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SYNTHESIS OF THIOETHER CONTAINING COPOLYMERS

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Eötvös Loránd Tudományegyetem
—— Természettudományi Kar ——
— Budapest, 2020 —
Acknowledgements

I would like to thank, my supervisor Prof. Béla Iván and research fellow Dr. Szabó Ákos for providing guidance and feedback throughout this project. The meetings and conversations were vital in inspiring me to think outside the box, from multiple perspectives to form a comprehensive and objective critique.
# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Literature review</td>
<td>3</td>
</tr>
<tr>
<td>2.1</td>
<td>Thioether containing polymers</td>
<td>3</td>
</tr>
<tr>
<td>2.2</td>
<td>Dithiol redox responsive polymers</td>
<td>4</td>
</tr>
<tr>
<td>2.3</td>
<td>DODT polymerization</td>
<td>6</td>
</tr>
<tr>
<td>2.4</td>
<td>Thiol Michael addition</td>
<td>7</td>
</tr>
<tr>
<td>2.5</td>
<td>Advantages and potential application of thioether containing polymers</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Aim and tasks</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Experimental Section</td>
<td>12</td>
</tr>
<tr>
<td>4.1</td>
<td>Characterization of raw materials</td>
<td>12</td>
</tr>
<tr>
<td>4.2</td>
<td>Analysis</td>
<td>13</td>
</tr>
<tr>
<td>4.3</td>
<td>Thioether containing polymers synthesis</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Results and Discussion</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>Summary</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>25</td>
</tr>
</tbody>
</table>
List of figures

1 Synthetic approaches for obtaining sulphur containing polymers, which are grouped by their isolated variable: (A) for the carbon spacer between thioether units, (B) for the ratio of ethers to thioethers, and (C) for the polarity of sulfur centered group [9] .......................................................... 4

2 Base-catalyzed thiol oxidation [14] .......................................................... 5

3 Proposed mechanism of Radical Ring-opening Redox Polymerization, R3P of DODT [16] ................................................................................. 7

4 Two reaction mechanisms for the thiol-Michael addition. The base catalyzed mechanism is shown on the left in red while the mechanism corresponding to nucleophilic initiation is presented on the right in blue. Common species are shown in black and the targeted product in pink. (EWG = electron withdrawing group) [22] .......................................................... 9

5 Structural formula of DODT ................................................................. 12

6 Structural formula of PMDETA ............................................................ 12

7 Structural formula of PEGDA ............................................................... 13

8 Structural formula of THF ................................................................. 13

9 The formation of the P (DODT-co-PEGDA) copolymers ................... 17

10 The structure of the formed P (DODT-co-PEGDA) copolymers ........... 18

11 $^1$HNMR spectra of copolymers obtained 1- and 15-minutes reaction time. (50% molar ratio of DODT and 50% of PEGDA in feed) ................. 19

12 The gel permeation chromatograms of the polymer obtained in Experiment 1 ................................................................. 20

13 $^1$HNMR spectrum for 30 min sample in Experiment 3 .................. 21

14 The gel permeation chromatogram of the polymers obtained in Experiment 5 ................................................................. 22

15 The gel permeation chromatogram of the polymers obtained in Experiment 7 ................................................................. 23
List of tables

1. $M_n$ and average degree of polymerization of DODT and PEGDA monomeric units in the P(DODT-co-PEGDA) chains obtained at different reaction times (Experiment 1) .................................................................................................................. 19

2. $M_n$ and average amount of DODT and PEGDA monomeric units in the P(DODT-co-PEGDA) chains obtained at different reaction times (Experiment 4) .................................................................................................................. 21
Nomenclature

Other Symbols

$Al_2O_3$ Aluminium Oxide

$CDCl_3$ Deuterated chloroform

$CF_3COOH$ Trifluoroacetic acid

$CHCl_3$ Chloroform

HCl Hydrogen chloride

$M_n$ Molecular Weight

$Na_2SO_3$ Sodium sulfite

$pK_A$ acid dissociation constant

$wt\%$ Weight Percent

Acronyms / Abbreviations

$^1H$ NMR Proton Nuclear Magnetic Resonance

$DODT$ 3,6-dioxo-octane-1,8-dithiol

GPC Gel Permeation Chromatography

LCST lower critical solution temperature

PEGDA Poly(ethylene glycol) Diacrylate (Mn = 250 g/mol)

PEG Poly(ethylene glycol)

