SULFOXIDE-CONTAINING POLYMERS

New double stimuli responsive materials and nanocarriers for dermal delivery

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I hereby declare that the following thesis is the result of my own work and that no other sources than those cited were used. This thesis has not been submitted in any other previous doctoral procedure.

April 2021

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Abstract

The identification of new functional moieties and chemical reactions that are inspired by small molecules is crucial in modern nanotechnological research. Their incorporation into either polymer backbones or side group structures opens up new and innovative pathways for the development of dynamic and responsive polymer architectures.

In this regard, sulfoxide-containing polymers are materials that are governed by the outstanding physicochemical properties of the sulfoxide moiety. Its high hydrophilicity translates into polymers with very low cytotoxicity and excellent biocompatibility. Thus, making them interesting candidates for biomedical applications. However, this pure hydrophilicity also limits the potential of this interesting polymer class. Overcoming this limitation, to gain access to new adaptive and tailor-made sulfoxide-containing polymers with additional areas of applications, remains a challenge.

In this work, this challenge was approached in two ways. First, new dynamic and responsive properties of polysulfoxides were introduced via a rational molecular design. Here, by controlling the amphiphilic balance of alkyl sulfoxide groups a temperature-responsive polymer profile was realized. Furthermore, an additional stimuli response was achieved by utilizing the oxidation of the polar sulfoxides to the respective hydrophobic sulfones. As a result, the polymer properties could be extended from its pure hydrophilic nature to a multi-stimuli-responsive behavior.

Second, new interactions at the biointerface were assessed though the incorporation of sulfoxide moieties in colloidal systems. By decorating biocompatible nanogels with the outstanding skin interaction properties of sulfoxide groups, a promising new approach was developed to expand the toolbox of dermal delivery vehicles. Here, dimethyl sulfoxide-inspired nanogels showed the strong potential to increase dermal drug delivery while circumventing the skin disrupting disadvantages of the small molecule.

Overall, this thesis exemplifies the strong synergy between the unique properties of the sulfoxide moiety and its structure-property relationship in macromolecules. As a result, a new family of adaptive sulfoxide-containing polymers and colloids were developed with potential applications in bionanotechnology.

Zusammenfassung

Die Identifizierung neuer funktioneller Gruppen und chemischer Reaktionen, die von kleinen Molekülen inspiriert sind, ist entscheidend für die moderne nanotechnologische Forschung. Ihr Einbau entweder in Polymerrückgrate oder Seitengruppenstrukturen eröffnet neue und innovative Wege für die Entwicklung dynamischer und reaktionsfähiger Polymerarchitekturen.

In dieser Hinsicht stellen sulfoxidhaltige Polymere Materialien dar, die von den herausragenden physikochemischen Eigenschaften der Sulfoxidgruppe abhängen. Ihre hohe Hydrophilie führt zu Polymeren mit sehr geringer Zytotoxizität und ausgezeichneter Biokompatibilität. Das macht sie zu interessanten Kandidaten für biomedizinische Anwendungen. Allerdings schränkt diese reine Hydrophilie auch das Potenzial dieser interessanten Polymerklasse ein. Die Überwindung dieser Limitierung, um Zugang zu neuen adaptiven und maßgeschneiderten Polysulfoxide mit zusätzlichen Anwendungsgebieten zu erhalten, bleibt jedoch eine Herausforderung.

In dieser Arbeit wurde diese Herausforderung auf zwei Arten angegangen. Erstens wurden neue dynamische und responsive Eigenschaften von Polysulfoxiden über ein rationales Moleküldesign eingeführt. Hier konnte durch die Kontrolle des amphiphilen Gleichgewichts von Alkylsulfoxidgruppen ein temperaturabhängiges Polymerprofil realisiert werden. Darüber hinaus wurde eine zusätzliche Oxidationsabhängigkeit eingeführt, indem die polaren Sulfoxide zu den jeweiligen hydrophoben Sulfonen oxidiert wurden. Als Ergebnis weist das Polymer ein multiresponsives Verhalten auf.

Zweitens wurden neue Wechselwirkungen an der Bio-Grenzfläche durch die Einbindung von Sulfoxidgruppen in kolloidale Systeme untersucht. Durch die Dekoration von biokompatiblen Nanogelen mit den hervorragenden Hautinteraktionseigenschaften von Sulfoxidgruppen wurde ein vielversprechender neuer Ansatz entwickelt, um den Werkzeugkasten der dermalen Verabreichungsvehikel zu erweitern. Hier zeigten Dimethylsulfoxid-inspirierte Nanogele das starke Potenzial, die topische Wirkstoffabgabe zu erhöhen und gleichzeitig die hautstörenden Nachteile des kleinen Moleküls zu umgehen.

Insgesamt veranschaulicht diese Arbeit die starke Synergie zwischen den einzigartigen Eigenschaften der Sulfoxidgruppe und ihrer Struktur-Eigenschafts-Beziehung in Makromolekülen. Als Ergebnis wurde eine neue Familie adaptiver sulfoxidhaltiger Polymere und Kolloide mit potenziellen Anwendungen in der Bionanotechnologie entwickelt.

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1. Introduction

The demand for advanced and adaptive materials is omnipresent in modern society to address urgent global challenges such as green energy storage, plastic pollution, and personalized health care. To meet this demand, researchers increasingly turn to our surrounding nature and draw inspiration from its complex structure-property relationships, *i.e.* the ability to simultaneously control overall shape, internal morphologies, and chemical functionalities in defined nanoscopic systems.[1]

To meet such a level of control in synthetic polymeric systems, bottom-up strategies combine new responsive polymers with macromolecular self-assembly, colloidal chemistry, and interfacial physics in a systematic way.[2-4] The development of such artificial nanomaterials is anticipated to give versatile building blocks for advanced technologies in the field of biological, chemical and pharmaceutical sciences.

The foundation to control and tailor the properties of polymeric nanomaterials is to understand that macroscopic processes draw their versatile and adaptive features from highly cooperative interactions.[5] These can be either small chemical, conformational or architectural changes in a polymeric structure which, in their entirety, are then able to induce a significant response at the macroscopic level. The ability to precisely control these parameters is the basis of modern nanotechnological research.[6] Its innovative strength lays in the transfer of concepts and methodologies from synthetic organic chemistry to polymeric materials. In addition, the identification of new functional moieties and chemical reactions that are inspired by small molecules is crucial for this approach. Their incorporation into either polymer backbones or side group structures opens up new and innovative pathways for the development of dynamic and responsive polymer architectures.

In this regard, polymers and colloidal materials that contain sulfoxide groups have sparked growing attention among the polymer community, especially in recent years, owing to certain unique physicochemical properties of the sulfoxide moiety (see **Fig. 1**).[7-9] In fact, some of these polysulfoxides are known for decades for their ability to extract metal salts and antibiotics,[10-11] their application in organic synthesis and as physiologically active compounds, etc.[12-13] These interesting and versatile macromolecular properties can be traced back, in part, to the outstanding features that their low molecular weight analogues possess. That is why, this thesis focuses on the design and investigation of new sulfoxide-containing polymers in chemical environments where their low molecular weight sulfoxide equivalents have proved to be especially interesting.

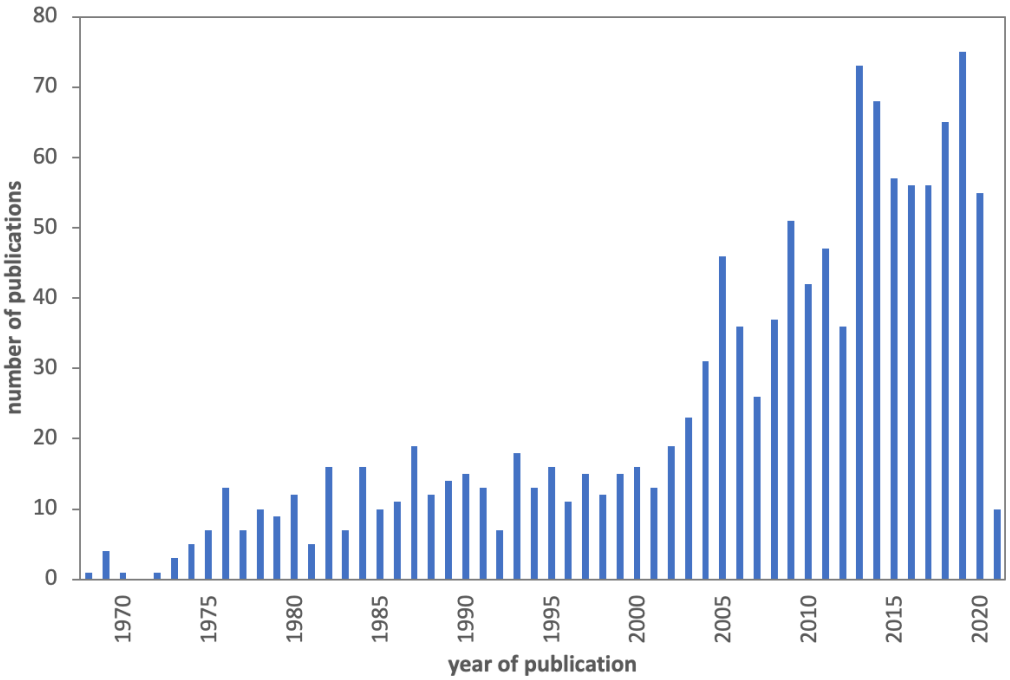


Fig. 1 While the number of publications dealing with sulfoxide-containing polymers remained constant over several decades, a recently growing interest is indicated trough the increase of published articles in the last passing years. (Data taken from https://pubmed.ncbi.nlm.nih.gov/, key words: sulfoxide containing polymer and poly(sulfoxide), March 2021)

The sulfoxide group as a versatile functional moiety itself is present in an ever-growing number of organic molecules that are important for applications in biology, chemistry, and material sciences.[14-17] Applications for this wide variety of low molecular weight sulfoxides span from their utilization as potent aprotic solvents, over chiral auxiliaries in advanced organic synthesis to penetration enhancers, and biological active substances. These properties stem from its exceptionally high polarity, its ability to form strong hydrogen bonds and the fact that it carries a stereogenic center.

The precise translation of these unique molecular properties into new polymeric materials remains a challenging topic. The incorporation of sulfoxides moieties into polymers was proposed to introduce stealth like character and antifouling properties similar to PEG.[9] Furthermore, polysulfoxides with catalytic activities and biological relevance are reported. Thus, sulfoxide-containing polymers possess both the characteristic properties of their low molecular weight analogues while additionally exhibiting new functions based on the embedding of a large number of sulfoxide groups in the polymer chain. Here, not only the functionality plays an important role, but the macromolecular architecture is also a crucial

factor. It has been shown further that the position of the sulfoxide groups in the macromolecule plays an important role in determining the polymers' functionality.

Taking all these aspects into account, this work, aims to understand the versatile properties of the sulfoxide functional group itself and, more precisely, its potential in a macromolecular and material science context. For this, first, the properties of the low molecular weight sulfoxides are briefly discussed after which a bridge is built to the macromolecular properties of modern sulfoxide-containing polymers.

1.1. Properties of low molecular weight sulfoxides

Sulfoxide compounds are chemical structures that carry a sulfinyl moiety which is covalently bonded at the sulfur atom to two carbon atoms. Naturally occurring sulfoxides are widely present in small concentrations in plants and animal tissues as *e.g.* fatty esters, glycosides, and sulfur-containing amino acids.[18] Their functions range from components of naturally occurring oils, and characteristic odors to chemopreventive activities, *i.e.* the retardation, blocking or reversing of the carcinogenic process by natural or synthetic agents.[16, 19]

Examples for industrially relevant sulfoxides are given by potent aprotic solvents like dimethyl sulfoxide and effective pharmaceutics like omeprazole, a leading gastric proton pump inhibitor. This wide variety of structural and functional aspects in low molecular weight sulfoxides is mainly attributed to their unique electronic structure, which will be discussed in more depth in the following chapters.

1.1.1. Physicochemical properties of sulfoxides

1.1.1.1. Electronic structure

Many physicochemical properties of low molecular weight sulfoxides are based on the unique electronic structure of the sulfur-oxygen bond.[15] The use of X-ray spectroscopy and theoretical molecular orbital calculations have shown that sulfoxide-containing small molecules are highly polarized exhibiting a localized net positive charge on the sulfur atom.[20] These findings together with a relatively short sulfur-oxygen distance (average bond length of 1.50 Å) indicate that the sulfoxide group resembles a hybrid from of three resonance structures (see **Fig. 2**). However, the first two structures (I and II) are predominantly observed in contrast to structure III which is energetically unfavored. While the highly polarized structure I mainly contributes for the donor properties of oxygen bonding events (sp^2 oxygen), structure II is considered to be responsible for the sulfur bond formation (sp^3 sulfur).

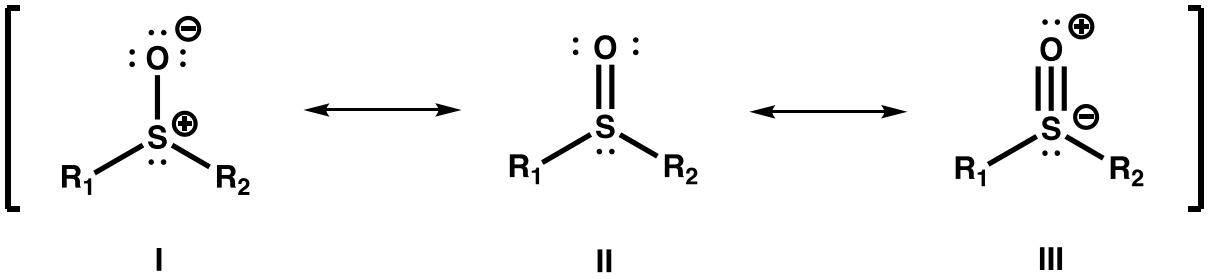


Fig. 2 Resonance structures of the sulfoxide group.

This discrepancy between oxygen and sulfur donor properties of the sulfoxide moiety came from observations that dimethyl sulfoxide coordinated to "harder" metals via the oxygen atom and to "softer" metals via the sulfur atom (see **Fig. 3**).[21] Such a behavior is in accordance to the HSAB principles. [22]

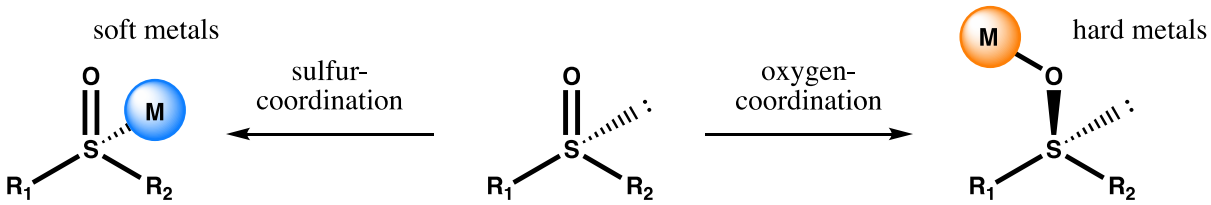


Fig. 3 Coordination modes of sulfoxide-containing molecules with soft and hard metal ions.

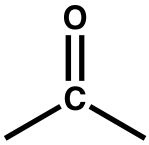
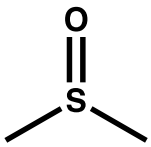
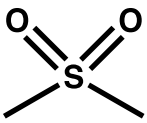
However, the ''hardness'' or ''softness'' of a metal ion can be further affected by the nature of the sulfoxide's substituents R_1 and R_2, where steric effects can force oxygen-bonding even in softer metal ions.[23] Thus, the intermolecular interactions of sulfoxide-containing molecules and the bidentate nature of the sulfoxide moiety itself are described as the result of a well-balanced interplay of electronic and steric factors.

1.1.1.2. Dipole moment and polarity

In general, the sulfur-oxygen bond length in sulfoxides and its corresponding sulfone analogues varies in the presence of different substituents attached to the sulfur center. However, on average, a S-O bond length of 1.45 Å is reported which is shorter than the calculated single bond with 1.60 Å and even slightly shorter than the predicted double bond length with 1.49 Å.[24-25] Thus, demonstrating a highly polarized sulfur-oxygen double bond character. This can also be seen for the example of dimethyl sulfoxide and dimethyl sulfone (see **Table 1**). Here, the sulfur-oxygen bond lengths are slightly shorter in the case of dimethyl sulfoxide and significantly shorter in case of the sulfone analogue compared to the calculated double bond

length. In contrast, the comparison between the S-O bond in dimethyl sulfoxide with the corresponding C-O bond in acetone shows a much shorter bond length for the carbonyl group with significantly less polarization (see **Table 1**). This further highlights the unique properties of the sulfoxide bond.

Table 1 S-O bond lengths and dipole moments of dimethyl sulfoxide and dimethyl sulfone indicate the highly polarized bond nature of the sulfur-oxygen linkage. In comparison, the corresponding C-O bond in acetone is much shorter and less polarized.[a]

Molecule	C-O and S-O bond length [Å]	Dipole moment [D]
	1.214	2.88
	1.485	3.96
	1.431	4.44

[a] Structural and physicochemical data are taken from *NIST Standard Reference Database* (see Reference [26]).

The evaluation of the dipole moments of various sulfoxides and sulfones gives another measure to quantify the polar nature of the sulfoxide moiety. It was found that the dipole moments for this functional group exhibit in average a value greater than 3.0 D in many sulfoxide-containing small molecules.[27] This is in agreement with the specific experimental data shown in **Table 1** for dimethyl sulfoxide and dimethyl sulfone. To bring this into perspective, the dipole moment of a sulfur-oxygen double bond would be zero if the electrons were equally shared between both the sulfur and oxygen atoms. In contrast, the sharp separation of both formal charges, *i.e.* a positively charged sulfur and a negatively charged oxygen, in a coordinative bond with a bond length of 1.45 Å would result into a dipole moment of around 7.0 D.[25] Thus, the observed lower value gives rise to the assumption of an unsymmetrical distribution of bonding electrons. In addition, the comparison to the respective carbonyl group in acetone shows that the C-O bond is significantly less polarized with an experimental dipole

moment value of 2.88 D (see **Table 1**) underlining further the special nature of the sulfur-oxygen bond.

