## *Synthesis and characterisation of aliphatic hyperbranched polyamidoamines and polyamides*

Simon James Aldersley

# Synthesis and characterisation of aliphatic hyperbranched polyamidoamines and polyamides

Simon James Aldersley



A thesis submitted for the degree of Doctor of Philosophy at the University of Durham

September 2002

**Abstract**

# Synthesis and characterisation of aliphatic hyperbranched polyamidoamines and polyamides

Simon J. Aldersley, Ph. D. Thesis, September 2002.

Dendrimers are perfectly branched macromolecules possessing large internal cavities and a known number and location of terminal groups. This unique architecture leads to many interesting properties and countless potential applications have been discussed. Their synthesis involves numerous repetitive steps, often requiring protection and deprotection chemistry and complex purification procedures. This limits their availability and leads to extremely high costs, a factor that has limited their use. Polyamidoamine (PAMAM) dendrimers, the first well-established series of dendrimers, were reported in the mid nineteen eighties.

For many applications the synthetic difficulties associated with dendrimers are so great that many potential applications are prohibited. Hyperbranched polymers are produced by a simpler synthetic route, the step growth polymerisation of $AB_x$ monomers in a one-pot procedure. They lack the architectural perfection of dendrimers but retain the large number of terminal groups and high degree of branching. Crucially, these polymers can be produced for a fraction of the cost of dendrimers.

The synthesis of hyperbranched analogues to both the full and half generation PAMAM dendrimers from $AB_2$ monomers is reported here. Attempts to extend this method to control the molecular weight, degree of branching and the terminal group functionality are discussed, as is the synthesis of a related series of polyamides. The characterisation of these materials and their physical properties are also described.

**Acknowledgements**

I make no apologies for the length of these acknowledgements, as without the support of any single one of the many people listed here (and many others who are not thanked explicitly) I would not be sitting here writing this today. People say that the completion of a PhD is an individual achievement, but if this is the case then I have done something wrong as I could not have done it on my own!

I would like to start my thanks back in Coventry and begin by mentioning the teachers at The Woodlands School and Tile Hill Wood School who gave me the support I needed to complete my secondary education. Special thanks must go to Mr. Greaves for his faith in my ability when I had none, to Mr. Banks who stimulated my interest in chemistry and to Mrs. Davies who nutured this interest through my 'A' levels.

From my time in Sheffield I would like to thank the staff of the chemistry department for their teaching ability and for constructing a degree program which gave the students the chance to develop their skills and interests without sacrificing the fundamentals of chemistry. I would like to thank Mike Turner for giving me a chance to do my first research in his laboratories and Ron Young who developed my skills and taught me many aspects of polymer chemistry. I would also like to thank my fellow students on the chemistry degree program for all their help throughout the course.

There are many people from my time in Durham who I must thank. First and foremost I would like to thank Jim who throughout my time here has seemed to know when to leave me alone to discover things for myself and when to offer me a helping hand when the going was tough. Also I would like to thank my other co-supervisor, Steve, who in addition to paying me (my bank-manager would like to thank-you personally for that one) has offered support through my three years both through practical advice and encouragement. Also at Unilever I would like to thank Rob and Ian for their help with the aqueous GPC and also for many other useful thoughts about the characterisation of hyperbranched polymers. From Durham (in no particular order) I'd like to thank Randal, Neil, Lian and Alan (for

helpful discussions and letting me use their equipment), Catherine, Ian and Jaroslava (for running all the samples I gave them and helping with my many 'urgent' requests), Dave (for help with MALDI and for allowing me to pick his brain for his (vast) knowledge of hyperbranched polymers), Alan (for fixing my computer regularly), Stuart L. (for help with IT and light-scattering), Stuart R. (for help with SEC theory and light-scattering), Mark (for help with MALDI), Andreas (for helping get this project off to flying start), Olli and Wilfried (for providing much advice throughout the last three years), Joseph (for useful discussions), Doug (for running analysis) and Alison (for all the little bits of help too numerous to mention and also for putting up with me for the last three years) and to the many members of the technical staff from the department who make life so much easier through their positive attitudes. Finally to all my fellow students, post-docs and the academic staff here in Durham many of whom have added to this project by giving me a little nugget of information and insight when I needed it most.

Which leaves the most important group of all, the ones who transcend all of the above geographical categories, my family. To my parents (in their various forms, genetic, step and grand) for all their support and help over the years, for believing in me and encouraging me along the way and for helping me achieve far more than I thought I ever could. Last (but definitely not least) I would like to thank Anna for her help and support throughout my period in Durham.

**Memorandum**

The work reported in this thesis has been carried out at the Interdisciplinary Research Centre in Polymer Science and Technology, Department of Chemistry, Durham University between October 1999 and September 2002. This work has not been submitted for any other degree either in Durham or elsewhere and is the original work of the author except where acknowledged by means of appropriate reference.

**Statement of Copyright**



**Financial Support**

I gratefully acknowledge the award of an Engineering and Physical Sciences Research Council (EPSRC) Industrial CASE Studentship by Unilever Research.

**Table of Contents**

# Chapter One

# Introduction

## 1 – Introduction

The phenomenon of branching in polymers has been known for many years, however the control of it is a new theme in polymer synthesis. Branched polymers are a class of polymers intermediate between linear and network polymers. They possess branch points in their structure from which two or more chains emanate. Branching is well known in synthetic polymers, for example in polyethylene, low density polyethylene (LDPE) is a branched variant of high density polyethylene (HDPE), which is essentially linear. There are significant differences in properties and end-uses of LDPE and HDPE consequent on the effects of branching.[1] Branching is also often seen in nature, for example glycogen is a highly branched natural polysaccharide.[2] Often branching is introduced deliberately into 'linear' polymers to improve performance or to aid processing, for example in the synthesis of linear low-density polyethylene (LLDPE).[3] In many syntheses of 'linear' polymers some degree of branching occurs inadvertently through side-reactions occurring in the polymerisation process. Multifunctional monomers can be added to bifunctional monomers to create branches in the polymer.

The synthesis of polymers containing a controlled number and position of branches is a more recent phenomenon. The synthesis of both star and comb polymers have been reported during the last few decades.[4] Star polymers possess a single focal point from which emanate a number of arms. Comb polymers are produced when the arms are attached to a polymer backbone, (Figure 1.1).

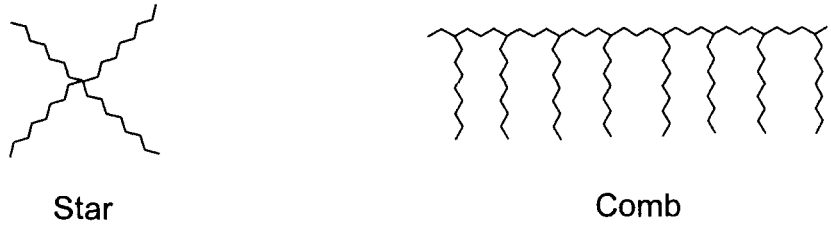



Figure 1.1 – A schematic view of the structure of a comb and a star polymer.

The first synthesis of star polymers was reported when the step-growth polymerisation of ϵ-caprolactam was initiated with cyclohexanone tetrapropionic acid and dicyclohexanone octapropionic acid to form four and eight arm star polymers, (Figure 1.2).[5] Stars can also be produced via a two-step synthetic route, in which a linear polymer is formed first and then undergoes a coupling reaction with a central core. The most common two-step synthetic strategy involves living anionic polymers being coupled to chlorosilanes, the first example being the coupling of polystyryl lithium to tetrachlorosilane.[6]

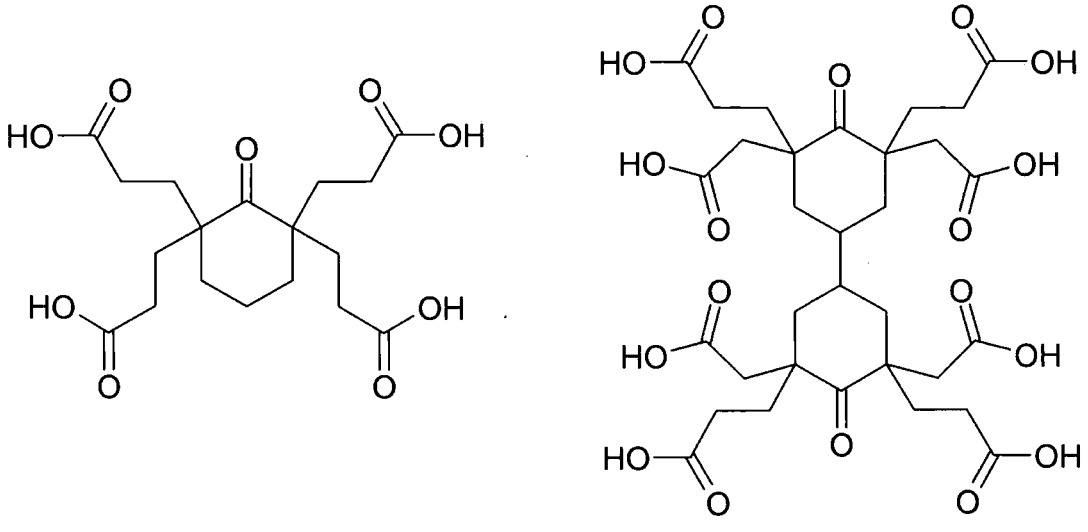



Figure 1.2 – Cyclohexanone tetrapropionic acid and dicyclohexanone octapropionic acid.

Combs can also be made via a one or two-step methodology. The first reported synthesis of combs involved the coupling of polystyryl potassium with the ester functions of poly(styrene-co-methyl methacrylate).[7] A one step method was pioneered by incorporating C-Li bonds into polydienes and using these as sites from which to initiate polymerisation.[8]

In recent years interest in polymers with controlled architecture has increased. The production of polymers with a known location and number of branches has become a synthetic challenge with well-defined products creating much interest. They are academically interesting materials and also have unique properties

suggesting their suitability for a variety of applications, (Section 1.1.2 and Section 1.2.4).

## 1.1 - Dendrimers

In 1978 the synthesis of an entirely new kind of perfectly branched macromolecule was reported.[9] This work signalled the genesis of a new class of polymeric materials, subsequently called dendrimers. A cascade reaction sequence of addition of acrylonitrile to a mono or diamine and reduction to amine was employed, (Figure 1.3). The product of the two reactions possesses two amine functionalities instead of one. Repetition of the two steps gives a product with four amine functionalities, forming what would now be termed a 'low-generation dendrimer'.

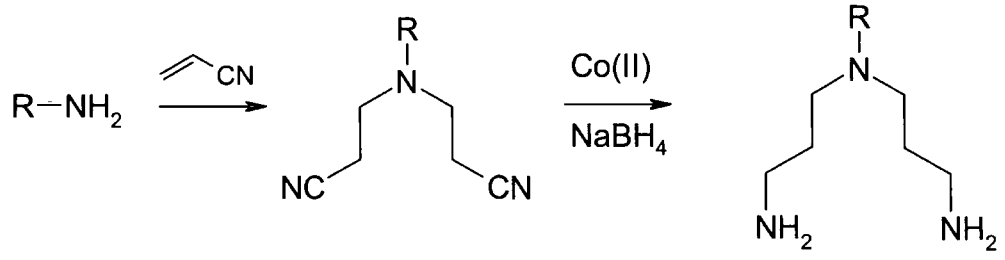



Figure 1.3 – Two-step cascade synthesis.

Aside from an isolated asymmetric example,[10] no more reports of such syntheses appeared until 1985, when the first report of the synthesis of polyamidoamine (PAMAM) dendrimers (Starburst™ polymers) appeared in the literature.[11] The synthesis involves the 1,4 conjugate addition, (Section 2.4) of an amine to methyl acrylate and subsequent amidation with ethylenediamine producing new amine functionalities upon which further conjugate additions can be carried out, (Figure 1.4). Repetition of this two step procedure leads to the build up of progressively larger dendrimers.

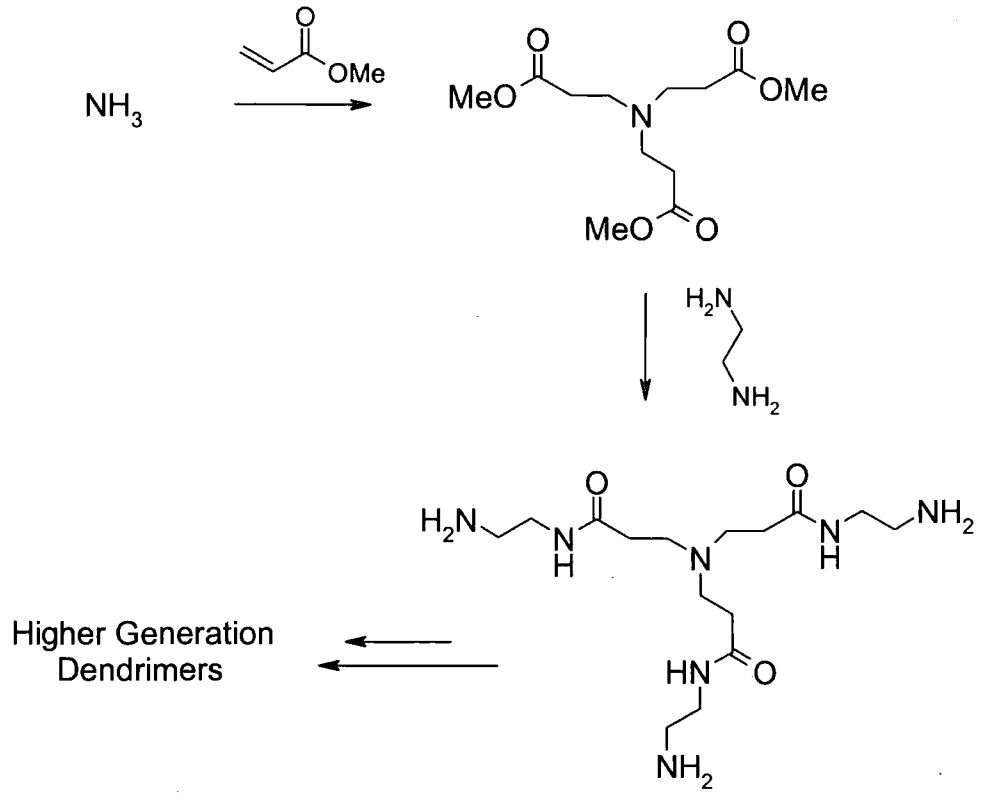



Figure 1.4 – The synthesis of PAMAM dendrimers.

Both reactions occur quickly and in good yields, but a large excess of the ethylenediamine (82 equivalents to get to generation 1, with 3 terminal amines) is needed to ensure reaction occurs at only one of the two amine groups. Synthesis of dendrimers up to generation 8 (384 end groups) had been reported by 1987.[12] Ideally this procedure builds up a perfectly branched structure with a known number of end groups, although it has since been shown that these materials possess a significant number of defects.[13] This synthesis, in common with other early dendrimer work, proceeded by what has now become known as the divergent route. Synthesis begins from a central core and proceeds outwards by addition of successive layers (generations), (Figure 1.5). In most examples of divergent synthesis, either protection and deprotection chemistry or large excesses of reagents are necessary to ensure the addition of a single generation at a time.

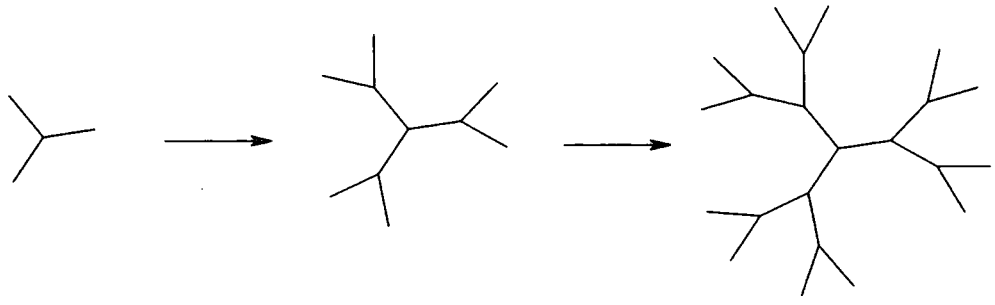


Figure 1.5 – A pictoral representation of dendrimer formation by divergent growth.

The convergent method was developed later, in an attempt to overcome the problems in the divergent approach caused by the rapid increase in the number of reactive groups at the periphery of the growing macromolecule. This can lead to incomplete reaction at the terminal groups or creation of defects by cyclisation. The convergent method consists of synthesising branched wedges (dendrons) and linking these to a central core once they reach the required size, (Figure 1.6).

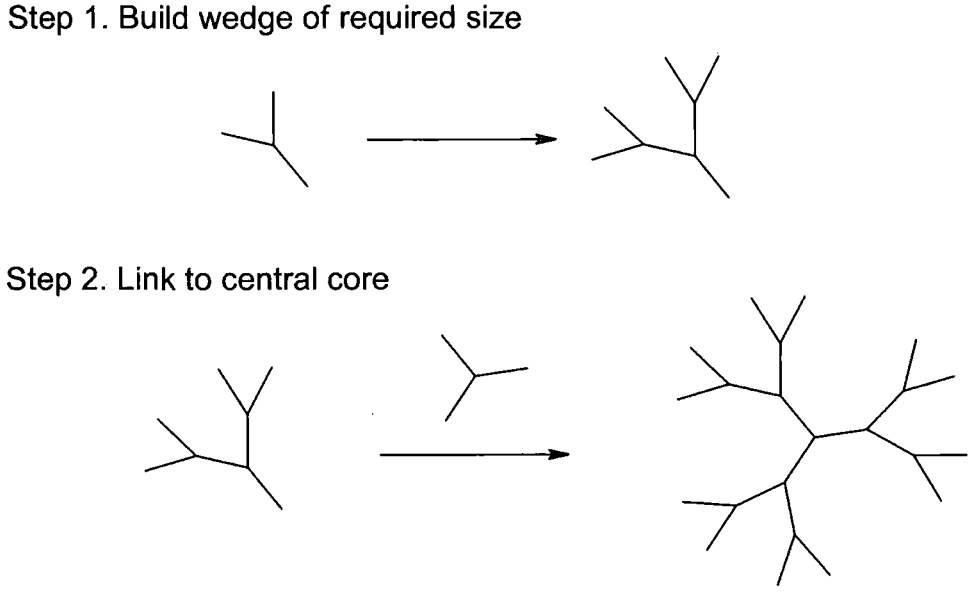



Figure 1.6 – A pictorial representation of the two steps required for convergent dendrimer synthesis.

