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*Mendeleev Commun.*, 2017, **27**, 574–576

Mendeleev Communications

# One-pot synthesis of poly(lactic acid) with terminal methacrylate groups for the adjustment of mechanical properties of biomaterials

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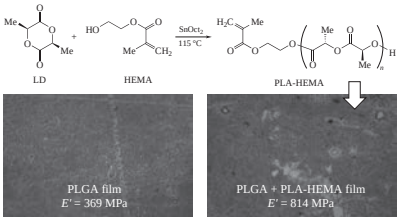
DOI: 10.1016/j.mencom.2017.11.012

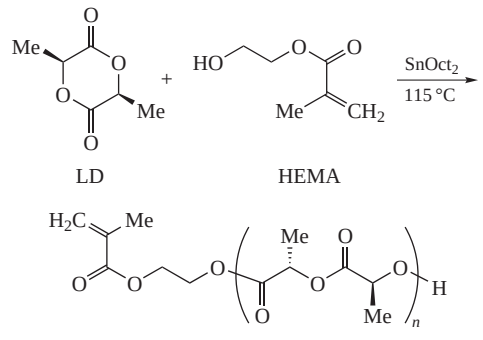
**Poly(lactic acid) with terminal methacrylate groups was synthesized in one pot using 2-hydroxyethyl methacrylate as initiator, whose content affected the polymer molecular weight. The impact of the obtained modified polymer cross-linking on the mechanical properties of PLA-based films was established.**




Poly(lactic acid) (PLA) is one of the leaders among numerous synthetic biodegradable macromolecules used for the construction of scaffolds for regenerative medicine and especially bone tissue engineering.[1–4] However, the PLA and other aliphatic polyesters lack their own reactive groups neccessary for controllable tuning of the material mechanical and biological properties. Moreover, PLA is relatively hydrophobic that results in low affinity to cells and biological fluids.[5,6]

One of the popular approaches for PLA modification is introduction of terminal double bonds or functional groups.[7–10] Herein, we have performed the one-pot synthesis of PLA-methacrylate with the maximum possible high molecular weight and tested its mechanical properties in regard to application as biomaterials.

To obtain PLA-methacrylate, the ring-opening polymerization (ROP) of lactide (LD) in the presence of tin(II) 2-ethylhexanoate (or stannous octoate, $SnOct_2$) and 2-hydroxyethyl methacrylate (HEMA) was carried out (Scheme 1).† Salt $SnOct_2$ was chosen because of its well-known activity in ROP of lactides, as well as FDA permission for its industrial application.[11–14]




**Scheme 1**

The structure of the product obtained was determined by $^1$H, $^{13}$C and $^1$H-$^{13}$C HMBC NMR spectroscopy. In the $^1$H NMR spectrum (Figure 1), the HEMA olefin protons resonate at 5.61 and 6.13 ppm and the signal of allylic Me group locates at

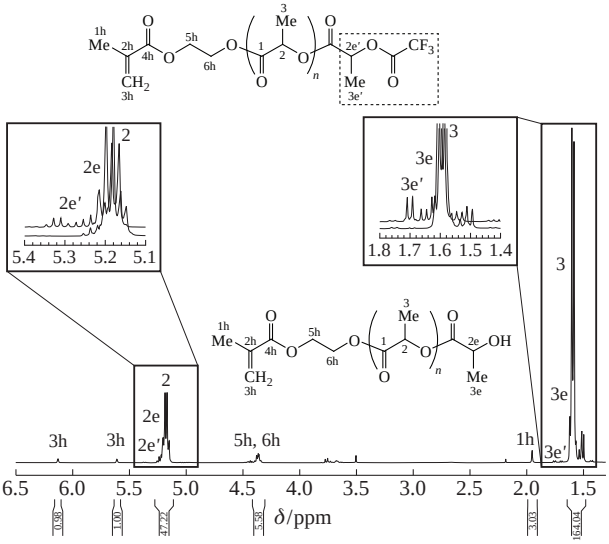



**Figure 1** $^1$H NMR (400 MHz, $CDCl_3$, 298 K) spectrum of PLA-HEMA (see Table 1, sample 2). The insets correspond to $^1$H NMR spectrum of TFAA-derivatized product.

