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Polymer-supported syntheses of some cyclic oligoamides and some cyclic alternating oligo(amide–ester)s

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Abstract

Cyclic oligoamides and alternating oligo(amide–ester)s have been prepared by a novel polymer supported method in yields ranging from 28–48%. In the case of the synthesis of cyclic oligo(undecanamide–undecanoate)s the cyclics obtained ranged in size up to ones having at least 288 ring atoms. The polymer beads recovered at the end of the syntheses contained material accounting for 25–48% of the bound starting monomers. The nature of this material is unclear but a significant fraction may be large cyclics wrapped round the network. Experiments to clarify this last point are in hand.

Keywords: Cyclic oligoamides; Alternating oligo(amide–ester)s; Polymer-supported synthesis

1. Introduction

Cyclic oligomers are of interest for several reasons. For example, they can serve as starting materials for entropy-driven ring-opening polymerisations [1–3], and, if they contain moieties which can take part in, for example, hydrogen-bonding and/or π-donor–acceptor interactions, they can have useful recognition properties [4].

It is well known that cyclic oligomers are present as minor components in the products from most step-growth polymerisations [5]. Typically the cyclic fraction is $< 2\%$ of the total product and isolation of the cyclic oligomers can be a tedious, inefficient and lengthy process. There is, therefore, a need for methods which allow cyclic oligomers to be synthesised in good yields and isolated easily. This paper describes studies of the polymer-supported (PS) syntheses of some cyclic oligoamides and cyclic alternating oligo(amide–ester)s. The attractive feature of these PS syntheses is that it is expected that at the end of each synthesis the cyclic products will be free in solution whereas the linear products will be bound to the insoluble supports and therefore easily removed by filtration. We have recently prepared cyclic oligomers (**1**) and (**2**) using a pseudo-high dilution method [6]. The products formed in that study have been used to facilitate the characterisation of some of the products formed in the present study.

The PS method used is outlined in Scheme 1. In Step A an *N*-*t*-Boc-protected amino acid is coupled through ester linkages to hydroxyl moieties on insoluble polymer beads. The ester linkage formed is one which will react smoothly with primary amines. In Step B the *t*-Boc protecting groups are removed and in Step C the amine groups are allowed to react with the active ester linkages to generate amide bonds. Two different types of amide-forming processes may occur. In the first, the amide-forming reactions may take place between *neighbouring* side chains (intersite reactions) to give, via 'chain extension', polymer-bound *linear* dimer, trimer, tetramer, pentamer, etc. The second type of amide-forming reaction involves reactions between the amine groups and the active ester linkage of the *same* side chain (intrasite reactions). Such reactions will lead to the formation of cyclic products and in the process of 'cyclisation' the product will become detached from the support. For the synthesis of cyclic *oligomers* both 'chain extension' and 'cyclisation' processes are needed and the average degree of polymerisation (DP) of the cyclic products will depend on the relative contributions of the two processes. For success the monomer must clearly be chosen such that a simple cyclisation of the monomer itself is unlikely or impossible. For example, the monomer could not be one where the cyclised monomer is simply an unstrained 6-membered ring, but it could be one where the cyclised monomer is a strained 'medium-sized' ring [7]. As the side chains get longer cyclisation is expected to become slower but long reaction times should allow most side

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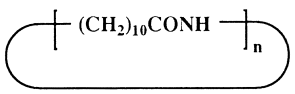

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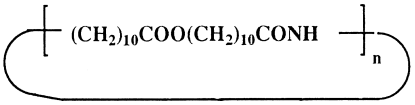

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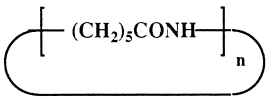

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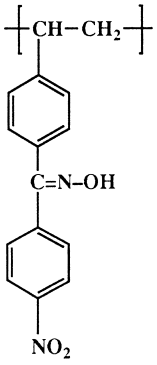

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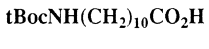

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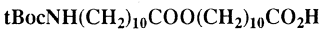