$PMDETA$ $N,N,N',N''-pentamethyl diethylenetriamine$
PNIPAM  poly(N-isopropylacrylamides)

R3P  Radical Ring-opening Redox Polymerization

RAFT  reversible-addition fragmentation transfer

THF  Tetrahydrofuran
1 Introduction

Click chemistry is a concept of highly efficient chemical reactions in which these reactions share some important common features: high reaction yields, benign reaction conditions and easily removable byproducts, stereospecific reaction coordinates and tolerance to diverse functional groups [1]. Due to allowing effective coupling of complementary functional groups, click reactions are not only utilized in organic chemistry but in fact, polymer science and material engineering [2] have also facilitated these reactions and transformed them into convenient, versatile and reliable coupling procedures [3]. Hence, it is used widely in generation of small molecules as well as crosslinked thin films and bulk materials.

Distinct class of conjugate(1,4) addition in which the strong nucleophilic attack on the β-carbon of an α, β-unsaturated carbonyl results in a negatively charged enolate, which called Michael addition reaction. This reaction generates C-C, C-N, C-S, C-O, and other C-X bonds, and such Michael addition products have been considered as important and very useful compounds in a broad range of organic syntheses [4]. Additionally, these reactions fulfill all the criteria which allows to classify them as “click” reactions. These can produce highly stereospecific and regiospecific products, and therefore the Michael addition reaction is an articulate, resilient, and extremely effective reaction which results in C-C bond under normal conditions [4].

Attempts to develop control over “click” reactions have been devoted to studying the relative reactivity of thiols with different catalysts combinations, which led to efficient yields of selective products. Accordingly, taking into account previous studies, advantages of the “click” nature offered by thiols have been exploited and implemented in a range of fields like chemical, biochemical, biological, physical, and engineering applications. In my work, completely new approach is exploited to form copolymers between a dithiol and diacrylate. It was found recently by Szabó et. al. that simultaneous oxidative coupling of dithiols and thiol-acrylate Michael addition may take place in the presence of a base as catalyst and an oxidizing agent. For investigating this unique polymer synthesis reaction, 3,6-dioxa-octane-1,8-dithiol (DODT) was used to react poly(ethylene glycol) diacrylate (PEGDA) catalyzed by N,N,N’,N”-pentamethyl diethylenetriamine (PMDETA) and oxidized by
hydrogen peroxide to form sulfur-sulfur bonds at the same time, and thus form DODT-PEGDA copolymers containing PEGDA-sulfur, i.e. \( \beta \)-thioester, and disulfide bonds.
2 Literature review

2.1 Thioether containing polymers

In the past few years, sulfur-containing polymers have become increasingly relevant due to their good properties which make them useful for a wide range of applications. Due to their versatile properties, both chemical and physical, sulfur-containing polymers have been investigated as sensors, controlled drug release matrices and as new biomedicines [5]. On the other hand, polymers based on thioether linkages have not acquired significant interest compared to other sulfur containing polymers. As a result, most research dealt with only few types of thioether homopolymers and random copolymers, which put restriction on the applicable polymerization techniques or on the application of such kind of polymers. For instance, Matyjaszewski’s group used polyethylene glycol (PEG) as macroinitiator for the synthesis of thioether-PEG polymers for gene delivery application [6]. Frey et al. [7] and Hendrick group [8] mentioned cationic polymerization of PEG-thioether random copolymers and investigated certain aspects of the chemistry of the synthesized polymers. Until the present time, vast fields of uncovered chemistry of thioether based polymers still arises, which will be very useful for future research works. Recently, Deubel [9] pointed out that the synthesis of polythioethers from $\alpha,\omega$-alkylene thiols by step-growth polymerization results in polymers with clearly defined structure and provides control of the carbon spacer between monomer units. In this report [9] researchers used the step-growth technique with different dithiols and divinyl ethers, which led to the formation of two different series of poly(ether-thioethers) (PETE). In the first series, the carbon spacer length of thioethers was diverse, whereas spacer length between ethers kept constant, and constant lengths were maintained between the heteroatoms with different ratio of thioethers to ethers [9]. The first series was used for testing the effect of the spacer length on the thermal properties and electrolyte behavior of these thioether containing polymers. Certain physical properties, such as crystallization and conductivity, were also investigated. In the Figure 1, there shown three samples (PETE-1, PESO-1, and PES-1), [9], which represent the effect of the sulfur containing groups on polarity.
Fig. 1 Synthetic approaches for obtaining sulphur containing polymers, which are grouped by their isolated variable: (A) for the carbon spacer between thioether units, (B) for the ratio of ethers to thioethers, and (C) for the polarity of sulfur centered group [9].

