Functional macromolecules and
smart polymer networks
for ion separation, reduction and delivery

Bram Zoetebier

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FUNCTIONAL MACROMOLECULES AND SMART POLYMER NETWORKS
FOR ION SEPARATION, REDUCTION AND DELIVERY

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Chapter 1

General introduction

1.1 Introduction

Since decades, nature has been an inspiration for the fields of polymer chemistry and materials science. To date, it remains a challenge to mimic natural systems to attain their desired properties.¹⁻² Traditional polymers can generally meet particular parameters one at a time. For example mechanical properties can be improved but often without enhancement of other materials parameters. The same also holds for other properties. In contrast, natural polymers developed during genesis often possess a set of properties which have been simultaneously optimized to achieve a given task.³ Meanwhile, chemists are making progress in the synthesis of biomimetic materials with desired combination of mechanical properties, which may lead to synthetic replacements of macromolecules in living tissues, such as cartilage and muscles.⁴

In the field of materials science, chemical properties are combined with structural and surface properties, mimicking, for instance, the gecko foot and the lotus leaf. Self-assembly at different length scales, one of the key elements that nature presents to us, provides simple building blocks for otherwise difficult to achieve structures, which are preferentially assembled through supramolecular chemistry.⁵ The dynamic, stimuli-responsive character of these interactions provide adaptive reversible connections in many molecular processes and materials. For example, molecular recognition processes can trigger biological responses, awakening the field of biosensors and actuators.⁶

The *Mimosa pudica*, a plant which folds its leafs upon receiving a stimulus, is another fascinating example of the responsiveness of natural systems. Upon a touch or air movement, a release of chemicals is triggered which causes water removal and subsequent cell collapse, giving rise to the folding of its leafs.⁷

These are just a few examples of the materials and objects developed and evolved over time by nature. Biomimetics brings together scientists from different fields in an attempt to create *e.g.*, molecular-scale devices, nanomedicine, actuators, self-

assembling and self-healing materials and tools for molecular sensing and recognition.

In the related fields of stimulus responsive hydrogels and ionic polymer–metal composite actuators, research is focused on achieving comparable responses with synthetic materials. In this thesis attention will be paid to hydrogels and “unconventional” polymers that incorporate inorganic elements in their main chain.

1.2 Concept of this thesis

The concept of the research described in this thesis is centered around the synthesis, characterization and function of novel organometallic polyanions, polycations, and their corresponding hydrogels and the exploration of the use of these redox-responsive water-soluble or water-swellaable materials in metal nanoparticle fabrication and transfection. In addition, crown ether-functionalized aromatic polymers and organometallic polymers will be employed for ion separation and sensing.

Chapter 2 summarizes the field of stimulus responsive polymers, focusing on redox responsive hydrogels and their application in the fabrication of metal nanoparticles.

Chapter 3 describes the synthesis of polyferrocenylsilane (PFS) polyanion hydrogels, where covalent crosslinks were formed between strained alkynes and azide groups in a copper-free Huisgen cycloaddition reaction. The anionic organometallic hydrogels display a reversible collapse and reswelling upon chemical oxidation and reduction as they are switched between a zwitterionic and a polyanionic state. The hydrogels provide a facile platform for obtaining unaggregated metal nanoparticles (NPs) from selected metal cation salts.

Chapter 4 explores the use of PFS polycations in selective gene delivery applications. The positive charge of the cationic PFS condenses DNA into polyplex NPs in which DNA is surrounded by PFS chains. The polyplex particles have a

high positive charge at the surface which results in a high gene delivery efficiency. A PEG shell was added to prevent aggregation of the polyplexes and improve cell viability.

Chapter 5 focusses on PFS derivatives suitable for sensing applications. Different functionalities are readily attached to PFS chains, either prior to or after immobilization of these chains on electrode surfaces. In this chapter, PFS chains will be functionalized with crown ether moieties, providing surface-immobilized redox-active PFS films with ion recognition and sensing capabilities.

Chapter 6 describes various crown ether containing poly(arylene ether ketone)s (PAEKs). By incorporating crown ether units in the main chain of these aromatic polymers, monovalent ion-selective membranes and ionic polymer metal composite actuators were prepared. The suitability of these systems for potassium and lithium ion separation will be demonstrated.

Chapter 7 explores future research in the direction of actuators and artificial muscles, based on PFS polyanion hydrogels. Their redox induced switching between a zwitterionic and a polyanionic state results in a substantial swelling and collapse. Combined with the self-healing capabilities of adamantyl/ β -cyclodextrin crosslinks a stable platform for the preparation of actuators is expected.

The scope of this thesis is centered around the field of biomimetics, by finding opportunities in organometallic hydrogels and ionic polymer metal composite actuators as artificial muscles, stimulating cells to actively perform desired tasks upon introduction of a reporter gene to cells using designer polymers or the preparation of bioinspired ion recognition sensors.

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Chapter 2

Stimulus-responsive materials and hydrogels, honing in
on PFS hydrogels and metal nanoparticle formation

This chapter gives a broad introduction to the field of stimulus responsive polymers, focusing on redox responsive (hydro)gels and their application in the fabrication of metal nanoparticles.

2.1 Introduction

Stimulus-responsive polymers constitute a fascinating class of materials that can display dramatic changes in properties when addressed by stimuli. These triggered responses play an important role in the fields of bio sensing, drug delivery and microfluidics. Chemical and conformational responses can be induced by changing *e.g.*, temperature, mechanical stress, electro-magnetic irradiation, redox state, pH, or ionic strength. Such stimulus-responsive materials or as often called ‘smart materials’, may be dissolved in aqueous or organic media, absorbed onto or chemically tethered to interfaces, or the stimulus-responsive polymers may be chemically crosslinked, H-bonded and/or physically entangled in the form of (hydro)gels, depending on the targeted application.¹⁻²

The physical form of the stimulus-responsive polymers dictates the mobility of the polymer chains within variable dimensions, providing the opportunity of directing the response.³ In the case of polymer brushes, the response is directed in one dimension, due to the high grafting density at the surface. The same one-dimensional response is observed for surface confined (hydro)gels, whereas polymers in solution and non-confined hydrogels have a three-dimensional response. Figure 2.1 gives an overview of the dimensionality, stimuli and responses of stimulus-responsive materials.

In our studies, stimulus-responsive and other functional polymers were used as building blocks for the creation of various functional polymer architectures such as (surface confined) hydrogels, polymer-DNA complexes and sensors. In this chapter the advances and challenges in the area of polyelectrolyte based ‘smart materials’ will be discussed, starting with the introduction of polyelectrolytes which are one of the building blocks used in this research.

Figure 2.1. Dimensional changes of stimulus-responsive polymers caused by physical or chemical stimuli. Reprinted with permission from reference.³

2.2 Polyelectrolytes

Polyelectrolytes (or polyions) are polymers that are charged (strong polyelectrolytes) or chargeable (weak polyelectrolytes) in their nature. Polyions are water-soluble, degrade at a slow rate and do not alter normal cell function, which makes them - in principle - suitable for (bio)medical applications.⁴ Polyions are crucial in biological systems for gene expression regulation, cell-cell interactions and communication, and ligand-receptor binding.⁵⁻⁸

Most of the properties of polyions can be related to their charged macromolecular character. Polyion solution characteristics strongly depend on salt concentration, because this influences electrostatic interactions. In the absence of salt, polyions tend to adopt a more stretched conformation, compared to neutral polymers. Therefore, the osmotic pressure of polyion solutions is often several orders of magnitude higher than that of neutral polymers at similar polymer concentrations.⁹

However, the addition of salt can introduce charge shielding effects, reducing the electrostatic interactions between polyion repeat units, allowing the polymer chain to form a random coil.¹⁰

The stretched conformation of linear polyions as well as the electrostatic assembly of polyions with other charged entities is closely related to the ionic interactions between two point charges. The Coulombic force F and the potential energy of the interaction V of two charges Q_1 and Q_2 , separated by a distance r are described by:

$$F = \frac{Q_1 Q_2}{4\pi\epsilon_0\epsilon r^2} \qquad V = \frac{Q_1 Q_2}{4\pi\epsilon_0\epsilon r}$$

Where ϵ_0 is the dielectric permeability of free space and ϵ is the relative permeability or dielectric constant of the medium. For like charge interactions, the Coulombic force is positive and therefore the force is repulsive, while for opposite charge interactions the Coulombic force is negative and the force is attractive.¹¹ When considering point charges at sub nm distance, like in polyions, the Coulomb interaction at room temperature is several hundreds of kT , k being the Boltzmann constant ($1.38 \cdot 10^{-23}$ J/K), which is comparable to the strength of covalent bonds. Therefore polyions will have a stretched conformation and a strong interaction with oppositely charged (poly)ions.

2.2.1 Polyelectrolyte complexes

Next to the electrostatic interactions between salts and polyions, polyions can also strongly interact with oppositely charged polyions to form polyionic complexes. The mixing of solutions of polyanions and polycations leads to the spontaneous formation of insoluble complexes accompanied by the release of their counterions.¹²⁻¹³ The gain of entropy due to this release of counterions plays a key role in complex formation. The formation of these, more coiled and interdigitated complexes is governed by the strength and location of ionic sites, the polymer

chain rigidity, precursor chemistries, pH, temperature, ionic strength, mixing intensity, and other controllable factors.⁴ Complex formation is tunable, *i.e.*, the nature of the supramolecular architecture can be controlled by various conditions.¹² Besides electrostatic forces, the formation of complexes may rely on short range interactions such as van der Waals forces, hydrogen bonding and hydrophobic interactions.¹⁴⁻¹⁷ Since most synthetic polyelectrolytes consist of a hydrophobic backbone, hydrophobic interactions will take place in aqueous solutions. This is closely related to the hydrophobic effect,¹¹ originating from the strong tendency of water molecules to form hydrogen bonds with each other, causing the hydrophobic chains to be closely packed together and surrounded by the water molecules in order to retain the hydrogen bonding sites. The related unfavorable entropic effect results in an unusually strong attraction between the hydrophobic chains.^{11, 18}

Synthetic polyions are highly versatile materials with well-defined structures and properties. By tailoring the polymer molecular weight, side groups and charge density, their self-assembly capabilities can be directed to form micelles, membranes, and capsules.¹² In this way, complex structures can be formed in a straightforward bottom-up approach, allowing one to implement multiple functionalities by tuning the formation conditions. For example, varying the pH of weak polyelectrolyte solutions can influence the availability of charged groups, while adding salts to increase the ionic strength can reduce electrostatic repulsion between charged groups and favor electrostatic assembly.¹⁹⁻²¹

More controlled structures can be obtained by a technique called layer-by-layer (LbL) deposition, introduced by Decher et al.²² on flat substrates and later by Möhwald et al.²³ for the preparation of hollow polymer shells. This technique results, for flat substrates, in multi-layered uniform nanostructures by repeatedly dipping a substrate in solutions of oppositely charged polyelectrolytes. The composition, surface charge and thickness can be controlled by changing the type of polyelectrolyte, the reaction conditions and the number of dip and wash cycles during the LbL preparation.

In order to expand the library of achievable hierarchical platforms by polyions, many types of charged molecules and objects have been used as (whether or not sacrificial) templates, *e.g.*, microparticles,²⁴ nanoparticles (NPs),²⁵⁻²⁷ porous membranes,²⁸ carbon nanotubes,²⁹⁻³⁰ clay platelets³¹ and nucleic acids (Figure 2.2).³²⁻³³

Figure 2.2. Representation of building blocks used in LbL and their structures and applications. Reprinted with permission from reference.¹³

These LbL membranes have found numerous potential applications, especially in drug delivery, gene transfection, and biosensors.¹² In the LbL fabrication process, different functional molecules can be incorporated in between, or as, polyion layers. In this way, materials can be made for selective and controlled (drug) release.^{24, 34}

By using a sacrificial template, hollow structures can be prepared.^{23, 35} Multilayer capsules have drawn attention for controlled release studies and drug delivery. To produce these LbL capsules, colloidal templates are dipped in polyelectrolyte solutions and isolated, after which the template is removed (Figure 2.3). These hollow micro or nanocapsules prepared by LbL deposition generally display

permeability to small molecules.³⁶ This selective permeability can be exploited to generate controlled release systems.^{24, 37-38}

Figure 2.3. *LbL formation of vesicles using a sacrificial template. Reprinted with permission from reference.¹²*

By using templates, the shape can be adapted to the specific application, however some applications can do without templates. For instance, the inherent tunability of polyionic complex micelles shows great potential to perform complex functions *in vivo*.^{12, 39} These polyionic complex micelles have a high stability and low critical micelle concentration. The hydrophobic heads of typical micelles are replaced by polycations and polyanions, which form a complex, being the core of the micelle. The hydrophilic shell is formed by the use of block copolymers, having a hydrophilic block attached to the polyion blocks. By mixing the polycation and polyanion block-co-polymer solutions, spontaneous formation of polyionic complex micelles is achieved, based on similar complex formation as described earlier. These polyionic complex micelles are promising vehicles for the delivery of charged compounds to the body. The charged compounds can include plasmid

DNA,³³ oligonucleotides,⁴⁰⁻⁴¹ or small interfering RNA.⁴² While the neutral hydrophilic blocks can be chosen from a wide variety of polymers, the use of PEG is mostly preferred, due to its strong hydration ability, conformational flexibility and remarkably high biocompatibility. The fact that PEG is approved by the US Food and Drug Administration makes it easier to introduce the final product to the market.¹²

When the complexes are formed by combining polycations and DNA, whether or not combined with a hydrophilic block to form polyionic complex micelles, these complexes are referred to as polyplexes (Figure 2.4). These polyplexes have been widely applied in gene delivery (also known as transfection).^{4, 43-44} A well-known example of polymers for gene delivery are polyethylenimines (PEIs). PEI has a high positive charge density, with every third atom being a protonatable amino nitrogen atom. PEIs are able to form tight polyplexes, protect DNA against nucleolytic degradation, and deliver DNA into cells, without any targeting group needed.⁴³ Therefore, PEI is now often used as the benchmark for other transfection studies.

Figure 2.4. The condensation of DNA with a polycation into a polyplex.

Other forms of polyionic complexes include fibers, prepared by drawing the polyionic complexed film from the interface of two oppositely charged polyion solutions.⁴⁵⁻⁴⁶ Once the film is dried, it forms a strong fiber with an outside layer composed of one polyelectrolyte and an inside layer of the other.¹² Click chemistry was also introduced in the formation of polyionic complexes to produce polyplexes that are stable to dissociation in the presence of salt,⁴⁷ or to specifically prepare

multifunctional cationic polymers.⁴⁸ Hydrogels, in which the crosslinks in a three dimensional network are governed by ionic interactions between oppositely charged polyions, are yet another interesting addition to polyionic complexed materials. Hawker et al. employed ABA triblock copolymers, A being polyionic (cationic or anionic) blocks and B a PEG linker. The tunable hydrogels were formed based on self-organization of two oppositely charged triblock copolyelectrolytes through ionic interactions in water.⁴⁹ The robust and tunable hydrogels were found responsive to pH and salt concentration.

2.3 Stimulus-responsive (hydro)gels

Polymer gels are composed of a flexible crosslinked polymer network, swollen with a solvent filling the interstitial molecular space, capable of undergoing large deformations. These solvent swollen networks absorb a significant fraction, up to about 2000 times the polymer weight, of the corresponding solvent within its structure but will not dissolve.⁵⁰ The swelling ratio of these solvent insoluble networks is determined by the balance between the favorable osmotic forces, swelling the network, and the elastic restoring forces in the polymer network, preventing deformation.⁵¹ These networks are found in the form of macroscopic gels,⁵² thin film gels,⁵³ surface confined gel films,⁵⁴⁻⁵⁵ and micro- and nanogels⁵⁶ and are referred to as hydrogels in the case of water being the solvent. The characteristic structure and nature of these networks, inherent from the stimulus-responsive polymers incorporated, is responsible for their unique ability to undergo changes in response to environmental stimuli. The stimuli to which these networks are responsive are analogue to those of the constituting polymers, *e.g.*, temperature,⁵⁷ light irradiation,⁵⁸ electric field strength,⁵⁹ magnetic field strength,⁶⁰⁻⁶² redox state,⁶³ pH,⁶⁴⁻⁶⁵ ionic strength,⁶⁶ or combinations thereof.⁶⁷⁻⁶⁸ Such gels can for instance be used for controlled release of drugs or cosmetics, upon employing a specific stimulus.⁶⁹ They can also be useful as actuators,⁷⁰ sensors⁷¹ or microfluidic valves,⁷² or in more biological applications as injectable

biomaterials,⁷³ artificial muscles⁷⁴ and tunable surfaces for cell sheet engineering.⁷⁵⁻⁷⁶

Here, we focus on gels responsive to redox stimuli. These gels usually incorporate transition metals into their network-forming polymer chains, either as main chain constituents or included in side groups, or are composed of (semi)conducting polymers.⁷⁷⁻⁷⁸ Their addressability by redox stimuli allows one to alter properties such as polarity, which generally has a large influence on polymer chain stiffness and extension, and on their interactions with solvents. Redox responsiveness is therefore mainly of interest for actuator applications. Until now, relatively few examples of transition-metal-based redox-active gels and hydrogels have appeared in the literature.⁷⁷

2.3.1 β -Cyclodextrin-ferrocene based (hydro)gels

β -CD shows a high affinity for ferrocene in its reduced state due to its hydrophobic nature, whereas the oxidized state of ferrocene (Fc^+) exhibits a low affinity for β -CD due to the cationic charge.⁷⁹ This redox state dependent interaction between β -cyclodextrin (β -CD) and ferrocene offers the opportunity to prepare redox-responsive materials.

For example, a redox-responsive self-healing hydrogel material was produced by means of host guest interactions. A poly(acrylic acid) (PAA) possessing β -CD moieties was used as a host polymer, while a ferrocene containing PAA functioned as the guest polymer. Upon mixing, a transparent supramolecular hydrogel was formed. Redox stimuli induced a sol-gel transition which can control the self-healing properties of the hydrogel (Figure 2.5).⁸⁰

Figure 2.5. a) β -Cyclodextrin forms an inclusion complex with ferrocene, while upon oxidation to ferrocenium the complex is disrupted. b) Oxidized surfaces of the broken hydrogel don't heal. Upon reduction the gel regains its self-healing properties. Adapted from reference.⁸⁰

A similar type of hydrogel, containing poly(acryl amide) chains with both ferrocene and cyclodextrin moieties, was demonstrated as an actuator, displacing a small load.⁸¹ These types of β -CD/ferrocene gels were investigated by a variety of research groups,⁸²⁻⁸⁵ with the work of the Harada group having the highest impact.⁸⁶⁻⁸⁸

A dual responsive hydrogel was formed by using β -CD functionalized quantum dots and ferrocene functional p(DMA-*b*-NIPAm). While the β -CD/ferrocene interactions form a micellar type of structure with a QD core, the poly(*N*-isopropylacrylamide) (PNIPAm) will physically crosslink above its lower critical solution temperature (LCST) by interchain aggregation. Lowering the temperature, oxidizing the ferrocene or introducing competing guest molecules will disassemble the gel.⁸⁹

2.3.2 Disulfide (hydro)gels

Disulfide bonds can be used in hydrogels, making them redox responsive.⁹⁰⁻⁹⁶ These disulfide bonds can be reduced to the corresponding thiols, hence reducing the crosslink density. This is of particular interest for biological applications, since glutathione (GSH), a tripeptide enzyme in cells, is able to serve as an electron donor in these reductions.⁹⁵

Redox induced macroscopic reversible changes in the mechanical properties of a hydrogel were obtained in a disulfide containing protein-hydrogel.⁹⁷ The macroscopic properties were tuned by conformational changes at the molecular level induced by protein folding-unfolding. Upon oxidation a disulfide bond was formed, accompanying the protein folding, drastically reducing the effective chain length between the crosslinks in the hydrogel (Figure 2.6a and b). By changing the physical and mechanical properties of the hydrogel, in this way, the oxidized hydrogel swelled less and became resilient and stiffer, exhibiting up to a fivefold increase in Young's modulus. These changes were fully reversible and could be cycled using redox potential. Another redox responsive biocompatible hydrogel was prepared by a double crosslinked poly(aspartic acid). By cleavage of the cystamine crosslinks, using dithiothreitol, a significant volume increase was realized, which was proportional to the amount of disulfide linkages (Figure 2.6c).⁹⁸

Figure 2.6. a) Protein folding switches. b) Dynamic protein hydrogels with reversibly tunable mechanical properties.⁹⁷ c) Volume change upon disulfide cleavage.⁹⁸ Adapted with permission from references.⁹⁷⁻⁹⁸

2.3.3 Metallo-(hydro)gels

Transition metal ions are found useful for introducing redox responsive properties into (hydro)gels. Hydrogels including crosslinks with metal cation centers undergo conformational changes induced by electrical potential, due to local changes in crosslink density. The presence of transition metal ions, including iron,⁹⁹ copper¹⁰⁰ and ruthenium,¹⁰¹⁻¹⁰² provides a simple and efficient way of producing redox-responsive gels that can be addressed externally.

Redox driven gel hardening was shown within a permanent covalently crosslinked polymeric hydrogel network. This gel hardening was caused by reversible crosslinks within the permanent network; the reversible crosslinks were switched between the strongly binding Fe^{3+} and weak to nonbinding Fe^{2+} . The addition of graphene oxide enhanced the response of the gels, making it possible to cycle between soft (Young's modulus of ~ 0.38 MPa) and hard (~ 2.3 MPa) states within 30 min.⁹⁹

Bipyridine metallo-hydrogelators have shown to be useful in the preparation of redox responsive hydrogels.¹⁰¹ A self-assembly motif was combined with bipyridine (bipy) to afford a functional ligand. While the ligand itself was unable to form a hydrogel, the Ru(II)(bipy)_2 analogue was, yielding a hydrogel over a wide pH range at different concentrations. The hydrogel was fluorescent, when excited at 470 nm, with an emission maximum at 630 nm, and would undergo a gel-sol transition upon oxidation of the metal center. A similar type of metallo-hydrogelator was used as Cd^{2+} sensor, showing a selective increase of fluorescence intensity at 470 nm upon chelation with Cd^{2+} .¹⁰³

Another bipyridine based redox responsive gel was formed with a Cu(I) complex in which the bipyridine ligand was bearing two cholesterol groups. The sol-gel transition could be induced upon reduction of the Cu(II) complex, followed by cooling of the solution to room temperature. Upon oxidation with NOBF_4 and heating of the mixture, the deep-green gel turned into a sol with a small amount of pale-blue precipitate.¹⁰⁰

Reversible redox-responsive gel-sol/sol-gel transitions were achieved in PAA aqueous solutions containing Fe(III)-citrate complexes. Due to the strong binding of trivalent cations such as Fe(III) to carboxylate groups, these ions were able to gelate PAA solutions, whereas Fe(II) ions did not crosslink PAA chains. Reduction of the Fe(III) ions by light resulted in the rapid transition to a PAA solution. Oxidation in air slowly recovered the weak hydrogel.⁷⁸

A self-oscillating redox-active gel was obtained by inducing the Belousov-Zhabotinsky (BZ) reaction within a ruthenium-bearing PNIPAm gel.¹⁰² The self-oscillating motion was produced by dissipating chemical energy from the oscillating BZ reaction, occurring inside the PNIPAm gel. The polymer had a LCST, because of the thermo sensitive NIPAm. The Ru(II) tris(2,2'-bipyridine) catalyst, for the BZ reaction, was covalently bound to the polymer. The LCST of the polymer in the oxidized Ru(III) state became higher than in the reduced Ru(II) state because of the charge increase of the catalyst.¹⁰⁴ Therefore, at constant temperature, the redox changes induced hydrophilic changes in the polymer gel, introducing a periodical swelling-deswelling of the gel. Tuning the hydrogel by a concentration difference of catalyst throughout the hydrogel resulted in a self-walking gel (Figure 2.7).

Figure 2.7. a) A self-oscillating redox-active gel obtained by inducing the Belousov-Zhabotinsky (BZ) reaction within a ruthenium-bearing PNIPAm gel directed by surface patterning b) Schematic representation of the gel bending c) Time-lapse images showing the trajectory of the hydrogel. Adapted with permission from reference.¹⁰²

An electrochemically responsive polymer hydrogel based on ionic crosslinking was prepared by a weakly crosslinked polyphosphazene which bore both oligo(ethylene glycol) chains and acidic side groups. The alkyl ethers were crosslinked by gamma radiation, while the acid groups were converted into carboxylate units. After cation exchange, with *e.g.*, Cu or Fe ions, the hydrogels expanded and contracted during the passage of an electric current.¹⁰⁵

2.3.4 Ferrocene based (hydro)gels

As shown in the section on β -cyclodextrin-ferrocene based (hydro)gels, ferrocene can be reversibly oxidized and reduced at ambient conditions by either chemical or electrochemical means, switching between a neutral (ferrocene) and positive (ferrocenium) state.¹⁰⁶ This charge change is accompanied by a small variation in size; ferrocene measures $4.1 \times 3.3 \text{ \AA}$ while the oxidized form, the ferrocenium ion, is $4.1 \times 3.5 \text{ \AA}$.¹⁰⁷ However, it is the charge difference and hydrophobicity changed, which have a big impact on the properties of ferrocene based materials, making ferrocene derivatives interesting building blocks for redox responsive materials.¹⁰⁸⁻¹⁰⁹

Ferrocenyl phenylalanine was demonstrated to self-assemble in water to form stable multi-stimuli-responsive hydrogels.¹⁰⁸ The proposed mechanism for gel formation starts with dimer formation, based on complementary π - π and hydrogen bonding between the ferrocenyl and benzene rings of the phenylalanino moieties and between both carboxylic acid groups. Subsequently, these dimers are hydrogen bonded in a side by side fashion to form tetramers which assemble into protofibrils, twisting into a matured fibril. The matured fibrils may undergo crosslinking, resulting in the gel network (Figure 2.8). The ferrocenyl groups are critical to the formation of the gel structure, as demonstrated by the fact that oxidation of the ferrocenyl moieties is accompanied by disassembly of the network. The network can also be reversibly assembled and disassembled by pH, temperature or shear stress.

Figure 2.8. The dimerization of ferrocenoyl phenylalanine, followed by fibril and network formation, yielding a multi-responsive hydrogel. Adapted with permission from reference.¹⁰⁸

The copolymerization of hydroxybutyl methacrylate and vinylferrocene, crosslinked with ethylene glycol dimethacrylate or *N,N'*-methylenebisacrylamide (MBAm), yields a redox-responsive polymer gel in which the hydrophobicity can be tuned by the oxidation state of the ferrocene moieties. In the oxidized state, the gel is hydrophilic, however upon reduction the gel becomes hydrophobic and selectively extracts butanol from aqueous solution.¹⁰⁹ Other redox-responsive gels reported in the literature include a ferrocenyl surfactant system showing controlled fluid viscoelasticity at extremely low DC voltages.¹¹⁰ Organometallic super-gelators with multiple stimulus-responsive properties were prepared from cholesterol-appended ferrocene derivatives. The corresponding cyclohexane-gel was found to have reversible gel-sol transitions upon oxidation, heating or applying shear-stress.¹¹¹

2.3.5 Conductive polymer based (hydro)gels

Conducting polymers generally have sp^2 hybridized carbon centers as their backbones, resulting in a molecule-wide delocalized set of orbitals.¹¹²⁻¹¹³ By oxidizing or reducing these polymers, charges are introduced which can influence properties such as conductivity¹¹⁴ and hydrophobicity.¹¹⁵ The accompanied movement of ions and water can induce changes in *e.g.*, volume, polymeric

entanglement and color.¹¹⁶ Especially the electrochemically driven volume changes of conductive polymers evoked the preparation of actuators.¹¹⁷⁻¹¹⁸

A polythiophene-based gel actuator was prepared by crosslinking the polymer with 6-bis(2-thienyl)hexane. Some preliminary force and extension measurements of this polymer gel in acetonitrile with tetrabutylammonium perchlorate as the electrolyte have been performed. Test cylinders were cut from the gel and the extension along the cylindrical axis was measured under an applied square wave pulse. It was found that the axial change in dimension was approximately 2%.¹¹⁷ Another example of a conductive polymer system used for its redox response is a polyaniline-based blend gel proposed as micro actuator valves for controlled release.¹¹⁸ These blend hydrogels were deposited on electrodes by electro polymerization and can be actuated electrochemically.

2.3.6 Tetrathiafulvalene based (hydro)gels

Tetrathiafulvalene (TTF) derivatives are well-known among reversible redox systems due to their three redox states, including radical cation and dication species, which are highly stabilized by the aromatic character of the 1,3-dithiolium rings (Figure 2.9).¹¹⁹ π - π stacking and Sulfur-Sulfur interactions yield conducting molecular stacks of TTF in the form of single crystals or thin films on polymeric supports.¹²⁰⁻¹²¹ This high molecular order leads to high charge carrier mobility, which together with the redox properties has led to a broad range of applications, including responsive hydrogels.¹²²⁻¹²³

Figure 2.9. Redox responsive properties of tetrathiafulvalene (TTF). Adapted with permission from reference.¹²³

A tetrathiafulvalene (TTF) organogel was formed consisting of low molecular weight gelator, containing the redox-active TTF group and a urea group, which can form intermolecular extended H-bonding. A gel-sol transition could be induced by chemical or electrochemical oxidation within 30 min. Upon reduction, followed by heating and cooling, the gel state was restored. The gel-sol transition was thought to be the result of positively charged TTF groups, impairing the bonding between adjacent urea groups and hence affecting gel formation.¹²⁴ Next to urea, the gelating group in the low molecular weight TTF gelators can be cholesterol and the system is also expandable with azobenzene units to make the gels, next to temperature and redox responsive, also light responsive.^{63, 123}

Some interesting reviews on redox responsive gels are available for further reading.^{77, 125}

2.3.7 Poly(ferrocenylsilane) (hydro)gels

Earlier, we described redox responsive (hydro)gels containing ferrocene moieties as pedant groups on a polymer or as the functional end groups of crosslinkers. Interestingly, not many polymers with ferrocene units in the backbone are known. Poly(ferrocenylsilane)s (PFSs)¹²⁶ are a prototype for main-chain ferrocene polymers, other examples as poly(ferrocenylenes),¹²⁷ poly(ferrocenylphosphines),¹²⁸ poly(ferrocenylgermanes)¹²⁹ and direct polymerization of dilithioferrocene complexes¹³⁰ have barely been investigated. Since 1992 the ring opening polymerization of silicon-bridged ferrocenophanes has opened up many opportunities in the preparation of high molecular weight ferrocene polymers.¹²⁶ Since then many different interesting materials for various applications have been prepared using PFSs, including nanostructured magnetic materials,¹³¹⁻¹³³ etch resists,¹³⁴⁻¹³⁵ self-assembled nanostructured materials,¹³⁶⁻¹³⁷ sensors,¹³⁸⁻¹⁴⁰ surface wettability switches¹⁴¹ and redox-active gels.^{77, 142} In this paragraph, recent developments in PFS (hydro)gels will be discussed.