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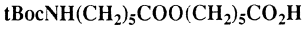
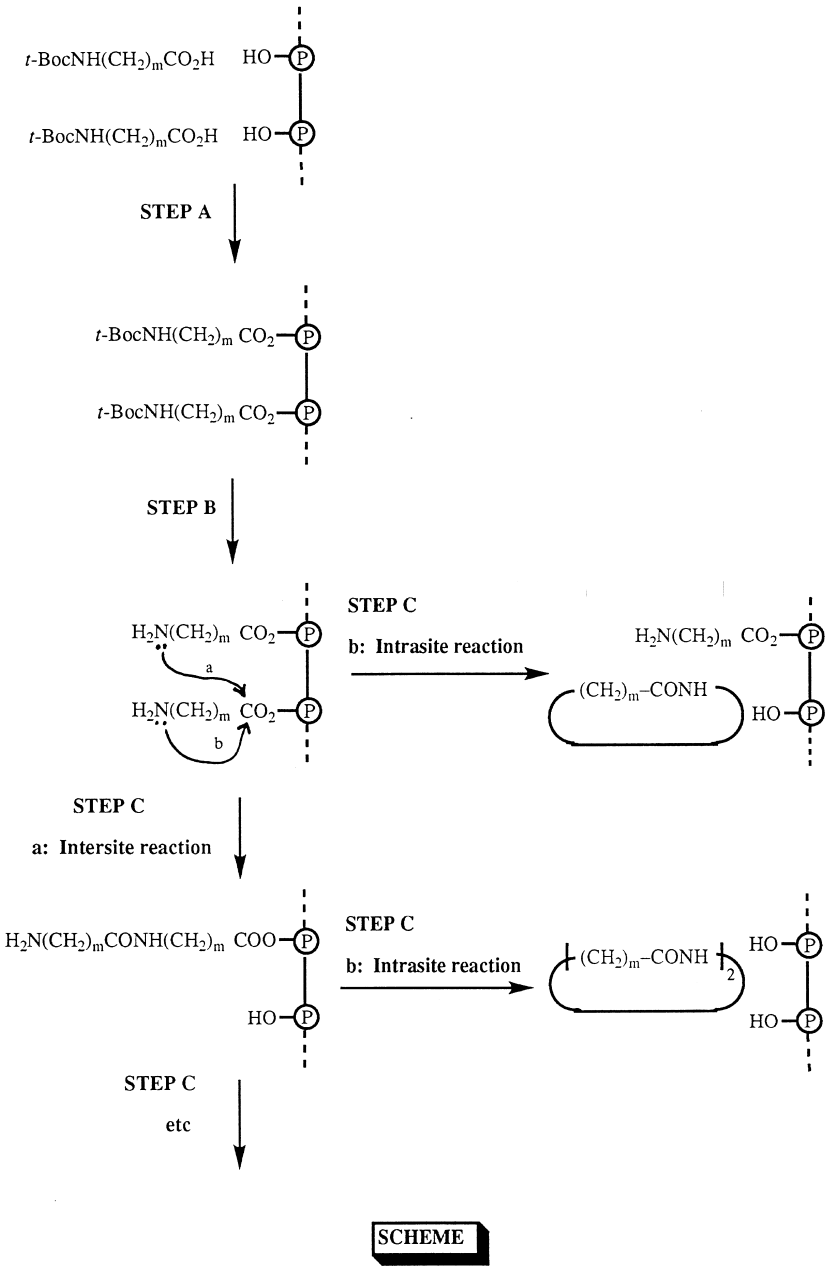


(8)

chains to cyclise. The attractive feature of this PS method is, as noted above, that it is expected that the *cyclic* oligomers will be released into solution whilst the *linear* products should remain bound to the insoluble support, thus facilitating separation.

Work related to this PS method has been published before, mainly in the context of trying to achieve 'site isolation' in reactions on polymer supports [8–10]. In these cases the target molecule is usually the cyclised monomer and 'chain extension' processes are undesirable. The most common example has been the 'solid phase' synthesis of cyclic peptides. Here a linear peptide is usually prepared on a polymer support and then cyclised [11–13]. However, Rothe and his coworkers have reported, mainly through conference proceedings [14–16], that complete 'site isolation' is not usually achieved in such syntheses of cyclic peptides and that the products contain many cyclic oligomers. More recently Rothe et al. have reported in some detail on the synthesis of cyclic oligomers of nylon 6 (**3**)[17] and of 12-hydroxydodecanoic acid and the 'dimer' of 6-hydroxyhexanoic [18]. In the former study products with as many as 280 ring atoms were *isolated*. Other relevant work has been carried out by Ford et al. [19] and the present author [20]. Ford et al. studied the cyclisation of 12-hydroxydodecanoic acid bound via a thiol ester linkage to polymer supports bearing thiol moieties. They showed that in comparison with the analogous non-polymeric reaction, the PS system allowed improved intramolecular cyclisation to give dodecanolactone, i.e. that a degree of 'site isolation' could be achieved. However, in addition to a modest yield of the cyclised monomer evidence for the formation of the cyclic dimer and trimer was also obtained. The present author has shown that in some circumstances cyclisations of ω-bromoalkanoates bound ionically to anion exchange resins give cyclised monomer and dimer in yields consistent with there being a degree of



Scheme 1. Step A: coupling of acid to the beads by esterification. Step B: removal of protecting group with TFA, then generation of free amine group by removal of proton with triethylamine. Step C: amide bond forming reactions. Letter 'P' within circle indicates polymer bead with, for example, residues (**4**).

'site isolation' [20]. The results from these various studies will be discussed below as appropriate together with those from the present work.

2. Experimental

Chromatographic, spectroscopic, and other general experimental details are as given previously [6]. Abbreviations: TFA = trifluoroacetic acid, DMF = dimethylformamide, DCCI = dicyclohexylcarbodiimide, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DIEA = diisopropylethylamine, TEA = triethylamine.

