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Oligomers based on cyanoacrylic acid esters

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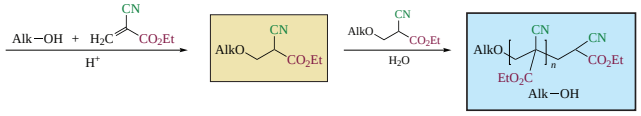
Ethyl 3-alkoxy-2-cyanopropanoates were prepared by the reaction of ethyl 2-cyanoacrylate with the corresponding linear alkanols C_6–C_{12} in acidic medium. Their treatment with water as a weak nucleophile resulted in elimination of the alkanol and the formation of oligocyanoacrylate terminated with the alkoxy group. The oligomers were studied by NMR spectroscopy, IR spectroscopy, MALDI-TOF mass-spectrometry and dynamic light scattering.



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The development of pharmacology in recent years has shown the promise of using polymer carriers for targeted drug delivery to organs, tissues, and specific cells.[1–4] Polymeric nanocarriers can be obtained in various size and structure. They are able to penetrate into living cells by the mechanism of membrane fusion, bypassing the stage of phagocytosis, followed by enzymatic release of the contents of the capsule. This allows them to be used for delivering chemically unstable compounds and plasmids to organelles and the nucleus.

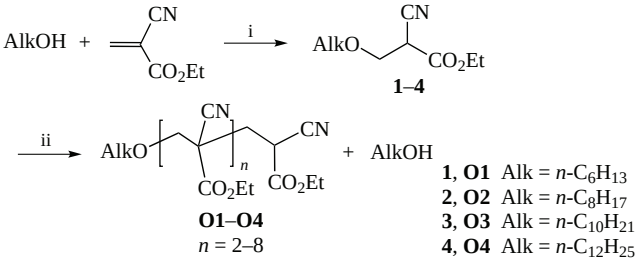
Among polymers, polycyanoacrylates possess unique properties that make them applicable in the design of nanocarriers. The principal property of cyanoacrylic monomers is to rapidly undergo anionic polymerization in the presence of weak nucleophiles, including traces of water,[5] which does not require the use of peroxide initiators in the system that destroy labile physiologically active substances. The second important property is the ability of cyanoacrylate polymers to biodegrade inside the body without the formation of toxic decay products, which ensures the safety of the carrier *in vivo*.[6]

Cyanoacrylate nanocapsules can be prepared by several approaches. The main approaches comprise interfacial polymerization and self-assembly procedures. These procedures offer their individual advantages and disadvantages when the design of optimized drug carrier systems is required. The most pharmaceutically important capsule parameters are the capsule radius distribution, capsule surface, and thickness and permeability of the capsule membrane.[3] Capsules of poly(alkyl cyanoacrylate) synthesized by interfacial polymerization have initially been introduced by Florence *et al.*[6] and Couvreur *et al.*[7] The similar process is described in works.[8,9]

The dispersion of an alcoholic solution of isobutyl cyanoacrylate and oil in water results in the formation of nanocapsules by interfacial polymerization with an average diameter of about 200–300 nm. Micellar DNA carriers were obtained in study.[10] Surfactant esters were synthesized differing in the architecture of hydrophilic–hydrophobic blocks. These particles contained a hydrophobic core and one or more active cyanoacrylate groups on the periphery capable of anionic polymerization and the formation of a hydrophilic polymer shell. An improved method[11] for the preparation of alkyl cyanoacrylate nanocapsules involves the intermediate synthesis of a well-defined adduct of a single monomer unit. This allows one to access capsules with thinner walls and, generally, with a more reproducible capsule structure.

The addition of fatty alcohols at alkyl cyanoacrylates was previously[12] revealed in the course of studies of reactions between CH-acids and cyanoacrylates. It was shown that strong nucleophiles are easily added to the electron-deficient double bond of alkyl cyanoacrylate.[13] The addition of weak nucleophiles, *e.g.*, fatty alcohols, required the use of acidic medium. Upon elimination of fatty alcohols, oligomers capable of self-organization into micelles could be synthesized.

In the present study, compounds **1**–**4** were obtained by adding the corresponding linear alkanols C_6–C_{12} to ethyl 2-cyanoacrylate in a non-aqueous medium, with a 10 mol% excess of alkanol having been used (Scheme 1). To prevent possible radical polymerization, 5 mol% hydroquinone was applied, while to prevent anionic polymerization it was necessary to create an acidic environment. The proton donor was a combination of 2-cyanoacrylic acid (5.5 mol%) highly soluble in both reagents and TsOH (3 mol%). The reaction was run for 6 h



Scheme 1 *Reagents and conditions*: i, $H_2C=C(CN)CO_2H$ (5.5 mol%), hydroquinone (5 mol%), TsOH (3 mol%), SO_2 (constant gas flow), 20 °C, 6 h; ii, H_2O, 20 °C.

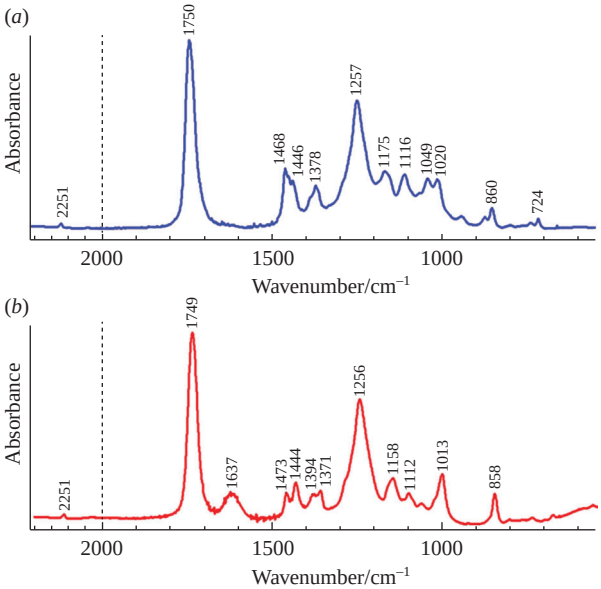


Figure 1 IR spectra of (*a*) compound **1** and (*b*) oligomer **O1**.

at room temperature with bubbling SO_2 gas[14] to prevent immediate polymerization.

