POLYMER-SUPPORTED SYNTHESES OF CYCLIC OLIGOMERS

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by

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ABSTRACT

This Thesis discusses the polymer-supported synthesis and characterisation of various cyclic oligomers such as esters, amides, and ester-amides. In order to study and make use of polymer-supported cyclo-oligomerisations, a number of polymer supports and monomers were first prepared.

Cyclic esters of ω-hydroxyalkanoic acids were prepared in good yield (30-65%) starting from Amberlyst 26 (bicarbonate form) and the ω-bromoalkanoic acid, from polymer-supported DBU and the ω-bromoalkanoic acid, or from a *para*-nitrobenzophenone oxime resin and the ω-hydroxyalkanoic acid. A careful investigation was carried out in order to understand the complicated processes involved in the cyclo-oligomerisation of ω-bromoundecanoic acid on Amberlyst 26 resin. The results indicate that the cyclic oligomers are actually formed from cyclo-depolymerisation reactions of linear polymers formed in the beads. Thus, high yields of cyclic oligoesters were observed by GPC in the Amberlyst 26 (bicarbonate form) catalysed cyclo-depolymerisation of linear polyesters. Improvements in the synthesis were achieved by the use of polymer-supported DBU and by the use of a *para*-nitrobenzophenone oxime resin. However, the formation of linear products was not avoided in either method. Thus, the reaction conditions still need to be further optimised.

Pure cyclic amides were prepared by using 4-hydroxy-3-nitrobenzoylated polystyrene, or preferably by using a *para*-nitrobenzophenone oxime resin. The poor solubility of the cyclic amides posed difficulties both for separation and for analysis. This prompted a study of the more soluble cyclic amide-esters. The cyclic amide-esters were obtained in 30-60% yield. Most of the products obtained were nearly free from linear oligomers. In both these types of cyclo-oligomerisations products were observed to be still remaining in the recovered beads. The nature of this part of the products was not clearly understood, though various experiments suggest that it is, at least in part, cyclic oligomers topologically trapped in the network of the beads.

GPC was used as the major analytical tool in this thesis. It proved to be extremely powerful and useful to identify and analyse the mixtures of cyclic and linear products.

In summary, cyclo-oligomerisation on polymer supports is an effective and easily carried out procedure for the synthesis of products rich in cyclic oligomers. It might provide a feasible way to prepare medium to large ring cyclic oligomers.

DECLARATION

This Thesis is submitted to the Faculty of Science for the Degree of Doctor of Philosophy at the University of Manchester, England, UK. It represents the author's research work carried out in this University from October 1992 to September 1995.

All the data and spectra presented in this Thesis are entirely authentic and original unless stated otherwise. No portion of this Thesis has been submitted in support of an application for any other degree or qualification of this or any other university or institute of learning.

NOTES ON COPYRIGHT

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PREFACE

The author graduated with a B.Sc. from the Department of Chemistry, University of Wuhan, Hubei, the People's Republic of China. He was awarded an M.Sc. in Polymer Chemistry three years later at the same university. He was then employed at Wuhan University for five years, first as an Assistant Professor and then as a Lecturer. Since August 1992, he has been enrolled as a full-time Ph.D. student carrying out research in the Department of Chemistry, University of Manchester, under the supervision of Professor P Hodge.

To my parents,
My wife, Weixiang,
and my lovely son, Sida

ABBREVIATIONS

1. General.

Boc	t-Butoxycarbonyl
BPA	Bisphenol A
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCC(I)	Dicyclohexylcarbodiimide
DCU	N,N'-Dicyclohexylurea
DIEA	Diisopropylethylamine
DNA	Deoxyribonucleic acid
DMF	N,N-Dimethylformamide
DP	Degree of polymerisation
DSC	Differential Scanning Calorimeter/Calorimetry
DVB	Divinylbenzene(s)
Ms	Methanesulfonyl
Phe	Phenylalanine
PEG	Poly(ethylene glycol)
PNP	*para*-Nitrophenol
Py	Pyridine
SBI	Spirobiindane
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

2. Monomers.

Aha	6-Aminohexanoic acid (6-aminocaproic acid)
Aua	11-Aminoundecanoic acid
Hha	6-Hydroxyhexanoic acid

Hua	11-Hydroxyundecanoic acid

3. Polymer supports.

PHNB-1	4-Hydroxy-3-nitrobenzoylated polystyrene(first preparation)
PHNB-2	4-Hydroxy-3-nitrobenzylated polystyrene
PHNB-3	4-Hydroxy-3-nitrobenzoylatedpolystyrene (second preparation)
PHPS	4-Hydroxyphenylthiomethylated polystyrene
PNO	*para*-Nitrobenzophenone oxime resins
SX1-beads	Polystyrene beads crosslinked with 1%DVB
SX2-beads	Polystyrene beads crosslinked with 2% DVB
PS-DBU	Polystyrene supported DBU with 1% DVB

4. Description of Nuclear Magnetic Resonance (NMR) spectra.

b	broad
d	doublet
m	multiplet
q	quartet
s	singlet
t	triplet

5. Mass spectra.

MS	Mass spectrometry
CI	Chemical ionisation
FAB	Fast atom bombardment
MALDI	Matrix assisted laser desorption ionisation

CHAPTER 1

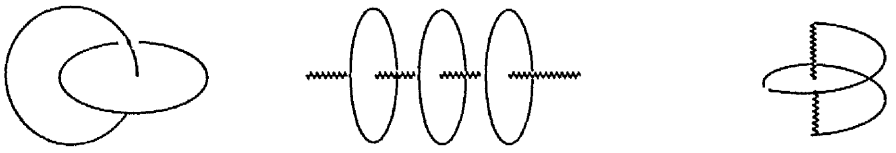
GENERAL INTRODUCTION

1.1 NOVEL POLYMER ARCHITECTURES

1.1.1 Some Novel Polymer Structures and Their Natural Occurrence

Over the last 50 years synthetic polymers based on long chain molecules have been studied intensively and countless synthetic polymers of this type have been developed for commercial applications. The chain-based polymers have three principle types of structure, i.e. linear, branched and crosslinked. Diversity of element and bond type results in a wide variety of polymers with different structures and properties.

By introducing cyclic units the variety of polymer structure types is increased significantly. For example, the cyclic units could be bound together, bound to linear units covalently, or bound to linear units physically. Cyclic units bonded together covalently form multicyclic supramolecules; cyclic units bonded physically together form catenanes, chain mails and knots; and cyclic units threaded onto chain units form rotaxanes. Recently, cyclic polymer-based supramolecular structures have been forming an interesting focus in so-called 'supramolecular chemistry'.



Catenane Polyrotaxane Knots

Figure 1.1 Cyclic polymer-based polymer supra-structures.

Cyclic macromolecules of topological interest actually exist in natural biosystems. A particularly important example is cyclic DNA. DNA is the genetic material of living organisms. It exists as a double-helix in which two complementary strands of DNA wrap round each other. Cyclic DNA has evolved in Nature to ensure the faithful duplication of a particular type of DNA. Because of the double-helix structure, a double-stranded cyclic DNA that contains no interruptions in its strand can be viewed as two multiply-

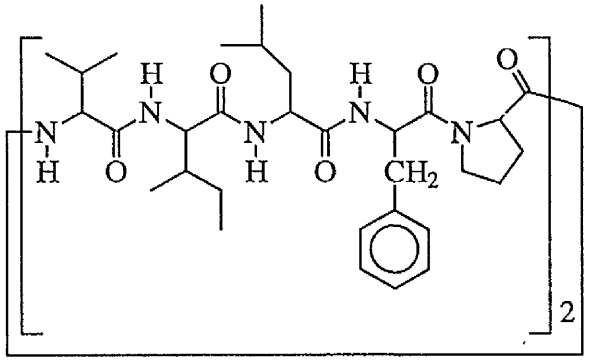
intertwined single-stranded rings. The first hint of the existence of circular DNA came from a genetic analysis in 1961.[1] When a large number of genes of the bacterium *Escherichia coli* were determined by gene crosses, the genes were found to form a single circular linkage map. Other studies indicated that the single-stranded DNA from bacterial virus(phage) ØX174 has no ends and is, therefore, also cyclic.[2] Sequencing work also confirmed the cyclic nature of the sugar-phosphate chain.[3,4] Since then, experimental results from electron microscopy and from biochemistry have shown that cyclic DNA is widely present in Nature and that all bacteria possess ring-shaped DNA.[5] Furthermore, catenated and knotted DNA rings also have been identified.[6]

Cyclic peptides and peptidomimics are another interesting class of cyclic biological molecules found widely in both animals and plants.[7] They perform a variety of biological roles, for example, as hormones, toxins, antibiotics, complexing agents and ionophores. Interest in cyclic peptide research began nearly 40 years ago when the cyclic decapeptide antibiotic gramicidin-S (see Figure 1.2) was discovered.[8] Since then the synthesis and modification of natural cyclic peptides has formed a very active area of protein biochemistry.[9] The interest has also involved studies of cyclodepsipeptides. In these compounds some of the constituent units are hydroxyacids rather than amino acids. Accordingly the building blocks are linked together both by ester and by amide bonds in the ring. A well-known example is valinomycin (see Figure 1.2), from the bacterium *Bacillus brevis*. It contains a 27-membered ring and is used as an antibiotic.

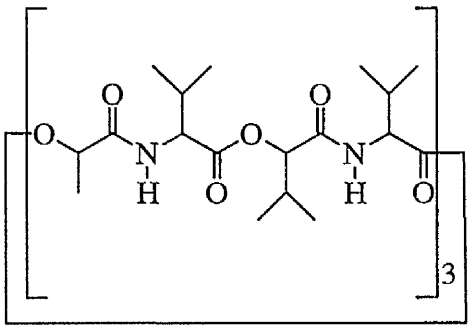
Macrolides are a further type of cyclic molecule present in many bacteria. They also have many important physiological activities. An example is nonactine. It consists of four tetrahydrofuran derivative units linked as shown in Figure 1.2.[10,11]

Cyclodextrins (CD) are cyclic oligomers of amylose consisting of 6, 7 or 8 glucose units (the α-, β- and γ-cyclodextrins respectively) which have been found in natural starch. Their function is unknown. Their cavities are 0.7 nm in depth with internal diameters of 0.45, 0.70 and 0.85 nm for α-, β- and γ-CD respectively.[12] They are able to accommodate both monomeric or polymeric guests. Therefore, they have attracted

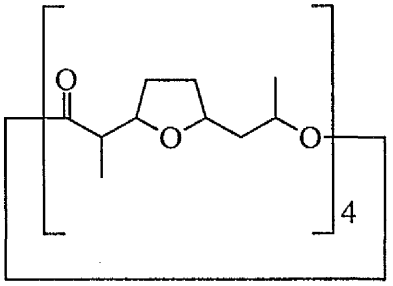
substantial interest recently and are expected to become increasingly important in supramolecular chemistry.



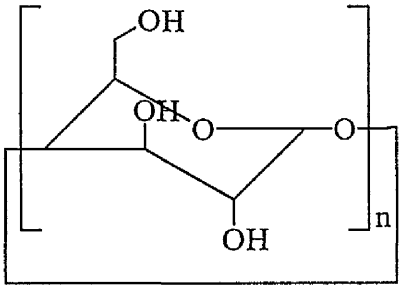
Gramicidin-S



Valinomycin



Nonactine



n = 6, 7, 8

Cyclodextrins

Figure 1.2. Cyclic oligomers in Nature.

1.1.2 Synthetic Approaches to Supramolecular Structures

It is not only because of their beautiful structures but also because of their special properties and their special functions in biosystems that macromolecules with novel topologies have been attracting chemists and biochemists for a long time.

Much attention has been focused recently on the design and synthesis of supramolecular structures.[13] Not all supramolecular polymer structures pose difficulties for the synthetic chemist. Star polymers, dendrimers and ladder polymers are classes of

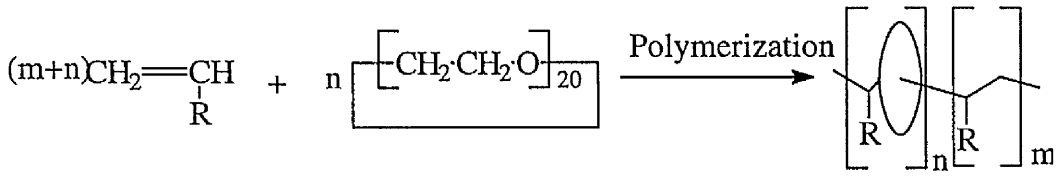
polymer which can be prepared relatively easily. However, despite dramatic progress in the last 20 years the synthesis of ring-based supramolecular structures (such as cyclic polymers and multicyclic polymers), especially those with non-covalently linked supramolecular structures (such as catenanes, mechanically linked polymers and polymer knots), still present a formidable challenge to the synthetic chemist. Obviously, classical polymerisations have little chance to produce identifiable polymers with supramolecular structures without the application of special techniques.

In the last 10 years, many new techniques have been developed and many breakthroughs have been made for the synthesis of supramolecular structures as illustrated by the examples below.

The synthesis of interlocked molecular rings, catenanes, is one of the greatest challenges in synthesis chemistry. They are probably formed in small quantities in some polymerisation reactions[14] but no separations or identifications have been possible. Stoddart *et al.*[15] have reported the synthesis and characterisation of a series of catenanes and multiply interlocked crown ether rings(olympianes) assembled from a macrocyclic polyether containing *p*-dialkoxybenzene units encircled by a tetracationic cyclophane containing bipyridinium or bis(pyridinium)ethylene units. Significant yields (20-60%) of catenanes or olympianes were obtained. More recently, Leigh[16] synthesized a new amide catenane in 20% yield in one practical step from two commercially available monomers. Many more analogous catenanes were prepared thereafter. It was believed the hydrogen bond is the driving force for this easy self-assembly of amide catenanes.

Rotaxanes and polyrotaxanes might be synthesized either by statistical threading or by molecular self-assembly. Gibson[17-19] and his coworkers have reported the synthesis of several kinds of polyrotaxanes. In their main method, to improve the threading yield, the cyclics were usually used as the solvent or cosolvent in a polymerisation. Examples are shown in Figure 1.3. Cyclodextrins threaded onto polymer main chains or side chains to form polyrotaxanes are also described in several papers.[20-23]

Polyrotaxanes have also been prepared by the polymerisation of rotaxane monomers in which the cyclics are bonded by guest-host affinity forces.[24]



R = C_6H_5– or –CN

Figure 1.3. Polyrotaxanes using a crown ether.

1.2 CYCLIC OLIGOMERS AND POLYMERS

1.2.1 Some Differences and Similarities between Cyclic and Linear Oligomers/Polymers

Cyclic polymers and oligomers are topologically distinct from their linear chain analogues and there are many differences in their properties. Thus, cyclic polymers and oligomers have no end groups. So the cyclic polymers and oligomers presumably never have traces of catalysts or initiators in their structures, while many linear polymer molecules have initiator residues at their ends. The chemistry of polymer end groups is obviously not applicable to cyclic polymers either. For instance, they cannot be crosslinked by end group coupling to form higher molecular weight molecules or networks. Neither is it possible to measure the molecular weight by end group assay.

Due to the topological difference, there are some interesting differences in the main chain reactions and the formation of polymer networks from cyclic oligomers or polymers. Thus, when a single bond is broken in a cyclic polymer, the product is quite different from those formed by random cleavage of a bond in a linear polymer: see Figure 1.4. Cyclics form chains of similar mass. By contrast, chain polymers form two smaller chain fragments, which may or may not have similar molar masses. There are similar differences when two molecules together are linked together.

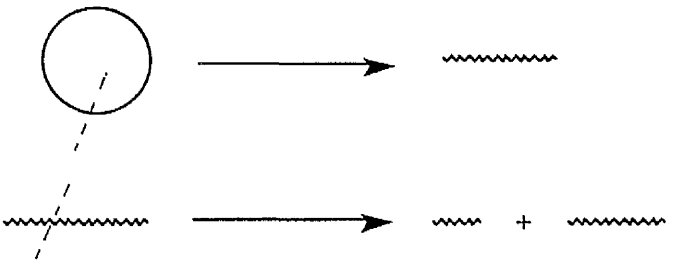


Figure 1.4. Cleavage reaction of a linear molecule and a cyclic molecule.

Many cyclic oligomers and polymers have some kind of guest-host effects. This new feature arises from the cavities resulting from the circular geometrical shape of the molecules.

Many kinds of cyclic oligomers with ester and amide bonds can be polymerised by ring-opening reactions to form huge molecules. This is attractive commercially as a means to improve the processability of many kinds of polymeric materials since the cyclic oligomers usually have improved solubility and lower melting temperatures as compared with their linear oligomers.

1.2.2 Identification and Characterisation of Cyclic Oligomers/Polymers

Currently characterisation of cyclic oligomers and polymers is largely carried out by comparing cyclic polymers with their linear analogues. The topic has been reviewed by Edwards.[25] The following are some of the more important characterisation techniques used.

Physical Properties

It has been reported that there are a lot of differences in the physical properties of cyclic oligomers and their linear counterparts, such as bulky density,[26] bulky viscosity,[27] refractive index,[26] melting point and solubility.

Nuclear Magnetic Resonance Spectra

The small cyclic oligomers of some types have unique NMR chemical shifts which change as the DP increases. This characteristic permits the identification of individual cyclic oligomers. A few examples are listed in Table 1.1

Table 1.1 Chemical shift differences of small cyclic oligomers.

NMR	Chain unit	Chemical shift (δ ppm)	Reference
^{13}C	$[OCH(CH_3)CH_2\underline{C}O]$	169.93(M_3); 169.59(M_4); 169.28(M_5); 169.21(M_6); 169.185(M_7); 169.145(M_8); 169.125(M_9); 169.105(M_{10})	28
^{29}Si	$-[(CH_3)_2\underline{Si}O-]$	-19.65(M_4); -22.01(M_5); -22.63(M_6); -22.94 (M_7); -22.99(M_8); -22.89(M_9); -22.78(M_{10});	29

End Group Analysis

The most convincing and direct method to demonstrate the cyclic nature of cyclic polymers and oligomers is the analysis of end groups. The analysis of end groups could be carried out either by just one technique or by combining several analytical techniques.

The possible techniques might be the following.

- NMR spectroscopy using, for example, the following nuclei: ^1H, ^{13}C, ^{31}P, ^{19}F, ^{29}Si.
- Mass spectrometry. For example, CI/EI-MS, FAB-MS, MALDI-MS.
- Elemental analysis, for example, for Br, Cl, S, F or I present in end groups.
- Titration of acidic or basic end groups. For example, NH_2 or COOH.
- End group reactions (both quantitative and qualitative).

Chromatography

Cyclic polymers and oligomers have different chromatographic behaviour to their linear analogues due to the differences in molecular shape and the lack of end groups.

Gas chromatography (GC) and gas-liquid chromatography (GLC) have been used in the analysis of some stable and volatile cyclic oligomers, such as cyclic oligomers of poly(ethylene glycol)[30] and polysiloxanes.[31] The combination of GC or GLC with mass spectrometer such as CI/EI-MS or FAB-MS gives very convenient and powerful techniques[32,33] but for most of research their availability is limited.

High performance liquid chromatography (HPLC) has been widely used in the analysis and separation of cyclic oligomers of polyamides[34,35] and polyesters.[36] It can provide information on cyclics with molecular weight up to about 1000 amu.

From low molecular weight cyclic oligomers to high molecular weight cyclic polymers, high performance gel permeation chromatography (GPC) is of major importance both in the identification and the characterisation of cyclic oligomers and polymers.[36] It can provide information on the molecular weight, the distribution and the cyclic content. In some cases the preparative GPC is useful for the separation of cyclic polymers from their linear analogues.

Thin layer chromatography (TLC) has also been used for the quick separation of small cyclic oligomers.[37] This technique is not widely applied, however, because of its limited efficiency and semi-quantitative nature.

1.2.3 Synthesis of Cyclic Oligomers/Polymers

1.2.3.1 Reaction methods and techniques

In general the formation of rings containing a large number of ring atoms is statistically unlikely and accordingly special reaction conditions or techniques are required to obtain large rings.

High Dilution

In a normal condensation polymerisation the cyclisation of a chain molecule is a process which is in competition with the polymerisation reaction. The formation of cyclic oligomers is the result of an intramolecular reaction (first-order kinetics), whereas polymerisation is a second-order reaction. This fact constitutes the basis of the well-known 'high dilution principle' of Ruggli and Ziegler,[38,39] which was devised to obtain higher yields of cyclic oligomers. By using low concentrations the first order reaction is better able to compete with the second order reaction.

Synthesis using high dilution techniques requires the slow admixture of reagents (*ca.* 8~24 hours or more) and/or a very large volume of solvent (concentrations of less than 5 mmol per litre). The former technique which affords the reactive intermediates in very high dilution by slow feeding of reactants is also called 'pseudo-dilution'.

Interchange Method

The fact that the thermal depolymerisation of certain condensation polymers in the presence of catalysts can give good yields of cyclic oligomers has been known since 1940 as a result of the work of Carothers and his coworkers.[40] A theory formulated by Jacobson and Stockmayer,[41] discussed in the next section, can satisfactorily predict the equilibrium concentration of each cyclic oligomer. Commonly, the type of systems studied in this way involve polyesters or polyamides.

Surface Reactions

A typical surface reaction affording high yields of medium rings was reported by Ruzicka.[42,43] In this diacids were condensed on the surface of sodium "balls" to give cyclic molecules. Improved yields, 40% to 90% for medium-sized rings, were obtained by the use of diacid esters.[44] It has been suggested that the two ends of the reactant molecules might become attached to the surface of the metal thereby bringing them into close proximity.

Biphase or Triphase Reactions

Multiphase reaction techniques which achieve 'pseudo dilution' have been developed by Regen.[45,46] In these techniques the starting materials are soluble in phase one (I), whilst the cyclisation takes place in phase two (II). If phase II is a liquid solvent phase, then suitable phase transfer catalysts may be needed to transfer reactants from phase I to phase II so that they are present at low concentrations. If phase II is a polymer-supported catalyst, the solvent might not be needed (illustrated in 1.3.2.3). By use of such techniques, excellent cyclisation yields were usually obtained.

Template Effects

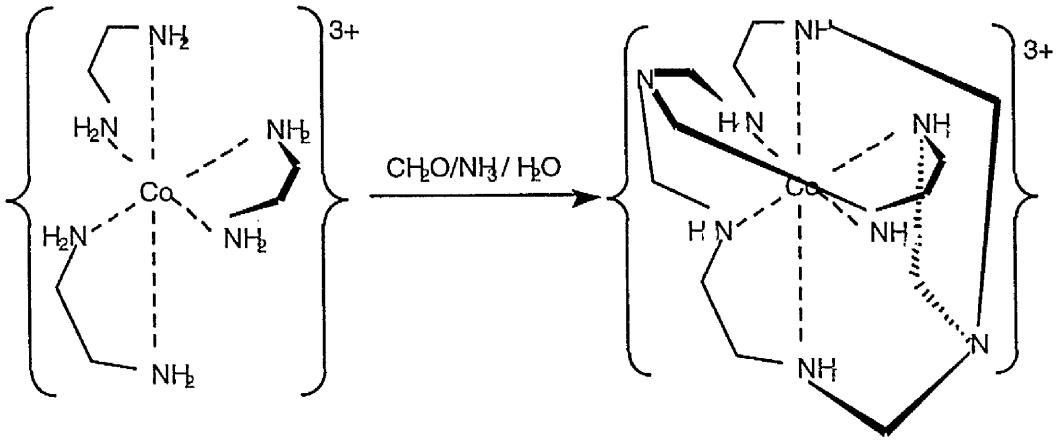


Figure 1.5. An example of a template effect by a cobalt ion.

The action of a template is to bring the reacting ends together and so favour cyclisation over polymerisation. The usual approach, as exemplified in Figure 1.5, is to hold the reactive groups in the correct orientation by means of a metal ion. In this case this encourages the multi-step cyclisation reaction illustrated. This reaction gives the tricycle containing 20 ring atoms in 95% yield.[47]

Another example of template effects which has been widely used is the preparation of cyclic poly(oxyethylene)s with molecular weight from 220 up to 20,000 in the presence of sodium or potassium ions; see Figure 1.6.[30,48-51]

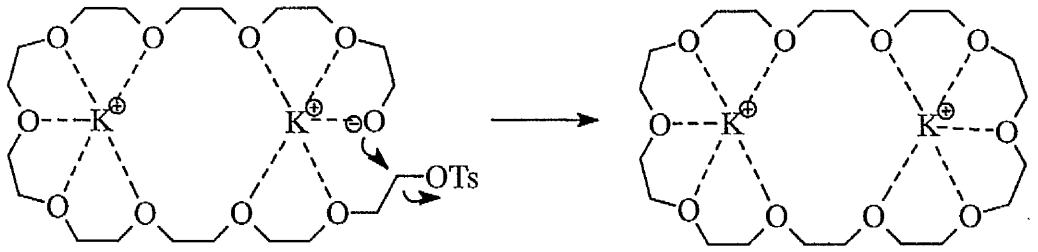


Figure 1.6. The organising power of potassium ions.

Structural Factors

There are some kinds of cyclic oligomers which can be prepared readily by polymerisation due to their structures. The drastic restriction of the conformational flexibility of parts of the oligomer chains favours ring closure for suitable conformations. This is so-called the 'rigid groups' principle. A good example is the ready formation of macrocyclic oligoalkynes as reported by Sondheimer *et al.*[52] Large sized cycloalkanes could be prepared by hydrogenation of these cyclic oligoalkynes.[53] Cyclic ester and cyclic amide oligomers containing spirobiindane (SBI) and similar structures (BPA, etc) were prepared readily in high yield (from 50 to 95%) even in relatively concentrated solutions.[54]

1.2.3.2 Jacobson-Stockmayer ring-chain equilibrium theory

Ring-chain equilibria are involved in many polymerisations and they provide a major route to certain cyclic oligomers and polymers. Semlyen has reviewed the systems which involve ring-chain equilibria.[55]

Polymerisations by both step growth reactions and chain reactions may generate equilibria of cyclic oligomers and chain oligomers or polymers. Typical examples for step growth reactions are the polycondensations of diacids with diols and of diacid dichlorides with diamines. Not only the ends of the molecules may react with each other. An end group of a molecule may also react with an internal ester or amide group or two internal ester or amide groups may react with each other by a transesterification or a transamidation reaction. In all cases, intramolecular reactions result in cyclic molecules. Ring opening polymerisation of cyclic oligomers can also establish ring-chain equilibria. Two prominent examples are the cationic ring-opening polymerisation of heterocycles and the metathesis reaction of cycloolefins. Here the active ends (i.e. the cationic species or the transition metal carbene) may react with each functional group (i.e. the heteroatom in the case of cationic polymerisation or the carbon-carbon double bond in the case of the metathesis reaction) along the chain (back-biting reaction) or with the functional group at the other end of the same molecule (end-biting reaction) to form cyclic molecules.

Many workers[56] have developed theories to apply to systems of various polymer chain types in order to allow the calculation of the distribution and equilibrium concentrations of cyclic oligomers. A well-known cyclisation theory for polymers obeying Gaussian statistics is called the Jacobson-Stockmayer theory.[41] According to this theory, the ring-chain equilibrium constant K_x of a cyclic oligomer with a degree of polymerisation x is proportional to $x^{-5/2}$.

$$K_x \propto x^{-5/2}$$

It should be noted that K_x, which it can be shown to a first approximation is equal to the cyclic concentration, is independent of the initial monomer concentration. Consequently, for each system, a maximum initial monomer concentration can be found up to which only cyclics are formed. On the other hand, ring formation can be kinetically enhanced or depressed. For example, in the early stage of cationic polymerisations, a kinetic enhancement of macrocyclic formation becomes evident if the heteroatom carrying the initiating group is much more reactive towards the growing centre than the other heteroatoms along the growing chain. Similarly, if the rate constant of the intramolecular reaction of the heteroatom carrying the initiating group to the growing end is larger than that of the addition reaction of the monomer to the growing end. A good example would be the cationic ring-opening polymerisation discussed in detail by Matyjazewski.[57]

Kinetic depression will occur if the rate of the addition reaction of the monomer to the growing end is much faster than that of any back-biting reaction. In this case, the formation of cyclics does not start before the monomer is completely consumed. Examples are the metathetical polymerisation of strained cycloolefins with low activity catalysts,[58] and the anionic polymerisation of ω-caprolactone.[59]

The Jacobson-Stockmayer theory is the first theory describing the typical ring-chain equilibrium of polymerisation and the theoretical predications of equilibrium concentrations of cyclic oligomers and polymers by this theory are in good agreement with the experimental results in many cases. However, its basic assumption is that unstrained rings formed from chains of sufficient length and flexibility obey Gaussian statistics. This limits it being applied widely. An alternative approach which is called the direct computation method makes no such assumption. It thus has wider application. This new approach has been applied successfully to calculate the concentrations of cyclics in a number of ring-chain equilibrates such as the hydrolysis of dichlorosilane of dimethyldichlorosiloxane, the oligomerisation of sodium metaphosphates and the polymerisation of ω-caprolatam.[60]

1.2.3.3 Reactions and examples

There are many ways to prepare cyclic oligomers and polymers. These can be classified by the different starting materials as follows:

- *Ring monomers*: The cyclic oligomers might be obtained from ring monomers by ring opening polymerisation by the use of a suitable initiator and conditions, or by melt polymerisation.

- *Bifunctional monomers*: Cyclic oligomers and polymers can be prepared by the polycondensation or polyaddition of bifunctional monomers.

- *Linear polymers*: Linear polymers might be cyclised by the use of a coupling reagent or be depolymerised either by pyrolysis or by catalysed depolymerisation in solution to produce cyclic polymers or oligomers.

The synthetic methods can also be classified by the different reaction types as follows.

- *Polymerisation*: Most polymerisations can produce cyclic oligomers. These include polymerisations such as metathesis polymerisation, electron transfer polymerisation, polycondensation, melt polymerisation and ring-opening polymerisation.

- *Depolymerisation*: The depolymerisation method includes the pyrolysis and catalysed depolymerisation of linear polymers in solution.

- *Polymer coupling reactions*: Coupling of the end groups might be achieved either by a coupling reagent or by activating a polymer end.

In the following sub-sections some specific examples are considered which illustrate some of the methods of synthesis mentioned above.

Polyaddition Reaction

Two interesting methods for preparing macrocyclic hydrocarbons have been described by numerous authors.[61] One is the metathesis reaction of cycloolefins, the other is the electron transfer oligomerisation of divinylidene compounds.

The metathesis reaction of a cycloolefin is a polymerisation reaction which produces cyclic hydrocarbon oligomers. A suitable catalyst is WCl_6 in conjunction with $EtAlCl_2$ or Me_4Sn. The mechanism involves the formation of a metal carbene complex which reacts with the olefin to form a metallacyclobutane intermediate and then, by decomposition of the latter, the formation of a new metal carbene complex.[62] The new carbene complex can be regarded formally as the insertion product of a cycloalkene into the metal-carbene bond. Cyclic oligomers are then formed by the back-biting reaction of a long chain carbene complex. The results obtained were in agreement with the Jacobson-Stockmayer theory as mentioned before.[63] GPC analysis of an homologous series of oligomers and polymers as generated from the tetramer of cyclododecene, $C_{48}H_{88}$, shows that no oligomer is particularly favoured although the tetramer of cyclododecene was chosen as the starting olefin. Because of the relatively large difference in molecular weight between the single oligomers, the cyclics could be separated by preparative chromatography.

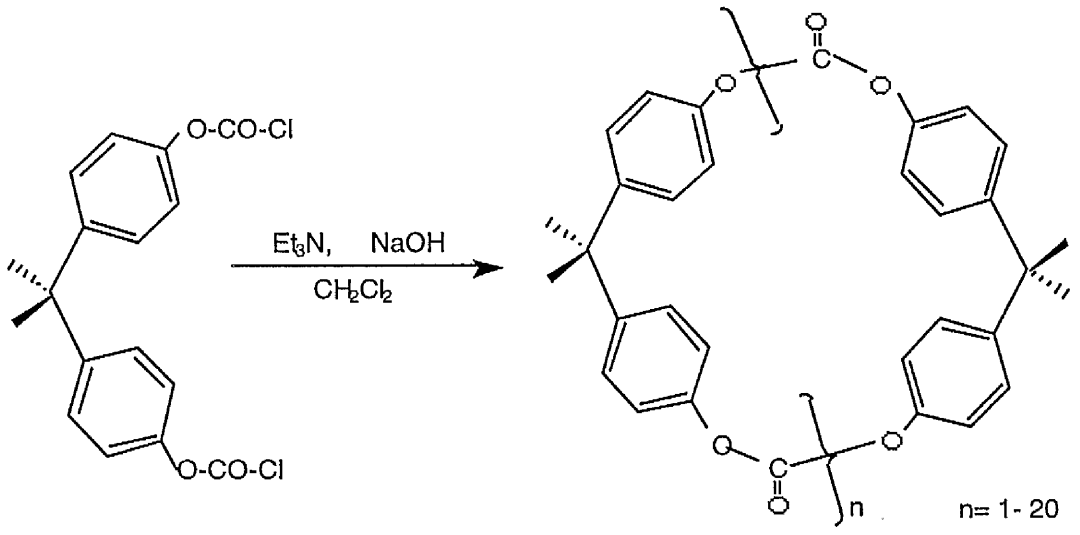
Another interesting class of cyclic hydrocarbons are the oligomers of 1,1-diphenylethene (DPE) and its analogs synthesised by electron transfer reactions as reported by Szwarc *et al.*[64] There are a lot of potential monomers for this reaction. Some of them, with a favoured geometrical structure, tend to give high yields of dimer. Others do not favour a certain oligomer and usually afford oligomeric cyclophanes with the degree of polymerisation between 2 to 6.

Polycondensation and Other Step Growth Reactions

It has been known for many years that cyclic oligomers are present in the products of most condensation polymerisations.[61,65] However, it is very difficult to isolate and purify them due to their small proportion (usually <5%) and their similarity to their linear chain analogs. In order to increase the yield of cyclic oligomers, the high dilution technique has been used frequently. Polycondensation is a useful reaction to make cyclic polyamides,[66] polyesters,[31,61] polyethers,[30,32,48] polyurethanes[67,68] and polysiloxanes.[61] Much effort has been made to look for methods to afford cyclic oligomers and polymers of these general types in high yield.

Recently, many efforts have been made to synthesize aromatic esters, especially carbonates, derived from bisphenol A (BPA) and its analogs. Brunelle[54] has reviewed the advances made recently of this kind of oligomerisation. A wide range of monomers similar to BPA and SBI have been studied and many techniques have been exploited to synthesize their cyclic carbonate esters with a view to improving the processability of polycarbonates. Generally, the cyclisation is carried out via an interfacial hydrolysis reaction of a bis(chloroformate) under pseudo-dilution conditions, with triethylamine in conjunction with sodium hydroxide as the catalyst: see Figure 1.7. The cyclic products could be obtained in as much as 95% yield. A typical distribution calculated by HPLC analysis[69] shows the formation of 5% of the dimer, 18% of the trimer, 16% of the tetramer, 12% of the pentamer, 9% of the hexamer and 10-15% of the higher oligomers and polymers. The recent mechanistic studies indicates that the cyclisation is a kinetically-controlled process.[54]

Among the BPA analogs, the spirobiindane structure is by far the most interesting unit to be used to build up cyclic oligomers with a favourable structural effect. A variety of bifunctional monomers based on SBI structure have been synthesized and employed to make cyclic oligomers containing mixed units such as amide, ester, imide and siloxane.[70,71]



bis(chloroformate)

Figure 1.7. Cyclisation polycondensation of the bis(chloroformate) of BPA.

Ring-opening Polymerisation

Ring-opening reactions are the most common method to obtain cyclic oligomers and polymers. Many commercially available cyclic monomers can be polymerised by catalysts to achieve ring-chain equilibria. The cyclic oligomers could be prepared from the cyclic monomers by cationic polymerisation[72] or by anionic polymerisation.[77] For example, cyclic monomers including ethers acetals, sulphides, amines and siloxanes (as shown in Figure 1.8) can be polymerised to give cyclic oligomers.

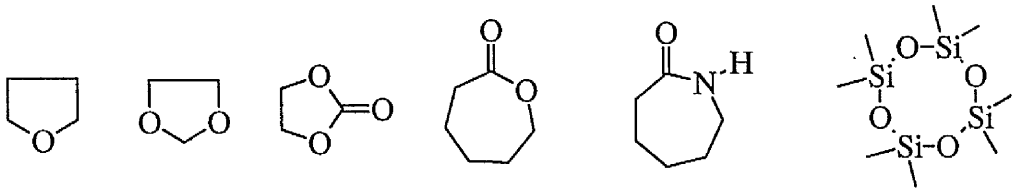


Figure 1.8. Some available types of cyclic monomers.

Synthetic aspects of macrocyclisation in cationic ring-opening polymerisation have been reviewed by Goethals[73] and Penczek.[74] Many factors influence the yields of the cyclics and the distributions. Thus, the content and distribution of the macrocycles depends very much on the monomer structure. For example, ethylene oxide and its derivatives with small substituents result in a series of cyclic oligomers starting from the dimer, while ethylene oxides with bulky substituents yield the corresponding cyclic tetramers with high preference by cationic polymerisation.[75]

It is even more interesting that different cyclic oligomers can be formed depending on the initiator used. Thus, when THF is polymerised cationically in nitromethane with CF_3SO_3H as the initiator (see Figure 1.9), cyclic oligomers from the trimer to the octamer are formed as demonstrated by gas chromatography. On the other hand, when $CF_3SO_3CH_3$ is used as the initiator, the polymerisation merely gives a small amount of the cyclic oligomers.[76]

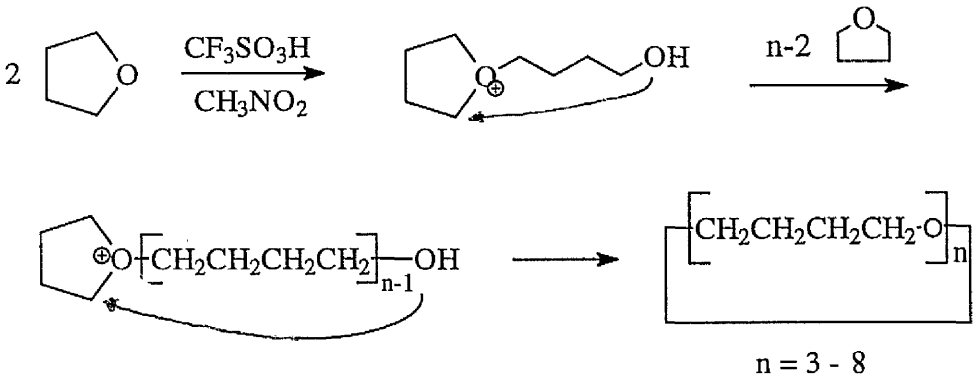


Figure 1.9. Cationic ring-opening polymerisation of THF.

Anionic ring-opening polymerisation can also afford cyclic oligomers. The yields and distributions are closely dependent on the initiator. An interesting initiator is the lithium salt of ω-caprolactam (Eclam). This can produce cyclic products effectively;[77] see, for example, Figure 1.10.

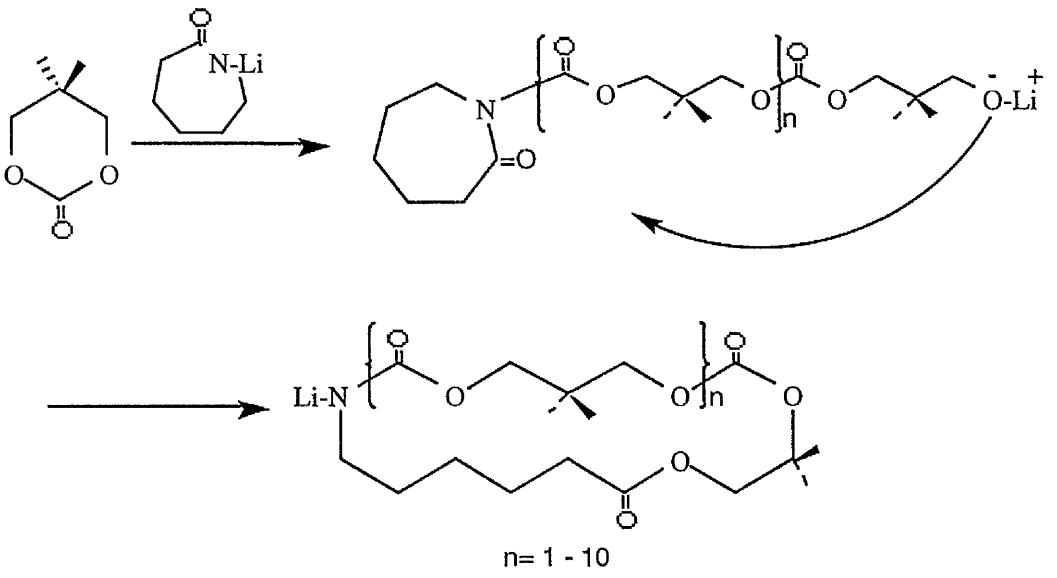


Figure 1.10. Anionic polymerisation of a cyclic carbonate initiated by Eclam-Li.

Depolymerisation Reactions

Cyclic oligomers can be prepared from a high molecular weight linear polymers either by pyrolysis or by catalysed depolymerisation in solution.

A series of papers devoted to the preparation and isolation of cyclic oligoamides of nylon 6, nylon 6-10 and nylon 6-6, appeared as early as the 1950s.[78-81] Cyclic oligomers of nylon 6 were prepared at temperatures of 800 K in the presence of water. After establishing a ring-chain equilibrium in the polymer melt, there was, on quenching, about 12% by weight of the cyclic oligomers that could be extracted from the polymer chip using hot water or boiling aqueous methanol.[82]

Cyclopolysiloxanes are also well-studied by many workers in order to show the differences in the properties between the cyclic and the linear oligomers. A mixture of cyclic oligomers can be prepared from the cyclic tetramer by melt polymerisation and can be separated by GPC.[83]

Depolymerisation of high molecular weight poly(ε-caprolactone) in solution or in bulk in the presence of catalyst (such as $Bu_2Sn(OMe)_2$) was reported by Hocker[84] to afford high yields of cyclic oligomers.

Coupling of Polymer End Groups

The coupling techniques use directly either the polymers or the polymeric ions. The coupling reactions may take place in two different ways.[85] In one way the polymer end groups can be coupled together by a coupling agent with bifunctional groups. In the other way the polymer end groups may be activated so that the two ends can be coupled together to form cyclics.

There are many bifunctional or multifunctional polymers available from which to make cyclic polymers and oligomers by coupling techniques. These include living polymer anions and PEGs.

Potassium naphthalene is an initiator used by several workers for the anionic polymerisation of styrene[86-88] to make the dianionic living polymer: see Figure 1.11. The two living polymer ends have been coupled by the bifunctional electrophile α,α'-dibromo-p-xylene to form cyclic styrenes with molecular weights as high as 450,000 as measured by light scattering method. Polysiloxane chloride[89] was also used as coupling reagent in this kind of cyclisation.

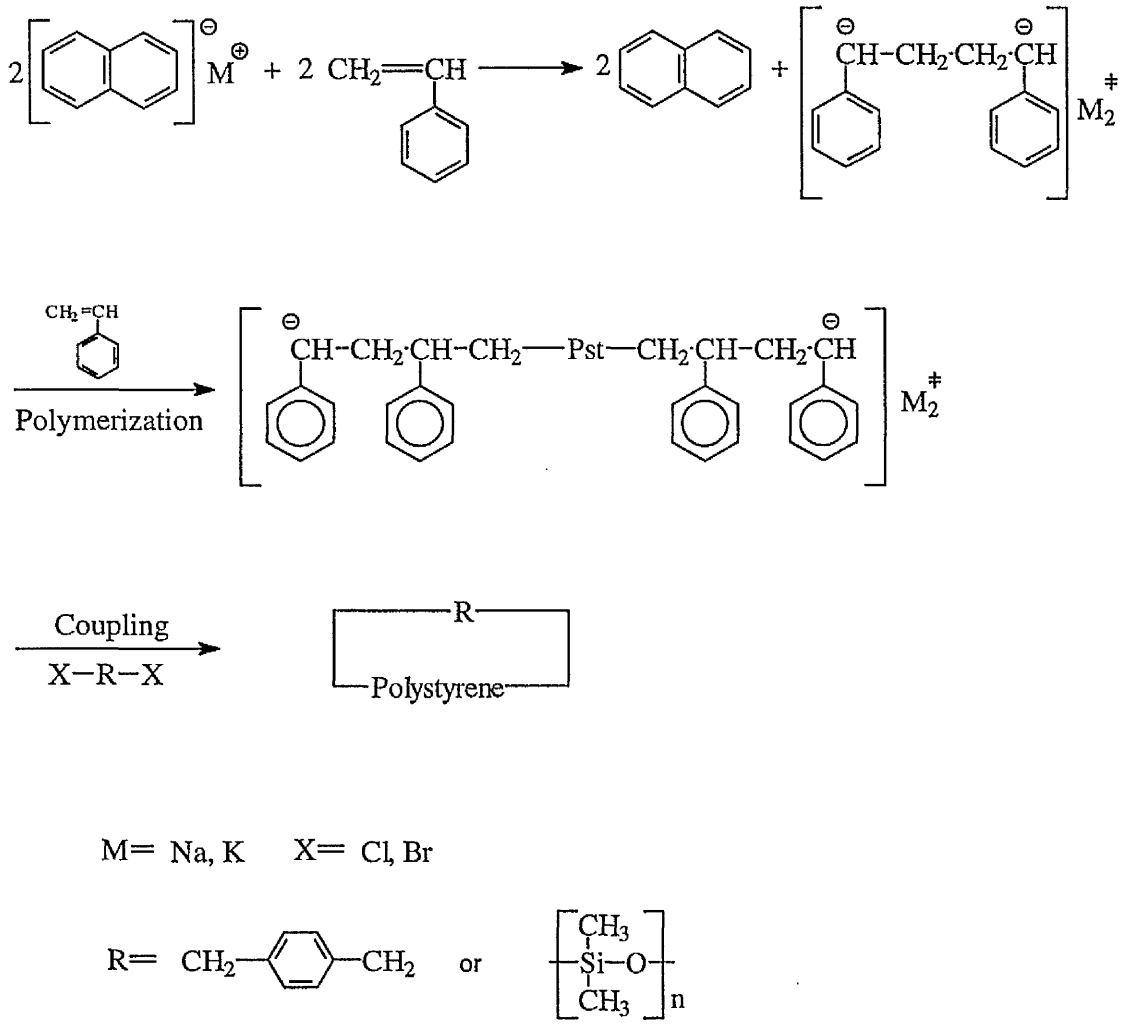


Figure 1.11. Cyclisation of dianionic polystyrene.

Many methods have been employed to activate polymer end groups to produce cyclic polymers unimolecularly.[85,90,91] In the Manchester laboratories, dichloromethane was used successfully to couple PEGs with an average molecular weight of up to 10,000. Using a pseudo-high dilution approach this gave high yields of cyclic acetal-linked PEG rings: see Figure 1.12.[49] *p*-Toluenesulfonyl chloride and sodium hydroxide were also employed by Booth[50] to activate the ends of PEGs. This produced cyclic PEGs in 50-85% yields with molecular weights of up to 20,000: see Figure 1.12.

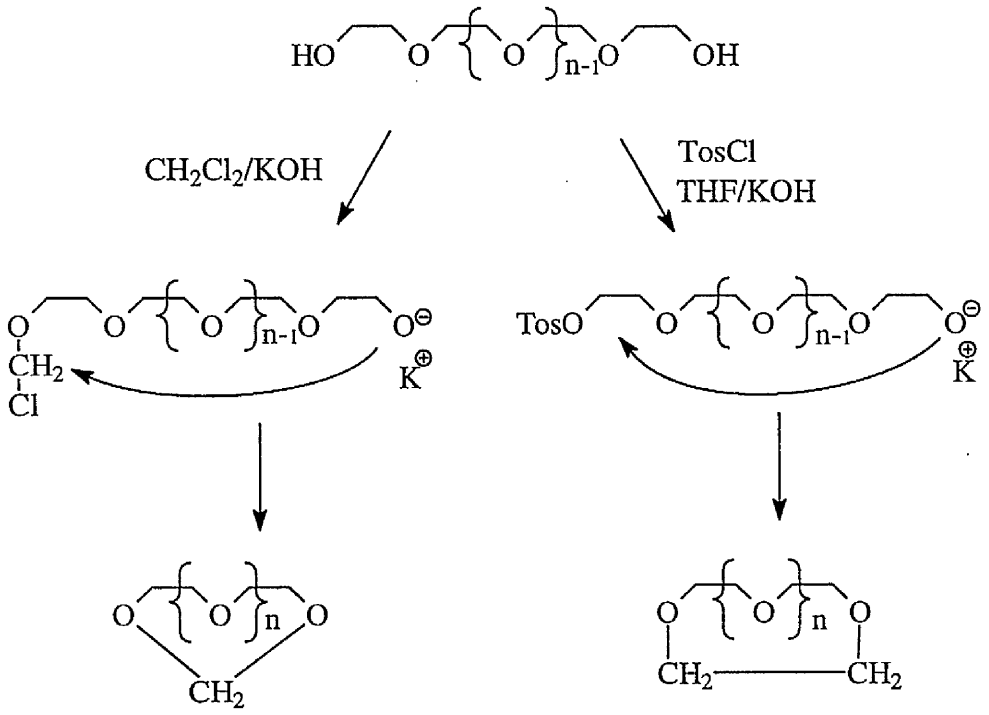


Figure 1.12. Coupling PEG end groups by different methods.

1.3 POLYMER-SUPPORTED CYCLISATIONS

1.3.1 Polymer-Supported Reactions

The idea of performing chemical reactions on polymer supports has been developed enormously since Merrifield's first reports of solid-phase peptide synthesis in 1963. Like solid phase peptide synthesis, other polymer-supported syntheses have obvious advantages. These include the following.

- Easy separation of supported and non-supported species.
- Polymer-supported species can be recovered for re-use.
- Potentially easy automation of the reaction systems.

In addition to these, there are many further characteristics of polymer-supported reactions, such as 'site isolation', steric hindrance and microenvironmental effects, which are different from reactions in solution. As a consequence of these features, polymer-

supported reactions have found many applications in organic synthesis, organic mechanistic studies and other areas.[92]

1.3.2 Polymer-supported Cyclisations

In the past 30 years, with the flourishing interest of research into the structure and function relationships of cyclic peptides, many efforts have been devoted to the development of methods which can result in the rapid and convenient synthesis of cyclic peptides. There are several advantages to be found in the use of polymer-supported cyclisations. The advantages are as follows.

(1) The site-isolation in polymer networks creates a pseudo high dilution microenvironment that can favour intramolecular cyclisation (refer to 1.3.2.1). For instance, coupling two ends of a peptide in solution to form a cyclic peptide must be performed at high dilution in order to favour the desired intramolecular reaction. In the solid phase approach, in contrast, there appears to be a reduced tendency for the interchain reactions that would result in polymeric by-products.

(2) Faster ring-closure and higher yields are obtained as compared with solution procedures.

(3) Easy separation is the most useful feature. Generally, the cyclic products are very difficult to separate from their linear counterparts. In a polymer-supported cyclisation, in favourable circumstances, the cyclisation reaction is an end-biting cyclisation that releases the cyclics into the solution while the linear species remain fastened on the resin. In such circumstances, the separation of the linears and cyclics will just involve filtration of the polymer from the cyclics in solution.

(4) The desired peptide sequence can be assembled on the polymer support first, then cyclised. Hence, the whole process can be automated or carried out without tedious practical procedures.

1.3.2.1 Site Isolation

The site isolation effect in polymer-supported reactions has been of considerable interest for many years and has been reviewed by several authors.[93-95] Initially, this kind of work was aimed at obtaining evidence on certain aspects of the nature of the solid support and in particular to answer the question of whether or not quantitative reaction between all the functional sites on the resin could be achieved. In the early period of resin-supported synthesis, it was often assumed that functional sites on lightly crosslinked poly(styrene-divinylbenzene) beads were isolated and that their reactions were analogous to reactions in solution at high dilution.[96,97] It was demonstrated by many authors that, for example, intramolecular oligomerisations could more favourably compete with intermolecular (intersite) oligomerisations on resins compared with the same reactions carried out in solution at similar concentrations.[97] In special cases, there has been evidence of site isolation for a long time.[48,98]

Many authors have devoted time and effort to quantifying site-site interactions. To what extent, for example, is it a function of the polymer morphology and the level of loading and how complete can it be? In Table 1.2 a few examples are listed. The results show that in general intersite reactions can occur readily even with a very low loading of substrate. It has become more and more clear, however, that site-site interactions can occur readily and that successful site isolation is usually a kinetic phenomenon.[99,101-103] The distribution of products depends on the relative rates of the competing reactions and this depends on many factors, for example, on the rates of diffusion of solutes into the beads and on the mobility of the polymer chains. In the presence of very rapid intramolecular reactions or reactions with soluble reagents very little site-site interaction usually occurs, but with slower reactions or in the absence of competing reactions the site-site reaction dominates. The most influential factors are summarised briefly in Table 1.3.[104-106]

Table 1.2. Quantitative experiments estimating the extent of intersite reactions.[a]

Loading (mmol/g)	Site-site reaction	Yield (%)	Reference
1.0	–COOH converted into anhydride	80	99
0.5	–SH oxidised to disulfide by Fe^{+3} and air	75	100
0.05	–COOH converted into anhydride	53	100
0.01	$-CH_2Cl + HS(CH_2)_4SH$	94	101

[a] All polymer supports used were lightly crosslinked (typically 1% or 2%) gel-type polystyrene resins. Yields refer to intersite reaction yield.

Table 1.3. Factors favouring intra-site reactions and inter-site reactions.

	Intra -site reactions	Inter -site reactions
Functionality:	low loading	high loading
Support:	high crosslinking	low crosslinking
	rigid backbone	flexible backbone
	short rigid spacer if any	long flexible spacers
	non-swelling or charged substituents	extensive swelling
Reaction:	rapid reaction	slow reaction

There is no clear line dividing between when and when not intra-site reactions can take place efficiently. To perform an intra-site cyclisation, a quick reaction, a highly crosslinked support, and a few more favouring conditions should be adopted to minimise the inter-site reaction. On the other hand, to carry out a cyclo-oligomerisation which

needs site-site interactions to achieve oligomerisation, a slow reaction, and a lightly crosslinked support would be helpful.

1.3.2.2 Polymer-supported Lactamisation

There are two common strategies used to perform cyclisations on resins. These are outlined in Figure 1.13. Most cyclisations involve solid peptide synthesis. Strategy A involves the following reaction steps.

- Side-chain anchoring.
- Stepwise solid phase assembly of the linear peptide sequence, protecting functional groups as necessary.
- Orthogonal deprotection to liberate selectively the two end groups.
- Efficient activation of one or both end groups.
- Carrying out the cyclisation reaction.
- Detaching the cyclic product.