*2.1. Synthesis of polystyrene beads with oxime moieties (**4**)*

These were prepared from 1% crosslinked polystyrene beads according to the procedures of DeGrado and Kaiser [21]. As estimated from the increase in weight of the beads they contained 2.42 mmol g^{-1} of oxime residues (**4**). By elemental analysis the beads contained 6.77% nitrogen which corresponds to a loading of 2.40 mmol g^{-1}. The beads had ν_{max} (KBr disc) 3600–3500 and 1600 cm^{-1}.

2.2. N-t-Butoxycarbonyl-11-aminoundecanoic acid (**5**)

This compound was prepared as described previously [6].

2.3. Typical attachment, deprotection and cyclo-oligomerisation procedures: cyclo-oligomerisation of 11-aminoundecanoic acid bound to polymer beads (**4**)

Attachment: *N-t*-Butoxycarbonyl-11-aminoundecananoic acid (**5**) (6.60 g, 22 mmol) in dichloromethane (30 ml) containing DMAP (3% v/v) or pyridine was mixed with DCCI (2.30 g, 11 mmol) in tetrahydrofuran (5 ml) at 10°C and the mixture was left for 15 min. Polymer beads (**4**) (4.15 g, 10 mmol) were then added and the mixture stirred at room temperature for 24 h. The beads were filtered off, Soxhlet extracted with dichloromethane for 10 h, and dried. This gave active ester beads (5.65 g, 1.28 mmol g^{-1} of bound acid), ν_{max} (KBr disc) 1770 (active ester) and 1709 cm^{-1} (Boc).

Deprotection: The active ester beads (4.00 g) were treated with TFA in dichloromethane (1 vol:2 vols; 20 ml) at 10°C for 1 h then the beads were filtered off, washed with dichloromethane (100 ml) and dried. They had ν_{max} (KBr disc) 1772 cm^{-1} (active ester).

Cyclo-oligomerisation: (a) The active ester beads prepared above were suspended in DMF (30 ml) containing DIEA (2.5 ml) for 7 days at 20°C. The beads were then filtered off and washed with hot (60°C) DMF (2 × 10 ml). The beads were also washed with TFA in hot (50°C) chloroform (1 vol:2 vols; 3 × 20 ml). The combined extracts were concentrated then precipitated into methanol. The precipitate was recovered, dried, extracted with DMF at 60°C and the solid filtered off. The filtrate was evaporated to dryness (290 mg, 31% yield). The residue had ν_{max} 1640 cm^{-1} and was analysed by g.p.c., using the procedures described before [6]. The g.p.c. results are presented in the text. The f.a.b.m.s. showed peaks at *m/e* 184, 367, 550, 734, 917 and 1100 corresponding to the series of ions $(M + 1)^+$ to $(6M + 1)^+$. The material which was insoluble in DMF (131 mg, 14% yield) had essentially the same infrared spectrum as that of the DMF-soluble material. Due to the method of isolation the linear oligomers would be present as the TFA salts. By elemental analysis this material contained 0.26% fluorine indicating [6] an average degree of polymerisation of 120.

(b) Cyclic nylon 11 oligomers were also synthesised using TEA in place of DIEA. Similar results were obtained.

(c) In some syntheses of cyclic nylon 11 oligomers the neutralisation of the salt formed during the removal of the *t*-butyloxycarbonyl group was carried out as a separate step. That is the excess of DIEA or TEA and their TFA salts were washed from the beads before the latter were set aside to allow cyclisation to take place. Again similar results were obtained. Addition of a few drops of acetic acid did not appear to catalyse the cyclisation reaction [21].

(d) In the experiments which formed the amide-esters, no TFA was used in the extraction: the beads were simply extracted using boiling chloroform and the extract analysed by ^1H n.m.r. spectroscopy, g.p.c., and f.a.b.m.s. The g.p.c. and f.a.b.m.s. results are presented in the text.

2.4. (t-Butoxycarbonyl-6-aminohexanoyl)-D,L-methionine(**6**)

(a) *N-t-Butoxycarbonyl-6-aminohexanoic acid:* A solution of 6-aminohexanoic acid (50.0 g, 380 mmol) in DMF–water (10:6 v/v, 400 ml) was treated with *t*-butoxycarbonyl azide [22] (55.0 g, 380 mmol) for 1 h. The pH was then raised to between 9.5 and 10.5 and held in this range during the course of the reaction by the careful addition of 2 N aqueous sodium hydroxide. The reaction mixture was left for 18 h, then acidified (Congo Red) by the addition of 2 N hydrochloric acid, and extracted with ether (2 × 200 ml). The extracts were dried and the solvent evaporated off under vacuum. The desired product (54.0 g, 62%) was initially an oil but it slowly crystallised. The crystals had m.p. 35–38°C (lit. [23] 41–42°C) and ν_{max} (film cast from chloroform) 1710 (carboxyl) and 1683 cm^{-1} (*t*-Boc carbonyl).

(b) *(t-Butoxycarbonyl)-6-aminohexanoic acid p-nitrophenyl ester:* The acid described immediately above was converted into the *p*-nitrophenyl ester (60% yield) using the procedure described previously for the synthesis of the corresponding aminoundecanoic acid derivative [6], and was used directly in the next step.