The first report of convergent synthesis[14,15] used a two-step process involving reaction of a benzylic bromide with a phenolic alcohol, followed by conversion of

the unreacted alcohol unit to bromide by reaction with carbon tetrabromide and triphenylphosphine, (Figure 1.7).

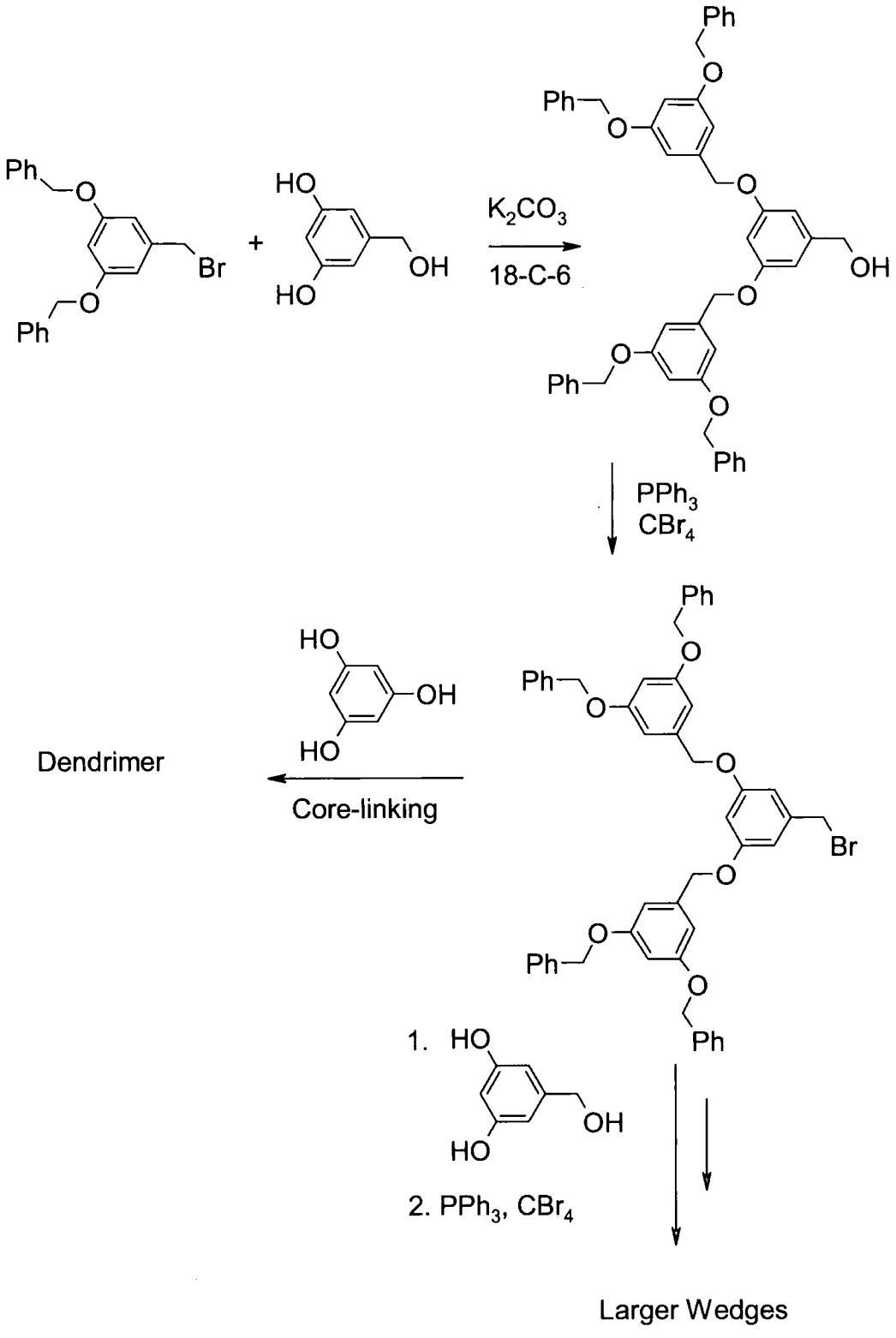



Figure 1.7 – Convergent synthesis of dendrimers.

Both convergent and divergent growth have associated problems. The divergent approach may lead to surface defects as the generation number increases, and use of excess reagent can lead to purification problems. The convergent approach suffers from steric constraints when the dendrons to be attached to the core become too large and is generally more synthetically challenging. Whichever method of dendrimer synthesis is used, it is always very time consuming, often difficult and thus expensive. Attempts have been made to develop an easier synthetic route to dendrimers. A number of different approaches have been researched, however despite the promises of easier synthesis offered by these methods the cost of dendrimers remains high and severely limits their availability.

A branched monomer has been used to reduce the number of steps necessary to reach higher generations. Instead of using a classical $AB_2$ monomer a larger $AB_4$ monomer of the next generation is employed, (Figure 1.8).[16,17]

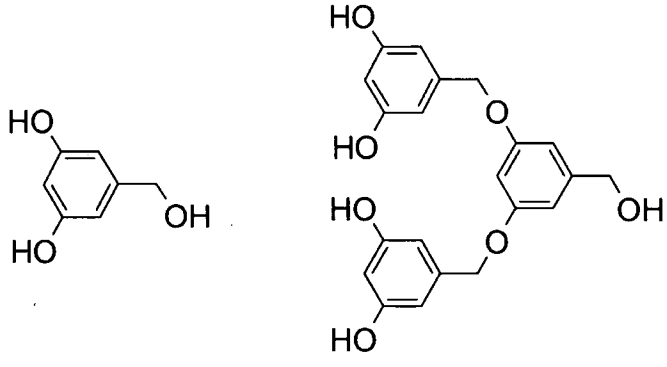



Figure 1.8 - An example of a branched monomer.

In a similar approach a diprotected monomer which has two different protecting groups on the A and B functionalities, Ap'-Bp"$_2$ is used and by selective deprotection and coupling a trimer is produced, (Figure 1.9).[18] Less reactions are necessary to access higher generations with a 255-mer being produced in only nine synthetic steps. This approach has been termed double exponent growth, but is limited by the necessity of orthogonal protecting groups and problems with steric crowding.

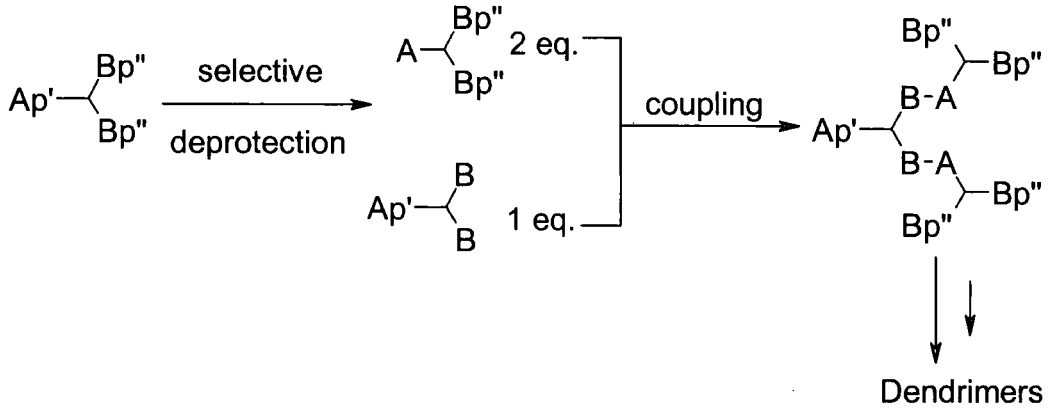



Figure 1.9 – Double exponent dendrimer growth.

Solid phase techniques[19] utilised in peptide synthesis have also been adapted for dendrimer synthesis, with PAMAM dendrimers having been grown on the surface of amine functionalised resins.[20] The resin beads can be washed easily to remove the excess reagents and the PAMAM dendrimers can be cleaved from the resin after synthesis. The physical separation of the reaction sites may also allow production of more homogenous materials. The dendrimer coated beads provide particles with a very high loading of amines on the surface and have themselves been used as new resins.

### 1.1.1 - Physical properties of dendrimers

In addition to the elegance and intuitive beauty of dendrimers their anomalous properties compared to those of linear polymers have engendered much interest. True comparison between a dendrimer and a linear polymer containing the same number of repeat units and functionalities is difficult due to problems with the exact synthesis of the linear isomers. One example of synthesis of a linear polymer with exactly the same number of repeat units and pseudo chain ends up to the equivalent of a generation six dendrimer has been reported. This study confirmed the uniqueness of the architecture of dendrimers.[21]

The differences between dendrimers and linear polymers manifest themselves at higher molecular weights (generations). Until generation four there was seen to be little difference in the hydrodynamic volumes (size in solution) of linear and dendritic isomers, however above generation four the increase of the

hydrodynamic volume of the dendrimers does not keep pace with that seen in linear polymers, suggesting that they have a very compact structure. This and other results indicate that at higher generations the unique architecture of dendrimers leads to anomalous properties compared to the linear equivalents. Further studies have confirmed this transition of shape at higher generations by showing clear changes in behaviour after the shape change.[22] The compact structure of high generation dendrimers has been explained by the back-folding of surface groups giving a density maximum at the core[23] (although there is some disagreement with this hypothesis[24]). Despite the difficulties in comparing linear polymers and dendrimers some important trends have been described.

One of the most feted properties of dendrimers is their intrinsic viscosity behaviour. Linear polymers (in accordance with the Mark-Houwink-Sakurda equation) show a linear increase in a plot of the logarithm of the intrinsic viscosity against the logarithm of molecular weight. For dendrimers a maximum is seen at a certain generation number above which the intrinsic viscosity drops with increasing molecular weight, (Figure 1.10).[25,26,27] This behaviour has been rationalised by postulating the adoption of a globular shape at a certain generation with the decrease in intrinsic viscosity occurring at molecular weights above this shape change.

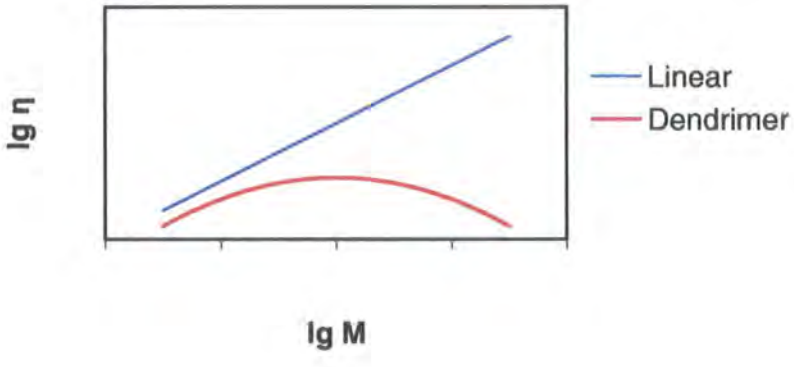



Figure 1.10 - A schematic view of the intrinsic viscosity behavior of dendrimers and linear polymers.

Generally dendrimers show much higher solubility than their linear analogues, often being soluble in a wider range of solvents than the linear polymer and also

show much greater solubilities in those solvents, for example this behaviour is seen in convergent polyester dendrimers.[28] This increased solubility is generally explained by the architecture of dendrimers and the high number and accessibility of their terminal groups.

The melt viscosity of linear polymers generally obeys a power law with respect to molecular weight, termed Rouse behaviour.

$$\eta_o = KM^a$$

For low molecular weights a = 1.0, whilst above a certain molecular weight ($M_c$) entanglement effects dominate and a = 3.4. Due to their highly congested surfaces and high degree of branching, entanglements are prevented in dendrimers and no $M_c$ is seen. The plot of melt viscosity against molecular weight is non-linear at low molecular weights, with significant curvature seen, (Figure 1.11).[29]

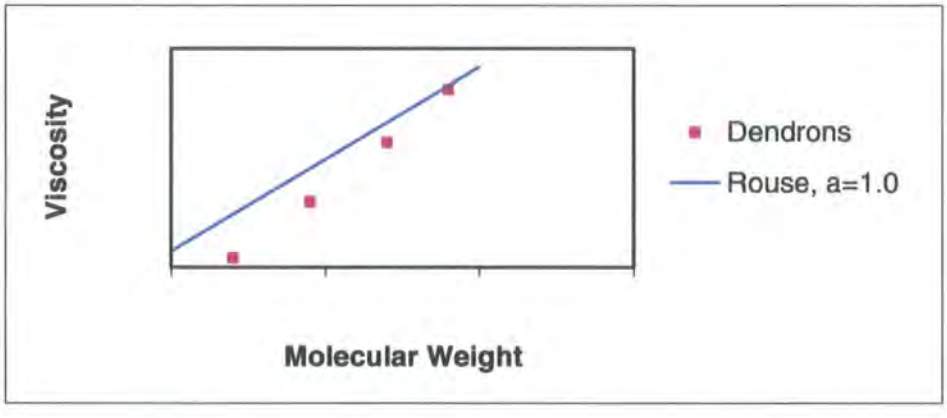



Figure 1.11 – The curvature seen in the plot of melt viscosity against molecular weight at low molecular weights.

The glass transition behaviour of linear polymers is known to correlate with chemical constitution. The glass transition temperature ($T_g$) increases as molecular weight increases to a maximum ($T_{g\infty}$) above which further increases in molecular weight have no effect.[30] For dendrimers the same qualitative behaviour is observed, although the unusual architecture means that the large number of

chain ends dominate and the traditional equations must be modified to allow for this, especially in dendrimers which can hydrogen bond.[31]

### 1.1.2 - Utility of dendrimers

Since their introduction, many possible applications for dendrimers have been suggested. Potential commercial applications are limited to those that can accept the huge cost of these materials. Dendrimers are commercially available, but the cost (250mg of generation four PAMAM dendrimer costs £36.30)[32] limits research into their applications to extremely high added value products. Such research has focused on three main areas, medicine, host-guest chemistry and catalysis, where the small quantities necessary and high value of the products makes the cost more bearable.

In medicinal applications the prospect of amplified binding through the numerous surface groups exists,[33] there are prospects for their use in magnetic imaging chemistry[34] and PAMAM dendrimers show an ability to transfer biomolecules into cells.[35,36] One potentially major limiting factor in the use of PAMAM dendrimers for medicinal uses is their high cytotoxicity.[37]

In the field of host guest chemistry the ability to shield the core of the dendrimer (at least to some extent) from the medium has generated much interest in applications calling for site isolation. Examples include the isolation of chromophores to improve luminescence properties[38,39] and in production of redox active couples.[40] The ability to complex guests away from the medium has also led to much interest, for example in 'the dendritic box' dye molecules were physically trapped in the core of a dendrimer with bulky surface groups.[41]

In catalysis it is hoped that dendrimers can offer the advantages normally associated with homogenous catalysis (faster kinetics and ease of access to the catalytic site) with the ease of recovery of heterogeneous catalysts.[42] There are advantages both in putting the catalytic function at the core and also in locating it at the periphery. When putting the functionality at the core beneficial interactions

between the substrate and the core maybe seen,[43] whilst if the periphery is used multiple catalytic sites maybe incorporated allowing a higher catalytic loading.[44]

This commentary on the synthesis, characterisation, properties and potential applications of dendrimers has been included here as background material. It has been kept brief deliberately because the primary focus of this work is in the area of hyperbranched polymers. The field of dendrimers has been and remains the subject of intensive research and many elegant syntheses and studies of structure and behaviour have appeared. The interested reader can access this work via the numerous papers, reviews and books available on this subject.

## 1.2 - Hyperbranched polymers

The difficulties in obtaining dendrimers on a large scale led to investigations of easier syntheses of similar materials. This in turn caused a renaissance into research into synthesis of hyperbranched polymers, which had been discussed in detail many years previously.[45] Hyperbranched polymers are less perfect, less controlled versions of dendrimers, (Figure 1.12). They lack the perfect architecture of dendrimers, however this reduction in perfection is accompanied by easier syntheses, with hyperbranched polymers typically being produced via a one-pot polymerisation, comparable in ease to traditional step-growth reactions.

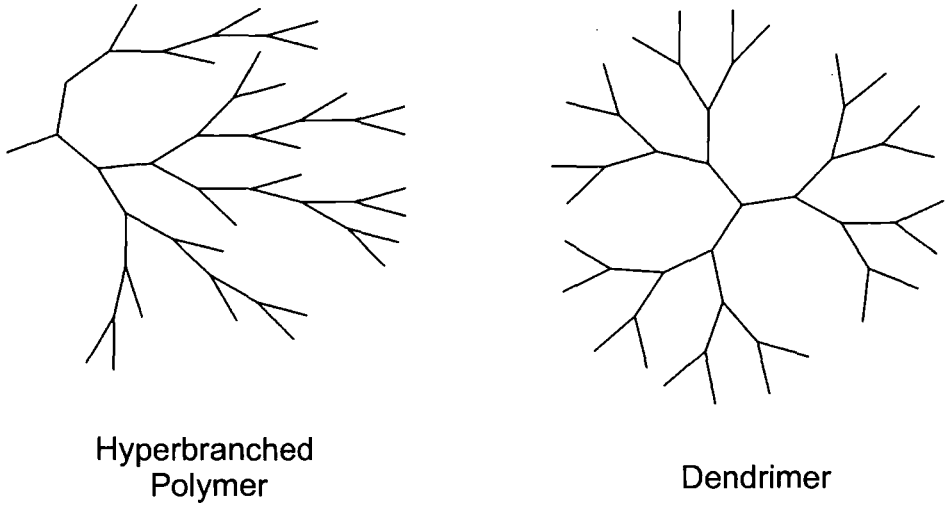



Figure 1.12 – Schematic view of the difference in architecture between dendrimers and hyperbranched polymers.

The first modern report of hyperbranched polymer synthesis was driven by the desire for large amounts of 'dendrimers' to test as rheological control agents. The polymerisation of $AB_2$ monomers to produce hyperbranched polymers was used as an alternative to the expensive dendrimer synthesis.[46,47]

A modified Suzuki type process was used to produce polyphenylene hyperbranched polymers, (Figure 1.13) and (relatively) large amounts of material were produced at a fraction of the cost of synthesising dendrimers. Since this work many groups have looked at the field of $AB_x$ polymerisations, often as low cost/large scale dendrimer analogues.