† All used chemicals were purchased from Sigma-Aldrich and the solvents, from Vekton. Lactide was twice recrystallized from toluene and dried overnight in vacuum desiccator at 30 °C prior to polymerization. HEMA was used without additional purification.

The polymerization was performed by stirring the solution of LD, $SnOct_2$ (0.1 mol%) and HEMA in toluene at 115 °C. After toluene vacuum removal, the polymerization proceeded in bulk under evacuation for 3 h. $^1$H NMR (400 MHz, $CDCl_3$, 298 K) $\delta$: 1.59 (d, 3H, H-3, $J$ 7.1 Hz), 1.95 (m, 3H, H-1h), 4.36 (m, 4H, H-5h and H-6h), 5.17 (q, 1H, H-2, $J$ 7.2 Hz), 5.60 (m, 1H, H-3h′), 6.13 (m, 1H, H-3h″). $^{13}$C NMR (125 MHz, $CDCl_3$, 298 K) $\delta$: 17.0 ($C^3$), 18.4 ($C^{1h}$), 62.2 and 67.8 ($C^{5h}$ and $C^{6h}$), 69.2 ($C^2$), 126.4 ($C^{3h}$), 136.0 ($C^{2h}$), 167.1 ($C^{4h}$), 169.8 ($C^1$).

**Table 1** Polymerization of LD in the presence of different HEMA quantities.[a]

| Sample no. | HEMA (mixture, mol%) | Yield (%) | $M_n$(theor.)[b] / g mol$^{-1}$ | $M_n$(GPC)[c] / g mol$^{-1}$ | $M_w/M_n$ | $[\eta]$ / cm$^3$ g$^{-1}$ | $F_n$[d] (%) | HEMA (product, mol%)[e] |
|---|---|---|---|---|---|---|---|---|
| 1 | 5.0 | 32 | 1 250 | 1450 | 1.11 | 2 | 73 | 5.1 |
| 2 | 2.5 | 22 | 1 570 | 1624 | 1.11 | 3 | 65 | 4.4 |
| 3 | 1.3 | 61 | 9 100 | 2088 | 1.11 | 6 | 59 | 2.8 |
| 4 | 0.6 | 58 | 20 400 | 2610 | 1.12 | 7 | 51 | 1.7 |
| 5 | 0.1 | 73 | 118 200 | 3364 | 1.17 | 10 | 15 | 0.1 |
| 6 | 0 | 85 | 126 700 | 9280 | 1.31 | 50 | - | - |

[a] Conditions: in bulk of LD, 115 °C, 3 h, [$SnOct_2$] = 0.1 mol% *vs.* [LD]. Values are given as mean ones and the average deviation is 5%. [b] For samples 1–5: $M_n$(theor.) = ([LD]/[HEMA])$M_r$(LD)×Yield + $M_r$(HEMA); for sample 6: $M_n$(theor.) = ([LD]/[$SnOct_2$])$M_r$(LD)×Yield. [c] Experimental value determined by GPC *vs.* polystyrene standards and corrected by a factor 0.58.[16,17] [d] Calculated from $^1$H NMR spectra as follows: $F_n$ = [$I$(1h)/$I$(3e)]×100, see Figure 1 for assignments. [e] Calculated from $^1$H NMR spectra as follows: HEMA(product, mol%) = [$I$(1h)/$I$(3)]×100, see Figure 1 for assignments.