The results of this research shows a rising tendency in molecular weight through the whole process, where the use of monomer with long spacers decreases the rate of the reaction, while the weight average molecular weight rises faster than the number average molecular weight, which leads to higher polydispersity of this particular reaction. Thioether functional polymers present stable structures for precise targeting for different biomedical applications, and can be considered as smart materials due to their unique oxidation possibilities. For example, hydrophobic thioethers undergo oxidation to polar sulfoxides and sulfones until exposure to $H_2O_2$ oxidants, which results from hydrophobic to hydrophilic transition as reactive oxygen sensitive material [10].

2.2 Dithiol redox responsive polymers

Recent studies on base-catalyzed thiol oxidation mechanism showed high effectiveness of polymerization of dithiols to high molecular weight polysulfide polymers through an oxidation mechanism. Disulfide bonds have been integrated into polymers in different ways, for example, disulfide cross-linkers, self-assembled redox-responsive polymers, linear and
dendritic biodegradable polymers, redox-responsive drug conjugates [7]. Such structures
decay to C-C bond based polymers or low molecular weight compounds due to the disulfide
reduction, which limits the degree of degradation of polymer chains. In several examples,
direct integration of disulfides into polymer structures would help to perform a faster degra-
dation process. As well known, thiols are more acidic compared to alcohol analogues, which
allows deprotonation under milder conditions. For instance, the $pK_a$ of ethyl alcohol is
16 [11] and $pK_a$ of ethyl mercaptan is 10.5 [12]. Deprotonated thiolate anion can participate
in different processes, which lead to disulfide formation. At one side, this is a single electron
transfer process [13], which results in oxidation of thiyl radicals as the rate-determining
step [14]. In order to form disulfide bond, thiyl radicals should couple fast with each other.
On a different side of the spectrum, nucleophilic thiolate anion attacks the disulfide bond,
which leads to formation of new disulfide and thiolate anion. This self-promoting cycle of
base catalyzed thiol oxidation is illustrated in Figure 2.

![Fig. 2 Base-catalyzed thiol oxidation [14]](image-url)
An advantage of the use of disulfides for the formation of new disulfide, which eliminates the potential for over-oxidation. Stronger oxidizing agents could not stop at the disulfide, but rather continue to go towards sulfonic acids [14, 15].

2.3 DODT polymerization

The polymerization of 3,6-dioxa-octane-1,8-dithiol (DODT) was carried out by oxidation of the thiol groups of the monomer with $H_2O_2$ aqueous solution performed under air in the presence of an amine base catalyst. This type of reaction called living radical ring-opening redox polymerization (R3P) by the authors, Rosenthal-Kim and Puskas [16], and they applied this process for the coupling of dithiol-telechelic polyisobutylene chains too. This type of reaction shows features of green chemistry, because of the convenient reaction conditions, that is, ambient temperature and pressure. As can be seen in Figure 3 the proposed mechanism shows that the thiols are converted to thiolate dianions by the base, and easily oxidized from the thiolate dianion to thiyld diradical by the addition of $H_2O_2$ [16]. Subsequently, the diradical monomers form cyclic dimers, which tends to change its state. In such state, the disulfide bonds can be potentially taken into account as an additional or opening site. Considering, that larger ring has the ability to recombine, which leads to the exponential growth of $M_n$ as displayed in Figure 3. Under certain conditions, the rings can stay open and create thiol end groups, but there were conditions, where no thiol end groups can be observed.
Fig. 3 Proposed mechanism of Radical Ring-opening Redox Polymerization, R3P of DODT [16]