This strategy mainly used in the synthesis of cyclic peptides. The cyclisation may occur between side chain and side chain of amino acids such as by bisulfide bridge formation,[107,108] or between the N-terminal residue and a side chain,[109] or between the N-terminal residue and the C-terminal residue (so-called head-to-tail cyclisation). The last has been developed only a few years ago and is quite successful as many papers report.[110] In these approaches, the polymer support is usually a modified Merrifield resin[111,112] such as *p*-alkoxybenzylamide (PAM), *p*-alkoxybenzyl alcohol (PAC),[110] *p*-tris(alkoxy)benzylamide (PAL).[112,113]

Strategy B is an end-biting cyclisation involving a reactive anchoring end. Such a synthesis may include the following steps.

- End-anchoring of the C-terminal of an appropriate amino acid or peptide.
- Assembly of the desired peptide sequence using Merrifield procedures.

- Efficient activation of the C-terminal residue.
- Deprotecting the N-end, thus freeing the amino group.
- Head-to-tail cyclisation to form the desired cyclic product which is thus released from the resin into the solution.

This strategy has been successfully employed in practice using Fridkin's active hydroxyl resin,[96] Flanigan and Marshall's safety-catch method[114] and, more recently, Kaiser's oxime resin[115]: see Figures 1.14 and 1.15.

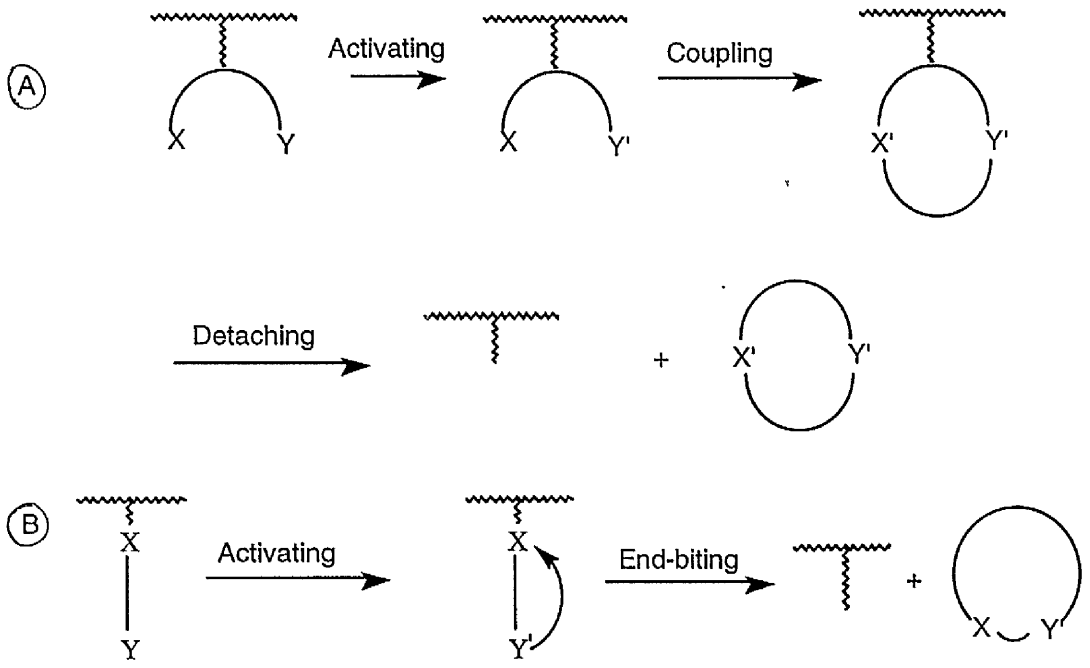


Figure 1.13. Strategies for carrying out cyclisations on a resin.

In Fridkin's method, the protected peptide fragment is attached through the carboxylic acid moiety of the peptide to the phenolic hydroxyl group to a 4-hydroxyl-3-nitro-polystyrene resin ('A' in Figure 1.13), the N-terminal is deblocked, cyclisation occurs and the cyclic peptide product is released from the support. Their studies have shown that many small peptide fragments can be cyclised successfully on the resin in good yield. However, due to the high reactivity of the ester linkage the use of this resin permits no assembling of a peptide on the resin and it is very difficult to efficiently attach

the peptide fragment to the support. The latter means that it may be necessary to use an excess of the possibly valuable peptide to get a reasonable loading.

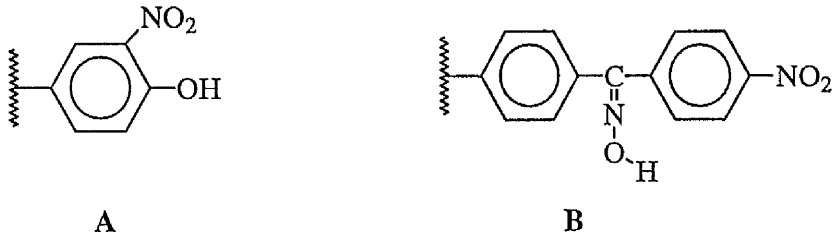


Figure 1.14. Fridkin's active hydroxyl resin (A) and Kaiser's oxime resin (B).

Flanigan and Marshall's method is similar to Fridkin's, but the ester linkage binding the peptide to the resin is only activated immediately prior to the cyclisation: see Figure 1.15. Activation is achieved by oxidising the thioether moiety into a sulphone moiety.

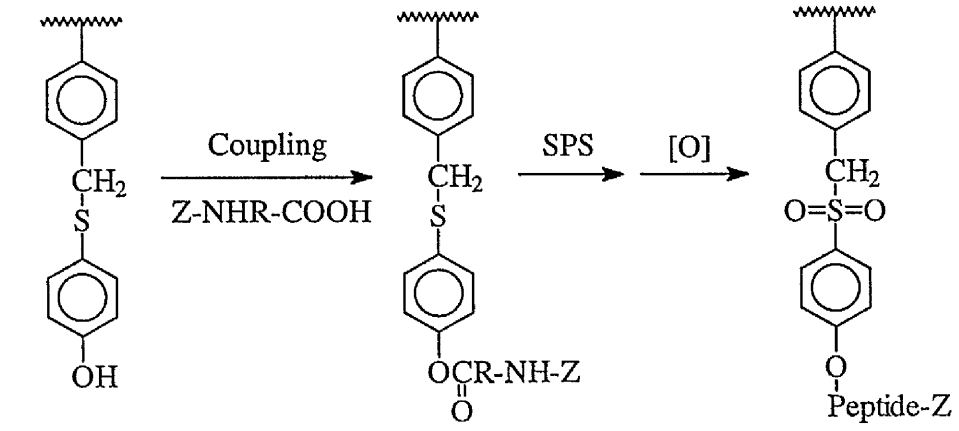


Figure 1.15. The "safety-catch" method by Flanigan and Marshall.

Kaiser's oxime resin provides a good balance between reactivity and practical use. It allows the peptide sequence to be assembled on the resin first. Then, after deprotecting the N-termini, cyclisation occurs on the resin to release cyclic peptide. It has been demonstrated to be a very successful support.[116,117]

1.3.2.3 Polymer-supported Lactonisation

Many efforts have been devoted to obtaining cyclic macrolides by the use of polymer-supported reactions.

Unsubstituted polystyrene beads in the presence of boron trifluoride were used by Scott[118] to assist the macrolactonisation of ω-hydroxyalkanoic acids (from 12 to 18 carbon atoms). The obtained yields were from 43-84%. It is not clear why this approach should be successful.

A polymer-supported bis(diphenylphosphino)ferrocene-$PdCl_2$ catalyst (abbreviated to Pddp-$PdCl_2$) was prepared by Stille *et al.*[119] and was used to catalyse the formation of large-ring keto lactones having from 9 to 27 carbon atoms: see Figure 1.16. Medium yields (30-70%) were obtained in most of the reactions studied.

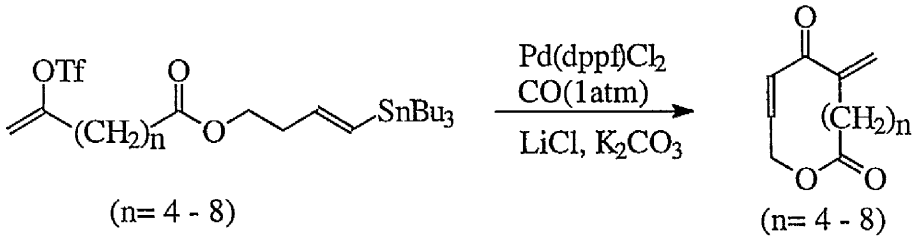


Figure 1.16. Polymer-supported "Palladium" as a ring closure catalyst.

A mixture of polymer-supported triphenylphosphine and diethyl azodicarboxylate (DEAD) was reported by Amos[120] to bring out the lactonisation of hydroxycarboxylic acids: see Figure 1.17.

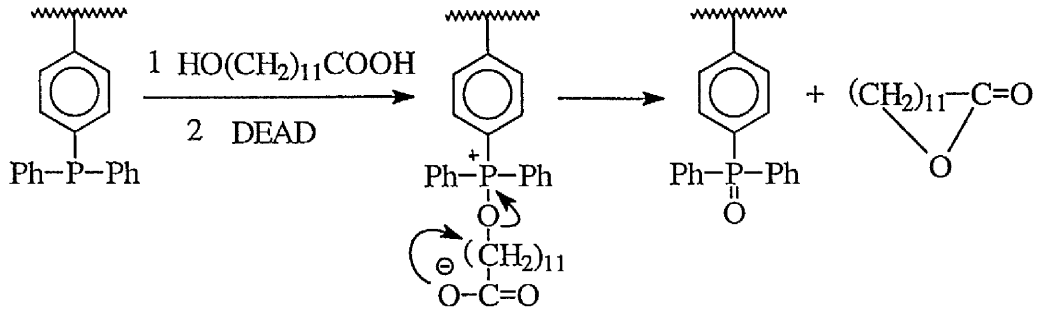


Figure 1.17 Lactonisation using a polymeric diphenylphosphine.

Regen[121] has reported that a 1% crosslinked polystyrene gel bearing quaternary phosphonium residues as a triphase catalyst, catalyses the lactonisation of the mesylates of ω-hydroxyl acids having from 11-14 carbon atoms. The reaction system is illustrated in Figure 1.18. The lactones were obtained in yield 47-72%. It was suggested that the site-isolation effect was involved in the formation of the big ring lactones.

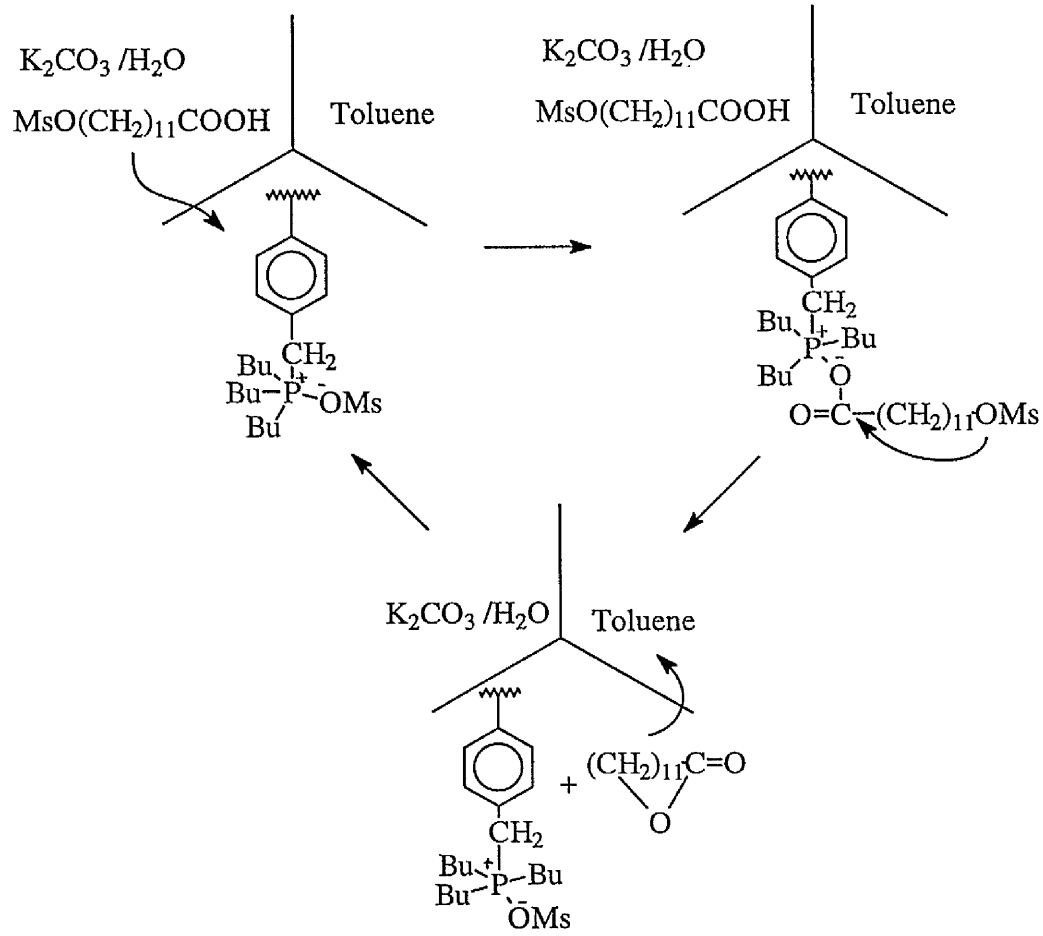


Figure 1.18. Lactonisation using a polymer-supported phase transfer catalyst.

Cyclisations of 12-hydroxydodecanoic acid on polymeric supports have been studied by Ford[122] using thiol ester activation in the presence of Hg^{2+} ions (as shown in Figure 1.19). The best yield of the simple lactone was 13%. The cyclic dimer was formed in a yield of 19%.

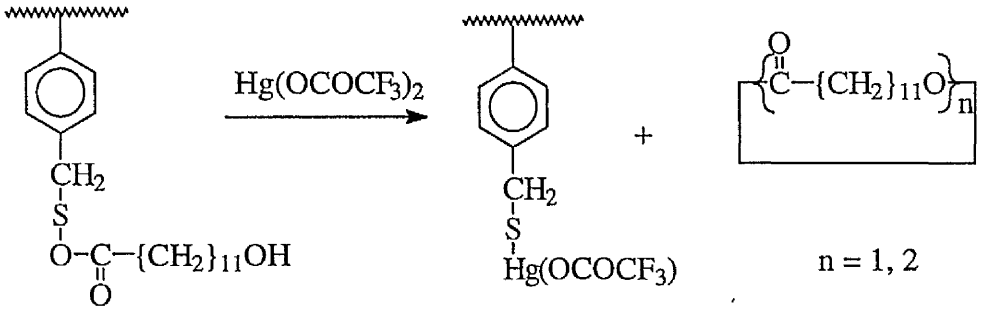


Figure 1.19. Lactonisation using a polymer-supported thioester

Macrolactones having from 11-15 ring carbon atoms were synthesized from ω-bromoalkanoic acids by Tomoi[104] by using a polymer-supported 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). The latter served as a dehydrobromination agent. The starting ω-bromoalkanoic acids were converted into lactones in yields of 30-61%. Some oligomers were present in the product but their size distribution and whether they were linear, cyclic or both was not established.

1.3.3 Polymer-Supported Cyclo-oligomerisations

As mentioned in Section 1.3.2.1, polymer-supported reagents can readily take part in inter-site or intra-site reactions. The former produces monomeric cyclics and the latter produces linear oligomers, which could undergo intra-site reactions affording cyclic oligomers. Whether the polymer-supported reactions go through inter-site or intra-site reaction depends on many conditions as summarised in Table 1.3. In practice, in many cases the cyclisation system not only produces single cyclics but also produces cyclic oligomers.

The polymer-supported cyclo-oligomerisation aims to utilise inter-site reactions to advantage. It has been emerging in the last few years as a novel method to prepare cyclic oligomers. The relevant studies have been carried out mainly by Röthe's group[123,124] and by Hodge's group.[125] However, there is still a lack of general understanding of these reactions and more investigations are needed. The work described in this Thesis aims to develop the methods and increase understanding.

Cyclic Peptide Oligomers

It is often found that cyclic oligomers are produced as by-products from the cyclisation of linear peptides. The phenomenon of 'cyclo-dimerisation' in cyclic peptide synthesis has been reported by many authors.[102,126]

Rebek[129] described a cyclo-oligomerization of glycine on a polymer-supported nitrophenol in a short communication. The identity of the cyclic oligomers was, however, only demonstrated by a negative ninhydrin test.

Röthe *et al.*[102,106,127] studied in detail the on-resin cyclo-oligomerisation of some oligopeptides. In their studies, they used both Fridkin's active hydroxyl resin and the "safety-catch" method of Flanagan and Marshall. Different solvents, temperatures, loadings of monomer, degrees of crosslinking and morphology of support were tested. The results showed that the cyclo-oligomerisation could produce products in high yields (20-80%) consisting of cyclic peptides having from 3-30 peptide residues. The solvent and linear peptide structure were the most important influences on the formation of the cyclic oligomers.

Nishino *et al.*[116] studied the cyclisation of tetrapeptides, iturin A analogs, on a Kaiser oxime support. Their results, summarised in Table 1.4, show that the distribution of cyclic peptide oligomers obtained depends not only on the loading of the linear oligomer and the solvent, but also on the sequence of the linear peptide.

Table 1.4. The dependence of the cyclic oligomer distribution on the peptide sequence.[a]

Sequence of peptide	Total yield (%)	Distribution (%)		
		Mono	Dimer	Higher
Arg(Tos)-Gly-Asp(OcHex)-Phg	65	75	20	5
Phg-Arg(Tos)-Gly-Asp(OcHex)	65	50	25	25
Asp(OcHex)-Phg-Arg(Tos)-Gly	70	40	40	20
Gly-Asp(OcHex)-Phg-Arg(Tos)	53	10	–	–

a Cyclisations carried out on Kaiser Oxime resin at r.t. and at similar loading. Phg = phenylglycine; cHex = cyclohexyl.

Cyclic Amide Oligomers

Cyclic caprolactam oligomers were prepared in 69% yield by Röthe *et al.*[106,124] carrying out cyclo-oligomerisations using Flanagan and Marshall's procedure with the dimer of 6-aminohexanoic acid as the starting monomer. Cyclic products with up to 40 aminohexanoic acid units were detected by GPC, separated by HPLC, and characterised by field desorption mass spectrometry. It was also mentioned in their paper[106] that analogous procedures using ω-aminoundecanoic acid and using ω-aminododecanoic acid afforded mainly the cyclic dimers.

Cyclic Ester Oligomers

As noted above, cyclic ester oligomers were present in the products from many of the polymer-supported lactonisations.[95,104] However, they were viewed as by-products and they were not well characterised, except that Ford[95] isolated the dimer of 11-hydroxydodecanoic acid.

Röthe[123] *et al.* reported the synthesis of cyclic ester oligomers of 11-hydroxydodecanoic acid and the linear dimer of 6-hydroxycaproic acid by using Flanigan and Marshall's "safety-catch" method[114]. The cyclizations were carried out in the presence of DBU, a strong organic base. The reaction produced a 32% yield of cyclic oligomers of 11-hydroxydodecanoic acid having DPs from 2-7 and a 54% yield of cyclic oligomers of di-ω-hydroxycaproic acid with DPs from 1 to 5.

Work reported by Hodge *et al.*[125] recently indicated a feasible way to make cyclic oligomers by favouring the inter-site reactions on ion exchange resins. ω-Halogenoalkanoic acids were fastened at high loading onto a commercial macroporous anion-exchange resin (Amberlyst A26) through the carboxylic moiety. Heating the heavily loaded resin results in the formation of cyclic oligomers in yields of between 44-74% with the average degree of polymerisation($\overline{DP}$) of from 9 to 25 respectively: see Figure 1.20. The cyclic nature of the product was characterised by FAB, GPC and topological trapping.[128]

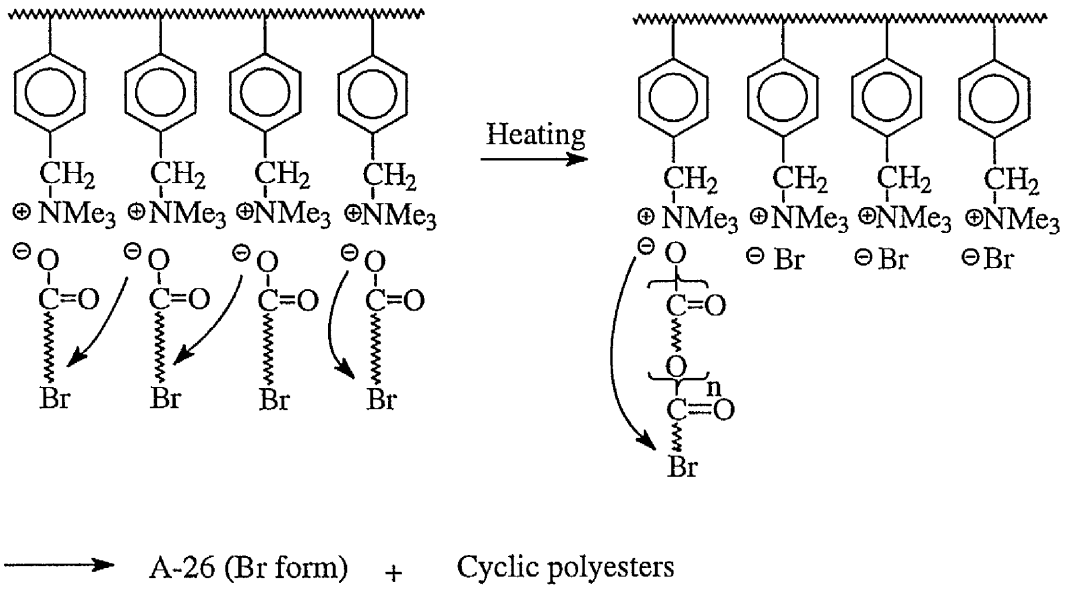


Figure 1.20. Cyclo-oligomerisation of ω-halogenoalkanoic acids on an anion-exchange resin.

1.4 OBJECTIVES OF PRESENT WORK

The general aims of the project described in this Thesis are to develop feasible ways to synthesise cyclic oligomers by means of polymer-supported reactions, especially the synthesis of cyclic oligoamides and esters. The project is, therefore, concerned with the following aspects.

1. To synthesize and evaluate suitable monomers and suitable polymeric supports.
2. To optimise the cyclo-oligomerisation reaction.
3. To develop methods to purify, identify, and characterise the cyclic oligomers produced.
4. To develop a better understanding of the basic chemistry of the cyclisation reaction on polymeric beads.

CHAPTER 2

CYCLIC OLIGOESTERS

Part 1

Understanding the Cyclisation of 11-Bromoundecanoic Acid on Amberlyst-26

2.1 INTRODUCTION

In previous work in Professor P Hodge's laboratory cyclic esters were prepared from 11-bromoundecanoic acid simply by the use of Amberlyst-26 (A-26) supported bicarbonate.[125] The products were substantially characterised by Semlyen's group[128] at the University of York. The cyclic polymers, obtained in yields of 40-70%, were believed to be formed by the nucleophilic attack of carboxylate anions on the carbon bearing the bromine group. This is shown in Figure 1.20. In our continuing studies it has been found that the yields of cyclic product were not constant and the composition of the products was more complex than expected. This prompted us to investigate this polymer-supported cyclisation in greater detail. By a deeper understanding of the cyclisation reaction on the resin beads, it was thought that it would be possible to optimise this cyclisation reaction and to design better polymer-supported systems for the preparation of cyclic oligomers.

This chapter deals mainly with some aspects of the mechanism of the cyclo-oligomerisation on Amberlyst A26. An important part of this work was to identify the cyclic oligomers by gel permeation chromatography (GPC) and by fast atom bombardment mass spectrometry (FAB-MS). The detailed instrumental methods and the conditions used are described in the Experimental Section (Chapter 7). In order to 'calibrate' both the GPC and the FAB-MS an initial aim was to prepare authentic samples of linear oligomers of 11-hydroxyundecanoic acid. It would then be easier to clearly distinguish between cyclic products and linear products.

2.2 SYNTHESIS OF LINEAR OLIGOMERS OF 11-HYDROXY-UNDECANOIC ACID

2.2.1 Synthesis of 11-Hydroxyundecanoic Acid (1a) and Related Monomers

11-Hydroxyundecanoic acid (**1a**), its dimer (**2**) and linear oligomers (**3a**) were prepared for model reactions, and for use as calibrants for the identification of all the

possible linear oligomers. The C_{11} acid was selected because 11-bromoundecanoic acid is available commercially in >99% purity and cyclisation to give the monomeric cyclic lactone is unlikely because the lactone is a medium-sized ring. 12-Hydroxydodecanoic acid (**1b**) itself is commercially available, but with a relatively poor purity. However, two to three recrystallisations from chloroform-methanol afforded crystals of 12-hydroxydodecanoic acid suitable for use in the reactions of interest.

In previous studies 11-hydroxyundecanoic acid was prepared by Lycan[130] by ozonolysis of ω-hydroxydodecene. Szantay[131] has described the hydrolysis of 11-bromoundecanoic acid in the presence of strong base to afford 11-hydroxyundecanoic acid. In the present work the hydrolysis of 11-bromoundecanoic acid to 11-hydroxyundecanoic acid was achieved by heating 11-bromoundecanoic acid in an excess of potassium hydroxide in water at 100 °C for 7 days (Scheme 2.1). The resulting potassium salt of 11-hydroxyundecanoic acid was recrystallised three times from ethanol in order to free the product of potassium bromide and starting materials. The 11-hydroxyundecanoic acid could be generated from the salt by acidifying the aqueous solution. After careful recrystallisation from ethyl acetate, needle-like crystals of 11-hydroxyundecanoic acid were obtained in an overall yield of about 50 percent. The

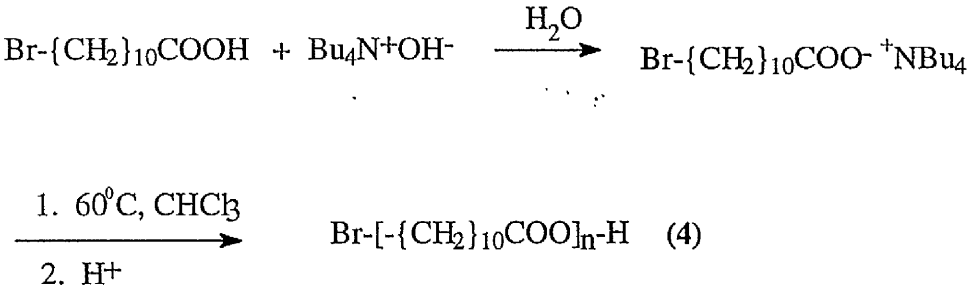
$$\text{Br-}\{CH_2\}_{10}\text{COOH} + \text{KOH} \xrightarrow{H_2O} \text{HO-}\{CH_2\}_{10}\text{COOK}$$

$$\xrightarrow{H^+} \text{HO-}\{CH_2\}_{10}\text{COOH} \quad (\mathbf{1a})$$

Scheme 2.1. Synthesis of 11-hydroxyundecanoic acid

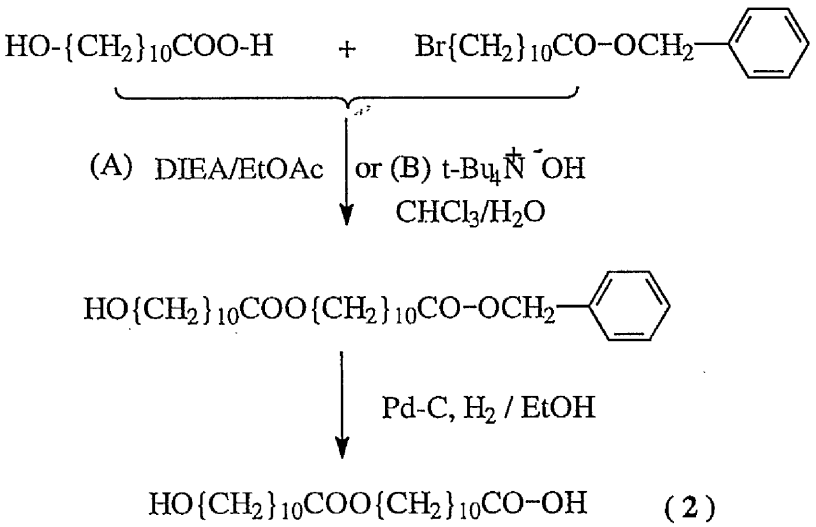
synthesis probably proceeds via poly(undecanoate). To expedite the reaction and improve the yield, the polymer intermediate was synthesised first in a separate step by the use of tetra-(n-butyl)ammonium hydroxide in a phase transfer catalysed reaction: see Scheme 2.2.[132] The polyesters of 11-bromoundecanoic acid could be prepared in high

yield and with high molecular weight. Purification of the polymer was achieved readily by precipitation from methanol. The polymer, which contained very few bromo-end groups, was hydrolysed using an excess of potassium hydroxide in THF-water as solvent. This produced the potassium salt of 11-hydroxyundecanoic acid in high overall yield.



Scheme 2.2. Synthesis of bromo-ended polyesters by a phase transfer catalysed reaction.

The synthesis of the linear dimer was achieved using the reactions shown in Scheme 2.3. Initially the benzyl ester of 11-bromoundecanoic acid was prepared by reacting the acid with benzyl alcohol in the presence of an acid catalyst. Two catalysts were then tried for the coupling of 11-hydroxyundecanoic acid (**1a**) with the 11-bromoundecanoic acid benzyl ester as shown in Scheme 2.3. Method A used di-isopropylethyl amine (DIEA) as



Scheme 2.3. Synthesis of the linear dimer of 11-hydroxyundecanoic acid.

the base and ethyl acetate as solvent. The mixture was heated under reflux for 72 h. This gave the dimer benzyl ester in 57% yield. Recrystallisation of this product from a mixture of cyclohexane and di-isopropyl ether afforded the pure product as shown by the ^{1}H NMR spectrum and elemental analysis. However, GPC shows this product contains only 95% of the dimeric ester. The trimer and tetramer esters also are present, to the extent of about 3 percent and 1.5 percent of the total product. These might be formed by the self condensation of 11-hydroxyundecanoic acid since 11-hydroxyundecanoic acid is easily oligomerised at higher temperatures.[130] In Method B a phase transfer catalysed reaction was used to couple 11-hydroxyundecanoic acid and 11-bromoundecanoic acid benzyl ester. The phase transfer catalysed reaction was carried out at 60 °C for 24 h. This yielded 44% of the dimer benzyl ester. The trimeric and tetrameric benzyl esters were again observed in the GPC trace to the extent of about 1.0 and 2.5 percent respectively of the total product. Removal of the ester protecting group was easily achieved using hydrogen and palladium-charcoal.

2.2.2 Linear Oligomers of 11-Hydroxyundecanoic Acid and 12-Hydroxydodecanoic acid (3a and 3b respectively)

Having successfully prepared 11-hydroxyundecanoic acid (**1a**) and having 12-hydroxydodecanoic acid (**1b**), the preparation of the linear oligomers was investigated. Melt polymerisation is an ideal method for the preparation of linear oligoesters from their hydroxy acid monomers and accordingly this method was investigated starting with both the C_{11} and C_{12} hydroxy acids. The results are summarised in Table 2.1. The yields were nearly quantitative and the products did not need any purification treatment. The NMR spectra of these oligomeric esters show, as expected, the hydroxymethylene end groups at δ 3.70 ppm and the ester methylene groups at δ 4.20 ppm. The degrees of polymerisation were calculated from the integration ratios of these signals. The ^{13}C NMR spectra of the oligomers showed clearly different signals due to both types of end group and the main chain. The peaks in the GPC traces were assigned to the oligomers with different DP. The availability of the linear monomer, cyclic monomers (purchased

from Aldrich) and the prepared dimer of the C_{11} acid allowed the certain assignment of the monomer peaks and the dimer peak in the GPC of the linear oligomers of 11-hydroxyundecanoic acid. Based on the assignment of the peaks, the average molecular weights were calculated by counting the areas of the peaks by use of the classical method. The results are summarised in Table 2.1.

Table 2.1. Summary of the synthesis and analysis of the linear oligomers of 11-hydroxyundecanoic acid (1a) and 12-hydroxydodecanoic acid (1b).

Linear Product No.	Mono -mer	Book reference	Reaction			$\overline{DP}$ (NMR)[a]	$\overline{DP}$ (GPC)[b]	Cyclic (%)[c]
			Time (hr)	Temp (°C)	Yield (%)			
3a	**1a**	2-55RP	30	110	95	2.84	3.26	4.5
3a	**1a**	2-55RP1	24	110	97	2.42	2.88	<5
3b	**1b**	2-67L1	48	110	100	2.86	2.91	<2.5

[a] 200 Hz ^{1}H NMR. [b] Calculated from the GPC traces based on peak assignment.
[c] Obtained from GPC traces by counting the peak area. The estimated errors for b and c are likely to be up to 10% of the value.

As seen from Table 2.1, the DPs calculated from the GPC traces are very close to those determined by the NMR method. This indicates that the peak assignments are correct.

It is interesting to note that the FAB-MS showed that there were small cyclic oligomers present in the linear oligoester samples. Their intensities were far larger than the peaks due to the linears, although GPC showed that the cyclics were present at less than 5% of the total sample. This suggests that the cyclic oligomers are far more easily detected by the FAB-MS method than are the linear oligomers. The FAB-MS histogram of oligomers **3a** is attached in the Appendices(**1**). The results for product **3a** are summarised below.

Linear product 3a.

Cyclic series: 185(M_1+1, 81.8%), 369(M_2+1, 100), 554(M_3+1, 34.5), 738(M_4+1, 12.7), 921(M_5+1, 3.6).

Linear series: 203(M_1+1, 18.2%), 386(M_2+1, 38.2), 571(M_3+1, 67.3), 755(M_4, 63.6), 940(M_5+1, 23.6), 1124(M_6+1, 3.6), 1309(M_7+1, 0.09).

These FAB-MS results are similar to those obtained with other cyclic mixtures, as mentioned in Chapter 3. The conclusion seems to be that the cyclic esters are more easily detected in the products under the particular conditions used. FAB is therefore little use in analysing reaction products. GPC is, therefore, a more promising method to determine the cyclic content in a mixture of cyclic and linear oligomers. A more detailed discussion is given in Section 2.8.1.

2.3 A STUDY OF THE LOADING PROCESS

2.3.1 Effect of Variations in the Loading Conditions

The study of the loading of 11-bromoundecanoic acid was expected to provide information on the nature of the loaded monomers prior to carrying out the cyclisation process, in particular to determine if any reactions occurred during the loading process itself. Amberlyst A26, a strong base anion exchange resin produced by Rohm and Haas Ltd, was converted from the original chloride form into the bicarbonate form by washing the as-purchased beads with excess aqueous $NaHCO_3$ using a column technique.

Effect of Loading Ratio

Previous researchers[125,128] loaded 11-bromoundecanoic acid onto the Amberlyst 26 bicarbonate using methanol as the solvent. Initially, with methanol as the solvent, the feed ratio (moles of monomer used per resin-supported HCO_3^- mole) was varied in the loading procedure. In each case a suspension of the resin was stirred with a solution of

the monomer for 24 h at 20 °C. The resin beads were then recovered and the beads and the filtrate analysed, the latter by ^{1}H NMR spectroscopy. The results are summarised in Table 2.2. Clearly, the loading achieved using methanol solutions was satisfactorily high when only an equivalent number of moles of 11-bromoundecanoic acid was used.

Table 2.2. Loading in methanol.

	Experiment 1	Experiment 2	Experiment 3	Experiement 4
Ratio of Br/Amb[a]	1.5:1	1:1	0.75:1	0.5:1
Loading of beads achieved (mmol/g)[b]	1.56	1.63	1.34	1.06
Ester % in solution[c]	16.0	25.4	25.9	26.5
DP of esters in solution[d]	1.19	1.34	1.35	1.36

[a] The number of moles of 11-bromoundecanoic acid used per Amberlyst-supported HCO_3^- group. [b] Loading time 24 h at 20 °C. [c] Percentage of carboxylic acid end groups esterified in solution. [d] DP of oligomers in solution.

The ^{1}H NMR spectra of the unloaded materials in solution indicated the presence of significant amounts of oligomers and, moreover that small amounts of them were present as methyl esters. The latter might result from methylation by the solvent. The degree of esterification of the materials in solution did not vary very much when the ratio was less than 1:1. Since it was anticipated that the linear methyl esters would not produce cyclic products according to the proposed mechanism,[125] we sought to avoid the formation of these esters during the loading procedure.

Effect of Loading Solvents

Using the usual procedure given above, loading in different solvents was carried out in an attempt to find better solvents which could avoid methylation and yet afford reasonably heavily loaded beads. N,N-Dimethylformamide (DMF), acetone, ether, toluene, chloroform and dichloromethane (DCM) were tried. The results are summarised in Table 2.3.

Table 2.3. Loading of 11-bromoundecanoic acid onto the bicarbonate form of Amberlyst A26 in different solvents[a].

Solvent	DMF	Acetone	Ether	Toluene	$HCCl_3$	DCM
Loading achieved (mmol/g)	0.49	0.87	0.90	0.94	0.96	1.08
Ester % in solution[b]	–	53.7	32.4	41.2	37.9	37.1
DP of oligomers in solution[c]	–	2.16	1.48	1.70	1.61	1.59

[a] Loading at 20 °C for 24 h. [b] Percentage carboxylic acid end groups esterified in solution. [c] DP of oligomers in solution.

From the loading experiments, it can be seen that none of the present solvents were able to afford as high a loading as that obtained using methanol. DMF and acetone gave lower loadings than the other solvents. This is probably because of the better solubility of the smaller oligomers in these solvents and the poorer solubility of the oligomers in methanol.

Effect of Loading Time

Apart from the feed ratio and the choice of loading solvent, further study showed that the loading time is also an important factor which affects the loading of the Amberlyst beads. Using the same loading and analysis procedures as before, 11-bromoundecanoic

acid was loaded onto the Amberlyst A26 bicarbonate using various contact times and with acetone as the solvent. As can be seen from Table 2.4, the maximum loading was achieved at 4 h and a longer time resulted in lower loadings. The degree of oligomerisation of unloaded materials in solution increases with the longer loading time.

Table 2.4. Loading of 11-bromoundecanoic acid in acetone onto the bicarbonate form of Amberlyst A26 for the various reaction times.[a]

		Expt. 1	Expt. 2	Expt. 3	Expt. 4	Expt. 5	Expt. 6
Loading time (hr)		0.5	1	2	4	18	24
Loading achieved (mmol/g)		1.17	1.30	1.35	1.42	0.92	0.87
DP of oligomers in solution		1.06	1.18	1.35	1.54	1.88	2.26
End groups[b]	Br (%)	>95	>95	>95	92.8	86.6	–
	Cl (%)	–	–	–	3.2	4.6	–
	OH (%)	–	–	–	4.0	8.8	–
DP of oligomers in beads[c]		5.86	5.94	6.20	5.24	6.08	–
End groups[c]	Br (%)	50.0	38.4	34.2	50.7	20.9	–
	Cl (%)	29.5	31.5	30.5	23.0	33.5	–
	OH (%)	20.5	27.8	35.2	26.3	45.6	

[a] Feed ratio 1:1 was used in all entries. Loading carried out at 20 °C. [b] DPs and end groups of linear oligomers present in solution. Samples were obtained by removing the beads and solvent and measured by 200 Hz H NMR. [c] DPs and end groups of linear oligomers present in bead. Samples were obtained by TFA extraction from beads and measured by 200 Hz H NMR.

Since the discovery that there were substantial amounts of oligomerisation in solution, in the present experiments we introduced the use of TFA/chloroform mixed solvent to extract the bound materials from the loaded beads. The TFA/chloroform extraction procedure was usually able to recover over 95% of the loaded monomer and

oligomers from the beads. The analysis of the extracted product provided useful information about the form of the species present in the loaded beads. The NMR spectral measurements showed that the degree of polymerisation of the extracted products is around 6 after carrying out the loading, washing, drying and storing procedures. This is probably because oligomerisation in the resin beads was still going on during each of the processes of washing, drying and storing. Since the loading time is relatively short and at low temperatures, it is likely that the DP of the extracts is mainly a result of the long drying time. However, to prove this point the wet beads were extracted after loading in acetone for just 2 h. The GPC indicates that at this stage there are mainly only small oligomers present in the resin beads (shown in Figure 2.1). After drying for 24 h in a vacuum at 30 °C, the extract of the same beads has a large fraction of higher molecular weight oligomers present and some small cyclics. Thus, substantial reactions occur during the drying period(see more detailed experiments in section 2.5).

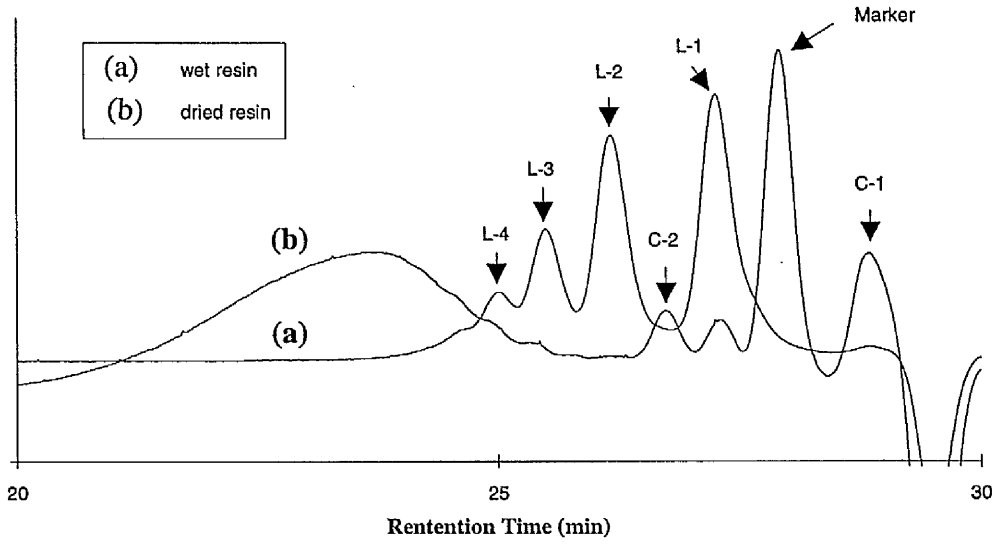


Figure 2.1. The GPCs of extracts from wet resin and dried resin (obtained using GPC apparatus B).

End Group Analysis

The TFA/chloroform extracts from the loaded beads were studied by ^1H NMR spectroscopy to determine the nature of the end groups present. There were three kinds of end groups present in the TFA/chloroform extract:

$Br–C\underline{H}_2–$: $\delta = 3.45$ (a triplet with J = 6.5)

$Cl–C\underline{H}_2–$: $\delta = 3.53$ (a triplet with J = 6.4)

$HO–C\underline{H}_2–$: $\delta = 3.65$ (a triplet with J = 6.5)

The analysis of the end groups (see Table 2.4) shows that the longer loading times produce a majority of hydroxyl-ended oligomers in the resin beads. Further study showed that higher temperature drying or longer storage times results in a further increase in the fraction of hydroxyl-group ended linear oligomers.

The appearance of the chloro-ended oligomers can easily be explained. As purchased Amberlyst A26 is fully in the chloride form. The exchange with the bicarbonate anions is incomplete and hence the Amberlyst A26 bicarbonate used for the loading process contains chloride anion. The latter will react in an S_N2 process with some of the bromo-ended species to displace bromide. The chloro-ended species, once formed, would be expected to be less reactive in any subsequent nucleophilic substitution reactions than the bromo-ended species.

2.3.2 Conclusions

It is clear, that the loading process is more complex than originally thought. The experiments and analyses in this section indicate that there are at least six different reactions simultaneously taking place in the resin beads.

Neutralisation: The polymer-supported bicarbonate reacts with the monomer in an acid-base reaction, affording bound monomers in the support.

Oligomerisation: The loaded monomer molecules react with one another producing loaded linear oligomers.

Cyclisation: The intramolecular cyclisation of supported monomer or oligomer produces cyclic oligomers. Obviously, this reaction is limited in extent.

Hydrolysis: The bromine end-groups are hydrolysed quickly to hydroxyl end-groups in the presence of polymer-supported bicarbonate.

Substitution: The polymer-supported chloride, remaining after the exchange with bicarbonate, substitutes the bromine of the oligomers producing chlorine-ended oligomers. These are relatively resistant to the hydrolysis reaction.

Ion exchange: The excess of monomer in the solution may exchange with the oligomers in the polymer support to release free linear oligomers into the loading solvent.

Methylation: When methanol is used as the loading solvent, the linear oligomers, and possibly the monomer itself can be methylated to give methyl esters.

The possible reaction was illustrated in Figure 2.2.

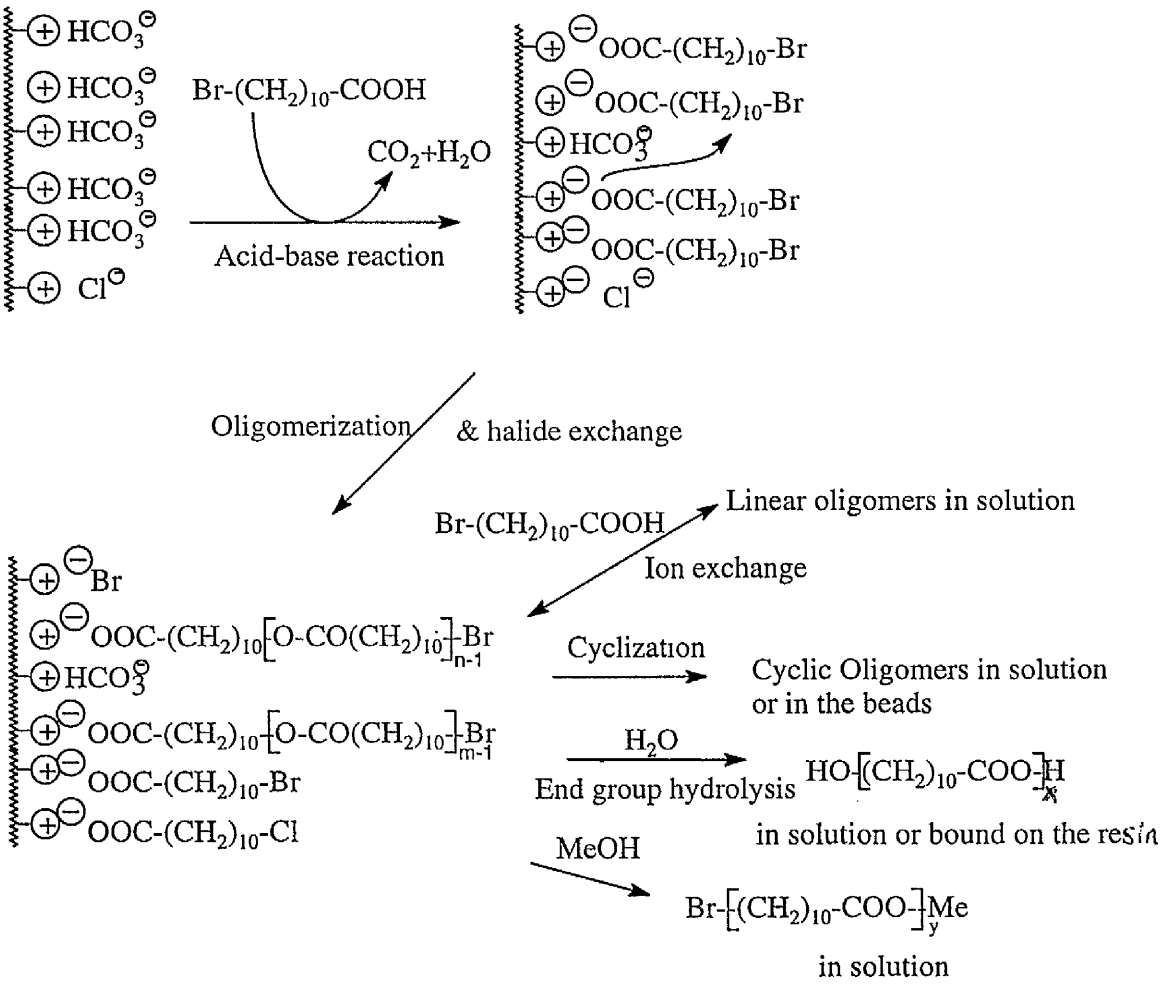


Figure 2.2. Possible reactions occurring during the loading procedure.

2.4 THE CYCLISATION REACTION ON AMBERLYST-26 BEADS

2.4.1 Cyclisation in Flow Column and Soxhlet Extractor

Originally, it was thought that not only would all the monomer molecules be fastened to the Amberlyst beads by an ionic link, but also the linear oligomers. This prompted us to carry out the cyclisation with the beads in the thimble of a Soxhlet apparatus and, more elegantly, in a column with flowing solvent and heating jacket in an attempt to wash off the cyclic oligomers as they were formed. The analysis of the fractions of the product

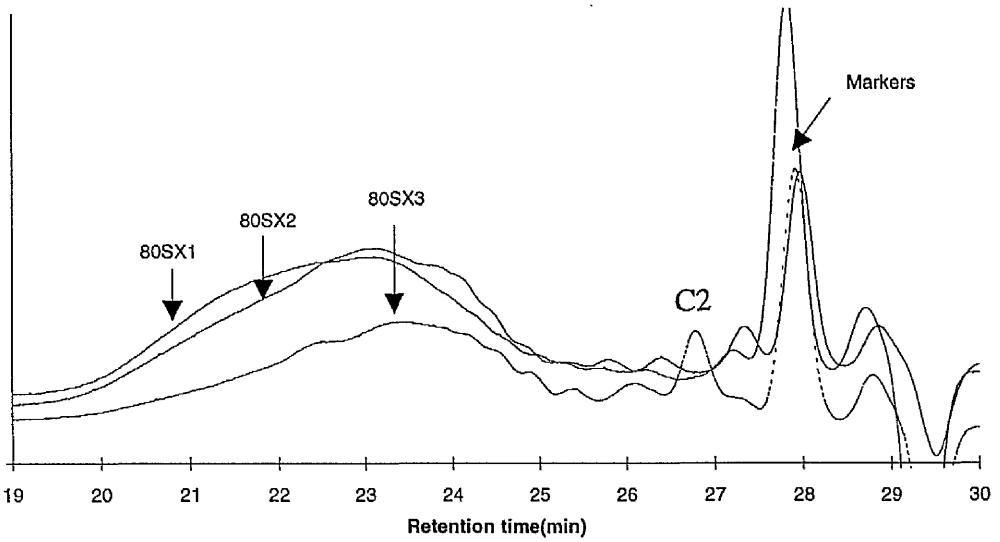
obtained by using a Soxhlet apparatus and a flowing solvent column are listed in Table 2.5. Their GPC traces, synthesised by computer, are shown in Figures 2.3 and 2.4.

Table 2.5. Cyclisations of 11-bromoundecanoic acid in Soxhlet apparatus and in a flow column

	Flow column cyclisation in chloroform[a]				Chloroform fractions from extraction;[b] in Soxhlet		
Sample Reference Number	57C1	57C2	57C3	57C4	80SX1	80SX2	80SX3
Time (min)	15	45	105	180	15	30	60
Yield (%)	41	26	6	1	73	8	6
Mn (GPC)[c]	2245	2009	1592	1425	2578	2071	2045
Mn (NMR)	2484	1343	860	860	–	–	–
DP (NMR)[d]	13.5	7.3	4.7	4.7	–	–	–
End Groups Br%	48	28	23	17			
End Groups Cl%	12	23	23	22	–	–	–
End Groups OH%	40	54	54	61			

[a] Cell volume 15 ml, flow rate: 3 ml/min. [b] Soxhlet thimble volume: 50 ml; solvent siphoned every 15 minutes. Beads loaded from methanol: loading = 1.63 mmol/g. [c] Only the main peaks included. The single small oligomer peaks are excluded. PEGs as calibrants. [d] From 200 Hz ^{1}H NMR spectra.

Essentially the results from the flow column experiments were in agreement with the results from the Soxhlet experiments. They both show that the reactions are substantially complete in 15 minutes. The higher molecular weight oligomers come off first, then, the small oligomers. Also, that the reactions produce mostly linear oligomers with relatively more cyclic oligomers in the later fractions. The total yield of cyclic products might not be over 10% according to the GPC identification (see later). It is important to note that the linear products had been washed off.



SX1, SX2, SX3 refer to Table 2.5.

Figure 2.3. The GPC traces from cyclisation reaction at 60 °C in a Soxhlet apparatus (GPC apparatus B).

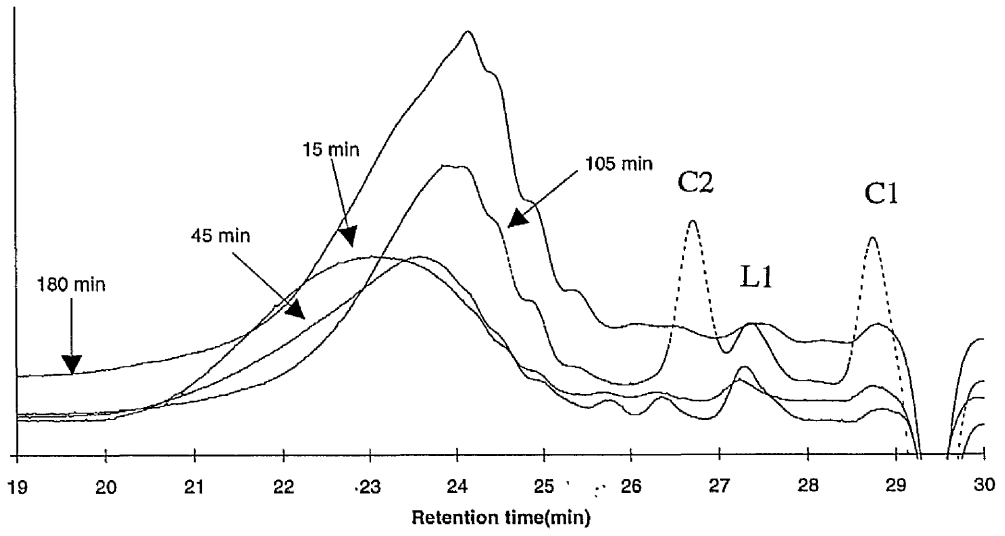


Figure 2.4. The GPC traces from the flow column reaction (GPC apparatus B).

2.4.2 Cyclisation with the Amberlyst Beads in Suspension

The suspension reaction (SS) product is quite different from the flow column and Soxhlet reaction products. The SS reaction gives more small cyclics without small linears together with a significant portion of higher molecular weight oligomers. Taken together the results suggest that the cyclisation is more likely to have a back-biting reaction mechanism rather than a head-to-tail reaction. The following studies aimed to clarify this situation.