1.95 ppm. In $^1$H-$^{13}$C HMBC spectrum (Figure 2),[†] carbonyl group of HEMA fragment is observed at 169.8 ppm manifesting its long-range correlations with protons of the double bond, methyl group and glycol moiety. Moreover, PLA carbonyl units next to HEMA (170.0 and 175.3 ppm in $^{13}$C dimension) correlate with glycol protons of HEMA. Treatment of PLA-HEMA with trifluoroacetic anhydride (TFAA) led to appearance of new deshielded $^1$H signal for PLA methyl group at 1.70 ppm (Figure 1) correlating with new $^{13}$C signals at 168.9 ppm and attributed to terminal trifluoroacetyl fragment. This observation confirms the presence of both covalently bound HEMA fragment and terminal hydroxyl groups in the polymer. This is in agreement with mechanism of lactide ROP when hydroxyl-bearing methacrylate acted as an initiator. The data in Table 1 (parameter $F_n$) show that some capping groups are methacrylate, while some other should be carboxylic, because lactic acid and water can also serve as competitive initiators.[16]

In all cases, the time of polymerization was fixed at 3 h according to the previously performed optimization of the PLA synthesis in the absence of HEMA.[11] Also, in all experiments the same concentration of $SnOct_2$ (0.1 mol% *vs.* LD amount) was used. Therefore, any changes in polymer characteristics were caused only by addition of HEMA in the polymerization mixture.

According to NMR, GPC and viscosimetry data (see Table 1), the ROP of LD with relatively small amount of HEMA allowed us to obtain the product with relatively high molecular weight (MW) and its quite narrow distribution. The increase in molar part of HEMA in the initial reaction mixture resulted in the polymer with lower yield and MW. Nevertheless, this led to the growth of HEMA content in the polymer composition (see Table 1, parameter $F_n$). According to the published data, $SnOct_2$ itself is a poor initiator of ROP.[12–15] Most likely, the hydroxyl-containing compounds, such as lactic acid and water, play a role of initiators of polymerization. The addition of HEMA initiates the chain growth, and the increase in its fraction in [LD]/[HEMA] molar ratio should raise the number of chain initiation acts. Thus, raising HEMA content should increase the number of macromolecules with smaller MW.

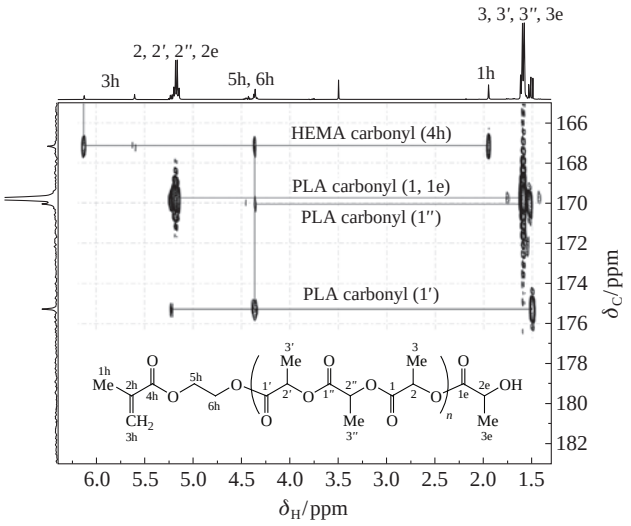



**Figure 2** $^1$H-$^{13}$C HMBC NMR spectrum of PLA-HEMA (see Table 1, sample 2). NMR correlations are due to the covalent bond between HEMA and PLA.

A good correspondence between theoretical MW and that obtained by GPC was observed at high HEMA concentrations. However, this was not valid when initial HEMA content in polymerization mixture was low, which can be explained by participation of lactic acid and water admixtures in initiation of polymerization. The small functionality value (see Table 1) at low HEMA content is in a good agreement with such an explanation. These results seem to be a feature of polymerization in the presence of stannous octoate, which can reversibly activate alcohols present in the polymerization mixture. This situation is different from described earlier,[17] when vinyl ester was a part of ROP initiating complex, and high-molecular polymers possessing functionality above 80% were obtained.