This unsymmetrical distribution of electrons and therefore high polarization enables the sulfoxide group to form a variety of intermolecular electrostatic interactions. These include, for example, the observed high boiling points (see **Chapter 1.1.1.4.**) and potent solubilizing properties of both dimethyl sulfoxide and dimethyl sulfone (see **Chapter 1.2.2.**). Both compounds are not only able to solubilize polar compound but especially π-electron rich molecules like naphthalene and biphenyl by interacting with the highly positively charged sulfur atom of the solvent molecules.[28]

1.1.1.3. Chirality

Besides the electronic structure, stereochemical aspects of the sulfoxide moiety have to be taken into account to fully understand its outstanding properties. Due to the lone electron pair at the sulfur atom, compounds with a chemical formula of R_1R_2SO exhibit a pyramidal geometry. This is quite different from that of R_1R_2CO molecules where the three atoms that are directly attached to the carbon are planar. In the case of different substitute ($R_1 \neq R_2$), this pyramidal geometry ultimately highlights another unique feature of the sulfoxide group; its inherent chiral nature.

This chiral nature can be extended to other compounds. For example, the polarized sulfur-oxygen bond enables both the sulfur and oxygen centers to coordinate to Lewis acids and transition metals, thus forming chiral transition-state geometries. In addition, the chiral sulfoxide group enables important asymmetric transformations in modern organic synthesis. A considerable amount of research was devoted to explore the asymmetric synthesis of small molecules,[17, 29-30] natural products,[16, 31] and biologically active compounds[14] as well as the applications of chiral sulfoxide ligands[32-33] in advanced organic catalysis.[34] For further details on the utilization of low molecular sulfoxides in advanced organic synthesis and catalysis, the reader is referred to **Chapter 1.2.3.**.

The effectiveness of the sulfoxide group as chiral moiety can be divided into three major aspects. First, its efficiency as bearer of the chiral information. Here, centered at the sulfur atom, the stereoelectronic differences between the three different substituents namely the oxygen atom and the two alkyl and/or aryl groups in combination with a lone pair of electrons allows for the formation of a well-defined and robust chiral environment (see **Fig. 4**).[15, 35] Second, its high optical stability is based on the high activation energy for the pyramidal

inversion of the sulfoxide structure. Investigations on various sulfoxides showed that thermal racemization of the sulfoxide group only occur at around 200 °C with a significant rate, thus making it robust for a broad range of reaction conditions.[36-37] And last, this allows for the accessibility of both enantiomers via the preparation of chiral non-racemic low molecular weight sulfoxides with an expected high enantiomeric purity.[29-30, 38]

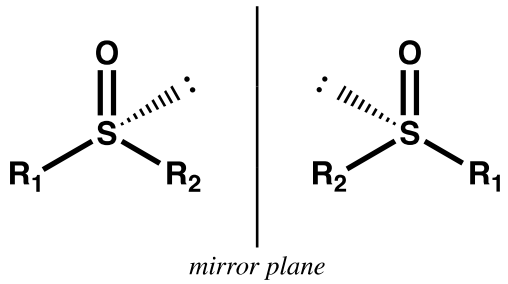


Fig. 4 A robust chiral configuration is observed for the sulfoxide functional group with two different substituents (R_1 and R_2), a bound oxygen atom and a lone pair of electrons centered around the sulfur atom.

The importance in understanding and controlling the sulfoxide chirality is also demonstrated in a variety of biologically significant molecules in which a stereogenic sulfoxide group translates into a pair of enantiomers with potentially different stereochemical properties in the human metabolism. This gives rise to the development of potentially new sulfoxide-containing pharmaceuticals in which both enantiomers can be evaluated for their biological role (see **Chapter** 1.2.1.).

1.1.1.4. Hydrogen bonding

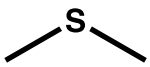
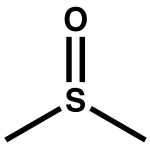
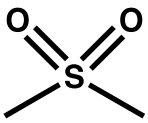
Owing to the highly polarized and unique dipole structure (see **Chapter** 1.1.1.1.), the sulfoxide group is able to form hydrogen bonds with various hydrogen donors by utilizing the oxygen atom in its sulfur-oxygen-bond.[39] In general, hydrogen bonding is considered as a weak attractive force which is taking place between two electronegative atoms sharing one proton with one another. The energy for hydrogen bonds can range from 10 to higher than 100 kJ/mol and is classified accordingly as weak to up to very strong interactions.[40] It is considered as one of the most significant and important chemical bonds in the field of chemical and biological sciences.

The tendency to form strong hydrogen bonds explains another remarkable physicochemical property of low molecular weight alkyl and/or aryl sulfoxides; their

hygroscopic nature. As a result, many sulfoxide-bearing compounds are quite easily dissolved in water or other protic solvents such as alcohols. This behavior can be attributed to the strong hydrogen bonding between the sulfur-oxygen bonds and water molecules in close similarity to the auto-association behavior.[41]

As described before, the polar sulfur-oxygen linkage with a partially positive charge on the sulfur and a partially negative charge on the oxygen atoms allows for the strong interaction with other polarized molecules. The evidence for strong intermolecular interactions is for example found for the boiling points and melting points of sulfoxides (and sulfones) compared to the corresponding sulfides. As a representative example the melting points, boiling points, and densities of dimethyl sulfide, dimethyl sulfoxide and dimethyl sulfone are compared (see **Table 2**). Here, the increasing values for the melting points (T_m), boiling points (T_b), and densities (r^{20}) account for the strong intermolecular interactions of the oxidized dimethyl sulfoxide and dimethyl sulfone compared to its sulfide analogue.

Table 2 Melting points (T_m), boiling points (T_b), and densities (r^{20}) of dimethyl sulfide, dimethyl sulfoxide and dimethyl sulfone show the strong intermolecular interactions of highly polarized dimethyl sulfoxide and dimethyl sulfone compared to its sulfide analogue.[a]

Molecule	T_m [°C]	T_b [°C]	r^{20} [g cm^{-3}]
	-98	37	0,85
	18	189	1,10
	107-110	238	-

[a] Physicochemical data are taken from *GESTIS-Stoffdatenbank*.

This trend can be explained through the auto-association behavior of sulfoxides. As one of the simpler examples, this was extensively studied for neat dimethyl sulfoxide. At room temperature, pure dimethyl sulfoxide molecules form a linear intermolecular association. This resembles a chain-like polymeric structure and is based on the dipole-dipole interactions of neighboring sulfur-oxygen bonds (see **Fig. 5(a)**).[42] However, with changing temperature and dilution, this linear association complex transforms to a dimer (see **Fig. 5(b)**).[39, 43-44]

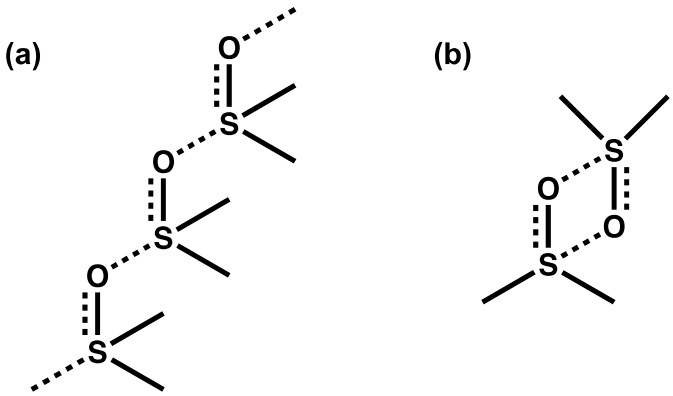


Fig. 5 Auto-association of dimethyl sulfoxide at **(a)** room temperature and **(b)** elevated temperature in dilution.

1.1.1.5. Electrochemical properties

The sulfur atom in sulfoxides has an intermediate oxidation state of +IV. Hence, the sulfoxide functional group can be reduced to thioethers with an oxidation state of +II and can be oxidized to the respective sulfones with an oxidation state of +VI (see Fig. 6).[45] As a result, the switching of these redox states can be used in reversible redox reactions. Another example are dithioether linkages, in which both sulfur atoms have an oxidation state of +I.

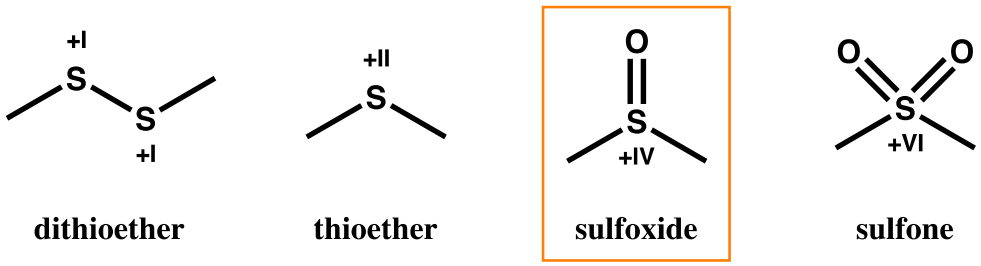


Fig. 6 Sulfur can be found in a variety of oxidation states. Besides the sulfoxide group with an oxidation state of +IV, further prominent examples include thioethers with S(+II), redox active dithioether linkages with S(+I), and sulfone groups with a sulfur oxidation state of S(+VI).

Based on the different oxidation states of the central sulfur atom, the corresponding functional groups exhibit unique properties. While sulfoxide groups are able to introduce chirality (see **Chapter** 1.1.1.3.) and good water solubility due to strong hydrogen bonds with water (see **Chapter** 1.1.1.4.),[41] thioether- and sulfone-containing compounds are known to show differing physicochemical properties. Thioether groups are highly hydrophobic and relatively flexible moieties that contribute to water insoluble compounds and less mechanically robust polymer materials.[46] In contrast, sulfones are known to be tough materials with high thermal resistance in which the sulfone groups only form relatively weak hydrogen bonds.[45,

[47] Additionally, dithioether bonds allow for the opportunity to introduce redox-responsive linkages in materials. The respective sulfur-sulfur bonds are quite stable and can be isolated under standard conditions. This represents a significant advantage over the often unstable and explosive peroxide-containing compounds.[48]

Overall, the drastic property changes between the different oxidation states allows to design compounds and materials with remarkable responsiveness. Such redox stimuli responsiveness may for example allow for the reversible switching of highly hydrophilic sulfoxide moieties to more rigid and hydrophobic thioether or sulfone groups with stark altered properties and applications. Thus, having the potential to introduce additional levels of variability to synthetic materials (see **Chapter 3.1.**).

1.2. Applications of low molecular weight sulfoxides

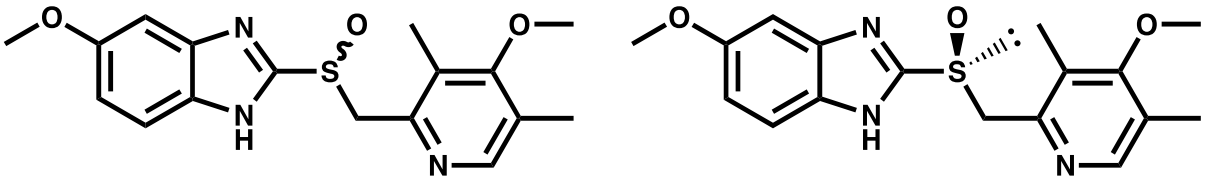
In the previous section the remarkable properties of the sulfoxide functional group were discussed. Based on its unique polar electronic structure it is used in advanced organic chemistry ranging from the introduction of chirality, and hydrophilicity to the utilization of redox responsiveness. Based on these properties a variety of interesting sulfoxide-containing low molecular weight compounds are reported. In the following sections some selected examples are given to show how defined properties of the sulfoxide functional group translate into the function of low molecular weight compounds.

1.2.1. Biological active sulfoxides

A number of biological active molecules exhibit a chiral sulfoxide moiety in their molecular structure.[15, 49] Thus, these compounds can exist as a pair of enantiomers with different pathways of *e.g.* metabolic activity and enzyme inhibition based on their stereogenic properties. In order to take this into account new guidelines and policy statements of the *United States Food and Drug Administration* (FDA) require the synthesis and determination of biological activity of both enantiomers of a pharmaceutically interesting chiral sulfoxide when proposed as a new potential stereoisomeric drug.[50]

One of the globally most profitable drugs in the year 2000 with a net selling worth of 6.2 billion US $ was the low molecular weight chiral sulfoxide *Omeprazole* (see **Fig. 7**). It is used as the leading gastric proton pump inhibitor.[51] However, racemic *Omeprazole* showed a so-called inter-individual variability in terms of pharmacokinetics which decreased its efficacy.

These findings lead to the development of the *(S)*-enantiomer of *Omeprazole*, *Esomeprazole* (see **Fig. 7**), which proved to be clinically superior in terms of bioavailability and potency.[52] This example shows the importance of the chirality that the sulfoxide moiety introduces into a bioactive molecule and its resulting metabolic effectiveness.



Omeprazole *(AstraZeneca)* **Esomeprazole** *(AstraZeneca)*

Fig. 7 Molecular structures of racemic gastric proton pump inhibitor *Omeprazole* and optically pure *(S)-Omeprazole* also known as *Esomeprazole*. The compounds illustrate the importance of chiral purity regarding the metabolic efficacy; *Esomeprazole* is pharmaceutically much more effective compared to *Omeprazole*.

Another interesting example is *Sulindac*, a sulfoxide-containing non-steroidal indene derivate used as an antiarthritic compound. It is administered as racemate, from which the prodrug is reduced to its active sulfide form.[53] It is noteworthy, that the fully oxidized sulfone derivate was found to be a complete inactive metabolite.[31] This example shows very well the interplay of chirality and oxidation state of the active sulfoxide compound in terms of its efficacy as pharmaceutical active molecule.

Other important biological active sulfoxides include the class of amino acid sulfoxides which are responsible for antibiotic activities,[54] the regulation of cholesterol catabolism[55] as well as for flavors and aroma precursors.[56] Furthermore, sulfoxides can act as inhibitors of uric acid biosynthesis,[57] which can prevent gout and is associated to help with diabetes and kidney stones. In addition, an acyl-CoA:cholesterol *O*-acyltransferase (ACAT) inhibitor,[58] potassium channel opener[59] and calcium channel antagonist,[60] antitumor and anticancer drugs[61-62] and, an immunosuppressor[63] are reported as sulfoxide-containing bioactives.

Overall, the chirality of sulfoxides exemplifies the importance of evaluating structure-activity relationships for drug enantiomers. Given the interest and value that chirality of sulfoxides holds in physiological challenges more comparable examples of sulfoxide-containing bioactives are currently developed and can be expected on the market.

1.2.2. Dimethyl sulfoxide (DMSO)

Dipolar aprotic solvents like acetonitrile, dimethylacetamide, dimethylformamide, nitrobenzene, and dimethyl sulfoxide are characterized, through their high dielectric constant (e > 15) and dipole moments (m > 3D).[64] Among these dipolar aprotic solvents, dimethyl sulfoxide (DMSO) is one of the most prominent and widely used example. Its importance ranges from its high solvent power for a wide variety of organic and inorganic compounds, its utilization in advanced organic and polymer chemistry to its physiological applications.[65]

DMSO in its pure state is an odorless, colorless, and hygroscopic liquid at room temperature. Its chemical structure resembles mainly two resonance hybrids with a polarized sulfur-oxygen bond (see **Chapter** 1.1.1.1., Fig. 2 structures I and II with R_1 and R_2 as methyl groups). Based on this polarization the molecule exhibits two proton acceptor sites; the oxygen atom with the highest electron density and the sulfur atom. While formally carrying a partially positive charge, this sulfur atom has a lone pair of electrons with nucleophilic properties. Thus, this unique electronic structure leads to strong polar intermolecular interactions *e.g.* auto-association (see **Chapter** 1.1.1.4.).

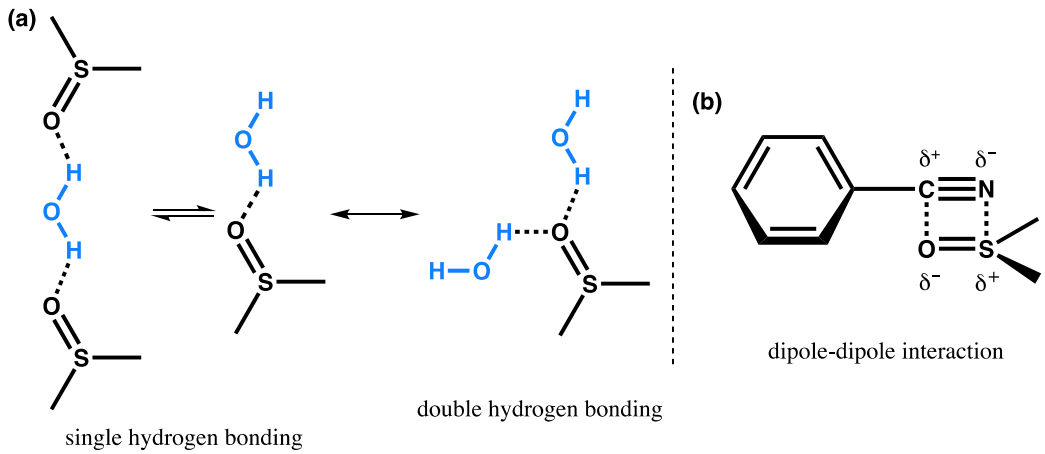


Fig. 8 Illustration of bonding events of DMSO with **(a)** water in binary mixtures (single and double hydrogen bonding with respect to DMSO) and **(b)** compounds exhibiting strong dipolar bonds.

