

# Reactions of chemical transformation of unsaturated co-polyesteramide

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## Abstract

The article deals with the obtaining of functional polymers, which are prospective in the form of biodegradable carrier polymers for covalent bonding of medicaments and bioactive compounds with them, as well as for pharmaceuticals delivery systems, micro- and nano capsulation etc. They are obtained as a result of chemical transformation by means of additive reaction of unsaturated/saturated polyesteramide containing unsaturated bonds with thioglycolic acid, 2-mercaptoethanol and  $\beta$ -alanine.

**Keywords:** *unsaturated/saturated polyesteramides, thioglycolic acid, 2-mercaptoethanol,  $\beta$ -alanine, functional polymers*

## Introduction

Polyesteramides (PEA) on the basis of natural aminoacids, aliphatic diols and dicarboxylic acids represent relatively new family of biodegradable polymers. The complex of beneficial properties characteristic for aliphatic polyesters and polyamides are combined in these polymers: biodegradation ability (polyesters), hydrophilic properties, high biocompatibility with tissues and desirable mechanical properties in case of average (30-50 thousands) molecular masses (polyamides) (Katsarava, Beridze, Arabuli, Kharadze, Chu, Won C, 1999; Villuendas, Iribabarren & Munoz-Guerra, 1999). Polyesteramides are prospective materials from the viewpoint of their application in surgery, pharmacology, and tissue engineering. Further improvement of PEA properties and respectively, further expansion of application area is possible via their functionalization with insertion of chemically active groups into polymeric chains (Jokhadze, Chu, Tugushi, & Katsarava, 2006) or hydrophobic groups (Neparidze, Machaidze, Zavrashvili, Mazanashvili, Tabidze, Tugushi, & Katsarava, 2006).

Functionalization of polymers creates the possibility of their bonding with medicaments and bioactive substances by chemical bonds enables their numerous transformations with the purpose of further modification of properties. One of the prospective ways of functionalization of polymers is the insertion of unsaturated bonds both into the basic and side chains of macromolecules (Lou, Detrembleur, Lecomte, & Jerome, 2002; Domb, Martinowitz, Ron, Giannos, & Langer, 1991). Insertion of desirable functional groups into macromolecules, as well as numerous inoculation reactions, structurization of polymers (sewing), co-polymerization, hybridization with other unsaturated polymers, e.g. with polysaccharides (acryloyl dextrane etc.) for receipt of multifunctional biodegradable hydrogels etc. are possible via bonding with unsaturated bonds.

## Working Methodology

The goal of the presented work was to study the reactions of chemical transformation of unsaturated-saturated polymer containing unsaturated bonds with the purpose of further receipt of functional polymers. By functional polymers such macromolecular systems are meant, which have either active functional groups well-known in chemistry, or the groups (hydrophobic, catalytic, stereospecific, matrix, photoactive, photochromic, electricity-conducting etc.) which stipulate specific properties of polymeric materials. Furthermore, the mentioned group may be inserted both into basic and side chains of macromolecules.

For chemical modification/transformation we selected unsaturated, biodegradable co-polyesteramide (FA/840/60-Leu-6), which contains unsaturated bonds in basic chain with polycondensation of p-nitrophenyl ethers of fumaric and sebacylic acids and di-p-toluolsulfoacid salts of bis-(L-leucine)-1,6-hexylene diesters (Guo, Chu, Chkhaidze & Katsarava, 2005; Chkhaidze, Tugushi, Kharadze, Gomurashvili, Chu, & Katsarava, 2011). Selection of co-polyesteramide FA/840/60-Leu-6 as research subject was preconditioned by its good film-formation ability on the one hand and by very high concentration of double bonds on the other.