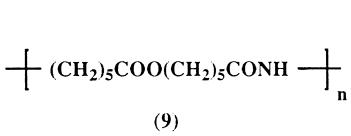
(c) *N-(t-Butoxycarbonyl-6-aminohexanoyl)-*D,L*-methionine (**6**):* The above *p*-nitrophenyl ester (10.6 g, 30 mmol) was dissolved in DMF (50 ml) and the solution added dropwise over 1 h to a solution of D,L-methionine (5.3 g, 35.5 mmol) and sodium hydroxide (1.5 g) in a mixture of DMF–water (100 ml, 1 vol:1 vol) at 20°C. After 24 h the mixture was acidified with 2 N hydrochloric acid and extracted with ether (3 × 200 ml). Evaporation of the dried extract gave the desired product (**6**) (30% yield). After recrystallisation from ethyl acetate–toluene, it was obtained as white needles m.p. 99.5–100.5°C. It had δ 1.25–1.70 (*m*; 15H; *t*Boc plus $CH_2CH_2CH_2$), 1.90–2.30 (*m*; 7H; $CH_2CH_2SCH_3$ plus CH_2CO), 2.55 (*m*; 2H; CH_2S), 3.12 (*t*; 2H; CH_2N), 4.70 (*m*; 1H; α − H of met), 6.93 (*d*; 1H; CONH) and 7.41 ppm (*br*; 1H; CONH). Found: C 53.1, H 8.3, N 7.7; $C_{16}H_{30}N_2O_5S$ requires C 53.0, H 8.3, N 7.7%.

2.5. (t-Butoxycarbonyl-11-aminoundecanoyl)-11-oxyundecanoic acid (**7**)

This compound was prepared as described previously [6].

2.6. (t-Butoxycarbonyl-6-aminohexanoyl)-6-oxyhexanoic acid (**8**)

(a) *6-Bromohexanoic acid benzyl ester:* 6-Bromohexanoyl chloride (23.1 g, 100 mmol) in chloroform (20 ml) was added dropwise into a solution of benzyl alcohol



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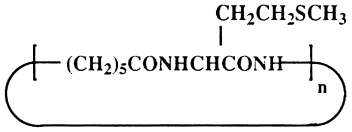

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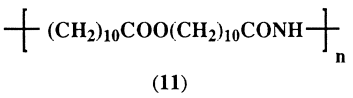

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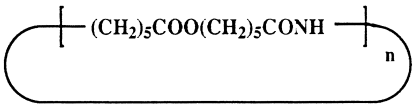

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(12.0 g, 110 mmol) and triethylamine (11.2 g, 110 mmol) in chloroform (80 ml) at 0–10 °C. The reaction mixture was kept at 20 °C for 24 h and was then diluted with chloroform (100 ml) and washed successively with 1 N hydrochloric acid, 5% aqueous sodium bicarbonate, and brine. Evaporation of the dried solution afforded an oily product (26.5 g), ν_{max} (film) 1735 cm^{-1}, which was used directly in the next step.

(b) *(t-Butoxycarbonyl-6-aminohexanoyl)-6-oxyhexanoic acid benzyl ester:* A mixture of *N-t*-butoxycarbonyl-6-aminohexanoic acid (10.0 g 44 mmol), the ester prepared in (a) (11.8 g, 44 mmol), diisopropylethylamine (5.6 g, 44 mmol) and ethyl acetate (10 ml) was stirred and heated at reflux temperature for 36 h. The cooled mixture was added to water (250 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 ml). The combined extracts were dried and the solvent evaporated. The oily residue (16.0 g) was purified by column chromatography over silica gel with ethyl acetate–cyclohexane (1 vol: 4 vols) as the eluant. This gave the desired product (12.4 g, 66%) as an oil, ν_{max} (film) 1734, and 1715 cm^{-1}, which was used directly in the next step.

(c) *(t-Butoxycarbonyl-6-aminohexanoyl)-6-oxyhexanoic acid (**8**):* The product described in (b) (12.4 g) was dissolved in THF (100 ml), palladium on charcoal (1.2 g, 20%) was added and the mixture shaken for 8 h under an atmosphere of hydrogen. The catalyst was then filtered off and the solvent evaporated off. The oily residue was recrystallised from ether–petroleum ether (b.p. 40–60°) (1 vol:4 vols). This gave crystals (6.43 g), m.p. 34–35°C, ν_{max} (film) 1728, 1714, and 1688 cm^{-1}. This product had δ 1.30–1.45 (*m*; 17H: *t*-Boc plus 4 × CH_2), 1.65 (*m*; 4H; 2CH_2), 2.30 (*t*; 2H; CH_2CO), 2.35 (*t*; 2H; CH_2CO), 3.10 (*q*; 2H; CH_2N), 4.10 (*t*; 2H; CO_2CH_2) and 6.60 ppm (*br*; 1H; CONH). Found: C 59.1, H 9.2, N 4.1; $C_{17}H_{31}NO_6$ requires C 59.1, H 9.0, N 4.1%.