DMSO forms strong intermolecular interactions with water molecules, too. It is able to disrupt the dynamic donor and acceptor balance in water though the ability to form up to two hydrogen bonds with its two oxygen lone pair electrons (see Fig. 8(a)). These hydrogen bonding interactions are reported to lead to different dynamic complex species in solution and determine the overall hydrophilic solution properties.[66]

Additionally, DMSO can build strong dipole-dipole complexes with nitrile- and ketone-containing molecules (see **Fig. 8(b)**).[64] Thus, further highlighting its solubilizing versatility. In addition to the solvent application, the shown properties also promote DMSO to be used as low molecular weight organic additive in the field of biomedicine. Here, it is utilized routinely *e.g.* as a denaturant, osmolyte and cryoprotective agent to study protein properties.[67-69] In the latter example, DMSO acts as cryoprotective agent, due to its ability to effectively disrupt water hydrogen bonding. This prevents ice formation and consequently inhibits cell and tissue damage during storage.[70]

1.2.3. Sulfoxides in organic synthesis and catalysis

The utilization of low molecular weight sulfoxides in modern organic synthesis is manifold. Their applications range from basic organic reagents, and chiral motifs in asymmetric synthesis to sulfoxide-containing ligands used for organometallic catalysis. Thus, it is not surprising that one of the most important reaction in synthetic organic and medicinal chemistry involves the use of dimethyl sulfoxide as an oxidation agent.

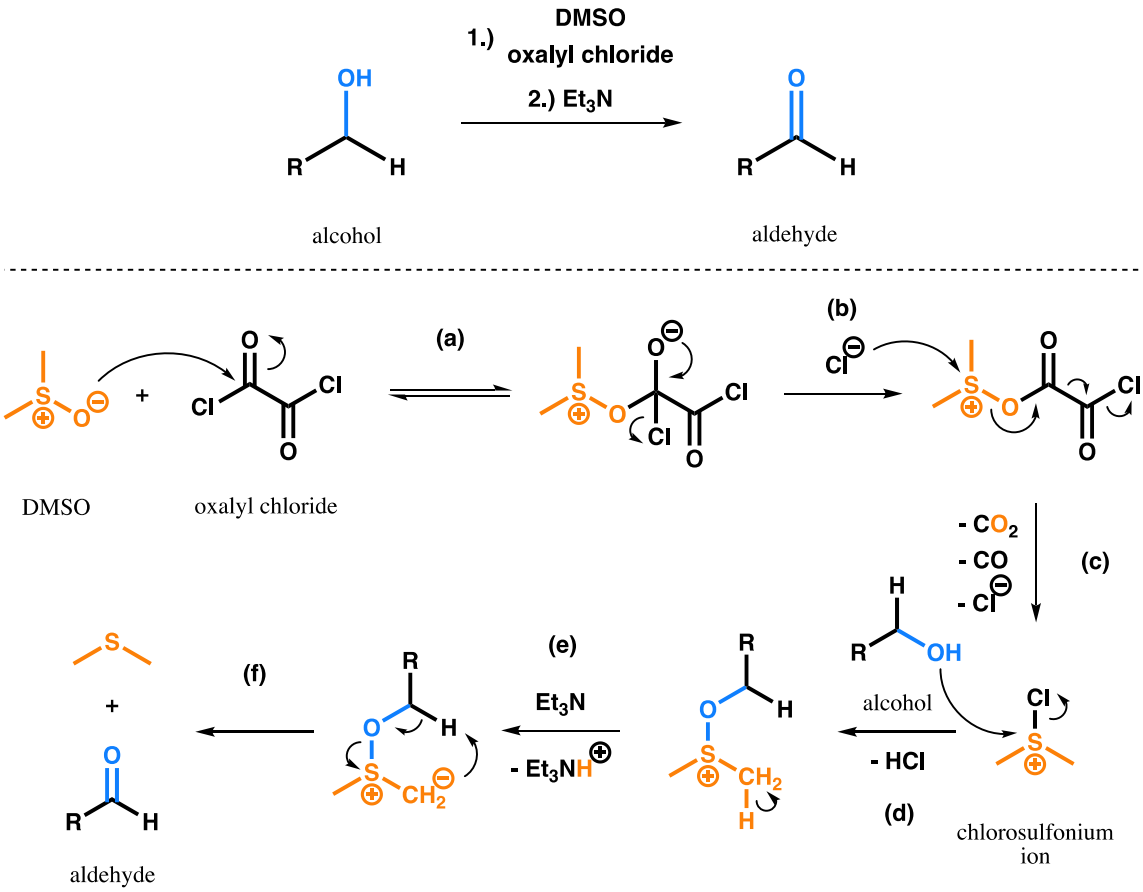


Fig. 9 The *Swern* oxidation reaction can be utilized to oxidize an alcohol to the respective aldehyde using DMSO and oxalyl chloride under basic conditions.

The *Swern* oxidation offers the transformation of alcohol groups to the respective aldehydes under mild basic conditions making it a versatile tool in the synthesis of various natural products (see **Fig. 9**). In general, the *Swern* oxidation reaction exploits the highly polarized sulfur oxygen bond in DMSO. Here, the oxygen atom is able to add via a nucleophilic addition reaction to the oxalyl chloride (see **Fig. 9(a)**). The resulting intermediate is quite unstable and reacts with a chloride ion (see **Fig. 9(b)**) to a highly reactive chlorosulfonium ion (see **Fig. 9(c)**). This is then able to react with an alcohol (see **Fig. 9(d)**). With the help of a base (see **Fig. 9(e)**), a final rearrangement occurs and the oxidation to the respective aldehyde compound is completed with the release of dimethyl sulfide as side product (see **Fig. 9(f)**).

One interesting example for the successful utilization of the *Swern* oxidation reaction is the final step in the total synthesis of the sesquiterpene dialdehyde isovelleral by Thompson and Heathcock (see **Fig. 10**).[71] In this synthesis the superiority of the *Swern* protocol is its mild and basic reaction conditions. This is in contrast to the acidic conditions of the *Jones* oxidation, which uses sodium dichromate in diluted sulfuric acid and could induce a possible rearrangement of the acid-sensitive cyclopropanemethanol moiety as side reaction.

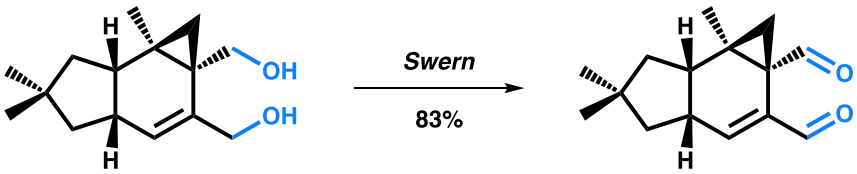


Fig. 10 Utilization of the *Swern* oxidation reaction to synthesize the acid-sensitive sesquiterpene dialdehyde isovelleral.

Another unique feature of the sulfoxide group which is extensively exploited in modern organic synthesis is its inherent chiral nature. One of the most prominent and powerful examples for the asymmetric transformation directed by a chiral sulfoxide group is the diastereoselective reduction of β-keto sulfoxides. First developed by Solladié and Kosugi, this methodology allows transferring the chirality from a sulfur atom to a carbon atom. This is achieved by appropriately choosing the stereocenter at the sulfur atom in the starting low molecular weight sulfoxide compound and the reduction conditions (see **Fig. 11**).[72]

Employing DiBAL-H as reducing agent, an initial intramolecular hydride transfer occurs through a six-membered cyclic transition intermediate. This intermediate forms an oxygen aluminum coordinative bond with the oxygen atom of the sulfoxide moiety, thus

directing the formation of the S_C,R_S-configurated β-hydroxy sulfoxide in good yields with high diastereoselectivities (see **Fig. 11(a)**).

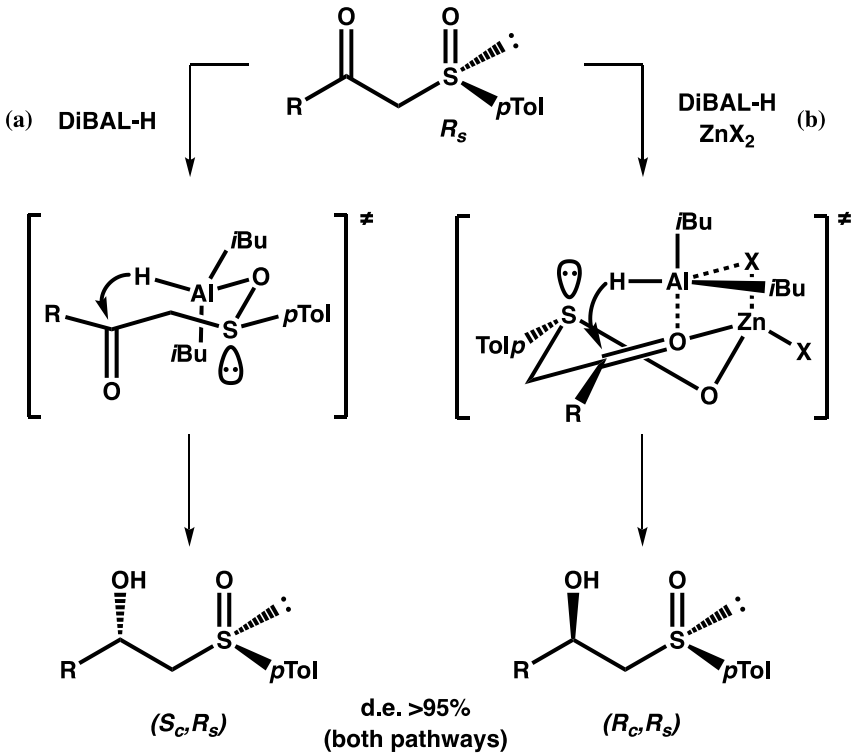


Fig. 11 The diastereoselective reduction of (*R*)-β-keto sulfoxides can be controlled via the presence of a chiral sulfoxide moiety and the suitable reduction reagent; **(a)** DiBAL-H and **(b)** DiBAL-H/ZnX_2.

In contrast, the utilization of the DiBAL-H/ZnX_2 results in the inversion of the diastereoselectivity leading nearly exclusively to the respective R_C,R_S-configurated β-hydroxy sulfoxide. This reaction route involves the initial formation of a chelation complex between both oxygen atoms of the sulfoxide and β-carbonyl functional groups with the zinc halide. The subsequent hydride attack from DiBAL-H occurs then on the less hindered site of the carbonyl group leading then to the final product (see **Fig. 11(b)**).

The previous example for the DiBAL-H/ZnX_2 system shows very well the interplay of the strong electron donor properties of the sulfoxide group and its chirality. Hence, chiral sulfoxide groups that are incorporated into metal binding ligands have emerged as superior and versatile compounds in enantioselective homogeneous catalysis. One of the earliest examples for the utilization of such ligands with a chiral center only at the sulfur atom was reported by Khiar and coworkers.[34] This bis(sulfoxide) ligand with C_2-symmetry was employed for the

Fe-catalyzed Diels-Alder reaction between an *N*-substituted acrylamide and cyclopentadiene (see Fig. 12(a)).

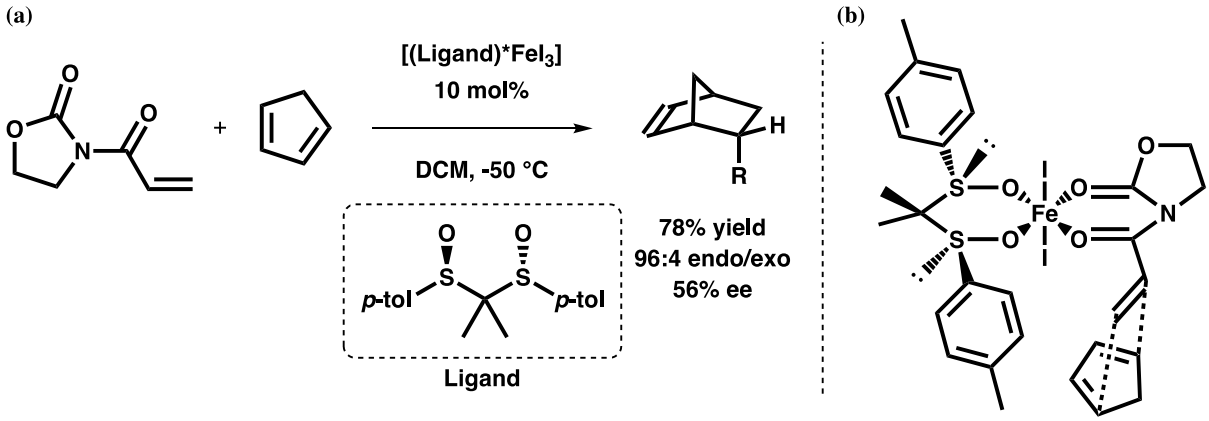


Fig. 12 The bis(sulfoxide) ligand with two chiral sulfur centers reported by Khiar and coworkers enable **(a)** the diastereoselective Diels-Alder reaction between an *N*-substituted acrylamide and cyclopentadiene. The directing function of the sulfoxide ligand is realized through **(b)** a proposed dual-six-membered bicyclic metal complex.

The bicyclic Diels-Alder product is obtained with exceptional diastereoselectivity in high yields and good enantiomeric excess (*ee*). The chiral bidentate ligand is hypothesized to bind through its two oxygen atoms of the sulfoxide groups to form a dual-six-membered bicyclic metal complex (see Fig. 12(b)). The enantioselectivity is explained based on the selective approach of the cyclopentadiene compound in trans position to the bulky aryl sulfoxide substituent of the bis(sulfoxide) ligand.

1.2.4. Sulfoxides as dermal penetration enhancers

To enhance dermal drug delivery specific chemical structures have been established as chemical penetration enhancers.[73-74] Such molecules include alcohols, fatty acids, pyrrolidones, phospholipids, sulfoxides, and others, which have been shown to effectively disrupt the highly ordered stratum corneum (SC) and dramatically increase drug permeation as a result.[75-76]

Amongst these chemical accelerants, dimethyl sulfoxide (DMSO) is known as one of the most potent and effective example.[74] It is an aprotic solvent with an inherent amphiphilic nature (see **Chapter** 1.2.2.) and the ability to promote permeation of both hydrophilic and lipophilic compounds.[77] While the mechanism is still not completely clarified, it is suggested that the penetration enhancing properties stem from two features: First, DMSO is able to

denature skin proteins, thus disturbing the integrity of the corneodesmosomes and corneocytes. For instance, it is able to change the intercellular keratin confirmation from α-helical to β-sheets.[78] Second, due to its amphiphilic nature, it can strongly interact with the lipid bilayers, thereby distorting their packing geometry.[79] As a consequence, the functional sulfoxide groups uniquely accelerate molecular penetration by channeling drugs though the perturbated skin barrier.

These findings are supported by molecular dynamics simulations of dermal cell membranes in the presence of DMSO.[80-81] Initially, DMSO facilitates the fluidity of the lipid bilayer and induces its thinning (see **Fig. 13(a, b)**). This can lead to the formation of pores in the cell membrane and as consequence lets water into the lipid bilayer (see **Fig. 13(c)**). If enough water molecules flow into the membrane, reorganization of the lipid head groups takes place to minimize the Gibb's free energy of the system. Finally, this disintegration of the lipid bilayer structure allows for the facilitated transport of drug compounds (see **Fig. 13(d)**).

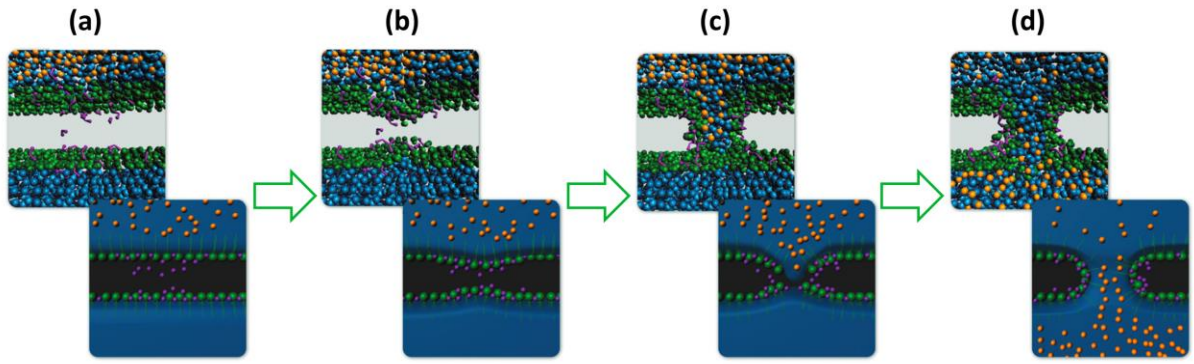


Fig. 13 Molecular dynamics simulation of the lipid bilayer membranes of skin indicate pore formations in the presence of aqueous dimethyl sulfoxide (DMSO, 10 mol%). DMSO facilitates the fluidity of the membrane **(a)** leading to its thinning **(b)** and ultimately to the formation of pores **(c)** and channelling of drug compounds **(d)**. Colour code: DMSO (purple), water molecules (blue), lipid head groups (green), and drug compounds (orange). (Adapted with permission from *Taylor & Francis*, see Reference [82])

Although effective, the dermal protein and bilipid layer disruption can lead to skin irritations and long-term damages of the protective features of human skin.[83-84] In addition, the disturbed barrier does not allow for restricting DMSO and drug molecules to specific skin layers, thus causing systemic exposure and corresponding side effects.

