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SYNTHESIS OF NOVEL SURFACE ACTIVE METHACRYLATE MONOMERS BASED ON *e*-CAPROLACTONE

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Abstract. The interaction of ε-caprolactone with methacrylic acid has resulted in formation of 6-methacryloylhexanoate which was subsequently converted into the corresponding chloroanhydride *via* the reaction with phosphorus trichloride. The reaction of chloroanhydride with poly(ethylene glycol) or poly(ethylene glycol) monomethyl ether yielded the corresponding surface active methacrylate monomers. During interaction of the hydroxyl group of poly(ethylene glycol) containing the monomer with the excess of phosphoryl chloride phosphate-containing monomer was synthesized. The synthesized monomers exhibit surfactant properties and reduce the surface tension at the aqueous solution – air interface.

Keywords: ε-caprolactone, methacrylates, phosphates, poly(ethylene glycol), surface activity, surface tension.

1. Introduction

Surface active monomers (surfmers) are widely utilized for the development of surface active oligomers and polymeric colloids with a functionalized interface [1-4]. During the emulsion copolymerization, the surfmer molecules are located predominantly on the monomer droplet-water interface thus acting as surfactants stabilizing the emulsion and comonomers. Subsequently surfmer units incorporated into the polymer structure provide effective stabilization of the polymer colloid. The process of surfmer-assisted emulsion polymerization is well described by the known mechanism of emulsion polymerization [5]. The polymerizable fragments of surfmers retain their polymerizability. Nowadays, a board assortment of anionic, cationic or nonionic maleate [6-10], (meth)acrylate [11-13], maleimide [14, 15] and styrene [16, 17] surfmers containing polymerizable fragment either in hydrophilic or in the hydrophobic block is known.

The use of various traditional monomers and surfmers having the necessary polymerization activity and the preselected type of surface activity, and containing defined functional groups, during copolymerization allows developing polymers with predicted micro-and macrostructure and colloidal properties [18]. Such materials were found to be efficient carriers of drugs [19-21] and nucleic acids [22, 23].

Among the variety of monomers for development of surface active copolymers for efficient conjugation of drugs and nucleic acid [24, 25], functional methacrylate monomers, namely N,N-dimethylaminoethyl methacrylate (DMAEMA) and 2-hydroxyethyl methacrylate (HEMA), have been widely used for obtaining such copolymers [26, 27]. Therefore a number of studies are focused on the synthesis of novel types of surface (meth)acrylate surface active monomers and their application for development of polymeric drug carriers [28-30].

Surface active (meth)acrylate monomers are mostly synthesized by acylation of hydroxyl groups of corresponding hydroxy acids with different length of aliphatic chain, or amino groups (such as the primary amino group in octadecylamine) with chloroanhydrides of acrylic and methacrylic acids [31].

Various surface active monomers that have polymerizable group and a functional group separated from each other *via* spacers of different lengths and nature are interesting prospects for developing the novel types of surface active copolymers. Various fragments of bifunctional compounds (diols, dicarboxylic acids, diamines, *etc.*) that are used as spacers could be incorporated into the surfmer structure via successive interaction due to their functional groups. However, selective transformation of one from two equally reactive functional groups is quite problematic. As a result, the final product contains impurities of bifunctional derivatives which is a serious issue in case of monomer synthesis.

Such problems can be omitted by using various heterocyclic reagents (oxyranes, lactones, sultones, *etc.*) since they are known to selectively form monosubstituted derivatives in ring opening reactions under mild conditions. Lactones of corresponding carboxylic acids are particulary promising reagents for incorporation of hydrophobic spacers. The utilization of lactones of different carboxylic acids and with various ring sizes allows varying hydrophilic-lipophilic balance (HLB) and the position of polymerizable fragment relative to other functional groups in the surfmer molecule.

Depending on ring size, nature of reagents and the reaction conditions, lactones are known to form either alkoxy or acyl-substituted derivatives [32]. Thus, acylation of HEMA by caprolactone yields acyl-substituted of 6-hydroxyhexanoic acid, namely 2-(methacryloyloxy)ethyl 6-hydroxyhexanoate [33,34] and hydroxyethylcaprolactone acrylate (HECLA) [35]. These monomers are successfully applied for creation of polymeric materials of biomedical application [36-38]. We consider the reaction of lactones with unsaturated carboxylic acids leading to formation of the corresponding alkoxy derivatives to be a promising approach for synthesis of monomers with the polimerizable fragment and a free carboxylic group separated by the polymethylene spacer of defined length. Moreover, the presence of reactive carboxylic group allows using such derivatives of ω-hydroxycarboxylic acids as intermediates for development of novel types of surface active monomers.