2.7. Linear alternating oligo(hexanamide–hexanoate)s (*9*)

(a) *Tosylate salt of 6-aminohexanoic acid benzyl ester:* A mixture of 6-aminohexanoic acid (13.1 g, 100 mmol), *p*-toluenesulphonic acid monohydrate (20.9 g, 110 mmol), benzyl alcohol (11.8 g, 110 mmol) and toluene (150 ml) was stirred and heated under reflux. A Dean–Stark trap was used to collect the water formed and the reaction was stopped when no more water formed.

The layer of white syrup which had formed was separated and washed with cold toluene. It solidified (38.4 g, 98%). This was used directly in the next reaction.

(b) *N-(6-Bromohexanoyl)-6-aminohexanoic acid benzyl ester:* The product from (a) was deprotonated by stirring with 1 N aqueous sodium bicarbonate (100 ml) and dichloromethane (100 ml) to afford a solution of the free amino ester. Triethylamine (15 ml, 110 mmol) and 6-bromohexanoyl chloride (12.0 g, 51 mmol) were carefully added to the stirred solution at 0°C, then the mixture was set aside for 24 h. It was then washed successively with 5% aqueous sodium bicarbonate, 1 N hydrochloric acid, and water and dried. Evaporation of the solvent gave a solid (20.0 g) which recrystallised from ether–petroleum ether (b.p. 40–60°) (1 vol:4 vols) to give white crystals (18.0 g), m.p. 47–48°C, ν_{max} (film) 1725, 1637, and 1543 cm^{-1}.

(c) *N-(6-Bromohexanoyl)-6-aminohexanoic acid:* The above ester (18.0 g) was debenzylated as described in the preparation of acid (**8**) above. This gave white crystals (10.0 g, 72%), m.p. 65–67°C, ν_{max} (film) 3301, 1701, 1632 and 1535 cm^{-1}. The product had δ 1.30–1.50 (*m*; 6H; 3 × CH_2) 1.65 (*m*; 4H; 2 × CH_2), 1.88 (*m*; 2H; CH_2), 2.20 (*t*; 2H; CH_2 CO), 2.35 (*t*; 2H; CH_2CO), 3.25 (*q*; 2H; CH_2N), 3.40 (*t*; 2H; CH_2Br) and 5.55 ppm (*br*; 1H; CONH). Found: C 47.3, H 7.2, N 4.7, Br 25.9; $C_{11}H_{22}BrNO_3$ requires C 47.8, H 7.2, N 4.6, Br 25.7%.

(d) *Linear alternating oligo(hexanamide–hexanoate)s (**9**):* A mixture of the above acid (449 mg, 1.0 mmol), aqueous tetra-*n*-butylammonium hydroxide (0.649 g of 40%, 1.0 mmol) and chloroform (6 ml) was vigorously stirred under reflux for 2 h. The mixture was then cooled and the organic layer added to acetone (100 ml) containing 2% acetic acid. The precipitate was collected and dried (298 mg, 78%), ν_{max} (film) 1728, 1638 and 1541 cm^{-1}. Found: Br 4.24%, corresponding to a DP of 4.9. By g.p.c. the sample consisted mainly of linear oligomers from the trimer to the dodecamer, with the major component being the tetramer. It had δ 1.20–1.80 (*m*; 12H; 6 × CH_2), 2.20 (*t*;

Table 1
Polymer-supported syntheses of cyclic oligomers[a]

Entry	Bound acid	Loading[b] (mmol g^{-1})	Product	Yield of cyclic oligomers (%)		Weight increase of recovered beads[d]	Equivalent % of monomer
				Initial extract[c]	TFA–$CHCl_3$ extract		
1	(**5**)	1.28	(**1**)	31	14	56	48
2	(**6**)	0.73	(**10**)	28	11	6	25
3	(**7**)	0.27	(**2**)	48	–	4	35
4	(**7**)	0.59	(**2**)	44	–	11	35
5	(**8**)	0.71	(**12**)	29	–	9	40

[a] Acids bound to polymer beads (**4**). Cyclo-oligomerisation carried out in DMF at 20°C for 7 days.
[b] Estimated by increase in weight of beads.
[c] Material in reaction solvent plus that extracted with hot chloroform.
[d] Weight of recovered beads in excess of that expected if all the bound monomer gave soluble cyclics.

2H; C*H*$_2$CONH), 2.35 (*t*; 2H; CH_2CO_2), 3.25 (*m*; 2H; CH_2N), 3.50 (*t*; $BrCH_2$ end groups), 4.04 (*t*; 2H; CO_2CH_2) and 6.00 ppm (*br*; 1H; CONH).