1.3 Sulfoxide-containing polymers

As we have seen in the previous sections, the sulfoxide group is a very interesting functional moiety due to its manifold unique physicochemical properties. With its highly dipolar nature it has been increasingly utilized as useful structural element to promote hydrophilicity in low molecular weight compounds via strong hydrogen bonding such as in DMSO (see **Chapter** 1.1.1.4. and **Chapter** 1.2.2.) and as solubilizing and penetration enhancing agents at the interface of biology and chemistry (see **Chapter** 1.2.4.) Additionally, the introduction of chirality has proven to be an essential element in modern organic synthesis (see **Chapter** 1.2.3.) and in the development of new drugs in the pharmaceutical sciences (see **Chapter** 1.2.1.).

Consequently, the sulfoxide group is used to translate and introduce these physicochemical properties into the fields of polymer and materials sciences. In recent years, the development of new non-ionic polar polymers has played a crucial role in facing challenges in the biomedical field such as in drug delivery. As a result, new sulfoxide-based materials have emerged to address these challenges.

1.3.1 Classes of sulfoxide-containing polymers

The position of the sulfoxide moiety in the polymer architecture can dictate its macromolecular properties. While this can influence its synthetic feasibility, it is also important for the overall function of the polymer in the final application. Hence, it may be beneficial to distinguish sulfoxide-containing polymers regarding their polymer architecture. That is why in the following, polysulfoxides are classified into polymers bearing the sulfoxide moiety in the polymer backbone, *i.e.* main chain polysulfoxides, and polymers where the sulfoxide group is incorporated as pending group, *i.e.* side group polysulfoxides (see Fig. 14).

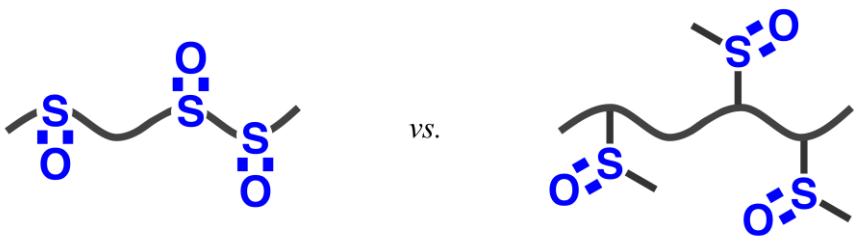


Fig. 14 Sulfoxide-containing polymers can be distinguished based on the position of the sulfoxide groups in the polymer architecture, *i.e.* main chain vs. side group polysulfoxides.

In the following sections, the structural properties of different examples for main chain polysulfoxides and side chain polysulfoxides are discussed. Subsequently, the respective polymerization routes are elaborated.

1.3.1.1. Main chain polysulfoxides

The subgroup of sulfoxide-containing polymers in which the sulfoxide moiety is present in the polymer backbone can be further divided with respect to the structural nature of the polymer backbone. Hence, this subgroup includes aliphatic, arylene and mixed aliphatic/arylene polymers. In the first class, different aliphatic polysulfoxides are reported (see **Fig. 15**). Examples for these polymers are polyethylene sulfoxide (PES) (see **Fig. 15(a)**) and polypropylene sulfoxide (PPS) (see **Fig. 15(b)**).[85-86] These polymers exhibit a solely aliphatic ethylene (C_2) backbone with a branching methyl group in the case of the poly propylene polymers. Both polymers closely resemble the well-known structures of polyethylene glycol (PEG) and polypropylene glycol (PPG) in which the bridging oxygen atom is replaced with a highly polar sulfoxide group.

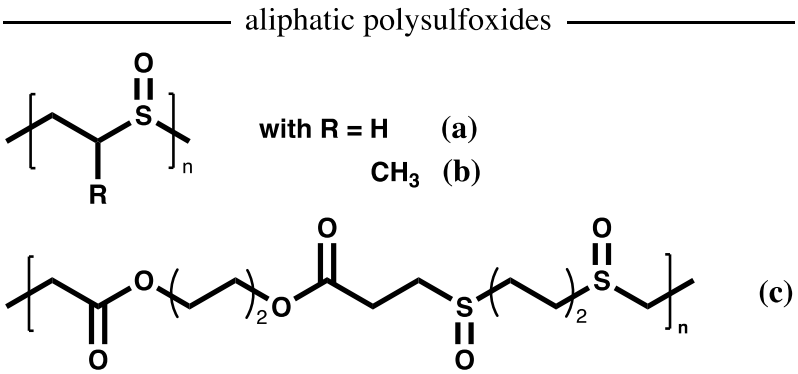


Fig. 15 Aliphatic main chain polysulfoxides exhibit an ethylene backbone which can include additional functional linkages like ester bonds. Examples are **(a)** polyethylene sulfoxide (PES), **(b)** polypropylene sulfoxide (PPS), and **(c)** sulfoxide-containing polyesters.

Another example is given by sulfoxide-containing polyesters (see **Fig. 15(c)**).[87] Here, the aliphatic parts of the polymer backbone with the incorporated sulfoxides moieties are connected through biodegradable ester bonds, thus introducing an additional backbone functionality. Both shown polymers, the solely aliphatic and the ester linked polysulfoxides, are in particular characterized through their increased chain flexibility which is based on the tetrahedral sp^3-carbons.

The second subgroup includes the arylene polysulfoxides (see Fig. 16). These polymers are mainly characterized by the incorporation of one or several aryl groups into the repeating units of the polysulfoxide. One simple example is given by poly(*p*-ethyl benzene sulfoxide) in which the sulfoxide group is directly connected to one single benzene ring and an ethyl spacer (see Fig. 16(a)).[88] In contrast to that, polysulfoxide **(b)** in Fig. 16 exhibits several arylene groups in its polymer backbone.[89-90] Here, ether bonds as well as sulfoxide groups function as linkages between the ring structures in each repeating unit (see Fig. 16(b)).

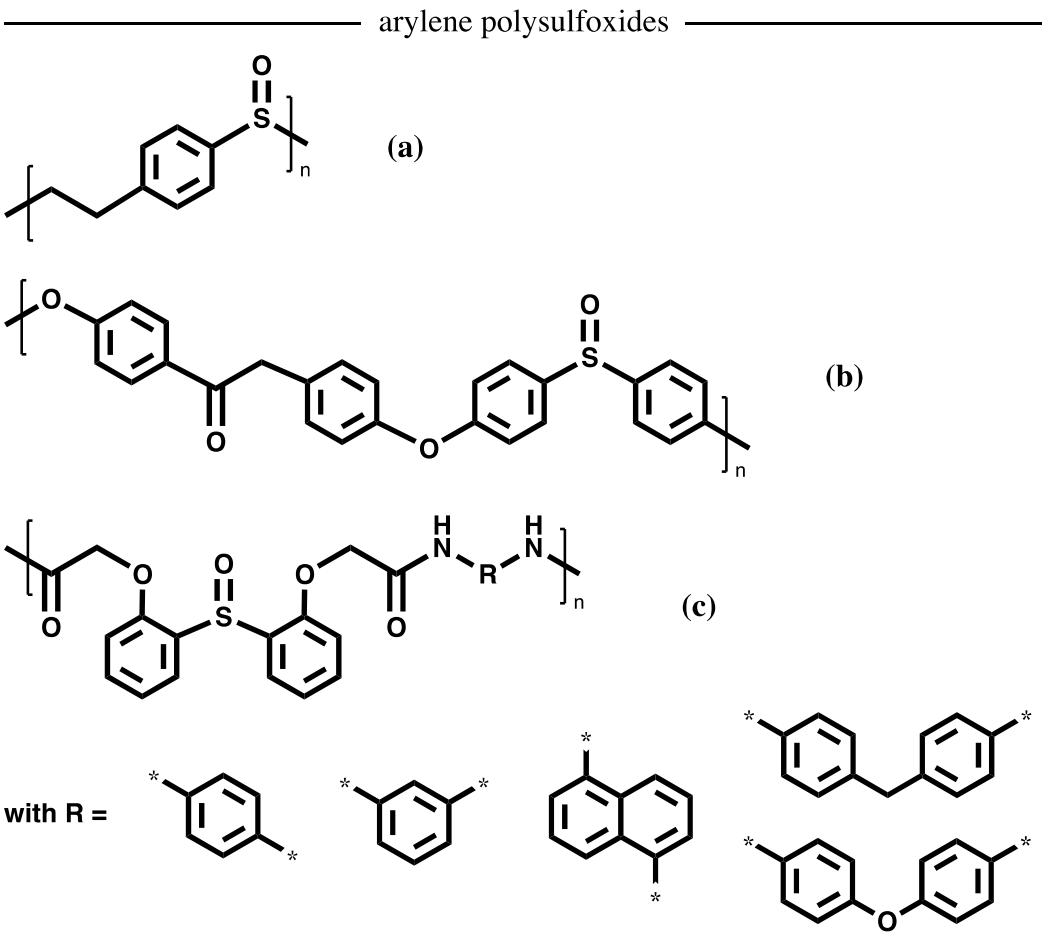


Fig. 16 Arylene polysulfoxides are characterized through their incorporation of one or more substituted aromatic benzene rings in their repeating units. Examples are **(a)** poly(*p*-ethyl benzene sulfoxide), **(b)** deoxybenzoin-containing polysulfoxides, and **(c)** arylene poly(ether-amide-sulfoxide).

Finally, the introduction of further backbone functionality such as biodegradable amide groups is reported to increase the polymers' variability, *e.g.* in the case of arylene poly(ether-amide-sulfoxide)s (see Fig. 16(c)).[91-92] Overall, due to the planar and rigid benzene rings the chain flexibility of arylene polysulfoxides is generally more hindered than in aliphatic

polysulfoxides. However, through incorporation of functional units such as ether bonds this structural rigidity can be countered.

The third subgroup is based on mixed aliphatic/arylene polysulfoxides. Here, the repeating units of the polymer contain both aliphatic and arylene structural elements successively connected to each other (see Fig. 17).[93-94] Hence, these polysulfoxides exhibit further increased chain flexibility compared to their pure arylene sulfoxide analogues.

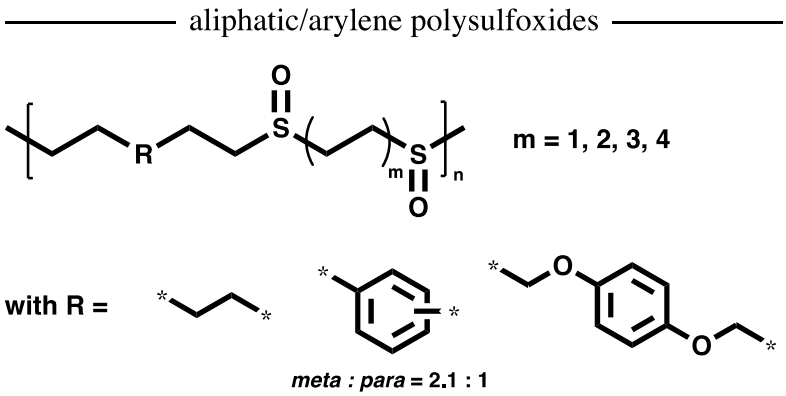


Fig. 17 Mixed aliphatic/arylene polysulfoxides comprise both aliphatic and arylene structural elements which are connected successively to each other.

1.3.1.2. Side group polysulfoxides

The subgroup of sulfoxide-containing polymers in which the sulfoxide group is present as side group of the polymer can be also further divided with respect to its polymer backbone. Hence, this subgroup includes polyethylenes, polyethylene oxides, polypeptides, poly(meth)acrylates, poly(meth)acrylamides, and conjugated polymers with a semi-conductive backbone.

Regarding the first group of sulfoxide-containing polyethylenes, the simplest ones are poly(*alkyl* vinyl sulfoxide)s (see Fig. 18(a)).[95-96] These polymers exhibit a pure aliphatic ethylene backbone with different *alkyl* sulfoxide side groups. This polymer class closely resembles the well-known structure of polyvinyl ethers in which the ether group is replaced with a polar sulfoxide group. The functional sulfoxide moieties themselves are closely connected to the polymer backbone. In the case of poly(*arylene* vinyl sulfoxides)s the polyethylene backbone and the *alkyl* sulfoxide side groups are separated by a benzene moiety, which places the sulfoxide group further away from the polymer backbone (see Fig. 18(b)).[97]

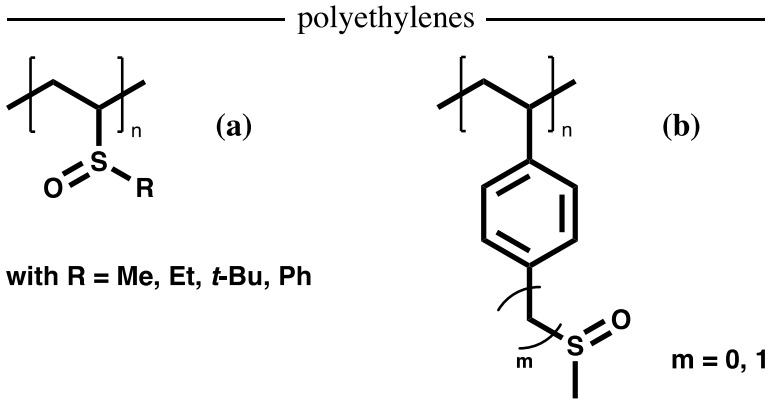


Fig. 18 Examples for side group polysulfoxides based on a polyethylene polymer backbone are **(a)** poly(*alkyl* vinyl sulfoxide)s and **(b)** poly(*arylene* vinyl sulfoxide).

Similarly to the sulfoxide-containing polyethylenes, sulfoxide-functionalized polyethylene oxides exist, too. A prominent example is poly(methyl glycidyl sulfoxide) (see Fig. 19(a)).[98] Here the alkyl sulfoxide functional group is introduced at the α-position with respect to the ethylene oxide repeating unit. On the other hand, poly(oxyethylene sulfoxide) shows the pending sulfoxide side group at the β-position (see Fig. 19(b)).[99] Both polymers are characterized through their hydrophilic polyethylene glycol backbone and hydrophilic sulfoxide side groups. In addition, sulfoxide-functionalized polypeptides are also developed. Here, various alkylated poly-*L*-methionine sulfoxides exhibit not only a hydrophilic peptidic backbone but additional chirality due to the chiral nature of the *L*-methionine sulfoxides amino acid (see Fig. 19(c)).[100-102]

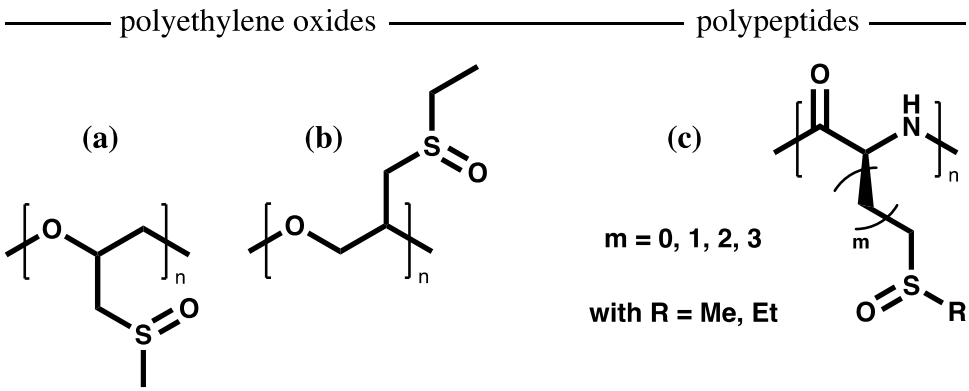


Fig. 19 Side group polysulfoxides based on a polyethylene oxide and polypeptide polymer backbone are **(a)** poly(methyl glycidyl sulfoxide, **(b)** poly(oxyethylene sulfoxide)s, and **(c)** poly(*alkyl* sulfoxide amide)s.

A growing class of side group sulfoxides is based on poly(*meth*)acrylate and poly(*meth*)acrylamide polymer backbones. Here, a wide variety of different sulfoxide-

containing side groups are introduced; From incorporation of linear alkyl sulfoxide groups in poly(methyl sulfoxide (*meth*)acrylate) (see Fig. 20(a)),[13, 103] over cyclic (cyclopropyl or cyclohexyl) sulfoxides in poly(cycloalkyl sulfoxide (*meth*)acrylate)s (see Fig. 20(b))[104] to the introduction of more complex variations of side group functionalities in poly(*alkyl* arylene sulfoxide acrylate)s (see Fig. 20(c)).[105] In the case of the poly(*meth*)acrylamides further functionalities are introduced such as perfluoroalkyl groups in poly(perfluoroalkyl sulfoxide (*meth*)acrylamide)s (see Fig. 20(d))[106-107] as well as secondary cycloalkyl amide groups, namely poly(cyclohexyl sulfoxide acrylamide) (see Fig. 20(e)).[104] Overall, these examples show the wide variety of side group functionalities that can be utilized in the pending groups of the respective poly(*meth*)acrylates and poly(*meth*)acrylamides. Moreover, it demonstrates the tolerance of two or more functional moieties in one side group.