Cyclisation at 40 °C

The cyclisation reaction was carried out in dichloromethane at 40 °C by heating a suspension of the beads under reflux. The products present in the early stages were mainly linear oligomers, and more than 50% of the total end groups were hydroxyl groups. The average molecular weight was calculated from the NMR analysis. These results are summarised in Table 2.6.

Table 2.6. Cyclisation on Amberlyst beads in dichloromethane at 40 °C.[a]

Sample reference	1-78C4	1-78C25	–
Reaction Time (h)	4	24	72
Weight of product (g)	0.679	0.164	0.07
Yield (%)	81	20	8
DP (NMR)	4.0	3.5	–

[a] Loading 0.72 mmol/g from acetone. TFA/chloroform extract had an average DP of around 2.9. All the yields are calculated based on the theoretical cyclic yield. Hence, if linear oligomers are present, the yields may be over 100%.

The GPC analysis (GPC Apparatus C) of the products showed that there was not much cyclic material present in these products (estimated at less than 5%). The average degree of polymerisation did not change significantly during the cyclisation. It seems that at 40 °C the solvent mainly extracted linear oligomers formed in the Amberlyst beads.

Cyclisations at 80 °C

There are clearly two families of oligomers present in the product formed at this temperature as shown by the GPC-C traces. One of the fractions is the small cyclic oligomers with DP from 2 to 14 (shown in Figures 2.5 and 2.6; GPC B and C traces). Another major fraction is the polymers with relatively high molecular weight. ^{1}H NMR spectra indicated that the end groups are mainly hydroxyl groups (more than 50%).

The cyclisation was carried out at 80 °C in various solvents. The results show that there are slight differences in the molecular weights of the polymer fractions obtained when different solvents were used. The molecular weights are in the order: Toluene > DMF > CCl_4 > Toluene (flow column). This may be explained by the different swelling abilities of the Amberlyst beads in these solvents. Although all of the reactions produced more cyclic oligomers than the Soxhlet and flow column reactions, the use of DMF and toluene seems to give a higher percentage of the cyclic dimer.

The distribution pattern obtained, i.e. the rapid formation of linear oligomers coupled with a greater yield of cyclics when the linears are left in contact with the resin, suggests that the cyclic oligomers are formed by a depolymerisation reaction which involves ring-chain equilibrium and a back-biting reaction. Similar distribution patterns have been reported before in many papers studying the ring-chain equilibrium phenomena that can occur in ring-opening polymerisation[133] or in catalysed depolymerisation.[84] The operation of such a mechanism in the present cyclisation explains why the suspension reaction system is more effective than the Soxhleting and flow column reaction systems for the production of cyclics.

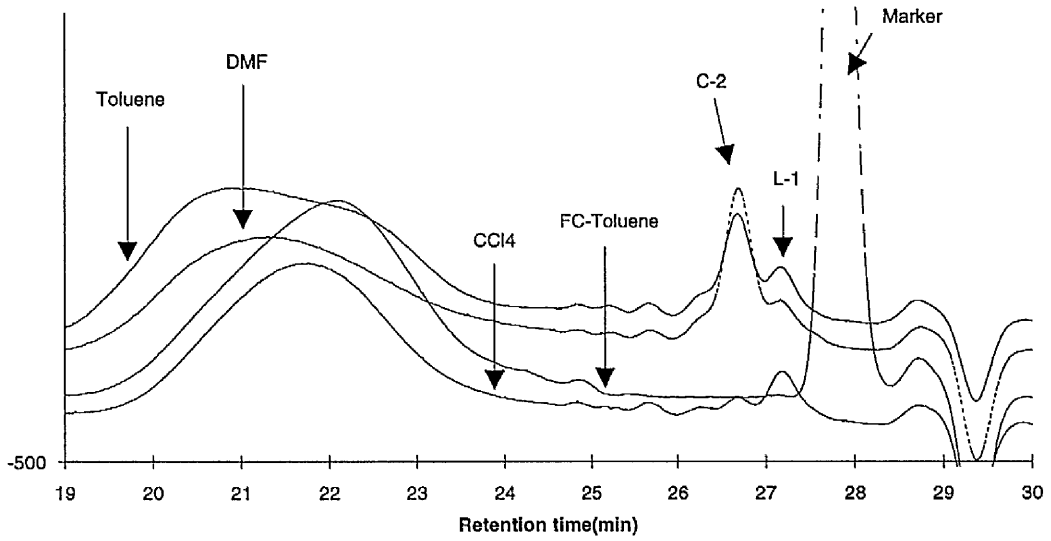


Figure 2.5. Cyclisation on Amberlyst at 80 °C in various solvents; GPC Apparatus B charts.

FC-Toluene: product was obtained by using a column with warm toluene eluent at a flow rate of 2-3 ml/min and 80 °C.

Table 2.7. Cyclisations using loaded beads in various solvents at 80 °C.[a]

Reference name	1-80CC1$_4$	1-80Tu	1-80CTu	1-80DMF
Solvent	CCl_4	Toluene	Toluene	DMF
Reaction Time (h)	24	24	3	24
Method	SS	SS	Flow column	SS
Yield (total)[b]	97	91	57	76
Mn (GPC B)	4680	6704	3954	4937
Cyclic yield by weight (%)[c]	16	20	<10	25
End groups (OH%)	50	71	54	80

[a] Resin loaded from methanol for 24 h. Loading: 1.62 mmol/g. TFA/chloroform extract: M_n = 1923 (GPC B); end groups: OH% (50); Br% (30) and Cl% (20). Cyclisation is carried out at 80 °C. [b] Based on the theoretical yield of pure cyclic oligomers. [c] Identified by GPC-C and calculated by peak area (cyclic oligomers)/total area of RI response.

Achieving ring-chain equilibrium needs time, and higher reaction temperatures could well expedite the reaction. In general, the distribution of small cyclic oligomers in a ring-chain equilibrium can usually be predicted for solution reactions by the Jacobson-Stockmayer equation. However, in the present polymer-solvent biphase system, the situation is more complicated because not all the oligomers will diffuse freely in and out of the Amberlyst beads.

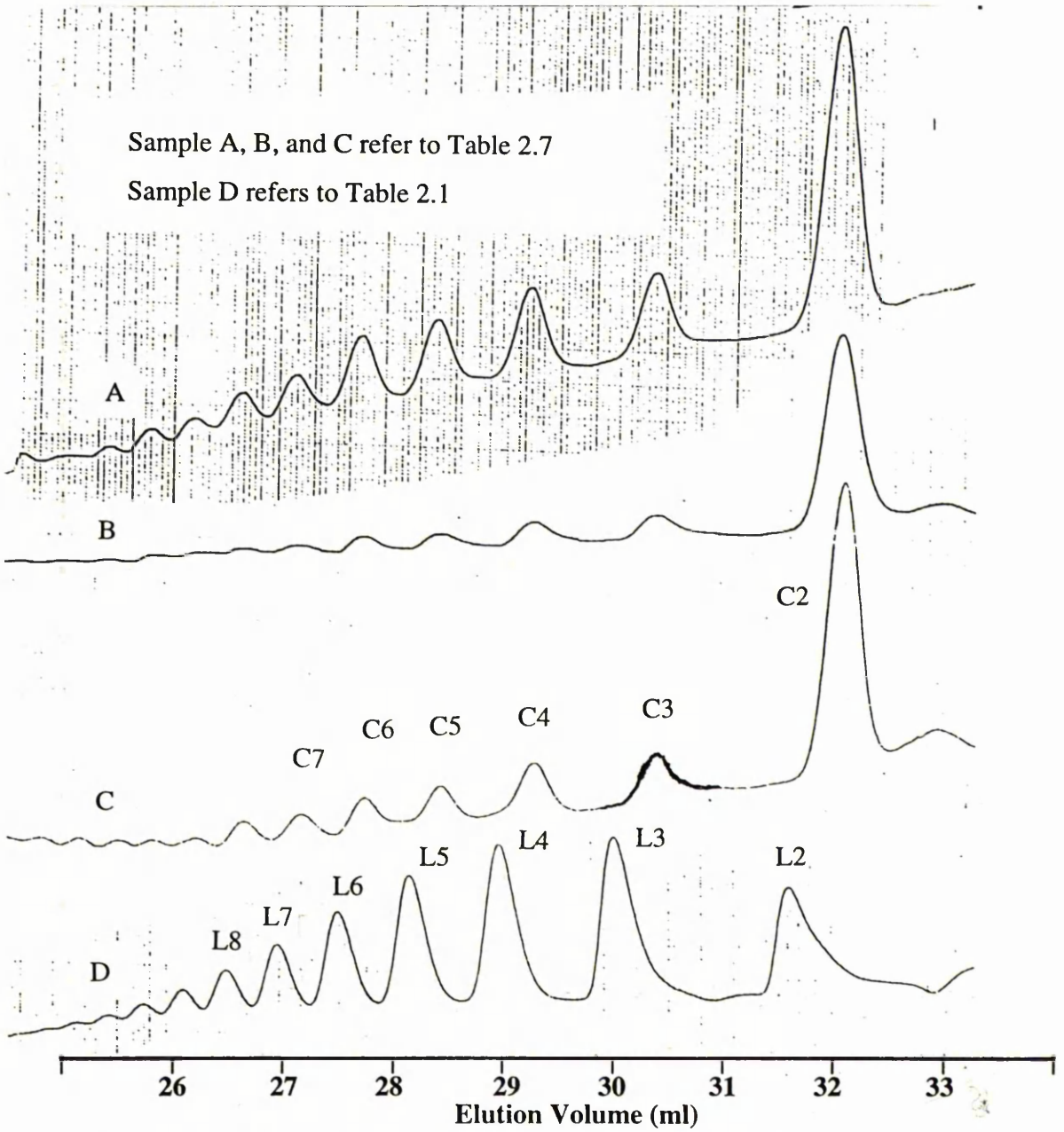


Figure 2.6. Cyclic oligomer fraction from cyclisation at 80 °C in various solvents Obtained by Appratus: GPC-C. High Mw fraction not shown here

A: in CCl_4; B: in DMF; C: in Toluene; D: linear oligoester 3a.

2.4.3 Conclusions

The results obtained so far show that the loading of 11-bromoundecanoic acid onto the bicarbonate form of Amberlyst A26 beads results in some oligomerisation during the loading process. On heating the loaded resin beads further oligomerisation occurs to give mainly linear oligomers rather than cyclic oligomers and the oligomers are mainly hydroxyl group ended. If the linear oligomers are not removed but are allowed to stay in the presence of the Amberlyst beads, cyclic oligomers are formed, probably by a back-biting reaction.

2.5 EXTRACTION OF THE RESIN BEADS AFTER STORAGE AND AFTER HEAT TREATMENT

In the previous section (2.4), it had been found that there were large amounts of linear oligomers present in the products from the Soxhlet and flow column cyclisations. In the experiments described in this section beads which had been loaded and stored at 20 °C for 5 days were extracted, and so too were the same beads after being heated in the dry state at 60 °C for 24 h. Two extraction procedures were used. The first just involved thoroughly washing with chloroform and thus removed *unbound* material. The second procedure involved washing with a mixture consisting of 75% dichloromethane and 25% TFA. The reagent extracts more than 95% of the *bound* material and does not hydrolyse the other groups during the extraction. The results are summarised in Table 2.8.

It is clear from the results that the higher molecular weight oligomers become detached from the beads and heating the beads, even in the dry state, brings about chain-forming reactions.

Table 2.8. Products extracted from stored beads and from stored and heated beads.

	Chloroform extracts		Dichloromethane/TFA extracts	
	Stored beads[a]	Stored and heated beads [b]	Stored beads	Stored and heated beads
Yield of oligomers	59%	69%	40%	30%
DP by NMR	10.9	14.2	8.6	6.5
$\bar{M}_n$ by GPC	2282	2982	850	800

[a] Negligible material extracted from freshly loaded beads. The beads were loaded using acetone, dried at 40 °C for 12 h and stored at 20 °C for 5 days.

[b]: Beads were heated at 60 °C for 5 days.

2.6 SOME MODEL REACTIONS

As discussed in earlier sections, the initial polymer-supported reactions produce linear oligomers of 11-bromoundecanoic acid in the solution surrounding the beads. Moreover, the majority of these linear oligomers have hydroxyl end groups. The purpose of the model reactions discussed in this section was to show that the bicarbonate form of Amberlyst A26 is capable of catalysing the cyclisation of these oligomers. Accordingly the oligoesters (**3a** and **3b**) previously prepared from 11-hydroxyundecanoic acid and 12-hydroxydodecanoic acid were treated with the bicarbonate form of Amberlyst A26 in various solvents. At the end of the reaction period the beads were filtered off, the solvent evaporated off, and the products analysed by GPC, ^{1}H NMR spectroscopy, and FAB-MS. The results are summarised in Table 2.9.

$$H\text{-}[\text{-}O\{CH_2\}_xCO]_n\text{-}OH$$

3a: x = 10; **3b**: x = 11

A summary of model reaction results is listed in Table 2.9. The results show that chloroform is the best of the solvents used for the reaction. With THF and toluene, less

than 20% of cyclic oligomers were formed. The results also show that during the cyclisation reactions the oligomers increase in molecular weight. The molecular weight increases might, at least in part, be due to the loss of low molecular weight linear oligomers which become bound to the Amberlyst beads.

Evidence for the formation of cyclic oligomers was given by the GPC analysis(GPC apparatus C) and by FAB-MS spectra. In the GPC traces, the corresponding linear oligomers give a series of peaks. After heating the linear oligomers with the Amberlyst-supported bicarbonate, a new series of peaks appeared which were eluted slightly later than their corresponding linear oligomers (see Charts in Figure 2.7).

In the FAB-MS spectra of the products, peaks due to cyclic oligomers are present. Peaks due to the smaller linears, i.e. linear monomer, dimer and trimer, are absent or very weak. This phenomenon might be the result of the strong absorption of the smaller linear oligomers to the Amberlyst beads.

When 11-hydroxyundecanoic acid was used in place of the linear oligomers, only *ca.* 2% of the monomer was found in the solution, and the IR spectrum of the beads showed there was no ester bonds formed in the resin beads. These observations indicate that oligomers are needed for cyclisation (back-biting) to occur.

Table. 2.9 The summary of cyclizations catalysed by the bicarbonate form of Amberlyst 26 beads

Entry	Sample Ref.	Substrate	DP of Substrate	Concentration (g/ml)[a]	Feeding Ratio[b]	Reaction Solvent	Time (hr)	Yield[c] (%)	Product DP by NMR	Product DP(GPC)	Cyclic content (%,) by GPC[d]
1	55am2	**3a**	2.84	0.022	0.27	$CHCl_3$	72	66	8.34	5.85	37
2	55am3	**3a**	2.42	0.022	0.14	THF	72	74	6.10	4.83	18
3	55am4	**3a**	2.42	0.022	0.27	Toluene	72	52	3.81	3.32	14
4	67c3	**3b**	2.86	0.027	0.27	THF	72	78	4.60	4.40	12
5	67c4	**3b**	2.86	0.010	0.25	$CHCl_3$	72	92	5.30	4.90	40

[a]: Grams of feeding oligomers per ml of reaction solvent.

[b]: Grams of oligomer per gram of A-26 HCO_3^-; resin HCO_3 content is 3.89 mmol/g. All reactions were carried out at 55 °C.

[c]: Total yield of mixture of cyclic and linear oligomer.

[d]: Calculation based on the identification of the cyclic oligomers. The total area of cyclic oligomers of the identifiable cyclic peaks with DP up to 7 in GPC traces was counted. The cyclic percentage equals (cyclic area / total area) x 100. The yield is, therefore, based on weights not the number of molecules.

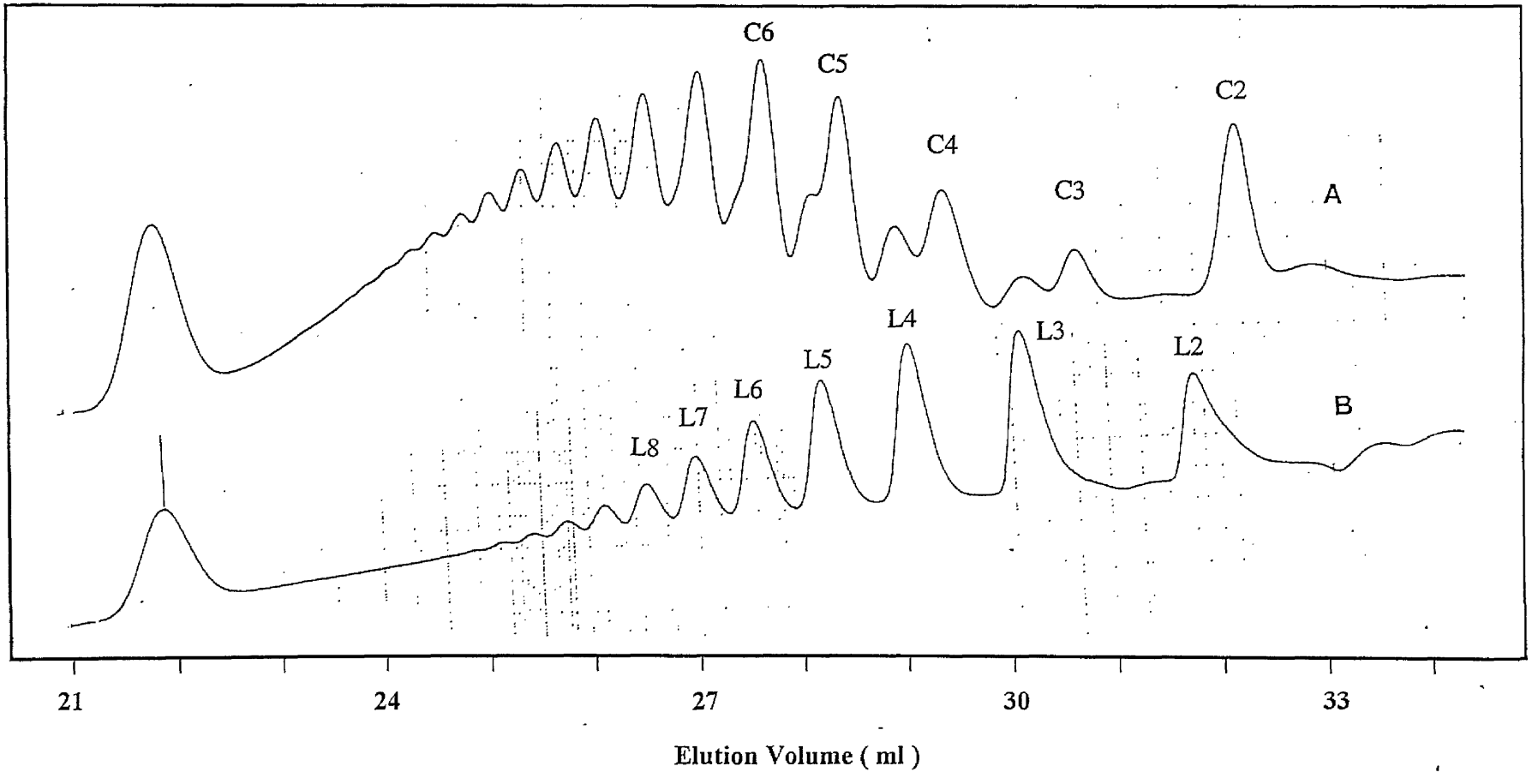


Figure 2.7 GPC-C traces of cyclic product (A) and linear substrate 3a (B)

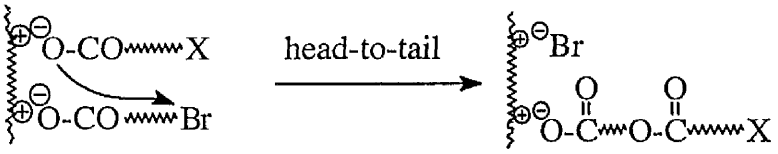
Sample A refers to entry 3 in Table 2.9; sample B refers to entry 2 in Table 2.1.

2.7 SUMMARY OF THE CYCLISATION MECHANISM

The mechanism of the cyclo-oligomerisation of 11-bromoundecanoic acid on the bicarbonate form of Amberlyst 26 is much more complicated that was expected. Summarising the results and conclusions from Sections 2.2 to 2.6, in this section we try to understand some aspects of this reaction system and to give reasonable explanations of the relevant results.

The following are the main features of the cyclo-oligomerisation reactions.

(1) During the loading, storing and heating of the bicarbonate form of the Amberlyst beads, chain growth occurs on the beads by the following reaction(see Figure 2.8).



X = Br; Cl; OH

Figure 2.8 Chain growth reaction in the Amberlyst beads

In the later stages of the cyclo-oligomerisation process some chain growth may also occur by transesterification. Typical $\overline{DP}$s obtained are from 3 to 20.

(2) At the same time as the ester forming reactions, some (>50%) of the terminal bromo groups are hydrolysed to give hydroxyl end groups. This appears to be a new reaction. At the same time, un-exchanged chloride anions react with bromo-end groups to give chloro-end groups. The latter are relatively inert.

(3) The lower molecular weight linear oligomers (DP 1 to 3) are more firmly bound to the beads than the higher molecular weight linear oligomers. The latter are released from the beads and pass into solution. They are removed from the reaction system in the Soxhlet and flow experiments. The Soxhlet procedure can also remove the small linears to some extent.

(4) A small fraction of the bound bromo-ended oligomers probably cyclise as originally envisaged to give cyclic dimers to pentamers.

(5) The hydroxyl-ended oligomers (but not monomer) undergo cyclisation when treated with the bicarbonate form of Amberlyst A26. Chloroform is the best solvent of those studied for this reaction and in this solvent up to 40% yields of cyclics can be obtained. These have DPs up to *ca.* 10 to 14.

(6) All the above processes occur in one-pot when loaded Amberlyst beads are stirred in solvent at reflux temperature. The combined yields of linears and cyclics are 50-70% by weight.

(7) There might be four different types of reaction to produce the cyclic oligomers from the Amberlyst-supported oligomers (as shown in Figure 2.9). As noted above, head-to-tail cyclisation (a) probably only occurs to a small extent. Head-to-tail cyclisation (b) appears to be unlikely on mechanistic grounds. Types of cyclisation (c) and (d), especially the latter, appear to be the most likely mechanisms operating in the present case.

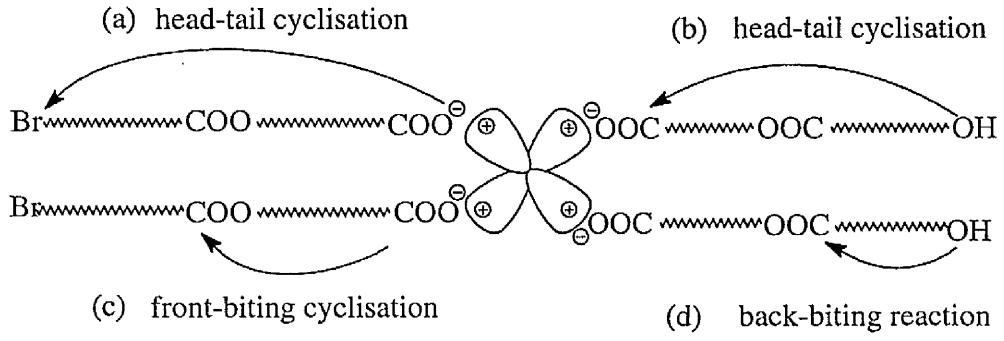


Figure 2.9 Possible routes for the formation of cyclic oligomers.

2.8 CHARACTERISATION OF CYCLIC PRODUCTS

In the course of the studies described in the previous sections of this chapter it was necessary to develop the means to determine the cyclic oligomers content of the various

products and fractions. Two characterisation methods played a key role: GPC and FAB-MS. The results obtained with these methods are now discussed here in more detail.

2.8.1 GPC Results

To identify the cyclic oligomers in GPC traces, it is necessary to know the retention volumes of all the possible linear oligomers which may be present. It is, therefore, very important to have available the linear oligomers with the different possible end groups, i.e. hydroxyl, bromo and chloro. Hydroxyl-ended linear oligomers were prepared as described before. Bromo-ended linear oligomers were prepared by a phase transfer catalysed oligomerisation of 11-bromoundecanoic acid in the presence of tetrabutylammonium hydroxide.[132] ^{1}H NMR spectra indicated that chloro-ended oligomers were present in certain samples. The latter were assigned to an otherwise unidentified family of peaks present in the GPC traces of these samples. The GPC peaks for this family were not found for samples for which the NMR spectra indicated that they did not contain chloro-ended oligomers. Certain samples were, of course, available commercially. These include 11-bromoundecanoic acid, 11-hydroxyundecanoic acid, and the lactone of the later. Details of the various syntheses are given in the Experimental Section.

The GPC C equipment consisted of four 300x10 mm column, packed with mixed E, 3μ 500A PL gel. It is an extremely powerful analytical apparatus for separating the oligomers. The experiments showed that this column set could separate the oligomers with a molecular weight difference of about 200 up to a molecular weight of *ca.* 1000. All the GPC charts were obtained with a column pressure in the range 8.2 to 9.0 MPa. Instead of retention volumes all the results are equivalently represented by retention times in Figure 2.10 and 2.11. All the retention times were corrected to internal standards.

The fitted formulae of logarithm molecular weight (Mw) of a particular oligomer versus retention time (T) are as follows:

Chlorine ended:	Log(M) = 6.015 - 0.0327t	r^2 = 0.9995
Bromine ended:	Log(M) = 6.085 - 0.0338t	r^2 = 0.9991
Hydroxyl ended:	Log(M) = 6.209 - 0.0352t	r^2 = 0.9993
Cyclics:	Log(M) = 6.279 - 0.0361t	r^2 = 0.9995

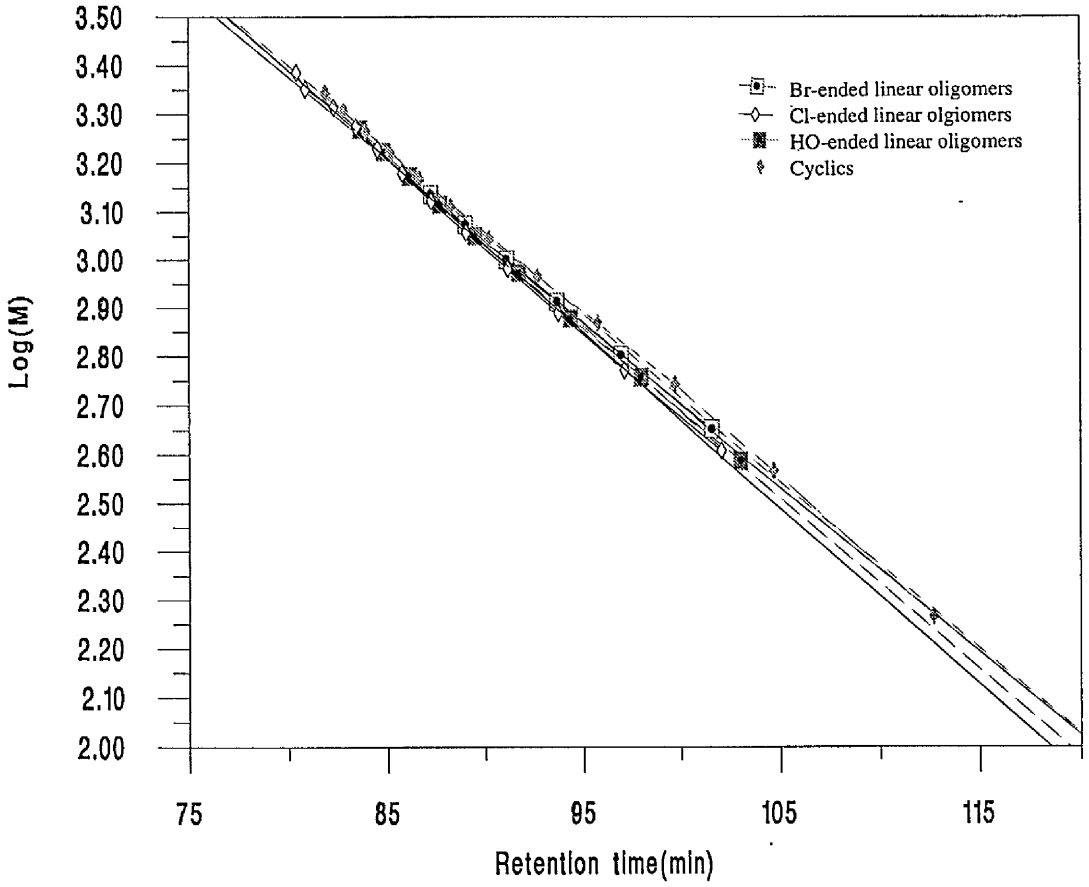


Figure 2.10. LogM-retention time plots for cyclic and linear oligomers.

From Figure 2.10 it is clear that there is only a slight difference between any two lines. This is probably due to two factors. Firstly, there are weight differences between the end groups. The oligomers with the same DP should have retention times in the

following order according to their molecular weight: see Table 2.10. Thus, there are different LogM-t lines even if the oligomers are of the same DP.

Cyclic > COOMe > OH > Cl > Br

Table 2.10. The weight differences of different end groups.

End group	Br	Cl	HO	Cyclic	COOMe
Molecular weight difference relative to the cyclic oligomer	80.9	35.5	18.0	0	14.0

Secondly, the Log(M)-t equation might not be accurate in describing the oligomers with different end groups. The major mechanism of the GPC separation process is size exclusion. The elution volume of molecules is affected mainly by their sizes not their molecular weights. Considering the size differences of the end groups, they make little contributions to the overall molecular sizes, so it should be more accurate to plot Log(DP) against retention time. Figure 2.11 shows this plot. It is now clear that there is not much difference between the retention times of the Cl-/ Br-ended oligomers, but there is a significant difference between Cl/Br and OH, Cl/Br and cyclics, OH and cyclics. In fact, there is good resolution in the GPC traces between Cl/Br and OH, OH and cyclic, Br/Cl and cyclics.

The plot for cyclic oligomers is displaced towards longer retention times compared to all the plots for the linear oligomers. Similar differences have been reported in many other comparisons of cyclic and linear polymers.[134,135]

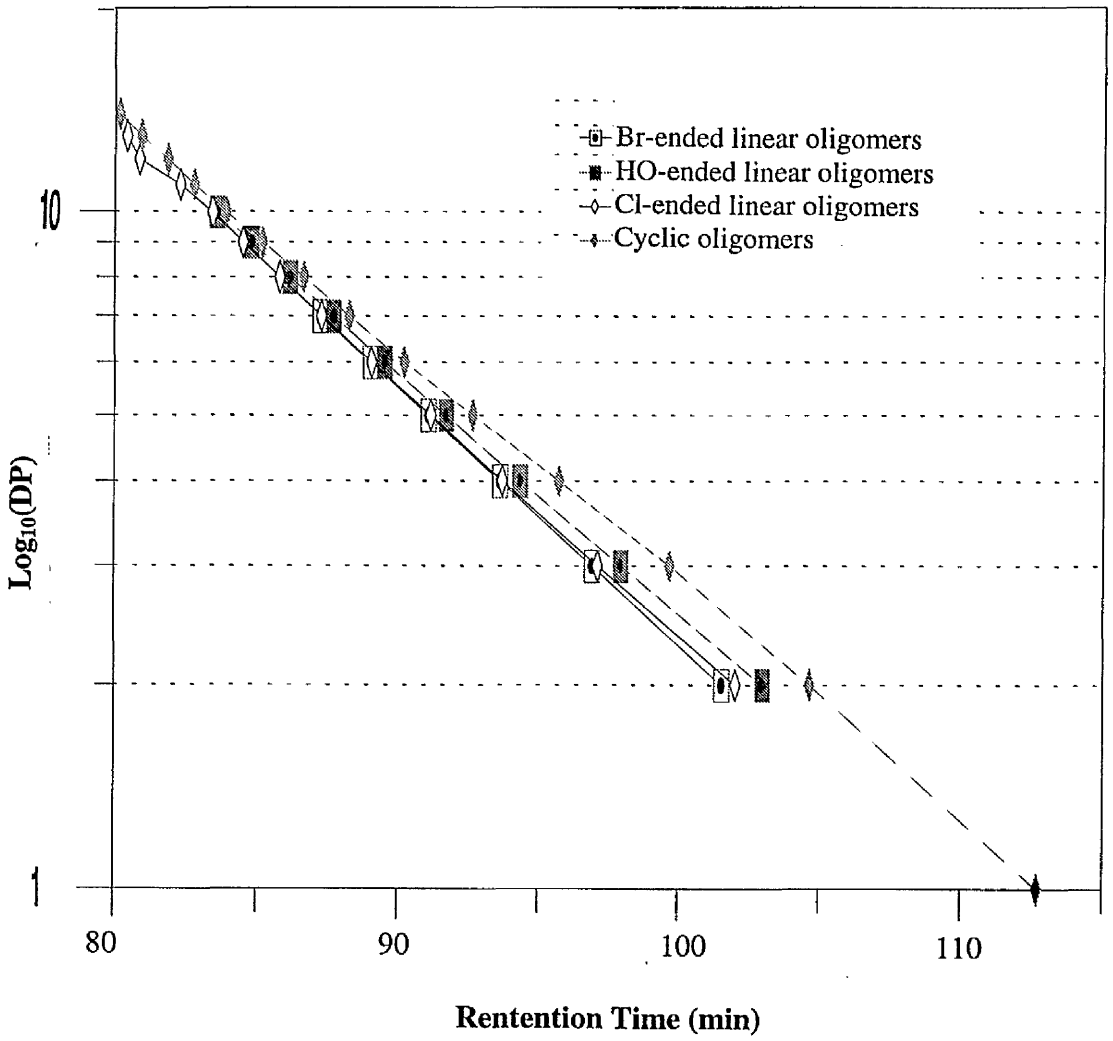


Figure 2.11. Log DP-retention time plot of oligomer traces.

2.8.2 FAB-MS

Fast atom bombardment mass spectrometry is a useful tool for the analysis of cyclic oligomers. However, it has obvious limits because the intensity of the peaks of charged molecules or fragments is clearly related to the ease of vaporisation of the molecules. Thus, some molecules or fragments may be very easily vaporised to produce a very strong peak current even though they are present in the sample in only very small amounts. On the other hand, some materials or fragments may be very difficult to vaporise. Generally speaking, the bigger the molecular weight, the more difficult it will be for the molecular ions or fragments to be vaporised.

This phenomenon was observed with the mixtures of cyclic and linear oligomers. The cyclic oligomers proved to be much more easily detected than their counterpart linear oligomers. For example, sample containing 20% (or less) of cyclic oligomers may only display strong peaks due to cyclic molecular ions.

An example of a FAB-MS is that of the product obtained by the cyclisation of the linear oligomers of 11-hydroxyundecanoic acid. This has been considered in Table 2.9, entry 1, and by GPC it contains *ca.* 37% of cyclic molecules. The FAB-MS is summarised in Table 2.11. Sodium chloride was added in order to produce a family of ions 23 units heavier.

Other examples of FAB-MS are given in Tables 2.12 and 2.13. These are for the products previously reported in Table 2.9, entries 2 and 3 respectively. They respectively contain 18% and 14% of cyclic oligomers.

Table 2.11. FAB-MS peak intensities of reaction product from experiment summarised in Table 2.9, entry 1.[a]

	m/z	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9
Cyclic products	M+1	185 (52.7)	369 (100)	554 (69.1)	738 (60)	923 (36.4)	1106 (9.1)	1292 (3.6)	–	–
	M+23	–	392 (100)	576 (41.8)	760 (34.5)	944 (21.8)	1128 (5.8)	1314 (2.3)		
Linear products	M+1	–	–	–	–	–	–	–	–	–
	M+23	–	–	594 (10.9)	778 (6.3)	962 (2.4)	1146 (1.3)	1332 (0.6)	1515 (0.5)	1700 (0.3)

[a] Intensities in brackets relative to the strongest peak in the spectrum.

Table 2.12. FAB-MS peak intensities of reaction product from experiment summarised Table 2.9, entry 2.

	m/z	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9
Cyclic products	M+1	185 (80.0)	369 (100)	554 (34.5)	737 (10.9)	923 (4.5)	–	–	–	–
	M+23	–	392 (18.1)	576 (10.0)	–	–	–	–	–	–
Linear products	M+1	–	–	572 (26.4)	756 (27.3)	940 (10.5)	1124 (3.6)	1309 (1.3)	–	–
	M+23	–	–	594 (34.0)	778 (43.6)	962 (19.3)	1146 (7.5)	1332 (3.1)	1515 (1.4)	1700 (0.6)

Table 2.13. FAB-MS peak intensities of cyclic product from experiment summarised in Table 2.9, entry 3.

	m/z	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8
Cyclic products	M+1	185 (94.5)	370 (100)	554 (36.4)	738 (10.9)	922 (3.6)	–	–	–
	M+23	–	392 (14.5)	576 (6.4)	–	–	–	–	–
Linear products	M+1	–	–	388 (36.4)	572 (61.8)	756 (49.1)	940 (15.5)	1309 (1.12)	–
	M+23	–	410 (23.6)	594 (46.4)	778 (45.5)	962 (18.2)	1146 (3.31)	1332 (1.4)	1516 (0.5)

Comparing the FAB-MS intensities of the same oligomer series in Tables 2.11-2.13 with their GPC traces, it is possible to make the following conclusions.

(a) The cyclics generally give much stronger FAB-MS peaks than their linear counterparts.

(b) The addition of sodium chloride to the sample increases the intensities of the FAB-MS peaks due to the linears but not those due to the cyclics.

(c) It is not easy to deduce any simple relationship between peak intensities in the FAB-MS and those of the corresponding species in the GPC traces.

CHAPTER 3

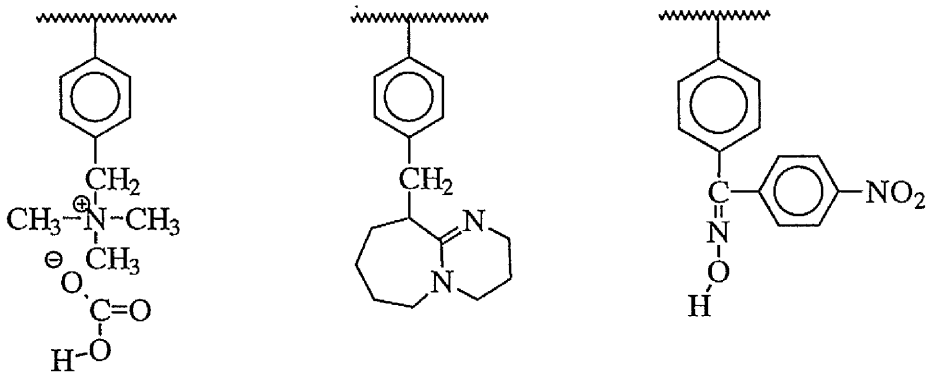
CYCLIC OLIGOESTERS

Part 2

Other Syntheses of Cyclic Oligoesters by the Use of Polymeric Supports

3.1 INTRODUCTION

This Chapter discusses two further approaches to the synthesis of cyclic oligoesters. In Chapter 2 the cyclisation of ω-bromoundecanoic acid using the anion exchange resin Amberlyst 26 (see structure **A-26** in Figure 3.1) was discussed. These reactions produced good yields of cyclic oligomers, but the products were mixtures of cyclic oligomers and bromo-, hydroxyl- and chloro-ended linear oligomers. This makes the analysis of such reactions and the separation of the products difficult. To reduce the complexity of the GPC traces of the products, and to help in the identification of the cyclic oligomers, two further approaches to the synthesis of cyclic oligomers were investigated which might produce less complex mixtures of products.



A-26 HCO_3 **PS-DBU** **PNO**

Figure 3.1. Polymer supports for synthesis of cyclic esters

One of these further approachs is to use organic bases instead of bicarbonate anions, that is to use materials such as polymer-supported 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (see structure **PS-DBU** in Figure 3.1). This polymer-supported organic base cannot hydrolyse the bromine end-groups to hydroxyl groups and there cannot be any linear products with chloro end-groups. Thus, the cyclisation reaction would probably only involve the simple nucleophilic cyclisation mechanism as proposed in previous papers.[125,128] The product would therefore be expected to contain only cyclic oligomers and linear oligomers bearing bromine end groups. The cyclisation of 14-bromotetradecanoic acid using polymer-supported DBU has been studied recently by

Tomoi *et al.*[104] They were mainly interested in the synthesis of the lactone of the monomer and they sought to optimise the reaction system for the production of this product. The maximum yield of the lactone was 57%. They commented that cyclic oligomers were also formed but no analysis of these was carried out. Our work on this approach is described in Section 3.2.

Still a further approach to the synthesis of cyclic oligoesters is based on the same principles as those already discussed. It differs from the others, however, in that instead of binding the linears to the support by ionic bonds they are bound by covalent bonds. Since covalent bonds will be less easily broken than ionic bonds, the processes should be simpler and the products purer. Such a system has been studied by Ford *et al.*[122]. They studied the cyclisation of 12-hydroxydodecanoic acid bound to polymeric supports via a thiol ester linkage which was then activated by the presence of Hg^{2+} ions (shown in Chapter 1, Figure 1.19, p. 48). Cyclic monomer (13%) and dimer (19%), but no higher cyclic oligomers, were isolated by flash chromatography.

Very recently whilst the present studies were in hand, Röthe *et al.*[123] described work on the cyclisation of 12-hydroxydodecanoic acid and the linear dimer of ω-hydroxycaproic acid bound via ester linkages to (4-hydroxyphenylthiomethyl) polystyrene beads (as shown in Figure 3.2). The ω-hydroxydodecanoic acid was attached to the 1% crosslinked polystyrene beads by a phenyl ester bond. The polymer-bound ester was activated by oxidising the sulfide group to a sulfone group. After deprotection of the terminal hydroxyl group using acid, the cyclisations were carried out in the presence of DBU in THF. For the 12-hydroxydodecanoic acid monomer the yield of cyclic oligomers was 32% with DPs ranging from 2 to 7. For the dimer of ω-hydroxycaproic acid monomer, the yield of cyclic oligomers was 54% with DPs ranging from 1 to 5. The products were separated using a silica gel column and gradient elution. Whether linear oligomers were present in the product was not mentioned. The cyclic oligomers were characterised by Field Desorption Mass Spectrometry and by DSC.

Our approach aims to simplify Röthe's approach by fastening unprotected ω-hydroxyundecanoic acid onto a polymeric oxime resin (see PNO in Figure 3.1) and to optimise the reaction conditions in order to avoid the release of linear oligomers. Our work on this approach is described in Section 3.3.

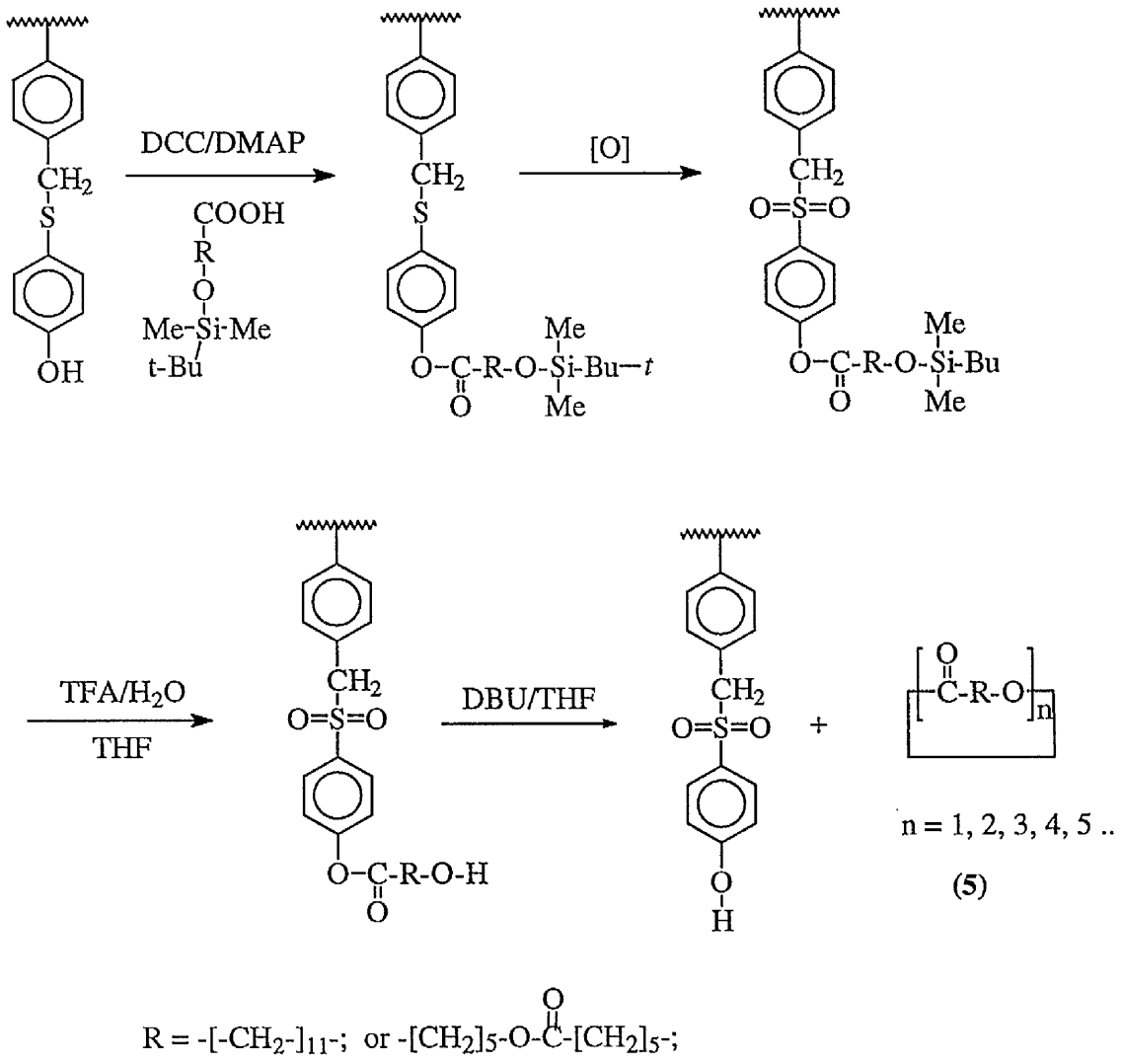


Figure 3.2. Röthe's 'safety catch' method for the synthesis of cyclic esters.

3.2 THE USE OF POLYMERIC ORGANIC BASES

Bicyclic amidines such as 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) or 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) are useful as reagents in synthetic organic chemistry.[136] The reagents DBN and DBU can bring about efficient

dehydrohalogenation under mild reaction conditions.[137] They can also be used for the esterification of carboxylic acids with alkyl halides[138] and for the alkylation and acylation of active methylene compounds.[139]

3.2.1 Synthesis of Polymer-supported DBU

Polymer-supported 1,8-diazabicyclo[5,4,0]-undec-7-ene(see Figure 3.3) was prepared by Tomoi[104,140] and applied to the synthesis of large ring lactones from the corresponding ω-bromoalkanoic acids. In the present work, the polymeric DBU was prepared by the same method as Tomoi used, that is from a Merrifield polymer (chloromethylated polystyrene) and lithiated DBU (see Figure 3.3). DBU can be lithiated by stirring dry DBU with n-butyl lithium at low temperature just before use.

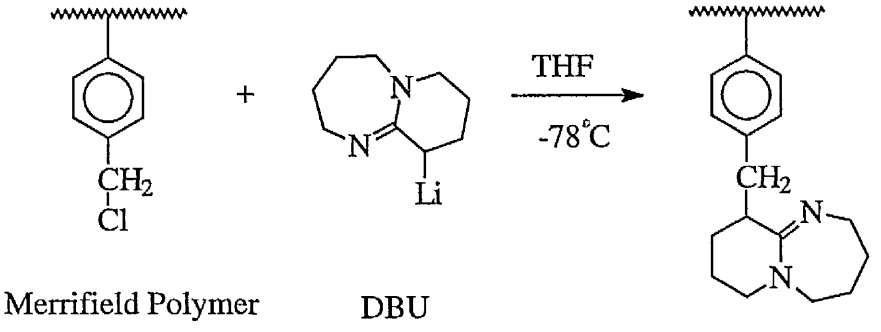


Figure 3.3. Synthesis of polymer-supported DBU.

In order to obtain polymer-supported DBU of high functionality, a Merrifield polymer with a high content of chlorine (4.3 mmol/g) was reacted with lithiated DBU in THF. The polymeric product was found to have a chlorine content of 8.66% (2.44 mmol/g) and a nitrogen content of 3.48% (1.24 mmol DBU/g). Clearly not all the chloromethyl groups reacted. Repetition of the same reaction on the initial product afforded polymer beads with a chlorine content of 5.08% (1.47 mmol/g) and a nitrogen content of 4.01% (1.43 mmol DBU/g). Since chloromethyl residues in the polymer beads are potentially reactive to carboxylic acids in the presence of DBU (see Figure 3.4), attempts were made to react the remaining chloromethyl groups with an excess of butyl lithium solution in THF. This method failed, however, to eliminate the chlorine residues.

In the future, an improvement might be obtained by the use of a lower loaded Merrifield polymer (1.0 to 2.0 mmol Cl/g) or by a better capping techniques to block the free chloromethyl residues.

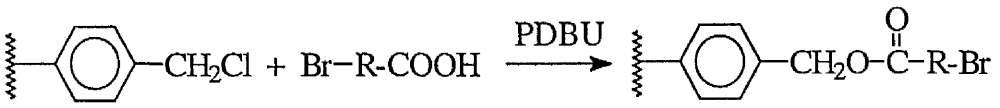


Figure 3.4 A side reaction of chloromethyl residues

3.2.2 Preparation of Cyclic Oligomers Using the Polymer-supported DBU Resin

No pre-loading procedure was used. The reaction was simply carried out by stirring a mixture of the PS-DBU and the monomer in a solvent at 58 °C. The products were analysed by GPC (see Figure 3.5 for a typical trace), ^{1}H NMR spectroscopy and FAB-MS. The results are summarised in Table 3.1.

As shown in Table 3.1, the cyclic contents of the obtained products were in the range of 25% to 45%, and the average DPs of the products were very small. The ^{1}H NMR spectra showed that hydroxymethylene end-groups (HO-CH_2) were absent, which indicates that the hydrolysis reaction which transformed bromo end-groups into hydroxyl end groups in the system discussed in the last chapter is absent in the present system. The mechanism to produce cyclics is almost certainly the nucleophilic attack of carboxylate anions on bromo groups as suggested in the previous work.[125,128]

Table 3.1. Cyclizations on PS-DBU

Entry	Notebook Ref.	Monomer[a]	Feed [M](mol/cm^3)	Conc.[b] R (mmol/g)	Reaction Solvent	Temp. (°C)	Reaction Time(hr)	Yield[c] (%)	Cyclic content (%)[d]	Overall by GPC[e]	DP by NMR[f]
1	82DA	A	0.075	0.53	THF	60	36	64	39	1.9	2.6
2	82DB	A	0.033	0.30	$CHCl_3$	60	36	59	45	1.8	2.5
3	82DC	B	0.018	0.16	$CHCl_3$	60	36	61	25	1.4	1.6

[a]: A = 11-bromoundecanoic acid; B = N-(11-bromoundecanoyl)-aminoundecanoic acid. [b]: [M] = concentration of monomer in solution(mol/l, M); R = the number of moles of monomer (mmol) per mmol of DBU unit. [c]: Obtained yield. Calculation based on the weight of feed monomers, i.e., yield = weight of product assuming it is cyclic divided by maximum possible yield of cyclics. [d]: Calculation based on the identification of the cyclic peaks on the GPC traces. The cyclic content is obtained by {the total area of cyclic oligomers divided by total peak area.}. [e]: For all the mixture(not only for the cyclic or the linear), estimated by classical method from the GPC traces, i.e., area counting or paper-weighing. [f]: Determined using a 200 Hz NMR instrument.

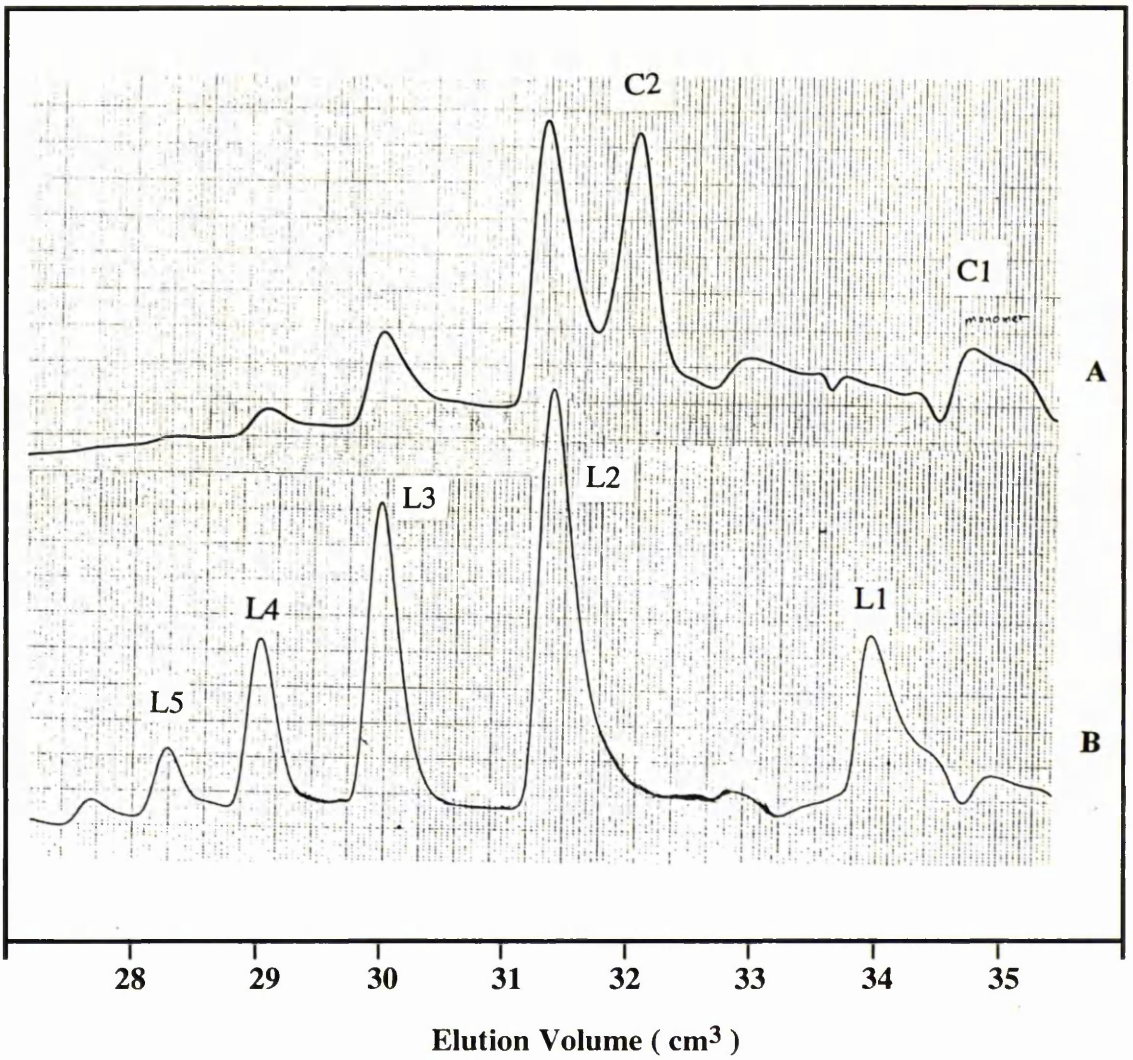


Figure 3.5 GPC-C traces of cyclic esters prepared by use of PS-DBU

A: Products from entry 2 (Table 3.1); B: Linear oligomers of bromoundecanoic acid.

