Cyclic polyesters: 1. Preparation by a new synthetic method, using polymer-supported reagents

B. R. Wood, P. Hodge* and J. A. Semlyen†
Chemistry Department, University of York, Heslington, York YO1 5DD, UK
**Chemistry Department, University of Manchester, Oxford Road, Manchester M13 9PL, UK*
(Received 4 October 1992)

A new method of synthesizing cyclic polyesters is described, using polymer-supported reactions. This method involves the attachment of ω-bromocarboxylate anions to the surface of an ion-exchange resin, followed by polymerization and cyclization by inter- and intramolecular alkylation reactions, respectively. The polymerization reaction results in the formation of oligomeric chain polyester molecules that remain bound to the resin by the carboxylate anion end group. The cyclization reaction results in the detachment of the cyclic product from the resin support. The cyclic polyester $[(CH_2)_{10}CO.O]_x$ obtained was divided into a series of sharp fractions using preparative g.p.c. and each fraction was examined by analytical g.p.c. The cyclic nature of the polyester product was established by n.m.r. spectroscopy and by fast atom bombardment (f.a.b.) mass spectrometry. The f.a.b. mass spectrum of a fraction showed a series of spectral lines corresponding to $[(CH_2)_{10}CO.O]_x$ with $x = 2$–7. The cyclic products were directly compared with analogous linear polymers.

(Keywords: cyclic polymers; polymer-supported reaction; polymerization)

INTRODUCTION

The first reports[1,2] of the fractionation of a synthetic cyclic polymer described how cyclic poly(dimethylsiloxane) (with up to 1000 skeletal bonds) was obtained as a number of sharp fractions by preparative g.p.c. These were then later fully characterized[3]. Since then, a range of cyclic polymers have been obtained and studied, including cyclic polysiloxanes $[R(CH_3)SiO]_x$, $4 < x < 500$ (where R = H, CH=CH$_2$ and C_6H_5)[4–6], cyclic polystyrene[7,8], cyclic polybutadiene[9] and other organic cyclic polymers[10]. Recently, cyclic polycarbonates have been reported[11]. These are the first cyclic polymers to have commercial applications[12]. Cyclic polymers are at last establishing a place alongside the familiar linear polymers in synthetic polymer chemistry; they are already well known in natural polymer chemistry where, for example, deoxyribonucleic acids (DNA) often occur in cyclic forms[13,14].

Cyclic polymers prepared by bulk polymerization reactions, i.e. using melt or solution techniques, are usually only obtained in very small yields and lengthy purification procedures have to be used in order to separate them from their chain analogues[3]. Merrifield[15] introduced the technique of 'solid phase' peptide synthesis using polymer-supported reagents. Since then, polymer-supported organic reactions have been extensively investigated[16]. The use of polymer-supported quaternary ammonium salts was first described by Cainelli[17,18] and this technique has been successfully applied to the synthesis of hindered esters[19,20]. Currently, we are investigating the use of polymer-supported reagents to prepare cyclic polymers. In this present investigation, a cyclic polyester was prepared by the exploitation of an intramolecular alkylation reaction of an ω-bromocarboxylic acid using an anion-exchange resin (*Figure 1*). Evidence is provided for the formation of cyclic oligomeric and polymeric esters, using techniques such as g.p.c., ^{1}H n.m.r. spectroscopy and mass spectrometry.

This first use of polymer-supported reagents for the preparation of cyclic polymers offers several advantages over conventional preparative procedures; for example, excess and spent reagent should easily be removed from the final reaction mixture. Also, the use of polymer supports makes it possible to perform reactions on columns, where the reagents can be regenerated. Such an approach would simplify any scale-up procedures.

EXPERIMENTAL

Materials

11-Bromoundecanoic acid [Br-$(CH_2)_{10}$-COOH] and Amberlyst A-26 anion-exchange resin [polymer-$C_6H_4N^+$-$(CH_3)_3Cl^-$] were supplied by Aldrich Chemical Co. Ltd. The anion-exchange resin was subsequently converted to the bicarbonate form [polymer-$C_6H_4N^+(CH_3)_3{}^-HCO_3$] for the cyclization reactions. This was achieved by washing the resin with an excess of a saturated aqueous potassium hydrogen carbonate solution using an ion-exchange column (i.e. a solution volume equivalent to ≈10 times the bed volume of the ion-exchange column). After sequential washing with deionized water, methanol, acetone and diethyl ether, the resin was dried by drawing air through the column using a water pump. The resin

