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First comb-like copolymer of poly(ethyl 2-cyanoacrylate) grafted as a side-chain to dextran

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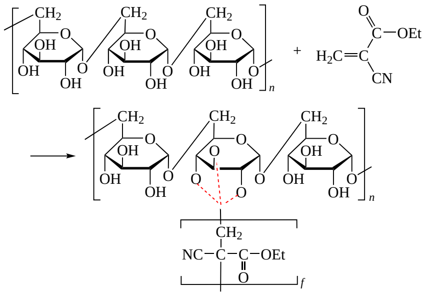
The first comb-like cyanoacrylic copolymer was synthesized by anionic polymerization of ethyl 2-cyanoacrylate in an aqueous solution of dextran of $M_w = 50 \pm 5$ kDa. The copolymer was explored by NMR and Fourier IR spectroscopy, as well as by MALDI-TOF mass-spectrometry methods. It contains up to 10 cyanoacrylate units grafted to anhydroglucose cycles of dextran main chain, multi-substituted glycose units were not detected.



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The C=C double bond of ethyl 2-cyanoacrylate (ECA) is highly polarized and would undergo instant polymerization *via* anionic mechanism in the presence of trace amounts of water.[1,2] This allowed its use in numerous ‘instant’ adhesive compositions, including medical adhesives, as well as in nano-capsules and polymeric drug delivery systems.[3–7] Ethyl 2-cyanoacrylate is relatively inert in radical polymerization and does not copolymerize with common acrylates and methacrylates, and its extremely high reactivity poses difficulties in the synthesis of both statistical and block copolymers with most monomers and polymers.[8,9] To date, only a few statistical and block copolymers of cyanoacrylates with other monomers have been synthesized.[10]

In this work, the anionic polymerization of ECA in an acidic aqueous solution of dextran was performed, which gave a comb-shaped block copolymer. The reaction was carried out in an aqueous medium using a polysaccharide with $M_w = 50 \pm 5$ kDa in the presence of citric acid as a polymerization retardant (pH 3–4). Depending on the ratio of dextran to ECA, copolymers **1**–**5** are formed, differing in composition and solubility (Table 1).

The structure of the polymers was studied using NMR and Fourier-transform infrared spectroscopy, however, the most informative results were obtained using MALDI-TOF mass spectrometry despite this method not being quantitative. The FTIR spectrum of the copolymer shows signals of anhydrous glucose rings of dextran and units of poly(ethyl-2-cyanoacrylate) (PECA). The band for the nitrile group is most characteristic.

For the convenience of decoding the MALDI-TOF mass spectra of the copolymer, the original dextran, and a model PECA obtained by anionic polymerization in an aqueous medium in the absence of polysaccharide were recorded under similar conditions. In the spectrum of the model PECA there is a sequence of peaks for oligomers with a degree of polymerization $n = 3$–22 with a difference between peaks corresponding to the mass of a monomeric unit $m/z = 125$. The mass values for the peaks in this series correspond to oligomers containing a terminal hydroxy group at the proximal end of the macromolecule and a hydrogen at the distal end. The first peak of the series has a mass of $m/z = 416$, which corresponds to a fragment consisting of three units of ECA with an attached water molecule and a sodium

Table 1 Properties of dextran–poly(ethyl 2-cyanoacrylate) copolymers **1**–**5** depending on the composition of the reaction system.[a]

Sample	Molar ratio dextran–ECA in the reaction system	Molar ratio dextran–PECA units in copolymer[b]	Solubility in	Degree of polymerization (m) in ECA block[c]	Average number of anhydroglucose cycles (k)[c]
1	3 : 1	3 : 1	H_2O	3–7	3–4
2	1.5 : 1	1.5 : 1	H_2O	3–10	4–5
3	0.75 : 1	0.75 : 1	H_2O; DMSO	3–10	4–6
4	0.5 : 1	0.35 : 1	DMSO	3–12	4–6
5	0.25 : 1	0.1 : 1	DMSO	3–15	6–7

[a] Citric acid (2 mg ml^{-1}) was used as retardant. [b] According to CHNX data. [c] Average distance between graft nodes (according to MALDI-TOF data).