3.2.3 An Attempt to Prepare Cyclic Oligomers by the Use of Amberlyst A-21

An attempt to prepare cyclic oligomers was made using the commercial polymer-supported weak organic base Amberlyst A-21. This contains benzyldimethylamine residues, 3.7-4.0 mmol/g: see Figure 3.6. Using similar reaction conditions to those used in the reactions summarised in Table 3.1, 11-bromoundecanoic acid was used as the monomer. However, very poor yields (10-20%) were obtained from the cyclisation reactions, although about 30-50% of the product was cyclic oligomers. Quaternisations,

as shown in Figure 3.6, might be responsible for the poor yields. This reaction would attach the monomers onto the polymer beads.

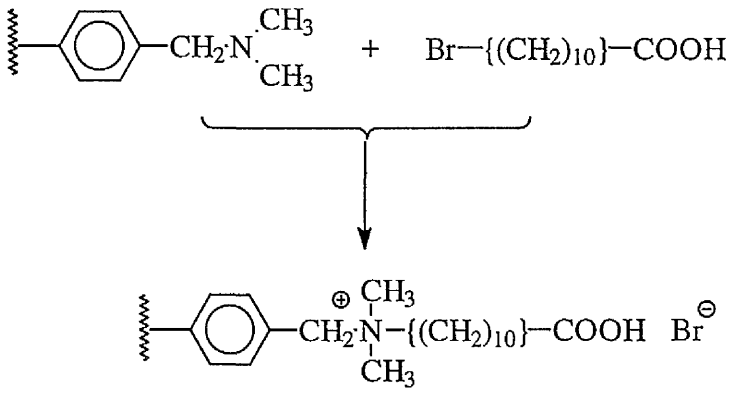


Figure 3.6. Quaternisation reaction of Amberlyst 21 resin.

3.3 THE USE OF A POLYMERIC OXIME RESIN

Polymer-supported oximes have been widely used recently in the synthesis of both linear polypeptides[141] and cyclic peptides.[116,117,142] They have many attractive features such as allowing the rapid consecutive assembly of aminoacids on the solid support, rapid aminolysis, and providing a labile active ester linkage on the solid support which could benefit both the nucleophilic cleavage of C-end protected amino acids and the intramolecular cyclisation-cleavage to produce cyclic peptides or peptidomimetrics.[116,117,142,143]

Polymer-supported oximes do not appear to have been employed before for the synthesis of cyclic oligoesters and linear esters.

3.3.1 Preparation of the Polymer-Supported Oxime

The polymer-supported oxime was prepared using a literature method.[141] Crosslinked-polystyrene beads (2% crosslinked) were acylated using *p*-nitrobenzoyl chloride and aluminium trichloride. The product was characterised by FT-IR

spectroscopy (carbonyl band at 1665 cm^{-1}) and by elemental analysis (2.29 mmol of N/g). The ketone groups were converted into oxime groups by treating the resin beads with hydroxylamine and pyridine. By elemental analysis for nitrogen the product contained 2.07 mmol of oxime residues per gram. An FT-IR spectrum of the oxime resin showed no band at 1665 cm^{-1}, indicating that the oxime-forming reaction was quantitative.

3.3.2 Coupling the Hydroxy Acid Monomers to the Polymer-Supported Oxime

N,N'-Dicyclohexylcarbodiimide (DCC or DCCI) is probably the most widely used reagent for peptide coupling[144,145] and for a wide variety of other coupling reactions between acidic species and nucleophiles[146,147] such as between acids and alcohols,[150,151] phenols,[144,146,148] thiols[122] and N-tosylamines.[149] 4-Dimethyl-aminopyridine (DMAP) is frequently used as a catalyst to accelerate the formation of esters and thioesters.[150,151]

The polymer-supported ω-hydroxyalkyl active esters prepared by Ford[122] and by Röthe[123] were prepared using DCC coupling. Both of these authors used *tert*-tetrabutyldimethylsilyl (TBDMS) groups to protect the hydroxyl groups in the DCC-mediated coupling reactions so as to avoid possible oligomerisation of the monomers. However, to protect and deprotect the hydroxyl group by TBDMS is a tedious multiple reaction route. Moreover, the protected ω-hydroxyalkyl acid monomers are not stable to moisture or an acid environment. In order to avoid using protecting and deprotecting procedures, the polymer-supported oxime was coupled directly with the ω-hydroxyalkyl carboxylic acid using DCC: see Figure 3.7. Although some oligomerisation of the hydroxy acid may occur on the resin or in solution, see Figure 3.8, this was not considered to be a problem because the product was to be used in a cyclo-oligomerisation reaction.

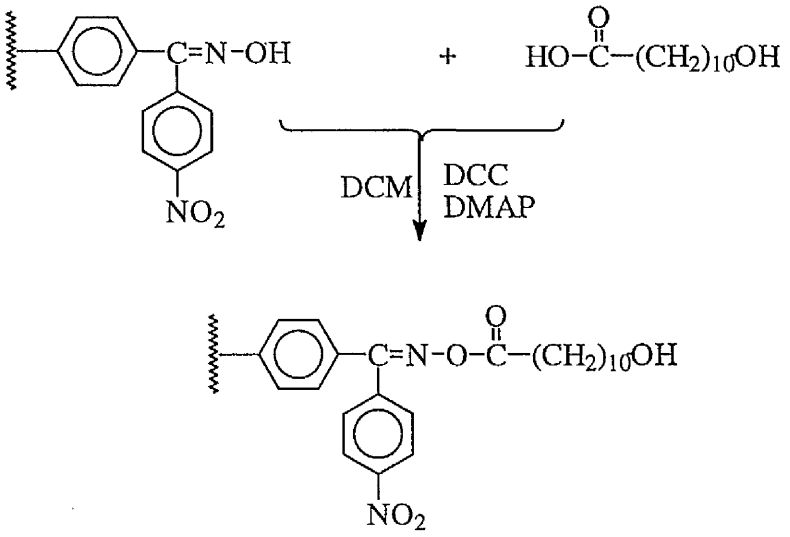


Figure 3.7. Coupling the ω-hydroxyalkyl acid onto the polymer-supported oxime resin.

$$HO{-}(CH_2)_{10}COOH + HO{-}(CH_2)_{10}COOH \xrightarrow[DMAP]{DCC} HO{-}\{(CH_2)_{10}COO\}_n H \quad n= 2, 3, \ldots$$

Figure 3.8. The competing reactions in the coupling procedure.

In practice, it was found that the coupling reactions were very effective and the coupling yields were excellent (around 80% of the feed monomer). This might be due to the stronger acidity of the hydroxyl groups in the oxime structure, which enables the hydroxyl groups of the oxime to be more actively involved in the coupling reaction than those of the monomers. Oxime beads with different loadings of monomers were prepared by using different feed ratios. The results are summarised in Table 3.2.

Table 3.2. Summary of the coupling reactions*.

Entry	Notebook Reference	Feed (mmol/g)[a]	Loading achieved			Coupling Yield (%)	DP[e]
			(mmol/g)[b]	(w/w%)[c]	(%)[d]		
1	2-65r	2.50	1.35	25.0	30.3	72	1.35
2	2-80r	1.86	1.19	22.0	25.6	82	1.33
3	2-85r	1.24	0.76	14.1	14.9	80	1.20

* All reactions were carried out on SX1-PNO resin.

[a] Millimoles of 11-hydroxyundecanoic acid per gram of oxime resin. [b] Estimated by weight increase. [c] Weight percentage. [d] The average numbers of monomer units per 100 styrene units. [e] Calculation based on the integration of ^{13}C NMR (125 Hz, T1 = 30s) spectra of swollen beads. DP = [integration at δ64.5 / integration at δ62.5] + 1.

The ^{13}C NMR spectrum of the swollen loaded (see Figure 3.9) beads proved that the coupling reaction produced oligomers on the polymer support and that the average degree of oligomerisation was from 1.20 to 1.35. From the point of view of the coupling reactions, this implies that 65-80% of the coupling reaction took place between monomer molecules and the OH groups of the oxime support and that only 35-20% of the coupling reaction took place between loaded monomers and monomers in solution, or between linear oligomers in solution and the OH groups of the support oxime. This suggests that the formation of the oxime active esters is 3 to 4 times more rapid than the formation of normal ester linkages on the polymer support (formed between the hydroxyl groups of supported species and the acid groups of the monomers).

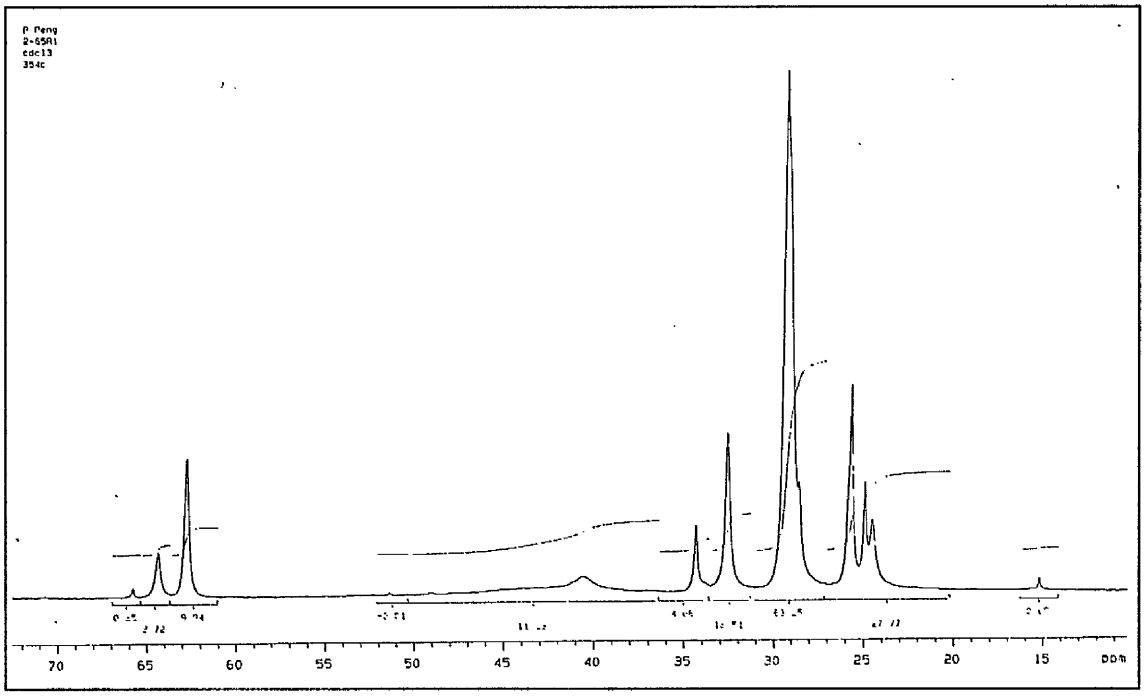


Figure 3.9 ^{13}C NMR spectrum of PNO resin loaded with 11-hydroxylundecanoic acid.

3.3.3 Cyclisation Reactions

Cyclisations of the polymer-supported hydroxy acid were brought about by treatment with an organic base in an organic solvent. The results are summarised in Table 3.3. The reactions gave oligoesters in yields of 65-93% with a cyclic content of 30-50%. The cyclic oligomers were identified by GPC (see Figure 3.10) as being from the cyclic monomer up to the cyclic hexamer (the resolution limit). The following sub-sections discuss the effect of the various reaction parameters.

Base

The tertiary amines DBU and DIEA were used to bring about the cyclisation reactions. The results, entry 1, showed that DIEA was not able to effectively bring about the reaction on the polymer support and only a 10% yield of oligoesters was produced at room temperature. It may be that DIEA is not a sufficiently strong base to activate the hydroxyl group of the supported monomers. DBU did, however, successfully catalyse the

cyclo-oligomerisation reaction and accordingly it was used for all the subsequent reactions.

Solvent

THF, $CHCl_3$, DCM and toluene were all tried as reaction solvents. The cyclisations in THF and toluene produced a significant product fraction of high molecular weight, which could not be identified as either cyclic or linear. The variation of solvent does not seem to influence the yield of cyclic oligomers and chloroform was adopted as the solvent for most of the subsequent studies.

Loading

It is clear from Table 3.3 that the average DP of the products is closely dependent on the loading of the polymer beads and the solvent. A higher loading produces products having a higher DP despite the variations of the conditions such as the concentration of the DBU, and the reaction time. Lower loadings tend to afford more cyclic oligomers.

The formation of linear oligomers

The present polymer-supported cyclo-oligomerisation is supposed to produce a product free of linear oligomers but in practice this did not prove to be the case. In the active ester linkage approach, the linear oligomers might be released from the support by hydrolysis due to the presence of moisture. Although all the reactants used were carefully dried, substantial amounts of linear oligomers were still present in the final product.

In the present study no special experiments were carried out in an attempt to understand the formation of the linear oligomers and this phenomenon still needs further investigation.

Table 3.3 Cyclisations of 11-hydroxyundecanoic acid on the oxime resins at 20 °C

Entry	Notebook Reference	Loading (mmol/g)	Reaction solvent	Reaction time (hr)	DBU concentration (mole/l)	Yield (%)	Cyclic Product		DP[b]	
							(%)[a]	DP (GPC)	by GPC	by NMR[c]
1	65d	1.35	THF	120	DIEA	10		-		8.0
2	65e	1.35	$CHCl_3$	120	0.25	92	69	2.7	3.2	3.6
3	65f	1.35	THF	120	0.17	90	17	2.8	6.3	7.4
4	65g	1.35	DCM	120	0.17	80	18	2.6	5.4	10.1
5	65a	1.35	THF	120	0.135	90	27	2.8	4.5	8.2
6	65b	1.35	Toluene	120	0.0075	85	28	2.0	4.1	9.0
7	65c	1.35	THF	120	0.0075	81	44	2.3	3.5	10.4
8	80e	1.19	$CHCl_3$	36	0.1	91	27	2.6	3.6	4.5
9	80a	1.19	$CHCl_3$	36	0.21	87	33	2.2	3.1	4.3
10	80c	1.19	$CHCl_3$	36	0.25	95	27	2.3	3.4	4.0
11	80b	1.19	$CHCl_3$	36	0.45	89	36	2.3	3.1	4.0
12	80d	1.19	$CHCl_3$	36	1.0	88	27	1.8	2.9	3.6
13	85a	0.76	$CHCl_3$	36	0.45	91	36	2.7	2.6	3.4
14	85b	0.76	$CHCl_3$	36	0.25	86	37	2.7	2.8	3.4
15	85c	0.76	$CHCl_3$	36	0.1	65	51	3.2	2.7	3.3

[a]: Calculation of cyclic content based on the GPC-C identification. The area of cyclic peaks from monomer ring to hexamer ring was counted. [b]: Average DP of mixture products. [c]: 500 Hz H NMR spectrometer was used.

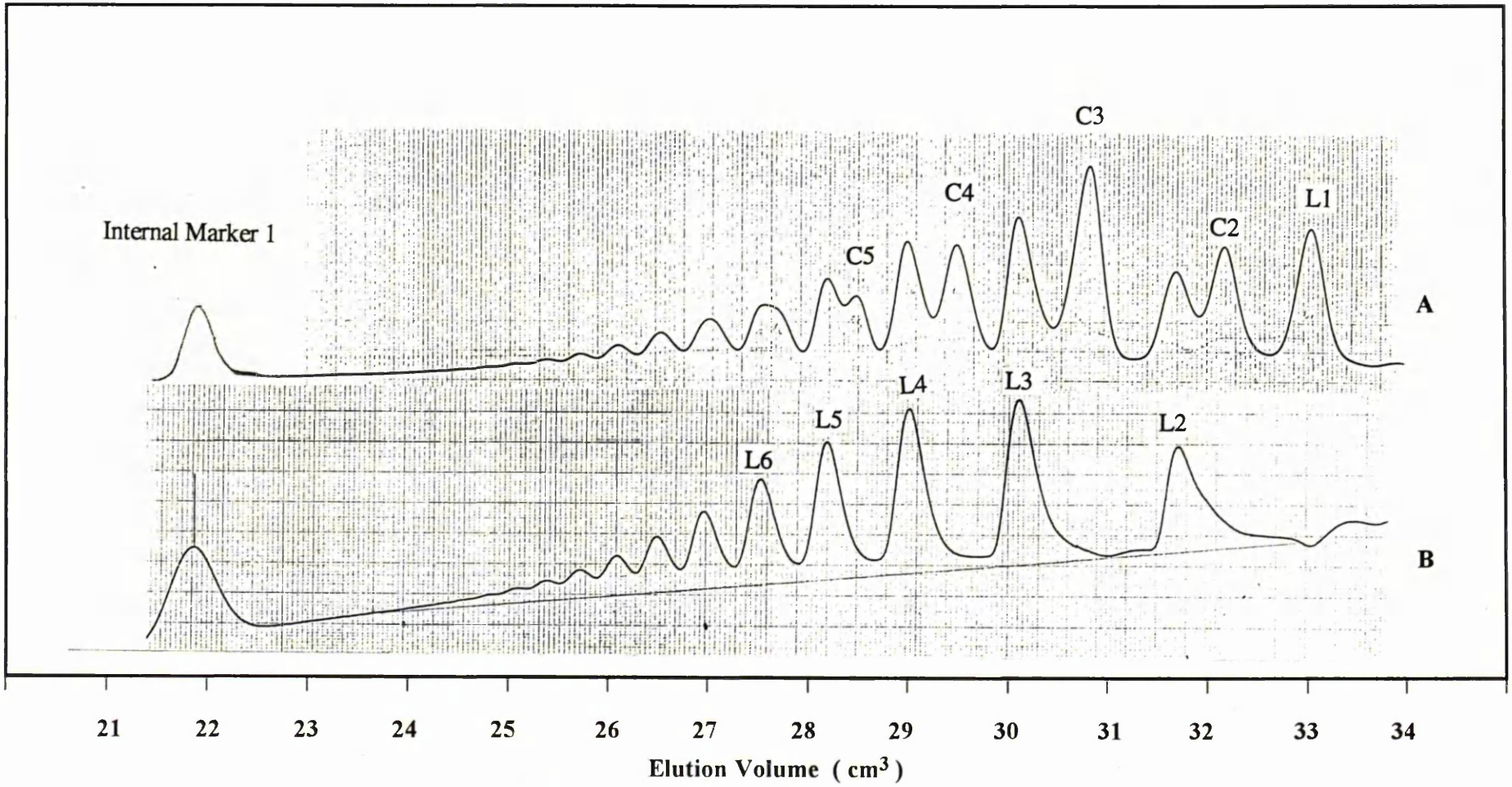


Figure 3.10 GPC-C trace of cyclic oligoesters prepared by use of SXI-PNO resin.

A: cyclic sample from entry 15 (tab. 3.3) ; B: linear ester 3a.

CHAPTER 4

SYNTHESIS OF CYCLIC OLIGOAMIDES

4.1 INTRODUCTION

Cyclic oligoamides have attracted a great deal of attention in the last decade.[31,82] Cyclic oligoamides are usually formed in ring-opening polymerisations or in the thermal depolymerisation of polyamides or copolyamides.[78-81] Many of these studies have been concerned with cyclic Nylon 6.[152,153] The isolation of the cyclic amides has largely relied on the solvent extraction of polyamide melt chips. Since many polyamides are poorly soluble in common solvents, which poses great difficulties for their separation and characterisation, the composition of cyclic amide fractions prepared by extraction are very much subject to the solvent used. In most cases, only small cyclic amide oligomers (from monomer up to hexamer) have been detected in extracts by HPLC analysis[152,153] and by FAB-MS.[153]

Polyamides are of great importance in modern materials science and industry. Cyclic oligoamides are potential precursor polymers for easy processing and they are ideal model compounds for structural research. Cyclo-oligomerisation on polymer supports could provide a novel method for the preparation of cyclic amide oligomers.

Cyclo-oligomerisations of ω-aminoalkanoic acids on polymer supports have been reported in a few papers by Röthe *et al.*[102,106,127] in connection with the debate about site-site interactions in solid phase peptide synthesis. The cyclic oligomers detected from the dimer of 6-aminohexanoic acid were of up to 40 repeating units.[106] Recently, the same author conducted a preparative separation of these cyclic amides by GPC and reverse phase HPLC. The separated cyclic amide oligomers accounted for 69% of the loaded monomer weight.[124] Finally, Röthe reported very briefly on the cyclo-oligmerisation of 11-aminoundecanoic acid.[106]

The research described in this Chapter is concerned with the cyclo-oligomerisation of 11-aminoundecanoic acid on polymer supports. Several polymer supports with active ester groups have been studied. Since the cyclic oligomers were generally obtained in poor yield and they were mainly small cyclic oligomers, some effort

was made to investigate the unrecovered material remaining in the polymer supports. The reactions involved are summarised in Figure 4.1.

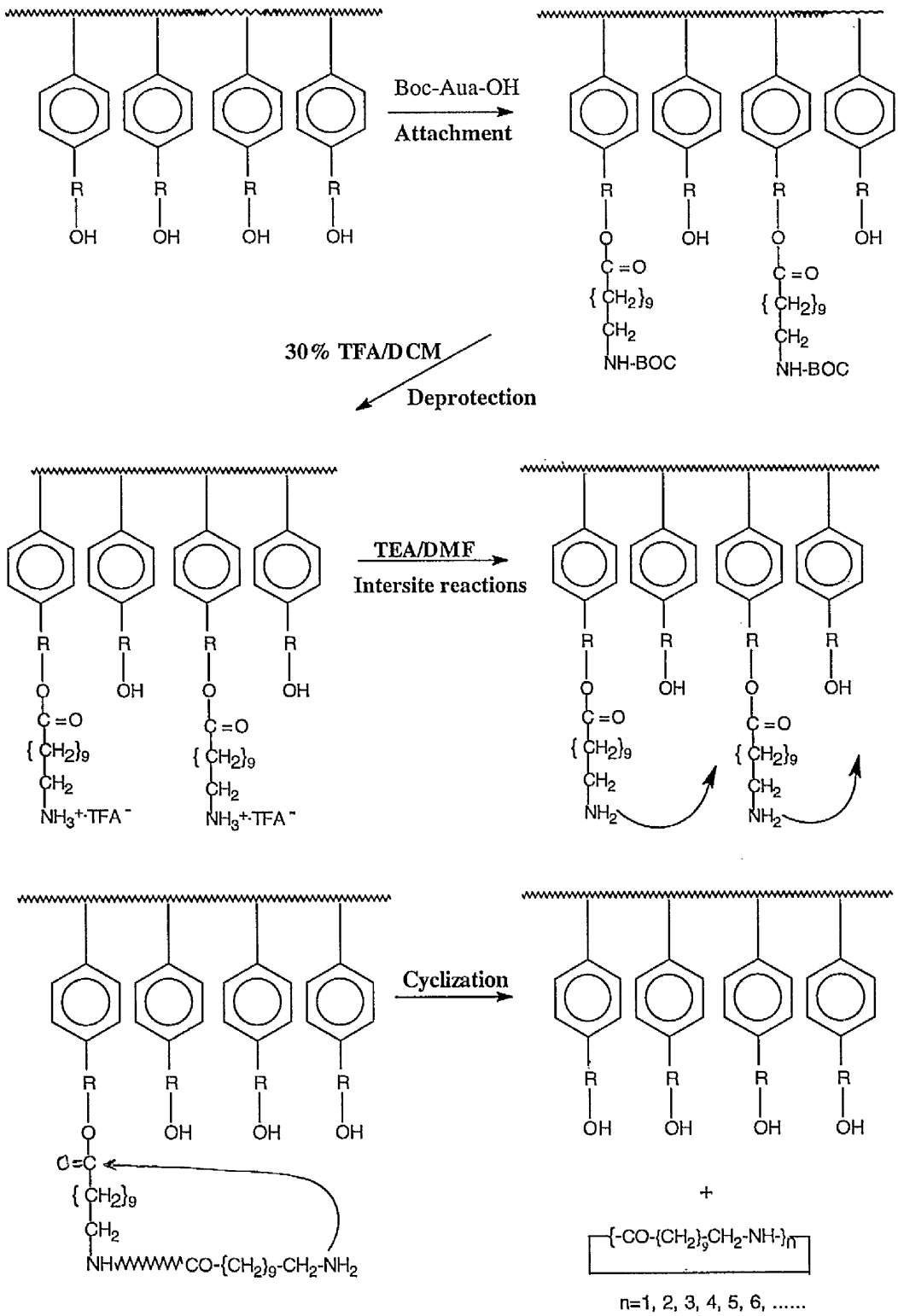


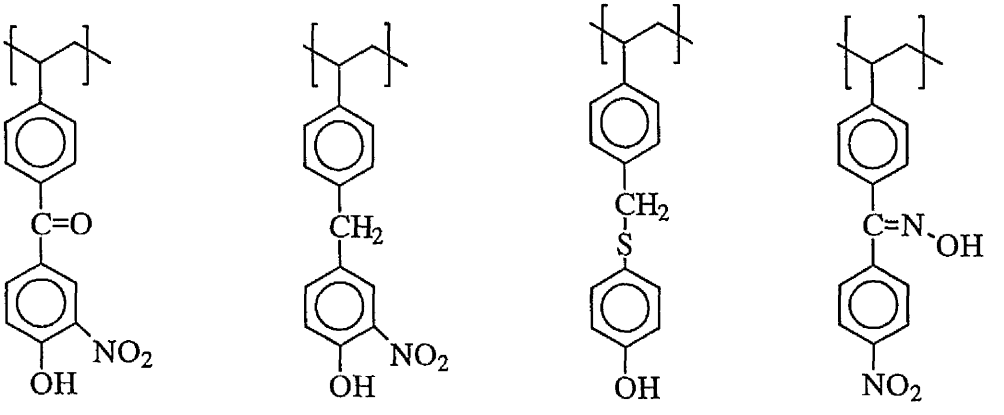
Figure 4.1. Reactions involved in the preparation of cyclic oligoamides.

Polymer supports refer to Figure 4.2

4.2 PREPARATION OF POLYMER SUPPORTS AND THE ATTACHMENT OF THE MONOMERS

4.2.1 Synthesis of the Polymer Supports

In general, the techniques used in cyclising linear peptides on a solid support can also be used to prepare other cyclic amides. Many techniques have been developed for peptide cyclisation[96,114,115,154] (refer to Chapter 1, Section 1.3.2.2), but of these techniques only active ester supports are potentially useful for the cyclo-oligomerisation of ω-aminoalkanoic acids and ω-amino aromatic acids because these monomers have no side groups available for anchoring the monomer to the support. Several well-known 'active ester' polymer supports have been extensively used in solid phase peptide synthesis. These are shown in Figure 4.2.



PHNB-1, PHNB-3, PHNB-2, PHPS, PNO

Figure 4.2. Structure of polymer supports.

For the present studies these polymer supports were prepared according to the literature methods referenced in Table 4.1. PHNB-1 and 3 resins were obtained by Friedel-Crafts acylation reactions of unfunctionalised crosslinked polystyrene beads with 4-chloro-3-nitrobenzoyl chloride in the presence of aluminum trichloride, followed by the hydrolysis of the *para*-chloro group to a hydroxyl group. PHNB-2 was prepared by a

Table 4.1. Preparation and Characterisation of Various Polymer supports[a]

Designation	Percentage of Cross-linking	Loading[b] (mmol/g)	Degree of Substitution[c]. (%)	Chlorine residues (% Cl)	Key IR bands (KBr disc, cm^{-1})	Reference for preparation
PHNB-1	2%	2.10	33.5	1.5	1660, 1620, 1538, 1291	Cohen *et al.*[154]
PHNB-3[d]	8%	2.0	31.1	0.3		
PHNB-2	2%	1.84	26.6	0	1658, 1621	Kalir *et al.*[155]
SX1-PHPS	1%	1.59	21.2	0	3412, 1598	Flanigan *et al.*[114]
SX2-PHPS	2%	1.59	21.2	1.6		
SX1-PNO	1%	2.40	41.3	-	3550, 1600, 1520, 757	Kaiser *et al.*[141]
SX2-PNO	2%	2.29	38.2	-		

[a]: Unless indicated otherwise microporous beads of particle size 150 - 425 mesh. [b]: millimoles of active OH per gram resin, calculated by elemental analysis. [c]: number of substituted functional groups per 100 styrene units. [d]: microporous; 20-60 mesh.

Friedel-Crafts reaction of unfunctionalised polystyrene beads with 4-chloromethyl-2-nitrophenol. The PHPS resins were prepared by reacting Merrifield resins with the potassium salt of *p*-hydroxythiophenol.[114] PNO (Kaiser oxime resin) was synthesised as described in the previous Chapter by the use of a Friedel-Crafts acylation of polystyrene beads with 4-nitrobenzoyl chloride, followed by reaction with hydroxylamine and pyridine. The prepared polymer supports were well washed and then dried in a vacuum oven. The IR spectra and elemental analyses are as summarised in Table 4.1.

The obtained resins have loadings of between 1.59-2.40 mmol of active functional groups per gram of resin, which are equivalent to 21%-41% substitution of the styrene units.

In some cases chlorine residues were detected by elemental analysis. The chlorine residues in the PHPS resins were possibly in the form of $-CH_2Cl$. These are reactive to free amino groups and thus potentially could terminate the cyclisation reaction. Therefore, repeat reactions were carried out in order to eliminate the chlorine residues. The chlorine residues in PHNB-1 and 3, on the other hand, were considered to be harmless in the cyclisation reaction. The reaction used to prepare PHNB-2 was not expected to leave any chloro or other reactive residues in the beads.

4.2.2 Loading of Monomer

Loading reaction

The loading of the monomers onto the various hydroxy-containing supports was carried out by DCC coupling reactions and by symmetrical anhydride reactions. The former procedure has already been described in Section 3.3.2. Symmetrical anhydride coupling procedures consume twice as much monomer as the direct coupling reaction by DCC, but they avoid the formation of DCU in the polymer beads and therefore have an advantage in some circumstances: see Figure 4.3.

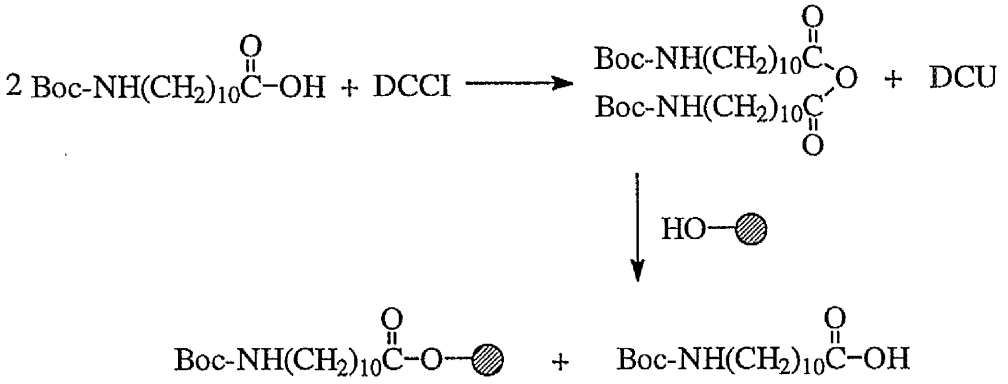


Figure 4.3. Symmetric anhydride coupling procedure.

Catalyst

Dimethylaminopyridine is one of the cheapest and most efficient catalysts employed in the DCC coupling reactions to expedite the decomposition of the DCC intermediate.[150,151] It is widely used in DCC-mediated coupling reactions to prepare amides and peptides.[144,145]

Washing solvent

Mixtures of DCM-methanol were developed as a solvent system to wash away the DCU from the resins in solid peptide synthesis. This solvent system is quite effective to remove unused reactants and DCU from the polystyrene beads. The typical mixture is 50/50 to 70/30 (DCM/MeOH).

4.2.3 Estimation of Loading

By weight increase

The monomer loadings were estimated by increase in weight of the resins. The loading of a Boc-blocked resin is calculated as follows:

$$\text{Loading (mmol/g)} = [W_f - W_s/(M \,.W_f)] \times 1000$$

Table 4.2 Loadings of Monomer and Yields of Cyclization of Boc-Aua on Polymeric Supports

Entry	Support	Amount of monomer used (mmol/g of resin)	Coupling Yield (%)	Loading of monomer (mmol/g)	Cyclo-oligomerisation Reaction			
					Solvent	Temperature (°C)	Time (days)[a]	Yield (%)
1	PHSP	2.9	21[d]	0.65	DCM	r.t.	6	12
2	PHNB-1	2.5	23 [d]	0.91	DCM	r.t..	4+8	13
3	PHNB-1	4.5	20 [e]	0.73	DCM	r.t.	8	7
4	PHNB-2	6.0	15 [e]	1.00	DCM	r.t.	1+5	8
5	PHNB-2	4.5	24 [d]	0.86	DMF[b]	60-80°	3+5	12
6	PHNB-2	4.5	24 [d]	0.86	DMF	r.t.	1+2	10
7	PHNB-1	4.5	22 [d]	0.82	Toluene	r.t.	3	5
8	PHNB-1	4.5	22 [d]	0.82	DMF	r.t.+60°	3+1	11
9	PHNB-2	4.5	12 [e]	0.48	DMF	r.t.+150	1+2	11
10	PHNB-3	4.5	8, 10 [f]	0.47	DMF	r.t.	3	14
11	SX2-PHPS	2.5	23, 20 [f]	0.83	DMF	r.t.+70°	3+5	9
12	SX2-PNO	2.0	65 [d]	0.98	DMF	r.t.	3	12
13	SX1-PHPS	2.0	55 [d]	0.85	DMF	r.t.	7	15
14	SX1-PNO	2.5	76 [d]	1.28	DMF	r.t.	7	16

[a]: + indicates successive reaction times. [b]: Deprotected by HBr/HOAc. [c]: TFA/Chloroform solvent(1/1, v/v); [d]: DCC coupling in presence of DMAP. [e]: Symmetric anhydride coupling in presence of pyridine. [f]: Coupling reaction was repeated twice.

where W_f is the final obtained resin weight in grams, W_s is the start resin weight, M is the molar mass of the monomer residue.

The loadings, shown in Table 4.2, were found to be in the range of 0.50-1.00 millimoles per gram. This is equivalent to 10-20% of the phenyl groups in the polymer beads bearing a monomer.

By titration

In some cases the loadings of the resins were also estimated by reacting the resins (0.100 g) with an excess of benzylamine (0.3 M in toluene) and back-titrating with perchloric acid (0.01M in acetic acid) with methyl violet as the indicator.[156] The results are shown in Table 4.3. Although the loadings calculated from the titration are slightly higher than those calculated from the weight increases, the experiments show that the values estimated by the weight increases are reasonably accurate.

Table 4.3. Comparison of the Loading Estimated by Two Methods

Entry in Table 4.2	9	12
Estimation by weight increase (mmol/g)	0.48	0.98
Estimation by titration (mmol/g)	0.60-0.70	1.00-1.05

Benzylamine reaction

The Boc-blocked Aua-resin whose preparation is summarised in Table 4.2, entry 4, (loading: 1.00 mmol/g, 0.485 g, 0.49 mmol) was reacted with an excess of benzylamine (0.306 g, 2.86 mmol) at room temperature for 1 day. The resin was then filtered off. The filtrate was washed with 1N HCl, 5% $NaHCO_3$, H_2O and purified on a small 20 x 2 cm silica column to afford as a solid product (0.180 g, 94%), m.p.: 107-108 °C, of the N-tBoc aminoundecanoic acid benzylamide. ^1H NMR spectroscopy confirmed the structure.

This reaction confirmed that, in this case at least, the loading estimated from the weight increase properly described the loading of the resin.

Soxhleting experiment

In the coupling reactions, there is the possibility of producing DCCI derivatives and DCU residues which might not be completely washed away from the resins. In order to confirm the effectiveness of the washing procedures, Soxhleting was used to extract the last traces. The resins from entry 3, 4, 5 and 10 were soxhleted using DCM/MeOH (1:1) overnight. The results showed that very little was extracted by the solvent and that there were no obvious weight losses of the loaded resins. This seems to show that the washing procedures were reasonably effective for the removal of the DCU, unreacted Boc-monomer, and DCCI side-products.

4.2.4 Characterisation of Loaded Beads

IR spectra

The IR spectra of all the Boc-monomer active resins showed bands at around 1750-1775 cm^{-1} (-CO-O-resin) and 1690-1715 cm^{-1} (Boc). The conversion of the PHPS sulfide resins into sulfone resins was easily monitored by IR spectroscopy because the ester band asymmetric vibration in the sulfide resin occurred at 1758 cm^{-1} and was shifted to 1763 cm^{-1} after oxidation.

^{13}C NMR spectra

^{13}C NMR spectra of the loaded resins were obtained using a 125 Hz ^{13}C NMR spectrometer with D_1 = 15s. The spectra showed clearly the presence of monomer moieties in the resin. A typical spectrum is shown in Figure 4.4.

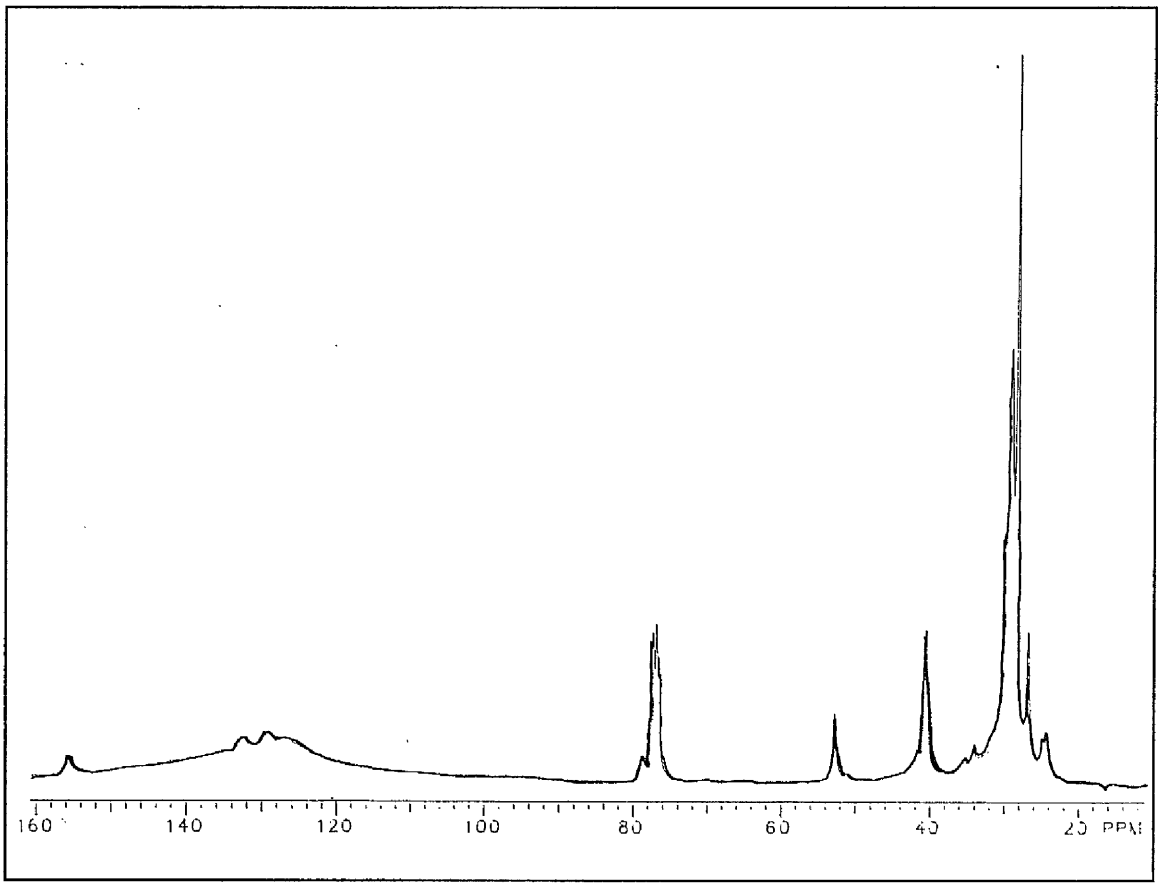


Figure 4.4. ^{13}C NMR spectrum of loaded polymer beads described in Table 4.2, entry 3.

4.2.5 Efficiency of Coupling Reactions

The DCC coupling reaction is a convenient and monomer-saving coupling reaction. It usually couples the monomer to the beads in high yield and produces polymer beads with a reasonable loading compared with the symmetrical anhydride method. Since recycling the monomer was not easy and was tedious, from both points of view, the DCC coupling reaction is preferred.

Some difficulties in fastening peptide monomers onto a PHNB resin were encountered in Fridkin's research.[96] It was also found in the present work that with the PHNB resins the coupling reactions were incomplete. Accordingly in most cases a second coupling reaction was necessary in order to achieve satisfactory loadings. PHPS resins were also found not to be easily loaded and reasonably high loadings (i.e. around 1

mmol/g) were obtained by carrying out the coupling procedure twice(entry 11 in Table 4.2). PNO resins were found to be the best beads with an easy loading of monomers to a reasonably high loading without the need for any repetitive coupling procedures. The coupling yields and loading conditions were as shown in Table 4.2.

4.2.6 The Stability of Loaded Resin Beads

The active esters of resins PHNB-1 and 3 are more active than those of PHNB-2 and they may suffer more hydrolysis than those on the PHNB-2 resin during storage, deprotection and cyclisation steps. A titration showed that the loaded PHNB-1 resins of entries 7 and 8 (Table 4.2) had a loading of 0.1-0.2 mmol/g after one month in storage at room temperature (original loading was 0.82 mmol/g). Thus, more than 70% of the active ester groups were hydrolysed.

The active esters prepared from resins PHNB-2 and PNO are relatively stable and by titration there was no obvious hydrolysis during storage and during the deprotection procedure.

4.3 MODEL COMPOUNDS

In order to characterise the cyclisation products, a series of model compounds were prepared. They were needed to help in the assignment of the signals in the NMR spectra of reaction products and the peaks in the HPLC and/or GPC traces. A knowledge of the properties of the model compounds was also helpful for predicting the properties of the target molecules.

4.3.1 Cyclic Oligoamides

11-tBoc-Aminoundecanoic acid *p*-nitrophenyl ester was prepared. The t-Boc group was removed and the product was allowed to react in a dilute solution in DMF (4×10^{-3} M) at 20 °C. After four days the total yield of isolated product was 60%. ^{1}H and

^{13}C NMR and IR spectral data of this sample were consistent with it being a mixture of cyclic oligomers. Interestingly, the ^{1}H NMR spectra (see Figure 4.5) showed slight differences in the chemical shift of the amide protons (CONH-) from the cyclic monomer to the cyclic pentamer: see Table 4.4.

Table 4.4. ^{1}H NMR Chemical Shifts of the Amide Protons of Cyclic Oligomers of Nylon 11.

DP of cyclic Nylon 11	1	2	3	4	5
Shift δ ppm	5.37	5.56	5.74	5.85	5.93

Chemical shifts were recorded in $CDCl_3$ at 25 °C.

The percentage composition of the cyclic oligomers product as found by integration of the ^{1}H NMR spectral shifts and the values calculated from HPLC and from GPC traces are given in Table 4.5. A typical GPC trace is shown in Figure 4.6 and a typical HPLC trace is shown in Figure 4.7. Both the GPC analysis and the NMR analysis indicated that the product was a mixture of cyclic oligomers together with a small amount of cyclic monomer. The product possibly only represents the yield of chloroform-soluble product because of the poorer solubility of the larger oligomers. Small samples of the cyclic 'dimer' and 'trimer' of modest purity were isolated by preparative HPLC as described later.

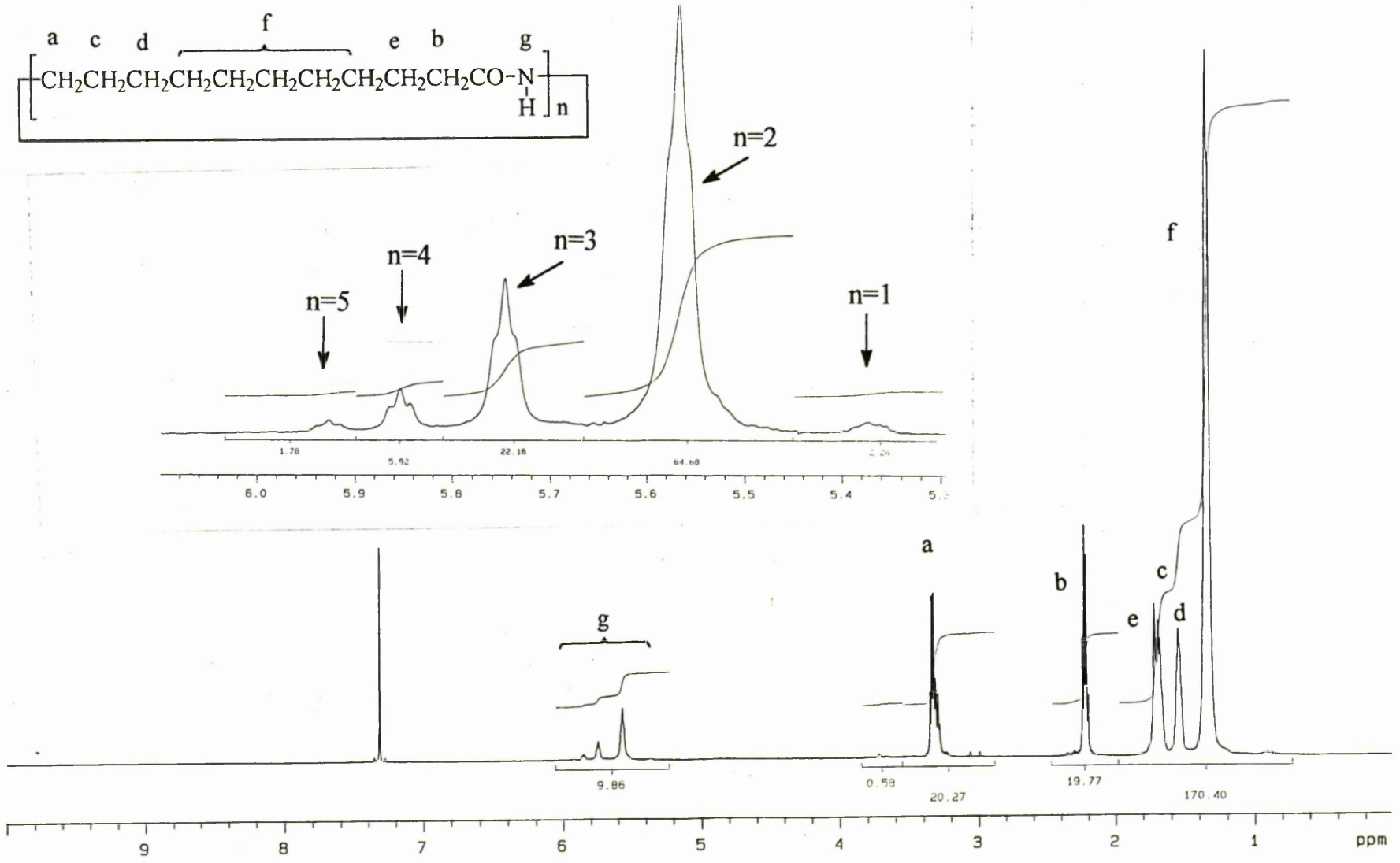


Figure 4.5. ^{1}**H NMR Spectrum of Cyclic Nylon 11s**

(This sample is referred to section 4.3.2, ^{1}H NMR recorded by a 500 Hz NMR for a solution of $CDCl_3$)

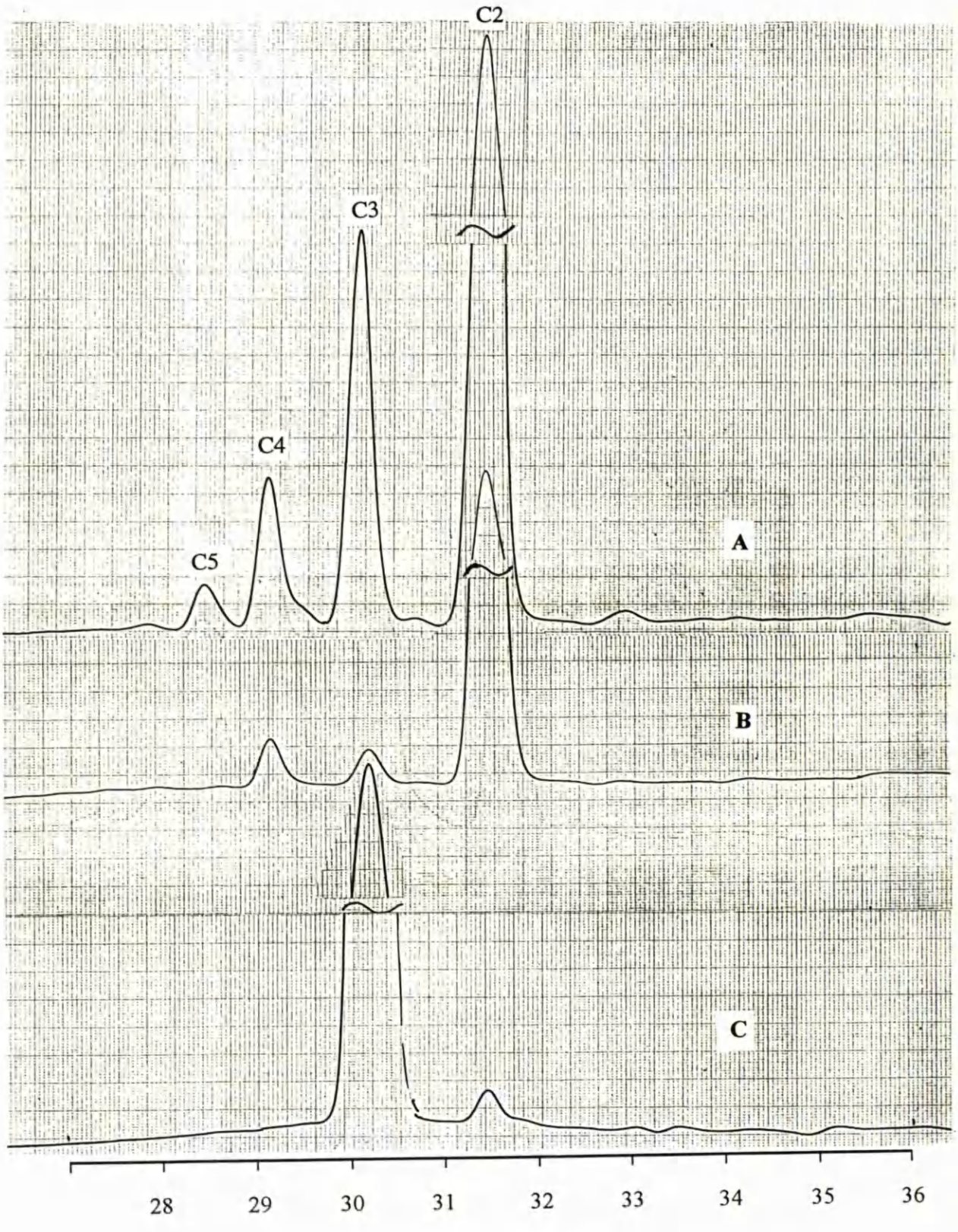


Figure 4.6 GPC-C traces of cyclic Nylon 11s

A: The sample referred to Section 4.3.1. B: Cyclic amide "dimer" separated by preparative HPLC. C: Cyclic amide "trimer" separated by preparative HPLC.

Table 4.5. The Percentage Composition of The Cyclic Product From Reaction of 11-Aminoundecanoic Acid *p*-Nitrophenyl Ester.

DP	1	2	3	4	5	6	$\bar{M}_n$
^{1}H NMR[a]	2.3	66.8	22.9	6.1	1.9	--	2.4
HPLC[b]	1.7	61.1	37.2	--	--	--	--
GPC(Wi%)[c]	0.3	62.5	23.5	9.9	3.3	0.6	--
(Ni%)[d]	0.7	73.3	18.4	5.8	7.7	1.4	2.7

[a]: Calculated from ^{1}H NMR(500 MHz) NH signals. All data are area percentage except in **d**. [b]: Calculated from HPLC peaks. Monitored by UV at 210 nm. Number percentage might not be worked out since the ε (absorption coefficient) are unavailable. [c]: Calculated from GPC peaks. Monitored by Refractive Index detector. Area percentage of peaks should represent the weight percentage of peaks. [d]: Number percentages obtained from area percentages for convenient comparison to NMR results.

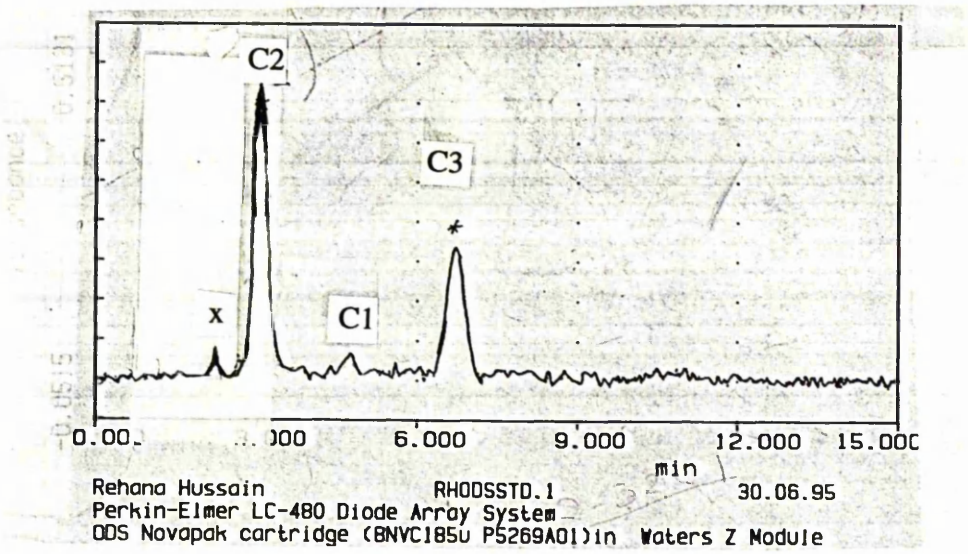


Figure 4.7. Elution curve from analytical HPLC of cyclic Nylon 11s [eluant methanol-water(80:20); UV monitor set at 210 nm].