The MW is an important parameter for application of the polymer in biomaterials construction. The MW of the PLA-HEMA obtained here (see Table 1, samples 4 and 5) was higher than that for the samples obtained earlier.[7] This could be due to higher [LD]/[HEMA] molar ratios used in our study. The scaffold could be obtained in the form of films (by solvent evaporation[20]) or supermacroporous matrices (*via* thermally induced phase separation[11]). Both methods require application of polymer with MW high enough to provide effective phase separation and acceptable mechanical properties of material. Obviously, the MW of obtained PLA-HEMA samples is too low to form the materials with acceptable mechanical properties. Therefore, to produce satisfactory materials, poly(lactic-co-glycolic acid) (PLGA) with higher MW was used as matrix-forming polymer, to which PLA-HEMA was added. Note that the MW of obtained PLA-HEMA was high enough, so the MW of the prepared PLGA + PLA-HEMA additive was not reduced significantly. The effective physical interaction of PLA-HEMA with matrix-forming polymer chains should provide the control of mechanical properties.

Thus, we have achieved regulation of scaffold mechanical properties based on the application of mono-functional PLA-methacrylate derivative and low-molecular-weight dimethacrylate as a cross-linker. This method is quite different from earlier published one based on the use of tetra-functional star-shaped PLA.[19] To estimate the effect of PLA-HEMA crosslinking on the

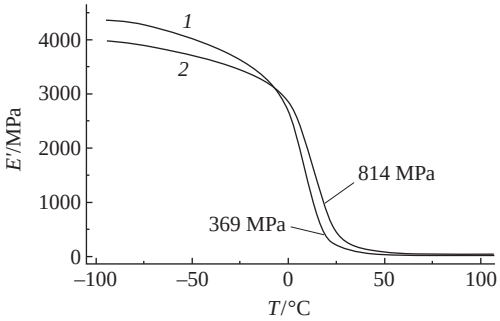



**Figure 3** Dynamic mechanical analysis of PLGA-based films after UV-initiated radical reaction: (*1*) PLGA, (*2*) PLGA + PLA-HEMA + EGDMA. Conditions: 5 K $min^{-1}$, frequency 1 Hz.

mechanical properties of materials, two different PLGA-based films were obtained.‡ Both half-dried film samples were exposed to UV light (125 W mercury lamp, Philips) with a wide radiation spectrum and a constant intensity for 20 min. The film with PLA-HEMA was clouded after UV irradiation. This effect could be indirectly related to the free-radical reaction of EGDMA with methacrylate group of PLA-HEMA, followed by formation of phase-separated globules.[18] After drying, both films were tested by dynamic mechanical analysis (DMA, Netzsch).

As shown by DMA, the control film containing only PLGA was destructed already at 50 °C (Figure 3, curve *1*). Another film with PLA-HEMA additive had a modulus of elasticity increased by 100% at the glass transition temperature (*cf*. PLGA film, curve *2*). Moreover, the film with PLA-HEMA was stretched but not destroyed till the termination of analysis at 150 °C. Thus, it can be assumed that cross-linked PLA-HEMA and matrix polymer interact with each other. It means that EGDMA links not only two short PLA-HEMA chains but also PLGA macromolecular coils, with which the PLA tails of PLA-HEMA are interlaced. These results reveal a positive effect of terminal double bonds of PLA-HEMA on improvement of mechanical properties of formed materials.

In summary, PLA-HEMA samples with quite high MW have been synthesized by ROP of lactide in the presence of HEMA. First experiments towards the control of mechanical properties of PLA-based materials have demonstrated the possibility of using such polymers to tune the strength of the materials by UV curing.

This study was supported by the Russian Ministry of Education and Science (state contract no.14.W03.31.0014, megagrant).