---

† To whom correspondence should be addressed

0032-3861/93/143052-07

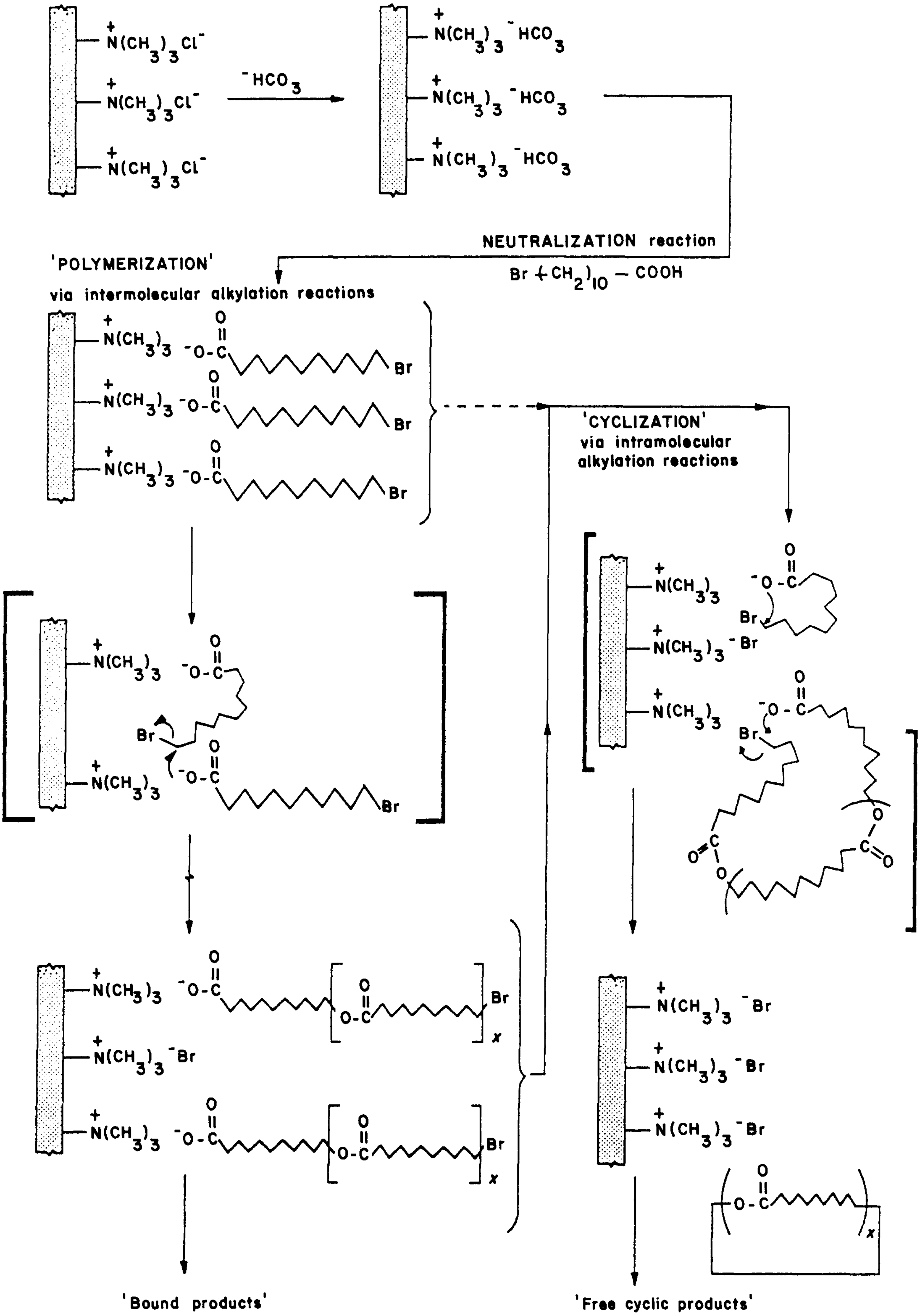

Figure 1 Schematic representation of the polymer-supported synthesis of a cyclic polyester

was dried further in a vacuum oven (5 mm Hg) at room temperature for ≈24 h. The concentration of bicarbonate ions residing on the dried anion-exchange resin was determined by back-pH titration using hydrochloric acid (0.02 M) and was found to be ≈1.8 mmol g^{-1}.

Reaction procedure

Essentially the reaction was performed in two parts, i.e. neutralization of the resin involving the displacement of bicarbonate ions by ω-bromocarboxylate ions and polymerization and cyclization of the ω-bromocarboxylate anions residing on the resin, by intermolecular and intramolecular alkylation reactions. Only the cyclized products obtained via intramolecular alkylation reactions were released from the resin.

Neutralization. The bicarbonate form of the anion-exchange resin (≈80 g) was neutralized by a methanolic bromoundecanoic acid solution, i.e. the dried resin (bicarbonate form) was placed in a 500 ml round-bottom flask along with the methanolic bromoundecanoic acid solution (0.144 mol in 300 ml MeOH). The mixture was stirred continuously at room temperature using an overhead stirrer for 48 h. The neutralized resin was collected by filtration and then washed with methanol, deionized water and acetone. The washed resin was then dried in a vacuum oven (≈5 mm Hg) at room temperature for ≈24 h.