4.3.2 Linear Oligoamides

Synthesis of the linear dimer: $CF_3COOH\text{-}NH_2(CH_2)_{10}CONH(CH_2)_{10}COOH$

This was synthesised as outlined in Figure 4.8. It was fully characterised by elemental analysis and infrared, ^1H and ^{13}C NMR spectroscopy.

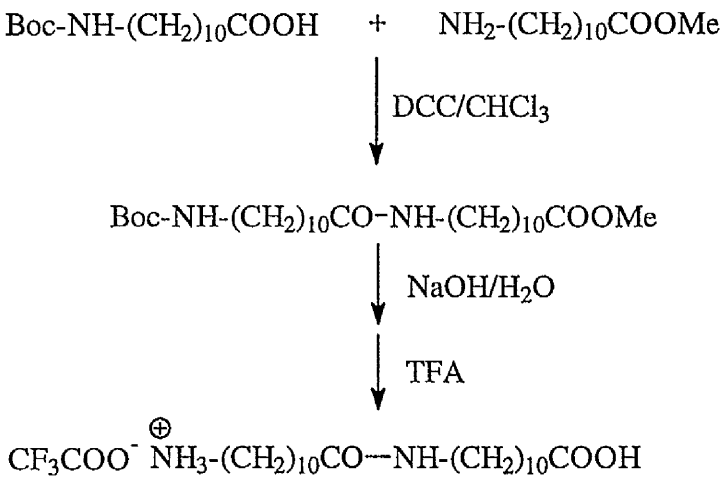


Figure 4.8. Synthesis of the TFA salt of linear dimer of Nylon 11.

Synthesis of the linear oligomers: $(CF_3COOH\text{-}NH_2(CH_2)_{10}CO\{NH(CH_2)_{10}CO\}_xOH)$

Linear oligomers of 11-aminoundecanoic acid were prepared by a similar method to that used for the synthesis of the cyclic oligoamides but the solution in DMF was at a concentration of 0.1 M. Treatment of the product with alkali removed the active ester end groups. The final product was found to be poorly soluble in chloroform, DMF and other common solvents. Accordingly a TFA/chloroform mixture had to be used as the solvent to reprecipitate the product and this resulted in the isolation of the TFA salt of the linear oligomers. The final product, obtained in 80% yield, was found to have an average degree of polymersition around 10 (by NMR spectroscopy and elemental analysis).

The model oligomers showed very important ^1H NMR chemical shift differences between the $-CH_2-$ next to the amino end groups ($-CONHC\underline{H}_2-$ or $NH_2C\underline{H}_2-$) and the $-CH_2-$ next to the amide groups in the main chain. This difference made it possible to

estimate the end groups and hence to calculate the degree of polymerisation of the linear oligomers.

4.4 POLYMER-SUPPORTED CYCLO-OLIGOMERISATIONS

4.4.1 Deprotection

N-Deprotection of the polymer-bound amino acid was generally carried out using either TFA in DCM (1:1) or HBr in acetic acid (33%). Both reagents work very well for the deprotection of the Boc group and this reaction can be monitored easily by the IR spectra of the resins. The TFA in DCM reagent seems to be the more convenient and mild. In solution at room temperature the complete deprotection usually takes 30 min to 1 h. For the substrates on the polymeric beads, a 1 h reaction period for deprotection is usually adopted in most solid phase peptide syntheses. In the present work, in order to guarantee quantitative removal of the Boc groups, a longer deprotection time (normally from 1 to 2 h) was adopted.

4.4.2 Cyclo-oligomerisation on Polymeric Supports

Cyclo-oligomerisations were carried out in the presence of triethylamine or di(isopropyl)ethylamine. When the oxime resin was used, a few drops of acetic acid were added as a catalyst[115, 116]. The aminolysis-cyclisation appeared to be a slow reaction. For many of the cyclisations described in Table 4.2, the reaction was actually terminated without completion of the cyclisation. The latter was deduced from the fact that many recovered beads showed positive Kaiser tests, especially when shorter reaction times were used. In order to accelerate the reaction, in many cases, a second reaction period was used. Usually this reaction was a few days at a higher temperature.

The cyclisations were carried out in different solvents, at different temperatures and for different times. The results are summarised in Table 4.2. In all entries, the cyclic

products were obtained in poor yields, between 5% and 16%. The use of different resins, monomer loadings and reaction times made no noticeable difference to the yield of cyclics. This suggests that this part of the cyclic materials, perhaps, just represented a small part of the solvent-soluble products and that a significant part of the cyclic products remained in the resins.

4.4.3 Separation and Purification

The cyclic product was easily separated. Thus, the crude product was obtained by removing most of the reaction solvent and followed by precipitation into water to wash away the TEA, TFA salt and catalyst. Reprecipitation into water yielded white precipitates. Since the monomer is soluble in water (TFA salt), and the linear oligomers are poorly soluble in chloroform, DMF and the reaction solvent, it was expected that only cyclic oligomers would be obtained by this procedure. As recrystallisation may result in some loss of the cyclic products, the precipitates were used directly for the HPLC analyses and for the GPC analyses.

To understand more clearly the effect of recrystallisation, the cyclic product from entry 8, Table 4.2, was recrystallised from ethyl acetate. This afforded a white solid powder, m.p. 145-148 °C. Elemental analysis and NMR spectroscopy show the purity of the solid was >95%. The GPC analysis of the recrystallised material showed that it consisted mainly of the cyclic dimer and trimer. However, GPC analysis of the original sample (before crystallisation) showed it contained cyclic monomer and higher cyclic oligomer peaks. Thus, the ethyl acetate recrystallisation resulted in the loss of some higher cyclic oligomers.

4.5 ANALYSIS OF CYCLIC PRODUCTS FROM POLYMER-SUPPORTED SYNTHESES

The problem of the separation of ε-caprolactam cyclic oligomers has existed since the early 1950s, as they are a major constituent of the waste product from the production

of Nylon 6 fibres. Much effort has been devoted to try to develop a rapid and reliable analysis of the individual cyclic oligomers in this product. Heikens[157] obtained the cyclic dimer, trimer and tetramer by the fractional sublimation of a methanolic extract. Röthe[158] separated the cyclic oligomers by paper chromatography and determined the individual components by calorimetry. Gas-liquid chromatography (GLC) was utilised in the determination of the cyclic oligomers of Nylon 6 for the first time by Mori *et al.*[159] in 1970, but this method is not entirely satisfactory as it requires the reduction of the cyclic oligomers to the corresponding amines first. About the same time, Mori and Takeuchi[160] published an analytical procedure based on a GPC method and attained a good separation of ε-caprolactam and its cyclic oligomers up to the hexamer on a Sephadex G-15, G-25 and Bio-Gel P-4 columns. Subsequently, many results were reported using Sephadex columns.[82,161]

The introduction of high performance liquid chromatography (HPLC) by Krajnik *et al.*[35] in 1982 brought about a major improvement in the analysis of cyclic amino acid oligomers, especially ε-caprolactam cyclic oligomers and 12-dodecanolactam cyclic oligomers. They used a C_{18} reverse phase (RP-18) column and a methanol-aqueous acetic acid mixture (30:70) as the eluent to separate the ε-caprolactam and its cyclic oligomers. They achieved a good separation. The 12-dodecanolactam and its cyclic oligomers were also well separated on a RP-18 column using aqueous acetic acid-methanol (20:80) as the eluent. Many systems have been developed since.[34,162]

The analysis of 11-undecanolactam and its cyclic oligomers has not been found in the literature. In the present work several approaches were made to analyse the cyclic oligomer samples. Some of these methods have already been discussed in connection with the analysis of the model compounds (Section 4.3).

4.5.1 NMR Analyses

^{1}H NMR spectroscopy was used in the characterisation of cyclic oligoamides for two purposes. Firstly, it was used for confirming the chain structure of the cyclic

oligomers and for detecting impurities in the samples. No end groups were found in most of the samples and the tiny amount of impurity detected were identified as the plasticiser dioctyl phthalate. This could not be removed by precipitation from water. Secondly, as mentioned in Section 4.3.1, it was found that the chemical shifts of the protons on the amide groups (CO-N<u>H</u>-) changed with the degree of oligomerisation of the cyclic oligomers (see Table 4.4). Thus, by expanding, assigning and integrating NMR peaks between δ5.3-6.2 ppm, it was possible to determine the proportions of the individual cyclic oligomers. The separated cyclic dimer and trimer (see below) helped in the assignment of the signals of the dimer and the trimer. Others were assigned accordingly. For example, the NMR spectrum of the cyclic product from entry 3, Table 4.3, had two major peaks at δ5.60 and δ5.77. This implied the presence of only two oligomers and by integrating the two peaks, the proportions of two cyclic oligoamides was found to be 63% (dimer) and 37% (trimer). Similarly, the composition of the cyclics from entry 5 was found to be 40% of cyclic dimer and 60% of cyclic trimer. This phenomenon of differences in the ^{1}H NMR spectra as a function of ring size has not been found in literature so far. The technique might be used for the quick analysis of cyclic oligomers extracted from the industrial products.

4.5.2 HPLC Analysis

HPLC analysis proved to be a very powerful method for the separation of some of the small cyclic amide oligomers. A Waters ODS column Novapack cartridge (10 x 8 mm, 5μ particle size) was used with the UV detector set at 210 nm. Results showed that both 80/20 methanol/water and 75/25 methanol/water were able to separate the small cyclic oligomers up to the trimer. The 80/20 methanol/water mixture eluting at 2 ml/min was good for the rapid analysis of the small cyclic oligomers. The cyclic dimer and trimer were isolated by preparative HPLC, and proved to be useful to identify the dimer and trimer in various reaction products. The cyclic monomer eluted between the dimer and trimer. Tables 4.6 and 4.7 summarise the HPLC solvents used with retention times

and the analysis results respectively. The retention times were heavily dependent on the water content of the solvent system. Accordingly, the retention times may not be constant for different batches of analyses. Therefore, calibration with a standard sample was necessary for every batch. Figure 4.7 shows an example of an HPLC trace.

Table 4.6. The retention times of cyclic oligomers on Nylon 11 in various solvent systems.

Solvent: Eluant ratio of $MeOH/H_2O$	Flow rate ml/min	Retention times (min) of cyclic oligomers				
		monomer	dimer	trimer	higher	unknown
100/0	2	No separation achieved				
80/20	1	6.00	5.25	7.91	10.59	
80/20	2	3.30	2.68	4.17	5.53	2.49
75/25	1	10.40	6.79	13.16	17.17	
75/25	2	5.23	3.40	7.04		
60/40	2		14.81	14.81		

HPLC analysis only separated the small oligomers in the crude cyclic samples. Since the molar extinction coefficient of individual cyclic oligomers and impurities were not available, the UV monitoring method does not permit the proportions of the cyclic oligomers in the samples to be estimated quantitatively.

Table 4.7. HPLC analysis of crude cyclic products.[a]

Entry[b]	Unimer	Dimer	Trimer	Higher
1		63.2	20.0	
2		55.1	23.0	
3		54.3	36.5	
4		45.9	23.1	
5		35.5	34.2	
6	1.7	29.8	48.8	
7		45.1	42.8	
8	15.8	30.9	30.5	11.1
9		27.9	28.8	27.3
10		39.3	41.8	3.15
13	–	60.5	38.0	

[a] Conditions: see Section 7.1; percentages were obtained by area integration.

[b] Sample entry numbers are as given in Table 4.2.

4.5.3 GPC Analysis of Cyclic Products

There seems to be no relevant research reported on the analysis of cyclic oligomers of Nylon 11 by GPC. Several research groups have analysed ε-caprolactam and its cyclic oligomers using Sephadex columns.[82,160,161] Generally, Sephadex columns contain water-based gel stationary phases used with water-based eluents. Cyclic oligomers of 11-aminoundecanoic acid are poorly soluble in water and only partially soluble in cold methanol. They are more soluble in chloroform and ethyl acetate. Therefore, the Sephadex gels are not a good choice of GPC system to run the present cyclic samples.

The GPC-C system available in the Manchester polymer laboratory provided an excellent means for analysing the cyclic samples. This GPC system is equipped with a

stationary phase of macroporous polystyrene beads with a particle size of around 3μ (500 Å) and has been proven to be powerful in separating small oligomers. Chloroform is used as the eluent.

To test the ability of chloroform to dissolve the cyclic amide oligomers, a typical cyclic sample (see entry 13, Table 4.2) was treated with boiling chloroform and filtered. The warm solution was injected into the sample loop immediately. The GPC trace obtained showed peaks due to cyclic oligomers from the dimer up to the octamer (see Figure 4.9 A). However, fearing possible column blockage because of the poor solubility of the bigger oligomers, in future experiments the cyclic oligomer samples were prepared in a different way, i.e. the sample was heated with chloroform, the mixture cooled to room temperature, and the insoluble material removed by filtration. Thus, the results of the GPC analysis only represent the chloroform-soluble part of the cyclic oligomers present.

In a typical GPC trace, only the cyclic oligomers from monomer to hexamer were seen; no higher oligomer peaks could be observed (see Figure 4.9B). Most of the cyclic fractions were just the dimer and trimer. They accounted for more than 65% of the total peak area due to the cyclic oligomers. Accordingly, the average degree of oligmerisation was between 2 to 3. The analysis results are shown in Table 4.8, a log (molar mass) v retention time plot is shown in Figure 4.10, and typical distribution curves are shown in Figure 4.11.

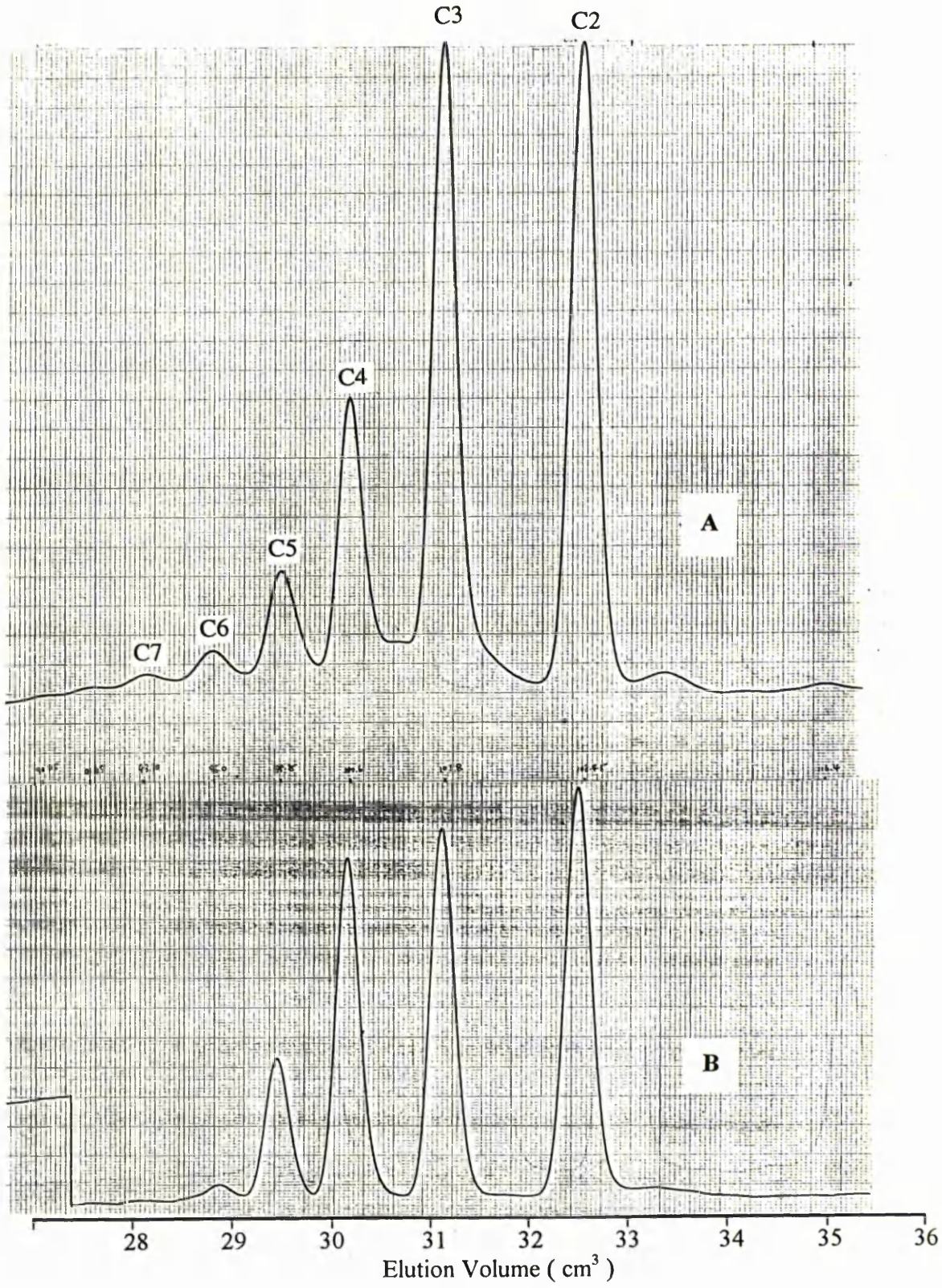


Figure 4.9. GPC-C traces of cyclic oligoamides.

A: The sample refers to in Table 4.2, entry 13: the sample was treated with boiling chloroform and analysed immediately. B: Cyclic oligoamides referred to in Table 4.2, entry 7: the sample was treated with boiling chloroform, cooled, and filtered.

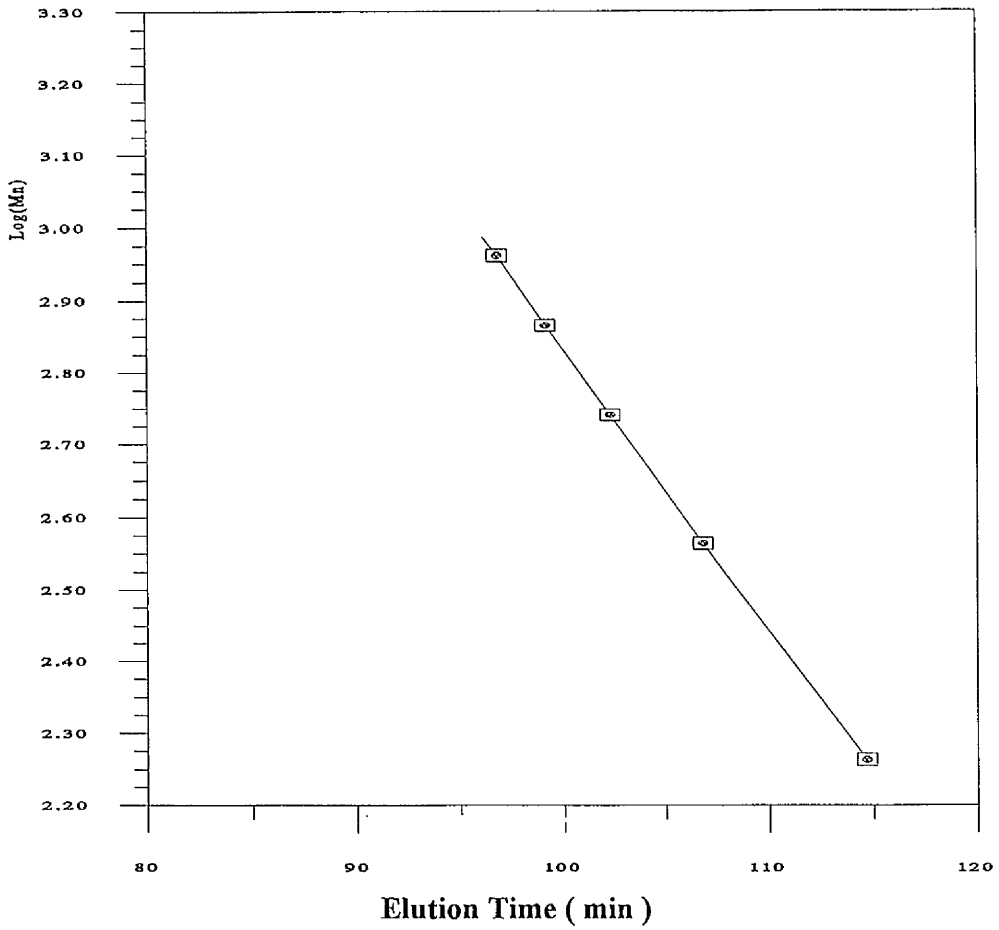


Figure 4.10. Log (molar mass) *v* Elution Time Plot for Cyclic Nylon 11s.

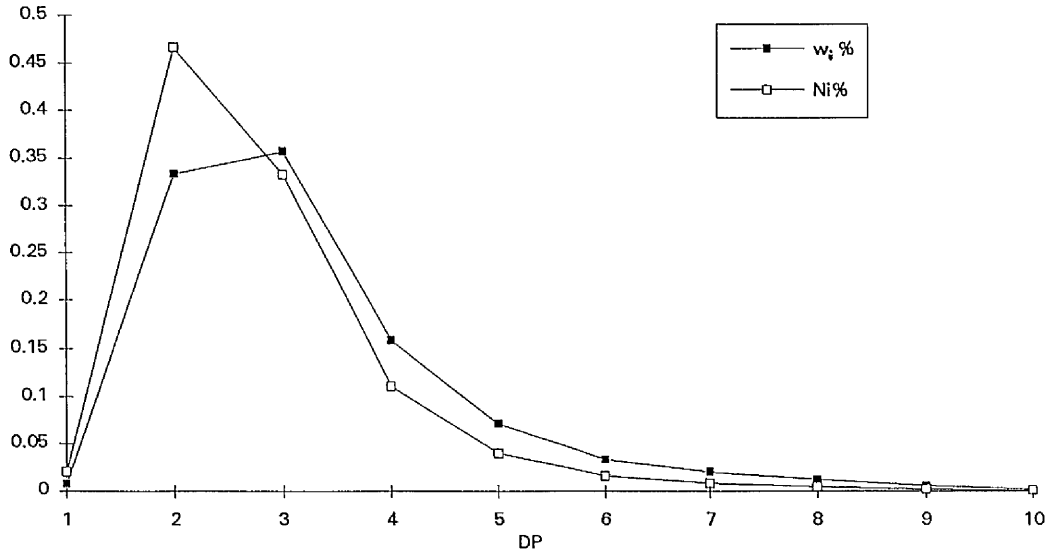


Figure 4.11. Weight Distribution and Number Distribution of Cyclic Oligomers

This sample referred to entry 13 in Table 4.2.

Table 4.8 Area Percentages of Cyclic Oligomers of Nylon 11s Calculated from GPC-C Traces

Entry No.	Sample	Percentage of each DP										
in Tab. 4.2	Reference.	1	2	3	4	5	6	7	8	9	10	$\overline{DP}$
5	1-32c3	-	45.6	54.4	-	-	-	-	-	-	-	2.44
7	1-40Tu	-	33.4	28.8	25.8	10.7	1.3	-	-	-	-	2.85
9	1-46c1	-	52.1	46.4	1.5	-	-	-	-	-	-	2.39
10	1-42c1	-	51.1	41.7	5.53	1.67	-	-	-	-	-	2.43
11	1-20c1	-	43.1	37.3	15.1	4.5	-	-	-	-	-	2.58
12	1-61c1	9.9	32.7	27.1	20.9	9.0	0.3	-	-	-	-	2.36
13	2-32c1	0.7	33.4	35.7	15.9	7.1	3.4	2.0	1.2	0.5	0.2	2.80
14	2-63c1	1.0	51.6	38.8	7.2	1.5	-	-	-	-	-	2.40

4.5.4 FAB-MS Analysis of Cyclic Products

Mass spectrometry (MS) has been used, in conjunction with GPC and HPLC methods, to identify the cyclic oligoamides in the extracts from Nylon-6 by a few authors.[152,153] Electron impact mass spectrometry (EI-MS) detected low molecular weight oligomers from monomer to pentamer, but the oligomers from the hexamer to decamer and higher are not sufficiently volatile to volatilise without decomposition and they therefore remain undetected. FAB-MS is useful for the detection of higher molecular weight oligomers (above 1100 Da up to the resolution limit, normally at *ca.* 2000 Da) present in mixtures of cyclic oligomers.

In the present work in-house measurement of the FAB-MS of cyclic products showed the presence of cyclic oligomers of Nylon 11 from the monomer up to the hexamer (1100 Da). No molecular ions of higher oligomers were observed in the FAB-MS histograms. The results are summarised in Table 4.9. A typical histogram is shown in Figure 4.12. Due to the differences in volatility the FAB-MS signal intensities do not quantitatively reflect the proportions of the oligomers present.

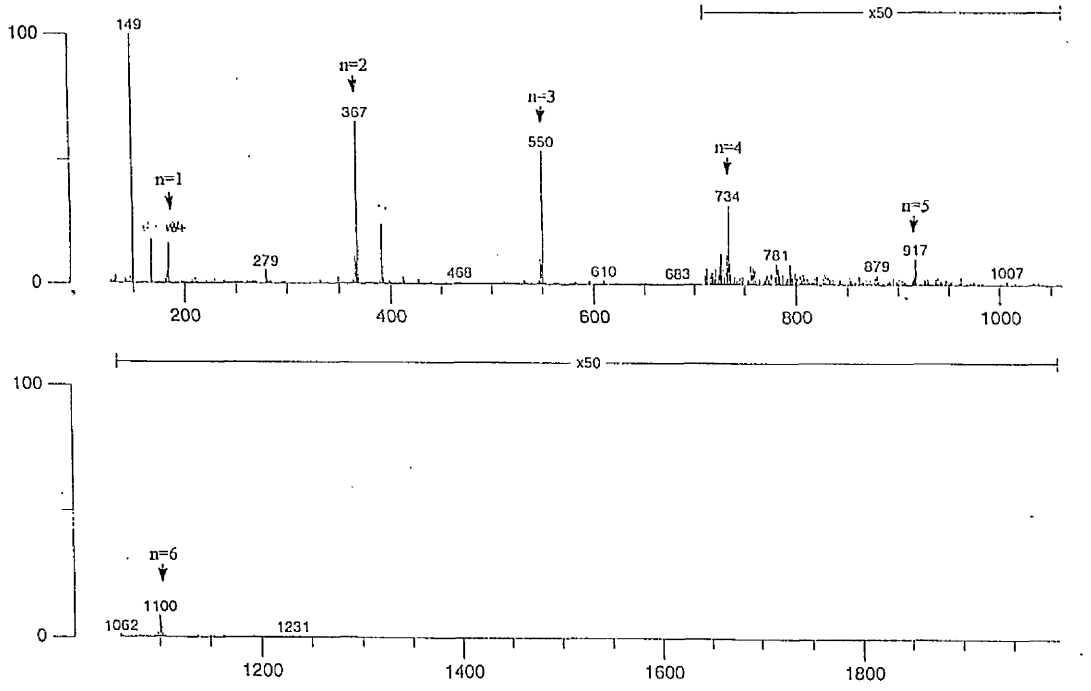


Figure 4.12. FAB-MS Histogram from the sample referred to entry 9 in Table 4.2.

Table 4.9. FAB-MS analysis of cyclic oligomer fractions.

Entry number[a]	Oligomers detected					
	M_1	M_2	M_3	M_4	M_5	M_6
5	184	367	550	-	917	-
6	184	367	550	-	-	1099
8	184	367	550	-	-	1100
9	184	367	550	734	917	1100
10	184	367	550	734	917	1100
11	184	367	550	734	917	1100
12	184	367	550	734	917	1100
13	184	367	550	734	917	1100
14	184	367	550	734	917	1100

[a] Samples are those referred to in Table 4.2 with the corresponding entry numbers.

4.6 POLYAMIDES REMAINING IN THE POLYMER BEADS

As can be seen from Table 4.2, cyclisation yields were poor (5-16%) and, as seen from Table 4.8, the products were mainly cyclic dimer and trimer plus a small fraction of higher oligomers (up to the hexamer). These conclusions are supported by the NMR, HPLC, GPC and FAB-MS analyses discussed in Section 4.5. It is clear from these results, however, that *ca.* 80% of the original monomer is unaccounted for. Attempts were made to account for this 'lost' material.

The deprotection procedure could have brought about the cleavage of some of the active ester linkages thus causing some of the loaded monomer to be lost. A deprotection experiment carried out under typical conditions showed that the loss of monomers from the resin is less than 5%. The separation steps could also have caused product loss. Nevertheless the majority of the product was believed to be still remaining in the polymer beads. This section mainly deals with this part of the reaction product.

Table 4.10 Summary of Changes in Weight of Polymer Supports During the Cyclo-oligomerisation

Entry No. in Table 4.3	Notebook Ref.	Resin weight changes in cyclo-oligomerisation						TFA/chloroform extraction				Total Yield[h] (%)
		Starting weight of beads(g)[a]	Weight of loaded beads(g)	Weight of recovered beads(g)	Weight Increase (g).	Monomer remaining[b] (%)	Kaiser test[c]	Weight of beads (g)[d]	Yield[e] (%)	$\overline{DP}$ E.A.[f]	NMR[g]	
4	1-31r7	2.14	3.00	2.39	+0.19	46	+	2.37	5.1	105	--	13
5	1-32r8	3.78	5.00	4.20	+0.42	53	+	3.95	28.3	41	28	40
6	1-32r13	4.17	5.51	4.68	+0.51	62	++	4.54	17.4	108	--	27
7	1-40rtu	1.54	2.00	1.64	+0.10	34	++	--	--	--	--	--
8	1-44r4	3.47	4.51	3.80	+0.34	51	+	3.56	34.0	63	--	45
9	1-46r1	3.88	4.50	4.05	+0.17	45	-	3.80	74.7	57	75	87
10	1-42r3	4.00	4.62	4.30	+0.30	75	+++	--	--	--	--	--
11	2-20r3	2.00	2.62	2.30	+0.30	75	+	2.14	14.5	25	31	23
12	1-63r3	3.60	5.00	4.30	+0.70	78	-	4.05	30.0	113	98	42
13	2-32c1	4.50	6.00	5.30	+0.80	77	+	5.13	16.7	15	--	32
14	2-63c1	3.00	4.72	3.87	+0.87	78	-	3.32	29.4	95	72	46

[a]: Functionised polymer supports, referring to Table 4.2. [b]: Percentage of monomer remained in the recovered beads, which is equal to (weight increase of recovered beads / calculated weight of cyclic products based on loading). [c]: +: slightly blue; ++ : blue; +++: purple; -: negative. [d]: Weight of recovered beads after TFA/Chloroform extraction. [e]: Yields of TFA/chloroform extracted products. [f]: Estimation based on fluorine and nitrogen analysis, $\overline{DP}$ = 4.07 x N% / F%. [g]: Calculation based on 500 Hz ^{1}H NMR, $\overline{DP}$ = [Integration at $\delta_{2.22}$] / [Integration at $\delta_{2.80}$]. [h]: Yield from reaction solvent plus yield from TFA/$CHCl_3$ extration.

4.6.1 Increase of Weight of Recovered Resins

The first important evidence towards explaining the poor yields was the remarkable weight increases of the resins recovered from the cyclo-oligomerisation reactions. These are shown in Table 4.10. The results show that the average weight increases of the recovered beads correspond to yields of 10-40%. This in turn corresponds to 30-80% of the monomer species still remaining in the resin beads.

4.6.2 Control Experiment

To make sure the weight increase was not due to a contaminant such as DCU remaining after the DCC coupling reaction, a control experiment was carried out in which 6-aminohexanoic acid was cyclised to ε-caprolactam on the support. Thus, t-butoxycarbonyl-6-aminohexanoic acid (Boc-Aha-OH) was attached onto polymeric support (PHNB-2), followed by the same cyclisation conditions and workup procedure as used with 11-butoxycarbonylaminoundecanoic acid. The results are summarised in Table 4.11. These controlled experiments show that the cyclisation of t-Boc-Aha-OH on the same resin gave both a good yield and no increases in the weight of the support. Thus, the gain in weight of the previous resins was not apparently due to impurities produced by the coupling reaction.

Table 4.11. Cyclisation of Boc-Aha on PHNB-2 resin.

Entry number	Loading of monomer (mmol/g)	Reaction Solvent	Reaction Temperature (C)	Isolated Yield (%)	Increase in resin weight
A1	0.70	DMF	20	69	nil
A2	0.70	DCM	20	65	nil
A3	0.78	DCM	20	74	nil
A4	0.65	DMF	20	64	nil

4.6.3 ^{13}C NMR Spectral Analysis of Recovered Beads

The ^{13}C NMR spectrum of the swollen beads recovered from the experiment summarised in Table 4.2 entry 8 was recorded in deuterated chloroform at 75 MHz with D_1 = 15s (see Figure 4.13). In addition to signals due to the polystyrene support the spectrum showed peaks between 20-40 ppm, indicative of the presence of Nylon 11 which could be either linear or cyclic, oligomeric or polymeric. It is, therefore, clear that the increase in weight of the support is due to the presence of Nylon 11 in some form, possibly linear, possibly cyclic, or both.

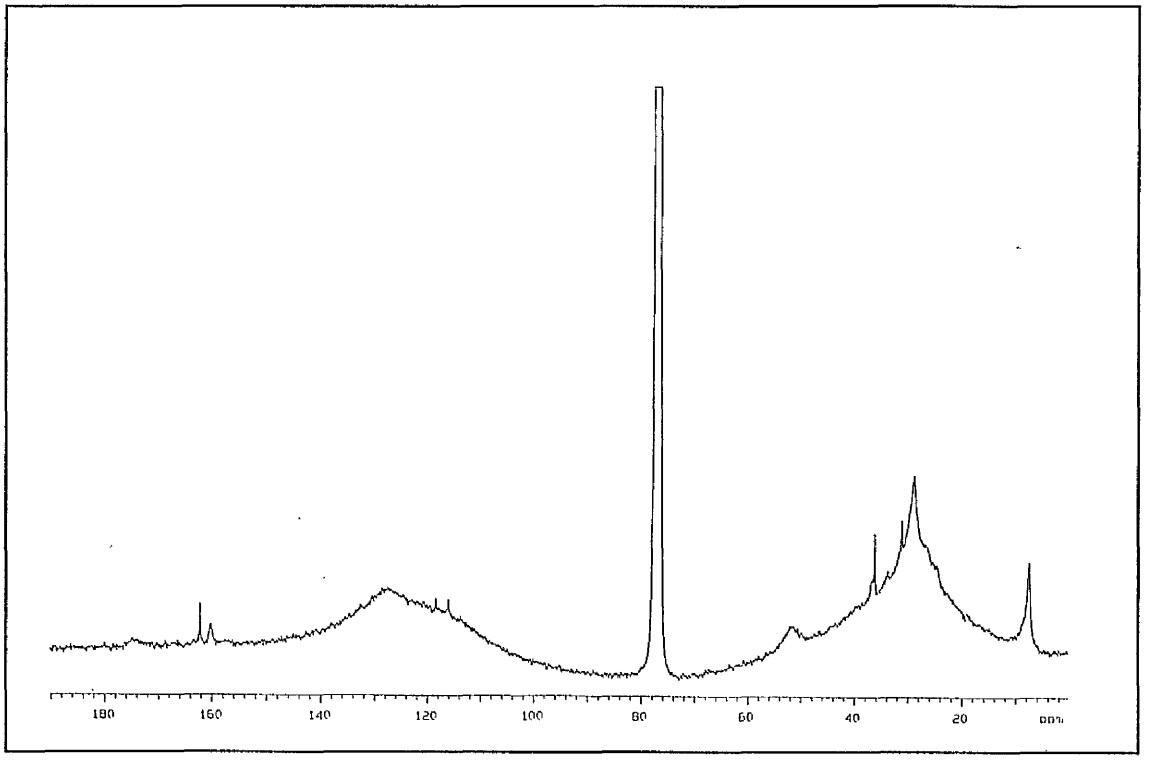


Figure 4.13. ^{13}C NMR of recovered polymer supports from entry 8 in Table 4.2.

4.6.4 IR Spectra

The IR spectra of the cyclic amide products which were soluble in chloroform have bands in the carbonyl region which overlap with bands due to the PHNB supports.

This makes it difficult to identify for certain carbonyl bands in this region due to Nylon 11. In spite of this, strong absorbencies at 1640-1650 cm^{-1} (amide I frequency) were observed in virtually all the recovered resins. The IR spectra of the recovered oxime resin (PNO) showed clearly that there were strong extra bands at 1640 cm^{-1}. The infrared spectrum (carbonyl region only) of a typical recovered support is shown in Figure 4.14.

The IR spectra of the recovered resins show no observable bands due to either Boc-moieties (1700-1715 cm^{-1}) or active ester moieties (1770-1775 cm^{-1}). This suggests that if the residual Nylon 11s are linear they must be greater than oligomers.

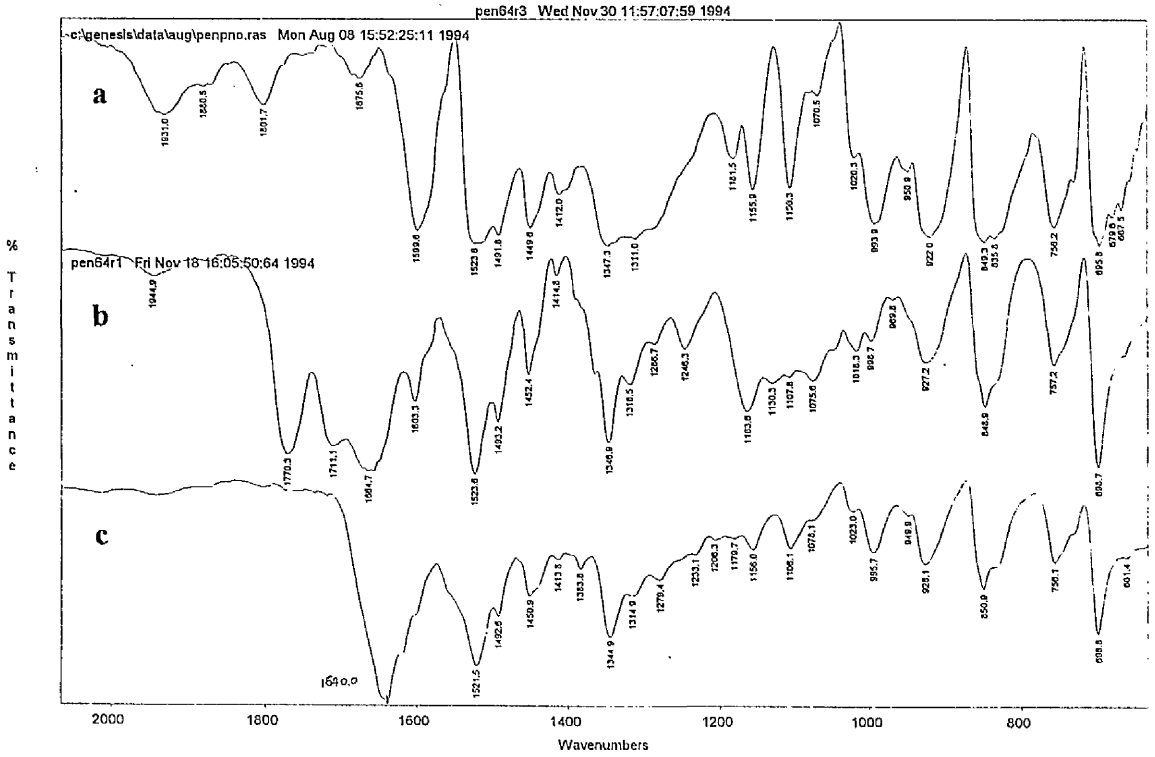


Figure 4.14. Carbonyl region of the IR spectrum of the recovered polymer oxime supports (PNO) from the experiment summarised in Table 4.2 entry 14.

a: Functionised PNO beads before loading. **b**: PNO beads loaded with monomers. **c**: Recovered PNO beads after cyclo-oligomerisation.

4.6.5 End-Group Analyses

It is clear from the results presented so far that the recovered beads contained some Nylon 11. In order to determine whether this was linear or cyclic and, if the former, what its molecular weight was, some end group analyses were carried out.

To cleave any remaining active ester linkages and thus release any linear product still bound to the resin, the recovered resin from the experiment summarised in Table 4.2 entry 5 (4.20 g) was reacted with benzylamine (5.0 ml) at room temperature in DCM (20 ml) for 1 day. The resin was then filtered off, washed and dried (4.04 g). The filtrate was evaporated to dryness and the residue dissolved in $CDCl_3$. The ^1H NMR spectrum of the solution showed no signals between 0 to 4 ppm. This indicates that the treatment with benzylamine did not release any monomer or small linear oligomers.

The Kaiser test was developed by Kaiser *et al.*[163] to check the completion of the acylation reaction in the solid phase synthesis of peptides (refer to Section 7.3 for details). It involves treating the sample with ninhydrin. A positive test gives a bluish-purple colouration. The test works for primary amino groups in α-amino acids, peptides, and aliphatic amines,[164,165] but it is more frequently used for the determination of the α-amino group in amino acids and proteins. In the present work an on-resin cyclisation (see Table 4.2 and 4.10, entries 2, 5, 11) was monitored using the Kaiser test. It was found that the Kaiser test was still positive after a 12 day reaction period at room temperature. A few reactions with the same monomer and resin were therefore carried out for a further reaction period and at a higher temperature. The results are reported in Table 4.10. Kaiser tests were carried out after Soxhleting the recovered beads in an attempt to eliminate interference by impurities. The results were positive for the cyclisations carried out at room temperature even after a few days (entries 4, 6, 7, 10) and even more than 10 days (entries 2, 5, 11). These results mean that free amino ends still existed in the polymer beads, possibly due to either incomplete reactions and/or hydrolysis. Most of the recovered resin beads from the reactions carried out for extended reaction periods at higher temperatures (Table 4.10, entries 5, 8, 9, 11) gave negative or

nearly negative Kaiser tests. Recovered PS-PNO beads (entry 12, 14 in Table 4.2) tends to give negative Kaiser tests suggesting that these beads were the best to use.

These results indicate that linear molecules are present in the beads unless vigorous reaction conditions are used. After a prolonged period they react but it is not clear whether it is to afford linear or cyclic products.

4.6.6 Extracting the Recovered Beads Using Trifluoroacetic Acid

Many of the above results indicate that in general most of the reaction product was trapped within the resin beads and was not removed by washing with hot chloroform.

There are two possible explanations for products being trapped. One is that linear and/or cyclic polyamides are formed but they are very insoluble. If so, this part of the product could be extracted by the use of a more powerful solvent. The second explanation is that cyclic polymers are formed but that they are topologically trapped in the polymer matrices: see Figure 4.15. This part of product could not be extracted by solvent. It could only be removed by destruction of either the polymer network or the cyclic oligomers themselves.

Trifluoroacetic acid and meta-cresol are frequently employed to dissolve the insoluble polyamides or peptides. This is because the acid and phenol break the many of the H-bonds present in polyamides or peptides. To extract the polyamides from crosslinked, and therefore insoluble, polymer beads the solvent needs to dissolve the polyamides fully and also have a good ability to swell the polymer beads. The two requirements seem to be contradictory but to balance the two requirements, a TFA-chlorform mixture was employed. This proved to be able to extract further quantities of Nylon 11 oligomers. The results are shown in Table 4.10.

From the results in Table 4.10, it can be seen that the combined total products accounted for 55% to 90% of the original monomer. However, 10%-45% of the product remained in the polymer beads.

The TFA-chloroform extracted beads gave a negative Kaiser test, but ^{13}C NMR spectra still indicated the presence of polyamides in the beads. Thus, a certain percentage of the product still remains in the resin beads and it cannot be extracted by TFA-chloroform. It might be trapped cyclic oligomers or trapped linear oligomers which were sufficiently large that they could not be extracted by the TFA-chloroform mixture. The trapping of cyclic oligomers would not be surprising as it has been shown that generating networks in the presence of cyclic oligomers leads to a portion of the cyclics becoming trapped topologically(see Figure 4.15). Thus, Semlyen *et al.*[174] were able to trap 25% of the rings of a cyclic polydimethylsiloxane of $\bar{DP}$ 50 by generating a polydimethylsiloxane network in their present work.

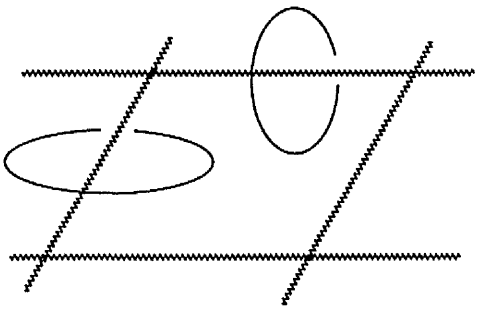


Figure 4.15 Possible Topologically Trapped Cyclic Products

The TFA-chloroform extracts were analysed by elemental analysis and ^{1}H NMR (500 Hz) spectroscopy (see Figure 4.16 for example). Both techniques showed the presence of end groups, $CF_3COO^{-+}NH_3CH_2$-, but in only very small amounts. The average DPs calculated from the elemental analyses and the NMR experiments were in the range of 15-105: see Table 4.10. The products extracted from the PNO resin had the

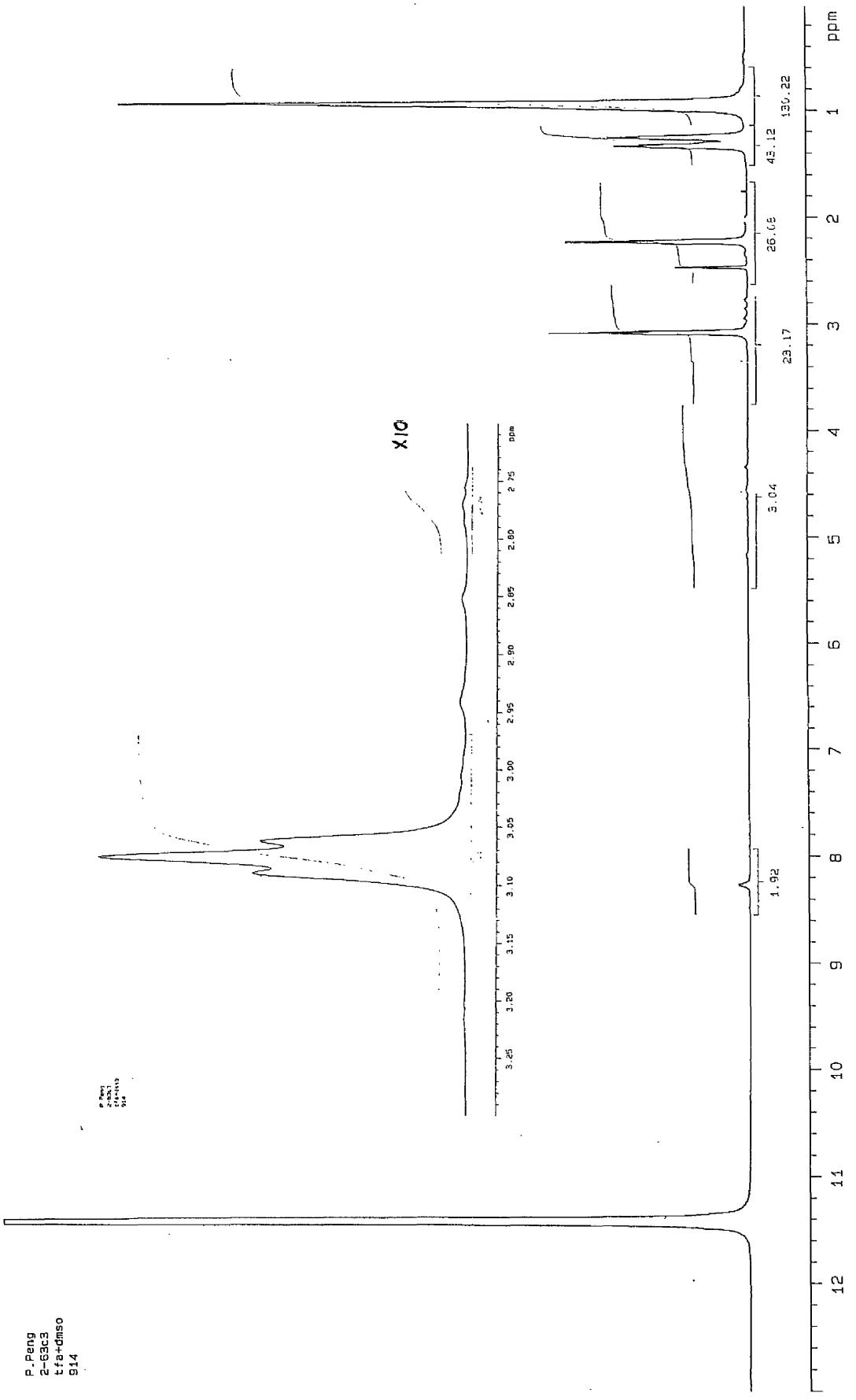


Figure 4.16 ^{1}H NMR Spectrum of TFA/Chloroform Extract from Entry 14 in Table 4.10.

largest $\overline{DP}$s. FAB-MS experiments failed to detect any products in these samples other than cyclic oligomers from the trimer to the hexamer.

GPC analysis of the TFA-chloroform extracts is to be carried out at RAPRA. It is proposed to use meta-cresol as the eluent at 120 °C.

4.7 CONCLUSIONS

Cyclo-oligomerisations of 11-aminoundecanoic acid attached through active ester linkages to polymer supports were carried out. Extraction of the final polymer beads with hot chloroform afforded the equivalent of 5%-20% yields of cyclic oligomers which were shown by HPLC and FAB-MS analysis to contain cyclics from the monomer to the hexamer. Extraction of the chloroform-washed beads with TFA-DCM gave material equivalent to a further 5%-75% yield of Nylon 11. FAB-MS studies indicated that these extracts also contained some cyclic trimer, tetramer, pentamer and hexamer. The latter represents the largest cyclic that we could detect by FAB-MS. End group analysis indicated that the latter materials had average DPs of 15-105. Given that these fractions contained some cyclics the average DPs of the linears present will be higher, corresponding to $\overline{M}_n$ of from *ca.* 3,000 to 20,000. It seems unlikely that such large linears could be formed in the beads, especially as linear Nylon 11s of significant molecular weight are exceedingly insoluble in all known solvents.

Even after extraction with TFA/DCM the recovered polymer supports still contained polyamide corresponding to 10%-45% of the original monomer. It is not clear whether this was cyclic or linear Nylon 11, or both. Other researchers in the Manchester group are preparing resin beads where the network can be broken down easily to release all the Nylon 11s present inside the beads.

Comparing the different active ester supports, supports PNO and PHNB-2 gave higher yields of products than the others.

It was noted earlier that Röthe *et al.*[106] studied the synthesis of cyclic nylon 11 oligomers. They reported that the main product was the dimer. No yields were given. It seems likely that in their study the beads were not extracted as thoroughly as in the present work, and that in general they simply failed to isolate higher oligomers.

It is clear that the work described in this chapter has been hampered by the poor solubility of these polyamides. This prompted the study of the cyclo-oligomerisation of a monomer containing ester linkages. The products in this case were amide-esters. The results of this study are considered in the next chapter.

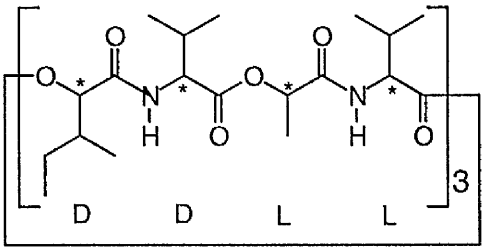
CHAPTER 5

SYNTHESIS OF CYCLIC OLIGO(AMIDE-ESTER)S

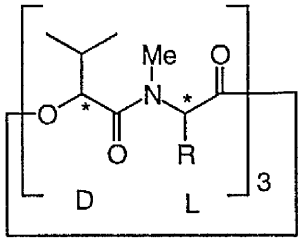
5.1 INTRODUCTION

Cyclic oligomers of amide-esters have very important roles both in biomedical applications and the materials industry. The most important cyclic amide-esters are the depsipeptides. Some of these not only occur in Nature and are known to serve important functions including the transport of ions through cell membranes, but also they are well-known antibiotics.[166] The alternated ester-amide bonds in the cyclic structures contribute in a major way to their unique biological activity.

Some of the best-known naturally occurring cyclodepsipeptides are Valinomycin, Enniatin A, Enniatin B, Enniatin C, Beauvericin and Monomycin. Some typical structures are listed below[166].



Valinomycin



Enniatins B

Figure 5.1. Some naturally occurring cyclic amide-esters.

The alternated polyamide-esters can be expected to have a better solubility and processability than the corresponding polyamides, and different properties from the corresponding random copolymers. Cyclic oligomeric amide-esters are the ideal pre-polymerised monomers for use in ring-opening polymerisations to produce very high molecular weight products.

In Chapter 4, the cyclic and linear polyamides of 11-aminoundecanoic acid were found to have a poor solubility in most organic solvents, and this posed great difficulties

for their characterisation and the understanding of the cyclisation on the polymer supports. In order to get a reasonable solubility of the cyclic products, one possiblity is to decrease the hydrogen-bonding between the polyamide molecules. The alternating amide-ester polymers have reduced hydrogen-bonding and so should have a better solubility. This should faciliate their characterisation by GPC, NMR and mass spectrometry.

Another interesting point concerning the amide-ester polymers (both cyclic and linear) is their unique hydrogen bonding structures, which will probably be the driving force for molecular self-assembly. Recently, an amide-based catenane has been prepared by Leigh[16] in a one step reaction with a yield of up to 20%: see Figure 5.2. The hydrogen bonding is considered the key factor in the self-assembly of these catenated molecules.