2.4 Thiol Michael addition

During the past decades, thiol-ene chemistry had many prosperous polymeric applications for the synthesis of monomers, polymers and for surface modifications [17]. On the basis of a wide variety of reactants, high thermodynamic driving force, fast reaction rate in simply removable solvents, insensibility to oxygen, regioselectivity and moderate conditions, the thiol-ene addition is among the “click” reaction type. As known from various studies, thiol-ene mixtures present considerable advantage for the formation of copolymers, like low shrinkage, self-initiation and latitude formation, because the large number of double bond containing monomers are able to react with thiols [18]. There are two mechanisms
that are described as thiol-ene addition: the first one is anti-Markovnikov addition when the compound is electron rich, and the second is thiol Michael addition for unsaturated compounds in the presence of a catalyst [19]. Michael addition is a nucleophilic addition of carbanion or different nucleophile (primary amine or thiol) to an $\alpha, \beta$-unsaturated carbonyl compound. It belongs to the large class of the conjugate addition reactions. This is one of the most useful ways of soft C-C bond formation [20]. In thiol Michael addition the reaction with negligible amounts of byproducts can be catalyzed by primary and secondary amines. However, according to the work of Sharpless [21], the thiol Michael addition should be eliminated as true click reaction, because it is used directly to remove byproducts. Nevertheless, the thiol-Michael addition is a crucial method for advanced polymer material formation. Common examples of Michael acceptors are acrylates, maleimides, acrylamides, methacrylates [22]. Two mechanisms exist that describe the thiol-Michael addition. As can be seen in Figure 4, the process starts with nucleophilic attack (2) of the amine (AM) on the ene (EN), which leads to zwitterion (ZW). The carbanion of (ZW) deprotonates the thiol to form thiol-anion (TA). Moreover, the zwitterion can undergo through aza-Michael addition [10], where TA is potent nucleophile and attacks an ene (4) resulting in an anionic product (AP). The targeted neutral product (Pr) and thiolate produced by deprotonation of the thiol (7) activate an anionic chain reaction, which are in charge for the rapid rate of this process. In order to terminate this reaction, cation (Cn) from reaction (3) react with AP (6), which causes formation of side products (NP).
2 Literature review

Fig. 4 Two reaction mechanisms for the thiol-Michael addition. The base catalyzed mechanism is shown on the left in red while the mechanism corresponding to nucleophilic initiation is presented on the right in blue. Common species are shown in black and the targeted product in pink. (EWG = electron withdrawing group) [22]

2.5 Advantages and potential application of thioether containing polymers

As well known from the past, antiseptic and healing properties of sulfur helped to create remarkable history in alchemy and medicine, which had significant influence in modern chemistry. One of the first plastic and rubber materials was synthesized from sulfur-containing polymers [23]. The exceptional properties of the S-S bonds make them biologically and synthetically beneficial. For instance, disulfide-bonded drug delivery [24] has been used in the biomedical field in the last 50 years, because their reductive property and selective
sensitivity. As for the synthetic possibilities of the disulfide bond, it is usually overshadowed because of their biodegradation. The demand for greener synthetic polymers put disulfide bonds as one of the leading synthetic strategies for green chemistry, because of the mild reaction conditions for their formation. It should be noted, that the simplicity of the thiol-ene chemistry and its efficiency make it possible to use this chemistry for both the synthesis of the starting monomers and the formation of macromolecules. Modifying polymers with the purpose of introducing the necessary functional groups and the broad range of starting materials makes this process attractive even for the derivatization of industrial polymers, such as polybutadiene homopolymers, copolymers and block copolymers, up to systems based on chitosan, polyoxazoline and polypeptides [25]. By means of the thiol-ene chemistry, linear polythioethers can also be obtained, as well as polymer-analogous transformations of linear polymers, giving them the necessary properties, for example, introducing biologically active molecular fragments into their structure. Thioether containing polymers have also been designed to be combined with other stimuli responsive moieties to construct multi-responsive systems. Random copolymers, such as of N-isopropylacrylamide (NIPAM) and thioethers were synthesized by reversible-addition fragmentation transfer (RAFT) polymerization. The resulting polymers possess lower critical solution temperature (LCST), which helps to change some properties of such polymers [26]. For instance, Chen and his team established a thermal and oxidation, dual responsive poly(β-thioether ester) by thiol-ene polymerization of PEG diacrylate and 1,2-ethanedithiol by thiol-ene polymerization of PEG diacrylate and 1,2-ethanedithiol monomers [27]. Even so, the biodegradable thioether containing polymers could be more preferable in the form of in vivo, therefore the thioether containing polypeptides and polyesters are progressively developing.
3 Aim and tasks

The major aim of my research is related to the investigation of the kinetics of the synthesis of thioether copolymers and investigating the effect of reaction time on the formation of sulfur containing copolymers between 3,6-dioxa-octane-1,8-dithiol (DODT) and poly(ethylene glycol) diacrylate (PEGDA) by click reaction. Achieving this aim required solving the following specific tasks:

- Establishing the regularities of the of l DODT and PEGDA in homogeneous and heterogeneous systems, and finding the formation conditions for copolymers with a preferably random or block-type distribution of comonomer units;

- improvement of the methods for the synthesis of DODT and PEGDA copolymers by the thiol-ene addition, and identification of ways to regulate the composition and structure of the copolymers;

- identification of optimal conditions for the synthesis of well-defined copolymers and development of predictive methods for calculating the kinetics of intramolecular cyclization taking into account the composition and distribution of functional groups in the macromolecules.
4 Experimental Section

4.1 Characterization of raw materials

3,6-dioxa-octane-1,8-dithiol (DODT) which formula is \( C_6H_{14}O_2S_2 \) was purchased at the firm «TCI»(Tokyo) used without further purification (MW= 182.30 g/mol); purity > 95%. Its structure is presented on Figure 5.

\[
\text{HS} - O - O - \text{SH}
\]

Fig. 5 Structural formula of DODT

N,N,N’,N”,N”-pentamethyl diethylenetriamine (PMDETA) which formula is \( C_9H_{23}N_3 \) was purchased at the firm «TCI» (Tokyo) used without further purification (MW= 173.30 g/mol); purity > 99.0 %. Its structure is visualised on Figure 6.

\[
\text{CH}_3 - \text{N} - \text{CH}_3 \quad \text{CH}_3 - \text{N} - \text{CH}_3
\]

Fig. 6 Structural formula of PMDETA

Poly (ethylene glycol) diacrylate (PEGDA) was purchased at the firm «Sigma-Aldrich», (United States) used with purification by passing through a column filled with basic \( \text{Al}_2O_3 \) (\( M_n= 250 \) g/mol) and its structural formula is represented at Figure 7.
4 Experimental Section

4.1 Materials

Tetrahydrofuran (THF) which formula is \(C_4H_8O\) was purchased at the firm «VWR» (United States) used without further purification (MW= 72.11 g/mol); purity > 99.0%. Its structure is often depicted according to Figure 8.

\[
\text{Fig. 7 Structural formula of PEGDA}
\]

Hydrogen peroxide solution which formula is \(H_2O_2\) was used as 30% (w/w) in aqueous solution and purchased at the firm «Sigma-Aldrich», (United States), (MW= 34.0 g/mol). In addition, materials that used in some of the synthesis as additives in alcohol solution are trifluoroacetic acid (\(C_3F_7COOH\)) purchased from «Sigma-Aldrich», (United States) and powder of sodium sulfite (\(Na_2SO_3\)).

4.2 Analysis

To analyze \(^1H\text{NMR}\) spectra of the obtained copolymers were recorded on a Varian 500 MHz spectrometer. Polymer samples were dissolved in deuterated chloroform (\(CDCl_3\)) because it helps to avoid recording of a large interfering signal and plays the role of non-polar solvent. Based on the NMR integrals, average degree polymerization of the two types of monomers units DODT and PEGDA could be determined. Also, it is possible to calculate the
number of average molecular weight (Mn) of the obtained copolymers. Molecular weights of the synthesized polymers were determined by gel permeation chromatography (GPC) applying tetrahydrofuran as eluent with 0.3 ml/min flow rate at 35°. Each sample undertakes a virtual separation run, which is dynamically presented in three ways in the software: a virtual column, the collected fractions, and a virtual chromatogram. These three steps show the simultaneous view of main aspects of the process to illustrate the interrelation between the experiment and the obtained chromatogram. The raw data is the chromatogram and with the calibration curve it can converted to molecular weight distribution. The number average molecular weight of the polymer is also known from the gel permeation analysis (GPC), which also helps to determine the molar mass distribution of the polymer. Number average molecular weight described as the total weight of polymer divided by the total number of molecules and expressed by formula [28]:

\[
\overline{M}_n = \frac{\sum_i N_i M_i}{\sum_i N_i}
\]

, where \(N_i\) is the number of molecules of molecular weight of \(M_i\).