3. Results and discussion

The main aim of the present study was to determine whether the synthetic approach outlined in Scheme 1 could be used successfully to prepare various cyclic oligoamides in good yields. Oligoamides were selected for this study because the synthetic reactions used are analogous to those used in peptide synthesis. As mixtures of oligomers were quite acceptable no attempt was made to achieve 'site isolation'. Thus, loadings as high as could be conveniently achieved were used. To prevent the formation of substantial proportions of cyclic monomers, the monomers used each contained more than eight chain atoms [7].

Polymer-supported active esters have often been used in peptide synthesis [12, 13, 24]. One of the most successful types and the one used in the present study, is that prepared by acylation of polymer beads containing the oxime residues (**4**). Acylation of 1% crosslinked polystyrene beads with 4-nitrobenzoyl chloride in the presence of aluminium trichloride followed by reaction with hydroxylamine and pyridine according to the procedures of DeGrado and Kaiser [21], gave beads containing 2.40 mmol g^{-1} of residues (**4**), corresponding to a degree of substitution of 0.41.

The readily available 11-aminoundecanoic acid was selected as the first substrate for investigation using the synthetic method outlined in Scheme 1. In this case the formation of cyclic monomer is not favourable [7] and when incorporated into oligomers or polymers this monomer contributes 12 chain atoms. *t*-Boc-11-Aminoundecanoic acid (**5**) was prepared from 11-aminoundecanoic acid as before [6] and attached to beads (**4**) by esterification brought about using DCCI catalysed by DMAP or pyridine: see Table 1, entry 1. The amount of bound acid (**5**) was estimated from the gain in weight of the beads. The *t*-Boc protecting group was removed by reaction with TFA and the cyclo-oligomerisation was carried out by suspending the beads in DMF containing DIEA at 20°C for 7 days. Kaiser tests [25] for the presence of free *p*-amines in the beads indicated that the aminolysis reactions needed this length of time to proceed to completion. Syntheses were also carried out using TEA in place of DIEA and in some cases the excess of base and the TFA salt were washed from the beads before they were set aside to allow the cyclisation to proceed. All these reactions produced essentially the same results so, as in previous studies [13, 17], for convenience the cyclisations were carried out in the presence of the excess base. Some difficulty was experienced in extracting the products from the beads and TFA was used as a cosolvent in order to disrupt the hydrogen-bonding interactions between the products and so enhance their solubilities. Even so the main fraction (DMF-soluble) isolated corresponded to a yield of only 31%. The g.p.c. analysis of this fraction indicated that it consisted almost entirely ($>$ 95%) of cyclic oligo(undecanamide)s (**1**). The proportions of these cyclics, by weight, were: the monomer 1.2%, dimer 50.3%, trimer 37.1%, tetramer 7.1%, pentamer 2.7% and hexamer 1.6%. In support of this the f.a.b.m.s. displayed peaks for all these six cyclic oligomers. The minor fraction isolated (DMF-insoluble but soluble in TFA–chloroform) corresponded to only a 14% yield. By elemental analysis it had an average degree of polymerisation of 120. Linear nylon 11s of DP $>$ 20 are almost certainly insoluble in TFA–chloroform [6] so, since cyclics are more soluble than the corresponding linears [6], a major part of this fraction is almost certainly cyclics with a significant proportion being rings larger than the hexamer. The cyclic dimer (**1**; $n = 2$) was reported by Rothe to be the main cyclic product from a related PS reaction system using a different type of active ester linkage, and it was also reported that cyclic oligomers up to the hexamer were present but few other details were given [16].

The next substrate studied was the 6-aminohexanamide–methionine derivative (**6**): see Table 1, entry 2. This was prepared as described in the experimental section. It was bound to the polymer beads (**4**) and cyclo-oligomerised using the same procedure as that described in the preceding example. In this case the amount of material recovered from

Table 2
Cyclo-oligomerisation of polymer-supported acid (**7**):[a] composition of cyclic oligomer (**2**) fractions[b]

Loading of acid (**7**) (mmol g^{-1})	Monomer	Dimer	Trimer	Tetramer	Pentamer	Hexamer	Heptamer	Octamer	Higher oligomers
0.27	59.3	21.7	10.3	4.6	1.7	1.0	0.6	0.2	0.6
0.59	30.1	33.0	18.2	9.2	4.1	2.5	1.4	0.6	0.9

[a] Reaction are those summarised in Table 1, entries 3 and 4.
[b] Analysis made by GPC. Figures given are the wt% of each cyclic oligomer in the cyclic functions.

the beads accounted for only 28% of the starting monomer. It was exceedingly insoluble but gave an *FT*i.r. spectrum consistent with it being cyclic oligomers (**10**) and in support of this the f.a.b.m.s. displayed clear peaks corresponding to the presence of all the cyclic oligomers from the monomer to the pentamer. In view of the small amount of material produced and its very poor solubility no further work was carried out on this material.