The PFS main chain is hydrophobic with a polymer backbone consisting of alternating ferrocene and organosilane units. The silane units provide opportunities for side-chain functionalization, while the ferrocene units give rise to the redox-responsive properties of PFS (Figure 2.10).

Figure 2.10. Typical double wave CV curve for PFS with the most used polymers for PFS hydrogels.

All of the recently developed PFS (hydro)gels were synthesized starting from poly(ferrocenyl(3-halopropyl)methylsilane).^{67, 143-146} The halopropyl side chains serve as a versatile handle on this PFS as these groups can be used to introduce cationic or anionic side groups¹⁴⁷ to render the polymer hydrophilic, and allow one to crosslink the polymer into a network. Poly(ferrocenyl(3-chloropropyl)-

methylsilane) was introduced by Vancso *et al.* as a base for the preparation of a stable polycation.¹⁴⁸

Poly(ferrocenyl(3-iodopropyl)methylsilane) was functionalized with acrylate groups to yield a photocrosslinkable PFS.⁶⁷ The crosslinking was done in the presence of NIPAm and MBAm providing homogeneous hydrogels, in which the mechanical properties are highly dependent on the included amount of PFS, which serves as a multifunctional crosslinker. The thermo-responsive properties of these gels could be altered up to 2 °C by changing the oxidation state of the PFS.

A similar acrylate functional PFS was used to prepare microgels by microfluidics.¹⁴⁴ In this case the PFS chains were crosslinked without other monomers yielding monodisperse organogel beads (Figure 2.11). Next to organogels, also hydrogel microbeads were prepared. For this, PFS was functionalized with vinylimidazolium side groups, which made the polymer cationic and water-soluble.¹⁴⁴ In similar fashion, the microgels were prepared by droplet formation in microfluidic channels and subsequent UV-crosslinking. A fluorescent dye was incorporated in the microgels as a molecular cargo and released upon oxidation of the microgels in aqueous environment.¹⁴⁴

Figure 2.11. a) PFS microgels prepared by microfluidics b) PFS hydrogel microbeads, releasing payload upon oxidation. Adapted with permission from reference.¹⁴⁴

Thin film gels of PFS were prepared by LbL assembly¹⁴⁵ and by spin-coating¹⁴⁶ on amino functionalized ITO electrodes. The LbL gels were prepared by sequential dip-coating of the substrate in solutions of poly(ferrocenyl(3-bromopropyl)-methylsilane) and PEI. The layers are crosslinked using an amine alkylation reaction between the bromopropyl side groups of the PFS and the amine groups of PEI. The thin PFS/PEI gels were effective for the electrochemical sensing of ascorbic acid and hydrogen peroxide (Figure 2.12).¹⁴⁵

Figure 2.12. a) Schematic representation of a LbL PFS-PEI film on an ITO electrode, used as sensor for H₂O₂, and b) the amperometric response of the sensor. Reprinted with permission from reference.¹⁴⁵

PFS hydrogels can also be prepared from cationic or anionic functionalized PFS rather than rendering the gel hydrophilic by the crosslinking groups or by using hydrophilic polymers as crosslinkers.¹⁴⁹ A recent example is the preparation of a PFS polyanionic hydrogel, formed by introducing a controlled amount of anionic sulfonate groups and crosslinkable azide groups onto a PFS chain.¹⁴³ A 4-arm PEG functionalized with the strained alkyne bicyclononyne was used to crosslink the polyanion by a strain promoted azide-alkyne cycloaddition. The hydrogel showed a significant volume change upon oxidation and reduction.

2.4 *Redox formed metal nanoparticles*

Compared to bulk catalysts, metal nanoparticles (NPs) attract much interest as catalyst materials, due to the high surface-to-volume ratio and their extreme surface activity.¹⁵⁰ It was calculated that the forward reaction rate constant and activity of metallic NPs changes exponentially as function of size.¹⁵¹ Therefore much research has been done on the use of noble metal NPs for many types of organic and inorganic reactions.¹⁵⁰ Traditionally, these nanocatalysts are used in colloidal solutions,¹⁵²⁻¹⁵³ adsorbed onto bulk supports,¹⁵⁴⁻¹⁵⁷ and as lithographically fabricated arrays of nanocatalysts.¹⁵⁸

Next to catalysts, noble metal NPs attract attention due to their promising applications in optical, electronic, sensing, biomedical and energy devices.¹⁵⁹ The properties of these NPs strongly depend on their size, morphology, composition, crystallinity, and surface structures.¹⁶⁰⁻¹⁶¹ Therefore many efforts have been made to optimize noble metal NP formation. Here, we report on the most recent research on redox-formed metal NPs; a straightforward way of preparing those metal nanocatalysts by the reduction of the corresponding metal salts.¹⁶²

The redox formation of metal NPs is based on electron transfer from a reductant to the metal cations. The oxidation potential (E_0) of the reductant should be lower than that of the metal cation to be able to reduce the metal cation to metal(0) (Figure 2.13).

Figure 2.13. *Reduction of silver ions to metallic silver by ferrocene.*

The Fe(II) of the ferrocene units in PFS was shown to reduce silver ions into AgNPs. In this way, tubular micelles composed of polymethylvinylsiloxane and PFS were used to synthesize one-dimensional arrays of AgNPs (Figure 2.14).¹⁶³

Figure 2.14. a) Tubular micelles composed of polymethylvinylsiloxane and PFS, used for AgNP synthesis b) TEM image of the AgNP containing micelles. Reprinted with permission from reference.¹⁶³

Another polymeric reducing agent, which has been studied widely in the last years, is polyaniline. Polyaniline is a conducting polymer with an oxidation potential of 0.7-0.75 V,¹⁶² making it possible to reduce metal ions such as Ag⁺,¹⁶⁴⁻¹⁶⁶ Au³⁺,¹⁶⁷⁻¹⁶⁹ Pt²⁺¹⁷⁰ and Pd²⁺¹⁷¹ or alloys thereof.¹⁷² Polyaniline gold and silver nanocomposite materials are often prepared as Surface-Enhanced Raman Spectroscopy (SERS) active substrates.^{166, 173} Other examples of applications are silver nanowires,¹⁶⁴ gold,¹⁷⁴ platinum¹⁷⁰ and palladium¹⁷¹ catalysts and bistable memory devices.¹⁷⁵ Han et al. prepared magnetic Fe₃O₄/PANI core-shell particles for the *in situ* preparation of PdNP catalysts. The PANI shell reduces an aqueous solution of PdCl₂, resulting in a composite PANI/Pd shell with PdNPs of about 3 nm (Figure 2.15). The magnetic retrievable catalysts were successfully employed in the catalytic reduction of nitro aromatic compounds in the presence of NaBH₄ and in Suzuki cross-coupling reactions.¹⁷⁶

Figure 2.15. a) Schematic representation for the formation of Fe₃O₄/PANI/PdNPs core/shell hybrids and b) a high resolution TEM image of the PANI/PdNP shell. Reprinted with permission from reference.¹⁷⁶

Next to polyaniline, other conductive polymer systems were applied for the in-situ formation of particles. PEDOT:PSS was successfully used for the preparation of AuNPs,¹⁷⁷ poly(phenylene vinylene) yielded Core/shell Ag/polymer nanostructures,¹⁷⁷ conglomerates of rice-grain AuNPs were formed by Au³⁺ reduction with polypyrroles and poly(2-aminothiophenol) was shown to yield AuNPs as small as 2 nm.¹⁶⁹

Interesting for the use in diagnostic and therapeutic applications are the PEG-coated metal NPs prepared through reduction of metal cations with 3,4-dihydroxyphenylalanine-containing PEG polymers. Simultaneous to the reduction of the metal salts, a PEG-tethered crosslinked shell was formed on their surfaces. These PEG-functionalized particles were stable in physiological ionic strengths.¹⁷⁸

Protic ionic liquids, octylammonium formate and bis(2-ethyl-hexyl)ammonium formate, were shown to produce metal NPs from metal trichlorides in DMF or water. The ionic liquids and solvent combinations were shown to strongly affect the formation, growth, shape and size of metal NPs.¹⁷⁹

Silver citrate was shown to produce AgNPs when confined in nanodomains of charged and neutral matrices. Citrate is often used in the synthesis of metal NPs, for its role as reductant, complexant and stabilizer.¹⁸⁰⁻¹⁸² When using a high citrate concentration $[\text{citrate}]/[\text{Ag}^+] \gg 1$, silver citrate is stable in bulk solution. While reduction to metallic silver is absent under these bulk conditions, introduction of confined nanodomains led to the decomposition of the silver citrate complexes and formation of AgNPs.¹⁸³

Redox-active solid biosubstrates made of squid suckerin proteins enable the synthesis of spherical and plate-like AuNPs. The high tyrosine content of suckerins provides a reducing environment which is suitable for NP growth both in solution as well as in the form of solid films or more complex micro and nanostructures. By a straightforward dip coating method using solid supports, application, could be extended to morphologies suitable for solid state biosensors.¹⁸⁴

The proteins ferredoxin-NADP⁺ reductase (FNR) and ferredoxin (FD), extracted from spinach leaves, were used in sunlight-mediated synthesis of AgNPs. To prepare AgNPs, an aqueous solution of silver nitrate (AgNO₃) was mixed with FNR/FD and exposed to sunlight, turning the solution yellowish brown. Similar procedure in the dark yielded no color change or AgNPs, suggesting that the FNR/FD can only undergo electron transfer in the presence of light. The protein-stabilized AgNPs were demonstrated to be catalytically active towards the degradation of hazardous organic dyes, exhibited antimicrobial activity and were useful in the detection of mercury ions, resulting in discoloration of the yellow AgNP solution upon exposure to Hg²⁺ (Figure 2.16).¹⁸⁵

Figure 2.16. AgNP solutions, used in the colorimetric detection of mercury ions. Reprinted with permission from reference.¹⁸⁵

Protein mediated synthesis of AuNPs was achieved by using alcohol oxidase (AOx) under alkaline conditions. The AOx protein surface was exploited for its spontaneous native reaction, driven by the enzyme, resulting in AOx stabilized AuNPs. The capping AOx molecules retained their native structure and ability to generate H₂O₂ from alcohols. The *in situ* generated H₂O₂ was used for the oxidative polymerization of a polyaniline shell around the particles. Subsequently these particles were immobilized on a glassy carbon electrode using chitosan and Nafion polymers. These functionalized electrodes displayed a linear current response against ethanol with a low detection limit.¹⁸⁶

2.4.1 Gel stabilized metal nanoparticle formation

The production of metal NPs often requires the use of organic ligands, salts, surfactants or other capping agents,¹⁸⁷⁻¹⁸⁸ which may significantly reduce their

(catalytic) activity.¹⁸⁸ NP fabrication inside a polymer network circumvents these issues and suppresses excessive growth of the particles.¹⁸⁹

Although polymer networks have already been used for about 20 years in the synthesis of noble metal NPs,¹⁹⁰ this method is still of recent interest due to the wide variety of applications for the resulting particles and particle-polymer composites.

For example, tyrosine containing oligopeptide based organogelators were used for the *in situ* preparation and stabilization of Ag and AuNPs. The redox active tyrosine residues were utilized to reduce the metal ions to their corresponding metals, while the gelator peptides retained their gelation properties. Fibers prepared from these gelators were shown to produce aligned AuNPs along the fibers, which may open up applications for supramolecular devices.¹⁹¹

Core-shell-type PS-PNIPAm particles, synthesized by conventional emulsion polymerization of PS and NIPAm, followed by seeded emulsion polymerization of NIPAm and MBAm, were used to form AgNPs inside the thermosensitive shell.¹⁹² The NPs were formed by the reduction of silver ions (AgNO_3), soaked to the PNIPAm shell, with NaBH_4 (Figure 2.17).¹⁹³ The catalytic activity of these PS-PNIPAm-Ag composites was assessed by photometric monitoring of the reduction of 4-nitrophenol with an excess of NaBH_4 . It was demonstrated that the catalytic activity can be modulated by temperature over one order of magnitude.¹⁹⁴

Figure 2.17. a) Schematic representation of the thermal response of the PNIPAm shell in which metallic NPs are embedded. b) Cryo-TEM image of the PS-PNIPAm core shell particles with PdNPs embedded in the PNIPAm shell. Reprinted with permission from reference.¹⁹⁴

Next to catalysis, gel supported NPs were also shown to be suitable as SERS substrates.¹⁹⁵ Polysaccharide alginate gel beads were used as photochemically active substrates for the formation of gold, silver and bimetal nanoclusters. The gel served as reductant under photoirradiation and as stabilizer for the formed metal NPs (Figure 2.18). Among the prepared substrates, alginate-stabilized Au gave the best results for SERS detection with an enhancement factor in the range of 10^4 and detection limits in the sub-picogram level (tested with 2-aminothiophenol and 1,10-phenanthroline).

Figure 2.18. Various polysaccharide alginate gels stabilized Ag, Au and Ag/AuNPs. Reprinted with permission from reference.¹⁹⁵

Surface initiated atom-transfer radical polymerization (SI-ATRP) allows one to grow polymer brushes of a desired length from a surface. These brushes can be directly grown inside microchannels and by adding a low amount of bifunctional monomer, a surface immobilized polymer gel film on the channel walls can be obtained. These gel films were loaded with Ag and PdNPs by the *in situ* reduction of AgNO_3 and $\text{Pd}(\text{NO}_3)_2$ with NaBH_4 . The heterogeneous catalyzed reduction of 4-nitrophenol and the Heck reaction demonstrated the wide applicability of these catalytic devices.¹⁹⁶

Wound-dressing alginate hydrogel fibers were produced by wet-spinning into a CaCl_2 precipitation bath followed by chemical crosslinking of the alginate hydroxyl groups with glutaraldehyde to ensure stability. The hydrogel fibers were loaded with silver ions by ion exchange from a AgNO_3 solution, after which excess

AgNO_3 was removed and AgNPs were formed inside the fibers by reduction with NaBH_4 . The alginate network could be enzymatically degraded with alginate lyase, yielding AgNPs with a size of 11.5 ± 5.9 nm. As expected, the AgNP loaded fibers enhanced the wound healing; however the bare AgNPs, obtained after network degradation, performed superior.¹⁹⁷

Another gel for wound dressing was prepared by gamma irradiation. A mixture of polyvinyl alcohol, cellulose acetate and gelatin was dissolved in water, made oxygen free and exposed to gamma rays. The resulting hydrogel was swollen with an aqueous AgNO_3 solution and again made oxygen free and exposed to gamma rays. The obtained AgNPs had a mean diameter ranging from 38.6 to 60.1 nm depending on the concentration of the AgNO_3 solution used to swell the hydrogels. The antibacterial ability of the gels was enhanced by increasing the AgNO_3 content.¹⁹⁸

An amphiphilic bis-imidazolium gelator was used for the stabilization and preparation of AuNPs. The hydrogels were prepared in an ethanol-water mixture of the gelator and HAuCl_4 and aged overnight. To prepare the NPs, 12 equivalents (with respect to Au^{3+}) of an aqueous solution of NaBH_4 were added. Obtained NPs were of homogenous size and geometry with sizes of ca. 5 nm and a well-defined icosahedral geometry. Furthermore, the gelator also acted as the stabilizing ligand of the NPs, allowing the recovery of the NPs by disassembling the gel without aggregation of the inorganic colloids.¹⁹⁹

Figure 2.19. a) Structure of the amphiphilic bis-imidazolium gelator b) HRTEM image of formed AuNP c) The corresponding power spectrum (FFT) d) And the structural 3D atomic model of the icosahedral morphology. Reprinted with permission from reference.¹⁹⁹

2.4.2 Metal nanoparticles formed in PFS (hydro)gels

This thesis will mainly be focused on the use of the redox responsive PFS, in particular in the form of hydrogels, for the preparation of metal NPs.

Owing to the redox responsive properties of ferrocene, with an oxidation potential around 0.4 V (vs. SHE), PFSs can reduce metal salts with higher oxidation potentials to their metallic state yielding the corresponding metal NPs. Table 2.1 lists metals that were successfully reduced by PFS hydrogels with their corresponding oxidation potential (vs. SHE).²⁰⁰

Table 2.1. Oxidation potentials of common half-reactions in aqueous solution.

Half- reaction		E ₀ vs SHE (V)	
Ag ⁺	+ e ⁻	Ag	+ 0.80
AuCl ₄ ⁻	+ 3e ⁻	Au	+ 4 Cl ⁻ + 1.00
PdCl ₄ ²⁻	+ 2e ⁻	Pd	+ 4 Cl ⁻ + 0.64
PtCl ₄ ²⁻	+ 2e ⁻	Pt	+ 4 Cl ⁻ + 0.76
Ir ³⁺	+ 3e ⁻	Ir	+ 1.16
Rh ³⁺	+ 3e ⁻	Rh	+ 0.76
[Ferrocenium] ⁺	+ e ⁻	Ferrocene	+ 0.40

A dual-responsive hydrogel system was prepared by UV-copolymerization of a mixture of PFS chains bearing acrylate side groups, NIPAm and MBAm in THF.

Figure 2.20. a) TEM image of AgNPs inside the hydrogel and antibacterial test on the b) PNIPAm hydrogel and c) hydrogel AgNP composite after incubation for 24 h at 37 °C. Reprinted with permission from reference.⁶⁷

The redox activity of the PFS chains in the hybrid hydrogels were used for the facile preparation of AgNPs inside the PFS-PNIPAm network. These composites showed a strong antimicrobial activity towards *Escherichia coli* while maintaining a high biocompatibility with cells (Figure 2.20).⁶⁷

Thin film PFS hydrogels were formed by the crosslinking of poly(ferrocenyl(3-bromopropyl)methylsilane) with *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA). The ferrocene containing redox-active PFS chains of the thin hydrogel films could be used as a reducing environment for the in-situ formation of PdNPs (Figure 2.21). These PFS hydrogel-nanoparticle composites were employed directly in the electrocatalytic oxidation of ethanol showing a pronounced catalytic activity.¹⁴⁶

Figure 2.21. *AFM measurements on a) PFS-Br/PMDETA hydrogel thin film on ITO, b) Pd-loaded hydrogel thin film before catalytic experiments and c) Pd hydrogel thin film after catalytic experiments. Scan size: 500 nm × 500 nm. Reprinted with permission from reference.¹⁴⁶*

2.5 References

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Chapter 3

Redox-responsive organometallic hydrogels for in-situ metal nanoparticle synthesis

A new class of redox active hydrogels composed of poly(ferrocenylsilane) polyanions or polycations and poly(ethylene glycol) chains were assembled, using a copper-free azide-alkyne Huisgen cycloaddition reaction. The organometallic anionic hydrogels displayed reversible collapse and reswelling upon chemical oxidation and reduction, respectively. Both cationic and anionic hydrogels formed relatively well-defined, unaggregated nanoparticles (NPs), yielding a diameter of 8.2 ± 2.2 nm (PdNPs) and 1.9 ± 0.3 nm (PtNPs) from K_2PdCl_4 and K_2PtCl_4 salts.

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3.1 Introduction

Stimulus-responsive gels are attracting much attention due to their interesting behavior as well as to many potential applications.¹⁻⁸ Such gels can *e.g.*, be used for controlled release of drugs or cosmetics, upon employing a specific stimulus.⁹⁻¹⁰ They can also be useful as actuators, artificial muscles or microfluidic valves.¹¹⁻¹² Typical stimuli used to date include changes in temperature,¹³ pH,¹⁴⁻¹⁵ ionic strength,¹⁶ electric field strength,¹⁷ light intensity,⁷ and variations in magnetic field strength.¹⁸⁻²⁰ Gels responsive to redox-stimuli usually incorporate transition metals into network-forming polymer chains, either as main chain constituents or included in side groups, or are composed of (semi)conducting polymers.²¹⁻²² Their addressability by redox stimuli allows one to alter properties such as polarity, which generally has a large influence on polymer properties such as chain stiffness and extension, and on interactions with solvent. Redox responsiveness therefore is of interest for actuator applications. Until now, relatively few examples of transition-metal-based redox-active gels and hydrogels have appeared in the literature.²² For example, copolymerization of vinylferrocene with acrylamide and *N,N'*-methylenebis(acrylamide) led to a random copolymer gel with potential use as a glucose biosensor.²³⁻²⁴ A poly[(*N*-isopropylacrylamide)-*co*-vinylferrocene] gel was produced which displayed electrochemically and thermally controllable phase transitions.²⁵ A self-oscillating redox-active gel was obtained by inducing the Belousov-Zhabotinsky (BZ) reaction within a ruthenium-bearing *N*-isopropylacrylamide gel.²⁶⁻²⁷ Other redox-responsive gels reported in the literature include a ferrocenyl surfactant system showing controlled fluid viscoelasticity,²⁸ and polyaniline-based gels as *e.g.*, actuators for controlled release²⁹ or catalysis.³⁰ Self-healing, supramolecular materials using PAA modified with β -cyclodextrin as a host polymer and PAA with ferrocene pendant groups as a guest polymer were also reported. By using chemical oxidation and reduction, a reversible sol–gel phase transition could be induced in this system.³¹

Organometallic polymers possessing skeletal transition metals show great promise as constituents of redox-responsive polymer gels.^{22, 32-35} Among this class of organometallic polymers, poly(ferrocenylsilanes), PFS, are raising much interest due to the useful chemical, redox, optical, thermal, and magnetic properties of these materials.³⁶⁻⁴⁰ A variety of polymerization methods have been developed, including living anionic ring-opening polymerization yielding homopolymers and block copolymers, transition metal-catalyzed ring-opening polymerization and photocontrolled living polymerization, broadening the range of accessible PFSs.³⁶⁻³⁸

While the crosslinking chemistries of poly(ferrocenylsilane) networks based on PFS chains soluble in regular organic solvents have been reported,^{32-35, 41-42} few accounts have appeared on crosslinking approaches for water-soluble PFSs.⁴³⁻⁴⁴ We reported the first examples of metal nanoparticle (NP) fabrication mediated by main-chain redox-active polymer hydrogels.³³⁻³⁴ PFS-based hydrogels were shown to provide a confined, reducing environment, allowing one to convert silver salts into defined, unaggregated metal NPs without employing external reducing agents.^{33-34, 45} The production of metal NPs often requires the use of organic ligands, salts, surfactants or other capping agents,⁴⁶⁻⁴⁷ which may significantly reduce their (catalytic) activity.⁴⁷ NP fabrication inside a polymer network circumvents these issues and suppresses excessive growth of the particles.⁴⁸ Here we describe the synthesis of a PFS polyanion hydrogel, where crosslinks were formed between strained alkynes and azide groups in a copper-free Huisgen cycloaddition reaction,⁴⁹⁻⁵⁰ and its use in the in-situ formation of palladium and platinum NPs. Palladium and platinum NPs are highly important catalytic materials and continue to attract growing interest due to their catalytic properties combined with a high surface-area to volume ratio.^{46, 51} Both metals are used extensively in hydrogenations,⁵²⁻⁵⁴ oxidations,⁵⁵⁻⁵⁶⁻⁵⁷ carbon-carbon bond formation,⁵⁸⁻⁵⁹ electrochemical reactions in fuel cells,⁶⁰ hydrogen storage,⁶¹⁻⁶³ and sensing applications.⁶⁴⁻⁶⁶

3.2 Results and discussion

In order to form a polyanionic poly(ferrocenylsilane) hydrogel with controlled degrees of crosslinking, a PFS polyanion with tunable amounts of crosslinkable azide groups was synthesized by side group modification of PFS **1** (Scheme 3.1). Negatively charged side groups were introduced using the carbon nucleophile α -lithioisobutylethanesulfonate.⁶⁷ Sulfonate ester carbanions enable one to attach alkanesulfonate ester moieties *e.g.*, to polymer backbones which, after deprotection, are turned into alkanesulfonate functionalities. Sulfonate ester carbanions have been shown to react for instance with carbonyl groups or with alkyl halides. Alkyl iodides react quickly with these carbanions, corresponding chlorides however are much less reactive.⁶⁸ The large difference in reactivity was exploited by forming PFS **1**, which contains both chloropropyl and iodopropyl moieties, in a halogen exchange reaction starting from poly(ferrocenyl(3-chloropropyl)methylsilane).⁶⁷ Treatment of PFS **1** with α -lithioisobutylethanesulfonate selectively displaced the iodo groups, giving PFS **2**. Sulfonate ester deprotection and the introduction of azide groups by displacement of the unreacted chloro groups was conducted in a single step, yielding the targeted PFS **3**.

Scheme 3.1. Synthesis of a crosslinkable poly(ferrocenylsilane) polyanion. PFS **1** was converted into a PFS featuring isobutylsulfonate side groups (**2**) using α -lithioisobutyl-ethanesulfonate. Treatment of PFS **2** with NaN_3 gave the water soluble PFS **3**.

For the formation of a polycationic poly(ferrocenylsilane) hydrogel with controlled degrees of crosslinking, a PFS polycation with tunable amounts of crosslinkable azide groups was synthesized by side group modification of poly(ferrocenyl(3-chloropropyl)methylsilane) (Scheme 3.2). In similar fashion as for the anionic polymer, the introduction of azide groups was done by displacement of the chloro groups on the chloropropyl side chains (PFS **6**) using NaN_3 . Polycationic PFS **7** was obtained by amination of the remaining chloro groups of PFS **6** with trimethylamine.

Scheme 3.2. Synthesis of a crosslinkable poly(ferrocenylsilane) polycation. Poly(ferrocenyl(3-chloropropyl)methylsilane) was converted into a PFS featuring azide side groups (**6**) using NaN_3 . Treatment of PFS **6** with trimethylamine gave the water soluble PFS **7**.

Polyanion **3** (or polycation **7**) and bicyclononyne (BCN) derivatized tetra-arm PEG solutions in MeOH were mixed, employing equimolar amounts of BCN and azide moieties in the gel-forming mixture (Scheme 3.3). The viscosity of the solution increased rapidly and gel formation was confirmed by the vial tilting method already within 2 minutes after mixing **3** and **4**. When water was used as a medium for crosslinking, gelation occurred within 30 seconds, thus providing less time for mixing. Gelation was allowed to proceed overnight. In order to completely remove MeOH, the gel was placed in Milli-Q water, which was replaced several times. The hydrogels were subsequently freeze-dried for FTIR analysis.

Scheme 3.3. Formation of a PFS polyanion hydrogel **5** by a copper-free azide-alkyne Huisgen cycloaddition reaction between PFS **3** and BCN-terminated four-arm star PEG **4** (left). Similar crosslinking reaction between PFS **7** and PEG **4** yields PFS polycation hydrogel **8**.

Figure 3.1 displays the FTIR spectra for PFS **3** and **7** and networks **5** and **8**. The absence of an azide stretching vibration absorption at 2094 cm^{-1} in the spectra of the hydrogels provides evidence for completion of the click reaction. Furthermore, the spectra display characteristic peaks of both PFS (774 , 1035 cm^{-1}), PEG (1098 cm^{-1}) and a carbonyl stretch absorption of the tetra-arm PEG at 1710 cm^{-1} .

Figure 3.1. FTIR spectra of PFSs **3** and **7** and networks **5** and **8**, showing the disappearance of the azide stretching vibration at 2094 cm^{-1} as the network is formed. a) Shows polyanionic PFS **3** and network **5**, b) shows polycationic PFS **7** and network **8**.

Upon swelling in deionized water, the PFS networks became amber transparent elastic hydrogels. Water-uptake and rheological measurements were performed from which the effective crosslink density could be calculated (Table 3.1), using polymer rubber theory⁶⁹:

$$G' = v_e RT \vartheta^{1/3}$$

With the effective crosslink density, v_e , the shear storage modulus, G' , and the polymer volume fraction.

Table 3.1. *Characteristics of hydrogels 5 and 8.*

	Storage modulus (G' , Pa)	Loss modulus (G'' , Pa)	Swelling ratio (by weight)	Effective crosslink density (v_e , mM)
Hydrogel 5	370 ± 5	65 ± 5	49.0	0.6
Hydrogel 8	$1.05 \cdot 10^4 \pm 90$	15 ± 2	18.5	11.2

The hydrogels could be reversibly oxidized and reduced electrochemically. For cyclic voltammetry, gels were built up layer-by-layer from PFS **3** and PEG **4** on a gold substrate, which served as working electrode, using an azidobutyl thioacetate self-assembled monolayer⁷⁰ for surface anchoring.

Cyclic voltammograms obtained after swelling of network **5** in aqueous NaClO_4 showed the two oxidation and reduction waves typical of poly(ferrocenylsilanes) at $E_{\text{ox1}} = 324$ mV and $E_{\text{ox2}} = 464$ mV, $E_{\text{red1}} = 397$ mV and $E_{\text{red2}} = 208$ mV, respectively (Figure 3.2a). Ferrocene units at alternating positions are oxidized first, followed by the oxidation of the ferrocene units located between ferrocenium sites at a higher potential.³⁹⁻⁴⁰ Peak currents showed a square root dependence on scan rate, indicating that the electrochemical processes are diffusion controlled (Figure 3.2b). Upon chemical oxidation, the hydrogel changed color from amber to green and turned back to amber upon reduction (Figure 3.3).