Therefore, the main purpose of this research was the synthesis of novel surfmers with poly(ethylene glycol) and phosphate fragments based on ε-methacryloyloxyhenaoic acid.

2. Experimental

2.1. Materials

Caprolactone (Sigma-Aldrich), triethylamine (Merck), phosphoryl chloride (Merck) and methacrylic acid (Sigma-Aldrich) were purified by distillation. Phosphorus trichloride was purchased from Merck and used without further purification. Poly(ethylene glycol) monomethyl ether 750 (PEG MME 750) with an average molecular weight of 750 g/mol and poly(ethylene glycol) 600 (PEG 600) with an average molecular weight of 600 g/mol were commercially available from Sigma-Aldrich. All solvents (hexane, ethyl acetate, dichloromethane, dioxane) were purchased from Merck and Sigma-Aldrich and purified according to known techniques prior to use [39].

2.2. Analysis

The individuality of the synthesized compounds was confirmed by thin layer chromatography using Silica gel 60 F_{254} (Merck) sheets. The hexane-ethyl acetate mixture (solvent ratios as 2:1, 1:1, and 2:1, respectively) was used as an eluent and the length of the solvent front was 100 mm. The chromatograms were developed in the iodine vapor. IR spectroscopy was used to determine the products. Spectra were recorded using Spectrod M80 spectrometr in a thin film (for liquid compounds) and in vaseline oil (for crystalline substances). ^{1}H-NMR spectra were recorded using a Brucker 150 spectrometr at a working frequency of 300MHz in DMSO-d_6. Sample concentration was 5–10 %, hexamethyldisiloxane was used as an internal standard. The structure and purity of synthesized compounds were additionally confirmed using micro elemental analysis. The concentration of carboxylic groups was determined by a potentiometric titration of a sample with 0.1 N solution of sodium hydroxide in ethanol [40].

2.3. Surface Tension

The characterization of synthesized monomers surface activity was characterized by surface tension measurements. The measurements were performed with a Du Noüy ring tensiometer at 293 K [41]. The critical micelle concentration (CMC) of monomers was determined from the inflection points on thesurface tension isotherms.

2.4. Synthesis

6-Methacryloyloxyhexanoic acid **2**. Mixture of 1 g (0.0098 mol) of caprolactone, 2.24 g (0.0261 mol) of methacrylic acid and 0.001 g of hydroquinone was kept at 228 K for 15 h in argon atmosphere. After removing the excess of methacrylic acid under reduced pressure, 1.12 g (58 %) of product (a white paste) was recovered. mp 303 K. Found acid value 281.16; calc. acid value 280.50. Found, %: C 59.56; H 8.33. $C_{10}H_{16}O_4$. Calc., %: C 60.00; H 8.05.

6-Methacryloyloxyhexanoyl chloride was synthesized *via* reaction of 6-methacryloyloxyhenaoic acid with phosphorus trichloride at 293 K according to the known technique [42].

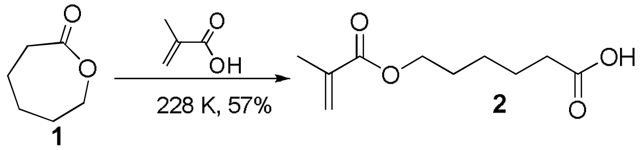
Poly(ethylene glycol)l-600-(6-methacryloyloxy) hexanoate **4a.** To a mixture of 10 g (0.016 mol) of PEG 600 and 0.4 g (0.004 mol) of triethylamine in 20 ml of dichloromethane, a solution of 0.9 g (0.004 mol) of 6-methacryloyloxyhexanoyl chloride in 5 ml of dichloromethane was added dropwise under stirring at 278 K. The reaction mixture was stirred for 5 h at 278 K and then for 7 h at ambient temperature. The precipitate was filtered off; the filtrate was diluted with 20 ml of water, and the monomer was extracted with butanone (10 ml×5) at 353 K under vigorous stirring. The butanone was removed from combined organic phase to give 2.8 g (90 %) of monomer. mp 300 K. Found, %: C 55.96; H 8.69. $C_{36.2}H_{68.8}O_{17.2}$. Calc., %: C 55.80; H 8.84.

ω-Methoxypoly(ethylene glycol) -750-(6-methacryloyloxy)hexanoate **4b**. To a solution of 3 g (0.004 mol) of PEG MME 750 and 0.4 g (0.004 mol) of triethylamine in 10 ml of dichloromethane, the solution of 0.9 g (0.004 mol) of 6-methacryloyloxyhexanoyl chloride in 5 ml of dichloromethane was added dropwise at 278 K under stirring. The reaction mixture was stirred for 4 h at 283–288 K, the precipitate was filtered off and the solvent was removed under reduced pressure to give 3.35 g (90 %) of monomer. mp 305–306 K. Found, %: C 56.28; H 8.79. $C_{43.6}H_{83.2}O_{20/3}$. Calc., %: C 56.18; H 8.93.