### 4.3 Thioether containing polymers synthesis

**Synthesis of P(DODT-co-PEGDA) copolymer**

A representative copolymerization of DODT and PEGDA in 50:50 molar ratio was performed as follows. First, 2.0 ml of DODT was dissolved in 24.0 ml THF. Subsequently, 1.68 ml PMDETA (1 equivalent to the –SH groups) and 2.80 ml PEGDA was added to the reaction mixture followed by the addition of 6 ml 6 wt% diluted aqueous solution of \(H_2O_2\) (the mixture of 1.2 ml 30 wt% \(H_2O_2\) solution and 4.8 ml distilled water). Then, 3.5 ml of samples were withdrawn at different reaction times. After 15 minutes reaction time, methanol was added to the opaque solution in which the obtained polymer was precipitated.
Synthesis of a P(DODT-co-PEGDA) during NMR analysis

A representative polymerization of DODT and PEGDA in 50:50 molar ratio was performed as follows. The volume of every reagent was divided by 36, and thus 0.05 ml of DODT was dissolved in 0.67 ml THF. Then, 0.08 ml PEGDA was added to the reaction mixture. When the test tube was transferred to the NMR laboratory, 0.05 ml of PMDETA (1 equivalent to the –SH groups) and 0.17 ml of 6 wt% diluted aqueous solution of \( H_2O_2 \) were added to the solution and the polymerization reaction began. During 15 minutes, NMR analyses were carried out 10 times in order to follow the reaction.

Synthesis with DODT monomer and PEGDA without \( H_2O_2 \)

The experiment without \( H_2O_2 \) addition was performed as follows. To the solution of 2.0 ml of DODT, 1.68 ml of PMDETA, 24.0 ml of THF and 2.8 ml PEGDA were added. Time frame of the reaction was from 1 min to 30 min, the volume of the reaction mixture was withdrawn in the amount of 3.5 ml at different reaction times, and the resulting polymer was precipitated in isopropanol.

Synthesis with DODT monomer and PEGDA with acid addition

In this experiment, 5 samples were obtained, instead of the usual 10 samples withdrawing technique. The quantities of the reagents were divided by 8 from the original experiment. This technique itself differed from the previously performed experiments, because in each sample, the amounts of reactants were as follow: 0.25 ml DODT, 0.21 ml PMDETA, 3 ml THF, and then pre-mixed solutions of 0.35 ml PEGDA and 0.75 ml 6 wt% \( H_2O_2 \) were added to the vials. The time frame of the reaction was from 1 min to 15 min. Half of the withdrawn samples were poured in methanol containing 0.3 ml \( CF_3COOH \) and 370 mg \( Na_2SO_3 \). It should be noted that this experiment was varied, depending on the results obtained. For example, in one variation, only the composition of the pre-mixed 5 vials of the methanol mixture was changed, particularly only \( CF_3COOH \) or \( Na_2SO_3 \) were added.
Synthesis with DODT monomer and PEGDA with chloroform addition

In this experiment 5 samples were considered. The method was different from the previous ones. In each sample the following amounts of reactants were added: 0.25 ml DODT, 0.21 ml PMDETA, 3 ml THF, 0.35 ml PEGDA and 0.75 ml 6 wt% $H_2O_2$ were added to the vials. The time frame of the reaction was from 1.5 min to 9 min. The withdrawn samples were poured in in pre-mixed solution of 10 ml $CHCl_3$ and 10 ml HCl (0.1 M) solution in water. After withdrawal, the resulting two-phase mixtures were shaken, in order to clearly see the border between the two systems. The upper phase is the aqueous phase, which should be removed with the help of a separatory funnel. After successful separation, the lower layer was placed in a rotary evaporator for further gentle removal of chloroform from samples by evaporation. The obtained copolymers were dried in air and under vacuum until constant weight.
5 Results and Discussion

The study of thioether containing copolymer causes great interest in the wide range of industries. Therefore, $^1$HNMR spectroscopy were used to analyze the number-average molecular weight of formed P(DODT-co-PEGDA) copolymer. Gained data showed NMR spectra allied with chemical shift of protons in various environments, NMR integration, and the effect of the solvent to a polymer [29]. In the discussion of the obtained results, an $^1$HNMR spectrum of a product present information on where the small peaks of the end groups can be seen along with a set of impurities due to catalyst, solvents, and byproducts. Reaction shown in Figure 9 can be accomplished using a thiol-ene coupling reaction, which undergoes by the oxidative polymerization of DODT in the presence of acrylate groups produced a new copolymer. The Michael-type addition reaction is advantageous for copolymers formation because thiols and alkenes couple under physiological conditions, with no by-products, and no need for free radical initiating chemicals. Eventually this polymerization produces a polymer with n units derived from the poly (ethylene glycol) and dithiol [30].

