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Polymer-Supported Synthesis of Series of Macrocyclic Oligoesters[1]

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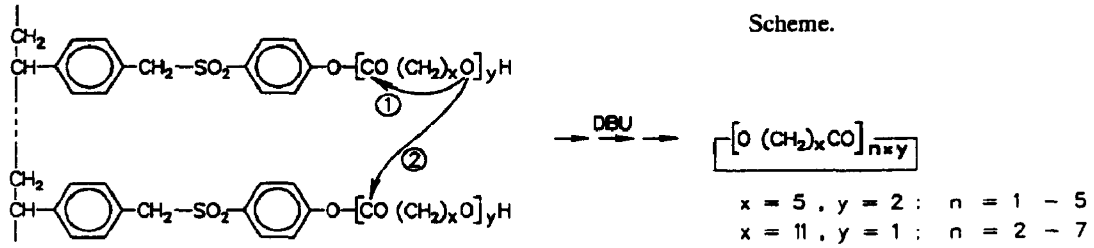
Abstract: ω-Hydroxydodecanoic acid and the linear dimer of ε-hydroxycaproic acid, resp., were attached to a cross-linked polystyrene by an activated ester bond. In the presence of strong tert. bases cyclo-oligomerization occurred on the resin yielding a series of macrocyclic rings which were isolated with up to 10 ω-hydroxy acid residues and 91 ring atoms.

Macrocyclic oligoesters of ω-hydroxy acids have gained increasing interest as well-defined model compounds for the corresponding polyesters[2]. Cyclizations of 12-hydroxydodecanoic acid on polymeric supports have been performed by Ford[3] using thiol ester activation in the presence of Hg^{2+} ions. Cyclic monomer and dimer but no higher cyclic oligomers could be isolated.

We report here on the cyclization of ω-hydroxydodecanoic acid and the linear dimer of ε-hydroxycaproic acid, which were attached to polystyrene by an active phenyl ester bond. A 1% cross-linked chloromethylated polystyrene was treated with 4-mercaptophenol to give (4-hydroxyphenyl thiomethyl)-polystyrene[4] and then esterified with the O-tert.butyldimethylsilyl-protected ω-hydroxy acid[3] with dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine. Subsequently, the sulfide bond was oxidized by 3-chloroperoxybenzoic acid in dioxane to yield the polymer-bound p-sulfonylphenyl ester[4]. Deprotection of the silyl group was performed with aqueous trifluoroacetic acid/THF[3]. The cyclizations were carried out in THF in the presence of strong bases, e.g. DBU or BEMP, for 100 h. Mixtures of cyclic oligoesters of ω-hydroxydodecanoic and di-ε-hydroxycaproic acid were obtained in 32 and 54% yield, resp., from the filtrate. They were separated by silica gel chromatography with cyclohexane/ethyl acetate (9:1 to 7:3) as eluent. The homologous di- to heptalactones of hydroxydodecanoic acid and a series of oligomerization products from the cyclic dimer to the decamer of ε-hydroxycaproic acid were isolated on a preparative scale. The scheme shows the principle of the cyclo-oligomerization reaction.



Scheme.

The yields of the rings decreased with increasing ring size (Table). However, no monomeric lactone of ω-hydroxydodecanoic acid was found in the oligomer mixture at all. This can be attributed to the strain in the 13-membered ring, which diminishes its formation tendency, and to the high loading of the hydroxy acid on the resin (0.98 mmol/g) corresponding to a rather concentrated (0.13 M) solution. At 0.03 M concentration on the resin ring-closure of the corresponding thiol ester[3] gave up to 13% of the monomeric lactone. These different results should not be explained by a reduced mobility of the polymeric support[3] but by the considerably higher activity of the p-sulfonylphenyl ester compared to the thiol ester leading to larger rings.

Table. Cyclic Oligomers of ω-Hydroxy Acids $c\text{-}[O(CH_2)_xCO]_m$ formed by Cyclo-oligomerization on Polymer Supports.

x	m	Mol-Wt.	Ring-Size	Yield (%)[a]	m.p.(°C)[b]	M+ (FD-MS)
5	2	228.3	14	15.4	111[c]	228
	4	456.6	28	14.6	30	457
	6	684.9	42	10.2	82	685
	8	913.1	56	7.6	61	913
	10	1141.4	70	6.2	90	1141
11	1	198.3	13	0		
	2	396.6	26	13.1	102[d]	397
	3	594.9	39	6.9	50	594
	4	793.2	52	4.6	88	793
	5	991.5	65	3.4	58	991
	6	1189.8	78	2.3	94	1190
	7	1388.1	91	1.7	66	1387

a) Yields are related to a loading (in mmol/g resin) for x = 5: 0.86, for x = 11: 0.98.
b) Determined by DSC analysis. c) Ref.[5]: 112-113°C. d) Ref.[5]: 101°C.

Thus, ring-closure on swellable polymer supports does not restrict the conformational flexibility of the bound linear chain. Instead, extensive intrapolymeric reactions occur leading to oligomerization followed by cyclization after every step.

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