10.1002/adfm.201906982>.
- (69) Mabeck, J. T.; Malliaras, G. G. Chemical and Biological Sensors Based on Organic Thin-Film Transistors. *Anal. Bioanal. Chem.* **2006**, *384* (2), 343–353. <https://doi.org/10.1007/s00216-005-3390-2>.
- (70) Galliani, M.; Diacci, C.; Berto, M.; Sensi, M.; Beni, V.; Berggren, M.; Borsari, M.; Simon, D. T.; Biscarini, F.; Bortolotti, C. A. Flexible Printed Organic Electrochemical Transistors for the Detection of Uric Acid in Artificial Wound Exudate. *Adv. Mater. Interfaces* **2020**, *7* (23), 1–7. <https://doi.org/10.1002/admi.202001218>.
- (71) Diacci, C.; Lee, J. W.; Janson, P.; Dufil, G.; Méhes, G.; Berggren, M.; Simon, D. T.; Stavrinidou, E. Real-Time Monitoring of Glucose Export from Isolated Chloroplasts Using an Organic Electrochemical Transistor. *Adv. Mater. Technol.* **2020**, *5* (3). <https://doi.org/10.1002/admt.201900262>.
- (72) Williamson, A. J.; Rivnay, J.; Kergoat, L.; Jonsson, A.; Inal, S.; Uguz,

- I.; Ferro, M.; Ivanov, A.; Sjöström, T. A.; Simon, D. T.; Berggren, M.; Malliaras, G. G.; Bernard, C. Controlling Epileptiform Activity with Organic Electronic Ion Pumps. *Adv. Mater.* **2015**, *27* (20), 3138–3144. <https://doi.org/10.1002/adma.201500482>.
- (73) Strakosas, X.; Seitanidou, M.; Tybrandt, K.; Berggren, M.; Simon, D. T. An Electronic Proton-Trapping Ion Pump for Selective Drug Delivery. *Sci. Adv.* **2021**, *7* (5), 1–6. <https://doi.org/10.1126/SCIADV.ABD8738>.
- (74) Bernacka-Wojcik, I.; Huerta, M.; Tybrandt, K.; Karady, M.; Mulla, M. Y.; Poxson, D. J.; Gabrielsson, E. O.; Ljung, K.; Simon, D. T.; Berggren, M.; Stavrinidou, E. Implantable Organic Electronic Ion Pump Enables ABA Hormone Delivery for Control of Stomata in an Intact Tobacco Plant. *Small* **2019**, *15* (43), 1–9. <https://doi.org/10.1002/sml.201902189>.
- (75) Hickner, M. A.; Pivovar, B. S. The Chemical and Structural Nature of Proton Exchange Membrane Fuel Cell Properties. *Fuel Cells* **2005**, *5* (2), 213–229. <https://doi.org/10.1002/fuce.200400064>.
- (76) Vincent, I.; Bessarabov, D. Low Cost Hydrogen Production by Anion Exchange Membrane Electrolysis: A Review. *Renew. Sustain. Energy Rev.* **2018**, *81* (May 2017), 1690–1704. <https://doi.org/10.1016/j.rser.2017.05.258>.
- (77) Tanaka, Y. Ion-Exchange Membrane Electrodialysis for Saline Water Desalination and Its Application to Seawater Concentration. *Ind. Eng. Chem. Res.* **2011**, *50* (12), 7494–7503. <https://doi.org/10.1021/ie102386d>.
- (78) Che, C.; Vagin, M.; Wijeratne, K.; Zhao, D.; Warczak, M.; Jonsson, M. P.; Crispin, X. Conducting Polymer Electrocatalysts for Proton-Coupled Electron Transfer Reactions: Toward Organic Fuel Cells with Forest Fuels. *Adv. Sustain. Syst.* **2018**, *2* (7), 1–7. <https://doi.org/10.1002/adsu.201800021>.
- (79) Couture, G.; Alaaeddine, A.; Boschet, F.; Ameduri, B. Polymeric Materials as Anion-Exchange Membranes for Alkaline Fuel Cells. *Prog. Polym. Sci.* **2011**, *36* (11), 1521–1557. <https://doi.org/10.1016/j.progpolymsci.2011.04.004>.
- (80) G.F. McLean *, T. Niet, S. Prince-Richard, N. D. An Assessment of AFC Technology. *Int. J. Hydrogen Energy* **2002**, *27*, 507–526.
- (81) Paulus, F.; Weiss, M. E. R.; Steinhilber, D.; Nikitin, A. N.; Schütte, C.; Haag, R. Anionic Ring-Opening Polymerization Simulations for Hyperbranched Polyglycerols with Defined Molecular Weights. *Macromolecules* **2013**, *46* (21). <https://doi.org/10.1021/ma401712w>.
- (82) Haag, R.; Sunder, A.; Stumbé, J.-F. An Approach to Glycerol Dendrimers and Pseudo-Dendritic Polyglycerols. <https://doi.org/10.1021/ja994363e>.
- (83) A. Sunder, H. Frey, R. M. Hyperbranched Polyglycerols by Ring-

