A Novel Approach to the Synthesis of Cyclic Oligo- and Poly-esters

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A new method for the synthesis of cyclic oligo- and poly-esters is described which affords readily isolated products that have a cyclic content of up to 74%; the method promises to be useful for the synthesis of topologically novel materials.

In recent years there has been an increasing interest in various molecules, including macromolecules, with novel topologies: for example, dendritic polymers[1] and polyrotaxanes.[2] Cyclic oligomers are one type that has been known for many years because most step-growth polymerisations produce a small cyclic fraction, typically <5% of the total product.[3] However, isolation and purification of the cyclic fraction is usually a lengthy process. If cyclic oligomers and polymers could be prepared more easily they could prove to be useful building blocks for the synthesis of various products with novel topologies: for example, cyclic polymeric liquid crystals,[4] polymeric catenanes (a true polymer 'chain') and 'chain-mail' polymer networks. Cyclic oligomers and polymers also provide an attractive synthetic approach to high-molecular-weight linear polymers *via* ring-opening reactions and for this reason much effort has been devoted recently to developing a route to cyclic polycarbonates using phase transfer-catalysed reactions.[5]

We now report a new approach to the synthesis of cyclic oligo- and poly-esters. The monomers used are ω-halogeno-carboxylic acids. To prepare cyclic products a given monomer is first attached to a commercial strong-base anion exchange resin as the carboxylate salt (**1a**). This is achieved either by reaction of the acid with the hydrogen carbonate form of the resin (**1b**) (Method A), or by preparation of an aqueous solution of the sodium or potassium salt of the acid followed by anion exchange with the chloride form of the resin (**1c**) (Method B). On heating a suspension of the bound carboxylate salt, polymerisation occurs by the carboxylate anion displacing halide:[6] see Scheme 1. The linear chain that is formed remains attached to the insoluble resin *via* the carboxylate end group. If, however, the end groups of a linear chain react together a cyclic oligomer or polymer (**2**) is formed and this, unlike the linear species, is not bound to the insoluble support. At the end of the reaction period, therefore, all the soluble (unbound) product should be cyclic. The success of the method obviously depends on there being no species present, other than the alkyl halide moieties of bound monomer, that can break the ionic linkage binding the linear species to the support. There should, for example, not be any other salts or any acids present.

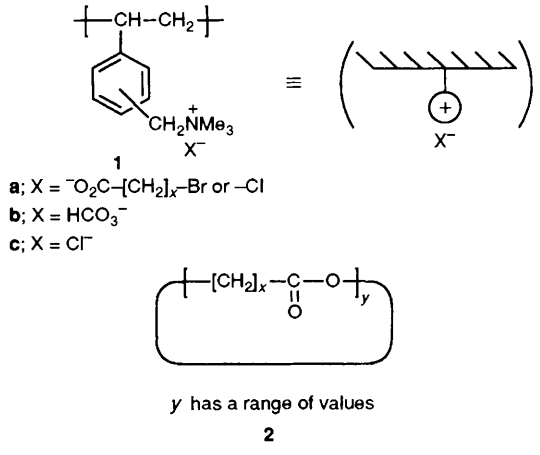
There appears to be only one previous related study and this was carried out in connection with the debate about 'site–site interactions' in 'solid phase' peptide synthesis.[7] Rothe's group bound various tri-, tetra- and penta-peptides to insoluble polymer supports *via* active ester linkages and then studied their cyclisation.[8] Whilst cyclised monomers, dimers or trimers were usually the main products, cyclic products

† This work was initiated whilst P. H. was at The University of Lancaster.

Table 1 Synthesis of cyclic oligomers

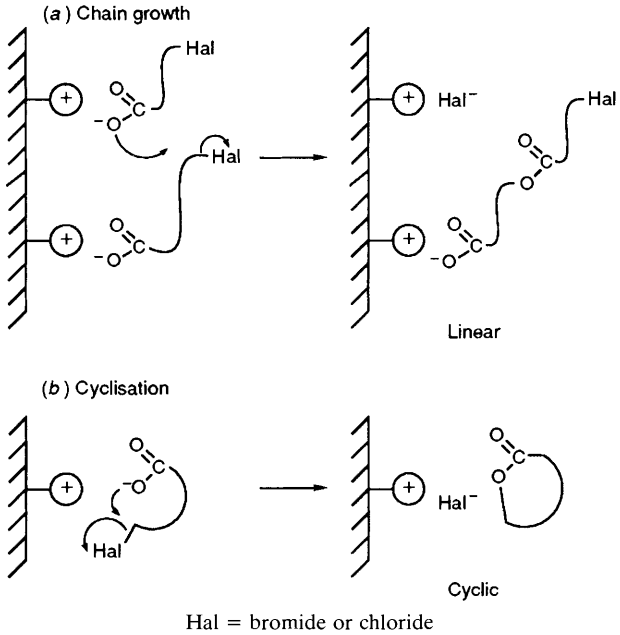
Reaction	Monomer	Synthetic method[a]	Loading[b]/ mmol g^{-1}	Reaction conditions[c]	Yield of monomeric lactone[d] (%)	Polymeric product Yield[e] (%)	$\bar{M}_n$[f]	$\bar{M}_w$[f]	$\overline{DP}$[g]	Cyclic content of polymeric product[h] (%)
1	$Br[CH_2]_4CO_2H$	A	2.44	I	93	—	—	—	—	—
2	$Br[CH_2]_5CO_2H$	A	2.35	I	94	—	—	—	—	—
3	$Br[CH_2]_{10}CO_2H$	A	0.82	II	—	92	2412	4172	13	76
4	$Br[CH_2]_{10}CO_2H$	B	1.74	II	—	75	2422	3270	13	60
5	$Cl[CH_2]_9CO_2H$	B	1.50	II	—	74	2427	2912	14	53
6	$Br[CH_2]_{10}CO_2[CH_2]_9CO_2H$	B	0.50	II	—	91	1542	2421	9	44
7	$Br[CH_2]_7CO_2H$ + $Br[CH_2]_{10}CO_2H$	B	1.13 + 0.82	II	—	*ca.* 80	3824	5736	25	50–70