‡ The first film was prepared by mixing 30 wt% of PLA-HEMA, 60 wt% of PLGA, 2 wt% of Darocur-1173 (photoinitator 2-hydroxy-2-methylpropiophenone, Sigma-Aldrich) and 8 wt% of ethylene glycol dimethacrylate (EGDMA) in $CH_2Cl_2$. The second film was produced only from PLGA with addition of Darocur-1173 and EGDMA. The solutions were stirred and after complete dissolution of components were poured onto polyethylene terephthalate, a flexible substrate, to obtain the polymer film after $CH_2Cl_2$ evaporation.

## References

1 S. Kobayashi and A. Makino, *Chem. Rev*., 2009, **109**, 5288.
2 P. Mainil-Varlet, B. Rahn and S. Gogolewski, *Biomaterials*, 1997, **18**, 257.
3 K. A. Athanasiou, G. G. Niederauer and C. M. Agrawal, *Biomaterials*, 1996, **17**, 93.
4 B. Eling, S. Gogolewski and A. J. Pennings, *Polymer*, 1982, **23**, 1587.
5 B. D. Ratner, *Biosens. Bioelectron*., 1995, **10**, 797.
6 K. J. L. Burg, W. D. Holder, C. R. Culberson, R. J. Beiler, K. G. Greene, A. B. Loebsack, W. D. Roland, D. J. Mooney and C. R. Halberstadt, *J. Biomater. Sci., Polym. Ed*., 1999, **10**, 147.
7 I. Barakat, Ph. Dubois, R. Jérôme and Ph. Teyssié, *J. Polym. Sci., Part A: Polym. Chem*., 1993, **31**, 505.
8 N. Sugai, T. Yamamoto and Y. Tezuka, *ACS Macro Lett*., 2012, **1**, 902.
9 M. R. Breteler, J. Feijen, P. J. Dijkstra and F. Signori, *React. Funct. Polym*., 2013, **73**, 30.
10 V. T. Shashkova, I. A. Matveeva, N. N. Glagolev, T. S. Zarkhina, A. V. Cherkasova, S. L. Kotova, P. S. Timashev and A. B. Solovieva, *Mendeleev Commun*., 2016, **26**, 418.
11 I. V. Averianov, V. A. Korzhikov and T. B. Tennikova, *Polym. Sci., Ser. B*, 2015, **57**, 336 (*Vysokomol. Soedin., Ser. B*, 2015, **57**, 281).
12 A. Kowalski, A. Duda and S. Penczek, *Macromolecules*, 2000, **33**, 7359.
13 D. R. Witzke, R. Narayan and J. J. Kolstad, *Macromolecules*, 1997, **30**, 7075.
14 J. P. Puaux, I. Banu, I. Nagy and G. Bozga, *Macromol. Symp*., 2007, **259**, 318.
15 H. von Schenck, M. Ryner, A. C. Albertsson and M. Svensson, *Macromolecules*, 2002, **35**, 1556.
16 A. Kowalski, A. Duda and S. Penczek, *Macromolecules*, 1998, **31**, 2114.
17 K. V. Zaitsev, Yu. A. Piskun, Y. F. Oprunenko, S. S. Karlov, G. S. Zaitseva, I. V. Vasilenko, A. V. Churakov and S. Kostjuk, *J. Polym. Sci., Part A: Polym. Chem*., 2014, **52**, 1237.
18 E. G. Vlakh and T. B. Tennikova, *J. Sep. Sci*., 2007, **30**, 2801.
19 P. Timashev, D. Kuznetsova, A. Koroleva, N. Prodanets, A. Deiwick, Yu. Piskun, K. Bardakova, N. Dzhoyashvili, S. Kostjuk, E. Zagaynova, Yu. Rochev, B. Chichkov and V. Bagratashvili, *Nanomedicine*, 2016, **11**, 1041.
20 V. Korzhikov-Vlakh, M. Krylova, E. Sinitsyna, E. Ivankova, I. Averianov and T. Tennikova, *Polymers*, 2016, **8**, 418.

*Received: 2nd March 2017; Com. 17/5190*