The poor solubilities of the above cyclic oligomers is due to their abilities to hydrogen-bond extensively. This prompted a study of the substrate (**7**), which has an ester linkage in the centre of the molecule and contains a total of 24 chain atoms. In this case the final cyclic oligomers (**2**) will have half the linkages between the hydrocarbon segments amides and half esters. Compound (**7**) was synthesised as described before [6] and was then bound to the polymer beads and subject to cyclo-oligomerisation using the procedures discussed above. In this case experiments were carried out at two different loadings: see Table 1 entries 3 and 4. In both cases the cyclic products were extracted easily with hot chloroform and the yields were 48% and 44%. The extractions were carried out without the use of TFA, because it was feared might it react with the ester linkages and thus open the rings. It should be noted here that however large the ring is it is only necessary for one ester linkage to react to transform the cyclic molecule into a linear molecule. They may, therefore, be particularly sensitive. As we have prepared and characterised the cyclics (**2**) and their linear analogues (**11**) before [6] the present products were easily characterised. The g.p.c. showed that in both cases the products were respectively 91% and 94% cyclics (**2**) and that the rings ranged in size from the unimer to at least the dodecamer. The rest of the extracted products were linear oligomers. The proportions of the cyclic

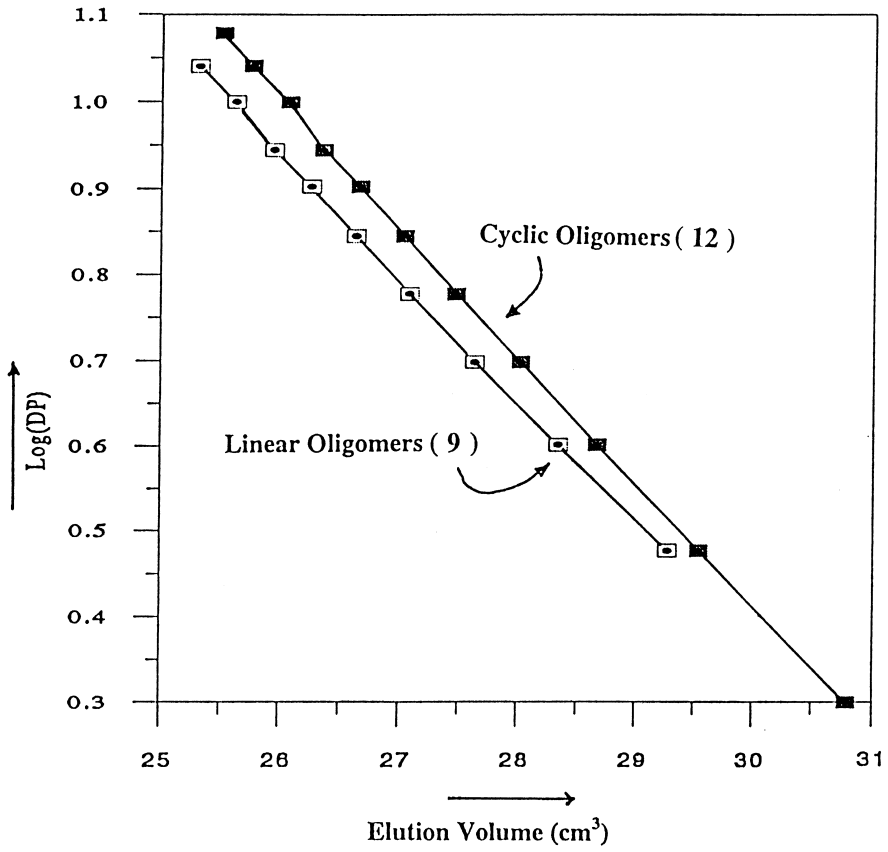

Fig. 1. Plots of log DP versus Elution Volume for cyclic oligomers (**12**) and linear oligomers (**9**). The g.p.c. conditions are as given previously [6].

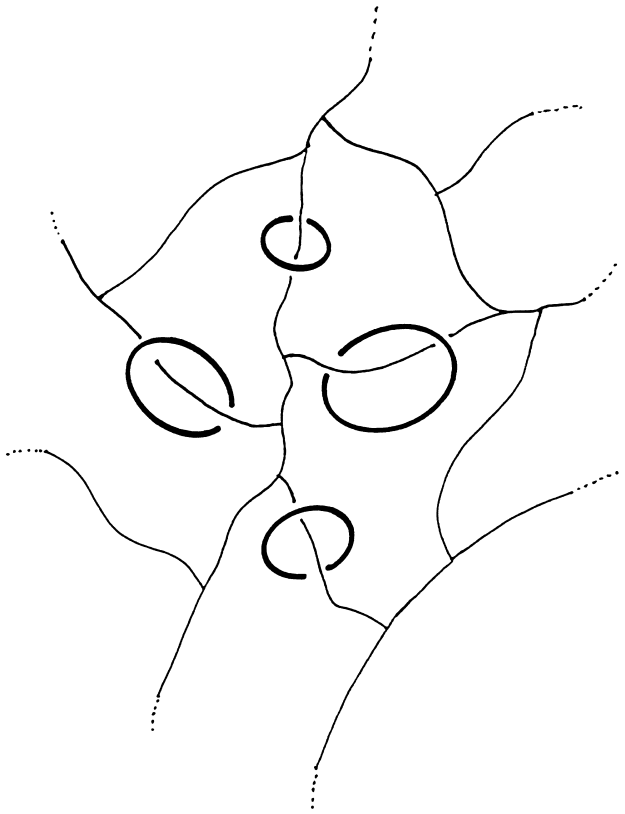

Fig. 2. Scheme showing how cyclic oligomers (———) may be trapped on a polystryrene network (———).