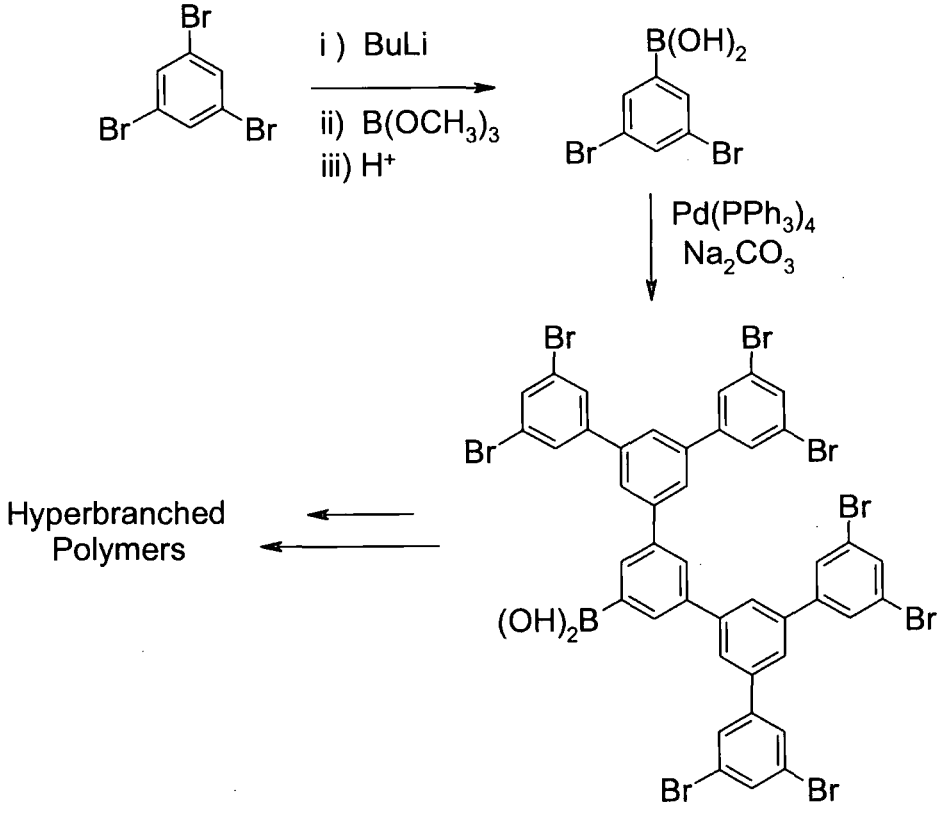



Figure 1.13 - Hyperbranched polyphenylene synthesis.

### 1.2.1 - Aspects of $AB_x$ polymerisations

Step-growth polymerisations involve reactions between pairs of mutually reactive functional groups that are initially provided by monomers. To form linear

polymers, difunctional monomers are needed, either of the A-B type, or a 1:1 mixture of A-A and B-B monomers, (Figure 1.14). To form linear polyesters for example, either an ω-hydroxy carboxylic acid (A-B) may be used, or a mixture of diacid and diol (A-A/B-B).

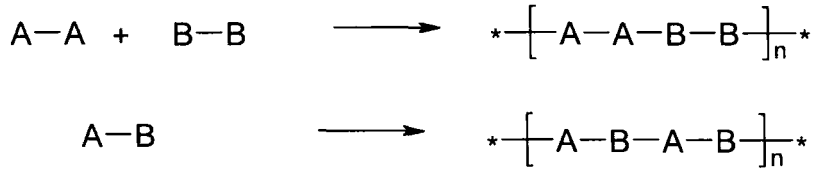



Figure 1.14 – Synthesis of linear polymers via step-growth polymerisations.

After the step-growth reaction has occurred the polymer chain is still difunctional and can react further, to build up longer chains. Each polymer chain grows at a much slower rate than in addition polymerisation, with the degree of polymerisation being linked to the conversion by the equation DP = 1/(1-p). This shows that at 95% conversion the average degree of polymerisation is only twenty. In order to attain a reasonable degree of polymerisation a high conversion is necessary. This leads to exacting requirements for the reactivity and purity of the monomers.

To allow the synthesis of hyperbranched rather than linear polymers, $AB_x$ monomers must be used rather than AB or A-A/B-B. The B groups can react with A groups, but neither A nor B can react with itself. The hyperbranched polymer is built up by step-growth reactions between A and B groups, (Figure 1.15). In addition to reactions involving the monomers, the A and B groups of the forming oligomers and polymers can also react with each other forming larger molecules. Each monomer, oligomer and polymer has one A group and n+1 B groups (two for the monomer, three for a dimer, four for a trimer etc.). As larger molecules are produced they have numerous B terminal groups.

The formation of bonds through the step-growth reactions are not controlled in any manner and the polydispersity is large with a mixture of small and large

molecules being seen in any one sample. As in the formation of linear step-growth polymers high molecular weight species are not created until the conversion is high and even in samples of high molecular weight polymer, monomers and oligomers are still present.

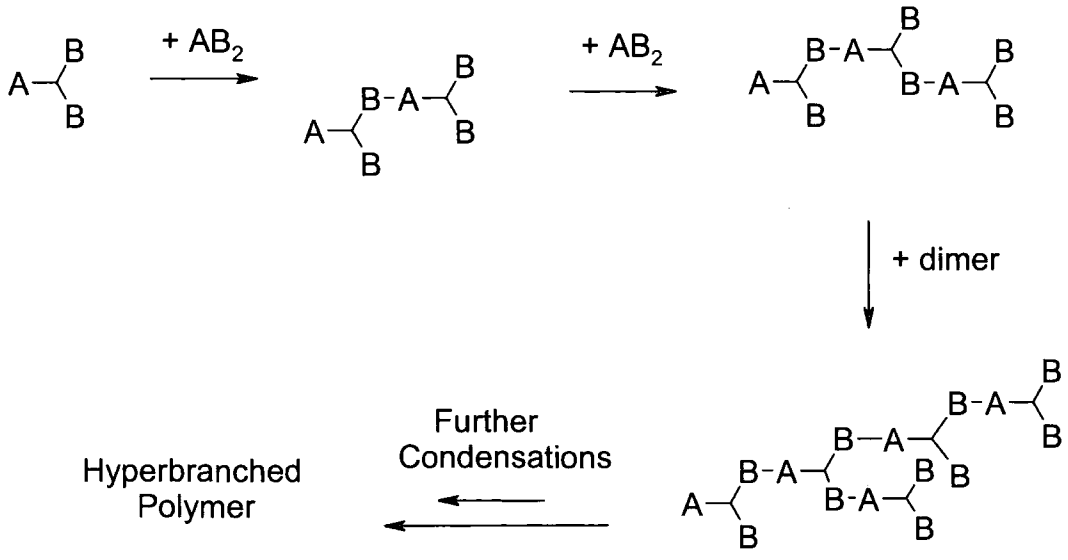



Figure 1.15 – A pictorial representation of how an $AB_2$ type monomer polymerises.

In the polymerisation of an $AB_2$ monomer once the degree of polymerisation exceeds two the phenomenon of isomerism becomes possible. The connectivity of the monomers maybe different as an A group can react with any of the available B groups and as the degree of polymerisation rises so does the number of possible isomers. This means that even in a (hypothetical) sample of hyperbranched polymer containing only molecules of one degree of polymerisation a huge variety of species would exist.

In linear polymers the units are joined together into long chains, whilst in dendrimers they are completely and perfectly branched. Hyperbranched $AB_2$ polymers fall between these two extremes containing a mixture of branched units (where both B groups have reacted), linear (where only one B group has reacted) and terminal (where neither B group has reacted), (Figure 1.16). There is also (if the molecule has not cyclised) one monomer unit possessing an unreacted A

group, termed the focal point. The amount of branching in a hyperbranched polymer is described as the degree of branching, (Section 1.2.5).

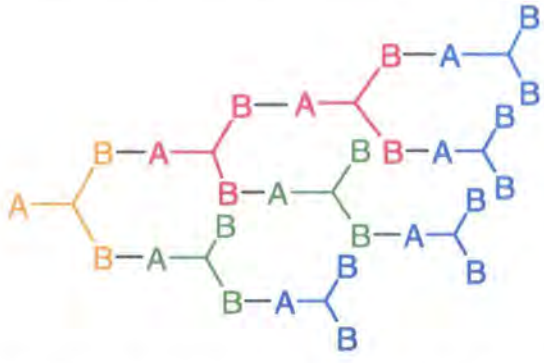


Figure 1.16 – The different types of unit seen in a hyperbranched polymer, terminal (blue), linear (green), branched (red) and the single focal unit (orange).

The polymerisation of an $AB_x$ monomer occurs through the reaction of an A group with a B group. Every growing polymer contains both of these groups and the potential for intramolecular reactions exists, (Figure 1.17). If this occurs then the polymer forms a cyclic species and cannot grow further through standard step-growth reactions. The formation of such cyclic species has been observed experimentally in the synthesis of hyperbranched polymers.[48]

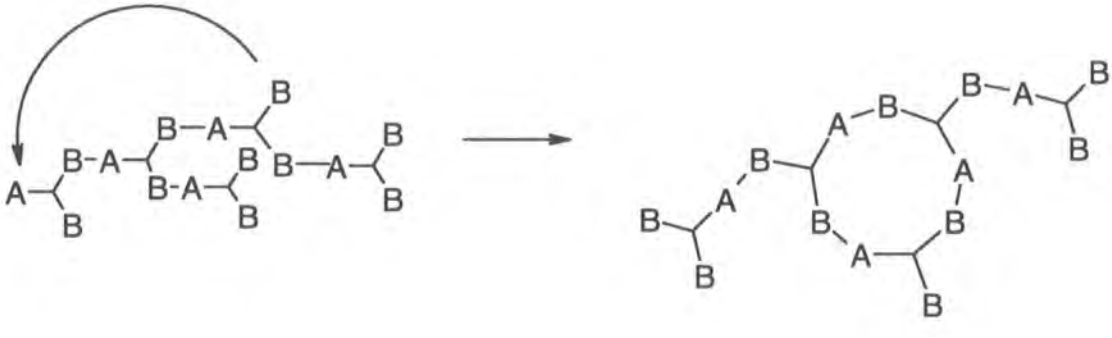


Figure 1.17 – The formation of cyclic species through intramolecular condensations.

The most common type of molecule used as a monomer for the formation of hyperbranched polymers is $AB_2$, but any molecule of the type $AB_x$ where $x>1$ can be used. Aside from $AB_2$ type monomers various other $AB_x$ monomers have been

studied.[49] Often these higher functionality monomers are used to alter the degree of branching, (Section 4.2).

### 1.2.2 – Alternative methods of hyperbranched polymer synthesis

Problems exist with $AB_x$ polymerisations, including the broad polydispersity of the polymers produced, the loss of focal point (A group) through side reactions or cyclisation and the non-commercial availability of suitable monomers.

To circumvent some of these difficulties attempts have been made to polymerise $AB_2$ monomers on a solid surface.[50] A monomer with a diiodo group was tethered to a solid support and the $AB_2$ monomer 1-ethynyl-3,5-diiodobenzene was added to a suspension of the support containing $Pd_2(dba)_3$ as a catalyst, (Figure 1.18). Competition between polymerisation in solution and on the resin surface was seen with some molecular weight control being possible in the polymer which had formed on the support surface. This polymer cannot undergo cyclisation and can be guaranteed after cleavage to possess one focal group per molecule. The polymers can be easily cleaned by washing away excess reagents, monomers, and unbound polymer.

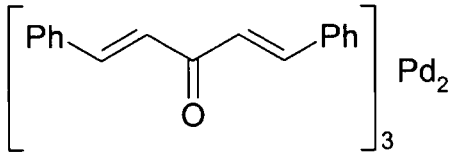



Figure 1.18 – Structure of $Pd_2(dba)_3$.

This methodology removes some of the problems of $AB_2$ polymerisations, however there have been a number of attempts to produce hyperbranched polymers through completely different synthetic routes.

The use of $A_2 + B_3$ systems that are prevented from forming a network has been investigated as an alternative method of synthesising hyperbranched polymers.[51] As it is necessary to stop the reaction so as to prevent a network forming, these

systems fail to meet most definitions of what constitutes a hyperbranched polymer. Gelation can occur at high conversions, nevertheless this method does provide a facile route to synthesise highly branched polymers. The ease of synthesis is increased as unlike $AB_2$ monomers there are many commercially available $A_2$ and $B_3$ systems. The first example of the use of the $A_2/B_3$ methodology,[52] as an alternative method of forming hyperbranched polymers was in the synthesis of polyamides. p-Phenylenediamine and 4,4'-oxyphenylene diamine were used as two alternative $A_2$ components with trimesic acid being used as the $B_3$ component, (Figure 1.19). These were polymerised by using triphenyl phosphite and pyridine as condensing agents (Section 3.2). The polymerisation was controlled to avoid gelation and the resulting polymers were soluble in organic solvents. Like conventional hyperbranched polymers prepared from analogous $AB_2$ monomers they contained a large amount of residual carboxylic acid groups.

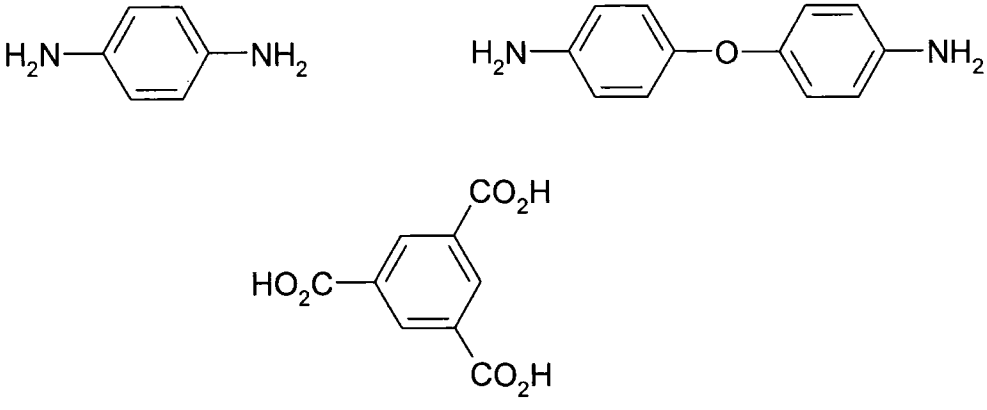



Figure 1.19 – The $A_2$ and $B_3$ monomers used to produce highly branched polymers.

To avoid the problems of network formation at high conversions a variant of the $A_2$ + $B_3$ methodology has been investigated in which the $B_3$ component is replaced by a $BB'_2$.[53] The polymerisation occurs in two stages, a fast reaction between the A and B groups, followed by a much slower reaction between the remaining A group and the two B' groups, (Figure 1.20). Essentially an $AB'_2$ monomer is produced in the first (fast) step, this then forms the hyperbranched polymer through polycondensation in the second (slow) step.

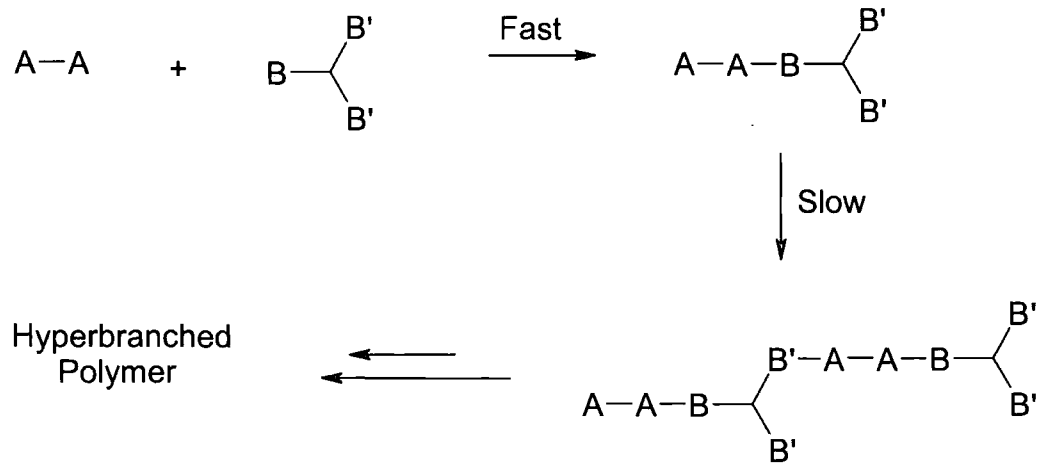



Figure 1.20 – A schematic view of an $A_2$ + $BB'_2$ polymerisation.

Hyperbranched polymers have been formed in this manner from two commercially available chemicals, 1-(2-aminoethyl)piperazine ($BB'_2$) and divinyl sulfone ($A_2$). The secondary amines of the 1-(2-aminoethyl)piperazine react quickly with the vinyl groups of the divinyl sulfone, forming predominantly dimers, which then go on to react more slowly through reaction between the remaining amine functionalities and the vinyl groups to build up polymers, (Figure 1.21).