Figure 3.2. a) Cyclic voltammetry curve of hydrogel **5** measured in 0.1 M NaClO_4 with a Pt counter electrode and Ag/AgCl reference electrode. The CV curve was measured at 5 mV/s. b) Peak currents display a square root dependence on scan rate, indicating that the electrochemical processes are diffusion controlled.

Oxidation of the anionic hydrogel was accompanied by a clear change in mechanical behavior: the gel collapsed and lost its elastic nature (Figure 3.4). Upon reduction the network reswelled and regained its elasticity. The observed collapse, shown in Figure 3.3, can be ascribed to electrostatic attraction between the positively charged ferrocenium units in the PFS main chain and the negatively charged sulfonate side groups of the polymer. Oxidation of the cationic hydrogel showed the opposite effect; the gel got swollen and retained its elastic nature (Figure 3.4). The observed swelling, shown in Figure 3.3, can be similarly ascribed to electrostatic repulsion between the positively charged ferrocenium units and the positively charged ammonium side groups of the polymer.

Figure 3.3. Response of the a) anionic (**5**) and b) cationic (**8**) hydrogels to chemical oxidation (50 mM $\text{Fe}(\text{ClO}_4)_3$) and reduction (50 mM sodium ascorbate).

Figure 3.4 shows the mechanical response of the anionic hydrogels to oxidation and reduction. The gels were equilibrated in Milli-Q water before the measurements.

Figure 3.4. Storage moduli (closed symbols) and loss moduli (open symbols) of a) hydrogel **5** and b) hydrogel **8** in pristine (■), oxidized (●) and reduced state (▼).

The redox activity of the hydrogels was employed for the in-situ formation of palladium and platinum NPs. Standard potentials for the reduction of noble metal salts such as H_2AuCl_4 (1.002 V), K_2PdCl_4 (0.915 V) and K_2PtCl_4 (1.188 V) to the corresponding metals indicate that PFSs may be used as reducing agents (see table 2.1). When hydrogel **5** was immersed in a solution of potassium tetrachloropalladate or potassium tetrachloroplatinate (5.0 mM, 1 oxidative equivalent with respect to the PFS ferrocene units). The hydrogel turned from orange to black within minutes in the case of palladium, for platinum this was within hours, after which the reaction was left overnight in the dark. In contrast, the cationic hydrogels turned slowly from orange to black, showing a gradual NP formation over time, after which the reaction was left overnight in the dark. The hydrogels showed a top surface covered with NPs, with a gradual transition towards pristine (not oxidized) cationic hydrogel at the bottom of the vials. The hydrogels were washed with Milli-Q water to remove unreacted salts and were freeze-dried for analysis.

Figure 3.5. TEM images of a/b) Pd and c) PtNPs formed inside hydrogel **5** at various magnifications.

TEM measurements show well-dispersed palladium and platinum NPs inside the gels, with a narrow size distribution (Figure 3.5). Images captured over larger areas demonstrate the uniformity and lack of aggregation of the formed NPs. The

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dimensions and size distribution of the Pd and PtNPs (Figure 3.6) was evaluated by measuring the diameter of at least 100 particles by TEM, yielding a diameter of 8.2 ± 2.2 nm (PdNPs) and 1.9 ± 0.3 nm (PtNPs).

Figure 3.6. a) Pd and b) PtNP size distribution histogram. Particle size distribution was obtained by measuring the diameter of at least 100 particles by TEM.

EDX was used to confirm the chemical nature of the particles and the hydrogel (Figure 3.7). Diffraction patterns obtained from the particles proved that Pd(0) and Pt(0)NPs were produced. Au and Ag metal NPs could also be produced from the mentioned salts using hydrogel **5**. The hydrogel supported NPs could be generated in microfluidics to yield catalytic devices, similar to previous research.⁷¹

Figure 3.7. *EDX spectra of the formed NPs inside the anionic hydrogel matrix a) PdNPs b) PtNPs. The Cu signals in the spectrum originate from the TEM grid.*

3.3 Conclusions

In summary, hydrogels of anionic poly(ferrocenylsilane) strong polyelectrolytes, with controlled degrees of crosslinking, were obtained by "Click" chemistry. The formed networks showed a strong swelling in water and could be reversibly oxidized and reduced chemically and electrochemically. Chemical oxidation and reduction led to a reversible collapse and reswelling of the network. The redox activity of both hydrogels was exploited successfully for the in-situ formation of rather well-defined palladium and platinum NPs.

3.4 *Experimental section*

Materials. (1*R*,8*S*,9*S*)-Bicyclo[6.1.0]non-4-yn-9-ylmethyl succinimidyl carbonate (>95%), *n*-butyllithium (1.6 M in hexanes), dimethyl sulfoxide (anhydrous), THF (anhydrous, inhibitor-free), phenol ($\geq 99.5\%$), trimethylamine solution (31-35 wt%, 4.2 M in ethanol), triethylamine (>99.5%), KI (>99%), NaN₃ (>99.5%), 15-crown-5 (98%), DMSO-*d*₆ (99.9 atom% D), and toluene-*d*₈ (≥ 99.6 atom% D) were obtained from Aldrich and used as received. THF-*d*₈ (99.5 atom% D) and CDCl₃ (99.8 atom% D) were purchased from Cambridge Isotope Laboratories. 4-Arm PEG amine (pentaerythritol) HCl salt ($M_n = 5000$ g/mol) was purchased from JenKem Technology USA. Potassium tetrachloropalladate and potassium tetrachloroplatinate was purchased from Strem Chemicals, Inc. (Newburyport, MA, USA). Methanol, DMSO, THF and diethyl ether were obtained from Biosolve, The Netherlands. Milli-Q water (Millipore) was used in all experiments. Acetone and DMF (extra dry, 99.8%) were purchased from Acros Organics. Isobutyl ethanesulfonate was prepared according to a literature procedure.⁶⁸

Techniques. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 MHz instrument at 400.1 and 100.6 MHz, respectively, in CDCl₃, DMSO-*d*₆, THF-*d*₈ or toluene-*d*₈. ¹H and ¹³C chemical shifts were based on the solvent residual signals. GPC measurements were carried out in THF (flow rate 2.0 mL/min) at 25 °C, using microstyragel columns (bead size 10 μm) with pore sizes of 10⁶, 10⁵, 10⁴ and 10³ Å (Waters) and a dual detection system consisting of a differential refractometer (Waters model 410) and a differential viscometer (Viscotek model H502). Molar masses were determined relative to narrow polystyrene standards. Rheological experiments were carried out with an UDS 200 rheometer (Anton Paar) using parallel plates (25 mm diameter) at 25 °C in the oscillatory mode with 0.1% strain and 1 Hz. Electrochemical measurements were carried out on hydrogels swollen in 0.1 M aqueous NaClO₄ using an Autolab, PGSTAT 10 electrochemical workstation. Cyclic voltammograms were recorded

between -0.1 and $+0.7$ V at scan rates between 5 and $100 \text{ mV} \cdot \text{s}^{-1}$, using a Ag/AgCl reference electrode, a Pt counter electrode, and a Pt working electrode. FTIR spectra were measured with a Bruker ALPHA on freeze-dried samples. TEM and EDX analyses were performed with a FEI (Philips) CM300ST equipped with a GATAN Tridiem energy filter ($2\text{k} \times 2\text{k}$ CCD camera), extra GATAN Ultrascan 1000 CCD camera ($2\text{k} \times 2\text{k}$), and a Noran System Six EDX analyzer with a Nanotrace EDX detector. The samples were prepared by sonication of small gel fragments in ethanol and depositing $7.5 \text{ }\mu\text{L}$ of the obtained dispersion on a Lacey carbon/Copper grid.

Poly(ferrocenylsilane) 1. PFS **1** was synthesized by Pt-catalyzed ring-opening polymerization of [1](3-chloropropyl)methylsilaferrocenophane (3.05 g , 10.0 mmol), followed by halogen exchange using KI.^{28f} At 90% conversion of Cl into I, **1** was isolated by precipitation in MeOH and dried under vacuum. Yield: 3.2 g (81%) of amber product. ^1H NMR (toluene- d_8 , δ , ppm): 0.52 (SiCH_3 , s, 3H); 1.00 (1-CH_2 , m, 2H); 1.82 (2-CH_2 , m, 2H); 2.95 ($3\text{-CH}_2\text{I}$, m, 2H); 3.30 ($3\text{-CH}_2\text{Cl}$, m, 2H); $4.05 + 4.10 + 4.27 + 4.29$ (Cp, m, 8H). ^{13}C NMR (toluene- d_8 , δ , ppm): -2.83 (SiCH_3); 12.02 (1-C); 18.52 (2-C); 29.32 ($3\text{-CH}_2\text{I}$); 48.23 ($3\text{-CH}_2\text{Cl}$); 70.50 (Cp-Si); $71.96 + 73.95$ (Cp). GPC (THF): $M_n = 2.72 \cdot 10^4 \text{ g/mol}$, $M_w = 4.98 \cdot 10^4 \text{ g/mol}$, $M_w/M_n = 1.83$.

Poly(ferrocenylsilane) 2. Isobutylsulfonate side groups were attached to **1** (1.50 g , $3.5 \text{ mmol CH}_2\text{-I}$ units) by alkylation with α -lithioisobutylethanesulfonate at $-55 \text{ }^\circ\text{C}$, using reaction conditions adapted from earlier work.²¹ A solution of isobutylethanesulfonate (2.49 g , 15.0 mmol) in dry THF (20 mL) was cooled under argon to $-80 \text{ }^\circ\text{C}$, and $n\text{-BuLi}$ (7.5 mL , 12 mmol) was added dropwise. After stirring for 60 min , DMSO (7.5 mL) and a solution of **1** (1.50 g , $3.5 \text{ mmol CH}_2\text{-I}$ units) in THF (40 mL) was added dropwise. Stirring was continued at $-55 \text{ }^\circ\text{C}$ for 13 h . The reaction was terminated at $-55 \text{ }^\circ\text{C}$ by adding phenol (0.85 g , 9.0 mmol) in THF (5 mL). Polymer **2** was isolated by repeated precipitation in MeOH and dried under vacuum. Yield: 1.4 g (86%) of an amber solid. ^1H NMR (THF- d_8 , δ ,

ppm): 0.51 (SiCH₃, s, 3H); 0.96 (1-CH₂, m, 2H); 0.96 (CH₃, d, $J = 6.7$ Hz, 6H); 1.31 (ethane CH₃, d, $J = 6.7$ Hz, 3H); 1.49 + 1.60 (2-CH₂, m, 2H); 1.60 + 2.02 (3-CH₂, m, 2H); 1.97 (CH, m, 1H); 3.18 (4-CH₂, m, 1H); 3.54 (3-CH₂Cl, m, 2H); 3.93 (SO₃CH₂, d, $J = 6.5$ Hz, 2H); 4.01 + 4.04 + 4.08 + 4.23 (Cp, m, 8H). ¹³C NMR (THF-d₈, δ , ppm): -2.86 (SiCH₃); 14.73 (ethane CH₃); 16.98 (1-C); 19.11 (isobutyl CH₃); 22.30 (2-C); 29.45 (CH); 35.26 (3-C); 48.78 (3-CH₂Cl); 56.54 (4-C); 71.26 (Cp-Si); 72.0-72.4 + 74.0-74.4 (Cp); 75.46 (SO₃CH₂). GPC (THF): $M_n = 1.79 \cdot 10^4$ g/mol, $M_w = 4.06 \cdot 10^4$ g/mol, $M_w/M_n = 2.27$. Percentage of CH₂Cl moieties: 10 mol%.

Poly(ferrocenylsilane) polyanion 3. The isobutylsulfonate ester groups of **2** (1.4 g) were deprotected using NaN₃ (2.50 g, 38.5 mmol), initially in THF (150 mL) and methanol (100 mL) at 55 °C. After 24 h, THF and methanol were evaporated, and deprotection was continued in DMSO (60 mL) at 45 °C for 48 h. Simultaneously, in DMSO, the 10 mol% chloride groups of polymer **2** were substituted by azide moieties. PFS **3** was purified by dialysis against Milli-Q containing trace amounts of sodium ascorbate and freeze-dried to yield the amber product. Yield: 1.30 g (100%). ¹H NMR (DMSO-d₆, δ , ppm): 0.44 (SiCH₃, s, 3H); 0.88 (1-CH₂, m, 2H); 1.07 (ethane CH₃, d, $J = 6.2$ Hz, 3H); 1.32 + 1.50 (2-CH₂, m, 2H); 1.32 + 1.90 (3-CH₂, m, 2H); 2.37 (4-CH₂, m, 1H); 3.31 (3-CH₂N₃); 3.98 + 4.18 (Cp, m, 8H). ¹³C NMR (DMSO-d₆, δ , ppm): -3.09 (SiCH₃); 15.36 (ethane CH₃); 15.70 (1-C); 21.53 (2-C); 35.67 (3-C); 53.88 (4-C); 70.33 (Cp-Si); 70.96 + 73.06 (Cp). ATR-FTIR: 2094 cm⁻¹ (azide).

Bicyclononyne (BCN) derivatized tetra-arm PEG 4.

(1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethyl succinimidyl carbonate (100 mg, 0.343 mmol) was dissolved in DMF (1 mL). Tetra-arm PEG amine 5000 (408 mg, 0.326 mmol) and triethylamine (70 μ l, 0.5 mmol) were dissolved in dry DMF (5 mL) and added to the BCN solution. The solution was stirred under argon for 20 h at 20 °C. The product was precipitated in cold diethyl ether, followed by centrifugation (3000 rpm, -20 °C) to isolate the polymer. The product was

redissolved in toluene and precipitated in cold diethyl ether, followed by centrifugation (3000 rpm, $-20\text{ }^{\circ}\text{C}$). Yield: 0.45 g of white powder. ^1H NMR (CDCl_3 , δ , ppm): 0.87 (m, 1H); 1.35 (m, 1H); 1.53 (m, 1H); 2.08-2.28 (m, 6H); 3.03 (m, 2H), BCN; 3.2–3.7 (EO, m); 4.08 (COOCH_2 , d, $J = 8.0\text{ Hz}$, 2H) 5.25 (NH, bs, 1H). ^{13}C NMR (CDCl_3 , δ , ppm): 156.81; 98.88; 70.2-70.7; 62.36; 46.13; 41.33; 29.31; 21.59; 18.39.

Anionic hydrogel 5 and cationic hydrogel 8. Polyanion **3** (50 mg, 0.13mmol r.u.) or polycation **7** (50 mg, 0.14 mmol r.u.) was dissolved in MeOH (0.2 mL) and mixed with a solution of BCN derivatized tetra-arm PEG **4** (1.0 eq.) in MeOH (0.1 mL). At this ratio, equimolar amounts of BCN and azide moieties were present in the gel-forming mixture. The viscosity was observed to increase until gel formation was confirmed by the vial tilting method. Typically, gelation was allowed to proceed overnight. In order to completely remove MeOH, the gel was placed in Milli-Q water, replacing the water several times. FTIR analysis of the gel after freeze-drying indicated that the azide signal, originating from polymer **3** or **7**, had disappeared.

Poly(ferrocenylsilane) 6. PFS **6** was synthesized by Pt-catalyzed ring-opening polymerization of [1](3-chloropropyl)methylsilaferrocenophane (0.89 g, 2.9 mmol), followed by halogen substitution using NaN_3 . The precipitated poly(ferrocenyl(3-chloropropyl)methylsilane) (0.77g, 2.51 mmol r.u.) was redissolved in 45ml THF. A solution of NaN_3 (0.35 g, 5.38 mmol) and 15-crown-5 (0.35 ml, 1.77 mmol) in 7.5ml DMSO was added and the mixture was stirred under nitrogen at $50\text{ }^{\circ}\text{C}$. At 18% conversion of Cl into N_3 , **4** was isolated by precipitation in MeOH and dried under vacuum. Overall yield: 0.7 g (79%) of amber product. ^1H NMR (toluene- d_8 , δ , ppm): 0.52 (SiCH_3 , s, 3H); 0.93 + 1.01 (1- CH_2 , m, 2H); 1.57 + 1.79 (2- CH_2 , m, 2H); 2.89 (3- CH_2N_3 , m, 2H); 3.28 (3- CH_2Cl , m, 2H); 4.04 + 4.08 + 4.27 (Cp, m, 8H). ^{13}C NMR (toluene- d_8 , δ , ppm): -2.99 (SiCH_3); 13.95 + 14.35 (1-C); 24.47 + 28.33 (2-C); 48.23 (3- CH_2Cl); 54.53 (3- CH_2N_3); 70.51 (Cp-Si); 71.93 + 72.09 + 73.83+ 74.01 (Cp). GPC (THF): $M_n = 6.04 \cdot 10^5\text{ g/mol}$, 66

$M_w = 1.06 \cdot 10^6$ g/mol, $M_w/M_n = 1.749$. GPC (THF, PFS-Cl): $M_n = 2.81 \cdot 10^5$ g/mol, $M_w = 4.89 \cdot 10^5$ g/mol, $M_w/M_n = 1.74$.

Poly(ferrocenylsilane) polycation 7. PFS **6** (0.7 g, 2.29 mmol r.u.) was dissolved in 15 ml THF, followed by the addition of 7.5 ml trimethylamine solution (4.2M in ethanol) and 7.5 ml DMSO. The mixture was stirred at 50 °C for 48 hours, after which the solvents were partially evaporated and 5 ml fresh trimethylamine solution was added. After 72 hours, the solution was left to cool to room temperature, was dialyzed against Milli-Q water containing trace amounts of sodium ascorbate and freeze-dried to yield the amber product. Overall yield: 0.73 g (98%) of amber product. ^1H NMR (DMSO- d_6 , δ , ppm): 0.47 + 0.52 (SiCH₃, s, 3H); 0.82 + 0.94 (1-CH₂, m, 2H); 1.62 + 1.74 (2-CH₂, m, 2H); 3.09 (N-CH₃ s, 9H); 3.32 (3-CH₂N(CH₃)₃, m, 2H); 3.35 (3-CH₂N₃, m, 2H); 4.04 + 4.08 + 4.15 + 4.23 (Cp, m, 8H). ^{13}C NMR (toluene- d_8 , δ , ppm): -3.34 (SiCH₃); 11.86 + 12.65 (1-C); 17.32 + 23.62 (2-C); 51.98 (N-CH₃); 53.59 (3-CH₂N₃); 67.62 (3-CH₂N); 68.09 (Cp-Si); 69.69 + 71.21 + 73.13 (Cp).

***In situ* formation of nanoparticles inside the hydrogels.** The water swollen anionic hydrogel **5** was immersed in a solution of potassium tetrachloropalladate or potassium tetrachloroplatinate (5 mM, 1 oxidative equivalent with respect to ferrocene units). The hydrogels were washed with Milli-Q water to remove unreacted salts and was freeze-dried for analysis.

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Chapter 4

DNA - Organometallic Polymer Polyplexes for Gene Delivery

The synthesis and characterization of polycationic poly(ferrocenylsilane)s (PFS) with tunable amounts of poly(ethylene glycol) (PEG) side chains are reported. These organometallic polycations were used for the condensation of DNA into polyplexes, which were analyzed for their size, zeta potential, aggregation behavior and application in transfection studies. The polyplexes had a diameter of around 100 to 150 nm in the dry state and 110 nm in 5.0 mM HEPES buffer depending on the degree of PEG grafting, as was established by atomic force microscopy and dynamic light scattering, respectively. Since the PFS-PEG/DNA polyplexes were stabilized by PEG chains, the polyplexes showed negligible aggregation in Dulbecco's Modified Eagle Medium (DMEM) and strongly reduced protein adsorption, as observed by surface plasmon resonance measurements. The transfection activities of the PFS-PEG/DNA polyplexes in Human Embryonic Kidney 293 T cells were comparable with those of polyplexes based on linear polyethylene imine (PEI). Importantly, although the PEI based polyplexes showed considerable cytotoxicity, the PFS-PEG/DNA polyplexes at equal doses exhibited an excellent cytocompatibility. In conclusion, PFS-PEG/DNA polyplexes are attractive formulations for the delivery of nucleic acid based drugs.

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4.1 Introduction

Gene therapy is a promising therapeutic modality for the treatment of many life-threatening and chronic diseases.¹⁻² In particular, non-viral gene delivery is attracting much attention due to its ability to overcome the immune and toxic reactions intrinsic to viral vectors, the straightforward low-cost synthesis involved and its versatility.³⁻⁵

Non-viral gene delivery includes approaches that rely on the use of positively charged lipids and polymers to bind and condense DNA. These cationic species spontaneously form complexes (referred to as lipoplexes and polyplexes, respectively⁶) when mixed with DNA, as a result of electrostatic interactions between the positively charged, generally amine, groups of the cationic species and the negatively charged phosphate groups of DNA.³ The complexation into nanoparticles is important to circumvent renal clearance, protect DNA against enzymatic degradation by nucleases and at the same time allow the DNA to pass through the endothelial layers of pathological tissues (the enhanced permeability and retention effect⁷) where they can enter the targeted cells by endocytosis.⁸

Although small size is in general considered favorable for delivery, interestingly, large, aggregated particles show in some cases a higher gene expression efficiency *in vitro* which was ascribed to the sedimentation of the particles onto the cells on the bottom of the well plates.⁹ On the other hand, small singular polyplexes exhibited improved gene expression *in vivo*.¹⁰ Comparing the toxicity of polyplexes and lipoplexes is non-trivial and it is dependent on the individual parameter sets of the specific systems. In a study of Kabanov *et al.* in which several lipid and polymeric gene delivery systems were evaluated with respect to their effectiveness and toxicity, polymeric systems had an efficiency higher than, or comparable to, lipid systems. These ensembles did not show serum dependence and were less toxic than the lipid based systems.³

An efficient way of reducing the cytotoxicity of polyplexes and increase their colloidal stability is PEGylation, which involves the attachment of poly(ethylene

glycol) (PEG) chains through both covalent¹¹⁻¹⁵ or non-covalent¹¹ bonds. Pre-PEGylation, where preformed block or comb copolymers are employed for the complexation of DNA, is the most commonly used technique.^{13-14, 16} When a bifunctional PEG is used, the extremities of the PEG shell can be functionalized with targeting molecules.^{12-13, 16}

An interesting case of pre-PEGylation was shown by Zhong *et al.*¹⁷ A low molecular weight triblock copolymer possessing a PEG middle block, PEI-PEG-PEI (4000-3000-4000 g/mol) was prepared, having a 3-fold higher transfection activity than linear polyethyleneimine (PEI) 25000. The polyplex conformation was proposed to have a flower-like structure, with PEI in the core condensing the DNA and PEG loops on the outside, shielding the surface positive surface charge of the polyplexes.

Post-PEGylation is used to ensure unhindered DNA complexation. The polyplexes are preformed, after which the PEG chains are reacted with the particle surface to create a protective shell.^{10-11, 15} In this way, it can be assured that targeting moieties are attached onto the complexes at the distal ends of the PEG shell, making them more accessible for their receptors.¹²⁻¹³ However, clinical application of post-PEGylation procedures may be hindered by the elaborate synthetic work needed to prepare the polyplexes.^{10, 18}

In view of these drawbacks of post-PEGylation, efforts have been made to develop a pre-made mixture of condensing, shielding and targeting agents for the direct preparation of polyplexes. These polyplexes were also used in transfection experiments after freezing and thawing, to test storage possibilities. Freeze-thawed and pre-made mixtures were both successfully applied for transfection, yielding efficiencies higher than their linear PEI (22 kg/mol) control polyplexes.¹⁸

To improve biodegradability, disulfide bonds, which are cleavable by intracellular reduction, can be used for the attachment of PEG.¹⁸⁻¹⁹ Alternatively, pH-sensitive hydrazone linkages can be used, which can be broken in endosomal environment, pH 5.²⁰

In addition to reducing cytotoxicity, PEGylation can increase colloidal stability and prevent aggregation under physiological conditions.^{10-11, 17, 21-22} The hydrophilic polymer shell reduces protein interaction and activation of the complement system (the complement system is a part of the immune system that helps to clear pathogens from an organism), thereby increasing the circulation time of the polyplexes.^{15, 22} Furthermore, the transfection efficiency of the polyplexes was reported to remain comparable or even to improve.^{17, 21, 23}

Recently, redox-active alkyl-ferrocene modified branched PEI was investigated as transfection agent. Polyplexes based on this polymer showed improved transfection efficiencies when compared to branched PEI (25 kg/mol) and Lipofectamine 2000. Oxidation of the ferrocene moieties increased the size and the zeta potential of the polyplexes and drastically reduced the gene transfection capabilities of the polyplexes.²⁴

Organometallic polymers have drawn interest by their interactions with DNA. Recently it was shown that the positively charged oxidized metal center of this kind of polymers could interact with the negatively charged phosphate groups of DNA.²⁵ In this case, efforts were focused on the structural replication of the anionic chiral template by poly(cobaltoceniumethylene).

An interesting class of versatile and inherently redox-active organometallic polymers encompasses poly(ferrocenylsilane)s (PFS).²⁶⁻²⁸ Water-soluble cationic poly(ferrocenylsilane)s were shown to be effective DNA condensation and transfection agents by Zhong *et al.*, who showed a higher transfection efficiency compared to pDMAEMA polyplexes.²⁹ However, significant agglomeration of the polyplexes was observed under physiological conditions, which limits their applicability *in vivo*. Similar polymers were used for the redox triggered release of Nile Red and paclitaxel.³⁰ By introducing about 25% of decyl hydrocarbon chains to the cationic polymer, it formed micellar assemblies of 100 nm which could be loaded with the aforementioned payloads. By varying the concentration of redox agents, control of the payload release profile was demonstrated. In addition,

a significantly higher transfection efficiency compared to the non-micellar polymer of Zhong *et al.* was observed. In this study we address the transfection efficiency, stability and protein adsorption of polyplexes formed from PEGylated cationic PFSs and DNA.

4.2 Results and discussion

A polycationic poly(ferrocenylsilane) with tunable amounts of PEG side chains was synthesized by side group modification of PFS **1** (Scheme 4.1). To introduce PEG side chains, PFS **1** was reacted with the sodium salt of monocarboxylic acid functional PEG (750 g/mol).

Scheme 4.1. Synthesis of poly(ferrocenylsilane) polycations with PEG side chains.

Successful substitution was confirmed by NMR (Figure 4.1) and FTIR (Figure 4.2). Next to the characteristic peaks for PFS, the methoxy endgroup signal of the grafted PEG sidechains was present in the ¹H NMR spectra at $\delta = 3.24$ ppm and in the ¹³C NMR spectra at $\delta = 58.04$ ppm. Furthermore, the signal associated with the oxyethylene groups of PEG is present in the ¹H NMR spectra at $\delta = 3.51$ ppm and in the ¹³C NMR spectra at $\delta = 69.76$ ppm. (Figure 4.1). Also, the peak of the

methyl groups present in the cationic NMe_3Cl units of polymer is clearly visible in the ^1H NMR spectra at $\delta = 3.11$ ppm and in the ^{13}C NMR spectra at $\delta = 52.00$ ppm. The targeted degrees of substitution were reached, as was confirmed by comparing the $\text{CH}_3\text{-Si}$ signals of the PFS main chain with the $\text{CH}_3\text{-O}$ signal of PEG in the ^1H NMR spectrum.

Figure 4.1. a) The structure, b) ^1H NMR and c) ^{13}C NMR spectrum ($\text{DMSO}-d_6$, δ , ppm) of the PFS- NMe_3Cl polymer with 25% PEG, used for the transfection studies.

Subsequently, positively charged moieties were introduced by amination of the iodopropyl side groups of PFS **2** using trimethylamine. Exchange of the iodide to chloride counterions further improved the water-solubility of the polycations. FTIR confirmed the expected functional groups; 1700 (carbonyl, PEG), 1632 and 1479 ($-\text{NMe}_3\text{Cl}$), 1111 (PEG), 1035 and 774 (PFS).

Figure 4.2. FTIR spectra of PFS polymers, used for the transfection studies. a) Full spectrum, b) detailed spectrum at 1750-500 cm^{-1} .

Polymer/DNA complexes were prepared by mixing PFS **3** with pCMV-GFP reporter plasmid with amine to phosphate (N/P) ratios ranging from 1–8 (mol/mol ratio) in a 5.0 mM HEPES buffer solution at pH 7.4. Increasing the ratio of amine (PFS cation) to phosphate (DNA) to 2 or higher resulted in condensation of PFS **3** and DNA into polyplex particles with diameters of about 110 nm (Figure 4.3a). AFM measurements on polyplexes with N/P ratio 4 deposited on silicon substrates show similar sizes (Figure 4.3b) although the measured height was significantly lower with respect to the diameter, suggesting a collapse of the particles upon drying. Dynamic light scattering (DLS) measurements in 5.0 mM HEPES buffer at pH 7.4 gave PFS/DNA polyplex diameters of about 110 nm for the PEGylated polyplexes and 120 nm for the non-PEGylated polyplex. Upon condensation of DNA at a N/P ratio of 2, the zeta potential switched from negative (–10 to –20 mV) to positive (+40 to +55 mV), indicating the inclusion of DNA inside the PFS polycations (Figure 4.3a).

Figure 4.3. a) Size and zeta potential of PFS/DNA polyplexes as a function of the N/P (mol/mol ratio) as measured by DLS in 5.0 mM HEPES buffer. The concentration was fixed at 100 $\mu\text{g/mL}$ and the incubation time was 30 minutes. b) AFM tapping mode image of polyplex particles on a silicon substrate, and the height profile of the white line shown in the image (inset) ($N/P = 4$).

The PEG side chains were used to reduce protein adsorption on the polyplexes. Next to shielding the positive core from the negatively charged proteins, these PEG side chains also introduce steric hindrance, stabilizing the polyplexes. Even though protein adsorption was still apparent after PEGylation of the PFS for polyplexes, it significantly decreased compared with the non-PEGylated PFS polyplexes (Figure 4.4b, the protein adsorption for non-PEGylated PFS polyplexes was set to 1). The same trend in BSA protein adsorption was found by Crielaard *et al.* for non-PEGylated versus PEGylated liposomes.³¹ However, upon PEGylation, the colloidal stability increased significantly (Figure 4.4b).