## Results

We have studied interaction of mercaptans and amines with unsaturated bonds of polyesteramide. Thioglycolic acid, 2-mercaptoethanol and aminoacid  $\beta$ -alanine were used as reagents. General pattern of transformations is presented in Figure 1:

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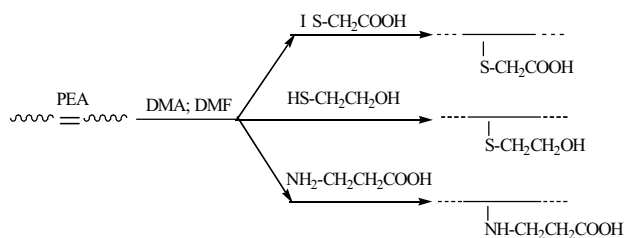


Figure 1. Reactions of chemical transformation of FA/840/60-Leu-6

Interaction with thioglycolic acid. Reaction proceeds according to the scheme presented in Figure 2. Based on common methodology unsaturated/saturated polymer **FA/840/60-Leu-6** (0,01 mole) was dissolved in 50 ml of DMA, then 0,04 moles of thioglycolic acid, 0,04 moles of sodium bicarbonate ( $\text{NaHCO}_3$ ), several water drops were added and reaction mixture was stirred at  $80^\circ\text{C}$  during 48 hours. Polymer was precipitated in the water, washed by water acidated by acetic acid, afterwards by distilled water and was dried in vacuum at  $50^\circ\text{C}$  over  $\text{P}_2\text{O}_5$ . Reaction yield was 89%.

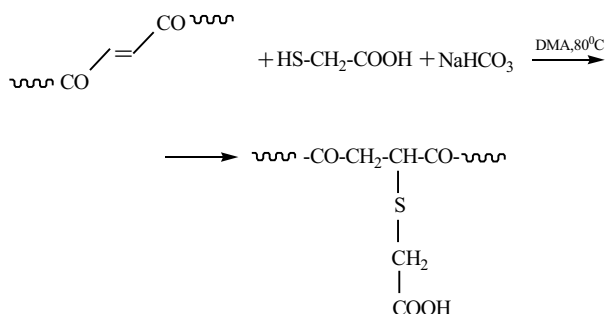


Figure 2. Reaction of chemical transformation of FA/840/60-Leu-6 by thioglycolic acid

Transformation degree (determined by titration) was 90.3%. Polymer transformation degree (t.d.) was determined by us with the use of potentiometric titration method (automated titrator "Radiometer") according to the following technique: 4 ml of 0,1N NaCl water solution was placed in the reactor of titrator and 5 ml of 96% ethanol was added to it, titrator pH (so-called end point) was fixed at 7,0 and then 10 ml of polymeric solution was added to 1 ml ethanol. Water solution of 0,1N NaOH was used by us as titrant. Transformation degree was determined according to the formula:

$$\text{t.d. (in \%)} = \frac{[M + k \cdot (M_{FL} - M)] \cdot V \cdot K \cdot 10^2}{k \cdot [a + (M_{FL} - M_{FNL}) \cdot V \cdot K \cdot 10^{-4}]}$$

where  $k$  is molar fraction in the polymer  $[\text{FA}-(\text{Leu-6})]_k$ ,  $a$  – weight of co-PEA sample in grams,  $b = \text{VK}10^{-7}$  is the amount of 0,1N NaOH consumed during titration of co-PEA sample ( $K$  is a correcting factor for water solution of 0,1N NaOH),  $V$  is the amount of 0,1N NaOH (in mkl) consumed for titration of co-PEA sample (neutralization of carboxylic groups).  $M$ ,  $M_{FL}$  and  $M_{FSL}$  are molecular masses of polymer saturated block 8-[Leu-6], untransformed (unreacted) unsaturated block  $[\text{FA}-(\text{Leu-6})]$  and transformed unsaturated block  $[\text{FA}-(\text{HS-CH}_2\text{-COOH})-(\text{Leu-6})]$  (to which thioglycolic acid was joined), i.e.:

$$\begin{aligned} M &= M_{8\text{-Leu-6}} \\ M_{FL} &= M_{\text{FA}-(\text{Leu-6})} \\ M_{FSL} &= M_{\text{FA}-(\text{HS-CH}_2\text{-COOH})-(\text{Leu-6})} \end{aligned}$$

Transformation degree determined via formula given above was equal to 90.3%. Mentioned composition of polymer is in good agreement with the data of elemental analysis (Table 1).