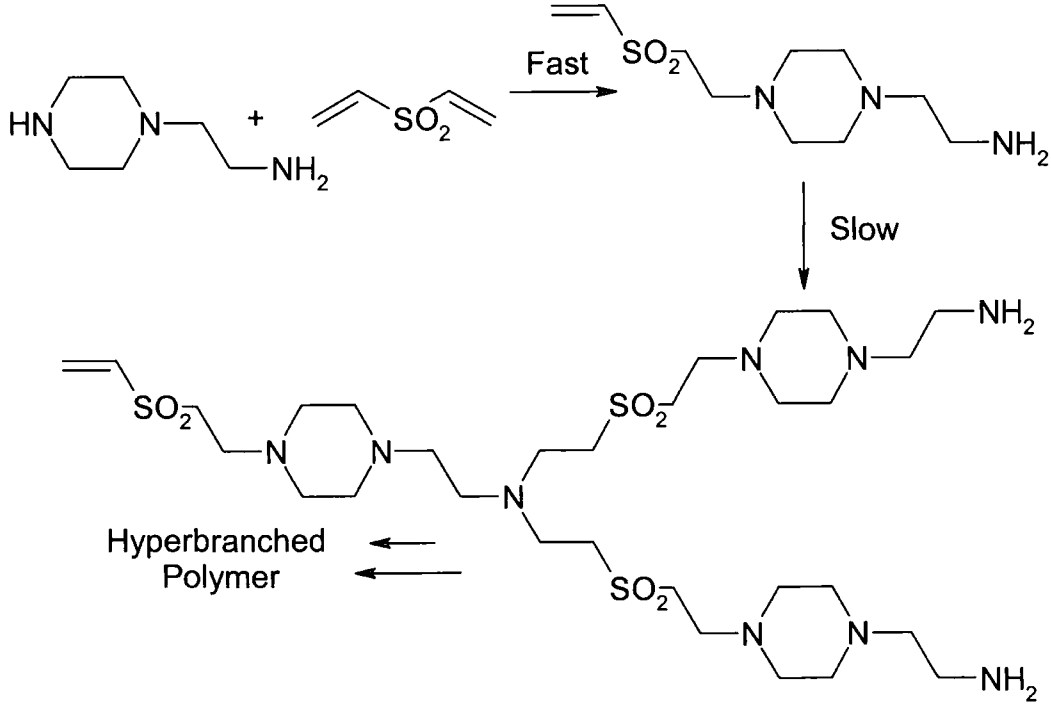



Figure 1.21 – Divinyl sulfone and 1-(2-aminoethyl)piperazine as an $A_2/BB'_2$ system.

A different approach to the synthesis of hyperbranched polymers involving the use of monomers with two different modes of activation has been reported.[54] Instead of $AB_2$ monomers an AB vinyl monomer is used. The A is a vinyl group, and the B is a pendant group which can be activated by an external stimulus to form a B* active group which is itself capable of initiating polymerisation of vinyl double bonds. This method has been termed self-condensing vinyl polymerisation (SCVP). This allows synthesis of highly branched polymers as upon dimerisation of two such externally stimulated monomers a species equivalent to an $AB_2$ monomer is produced. The vinyl group of the dimer can react with either a propagating centre or a B* group, and this dimer is thus equivalent to an $AB_2$ monomer, (Figure 1.22). Due to the different rate constants of the reactions occurring the kinetics of SCVP are very different to those for the production of hyperbranched polymers by step-growth polymerisation and the reaction leads to polymers with a higher polydispersity.

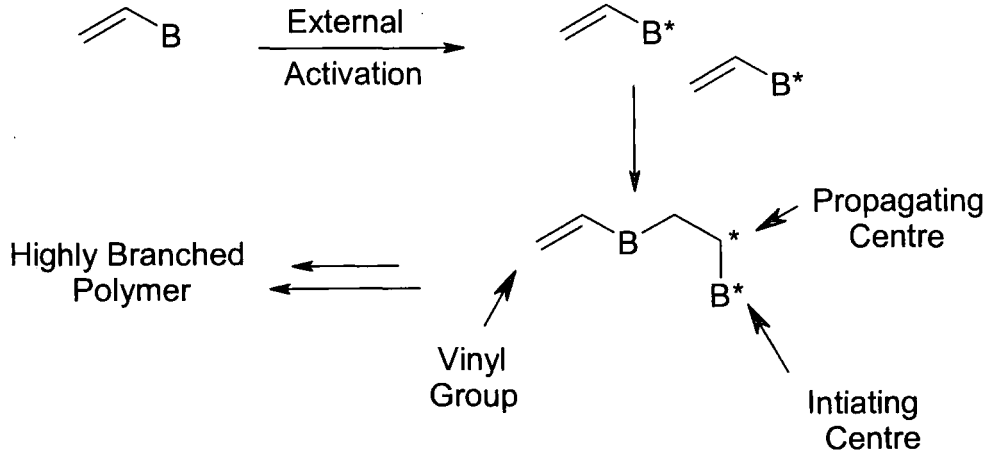



Figure 1.22 – The mechanism of self condensing vinyl polymerisation.

This methodology was illustrated with 3-(1-chloroethyl)-ethenylbenzene, in which the chlorine atom can be converted to an initiating site, (Figure 1.23). A sample of polystyrene was produced that was thought to be highly branched as it had very low intrinsic viscosity compared to linear polystyrene of a similar molecular weight.

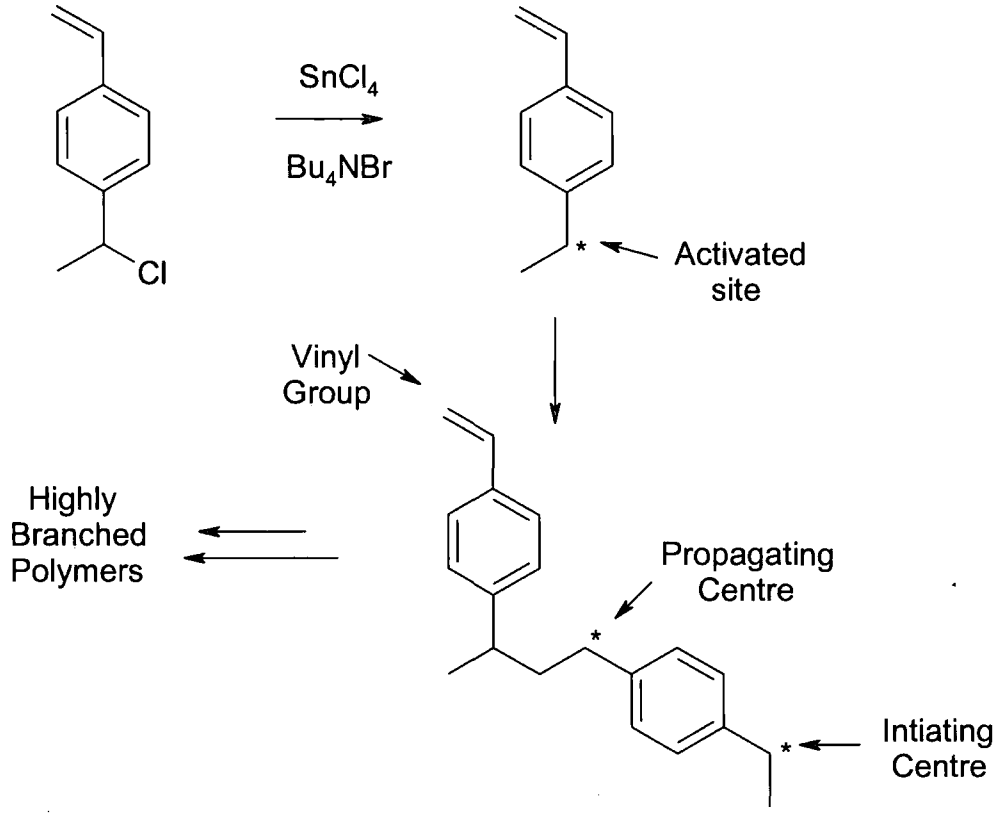



Figure 1.23 – The self-condensing vinyl polymerisation of 3-(1-chloroethyl)-ethenylbenzene.

The SCVP route has also been used to form highly branched molecules via living free radical polymerisation. Atom transfer radical polymerisation (ATRP) was used to polymerise p-(chloromethyl)styrene, which contains a benzylic chloride intiating species, and a polymerisable styrene group[55] and nitroxide based living free radical polymerisation has been used to produce highly branched polymers from a monomer containing a polymerisable styrene group and a nitroxide that can act as an initiating site bound to a benzylic carbon.[56]

Ring-opening reactions have also been used to prepare hyperbranched polymers in an approach which utilises the 'hidden' $AB_2$ nature of some cyclic species and has been termed multi-branching polymerisation.[57] 5,5-Dimethyl-6-ethenylperhydro-1, 3-oxazin-2-one, which has an amidic proton, was used as a monomer in the first example of this approach, (Figure 1.24). Primary or secondary amines were used as initiators and the polymerisation was catalysed by palladium salts. This system can form hyperbranched polymer as the primary amine formed by the ring

opening can react twice with a complexed vinyl, and therefore act as a $B_2$ group with the complexed vinyl acting as an A group.

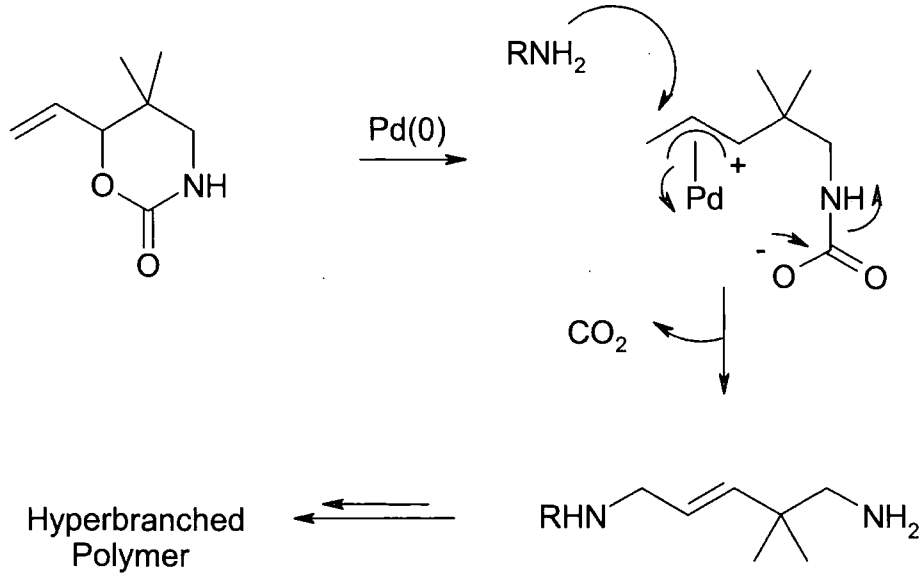



Figure 1.24 – Mechanism of multi-branching polymerisation of 5,5-dimethyl-6-ethenylperhydro-1, 3-oxazin-2-one.

Interest in the synthesis of highly branched 'linear' polymers has grown in recent years. These have the significant advantage over hyperbranched polymers that a standard industrial set-up can be used for their synthesis. By choice of the correct catalyst, temperature and pressure, highly branched polyethylene,[58,59] α-olefins[60] and ethylene functionalised vinyl copolymers[61] have been synthesised.

In a different approach to formation of highly branched polymers successive rounds of grafting of linear polymers may be used. Chains are grafted onto a linear polymer to form a comb and subsequent activation of the teeth of the comb allows them to accept a further round of grafting. Highly branched polymers are formed by successive iterations of this scheme. Early examples included the grafting of cationic chain-capped polyoxazolines to polyethyleneimine receivers and subsequent hydrolysis to give new secondary amine sites onto which further grafting could occur,[62] (Figure 1.25) and an anionic method involving the formation of pendant chlorine groups in polystyrene onto which new anionic polystyrene chains could be grafted.[63]

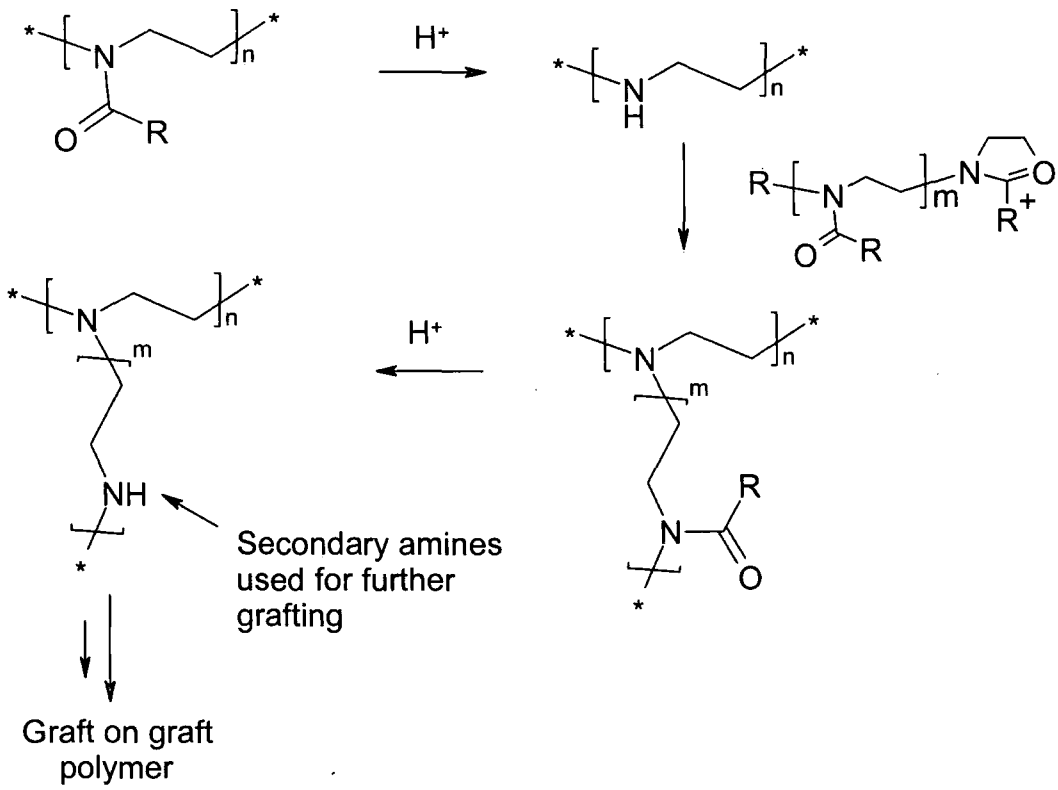



Figure 1.25 – Formation of highly branched polymers by grafting cationic polyoxazolines onto polyethyleneimine receivers.

A final method of forming branched polymers is the polymerisation of $AB_2$ monomers which are of the form A-polymer-$B_2$. The polymer chains of the macromonomer contain no branching, but as they are terminated by an A and a $B_2$ group they can be polymerised subsequently to form macromolecular hyperbranched polymers. The molecular weight of macromonomers can be substantial, and hence upon polymerisation high molecular weights are easily achieved. A series of hyperbranched poly($\epsilon$-caprolactones) were synthesised from the step-growth polymerisation of $AB_2$ functionalised macromonomers, (Figure 1.26), which were in turn formed from the ring-opening polymerisation of $\epsilon$-caprolactone, either initiated by benzyl alcohol followed by capping with a protected diol and deprotection,[64] or by initiation with a diol followed by deprotection.[65]

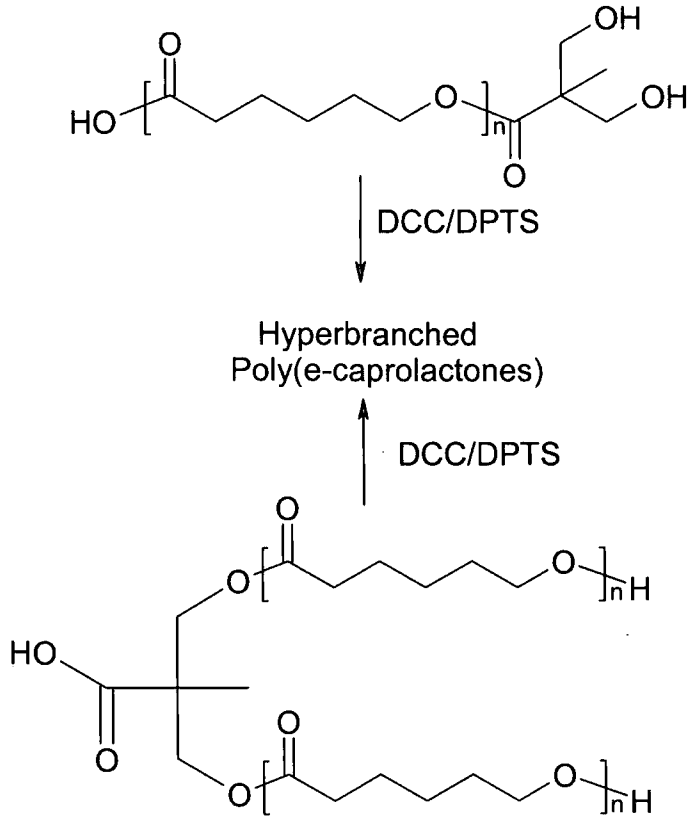



Figure 1.26 – Hyperbranched poly(ϵ-caprolactones) synthesised from macromonomers.

### 1.2.3 - Properties of hyperbranched polymers

Hyperbranched polymers have often been synthesised with the aim of producing lower cost materials than dendrimers with similar properties. It has become apparent that, although some similarities between the properties of the two classes of materials exist there are important differences and the utility of hyperbranched materials as alternatives to dendrimers depends entirely on the application in mind. Two factors dominate the behaviour of hyperbranched polymers, their high degree of branching and their large number of terminal groups. The predominance of these terminal groups leads to their nature having a large effect on the properties of the materials.

The higher solubility of dendrimers compared to linear polymers is also seen in hyperbranched polymers, with a consequent enhancement in both solubility and

the number of suitable solvents.[66] The pioneering work on hyperbranched polyphenylenes showed the importance of end-group identity with respect to the solubility of the polymers, when the polymer possessed non-polar end-groups it was soluble in non-polar solvents yet after modification to give a polar end-group solubility in water was seen.[46,47]

The anomalous intrinsic viscosity behaviour of dendrimers has led to much interest in the analogous behaviour of hyperbranched polymers. Most examples of hyperbranched polymers obey the Mark-Houwink-Sakurada equation used to describe linear polymers, ($[\eta] = KM^{a}$), albeit with a lower exponent a. For linear polymer the value of a is 0.5 in a theta solvent and is commonly between 0.65 and 0.75 for a random coil in a good solvent, whilst for hyperbranched polymers a is commonly below 0.5 even in a good solvent, (Figure 1.27).[67] In the special case of a hyperbranched polymer with DB = 1.00 (Section 1.2.5) then an intrinsic viscosity maximum may be seen.[68]

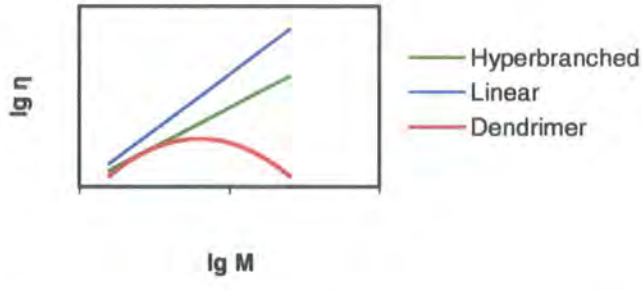



Figure 1.27 – A schematic view of the intrinsic viscosity behaviour of a dendrimer, a typical hyperbranched polymer and a linear polymer.