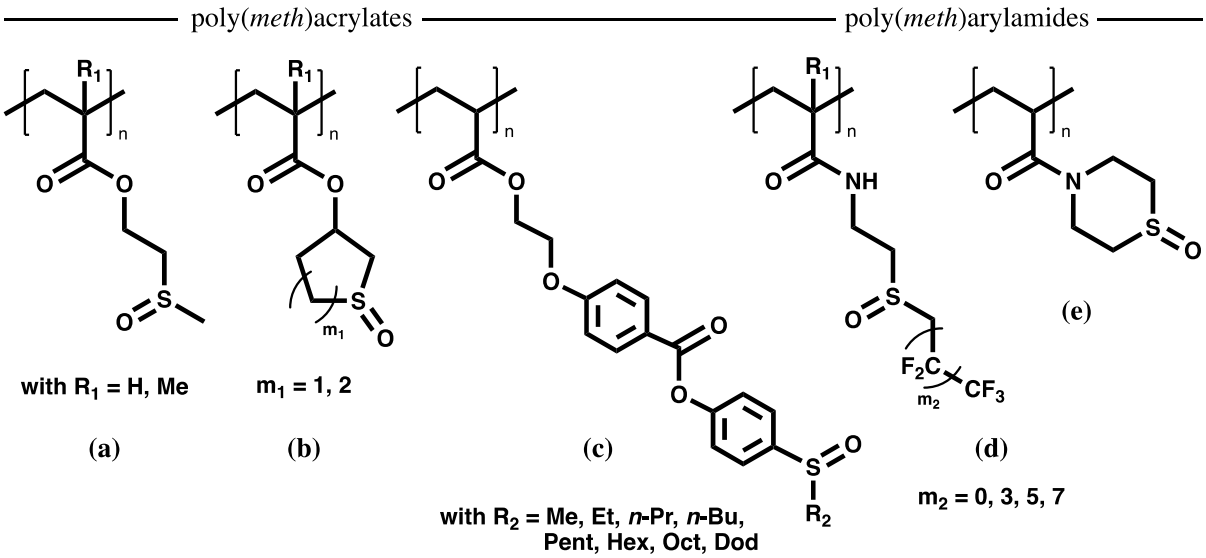


Fig. 20 A growing number of side group polysulfoxides based on a poly(*meth*)acrylate or poly(*meth*)acrylamide polymer backbone are reported. Examples are **(a)** poly(methyl sulfoxide (*meth*)acrylate)s, **(b)** poly(*cycloalkyl* sulfoxide (*meth*)acrylate)s, **(c)** poly(*alkyl* arylene sulfoxide acrylate)s, **(d)** poly(perfluoroalkyl sulfoxide (*meth*)acrylamide)s, and **(e)** poly(cyclohexyl sulfoxide acrylamide).

Finally, sulfoxide-functionalized polymers with a π-electron-conjugated polyalkylene backbone were developed. These semi-conductive polymers are characterized through a very rigid backbone architecture which defines high T_g and causes limited solubility due to π-π stacking and overall high hydrophobicity. However, through the introduction of hydrophilic sulfoxide moieties in the polymer side group like in poly(dipropargyl sulfoxide) (see Fig. 21(a))[108] and simple alkyl sulfoxide groups such as in poly(*alkyl* sulfoxide

thiophene)s (see Fig. 21(b))[109] this rigidity can be countered through additional polar and flexible side group structures. Thus, enhancing solubility and processibility.

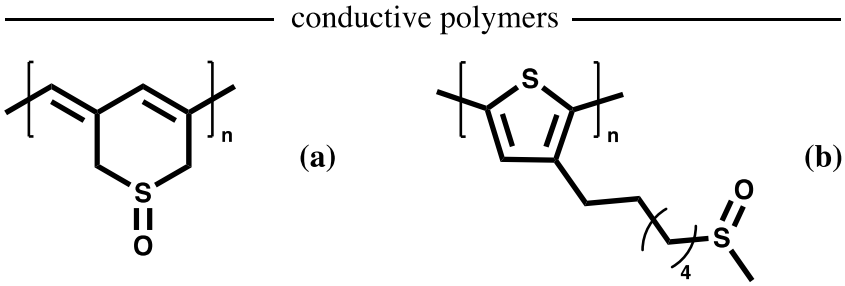


Fig. 21 Examples for side group polysulfoxides based on a conductive polymer backbone are **(a)** poly(dipropargyl sulfoxide) and **(b)** poly(alkyl sulfoxide thiophene)s.

1.3.2. Preparation of polysulfoxides

As seen in the previous section, a wide variety of sulfoxide-containing polymers are reported. Based on their polymer architecture, the sulfoxide group can be combined with additional functional moieties such as ether, ester and amide linkages as well as arylene and perfluoro groups. In all cases, the sulfoxide moieties can be located either in the main chain or side group of the respective polymer. The synthetic accessibility of these different polymer architectures requires robust and versatile polymerization techniques to ensure functional group tolerance. Hence, different polymerization methods are reported for the preparation of either main chain or side chain sulfoxide-functionalized polymers.[8]

1.3.2.1. Synthesis of main chain polysulfoxides

A general concept for the formation of main chain sulfoxide-functionalized polymers is based on the controlled oxidation of the respective main chain polysulfides (see Fig. 22). For this purpose, various oxidizing agents are reported. These include for example bromine, hydrogen peroxide, peracids, nitric acid, and tert-butyl peroxide. However, using these agents, difficulties in avoiding the oxidation reaction until the sulfone polymer analogues may arise.

In this manner, poly(phenylene sulfoxide) and poly(*p*-phenoxy phenyl sulfoxide) (similarly to the polymer structures shown in **Chapter** 1.3.1.1., Fig. 16) were prepared via oxidation with nitric acid or hydrogen peroxide. Importantly, no overoxidation to sulfonyl groups was reported.[110-111]

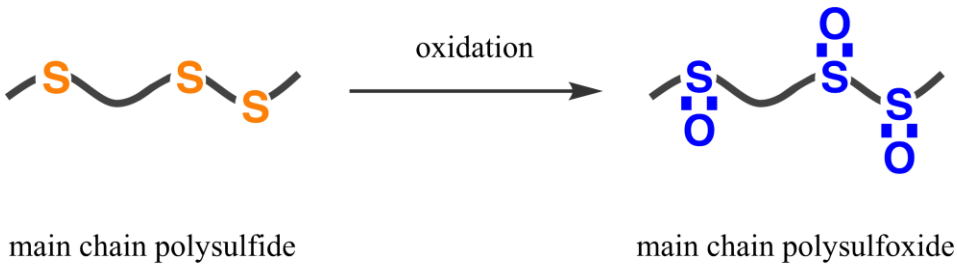


Fig. 22 A straightforward method to prepare main chain polysulfoxides is the controlled oxidation of the respective main chain polysulfides.

More recently, great efforts were made for the selective and quantitative conversion of atactic poly(propylene sulfide)s to the respective poly(propylene sulfoxide)s. The subsequent oxidation reactions were carried out in either homogenous or two-phase systems using stoichiometric equivalents of bromine, hydrogen peroxide, or *meta*-chloroperoxybenzoic acid.[9, 85, 112]

Furthermore, mixed aliphatic/arylene main chain polysulfoxides with different chain lengths between the sulfoxide moiety and arylene groups were synthesized. Here, in a first step, a step growth polymerization via polyaddition of different diolefins with dithiols was used to prepare the initial polysulfides (see Fig. 23). The resulting polymers were then oxidized with aqueous hydrogen peroxide to achieve the final polydisulfoxides with M_n = 1600 – 6500 g/mol and typically moderate to increased polydispersities of 1.23 – 2.77.[93-94]

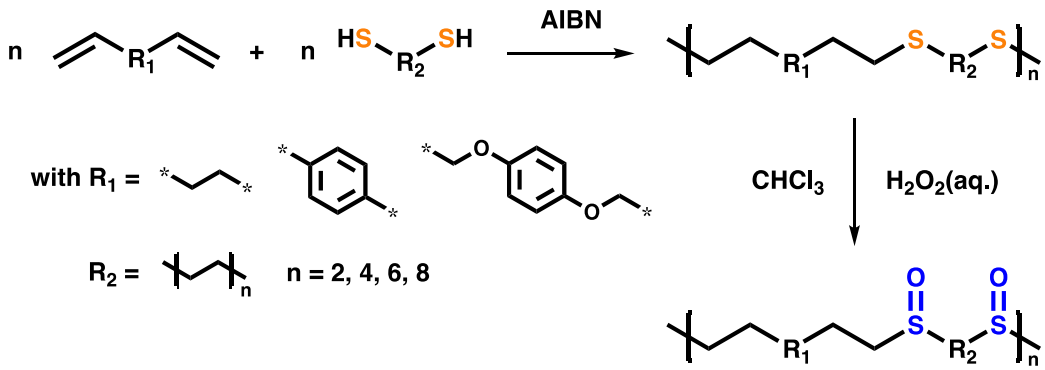


Fig. 23 Mixed aliphatic/arylene main chain polysulfoxides are prepared via initial thiol-ene polyaddition reaction between diolefins and dithiols and subsequent oxidation reaction of the resulting main chain polysulfide analogues.

Oxidation conversions were reported to reach up to 92% and were confirmed by spectroscopical analysis. In close similarity to this approach, a series of complex arylene poly(ether amide sulfoxide)s were synthesized via phosphorylation polycondensation, as

another step growth polymerization type, of functional dicarboxylic acids with diamines.[91-92] The utilization of chiral oxidation agents such as *N*-sulfonyl oxaziridines allowed also for the preparation of optically active main chain sulfoxide-containing polymers. For this, an asymmetric oxidation methodology was employed and, as a result, polysulfoxides with an enantiomeric excess (*ee*) of about 91% were achieved (see Fig. 24).[88]

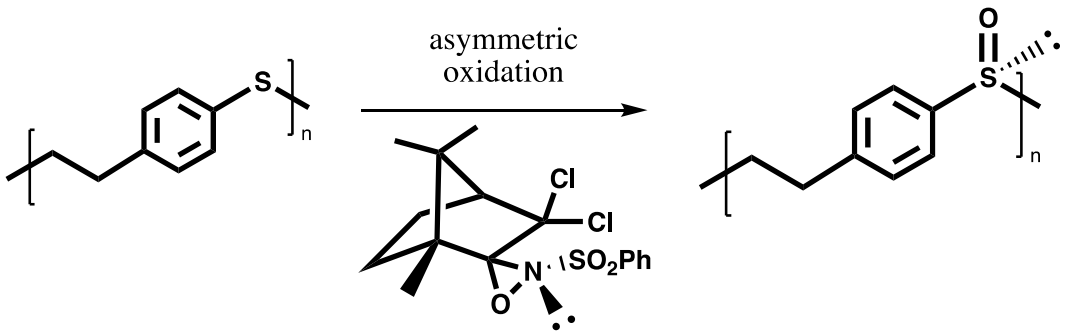


Fig. 24 The asymmetric oxidation of a main chain polysulfide can be realized by using *N*-sulfonyl oxaziridine as chiral oxidation agent.

Overall, these examples demonstrate that a wide variety of main chain polysulfoxides can be realized either by using simple oxidation reactions of already prepared polysulfides or initially synthetized functional polysulfides by step growth polymerizations. While these approaches are generally easy to perform, problems can arise from incomplete oxidation or even overoxidation events. Furthermore, polyaddition and polycondensation may prove to be challenging to achieve high molecular weight polymers with narrow polydispersities. To counter these problems the realization of other polymer architectures with different polymerization techniques are sometimes required such as controlled radical polymerizations.

1.3.2.2. Synthesis of side group polysulfoxides

The toolbox for the preparation of side group polysulfoxides is manifold. While the subsequent oxidation of the respective side group polysulfides is similar to the oxidation of their main chain polysulfide analogues, the direct polymerization of sulfoxide bearing monomers show great advantages (see Fig. 25). Such monomers include structures where the sulfoxide moiety is attached to the polymerizable vinyl group via aliphatic or aromatic spacers or directly connected as in vinyl methyl sulfoxide and vinyl phenyl sulfoxide (see **Chapter** 1.3.1.2. for structures). These monomers can be polymerized to achieve the sulfoxide-containing polymers without

subsequent post-polymerization oxidation procedures.[97, 113-114] In addition, this method can also be successfully applied for the preparation of different sulfoxide-bearing copolymers.[95]

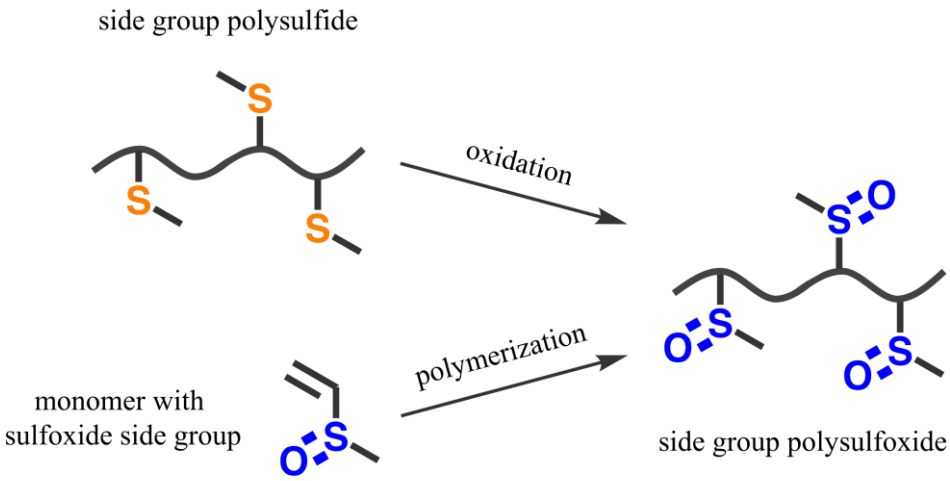


Fig. 25 The synthesis of side group polysulfoxides can be achieved either by oxidation of the respective side group polysulfides or through direct polymerization of the corresponding sulfoxide-bearing monomers.

Another approach focuses on polyether backbones bearing sulfoxide pending groups. For these materials, the ring opening polymerization of either α- or β-*alkyl* glycidyl sulfoxides (see Fig. 19) results in polymers closely resembling the structure of highly hydrophilic polyethylene oxide while allowing the introduction of an additional hydrophilic alkyl sulfoxide moiety.[98-99] More recently, the ring opening polymerization of different *alkyl* sulfoxide *N*-carboxyanhydrides led to a class of functional sulfoxides bearing polypeptides.[101]

While free radical or ring opening polymerization methodologies are powerful tools to introduce pending functional side groups, their lack in either controlling the molecular weight, molecular weight distribution and chain ends was found to limit their range of applications. Addressing this challenge, controlled radical polymerization techniques such as atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerization have emerged and the design and synthesis of side group sulfoxide-containing polymers shifted significantly. Hence, a wide variety of functional (*meth*)acrylate and (*meth*)acrylamide monomers were designed to enable the preparation of multi-functional polymeric materials. In past years, multiple examples of side group sulfoxide-functionalized poly(*meth*)acrylates and poly(*meth*)acrylamide are reported (see **Chapter** 1.3.1.2.). These examples range from the controlled polymerization of simple methyl ethylene sulfoxide acrylate[12-13, 103] and a family of further *alkyl*/*cycloalkyl* ethylene sulfoxide (*meth*)acrylates[104,

[115] to monomers with multiple functional groups such as arylene, ether, ester and perfluoroalkyl moieties.[105, 107] For all these variety of monomers, ATRP and RAFT polymerization ensures the functional group integrity along the polymerization reaction while allowing for tackling different polymer architectures like random or block copolymers, brushes and further branched polymer structures.

1.3.3 Properties and applications of polysulfoxides

As discussed in the previous sections, small molecular weight sulfoxides are utilized in a wide variety of applications that use their unique physicochemical properties (see **Chapter** 1.2.). These properties can be either fully or partially ascribed to the presence of one or more sulfoxide moieties in the molecular structure.

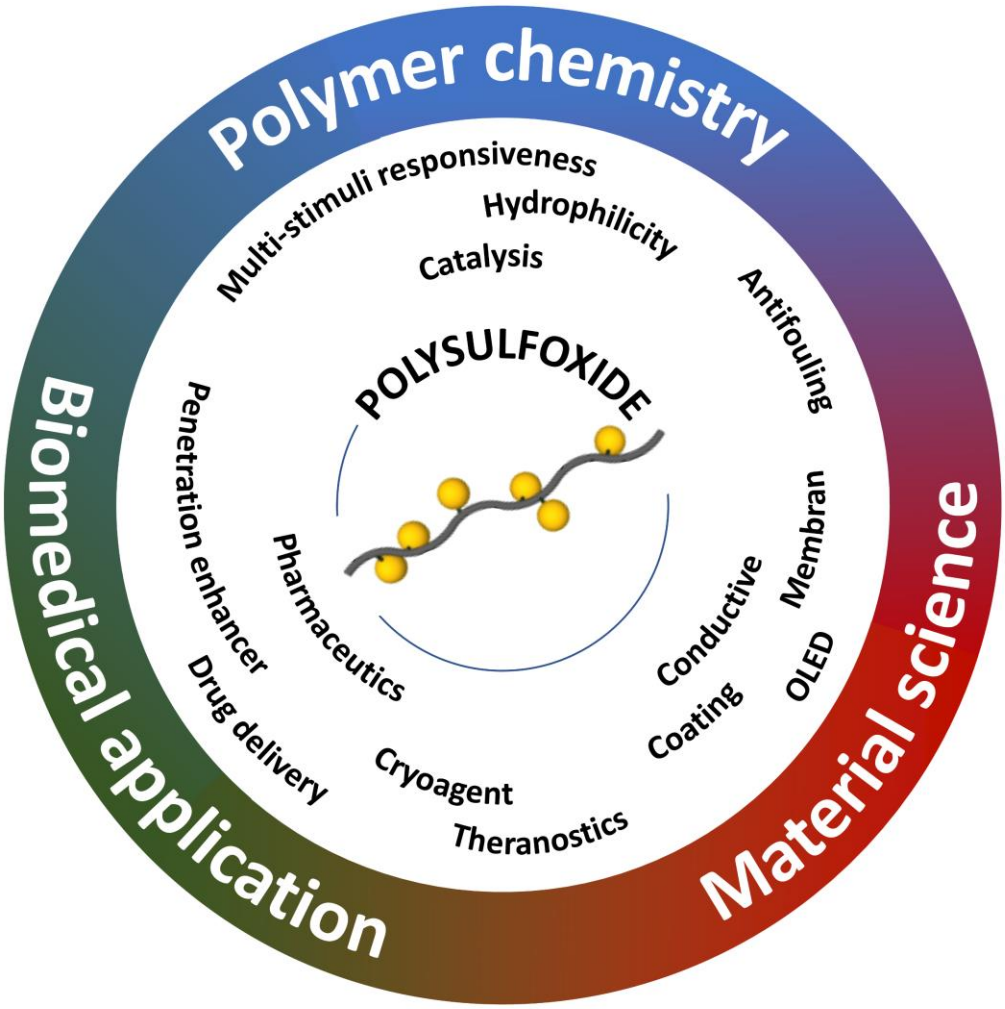


Fig. 26 The presence of sulfoxide groups as versatile functional moieties in a large and ever-growing number of polymeric compounds enables their use in the field of polymer chemistry, material sciences, and biomedical applications.