Cyclization. The cyclization reaction (and the consequent polymerization reaction) was carried out as follows: the dried resin was placed in a two-necked round-bottom flask, along with ≈400 ml of toluene. The temperature was raised to and maintained at 55°C. The reaction mixture was stirred continuously for the duration of the reaction (≈168 h), after which the reaction was terminated. The resin was collected by filtration, washed twice with toluene, and dried in a vacuum oven (≈5 mm Hg) at room temperature for ≈48 h. The toluenic product solution and the resin washings were collected in a pre-weighed flask and evaporated to dryness using a rotary evaporator. The weight of the products was recorded.

Liberation of bound 'linear' material. The 'linear' product residing on the resin was liberated via an additional esterification reaction, using an excess of methyl iodide as follows. The dried resin from the cyclization reaction was placed in a two-necked round-bottom flask and a toluenic methyl iodide solution (0.035 mol in 300 ml toluene) was added. The temperature was raised to ≈55°C and the reaction mixture stirred continuously. After ≈96 h the reaction was terminated. The resin was collected by filtration, washed twice with toluene, and dried in a vacuum oven (≈5 mm Hg). The liberated 'linear' product and the washings were collected in a pre-weighed flask, and evaporated to dryness using a rotary evaporator. The liberated product was weighed, and the yield subsequently determined.

Fractionation. The cyclic polymer was fractionated using preparative g.p.c.[2]. The column on the preparative instrument was supplied by Waters Chromatographic Division Millipore (UK) Ltd. It had a length of 120 mm and an internal diameter of 50 mm and was packed with Styragel with a nominal porosity of 100 nm. The instrument had an injection loop with a nominal volume of 10 cm^3. Toluene was used as the chromatographic solvent, at a flow rate of ≈20 $cm^3\,min^{-1}$. A Waters Associates R403 differential refractometer was used as the detector. The polymer sample to be fractionated was dissolved in toluene to give a solution concentration of ≈0.2 g cm^{-3} (i.e. 11 g in 60 cm^3). Six sample injections were made and 19 fractions were collected between each injection. The volume of solvent eluted from the column was measured in counts, which were equivalent to a volume of 50 cm^3 at each discharge from the instrument's fraction cutter. After the initial sample injection, the second and subsequent sample injections were made at predetermined count numbers to achieve a continuous collection of sample fractions.

The solvent was removed from each collected fraction by rotary evaporation. The toluenic fractions were contaminated with impurities (benzaldehyde and benzoic acid) resulting from the oxidation of toluene in the heated still of the g.p.c. instrument. These impurities were removed by several solvent extractions using methanol. Each fraction, redissolved in toluene, was shaken with ≈30 cm^3 methanol in a separating funnel and allowed to stand for ≈4 h to facilitate complete separation. The toluene layer was removed and evaporated to dryness. The methanolic washing procedure was repeated until no impurity peaks were observed on the analytical g.p.c. chromatograms. Each fraction was then subsequently collected in a pre-weighed flask and evaporated to dryness using a rotary evaporator.

Characterization

Gel permeation chromatography. Six 'cyclic' polyester fractions were analysed at RAPRA Technology Ltd by a g.p.c.-viscometric technique, providing a set of 'well characterized' molar mass calibrants for subsequent in-house g.p.c. measurements (see *Table 1*).

The liberated linear and cyclic polymers were also analysed in-house using analytical g.p.c. The instrument used was a Knauer HPLC/GPC equipped with a PL-gel 5 μm size exclusion column. Both were supplied by Polymer Laboratories Ltd. A Shimadzu RID-6A differential refractometer was used as the detector. Chromatographs were obtained for both polymer systems before and after fractionation and also before and after solvent extraction (*Figures 2–4*).

Table 1 G.p.c. data for the cyclic polyesters[a]

Fraction no.	Weight of product (g)	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$	Degree of polymerization
1	1.12	2800	1.06	15
2	1.51	2400	1.07	13
3	1.16	2300	1.09	12
4	1.45	1800	1.13	10
5	1.10	1600	1.16	9
6	1.36	1300	1.15	7
7[b]	0.56	1100	1.15	6
8[b]	0.41	950	1.15	5