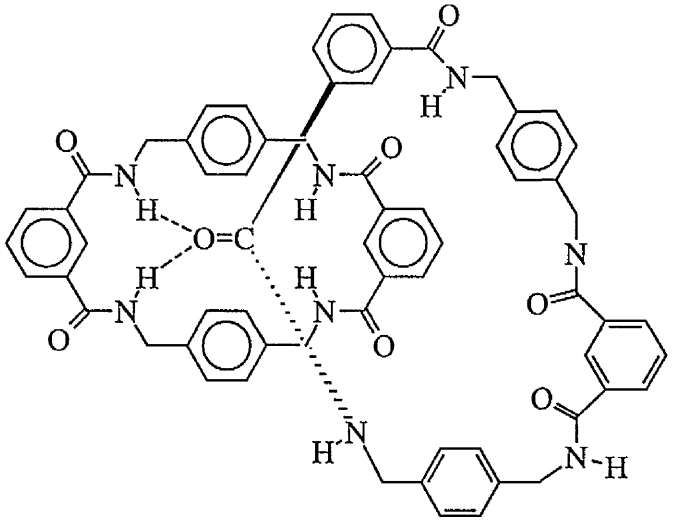


Figure 5.2. A novel amide catenane

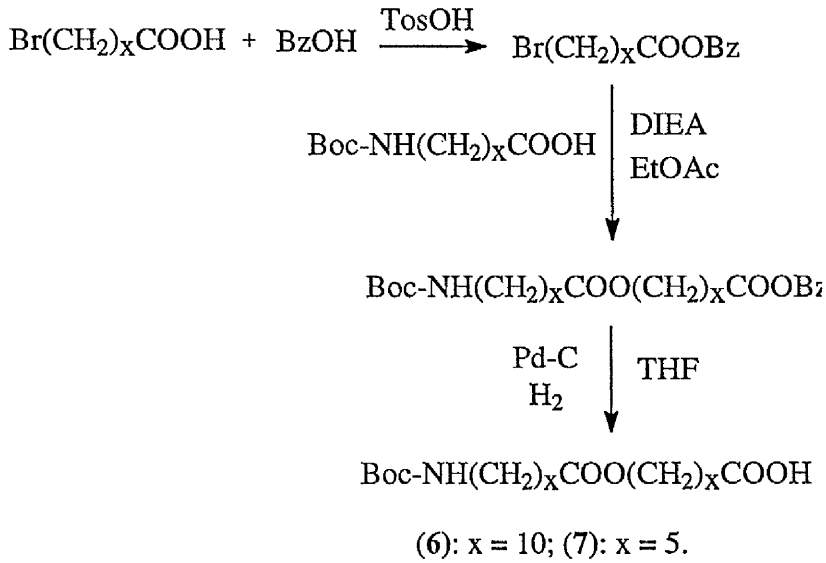
Synthetic cyclic alternated ester-amides are rarely recorded in the literature since the thermal depolymerisation of poly(amide-ester)s could only produce random cyclic ester-amides. It seems that only Goodman *et al.*[167] has separated and characterized an alternated ester-amide from a condensation polymerisation reaction.

The purpose of the present work was to study the on-resin cyclo-oligomerisation reaction using more soluble monomers than the pure amide monomers and hence to prepare cyclic ester-amides with an alternated structure. One of the key points of this work is to detect and identify the cyclic oligomers and to optimize the reaction conditions.

5.2 SYNTHESES OF MONOMERS

The syntheses of the monomers are outlined in Figure 5.3. Both of the synthetic routes have used benzyl protection of the carboxyl group and hydrogenolysis for the deprotection. Benzyl esters are readily prepared by many classical methods since benzyl alcohol is unhindered, relatively stable to acid, and cheap. It is also UV active, which means the ester can be visualized easily when using TLC or other chromatographic methods to detect or separate the products. The most useful property of benzyl esters is that they can be readily cleaved by catalytic hydrogenolysis[168] or hydrogen transfer hydrogenation[169-171] to afford very clean products because the yields are usually very good, up to 100%, the only products being the acid and toluene: see Figure 5.4.

Monomer 6 and 7



(6): x = 10; (7): x = 5.

Figure 5.3 (continued on next page)

Monomer 8 and 9

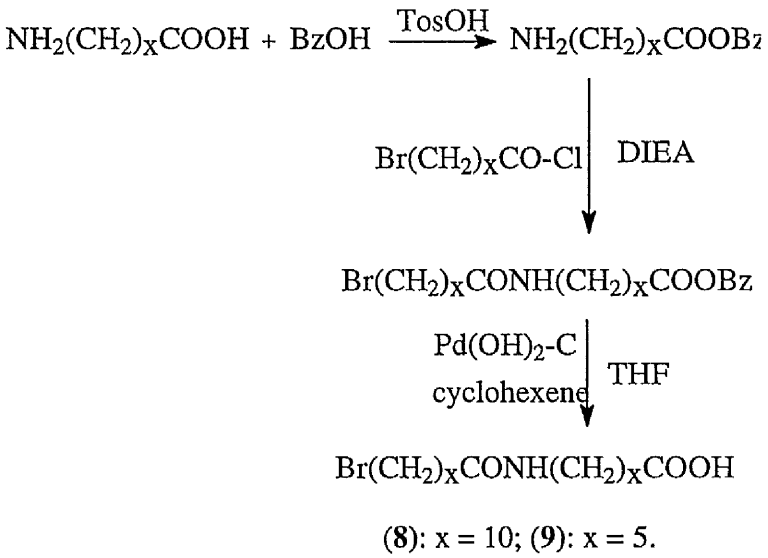


Figure 5.3. Synthesis of monomers 6, 7, 8 and 9.

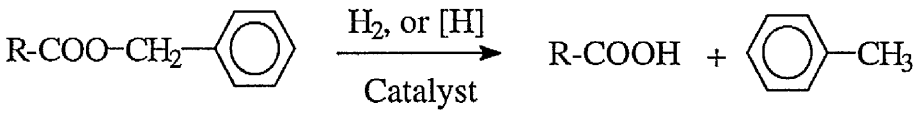


Figure 5.4. Debenzylation by hydrogenation.

5.3 PREPARATION OF LINEAR AND CYCLIC OLIGOMERS IN SOLUTION

5.3.1 Synthesis of Linear Oligomers

The linear oligomers were synthesized in order to calibrate the GPC and to identify the shifts of their groups in the ^{1}H NMR spectra.

A simple method reported by Hodge *et al.*,[132] which involved the phase transfer catalyzed polymerisation of ω-bromoalkanecarboxylate salts, was adopted to make the

linear oligomers of the amide-esters. This is outlined in Figure 5.5. The reaction conditions and the results are summarised in Table 5.1.

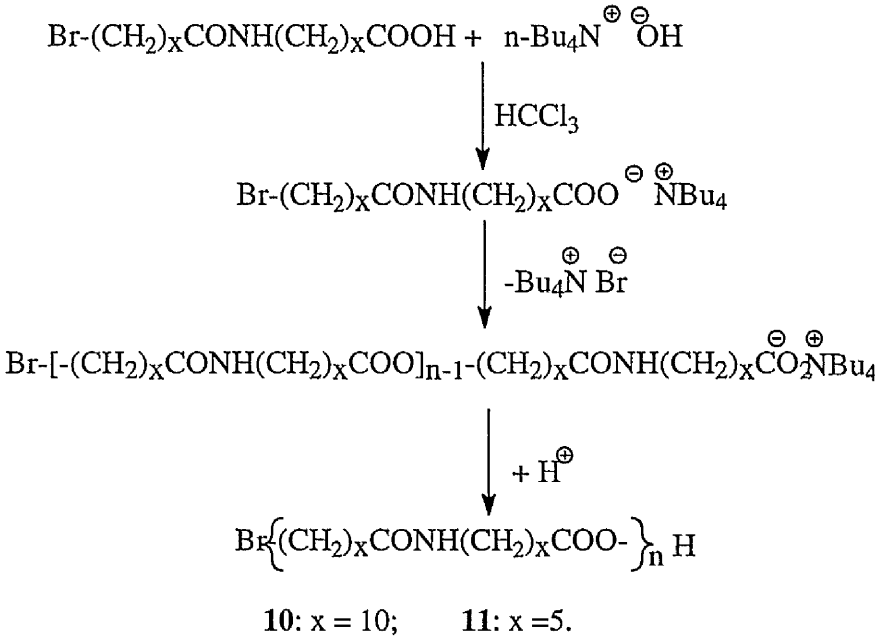


Figure 5.5. Synthesis of linear oligomers with bromo end groups.

Table 5.1 Synthesis of Linear Amide-ester Oligomers[a]

Polymer	Monomer x =	Concentration of monomer	Reaction time (h)	Reaction yield (%)	$\bar{D}P^b$	$\bar{M}_n{}^b$
10	10	0.17	2	78	3.51	1290
11	5	0.32	4	27	3.81	865

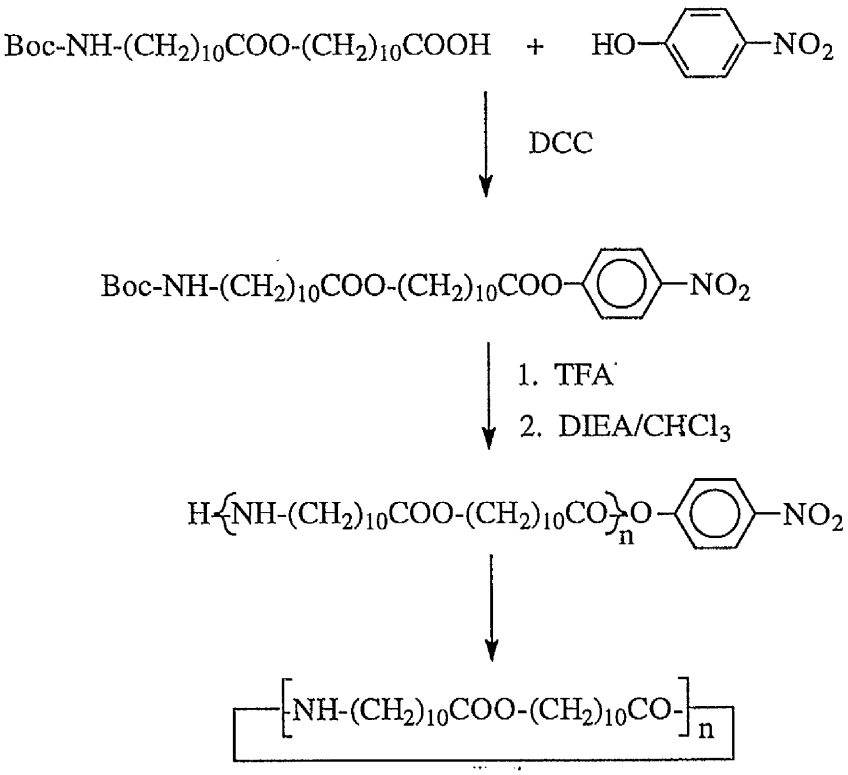
[a] Reactions were carried out in chloroform at 60 °C. [b]Calculated based on the end-group content determined by ^{1}H NMR spectroscopy (200 MHz NMR machine).

The product (**11**) was finally purified by passing down an Amberlite 15 (H^+ form) column. The GPC traces of the oligomers will be discussed in Section 5.6.2. In the GPC trace of (**10**) it was found there was about 15% of cyclic oligomers present. Almost 70%

of these cyclics was the cyclic dimer. It was also possible to identify cyclic trimer and tetramer. The FAB-mass spectrum of this sample showed the protonated peaks of the cyclic oligomers from the monomeric ring up to the tetramer (m/z 1472).

5.3.2 Synthesis of Cyclic Oligomers in Solution at High Dilution

The high dilution method is widely used for the synthesis of cyclic molecules. Condensation polymerisation at high dilution usually produces a mixture of cyclic oligomers. A greater dilution generally gives more rings. A typical concentration for high dilution is 10^{-3} M or less. In the present work cyclic oligomers (**12**) were synthesised by reaction of amino end groups with an active ester end group. The reaction involved are summarised in Figure 5.6.



(12)

Figure 5.6. Synthesis of cyclic amide-ester oligomers by the high dilution method.

Table 5.2. Model cyclisation in dilute solution[a].

Product	Notebook reference	Reaction concentration (M)	Yield (%)	Cyclic (%)	$\bar{DP}^b$	$\bar{M}_n$ (GPC)
12	2-75cl	0.0033	57	97	1.43	525

[a]: The reaction was carried out in chloroform at room temperature. [b]: Calculation based on the GPC-C peaks.

Table 5.2 shows the results obtained from conducting the cyclisation at 20 °C and a concentration of 3.3 x 10^{-3} M in chloroform. The final product (**12**) obtained was a mixture of cyclic oligomers with DPs from ranging 1 to 5 and containing about 3% of unknown oligomers. The ^{1}H NMR spectrum did not show any end groups. FAB-MS showed protonated peaks of cyclic oligomers: 368(100%, monomer); 736(dimer) and 1103(trimer).

5.4 COUPLING THE MONOMERS ONTO THE RESINS

The monomers (**6**) and (**7**) were attached onto various polymer supports by the use of DCC coupling reactions (see also Sections 3.3.2 and 4.2.2). An example is illustrated in Figure 5.7. The coupling reactions carried out are summarised below in Table 5.3.

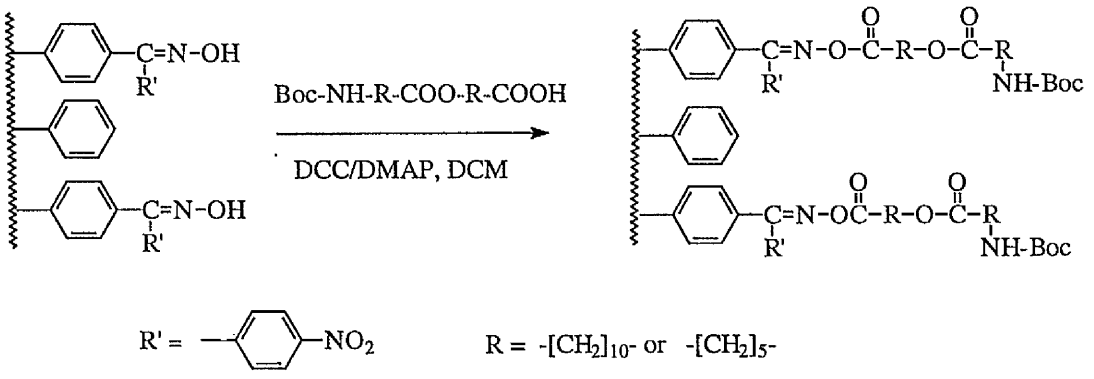


Figure 5.7. Coupling monomers onto the polymer support.

As seen from Table 5.3, more than 57% of the amount of the monomer used was coupled onto the support by a single coupling reaction step. Generally speaking, a higher feed ratio resulted in a higher loading on the beads. By using an appropriate feed ratio, it is possible to control the loadings on the beads.

Table 5.3. A Summary of the Coupling Reactions Carried Out.

Entry	Notebook Ref.	Mono -mer	Polymer support	Amount of monomer used (mol/mol)[a]	Amount of monomer used (mmol/g)[b]	Loading achieved (mmol/g)[c]	Coupling yield (%)[d]
1	2-38	**6**	SX2-PNO	0.46	1.03	0.55	72
2	2-65c	**6**	SX1-PNO	0.13	0.31	0.27	86
3	2-44c	**6**	SX1-PNO	0.43	1.03	0.55	68
4	2-44d	**6**	SX1-PNO	0.43	1.03	0.55	68
5	2-64a	**6**	SX1-PNO	0.47	1.13	0.59	72
6	2-45	**6**	SX1-PHPS	0.52	0.82	0.39	57
7	2-42a	**7**	SX2-PNO	0.75	1.70	0.91	76
8	2-42b	**7**	SX1-PNO	0.48	1.16	0.71	80

a Millimoles of monomer used per millimoles of active hydroxyl groups on the polymer support.

b Millimoles of monomer per gram of polymer support.

c milimoles of monomer per gram of polymer support.

d Calculation based on the feed monomer weight.

The infrared spectra of the loaded beads showed the presence of active ester groups(carbonyl) at 1750 cm^{-1}; simple ester carbonyl groups at 1730 cm^{-1}; Boc carbonyl groups at 1710 cm^{-1}; and amide carbonyl groups at 1640 cm^{-1} and 1545 cm^{-1}.

All the loaded beads were quite stable if kept away from moisture and heat. There was no noticeable active ester cleavage after 3 months storage in a refrigerator kept at 4 °C.

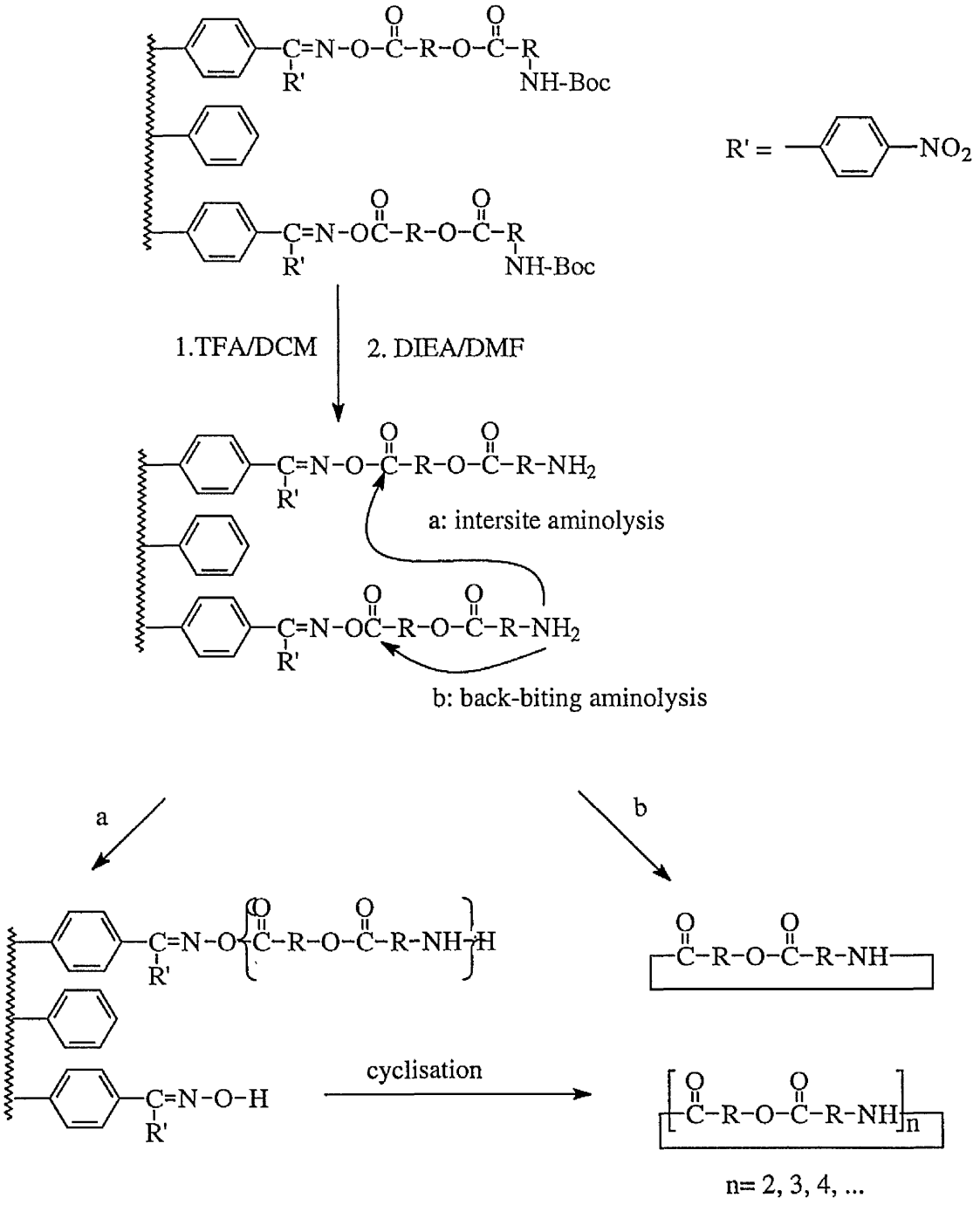
In this chapter, the oxime resins were chosen as the main supports to carry out the cyclisation reactions. Among the prepared polymer supports given in Table 5.3 (also discussed in the previous chapters), the oxime resin was found to be the easiest to load with the monomer and its loaded beads have a reasonable stability.

5.5 POLYMER-SUPPORTED CYCLISATIONS

5.5.1 Cyclisation Reactions

To determine optimal cyclisation conditions, several parallel reactions were conducted on the polymer beads. The reactions involved in the cyclo-oligomerisations are summarised in Figure 5.8.

The cyclisation of the deprotected polymer-bound monomers was expected to take place only in the resin beads. After normal procedures for deprotection and washing to generate free amino groups, the polymer beads were suspended in a suitable solvent, usually DMF, for at least 7 days in order to allow maximum cyclo-oligomerisation. The cyclisation was catalysed by acetic acid.[107,143] An experiment conducted by Nishino[143] showed that the cyclisation of a linear peptide on the Kaiser oxime resin could be accomplished in more than 70% yield in 24 h. In the present studies the cyclo-oligomerisation was found to be continuing even at 11 days. The reactions became slower as the reaction time increased and bigger cyclic oligomers were formed.[106]



(12): R= $(CH_2)_{10}$; **(13):** R= $(CH_2)_5$;

Figure 5.8. Cyclisation reactions on oxime resin.

5.5.2 Isolation of Cyclic Products by Different Methods

At the end of each cyclo-oligomerisation, the polymer beads were filtered off and the filtrate was collected. The beads were then washed in various ways as indicated in the footnotes of Table 5.4. The overall results were as summarised in Table 5.4. The "first batch" of cyclic products was the product obtained from the initial filtrate. The "second batch" was the product obtained by various washing procedures.

Table 5.4. Cyclo-oligomerisation Reactions*

Entry	Notebook Ref.	Support	Monomer[e]	Loading mmol/g	Time (days)	Yield(%) from each batch 1st	Yield(%) from each batch 2nd	Yield(%) Total
1	2-38c	SX2-PNO	**6**	0.55	5+2	14	31[a]	45
2	2-64c	SX1-PNO	**6**	0.27	7	--	48[c]	48
3[d]	2-44c	SX1-PNO	**6**	0.55	7	12	35[b]	47
4	2-44d	SX1-PNO	**6**	0.55	7	10	50[b]	60
5	2-64a	SX1-PNO	**6**	0.59	7	--	44[c]	44
6	2-45	SX1-PHPS	**6**	0.39	7+7	17	9[c]	25
7	2-42a	SX2-PNO	**7**	0.91	7	13	6[c]	19
8	2-42b	SX1-PNO	**7**	0.71	7	20	9[c]	28

* DMF was used as reaction solvent except where indicated.

a: Products obtained by Soxhlet extraction using chloroform; **b**: Product extracted by using TFA/chloroform (50/50) mixed solvent; **c**: Product extracted by a hot chloroform wash. **d**: Chloroform was used as cyclization solvent.

As can be seen from Table 5.4, the yields of the "first batch" of cyclic products were only about 10-20%. In entries 1, 3, 4, 6, 7 and 8 (Table 5.4), the "first batch" of cyclic products was obtained from the filtrate after the beads had simply been filtered off and washed with cold DMF or chloroform. As the ^{1}H NMR spectra and the GPC analysis proved, they were mainly the smaller cyclic oligomers, usually with a purity of more than

95% (calculated from the GPC chart), DP from 1 to 10 and as average of $\bar{DP}$ of around 2-3(see Table 5.5).

Table 5.5. Summary of Analyses of the 'first batch' of cyclic products.[a]

Entry number	Notebook reference	GPC-C analysis[b]				End group[d] (by ^{1}H NMR)
		$\bar{M}_n$	$\bar{DP}$	Cyclic (%)	Unknown(%)[c]	
1	2-38c1	695	1.9	95	5	trace
2	2-64c1	579	1.6	91	9	trace
3	2-44c1	1074	2.9	94	6	trace
4	2-44d1	398	1.1	90	10	trace
5	2-64a1	690	2.0	94	6	trace
6	2-45c1	793	2.2	80	20	trace
7	2-42a1	904	4.0	100	–	trace
8	2-42b1	1100	4.9	>95	<5	trace

a Entry numbers correspond to those in Table 5.4. **b**: All data were obtained based on the peak area counting or paper weighing method from GPC-C traces. **c**: (Total area of peaks due to cyclic oligomers)/total area of peaks. **d**: Amino end groups ($NH_2C\underline{H}_2$) detected by 500 Hz NMR at δ 2.5-2.9 ppm but the integrations were less than one in 50 repeat unit.

Seeing the relatively low yields of the "first batch" of cyclic products, it was assumed that there were larger oligomers still remaining in the polymer beads, as was the case with the cyclic amides discussed in Chapter 4. More vigorous conditions were therefore used in order to drive the cyclisation reaction and to extract the rest of the cyclic products.

In an attempt to drive a cyclisation to completion, the recovered beads from entry 1 (Table 5.4) were heated in chloroform in the presence of triethylamine for two days. The

beads were then filtered off and washed with hot chloroform. The product obtained in this way clearly showed two distinctly different molecular weight components. The higher molecular weight components had a molecular weight of around 25,300 (calibrated with polystyrene standards) and was obtained in about 12% yield. The lower molecular weight components, as shown in GPC(Figure 5.9 B), was obtained in about 19% yield and was identified by GPC ^{1}H NMR as being mainly cyclics. A second very small fraction of high molecular weight product was obtained by Soxhlet extracting the beads with hot chloroform. The results were summarised in Table 5.6.

Table 5.6. GPC analyses of cyclic products from boiling chloroform of entry 1, Table 5.4[a]

Reference	Yield	Low $\bar{M}_w$ cyclics[b]			High $\bar{M}_w$ cyclics[c]	
	(%)	Weight (%)	$\bar{DP}$	$\bar{M}_w$	Weight (%)	$\bar{M}_w$
2-38c2	31[d]	60	2.9	1060	40	25,300
2-38c3	4[e]	<5	–	–	>95	36,200

a: The calculations were based on the separation line (dot line) in Figure 5.9. **b**: The low molecular eight fraction in GPC trace was identifiable and the DP, Mw was calculated based on identification of individual cyclic oligomers by paper-cuting method. **c**: The polystyrene standard was used for the calculation of $\bar{M}_w$. **d:** Extracted with hot chloroform. **e:** Extracted using a Soxhlet apparatus and hot chloroform.

As seen from Table 5.6 and Figure 5.9, the results suggest that the cyclic oligomer that remained in the polymer beads could either have been polymerised in the boiling chloroform by ring-opening polymerisation or there might have been extensive chain growth in the polymer beads. In subsequent experiments milder conditions were, therefore, used to extract the remaining products in the beads.

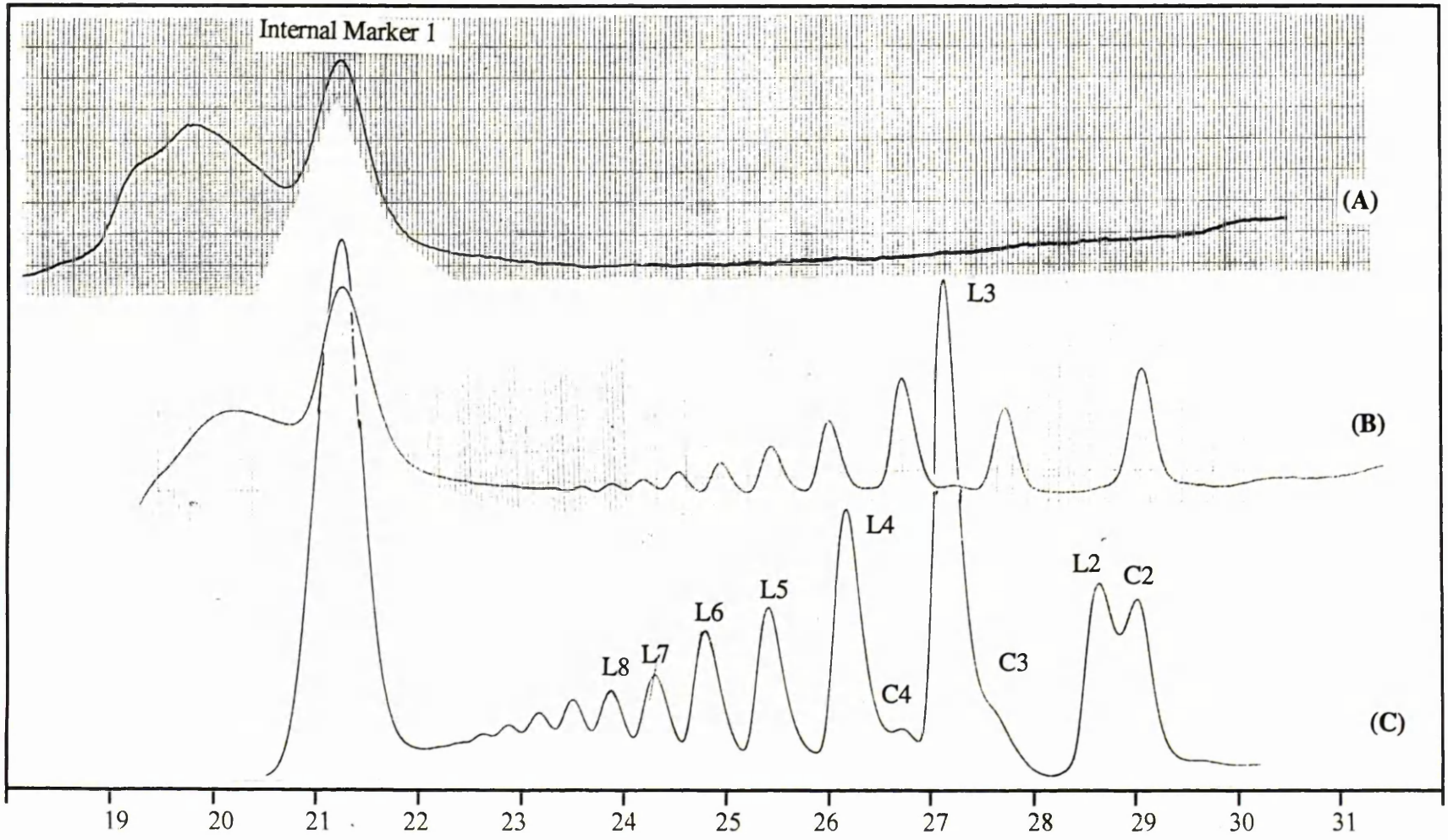


Figure 5.9. GPC Traces of Recovered "Cyclic Materials" Obtained by Boiling in Chloroform (by GPC apparatus C)

(A): High Mw materials obtained by Soxhleting (refers to Table 5.6, ref. 2-38c3). (B): Products obtained from chloroform solution after boiling (refers to Table 5.6, ref. 2-38c3). (C): Linear oligomers (**10**) prepared by phase transfer reaction(refer to Table 5.1).

In the case of the cyclo-oligomerisations summarised in entries 2 and 5(Table 5.4), hot chloroform(*ca.* 50 °C) was used to wash the resin beads and both of these reactions gave the cyclic oligomers in higher yields (48% and 44% respectively, see Table 5.6). The hot chloroform washing procedure was able to extract the small oligomers up to a maximum degree of polymerisation of 14-16, i.e. molecules with a molecular weight of around 5000, while the average $\overline{DP}$ of the oligomers was about 2. This result shows that nearly half of the cyclic oligomers produced in the polymeric beads were small cyclic oligomers with an average number of ring atoms of around 40-120, i.e. they were medium sized rings ($\overline{DP}$ from 2-6). These relatively large ring sizes can probably be explained by the conformation of the linear oligomers in DMF or chloroform solution. Thus, the linear amide-esters probably tend to adopt a folded or β-sheet confirmation, with the result that the distances between the end groups was greatly reduced compared with the situation when shorter monomers react with each other.

Another good solvent system for extracting polyamides from polymer beads(see Chapter 4) is TFA in chloroform. It does this by breaking the hydrogen-bonding between the molecules. TFA is a strong organic acid which is able to break the hydrogen bonds but it does not cleave the amide or ester bonds. Chloroform provides good swellability for the polystyrene beads in this mixed solvent. Simple tests showed the good solubility of the model linear amide-ester oligomers and polymers. Thus, a second extraction of the recovered beads considered in entries 3 and 4 of Table 5.4 with TFA/chloroform was carried out in order to extract bigger oligomers from the beads. Second crops of cyclic products from entry 3 and 4 were obtained in yields of 35% and 50% respectively(see Table 5.7). Attempts to extract more products from recovered beads after the hot chloroform washing of the beads considered in entries 6, 7 and 8 in Table 5.4 by using TFA in chloroform did not afford any more material.

Table 5.7. Summary of analysis of the cyclic products from the "second extraction" of various beads.[a]

Entry Number	Sample Reference	Yield %	Low $\bar{M}_w$ fraction[b]			High $\bar{M}_w$ fraction[c]		
			%	$\bar{DP}$	$\bar{M}_n$	%	M_{pk}	$\bar{M}_w$
3	2-44c2	35	31	5.0	1849	69	15000	15500
4	2-44d2	50	44	3.4	1253	56	11500	13800
6	2-45c2	9	>90	5.4	1997	–	–	–
7	2-42a2	6	100	8.3[d]	1886[d]	–	–	–
8	2-42b2	9	100	7.7	1740	–	–	–

a Entry numbers correspond to the same reactions presented in Table 5.4.
b DP up to 8, i.e. $M_n < 5000$, which consist of identifiable single peaks; $\bar{M}_n$ were obtained by calculation based on the areas of the single peaks.
c $DP > 8$, $M_w > 5000$; M_w estimated using polystyrene calibration.
d Only the low molecular weight components were present.

The TFA in chloroform extracts were analysed by GPC. A typical GPC trace is shown in Figure 5.12. It is evident that considerable amounts of large molecular weight material was present in the TFA/chloroform extracts. The GPC identifications show that the fractions with small molecular weight are almost cyclic oligomers but it is not known if the fractions of high Mw are cyclic or linear species. This is due to a lack of separation techniques. The oxime resin tends to give high yields of TFA extract, but the PHPS resin gives low yield of TFA extraction.

The cyclo-oligomerisation of monomer (7) gave low overall yield(19-28%) inspite of the use of various extraction procedure. On the other hand, these reactions give nearly pure small cyclic fractions.

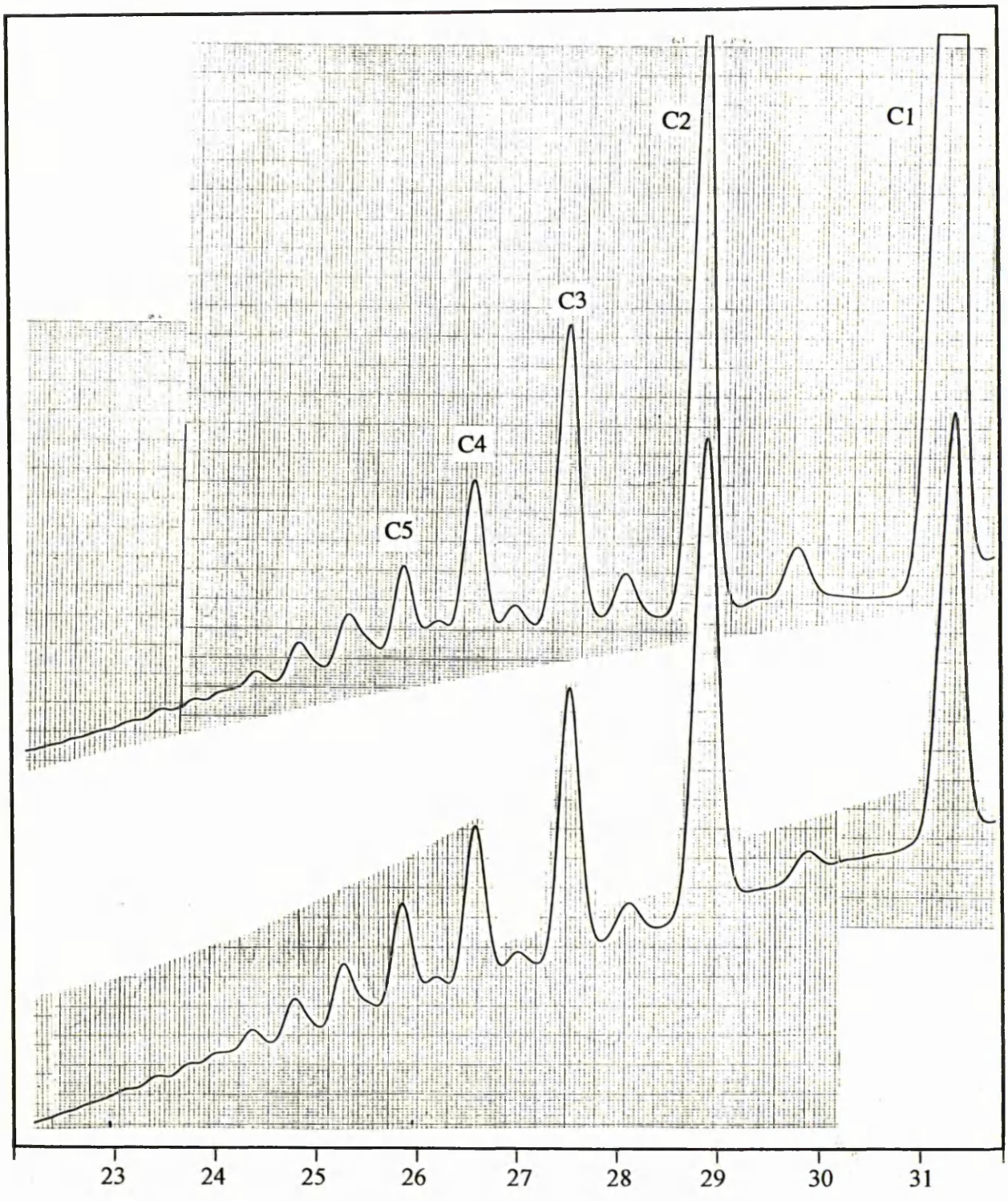


Figure 5.10. GPC Traces of Cyclic Amide-Ester Products (12)
Recorded by GPC Apparatus C. (A): "2nd batch" of cyclics of Entry 2 in Table 5.4. Sample ref. 2-64c; (B): "2nd batch" of cyclics of Entry 5 in Table 5.4. Sample ref. 2-64a.

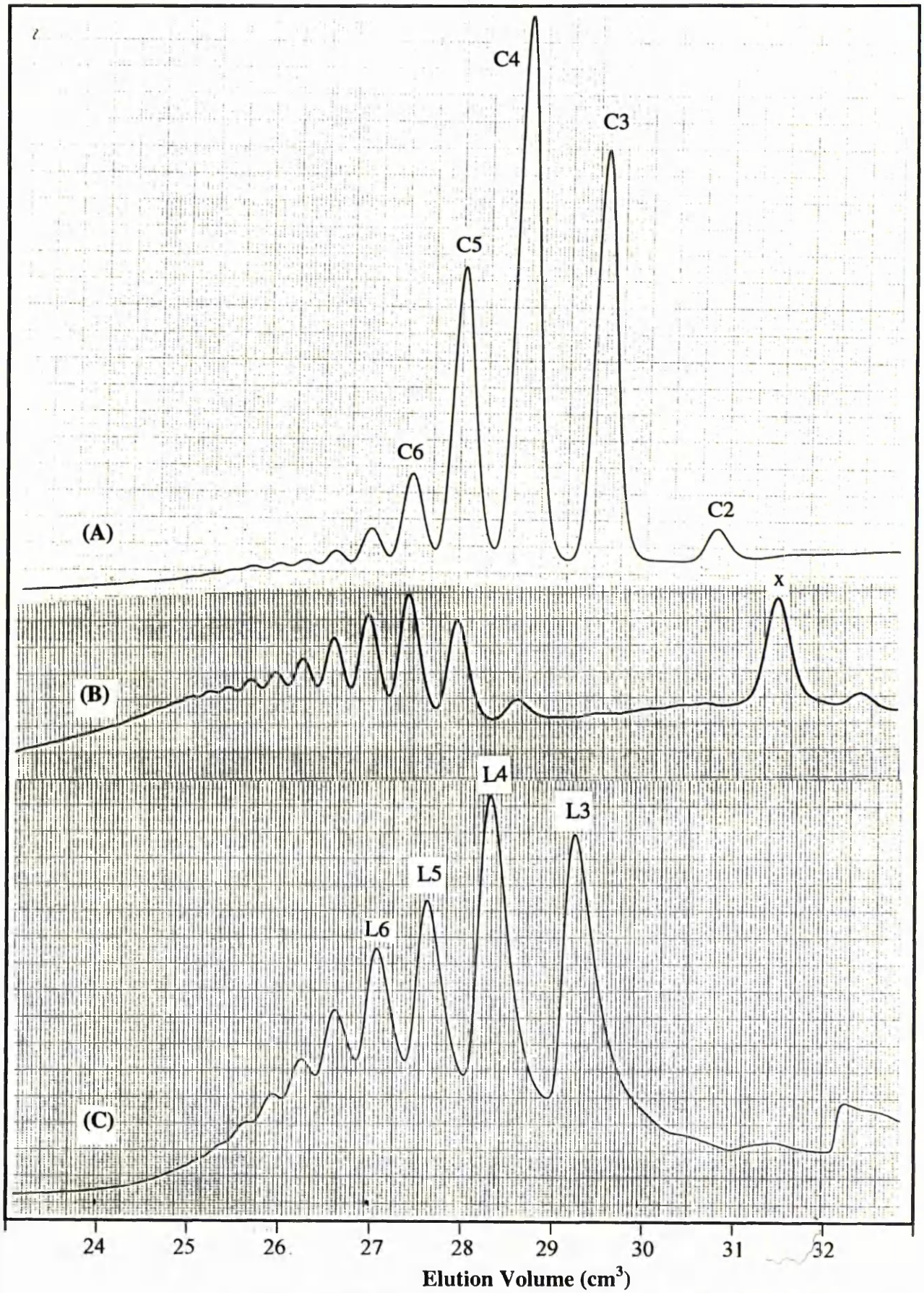


Figure 5.11. GPC Traces of Cyclic Amide-Ester Products (13)

Recorded by GPC Apparatus C. (A): "1st batch" of cyclics of Entry 7 in Table 5.4. Sample ref. 2-42a1; (B): "2nd batch" of cyclics of Entry 7 in Table 5.5. Sample ref. 2-42a2. (C): Bromo-ended Linear Amide-Esters (**11** in Table 5.1).

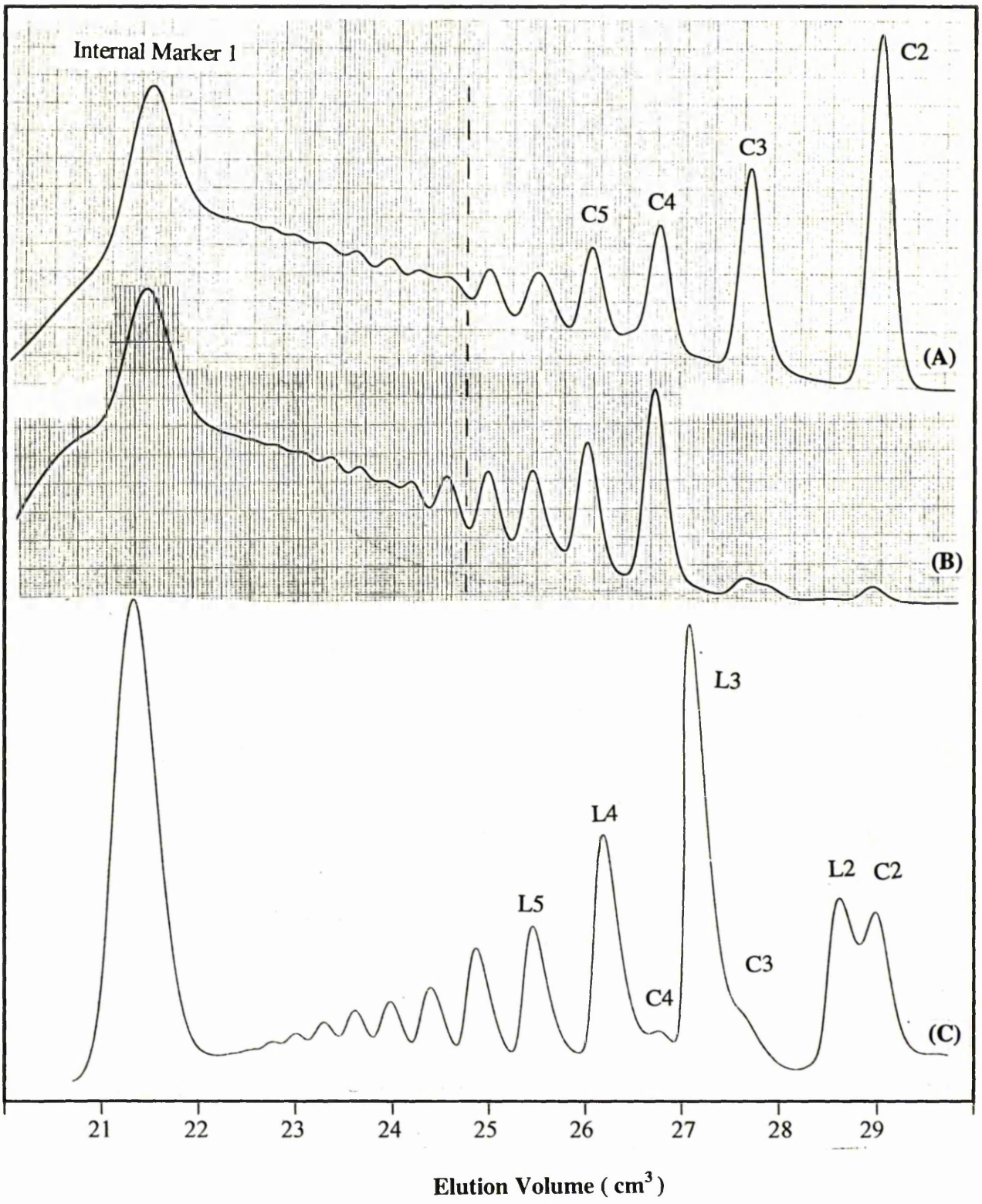


Figure 5.12. GPC Traces of TFA/Chloroform Extracts by GPC Apparatus C.
(A): Refer to entry 4 in Table 5.7, ref. 2-44d2; (B): Refer to entry 6 in Table 5.7, ref. 2-44c2; (C): Refers to linear oligomer **(10)** in Table 5.1.

In a summary, combining the two crops of cyclic oligomers, the total yield of the cyclic product was in the range of 40-60%. Different reaction solvents, degrees of crosslinking of the polymer support, and the loadings of the monomers on the beads do not have dramatic effects on the yields of cyclic product. However, the PHPS bead was not as productive as the oxime resins, even at extended reaction times. Also cyclo-oligomerisation using the monomer (**7**) (Boc-Aha-OH) produced relatively poor yields of cyclic oligomers compared to the reactions using monomer (**6**) (Boc-Aua-OH). The reasons for this are not clear

5.5.3 Purification and Fractionation.

It was found that reasonably pure cyclic oligomers could be obtained by precipitating the crude products into methanol. After two to three precipitations, the elemental analyses of the cyclic products were in agreement with their calculated value and the ^1H NMR spectra indicated that no DIEA salt and other impurities were present in the sample.

Attempts to fractionate the cyclic samples using various solvents showed mixtures of chloroform-methanol were a promising system to fractionate out the smaller cyclic oligomers by precipitation. The cyclic products from entry 1, reference 2-38c11, were fractionated by this method. The first fraction, 2-38c11, obtained using a mixture of approximately 50/50 methanol-chloroform, was obtained in a yield of 6.5%. GPC analysis showed that it consisted mainly of cyclic dimer and trimer, though small amount of cyclic oligomers with $\bar{D}$Ps from 1 to 10 were present. The second fraction obtained using 80/20 methanol-chloroform, 2-38c12, was obtained in 5.4% yield. The GPC analysis showed it was mainly cyclic monomer together with a small percentage of the cyclic dimer and trimer. These results are summarised in Table 5.8. The GPC traces are shown in Figure 5.13.

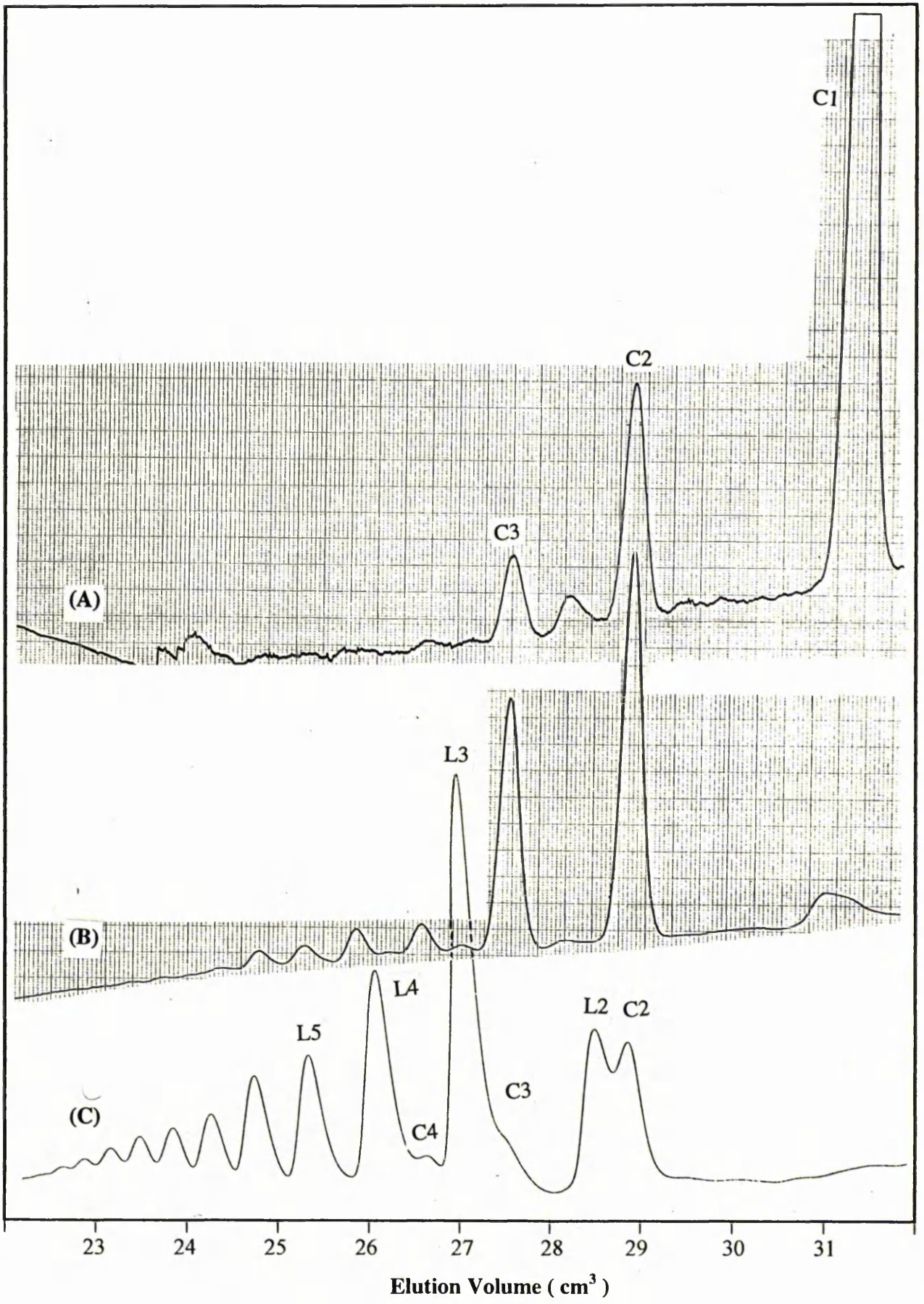


Figure 5.13. GPC Traces of Separated Fractions by GPC Apparatus C.
(A): A fraction obtained from 80/20 MeOH/CHCl3, referred to 2-38c12 in Table 5.8. (B): A fraction obtained from 50/50 MeOH/CHCl3, referred to 2-38c11 in Table 5.8. (C): Refers to linear oligomer **(10)** in Table 5.1.

Table 5.8. The fractionation of cyclic products from entry 1.[a]

Sample Reference	Yield[b] (%)	$\bar{M}_n$ (GPC)	$\bar{DP}$ (GPC)	End groups (500 Hz)	Cyclic (%) (GPC)	Linear (%) (GPC)
2-38c11	7	1270	3.5	Trace	96	4
2-38c12	5	423	1.2	Trace	97	3

a Product from reaction summarised in entry 1, Table 5.4.

b Yields were calculated based on the theoretical weight cyclic product.

5.5.4 Materials Trapped in the Beads

For each cyclo-oligomerisation reaction studied, the combined yields of the isolated products accounted for only about 50-60% of the loaded monomer. These yields are substantially better than those obtained with the cyclic polymer amides, possibly due to their better solubility. The rest of the product, which corresponds to around 30-40% of the loaded monomer, is however unaccounted for and the following disscussion is concerned with possible explanations for this.

First of all, it is possible that the deprotection step and washings of the loaded monomer may cause side-reactions which result in the loss of some monomer and oligomers. This loss is, however, usually expected to be less than 10% of the total loaded monomer as judged from the results obtained in the oligoamide study.

A major part of the shortfall was identified when it was found that the beads weighed more after reaction that would be expected if all the monomer had reacted. This weight gain accounts for a major part of the missing product. All the recovered beads gained in weight , the gain being equivalent to 20-35% of the initial monomer bound. The ^{13}C NMR spectra of the recovered beads showed signals due to ester linkages(-COO$\underline{C}H_2$ at δ

64.5 (ppm) and signals due to aliphatic methylene groups at 21 - 32 ppm. The amide (-CONHCH$_2$-) linkage would be expected to appear in the 40-50 ppm regin but this overlaps with the polystyrene main chain signals. The FTIR spectra showed strong carbonyl vibration frequencies at 1727 cm^{-1} (ester bond) and 1648 cm^{-1}(amide bonds). There were no detectable absorbancies due to active ester bonds. The latter would normally be at 1750-1775 cm^{-1}. A Kaiser test[163] on the recovered beads gave a negative result. Thus, it is evident that the beads contained a substantial amount of oligo/poly(amide-ester) and that it could be cyclic and/or linear. If it was linear it appears to be of high molecular weight as there is little evidence of end groups.

5.6 CHARACTERIZATION OF THE CYCLIC OLIGOESTER-AMIDE PRODUCTS

The cyclo-oligomerisations achieved using amide-bond formation produced satisfactory samples of the cyclic ester-amides derived from both the acid of "C_{11}" (**6**) and "C_6" series (**7**). Cyclic samples were also obtained by using the high dilution methods. Linear oligomers were obtained by using the phase transfer catalysed reaction starting with monomers (**8**) and (**9**). In this section, the characterisation data for these various oligomers is gathered together.

5.6.1 High resolution NMR

This technique is extremely valuable for detecting end groups. This is possible because the shifts of the H or C atoms in the end groups are slightly different from those of similar groups in the main chain. Table 5.9 summarises the data. Clearly determination of the number of repeat units per end group allows estimates of $\bar{M}_n$ to be made. The hydroxymethyl end groups is particularly easy to identify and integrate

accurately. It is possible to detect and integrate accurately one end group per 100 unit main chain units using a 500 Hz NMR machine.