Hyperbranched polymers are thought to be largely unentangled and their glass transitions to be due to different relaxation processes than those responsible for the glass transition in linear polymers with interactions between end-groups having a large effect. In the case of hyperbranched polyphenylenes[47] changing the end-groups from bromine to $(CH_3)_3Si$ caused the glass transition temperaure ($T_g$) to drop by around 80°C. The hypothesis that thermal relaxation is due to translational motion of the polymer chains has been supported by the demonstration of a good correlation between the $T_g$ of a series of hyperbranched

polyphenylenes with a given surface and that of the triphenylbenzene derivative with the same functional groups implying the relaxation mechanisms are similar in each case.[69] If the end-groups of a hyperbranched polymer are changed from a polar group to a short alkane chain a decrease in $T_g$ is observed due to loss of hydrogen bonding. If the alkane chains are increased in length then a rise in $T_g$ is seen due to crystallisation of the surface groups.[70] It has been suggested that the thermal properties are largely independent of the architecture of the polymer.[28] Varying the degree of branching in hyperbranched polymers from the statistical value of 0.5 (Section 4.2) has no effect on $T_g$.[71]

### 1.2.4 - Utility of hyperbranched polymers

Due to the lack of a well-defined structure and molar mass many of the possible applications discussed for dendrimers are not suitable for hyperbranched polymers. The lower cost of these materials has led to them being considered for numerous industrial applications as their one-step syntheses would allow mass production. They have little use as bulk materials as they tend to be very brittle (due to the lack of entanglements), however there are many applications in which their low viscosity and large number of functional groups would be an advantage. The earliest results from studies of the application of hyperbranched polymers have been in the areas of additives for commercial polymers to aid processing, as curing agents and as carriers of functional molecules such as drugs and dyes. It seems likely that in the future these applications will increase in number and hyperbranched polymers will become an important class of industrial polymers.

The large number of functional groups at the surface of hyperbranched polymers has led to investigations into their use as curing agents. A series of hyperbranched polyesters, which could be UV cured have been studied.[72,73] These showed a substantially lower viscosity than conventional curing agents and had excellent curing properties with short curing times. They allowed the production of high-solid content organic coatings without reducing the molecular weight of the coating resin. Hyperbranched polyesters with methacrylate groups attached at the surface have been used to produce radiation-curable resins.[74,75,76]

These were shown to have lower viscosities and higher curing rates than their linear analogues.

Due to the lack of mechanical strength of hyperbranched polymers they are not suitable for application as engineering materials. They have been investigated in blends with linear polymers as their low melt viscosity may cause them to improve the processability of the linear materials. Hyperbranched polyphenylenes have been shown to reduce the melt viscosity of linear polystyrene[47] and hyperbranched polyesters have been added to a variety of linear polymers leading to improvements in mechanical properties.[77,78,79] In addition to improving processability the use of modified hyperbranched polyesters as dye carriers into polyolefin blends has been described. The dye is homogenously distributed in the matrix allowing the polyolefin to become uniformly coloured.[78] It has been suggested that a number of different additives could be carried into thermoplastics (and other systems) in this manner.[80]

### 1.2.5 - Theory of hyperbranched polymerisations

The step-growth polymerisations of $AB_x$ monomers have been studied theoretically for many years.[81,82,83] The most quoted work in the field of hyperbranched polymer theory is still that derived as a special case by Flory from considerations of the formation of infinite networks.[45] To simplify the mathematics three assumptions were made about the polymerisations of $AB_x$ monomers,

i) Only reactions between an A group and a B group are allowed.
ii) No intramolecular reactions (to form cyclic species) are allowed.
iii) The reactions of a functional group are independent of molecular size.

Using these assumptions it was predicted that a highly branched polymer would be produced but that it would not undergo network formation. For an $AB_x$ system the number of unreacted A groups per molecule remains at one (the focal point), whilst the number of unreacted B groups becomes (x-1)(z+1) in a z-mer. Since the renaissance of work on hyperbranched polymers the statistics and kinetics of these polymerisations have been re-examined. Much of the recent theoretical

work has involved computer simulations of the polymerisations.[84,85,86,87] These simulations have attempted to predict many of the important features of the polymerisations and of the polymers produced.

To describe branching in an $AB_x$ system, Flory defined the branching probability as the fraction of B groups that had reacted ($\alpha = p_B$), or in terms of A groups ($\alpha = p/x$), where p is the fraction of A groups which have reacted. The branching probability $\alpha$ actually measures the probability of any given A group at a branch point being joined via a polymer unit to another branch point and is directly related to the conversion. To quantify better the degree of branching in hyperbranched systems alternative definitions have been suggested.

Four different types of sub-unit in a polymer synthesised from an $AB_2$ monomer were described, (Figure 1.28),[66]

i) The focal point.

ii) Dendritic units (D), which have no unreacted B groups.

iii) Linear units (L), which have one unreacted B group.

iv) Terminal units (T), which have two unreacted B groups.

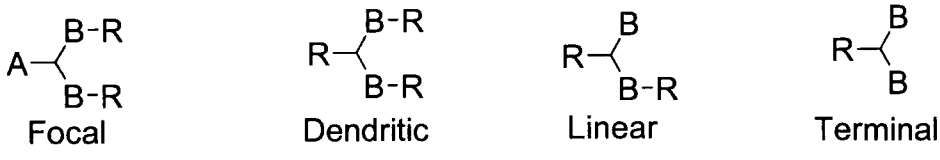



Figure 1.28 - The four types of sub-unit seen in the structure of a hyperbranched polymer.

The single unit at the focal point was ignored as its influence becomes insignificant as the molecular weight increases. The degree of branching (DB) of the polymers was defined as DB = (D+T)/(D+T+L). This definition (The Fréchet definition of degree of branching) is widely used, however the inclusion of terminal units gives unrealistically high values of DB for small molecules.

New equations for the degree of branching, which are valid at all molecular weights have been derived.[88] For $AB_2$ systems the expression DB = (2D)/(2D+L)

has been suggested. This equation (The Frey definition of degree of branching) eliminates the problems at low molecular weights seen with the earlier equation, resulting in more sensible values for DB at low molecular weights. It has the added advantage of not requiring the determination of the fraction of terminal units. The maximum value of DB (if one assumes equal reactivity of all A and B groups) using this definition is 0.5, however experimentally derived values are generally somewhat lower as complete conversion of A groups can never be achieved and linear units are generally less accessible than terminal. The conversion dependence of branching has also been calculated[89] which gives an idea of how the branching develops with time.

The possibility of cyclisation and the effect that this would have on the growth of hyperbranched polymers has also been studied. A kinetic model including size dependent cyclisation has been developed[87] and compared to the synthesis of a hyperbranched polyester. Good agreement between theory and experiment was seen including the observation that the degree of cyclisation rises with conversion. A detailed computer based lattice model has also been used to study cycle formation in the polymerisation of an $AB_2$ monomer.[84,90] These models again suggest that cyclic species are dominant at higher conversions and the growth of polymers can be frustrated through loss of A groups in cyclisation reactions.

Flory formulated an equation for the number of isomers obtained in the polymerisation of an $AB_x$ monomer. The individual x groups were considered to be distinguishable from each other (An $AB_2$ monomer was treated as an ABB' monomer) and the number of configurations ($N_c$) of a z mer was shown to be described by the relationship below.

$$N_c = \frac{((x+1)z - z)!}{((x+1)z - 2z + 1)!\, z!}$$

For an $AB_2$ (x=2) monomer this equation reduces to a simpler expression.

$$N_c = \frac{(2z)!}{(z+1)!\, z!}$$

This equation overestimates the number of isomers possible if the two B groups are indistinguishable. This is the case if the B groups are identical and there is free rotation around the A-B bond. Flory suggests that there are five possible arrangements for a trimer, whilst if free rotation is allowed four of these are indistinguishable, (Figure 1.29).

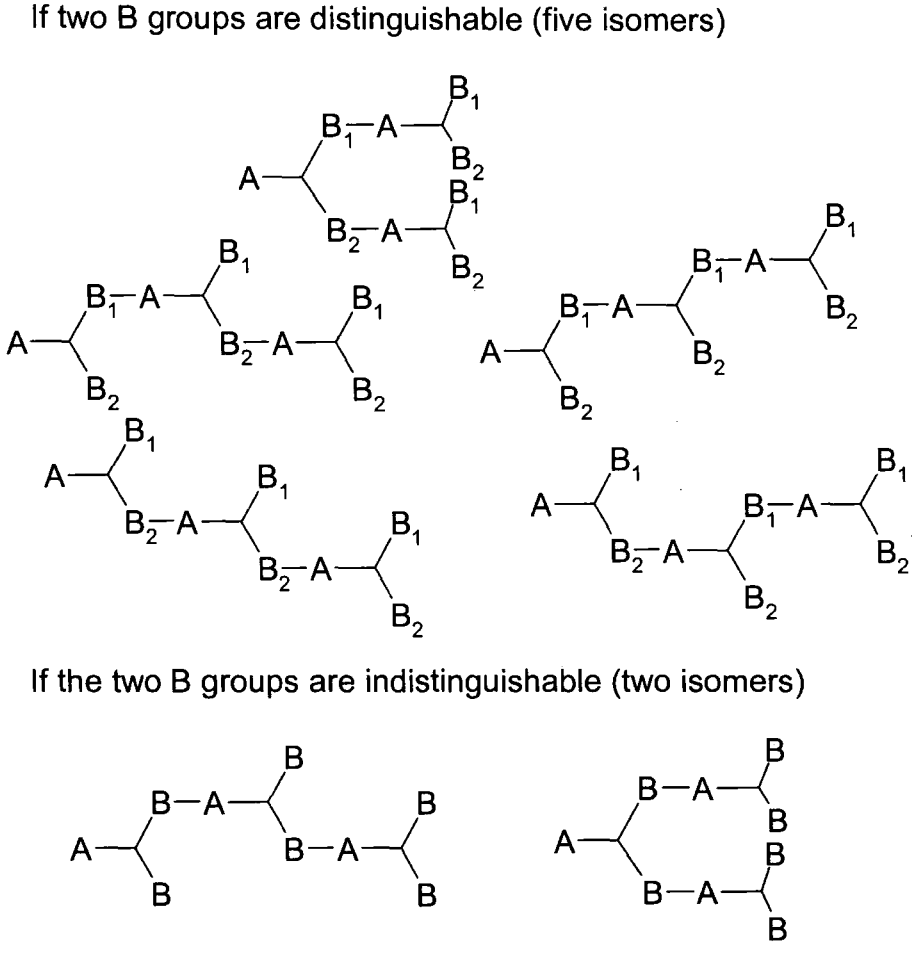



Figure 1.29 – The difference in number of isomers if B groups are distinguishable compared to the case when they are indistinguishable.

Degree of branching is not a measure of topology as two molecules that are very different in structure may have the same degree of branching, (Figure 1.30). The connectivity of a hyperbranched polymer[91] has been analysed using the Wiener index[92] which better defines the actual distribution of molecules. It cannot be measured experimentally and is only useful for theoretical studies.

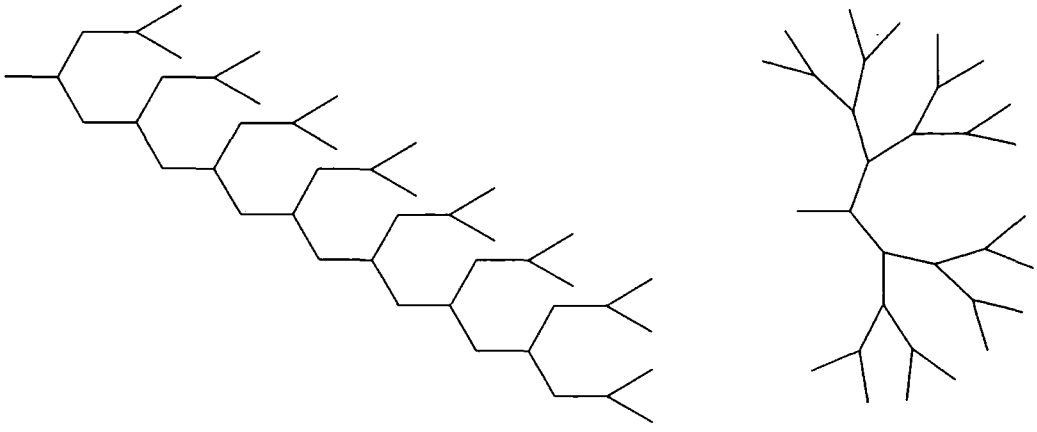


Figure 1.30 – Schematic representation of hyperbranched polymers with very different topologies, but both having a degree of branching of 1.

Flory derived an expression for the number average degree of polymerisation by substitution into his expression for the degree of branching.

$$\overline{x}_n = \frac{1}{1-p} = \frac{1}{1-\alpha x}$$

From first principles an equation for the weight average degree of polymerisation was obtained.

$$\overline{x}_w = \frac{1-\alpha^2 x}{(1-\alpha x)^2}$$

An expression for the polydispersity (PD) of the samples can be produced by combination of these two expressions.

$$PD = \frac{\overline{x}_w}{\overline{x}_n} = \frac{1-\alpha^2 x}{1-\alpha x}$$

This shows that there is expected to be a broadening of the molecular weight distribution as the reaction proceeds towards completion, as the weight average degree of polymerisation increases much faster than the number average. Indeed

for an $AB_2$ system as $\alpha$ tends to 0.5 polydispersity tends to infinity. These equations are somewhat in error as they ignore the effect of intramolecular reactions which may suppress growth. This causes large discrepancies at higher conversions and more recent studies have sought to include cyclisation in treatments of the molecular weight distribution of hyperbranched polymers.[84,90]

Many simulations to predict the properties of hyperbranched polymers have been reported. The intrinsic viscosity behaviour has been studied via a number of methods[91,93] which suggest that even hyperbranched polymers with a low degree of branching should possess a maximum in the plot of intrinsic viscosity against molecular weight, like that seen for dendrimers. This is not in agreement with the experimental results. Other properties that have been simulated include the behaviour of hyperbranched polymers under shear[94] and their phase behaviour in solution.[95]

### 1.3 - Aims of this work

Research into hyperbranched polymers has largely been directed at production of large-scale low cost analogues of dendrimers. Reports of hyperbranched polymers which are the analogues of important classes of dendrimers[96] have been produced and a comparison between their properties made. Despite this interest in hyperbranched analogues to dendrimers no such equivalents to the PAMAM dendrimers have been reported. Previous work at Durham[97] has shown the production of polyelectrolyte analogues but these are not suitable to replace dendrimers in many of the applications which have been discussed.

Production of analogues to the PAMAM dendrimers may allow the application of these hyperbranched materials to the potential uses of dendrimers for which cost is currently prohibitive. The aim of this work was the production of neutral soluble hyperbranched analogues to the PAMAM dendrimers, by an easy route allowing production on a relatively large scale (>10g) and at a fraction of the cost of the analogous dendrimers. It was intended to synthesise analogues of both the full generation (with amine surface) and the half generation (with ester surface)

PAMAM dendrimers. Also it was hoped to develop these strategies to include the production of similar dendritic materials.

## 1.4 - References


1 - Ehrlich, P. Mortimer, G. A. *Adv. Polym. Sci.* **1970**, *7*, 386

2 - Geddes, R. in *The Polysaccharides. Glycogen: A Structural Viewpoint*; Aspinall, G. O., Ed.; Academic Press: London, New York, **1985**; Vol. 3, p 209.

3 - Bork, S. *Kunstoffe – German Plastics* **1984**, *74*, 474.

4 - Hadjichristidis, N.; Pitsikalis, M.; Pispas, S.; Iatrou, H. *Chem. Rev.* **2001**, *101*, 3747.

5 - Schaefgen, J. R.; Flory, P. J. *J. Am. Chem. Soc.* **1948**, *70*, 2709.

6 - Morton, M.; Helminiak, T. E.; Gadkary, S. D.; Buecke, F. *J. Polym. Sci.* **1962**, *57*, 471.

7 - Decker, D. *Makromol. Chem.* **1969**, *125*, 136.

8 - Falk, J. C.; Scott, R. J.; Hoeg, D. F.; Pendleton, J. F. *Rubber Chem. Technol.* **1973**, *46*, 1044.

9 - Buhleier, E.; Wehner, W.; Vögtle, F. *Synthesis* **1978**,155.

10 - Denkewalter, R. G.; Kolc, J. F.; Lukasavage, W. J. *Chem. Abstr.* **1984**, *100*, 103 907; and US Pat. 4 289 872 (**1981**).

11 - Tomalia, D. A.; Baker, H., Dewald, J. R.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J. (Tokyo)* **1985**, *17*, 117.

12 - Tomalia, D. A.; Berry, V.; Hall, M.; Hedstrand, D. M. *Macromolecules* **1987**, *20*, 1164.

13 - Hummelen, J. C.; van Dongen, J. L. J.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1489.

14 - Hawker, C. J.; Fréchet, J. M. J. *J.Chem. Soc. Chem. Comm.* **1990**, 1010.

15 - Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

16 - Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252.

17 - Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 82.

18 - Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159.

19 - Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

20 - Swali, V.; Wells, N. J.; Langley, G. J.; Bradley, M. *J. Org. Chem.* **1997**, *62*, 4902.

21 - Hawker, C. J.; Malmström, E. E.; Franck, C. W.; Kampf, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 9903.

22 - Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *Macromolecules* **1993**, *115*, 4375.

23 - Lescanec, R. L.; Muthukumar, M. *Macromolecules* **1990**, *23*, 2280.

24 - De Gennes, P. G.; Hervet, H. *J. Phys. Lett. Fr.* **1983**, *44*, L351.

25 - Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401.

26 - De Brabander-van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1308.

27 - Tomalia, D. A.; Naylor, A.; Goddard, W. A. III *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.

28 - Wooley, K. L.; Fréchet, J. M. J.; Hawker, C. J. *Polymer* **1994**, *35*, 4489.

29 - Hawker, C. J.; Farrington, P. J.; Mackay, M. E.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1995**, *117*, 4409.