This approach led to the design and development of new sulfoxide-containing functional macromolecules which were then translated into functional materials with potential biomedical use and further interdisciplinary applications. Fig. 26 shows the versatility of such polymeric materials and their applications.

1.3.3.1. Polymer chemistry and organic synthesis

The introduction of sulfoxide groups can significantly enhance the properties of a given polymer. Based on the highly polar and partially ionic character of the sulfoxide moiety, polysulfoxides are reported to be utilized as catalysts for reactions via two- or three-phase transfer conditions.[114, 116] For instance, poly(hexamethylene sulfoxide) was found to catalyze the Swern oxidation of primary and secondary alcohols.[93] Likewise to the conventional Swern oxidation reaction with dimethyl sulfoxide (see **Chapter** 1.2.3.), octanol and undecane-6-ol were oxidized in this case to give the respective aldehydes or ketones in high yields.

1.3.3.2. Material science

The incorporation of few sulfoxide groups as pending moieties onto polymer chains was shown to keep the high melting temperatures (T_m's) while improve the mechanical and surface properties of functionalized polyethylenes. Additionally, these polymers can be used as compatibilizers and polymer solvents. The miscibility of such amphipathic sulfoxide-containing polymers with commonly known polymers was examined by evaluating glass transition temperatures (T_g's) of the polymer mixtures and T_g's of the native polymers by dynamic scanning calorimetry (DSC). As a result, polysulfoxides were found to exhibit good miscibility with *e.g.* poly(2-methyl-2-oxazoline) and poly(*N*-vinylpyrrolidinone).[94]

Furthermore, the exceptional dielectric constant (ε_r) of sulfoxide groups (see **Chapter** 1.1.1.2.), as another unique physicochemical property, emerged as a new way to meet the challenge for designing and developing new organic semiconductors with tunable and overall high dielectric constants. This is based on the fact that sulfoxide moieties have shown the potential to significantly enhance the performance of organic light-emitting diode displays (OLEDs) by promoting for example its electron carrier mobility.[109]

Another interesting aspect of polysulfoxides in material sciences is based on using the chirality of its functional units. That is why chiral, sulfoxide-containing polymers can be utilized as stationary phases in chiral high pressure liquid chromatography (HPLC) columns to separate pharmaceutically relevant bioactives.[88]

1.3.3.3. Biomedical applications and biomaterials

Sulfoxide groups are strong hydrogen bond acceptors and are therefore very hydrophilic. In polymers, side-group sulfoxide poly(*meth*)acrylates are known for their very low cytotoxicity and excellent biocompatibility with potential applications in pharmaceutical and medical sciences. In particular, poly(ethyl sulfoxide acrylate)s were investigated from early on to exhibit biological activity. Due to their strong inherent hydrophilicity, polysulfoxides were also proposed to have properties similarly to polyethylene glycol (PEG). Furthermore, functional polymers are developed by combining the properties of PEG with DMSO-like functionalities to achieve polymeric cryoprotectants (see **Fig. 27**). These poly(methyl glycidyl sulfoxide)s show extraordinary effective post-thaw recovery of *e.g.* 3T3 cells and normal human fibroblast cells.[98]

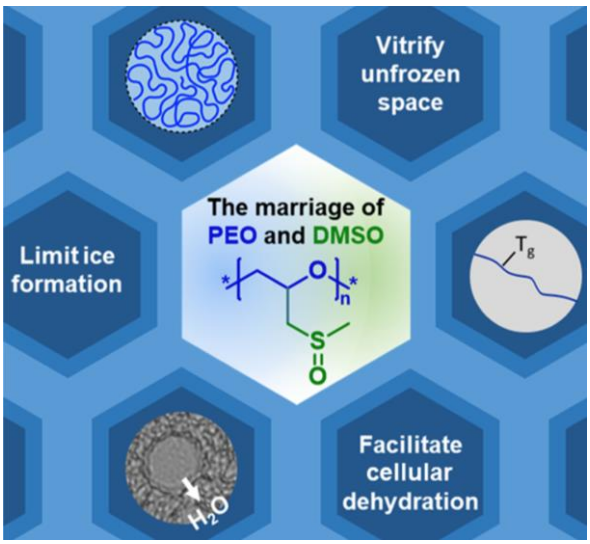


Fig. 27 Enhanced polysulfoxide-mediated cryopreservation using poly(methyl glycidyl sulfoxide). The polymer is proposed to mitigate the mechanical and osmotic stress that the freezing process imparts on cells by limiting the amount of water that freezes and facilitating cellular dehydration. (*Reproduced with permission of The Royal Society of Chemistry, see Reference* [98])

More recently, polysulfoxides have emerged as a very promising class of low-fouling polymer materials. Due to the presence of highly polar sulfoxide groups in the side group, sulfoxide-containing polymers were found to present exceptional solubility in water and other polar protic solvents. These properties enable the polymer to impart its superior low-fouling behavior to a wide variety of materials by functionalizing and/or decorating nanoparticles,[115] biomacromolecules[107, 117] and, surfaces (see **Fig. 28**).[118] These properties can also be used for the fabrication of sulfoxide-bearing functional membranes.[11, 119] Here, materials are

introduced that are permeable, especially for polar compounds. Other sulfoxide bearing membrane materials are reported to selectively remove petroleum and oil residues out of contaminated sewage water.[7]

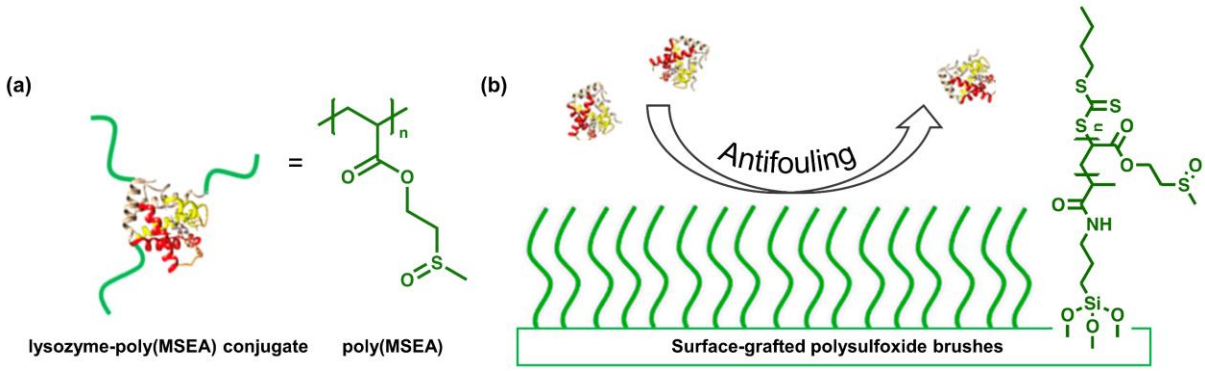


Fig. 28 Sulfoxide-containing polymers are increasingly used as potent antifouling building blocks. One prominent example is poly(2-(methylsulfinyl)ethyl acrylate) (poly(MSEA) which is used to *e.g.* **(a)** shield biomacromolecules such as proteins and **(b)** decorate surfaces to prevent biofouling processes. (*Adapted with permission from The Royal Society of Chemistry, see Reference* [117-118])

On the other hand, when sulfoxides are oxidized to the corresponding sulfones, the ability to form hydrogen bonds with water is dramatically reduced. Since this oxidation of sulfoxide-containing polymers can occur effectively as response to reactive oxygen species (ROS), polymers containing sulfoxide side groups show great potential for realizing oxidation-responsive drug-delivery systems.[120]

2. Motivation and aims

Modern nanotechnological research draws its strength from the identification of new functional moieties that are inspired by small molecules. Their incorporation into a variety of different polymeric architectures opens up new and innovative pathways for the development of dynamic and responsive polymer materials.

In this context, sulfoxide groups present outstanding physicochemical properties in both small molecules and polymers. As single small molecules, they are strong hydrogen bond acceptors and are therefore very hydrophilic. This property also translates well into macromolecular architectures. Hence, sulfoxide-containing polymers are known for their very low cytotoxicity, their excellent biocompatibility, and antifouling features with potential biomedical applications.

However, these properties are known for decades and limit the potential of this interesting polymer class. Thus, this work focuses on expanding the functional toolbox of polysulfoxides beyond their solely hydrophilic nature. This will lead to new tailor-made and adaptive polymers and open up additional areas of applications in advanced material and biomedical sciences. To approach this task two pathways were followed (see Fig. 29).

This thesis aims to

1. Understand and tune the amphiphilic balance of sulfoxide groups in polymers to achieve new dynamic and responsive properties
2. Translate known properties of polysulfoxides into new colloidal carriers to tune the specific interaction with biological systems

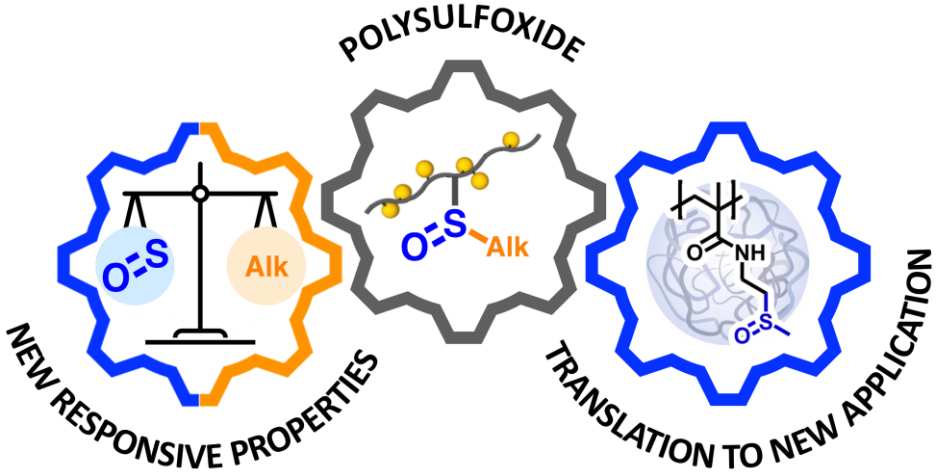


Fig. 29 The goal of this work lays in the expansion of the functional toolbox of polysulfoxides via understanding their structure-property relationship to introduce neu responsive properties and transferring them into new advanced applications.

In achieving these two goals the work in this thesis focused on the following projects:

AIM 1 ***Expanding the dynamic and responsive properties of sulfoxide-containing polymers (Chapter 3.1)*** To approach this goal, the rational design of a new class of alkyl sulfoxide functional monomers is developed. In these monomers, the central role of the sulfoxides is hypothesized to be twofold: on one hand, the strong hydrogen bond acceptors shall be combined with hydrophobic alkyl side groups to realize an amphiphilic structure. This is the foundation for potential thermo-responsive polymer properties. Here, the cloud point temperature is suggested to be tunable by varying the alkyl side chain, *i.e.* the hydrophilic-to-hydrophobic balance of the monomer. On the other hand, oxidation of the sulfoxides to the respective sulfones is assumed to reduce the polymers' hydrophilicity. Thus, a quantitative oxidation would result in a dramatically reduced water solubility. By controlling the conversion of sulfoxide to sulfone side groups, the cloud point temperature could be continuously decreased with an increasing number of sulfones per polymer. As a result, the polymer would exhibit an additional multi-responsive behavior (see **Chapter 3.1.**).

AIM 2 ***Polymeric mimicry of low molecular weight sulfoxide penetration enhancers and their translation into colloidal carriers (Chapter 3.2)*** The accurate tailoring of defined macromolecular interactions with the amphiphilic skin barrier is still challenging. To address this limited specificity, a new strategy shall be examined by combining biocompatible nanogels with the outstanding skin interaction properties of sulfoxide moieties. These chemical motifs are known from dimethyl sulfoxide (DMSO), a potent chemical penetration enhancer, which can often cause undesired skin damage upon long-term usage. By covalently functionalizing the nanogels' polymer network with such methyl sulfoxide side groups, tailor-made dermal delivery vehicles are developed to circumvent the skin disrupting properties of the small molecules. Key to an effective nanogel–skin interaction is assumed to be the specific nanogel amphiphilicity based on the unique properties of the sulfoxide moieties.

To address this task, two aspects have to be realized. First, a synthetic strategy has to be developed that allows decoupling the chemical functionality from the colloidal features, *i.e.* nanogel crosslinking density, size distribution to ensure accurate comparability between the anticipated nanogels (see **Chapter 3.2.1.**).

Second, the DMSO-inspired sulfoxide-based nanogels need to be synthesized and investigated to potentially show increased delivery efficiency while circumventing the skin disrupting disadvantages of the small molecule (see **Chapter 3.2.2.**).

3. Results and discussion

In the following chapters the published articles are presented, and the contribution of the author is specified. Furthermore, the respective publications are brought into context to the presented motivation and aims. In the end, an outlook is given for each chapter. All publication in this work were subjected to a peer review system of international journals.

3.1. Thermo- and oxidation-sensitive poly(meth)acrylates based on alkyl sulfoxides: dual-responsive homopolymers from one functional group

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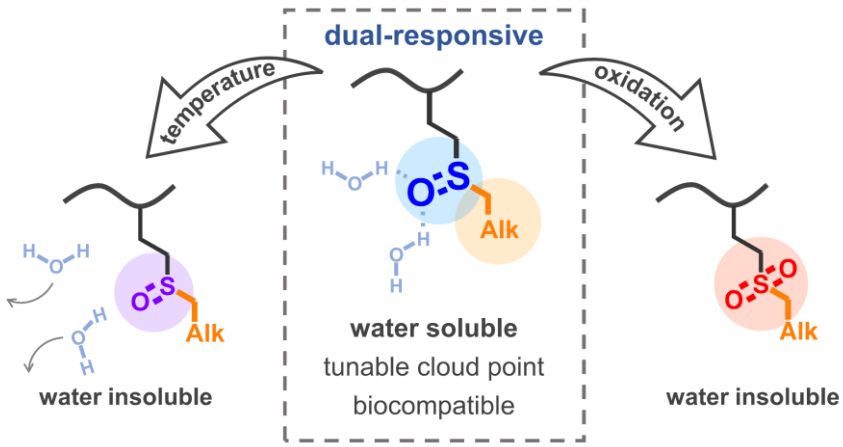

Fig. 30 Alkyl sulfoxide side groups introduce thermo- and oxidation-sensitivity into poly(*meth*)acrylates, thus realizing new dual-responsive homopolymers based on one functional group. (Reproduced with permission of *The Royal Society of Chemistry*, see Reference [121])

Author contribution. In this work the main author contributed with the complete design, synthesis and characterization of all sulfoxide-containing monomers and multi-stimuli-responsive poly(*meth*)acrylates, analyzing their transition temperatures and oxidation-responsiveness, evaluation of the cytotoxicity results with the collaboration partners, and writing the manuscript.

Contribution of this work to realize AIM 1. To expand the dynamic and responsive properties of sulfoxide-containing polymers, the rational design of a new class of alkyl sulfoxide

functional monomers was achieved. For this, the outstanding properties of alkyl sulfoxide groups were systematically varied. Such functional moieties are strong hydrogen bond acceptors, very hydrophilic, and ensure good biocompatibility. In addition, they can be oxidized to the more hydrophobic sulfones upon reaction with reactive oxygen species, *e.g.* H_2O_2. These two features were used in a rational molecular design to overcome the solely hydrophilic nature of sulfoxide-containing polymers and realize an additional thermo- and oxidation-responsive behavior.

This was achieved in two ways. First, the thermo-responsive behavior can be tuned by balancing sulfoxide-water hydrogen bonds and hydrophobic interactions of the respective alkyl side chains. Following this molecular design, we found that systematically varying the sulfoxides' alkyl groups can be used to tune the thermo-responsive properties of the polymers. Second, an additional oxidation response is introduced by utilizing the oxidation of the sulfoxides to the respective sulfones. This decreases the polymer's overall hydrophilicity, thus reducing the cloud point temperature. As a result, the polymer exhibits a multi-responsive behavior.

Consequently, this study has demonstrated the high potential of a rational molecular design to introduce additional responsive properties to a class of well-established functional polymers. Hence, our synthetic strategy represents a simple yet powerful expansion of the functional sulfoxide-containing polymer toolbox. This unique combination of thermal and oxidation response in one single functional unit, its facile synthesis, well-controlled polymerization, and biocompatibility is the starting point for the preparation of highly sophisticated materials for a wide variety of applications.

3.1.3. Outlook – Thermo- and oxidation-sensitive materials from polysulfoxides

3.1.3.1. Preparation of thermo- and oxidation-responsive nanogels

Successfully expanding the functionality of sulfoxide-containing polymers via a rational molecular design is a crucial step towards advanced materials. In particular, poly(*n*-propyl sulfoxide ethyl *meth*acrylate) (P(*n*Pr-SEMA)) is a promising candidate for biomedical applications due to its cloud point temperature (T_{cp}) close to human body temperature (36 °C). In close similarity to the widely used poly(*N*-isopropyl acrylamide) (P(*N*IPAm)), this thermo-sensitivity can be exploited to build different functional polymer architectures. These structures range from *i.e.* block copolymers to more complex three-dimensional crosslinked polymer colloids like nanogels.