[ω-(Phosphonooxy)poly(ethylene glycol)-600] 6-(methacryloyloxy)hexanoate **6**. To a mixture of 3.37 g (0.022 mol) of phosphotyl chloride in 15 ml of dioxane, the solution of 0.6 g (0.006 mol) of the monomer **4a** and 0.6 g (0.006 mol) of triethylamine in 10 ml of dioxane was added dropwise at 273–278 K under vigorous stirring. The reaction mixture was stirred for 2 h at 273–278 K. The precipitate was filtered off; excess of phosphoryl chloride was removed by distillation. The residue was diluted with 15 ml of dioxane and 1 ml (0.056 mol) of water. After stirring for 24 h at 273–278 K and removing of solvents under reduced pressure 3.56 g (94 %) of desired product was obtained. M. p. 301 K. Found, %: C 50.97; H 8.03. $C_{36.44}H_{72.88}O_{20.22}P$. Calc., %: C 50.57; H 8.43.

3. Results and Discussion

As it was mentioned earlier, the reaction of lactones with unsaturated acids could be a promising method for the development of monomers having the polimerizable fragment separated from the carboxylic group *via* the polymethylene spacer of the defined length. Thus, the interaction of caprolactone with methacrylic acid was studied first:



The reaction was carried out by heating the reagent mixture at different molar ratios at 228 K without using any catalysis and solvents. A nearly total conversion of lactone was achieved in 12 h of reaction under these conditions. The dependence of monoaddition product yield on the molar ratio of reagents is shown in Fig. 1.

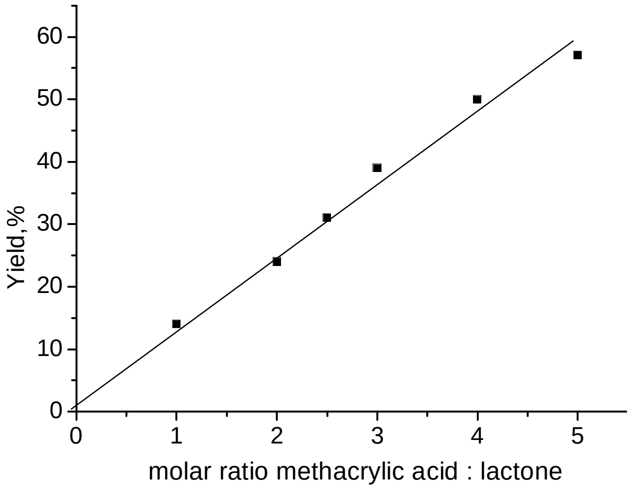


Fig. 1. The dependence of 6-methacryloyloxyhexanoic acid yield on the molar ratio of methacrylic acid:caprolactone

As expected, the telomerization of lactones was mostly observed for the equimolar ratio of reagents. With increasing concentration of methacrylic acid the yield of monomer **2** increased as well. For the 5-fold excess of methacrylic acid, 57–60 % yield of monomer **2** was achieved, the main by-products were the products of polyaddition of lactone. The utilization of catalysis did not lead to formation of desired monomer **2** with a satisfactory yield. The structure of methacrylate **2** was confirmed by IR and ^{1}H NMR spectroscopy and by functional and elemental analysis.

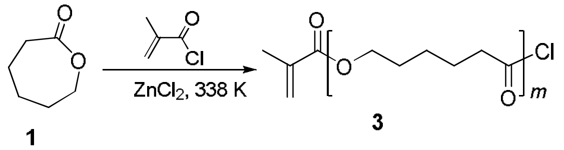
In IR spectrum of methacrylate **2** the following absorption bands are observed: 3300–2550 cm^{-1} (ν_{OH} in carboxylic acids), 1710 cm^{-1} ($\nu_{C=O}$ in acids), and 1724 cm^{-1} ($\nu_{C=O}$ in esters). The absorption band at 1190 cм$^{-1}$ corresponds to stretching of C–O bond in ester group. The presence of absorption bands at 3010 cm^{-1} (ν_{sCH} in $CHR{=}CH_2$), 3080 cm^{-1} (ν_{asCH} in $CHR{=}CH_2$) and 1640 cm^{-1} ($\nu_{C=C}$ in $CHR{=}CH_2$) indicates the presence of the polymerizable methacrylic fragment.