Fig. 9 The formation of the P (DODT-co-PEGDA) copolymers
After completing the first series of experiments (Experiment 1), 10 samples of copolymers were taken to analysis preparation phase, where, pre-weighted vials were used to undertake $^1$HNMR and GPC analysis. On the basis of outcome, that gives first experiment, it can be shown, that $^1$HNMR analysis helped to make visual illustration of formed copolymers (P(DODT-co-PEGDA)) presented in Figure 10.

![The structure of the formed P(DODT-co-PEGDA) copolymers](image)

Fig. 10 The structure of the formed P(DODT-co-PEGDA) copolymers

The evaluation of the 1H NMR spectra of the withdrawn samples is shown in Figure 11, where three triplets between 6 and 7 ppm illustrate C=C double bonds at the end of the chain in acrylate groups. Highest peak at 3.62 ppm presents O-CH2 methylene protons adjacent to the etheric oxygen. Area with major number of peaks from 2.89 to 2.65 ppm displays methylene protons attached to the thioether groups. Peaks between 4.5 and 4.0 ppm show in the saturated acrylate groups, where methylene protons adjacent to the ester group. Mn and average amount of DODT and PEGDA monomeric units in the copolymer chains can be determined from the obtained peaks and summarized in the Table 1.

Precise knowing of DODT and PEGDA content of formed copolymers helped for further investigation and corrections of the polymerization reaction. From the data of Table 1 it can be seen that the Mn values do not show any increasing tendency with time and the
Fig. 11 $^1\text{HNMR}$ spectra of copolymers obtained 1- and 15-minutes reaction time in Experiment 1. (50% molar ratio of DODT and 50% of PEGDA in the feed)

composition does not change considerably, too. It can be concluded that even at the time of the withdrawal of the first sample the polymerization was complete.

Table 1 $M_n$ and average degree of polymerization of DODT and PEGDA monomeric units in the P(DODT- co-PEGDA) chains obtained at different reaction times (Experiment 1)

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>$M_n$ (g/mol)</th>
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<th>PEGDA</th>
<th>$M_n$ GPC (g/mol)</th>
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<tr>
<td>9</td>
<td>4700</td>
<td>13</td>
<td>10</td>
<td>5100</td>
</tr>
<tr>
<td>11</td>
<td>4800</td>
<td>13</td>
<td>10</td>
<td>4700</td>
</tr>
<tr>
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<td>14</td>
<td>11</td>
<td>4200</td>
</tr>
<tr>
<td>15</td>
<td>4900</td>
<td>14</td>
<td>10</td>
<td>3400</td>
</tr>
</tbody>
</table>

On the gel permeation chromatograms (Figure 12) one monomodal peak can be seen indicating quite narrow molecular weight distribution. It shows that the size of the formed polymer chains does not change considerably in this reaction and in a chosen time region.

In the next experiment (Experiment 2), I tried to follow the reaction with $^1\text{HNMR}$ spectra recording. So, I performed reaction in $^1\text{HNMR}$ tube using deuterated THF and water, then took NMR spectra at the given reaction times. In the first experiment (Experiment 1), after the synthesis of a copolymer with a given ratio of PEGDA and DODT content...
in feed followed by the addition of equal molar amount of $H_2O_2$ solution, samples were withdrawn. However, there was not any considerable changes in the spectra related to the first one, recorded at 69 seconds reaction time in the next experiment (Experiment 3), the polymerization was performed without the addition of $H_2O_2$. Also in this case, the NMR spectra and the gel permeation chromatograms (and the calculated average PEGDA content and Mn) did not show considerable change in time. (Figure 13, Table 2) However, the calculated average degree of polymerization of PEGDA and DODT are in accordance with the expectation that alternating copolymer should be formed (since the monomeric units cannot react with themselves only with each other).
Fig. 13 $^1$HNMR spectrum for 30 min sample in Experiment 3

Table 2 $M_n$ and average amount of DODT and PEGDA monomeric units in the P(DODT-co-PEGDA) chains obtained at different reaction times (Experiment 4)

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>$M_n$ (g/mol)</th>
<th>DODT</th>
<th>PEGDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2900</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>2900</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>2600</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>3000</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>30</td>
<td>3000</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
Since in the previous experiment the polymer was precipitated in methanol with time, the methodics was slightly changed in Experiment 4. Here, every samples were withdrawn into pre-mixed solution $\text{CF}_3\text{COOH}$ and $\text{Na}_2\text{SO}_3$ in methanol. The aim of the addition of $\text{CF}_3\text{COOH}$ was to inactivate the PMDETA catalyst by salt formation while of $\text{Na}_2\text{SO}_3$ to inactivate the remaining $\text{H}_2\text{O}_2$. However, reaction was not successful, no yield of polymer came out of it. However, when the reaction mixture was added to the methanolic solution of only $\text{CF}_3\text{COOH}$ (Experiment IV), polymer products were precipitated later. In Figure 14, the GPC chromatogram of the precipitated polymer can be seen.