Figure 4.4. a) Relative protein adsorption (the protein adsorption for non-PEGylated PFS polyplexes was set to 1), determined by Surface Plasmon Resonance (SPR) and b) colloidal stability of polyplexes with different degrees of PEGylation (N/P = 4).

Transfection activity and cytocompatibility of the PFS/DNA polyplexes were tested and compared with polyplexes based on with linear PEI (25 kg/mol). The N/P ratio was set to the optimum values obtained from previous experiments (results not reported); for PFS 6/1 and for linear PEI 8/1 was used with 150 ng/mL pCMV-GFP reporter plasmid. The experiments were performed in medium with 0%, 5% and 10% of serum. The results of transfection and cell viability assays are summarized in Figure 4.5.

Among the tested polymers, unmodified PFS cation has the highest efficiency regardless of the serum content. Interestingly, even in 10% serum, the unmodified PFS cation has high transfection efficiency which shows the superior efficiency of PFS in cell transfection *in vitro*, regardless of the protein adsorption and agglomeration of the particles. These relatively high transfection efficiencies can be explained by sedimentation of the particles onto the cells on the bottom of the well plates.^{9, 32} This is supported by the lower transfection efficiency of the PEGylated cationic PFS polyplexes which have an only slightly lower zeta

potential, important for polyplex-cell membrane interactions,³³⁻³⁴ but a significantly reduced agglomeration.

Although the transfection efficiency decreased by PEGylation, it increased the cell viability during transfection in serum. By increasing the serum concentration, the cell viability decreased for the unmodified PFS cation, while for the PEGylated cations, the cell viability increased. This can be explained by the aggregation of the unmodified cationic PFS polyplexes (Figure 4.4). These charged aggregates interact with negatively charged cell membranes resulting in cell permeabilization and finally in cell death.

Figure 4.5. a) Cell viability and b) relative transfection efficiency (the transfection efficiency of bare DNA was set to 1) of polyplexes with different degrees of PEGylation, N/P (mol/mol) ratios were for PFS 6/1 and for linear PEI 8/1.

When comparing PFS at a higher degree of PEG grafting, with linear PEI, the cell viability and transfection efficiency for PFS polyplexes is comparable or higher. In combination with the facile side group modification of PFS, desired membrane disruptive peptides or targeting units could be incorporated during the synthesis, which is a promising future strategy to increase the transfection activity of the polyplexes and to render them cell specific.³⁵⁻³⁶

4.3 Conclusion

In this study, it was shown that cationic PFS is an interesting polymer for transfection studies. The cationic PFS polyplexes were stabilized by short PEG side chains increasing their colloidal stability and reducing protein adsorption onto their surface. These PEGylated polyplexes did not compromise, in contrast to *e.g.*, PEI-bases formulations, the cell viability. Even though, the transfection efficiency of the PFS-polyplexes was reduced by PEGylation, the efficiency of the PEGylated PFS polyplexes remained comparable to non-PEGylated linear PEI polyplexes. These results show the opportunity to prepare tailor-made cationic polyplexes based on the versatility of cationic PFS.

4.4 Experimental section

Materials. Trimethylamine solution (31-35 wt%, 4.2 M in ethanol), potassium iodide (99%), iodoethane (99%), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer (HEPES), deoxyribonucleic acid sodium salt from salmon testes, 3-mercapto-1-propanesulfonic acid sodium salt (90%), Bovine Serum Albumin ($\geq 99\%$), dicyclohexano-18-crown-6 (98%), 15-crown-5 (98%), $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$, DMSO- d_6 (99.9 atom% D), and toluene- d_8 (≥ 99.6 atom% D) were obtained from Aldrich and used as received. CDCl_3 (99.8 atom% D) was purchased from Cambridge Isotope Laboratories. pCMV-GFP plasmid DNA was obtained from PlasmidFactory GmbH & Co. KG, Bielefeld, Germany. O-[2-(3-Succinylamino)-ethyl]-O'-methyl-polyethylene glycol (PEG average $M_n = 750$ g/mol) was purchased from Rapp Polymere GmbH (Tübingen, Germany). Methanol, DMSO, THF and diethyl ether were obtained from Biosolve, The Netherlands. Milli-Q water (Millipore) was used in all experiments. CellTiter 96[®] One Solution Cell Proliferation Assay (MTS) was purchased at Promega, Madison, WI.

Techniques. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz instrument at 400.1 and 100.6 MHz, respectively, in CDCl_3 , DMSO- d_6 or toluene- d_8 . ^1H and ^{13}C chemical shifts were based on the solvent residual signals.

GPC measurements were carried out in THF (flow rate 2.0 mL/min) at 25 °C, using microstyragel columns (bead size 10 μm) with pore sizes of 10^6 , 10^5 , 10^4 and 10^3 Å (Waters) and a dual detection system consisting of a differential refractometer (Waters model 410) and a differential viscometer (Viscotek model H502). Molar masses were determined relative to narrow polystyrene standards. FTIR spectra were measured with a Bruker ALPHA on freeze-dried samples. The hydrodynamic particle size was measured on a Zetasizer Nano ZS (Malvern, Worcestershire, United Kingdom). This device uses a 4 mW 633 nm laser and measures the backscattering at a 173° angle. A delay time of 10 minutes after sample insertion was used for each measurement. The measured sample concentration was ~ 5 mg/ml. AFM measurements were performed on cleaned silicon substrates using a Multimode AFM with a Nanoscope V controller (Bruker, Santa Barbara, California, USA) in tapping mode using silicon nitride cantilevers with resonance frequency $f_0 = 50\text{--}80$ kHz and spring constant of $k = 0.35$ N/m (Bruker, Camarillo, California, USA). SPR measurements were performed in a SPR setup in Kretschmann configuration. For fluorescent imaging a Keyence BZ-9000E (Keyence, Osaka, Japan) device was used.

Poly(ferrocenylsilane) 1. PFS **1** was synthesized by Pt-catalyzed ring-opening polymerization of [1](3-chloropropyl)methylsilaferrocenophane (3.0 g, 9.85 mmol) in THF, followed by halogen exchange using KI.³⁷ PFS **1** was isolated by precipitation in MeOH and dried under vacuum. Overall yield: 2.65 g (68%) of amber product. ^1H NMR (toluene- d_8 , δ , ppm): 0.52 (SiCH₃, s, 3H); 1.00 (1-CH₂, m, 2H); 1.82 (2-CH₂, m, 2H); 2.95 (3-CH₂I, m, 2H); 4.05 + 4.10 + 4.27 + 4.29 (Cp, m, 8H). ^{13}C NMR (toluene- d_8 , δ , ppm): -2.83 (SiCH₃); 12.02 (1-C); 18.52 (2-C); 29.32 (3-CH₂I); 70.50 (Cp-Si); 71.96 + 73.95 (Cp). GPC (THF): $M_n = 2.2 \cdot 10^4$ g/mol, $M_w = 4.5 \cdot 10^4$ g/mol, $M_w/M_n = 2.07$.

Poly(ferrocenylsilane) 2. For 10% PEGylated PFS, 46.6 mg O-[2-(3-Succinylamino)ethyl]-O'-methyl-polyethylene glycol (0.051 mmol, $M_n = 750$ g/mol) was dissolved in methanol (10 mL). Sodium hydroxide (0.051

mmol) was added to the flask and the reaction was continued at room temperature overnight. Methanol was evaporated and the formed salt was dissolved in DMSO (3 mL). PFS **1** (200 mg, 0.51 mmol r.u.) was dissolved in THF (10 mL) and the solution of PEG salt was added to the mixture. 15-Crown-5 (10 μ L, 0.051 mmol) was added and the reaction was continued at 45 °C for 4 days. The same procedure was used for PFS with 25% of PEG side chains. ^1H NMR (CDCl_3 , δ , ppm): 0.47 (SiCH_3 , s, 3H); 0.87 + 1.01 (1- CH_2 , m, 2H); 1.67 + 1.88 (2- CH_2 , m, 2H); 2.48 ($\text{O}-\text{C}=\text{O}-\text{CH}_2$, m, 2H); 2.64 ($\text{N}-\text{C}=\text{O}-\text{CH}_2$, m, 2H); 3.22 + 4.04 (3- CH_2 , m, 2H); 3.37 (MeO, s, 3H); 3.43 (N- CH_2 , m, 2H); 3.64 (PEG, m) 4.00 + 4.23 (Cp, m, 8H). ^{13}C NMR* (CDCl_3 , δ , ppm): -2.98 (SiCH_3); 12.43 + 18.32 (1-C); 23.45 + 28.85 (2-C); 30.79 ($\text{O}-\text{C}=\text{O}-\text{CH}_2$, m, 2H); 29.53 ($\text{N}-\text{C}=\text{O}-\text{CH}_2$, m, 2H); 67.33 (3- CH_2 , m, 2H); 59.18 (MeO, s, 3H); 39.32 (N- CH_2 , m, 2H); 70.59 (PEG, m) 71.59 + 73.41 (Cp). *Based on C-H correlated NMR. ATR-FTIR: 1700 (carbonyl, PEG), 1111 (PEG), 1035 and 774 (PFS) cm^{-1} .

Poly(ferrocenylsilane) 3. PFS **1** (1.0 g, 2.53 mmol r.u.) was dissolved in THF (20 mL). Trimethylamine solution (10mL, 4.2M in ethanol) and DMSO (6.5 mL) were added to the solution. After 24 hours at room temperature, the product had precipitated in the reaction flask. THF was evaporated and fresh DMSO (10 mL) and trimethylamine (5 mL, 21 mmol) were added to the precipitate. After 3 days, the product was precipitated in THF. An orange solid was obtained (0.90 g, 2.03 mmol, 80%). PFS **3** was obtained through ion exchange by dialysis against 0.1 M aqueous NaCl for 1.5 day continuing with 1.5 day dialysis against Milli-Q water, followed by freeze-drying yielding the product as an amber foam with typical yields around 70%. The same procedure was used for PFS with PEG side chains (PFS **2**). ^1H NMR ($\text{DMSO}-d_6$, δ , ppm): 0.44 + 0.52 (SiCH_3 , s, 3H); 0.83 (1- CH_2 , m, 2H); 1.52 + 1.74 (2- CH_2 , m, 2H); 2.13 ($\text{O}-\text{C}=\text{O}-\text{CH}_2$, m, 2H); 2.19 ($\text{N}-\text{C}=\text{O}-\text{CH}_2$, m, 2H); 3.10 (N- CH_3 s, 9H); 3.15 (N- CH_2 , m, 2H); 3.23 (MeO, s, 3H); 3.39 + 3.40 (3- CH_2 , m, 2H); 3.50 (PEG, m) 4.00-4.23 (Cp, m, 8H). ^{13}C NMR ($\text{DMSO}-d_6$, δ , ppm): -3.38 (SiCH_3); 11.90 (1-C); 17.28 + 27.34 (2-C); 30.79*

(O-C=O-CH₂, m, 2H); 29.53* (N-C=O-CH₂, m, 2H); 38.37 (N-CH₂); 51.98 (N-CH₃); 58.02 (MeO); 63.81 + 67.63 (3-CH₂); 69.22-70.42 (PEG) 70.9-71.4 + 73.09 (Cp) 177.56 + 178.20 (C=O). *Not observed anymore. ATR-FTIR: 1632 and 1479 (–NMe₃Cl) cm^{–1}.

Polyplex formation. Polymer/DNA complexes were prepared in variety of amine/phosphide (N/P) ratios ranging from 1 to 8 in 5mM HEPES buffer solution, vortex mixed for 5 seconds and incubated at room temperature for 30 minutes.¹⁷

Protein adsorption. The SPR gold discs (gold thickness was 45 nm, XanTec Bioanalytics GmBh, Dusseldorf, Germany) were, after cleaning with piranha, functionalized with sodium 3-mercapto-1-propanesulfonate (1.0 mM in Milli-Q water). To measure the protein adsorption on the polyplex particles, the substrate was mounted in the SPR setup and polyplex particles were first adsorbed to the monolayer. Excess particles were washed away with buffer, after which a Bovine Serum Albumin (BSA) solution was passed over the substrate.

Cell culture. Human Embryonic Kidney 293 T cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS, 100 U/mL penicillin and streptomycin (GIBCO) at 37 °C in a humidified 5% CO₂-containing atmosphere.

Transfection experiments. Transfection experiments were performed using 150 ng/mL of pCMV-GFP reporter plasmid. The cells were plated in 96-well plates ($0.8\text{--}1.0 \times 10^4$ cells/well) and cultured in 0.1 mL/well DMEM medium containing 10% FBS for at least 24 h until 60-70% cell confluence was reached. They were then washed once with fresh PBS buffer and incubated in the DMEM medium with 0%, 5% or 10% FBS for transfection. The cells were treated with 10 µL of the polyplex dispersion for 1 h at 37 °C in a 5% CO₂-containing atmosphere. Next, the medium was replaced with DMEM medium containing 10% FBS and the cells were further incubated for another 47 h. All the transfection experiments were done in quadruplicate. A transfection formulation with linear PEI (25 kg/mol) prepared at an optimal N/P ratio of 8/1 was also applied as positive control.

Cell viability assay. Relative cell viability was evaluated by CellTiter 96[®] One Solution Cell Proliferation Assay (MTS) (Promega, Madison, WI). In brief, 20 μ L MTS was added carefully to each well, including untreated cells (cells not exposed to polyplexes). After 4 hours in culture the cell viability was determined by measuring the absorbance at 490 nm using a 550 BioRad plate-reader (Bio-Rad, Hertfordshire, UK).

Transfection efficiency assay. GFP gene expression in transfected cells was determined by quantification of the fluorescence intensity of GFP. After transfection, the cells in a 96-well plate were washed twice with PBS buffer and incubated with cell lysis buffer (100 μ L) at 4 °C for 20 min. The cell lysates were collected, centrifuged to pellet cellular debris, and 90 μ L of cell lysate was transferred in a 96-well black plate to determine fluorescence intensity of GFP with excitation and emission wavelengths of 488 nm and 520 nm, respectively. Background fluorescence/auto-fluorescence was also determined using untreated cells as a blank control. The total recovered protein concentration in the cell lysate from each well was estimated with a BAC kit. The amount of protein was normalized from a BSA standard curve. GFP gene expression was calculated as fluorescence intensity (FI) normalized against protein concentration and expressed as arbitrary units (a.u.)/mg protein.

4.5 References

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Chapter 5

Selective ion sensing by crown ether-bearing poly(ferrocenylsilane)s

The synthesis and characterization of poly(ferrocenylsilanes) (PFSs) possessing pendant crown ether moieties are reported. Gold electrodes were chemically modified with these redox responsive organometallic PFS chains for electrochemical ion recognition. Cyclic voltammetry (CV) measurements were performed on these electrodes in 100 mM LiClO₄ as electrolyte, showing the typical double wave voltammograms for PFS. However, upon the addition of KClO₄ a third oxidation peak emerged at a higher potential was formed. The lower detection limit of KClO₄ in 100 mM LiClO₄ was estimated to be 3 μM.

5.1 Introduction

This chapter describes the formation and redox characteristics of gold electrodes modified with crown ether bearing redox responsive organometallic poly(ferrocenylsilane) (PFS) chains and their use in the electrochemical detection of cations.

Electrochemical sensing platforms, based on the modification of electrode surfaces with electroactive species, are drawing much attention due to their application potential in *e.g.*, electrocatalysis,¹⁻² amperometric biosensors,³⁻⁴ and ion recognition.⁵⁻⁷ Often, ferrocene is used as the electroactive species for these molecular receptors and sensing materials and its derivatives are used as a mediator or label for the transformation of recognition information to an electrical signal.⁸⁻¹⁰ To prepare a molecular recognition sensor, a host molecule is needed which selectively binds the guest analyte and which is linked to and located in the vicinity of the electroactive species.¹¹

For cation recognition, chelating agents and macrocycles such as crown ethers, cryptands and calixarenes have proven to be efficient units.¹² This research was focused on crown ethers as host molecules for cations; these structures are able to selectively bind specific cationic species due to the ion-dipole interaction of the positively charged metal ion with the negatively polarized oxygen atoms.¹³ Besides their specific binding with cations, crown ethers can also function as ion carriers.¹⁴ The combination of ferrocene with crown ethers for ion recognition has been a topic of interest in the past decades.¹⁵⁻¹⁷ Crown ethers containing a conjugated linkage with ferrocenes reveal a shift in the oxidation potential of ferrocene upon the binding of Na⁺, K⁺, and Mg²⁺ guest cations.¹⁸ The oxidation potential of ferrocene was shifted to more positive potentials. The magnitude of the shift depends on the charge:radius ratio of the cationic species, Mg²⁺ producing the largest shift and K⁺ the smallest.

By using a pyrrole functionalized ferrocene crown ether, the redox-active host could be coated on electrode surfaces by electrooxidative polymerization. These

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modified electrodes were successfully used for the amperometric recognition of Ca^+ and Ba^+ in organic solvents.¹⁹⁻²⁰

Recently the preparation of electrochemical sensors based on PFS was described by Sui et al.²¹ Chemically modified electrodes, decorated with covalently tethered poly(ferrocenyl(3-iodopropyl)methylsilane) chains, were presented as a robust, highly tailorable platform for redox-active interfaces. The modified electrodes were directly applied as electrochemical sensor for ascorbic acid, exhibiting a high sensitivity and stability. It was shown that this method can be extended to multilayers of PFS with polyethyleneimine (PEI).³ The PEI readily forms covalent bonds with the unreacted halopropyl groups of the PFS by means of an amine alkylation reaction, yielding covalently connected, redox-active multilayer thin films. The PFS/PEI multilayers were effective for the electrochemical sensing of ascorbic acid and hydrogen peroxide and showed improved sensing performance at higher bilayer numbers.

The sensitivity of ascorbic acid sensors based on ferrocene derivatives was further improved by the use of polyionic liquids. PFS, functionalized with methylimidazole side groups, was found well-soluble in the ionic liquid 1-ethyl-3-methylimidazolium ethyl sulfate. The direct cathodic reduction of this polymer/ionic liquid solution generated a robust redox-active graft on the electrodes.²² A drawback to these redox-active grafts is the lack of facile chemical handles for (sensor) modification.

As discussed above, different functionalities are easily introduced by side-group modification of poly(ferrocenyl(3-iodopropyl)methylsilane) and it has been shown that thin and dense redox-active films can be immobilized on electrode surfaces. Combined with crown ethers, for molecular recognition, this would be a very suitable ion recognition and sensing platform. The first ion sensing results of this type of crown ether functionalized PFS are presented below.

5.2 *Results and discussion*

For the fabrication of the ion recognition sensor, based on PFS, 4'-hydroxybenzo-18-crown-6 was synthesized from benzo-18-crown-6. The procedure via acylation of benzo-18-crown-6, followed by a Baeyer-Villiger oxidation and hydrolysis is presented in Scheme 5.1.

Scheme 5.1. Synthesis of 4'-hydroxybenzo-18-crown-6 (**3**).

The successful synthesis of **3** was confirmed by ^1H NMR and FTIR spectroscopy. To attach these crown ether moieties to the iodopropyl sidechains of poly(ferrocenyl(3-iodopropyl)methylsilane) (PFS **4** in Scheme 5.2), PFS **4** was reacted with the phenolate anion of 4'-hydroxybenzo-18-crown-6, prepared with the phosphazene base P1-t-Bu-tris(tetramethylene) at 0 °C. Successful substitution was confirmed by ^1H NMR and FTIR spectroscopy. Next to the characteristic peaks of PFS, the oxyethylene groups of the crown ether side chains were present in the ^1H NMR spectra at $\delta = 3.50\text{--}4.35$ ppm and in the FTIR spectrum at 1105 cm^{-1} . The degrees of substitution were calculated by comparing the SiCH_3 signal at 0.52 ppm with the signal of the aromatic protons of the benzo-18-crown-6 at 6.35–6.78 ppm. The crown ether substitution was 75%, leaving 25% reactive iodopropyl groups for surface tethering.

Scheme 5.2. Reaction of PFS **4** with the phenolate anion of 4'-hydroxybenzo-18-crown-6, yielding PFS **5**.

The modification of gold electrode surfaces was achieved by the amine alkylation reaction of the unreacted iodopropyl groups of PFS **5** with the cysteamine monolayer on the gold electrode surface, yielding a covalently bound, redox-active polymer layer for molecular recognition. Alternatively, PFS **4** was tethered to the electrode surface via a cysteamine monolayer to yield a PFS layer with some reactive iodopropyl groups remaining (Scheme 5.3).

Scheme 5.3. Schematic representation of the surface modification of electrodes with PFS **4** followed by the attachment of crown ether groups for molecular recognition.

These remaining reactive groups were used to attach 4'-aminobenzo-18-crown-6, yielding a crown ether-bearing PFS film on the electrode surface. The disadvantage of this method is that the degree of crown ether substitution is unknown. The

electrode surfaces were analyzed by FTIR, confirming the characteristic absorptions of PFS (1165 cm^{-1} , asymmetric ring in-plane vibration of ferrocene, and 1037 cm^{-1} , the out-of-plane C–H vibration of ferrocene) and crown ether (1105 cm^{-1} , the C–H stretching of the crown ether) (Figure 5.1).

Figure 5.1. FTIR spectra of PFS 4 and 4'-aminobenzo-18-crown-6 functionalized PFS, immobilized on the gold electrode surface.

The crown ether PFS modified gold electrodes were employed as the active component in electrochemical sensors. Figure 5.2 shows the electrochemical response of gold electrodes decorated with a layer of PFS 5. The dashed line represents the CV curve measured in pure electrolyte, 100 mM LiClO_4 , revealing the typical double wave oxidation and reduction voltammogram of PFS. Upon addition of $20\text{ }\mu\text{M}$ of KClO_4 , potassium ions being suitable guest cations for 18-crown-6, a third oxidation peak emerged. Contrary to the expectation based on earlier research,^{6, 19} the formed third oxidation peak did not increase in intensity upon the successive additions of KClO_4 . Instead, the oxidation peak started to shift towards higher potentials when the total concentration of KClO_4 reached $160\text{ }\mu\text{M}$.

Figure 5.2. a) The electrochemical response of a gold electrode with a layer of PFS 5 upon addition of small amounts of KClO_4 using 100 mM LiClO_4 as electrolyte. b) Zoomed in on the region of interest.

To confirm that the electrochemical response of the sensor was due to the addition of small amounts of potassium ions, a control experiment was performed, where small amounts of LiClO_4 were added to the electrochemical setup with 100 mM KClO_4 as electrolyte. Results are shown in Figure 5.3, revealing the lack of any third oxidation peak.

Figure 5.3. The electrochemical response of a freshly prepared gold electrode with a layer of PFS 5, upon addition of small amounts of LiClO_4 to 100 mM KClO_4 electrolyte.

For the gold electrodes, which were coated with PFS **4** and subsequently reacted with 4'-aminobenzo-18-crown-6, similar sensing experiments were performed. The dashed line in Figure 5.4 represents the blank measurement in 100 mM LiClO₄ electrolyte. The electrochemical response of these electrodes is one order of magnitude higher than that of the electrodes modified with PFS **5**, indicating a response of more ferrocene units, which suggest a thicker or more dense PFS layer. Furthermore, these electrodes show a electrochemical response to the addition of KClO₄ at concentrations as low as 3 μ M. However, the response does not show a clear relation between the peak area and amount of potassium ions added, which would be desired for any quantitative ion recognition sensor.

Figure 5.4. a) The electrochemical response of a gold electrode with a layer of PFS **4**, followed by functionalization with 4'-aminobenzo-18-crown-6, upon addition of small amounts of KClO₄ using 100 mM LiClO₄ as electrolyte. b) Zoomed in on the region of interest.

5.3 Conclusion

Gold electrodes were successfully modified with crown ether bearing redox responsive organometallic poly(ferrocenylsilane) (PFS) chains and tested for the electrochemical detection of cations. Both systems, with premade crown ether-

functionalized PFS and with crown ethers bound to surface-anchored PFS layers, showed an electrochemical response to potassium ions. The first detected observation of deviations in the standard CV curve measured in LiClO_4 was at a KClO_4 concentration as low as 3 μM . A detailed understanding of the electrochemical process is needed prior to device construction.

5.4 Experimental section

Materials. Benzo-18-crown-6 (98%), 4'-aminobenzo-18-crown-6 (technical), Eaton's reagent, potassium iodide (99%), iodoethane (99%), dicyclohexano-18-crown-6 (98%), $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$, toluene- d_8 (≥ 99.6 atom% D), THF- d_8 (99.5 atom% D), CDCl_3 (99.8 atom% D), DMSO- d_6 (99.9 atom% D), $\text{LiOH} \cdot \text{H}_2\text{O}$ ($> 98\%$), Na_2HPO_4 ($> 99\%$), Na_2SO_3 ($> 98\%$), Na_2SO_4 (anhydrous, $> 99\%$), NaHCO_3 ($> 99.7\%$), LiClO_4 ($\geq 98\%$), KClO_4 ($\geq 99\%$) and NaClO_4 ($\geq 98\%$) were obtained from Aldrich and used as received. *m*-chloroperbenzoic acid (*m*-CPBA, 77%) were obtained from Aldrich and dried before use. Methanol, THF, DMF and dichloromethane were obtained from Biosolve, The Netherlands. Milli-Q water (Millipore) was used in all experiments. Glacial acetic acid was obtained from Merck, USA.

Techniques. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz instrument at 400.1 and 100.6 MHz, respectively, in CDCl_3 , DMSO- d_6 , THF- d_8 or toluene- d_8 . ^1H and ^{13}C chemical shifts were based on the solvent residual signals. GPC measurements were carried out in THF (flow rate 2.0 mL/min) at 25 °C, using microstyragel columns (bead size 10 μm) with pore sizes of 10^6 , 10^5 , 10^4 and 10^3 Å (Waters) and a dual detection system consisting of a differential refractometer (Waters model 410) and a differential viscometer (Viscotek model H502). Molar masses were determined relative to narrow polystyrene standards. FTIR spectra of the polymer powder samples were measured with a Bruker ALPHA. The polymer layers were analyzed by a Bruker Vertex 70v by using grazing angle FTIR. Cyclic voltammetry (CV) was carried out

with PFS films on gold substrates in aqueous electrolyte (0.1 M) using an Autolab PGSTAT 302N electrochemical workstation. Cyclic voltammograms were recorded between 0.0 V and +0.9 V at different scan rates, using a Ag/AgCl reference electrode and a Pt counter electrode. The sensing of different ions was performed by using the immobilized PFS films on gold as the working electrode and aqueous LiClO₄ (0.1 M) as the electrolyte solution. Successively, aqueous KClO₄ solution (0.1 M) was added to the measurement cell and mixed thoroughly before measuring the next CV curves.

4'-Acetylbenzo-18-crown-6 1. Benzo-18-crown-6 (1.48 g, 4.74 mmol), 1.1 equivalent glacial acetic acid (0.31 g, 5.21 mmol) and Eaton's reagent (4.3 mL) were mixed under argon. The mixture was stirred for 6 hours and Milli-Q water (25 mL) was added. The mixture was neutralized with NaHCO₃ and extracted three times with CH₂Cl₂ (50 mL). The CH₂Cl₂ layer was dried over Na₂SO₄, and evaporated in vacuo to yield a 1.62 g mixture of 4'-acetylbenzo-18-crown-6 (69 mol%) and benzo-18-crown-6 (31 mol%). ¹H NMR (400 MHz, CDCl₃, δ): 2.54 (s, 3H, CH₃), 3.66-3.80 + 3.88-3.98 + 4.21 (m, 20H, 18C6), 6.87 (m, 1H, Ar *m*-CH₂), 7.53 (m, 2H, Ar *o*-CH₂).

4'-Acetatobenzo-18-crown-6 2. To a solution of unpurified 4'-acetylbenzo-18-crown-6 (1.62 g, 3.27 mmol 4'-acetylbenzo-18-crown-6) in CH₂Cl₂ (100 mL), a solution of *m*-chloroperbenzoic acid (6.2 g, 35.9 mmol) in 55 mL CH₂Cl₂ was added. After the mixture was stirred for 2 days under nitrogen atmosphere, the solution was filtered over a POR3 glass filter and subsequently washed with 5% aqueous Na₂S₂O₃ (100 mL) and a saturated solution of NaHCO₃ (2 × 100 mL). Then, the organic layer was dried over Na₂SO₄, and evaporated in vacuo to yield 1.60 g of a yellow oil. ¹H NMR (400 MHz, CDCl₃, δ): 2.27 (s, 3H, CH₃), 3.58-3.79 + 3.88-3.95 + 4.10-4.18 (m, 20H, 18C6), 6.59-6.65 (m, 2H, Ar *o*-CH₂), 6.85 (m, 1H, Ar *m*-CH₂). IR: ν = 1757 (s, C=O), 1201 (s, C-O) and 1125 (s, C-O) cm⁻¹.

4'-Hydroxybenzo-18-crown-6 3. Unpurified 4'-acetatobenzo-18-crown-6 (1.46 g, 3.94 mmol) was dissolved in a mixture of CH_2Cl_2 (80 mL) and MeOH (120 mL). The mixture was purged with nitrogen for 1 h, before adding a solution of $\text{LiOH} \cdot \text{H}_2\text{O}$ (0.65 g, 15.5 mmol) in MeOH (10 mL). After stirring under nitrogen for 24 h, the mixture was neutralized with 2.0 M HCl and dried in vacuo. To the aqueous residue, Milli-Q water (10 mL) was added, followed by extraction with CH_2Cl_2 (3×50 mL). The CH_2Cl_2 layer was dried over Na_2SO_4 , and evaporated in vacuo. The product was purified by passing it over a short silica column (eluent $\text{CH}_2\text{Cl}_2 : \text{MeOH} = 95 : 5$ vol/vol). After drying, the product (0.56 g) contained 17 mol% and benzo-18-crown-6. ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 3.65-3.78 + 3.85-3.89 + 4.03-4.09 (m, 20H, 18C6), 6.32 (dd, $J = 2.5$ and 8.5 Hz, 1H, Ar *o*- CH_2), 6.41 (d, $J = 2.5$ Hz, 1H, Ar *o*- CH_2), 6.69 (d, $J = 8.5$ Hz, 1H, Ar *m*- CH_2). ATR-FTIR: 3455 (w, OH), 1216 (s, C-O) and 1126 (s, C-O) cm^{-1} .