- Opening Multibranching Polymerization. *Macromol. Symp.* **2000**, *153*, 187–196.
- (84) Izunobi, J. U.; Higginbotham, C. L. Polymer Molecular Weight Analysis by ¹H NMR Spectroscopy. *J. Chem. Educ.* **2011**, *88* (8), 1098–1104. <https://doi.org/10.1021/ed100461v>.
- (85) Sunder, A.; Hanselmann, R.; Frey, H.; Mu, R. Controlled Synthesis of Hyperbranched Polyglycerols by Ring-Opening Multibranching Polymerization. <https://doi.org/10.1021/ma990090w>.
- (86) Yang, Q.; Sheng, M.; Henkelis, J. J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D. E. Explosion Hazards of Sodium Hydride in Dimethyl Sulfoxide, N, N-Dimethylformamide, and N, N-Dimethylacetamide. *Org. Process Res. Dev.* **2019**, *23* (10), 2210–2217. <https://doi.org/10.1021/acs.oprd.9b00276>.
- (87) Leliège, A.; Barik, S.; Skene, W. G. Photopatternable Electrochromic Materials from Oxetane Precursors. *ACS Appl. Mater. Interfaces* **2014**, *6* (9), 6920–6929. <https://doi.org/10.1021/am500726n>.
- (88) Omar, O. H.; Gatta, S.; Tangorra, R. R.; Milano, F.; Ragni, R.; Operamolla, A.; Argazzi, R.; Chiorboli, C.; Agostiano, A.; Trotta, M.; Farinola, G. M.; Chimica, D.; Aldo, B. Synthetic Antenna Functioning As Light Harvester in the Whole Visible Region for Enhanced Hybrid Photosynthetic Reaction Centers. **2016**. <https://doi.org/10.1021/acs.bioconjchem.6b00175>.
- (89) Ichinose, N.; Ura, H. Concentration Dependence of the Sol-Gel Phase Behavior of Agarose-Water System Observed by the Optical Bubble Pressure Tensiometry. *Sci. Rep.* **2020**, *10* (1), 1–9. <https://doi.org/10.1038/s41598-020-58905-8>.
- (90) Kim, E.; Xia, Y.; Whitesides, G. M. Micromolding in Capillaries: Applications in Materials Science. **1996**, *7863* (Figure 1), 5722–5731.
- (91) Galama, A. H.; Hoog, N. A.; Yntema, D. R. Method for Determining Ion Exchange Membrane Resistance for Electrodialysis Systems. *Desalination* **2016**, *380*, 1–11. <https://doi.org/10.1016/j.desal.2015.11.018>.
- (92) Abbina, S.; Vappala, S.; Kumar, P.; Siren, E. M. J.; La, C. C.; Abbasi, U.; Brooks, D. E.; Kizhakkedathu, J. N. Hyperbranched Polyglycerols: Recent Advances in Synthesis, Biocompatibility and Biomedical Applications. *J. Mater. Chem. B* **2017**, *5* (47), 9249–9277. <https://doi.org/10.1039/c7tb02515g>.
- (93) Wilms, D.; Wurm, F.; Bo, P.; Kemmer-jonas, U.; Frey, H. Hyperbranched Polyglycerols with Elevated Molecular Weights: A Facile Two-Step Synthesis Protocol Based on Polyglycerol Macroinitiators. *Control* **2009**, 3230–3236.
- (94) Kainthan, R. K.; Muliawan, E. B.; Hatzikiriakos, S. G.; Brooks, D. E. Synthesis , Characterization , and Viscoelastic Properties of High

- Molecular Weight Hyperbranched Polyglycerols. **2006**, 7708–7717.
- (95) Tong, X.; Lai, J.; Guo, B.-H.; Huang, Y. A New End Group Structure of Poly(Ethylene Glycol) for Hydrolysis-Resistant Biomaterials. *J. Polym. Sci. Part A Polym. Chem.* **2011**, 49 (6), 1513–1516. <https://doi.org/10.1002/pola.24562>.
 - (96) Cherian, D.; Lienemann, S.; Abrahamsson, T.; Kim, N.; Berggren, M.; Simon, D. T.; Tybrandt, K. Soft Iontronic Delivery Devices Based on an Intrinsically Stretchable Ion Selective Membrane. **2021**, 6 (4).
 - (97) Blum, A. Perspectives | Brief Communication The Madrid Statement on Poly- And. *Environ. Health Perspect.* **2015**, 123 (5), A107–A111. <https://doi.org/10.1021/es201662b.Fei>.
 - (98) Houde, M.; Martin, J. W.; Letcher, R. J.; Solomon, K. R.; Muir, D. C. G. Biological Monitoring of Polyfluoroalkyl Substances: A Review. *Environ. Sci. Technol.* **2006**, 40 (11), 3463–3473. <https://doi.org/10.1021/es052580b>.
 - (99) Mantione, D.; Stavrinidou, E.; Pavlopoulou, E.; Istif, E.; Dufil, G.; Vallan, L.; Parker, D.; Brochon, C.; Cloutet, E.; Hadzioannou, G.; Berggren, M. Thiophene-Based Trimers for in Vivo Electronic Functionalization of Tissues. *ACS Appl. Electron. Mater.* **2020**, 2 (12), 4065–4071. <https://doi.org/10.1021/acsaelm.0c00861>.
 - (100) Elschner, A.; Kirchmeyer, S.; Lövenich Wilfried; Merker, U.; Reuter, K. *PEDOT: Principles and Application of an Intrinsically Conducting Polymer*; CRC Press, 2010.

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