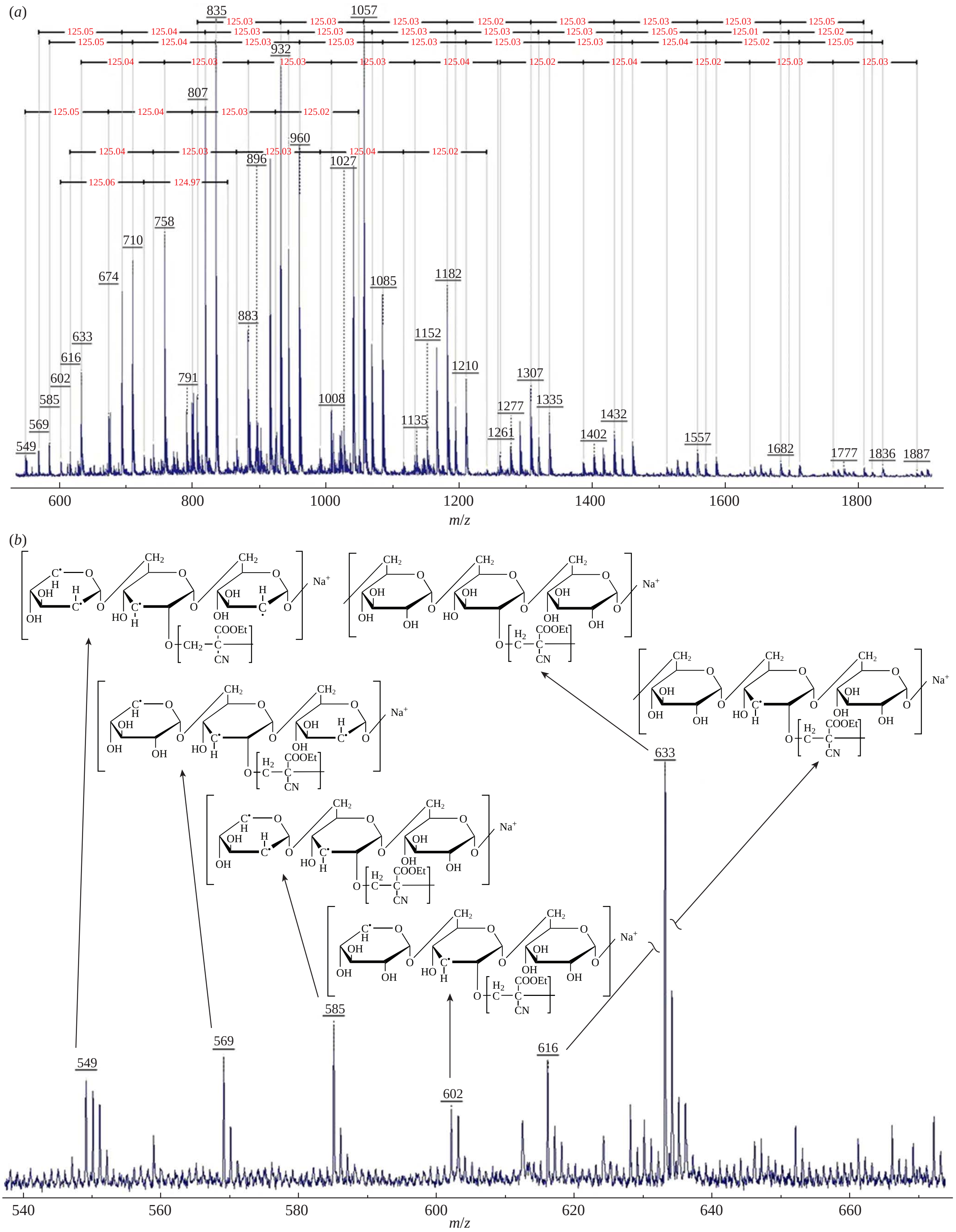

Figure 1 MALDI-TOF mass spectrum of sample **2**: (*a*) full spectrum, (*b*) the region of initial sequence peaks.