Poly(ferrocenylsilane) 4. PFS **4** was synthesized by Pt-catalyzed ring-opening polymerization of [1](3-chloropropyl)methylsilaferrocenophane (3.0 g, 9.85 mmol) in THF, followed by halogen exchange using KI.²³ PFS **4** was isolated by precipitation in MeOH and dried under vacuum. Overall yield: 2.65 g (68%) of amber product. ^1H NMR (toluene- d_8 , δ , ppm): 0.52 (SiCH_3 , s, 3H); 1.00 (1- CH_2 , m, 2H); 1.82 (2- CH_2 , m, 2H); 2.95 (3- CH_2I , m, 2H); 4.05 + 4.10 + 4.27 + 4.29 (Cp, m, 8H). ^{13}C NMR (toluene- d_8 , δ , ppm): -2.83 (SiCH_3); 12.02 (1-C); 18.52 (2-C); 29.32 (3- CH_2I); 70.50 (Cp-Si); 71.96 + 73.95 (Cp). GPC (THF): $M_n = 1.86 \cdot 10^5$ g/mol, $M_w = 2.97 \cdot 10^5$ g/mol, $M_w/M_n = 1.60$.

Poly(ferrocenylsilane) 5. Benzo-18-crown-6 side groups were attached to **4** by reaction with the phenolate anion of 4'-hydroxybenzo-18-crown-6 at 0 °C. A solution of 4'-hydroxybenzo-18-crown-6 (300 mg, 15.0 mmol) in anhydrous THF (5 mL) was cooled under argon to 0 °C in an ice bath, and Phosphazene base P1-*t*-Bu-tris(tetramethylene) (220 mg, 0.7 mmol) was added dropwise. After stirring for 12 h, a clear green solution was formed to which a solution of **4** (200 mg, 0.5 mmol r.u.) in anhydrous THF (5 mL) was added dropwise, followed

by dropwise addition of anhydrous DMSO (1 mL). Stirring was continued at room temperature for 24 h. Polymer **5** was isolated by repeated precipitation in cold MeOH and dried under vacuum to yield the product as an amber solid. ^1H NMR (THF- d_8 , δ , ppm): 0.52 (SiCH₃, s, 3H); 1.06 (1-CH₂, m, 2H); 1.86 (2-CH₂, m, 2H); 3.25 (3-CH₂, m, 2H); 3.50-4.35 (Ferrocene + crown ether, m, 28H) 6.35-6.78 (Ar CH, m, 3H). ATR-FTIR: 1165 (s, PFS) 1105 (s, C-O, crown ether), 1037 (s, PFS) cm^{-1} .

Gold electrode functionalization with cysteamine. Gold substrates (100 nm Au on 10 nm Cr on silicon) were cleaned with piranha solution and extensively rinsed with water and ethanol. Cysteamine SAMs were prepared by immersing gold substrates in ethanol solutions containing 0.1 wt% cysteamine for 6 h. The substrates were then rinsed with ethanol, dried in a stream of N₂, and immediately used for PFS attachment.

Immobilization of PFS on gold electrodes. A solution of PFS (**4** or **5**) in THF (1 mg/mL) was deposited on the amine-functionalized gold electrodes. Another drop of PFS-I solution was added onto the surface after the THF was evaporated (~1 h). Then the substrates were left to react overnight at 50 °C in a vacuum oven. The PFS modified substrates were soaked three times in THF for 2 hours to remove physisorbed polymer chains.

Crown ether functionalization of PFS-I modified gold electrodes. The PFS-I functionalized gold electrodes were immersed in THF (3.75 mL) and the solution was purged with nitrogen for 20 min. A solution of 4'-aminobenzo-18-crown-6 (20 mg, 0.061 mmol) in DMF (1.5 mL) was added and the substrates were left to react overnight. The substrates were rinsed with DMF and THF and dried in a stream of N₂.

5.5 References

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Chapter 6

Synthesis and applications of poly(arylene ether ketone)s
bearing skeletal crown ether units

6.1 General introduction

This chapter described the synthesis of various novel sulfonated and non-sulfonated PAEKs (SPAEEKs) containing crown ether units in the main chain. Two different crown ethers, based on dibenzo-18-crown-6, were synthesized and used as monomer in a step growth polymerization to form crown ether containing PAEKs and SPAEEKs. The synthesis of the first crown ether monomer, 4,4'(5')-di(hydroxybenzo)-18-crown-6, is described in Part 1 of this chapter. The second monomer, di(fluorobenzophenone)-18-crown-6, is introduced in Part 3.

Part 1 describes the fabrication and characterization of membranes based on SPAEEKs. Diffusion dialysis revealed a reduced potassium ion diffusion in the crown ether containing SPAEEK membranes compared with the SPAEEK membranes without crown ether moieties.

In Part 2, the preparation of blend membranes containing commercial sulfonated poly(ether ether ketone) (SPEEK) and synthesized crown ether containing poly(arylene ether ketone) (CPAEK) is described. The ion transport characteristics of these membranes was determined for the monovalent ions Li^+ and K^+ and the separation of these ions by these cation exchange membranes was investigated. It was found that the use of blend membranes of CPAEK with SPEEK enhanced the K^+ over Li^+ selectivity by a factor of 4 compared with pure SPEEK membranes.

Next to membrane applications, these polymers were tested as ionic polymer composite actuators. To this extend, sulfonated PAEKs (SPAEEKs) and crown ether containing SPAEEKs were synthesized and solution casted into membranes. The membranes were coated with platinum, soaked with an ion solution and a voltage was applied to test the actuator performance. The crown ether containing SPAEEK actuators displayed improved actuation performance compared with the SPAEEK actuators without crown ether. Furthermore, the bending was dependent on the type of ion used.

This chapter will start with the three different parts, including a short summary and conclusions, followed by a common experimental section at the end of the chapter.

Chapter 6 – Part 1

Synthesis of poly(arylene ether ketone)s bearing skeletal crown ether units for cation exchange membranes

Poly(arylene ether ketone)s (PAEKs) are the most commonly known high performance materials used for ion exchange and fuel cell membranes. Described here is the design of novel sulfonated and non-sulfonated PAEKs (SPAEEKs) containing crown ether units in the main chain, which can be used in sensing applications and ion-selective membranes. To this end, 4,4'(5')-di(hydroxybenzo)-18-crown-6 is synthesized and used as monomer in a step growth polymerization to form crown ether containing PAEKs and SPAEEKs. The successful synthesis of PAEKs containing 18-crown-6 and sulfonate groups is confirmed by gel permeation chromatography, FTIR and NMR spectroscopy. Membranes are fabricated from the sulfonated polymers. Potassium ion transport properties of the SPAEEK and crown ether containing SPAEEK membranes are assessed by diffusion dialysis. Potassium ion diffusion in the crown ether containing SPAEEK membranes is almost four times lower than K^+ diffusion in the native polymer membranes, without crown ether.

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6.2.1 Introduction

Integral membrane proteins such as ion channels can gate the flow of ions in and out of cells by adopting closed and open states. Controlled by different mechanisms such as membrane potential or binding of a ligand, ion channels are of central importance for many biological functions (*e.g.*, cell-cell communications, muscle contraction) by allowing the movement of particular ionic species across the membrane.¹⁻³ In view of the central role played by ion channels in biology, synthesis and development of artificial ion channels are of great importance for creating new functional materials. A combination of the biological ion transport mechanism with polymer chemistry has opened many avenues in materials science, particularly in sensing applications and in the area of ion selective membranes.⁴⁻⁶ Crown ethers are widely used as guest molecules for ions and attract great interest in terms of mimicking the biological ion transport mechanism. These structures are able to selectively bind specific cationic species due to the ion-dipole interaction of the positively charged metal ion with the negatively polarized oxygen atoms.⁷ Besides their specific binding with cations, crown ethers can also function as ion carriers.⁸ Moreover, the stacking ability of the crown ether moieties makes them a potential candidate for the design of one-dimensional ion channels.⁹ Therefore, several interesting molecular architectures including crown ether polymers have been designed in the context of synthetic ion channels and responsive materials.¹⁰⁻¹¹ Polymers containing crown ethers are widely used in polymer chemistry and have been around for a long time.¹² The first example of such a polymer, bearing crown ethers in the main chain, was published by Feigenbaum and Michel.¹³ These authors reported a polyamide that extracted alkali cations from aqueous metal chlorides. Other polymer configurations followed soon, including end-functionalized polymers¹⁴⁻¹⁶ or polymers with pendant crown ether groups.¹⁷ Nowadays, these crown ether containing polymers are still intensively studied, due to their potential use in ion recognition,¹⁸⁻¹⁹ supramolecular assemblies²⁰⁻²³ and self-healing gels.²⁴⁻²⁷ Recent work on main chain crown ether containing

supramolecular polymers includes processing by electrospinning to form nanofibers,²¹ polymers responsive to heat, pH, potassium cations or competitive ligands^{20, 22} and interesting cases where linear supramolecular polymers constructed of AB-type monomers formed supramolecular fibrils which subsequently self-organized into cross-linked networks.²⁶ The thermo- and pH-responsive sol-gel transition of similar gels was successfully employed for the controlled release of rhodamine B.²⁴ Other gels were prepared with multifunctional supramolecular monomers,²⁵ results including self-healing gels, showing 100% recovery even under 10,000% strain in less than ten seconds.²⁷ Recently, fluorescent supramolecular polymers were prepared for sensing applications.²⁸⁻²⁹

Poly(arylene ether ketone)s (PAEKs) are the most commonly known high performance materials that have been extensively studied as actuators, and as ion exchange and fuel cell membranes.³⁰⁻³⁴ PAEKs belong to the class of aromatic polyethers³⁵ and possess outstanding thermal stability, chemical resistance, processability and mechanical properties.³⁶ To date, incorporation of various chemical moieties and post modification reactions of PAEKs have been investigated.³⁷⁻⁴¹ However, the major current challenge in ion exchange membrane development is how to improve the selective transport of a specific ion with a very high degree of specificity. To our knowledge, there are no examples of PAEKs or even of aromatic polyethers such as poly(sulfone)s or poly(ether sulfone)s with crown ether moieties incorporated in their main chain. Crown ether containing PAEKs would alter the specific ionic selectivity and are valuable for the development of ion selective membranes and electrodes.

Here we report the design of novel sulfonated copoly(arylene ether ketone)s containing crown ether moieties in the main chain. The synthesized polymers were characterized by gel permeation chromatography, NMR and FTIR spectroscopy and their thermal and film forming properties were investigated. Diffusion dialysis experiments for potassium ions were performed as a proof of concept for the use of these membranes as ion selective materials and to elucidate the influence of crown ether moieties in the PAEK main chain on ion transport.

6.2.2 Results and discussion

In the present work, we describe the direct incorporation of dibenzo-18-crown-6 units into a poly(arylene ether ketone) main chain as repeating unit. In the employed step-growth polymerization, a hydroxyaryl-containing crown ether was required. Accordingly, 4,4'(5')-di(hydroxybenzo)-18-crown-6⁴²⁻⁴³ was synthesized (Scheme 6.1). Copolymers were synthesized by polycondensation of 4,4'-difluorobenzophenone with bisphenol A (BPA) and 4,4'(5')-di(hydroxybenzo)-18-crown-6 at 175 °C in NMP (Scheme 6.2). The copolymers were designated as S(x)C(y)PAEK where x and y represent the mol percentages of SDFBP and crown ether monomers. The molar masses of the polymers were measured by GPC and the results are summarized in Table 6.1.

Scheme 6.1. Synthesis of 4,4'(5')-di(hydroxybenzo)-18-crown-6.⁴²⁻⁴³

Scheme 6.2. Polycondensation procedure for PAEKs bearing crown ether units in their main chain.

Table 6.1. Molecular characteristics of PAEK and CPAEKs

Polymer	M_n^a (g/mol)	PDI ^b -	Yield (%)	SDFBP ^c (mol%)	18C6 ^d (mol%)
PAEK	16000	1.6	88	-	-
C(25)PAEK	18000	1.8	87	-	21
C(50)PAEK	14000	2.9	88	-	43
C(75)PAEK	21000	1.8	88	-	66
S(25) PAEK	33000	2.0	91	21	-
S(25)C(75)PAEK	29000	5.9	82	26	68

^a M_n : number average molar mass by GPC, relative to polystyrene standards. ^b PDI: (M_w/M_n), polydispersity index. ^c the incorporated mol% SDFBP by ^1H NMR. ^d the incorporated mol% 18C6 by ^1H NMR.

NMR studies confirmed the chemical structure of PAEK (Figure 6.1) and CPAEK (Figure 6.2). The characteristic peak of the methyl groups present in the BPA units of PAEK is clearly visible in the ^1H NMR spectra at $\delta = 1.74$ ppm and in the ^{13}C NMR spectra at $\delta = 31.1$ ppm. Also, the carbonyl carbon of the DFBP units was present in the ^{13}C NMR spectra at $\delta = 194.3$ ppm (Figure 6.1c). Furthermore, the signal associated with the hydroxy groups of BPA is missing in the spectrum of PAEK, confirming successful polymerization.

Figure 6.1. a) Structure b) ^1H NMR spectrum and c) ^{13}C NMR spectrum of PAEK.

When 4,4'(5')-di(hydroxybenzo)-18-crown-6 was included in the step growth polymerization, signals of the incorporated crown ether became clearly visible. Peaks O and P (Figure 6.2), ^1H NMR at $\delta = 4.06 - 4.19$ ppm belong to the protons present in the oxyethylene groups of the crown ether, while peaks M and Q in the ^1H NMR spectrum originate from the phenyl rings of the crown ether units (Figure 6.2).

Figure 6.2. a) Structure b) ^1H NMR spectrum and c) ^{13}C NMR spectrum of CPAEK.

Corresponding peaks in the ^{13}C NMR spectrum are shown in Figure 6.2c. When increasing the crown ether feed ratio in the reaction mixture, the crown ether content in the polymer increased correspondingly (Table 6.1). When introducing SDFBP in the polymerization, the polymer became soluble in DMSO. In the ^1H NMR spectra, measured in $\text{DMSO}-d_6$, new peaks emerged. Most evident is the peak related to protons in between the sulfonate and carbonyl groups (Figure 6.3, peak N and Figure 6.4 labeled B). The signal of these protons is shifted downfield and can be related to the mol percentage of sulfonated monomer introduced in the reaction mixture.

Figure 6.3. a) Structure b) ^1H NMR spectrum and c) ^{13}C NMR spectrum of SPAEK.

Combining all monomers, bisphenol A, 4,4'(5')-di(hydroxybenzo)-18-crown-6, DFBP and SDFBP, the NMR spectra became complex. The molar percentages were calculated with the non-overlapping ^1H NMR signals (DMSO- d_6 , δ) 3.87 + 4.10 (16H), 8.33 (2H) and 1.66 (6H) corresponding to protons from the crown ether, the SDFBP and the bisphenol A units (Figure 6.4).

Figure 6.4. a) Structure and b) ^1H NMR spectrum S-CPAEK.

The chemical structure of the synthesized polymers was also confirmed by FTIR spectroscopy. Figure 6.5 shows the FTIR spectra of PAEK, C(75)PAEK, S(25)PAEK and S(25)C(75)PAEK. In the spectra, all polymers showed an absorbance at 1650 cm^{-1} , which is related to the carbonyl stretching of Ar-C(=O)-Ar moieties. The typical C=C aromatic stretching bands were observed at 1590 cm^{-1} and 1495 cm^{-1} . The crown ether containing polymers showed, next to the characteristic absorption bands of PAEK, also the characteristic C–O–C stretching signals of the crown ether at 1058 and 988 cm^{-1} .⁴⁴ Furthermore, the absorbance values at these frequencies increased with increasing crown ether content in the polymer. This confirms the successful incorporation of dibenzo-18-crown-6 units into the polymer.

Figure 6.5. FTIR spectra of PAEK, C(75)PAEK and sulfonated copolymers.

Also the stretching vibration absorption of phenyl ether (C=C-O) groups at 1120 cm^{-1} became stronger. In addition, absorption bands of the aromatic ether (Ar-O-Ar) linkages formed during polycondensation, around 1229 cm^{-1} , were observed for all polymers synthesized. Sodium sulfonate has asymmetric and symmetric stretching vibrations at 1080 cm^{-1} and 1030 cm^{-1} .⁴⁵ The observed band at 1030 cm^{-1} confirmed the introduction of sulfonate groups into the polymer chains.

Thermal characteristics of the synthesized polymers were determined by TGA and DSC under N_2 atmosphere. The results of thermogravimetric analysis, summarized

in Table 6.2, shows that crown ether incorporation influenced the thermal stability of the polymers.

Table 6.2. *Thermal properties of PAEKs and CPAEKs.*

Polymer	T_g^a (°C)	T_5^b (°C)	Char yield ^c (%)
PAEK	162	488	43
C(25)PAEK	144	430	42
C(50)PAEK	143	407	42
C(75)PAEK	143	390	45
S(25)PAEK	180	454	47
S(25)C(75)PAEK	158	285	31

^a Glass transition temperature. ^b Temperature corresponding to 5% weight loss. ^c Residual mass percentage after heating to 900 °C.

Thermal characteristics of the synthesized polymers were determined by TGA and DSC under N₂ atmosphere. The results of thermogravimetric analysis, summarized in Table 6.2, shows that crown ether incorporation influenced the thermal stability of the polymers. PAEK exhibits a high thermal stability and showed only 5% weight loss at 488 °C, while C(25)PAEK, C(50)PAEK, and C(75)PAEK copolymers began to decompose at 430 °C, 407 °C, and 390 °C, respectively. CPAEKs display a lower thermal stability due to the fact that the crown ether units are more sensitive to thermal degradation than the thermally stable bisphenol A moieties of PAEK.

Figure 6.6. *TGA curves of PAEK, C(75)PAEK and sulfonated copolymers.*

TGA curves of the polymers are shown in Figure 6.6. PAEK exhibited a one-stage degradation profile and the weight loss around 500-600 °C was assigned to intramolecular thermal cleavage of benzophenone units.⁴⁶⁻⁴⁷ C(75)PAEK copolymer also showed one weight loss step with a maximum at 414 °C, indicating that thermal decomposition was mainly due to crown ether degradation.⁴⁸⁻⁴⁹ S(25)PAEK copolymer displayed high thermal stability (5% weight loss at 454 °C), comparable to PAEK. A three-step degradation profile was observed for S(25)C(75)PAEK. The first weight loss at around 250 °C, typically assigned to desulfonation processes,⁵⁰ is followed by loss of crown ether units and decomposition of the polymer main chain. The char yield for PAEK and the CPAEK and sulfonated copolymers remained in the 31-47% range.

The glass transition temperatures (T_g 's) were measured by differential scanning calorimetry (DSC). As shown in Table 6.2, PAEK has a T_g of 162 °C which is in good agreement with literature values.⁵¹⁻⁵² PAEK has rigid arylene linkages that allow limited segmental motion and consequently this polymer has a relatively high T_g . However, crown ether incorporation in the polymer backbone lowered the T_g by around 20 °C for all compositions synthesized. Similar trends have been observed for crown ether containing polyamides and polyimides.⁵³ This implies that crown ether moieties enhance chain flexibility, which may be attributed to the aliphatic ether bonds present in these macrocycles. In addition, the crown ether units likely increase free volume, which also contributes to a decrease in T_g . The introduction of sulfonate groups into PAEK and C(75)PAEK increased the T_g by around 15 °C. Here, intermolecular ion-dipole interactions hinder the chain mobility.⁵⁴ No crystallization or melting peaks were observed in the DSC traces, indicating an amorphous polymer structure.

The amorphous structure of the polymers synthesized was further confirmed by X-ray diffraction measurements. In all cases broad amorphous scattering was observed and crystalline reflections were completely missing.⁵⁵⁻⁵⁶

Table 6.3. *Solubility characteristics of PAEK and CPAEKs.*

Polymer	NMP	DMF	DMAc	DMSO	THF	CHCl ₃	CH ₂ Cl ₂
PAEK	+	+	+	-	+	+	+
C(25)PAEK	+	+	+	-	+	+	+
C(50)PAEK	+	+	+	+/-	+	+	+
C(75)PAEK	+/-	+/-	+/-	+/-	-	+/-	+/-
S(25)PAEK	+	+	+	+	-	-	-
S(25)C(75)PAEK	+/-	+/-	+/-	+	-	-	-

Solubility at room temperature: + fully soluble; +/- partially soluble; - insoluble.

The solubility of the synthesized polymers in common organic solvents is summarized in Table 6.3. The solubility of the polymers was tested by dissolving 20 mg of polymer in 1.0 mL of solvent. PAEK, C(25)PAEK, and C(50)PAEK showed a high solubility in polar aprotic solvents, such as NMP, DMF and DMAc, at room temperature. These polymers also dissolved in moderately polar solvents like THF, dichloromethane and chloroform. However, both PAEK and C(25)PAEK were not soluble in DMSO at room temperature. PAEK, C(25)PAEK, and C(50)PAEK exhibited solubility in common organic solvents due to their amorphous structure. In contrast, C(75)PAEK showed partial solubility in polar aprotic solvents as well as in moderately polar solvents. Although C(75)PAEK also has an amorphous structure, its increased crown ether content apparently lowers the solubility of this polymer. The solubility change can be explained by stacking of crown ether units in the main chain.⁵⁷⁻⁵⁸ The phenyl rings in dibenzo-18-crown-6 may favor π -stacking interactions.^{57, 59} The sulfonated PAEK and CPAEK were only soluble in the aforementioned polar aprotic solvents.

Table 6.4. *S(25)PAEK and S(25)C(75)PAEK membrane properties.*

Membrane	d_{wet} (μm)	Swelling (%)	Permselectivity (%)
S(25)PAEK	50 ± 3	17 ± 1	82 ± 1
S(25)C(75)PAEK	40 ± 5	22 ± 3	77 ± 2

The fabricated membranes were characterized in terms of permselectivity and swelling. Membrane permselectivity is a measure of how well the membrane permits the transport of cationic species while restricting the passage of anionic ones. Membrane permselectivities are listed in Table 6.4. S(25)PAEK and S(25)C(75)PAEK have permselectivities of around 80%. Membranes with a sulfonation degree of 65% have permselectivities of around 90%.⁶⁰ Membranes with low fixed charge densities (low degrees of sulfonation) exhibit low permselectivities, likely due to less effective anion exclusion.⁶¹ S(25)C(75)PAEK had a slightly lower permselectivity compared with S(25)PAEK. The presence of crown ether in the polymer backbone increases the counter-ion (K^+) sorption in the membrane, which may reduce the effective fixed charge density. For this reason, the membrane is probably slightly less able to exclude co-ions (Cl^-).

Water plays a critical role in ion transport within membranes. The measured water content for a S(25)PAEK membrane was 17%. Introduction of crown ether units into the SPAEK backbone slightly increased the water content in the membrane due to the hydrophilic ether groups of the crown ether. This also contributes to a decrease in fixed charge density of the membrane.

Donnan dialysis is an ion exchange membrane process, in which a concentration gradient over the membrane is the driving force for the transport of ions from the concentrated side of the membrane to the lower concentration side.⁶² Potassium ion transport properties of S(25)PAEK and S(25)C(75)PAEK membranes were evaluated using a two compartment Donnan dialysis set up with the membrane under investigation positioned between the two compartments. Figure 6.7a shows the change in K^+ concentration of the feed and receiving side with time for S(25)PAEK and S(25)C(75)PAEK membranes. At the initial stages of the operation, K^+ diffusion in the S(25)C(75)PAEK membrane was almost four times lower than that of the native polymer without crown ether (Figure 6.7b). PVA-based poly(crown ether) showed similar effects for potassium picrate, with a two-fold decrease in permeability due to strong crown ether-cation interactions.⁶³

Figure 6.7. a) Change in K^+ concentration in the feed and receiving compartments for the membranes at 25 °C and b) K^+ flux through the membranes in time.

These results confirmed the potassium selective nature of the dibenzo-18-crown-6 in the synthesized polymer.⁶⁴ For non-porous membranes, diffusion of the ionic species in the membrane is the rate limiting step and transport of ions within the membrane is controlled by the exchange rate of ions. For the S(25)PAEK membranes, where only sulfonate groups are present and which does not contain crown ether moieties, potassium ion transport is facilitated by a vehicle mechanism from sulfonate group to sulfonate group.⁶⁵ The mobility of the ions depends on the exchange kinetics between H^+ and K^+ ions at the sulfonate group, the swelling state of the polymer matrix and the diffusional jump distance between the carrier (sulfonate) groups.⁶⁶ In addition to sulfonate-cation interactions, crown ether-cation complexation also influences the overall potassium ion transport in the S(25)C(75)PAEK membrane. In the synthesized crown ether polymers, the relative amount of crown ether in the membrane was kept higher than that of the SO_3^- groups, to be able to investigate the contribution of the crown ether moieties to cation transport. The dialysis results show that the presence of the crown ether units hinders the transport of K^+ ions by introducing additional interactions (Figure 6.8), as the crown ether is selective for K^+ . The crown ether polymer can bind a K^+

ion by sandwiching it between two crown ether units.⁶³ Moreover, dibenzo-18-crown-6 can form a 1:1 crown ether ring-to-cation complex with potassium ion.⁶⁴ Finally, SO_3^- and the crown ether can accommodate the cation together.⁶⁷ These interactions significantly affect the diffusion behavior of potassium ions in the S(25)C(75)PAEK membranes, resulting a decrease in the transport of these ions through the membrane.

Figure 6.8. Schematic illustration of potassium ion and S(25)C(75)PAEK interactions.

6.2.3 Conclusions

A series of novel crown ether containing poly(arylene ether ketone)s (CPAEK)s and sulfonated CPAEKs were successfully synthesized with reasonably high molecular weights. For this study, dihydroxy-functionalized crown ethers were employed as monomer. Structural and thermal properties of the synthesized polymers were investigated. DSC and X-ray diffraction analysis confirmed that the polymers are amorphous. Membranes were fabricated from crown ether containing sulfonated PAEKs. In Donnan dialysis, the crown ether containing SPAEK membranes formed complexes with potassium ions which resulted in a lower K^+ diffusion compared with native sulfonated PAEK polymer films.

The idea of incorporating crown ether moieties into the SPAEK backbone could potentially be used for monovalent ion separation. Moreover, this new membrane material could inspire innovations in ion selective electrodes and ion sensors.

Chapter 6 – Part 2

Monovalent cation separation with crown ether containing poly(arylene ether ketone) / SPEEK blend membranes

Blend membranes of sulfonated poly(ether ether ketone) (SPEEK) and poly(arylene ether ketone) (PAEK) derivatives containing crown ether units in the main chain (CPAEK) were prepared and characterized in terms of water swelling and ion exchange capacity (IEC). The miscibility of the polymers was verified by DSC and HR-SEM. Ion transport characteristics of the membranes were established for the monovalent ions Li^+ and K^+ and the separation of these ions by the cation exchange membranes was investigated. Diffusion experiments for aqueous KCl, LiCl and their mixtures were carried out with pure SPEEK membranes as well as with the CPAEK/SPEEK membranes. Blending significantly decreased the ion permeability due to cation-crown ether complexation and increased the hydrophobicity of the matrix. The K^+ over Li^+ selectivity of the SPEEK membrane was enhanced by blending SPEEK with CPAEK by a factor of nearly 4, indicating that the presence of a crown ether polymer changes the relative transport of the ions in the membrane.

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6.3.1 Introduction

Cation exchange membranes (CEMs) have been widely used in electrodialysis,⁶⁸⁻⁶⁹ fuel cells^{31, 70} and diffusion dialysis.⁷¹⁻⁷² CEMs are made from ionic polymers that have negatively charged moieties bound covalently to the polymer backbone. This makes CEMs selectively permeable to positively charged species, yet almost impermeable to anions. Therefore oppositely charged ions can be separated with such membranes. However, the major current challenge in ion exchange membrane development is how to improve the selective transport of a specific ion with a very high degree of specificity.