[a] Measurements performed at RAPRA using a g.p.c.-viscometric technique

[b] In-house measurements

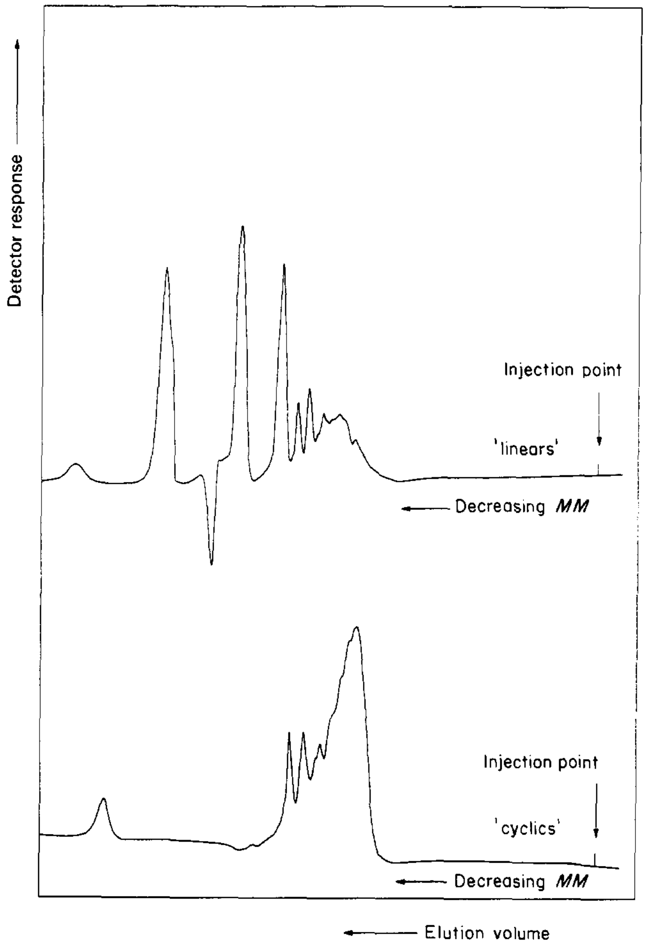

Figure 2 G.p.c. of the unfractionated bound product and the product later identified as cyclic polyester

Spectroscopic methods. The ^{1}H n.m.r. spectra of the polymer fractions were analysed using a Bruker MSL 300 MHz n.m.r. spectrophotometer, with deuterated chloroform as the solvent. The mass spectra of the cyclic and linear polymers were obtained using an Autospec f.a.b. mass spectrometer.

RESULTS AND DISCUSSION

The polymer-supported reaction gave liberated 'cyclics' in a yield of 11.8 g from an initial monomer weight of 38.2 g (0.144 mol). The weight of 'linear' polymer residing on the resin support after the cyclization reaction was found to be 10.6 g.

Gel permeation chromatography

G.p.c. showed that the cyclic polymers were obtained as a series of narrow molar mass fractions (*Figure 3*), with fractions ranging from 125 mg to 1.1 g. G.p.c. also showed that the toluene oxidation products (benzaldehyde and benzoic acid) could be removed from the sample fractions by solvent extraction, using methanol and fresh toluene (*Figure 4*). Each of the 19 sample fractions typically required ≈24 h to accomplish purification to an acceptable level, as shown by g.p.c.

G.p.c. showed that the unfractionated 'linear' polymer obtained by reaction of the non-cyclized polyester (residing on the support) with methyl iodide, had a similar molar mass range as the 'cyclic' polyester product (*Figure 2*).

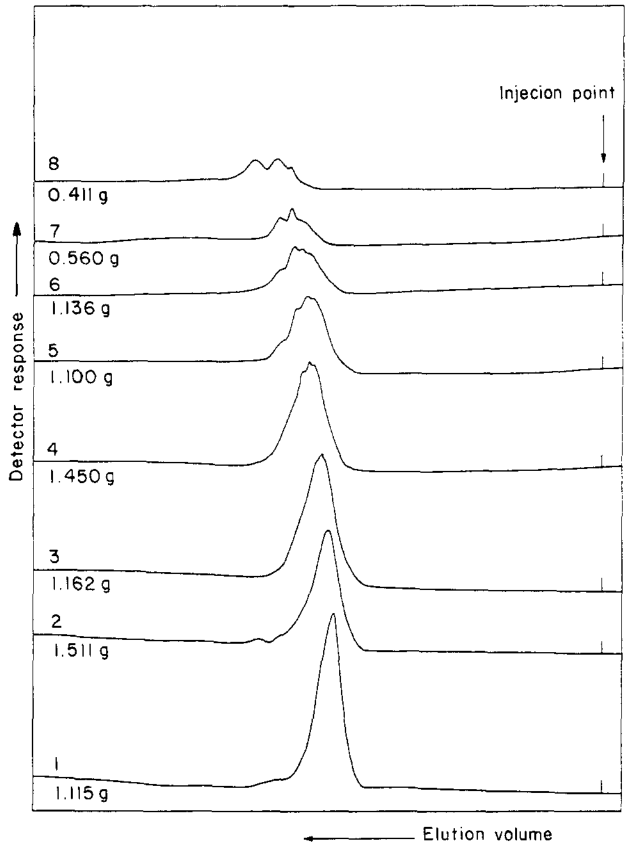

Figure 3 G.p.c. of the fractionated cyclic polyester product (the first eight fractions are shown together with their weights)