ion. Ionization during laser desorption/ionization occurs due to the attachment of a sodium ion, which is typical in cases where there is an excess of them in the substrate.[11]

As is known, due to the high concentration of intermolecular hydrogen bonds and low absorbance at the wavelength of the laser used, polysaccharides do not form molecular ions under laser desorption/ionization conditions.[12] In the dextran spectrum, peaks for oligomers with a degree of polymerization $n = 4$–10 with a mass difference between peaks in the series $m/z = 162$ are present. The masses correspond to oligomers containing a terminal hydrated unit from the non-reducing end of the polysaccharide.

The first member of the sequence has m/z = 671 and represents a tetramer of anhydrous glucose ionized by a sodium cation. In the MALDI-TOF mass spectrum of the comb-shaped copolymer **2** (Figure 1) there are seven sequences in which the peaks differ by the mass of the monomeric unit of ECA's m/z = 125. The difference in mass of the first members of the sequences forms a sequence with a mass difference multiple of the weight of the anhydrous glucose unit of dextran m/z = 162. The fragmentation mechanism of the main chain of the dextran copolymer under laser desorption/ionization conditions differs from the fragmentation of the macromolecules of the original dextran. The fragmentation of dextran occurs through acetal bonds between anhydrous glucose cycles, while the cleavage of the main chain of the copolymer occurs through the cleavage of acetal bonds and carbon–carbon bonds, C^2–C^3 and C^3–C^4 between vicinal hydroxy groups.[13]

Signals corresponding to the respective fragments are observed in the copolymer spectrum. The change in the fragmentation mechanism may be related to the presence of residual water and acid in the mixture. Changes in the electronic spectrum of the copolymer result from introducing two chromophoric groups (CO_2Et and CN) into the macromolecule. Apparently, ethoxycarbonyl and nitrile groups present in the PECA blocks would increase the proportion of laser ionizing radiation absorbed by the macromolecule as a whole. MALDI-TOF mass spectrometry is not a quantitative method of analysis, however, the analysis of spectra allows one to estimate parameters of both the main and side chains of the comb-shaped grafted copolymer and to draw important conclusions. No peaks for disubstituted anhydrous glucose rings were found in the spectrum. The degree of polymerization of cyanoacrylate fragments in the water-soluble grafted copolymer is m = 3–15 while the average number of anhydrous glucose units between grafted macromolecules is k = 3–7 (see Table 1). Of interest is the formation of grafted copolymers in aqueous solutions despite the high sensitivity of cyanoacrylic acid esters to trace amounts of water. It is known that in organic solvents, primary alcohols can add to the C=C double bond of cyanoacrylates to form 3-alkoxy-2-cyanopropanoates, while in water poly(alkyl 2-cyanoacrylates) with terminal alkoxy capping groups can form.[14] However, the initiation of anionic polymerization by secondary alcohols in aqueous medium under conditions of competition with hydroxyl anions of water has been herein discovered for the first time.

Studies on the biological activity of the synthesized block copolymers revealed their unexpectedly high cytotoxicity for human fibroblasts in cell culture experiments. This may be related to the known characteristics of the interaction of amphiphilic copolymers containing hydrophilic and hydrophobic fragments with the plasma membrane.[15,16] The combination of two non-toxic polymers, dextran blood substitute and surgical adhesive PECA, led to the formation of a highly toxic amphiphilic grafted comb-shaped block copolymer capable of piercing the membranes of living cells. As a result of the MTT assay on the HEK293 cell line, it was established that the LD_{50} of the obtained copolymer is 4.62 ± 0.23 μg μl^{-1}.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.10.035.

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