In order to exclude the fact that either some group of polyesteramide or thioglycolic acid closely conjoint with the polymeric chain has experienced titration. Saturated polyesteramide 8-Leu-6 +  $\text{HS-CH}_2\text{-COOH}$  +  $\text{NaHCO}_3$  was used as a control system. A control experiment was conducted under conditions of above reaction (reaction in 50 ml of DMA, 0,01 moles of polymer, 0,04 moles of thioglycolic acid, 0,04 moles of sodium bicarbonate ( $\text{NaHCO}_3$ ), several water drops, temperature  $80^\circ\text{C}$ , stirring within 48 hours) and the polymer was also separated and purified by the similar technique as described above.

The titrant consumption was not registered during control polymer titration under the abovementioned conditions. There is no other way of titration of one or another group of polymers by alkali. Thioglycolic acid is not bonded with polymer as well, so it was completely washed away during polymer purification (thioglycolic acid doesn't bond with polyesteramide chain with formation of some persistent complex). This experiment testifies that thioglycolic acid is bonded by covalent bonds (namely, sulfide C-S-C bond) with FA/840/60-Leu-6 polyesteramide containing unsaturated bonds.

Fourier infrared spectra (FTIR) of initial and transformed polymers given in Figure 3 confirm the same fact. As it can be seen an absorption band of sulfide bond is clearly visible in spectrum of transformed polymer in the area of  $\sim 750 \text{ cm}^{-1}$ .

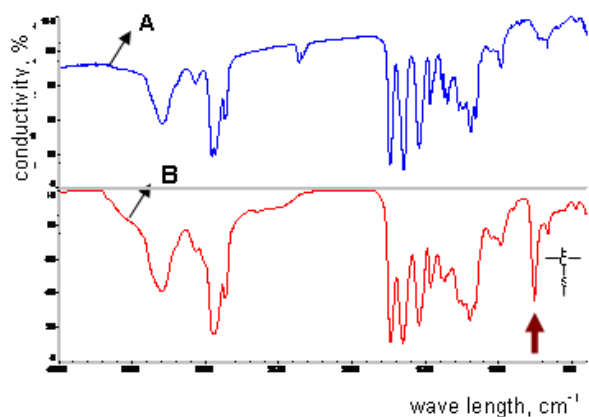


Figure 3. FTIR spectra: A – FA/860/40-Leu-6, B – FA/860/40-Leu-6 + HS-CH<sub>2</sub>-COOHOH

Interaction with mercaptoethanole. Reaction proceeds according to the scheme presented in Figure 4. Based on common methodology unsaturated/saturated polymer – FA/840/60-Leu-6 (0,01 mole) was dissolved in 50 ml of DMA, then 0,04 moles of mercaptoethanol, 0,04 moles of sodium bicarbonate (NaHCO<sub>3</sub>), several water drops were added and the reaction was carried out at 80°C within 48 hours. Obtained substance was precipitated in water, washed by water and dried in vacuum at 50°C on P2O<sub>5</sub>. Reaction yield was 92%.

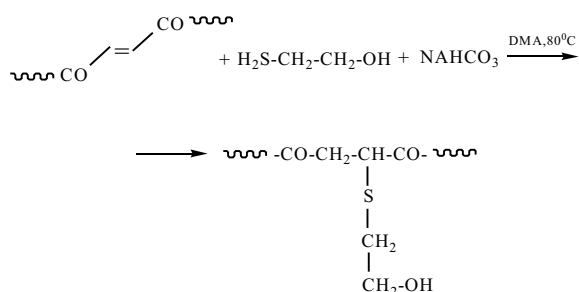


Figure 4. Reaction of FA/8-40/60-Leu-6 chemical transformation by mercaptoethanol