The IR spectrum of ethyl 2-cyano-3-(hexyloxy)propanoate **1** contains the band at 2251 cm^{-1} for the nitrile group and the band at 1750 cm^{-1} for the ester carbonyl group [Figure 1(*a*)]. The bands in the range 860–1468 cm^{-1} refer to the vibrations of the C–H aliphatic bonds. Elemental analysis data of products **1**–**4** confirm well the theory.

The resulting monomers **1**–**4** would lose the alcohol molecule upon hydrolysis[15] and can thus form cyanoacrylate oligomers which, at the same time, contain a terminal aliphatic hydrophobic substituent (see Scheme 1). The IR spectrum of the **O1** oligomer, compared to the spectrum of the starting compound **1**, contains a new band at 1637 cm^{-1}, apparently related to a carbonyl group of some other type [see Figure 1(*b*)].

The resulting oligomers **O1**–**O4** contain a terminal aliphatic hydrophobic substituent and thus can serve as surfactants capable of self-organization with subsequent formation of nanoparticles. Analysis of the MALDI-TOF mass spectrum of the **O1** oligomer (Figure 2) confirms that the polymerization proceeds according to the stated mechanism. In the spectrum, one can observe peaks for products with different molecular weights with a step between them about 125.3, which corresponds to the mass of one unit of the oligomer.

A similar regularity is observed for oligomers **O2**–**O4** (see Online Supplementary Materials). Based on the obtained oligomers, a series of water-filled nanocapsules of various hydrophobicity was synthesized. Depending on the production conditions, their shape can be changed from a solid nanoparticle to hollow capsules, the creation of which requires the use of a two-phase aqueous system of a dispersed medium. The particles were studied by dynamic light scattering (Table 1). According to the obtained particle distribution diagrams, there are three types of signals. The first belongs to micelles formed by a fatty alcohol (8–15 nm region), the second belongs to capsules (30–100 nm region), and the third (500–600 nm region) belongs to agglomerates of spherical capsules.

Table 1 Investigation of oligo(ethyl 2-cyanoacrylate) particles by dynamic light scattering.

Oligo-mer	Alk	Alk length/ nm	Capsule size/ nm	AlkOH micelle size/nm	Size of agglomerates of spherical capsules/ nm
O1	*n*-C_6H_{13}	1.23	36.1	–	–
O2	*n*-C_8H_{17}	1.54	62.2	13.1	–
O3	*n*-$C_{10}H_{21}$	1.85	80.9	9.5	559.8
O4	*n*-$C_{12}H_{25}$	2.16	90.6	–	586.1

The sizes of oligo(ethyl 2-cyanoacrylate) capsules formed as a result of self-organization depend on the length of the molecule and grow with elongation of the terminal aliphatic substituent (see Table 1). When capsules are formed from **O1**, micelles formed from hexanol do not appear due to the insufficient length of its aliphatic group and essentially high solubility of hexanol in water. Oligomer **O4** also does not form micelles during the formation of its capsules, which is due to the fact that dodecanol is poorly soluble in water. The diameters of micelles formed in cases of **O2** and **O3** are almost the same being 9 and 13 nm, respectively.

In summary, several fatty alcohols were added at a highly polarized double bond of ethyl 2-cyanoacrylate in the presence of 2-cyanoacrylic acid. Elimination of these alcohols in aqueous medium leads to the formation of oligomers possessing surfactant properties and being promising for the creation of polymeric drug carriers.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.040.

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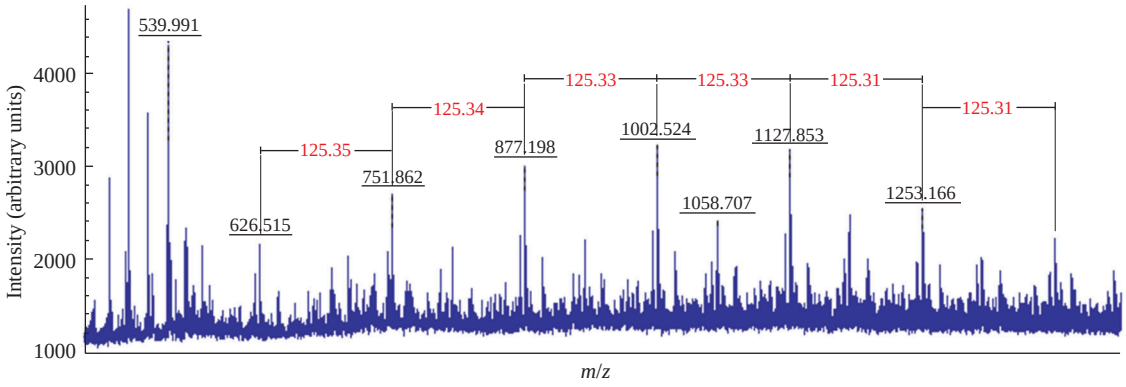

Figure 2 MALDI-TOF mass spectrum of oligomer **O1**.

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