In NMR spectrum of the compound **2** two signals with chemical shifts of 5.55 ppm (s,1H, CH_2=) and 6.09 ppm (s, 1H, CH_2=) correspond to protons of the methylene group. This can be explained by *cis*- or *trans*-position of the mentioned protons relative to the carbonyl group. The signal of methylene cis-proton is shifted downfield. Proton peak of the methacrylate methyl group is located at 1.95 ppm (s, 3H, CH_3–C=).

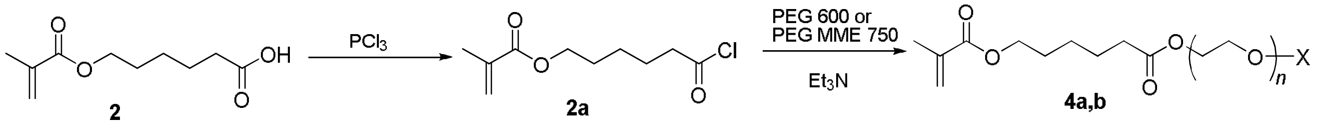
The attempt to synthesize the corresponding maleate monomers via similar interaction of caprolactone with maleic acid was unsuccessful. As a result of the reaction, the mixture of products of mono-, di-, and polyaddition of lactone to the maleic acid was obtained.

The targeted maleates were not extracted even when the significant excess of maleic acid was used in the reaction.

Synthesis of 6-methacryloyloxyhexanoyl chloride *via* interaction of caprolactone with methacryloyl chloride was attempted. This chloroanhydride is considered to be a promising intermediate compound for developing the novel types of surfmers. Oxygen-containing heterocycles, *e.g.* oxyranes or tetrahydrofuran, are known to react with acryloyl chloride in the presence of Lewis acids forming corresponding ω-chloroalkylic esters [43]. Thus, it was expected that the similar reaction of caprolactone with mehacryloyl chloride would lead to formation of corresponding chloroanhydride. However, heating of lactone **1** with methacryloyl chloride at 338 K in the presence of zinc chloride led to telomerization of lactone yielding the product **3** (m = 8–10):



The presence of terminal methacrylic fragment was confirmed by IR spectroscopy, namely by absorption band at 1630–1650 cm^{-1}. This band is characteristic for conjugated C=C bond in methacrylates. The reaction of caprolactone with acetyl chloride under same conditions led to similar results. Therefore, the corresponding chloroanhydride **2a** was synthesized by the reaction of methacrylate **2** with phosphorus trichloride at 293 K during 12 h. The utilization of $SOCl_2$ aimed at synthesis of the corresponding chloroanhydride **2a** is inadmissible due to the partial interaction of HCl with C=C bond during the reaction.

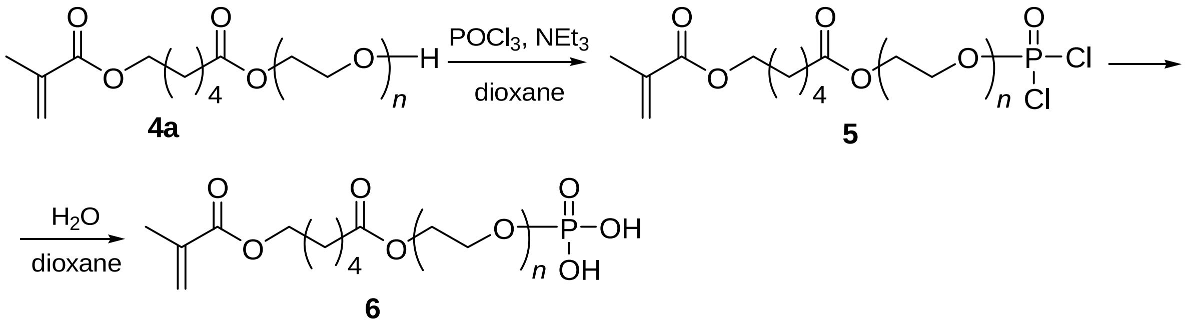


X = H (a); Me (b)

To synthesize the monoacyl derivative of poly(ethylene glycol) 5-fold excess of PEG 600 was used. The equimolar ratio of reagents was utilized for the interaction of chloroanhydride **2a** with PEG MME 750. The reactions were carried out at 278–303 K in dichloromethane or hexane.

The ester **4a** bearing a free hydroxyl group was used as an intermediate compound for synthesis of the surface active phosphate monomer, as polymers with phosphate groups find a wide variety of applications in different fields of biomedicine [44-46].