In case of 2- mercaptoethanol, polymer's transformation degree was assessed using hydroxyl number, which was determined with the use of phthalic anhydride solution in pyridine. Phthalic anhydride is connected with compound under investigation by heating with formation of ester on the basis of one carboxylic group and salt with pyridine on the basis of another carboxylic group. 10 ml of distilled water was added to solution under investigation and free carboxylic groups were titrated by 0.5 N NaOH in the presence of phenolphthalein until pink coloring was reached. Hereof:

$$H.N \frac{\text{calculated}}{\text{det er min ed}} = \frac{5,44}{2,85}$$

Transformation degree is equal to 95%. Received transformation degree is in good agreement with the data of elemental analysis (Table 1).

In order to exclude the fact that either some group of polyesteramide, or 2-mercaptoethanol closely conjoint with the polymeric chain was not reacted with phthalic anhydride, the control system, saturated polyesteramide 8-Leu-6 + HS-CH<sub>2</sub>-CH<sub>2</sub>-OH + NaHCO<sub>3</sub>, has been used.

**Table 1.** Elemental analysis of compounds obtained via FA/8-40/60-Leu-6 transformation by thioglycolic acid and mercaptoethanol

Polymer	Brutto formula (average mol. mass)	Calculated/determined, %			
		C	H	N	S
R=SCH <sub>2</sub> COOH	(C <sub>28</sub> H <sub>50</sub> N <sub>2</sub> O <sub>8</sub> ) <sub>0,08</sub> -	61,80	9,04	5,46	2,50
	(C <sub>24</sub> H <sub>40</sub> N <sub>2</sub> O <sub>8</sub> S) <sub>0,028</sub> (C <sub>22</sub> H <sub>38</sub> N <sub>2</sub> O <sub>8</sub> ) <sub>0,04</sub> (509,04)	59,65	8,97	5,42	2,69
R=SCH <sub>2</sub> CH <sub>2</sub> OH	(C <sub>28</sub> H <sub>50</sub> N <sub>2</sub> O <sub>8</sub> ) <sub>0,08</sub> -	62,48	9,30	5,52	2,53
	(C <sub>24</sub> H <sub>42</sub> N <sub>2</sub> O <sub>7</sub> S) <sub>0,028</sub> (C <sub>22</sub> H <sub>38</sub> N <sub>2</sub> O <sub>8</sub> ) <sub>0,02</sub> (505,57)	60,76	9,29	5,24	2,24

Control experiment was conducted by us under conditions of the abovementioned reaction (reaction in 50 ml of DMA, 0,01 moles of polymer, 0,04 moles of 2-mercaptoethanol, 0,04 moles of sodium bicarbonate (NaHCO<sub>3</sub>), several water drops, temperature 80°C, stirring within 48 hours) and the polymer was also separated and purified by the similar technique as described above. Hydroxyl number was not identified in control polymer. There is no other way of interaction of one or another group of polymers with phthalic anhydride. 2-mercaptoethanol is not bonded with polymer as well, i.e. it was completely washed away during the polymer purification (so, 2-mercaptoethanol doesn't bond with polyesteramide chain with formation of some persistent complex).

Interaction with β-alanine. Reaction proceeds according to the scheme presented in Figure 5. Based on common methodology unsaturated/saturated polymer – FA/840/60-Leu-6 (0,01 mole) was dissolved in 50 ml of DMA, then 0,04 moles β-alanine, 0,04 moles of NEt<sub>3</sub> were added. Reaction was conducted at 100-110°C within 96 hours. Obtained compound was precipitated in water, washed by water and dried in vacuum at 50°C on P2O<sub>5</sub>. Reaction yield was 69%.