To date, most of the research on cation exchange membranes has focused on monovalent/divalent ion selectivity improvements (*e.g.*, separation of $\text{Na}^+/\text{Mg}^{2+}$). CEMs with a thin layer of a conducting polymer, such as polypyrrole or polyaniline, were developed for that purpose. The presence of a conducting polymer on the surface of cation exchange membranes decreased the permeation of divalent ions, therefore an improved monovalent over divalent ion selectivity was observed.⁷³⁻⁷⁴ In recent studies, layer-by-layer deposition of polyelectrolytes onto CEMs was employed to enhance monovalent over divalent ion selectivity.⁷⁵⁻⁷⁷

Crown ethers, widely used as host molecules, are able to selectively bind specific cationic species due to the ion-dipole interaction of the positively charged metal ion with the negatively polarized oxygen atoms.⁷ The host-guest interactions between crown ethers and various guests (*e.g.*, cations) generated interest in the development of various well-defined, crown ether containing polymers. For example, Tunca et al. and Alexandratos et al. have reviewed crown ether polymer synthesis and the functionalization of pre-formed polymers with crown ether moieties.^{12, 78} These authors showed that the choice of the polymer matrix for crown ether incorporation greatly influences the complexation ability of crown ethers; for example, it is important to use a hydrophilic polymer matrix to achieve a high degree of ion complexation.⁷⁸ Van de Water et al. synthesized a polar azathia crown ether-functionalized poly(glycidyl methacrylate) resin for membrane

applications. This hydrophilic resin exhibited selectivity towards Ag^+ ions in the presence of Cu^{2+} , Zn^{2+} and Cd^{2+} ions.⁷⁹

Owing to their high ion selectivity, liquid membranes are an interesting alternative to conventional membranes.⁸⁰ Selective receptor molecules for cationic as well as anionic, organic, or inorganic species are used as carriers in liquid membranes for selective ion transport.⁸¹ Carrier-facilitated ionic permeability can be induced by crown ethers as well as by crown ether-containing polymers.⁸²⁻⁸³ Despite the high selectivity of liquid membranes, their applications are still restricted due to their limited stability.⁸⁴

Various researchers have prepared self-standing membranes with crown ether polymers.^{63, 85-87} For instance, to a polymer consisting of alternating co-monomers of ethylene and maleic anhydride, crown ethers were attached as side groups. Simultaneous to the attachment of the crown ethers, carboxylic acid groups were formed which enable active ion transport.⁸⁵ Another example for self-standing membranes with crown ether polymers consists of a polymer that contains pendant crown ether moieties, synthesized by the reaction of poly(vinyl alcohol) (PVA) with formyl derivatives of crown ethers. This polymer was capable of forming mechanically strong films, and had different permeabilities for metal picrates compared with PVA films.⁶³ In addition, Nafion membranes impregnated with crown ethers⁸⁸⁻⁹⁰ were also investigated, but a major drawback of crown ether impregnation for these membranes was that the crown ethers leached out under the applied electric potentials.⁸⁹

Sulfonated poly(ether ether ketone) (SPEEK) has been used as cation exchange membrane material owing to its excellent chemical and mechanical stability.⁹¹⁻⁹³ Unfortunately, SPEEK membranes lack specific ion selectivity and the need for specificity has driven efforts aimed at their modification.^{30, 94} Polymer blending is a versatile and cost-effective method for creating new functional materials,⁹⁵ but obtaining homogenous blends is limited by the degree of miscibility of the polymers.^{94, 96-98} Although the use of SPEEK membranes for monovalent-divalent

ion separation has been reported, there are only few reports in the literature on the use of ion exchange membranes for the separation of two monovalent ionic species.^{30, 99}

We recently reported on the synthesis of a novel main-chain crown-ether-containing poly(arylene ether) ketone (CPAEK) and its sulfonated derivatives applicable for membrane applications.⁸⁷ In the present study, we blended PAEK and CPAEK polymers with a hydrophilic polymer, SPEEK, to prepare hydrophilic thin films. Polymer blending was performed as a method to improve the processability of the hydrophobic crown ether containing membrane and allow membrane film formation. CPAEK in which the crown ether is covalently bound to the polymer backbone is used, as simple blending of the crown ether with the polymer matrix makes the crown ether very susceptible to leaching out of the crown ether. Our aim was to tailor the monovalent ion transport properties of the SPEEK membranes by exploiting the presence of crown ethers in the polymer backbone. Membranes with different blending ratios of PAEK/SPEEK and CPAEK/SPEEK were prepared. The miscibility of these polymers was investigated by DSC and HR-SEM. Single and mixed ion transport properties of the SPEEK and CPAEK/SPEEK membranes for K^+ and Li^+ ions were assessed by diffusion dialysis.

6.3.2 Results and discussion

PAEK and CPAEK were synthesized according to a literature procedure.⁸⁷ The molecular structures of the polymers are shown in Figure 6.9. Polymer blend membranes of PAEK/SPEEK and CPAEK/SPEEK were prepared by solution-casting.

Figure 6.9. Molecular structure of a) PAEK, b) CPAEK, and c) SPEEK polymers used for the preparation of the CPAEK/SPEEK and PAEK/SPEEK blend membranes.

The thermal characteristics of the membranes were determined with DSC and TGA under a nitrogen atmosphere. A detailed understanding of the thermal properties is needed to be able to correlate these properties with the miscibility of the polymers. Thermodynamically, miscible polymer blends can be achieved when the free energy of mixing has a negative value, a condition induced by specific interactions such as hydrogen bonding, dipole-dipole interactions or acid-base interactions between the polymers in the mixture.¹⁰⁰⁻¹⁰² DSC is often employed to study the miscibility of the polymers of interest by analyzing the glass transition temperature (T_g) of the blend.¹⁰¹ A single T_g , intermediate to the T_g values of the individual components, is often taken as an evidence of polymer/polymer miscibility.¹⁰² However, the glass transition temperature is not an ideal indicator for the thermodynamic miscibility of the polymers. T_g is rather a measure of the state of dispersion.¹⁰³ Moreover, a single T_g indicates that the domain size of the homogenous polymer/polymer dispersion is at least smaller than the proposed resolution limit of DSC for domains.^{100, 103-104} Generally, a minimum detectable domain size for DSC is in the range of 10-50 nm.^{101, 104-105} Partially miscible blends exhibit two T_g values, however in such cases, T_g values differ slightly from those of the pure polymers.^{104, 106} In case of completely immiscible blends, two T_g values can be observed and they are similar to those of the individual components.¹⁰⁴

Table 6.5 lists the T_g values of the starting materials and the blend membranes prepared in this study. SPEEK exhibits a glass transition temperature around 205 °C, which is in good agreement with literature values.¹⁰⁷ The pure CPAEK and PAEK polymers show a glass transition temperature of 144 °C and 162 °C, respectively. The CPAEK/SPEEK (40/60) blend exhibits two T_g values. The lower T_g is similar to that of CPAEK. The higher T_g is decreased by 26 °C compared with the T_g of pure SPEEK. For CPAEK/SPEEK (60/40), also two T_g values are observed, although the depression of the higher T_g in this case is about 20 °C.

Table 6.5. T_g values of the pure and the blend membranes.

	$T_{g,1}$ (°C)	$T_{g,2}$ (°C)
PAEK	162	-
CPAEK	144	-
SPEEK	-	205
CPAEK/SPEEK (40/60)	145	179
CPAEK/SPEEK (60/40)	144	185
PAEK/SPEEK (40/60)	159	202

The shifts in glass transition temperature provide indication for the partial miscibility of CPAEK and SPEEK. In the CPAEK/SPEEK blend systems, the first T_g indicates the presence of a CPAEK phase. The shifts of the second, higher glass transitions towards lower temperatures indicate partial miscibility of CPAEK in the SPEEK rich phase.¹⁰⁸ The PAEK/SPEEK blend exhibits immiscible characteristics. In this case, the blend clearly demonstrates the two T_g values that correspond to the respective pure components.

Figure 6.10a shows thermogravimetric curves for SPEEK, CPAEK and PAEK. The first thermal decomposition of SPEEK around 290 °C is associated with the degradation of sulfonic acid groups and the second decomposition stage at 527 °C is related to thermal degradation of aromatic moieties.^{47, 50} PAEK exhibits a one-stage degradation with a maximum weight loss around 550 °C indicating the

degradation of aromatics.⁴⁶⁻⁴⁷ CPAEK is more sensitive to thermal degradation as compared with PAEK and shows two main degradation steps. The first weight loss step around 400-450 °C is due to the loss of crown ether units from the polymer.^{53, 87} This is followed by decomposition of thermally stable aromatic moieties.⁴⁶⁻⁴⁷

Figure 6.10. TGA curves of a) SPEEK, PAEK, and CPAEK and b) blend membranes.

Figure 6.10b shows the thermal decomposition behavior of the blend membranes. A three-stage thermal degradation profile was observed for the CPAEK/SPEEK (40/60) membrane. In contrast to the SPEEK membranes, desulfonation started at a slightly higher temperature (310 °C) and occurred over a more narrow temperature range. This was probably caused by an interaction between the crown ether units of the CPAEK and the sulfonic acid groups of SPEEK. When the CPAEK weight ratio in the blend was increased, the CPAEK/SPEEK (60/40) membrane showed no weight loss around 310 °C. Instead, the thermal degradation started at 454 °C, which is possibly associated with the loss of sulfonic acid and crown ether groups. The PAEK/SPEEK (40/60) membrane exhibited a three stage thermal degradation profile. The first weight loss around 250 °C is ascribed to the loss of residual NMP in the membrane that continues with desulfonation and finally with decomposition of the thermally stable aromatic groups.

The microstructure of the blend membranes was investigated using HR-SEM. Photographs of sample cross sections are displayed in Figure 6.11. In Figure 6.11a, images of a PAEK/SPEEK (40/60) blend are shown at different magnifications, revealing the presence of micrometer-size, droplet-shaped PAEK domains (dotted line), surrounded by SPEEK. For comparison, the morphology of pure SPEEK is displayed in Figure 6.11b. Clearly, the PAEK/SPEEK (40/60) membrane exhibited macroscopic phase separation. PAEK and SPEEK apparently lack the specific interactions necessary to form miscible blends of these polymers.^{95, 109} In contrast, CPAEK/SPEEK (40/60) and (60/40) membranes did not exhibit any signs of macroscopic phase separation. HR-SEM images of these membranes showed smooth morphologies where micrometer-size, droplet-like features were completely absent (Figure 6.11c and d).

These results are in agreement with the DSC observations and indicate that favorable intermolecular interactions exist between CPAEK and SPEEK. The SPEEK polymer in the CPAEK/SPEEK membranes was in the sulfonic acid (H^+) form. In an aqueous environment, protonation of water results in formation of hydronium ions (H_3O^+) which can form proton bridges with the six oxygen atoms present in the 18-crown-6 cavity, creating a stable complex.¹¹⁰⁻¹¹¹ In our case, the ionic groups of SPEEK and the dibenzo-18-crown-6 moieties of CPAEK can interact with H_3O^+ simultaneously, which may favor miscibility of the two polymers (Figure 6.12).

Figure 6.11. HR-SEM of a) PAEK/SPEEK, b) SPEEK, c) CPAEK/SPEEK 40/60 and d) CPAEK/SPEEK 60/40 membranes.

Figure 6.12. Schematic illustration of ion-dipole interaction between SPEEK and CPAEK polymer chains.

In CPAEK/SPEEK systems, the crown ether and the sulfonic acid groups together can accommodate H_3O^+ ions or metal cations. Such ion-dipole interactions are known to play a role in forming compatible blends.⁶⁷ Ion-dipole interactions have also been reported for poly(ethylene oxide)/ polystyrene sulfonate (PEO/PSS) blends in the presence of a lithium salt.⁹⁶ PEO is able to bind alkali metals just as crown ethers do; the lithium ion is situated in the electron-rich environment of the ethers' oxygen atoms of the PEO chain and also interacts with the ionic groups of PSS.⁹⁶ Another study showed that disulfonated poly(arylene ether sulfone) and poly(ethylene glycol) (PEG) form compatible blends due to strong ion-dipole interactions between potassium ions located between the sulfonate groups of poly(arylene ether sulfone) and PEG.¹¹²⁻¹¹³

Figure 6.13 shows the water swelling, indicated by blue squares, and the ion exchange capacity (IEC), represented by red dots, of the SPEEK and

CPAEK/SPEEK membranes as a function of the CPAEK mass ratio. In agreement with the literature, the SPEEK membranes exhibit 20 wt% swelling in water.^{31, 47} CPAEK is a hydrophobic polymer and the CPAEK film shows only 3 wt% swelling in water. Blending SPEEK with CPAEK increases the hydrophobicity of the membranes and the water content of the membranes linearly decreases with increasing CPAEK mass ratio.

Figure 6.13. Water swelling and IEC of SPEEK and SPEEK/CPAEK membranes.

The IEC of the blend membranes decreases with increasing CPAEK content. As the ionic groups (sulfonate groups) become increasingly surrounded by hydrophobic domains, relatively less sulfonate groups are available for ion exchange.⁹⁴

The Li^+ and K^+ transport properties of the SPEEK and CPAEK/SPEEK blend membranes were evaluated with a Donnan dialysis setup, with the membrane under investigation positioned between the feed compartment and the receiving compartment. The ion concentration difference between the feed compartment and the receiving compartment causes a transport of potassium (or lithium) ions from the feed side to the receiving side. Table 6.6 shows the Li^+ and K^+ fluxes at the initial stage of the operation for the single-ion and mixed-ion diffusion experiments.

The Li^+ ion has a larger hydrated radius (0.34 nm) than the K^+ ion (0.23 nm).¹¹⁴⁻¹¹⁵ The mobility of the Li^+ ions in Nafion membranes is greater than that of the K^+ ions.¹¹⁶⁻¹¹⁷ However, for single ion diffusion, SPEEK and blend membranes exhibit lower ion fluxes for Li^+ ions than for K^+ ions.

Table 6.6. *Ion fluxes of the membranes for single-ion and mixed-ion diffusion.*

Membrane	$J_{\text{Li}^+,\text{single 15min}}$ ($\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$) 10^{10}	$J_{\text{K}^+,\text{single 15min}}$ ($\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$) 10^{10}	$J_{\text{Li}^+,\text{mixed 15min}}$ ($\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$) 10^{10}	$J_{\text{K}^+,\text{mixed 15min}}$ ($\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$) 10^{10}
SPEEK	47 ± 5	113 ± 8	24 ± 4	65.8 ± 1.0
CPAEK/SPEEK (40/60)	7.8 ± 1	31 ± 13	2.7 ± 0.5	37.6 ± 0.1
CPAEK/SPEEK (60/40)	5.1 ± 0.4	7.1 ± 1	~ 0	3.9 ± 0.1

As a general trend, it is observed that blending CPAEK with SPEEK reduces the ion flux of both ions, compared with pure SPEEK membranes. This is partially caused by the dependence of the ion flux on the membrane water content, since ion mobility is closely related to the extent of water swelling of the matrix and diffusion rate of water molecules in the membrane.¹¹⁸ The water molecules facilitate the transport of cationic species (K^+ and Li^+) from one sulfonate group to the next.⁶⁵ Increasing the CPAEK content in the membrane significantly reduces the water uptake of the membranes; therefore ion fluxes decrease.

Another reason for the reduced ion flux is the cation complexation by the crown ether moieties in the CPAEK polymer backbone. In previous research, we reported that the K^+ flux for sulfonated poly(arylene ether ketone) (SPAEK) membranes is almost 4 times higher than for SPAEK membranes with crown ether moieties incorporated in the main chain.⁸⁷ Kimura et al. obtained similar results for PVA-based poly(crown ether)s, which were ascribed to the strong interactions between crown ethers and cations.⁶³ Bhattacharyya et al. investigated the mobility of alkali metal ions in dibenzo-18-crown-6-loaded Nafion-117 membranes. In these

membranes, the mobility of Li^+ and Cs^+ ions was found to be extremely low relative to their mobility in pure Nafion-117 membranes.⁸⁸ These results indicate that the cation complexing ability of crown ethers changes the mobility of these ions in the membranes.

Dibenzo-18-crown-6 can form complexes with K^+ , Li^+ and Na^+ ions, however the K^+ ion complex with dibenzo-18-crown-6 is stronger than that with Li^+ and Na^+ ions^{64, 119} therefore increasing the CPAEK content influences the K^+ ion flux more significantly than the Li^+ ion flux. For the CPAEK/SPEEK (60/40) membrane, the K^+ ion flux decreased 16 times compared to that of the pure SPEEK membranes, against only 9 times for Li^+ ions. Therefore, single ion diffusion experiments confirm the potassium selective nature of the CPAEK polymer.

Ion fluxes in mixed-ion experiments with Li^+ and K^+ ions are lower than in the single-ion transport experiments. This may be related to a competition between Li^+ and K^+ ions for the available ion exchange sites (SO_3^- groups) in the membrane.¹¹⁹⁻¹²⁰ Since ion fluxes are related to the gradient of fractional occupancy of the SO_3^- sites by a specific ion, one can speculate that in the competition between Li^+ and K^+ ions for the available ion exchange sites, the increased hydrophobicity of the membrane and the crown ether-ion complexation¹²⁰ lead to lower ion fluxes.

Figure 6.14 shows the K^+/Li^+ selectivity change in time for the single-ion and mixed-ion diffusion experiments. For single-ion diffusion, SPEEK and CPAEK/SPEEK membranes show almost similar selectivities. The SPEEK membrane exhibits the same K^+/Li^+ selectivity in the mixed-ion experiment as in the single-ion experiment.

Figure 6.14. Membrane potassium over lithium ion selectivity change in time during a) single-ion diffusion and b) mixed-ion diffusion.

In the mixed-ion experiment, the K^+/Li^+ selectivity of the CPAEK/SPEEK (40/60) membrane is 3.8 times greater than for SPEEK membranes in the initial stage of the diffusion. The CPAEK/SPEEK (60/40) membrane is only permeable to K^+ ions during the first 15 minutes of the operation. As mentioned before, Li^+ and K^+ ions compete for the available SO_3^- sites in the SPEEK membrane.⁶⁶ This applies to CPAEK/SPEEK membranes as well, but in this case, transport is also affected by complex formation between Li^+ and K^+ ions and dibenzo-18-crown-6. These interactions combined determine the selectivity of the membranes.

The blend membranes only show the higher selectivity in the initial stage of operation. This can be most probably explained by the decreasing availability of crown ether sites for complex formation with the ions during Donnan dialysis, diminishing the complexation rate due to the lack of available crown ether binding sites at longer operation times. The CPAEK/SPEEK membrane's selectivity decreases to values comparable to those of the pure SPEEK membrane from 45 minutes on. The results of the mixed-ion experiments suggest that not only the presence of crown ether moieties in the membrane matrix, but also the increased hydrophobicity of the membrane, influences the relative mobility of K^+ and Li^+ ions in the initial stage of the operation. Overall, the CPAEK/SPEEK blend

membranes have demonstrated their utility in the separation of monovalent ions. Regeneration of these mechanically robust membranes by acid treatment allows one to restore their selectivity, which implies that their arrangement in series could lead to an effective, continuous ion separation process.

6.3.3 Conclusions

This study explored the selective permeability of crown-ether-containing PAEK blend membranes for monovalent ions (K^+/Li^+). CPAEK/SPEEK and PAEK/SPEEK membranes were prepared by solution blending the two polymers of interest in different weight ratios, and their morphology and thermal characteristics were investigated. Membranes made from PAEK and SPEEK exhibited macroscopic phase separation, as was established by DSC and HR-SEM. CPAEK and SPEEK, however, were found to be partially miscible. The IEC and water content of the membranes decreased with increasing CPAEK content in the membrane. Single and mixed ion transport characteristics of SPEEK and CPAEK/SPEEK membranes for K^+ and Li^+ ions were assessed by Donnan dialysis. The presence of the hydrophobic crown ether polymer in the matrix resulted in a lower ion transport for both single and mixed ion diffusion cases. However, in the initial stage of mixed-ion diffusion experiments, CPAEK/SPEEK membranes exhibited selectivity towards K^+ ions over Li^+ ions.

Chapter 6 – Part 3

Electromechanical performance of a crown ether containing ionic polymer-metal composite actuator

The development of new ionic polymer-metal composite actuators enables breakthroughs as biomimetic robots, sensors and artificial muscles. In the present work a new ion selective polymer actuator concept is developed that could mimic natural muscle-like motion. For this purpose, sulfonated PAEK (SPAEK) and crown ether containing SPAEK were synthesized. The successful synthesis of SPAEK and dibenzophenone-18-crown-6 containing SPAEK was confirmed by gel permeation chromatography, FTIR spectroscopy and NMR spectroscopy. Membranes were fabricated by a solution-casting method. The crown ether containing SPAEK actuator displayed improved actuation performance compared with the SPAEK actuator without crown ether units. Also, the incorporation of crown ether units in the polymer backbone resulted in an ion-selective bending displacement. S(25)C(50)PAEK actuators show an increased bending displacement of 28% for Na⁺ and 20% for K⁺ ions, compared to S(25)PAEK. However, at higher frequencies, the S(25)C(50)PAEK actuators with K⁺ ions perform equal to S(25)PAEK, while for Na⁺ ions the crown ether-bearing S(25)C(50)PAEK remains superior.

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6.4.1 Introduction

A variety of polymers have been developed to imitate natural motions. In particular, polymers that exhibit deformations in response to applied voltages,¹²¹ which makes them promising candidates for use in biomedical devices,¹²² biomimetic robots,¹²³ artificial muscles¹²⁴ and biomimetic sensors¹²⁵ have raised much interest. Specifically, conducting polymers¹²⁶⁻¹²⁷ and ionic polymer-metal composites (IPMCs)¹²⁸ have been employed in the development of muscle-like actuators. IPMCs undergo a large bending displacement under a low applied voltage (1-5 V)¹²⁹⁻¹³⁰ and are currently considered as suitable candidates for mimicking biological muscle motion.

IPMCs consist of a hydrated ionic polymer membrane and metal electrodes, typically Pt or Au, plated on both surfaces of the membrane.¹²⁴⁻¹²⁵ The ionic polymer has covalently bound negative or positive charges that are neutralized by oppositely charged mobile counter ions. Under an applied voltage, for a polyanionic membrane, the solvated mobile cations move towards the negatively charged electrode. Redistribution of the cations and water molecules, as shown in Figure 6.15, results in swelling near the negative electrode, shrinkage near the positive electrode, and bending of the IPMC actuator.¹²⁴

Figure 6.15. Schematic illustration of an actuator without (left) and with (right) applied potential.

Nafion is considered a benchmark membrane for IPMC technology¹³¹⁻¹³² and many current studies focus on the improvement of the Nafion actuator performance.¹³² Nafion is a perfluoro-sulfonyl fluoride copolymer from DuPont commonly used for membranes (Figure 6.16). The polymer is significantly different than other fluorocarbon polymer, since it functionally interacts with its environment, whereas perfluorinated polymers are valued for their inertness.¹³³

Figure 6.16. Structure of Nafion, a perfluoro-sulfonyl fluoride copolymer.

As an alternative to Nafion, to further improve the performance of the IPMC actuators in terms of bending response, researchers work on designing new membrane materials with controlled levels of polar functionality. Sulfonated polymers such as poly(arylene ether sulfone)s,¹³⁴ poly(vinyl alcohol)s,¹³⁵⁻¹³⁶ poly(styrene)s,¹³⁷ poly(phenyl sulfone)s¹³⁸ and a sulfonated poly(ether ether ketone)-poly (vinylidene fluoride)¹³⁹ blend have been investigated within this context.

In muscles, membrane proteins are ion selective and gate the flow of K⁺ and Na⁺ ions in and out of cells by adopting closed and open states.^{1, 3, 140} The selective transport of these ions is of central importance for muscle contraction and expansion. The ion selectivity of crown ether-containing polymer membranes⁸⁷ could potentially yield ion selective actuation, as natural muscles do. Crown ethers can selectively bind specific cationic species due to the ion-dipole interaction of the positively charged metal ion with the negatively polarized oxygen atoms of the crown ether.⁷ Therefore, crown ethers and crown ether polymers are often employed to develop artificial ion channels.¹⁴¹⁻¹⁴²

To date, sulfonated polymers^{134, 137-138} and crown ethers¹⁴³ have been used for IPMC applications. The combination of both, by incorporation of crown ether functionality in SPAEK will alter the specific ion selectivity and has potential in terms of mimicking natural muscle-like motions.

Here, we describe the synthesis of SPAEK with crown ether moieties in the main chain and its use in the fabrication of IPMC actuators. The ion dependent actuation performance of SPAEK and crown ether containing SPAEK IPMC actuators was investigated.

6.4.2 Results and discussion

In the preceding part of this chapter, we describe the direct incorporation of 4,4'(5')-di(hydroxybenzo)-18-crown-6 into a poly(arylene ether ketone) main chain as repeating unit. The preparation of this bifunctional crown ether was a three step reaction with elaborate purifications. In this part, we describe the use of di(4-fluorobenzophenone)-18-crown-6 (DFBP18C6), which was prepared by a one-step acylation of dibenzo-18-crown-6 with 4-fluorobenzoic acid (Scheme 6.3).

Scheme 6.3. Synthesis of di(4-fluorobenzophenone)-18-crown-6 (DFBP18C6).

The synthesized di(4-fluorobenzophenone)-18-crown-6 was used in a polycondensation reaction yielding S(25)C(50)PAEK (Scheme 6.4). NMR studies confirmed the chemical structure of S(25)PAEK (Figure 6.3) and S(25)C(50)PAEK (Figure 6.17). The characteristic peak of the methyl groups present in the bisphenol A (BPA) units of PAEK is clearly visible in the ¹H NMR spectra at $\delta = 1.66$ ppm (Figure 6.17, peak denoted with A) and in the ¹³C NMR spectra at $\delta = 30.5$ ppm.

Scheme 6.4. Polycondensation procedure for sulfonated crown ether-containing poly(arylene ether ketone) $S(x)C(y)$ PAEK.

The synthesized di(4-fluorobenzophenone)-18-crown-6 was used in a polycondensation reaction yielding $S(25)C(50)$ PAEK (Scheme 6.4). NMR studies confirmed the chemical structure of $S(25)$ PAEK (Figure 6.3) and $S(25)C(50)$ PAEK (Figure 6.17). The characteristic peak of the methyl groups present in the bisphenol A (BPA) units of PAEK is clearly visible in the ^1H NMR spectra at $\delta = 1.66$ ppm (Figure 6.17, peak denoted with A) and in the ^{13}C NMR spectra at $\delta = 30.5$ ppm. Also, the carbonyl carbon of the DFBP units is present in the ^{13}C NMR spectra at $\delta = 193.1$ ppm (Figure 6.17c). Furthermore, the signal associated with the hydroxy groups of BPA is absent in the spectrum of PAEK, confirming successful polymerization. Most evident for the introduction of SDFBP is the peak related to protons in between the sulfonate and carbonyl groups at 8.21 ppm (Figure 6.17b peak B and Figure 6.3, peak N). The signal of these protons is shifted downfield and this can be related to the molar percentage of sulfonated monomer introduced in the reaction mixture.

Figure 6.17. a) Structure, b) ^1H NMR spectrum and c) ^{13}C NMR spectrum of S(25)C(50)PAEK recorded in $\text{DMSO}-d_6$.

When di(4-fluorobenzophenone)-18-crown-6 is included in the step growth polymerization, the signals of the incorporated crown ether become clearly visible. The ^1H NMR peaks at $\delta = 3.9 + 4.2$ ppm, C in Figure 6.17 represent the protons present in the oxyethylene groups of the crown ether. Corresponding peaks in the ^{13}C NMR spectrum are shown in Figure 6.2b.

The molar percentages are calculated from the non-overlapping ^1H NMR signals ($\text{DMSO}-d_6$, δ) 3.9 + 4.2 (16H), 8.21 (2H) and 1.66 (6H) corresponding to protons from the crown ether, the SDFBP and the bisphenol A units, respectively (Figure 6.17, Table 6.7).

S(25)PAEK and S(25)C(50)PAEK possess molar masses (M_n) of 33 and 19 g/mol respectively, sufficient for creating entanglements, necessary for preparing membranes of high mechanical stability. The polydispersity index of S(25)PAEK measured by GPC ($M_w/M_n=2.0$) is typical for polymers prepared by polycondensation. However S(25)C(50)PAEK has a relatively high polydispersity index ($M_w/M_n=4.0$). This high PDI index can be partially related to the GPC measurement, in which LiBr is used in the eluent. This polymer features both crown ether units and sulfonate pendant groups, which likely interact with Li^+ and may influence the interactions with the stationary phase of the GPC column.⁸⁷

Table 6.7. *Polymer characteristics of S(25)PAEK and S(25)C(50)PAEK.*

Polymer	M_n^a (kg/mol)	PDI ^b -	Yield (%)	SDFBP ^c (%)	18C6 ^d (%)
S(25)PAEK	33	2.0	91	21	-
S(25)C(50)PAEK	19	4.0	88	25	43

^a Mn: number average molar mass by GPC, relative to polystyrene standards.

^b PDI: (Mw/Mn), polydispersity index. ^c The incorporated mol% SDFBP as determined by

¹H NMR. ^d The incorporated mol% 18C6 as determined by ¹H NMR.

FTIR spectroscopy was performed to confirm the chemical structure of the synthesized polymers. Figure 6.18a shows the FTIR spectra of S(25)PAEK and S(25)C(50)PAEK. The absorbance at 1650 cm⁻¹ indicates the carbonyl stretching of Ar-C(=O)-Ar moieties while the absorbance bands at 1590 cm⁻¹ and 1497 cm⁻¹ are due to C=C stretching of aromatics. S(25)PAEK and S(25)C(50)PAEK exhibit an absorbance at 1236 cm⁻¹ attributed to the formation of (Ar-O-Ar) linkages during polycondensation. The characteristic asymmetric and symmetric stretching vibrations of sodium sulfonate are visible at 1080 cm⁻¹ and 1013 cm⁻¹.⁴⁵ Furthermore, S(25)C(50)PAEK shows the C-O-C stretching signals of the crown ether at 1128 cm⁻¹.¹⁴⁴⁻¹⁴⁵ This absorbance band confirms the presence of crown ether moieties in the polymer chain.

The thermal properties of the synthesized polymers were characterized by TGA and DSC under N₂ atmosphere. As shown in Figure 6.18b, S(25)PAEK exhibits a two-stage degradation profile. The first weight loss between 200 °C and 250 °C is due to desulfonation of the polymer chains.⁵⁰ The second weight loss step at 490 °C indicates decomposition of the aromatic units.⁴⁶⁻⁴⁷ S(25)C(50)PAEK undergoes the first weight loss around 180 °C, which can be ascribed to the loss of residual NMP. The thermal degradation of S(25)C(50)PAEK starts around 400 °C, probably linked to the combined desulfonation and loss of crown ether groups, and continues with the decomposition of the thermally stable aromatic groups of S(25)CF(50)PAEK.⁸⁷

Figure 6.18. a) FTIR spectra and b) TGA curves of S(25)PAEK and S(25)C(50)PAEK copolymers.

Table 6.8. Thermal properties of S(25)PAEK and S(25)C(50)PAEK copolymers.

Polymer	T_g^a (°C)	T_5^b (°C)	Char yield ^c (%)
S(25)PAEK	180	454	47
S(25)C(50)PAEK	167	404	45

^a Glass transition temperature. ^b Temperature corresponding to 5% weight loss. ^c Residual mass percentage after heating to 900 °C.

As shown in Table 6.8, crown ether incorporation influences the thermal stability of the polymer. S(25)PAEK displays high thermal stability with a weight loss of only 5% at 454 °C. Crown ether moieties on the other hand are relatively sensitive to thermal degradation.⁸⁷ Therefore, S(25)C(50)PAEK displays a lower thermal stability, with 5% weight loss at 404 °C. The char yields for S(25)PAEK and the S(25)C(50)PAEK are 47% and 45%, respectively.