The surfmer **6** was synthesized by the reaction of the compound **4a** with the excess of $POCl_3$ followed by hydrolysis of resulting chlorophosphate:



For the synthesis of monophospahates the monomer **4a**: $POCl_3$: triethylamine ratio was as 1:5:1. The reaction was carried out at temperatures less then 283 K in dioxane or dichloromethane. The resulting chlorophosphate **5** underwent hydrolysis at 273–278 K during 24 h. Interestingly, the direct one-step interaction of **4a** with P_2O_5 leads to formation of the strongly coloured product.

IR spectra of surfmers **4a,b** contain both characteristic absorption bands of methacrylate fragments and an absorption band at 1104 cm^{-1} attributed to poly(ethylene glycol) fragment ($\nu_{C\text{-}O}$). IR spectrum of a phosphate monomer **6** contains absorption bands at 1100 cm^{-1} ($n_{asP\text{-}O}$) and 1000–740 cm^{-1} ($n_{sP\text{-}O}$).

To study colloidal properties of the synthesized monomers, the surface tension isotherms of their aqueous solutions were measured and their critical micelle concentrations and the surface tension above CMC were determined. The surface tension isotherms of the aqueous solutions of the synthesized surface active monomers are shown in Fig. 2.

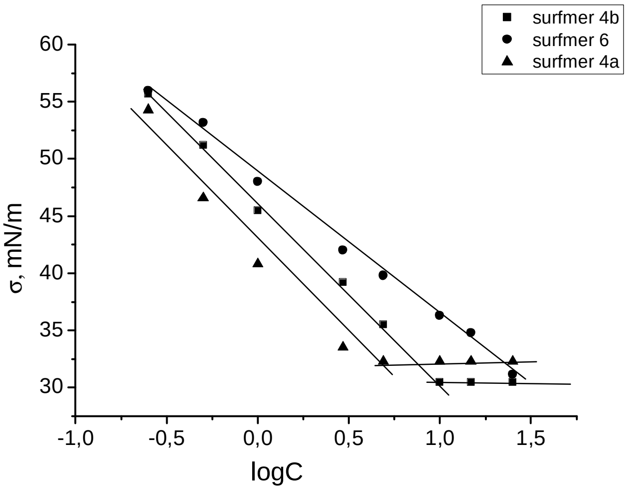


Fig. 2. Surface tension isotherms of surfmers **4a,b** and **6**

The synthesized monomers are typical surfactants, since they reduce the surface tension on aqueous solution – air interface. The surfmers **4a,b** containing poly(ethylene glycol) fragments manifested good solubility in water and high CMC values. The CMC values of the monomers as well as surface tension above CMC were determined from the inflection points on the surface tension isotherms. The CMC for surfmer **4a** was 4.9 % and the surface tension above CMC was 32.3 mN/m. The CMC for surfmer **4b** was 10 % and the surface tension above CMC was 30.5 mN/m, respectively. The absence of inflection point on the surface tension isotherm of the monomer **6** could be explained by its strong hydrophilic character due to the presence of long poly(ethylene glycol) chain and the phosphate group.

4. Conclusions

It was established that the interaction of ε-caprolactone with the excess of methacrylic acid led to the formation of 6-methacryloyloxyhexanoic acid. The synthesized compound is a promising intermediate for the development of novel types of surface active methacrylate monomers. The resulted 6-methacryloyloxyhexanoic acid was used for synthesis of non-ionic surfmers containing poly(ethylene glycol) fragments and their phosphate derivatives. The developed monomers are typical surfactants and reduce the surface tension on the aqueous solution–air interface.

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СИНТЕЗ НОВИХ ПОВЕРХНЕВО-АКТИВНИХ МОНОМЕРІВ МЕТАКРИЛАТНОГО ТИПУ НА ОСНОВІ ε-КАПРОЛАКТОНУ

Анотація. *Реакцією ε-капролактону з метакриловою кислотою одержано 6-метакрилоїлоксигексанову кислоту, яку взаємодією з фосфор трихлоридом перетворено у відповідний хлороангідрид. Реакцією зазначеного хлорангідриду з монометиловим етером поліетиленгліколю та поліетиленгліколем синтезовано поверхнево-активні мономери метакрилатного типу. Реакцією поліетиленгліколевого похідного за гідроксильною групою, з надлишком фосфор оксохлориду синтезовано відповідний фосфатовмісний мономер. Отримані речовини є типовими поверхнево-активними речовинами, які суттєво знижують поверхневий натяг на межі водний розчин-повітря.*

Ключові слова: *ε-капролактон, метакрилат, фосфат, поліетиленгліколь, поверхнева активність, поверхневий натяг.*