In this regard, initial experiments were performed to translate *n*-propyl sulfoxide ethyl *meth*acrylate (*n*Pr-SEMA) into multi-stimuli-responsive nanogels. Here, both the thermo- and oxidation-sensitive features of the resulting nanogels are expected to solely depend on the amphiphilicity of the introduced alkyl sulfoxide groups similar to the respective homopolymers (see **Chapter** 3.1.).

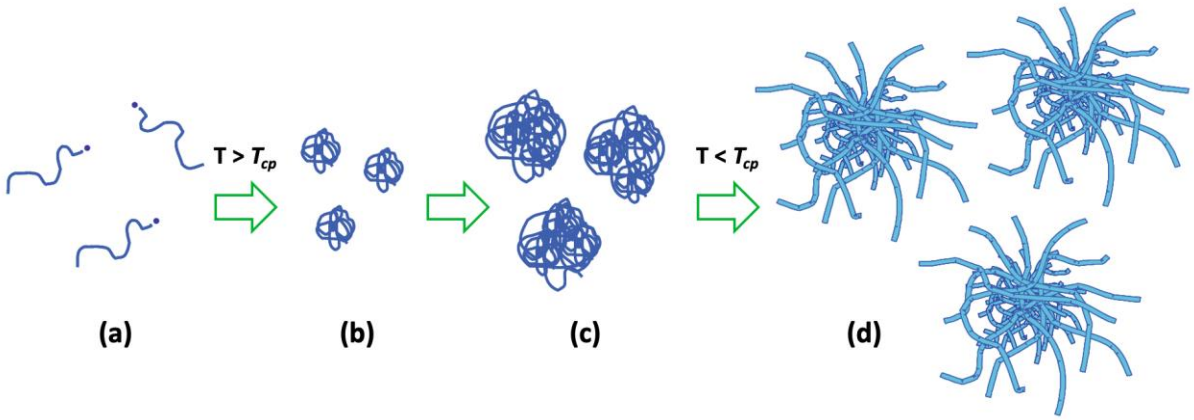

Fig. 31 Simplified mechanism of thermo-responsive nanogel formation via precipitation polymerization. After initiation, the oligoradical formation **(a)** proceeds until a critical chain length is reached while the reaction temperature (T) is over the cloud point temperature (T_{cp}). As consequence, the polymer collapses to give precursor particles **(b)**. The growing particles **(c)** are fed through further addition of monomers and crosslinker. After the polymerization, cooling down the dispersion below the T_{cp} initiates the swelling of the final nanogels **(d)**. (Adapted with permission from *Springer Nature*, see Reference [122])

To prepare such multi-responsive nanogels, precipitation polymerization was identified as a suitable synthetic pathway (see Fig. 31). This process starts from an initial homogenous phase in which the monomer, crosslinker, initiator, and surfactant are completely soluble. The system turns then into a heterogenous polymerization process upon initiation of the reaction, *i.e.* the forming polymer becomes insoluble, thus is precipitating. In this special case, the precipitation of the polymer is not solely directed through the nature of the solvent but also through the thermo-responsive property of the reacting polymer chain itself. Meaning, the forming polymer chains collapse when reaching a critical length and form precursor particles if the reaction temperature is higher than the polymer's T_{cp}. In the end, the final swollen nanogels are achieved after the reaction is cooled down to room temperature.

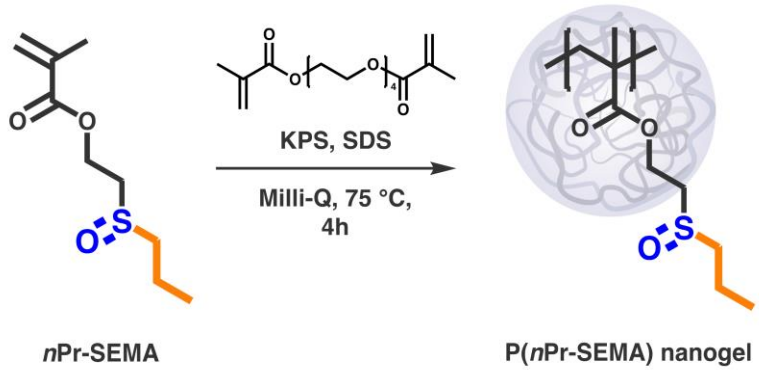

Fig. 32 Reaction scheme for the preparation of P(*n*Pr-SEMA) nanogels via precipitation polymerization.

Consequently, using this technique, P(*n*Pr-SEMA) nanogels were prepared as follows (see Fig. 32). Briefly, *n*Pr-SEMA (18 mg, 88.3 mmol, 1 eq.) and tetraethylene glycol dimethacrylate (TEGDMA, 1.2 mg, 3.52 mmol, 4 mol% w.r.t the monomer) were dissolved in 1 mL sodium dodecyl sulfate solution (SDS, 1 mg/mL). Subsequently, potassium persulfate (KPS, 1.2 mg, 4.40 mmol, 5 mol%) was dissolved in 100 µL Milli-Q water and both aqueous solutions were purged with nitrogen for 10 minutes. Afterwards, the monomer solution was placed in a preheated oil bath for another 10 minutes at 75 °C. The polymerization was then started via the addition of the KPS solution. The reaction was stopped after 4 hours, cooled down to room temperature and dialyzed against distilled water.

The nanogels were characterized by dynamic light scattering (DLS) measurements at different temperatures to account for the expected thermo-responsive properties of the colloids. The results of these measurements are shown in Fig. 33.

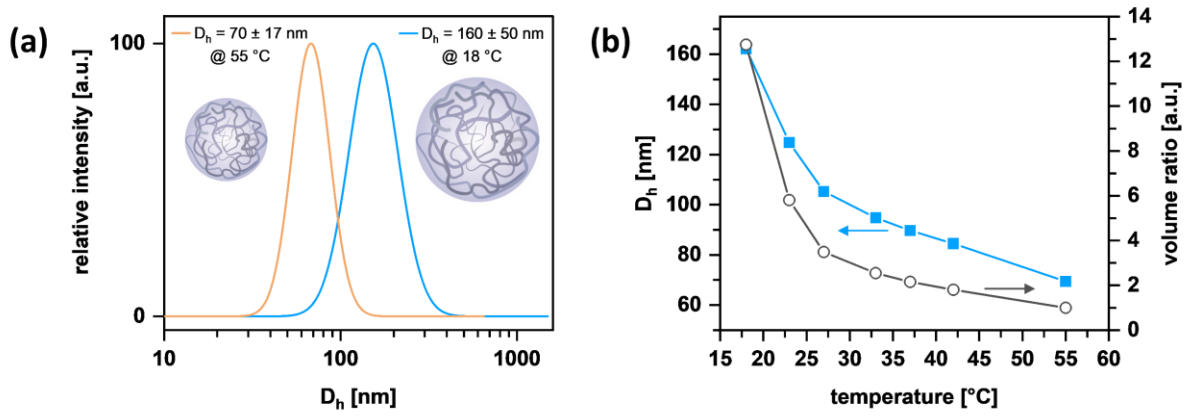

Fig. 33 Dynamic light scattering (DLS) measurements of P(*n*Pr-SEMA) nanogels were performed at temperatures ranging from 18-55 °C at a scattering angle of 90°. **(a)** Representative DLS curves at 18 °C and 55 °C indicate the presence of swollen nanogels at lower temperatures and collapsed colloids at an elevated temperature, respectively. This underlying trend becomes more evident in the **(b, blue)** hydrodynamic radius *vs.* temperature plot and **(b, grey)** the respective volume ratios *vs.* temperature plot.

At lower temperatures, the DLS measurements indicate that the nanogels are highly swollen based on the favorable interaction of the polymer network with water molecules. This effect is further evident for the nanogel sizes at 18 °C and 55 °C (see **Fig. 33(a)**). Here, a reduction in size from initial 160 ± 50 nm to 70 ± 17 nm is observed. Hence, giving a strong evidence for a thermo-responsive behavior. Looking into this in more detail, a trend is observed regarding hydrodynamic radius (D_h) *vs.* temperature (see **Fig. 33(b), blue**). In contrast to the sharp cloud point temperatures for the linear P(*n*Pr-SEMA), the thermo-responsive profile of the respective P(*n*Pr-SEMA) nanogels shows a broader transition temperature range. One possible explanation could be that while significant parts of the three-dimensional network are collapsed at elevated temperatures, some smaller fragments may still remain solubilized contributing to a partial swelling. This trend becomes more evident when looking into the swelling ratios of the nanogels. As an example, the volume of the nanogel network from the fully collapsed state at 55 °C increases to nearly 13-fold at the fully swollen state at 18 °C (see **Fig. 33(b), grey**).

Overall, these initial synthetic and physicochemical results are encouraging for further evaluations. On the synthesis part, additional efforts have to be taken to optimize the precipitation polymerization process *i.e.* evaluating the influence of monomer, initiator, and surfactant concentrations on the resulting colloidal properties. Regarding the multi-stimuli-responsiveness, oxidation experiments with *e.g.* hydrogen peroxide or *meta*-chloroperoxybenzoic acid have to be carried out to prove the additional oxidation-response of

the presented nanogels. With this in hand, it is strongly assumed that such thermo- and oxidation-sensitive soft colloids can make a significant contribution to the functional toolbox of nanogels for a wide variety of application, especially in the biomedical field.

3.1.3.2. Enhanced design of new thermo- and oxidation-responsive monomers

Having shown the possibilities to incorporate alkyl sulfoxide *meth*acrylates, (especially *n*Pr-SEMA) into complex polymer structures, *e.g.* nanogels, the topic of thermo- and oxidation-sensitive monomers can also be addressed on a more fundamental research basis. The combination of two response mechanisms in one monomer and even in one functional group is clearly a huge step in overcoming disadvantages that stem from otherwise necessary copolymerization strategies and lead towards polymers with a more complex responsive profile.

Thus, the exploitation of the delicate amphiphilic balance of hydrophilic sulfoxide groups with varying hydrophobic alkyl moieties remains a key feature in introducing an effective thermal response. Translating this hydrophobic/hydrophilic tunability to sulfide-based monomers would mark another big step towards another type of highly adaptive multi-responsive polymers. This is based on the fact that besides the anticipated thermal response of such monomers, the oxidation reaction of sulfides to sulfoxides is a fast, easy and reversible transformation. So, it is not surprising that researchers have used the oxidation response of sulfide groups for a wide variety of stimuli-responsive materials.[120]

Yet, the design of both thermo- and oxidation-sensitive monomers that include a sulfide moiety in its structure remains challenging. This challenge stems largely from the strong hydrophobic character of the thioether group making it necessary to counter it with a strong hydrophilic group. Only by doing so, a balanced amphiphilic chemical structure is achieved which could then exhibit a thermo-responsive behavior.

To approach this task, two new monomers were designed and synthesized (see **Fig. 34**). The rational design of these two monomers follows the basic thought that changing the hydrophilicity of a polymer can be achieved via two ways. The first monomer, methyl thioethyl acrylamide, is an example for the incorporation of the hydrophilic moiety *i.e.* the amide bond, at the backbone of the polymer (see **Fig. 34(a)**). In contrast to that, a hydrophilic diethylene glycol is introduced as pending group in the second monomer (methyl thio(diethylene glycol) *meth*acrylate) (see **Fig. 34(b)**).

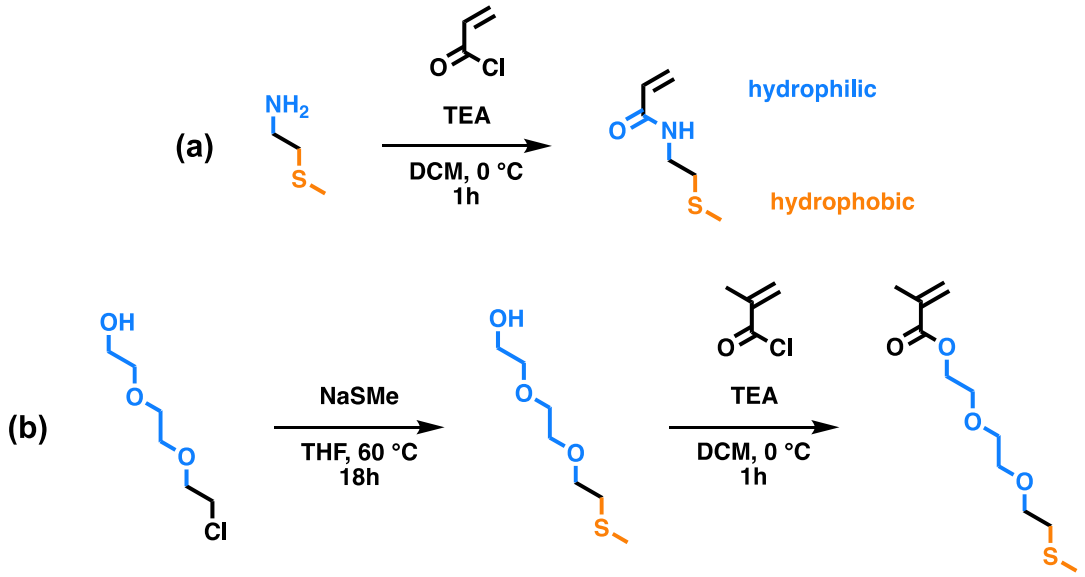

Fig. 34 Synthesis routes of methyl thioethyl acrylamide **(a)** and methyl thio(diethylene glycol) *meth*acrylate **(b)**. Both monomers are designed to exhibit a hydrophobic and oxidation-responsive sulfide group in combination with different hydrophilic structural elements.

Regarding the synthesis, for both monomers the *meth*acrylation and acrylamidation, respectively, follows the same synthesis procedures as described in the published article (see **Chapter** 3.1.). The methyl thiolation using sodium methanethiolate is described in the literature.[123] Briefly, 2-[2-(2-chloroethoxy)ethoxy]ethanol (567 mg, 3.36 mmol, 1 eq.) and sodium methanethiolate (236 mg, 3.36 mmol, 1 eq.) were dissolved in 26 mL dry THF under a nitrogen atmosphere. The solution was heated to 60 °C and stirred for 18 hours. Subsequently, the reaction mixture was allowed to reach room temperature, diluted with ethyl acetate and washed twice with saturated sodium bicarbonate and ones with distilled water. After the organic layer was dried over sodium sulfate, the solvent was evaporated in *vacuo* and the product was afforded as a pale-yellow oil (454 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 – 3.57 (m, 10H, -CH_2-), 2.70 (s, 2H, -CH_2-S-), 2.29 (s, 1H, -OH), 2.15 (s, 3H, -S-CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 72.60, 70.66, 70.54, 70.46, 61.92, 33.59, 16.15 ppm.

Having successfully synthesized both monomers their anticipated thermo-responsive polymer properties were assessed. Also, to ensure comparability, the polymerization reaction was conducted according to the published RAFT procedures extensively elaborated in the published paper. However, before the thermal response could be determined, unfortunately, the resulting initial polymers were not water soluble in the first place. Hence, indicating that the hydrophobic contribution of the thioether group is already dominating the overall macromolecular polymer properties at room temperature.

A possible solution to this observation could be to either relocate the thioether group and/or increase the hydrophilic contribution of the polar moiety. It is proposed that these both aspects can be further assessed the best for the methyl thio(diethylene glycol) methacrylate monomer. The success of this approach would pave the way for a next generation of multi-responsive functional monomers with versatile and highly adaptable features.

3.2. Polymeric mimicry of low molecular weight sulfoxide penetration enhancers and their translation into colloidal carriers

The following sections address an important expansion of the currently available portfolio of nanocarriers for dermal delivery applications; rational design of molecular functionality to tailor the properties of nanogels to the challenging biological barrier of skin. For this, aspects from nanobiotechnology were combined with colloidal chemistry, physicochemical characterizations, and biological investigations in a new way.

While colloidal nanogels have evolved as promising non-irritating delivery vehicles to increase dermal bioavailability of therapeutics, the accurate tailoring of defined interactions with the amphiphilic skin barrier is still challenging. This drastically limits their ability to address an increasing task: the delivery of hydrophobic drugs. Thus, addressing this limited specificity by combining biocompatible nanogels with the outstanding skin interaction properties of sulfur-based moieties *i.e.* methyl sulfoxide groups represents a promising new approach to increase their therapeutic potential.

Key to this proposed effective nanogel-skin interaction is assumed to be the specific nanogel amphiphilicity. This is examined by comparing the delivery efficiency of sulfoxide-based nanogels (NG-SOMe) with their corresponding thioether- and sulfone-functionalized analogues. However, the preparation of such precisely tailored functional nanogels is still in its infancy. To ensure accurate comparability between these particles, special attention was paid on using a synthetic strategy that allows decoupling the chemical functionality from the colloidal features, *i.e.* nanogel crosslinking density, size distribution, to some extent. For this, a post-polymerization modification approach was successfully employed for the generation of the different nanogels from one batch of reactive precursor nanoparticles. The resulting comparability enabled to accurately correlate topical delivery efficacy, skin compatibility, and cytotoxicity with the chemical network functionality (see publication in **Chapter 3.2.1.**).

Following this approach, a library of amphiphilic nanogels with similar colloidal features and varying network functionality was prepared. It was demonstrated that the DMSO-inspired sulfoxide-based nanogels showed the highest delivery efficiency while circumventing the skin disrupting disadvantages of the small molecule DMSO. It is suggested that this specific performance of the NG-SOMe nanogels is directly induced by the amphiphilic sulfoxide groups interacting with the proteins and lipids of the skin barrier, thus increasing the NGs' retention in the stratum corneum. It is proposed that this enables the nanogels to serve as drug reservoir, which enhances the local concentration of payloads in the upper skin layer. In combination with

an increased skin hydration, the diffusion of the payloads into the deeper skin layers (*i.e.* the viable epidermis) is increased without disrupting the skin barrier and risking systemic exposure (see publication in **Chapter** 3.2.2.)