DSC was employed in order to study the glass transition temperature (T_g) of S(25)PAEK and S(25)C(50)PAEK. S(25)PAEK shows a T_g of 180 °C, which is in good agreement with literature values.¹⁴⁶⁻¹⁴⁷ S(25)C(50)PAEK has a T_g of 167 °C, with crown ether units lowering the polymers T_g by around 13 °C compared with S(25)PAEK. This decrease in T_g can be attributed to the enhanced chain flexibility due to the aliphatic ether bonds present in these macrocycles. In addition, the presence of the crown ether units increases the free volume of the polymer, which

also contributes to a decrease in T_g . Previously, we observed similar behavior for crown ether-bearing SPAEK, synthesized with using the monomer 4,4'(5')-di(hydroxybenzo)-18-crown-6.⁸⁷ Moreover, T_g decreases have also been observed for polyamides and polyimides after incorporation of crown ether units.⁵³ Table 6.9 summarizes the membrane thickness, water swelling, and ion exchange capacity (IEC) of the S(25)PAEK and S(25)C(50)PAEK membranes. Water content is an important parameter affecting ion transport in membranes, as well as the actuation performance of IPMCs.¹³⁰ The mobile cations move through the water-swollen polymer and water facilitates cation transport from sulfonate group to sulfonate group.^{65, 148} Therefore, the mobility of the ions depends on the swelling degree of the matrix.⁶⁵ The water swelling of S(25)PAEK and S(25)C(50)PAEK membranes is 17% and 19%, respectively, which is comparable to values reported for Nafion membranes, which are in the range of 16% to 24%.^{121, 129-130, 134, 149} The S(25)C(50)PAEK membrane seems to exhibit slightly higher water swelling compared with the S(25)PAEK membrane. This can be due to the hydrophilic ether groups of the crown ether.¹⁵⁰

Table 6.9. *S(25)PAEK and S(25)C(50)PAEK membrane properties.*

Membrane	d_{wet}^a (μm)	Swelling (%)	IEC (mol/kg)
S(25)PAEK	50 ± 5	17 ± 1	0.71 ± 0.01
S(25)C(50)PAEK	45 ± 3	19 ± 2	0.86 ± 0.01

^a Thickness of the wet membrane.

The performance of IPMC actuators is strongly influenced by the ion exchange capacity (IEC). The IEC expresses the amount of available fixed (ionic) sites for interaction with the mobile cations. Therefore IPMCs with high IEC values have better actuation performance.¹³⁸ The S(25)PAEK and S(25)C(50)PAEK membranes have an IEC of 0.71 mol/kg and 0.86 mol/kg, respectively. Incorporation of crown ether units in the SPAEK backbone increases the IEC due to the ion-dipole interactions between the Na^+ and K^+ ions in the membrane and the

negatively polarized oxygen atoms of dibenzo-18-crown-6 (DB18C6).¹⁵¹ This adds up to the amount of sulfonate moieties present in the polymer and thus contributes to the observed IEC.

Figure 6.19 shows the surface and morphology of the S(25)PAEK IPMC actuator; the presence of a densely deposited Pt layer on the S(25)PAEK membrane is clearly visible. Surfaces and cross sections of the corresponding crown ether containing polymer membranes were very similar.

Figure 6.19. HR-SEM images of a) a S(25)PAEK membrane cross section without Pt coating, and b) a S(25)PAEK IPMC actuator cross section, and c) the surface of the actuator.

The bending performance of IPMCs is strongly dependent on the electrode properties.¹⁵² The Pt coating is important for eliminating large voltage drops away from the contact electrode by decreasing the surface resistance of IPMCs.¹⁵³ A lower surface resistance enhances the conductivity through the membrane,

resulting in an improved actuation performance.¹⁵³⁻¹⁵⁴ Repetitive reduction of the Pt layer during application of the electrode increases the hardness of the electrode and ensures a defect-free electrode layer.¹⁵⁴ An electrode layer with cracks on the surface has high electrical resistance and allows water evaporation, resulting in lower actuation performance.¹⁵⁴⁻¹⁵⁵ Consequently, the actuator performance is sensitive to the electrode layer properties and thickness.¹⁵²

The SEM analysis shows that the Pt particles are homogeneously distributed over the membrane surface with a layer thickness of around 120 nm. Typical Pt layer thicknesses for IPCMs range between 1 and 20 μm . Interestingly, increased electrode layer thicknesses lead to enhanced bending performances.^{138, 149, 155} Despite our rather thin electrodes, the current was still uniformly distributed through the IPMC, albeit at a lower bending performance. Vargantwar et al. studied the effect of the Pt layer thickness on the actuation efficiency. The Pt electrode layer in their study was extremely thin after a single coating cycle, although the actual thickness is not specified in the paper. However, it allowed an uninterrupted current flow to obtain actuation.¹⁵² Another example is a microvalve system based on a Nafion IPMC actuator coated with a 177 nm thin Pt electrode layer. In spite of the thinness of the layer, the actuator performed effectively.¹⁵⁶

The electromechanical bending of the membrane cantilevers was quantified by measuring the tip displacement with respect to time. Figure 6.20 shows the responses of the K^+ saturated S(25)PAEK and S(25)C(50)PAEK actuators to a sinusoidal voltage applied at a frequency of 10 Hz. A similar bending response was also observed for the actuators in their Na^+ form. This bending was repeatedly observed and is due to the migration of hydrated cations (K^+ or Na^+ ions) and free water molecules under the sinusoidal voltage applied. The cations and water molecules migrate through the membrane, resulting in an asymmetric swelling of the IPMC matrix.¹⁵⁷⁻¹⁵⁸ The cathode side expands due to the accumulation of hydrated cations and free water molecules, whereas the anode side contracts, producing a bending towards the anode side (Figure 6.21).^{155, 159}

Figure 6.20. The displacement of a) *S(25)PAEK* and b) *S(25)C(50)PAEK* actuators under a 1.5 V sinusoidal voltage at 10 Hz.

As our focus was to develop a fast ion-selective actuator, the bending performance of the *S(25)PAEK* and *S(25)C(50)PAEK* IPMC actuators for both K^+ and Na^+ ions was compared at 1.5 V at frequencies of 10 Hz, 15 Hz and 20 Hz. An improved actuation performance of *S(25)C(50)PAEK* compared with *S(25)PAEK* was observed. Figure 6.22c shows an increase of 127 nm in the maximum displacement for a Na^+ saturated *S(25)C(50)PAEK* actuator at a voltage frequency of 10 Hz, compared with *S(25)PAEK*. For K^+ saturated actuators the difference was 88 nm at 10 Hz, but this decreased significantly at higher frequencies.

Figure 6.21. Schematic displacement (*d*) of an IPCM actuator. The swelling of the cathode side, due to the accumulation of cations and free water molecules, results in a bending towards the anode side of the membrane.

Figure 6.22. Frequency dependent displacement of S(25)PAEK and S(25)C(50)PAEK actuators saturated with a) Na⁺ and b) K⁺ ions. c) Δd is the maximum displacement difference between S(25)C(50)PAEK and S(25)PAEK actuators saturated with Na⁺ and K⁺ ions.

Figure 6.22 a and b show that the maximum tip displacement of Na⁺ saturated and K⁺ saturated actuators decreases with increasing frequency from 10 Hz to 20 Hz. This is due to the voltage polarity change becoming faster than the migration of K⁺ and Na⁺ ions and water molecules in the IPMC actuator, leading to less bending.¹³⁸ Slightly larger displacements were observed for Na⁺ saturated actuators compared to their K⁺ saturated counterparts. This could be explained by the larger hydrated radius of Na⁺ ions,¹¹⁴ facilitating the migration of more water molecules, resulting in a larger swelling and thereby displacement of the actuator. Guzman et al. formulated a model for the bending deformation of a Nafion IPMC actuator and

compared the bending performance of the actuator for five different types of cations. In agreement with our result, their computational and experimental results showed that the actuator saturated with Na^+ ions displayed larger bending deformations compared with the one saturated with K^+ ions.¹⁶⁰

Figure 23c shows that the improvement of crown ether incorporation diminishes in the case of the K^+ saturated actuators at higher frequencies. As there is not sufficient time for the K^+ ions to dissociate from the crown ether moieties (Figure 6.23), consequently, only K^+ ions interacting with the sulfonate groups (SO_3^-) contribute to the bending response at a frequency of 20 Hz. Dibenzo-18-crown-6 binds selectively to K^+ ions and complexes more strongly with K^+ ions compared with Na^+ ions.^{64, 151, 161} Therefore the Na^+ ions can more easily dissociate from the crown ethers under an applied potential.

Figure 6.23. Schematic illustration of S(25)C(50)PAEK IPMC actuator; a) sulfonate-cation interaction, b) 2:1 crown ether-cation complexation, c) 1:1 crown ether-cation complexation, and d) accommodation of a cation between SO_3^- group and crown ether.

The various cation-crown ether interactions, shown in Figure 6.23, increase the concentration of cations in the crown ether containing SPAEK membrane relative to that in the SPAEK membrane without crown ethers, as reflected in the higher IEC values. Moreover, also the water swelling slightly increases after incorporation of crown ether. These combined effects of crown ether incorporation improved the bending performance of the IPMC actuators.

The bending performance of the S(25)C(50)PAEK actuator is compared with previously reported results. The displacement was normalized for different-sized IPMCs and the strain was calculated according to a formula proposed in literature.^{138, 162} The maximum strain values for the Na⁺ and K⁺ forms of the S(25)C(50)PAEK actuator at a frequency of 10 Hz are $0.53 \pm 0.03 \cdot 10^{-6}$ and $0.47 \pm 0.01 \cdot 10^{-6}$, respectively. This is almost 9 times lower than the reported value for the Li⁺ form of a sulfonated poly(ether ether ketone) (SPEEK) IPMC actuator under 1.5 V at a frequency of 7 Hz.³² However, it is known that Li⁺ enhances the bending performance of IPMC actuators compared with Na⁺ and K⁺.¹⁶⁰ Moreover, the electrode thickness, which for the Li⁺-SPEEK case was about 80 times thicker, has a significant influence on the maximum tip displacement.¹⁵²

Although the bending performance of the S(25)C(50)PAEK actuator has to be improved further to be competitive with other IPMC actuators based on sulfonated polymers, crown ether incorporation increased the bending displacement by 28% for the Na⁺ ion (20% for K⁺) containing S(25)C(50)PAEK actuator relative to the native S(25)PAEK actuator. Moreover, the S(25)C(50)PAEK actuator exhibited an ion selective actuation performance, which was not observed for other sulfonated materials lacking crown ethers. Therefore, incorporation of crown ether moieties into the sulfonated polymer backbone constitutes an important contribution to the development of ion selective biomimetic actuators. While the enhanced performance of the crown ether containing S(25)C(50)PAEK, compared with S(25)PAEK, was retained at higher frequencies for Na⁺ ions, the enhanced performance diminished for K⁺ ions at frequencies exceeding 20 Hz. Moreover, the

performance of this actuator can potentially be tuned further by varying the degree and type of crown ether incorporation, the sulfonation degree of the polymer, and the thickness of the membrane and the electrode layers.

6.4.3 Conclusions

Sulfonated PAEK (SPAEEK) and crown ether containing SPAEEK were synthesized with molecular weights suitable for membrane preparation. Structural and thermal properties of the synthesized polymers were characterized using NMR and FTIR spectroscopy, TGA, and DSC. IPMC actuators were fabricated by electroless chemical deposition of a Pt layer on both sides of the membranes, resulting in electrode layers with thicknesses of around 120 nm. Actuation experiments demonstrated cation specific responses and bending degrees of the IPMC actuators. For both actuator types, with (S(25)C(50)PAEK) and without crown ethers (S(25)PAEK), when containing Na^+ ions, the actuators showed larger bending displacements than with K^+ ions. The incorporation of crown ether units in the polymer backbone resulted in an improved and ion-selective bending displacement. S(25)C(50)PAEK actuators showed an increased bending displacement of 28% for Na^+ and 20% for K^+ ions, compared with S(25)PAEK. However, at higher frequencies, the S(25)C(50)PAEK actuators with K^+ ions performed equal to S(25)PAEK, while for Na^+ ions the S(25)C(50)PAEK remained superior.

6.5 *Experimental section*

Materials. Dibenzo-18-crown-6 (98%), Eaton's reagent, 4,4'-difluorobenzophenone (DFBP, 99%), bisphenol A (BPA, $\geq 99\%$), 1-methyl-2-pyrrolidinone (NMP, anhydrous, 99.5%), CDCl_3 (99.8 atom% D), 4-fluorobenzoic acid (98%), tetraammineplatinum chloride hydrate ($[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2 \cdot x\text{H}_2\text{O}$, 98%), sodium borohydride (NaBH_4 , $\geq 99\%$), ammonium hydroxide (NH_4OH , 28.0-30.0%), hydrazine monohydrate ($\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, 98%), hydroxylammonium chloride ($\text{NH}_2\text{OH} \cdot \text{HCl}$, 99%), DMSO-d_6 (99.9 atom% D), NaOH ($> 98\%$), Na_2HPO_4 ($> 99\%$), Na_2SO_3 ($> 98\%$), Na_2SO_4 (anhydrous, $> 99\%$), NaHCO_3 ($> 99.7\%$) LiCl (99%), KCl (99%) and NaCl ($> 99\%$) were obtained from Aldrich and used as received. K_2CO_3 (99.9%) and *m*-chloroperbenzoic acid (*m*-CPBA, 77%) were obtained from Aldrich and dried before use. Methanol, DMSO, THF and dichloromethane were obtained from Biosolve, The Netherlands. Sulfonated poly(ether ether ketone) (SPEEK) with a sulfonation degree of 40% (SD 40) was obtained from FumaTech GmbH. Acetone, hydrochloric acid (37%) and DMF (extra dry, 99.8%) were purchased from Acros Organics, Belgium. Glacial acetic acid and Ethyl acetate (99.5%) were obtained from Merck, USA. Milli-Q water (Millipore) was used in all experiments.

Techniques. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz instrument at 400.1 and 100.6 MHz, respectively, in CDCl_3 or DMSO-d_6 . ^1H and ^{13}C chemical shifts were based on the solvent residual signals. Peak assignments were based on ^1H - ^{13}C correlated 2D NMR (HSQC) spectra. FTIR spectra were measured with a Bruker ALPHA. Gel permeation chromatography (GPC) measurements were performed using a Shimadzu GPC LC-20AD equipped with a Shodex LF-801 column and a refractive index detector, using NMP containing 0.5 mM LiBr as the eluent. GPC measurements for sulfonated polymers were carried out in NMP containing 5.0 mM LiBr, using PSS GRAM analytical 30Å and 1000Å GPC columns and a dual detection system consisting of a differential refractometer (Waters model 410) and a differential viscometer

(Viscotek model H502). Molar masses were determined relative to narrow polystyrene standards. All sample solutions were prepared at a concentration of $1 \text{ mg}\cdot\text{mL}^{-1}$ and filtered through a $0.45 \text{ }\mu\text{m}$ PTFE filter prior to a GPC run. Thermal gravimetric analysis (TGA) measurements were performed on a Perkin Elmer TGA 4000 under N_2 atmosphere at a linear heating rate $20 \text{ }^\circ\text{C min}^{-1}$. Samples (10 mg) were heated over a $30\text{--}900 \text{ }^\circ\text{C}$ temperature range. Differential scanning calorimetry (DSC) measurements were performed on a Perkin Elmer DSC 8000. Each sample (10 mg) was subsequently heated and cooled at a rate of $20 \text{ }^\circ\text{C min}^{-1}$ between $30 \text{ }^\circ\text{C}$ and $220 \text{ }^\circ\text{C}$ under N_2 atmosphere. This cycle was repeated four times. Glass transition temperatures (T_g 's) were determined from the second heating cycle. The microstructure of the membranes and the morphology of the IPMC actuator were analyzed with high-resolution scanning electron microscopy (HR-SEM) (Zeiss Merlin, GeminiSEM, Oberkochen, Germany). Sample cross sections were prepared by freeze fracturing the films in liquid nitrogen. After drying under vacuum, the membranes samples were coated with gold. X-ray diffraction measurements were performed using an XRD D2 Phaser Bruker instrument employing $\text{Cu K}\alpha$ radiation. The generator was set to 30 kV and 10 mA . Data was collected in the 2θ range of $10 - 40^\circ$ with an interval of 0.02° . The potassium concentration during the diffusion experiments was measured by BWB-XP flame photometer.

4,4'(5')-Di(acetylbenzo)-18-crown-6.⁴²⁻⁴³ Dibenzo-18-crown-6 (20.0 g, 55.5 mmol), 1.5 equivalent glacial acetic acid (10.0 g, 166.5 mmol) and Eaton's reagent (145 mL) were mixed under argon. The mixture was heated to $50 \text{ }^\circ\text{C}$ under argon and stirred overnight. About 250 g of ice was added to the cherry red mixture. The solid was filtered with a POR 3 glass filter and dissolved in 500 mL of CH_2Cl_2 . The organic layer was washed with 5% aqueous NaOH solution ($3 \times 150 \text{ mL}$) and brine (150 mL). The CH_2Cl_2 layer was dried over Na_2SO_4 , and evaporated in vacuo to yield 24.71 g (99%) of product as a light yellow solid with mp $192 \text{ }^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3 , δ): 2.55 (s, 6H, CH_3), 4.01-4.07 + 4.22-4.24 (m, 16H, 18C6), 6.86 (d, $J = 8.5 \text{ Hz}$, 2H, Ar *m*-CH), 7.49-7.58 (m, 4H, 156

Ar *o*-CH). ^{13}C NMR (100 MHz, CDCl_3 , δ): 26.26 (CH_3), 68.29, 69.48 (18C6), 111.02 (Ar C), 123.40 (Ar C), 130.45 (Ar C), 148.50 (Ar C-O), 152.82 (Ar C-O), 196.90 (C=O); ATR-FTIR: 1666 (s, C=O), 1266 (s, C-O) and 1129 (s, C-O) cm^{-1} .

4,4'(5')-Di(acetatobenzo)-18-crown-6.⁴²⁻⁴³ To a solution of 4,4'(5')-di(acetylbenzo)-18-crown-6 (24.64 g, 55.4 mmol) in CH_2Cl_2 (1.5 L), dried *m*-chloroperbenzoic acid (47.35 g, 274.4 mmol) and Na_2HPO_4 (20.7 g, 145.8 mmol) were added. After the mixture was stirred for 2 days under argon atmosphere, the solution was concentrated in vacuo and the organic layer was subsequently washed with 5% aqueous Na_2SO_3 (500 mL), a saturated solution of NaHCO_3 (3 x 500 mL) and brine (300 mL). Then, the organic layer was dried over Na_2SO_4 , and evaporated in vacuo to yield 23.16 g of product (86%) with mp 112 °C. ^1H NMR (400 MHz, CDCl_3 , δ): 2.25 (s, 6H, CH_3), 3.96-4.06 + 4.10-4.20 (m, 16H, 18C6), 6.60 (m, 4H, Ar *o*-CH), 6.81 (m, 2H, Ar *m*-CH). ^{13}C NMR (100 MHz, CDCl_3 , δ): 21.18 (CH_3), 68.70-69.91 (18C6), 107.36 (Ar C), 113.31 (Ar C), 113.42 (Ar C), 144.65 (Ar C-O), 146.47 (Ar C-O), 149.11 (Ar C-O), 169.83 (C=O); ATR-FTIR: 1747 (s, C=O), 1202 (s, C-O) and 1123 (s, C-O) cm^{-1} .

4,4'(5')-Di(hydroxybenzo)-18-crown-6.⁴²⁻⁴³ 4,4'(5')-Di(acetatobenzo)-18-crown-6 (18.9 g, 39.7 mmol) was dissolved in a mixture of CH_2Cl_2 (725 mL) and MeOH (900 mL). The mixture was purged with argon for 1 h, before adding an argon-purged solution of NaOH (6.1 g, 154 mmol) in MeOH (100 mL). The mixture was neutralized with concentrated HCl after stirring under argon for 24 h and dried in vacuo. The crude product was dissolved in MeOH (200 mL) and CH_2Cl_2 (800 mL) was added. Solids were filtered off and the filtrate was dried in vacuo. The product was redissolved in MeOH (100 mL) and crystallized by adding Milli-Q water (750 mL), yielding 12.8 g of pure product (82%), mp 212 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 3.74-3.87 + 3.91-4.04 (m, 16H, 18C6), 6.24 (dd, $J = 2.5$ and 8.5 Hz, 2H, Ar *o*-CH), 6.39 (d, $J = 2.5$ Hz, 2H, Ar *o*-CH), 6.72 (d, $J = 8.5$ Hz, 2H, Ar *m*-CH), 8.97 (s, 2H, OH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ): 67.5-69.4 (18C6), 101.1 (Ar *o*-C), 105.76 (Ar *o*-C), 114.15 (Ar *m*-C), 140.87 (Ar

C-O), 148.94 (Ar C-O), 151.80 (C-OH); ATR-FTIR: 3583 (w, OH), 1219 (s, C-O) and 1123 (s, C-O) cm^{-1} .

Poly (arylene ether ketone)s (PAEKs). A typical polycondensation was conducted as follows: A mixture of BPA (component A, 2.28 g, 10 mmol), DFBP (component B, 2.18 g, 10 mmol), and K_2CO_3 (1.57 g, 15 mmol) was dissolved in dry NMP (16 mL) and toluene (8 mL) in a three necked round-bottomed flask equipped with a magnetic stirring bar, Dean-Stark trap and thermometer. The content was heated to 150 °C for 4 h while removing water by azeotropic distillation. Heating was then continued at 175 °C for 20 h. The viscous solution was diluted with NMP and the polymer was precipitated in a 10-fold excess of cold ethanol. The solid was filtered off and dried *in vacuo* at 60 °C. For the CPAEKs (featuring crown ether units), part of the BPA was substituted by 4,4'(5')-di(hydroxybenzo)-18-crown-6, or part of the DFBP was substituted by DFBP18C6. For the SPAEKs (featuring sulfonate units), 25 mol% of the DFBP was substituted by SDFBP. The copolymers were designated as S(x)C(y)PAEK where *x* and *y* represent the mol percentages of SDFBP and crown ether monomers.

Synthesis of di(4-fluorobenzophenone)-18-crown-6. Dibenzo-18-crown-6 (19.97 g, 55.4 mmol), 1.01 equivalent 4-fluorobenzoic acid (15.65 g, 111.8 mmol) and Eaton's reagent (102.7 mL) were mixed under argon and stirred for 50 hours. Approximately 250 g of water and ice were added to the mixture. The mixture turned green and the solid was filtered with a POR3 glass filter and dissolved in 250 mL of CH_2Cl_2 . The organic layer was neutralized with a concentrated NaHCO_3 solution and evaporated *in vacuo* to yield the crude product as a light orange solid. Recrystallization from boiling ethyl acetate yielded di(4-fluorobenzophenone)-18-crown-6 (DFBP18C6) with a yield of 9.7 g (29.0%) of pure product with a melting point of 189 °C. ^1H NMR (CDCl_3 , δ , ppm): 4.04 + 4.23 (18C6, m, 16H); 6.86 (Ar *o*-CH, d, J = 8.3 Hz, 2H); 7.14 (F-Ar *o*-CH, m, 4H); 7.32 (Ar *m*-CH, dd, J = 8.3 Hz; J = 1.9 Hz, 2H); 7.41 (Ar *o*-CH, m, J = 1.9 Hz, 2H); 7.77 (F-Ar *m*-CH, m, 4H). ^{13}C NMR (CDCl_3 , δ , ppm): 68.60, 69.69 (18C6); 110.93 + 110.99 (Ar

o-C); 113.44 (Ar *o*-C); 115.25 + 115.47 (F-Ar *o*-C); 125.31 + 125.43 (Ar *m*-C); 130.10 + 130.17 (Ar C-C=O); 132.28 + 132.37 (F-Ar *m*-C); 134.47 + 134.50 (F-Ar C-C=O); 148.48 (Ar-crown C); 152.64 + 152.71 (Ar-crown C); 163.83 + 166.34 (C-F); 194.18 (C=O). ATR-FTIR: 1740 and 1638 (C=O); 1245 and 1129 (C-O).

Sulfonated 4,4'-difluorobenzophenone.⁴⁵ 4,4'-difluorobenzophenone (30 g) was dissolved in 65% fuming sulfuric acid (60 mL) in a 100 mL, three necked flask equipped with a stirrer bar and a nitrogen inlet/outlet. The solution was heated to 150 °C for 6 hours to produce a homogeneous solution. Then it was cooled to room temperature, and poured into 450 mL of ice-water. Next, 180.0 g of NaCl was added which produced a white solid. This was filtered and re-dissolved in 300 mL of Milli-Q water. The solution was neutralized with 2.0 M NaOH and 110.0 g NaCl was added to salt out the sodium form sulfonated monomer. The crude product was recrystallized from a 3:1 mixture of isopropanol and Milli-Q water (3/1 in volume). The product was obtained as white crystals with a yield of 87%.

Membrane fabrication. 20 wt% solutions of S(25)PAEK and S(25)C(75)PAEK were prepared in NMP at 60 °C. For the blend membranes a 20 wt% polymer solution was prepared with the desired ratio of CPAEK and SPEEK (SD 40) or PAEK and SPEEK (SD 40) in NMP. The membranes were defined as CPAEK/SPEEK (x/y) and PAEK/SPEEK (x/y), where x and y represent the weight percentages of the different polymers. The viscous solutions were cast on a glass plate with a 0.5 mm casting knife. After casting, the solvent was evaporated under N₂ atmosphere for 5 days at room temperature, followed by 5 days at 60 °C and 2 days at 110 °C under vacuum (9 mbar). Next, the membranes were peeled off from glass plate after immersion into water and then transferred into 1.0 M HCl to convert the Na-SPAEEK into H-SPAEEK. Afterwards, the membranes were rinsed several times with Milli-Q water.

Water swelling. The fabricated membranes were immersed in Milli-Q water for 24 hours to measure the wet weight of the membranes. Then the wet

membranes were subsequently dried at 60 °C for 24 hours. Membrane swelling was calculated by the following equation:

$$\text{Swelling} = \frac{m_{\text{wet}} - m_{\text{dry}}}{m_{\text{dry}}} \times 100\% \quad (1)$$

Here, m_{wet} and m_{dry} are the mass (g) of the wet and the dry membranes.

Ion exchange capacity. A titration method was used to determine the membrane ion exchange capacity (IEC).¹⁶² First, the membranes were converted into the sulfonic acid (H^+) form by stirring the membrane in a 1.0 M HCl solution for at least 15 hours. Subsequently the membranes were converted back into the sodium form by immersing them in a 2.0 M NaCl solution for 3 hours. The released amount of H^+ in the solution was then determined by titration with 0.1 M NaOH. The IEC ($\text{mmol} \cdot \text{g}^{-1}_{\text{dry membrane}}$) values were calculated with the following equation:

$$\text{IEC} = \frac{V_{\text{NaOH}}}{m_{\text{dry}}} \times C_{\text{NaOH}} \quad (2)$$

Here, V_{NaOH} is the added volume of NaOH solution (mL), m_{dry} is the mass of the dry membrane (g), and C_{NaOH} is the concentration of the NaOH solution ($\text{mmol} \cdot \text{mL}^{-1}$).

Permselectivity. The permselectivity of the membranes was determined by the Nernst potential method. In a two-compartment cell, KCl solutions of 0.50 M and 0.10 M are recirculated on each side of the test membrane. The membrane potential is measured by two reference electrodes. The permselectivity of the membranes was calculated by the following equation:

$$\text{permselectivity (\%)} = \frac{\Delta V_{\text{measured}}}{\Delta V_{\text{theoretical}}} \times 100\% \quad (3)$$

$$\Delta V_{\text{theoretical}} = \frac{RT}{zF} \ln \frac{C_2 \gamma_2}{C_1 \gamma_1} \quad (4)$$

Here, R is the gas constant ($\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$), T the temperature (K), z the electrochemical valence, F the Faraday constant ($\text{A}\cdot\text{s}\cdot\text{mol}^{-1}$), C_1 and C_2 the concentrations of the two solutions ($\text{mol}\cdot\text{L}^{-1}$) and γ_1 and γ_2 the activity coefficients of the two solutions.

Diffusion dialysis. Diffusion experiments were performed with a glass diffusion cell (70 mL) in which the two compartments were separated by the membrane under investigation, with an effective area of 12 cm^2 . For the single-ion diffusion experiments (Figure 6.24a), the receiving chamber contained an aqueous 10.0 mM HCl solution, while the feed chamber contained aqueous solutions of 10.0 mM KCl or LiCl. For the mixed-ion diffusion experiments (Figure 6.24b), an aqueous solution of 10.0 mM KCl and 10.0 mM LiCl was added to the feed chamber, while the receiving chamber contained an aqueous solution of 20.0 mM HCl.

The two compartments were stirred vigorously throughout the experiments. Every 15 min, a 0.1 mL sample was taken and analyzed. The potassium and lithium ion concentrations were measured with a BWB-XP flame photometer (BWB Technologies, Newbury, UK).

Figure 6.24. Schematic illustration of the glass diffusion cell for a) single-ion and b) mixed-ion diffusion experiments.

The specific ion flux through the membrane was calculated from the concentration change of the specific ion in the receiving compartment, as follows:

$$J_i = \frac{V}{A} \frac{dc_i}{dt} \quad (5)$$

where V (cm^3) is the volume of the receiving compartment, A (cm^2) is the membrane area and dc_i/dt ($\text{mol}\cdot\text{cm}^{-3}\cdot\text{s}^{-1}$) is the concentration change in time.

Membrane selectivity can be defined as:

$$\text{Selectivity} = \frac{J_i \Delta C_j}{J_j \Delta C_i} \quad (6)$$

where J_i ($\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$) is the flux and ΔC ($\text{mol}\cdot\text{cm}^{-3}$) is the concentration difference between the feed compartment and the receiving compartment.