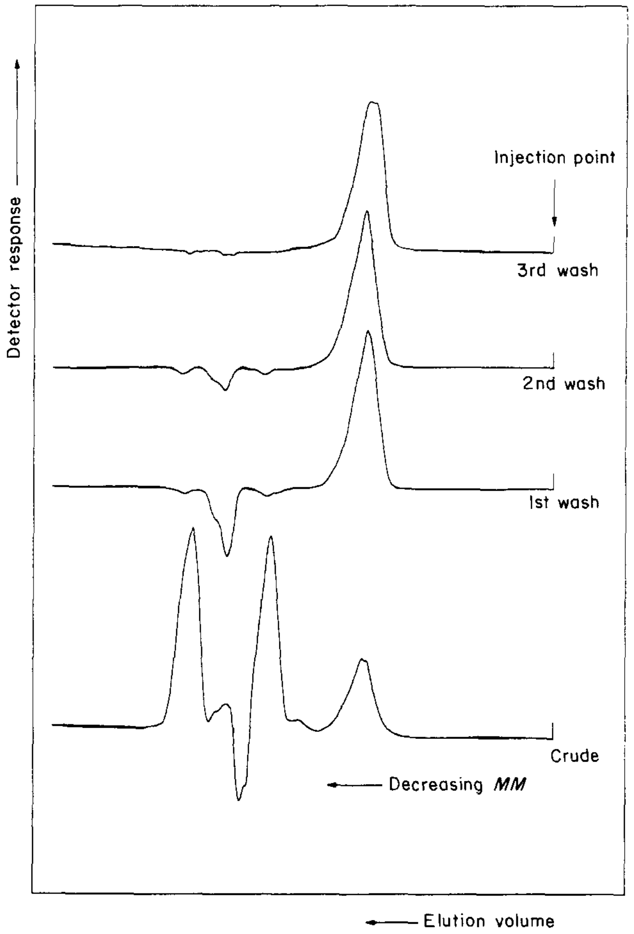

Figure 4 G.p.c. to demonstrate the removal of impurities from the cyclic polyester fractions by successive solvent extraction (fraction no. 2 is shown)

^1H *n.m.r. spectroscopy*

N.m.r. spectroscopy showed that the product obtained from the cyclization reaction had chemical shifts characteristic of a polymeric ester, i.e. chemical shifts due to protons adjacent to the ester groups at $\delta = 2.31$ and 4.27 ppm ($-CH_2CO.O-$ and $-CO.O-CH_2-$, respectively) and chemical shifts representative of the hydrocarbon chain separating the ester linkages $\delta = 1.62$ and 1.28 ppm (*Figure 5*). In addition, the n.m.r. spectra also showed chemical shifts corresponding to protons adjacent to a bromine atom $\delta = 3.4$ ppm ($-CH_2-Br$). The ratio of the integration heights for the signals $-CH_2-CO.O-$ and $-CH_2-Br$ was found to be $\approx 50:1$. If the product with a molar mass of $\bar{M}_n = 2400$ had been entirely linear the integration signal ratio would have been 13:1. Other signals due to protons of hydroxyl groups and methyl ester terminated groups were also observed. Again the integration heights were very small (i.e. $>50:1$) with respect to the protons of the ester group. This implied that some side reactions had occurred. Such side reactions may have taken place due to nucleophilic attack by bicarbonate or methanol residues.

The n.m.r. spectrum of the liberated material that was left bound to the resin after the cyclization reaction, showed chemical shifts indicative of methyl terminated polyesters and chemical shifts due to protons adjacent to bromine atoms; but the height of the integration signal was significantly larger than for the corresponding cyclization product, i.e. an integration ratio of $\approx 10:1$.

Mass spectrometry showed that the specimens were predominantly cyclic, with little evidence for bromine terminated chain species. The mass spectrum for cyclic fraction no. 8 (*Figure 6*) showed a regular series of spectral lines corresponding to exact multiples of the polyester repeat unit $[(CH_2)_{10}CO.O]_x$ (formula weight = 184.26). This could indicate the presence of polyester rings with $x = 2-7$, i.e. 24–84 bonds for the low molar mass fraction no. 8 (*Figure 6*).

The mass spectrum of a fraction of comparable molar mass for the liberated products from the resin, showed similar spectral lines to the cyclized products (although of lower intensity), with other spectral lines also present (*Figure 7*). This suggested that either some of the cyclic polyester remained on the resin after the cyclization reaction or formed *in situ* in the mass spectrometer. Apart from the spectral lines associated with cyclic products, the other lines could be associated with chain polyester products.

Cyclic polymers would be expected to be formed by the particular synthetic route chosen. Spectroscopic evidence, particularly f.a.b. mass spectrometry is in accord with this expectation. However, it is in the following paper that unequivocal direct evidence is presented for the cyclic nature of these polyesters[21].