3.2.1. *A versatile synthetic platform for amphiphilic nanogels with tunable hydrophobicity*

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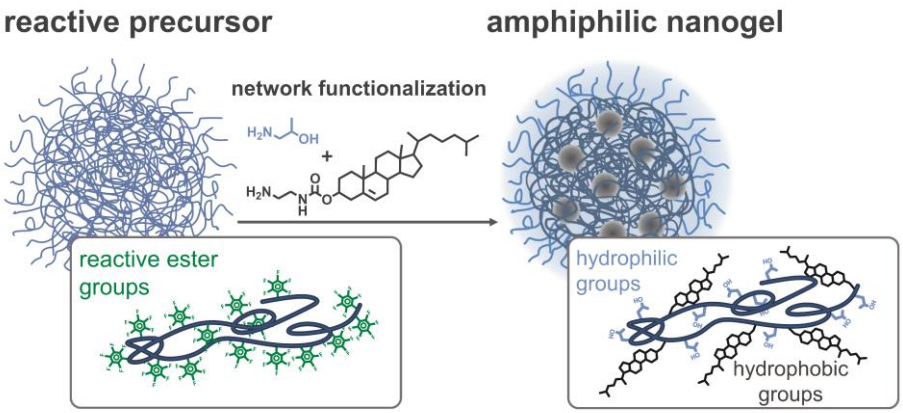

Fig. 35 The realization of three-dimensionally crosslinked reactive precursor nanoparticles facilitates the synthesis of amphiphilic nanogels via straight forward post polymerization functionalization while keeping most colloidal features constant. (Reproduced by permission of *The Royal Society of Chemistry*, see Reference [124])

Author contribution. In this work the author contributed with the synthesis and characterization of the linear amphiphilic polymers, analyzing their physicochemical properties, with transmission electron microscopy measurements and images of the respective amphiphilic nanogels.

Contribution of this work to realize AIM 2. The article addresses an important challenge in expanding the potential of polymeric nanogels: the introduction of tailor-made network functionality without changing the colloidal features. For this, aspects from polymer synthesis and polymer functionalization with colloidal chemistry, physicochemical characterizations and biological investigations were combined in a new way.

In particular, the preparation of dermal drug delivery vehicles that combine the beneficial aspects of sulfoxide polymer side groups and the colloidal features of nanogels faces various challenges. First, the different sulfur-based moieties should be homogenously incorporated into the three-dimensional polymeric network in a facile and efficient way. Second, the nanogels should maintain their structural and functional integrity in aqueous dispersion, *i.e.* not relying on critical micelle concentrations and not showing aggregation etc. Third, functional nanogels with similar colloidal features, *e.g.* particle size, size distribution, and homogenous morphologies are required to ensure a high degree of comparability that would enable accurate structure–property relations. Addressing these challenges allows for an accurate determination of the dermal delivery potential by investigating skin compatibility, toxicology, and dermal delivery efficacy.[125]

Conventional nanogel preparation methods are often based on radical copolymerization of vinyl-based monomers (styrenics, (meth)acrylates, (meth)acrylamides, etc.) and crosslinkers in heterogeneous systems ((mini)emulsion-based approaches). In these strategies, it is highly challenging to prepare nanogels with different chemical functionalities but comparable colloidal parameters. This can be attributed to the fact that different particle preparation methods are required to polymerize monomers with strongly opposing physicochemical properties (*e.g.* solubility). In case of monomers containing either hydrophobic thioether/sulfone moieties or hydrophilic sulfoxide groups, two different synthetic (mini)emulsion methods are required, respectively: For the hydrophobic monomers, a direct oil-in-water mini-emulsion procedure could be employed. In contrast, for the synthesis of the hydrophilic polymer network, an inverse water-in-oil mini-emulsion pathway would be more suitable. As a result of these different preparation pathways, nanogels with different network functionalities would vary strongly in their morphology, particle size, size distribution, crosslinking density, etc. These natural batch-to-batch variations hinder the accurate determination of their structure–properties relationships.[125]

To address this synthetic challenge, a facile and efficient post-polymerization modification strategy was developed in this work. Starting from pentafluorophenyl methacrylate (PFPMA), a master batch of cross-linked reactive pPFPMA precursor nanoparticles (Pre-NP) was prepared. This was achieved by free radical copolymerization of the PFPMA monomer with ethylene glycol dimethacrylate (EGDMA) as cross-linker in mini-emulsion using sodium dodecyl sulfate (SDS) as surfactant. The resulting particle dispersion was purified by repeated centrifugation/redispersion cycles in deionized (DI) water. Analysis by angle-dependent dynamic light scattering (DLS) and transmission electron microscopy

(TEM) directly after the synthesis showed well-defined particles with narrow size distribution.[125]

Following this methodology, this work has demonstrated the high potential of a reactive precursor platform approach to prepare nanogel with tailor-made functionalities without altering their colloidal features. As consequence, these functional nanogel are anticipated to reveal more accurate structure-property relationships at the biointerface when used as potential drug delivery vehicles.

3.2.2. *Sulfoxide-functionalized nanogels inspired by the skin penetration properties of DMSO*

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https://doi.org/10.1039/D0BM01717E

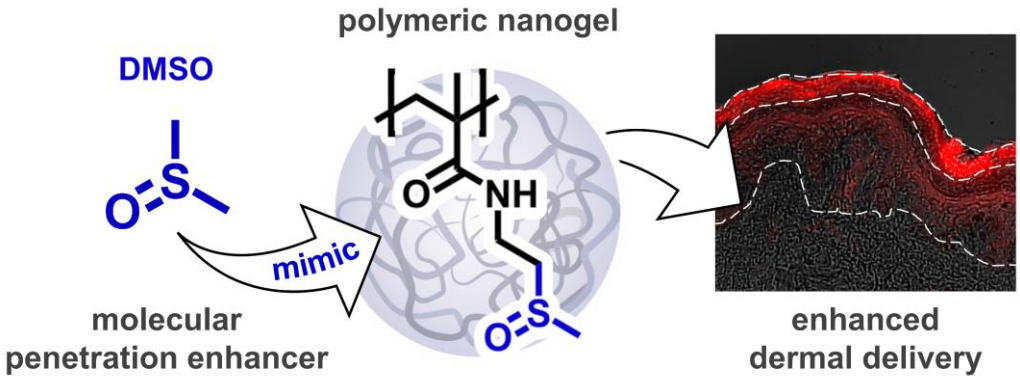

Fig. 36 The translation of the unique physicochemical and penetration enhancing properties of DMSO into biocompatible nanogels allows for the preparation of a new class of potent dermal drug delivery vehicles. (Reproduced by permission of *The Royal Society of Chemistry*, see Reference [125])

Author contribution. In this work the main author contributed with the synthesis and characterization of all functional linear polymers and their respective functional nanogels, analyzing their physicochemical properties, loading of the nanogels with the dye and model drug Nile red, evaluation of the skin delivery experiments and the cytotoxicity results with the collaboration partners, and writing the manuscript.

Contribution of this work to realize AIM 2. The article addresses an important expansion of the currently available portfolio of nanocarriers for dermal delivery applications: rational design of molecular functionality to tailor the properties of nanogels to the challenging biological barrier of skin. For this, aspects from nanobiotechnology were combined with colloidal chemistry, physicochemical characterizations and biological investigations in a new way.

While colloidal nanogels have evolved as promising non-irritating delivery vehicles to increase dermal bioavailability of therapeutics, the accurate tailoring of defined interactions with the amphiphilic skin barrier is still challenging. This drastically limits their ability to address an increasing task: the delivery of hydrophobic drugs. Thus, addressing this limited

specificity by combining biocompatible nanogels with the outstanding skin interaction properties of sulfur-based moieties *i.e.* methyl sulfoxide groups represents a promising new approach to increase their therapeutic potential.

Key to this proposed effective nanogel-skin interaction is assumed to be the specific nanogel amphiphilicity. This is examined by comparing the delivery efficiency of sulfoxide-based nanogels (NG-SOMe) with their corresponding thioether- and sulfone-functionalized analogues. However, the preparation of such precisely tailored functional nanogels is still in its infancy. To ensure accurate comparability between these particles, special attention was paid on using a synthetic strategy that allows decoupling the chemical functionality from the colloidal features, *i.e.* nanogel crosslinking density, size distribution, to some extent. For this, we successfully employed a post-polymerization modification approach for the generation of the different nanogels from one batch of reactive precursor nanoparticles. The resulting comparability enabled to accurately correlate topical delivery efficacy, skin compatibility, and cytotoxicity with chemical network functionality.

Following this approach, a library of amphiphilic nanogels with similar colloidal features and varying network functionality was prepared. It was demonstrated that the DMSO-inspired sulfoxide-based nanogels showed the highest delivery efficiency while circumventing the skin disrupting disadvantages of the small molecule DMSO. It is suggested that this specific performance of the NG-SOMe nanogels is directly induced by the amphiphilic sulfoxide groups interacting with the proteins and lipids of the skin barrier, thus increasing the NGs' retention in the stratum corneum. It is proposed that this enables the nanogels to serve as drug reservoir, which enhances the local concentration of payloads in the upper skin layer. In combination with an increased skin hydration, the diffusion of the payloads into the deeper skin layers (*i.e.* the viable epidermis) is increased without disrupting the skin barrier and risking systemic exposure.

Consequently, this study has demonstrated the high potential of a systematic synthetic platform approach to accurately determine the influence of tailor-made functionalities on the resulting physicochemical and biological properties. Having shown the potential of crosslinked sulfoxide-containing polymers as new dermal delivery vehicles, this work represents a starting point for the development of more advanced topical delivery nanomaterials, *e.g.* by incorporating additional stimuli-responsive loading and release properties.

3.2.3. Outlook – Next generation of advanced dermal delivery vehicles

Having shown the potential of crosslinked sulfoxide-containing polymers as a new class of dermal delivery vehicles, this work represents a starting point for the development of more advanced topical delivery nanomaterials. The shown system is a simple yet powerful example how a precisely tailored functional polymer can be used to passively adapt to the skin barrier and increasing its drug delivery efficacy.

The next generation of dermal delivery vehicles, however, would include additional levels of functionality and versatility to account for a more complex and adaptive therapeutic profile. Such an enhancement of the current methyl sulfoxide-functionalized nanogels could follow two pathways.

First, additional stimuli-responsive properties could be introduced into the nanogels' polymeric network. As shown in **Chapter** 3.1. this can be achieved by exploiting the delicate amphiphilic balance between hydrophilic sulfoxide moieties and hydrophobic alkyl groups. By doing so, a thermo- and oxidation-responsive nanogel can be designed. The possibility how this multi-stimuli-responsive nanogel can be actually prepared is discussed in detail in **Chapter** 3.1.2.1.. The utilization of such a multi-stimuli-sensitive dermal delivery vehicle would allow additional levels of loading and release profiles. In particular, the thermo-responsive feature could account for the inherent temperature gradient of human skin, enabling another route for controlled drug release. While the oxidation response could actively neutralize harmful reactive oxygen species which can be present in diseased tissue.

Second, the three-dimensionally crosslinked polymer network itself can be modified. Here, labile crosslinkers can be incorporated to respond to further environmental stimuli such as the skin's pH or reductive physiological conditions. The utilization of these responsive crosslinker would further allow to precisely adapt the drug delivery vehicles to the targeted skin. Moreover, by introducing these cleavable points in the polymeric network, the biocompatibility of the material can be significantly improved.

Overall, either of these pathways or even a smart interplay of both would translate into additional levels of versatility and adaptive features of the drug delivery system, thus opening the possibility to target even more complex physiological conditions.

4. Conclusion

The development of new advanced functional polymers with additional levels of materials' variability requires a strong understanding of the underlying structure-property relations. In sulfoxide-containing polymers these are largely governed be the unique features of the sulfoxide group. Its high hydrophilicity translates into polymers with very low cytotoxicity and excellent biocompatibility. Thus, making them interesting candidates for biomedical applications.

However, this pure hydrophilicity also limits the potential of this interesting polymer class. Overcoming this limitation would give access to new adaptive and tailor-made polysulfoxides with additional areas of applications in nanotechnology and material sciences. Yet, the realization of these materials remains largely unexplored. In this work, this open task was addressed in two distinct ways.

First, by understanding and tuning the amphiphilic balance of alkyl sulfoxide groups in polymers and colloids. New dynamic and response properties of sulfoxide-containing polymers were introduced via a rational molecular design. Here, by controlling the amphiphilic balance of alkyl sulfoxides a temperature-responsive profile was realized. This thermo-responsive behavior was tuned by balancing sulfoxide-water hydrogen bonds and hydrophobic interactions of the respective alkyl side groups. Furthermore, an additional oxidation stimuli response was achieved by utilizing the oxidation of the polar sulfoxides to the respective hydrophobic sulfones. As a result, the polymer properties could be extended from its pure hydrophilic nature to a multi-stimuli-responsive behavior (see **Chapter 3.1.**).

Following this approach, new materials with well-defined and robust thermo-responsive polymer properties were developed. In particular, poly(*n*-propyl sulfoxide ethyl *meth*acrylate) (P(*n*Pr-SEMA)) was found to be a promising candidate for biomedical applications due to its cloud point temperature close to human body temperature (36 °C). Initial experiments to translate *n*-propyl sulfoxide ethyl *meth*acrylate (*n*Pr-SEMA) into a new class of multi-stimuli-responsive nanogels via precipitation polymerization were very encouraging.

Second, by applying the unique properties of sulfoxide-containing polymers to dermal delivery applications. Here, it was demonstrated how a rational design of polymer functionality can be used to tailor the properties of nanogels to the challenging biological barrier of skin. Key to this rational design is the covalent functionalization of the nanogels' polymer network with methyl sulfoxide side groups. These chemical motifs are known for their outstanding skin interaction properties, *i.e.* from DMSO as chemical penetration enhancer. By

including these moieties into the nanogels, the properties of the small molecules were translated to the polymeric carriers. Such a rational design represents an important expansion of the currently available portfolio of nanocarriers for dermal delivery applications (see **Chapter** 3.2.).

To ensure accurate comparability between these particles, a new reactive precursor platform was developed as a synthetic strategy that allows decoupling the chemical functionality from the colloidal features, *i.e.* nanogel crosslinking density, size distribution (see **Chapter** 3.2.1.). Furthermore, it was demonstrated that the DMSO-inspired sulfoxide-based nanogels showed the highest delivery efficiency while circumventing the skin disrupting disadvantages of the small molecule DMSO (see **Chapter** 3.2.2.).

Overall, this thesis exemplifies the strong synergy between the unique properties of the sulfoxide moiety and its structure-property relationship in linear polymers and colloidal systems. On one hand, the precise tailoring of this structure-property relationship led to multi-responsive polysulfoxides with a more complex adaptive profile. On the other hand, it enabled the translation of sulfoxide moieties into new potent dermal drug delivery vehicles. As a result, this work extends the current available portfolio of sulfoxide-containing polymers and its applications. It lays the foundation for upcoming challenges in the engineering of this interesting polymer class.

Future perspectives of this polymer class may include the introduction of further reversibility to the sulfoxide/sulfone transition in the thermo- and oxidation-sensitive poly(*alkyl* sulfoxide *meth*acrylate) system via the utilization of special enzymes such as methionine reductases. In the field of material sciences, the two different bonding modes of the sulfoxide moiety and its stimuli-responsiveness could translate into polymeric support materials for metal catalysts with potential switchable catalytic activities. In addition, the chiral nature of the sulfoxide group could account for a completely new generation of asymmetric transformation reactions in modern organic synthesis mediated by tailor-made sulfoxide-containing polymers.

5. List of figures

6. List of tables

7. Bibliography

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8. Appendix

8.1. Curriculum vitae

For reasons of data protection, the curriculum vitae is not included in the online version.

8.2. List of Publications

04 **D. Işık**, A. A. Joshi, X. Guo, F. Rancan, A. Klossek, A. Vogt, E. Rühl, S. Hedtrich, D. Klinger *Sulfoxide-functionalized nanogels inspired by the skin penetration properties of DMSO*, Biomaterials Science, **2021**, *9*, 712-725. DOI: 10.1039/d0bm01717e.
https://doi.org/10.1039/D0BM01717E

03 **D. Işık**, E. Quaas, D. Klinger *Thermo- and oxidation-sensitive poly(meth)acrylates based on alkyl sulfoxides: dual-responsive homopolymers from one functional group*, Polymer Chemistry, **2020**, *11*, 7662-7676. DOI: 10.1039/d0py01321h
https://doi.org/10.1039/D0PY01321H

02 A. Gruber, **D. Işık**, B. B. Fontanezi, C. Böttcher, M. Schäfer-Korting, D. Klinger *A versatile synthetic platform for amphiphilic nanogels with tunable hydrophobicity*, Polymer Chemistry, **2018**, *9*, 5572-5584. DOI: 10.1039/c8py01123k
https://doi.org/10.1039/C8PY01123K

01 M. Giulbudagian, S. Hönzke, J. Bergueiro, **D. Işık**, F. Schumacher, S. Saeidpour, S. B. Lohan, M. C. Meinke, C. Teutloff, M. Schäfer-Korting, G. Yealland, B. Kleuser, S. Hedtrich and M. Calderón *Enhanced topical delivery of dexamethasone by β-cyclodextrin decorated thermoresponsive nanogels*, Nanoscale, **2018**, *10*, 469-479. DOI: 10.1039/c7nr04480a
https://doi.org/10.1039/C7NR04480A