Table 5.9. The Chemical Shifts of End Groups and Repeat Units in NMR Spectra of Oligoester-amides

δ ppm	^{1}H NMR(δ ppm)	^{13}C NMR(δ ppm)
-C<u>H$_2$</u>C<u></u>OOH end groups	2.28-2.35	179.5
-C<u>H$_2$</u>C<u></u>OO- repeat units	2.30 - 2.40	174.5
HO-C<u>H$_2$</u>- end groups	3.70	62.7
-COOC<u>H$_2$</u>- repeat units	4.00 - 4.20	64.3
-C<u>H$_2$</u>C<u></u>ONH- repeat units	2.22	171.9_{linear}; 172.8_{ring}
NH$_2$C<u>H$_2$</u>- end groups	2.75 - 2.90	35.4
CONHC<u>H$_2$</u>	3.15 - 3.25	33.7

5.6.2 GPC Analysis

GPC analysis is the most powerful of the common methods used to characterise oligomer samples. As expected the cyclic and linear samples have slightly different eluent volumes with the GPC equipment available in Manchester. The differences in the elution volumes of the cyclic and linear series was, however, small. Due to environmental temperature changes, pre-column blockages, pump pressure and baseline changes, a significant shift of elution volumes for all analytes was encountered from time to time. Therefore, in order to make the results comparable, internal standards were used. One was a polystyrene standard with a molecular weight of 17,000 Da. This is eluted just before the oligomers; elution volume around 21.30 cm^3. The other internal standard was an unknown compound, possibly water or ethanol present in the chloroform. This has an elution volume around of 37.0 cm^3 and it was eluted after all the oligomers.

Plots of the logarithm of the DP versus the elution volume for the cyclic oligomers (**12**) and linear oligomers (**10**) are shown in Figure 5.14. It is evident that the plot of cyclic oligomer (**12**) is parallel to the plot of the bromine-ended linear oligomers (**10**). The displacement of the molecular weight on the $\log_{10}(DP)$ is 0.10, i.e., $(DP)_r/(DP)_l=1.27$. This means the molecular weight of the cyclic oligomers is 1.27 times bigger than the linear oligomers at the same elution volume. Similar results were also reported for a cyclic polyether and linear polyether($M_r/M_l=1.4$)[135], and for a cyclic and linear polysiloxane($M_r/M_l=1.24$)[83].

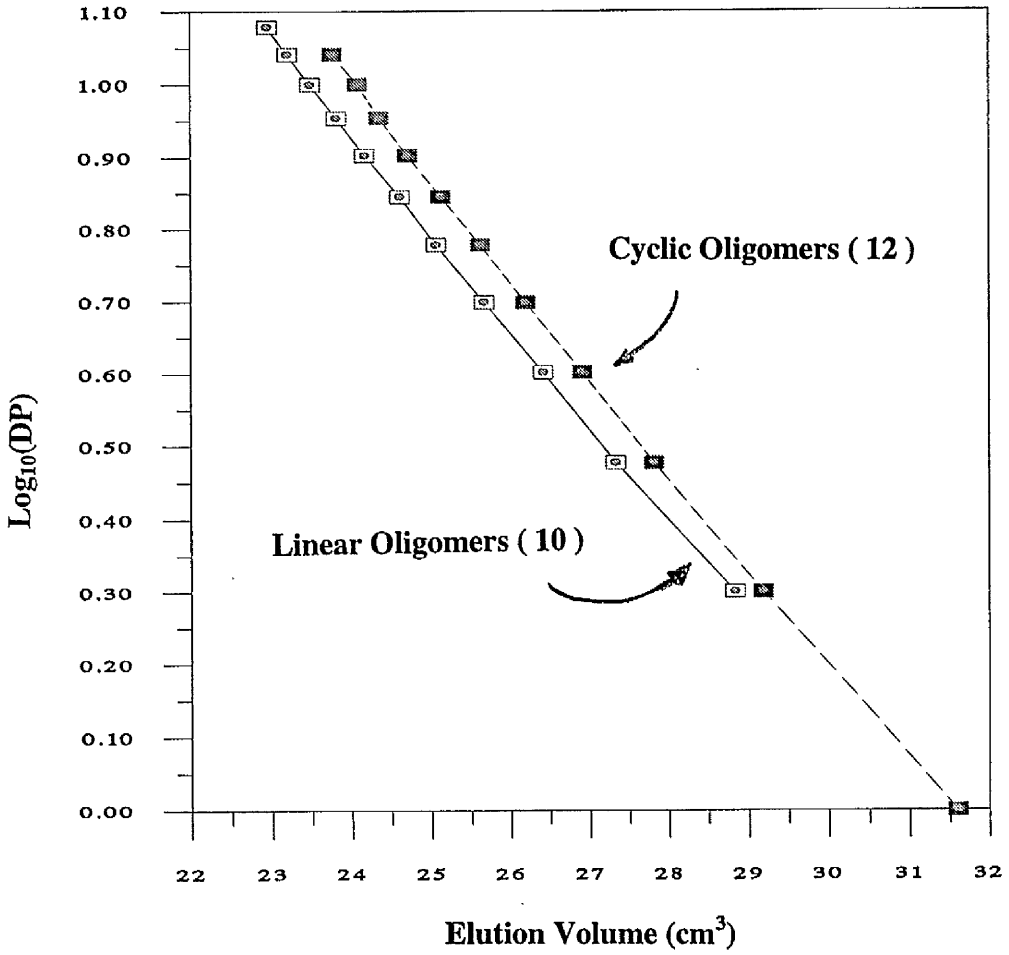


Figure 5.14 The $Log_{10}(DP)$ *vs.* Elution Volume Plot of Cyclic Oligomers (12) And Linear Oligomers (10)

Plots of the logarithm of the DP versus the elution volume for the cyclic oligomers (**13**) and linear oligomers (**11**) are shown in Figure 5.15. The displacement of the plot of linear oligomers (**11**) and the corresponding cyclic oligomers (**13**) is about 0.19 on the $\log_{10}$(DP) scale, i.e., $(DP)_F/(DP)_l$=1.57.

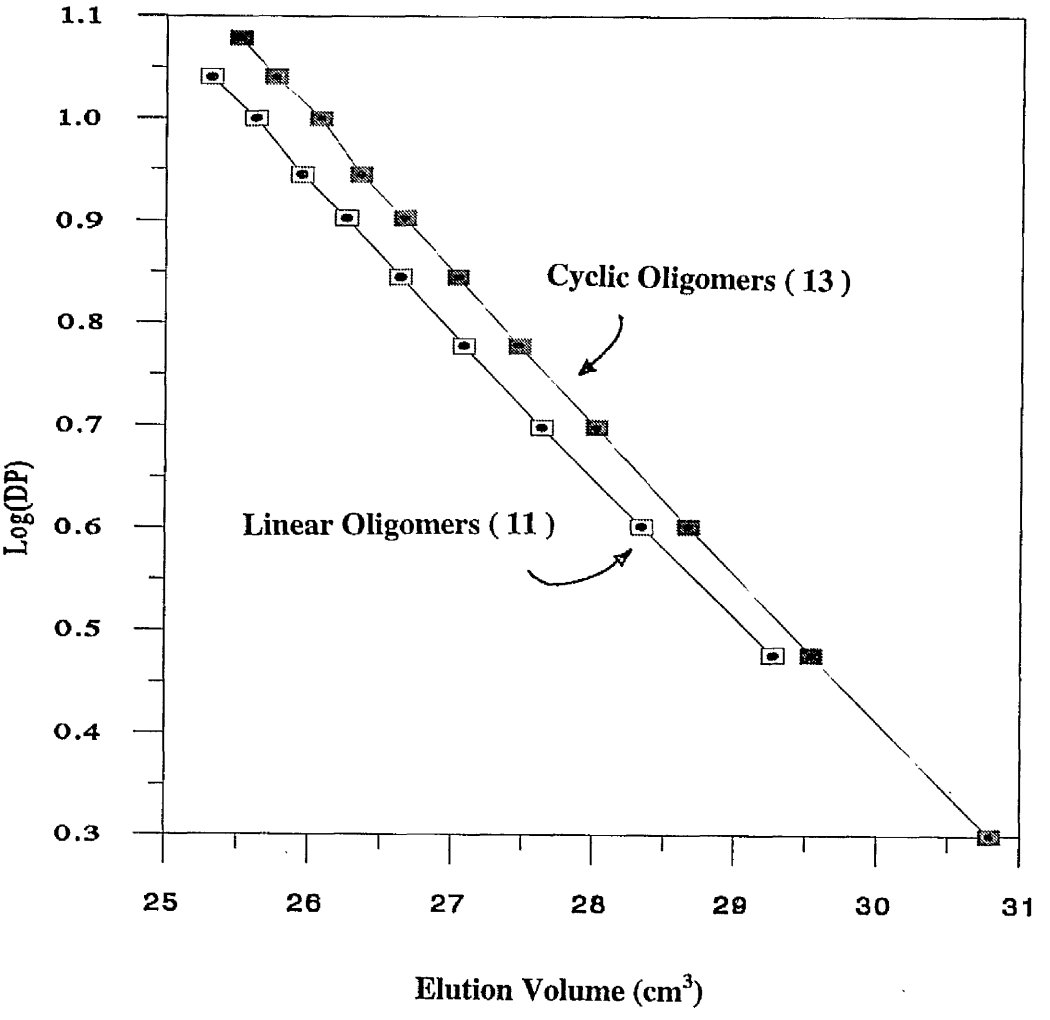


Figure 5.15 The Log_{10}(DP) *vs.* Elution Volume of Cyclic Oligomer(13) and Linear Oligomers (11)

5.6.3 FAB-Mass Spectrometry of Cyclic Amide-esters

FAB-Mass Spectrometry is an efficient method to determine the molecular weight of molecules up *ca.* 2500 Daltons. It results in little fragmentation of the molecules. Satisfactory FAB-MS were obtained for the "C_{11}" cyclic oligomers (structure **12**) up to a DP of 6. However, it was found the cyclic oligomers were much more volatile and a sample containing only 15% of "C_{11}" cyclics displayed the cyclic peaks as the major peaks(see Table 5.10). The method though valuable does not, therefore, permit the quantitative analysis of a sample. However, if no peaks due to cyclics appear in the spectrum, the sample almost certainly does not contain cyclics.

Table 5.10. FAB-MS data and Percentage of Linear Oligomers (10)[a]

	M_1+1	M_2+1	M_3+1	M_4+1	M_5+1	M_6+1	M_7+1	M_8+1
Cyclic(m/z)	368	736	1005	1472	--	--	-	-
Intensity[a]	7.1	44.6	4.07	1.1	--	--	-	-
Cyclic content(%)	0	9.2	2.9	2.1	-	-	-	-
Linear(m/z)	--	816	1183	1152	1920	2287	-	-
		818	1185	1154	1922	2291		
Intensity[b]		10.7	10.7	3.47	0.7	0.2	-	-
Linear (%)	0	10.0	25.2	14.3	9.1	7.6	5.2	14.0

[a]: This sample refers to that considered in Table 5.1. [b]: Relative to highest peak(as a percentage).

Table 5.11 is a summary of the FAB-MS results of the various cyclic samples. The histograms can be found in the Appendix.

Table 5.11 A Summary of FAB-MS Data of Cyclic Amide-esters

Entry Ref.	Notebook Ref.	M_1+1	M_2+1	M_3+1	M_4+1	M_5+1	M_6+1	M_7+1	M_8+1	M_9+1	M_{10}+1
1[a]	2-38c11	368	735	1103	1470	1837	2205	2579			
1[a]	2-38c12	368	735	1103	1470	1838	2205				
1[b]	2-38c2	368	736	1103	1470	1839	2207	2573			
2[c]	2-64c1	386		736	1104	1470	1837				
3[d]	2-44c2	-	735	1103	1470	1837	2205	2572			
4[c]	2-44d1		736	1103	1470	1839					
4[d]	2-44d2	368	736	1104	1471	1838	2205				
5[c]	2-64a1	368	736	1104	1471	1837	2206				
7[d]	2-42c2	228	455	682	910	1137	1364	1591	1819	2046	2273
7[c]	2-42c1	228	455	682	910	1137	1364	1593	1819		

a: Samples refer to the corresponding entries in Table 5.8. b: Samples refer to the corresponding entries in Table 5.6. c: Samples refer to the corresponding entries in Table 5.5. d: Samples refer to the corresponding entries in Table 5.7.

5.7 CONCLUSION

In conclusion, 40-60% yield of cyclic oligoamide-esters obtained by the cyclization of monomer (**6**) bound to the PNO resin. But, only 10-30% of cyclic oligomers were obtained from the cyclisation reaction of monomer (**7**) bound to the PNO resin. The hot chloroform wash of the polymer beads is the best method to extract cyclic oligomers from the polymer supports. GPC analysis showed that in the "first batch" of product more than 90% of products extracted by hot chloroform was cyclic oligomers having a degree of oligomerization between 1.5 to 3.5. This corresponds to 36-84 ring atoms in the ring. It is clear that oligomers (**12**) of 11-aminoundecanoyl-undecanoic acid are more soluble than the oligomers of 11-aminoundecanoic acid. Thus, better yields were obtained by using amide-ester monomers(**6** and **7**).

About 20-40% more products can be extracted by use of TFA/chloroform mixture, or hot chloroform. The TFA/chloroform generally had a larger molecular weight and contained up to 15% of non-identifiable larger oligomers(having molecular weight over 5000). So, the total identified cyclic oligomers can account for 30-45% of the theoretical yield calculated from the loaded resin.

CHAPTER 6

CONCLUSIONS

CONCLUSIONS

This chapter aims to bring together briefly the main conclusions from the work described in this thesis.

In Chapter 2 the cyclo-oligomerisations of 11-bromoundecanoic acid with the bicarbonate form of Amberlyst 26(A26) were discussed. It was known before this work began that these reactions were complex and the aim was to clarify the situation. It was found that the main reaction occurring in the early stages was oligomeristion to give linear oligomers. These could be washed off the beads after short reaction periods. A second reaction occurring in the early stage was the conversion of bromo-end groups into hydroxy-end groups. This appears to be a new reaction. Over extended reaction times, cyclic esters were formed by transesterification reactions on the linear oligomers. There was little evidence for the simple cyclisations envisaged in the early work, i.e., the displacement of bromo groups by carboxylate. However, experiments using the PS-DBU showed that such reactions can occur.

In Chapter 3, cyclo-oligomerisations were discussed where the alkanoic acids were bound covalently to polymer supports through active ester linkages. The best results were obtained using the Kaiser oxime-type resin. Here cyclic oligomeric esters were obtained in 17-69% yield, but they still contained significant amount of linears.

More successful results were obtained with cyclisations that produced amide links. This work was discussed in Chapters 4 and 5. These reactions gave pure cyclic Nylon 11s but the yields were only around 10-15%. This was attributed to the

insolubility of the polyamides. When the work was repeated using the more soluble ester-amides, the yields of cyclics achieved rose to 20-60%.

Since this work was carried out, Dr. Ruddick in these laboratories has successfully prepared pure cyclic undecanoates in *ca.* 80% yield by treating the crosslinked polymer-supported ω-hydroxyundecanate(see Figure 6.1), which was prepared from Merrield polymer and the ω-hydroxyundecanoic acid, with 0.2% of dibutyltin oxide in chlorobenzene at 130 °C. This result suggests that the difficulty in the methods discussed in this Thesis is the lability of the polymer-acid linkages and the poor solubility of many products.

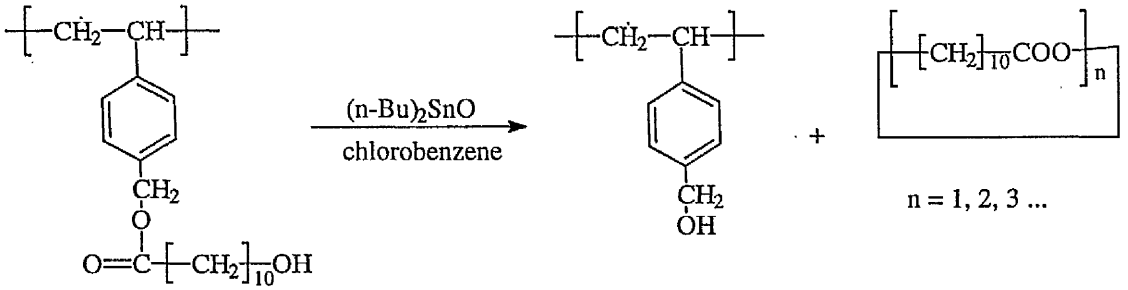


Figure 6.1 Cyclo-oligomerisation of polymer-supported 11-hydroxydecanoic acid bound *via* a stable covalent linkage.

CHAPTER 7

EXPERIMENTAL SECTION

7.1 DETAILS OF TECHNIQUES USED

7.1.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR instruments

Varian Gemini 200 NMR spectrometer.

Bruker AC300 NMR spectrometer.

Varian Unity 500 NMR spectrometer.

Conditions for recording spectrum

Soluble polymers and monomers: Solvent was used as indicated. Recorded at 25 °C except when indicated otherwise. The Gemini 200 MHz spectrometer was used for most measurements. The Unit 500 MHz spectrometer was used for detecting the end groups in samples with high molecular weights, and, where necessary, for a high resolution spectrum.

Polymer beads: ^{13}C NMR spectra were recorded at 75 MHz on the Bruker AC300 MHz NMR spectrometer or at 125 MHz on the Unity 500 spectrometer using a Wilmad 513 3PP 10 mm tube. Data was collected overnight with $D_1 = 15$. About 500 mg of sample was used.

7.1.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR Spectrometers

Except where indicated otherwise an ATI Mattson Genesis Series FTIR instrument equipped with a computer software package was used. It had a resolution of $<4\ cm^{-1}$.

The spectra of a few samples were measured on a Perkin Elmer 1710 Fourier Transform Infrared spectrometer.

Sample Preparation

Liquid samples were run as a film between two CsCl or NaCl plates.

Solid samples were prepared by one or other of two techniques: evaporated film and KBr disk.

Evaporated film: 1-2 mg of the solid sample were placed into a small sample vial and a few drops of the dichloromethane or chloroform were added to make a concentrated solution. Some of the solution was transferred onto a clean polished CsCl or NaCl plate and the solvent allowed to evaporate completely.

KBr disk: The solid sample (compound or polymer beads, 1-2 mg) was finely ground and mixed with a matrix of KBr. The matrix/sample mixture was then compressed to form a thin translucent disk.

7.1.3 Fast Atom Bombardment Mass Spectrometry (FAB-MS)

A Kratos Concept IS spectrometer of magnetic sector type was used for all mass spectroscopic measurements. The fast atom bombardment technique is available on this instrument. The ionisation is achieved by xenon atoms bombarding the sample matrix suspended in *m*-nitrobenzyl alcohol. It is calibrated to 2000 Da(m/z) but it was found that sometimes it had a systematic error of up to 2 m/z in the calibration range, especially in the range of m/z 1000-2000.

7.1.4 High Performance Liquid Chromatography (HPLC)

Analytical HPLC

Instrument was assembled in home from commercial components.

Column: Water ODS RP-18 silica column, 100 x 8 mm Novapack cartridge, 5μ size.

Mobile phase: 80/20 methanol/water (except where indicated otherwise).

Flow rate: 2 ml/min (except where indicated otherwise).

Monitor: a UV monitor at a wavelength of 210 nm. It was a Perkin Elmer LC-480 Diode Array Monitor system.

Temperature: room temperature (20 °C).

A software package was used for collecting the UV data and processing the data.

Preparative HPLC

Instrument was assembled in home from commercial components

Column: An ODS C-18 reverse phase column (21.4 x 250 mm dimensions + guard column).

Mobile phase: 80/20 methanol/water.

Flow rate: 15 ml/min.

Monitor: UV monitor at 210 nm.

Temperature: room temperature (25 °C).

7.1.5 Gel Permeation Chromatography (GPC)

The various sets of GPC apparatus used were assembled in house by Dr C Booth from commercial components.

GPC Apparatus A (GPC-A)

Solvent: DMA.

Column: PLgel 30 cm-2 x mixed B, 1 x 10μ 500 A.

Temperature: 74 °C.

Detector: Knauer HT Differential Refractometer.

Dector temperature: 60 °C.

Detector sensitivity: x 4

Injection volume: 100 μl.

Pump: Water 501.

Flow rate: 1 cm^3/min.

Chart speed: 1 cm/min.

Reference marker: H_2O.

The GPC-A was calibrated with a range of polystyrene standards of up to a molecular weight of 2.0 x 10^6. Average molecular weights were calculated from the charts by classical methods. The retention times were corrected to standard.

GPC Apparatus B (GPC-B)

Solvent: THF.

Column: PLgel 30 cm 10μ-2 x mixed B + 1, 500A.

Temperature: Ambient.

Detector: Waters 401 Differential Refractometer.

Dector temperature: 35 °C.

Detector sensitivity: 32, scale factor 10

Injection volume: 100 μl.

Pump: Knauer 64.

Flow rate: 1 cm^3/min.

Chart speed: 1 cm/min.

Reference marker-1: n-octane; retention time: 27.97 min.

Reference marker-2: an unknown solvent peak, retention time: 29.51 min; this marker was used when marker-1 was absent.

Sample concentration: 0.2%, i.e. 2 mg/ml.

GPC-B was calibrated with a range of polyethylene glycol standards with molecular weights of up to 1.8×10^6. The RI signal was collected by a computer fixed with a Waters GPC 6000 system. Molecular weights and distributions were obtained using this software package. The data files were reprocessed using common graphic programs to produce overlay charts.

GPC Apparatus C (GPC-C)

Solvent: chloroform.

Column: PLgel 30 cm x 4; mixed E, 3μ - 500 A.

Temperature: ambient.

Detector: Polymer Laboratories, GPC LC 1240 RI detector.

Detector temperature: 35 °C.

Detector sensitivity: 2×10^{-5} RIU/FS

Injection volume: 100 μl.

Pump: Gilson 307

Flow rate: 0.3 cm^3/min

Chart speed: 1 cm/min.

Reference marker 1: polystyrene Mw = 1.7×10^5, Mw/Mn = 1.04, retention time: 72.05 minutes at a pressure of 8.5 MPa.

Reference marker 2: unknown solvent contaminant: retention time: 125.0 minutes, at a pressure of 8.5 MPa.

All the retention times were normalised to the same standard for comparison.

GPC-C was calibrated up to 1.1×10^6 with polystyrene calibrants.

7.1.6 Other Techniques

Thin Layer Chromatography (TLC)

Plates: POLYGRAM SIL G/UV_{254} plates (10 x 50 mm), precoated with 0.25 mm silica gel containing fluorescent indicator UV_{254}.

Mobile phase: as indicated in the text.

Melting Points

All melting points were measured using Gallenkamp Melting Points Apparatus and are uncorrected.

Elemental Analyses

C, H, N and S elemental analyses were obtained in house using a Carlo Erba 1108 elemental analyser.

Fluorine analyses were done in house by a colorimetric method with a Cecil Instruments UV/VIS Spectrophotometer.

Chlorine and bromine analyses were carried out in house using potentiometric titration with a Metrohm Autotitration System.

7.2 SYNTHESIS OF POLYMERIC SUPPORTS

7.2.1 Amberlyst A26 (Bicarbonate Form)

Amberlyst A26 (Aldrich, 30 g) was loaded into a column and washed successively with water, acetone, DCM, acetone, water, saturated $KHCO_3$ solution (containing 500 g $KHCO_3$), water and acetone, and then dried. The loading of bicarbonate achieved was

determined by back-titration method using excess hydrochloric acid. Loading achieved: 3.80 mmol of HCO_3^- per g.

A more extensive washing procedure was used to obtain chloride-free Amberlyst A26 bicarbonate for the model reactions discussed in Chapter 2, Section 2.6. By elemental analysis it had: Cl%: 0 and the loading of bicarbonate was 3.89 mmol/g.

7.2.2 4-Hydroxy-3-nitrobenzoylated Polystyrene (PHNB-1 and -3)

3-Nitro-4-chlorobenzoic acid (500.0 g, 2.48 mole), thionyl chloride (500 g, 300 ml, 4.2 mole) and DMF (30 ml) were placed in a 1-L round-bottomed flask. The flask was fitted with a reflux condenser carrying a $CaCl_2$ drying tube leading to gas-absorption trap. The mixture was heated with stirring for 6 hours. The condenser was then set for downward distillation and the excess of thionyl chloride was distilled off. The viscous residue was transferred to a 1000 ml Claisen flask and distilled under reduced pressure collecting the fraction b.p. 158-160 °C/20 mmHg. This gave 4-chloro-3-nitrobenzoyl chloride (500.0 g, yield 91%).

A mixture of polystyrene (2% crosslinked, bead size 156-425 mesh, 50.0 g) and 4-chloro-3-nitrobenzoyl chloride (100.0 g) were added to a solution of aluminium trichloride (25.0 g) in dry nitrobenzene (300 ml). The mixture was stirred mechanically at 60 °C for 5 h and then poured into a mixture of DMF (150 ml), concentrated HCl (100 ml) and ice (150 g). The ensuing mixture was left overnight. The beads were collected on a filter and washed with DMF-H_2O (3:1) until the washings were colourless, then with warm DMF (60 °C) and finally with portions of methylene chloride-methanol (2:1). The beads were dried in a vacuum oven at 80 °C/1 mmHg overnight. The dried polymer obtained (79.0 g) had elemental analysis: N%: 3.00 (*ca.* 2.15 mmol/g); Cl%: 8.40 (*ca.* 2.37 mmol/g).

The above polymer was hydrolysed by two successive treatments with a mixture of benzyltrimethyl ammonium hydroxide in water (Aldrich, 40%, 130 ml), water (130 ml) and dioxane (260 ml), for 12 hours at 90 °C. The beads were then washed with warm dioxane. Acetic acid (30 ml) was added with stirring over 15 min. The polymer beads were then collected and washed successively with dioxane until the washings were neutral, and methylene chloride-methanol (2:1), then dried in a vacuum oven.

The product, polymer support PHNB-1, obtained (75 g) had by elemental analysis: N%, 3.0 (*ca.* 2.15 mmol/g); Cl%, 1.5 (*ca.* 0.42 mmol/g). The loading of functionalised groups (OH) was approximately 1.90 mmol/g as estimated by the weight increase and lower than 2.10 mmol/g as estimated by the nitrogen analysis. The beads had IR (cm^{-1}): 3400-3200, 1660, 1620, 1538, 1291, 760 and 702.

The product polymer support PHNB-3 was prepared similarly by using Amberlite XDE-30 (Aldrich, macroreticular) as the polymeric starting material instead of 2%-DVB crosslinked polystyrene beads. It had by elemental analysis: N% 3.1 (*ca.* 2.0-2.2 mmol/g); Cl%: 0.3 (<0.01 mmol/g). The loading of the OH group was 2.0 mmol/g as estimated by the weight increase. The beads had IR (cm^{-1}): 3400-3200, 1658, 1621, 1538, 1290, 761 and 700.

7.2.3 4-Hydroxy-3-nitrobenzylated Polystyrene (PHNB-2)

Hydrogen chloride gas was passed into a well-stirred mixture of *o*-nitrophenol (80.0 g, 0.58 mole), formaldehyde (40%, 135 ml, *ca.* 1.8 mole), concentrated hydrochloric acid (36%, 610 ml, *ca.* 6 mole) and concentrated sulfuric acid (8 ml) at 90-100 °C for 6 hours. After cooling, the mixture was extracted with benzene (250 ml). The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Adding anhydrous ethanol (100 ml) and cooling the mixture in the fridge gave crude 4-

hydroxy-3-nitrobenzyl chloride (40.0 g), m.p.: 60-65 °C. After recrystallisation from benzenes (25 ml) with the addition of light petroleum ether, a yellow powder was obtained, m.p.: 68-70 °C (lit.[173] 72-74 °C). Yield: 32.0 g (30%). Elemental analysis found (required): C%: 45.3(44.8); H%: 3.4(3.2); N%: 7.5(7.5); Cl%: 18.4(18.9). It had ^{1}H NMR ($CDCl_3$, δ ppm): 10.60(s, 1H, OH); 8.15(s, 1H, aromatic); 7.60(d, 1H, aromatic); 7.20(d, 1H, aromatic) and 4.55(s, 2H, CH_2Cl).

4-Hydroxyl-3-nitrobenzyl chloride (21.0 g, 0.11 mole) in nitrobenzene (220 ml) was stirred with 2% crosslinked polystyrene beads (10.5-150 mesh, 35.0 g) and the mixture was heated gradually to 65-70 °C. Aluminium trichloride (3.0 g) in nitrobenzene (20 ml) was then added; the reaction mixture became deep red and hydrogen chloride gas was evolved. Stirring was continued at 65-70 °C for 2 days. The polymer beads were filtered off, washed successively with chloroform, 1N HCl in dioxane-water (7/3, v/v), methanol and dried in the vacuum oven at 80 °C/1 mmHg. The product was a brown resin (51.0 g). It had N%: 2.6; Cl%: 0. The loading of the functional group (OH) was 1.85 mmol/g as measured by weight increase. This is roughly in agreement with the estimation by nitrogen analysis (1.84 mmol/g). It had IR (cm^{-1}): 3300-3200, 1630, 1538 and 1252.

7.2.4 4-Hydroxyphenyl-1-thiomethylated Polystyrene (SX1 and SX2-PHPS)

p-Mercaptophenol (Lancaster Synthesis, 94%+, 10.0 g, 75 mmol) was dissolved in DMF (50 ml). Potassium hydroxide (85%, 5.0 g, 76 mmol) was added to the stirred solution under a nitrogen atmosphere. The resulting solution was added to a suspension of Merrifield polymer beads (Fluka, 2.1 mmol Cl/g, 2%-DVB-crosslinked, 10.0 g, *ca.* 8.6 mmol) in DMF (50 ml) and the reaction mixture was heated under reflux for 5 h. The cooled suspension was filtered off and the resin beads washed succesively with HOAc/DMF (2/20, v/v, 100 ml), HOAc/EtOH/H_2O (10/50/50, v/v, 110 ml), H_2O (100 ml), methanol (100 ml) and acetone (50 ml). The final dried resin SX2-PHPS (11.82g)

had by elemental analysis: Cl%: 1.6; S%: 5.1 (1.59 mmol/g). The loading estimated by the weight increase is 1.72 mmol/g. The IR spectrum showed bands at 3412 cm^{-1} (–OH) and 1598 cm^{-1} (–S–CH_2).

The SX-1 PHPS resin was prepared similarly by using a 1% crosslinked Merrifield polymer (Fluka, 1.7 mmol Cl/g). A loading of 0.92 mmol/g was estimated by the weight increase. It had by elemental analysis: Cl% 0; S%: 5.1. The loading estimated by sulfur analysis is 1.59 mmol S/g.

7.2.5 The *para*-Nitrobenzophenone Oxime Polystyrene Resin (SX1- and SX2-PNO)

Polystyrene beads (2% crosslinked, 150-400 mesh, 20.0 g) were swollen in 1,2-dichloroethane (300 ml). p-Nitrobenzoyl chloride (15.0 g) was added to the mixture followed by the slow addition of aluminium trichloride (15.0 g) with vigorous stirring. The mixture was heated under reflux and well stirred for 10 h. The polymer beads were then collected by filtration and washed successively several times with dioxane-4N HCl (3:1, v/v), dioxane/water (3:1), dioxane, MeOH, DCM and ether, yielding the nitrobenzophenone resin (30.3 g). The IR spectrum of the beads showed strong bands at 1665, 1524 and 1310 cm^{-1}. Elemental analysis: N%: 3.2 (2.29 mmol/g). The loading estimated by the weight increase was 2.27 mmol/g.

The *p*-nitrobenzoylated resin was suspended in a mixture of ethanol (600 ml), pyridine (150 ml), and hydroxylamine hydrochloride (100 g). The mixture was heated under reflux with stirring for 24 h. The resin was then filtered off, washed successively with ethanol, ethanol/water (1/1, v/v), acetone and DCM. Drying gave oxime resin SX2-PNO (30.0 g). The IR band present in the starting material at 1665 cm^{-1} had disappeared. Elemental analysis: N%: 5.8 (2.07 mmol/g). The loading estimated from the weight increase was 2.27 mmol/g. It had IR (KBr disc, cm^{-1}): 3500-3600, 1600, 1519, 757 and 693.

The SX1-PNO resin was prepared by a similar procedure. Elemental analysis: N%: 6.77 (2.40 mmol/g). The loading estimated by the weight increase is 2.42 mmol/g. It had IR (KBr disc, cm^{-1}): 3500-3600, 1600, 757 and 693.

7.2.6 Synthesis of Polymer-supported DBU

THF (dried over Na, 100 ml) and DBU (dried and distilled over CaH_2, 12.2 g, 80 mmol) were mixed in a three-neck flask, which was fitted with a reflux condenser and a nitrogen inlet tube. The solution was well stirred in a dry ice bath and n-butyl lithium in hexane (1.6M, 45 ml) was added dropwise over a period of 2 h. After the addition was completed, the solution was stirred for an additional 2 h, and Merrifield polymer (Fluka, Cl content 4.3 mmol/g, 2% crosslinked, 11.2 g, 4.2 mmol) was added to the solution in 10 equal portions over a period of 3 h. The mixture was well stirred and allowed to warm to room temperature. After about 40 h, the reaction was terminated by the addition of methanol (10 ml). The polymer beads were recovered by using a sintered glass funnel, then they were washed thoroughly with THF/methanol, methanol, water/methanol, acetone and ether, and dried at 40 °C in vacuum, yielding PDBU (13.4 g). Elemental analysis: Cl%: 8.66 (2.44 mmol/g); N%: 3.48 (1.24 mmol/g). They had IR (KBr, cm^{-1}): 2920, 2852, 1620, 1510, 1448, 1421, 1322, 1110, 816 and 700.

In an attempt to reduce the chlorine content of the beads, the reaction was repeated once more. This gave polymer-supported DBU with a chlorine content of 5.08% (1.43 mmol/g) and a nitrogen content of 4.01 (1.43 mmol/g).

7.3 SOME GENERAL PROCEDURES

7.3.1 Coupling of Monomer onto A Polymer Support

Active esters of Boc-blocked monomers were prepared by two methods. The following procedure are typical.

Procedure A: Symmetric Anhydride Method.

Boc-blocked monomer(20 mmoles) was dissolved in CH_2Cl_2(40 ml) (THF was added in cases of poor solubility). The solution was cooled to -5 - 0 °C and DCC(10 mmole) was added. After 30 min at 0 °C, the mixture was filtered directly into a flask containing the polymer support(PHNB, 4.0 g) and pyridine(2.5 ml) in CH_2Cl_2(10 ml) and stirred at room temperature overnight. The polymer beads were washed successively with portions of CH_2Cl_2, CH_2Cl_2/MeOH(3:1, v/v), ether, and dried(soxhleted if necessary).

Procedure B: DCC-Coupling Method.

Boc-blocked monomer(10-15 mmoles) in DMF or DCM(15 ml) containing 3%(v/v) 4-dimethylaminopyridine or pyridine was stirred with PHNB (4.0 g, containing 6-8 mmoles OH) at 0 °C for 5 min and DCC (10-15 mmoles) in THF (10 ml)was added. Stirring was continued for 1 hour at 0-10 °C following 24 hours at room temperature. The active ester polymer was filtered off, washed with DMF(2x50ml), chloroform-methanol(1:1, v/v, 5x50ml)and ether (100 ml) and dried in a vacuum oven. Multiple coupling could result in a resin of higher loading.

7.3.2 Estimation of loading

By Measuring Weight Increase:

$$\text{Loading} = \frac{\text{loaded resin weight} - \text{start resin weight}}{(\text{molar mass of monomer residue}) \times (\text{loaded resin weight})}$$

By Titration of the Loaded Resin[156]*:*

Loaded resin(0.100g) was suspended in a toluene solution of benzylamine(0.3M, 1.50ml), and the mixture was well stirred for 20 minutes. Two drops of 1% chlorobenzene solution of methyl violet were added. The suspension was back-titrated to a green colour using 0.100 N standard perchloric acid in acetic acid. A blank sample was treated in the same manner. The loading of the resin was calculated according to the equation:

$$\text{Loading (mmol/g)} = \frac{[\text{volume(blank)} - \text{volume(sample)}] \times 0.100}{\text{loaded resin weight}}$$

7.3.3 Kaiser test[163]

Reagents:

Solution A: a 5% solution of ninhydrin in ethanol;

Solution B: a solution of phenol(0.8g) in ethanol(20 ml);

Solution C: a solution of KCN(2mg) in pyridine(100 ml).

Procedure:

The test was carried out in a small test tube. The polymer beads were suspended in the solution obtained by mixing 3 drops of each solution in the test tube, then placed in boiling water for 5 minutes. The colour change both in solution and on the beads was noted. The formation of a blue colour is stong evidence of the presence of amino groups.

7.3.4 Deprotection of *tert*-Butoxylcarbonyl Group

The deprotection of Boc-blocked polymer-supported monomers was carried out at room temperature or 0 - 10°C by treatment with TFA/CH_2Cl_2 (1:1 or 1:2, v/v) for 1 hour. Then, the beads were filtered off and washed successively with CH_2Cl_2, ether and dried under vacuum at room temperature.

7.4 EXPERIMENTS DISCUSSED IN CHAPTER 2

11-Bromoundecanoic acid(AR, Aldrich) was recrystallised from acetone. This afforded white crystals. m.p. 49 - 51 °C(Aldrich, 48 - 51 °C). 12-Hydroxydodecanoic acid(Fluka, 95%+, m.p.: 80 -82 °C) was recrystallized from chloroform-methanol twice. This gives white crystals, m.p. : 82 - 83 °C (lit.[130] 83 - 84 °C). All solvents were purified according to common methods. All resins and products were dried in vacuum oven at 40 °C in a vaccum oven at 20 mmHg at least for 24 hours, and 4 hours at 0.2 mmHg if not indicated.

7.4.1 Synthesis of 11-Hydroxyundecanoic Acid, Its Dimer and Linear Oligomers

7.4.1.1 11-Hydroxyundecanoic Acid (**1a**).

A solution of 11-bromoundecanoic acid(53.2 g, 0.2 mole) in water(300 ml) containing potassium hydroxide(AR., 85%, 30.0 g, 0.45 mole), was heated under reflux for one week. Then, the reaction solution was cooled to 0 °C and the precipitate was filtered off. The solvent was evaporated off the filtrate and the recrystalized twice from methanol. It was then dissolved in water(200 ml) and acidified to pH=1 by adding 6N HCl. The oil that found was extracted twice with ether(150 ml), and the extracts was washed with water and dried over $MgSO_4$. Evaporation of the solvent afforded a crude product which was recrystalized from ethyl acetate. This yielded white needle crystals(18.6 g, yield: 46.0%). m.p.: 66-67 °C (lit.[130] 65.5-66.0 °C).

^{1}H NMR ($CDCl_3$, δ ppm): 6.1-6.5(b, 1H, -O<u>H</u>); 3.65(t, 2H, C<u>H$_2$</u>-OH); 2.35(t, 2H, C<u>H$_2$</u>CO) and 1.7-1.2(m, 16H, -(C<u>H$_2$</u>)$_8$-).

IR(film, cm^{-1}): 3350(OH), 2917, 2849, 1692(CO), 1465, 1065 and 914.

Elemental analysis(required): C%: 65.50(65.35); H%: 11.10(10.90); Br%: 0.00(0).

^{13}C NMR($CDCl_3$, δ ppm): 179.98, 63.40, 34.57, 33.03, 29.94, 29.79, 29.66, 29.49, 29.40, 26.15 and 25.18.

7.4.1.2 Dimer (**2**) of 11-hydroxylundecanoic acid

(a) Coupling

11-Bromoundecanoate benzyl ester(refers to Section 7.7.1.2 *(a)*, 3.6g, 10 mmol), 11-hydroxyundecanoic acid(2.0 g, 10 mmol) and DIEA(1.5g, 12.5 mmol) were dissolved in ethyl acetate(8 ml) and heated at 80 °C for 72 hours. Then, the mixture was diluted with ethyl acetate(50 ml). The salt precipitates out and was removed by filtration. An oily product was obtained by removing the solvent under vacuum. Recrystallisation from cyclohexane twice and di-isopropylethyl ether once gave crystals (2.34g, yield: 49%). m.p. 48.5 - 50 °C.

Elemental analysis(required): C%: 72.76(73.07); H%: 10.15(10.14); N%: 0.0(0).

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 7.37(s, 5H, aromatic), 5.12(s, 2H, $C\underline{H}_2$-Ph), 4.05(t, J= 6.5 Hz, 2H, -$COOC\underline{H}_2$-), 3.64(t, J= 6.5 Hz, 2H, $HOC\underline{H}_2$-), 2.35(t, J= 7.5 Hz, 2H, $C\underline{H}_2COOCH_2$), 2.28(t, J= 7.5 Hz, 2H, $C\underline{H}_2COOH$), 1.60(m, 8H, 2-CH_2-) and 1.30(s, 24H, 6-CH_2-).

IR(film, cm^{-1}): 2917(s), 2850 (s), 1733(s), 1463(m), 1178(m), 741(w) and 697(w).

(b) Deprotection

The above "dimer" benzyl ester(2.3 g) was hydrogenated in ethanol(30 ml) under an hydrogen atmosphere with a Pd-C catalyst(20% Pd, 0.5 g) for 4 hours. Then, the catalyst was removed by filtration and the solvent was evaporated off under vacuum.

The residue was recrystallized from ether-petroleum ether(1:1, v/v) twice, affording white crystals(1.43g, overall yield: 37%), m.p. 39 - 41 °C. Elemental analysis(required): C%: 68.93(68.39); H%: 10.92(10.95).

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 4.75(b, 1H, HO-), 4.05(t, J= 6.5 Hz, 2H, -$COOC\underline{H}_2$-), 3.64(t, J= 6.5 Hz, 2H, $HOC\underline{H}_2$-), 2.34(t, J= 7.5 Hz, 2H, $C\underline{H}_2COOCH_2$), 2.29(t, J= 7.5 Hz, 2H, $C\underline{H}_2COOH$), 1.61(m, 8H, 2-CH_2-) and 1.29(s, 24H, 6-CH_2-).

IR(film, cm^{-1}): 3438(OH), 2917, 2850, 1735(CO ester), 1711(CO acid), 1466 and 1185(C-O-).

^{13}C NMR($CDCl_3$, δ ppm): 179.40($\underline{C}OOH$), 174.58($\underline{C}OOCH_2$), 64.69($COO\underline{C}H_2$), 63.51($HO\underline{C}H_2$), 34.90(1C), 34.43(1C), 33.16(1C), 29.98(1C), 29.88(1C), 29.84(2C), 29.79(1C), 29.67(2C), 29.60(1C), 29.51(1C), 29.10(1C), 29.00(1C), 26.40(1C), 26.18(1C), 25.49(1C) and 25.18(1C).

7.4.1.3 Synthesis of Linear Oligomers of 11-Hydroxyundecanoic Acid and 12-Hydroxydodecanoic Acid

*(a) Synthesis of Linear Oligomers (**3a**) of 11-Hydroxyundecanoic Acid*

11-Hydroxyundecanoic acid(3.00 g) was placed in a flask and heated under nitrogen at 110°C for 48 hours. The polymer(Sample Ref.: 2-55RP1, 2.82 g) has a number average molecular weight of 2.42(NMR).

^{1}H NMR($CDCl_3$, δ ppm): 4.06(t, J = 6.6 Hz, 1.15H, $COOC\underline{H}_2$), 3.65(t, J= 6.6 Hz, 0.85H, $HOC\underline{H}_2$), 2.35(t, J= 7.5 Hz, $C\underline{H}_2COOCH_2$), 2.29(t, J= 7.5 Hz, $C\underline{H}_2COOH$), {δ 2.35+δ2.29(2H)}, 1.65(m, 4H, 2-CH_2-) and 1.30(s, 12H, 6-CH_2-).

^{13}C NMR($CDCl_3$, δ ppm): 179.40($\underline{C}OOH$), 174.62($\underline{C}OOCH_2$), 64.91($COO\underline{C}H_2$), 63.29($HO\underline{C}H_2$), 34.84, 34.52, 33.03, 29.90, 29.84, 29.69, 29.59, 29.51, 29.08, 26.37, 26.17, 25.45 and 25.18.

IR(film, cm^{-1}): 3489(HO), 2918, 2851, 1731(ester), 1711(CO acid), 1465 and 1184(ester).

(b) Synthesis of Linear Oligomer (3b) of 12-Hydroxydodecanoic Acid

12-Hydroxydodecanoic acid oligomers were prepared by a similar method that used in the above section (a). This gave a product (**3b**, sample ref: 2-67L1 in Table 2.1) with a number average molecular weight of 2.86 (by NMR).

^{1}H NMR($CDCl_3$, δ ppm): 5.4-4.8(b, 0.4H, HO), 4.06(t, J = 6.5 Hz, 2.70H, $COOC\underline{H}_2$), 3.65(t, J= 6.6 Hz, 1.45H, $HOC\underline{H}_2$), 2.35(t, J= 7.5 Hz, $C\underline{H}_2COOCH_2$), 2.29(t, J= 7.5 Hz, $C\underline{H}_2COOH$), {2.35+2.29(2H)}, 1.65(m, 4H, 2-CH_2-), 1.30(s, 14H, 6-CH_2-).
IR(film, cm^{-1}): 3492(HO), 2918, 2851, 1727(ester), 1711(CO acid), 1468 and 1183(ester).

^{13}C NMR($CDCl_3$, δ ppm): 179.40($\underline{C}OOH$), 174.62($\underline{C}OOCH_2$), 64.93($COO\underline{C}H_2$), 63.48($HO\underline{C}H_2$), 34.89, 34.52, 33.11, 29.94, 29.87, 29.73, 29.63, 29.59, 29.54, 29.46, 29.11, 26.40, 26.20, 26.15, 25.49 and 25.18.

7.4.2 The synthesis of Chloro/ Bromo-ended Linear Oligomers

7.4.2.1 Chloro-ended Linear Oligoesters

Linear oligomers of 11-hydroxylundecanoic acid(Sample ref: 2-55RP, 0.55 g) were dissolved in chloroform(10 ml) and a few drops of DMF were added. Thionyl chloride(1 ml) was added to the solution at 0°C. The reaction was left overnight at room temperature. The solution was then evaporated to dryness. The residue was dissolved in THF(15 ml), and stirred with potassium bicarbonate solution(5%, 5 ml) overnight. The THF was then evaporated off and the residue re-dissolved in chloroform(30 ml) and washed by 1N aqueous HCl, and dried, affording a crystalline polymer(Sample ref.: 2-59-Cl, 0.52 g). Elemental analysis: Cl%: 5.5.

IR(film, cm^{-1}): 2919, 2851, 1732(CO ester), 1711(CO acid), 1465, and 1183(ester).

^1H NMR($CDCl_3$, δ ppm): 4.06(t, J = 6.6 Hz, 1.35H, $COOC\underline{H}_2$), 3.55(t, J= 6.6 Hz, 0.65H, $ClC\underline{H}_2$), 2.35(t, J= 7.5 Hz, $C\underline{H}_2COOCH_2$), 2.29(t, J= 7.5 Hz, $C\underline{H}_2COOH$), {δ 2.35+δ2.29(2H)}, 1.65(m, 4H, 2-CH_2-) and 1.30(s, 12H, 6-CH_2-). DP=1+ Integration at $\delta_{4.06}$/ Integration at $\delta_{3.55}$ = 3.08. ^1H NMR(200 MHz) showed no -CH_2-OH end groups present.

7.4.2.2 Bromo-ended Linear Oligoesters

The bromo-ended oligomer sample was obtained by heating under reflux using equal molar amount of n-tetrabutylammonium hydroxide in methanol with 11-bromoundecanoic acid in chloroform for 2 hours. The resulting solution was washed with 0.5 M aqueous hydrogen bromide, then water and dried over sodium sulfate. The bromo-ended oligomers were obtained by removing the solvent in vacuum(sample ref: 2-59Br). They had a DP(NMR) of 3.42, Br%: 10.8. ^{1}H NMR(200 MHz) showed no HO-CH_2-($\delta_{3.65}$) end groups present. IR(film, cm-1): 2917, 2849, 1732(ester), 1472 and 1182(ester).

7.4.3 Loading of 11-Bromoundecanoic Acid onto Amberlyst 26

Typical Procedure for Achieveing Loading :

A mixture of the bicarbonate form of Amberlyst 26 resin(3.89 mmol HCO_3^- /g, 1.00 g), and 11-bromoundecanoic acid(1.03 g), solvent(10 ml) were shaken for given time in room temperature. Then, the resin beads were filtered off and washed successively with acetone(2x20 ml), chloroform(20ml), acetone(30 ml) and ether and dried. Details of solvents and times used and the loadings achieved are summarisied in Table 2. 3 and Table 2.4.

TFA Extraction of In-Resin Oligomers for GPC Analysis

The loaded resin(usually 1-1.5 g) was suspended in TFA/chloroform solution(1/4, v/v, 8 ml) and shaken at room temperature for 15-30 min. The beads were then filtered off and washed with chloroform(3x10ml). Evaporation of the solvent gave an oily product which was re-dissolved in chloroform(50 ml). The solution was washed with aqueous sodium bicarbonate(5%, 2x20 ml) and dried over $MgSO_4$. Removing the solvent gave the extract which was dried and weighed. This procedure is able to recover over 95% of the calculated amount of oligomers. The GPC analysis results were given in Table 2.4 and Table 2.8.

7.4.4 Cyclo-oligomerisations

The following are general procedures for the experiments summarised in Table 2.5 and 2.9.

Suspension Reactions

Loaded resin(2.0g) was suspended in the solvents (20ml) and the mixture was heated for the given time at the given temperature. After cooling the reaction mixture, the beads were filtered off and washed with solvent(3x20 ml). Removing the solvent from the filtrate afforded the cyclic products. They were carefully weighed and analysed as discussed in Chapter 2.

Reaction by Using the Soxhlet Apparatus

This procedure was similar to that used for the suspension reactions but the beads were placed in the thimble of a Soxhlet apparatus instead of in a flask. The solvent was placed in the boiler.

Flow Column Reactions

The designed flow column was a water-jacketed chromatography column(20mmx50mm). Hot water(60 °C) was pumped through the jacket to keep the column at a constant temperature. Loaded resin beads(2.0 g) were placed in a thimble and suspended in the reaction solvent in the jacketed column. Fresh and warm solvent(60 °C) was introduced into the column by a Teflon tube. The volume of solvent staying in the column was about 20 ml. The flow rate was controlled at 2-3 ml/min.

7.4.5 Extraction Experiment of Heated Resin Beads

Loaded resin beads (1.00 g) were dried in vacuum oven at room temperature for a few hours. Then oven was then filled with nitrogen and the beads were heated at 40°C and at 60 °C. After cooling down, the beads were extracted by chloroform(4x5ml).

7.4.6 Cyclo-depolymerisation of Linear Oligoesters (3a and 3b) Catalysed by A26 Bicarbonate

The linear oligomers of 11-hydroxyundecanoic acid(**3a**, Ref. 2-55RP, 0.55g , *ca.* 1 mmol of OH) and bicarbonate form of Amberlyst-26 (2.00g, 7.8 mmol HCO_3^-) were suspended in chloroform(15 ml). The suspension was heated to 58°C for 72 hours. The beads were then removed by filtration and the filtrate was evaporated to dryness. This yielded a white solid(0.35 g, yield: 66%). This was analysed by GPC and ^{1}H NMR. Other reactions were carried out similarly. The results were summarised in Table 2.9.

7.5 EXPERIMENT DISCUSSED IN CHAPTER 3

7.5.1 Cyclizations of 11-Bromoundecanoic Acid on Polymer supported DBU Resin(PS-DBU)

These reactions are summarised in detail in Table 3.1. The general procedures were as follows.

PS-DBU resin was suspended in a solution of the monomer in chloroform and the mixture was stirred and heated at 58 °C for a given time. The polymer beads were then filtered off and washed. The filtrate was evaporated to dryness to yield the products, usually as a white solid. The solid was analysed by ^{1}H NMR and GPC. The results were summarised in Table 3.1.

7.5.2 Cyclo-oligomerization on Polymer-supported Oxime Resin(PNO)

These reactions are summarised in detail in Table 3.3. The general procedure used was as follows.

The loaded oxime beads were suspended in a chloroform solution of DBU and the mixture was shaken on a vibrator at room temperature for the time given. The polymer beads were filtered off and washed by chloroform. The filtrate and washings were washed with 1N hydrochloric acid twice, water, and passed a short silica column. Finally, the organic solvent was evaporated off to yield the solid products. These were analysed by GPC and ^{1}H NMR. The results were given in the Table 3.3.

7.6 EXPERIMENTS DISCUSSED IN CHAPTER 4

7.6.1 The Synthesis of Boc-Blocked Monomers

7.6.1.1 *t*-Butoxylcarbonyl-11-aminoundecanoic Acid

A three-necked round-bottom flask (1 L) equipped with a mechanical stirrer, thermometer and dropping funnel, was charged with a solution of sodium hydroxide(6.8g, 0.17 mole) in water(150 ml) and 11-aminoundecanoic acid(30.0g, 0.15 mole). The clear solution obtained was diluted with t-butyl alcohol(100 ml). To this well-stirred solution,

di-*t*-butyl dicarbonate(Aldrich, 97%+, 33.80 g, 0.15 mole) was added dropwise over an hour. A white precipitate formed. Additional sodium hydroxide(3.2g, 0.8 mole) in water(10 ml) was carefully added to the mixture in the flask. The solution became clear again. The pH was still between 7 and 8. This solution was left overnight, then acidified to Congo Red, and extracted by diethyl ether(200 mlx2). The combined extracts were washed with water(100 ml) then dried overnight. The solvent was evaporated off, then, the residue was dissolved in ethyl acetate-petroleum (1:1), and stored in a cool place. Needle-like crystals formed and were collected by filtration, and dried, to afford the product (38.0g, yield: 85.0%). m.p.: 69-70 °C.

^{1}H NMR($CDCl_3$, δ ppm): 4.50 (b, 1H, -CO-NH); 3.10(m, 2H, -NH-CH_2); 2.35(t, 2H, -CH_2-CO) 1.65(m, 2H, NH-CH_2CH_2); 1.45(s, 9H, Boc-) and 1.30(s, 12H, -$(CH_2)_6$-).

7.6.1.2 t-Butyloxylcarbonyl-6-aminocaproic Acid

A solution of 6-aminocaproic acid(50.0 g, 0.38 mole) in DMF-H_2O(10:6, v/v, 400 ml) was treated with t-butoxycarbonyl azide(crude product, 55.0 g, ca. 0.38 mole) for one hour. The pH was then raised between 9.5 to 10.5 and held constant during the course of the reaction by the addition of 2N NaOH. The reaction solution was left overnight and acidified to Congo Red by the addition of 2N HCl. The mixture was extracted twice with ether (200 ml). The combined extracts were dried then the solvent was evaporated off to give an oily product. This crude product was dissolved in aqueous Na_2CO_3 (150 ml, 0.50 mole), and the solution was extracted with ether twice. The aqueous layer was acidified to Congo red and extracted with ether again. Evaporating off

the ether gave a nearly pure oily product(54.0 g, yield: 61.5%.), which gradually crystallized. m.p. 35-38 °C(lit.[172] 39 °C).

^{1}H NMR($CDCl_3$, δppm): 4.7 (b, 1H, N-H); 3.10 (m, 2H, NH-CH_2) ; 2.30 (t, 2H, CH_2CO); 1.20-1.70 (m, 15H, Boc+(CH_2)$_3$ -) and 11.1 (s, 1H, COOH).