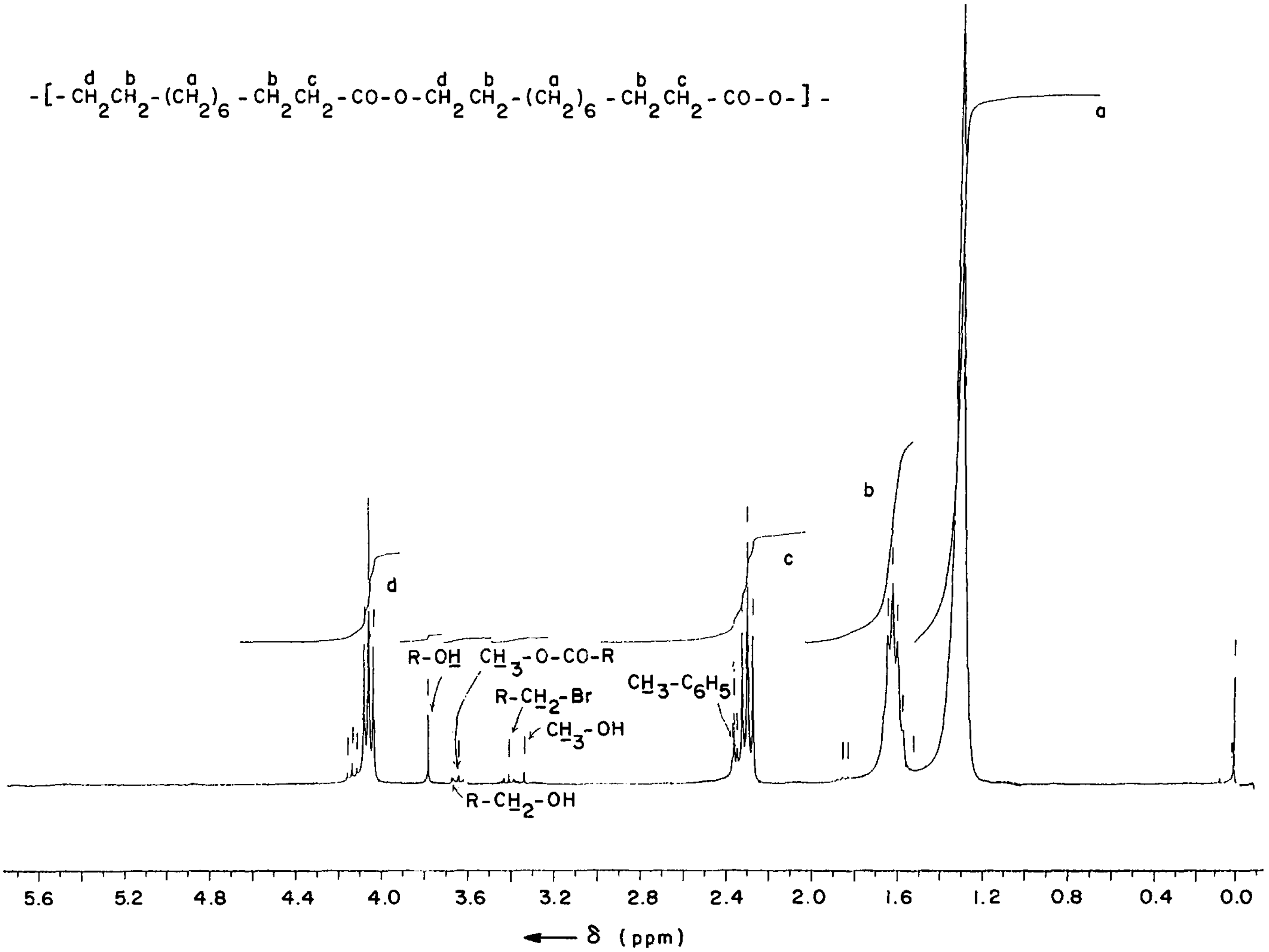

Figure 5 N.m.r. spectrum of cyclic polyester fraction no. 2

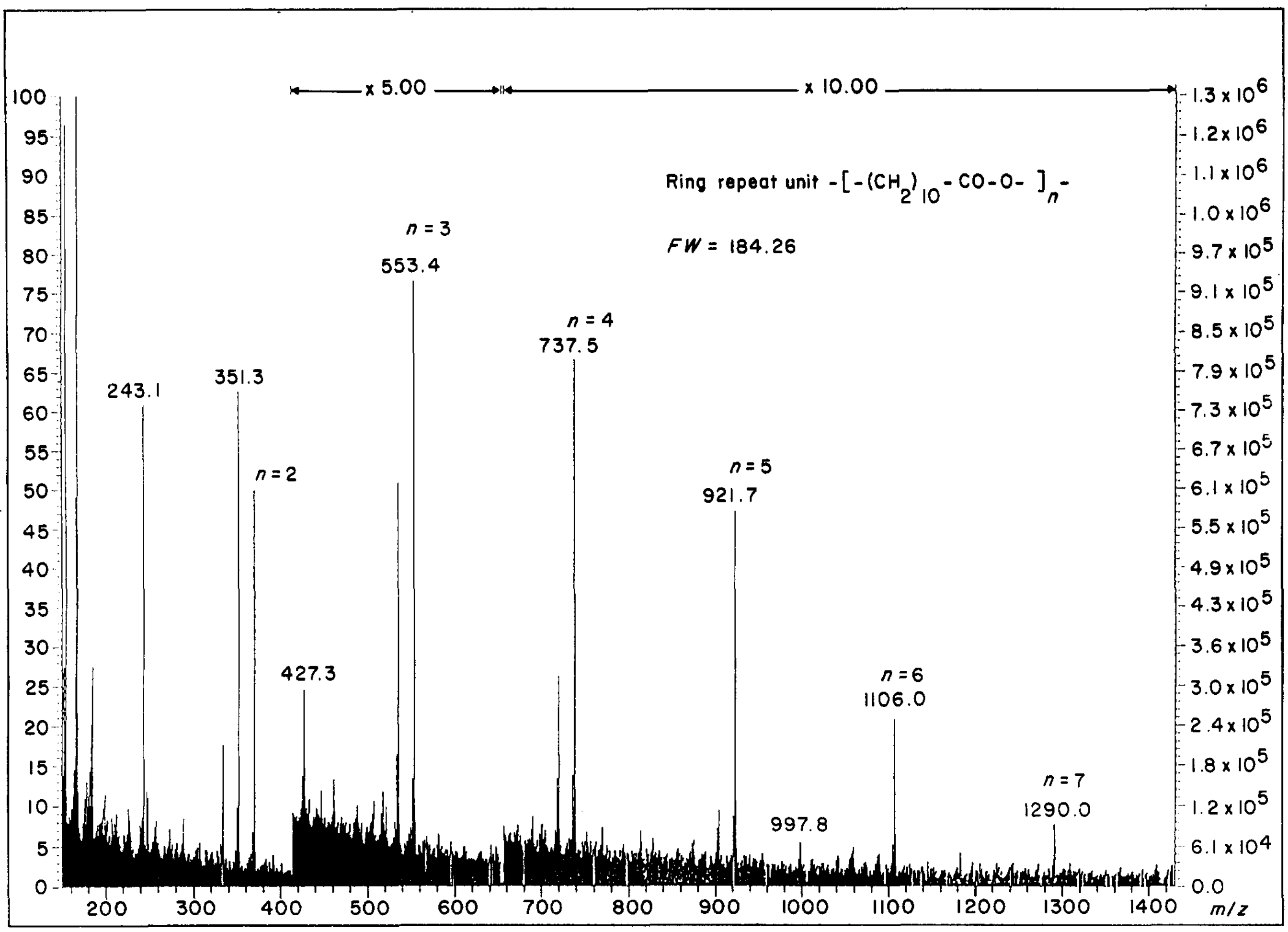

Figure 6 Mass spectrum for cyclic polyester fraction no. 8

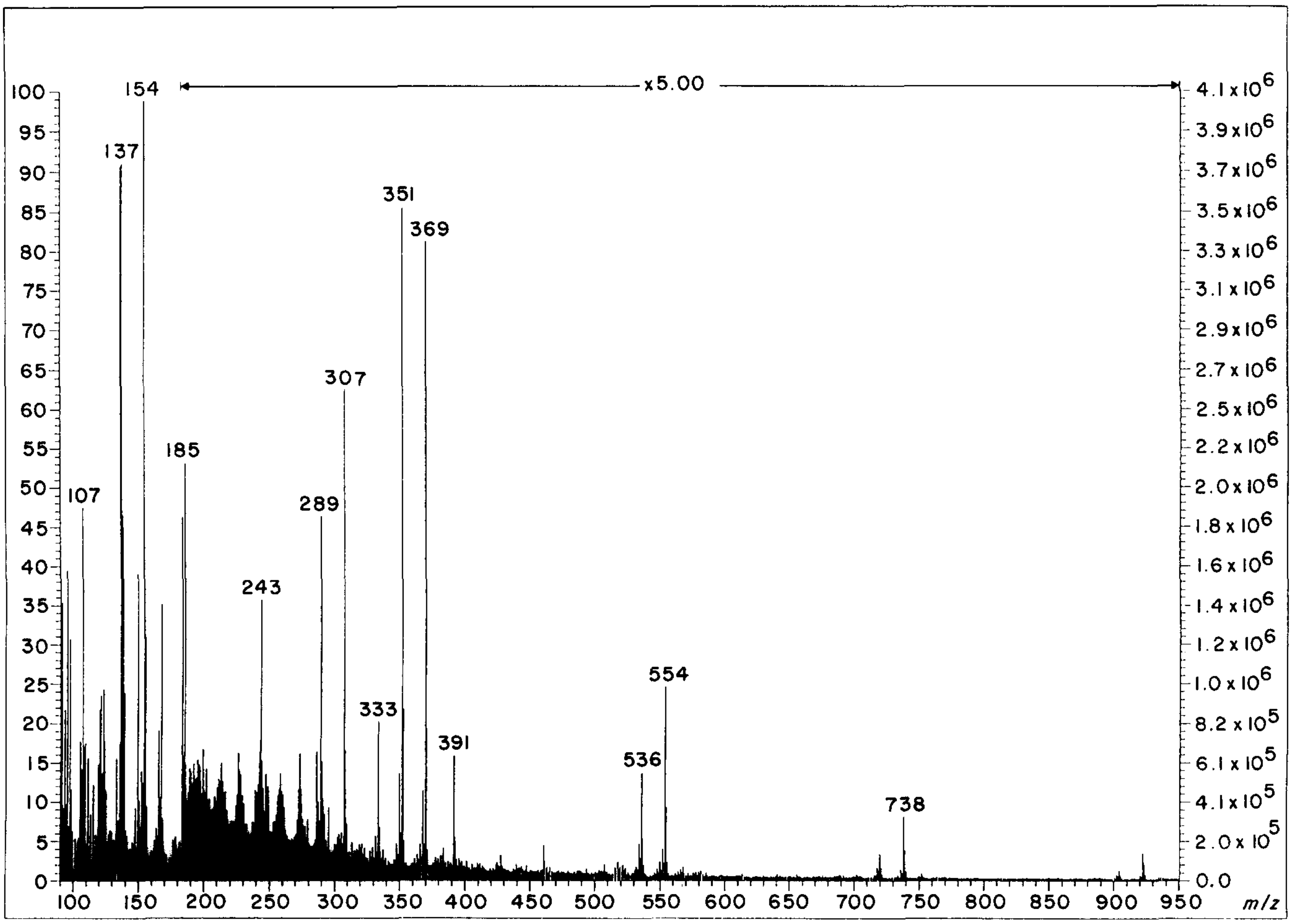

Figure 7 Mass spectrum for an unfractionated linear polyester sample

ACKNOWLEDGEMENTS

The authors are grateful to the Science and Engineering Research Council for financial support. The authors would like to thank Dr G. Barlow and Dr T. Dransfield (both of the University of York) for n.m.r. and mass spectra, respectively, and for helpful discussions.

REFERENCES

1 Dodgson, K. and Semlyen, J. A. *Polymer* 1977, **18**, 1265
2 Dodgson, K., Sympson, D. and Semlyen, J. A. *Polymer* 1978, **19**, 1285