30 - Adam, G.; Gibbs, J. H. *J. Chem. Phys.* **1965**, *43*, 139.

31 - Wooley, K. L.; Hawker, C. J.; Pochan, J. M.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 1514.

32 - Sold as 10% solution in methanol. Price from 2000-1 Aldrich Handbook of Fine Chemicals and Laboratory Equipment. Sigma-Aldrich, The Old Brickyard, New Road, Gillingham, Dorset, SP8 4XT.

33 - Posnett, D. N.; McGrath, H.; Tam, J. P. *J. Biol. Chem.* **1988**, *263*, 1719.

34 - Wiener, E. C.; Brechbiel, M. W.; Brothers, H.; Magin, R. L.; Gansow, O. A.; Tomalia, D. A.; Lauterbur, P. C. *Magn. Reson. Med.* **1994**, *31*, 1.

35 - Haensler, J.; Szoka, F. C. Jr. *Bioconjug. Chem.* **1993**, *4*, 372.

36 - Kukowska-Latallo, J.; Bielinska, A. U.; Johnson, J.; Spindler, R.; Tomalia, D. A.; Baker, J. R. Jr. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 4897.

37 - Duncan, R.; Malik, N. *Proc. Int. Symp. Control. Relat. Bioact. Mater.* **1996**, *23*, 105.

38 - Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286.

39 - Freeman, A. W.; Koene, S. C.; Malenfant, P. R. L.; Thompson, M. E.; Fréchet, J. M. J. *J. Am. Chem. Soc* **2000**, *122*, 12385.

40 - Dandliker, P. J.; Diederich, F.; Gross, M.; Knobler, C. B.; Louati, A.; Sanford, E. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1739.

41 - Jansen, J. F. G. A.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226.

42 - Tomalia, D. A.; Dvornic, P. R. *Nature* **1994**, *372*, 617.

43 - Brunner, H. *J. Organomet. Chem.* **1995**, *500*, 39.

44 - Lee, J.-J.; Ford, W. T.; Moore, J. A.; Li, Y. *Macromolecules* **1994**, *27*, 4632.

45 - Flory, P. J. Principles of Polymer Chemistry, chapter 9. Cornell University Press, Ithaca, New York, 1953.

46 - Kim, Y. H.; Webster, O. W. *J. Am. Chem. Soc.* **1990**, *112*, 4592.

47 - Kim, Y. H.; Webster, O. W. *Macromolecules* **1992**, *25*, 5561.

48 - Feast, W. J.; Keeney, A. J.; Kenwright, A. M.; Parker, D. *Chem. Commun.* **1997**, 1749.

49 - Miravet, J. F.; Fréchet, J. M. J. *Macromolecules* **1998**, *31*, 3461

50 - Bharati, P.; Moore, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 3391.

51 - Aharoni, S. M. *Polym. Adv. Technol.* **1995**, *6*, 373.

52 - Jikei, M.; Chon, S.-H.; Kakimoto, M.-A.; Kawauchi, S.; Imase, T.; Watanebe, J. *Macromolecules* **1999**, *32*, 2061.

53 - Yan, D.; Gao, C. *Macromolecules* **2000**, *33*, 7693.

54 - Fréchet, J. M. J.; Henmi, M.; Gitsov, I.; Aoshima, S.; Leduc, M. R.; Grubbs, R. B. *Science* **1995**, *269*, 1080.

55 - Gaynor, S. G.; Edelman, S.; Matyjaszewski, K. *Macromolecules* **1996**, *29*, 1079.

56 - Hawker, C. J.; Fréchet, J. M. J.; Grubbs, R. B.; Dao, J. *J. Am. Chem. Soc.* **1995**, *117*, 10763.

57 - Suzuki, M.; Ii, A.; Saegusa, T. *Macromolecules* **1992**, *25*, 7071.

58 - Kim, J. S.; Pawlow, J. H.; Wojcinski, L. M. II; Murtuza, S.; Kacker, S.; Sen, A. *J. Am. Chem. Soc.* **1998**, *120*, 1932.

59 - Guan, Z.; Cotts, P. M.; McCord, E. F.; McLain, S. J. *Science* **1999**, *283*, 2059.

60 - Johnson, L. K.; Killian, C. M.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 6414.

61 - Johnson, L. K.; Mecking, S.; Brookhart, M. *J. Am. Chem. Soc.* **1996**, *118*, 267.

62 - Tomalia, D. A.; Hedstrand, D. M.; Feritto, M. S. *Macromolecules* **1991**, *24*, 1435.

63 - Gauthier, M.; Möller, M. *Macromolecules* **1991**, *24*, 4548.

64 - Trollsås, M.; Atthoff, B.; Claesson, H.; Hedrick, J. L. *Macromolecules* **1998**, *31*, 3439.

65 - Trollsås, M.; Hedrick, J. L. *Macromolecules* **1998**, *31*, 4390.

66 - Hawker, C. J.; Lee, R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4583.

67 - Turner, S. R.; Voit, B. I.; Mourey, T. H. *Macromolecules* **1993**, *26*, 4617.

68 - Hobson, L. J.; Feast, W. J. *Chem. Commun.* **1997**, 2067.

69 - Kim, Y. H.; Beckerbauer, R. *Macromolecules* **1994**, *27*, 1968.

70 - Malmström, E.; Johansson, M.; Hult, A. *Macromol. Chem. Phys.* **1996**, *197*, 3199.

71 - Hawker, C. J.; Chu, F. *Macromolecules* **1996**, *29*, 4370.

72 - Johansson, M.; Hult, A. *J. Coat. Technol.* **1995**, *67*, 35.

73 - Johansson, M.; Malmström, E.; Hult, A. *J. Pol. Sci. Part A: Polym. Chem* **1993**, *31*, 619.

74 - Shi W. F.; Rånby, B. *J. Appl. Pol. Sci.* **1996**, *12*, 1937.

75 - Shi W. F.; Rånby, B. *J. Appl. Pol. Sci.* **1996**, *12*, 1945.

76 - Shi W. F.; Rånby, B. *J. Appl. Pol. Sci.* **1996**, *12*, 1951.

77 - Massa, D. J.; Shriner, K. A.; Turner, S. R.; Voit, B. I. *Macromolecules* **1995**, *28*, 3214.

78 - Schmaljohann, D.; Pötschke, P.; Hässler, R.; Voit, B. I.; Froehling, P. E.; Mostert, B.; Loontjens, J. A. *Macromolecules* **1999**, *32*, 6333.

79 - Mulkern, T. J.; Beck Tan, N. C. *Polymer* **2000**, *41*, 3193.

80 - Sunder, A.; Krämer, M.; Hanselmann, R.; Mülhaupt, R.; Frey, H. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3552.

81 - Stockmayer, W. H. *J. Chem. Phys.* **1943**, *11*, 45.

82 - Stockmayer, W. H. *J. Chem. Phys.* **1944**, *12*, 125.

83 - Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 58.

84 - Cameron, C.; Fawcett, A. H.; Hetherington, C. R.; Mee, R. A. W.; McBride, F. V. *Macromolecules* **2000**, *33*, 6551.

85 - Lee, Y. U.; Jang, S. S.; Jo, W. H. *Macromol. Theor. And Sim.* **2000**, *9*, 188.

86 - Galina, H.; Lechowicz, J. N.; Kaczmarski, K. *Macromol. Theor. And Sim.* **2001**, *10*, 174.

87 - Dušek, K.; Šomvársky, J.; Smrčková, M.; Simonsick, Jr., W. J.; Wilczek, L. *Polym. Bull.* **1999**, *42*, 489.

88 - Hölter, D.; Burgath, A.; Frey, H. *Acta Polymer.* **1997**, *48*, 30.

89 - Beginn, U.; Drohmann, C.; Möller, M. *Macromolecules* **1997**, *30*, 4112.

90 - Cameron, C.; Fawcett, A. H.; Hetherington, C. R.; Mee, R. A. W.; McBride, F. V. *J. Chem. Phys.* **1998**, *108*, 8235.

91 - Widmann, A. H.; Davies, G. R. *Comp. And Theor. Polymer Science* **1998**, *8*, 191.

92 - Wiener, H. *J. Am. Chem. Soc.* **1947**, *69*, 17.

93 - Aerts, *J. Comp. And Theor. Polymer Science* **1998**, *8*, 49.

94 - Lyulin, A. V.; Adolf, D.; Davies, G. R. *Macromolecules* **2001**, *34*, 3783 (see erratum *Macromolecules* **2001**, *34*, 8818.)

95 - Jang, J. G.; Bae, Y. C. *Polymer* **1999**, *40*, 6761.

96 - Uhrich, K. E.; Hawker, C. J.; Fréchet, J. M. J.; Turner, S. R. *Macromolecules* **1992**, *25*, 4583.

97 - Hobson, L. J.; Feast, W. J. *Polymer* **1999**, *40*, 1279.

# Chapter Two
# Synthesis of hyperbranched analogues of the polyamidoamine series of dendrimers

## Chapter Two – Synthesis of hyperbranched analogues of the polyamidoamine series of dendrimers

### 2.1 – Introduction

Polyamidoamines (PAMAMs) are a group of polymers that have a mixture of amines and amides within their repeat units. Such materials are unknown as linear polymers but in recent years there has been much interest in dendrimers with this structural feature. The synthesis of PAMAM dendrimers[1] involves the conjugate addition of an amine to methyl acrylate and subsequent amidation with ethylenediamine, (Figure 1.4). This produces new amine functionalities, which can undergo further conjugate addition to methyl acrylate. A perfectly branched structure is produced with alternating tertiary amines and amides in the repeat units. The terminal functionalities are either amines (full generations), (Figure 2.1) or esters (half-generations), (Figure 2.2).

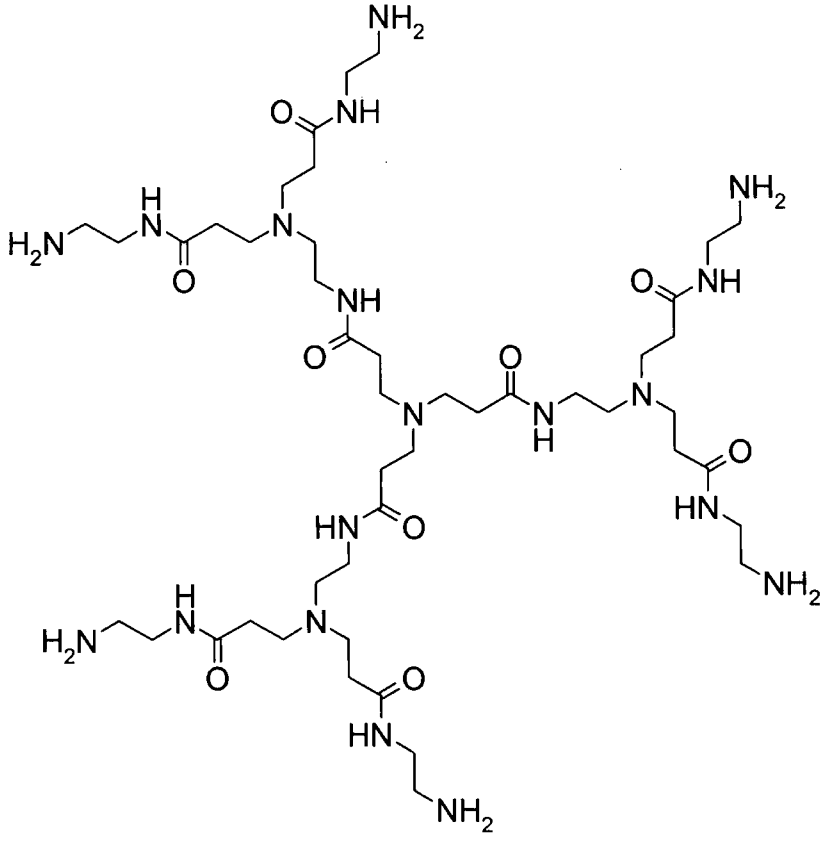


Figure 2.1 – Generation one PAMAM dendrimer, with amine end groups.

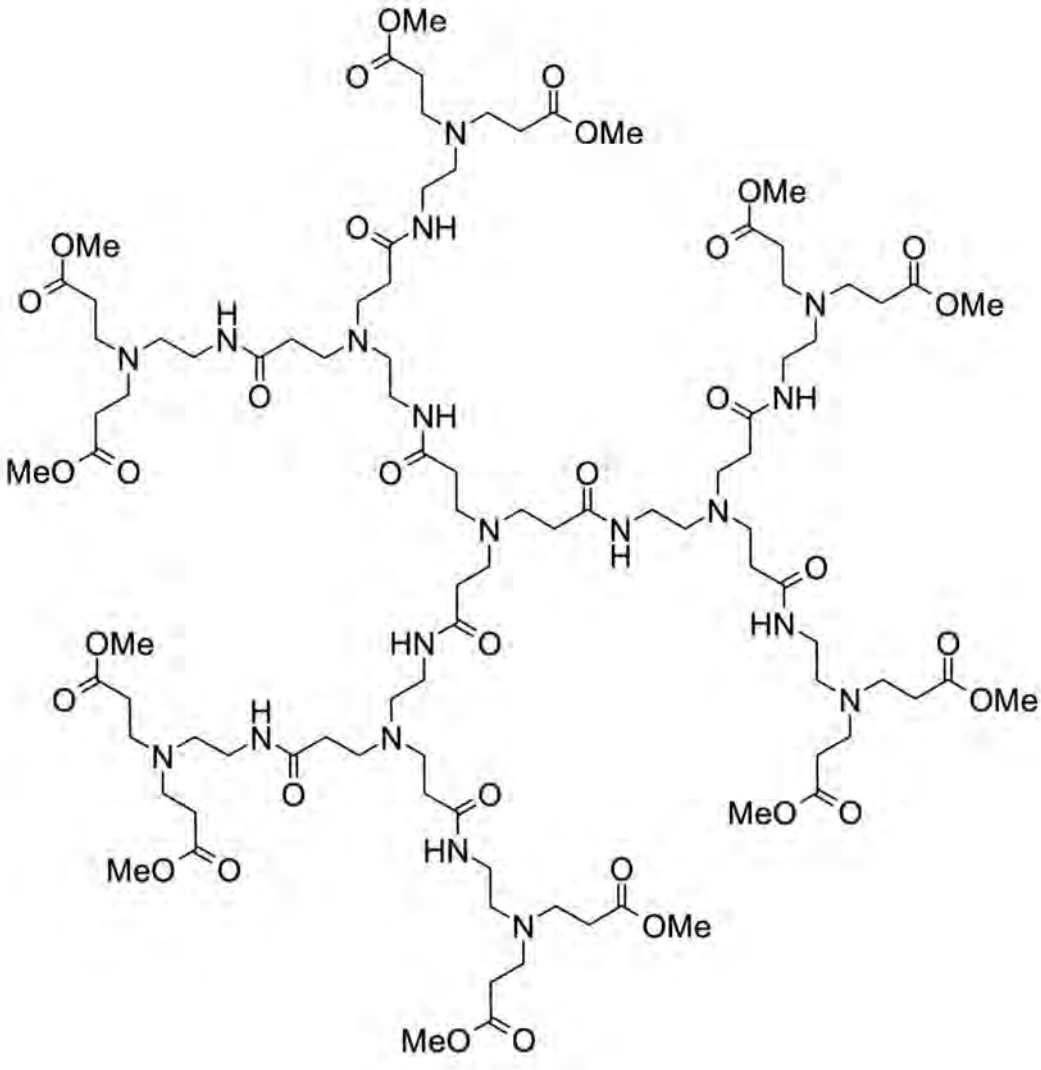


Figure 2.2 - Generation 1.5 PAMAM dendrimer, with ester end groups.

There has been a large amount of interest in dendrimers and their potential applications in recent years. There has been specific interest in the primary amine end groups and perfect architecture of PAMAM dendrimers, which has led to discussions of their potential use as 'artificial proteins' and as mimics of micelles and liposomes. There has been growing interest in the use of PAMAM dendrimers for medical research. Successes have been reported for their use as vectors for the transfer of genetic material into cells[2] and in their use as agents for drug delivery.[3]

Considering the interest in the PAMAM dendrimers there has been surprisingly little work on the area of hyperbranched PAMAMs. A method allowing the

synthesis of such materials should allow easier and cheaper production of a large amount of material, which although lacking the architectural perfection of dendrimers will still possess the high degree of branching and combination of tertiary amine and amide groups in the repeat units and primary amines at the termini. The lack of reported hyperbranched equivalents may be due to the difficulty in synthesising suitable $AB_x$ monomers, problems with the solubility of the polymers or in difficulties with their analysis.

The only aliphatic hyperbranched PAMAMs described prior to the work reported here are polyelectrolytes. The first examples of these were formed by melt polymerisation of N-acryoyl-α,ω-diaminoalkane hydrochlorides, (Figure 2.3).[4,5]

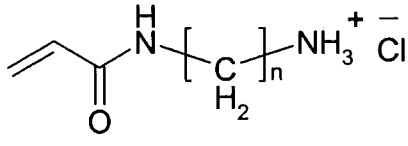


Figure 2.3 - The N-acryoyl-α,ω-diaminoalkane hydrochlorides polymerised to form polyelectrolyte PAMAMs.

When n=2, N-acryloyl-1,2-diaminoethane, the polymers obtained were shown by quantitative $^{15}N$ NMR to have a degree of branching close to 1, indicating few or no linear units. When this monomer is polymerised with tris(2-aminoethylamine), which acts as a $B_6$ core (Section 4.1) it was shown that the polymers retained their solubility as free bases. The core terminated hyperbranched PAMAMs showed solution viscosity behaviour similar to that of perfect dendrimers, with a maximum in the plot of solution viscosity versus molecular weight.[6]

The polymerisation of amino-methacrylate systems has also been investigated.[7] Only the monomer derived from N-methacryoyloyl-1,2-diaminoethane could be polymerised, (Figure 2.4), monomers derived from butane or propane did not undergo polymerisation, even at elevated temperatures. These materials were shown (unlike the polymers derived from N-acryoyl-α,ω-diaminoalkane hydrochlorides) to be soluble as the free bases, and if 10% of the N-

methacryoyloyl-1,2-diaminoethane hydrochloride is added to a polymerisation of N-acryloyl-1,2-diaminoethane hydrochloride the resultant polymers are soluble as the free bases.