products at the two loadings are summarised in Table 2. It is evident that the reaction carried out at the lower loading gave a significantly higher proportion of the cyclic unimer (24 ring atoms) thus suggesting that there was some 'site isolation' [8–10]. The f.a.b.m.s. of the present products confirmed the presence of cyclics from the unimer to at least the hexamer. It is interesting to note here that the rings produced in these syntheses are particularly large, the cyclic dodecamer, for example, has 288 ring atoms.

Finally we prepared the substrate (**8**), which contains an ester linkage in the centre of the molecule and a total of 14 chain atoms, and investigated the cyclo-oligomerisation: see Table 1 entry 5. In this case the yield of cyclic products extracted from the beads with hot chloroform was only 29% but by g.p.c. analysis it was entirely cyclics (**12**) ranging in size from the dimer to at least the decamer. The composition by weight was: cyclic dimer 1.6%; trimer 28.6%; tetramer 42.3%; pentamer 20.1%; hexamer 4.9%; heptamer 1.2%; octamer 0.4% and higher oligomers 0.9%. The f.a.b.m.s. clearly indicated the presence of cyclics from the unimer to the decamer: the latter having 140 ring atoms. To further assist the characterisation linear oligomers (**9**) were prepared by reaction of the benzyl ester of 6-aminohexanoic acid with 6-bromohexanoyl chloride, debenzylation of the product, followed by polymerisation under phase transfer conditions [26]. Having available the linears and cyclics allowed a plot of 'log DP' versus 'g.p.c. elution volume' to be made, see Fig. 1, thus facilitating identification of the cyclic peaks in the product from the PS reaction. In the range studied the displacement between the linear and cyclic plots for a given elution volume ranges from 0.043 to 0.065 'log DP' units corresponding to (DP ring)/(DP linear) ratios of 1.10 to 1.16. For cyclic dimethylsiloxanes a value of 1.26 was predicted and a value of 1.24 found [27]. With the cyclics (**2**) and linears (**11**) the value was ca. 1.20 [6].

The cyclic oligomers (**12**) are amide–ester analogues of the cyclic nylon 6s prepared by Rothe [17]. Rothe in his work, using a different active ester support, *isolated* the cyclic nylon 6 oligomer with 280 ring atoms [17] and detected nylon 6s with up to 320 ring atoms [16]. The present synthesis of cyclic oligomers (**12**) produced smaller, but still large, rings. It is possible that with more amide residues present hydrogen-bonding in a 'β-sheet' arrangement assists the formation of relatively large rings.

It will have been noted that the yields of cyclic oligomers extracted from the above PS reactions account for only 48% or less of all the bound monomers used. The question therefore arises as to the fate of the rest of the monomers. The weights of the recovered polymer beads indicated that they contained material corresponding to 25–48% of the original bound monomers: see Table 1. Consistent with this the *FT*i.r. spectrum of the beads used to prepare cyclic oligomers (**1**) displayed a strong carbonyl band due to amide linkages and the spectrum of the beads used to prepare oligomers (**2**) had both strong ester and amide carbonyl bands. In neither case were there detectable bands due to active-ester linkages or *t*-Boc groups. In agreement with this no material was released when each set of the beads were treated with benzyl amine, i.e. when any remaining active-ester linkages were cleaved. Thus, in each case the beads contain a substantial amount of oligo- or polyamide and this may be cyclic or linear. The material in the beads may be trapped for one or more of the following reasons.

First, they are sufficiently large linears that they are insoluble, even, in the case of simple polyamides, in the presence of hydrogen-bond breakers such as TFA.
Secondly, they are sufficiently large cyclics that they are insoluble.
Thirdly, they are large cyclics which are topologically trapped by being wrapped round the network: see Fig. 2.

In support of the last it is known that forming networks in the presence of rings can trap a significant fraction of the rings, especially if the rings are large [28]. The rings may become trapped even more efficiently when they are actually generated within the network as they are in this present case. We are currently seeking to solve this problem by preparing networks that can be degraded so as to release trapped material [29, 30].

4. Conclusions

Cyclic oligoamides and alternating oligo(amide–ester)s have been prepared by the novel polymer supported method outlined in Scheme 1 in yields ranging from 28–48%. In the case of the synthesis of cyclic oligo(undecanamide–undecanoate)s the cyclics obtained ranged in size up to ones having at least 288 ring atoms. The polymer beads recovered at the end of the syntheses contained oligo- and/or poly-amide material accounting for 25–48% of the bound starting monomers. The nature of this material is unclear but a significant fraction may be large cyclics wrapped round the network. Experiments to clarify this last point are in hand.

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