Preparation of the IPMC actuator. Following the characterization of the membranes in terms of swelling and ion exchange capacity, the membranes were used to prepare the IPMC actuators. To facilitate application of voltage across the membrane, both surfaces of the membranes were covered with platinum using an electroless plating method with two reduction steps.^{155, 163} In order to improve the bending performance of the actuators, a pre-treatment step was applied to the membranes. In this pretreatment step, the membranes were first roughened with sand paper to increase the surface area, followed by boiling in 1.0 M HCl for 30 min and subsequent rinsing in deionized water. For the first reduction step, the membranes were then immersed in 100 mL of a 5 wt% aqueous solution of $[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2$ overnight to induce ion exchange between H^+ to Pt^{2+} . The membranes were rinsed with deionized water again and stirred in 200 ml of deionized water at 40 °C. 3 mL of 5 wt% aqueous NaBH_4 solution was added every 30 min during 6 hours. During the addition of reducing agent, the temperature was gradually increased to 60 °C. After completion of the first plating series, the membranes were again washed with deionized water and boiled in 1.0 M HCl for 5h, followed by the second reduction step. Afterwards, the membranes were rinsed

once again with deionized water and then stirred in 240 mL $[\text{Pt}(\text{NH}_3)_4]\text{Cl}_2$ (0.5 mg Pt mL⁻¹) solution at 40 °C for 5h. Meanwhile, 5 mL of 5 wt% aqueous solution of NH_4OH was slowly added, followed by the addition of 6 mL of 20 wt% hydrazine hydrate solution and 3 mL of 5 wt% hydroxylammonium chloride at 60 °C over 4h. The resulting Pt covered membranes were boiled in 1.0 M HCl for 30 min and rinsed with Milli-Q water.

Characterization of the actuation performance. The electromechanical response of the membranes in both Na^+ and K^+ forms was measured in deionized water. To do so, the resulting IPMC actuators were soaked in 2.0 M NaCl or KCl solution overnight for complete ion exchange between H^+ and Na^+ or K^+ .^{155, 163} Finally, the actuators were cut into 0.7 cm × 3 cm pieces to prepare test cantilevers, rinsed with deionized water to remove excess salt (NaCl or KCl) and stored in deionized water. The actuator performance was measured using a laser Doppler vibrometer (Polytec GmbH, MSA-400 micro system analyzer). An AC voltage with a peak-to-peak amplitude of 1.5 V was applied across the electrodes at frequencies of 10 Hz, 15 Hz and 20 Hz.

6.6 References

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Chapter 7

Outlook: Supramolecular Redox-Responsive Hydrogels

In Chapter 3, redox active hydrogels were prepared by covalently connecting poly(ferrocenylsilane) (PFS) polyanions. These hydrogels were used as a reducing environment for the fabrication of metal nanoparticles from the corresponding metal salts. In this Chapter, β -cyclodextrin/adamantane host-guest interactions will be used to reversibly crosslink poly(ferrocenylsilane) polyanion chains. Due to the reversible crosslinks, the mechanical properties of the resulting supramolecular hydrogel are expected to differ notably from those of the covalently crosslinked poly(ferrocenylsilane) polyanions. For instance, the supramolecular PFS hydrogels possess self-healing properties. In addition, their mechanical properties may be influenced by adding competing guest molecules and therefore, these supramolecular hydrogels may be regarded as systems responsive to multiple stimuli. As a result of the strong swelling and collapse of poly(ferrocenylsilane) polyanion networks upon oxidation and reduction, these gels are of interest for the fabrication of actuators and artificial muscles.

7.1 Introduction

Redox responsive gels attract attention due to their interesting application as actuators, artificial muscles or microfluidic valves.¹ As opposed to the more classical stimuli such as changes in temperature² and pH,³ redox stimuli may offer fast switching between oxidation states and can be applied locally under external control, for instance by employing nanowires.⁴ Switching the oxidation states allows one to alter properties such as polarity, which generally has a large influence on polymer properties such as chain stiffness and extension, and on interactions with solvent. Redox-active gels often incorporate transition metals into their network-forming polymer chains, either as main chain constituents or included in side groups.⁵

Transition metal ions provide a simple and efficient way of producing redox-responsive gels that can be addressed externally, *e.g.*, by changing the local crosslink density. Using iron ions, a redox driven gel hardening, within a permanent covalently crosslinked polymeric hydrogel network, was achieved by reversible crosslinks which were switched between the strongly binding Fe^{3+} and weak to nonbinding Fe^{2+} .⁶ In another example, stable multiple-stimuli responsive hydrogels were formed by self-organization of ferrocenyl phenylalanine in water.⁷ Gel formation was based on complementary π - π and hydrogen bonding, which could be disrupted by oxidation of the ferrocene units as well as by pH, temperature or shear stress. In these examples, gel hardening or sol-gel transitions are induced by redox stimuli. Host guest interactions may also be used to construct hydrogels with reversible properties. β -Cyclodextrin (β -CD) is a widely used, fascinating host for a range of hydrophobic guests, including aromatic molecules, cholesterol, ferrocene and adamantane and their derivatives, which has led to responsive and self-healing materials.⁸ For instance, a transparent supramolecular hydrogel was formed upon mixing poly(acrylic acid) (pAA), functionalized with β -CD host moieties, with ferrocene-functionalized pAA. This inclusion complex gel was crosslinked further covalently, yielding a redox responsive actuator

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capable of displacing a small load upon oxidation and reduction.⁹ The current work was aimed at the preparation of a redox active hydrogel based on polyanionic poly(ferrocenylsilane) (PFS) chains bearing β -CD moieties and an adamantyl functionalized PEG star polymer, connected by reversible β -CD/adamantyl bonds. Such a hydrogel can be expected to display responsiveness to multiple stimuli, including redox stimuli and the presence of competing guest molecules. In Chapter 3, a polyanionic PFS hydrogel crosslinked covalently with poly(ethylene glycol) showed a twofold size reduction (measured in one dimension) upon oxidation.¹⁰ However, this hydrogel was relatively fragile, which may be due to the buildup of internal stresses during swelling and collapse, by inhomogeneous crosslinking. Here, in addition to exploring stimuli responsive properties, we aim to investigate the mechanical properties of a PFS polyanion hydrogel formed from supramolecular crosslinks, capable of redistributing the stresses of the network.

7.2 Results and discussion

In Chapter 3 a polyanionic PFS with controlled degrees of crosslinkable azide groups was synthesized (PFS **4**, Scheme 7.2) by partial halogen exchange and side group modification of poly(ferrocenyl(3-chloropropyl)methylsilane), followed by covalent crosslinking with strained alkynes employing copper-free "Click" chemistry. Here supramolecular crosslinking of this PFS polyanion was performed based on the interaction of β -cyclodextrin (β -CD) and adamantyl groups. In order to introduce β -cyclodextrin moieties to PFS **4**, 6-monodeoxy-6-mono(bicyclononyne)- β -cyclodextrin (β -CD **1**) was synthesized by the NHS ester reaction of 6-monodeoxy-6-mono(amino)- β -cyclodextrin with (1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethyl succinimidyl carbonate (Scheme 7.1). The synthesized β -CD **1** was coupled to PFS **4** by a strain-promoted alkyne-azide cycloaddition (SPAAC) yielding PFS **5** (Scheme 7.2).

Scheme 7.1. Synthesis of a bicyclononyne functional β -cyclodextrin **1**.

Scheme 7.2. a) Schematic drawing of the supramolecular hydrogel network. b) Synthesis of a supramolecular crosslinkable PFS polyanion. PFS **4** was coupled with β -CD **1** via a SPAAC reaction.

Although both β -CD and ferrocene moieties, which are well-known for their redox responsive supramolecular interaction,¹¹⁻¹² were present in PFS **5**, the polymer remained highly soluble in water and did not show any sign of gelation or viscosity increase. However, upon mixing with adamantyl functionalized 4-arm PEG, the viscosity of the mixture increased significantly. This demonstrates that the ferrocenylsilane units in the PFS chains do not form inclusion complexes with β -CD. By vial tilting, the difference in viscosity of the mixture of PFS **5** with adamantyl functionalized 4-arm PEG (vial in the blue clamp, right in Figure 7.1) and a reference mixture of PFS **5** with non-functionalized 4-arm PEG (on red clamp, left in Figure 7.1) is clearly visible. However, a stable gel was not obtained and the viscous liquid settled down at the bottom of the vial over time (minutes).

Figure 7.1. Image of two mixtures of PFS **5** with non-functionalized 4-arm PEG (left) and with adamantyl functionalized 4-arm PEG (right).

A new redox responsive hydrogel with reversible crosslinks was prepared by supramolecular inclusion complexation of β -cyclodextrin-functionalized PFS polyanion chains with adamantyl-functionalized 4-arm poly(ethylene glycol). The

polyanionic poly(ferrocenylsilane) serves as the redox responsive backbone, capable of significant collapse in its oxidized zwitterionic state, while the β -CD/adamantyl inclusion complex provides the hydrogel with self-healing properties.

Work in progress focuses on the crosslinking of this β -CD bearing polyanionic PFS with adamantyl functionalized 8-arm PEG, presuming that the use of a crosslinker with a higher degree of functionality will lead to a more stable redox-responsive hydrogel. In addition, the adamantyl groups could be replaced by azobenzene¹³⁻¹⁴ or benzimidazole¹⁵⁻¹⁶ moieties, yielding redox responsive hydrogels with light or pH triggered sol-gel transitions, respectively.

7.3 Experimental section

Materials. (1*R*,8*S*,9*S*)-Bicyclo[6.1.0]non-4-yn-9-ylmethyl succinimidyl carbonate (>95%), *n*-butyllithium (1.6M in hexanes), dimethyl sulfoxide (anhydrous), THF (anhydrous, inhibitor-free), phenol ($\geq 99.5\%$), KI (>99%), NaN₃ (>99.5%), THF-d₈ (99.5 atom% D), CDCl₃ (99.8 atom% D), DMSO-d₆ (99.9 atom% D), and toluene-d₈ (≥ 99.6 atom% D) were obtained from Aldrich and used as received. 4-arm PEG succinimidyl carboxymethyl ester (pentaerythritol) ($M_n = 5000$ g/mol) was purchased from JenKem Technology USA. Methanol, DMSO and THF were obtained from Biosolve, The Netherlands. Milli-Q water (Millipore) was used in all experiments. Acetone and DMF (extra dry, 99,8%) were purchased from Acros Organics. Isobutyl ethanesulfonate was prepared according to a literature procedure.¹⁷ 1-(*p*-Toluenesulfonyl)imidazole and 6-Monodeoxy-6-mono(tosyl)- β -cyclodextrin were prepared according to a literature procedure¹⁸ and subsequently, 6-Monodeoxy-6-mono(azido)- β -cyclodextrin and 6-Monodeoxy-6-mono(amino)- β -cyclodextrin were prepared according to another literature procedure.¹⁹

Techniques. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 MHz instrument at 400.1 and 100.6 MHz, respectively, in CDCl₃, DMSO-d₆, THF-d₈ or toluene-d₈. ¹H and ¹³C chemical shifts were based on the solvent 180

residual signals. GPC measurements were carried out in THF (flow rate 2.0 mL/min) at 25 °C, using microstyragel columns (bead size 10 µm) with pore sizes of 10^6 , 10^5 , 10^4 and 10^3 Å (Waters) and a dual detection system consisting of a differential refractometer (Waters model 410) and a differential viscometer (Viscotek model H502). Molar masses were determined relative to narrow polystyrene standards. FTIR spectra were measured with a Bruker ALPHA on freeze-dried samples.

6-Monodeoxy-6-mono(bicyclononyne)-β-cyclodextrin 1.

(1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethyl succinimidyl carbonate (135 mg, 0.463 mmol) was dissolved in DMF (1 mL) and purged with argon. 6-Monodeoxy-6-mono(amino)-β-cyclodextrin (500 mg, 0.441 mmol) and triethylamine (73 µL, 0.53 mmol) were dissolved in dry DMF (3 mL), purged with argon and added to the bicyclononyne (BCN) solution. The mixture was stirred under argon for 4 days at 20 °C. The product was crystallized in acetone (30 mL), washed with acetone and dried in vacuum to obtain the product as white crystals. ¹H NMR (CDCl₃, δ, ppm): 0.87 (BCN, m, 1H); 1.27 (BCN, m, 1H); 1.52 (BCN, m, 1H); 2.08-2.28 (BCN, m, 6H); 3.03 (BCN, m, 2H); 3.36 (β-CD, m, 16H); 3.63 (β-CD, m, 26H); 4.47 (β-CD, m, 6H); 4.83 (β-CD, m, 7H); 5.71 (β-CD, m, 14H).

Poly(ferrocenylsilane) 2. PFS **2** was synthesized by Pt-catalyzed ring-opening polymerization of [1](3-chloropropyl)methylsilaferrocenophane (3.0 g, 9.8 mmol), followed by halogen exchange using KI.²⁰ At 82% conversion of Cl into I, **2** was isolated by precipitation in MeOH and dried under vacuum. Overall yield: 3.28 g (88%) of amber product. ¹H NMR (toluene-*d*₈, δ, ppm): 0.52 (SiCH₃, s, 3H); 1.00 (1-CH₂, m, 2H); 1.82 (2-CH₂, m, 2H); 2.95 (3-CH₂I, m, 2H); 3.30 (3-CH₂Cl, m, 2H); 4.05 + 4.10 + 4.27 + 4.29 (Cp, m, 8H). ¹³C NMR (toluene-*d*₈, δ, ppm): -2.83 (SiCH₃); 12.02 (1-C); 18.52 (2-C); 29.32 (3-CH₂I); 48.23 (3-CH₂Cl); 70.50 (Cp-Si); 71.96 + 73.95 (Cp). GPC (THF): $M_n = 1.43 \cdot 10^5$ g/mol, $M_w = 2.97 \cdot 10^5$ g/mol, $M_w/M_n = 2.08$. GPC (THF, PFS-Cl): $M_n = 2.28 \cdot 10^5$ g/mol, $M_w = 4.90 \cdot 10^5$ g/mol, $M_w/M_n = 2.15$.

Poly(ferrocenylsilane) 3. Isobutylsulfonate side groups were attached to **2** (1.13 g, 2.4 mmol CH₂-I units) by alkylation with α -lithioisobutylethanesulfonate at -55 °C, using reaction conditions adapted from earlier work.²⁰ A solution of isobutylethanesulfonate (1.85 g, 11.1 mmol) in dry THF (18 mL) was cooled under argon to -80 °C, and *n*-BuLi (5.6 mL, 8.9 mmol) was added dropwise. After stirring for 60 min, DMSO (10 mL) and a solution of **2** (1.13 g, 2.4 mmol CH₂-I units) in THF (30 mL) was added dropwise. Stirring was continued at -55 °C for 16 h. The reaction was terminated at -55 °C by adding phenol (0.66 g, 7.0 mmol) in THF (5 mL). Polymer **3** was isolated by repeated precipitation in MeOH and dried under vacuum. Yield: 1.13 g (95%) of an amber solid. ¹H NMR (THF-d₈, δ , ppm): 0.51 (SiCH₃, s, 3H); 0.96 (1-CH₂, m, 2H); 0.96 (CH₃, d, *J* = 6.7 Hz, 6H); 1.31 (ethane CH₃, d, *J* = 6.7 Hz, 3H); 1.49 + 1.60 (2-CH₂, m, 2H); 1.60 + 2.02 (3-CH₂, m, 2H); 1.97 (CH, m, 1H); 3.18 (4-CH₂, m, 1H); 3.54 (3-CH₂Cl, m, 2H); 3.93 (SO₃CH₂, d, *J* = 6.5 Hz, 2H); 4.01 + 4.04 + 4.08 + 4.23 (Cp, m, 8H). ¹³C NMR (THF-d₈, δ , ppm): -2.86 (SiCH₃); 14.73 (ethane CH₃); 16.98 (1-C); 19.11 (isobutyl CH₃); 22.30 (2-C); 29.45 (CH); 35.26 (3-C); 48.78 (3-CH₂Cl); 56.54 (4-C); 71.26 (Cp-Si); 72.0-72.4 + 74.0-74.4 (Cp); 75.46 (SO₃CH₂). Percentage of CH₂Cl moieties: 18 mol%.

Poly(ferrocenylsilane) 4. The isobutylsulfonate ester groups of **3** (0.96 g) were deprotected in THF (20 mL) by adding a solution of NaN₃ (2.0 g, 38.5 mmol) in DMSO (30 mL) at 45 °C. After 24 h, THF was evaporated, and deprotection was continued in DMSO for 48 h. In DMSO, the 18 mol% chloro groups of PFS **3** were substituted by azide. After cooling, the solution was dialyzed against Milli-Q water containing trace amounts of sodium ascorbate and freeze-dried to yield the amber product. Yield: 1.30 g (100%). ¹H NMR (DMSO-d₆, δ , ppm): 0.44 (SiCH₃, s, 3H); 0.88 (1-CH₂, m, 2H); 1.07 (ethane CH₃, d, *J* = 6.2 Hz, 3H); 1.32 + 1.50 (2-CH₂, m, 2H); 1.32 + 1.90 (3-CH₂, m, 2H); 2.37 (4-CH₂, m, 2H); 3.31 (3-CH₂N₃); 3.98 + 4.18 (Cp, m, 8H). ¹³C NMR (DMSO-d₆, δ , ppm): -3.09 (SiCH₃);

15.36 (ethane CH₃); 15.70 (1-C); 21.53 (2-C); 35.67 (3-C); 53.88 (4-C); 70.33 (Cp-Si); 70.96 + 73.06 (Cp). ATR-FTIR: 2094 (azide) cm⁻¹.

Poly(ferrocenylsilane) 5. PFS **5** was prepared by mixing PFS **4** (150 mg, 0.07 mmol N₃) with β -CD **1** (160mg, 0.12 mmol BCN) in DMSO (5 mL). The reaction mixture was transferred into a dialysis tube after 3 hours and dialyzed against Milli-Q water. Freeze-drying yielded 241 mg (99%) of product in the form of orange foam. ¹H NMR (DMSO-d₆, δ , ppm): 0.42 (SiCH₃, s, 3H); 0.88 (1-CH₂, m, 2H); 0.87 (BCN, m, 1H); 1.07 (ethane CH₃, d, J = 6.2 Hz, 3H); 1.27 (BCN, m, 1H); 1.32 + 1.50 (2-CH₂, m, 2H); 1.48 (BCN, m, 1H); 1.32 + 1.90 (3-CH₂, m, 2H); 2.08-2.28 (BCN, m, 6H); 2.37 (4-CH₂, m, 2H); 3.03 (BCN, m, 2H); 3.36 (β -CD, m, 16H); 3.63 (β -CD, m, 26H); 3.98 + 4.18 (Cp, m, 8H). 4.46 (3-CH₂-triazole); 4.47 (β -CD, m, 6H), 4.83 (β -CD, m, 7H), 5.71 (β -CD, m, 14H).

Adamantyl derivatized tetra-arm PEG 6. To a solution of amantadine hydrochloride (377 mg, 2.01 mmol) and triethylamine (300 μ l, 2.17 mmol) in dry DCM (3 mL), a solution of tetra-arm PEG succinimidyl carboxymethyl ester (512 mg, 0.41 mmol NHS) in DCM (3 mL) was added. The solution was stirred under argon for 4 h at 20 °C. The product was dried under vacuum and dissolved in water. By centrifugation, the unreacted 1-adamantanamine was removed. Dialysis overnight (MWCO, 3500 g/mol) and freeze-drying yielded the product. ¹H NMR (CDCl₃, δ , ppm): 1.6 - 2.1 (adamantyl, br, 15H); 2.35 (CH₂C=O, s, 2H); 3.3 – 3.7 (EO, m); 6.47 (NH, bs, 1H).

Hydrogel 7. Polyanion **5** (~15 mg) was dissolved in 0.1 ml Milli-Q water and mixed with a solution of adamantyl derivatized tetra-arm PEG (~9 mg) in 0.1 ml Milli-Q water. Ratios having roughly equimolar amounts of adamantyl and β -CD moieties present in the gel-forming mixture were chosen. The solutions were thoroughly mixed and subsequently lyophilized and rehydrated to obtain a 20% polymer:water mixture. The viscosity was observed to slightly increase until a viscous fluid/gel was confirmed by the vial tilting method.

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Summary

In this thesis we tackle the synthesis, characterization and function of novel organometallic polyanions, polycations, and their corresponding hydrogels and explore the use of these redox-responsive water-soluble or water-swellaable materials in applications where either their charge or their redox activity leads to new opportunities, such as in metal nanoparticle fabrication and transfection. In addition, crown ether-functionalized aromatic polymers and organometallic polymers will be explored for ion separation and – sensing.

After a brief introduction and outline of the thesis, a broad introduction to the field of stimulus responsive polymers is given in **Chapter 2**. This literature overview is focused on redox responsive hydrogels and their application in the fabrication of metal nanoparticles.

Stimulus-responsive gels attract much attention due to their wide applicability in areas including sensing, controlled release, actuators and artificial muscles. In **Chapter 3** we describe the synthesis of polyferrocenylsilane (PFS) polyion hydrogels, where crosslinks were formed between strained alkynes and azide groups in a copper-free Huisgen cycloaddition reaction. The anionic organometallic hydrogels display a reversible collapse and reswelling upon chemical oxidation and reduction as they are switched between a zwitterionic and a polyanionic state.

Following the development of covalently crosslinked, redox responsive organometallic hydrogels we explored their ability to reduce transition metal salts to the corresponding metal nanoparticles (NPs) and observed that the hydrogels provided a facile platform for fabricating such nanoparticles. Salts of metal cations with selected redox potential were conveniently converted to unaggregated metal NPs without employing external reducing agents. The production of metal NPs often requires the use of organic ligands, salts, surfactants or other capping agents, which may significantly reduce their (catalytic) activity. Nanoparticle fabrication inside a polymer network circumvents these issues and suppresses excessive growth of the particles.

In addition to polyanions, PFS polycations are also explored in this project. **Chapter 4** shows the potential that PFS polycations have to be used in selective gene delivery applications. The positive charge of the cationic PFS condenses DNA into polyplex NPs in which DNA is surrounded by PFS chains. The polyplex particles have a high positive charge at the surface which results in a high gene delivery efficiency compared to conventional polymers used in cell transfection experiments such as polyethyleneimine (PEI).

PFS derivatives are suitable for sensing applications due to their excellent redox properties. Different functionalities are easily introduced by side-group modification. It has been shown that thin and dense redox-active films can be immobilized on electrode surfaces. **Chapter 5** combines these redox-active films with crown ethers, allowing specific cation recognition and sensing. Preliminary results, achieved with crown ether functionalized PFS films, show a response to μM cation concentrations.

Next to PFS, various crown ether containing poly(arylene ether ketone)s (PAEKs) were also synthesized and described in **Chapter 6**. PAEKs are the most commonly known high performance materials used for ion exchange and fuel cell membranes. By incorporating crown ether units in the main chain of these aromatic polymers, monovalent ion-selective membranes and ionic polymer metal composite actuators were prepared. The suitability of these systems for potassium and lithium ion separation was demonstrated.

In the outlook, **Chapter 7**, PFS polyanionic hydrogels were investigated further. The intriguing and substantial swelling and collapse upon reduction and oxidation were combined with the self-healing capabilities of β -cyclodextrin/adamantyl crosslinks. The resulting supramolecular hydrogel is a system responsive to multiple stimuli, including redox stimuli and the addition of competing guest molecules. By employing 8-arm instead of 4-arm crosslinking polymers, more mechanically robust hydrogels are expected to be formed.

Samenvatting

Dit proefschrift beschrijft de synthese, karakterisatie en toepassing van nieuwe organometallische polyanionen, polykationen, en hydrogels hiervan. Het gebruik van deze redox-responsieve wateroplosbare en water-zwelbare materialen is onderzocht in toepassingen waar hun lading of redox-activiteit tot nieuwe mogelijkheden leidt, zoals het maken van metaal nanodeeltjes en hun gebruik in transfectie. Daarnaast zijn ook kroonether gefunctionaliseerde aromatische en organometallische polymeren onderzocht op hun ionscheidend vermogen en op hun mogelijkheden om ionen te detecteren.

Na een korte inleiding en overzicht van dit proefschrift wordt er een uitgebreide inleiding gegeven op het gebied van stimulus responsieve polymeren in **Hoofdstuk 2**. Dit literatuuroverzicht is gefocust op redox responsieve hydrogels en hun toepassing in de fabricage van metaal nanodeeltjes.

Stimulus-responsieve gels trekken veel aandacht door hun brede toepasbaarheid op het gebied van sensoren, gecontroleerde afgifte van actieve stoffen, actuatoren en kunstmatige spieren. In **Hoofdstuk 3** beschrijven we de synthese van polyferrocenylsilaan (PFS) polyion hydrogels, waarin crosslinks gevormd zijn tussen gespannen alkyne en azide groepen in een kopervrije Huisgen cycloadditie reactie. De anionische organometallische hydrogels vertonen een reversibele krimp en swelling bij chemische oxidatie en reductie, waarbij ze tussen een zwitterionische en polyanionische toestand worden geschakeld.

Na de ontwikkeling van covalent gecrosslinkte, redox responsieve organometallische hydrogels hebben we hun vermogen om overgangsmetaal zouten te reduceren tot de overeenkomstige metaal nanodeeltjes onderzocht en hebben we vastgesteld dat deze hydrogels een geschikt platform bieden voor de fabricage van deze nanodeeltjes. Zouten van metaal kationen met geselecteerde redox potentialen werden eenvoudig omgezet tot ongeaggregeerde metaal nanodeeltjes zonder gebruik van externe reducerende middelen. Voor de productie van metaal nanodeeltjes zijn vaak organische liganden, zouten, oppervlakte-actieve stoffen of andere inkapselende middelen nodig, wat de katalytische

activiteit significant kan reduceren. Nanodeeltjes fabricage in een polymeer netwerk vermijdt deze problemen en onderdrukt excessieve groei van de deeltjes.

Naast polyanionen zijn ook PFS polykationen onderzocht in dit project.

Hoofdstuk 4 laat het potentieel van PFS polykationen zien in een toepassing voor gen afgifte. De positieve lading van kationisch PFS condenseert DNA tot polyplex nanodeeltjes, waarin DNA is omgeven door PFS ketens. De polyplex deeltjes hebben een hoge positieve lading aan het oppervlak, wat resulteert in een hoge gen afgifte efficiëntie vergeleken met conventionele polymeren zoals polyethyleneimine, die gebruikt worden in cel transfectie experimenten.

PFS derivaten zijn geschikt voor sensor toepassingen, gezien hun excellente redox eigenschappen. Verschillende functionaliteiten zijn eenvoudig te introduceren als zijgroep. Het is bekend dat dunne redox-actieve films met hoge dichtheid kunnen worden geïmmobiliseerd op het oppervlak van elektrodes. **Hoofdstuk 5** combineert deze redox-actieve films met kroonethers, wat gelegenheid biedt tot kation herkenning en detectie. Eerste resultaten, behaald met kroonether gefunctionaliseerde PFS films, laten een respons zien tot μM kation concentraties.

Naast PFS, zijn verscheidene kroonether bevattende poly(aryleenether ketonen) (PAEK) gesynthetiseerd en beschreven in **Hoofdstuk 6**. PAEK zijn de meest gangbare high performance materialen die gebruikt worden voor ion uitwisseling en brandstofcel membranen. Door het onderbrengen van kroonether eenheden in de hoofdketen van deze aromatische polymeren, zijn monovalent ion-selectieve membranen en ionische polymeer metaal composiet actuators geproduceerd. De geschiktheid van deze systemen voor kalium en lithium ion scheiding is gedemonstreerd.

In **Hoofdstuk 7** zijn PFS polyanionische hydrogels verder onderzocht. De intrigerende en substantiële swelling en krimp bij reductie en oxidatie zijn gecombineerd met zelfhelende eigenschappen van β -cyclodextrine/adamantaan crosslinks. De resulterende supramoleculaire hydrogel is een systeem dat responsief is voor meerdere stimuli, waaronder redox stimuli en de toevoeging van

competitieve gast moleculen. Door een 8-arm in plaats van een 4-arm vernetkend polymeer te gebruiken, wordt verwacht dat een meer mechanisch robuuste hydrogel zal worden gevormd.

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After more than 5 years, my adventure at the MTP group has come to an end. At the beginning of 2011 I started a Master project under the supervision of **Joost Duvigneau**. Next to the party life, I soon realized that I really liked working in the lab and doing research. In fact, **Joost** together with **Edit Kutnyánszky** (nowadays known as **Edit Brodskaya**) made me enthusiastic for the research life and before I knew it, I was spending evenings and weekends in the lab trying to get good results and learning a lot from them. Therefore, thanks to them, I am now writing the acknowledgements of my PhD Thesis. A PhD which was made possible by my promotor **Prof G. Julius Vancso** and my Assistant-promotor, but more importantly daily supervisor, **Dr. Mark Hempenius**, who entrusted this project to me.

After a relaxing period of windsurfing and traveling in Namibia with my brother, **Tim Zoetebier**, it was time to start my PhD here at MTP. Full of energy, with high hopes and big plans for the upcoming time, I arrived to the group, where I found a few PhD students, a gift from **Joost** for my Master project and not a single staff member. After watching the gift, a windsurf DVD, in **Edit's** office, without access to my own office, workspace or computer I looked out of the window and decided to call my brother. *It is windy and sunny! Do you have time? Ok, I'll pick you up, let's go windsurfing!*

Best start of a job, I would say!

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List of publications

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Redox-responsive organometallic hydrogels for in situ metal nanoparticle synthesis.

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Zoetebier, B.; Tas, S.; Vancso, G. J.; Nijmeijer, K.; Hempenius, M. A.,
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DNA - Organometallic Polymer Polyplexes for Gene Delivery.

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Tas, S.; Zoetebier, B.; Hempenius, M. A.; Vancso, G. J.; Nijmeijer, K.,
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Tas, S.; Zoetebier, B.; Sardan Sukas, Ö.; Bayraktar, M.; Vancso, G. J.;
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