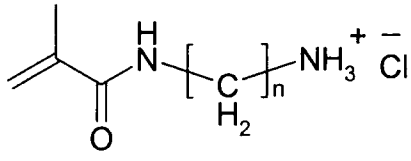


Figure 2.4 - N-methacryoyloyl-1,2-diaminoethane hydrochloride.

A series of amphiphilic hyperbranched PAMAM polyelectrolytes has also been reported.[8] These were synthesised by polymerisation of $AB_2$ monomers (Figure 2.5). The products will contain quaternary ammonium bromides in linear and dendritic segments with terminal tertiary amines. They have been studied as polymeric soaps.

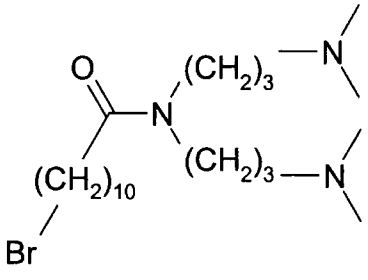


Figure 2.5 – Monomer used to synthesis amphilic hyperbranched polyelectrolytes.

## 2.2 – Outline of methodology for the synthesis of full generation hyperbranched analogues of PAMAM dendrimers

The intention in this work was to synthesise hyperbranched polymers from $AB_2$ monomers that were similar to the repeat units of the PAMAM dendrimers. The end groups of a hyperbranched polymer are the B groups of the monomer, and thus to form the full generation analogues (i.e. with amine end groups) an $AB_2$ molecule with amine B groups is required. It should be noted that the end groups of a hyperbranched polymer are often referred to as the 'surface groups', this

description has been avoided here as the end groups are often not located at the surfaces of the polymer.

The synthetic building block chosen for the synthesis of the full generation analogues was a triamine with two primary amines and one secondary amine. Primary and secondary amines have different reactivities and the first step of the synthesis is to selectively protect the primary amines whilst leaving the secondary amines unprotected, (Figure 2.6).

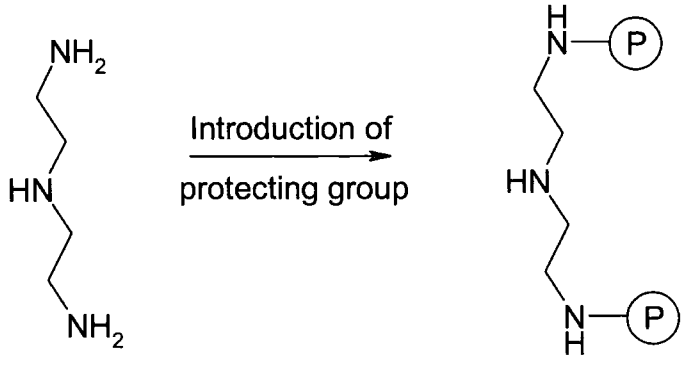



Figure 2.6 – Selective introduction of a protecting group (P) at the primary, but not the secondary amines of a triamine.

The (unprotected) secondary amine can then undergo conjugate addition with an acrylate. As the primary amines are protected this reaction will occur only at the secondary amine site and will introduce a single ester functionality, (Figure 2.7).

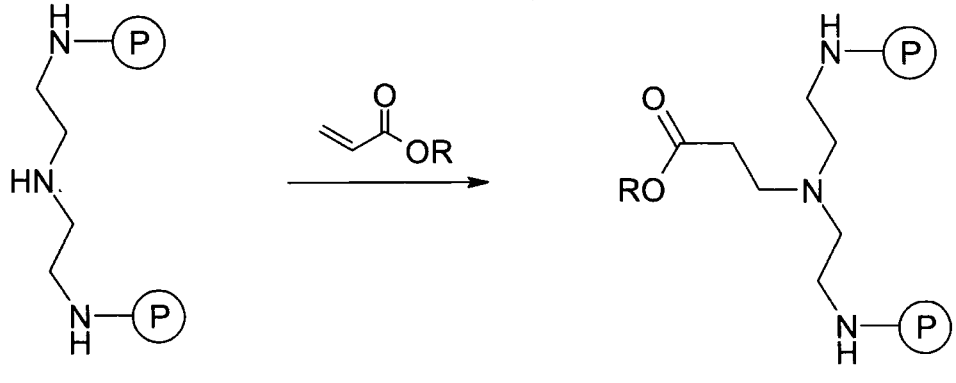



Figure 2.7 – Conjugate addition of the secondary amine of a selectively protected triamine to an acrylate.

The protecting groups can be removed from the primary amines to give an $AB_2$ monomer, which has an ester A group and amine B groups, (Figure 2.8). This will upon polymerisation give a hyperbranched polymer with alternating tertiary amines and amides in its repeat unit and primary amines at the termini.

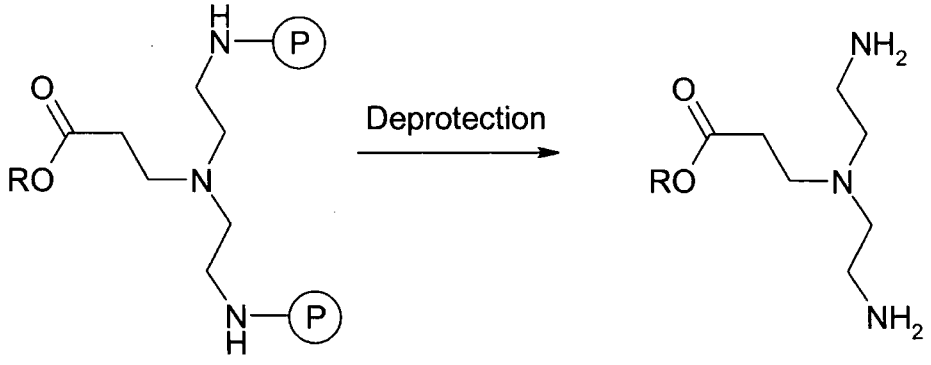



Figure 2.8 – Deprotection of primary amines to form the $AB_2$ monomer.

A primary amine and an ester group will undergo a condensation reaction with production of an alcohol. Through numerous such condensation reactions a hyperbranched polymer will be produced, (Figure 2.9).

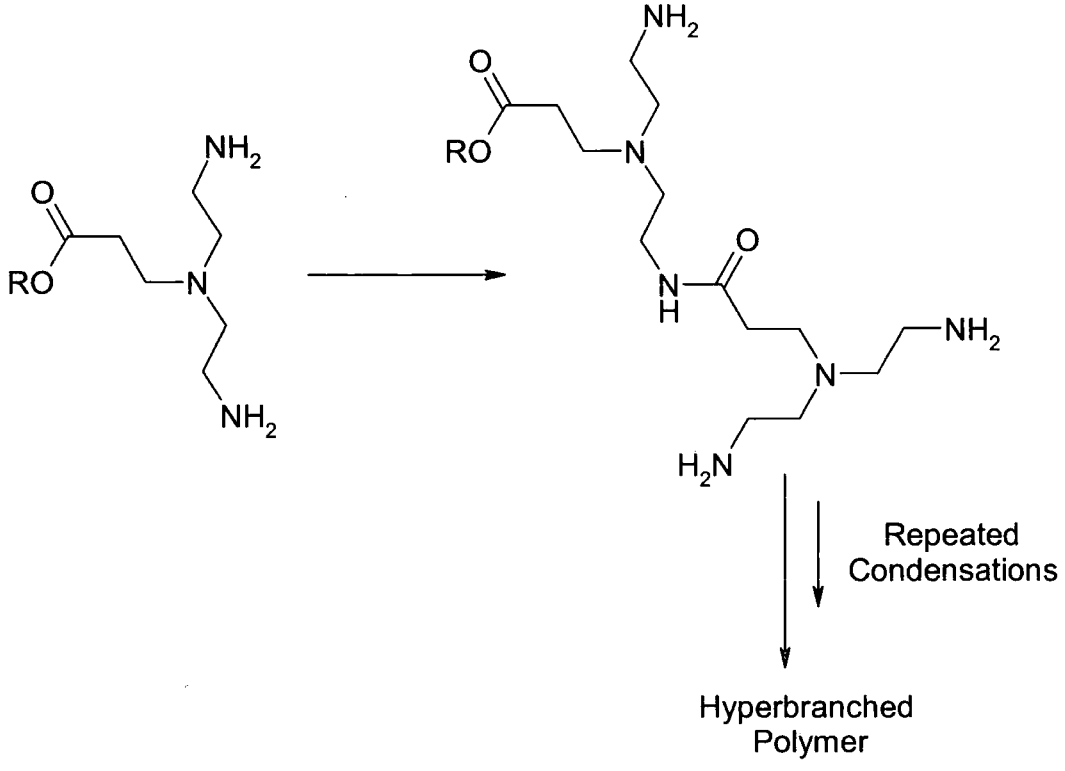



Figure 2.9 – Condensation reactions to produce a hyperbranched polymer.

## 2.3 – Selective protection chemistry

Protecting groups are used to block one reactive site in a molecule to allow a reaction to proceed selectively at a different site in the same molecule. It must then be possible to remove the protecting group to regenerate the original reactive site. The ideal protecting group must fulfil a number of criteria, it must be easy to selectively introduce in a clean reaction that proceeds in a good yield, must be stable to the conditions that are used in the subsequent reactions and must be easily removed in a clean reaction that does not require reagents or conditions that affect other functional groups in the molecule.

The t-butoxycarbonyl (Boc) protecting group was developed in the late 1950s[9,10,11] as a novel method of protecting amines and has since found widespread use in the field of peptide chemistry.[12,13] The Boc group forms a urethane linkage with amines and is stable to basic conditions, however due to the formation of a stable carbocation it is labile at low pH and is commonly removed with either hydrochloric or trifluoroacetic acid, (Figure 2.11). This forms an ammonium salt from which the neutral amine can be recovered either by neutralisation with base and extraction of the product into an organic solvent or alternatively by use of an ion-exchange column.

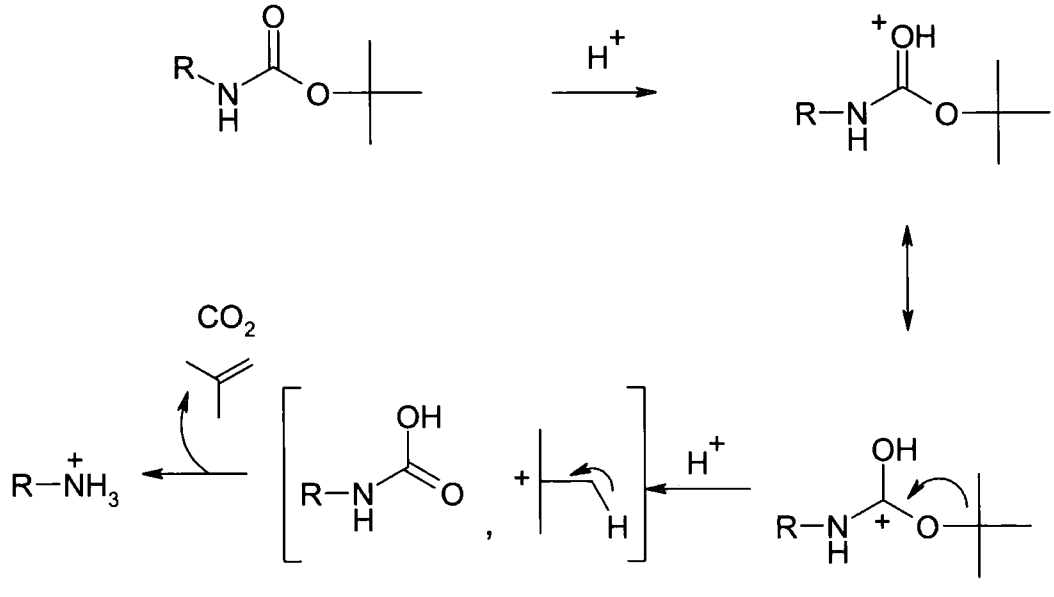



Figure 2.11 – Mechanism of the removal of the Boc protecting group with acid.

Addition of the Boc group to the two primary amines of a triamine leaving the secondary unprotected would provide a useful method to allow temporary protection of the primary amines. The method chosen to allow introduction of the Boc group at the primary amines utilised the selective chemistry of carbonyl diimidazole (CDI), (Figure 2.12).

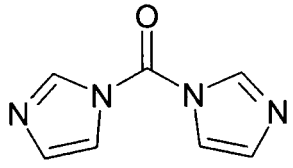


Figure 2.12 – Carbonyl diimidazole.

CDI has been used as a convenient alternative to phosgene, which is highly toxic and difficult to handle. It is prepared from phosgene[14,15,16] and possesses similar reactivity. The carbonyl group of CDI is strongly electrophillic due to the high degree of electron attraction exerted by the two adjacent heterocyclic substituents. Due to this electrophilicity CDI will undergo nucleophillic substitution with primary alcohols to form carbonates. In the case of tertiary alcohols the second substitution cannot proceed and even with an excess of alcohol and prolonged heating the carbonate cannot be formed, (Figure 2.13).

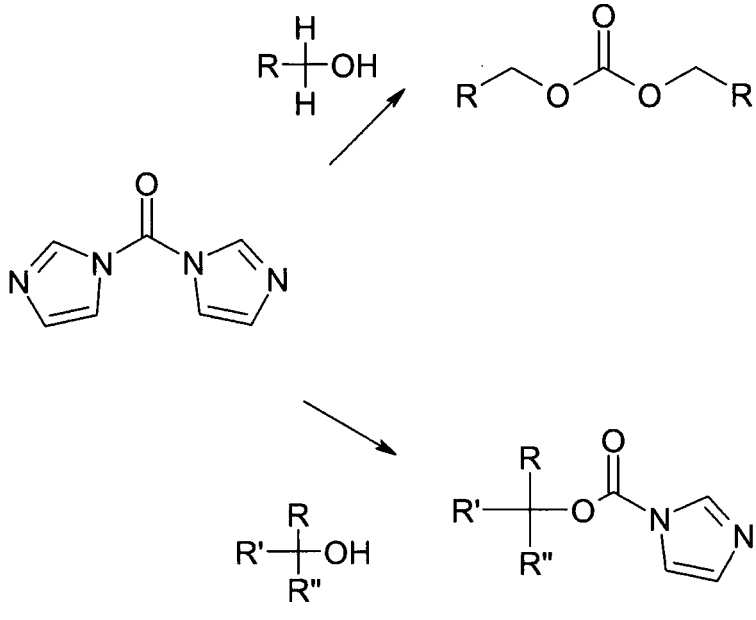


Figure 2.13 – Comparison of reaction of the CDI with primary and tertiary alcohols.

With t-butanol, t-butyl imidazole-N-carboxylate is the final product, which will undergo nucleophilic substitution by primary amines to form a carbamate. This reaction has been suggested as a method of introducing the Boc protecting group to amino acids[17] and has subsequently been shown to occur exclusively at primary amines, with no evidence for formation of carbamates with secondary amines.[18] This remarkable selectivity means that if t-butyl imidazole-N-carboxylate is introduced to a solution of a triamine Boc protection will only occur at the primary amines, whilst secondary amines remain unprotected. In practice it has proved to be more convenient to carry out this process as a one-pot procedure. The t-butyl imidazole-N-carboxylate is formed in solution with the triamine being added subsequently, (Figure 2.14).

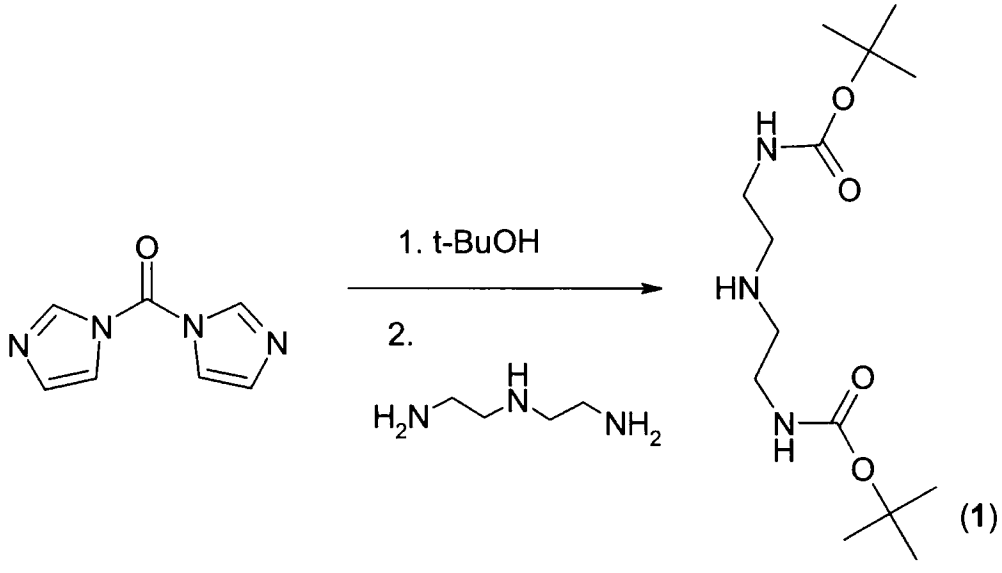



Figure 2.14 – The use of CDI to selectively introduce the Boc protecting group at the two primary amines of a triamine.

Using this simple procedure triamines could be Boc protected selectively at the primary functionalities in good yields without further purification.

### 2.4 – Functionalisation at the secondary amine

Conjugate addition is the addition of a nucleophile to an unsaturated system which is in conjugation with an electron withdrawing activating group. A conjugate acceptor must possess both an activating substituent and an unsaturated system.

Both activated alkenes and alkynes can be used as acceptors, with examples of activating groups (Y) including aldehyde, ketone, ester, nitro, sulfoxide and phosphonate, (Figure 2.15).


Figure 2.15 – The structure of conjugate acceptors.

The numbering system used to describe conjugate additions comes from early work on the addition to $\alpha,\beta$-unsaturated carbonyl systems, where the 1 position refers to the carbonyl oxygen and 4 to the $\beta$ carbon, (Figure 2.16). Although conjugate addition can occur at any site 2n atoms from the carbonyl carbon, the site two atoms distant (position 4) is by far the most common, with examples of 1,6 and 1,8 addition being much rarer.

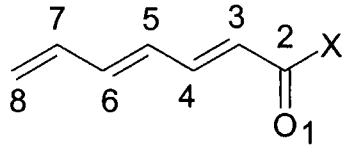



Figure 2.16 – The numbering of the positions in an unsaturated carbonyl system.