Fig. 14 The gel permeation chromatogram of the polymers obtained in Experiment 5

In a control experiment (Experiment 6), a copolymer was added to an $\text{Na}_2\text{SO}_3$-solution in methanol, and the copolymer was disappeared proving that $\text{Na}_2\text{SO}_3$ reduce the dithiol bonds results in the decomposition of the polymer chains. Since it seems that in the presence of $\text{CF}_3\text{COOH}$ the reaction goes further, in the next experiment (Experiment 7), methodic of copolymers obtaining changed significantly. So, instead of pouring into alcohol solution the withdrawn solution was pour out to pre-mixed solution of $\text{CHCl}_3$ and aqueous HCl solution.
Because the system was two-phased, it was separated with separatory funnel, and with the help of rotary evaporator chloroform were dried out from this solution. However, only two samples could be examined by GPC and $^1{HNNMR}$ whose results are shown in Figure 15.

![The gel permeation chromatogram of the polymers obtained in Experiment 7](image)

**Fig. 15** The gel permeation chromatogram of the polymers obtained in Experiment 7

The last experiments were focused on formation of copolymers in the alcohol and water free environment. Experiment was made with the same quantity of reagents as was taken in previous experiments with one exception of that, no $H_2O_2$ was poured. It was poured after 15 minutes and then was withdrawn to methanol. Reaction showed milky color, only after pouring of the $H_2O_2$. Very small amount of polymer was obtained in this process. Therefore, no analyses could be done because only two samples showed tendency of polymerization and very small amounts of polymers were obtained by centrifugation. However, when some alcohol was added to same reaction mixture, high yields were experienced. So, we can conclude that addition of water or an alcohol is necessary for the performance thiol-Michael addition for synthesis P(DODT-co-PEGDA) of this polymerization.
6 Summary

Click chemistry is a concept of highly efficient chemical reactions in which these reactions share some important common features, such as high reaction yields, benign reaction conditions and easily removable byproducts, stereospecific reaction coordinates and tolerance to diverse functional groups. Accordingly, taking into account previous studies, advantages of the “click” nature offered by thiols have been exploited and implemented in a broad range of fields, like chemical, biochemical, biological, physical, and engineering applications. The Michael-type addition reaction is one of the “click” chemistry mechanisms, which used for copolymer formation. Thiols and alkenes couple even under physiological conditions with no by-products, and there is no need for free radical initiating chemicals. In my work, I have attempted to investigate the effect of a novel unique process developed very recently, which is based on the simultaneous thiol-ene Michael addition and oxidative thiol coupling reactions. In the past few years, sulfur-containing polymers have gained increased interest due to their advantageous properties which make them useful for a wide range of applications. I have studied the reaction of 3,6-dioxa-octane-1,8-dithiol (DODT) with poly(ethylene glycol) diacrylate (PEGDA) in the presence of N,N,N’,N″,N″'-pentamethyldiethylenetriamine (PMDETA) catalyst and hydrogen peroxide as oxidizing agent. This reaction shows the features of green chemistry due to the use of ambient temperature and pressure. During the reactions, small amounts of samples were withdrawn at different reaction times, and alcohol was added to the opaque solutions in which the obtained polymers were precipitated. Analysis of the resulting polymer samples were carried out by \( ^1HNMR \) spectroscopy and gel permeation chromatography (GPC) for the determination of the number of average molecular weight \( (M_n) \) and the average amounts of DODT and PEGDA monomeric units in the obtained copolymers. My results conclusively indicate that the simultaneous thiol-ene Michael addition reaction and oxidative thiol-thiol coupling successfully resulted in P(DODT-co-PEGDA) copolymer formation under green chemistry conditions in a short reaction time. Moreover, it has been proved that the presence of water or alcohol is necessary for the formation of this copolymer.
References