IR(film, cm^{-1}): 3334(OH), 2977, 2936, 2866, 1710, 1526, 1455, 1367, 1278, 1252 and 1170.

7.6.1.3 Synthesis of N-t-butoxycarbonyl-11-aminoundecanoic Acid p-Nitrophenyl Ester

Into a solution of N-t-butoxycarbonyl-11-aminoundecanoic acid(6.02 g, 0.02 mole) in THF (30 ml), a mixture of *para*-nitrophenol(4.17g, 0.03 mole), DMAP(0.1 g), and DCC(6.18 g, 0.03 mole) in THF(20 ml) was added dropwise over a period of 30 minute at 0 - 10°C. The reaction mixture was well-stirred for further 24 hours. Then the THF was removed in vacuum. The residue was recrystallised from methanol twice, and cyclohexane once. This gave yellowish needles(5.8 g, yield: 58.8%), m.p. 57-58°C.

IR(film, cm^{-1}): 2919, 2849, 1754(active ester CO), 1683(carbonyl in Boc), 1615(aromatic ring), 1592, 1518(amide II), 1348, 1202, 1104(ester), 920 and 853.

^{1}H NMR($CDCl_3$, ppm): 8.28(d, 2H, J=9.13, aromatic H); 7.28(d, 2H, J=9.13, aromatic H); 4.50(b, 1H, -NH-); 3.10(tetra, 2H, J=6.4, -NH-CH_2-); 2.60(t, 2H, J=7.45, CH_2-CO); 1.76(m, 2H, NH-CH_2CH_2-); 1.45(s, 9H, Boc) and 1.30{b, 14H, -(CH_2)$_7$-}.

^{13}C NMR($CDCl_3$, δ ppm): 174.5, 174.0, 156.3, 148.5, 79.5, 51.7, 41.35, 40.41, 36.20, 31.38, 30.13, 29.63 and 28.43.

Elemental analysis(required): C%: 62.49(62.54); H%: 8.20(8.11); N%: 6.80(6.63).

7.6.2 Preparation of Linear Oligomers of 11-Aminoundecanoic Acid in Solution

7.6.2.1 N-(11-Aminoundecanoyl)-aminoundecanoic Acid

(a) 11-Aminoundecanoate Methyl Ester

11-Aminoundecanoic acid (20.0 g, 0.1 mol) was suspended in methanol(300 ml). Hydroden chloride gas was passed into the suspension until the solid disappeared. The solution was left overnight. Removing the solvent afforded a solid, which was recrystalised from methanol twice. This gave white needle crystals of 11-aminoundecanic acid methyl ester hydrochloride(22.5 g, yield: 90%). m.p.: 158-159.5 °C.

^1H NMR (δ ppm, 25 °C, D_2O): 3.67 (s, 3H, OMe); 2.97 (t, 2H, NH_3^+-CH_2-); 2.34 (t, 2H, -CH_2-CO-); 1.62 (m, 4H, NH_3^+-$CH_2C\underline{H}_2$+$C\underline{H}_2CH_2CO$) and 1.35 (s, 12H, 6-CH_2-).

IR (KBr disc, cm^{-1}): 2920, 2849, 1724, 1563 and 1176.

(b) N-(t-butoxylcarbonyl-11-aminoundecanoyl)-aminoundecanoic Acid Methyl Ester

The above 11-aminoundecanoic acid methyl ester hydrogen chloride (10.0 g, 0.04 mol), t-Boc-aminoundecanoic acid (12.4 g, 0.04 mole) and DCCI (8.24 g, 0.04 mole)

were dissolved in chloroform (60 ml) containing triethylamine (4.0 g, 0.04 mole) with vigorous stirring at 0 - 10 °C for 2 hours. The reaction was then carried out at room temperature for 24 hours. The reaction mixture was filtered and washed with 1N HCL, 5% aqueous sodium bicarbonate and dried. Removing the solvent afforded a white solid. Recrystallisation from THF-petroleum ether twice gave Boc-Aua-Aua-Ome as a white crystalline product (9.0 g, yield: 45%). m.p.: 81.5-83 °C. IR (film, cm^{-1}): 1724, 1704, 1679, 1640, 1528 and 1182.

^1H NMR (δ ppm, 25 °C, $CDCl_3$): 5.70 (b, 1H, CONH-CH_2); 4.60 (b, 1H, BocNH); 3.65 (s, 3H, OMe); 3.19 (q, 2H, CONH-CH_2-); 3.07(q, 2H, CONH-CH_2); 2.27 (t, 2H, CH_2-CO-); 2.13 (t, 2H, -CH_2-CO-); 1.58 (m, 8H, 2-CH_2-); 1.41 (t, 9H, Boc) and 1.24 (s, 24H, 6-CH_2-).

(c) N-(t-Butoxylcarbonyl-11-aminoundecanoyl)-aminoundecanoic Acid

The above Boc-Aua-Aua-OMe (8.86 g, 0.018 mole) was suspended in THF/H_2O/MeOH (1:1:1, v/v/v, 40 ml). Sodium hydroxide solution (0.8 g in 20 ml of the same mixed solvent) was added dropwise to the suspension at room temperature during a period of 60 min. The final solution was acidified to pH = 2 - 3 by the addition of 1 N hydrochloric acid and was then extracted by chloroform (5x100 ml). Removing the chloroform under vacuum gave a white solid which was recrystallised from THF-H_2O. This gave Boc-Aua-Aua-OH as a white solid (7.1g, yield: 75%). m.p.: 108 - 110 °C.

^1H NMR (δ ppm, 25 °C, $CDCl_3$): 5.70 (b, 1H, CONH-CH_2); 4.60 (b, 1H, BocNH); 3.65 (s, 3H, OMe); 3.19 (q, 2H, CONH-CH_2-); 3.07(q, 2H, CONH-CH_2); 2.27

(t, 2H, CH_2-CO-); 2.13 (t, 2H, -CH_2-CO-); 1.58 (m, 8H, 2-CH_2-); 1.41 (t, 9H, Boc) and 1.24 (s, 24H, 6-CH_2-).

IR (KBr disc, cm^{-1}): 3350, 2918, 2851, 1698(carbonyl in Boc), 1680, 1639, 1530, 1185 and 1174.

(d) N-(11-Aminoundecanoyl)-aminoundecanoic Acid

The Boc-Aua-Aua-OH(0.10 g) was stirred with TFA/chloroform(1:1, v/v, 5 ml) for 2 hours. The solution was evaporated to dryness. The residue was dissolved in acetone and precipitated from dry ether. A white powder of N-(11-aminoundecanoyl)-11-aminoundecanoic acid trifluoroacetic acid salt was obtained(0.06 g, yield: 57%).

IR(KBr disc, cm^{-1}): 3460(N-H), 2919, 2851, 1710(CF_3COOH), 1686(COOH), 1638(CO-NH I), 1543 (CO-NH II), 1472, 1202, 1191 and 1135.

Elemental analysis(required): C%: 57.62(57.8); H%: 9.34(9.1); N%: 5.70(5.6); F%: 11.38(11.4). This corresponds to an average degree of polymerisation, $\overline{DP} = 4.07 \times \frac{N\%}{F\%} = 2.04$.

^{1}H NMR(DMSO-d_6, δ ppm): 3.02(q, 2H, CONHCH_2, J=5.9 Hz); 2.79(m, 2H, NH_2CH_2, J=6.4 Hz); 2.20(t, 2H, J=7.15 Hz, CH_2CONH); 2.03(t, 2H, J=7.15 Hz, CH_2CO);1.50(b, 4H, -CH_2-) and 1.45(s, 8H, -CH_2-). From the NMR spectrum, the average degree of polymerisation, DP=Integration at $\delta_{2.20+2.03}$/ Integration at $\delta_{2.79}$ =2.0.

^{13}C NMR(DMSO-d_6, δ ppm): 174.5(COOH), 171.9(CONH), 35.42($NH_3^+CH_2$), 33.7($CONHCH_2$), 29.16, 28.98, 28.82(4C), 28.77(4C), 28.65, 28.57, 28.53, 27.00, 26.40, 25.78, 25.35 and 24.51.

IR(film, KBr, cm^{-1}): 3459(N-H), 2919, 2851, 1710(CF_3COOH), 1686(COOH), 1638(CO-NH I), 1543(CO-NH II), 1472, 1202, 1191 and 1135.

7.6.2.2 Linear Oligomers of 11-Aminoundecanoic Acid

Boc-Aua-OPNP(0.85 g, 0.002 mole) was dissolved in TFA/chloroform(1/1, v/v, 15 ml) and the mixture was left at 0 - 10°C for 60 minutes. The solvent was then removed under vacuum. The residue was dissolved in DMF(20 ml) containing DIEA(1.5 ml, 0.0086 mole) and well stirred at 20 °C for 5 hours. After precipitation with ether, the solid was collected and washed with 1N HCl, $NaHCO_3$, water and dried. The residue was dissolved in TFA/chloroform(1/1, v/v, 20 ml), and precipitated from methanol. This afforded the trifluoroacetic acid salt of the discussed product as a white solid(0.29 g, yield: 70-75%).

Elemental analysis: C%: 66.61; H%: 10.68; N%: 7.53; F%: 3.32. This corresponds to an average degree of polymerisatioin, DP= 4.07 x N%/F% = 9.2.

^1H NMR(TFA-d+DMSO-d_6, δ ppm): 3.12(b, 2H, $CONHCH_2$); 2.80(b, 2H, NH_2CH_2); 2.22(t, 2H, CH_2CO);1.38(b, 4H, -CH_2-); 1.10(s, 8H, -CH_2-). From the NMR spectrum, the average degree of polymerisation, DP = Integration at $\delta_{2.22}$ /Integration at $\delta_{2.80}$ = 10.2.

IR(disc, KBr, cm^{-1}): 3299(N-H), 2921, 2849, 1643(CO-NH I), 1555(CO-NH II), 1465 and 1438.

7.6.3 Preparation of Cyclic Oligomers of 11-Aminoundecanoic Acid in Solution

7.6.3.1 Cyclisation in High Dilution

The reaction described in the previous experiment(section 7.6.2.2) was repeated except that now the solvent was DMF(500 ml) and the reaction time was 96 hours. The product(0.34 g) was washed with 1N HCl, sodium bicarbonate solution and dried. Recrystallisation from chloroform-petroleum twice give pure cyclic product(0.21 g, yield: 57%).

Elemental analysis: C%: 71.88(72.09); H%: 11.36(11.54); N%: 7.75(7.64).

^{1}H NMR($CDCl_3$, δ ppm): 5.30-6.0(m, 1H, -NH-); 3.12(b, 2H, $CONHC\underline{H}_2$); 2.80(b, 2H, $NH_2C\underline{H}_2$); 2.22(t, 2H, CH_2CO);1.38(b, 4H, $-CH_2-$) and 1.10(s, 8H, $-CH_2-$).

^{13}C NMR($CDCl_3$, D_1=15, 40°C, δ ppm): 172.8(-CO-); 39.37+39.22(1C, $-NHCH_2$); 36.89+36.76(1C,); 29.40+29.30(1C); 28.97(1C); 28.94(2C); 28.53(1C); 26.64+26.58(1C) and 25.81+25.73(1C).

IR(KBr, cm^{-1}): 3295(s, N-H), 2916, 2847, 1642(s, CO-NH I), 1554(s, CO-NH II), 1464 and 1433.

7.6.3.2 Separation of Cyclic Dimer and Trimer

The cyclic oligoamide sample prepared in section (a) above was separated by HPLC on a RP-18 silica column. The fractions at 8.54 min and 16.50 min were collected and characterized by ^1H NMR and FAB-MS. The results show these two fractions were mainly cyclic dimer and trimer respectively, but both of them contaminated by a small portion of other oligomers. Their NMR data was assigned as below.

The dimer: ^1H NMR($CDCl_3$, δ ppm): 5.50(b, 2H, -NH-); 3.30(m, 4H, -NH-CH_2-); 2.15(m, 4H, CH_2CO-); 1.70-1.40(m, 8H, -$NHCH_2CH_2$+-CH_2CH_2CO-); 1.20(s, 24H, -$(CH_2)_6$-). HPLC(methanol/water; 80/20 v/v) and GPC(chloroform) indicated this sample with a purity of more than 95%. FAB-MS(m/z): 184(M_1+H^+, 8.3%); 367(M_2+H^+, 100%). m.p.: 174-175 °C.

The trimer: ^1H NMR($CDCl_3$, δ ppm): 5.80(b, 3H, -N<u>H</u>-); 3.25(m, 6H, -NH-C<u>H</u>$_2$-); 2.15(m, 6H, CH_2CO-); 1.90-1.40(m, 12H, -$NHC\underline{H}_2C\underline{H}_2$+-$C\underline{H}_2C\underline{H}_2CO$-); 1.20(s, 36H, -$(CH_2)_6$-). HPLC(methanol/water; 80/20 v/v) indicated more than 95% purity. FAB-MS(m/z): 184(M_1+H^+, 12.5%), 367(M_2+H^+, 2.5%) , 550(M_3+H^+, 100%) and 1099(M_6, 16%). m.p.: 169-170 °C.

7.6.4 Coupling, Deprotection and Cyclization Procedures for Cyclic Nylon 11s

These were carried out using the general procedures in Section 7.3. The following example is typical.

An Example: Coupling, deprotection and cyclisation of Boc-Aua-OH on PHNB-1 resin(entry 3 in Table 4.2):

Boc-Aua-OH(6.6 g, 22 mmol) in DCM(30 ml) was mixed with DCCI(2.3 g, 11 mmole) in THF(5 ml) at 0 - 10°C and the mixture was left for 15 min. Then, PHNB-1 beads(5.00 g, 10 mmol) were added to the mixture and more DCM(30 ml) was added with pyridine (5 ml). The reaction was left overnight. The beads were then filtered off and extracted by DCM for 10 hours using a Soxhlet. This gave the loaded PHNB-1 beads(6.3 g, loading: 0.73 mmol/g). The IR spectrum displayed the active ester carbonyl bond asymmetric vibration at 1750 cm^{-1}, carbonyl vibration of Boc at 1709 cm^{-1}. The loaded monomer units were deblocked using TFA/DCM(1:1, v/v, 20 ml) (1 hour), then, the resin beads were filtered off and washed and dried at room temperature in vacuum. The beads was shaken in DCM(30 ml) with TEA(10 ml) for 8 days, then, recovered. The filtrate was washed with 1N HCl, 5% aqueous sodium bicarbonate, and water, filtered and dried. Evaporating off the solvent afforded solid materials(55mg. yield: 6.4%). IR: 1639.5 cm^{-1}.

7.7 EXPERIMENTS DISCUSSED IN CHAPTER 5

All GPC measurements in Chapter 5 were carried out using the GPC-C equipment.

7.7.1 Syntheses of Monomers

7.7.1.1 N-(11-Bromoundecanoyl)-11-aminoundecanoic Acid (**8**)

(a) 11-Aminoundecanoic Acid Benzyl Ester

11-Aminoundecanoic acid(20.1g, 0.10 mole), *para*-toluenesulfonic acid monohydrate(20.9g, 0.11 mole), benzyl alcohol(11.8g, 0.11 mole) and toluene(150 ml) were mixed together in a 250 ml round bottom flask which was fixed with an Dean-Stark device. The mixture was heated under reflux until no more water was produced. The mixture was then cooled and the white syrup added into petroleum ether (200 ml) and well stirred. The solid product was filtered off and air-dried. The solid obtained(45.6g) was recrystalized from ethyl acetate(38.7g, yield: 83.2%). m.p.:70-75 °C. IR: 1729 cm^{-1}. The salt of benzyl ester(22.3g, 0.05 mole) so obtained was dissolved in chloroform(200 ml) and washed successively with aqueous sodium bicarbonate (5%), water(2x100ml) and dried over magnesium sulfate overnight.

(b) 11-Bromoundecanoyl Chloride

To a dichloromethane solution(50ml) of 11-bromoundecanoic acid(13.3g, 0.05 mole), a few drops of DMF were added, followed by thionyl chloride(6.6g, mmole). The reaction mixture was left overnight. The solvent and excessive thionyl chloride were then evaporated off to give the desire product as a yellowish oil(14.4g).

(c) Synthesis of $Br(CH_2)_{10}CONH(CH_2)_{10}COOBz$

The 11-aminoundecanoic acid benzyl ester solution prepared in section 7.7.1.1 *(a)* was diluted with chloroform(20ml) and added dropwise during half an hour into a solution of 11-bromoundecanoyl chloride in chloroform(10 ml) (in section 7.7.1.1 *(b)*). The resulting mixture was well stirred. TEA(7.0ml, 0.055mole) was added. After 24 hours the reaction mixture was washed successively by 5% aqueous sodium bicarbonate(2x100 ml), 1N hydrochloric acid(2x100 ml), water (2x100 ml) and dried over magnesium sulfate overnight. Evaporating the solvent from the filtrate afforded a white solid(16.5g). After recrystalization from ethanol, the product was obtained as needle crystals(15.0g, yield: 56%). m.p.: 82-84 °C.

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 7.35(s, 5H, aromatic); 5.12(s, 2H, $COOCH_2Ph$); 3.40(t, 2H, $BrCH_2$-); 2.35(t, 2H, CH_2CO); 1.80(m, 2H, -CH_2-); 1.60(m, 2H, -CH_2-); 1.40(m, 2H, -CH_2-) and 1.25(s, 10H, -CH_2-).

Elemental Analysis(required): C%: 64.94(64.7); H%: 8.94(8.98) N%: 2.71(2.60); Br%: 14.97(14.84); Cl%: 0.0(0). FAB-MS: *m/z*, 539(M+1).

IR (KBr, cm^{-1}): 2929(-CH_2) and1737(CO-O).

(d) Synthesis of $Br(CH_2)_{10}CONH(CH_2)_{10}COOH$

The product described in section *(c)* above (11.0 g) was dissolved in a suspension of $Pd(OH)_2$/C(10% Pd, Aldrich, 2.00g) in THF (200 ml) and cyclohexene (80 ml). The suspension was heated under reflux for 6 hours, then filtered. Evaporating off the solvent

afforded a white solid(9.0 g). Recrystallization of this product from chloroform gave star-like crystals(6.88 g, yield: 75%). m.p.: 97-98 °C.

Elemental Analysis(required): C%: 59.27(59.03); H%: 9.29(9.46) N%: 3.04(3.13); Br%: 17.43(17.65). FAB-MS: *m/z*, 447 and 449(M+1).

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 5.50(b, 1H, CO-NH); 3.40(t, 2H, $BrCH_2$-); 3.25(q, 2H, NH-C<u>H</u>$_2$); 2.35(t, 2H, CH_2CO); 2.18(t, 2H, CH_2CO); 1.85(m, 2H, -CH_2-); 1.60(m, 4H, -CH_2-); 1.45(m, 2H, -CH_2-) and 1.30(s, 24H, -CH_2-).

IR(KBr disc, cm^{-1}): 1694; 1632; 1536; 1471; 1223; 719 and 680.

7.7.1.2 Synthesis of Monomer (**6**) Boc-NH-$(CH_2)_{10}COO(CH_2)_{10}COOH$

(a) Synthesis of 11-Bromoundecanoic Acid Benzyl Ester

The 11-bromoundecanoic acid chloride(14.0 g, 0.05 mole) discribed in previous section (7.7.1.1 b) in chloroform(10 ml) was added dropwise over an hour into a solution of benzyl alcohol(6.00 g, 0.055 mole) and DIEA(7.5 g) in chloroform(10 ml) at 0 °C. The reaction mixture was left overnight, then diluted with chloroform(100ml), followed by washing with 1N HCl, 5% aqueous $NaHCO_3$ and brine. The chloroform layer was dried over $MgSO_4$ and evaporated to afford an oily product(15.0 g, yield: 84%). This was not purified further. IR(film, cm^{-1}): 2927; 2854; 1737; 1455; 1243; 1214; 1163 and 697.

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 7.35(s, 5H, aromatic); 5.12(s, 2H, CH_2-Ph); 3.40(t, 2H, $BrCH_2$-); 2.35(t, 2H, -CH_2CO); 1.80(m, 2H, $BrCH_2C\underline{H}_2$-); 1.65(m, 2H, $BrCH_2CH_2C\underline{H}_2$-); 1.40(m, 2H, -$C\underline{H}_2CH_2CO$-) and 1.30(s, 10H, -$CH_2$-).

(b) Synthesis of Boc-NH-$(CH_2)_{10}COO(CH_2)_{10}COOBz$

The above oily product(15.0, 0.042 mole) and Boc-Aua-OH (13.0 g, 0.043 mole) were dissolved in ethyl acetate(15 ml), then DIEA(5.6 g, 0.043 mole) was added to the solution. The mixture was heated under reflux for 24 hours with good stirring. The cooled reaction solution was diluted with more ethyl acetate then washed and dried using the usual procedure. The oily product(16.0 g) was purified on a silica column (30mmx400mm) with elution using 20% ethyl acetate-cyclohexane(v/v). This gave an oily product(12.5 g). The product solidified on storing. Recrystallisation from petroleum ether(40-60 °C) afforded white sheet crystals(9.5 g). m.p.: 44-45 °C. Overall yield: 38%. Elemental Analysis(required): C%: 71.02(70.92); H%: 9.78(9.97) N%: 2.47(2.43).

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 7.35(s, 5H, aromatic); 5.11(s, 2H, $COOC\underline{H}_2Ph$); 4.05(t, 2H, J=6.5Hz, $COOCH_2$); 3.08(q, J=6.5, 2H, -CH_2-NH-CO); 2.30(m, 4H, CH_2CO); 1.65(m, 2H, -CH_2-); 1.45(m, 2H, -CH_2-) and 1.30(s, 37H, -CH_2-).

IR(film, cm^{-1}): 2922(-CH_2); 2849; 1731(CO-O); 1683(amide I); 1536(amide II); 1167(CO-O) and 746, 698(aromatic).

(c) Syntheis of Boc-NH-$(CH_2)_{10}COO(CH_2)_{10}COOH$

The product(4.2 g) described in section *(b)* above was dissolved in ethanol(100 ml). Palladium on active charcoal(20%, Aldrich, 0.5 g) was added and the mixture was

shaken for 4 hours under a hydrogen atmosphere. The catalyst was then filtered off and the filtrate diluted with water(20 ml) and stored in a fridge. The small needle crystals which formed were collected(3.30 g, yield: 99%), m.p.:64-65°C.

Elemental Analysis(required): C%: 66.89(66.77); H%: 10.53(10.58); N%: 2.86(2.88). FAB-MS: *m/z*, 486(M+1) and 386(M-Boc).

^{1}H NMR($CDCl_3$, 25°C, δ ppm): 4.54(b, 1H, Boc-NH); 4.06(t, 2H, J=6.5Hz, O-CH_2Ph); 3.11-3.07(m, 2H, NH-CH_2); 2.38-2.25(hex, 4H, J=7.4 , 2-C$\underline{H}_2$CO); 1.60(m, 6H, 3-CH_2-); 1.44(s, 9H, Boc) and 1.29-1.27(s, 26H, 13 -CH_2-).

IR (film, cm^{-1}): 3361(CO$\underline{OH}$); 2918(-CH_2); 2852; 1725(CO-O); 1703; 1681(amide I); 1529(amide II); 1478; 1280; 1237 and 1174(CO-O).

7.7.1.3 Synthesis of Monomer (7) (Boc-NH-$(CH_2)_5$-CO-O-$(CH_2)_5$-COOH)

(a) 6-Bromohexanoic Acid Benzyl Ester

6-Bromohexanoyl chloride(Aldrich, 23.10g, 0.10 mole) in chloroform(20 ml) was added dropwise into a solution of benzyl alcohol (12.0 g, 0.11 mole) and triethylamine (11.2 g, 0.11 mole) in chloroform(80 ml) at 0-10 °C. The reaction mixture was kept for 24 hours at 20 °C. The mixture was then diluted with chloroform(100 ml), and washed successively with 1N HCl, 5% aqueous sodium bicarbonate, and brine and dried over $MgSO_4$. Evaporating off the solvent afforded an oily product(26.5 g). No further attempt was made to purify the oily product. IR (KBr, cm^{-1}): 1735.

^{1}H NMR($CDCl_3$, δ ppm): 7.35(s, 5H, aromatic); 5.10(s, 2H, $COOC\underline{H}_2Ph$); 3.50(t, 5%x2H, Cl-CH_2); 3.38(t, 95%x2H, Br-CH_2); 2.35(t, 2H, CH_2CO); 1.85(m, 2H, $BrCH_2$-$C\underline{H}_2$-); 1.65(m, 2H, -CH_2-) and 1.45(m, 2H, -CH_2-).

(b) Synthesis of Boc-NH(CH_2)$_5$-CO-O-(CH_2)$_5$-COOBz

A mixture of Boc-Aha-OH(10.0g, 43.4 mmole), Br(CH_2)$_5$-COOBz(11.8 g, 43.4 mmole), DIEA(5.6 g, 43.4 mmole) and ethyl acetate(10 ml) was stirred and heated under reflux for 36 hours. Isolation of the product using the procedure as described in section 7.7.1.2 *(b)* gave an oily product(12.5 g). This product was purified by flash chromatography on silica column (80/20 cyclohexane/ethyl acetate as eluent). This gave the desired product as a yellowish oil(12.4g, yield: 66%). Elemental Analysis(required): C%: 66.49(66.19); H%: 8.33(8.56) N%: 3.19(3.22).

IR(film, cm^{-1}): 1734(ester carbonyl); 1715(Boc carbonyl); 1516(amide), 1455; 1248, 1161(ester); 749 and 698.

^{1}H NMR($CDCl_3$, δ ppm): 7.35(s, 5H, aromatic); 5.12(s, 2H, $COOC\underline{H}_2Ph$); 4.50(b, 1H, CO-NH); 4.05(t, 2H, $COOCH_2$); 3.10(q, 2H, NH-CH_2); 2.35(t, 2H, CH_2CO); 2.30(t, 2H, CH_2CO); 1.65(m, 4H, -CH_2-) and 1.45-1.30(m, 13H, -CH_2-).

(c) Synthesis of Boc-NH-(CH_2)$_5$-CO-O-(CH_2)$_5$-COOH

The product discribed in *(b)* above was dissolved in THF(100 ml). The solution was stirred under hydrogen atomsphere with Pd-C as catalyst(20%, Aldrich, 1.2 g) for 8 hours(reaction monitored by TLC and IR). The catalyst was removed by filtration and the solvent removed from the filtrate by rotary evaporation. This afforded a nearly

quantitative yield of acid product. The oily product was recrystallised from 20% ether-petroleum(40-60°C). This gave a solid(6.4 g). m.p. 34-35°C.

Elemental Analysis(required): C%: 59.07(59.10); H%: 9.23(9.04); N%: 4.14(4.06). FAB-MS(*m/z*): 346(M+1); 246(M+1-Boc).

IR(KBr, cm^{-1}): 1728; 1714; 1688; 1524; 1265 and 1167.

^1H NMR($CDCl_3$, δ ppm): 6.60(1/4H, -CO-NH); 4.60(b, 3/4H, -CO-NH); 4.10(t, 2H, $COOCH_2$); 3.10(q, 2H, NH-CH_2); 2.35(t, 2H, CH_2CO); 2.30(t, 2H,CH_2CO); 1.65(m, 4H, -CH_2-) and 1.45-1.30(m, 13H, -CH_2-).

7.7.1.4 Synthesis of Monomer (**9**) (Br-$(CH_2)_5$-CO-NH-$(CH_2)_5$-COOH)

(a) Tosylate salt of 6-Aminocaproic Acid Benzyl Ester

A mixture of 6-aminocaproic acid(13.1g, 0.1 mole), *p*-toluenesulphonic acid monohydrate (20.9g, 0.11 mol), benzyl alcohol (11.8g, 0.11 mole) and toluene (150 ml) was stirred and heated under reflux. A Dean Stark trap was used to collect the water formed. The reaction was stopped when no more water formed. The white syrup which had formed was filtered and the solid was collected and washed with cool toluene. A white solid was obtained(38.4g, yield: 98%). This product was deprotonated by stirring with 1M aqueous sodium bicarbonate and DCM (100 ml) to afford a solution of free amino benzyl ester for use in the following reaction.

(b) Syntheis of Br-$(CH_2)_5$-CO-NH-$(CH_2)_5$-COOBz

The solution prepared in *(a)* above (20.5g, 0.5mole) was dissolved in chloroform(100 ml) with TEA (15 ml, 0.11 mole). 6-Bromohexanoyl chloride (Aldrich, 12.0g, 0.051mmol) was added dropwise into this solution at 0 - 10°C. After allowing 24 hours for the reaction, the product was isolated using a similar procedure as described in section 7.7.1.1 *(c)*. This gave a solid product (20.0g). Recrystallisation from ether-petroleum(1/5, v/v) ether gave white crystals(18.0g). m.p.: 47-48°C.

Elemental analysis(required): C%: 57.60(57.29); H%: 7.10(7.08); N%: 3.54(3.52); Br%: 19.38(20.06).

^{1}H NMR($CDCl_3$, δ ppm): 7.35(s, 5H, aromatic); 5.55(b, 1H, CO-NH); 5.10(s, 2H, CH_2-Ph); 3.40(t, J=6.7, Br-CH_2); 3.20(q, 2H, J=6.8, CO-NHCH_2); 2.35(t, 2H, J=7.3, CH_2CO); 2.15(t, J=7.5, 2H, CH_2CO); 1.85(m, 2H, -CH_2-); 1.60(m, 4H, 2-CH_2-) and 1.50-1.30(m, 6H, 3-CH_2-).

IR(KBr disk, cm^{-1}): 1725; 1637; 1543; 1266; 1188; 695 and 637.

(c) Synthesis of Br-$(CH_2)_5$-CO-NH-$(CH_2)_5$-COOH

The above benzyl ester was debenzylated by heating under reflux with cyclohexene(180 ml) in ethanol(300 ml) and palladium hydroxide on carbon(Aldrich, 10%, 3.5 g) as the catalyst. After completion of the reaction(monitored by TLC or IR), the catalyst was filtered off and the solvent evaporated. The residue was recrystallised from 50% water-ethanol. This gave white crystals(10.0g, yield: 72%). m.p.: 65-67°C.

Elemental analysis(required): C%: 47.25(46.76); H%: 7.19(7.20); N%: 4.74(4.56); Br%: 24.91(25.70). FAB-MS(*m/z*): 308 and 310(M+1)

^{1}H NMR($CDCl_3$, δ ppm): 5.55(b, 1H, CO-NH); 3.40(t, Br-CH_2); 3.25(q, 2H, CO-$NHCH_2$); 2.35(t, 2H, CH_2CO); 2.20(t, 2H, CH_2CO); 1.88(m, 2H, -CH_2-); 1.65(m, 4H, 2-CH_2-) and 1.50-1.30(m, 6H, 3-CH_2-).

IR(film, cm^{-1}): 3301, 2938, 2869, 1701, 1632, 1535 and 1265.

7.7.1.5 Synthesis of Boc-NH$(CH_2)_{10}$-CO-O-$(CH_2)_{10}$-COOPNP

Boc-Aua-O-Hua-OH(4.9 g, 10 mmole), *para*-nitrophenol(1.54g, 11 mmole), and DMAP(0.15 g) were dissolved in THF(40 ml) at 0°C. Then a THF(10 ml) solution of DCC(2.25g, 11 mmole) was added into the solution with vigorous stirring. The reaction mixture was filtered after 24 hours. The filtrate was evaporated to dryness and the residue recrystallised from ethanol-petroleum(1:2) twice and from diisopropylether once. This gave yellowish crystals(4.0 g, yield: 66%). m.p.: 102-105 °C.

Elemental analysis(required.): C%: 65.25(65.32); H%: 9.23(8.97); N%: 4.73(4.62).

^{1}H NMR($CDCl_3$, δ ppm): 8.26(d, 2H, -Ph-NO_2); 7.26(d, 2H, -Ph-NO_2); 4.50(b, 1H, CONH-); 4.05(t, J=6.8; $COOCH_2$-); 3.08(q, 2H, J=6.4, CONH-CH_2-); 2.60(t, 2H, J=7.4, CH_2CO-); 2.28(t, 2H, J=7.4, CH_2CO-); 1.76(m, 2H, -CH_2-); 1.65(m, 4H, 2-CH_2-); 1.60-1.44(s, 9H, Boc); 1.31(s, H, -CH_2-) and 1.27(s, H, -CH_2-).

IR(KBr, cm^{-1}): 3382; 2918; 1752; 1691; 1536; 1519; 1350; 1202; 1165 and 1143.

7.7.2 Syntheses of Various Linear Oligomers

(a) Synthesis of Linear Oligomers (10) (Br-[$(CH_2)_{10}CONH(CH_2)_{10}COO]_n$-H)

A mixture of Br-$(CH_2)_{10}CONH(CH_2)_{10}COOH$(0.449g, 1 mmol), *tetra*-n-butylammonium hydroxide in water(40%, 0.649g, 1 mmol) and chloroform(6 ml) were vigrously stirred and heated under reflux for 2 hours. The mixture was then cooled and the organic layer added to acetone(100 ml) containing 2% of acetic acid. The precipitate was filtered off and dried(0.28g, yield: 78%). Elemental Analysis: C%: 68.66; H%: 10.49; N%: 3.77; Br%: 4.24. The average molecular weight(Mn) was 1885 by calculation based on bromine analysis. This corresponds to $\overline{DP}$ = 4.9. The calculated percentages of C%: 68.81; H%: 10.81; N%: 3.65 were in good agreement with the results.

IR(film, cm^{-1}): 1728(s), 1638(s, amide I), 1541(m, amide II), 1468(m), 1273(m), 1238(m), 1208(s), 1182(m) and 816.

^1H NMR($CDCl_3$, δ ppm): 5.8-5.5(m, 1H, CONH-), 4.08(t, 1.6H, linear $COOCH_2$-), 4.03(m, 0.4H, ring $COOCH_2$-), 3.40(t, Br-CH_2, end group); 3.20(m, 2H, CO-$NHCH_2$-); 2.28(t, 2H, CH_2COO); 2.13(t, 2H, CH_2CONH); 1.60(b, 6H, -CH_2-); 1.50(s, 2H, -CH_2-) and 1.25(s, 24H, -CH_2-).

(b) Synthesis of Linear Oligomers (11) (Br-[$(CH_2)_5CONH(CH_2)_5COO]_n$-H)

A mixture of N-(6-bromohexanoyl)-aminohexanoic acid(0.50 g, 1.62 mmol), tetra-n-butylammonium hydroxide(40%, 1.05 g, 1.62 mmol) and chloroform(5 ml) was stirred vigorously for 30 minutes. The solvent was then removed under vacuum at 50 °C. The residue was re-dissolved in chloroform(4 ml), and heated under reflux for 4 hours, then, precipitated from THF. The isolated oily product was dissolved in chloroform(10 ml), and washed successively with acetic acid-water(1:20, v/v), water and dried over Amberlite 15 beads(H^+ form) and sodium sulfate. Removing the chloroform under vacuum afforded a solid product(0.1 g, yield: 27%). Elemental Analysis: N%: 5.1; Br%: 7.7.

^1H NMR($CDCl_3$, 25°C,δ ppm): 6.0(b, 1H, CONH); 4.04(t, 2H, $COOCH_2$-); 3.50(t, end groups, CH_2-Br); 3.25(m, 2H, $CONHCH_2$-); 2.35(t, 2H, CH_2COO); 2.20(t, 2H, CH_2CONH-) and 1.80-1.20(m, 12H, -$CH_2CH_2CH_2$-).

IR(film, cm^{-1}): 3313(m), 2936(m), 1725(s0, 1638(m), 1542(m), 1254(w), 1185(m) and 1169(m).

As discussed in Chapter 5(Table 5.1), the ^1H NMR spectrum and the GPC analysis indicate that the oligomers had a average DP = 3.8.

(c) Synthesis of $NH_2(CH_2)_{10}COO(CH_2)_{10}COOH$

Boc-$NH(CH_2)_{10}COO(CH_2)_{10}COOH$ (200 mg) was dissolved in dichloromethane(5 ml). TFA(2 ml) was added into the solution which was then left in room temperature for 1 hour. After removing the solvent under vacuum, the oily product

was redissolved in chloroform(2 ml) and precipitated from ether. The white crystals was collected by filtration and dried (190 mg, TFA salt, yield: 92%). m.p. 68-69°C.

Elemental analysis(required): C%: 57.49(57.60); H%: 8.65(8.80); N%: 2.87(2.80).

^{1}H NMR($CDCl_3$, 25 °C, δ ppm): 7.8(b, 3H, NH_3^+); 4.03(t, 2H, -$COOCH_2$-); 2.86(b, 2H, NH_3-CH_2); 2.25(q, 4H, CH_2CO); 1.60(m, 8H, CH_2) and 1.15(s, 24H, -CH_2).

IR(KBr disk, cm^{-1}): 2914(s), 2849(s), 1732(s), 1708(s), 1690(s), 1468(m), 1185(s) and 1133(s).

7.7.3 Cyclization of Boc-NH-$(CH_2)_{10}COO(CH_2)_{10}$COOPNP in Dilute Solution

The product prepared in Section 7.7.1.5 above Boc-Aua-O-Hua-PNP(0.61 g, 1.0 mmol) was deprotected by treatment with TFA in DCM(1:1, v/v, 8 ml)) for an hour, then, the solvent was removed under vacuum. The residue was dissolved in chloroform(300ml) and DIEA(5 ml), and stirred for 100 hours. After removing the solvent under vacuum, the residue was recrystallised from methanol twice. This afforded white crystals(0.21g, yield: 57%). m.p.: 97-100 °C.

Elemental analysis(required): C%: 70.93(71.89); H%: 11.08(11.24); N%: 3.62(3.81).

^{1}H NMR($CDCl_3$, δ ppm): 5.78+5.43(b, 1H, CONH); 4.10(m, 2H, $COOCH_2$); 3.25 (m, 2H, $CONHCH_2$); 2.30(m, 2H, CH_2CO); 2.15(m, 2H, CH_2CO); 1.60(m, 6H, 3-CH_2-); 1.50(m, 2H, -CH_2-) and 1.35(s, 24H, 12-CH_2-).

IR(film, KBr, cm^{-1}): 2914; 2848; 1727; 1640; 1535 and 1467.

As discussed in Chapter 5(Table 5.2), the ^{1}H NMR spectrum and the GPC analysis indicate that the oligomers had a average DP = 1.4.

7.7.4 Cyclo-oligomerisation of Loaded Polymer Beads(PNO)

The coupling, deprotection and cyclisation were carried out by a typical procedure described in Section 7.3.1. The oxime beads finally were filtered off from the reaction mixture and washed with DMF, $CHCl_3$, acetone, methanol, and ether. The filtrate was evaporated to dryness under vacuum under 50°C. The residue was then precipitated appeared from water and collected by filtration. The products could be purified by precipitation or fractionation by use the solvent systems described in Table 5.4, 5.5, 5.6 and 5.7.

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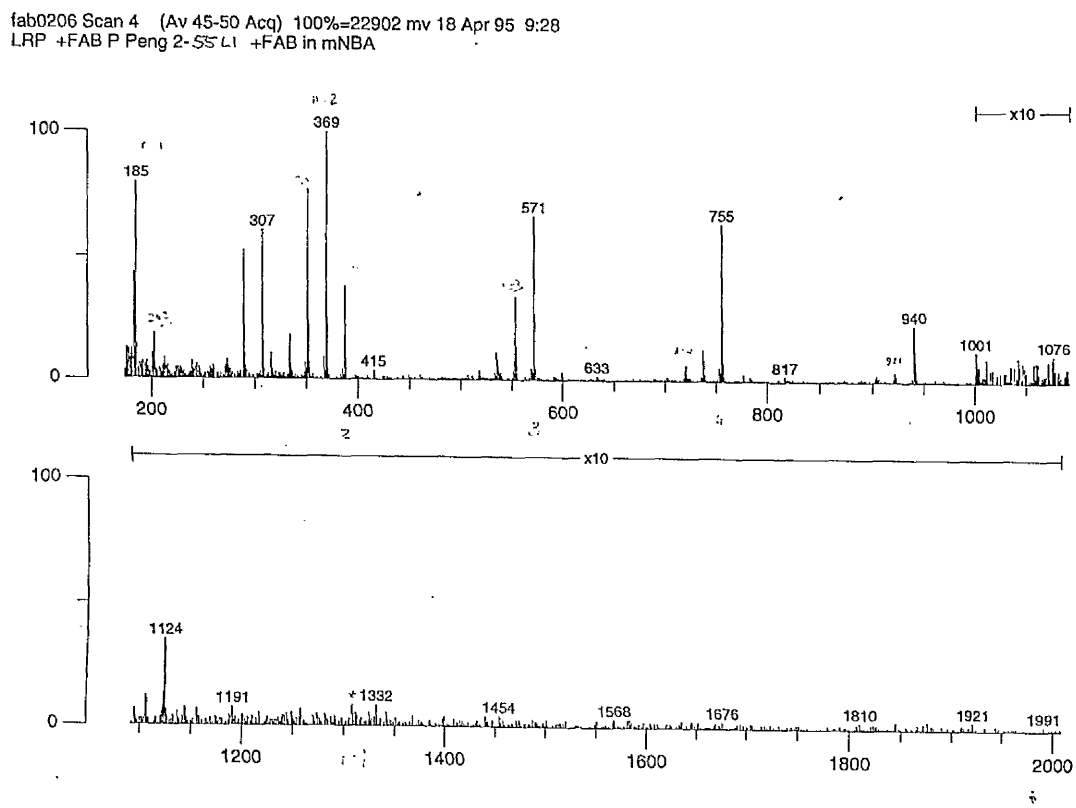
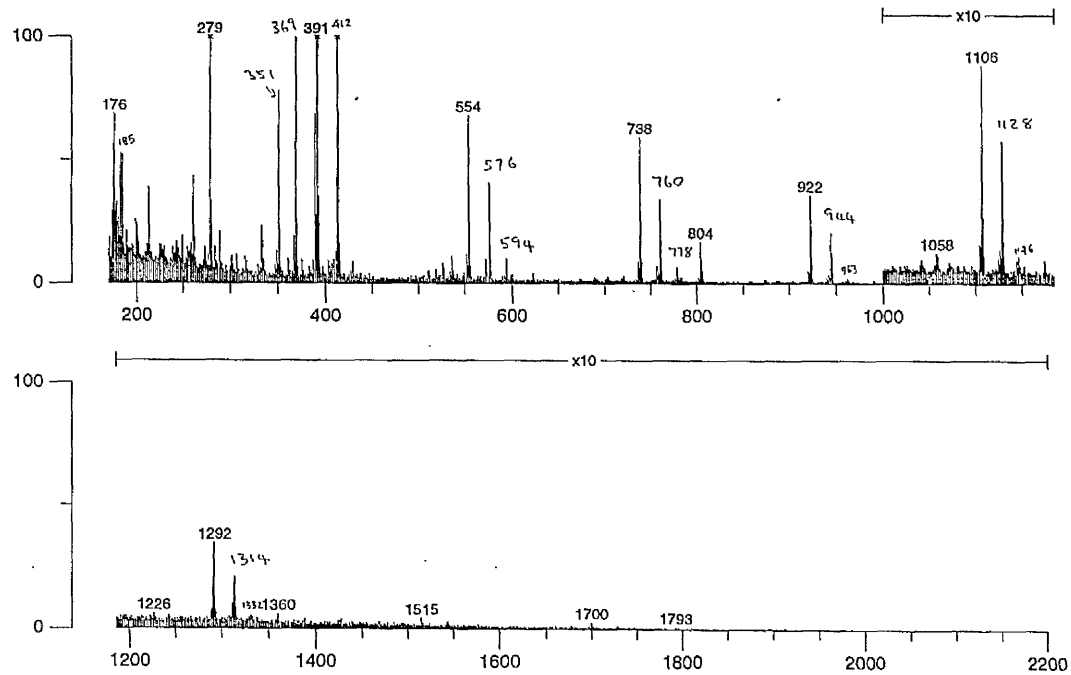
APPENDIX

Some histograms of FAB-Mass Spectra of cyclic esters, amide and amide-esters are given below:

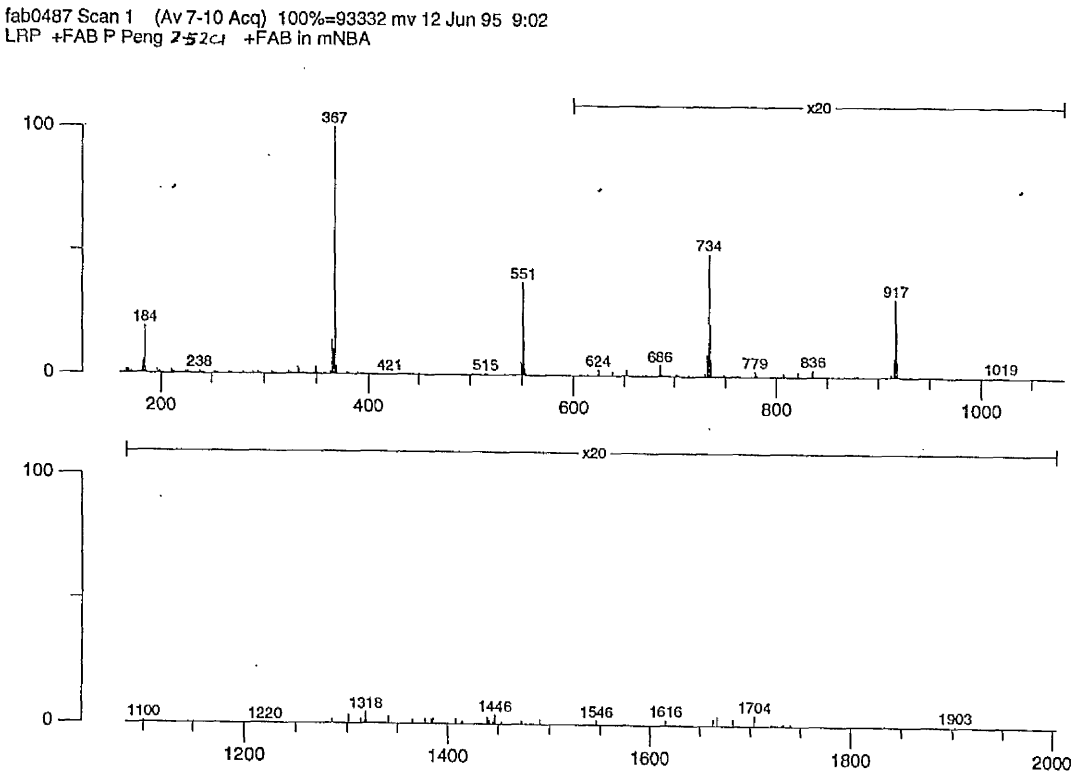
1 Linear Substrate (3a) in Table 2.1, sample reference 55RP.



2 Cyclic Products Obtained by A26 Catalysed Depolymerisation of Linear Substrate (3a). Refer to Entry 1 in Table 2.9.

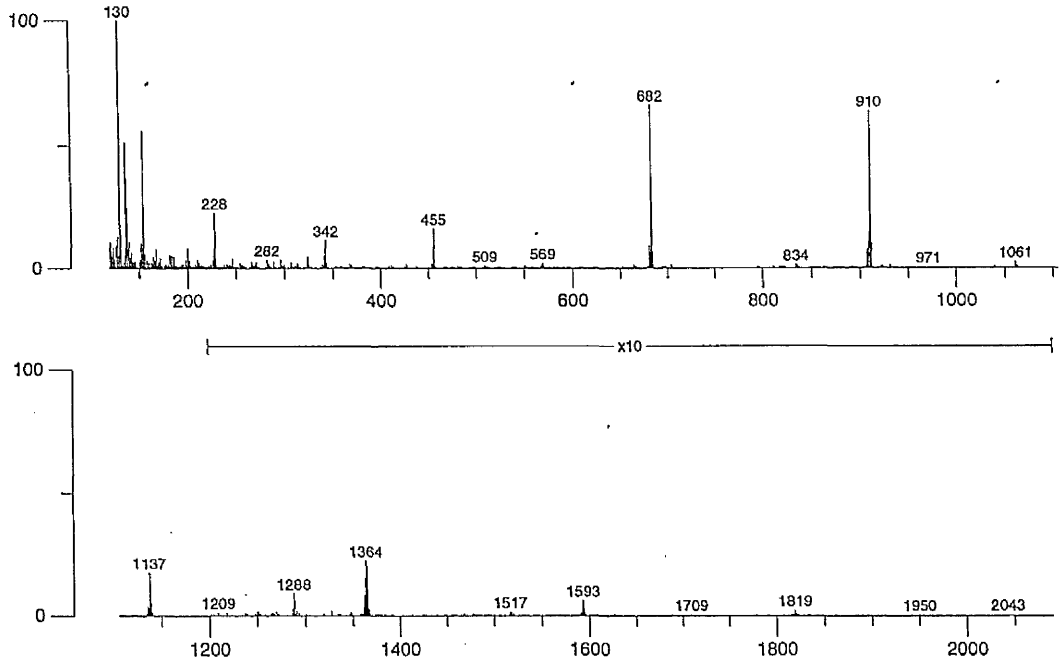


3 Cyclic Oligoamides Obtained from High Dilute Reaction(refers to section 4.3.1.)



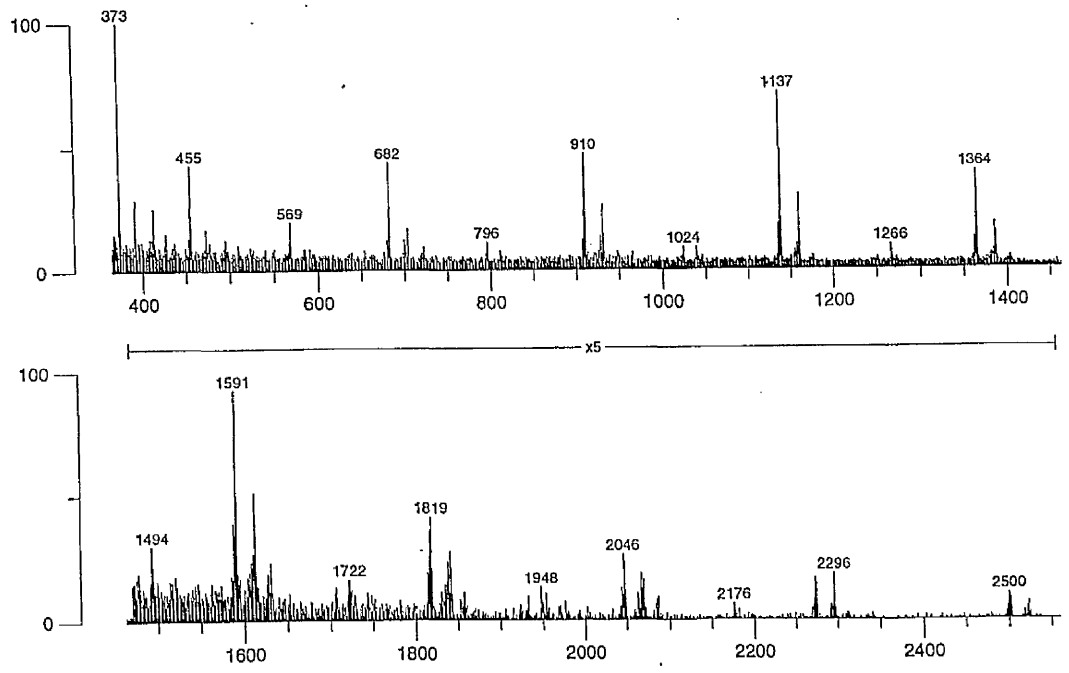
4 "First Batch" of Cyclic Products(entry 7 in Table 5.4) Prepared by PNO Resin.

fab0206 Scan 3 (Av 30-34 Acq) 100%=117722 mv 18 Apr 95 9:28
LRP +FAB P Peng 2-42c1 +FAB in mNBA



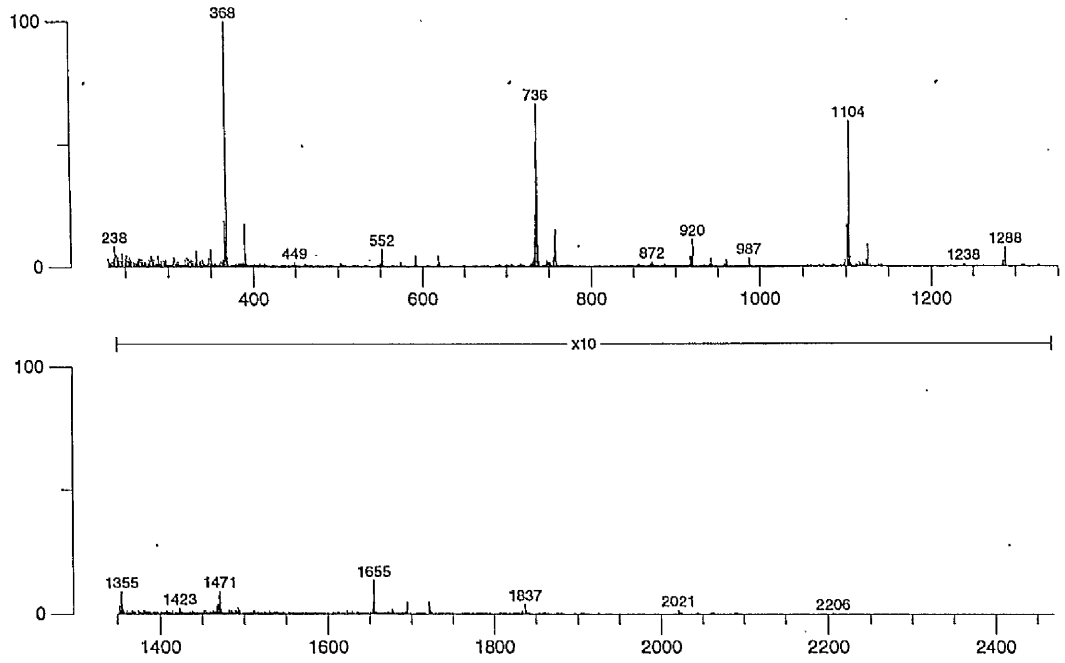
5 "Second Batch"of Cyclic Products(entry 7 in Table 5.4) Extracted by Hot Chloroform from Recovered PNO Resin.

FAB0308 Scan 1 (Av 3-10 Acq) 100%=8364 mv 20 Oct 95 10:05
LRP +FAB P Peng 2-42C3 +FAB in mNBA



6 Cyclic Oligo(ester -amide)(entry 5 in Table 5.4) Extracted Using Hot Chloroform

FAB0324 Scan 1 (Av 2-6 Acq) 100%=93911 mv 23 Oct 95 11:25
LRP +FAB P Peng 2-64a1 +FAB in mNBA



7 Cyclic Oligo(ester -amide)s (entry 4 in Table 5.4) Extracted Using TFA-Chloroform

AB0323 Scan 1 (Av 2-6 Acq) 100%=70689 mv 23 Oct 95 11:22
RP +FAB P Peng 2-44d2 +FAB in mNBA