[a] Method A: Polymer-supported salt prepared by treating the hydrogen carbonate form (3.81 mmol g^{-1}) of Amberlyst A26 with the monomer in aqueous methanol at 20 °C for 18 h. The resin beads were then recovered, washed with methanol and dried. Method B: Polymer-supported salt prepared by treating the chloride form of Amberlyst A26 (the washed commercial resin) for 6 h with an aqueous solution of the sodium or potassium salt of the monomer at 20 °C. The resin beads were then recovered, washed successively with deionized water, chloroform and diethyl ether, then dried. [b] Estimated from the gains in weight of the resin as a result of procedure A or B. [c] Conditions I: the polymer-supported salt was suspended in tetrahydrofuran and heated under reflux for 18 h. Conditions II: the polymer-supported salt was suspended in toluene and heated at 55 °C for 48 h. In both cases the product was recovered simply by washing with an organic solvent. [d] Isolated by distillation. [e] Estimated from the weight and loading of the initial polymer-supported salt and the weight of the soluble product. [f] Estimated by gel permeation chromatography using a Waters μ-Styragel 4-column set. Reaction 3 was repeated on a sufficient scale to allow preparative GPC. Six 'cyclic' polyester fractions were analysed at RAPRA Technology Ltd by a GPC-viscometric technique to give a set of molar mass calibrants. [g] Calculated from $\bar{M}_n$. [h] Calculated from the $\overline{DP}$ and the ratio (R) of the area of the $-CO_2CH_2-$ signal to the combined areas of the $Br-CH_2-$, $Cl-CH_2-$ and $HO-CH_2-$ signals in the 500 MHz ^1H NMR spectra using the equation: percentage cyclic = $100\,[1 - (\overline{DP}/R)]$.



containing up to nine monomer units (27 amino acid residues) were also formed. In the example most pertinent to the present study, an analogous cyclisation of the bound 'dimer' of 6-aminohexanoic acid afforded cyclic Nylon-6 polymers with from 2 to 46 amino acid units.[8]

Our results are summarised in Table 1. Conversion of 5-bromopentanoic and 6-bromohexanoic acids to their polymer-supported salts by Method A and heating the products in tetrahydrofuran (THF) gave the corresponding monomeric lactones in high yields (Table 1, reactions 1 and 2). However, when a similar reaction was carried out with 11-bromoundecanoic acid (reaction 3) the formation of the monomeric lactone was less favoured[9] and cyclic oligomers and polymers were the major product. The molecular weight was estimated by gel permeation chromatography (see Table 1, footnote *f*) to be $\bar{M}_n$ = 2412, corresponding to an average degree of polymerisation ($\overline{DP}$) of 13. The proportion of the product that was cyclic was estimated by end-group analysis. Elemental analysis did not detect (<0.3%) any halide. The 500 MHz ^1H NMR spectrum showed only small signals due to $Br-CH_2-$, $Cl-CH_2-$ (formed by halide exchange between monomer and bound chloride anion[10]), and $HO-CH_2-$ (probably due to hydrolysis catalysed by traces of acid or base). The combined



Scheme 1 Two processes occurring on polymer beads

areas of these signals were 1.8% of the $-CO_2CH_2-$ signal. This and the value of $\overline{DP}$ taken together indicate (see Table 1, footnote *h*) that the soluble polymeric product contained 76% of cyclic material. A somewhat cleaner product was obtained using Method B to prepare the supported salt (reaction 4) and this procedure was subsequently used for the other reactions reported. The products of all these reactions were characterised as for the product of reaction 3.

Fast atom bombardment mass spectrometry (xenon as ionizing gas) (FAB) on the products from reactions 3 and 4 clearly showed molecular ions (detection limit up to *m/z ca.* 1500) for cyclic oligomers from dimers to pentamers. The spectra were different from that of an analogous linear

polymer prepared by a phase transfer-catalysed reaction.‡ The products from reactions 5 and 6 showed molecular ions for all the cyclic products from dimers to heptamers and for dimers and trimers respectively.

Reaction 7 was carried out using an equimolar mixture of two acid salts attached to different polymer beads. The FAB spectrum of the soluble product clearly showed molecular ions for all the cyclic oligomers of the C_{11} acid from dimers to heptamers and for all the cyclic oligomers of the C_8 acid from dimers to undecamers. There was no evidence for cyclic co-oligomers indicating (Three Phase Test[11]) that the reactions do indeed take place on the beads and not *via* any soluble intermediates.

We are currently seeking to refine the method and to extend it to the preparation of other cyclic species including ethers formally derived from quinol and ethylene glycol.

We thank the SERC for financial support and for a studentship (M.P.H.).

Received, 30th December 1992; Com. 2/06884B

‡ Sample kindly prepared by Dr R. O'Dell by vigorously stirring a solution of 11-bromoundecanoic acid in chloroform at 60 °C with an aqueous solution of tetra-n-butylammonium hydroxide.

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