3 Semlyen, J. A. (Ed.) 'Cyclic Polymers', Elsevier, London, 1986
4 Richards, R. D. C. *PhD Thesis* University of York, 1988
5 Formoy, T. R. and Semlyen, J. A. *Polym. Commun.* 1989, **30**, 86
6 Clarson, S. J. and Semlyen, J. A. *Polymer* 1986, **27**, 1633
7 Geiser, D. and Höcker, H. *Macromolecules* 1983, **16**, 843
8 Roovers, J. and Toporowski, P. M. *Macromolecules* 1983, **16**, 843
9 Roovers, J. *Macromolecules* 1988, **21**, 1517
10 Höcker, H. in 'Cyclic Polymers' (Ed. J. A. Semlyen), Elsevier, London, 1986, Ch. 6
11 Brunelle, D. J. and Shannon, T. G. *Macromolecules* 1991, **24**, 3035
12 Stinson, S. *Chem. Eng. News* 1989, 18 September, 8
13 Freifelder, D., Kleinschmidt, A. K. and Sinsheimer, R. L. *Science* 1964, **146**, 254
14 Wang, J. C. in 'Cyclic Polymers' (Ed. J. A. Semlyen), Elsevier, London, 1986, Ch. 7
15 Merrifield, R. B. *J. Am. Chem. Soc.* 1963, **85**, 2149
16 Hodge, P. and Sherrington, D. C. (Eds) 'Polymer Supported Reactions in Organic Synthesis', Wiley, Chichester, 1980
17 Cainelli, G. and Manescalchi, F. *Synthesis* 1975, 723
18 Cainelli, G., Contento, M., Manescalchi, F. and Plessi, L. *J. Chem. Soc. Commun.* 1982, 725
19 Moore, G. C., Foglia, T. A. and McGahan, T. J. *J. Org. Chem.* 1975, **44**, 2425
20 Cardillo, G., Orena, M., Porzi, G., Sandri, S. and Tomasini, C. *J. Org. Chem.* 1984, **49**, 701
21 Wood, B. R., Joyce, S. J., Scrivens, G., Semlyen, J. A., Hodge, P. and O'Dell, R. *Polymer* 1993, **34**, 3059