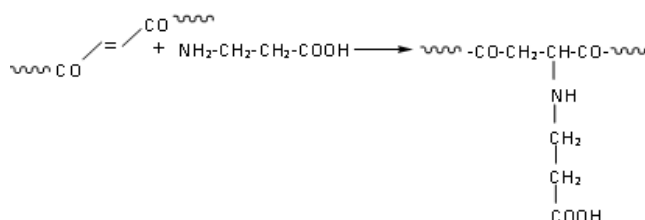


Figure 5. Reaction of FA/8-40/60-Leu-6 chemical transformation by  $\beta$ -alanine

Transformation degree was determined by us with the use of potentiometric titration and the abovementioned formula (Interaction with thioglycolic acid). Transformation degree determined by this method was equal to 24.2% that is significantly less than transformation with the participation of thio-compounds.

The course of a reaction was also confirmed by means of UV-spectroscopy (Figure 6, A, B), via reduction of intensity of absorption band characteristic for double bonds at 260 nm.

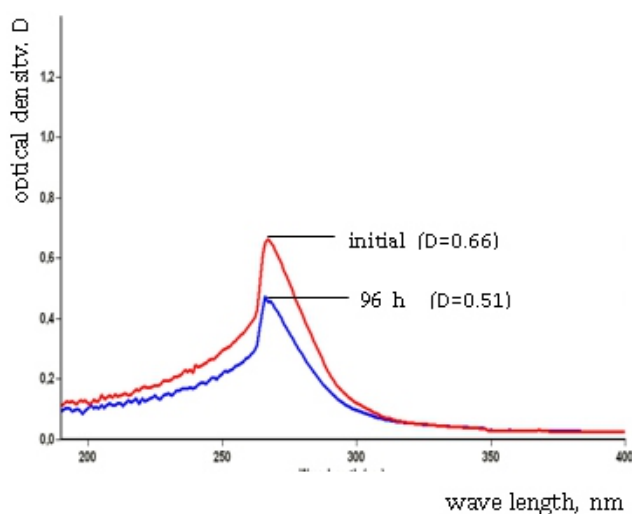


Figure 6. UV spectrum of product received by chemical transformation of FA/840/60-Leu-6 by  $\beta$ -alanine in DMF,  $c=10^{-3}$  mole/l: A – initial polymer, B – after 96-hour transformation

Transformation degree, determined by means of UV-spectrophotometry (according to the data presented in Figure 6) was equal to 22.7% which is in good agreement with the titration data (24.2%).

It is known that the reactions of aliphatic amines with nucleophiles (to which the double bond of fumaric acid residue belongs in this case) are catalyzed by soft organic acids (bifunctional catalysis). That is why in this reaction we used glacial acetic acid (we added several drops – catalytic amount of acetic acid to the reaction mixture parallel to abovementioned composition). Transformation degree of obtained product, which was determined using potentiometric titration was 47.1% that clearly testifies catalytic impact of acetic acid.

In order to exclude the fact that during the analysis titration of  $\beta$ -alanine carboxylic groups took place, which are covalently bonded with polymer and not  $\beta$ -alanine not entering into reaction and complexed with polymer, and not acetic acid used as catalyst. In all cases we have conducted control experiment with the use of unsaturated polyesteramide 8-Leu-6 + H<sub>2</sub>N-CH<sub>2</sub>-CH<sub>2</sub>-COOH (+CH<sub>3</sub>COOH in catalytic reaction).

The titrant consumption during control polymer titration was not registered. There is no other way of titration of one or another group of polymer by alkali. Also neither  $\beta$ -alanine nor acetic acid is bonded with polymer, so they are completely washed away during polymer purification. This experiment

testifies the fact that  $\beta$ -alanine is connected by covalent bonds (by aminogroup – C-NH-C bond) with FA/840/60-Leu-6 polyesteramide containing unsaturated bonds.

## Conclusion

Conducted chemical transformations allow us to make conclusion that obtained functional polymers are prospective in form of biodegradable carrier polymers for covalent bonding of medicaments and other bioactive compounds with them, as well as for pharmaceuticals delivery networks, micro- and nano capsulation, medications transportation, etc.

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