The mechanism of these additions is thought to be nucleophilic addition to the double bond to form a delocalised carbanion. Combination with an electrophile gives a neutral addition product, (Figure 2.17). This mechanism ensures that 1,4 addition occurs to the exclusion of 1,3 as the carbanion which would be produced by attack at the 3 position would not be stabilised by resonance.

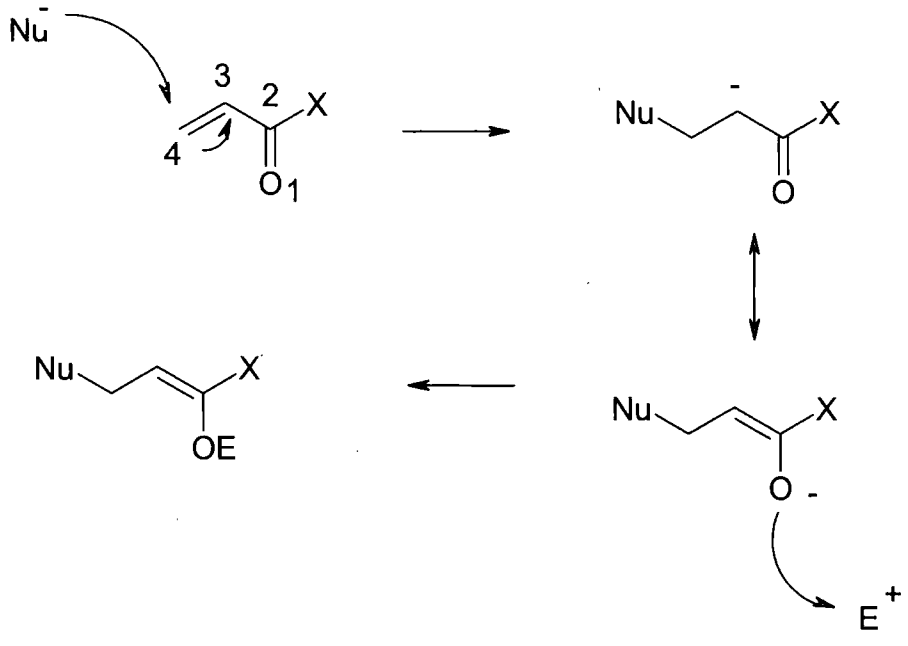



Figure 2.17 – Proposed mechanism of 1,4 conjugate addition.

The first conjugated addition was reported by Kommenos[19] however conjugate additions of carbon nucleophiles was popularised by Arthur Michael. He described work on the conjugate addition of sodium salts of malonates and ß-ketoesters to ethyl cinnamate, (Figure 2.18).[20,21]

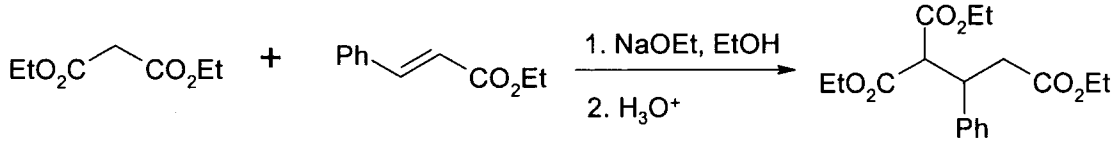



Figure 2.18 –The 1,4 conjugate additions of carbon nucleophiles reported by Michael.

Since this work many stabilised carbanions have been used in conjugate additions and such reactions are commonly termed Michael additions. Various types of nucleophile have been used in 1,4 conjugate additions with the use of heteroatom nucleophiles often being referred to as 'Michael-type' addition. The reaction of a nitrogen nucleophile in a conjugate addition is usually performed in solvent. Basic catalysis can be employed although the use of preformed nitrogen anions gives exclusively 1,2 addition. Both primary and secondary amines usually react readily without catalysis at room temperature and problems with over alkylation

are sometimes seen with extended heating. In this work the objective was to functionalise at the unprotected secondary amine of the diprotected triamine (**1**) using a 1,4 conjugate addition of this nucleophile to an acrylate. The addition of secondary amines to acrylates is well known, an early example being the addition of 2-methyl-3-methylamino propionic acid methyl ester to methyl acrylate, (Figure 2.19).[22]

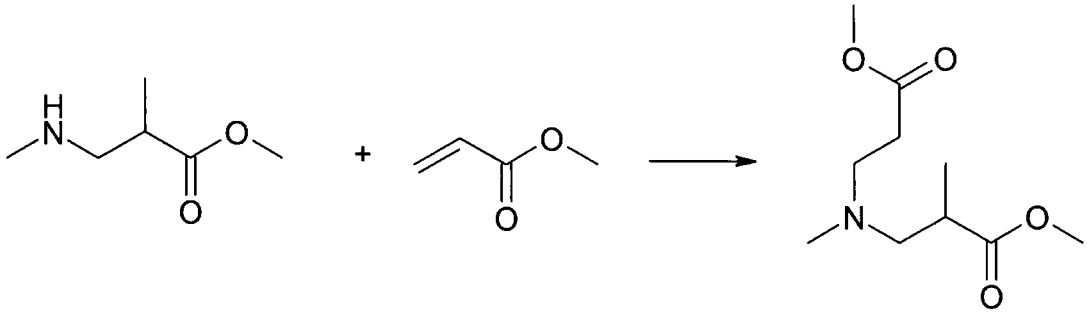


Figure 2.19 – Conjugate addition of a secondary amine to methyl acrylate.

The mechanism of this reaction appears to be 3,4 addition, however the reaction occurs through an enol intermediate which isomerises to form the final product, (Figure 2.20). The net result of the reaction is addition to the C=C double bond but the mechanism is 1,4 conjugate addition.

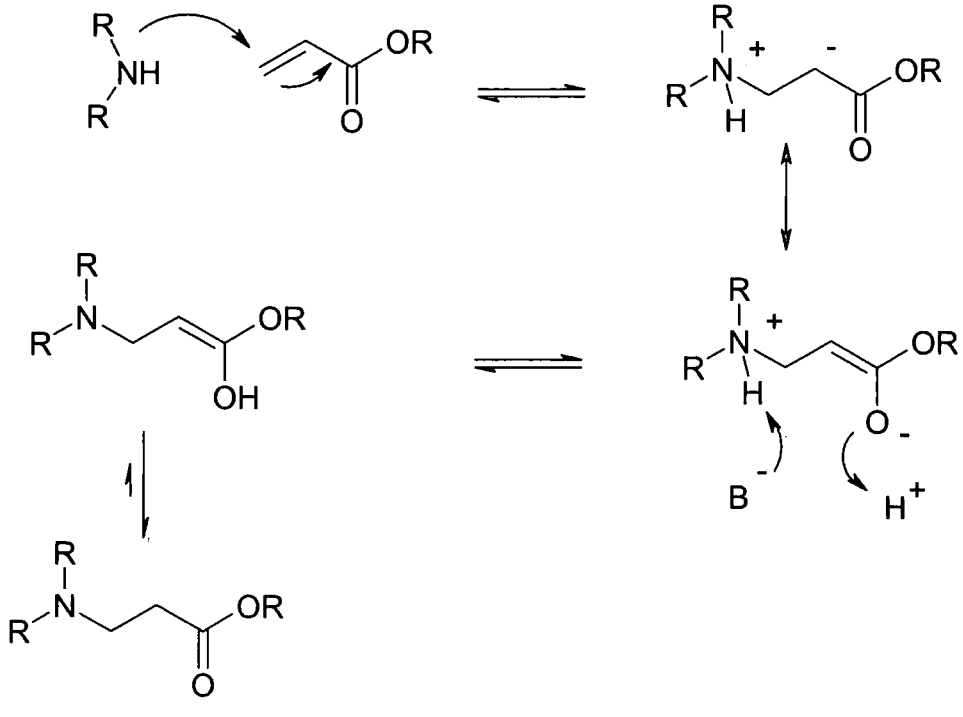


Figure 2.20 – Mechanism of 1,4 conjugate addition of a secondary amine to an acrylate.

The conjugate addition of the unprotected secondary amine to a range of acrylates was used to produce protected $AB_2$ monomers, (Figure 2.21).

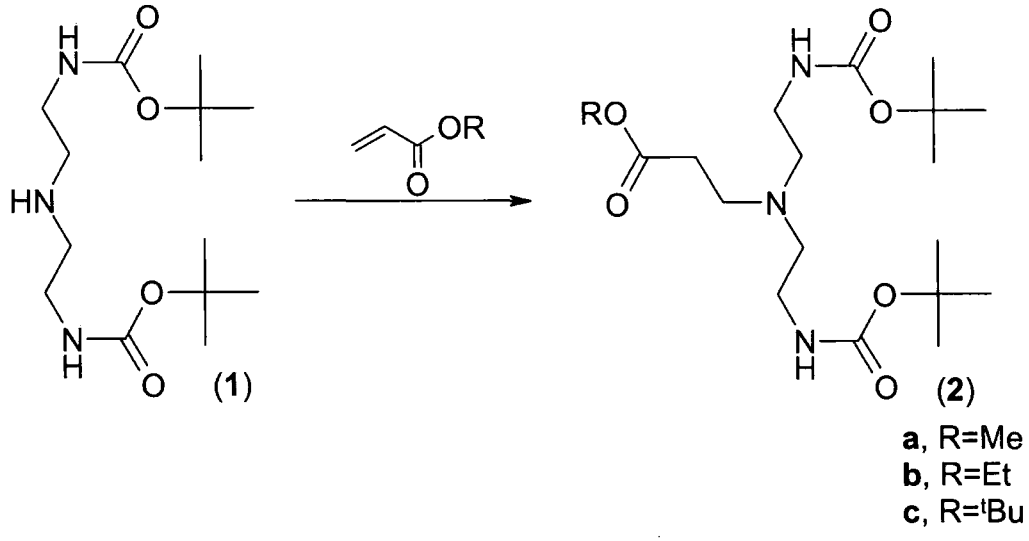



Figure 2.21 – Addition of diprotected triamine to an acrylate.

The reaction was carried with R as methyl, ethyl and t-butyl, to produce monomers with three different leaving groups. In the case of the acrylates of primary alcohols it was found to be necessary to use as a solvent an alcohol ROH which matched the functionality in the acrylate (R) to prevent formation of a product mixture by ester interchange. Heating caused formation of side products which were difficult to remove after synthesis and it was found to be preferable to use longer reaction times at lower temperatures. In all investigated systems the products were oils that had to be purified by column chromatography.

## 2.5 – Polymerisation attempts

The formation of an amide can be achieved via the acylation of amines with carboxylic esters, (Figure 2.22). This route to amides is less common than the use of acid chlorides and acid anhydrides but is mild and effective and is commonly used to form peptides from amino acids, usually using specially developed active esters.[23,24,25]

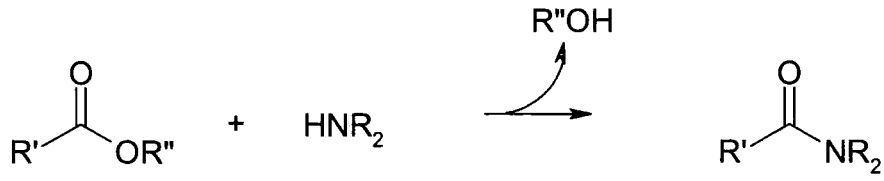



Figure 2.22 – Acylation of amines by carboxylic esters.

The reaction appears to be a nucleophilic substitution at the carbonyl, however there seems to be a wide variation in mechanism depending on the structure of the reactants, the reaction media and catalysis. Two pathways exist, the reaction proceeding either through a tetrahedral intermediate or via a synchronous displacement, (Figure 2.23).[26]

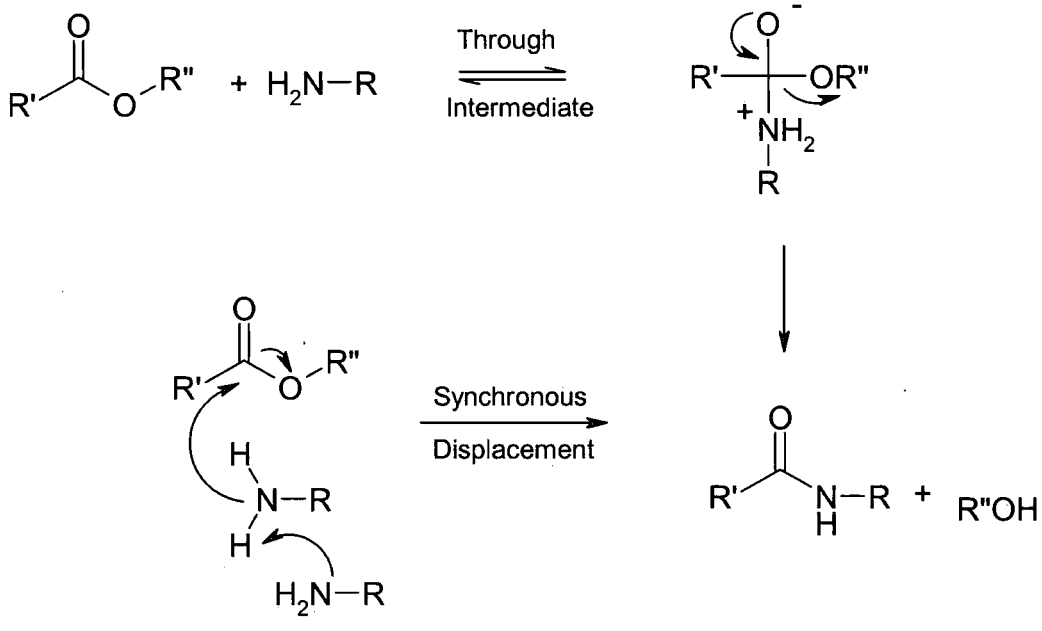



Figure 2.23 – The two mechanisms proposed for the acylation of amines by carboxylic esters.

The conditions necessary for the reaction to occur vary widely depending on the nature of the substrates. If the ester possesses electron withdrawing substituents and/or the amine is very nucleophilic the reaction may be fast, even at temperatures below ambient. With poorly nucleophilic amines the reaction can be very slow, even with heating. The reaction can be either base or acid catalysed,

although in basic conditions a proton donor is necessary to assist leaving group removal.

### 2.5.1 – Attempted polymerisation via 'free amine' monomers

Prior to their polymerisation via polyamidation the potential $AB_2$ monomers needed to be deprotected by removing the Boc groups from the two primary amines. The Boc groups can be cleaved by moderately strong acids via acidolysis, (Figure 2.11). The two most commonly used acids for this purpose are hydrochloric acid or trifluoroacetic acid the latter also being used as the reaction solvent. The neutral amines are usually recovered from the protonated salt products in one of two ways. With neutral amines that are preferentially soluble in organic solvents the aqueous phase can be neutralised with base and the deprotected amine extracted into an organic solvent. An alternative, which is useful for amines that are preferentially soluble in the aqueous phase is to use an ion-exchange resin to achieve the neutralisation and subsequently to remove the water.

Both techniques were attempted. Deprotection with a base followed by extraction into organic solvent proved unsuccessful, with all organic material remaining in the aqueous phase. Attempts at ion-exchange chromatography also proved unsuccessful. As this is an aqueous phase technique this cannot be due to lack of solubility and it is believed that the inability to recover the deprotected monomers from the column was due to their binding to the resin material. To prove this hypothesis a related monomer which had a chromophore attached at the potential A group was synthesised, (Figure 2.24). This was deprotected by acid hydrolysis and then introduced to the ion-exchange column its progress being monitored by observation of the progression of the bright yellow colour.

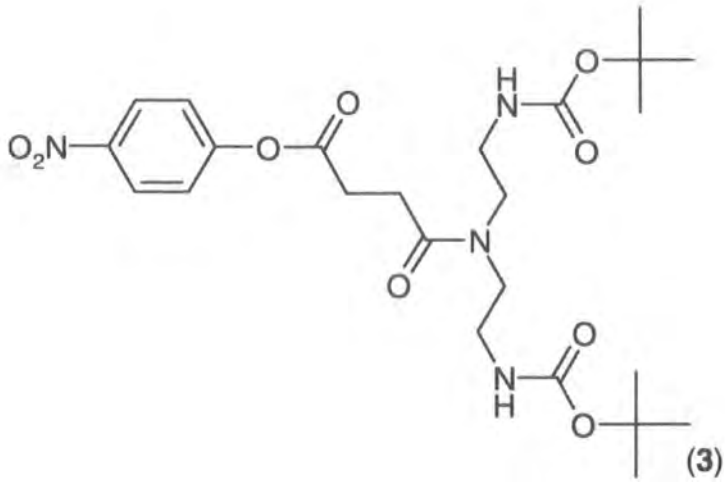



Figure 2.24 – An $AB_2$ monomer with a chromophore attached at the A group.

When this was introduced on to the column a yellow ring formed, which was not removed even on washing with a vast amount of water, (Figure 2.25). This suggested that the deprotected material was binding irreversibly to the column material.

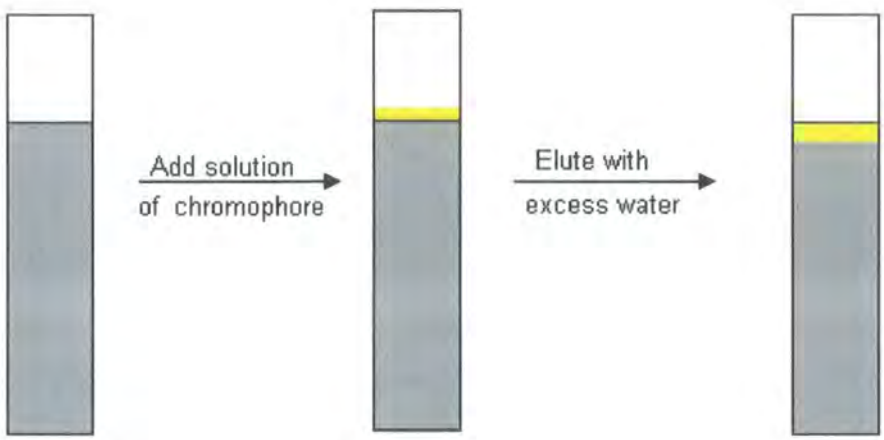



Figure 2.25 – Schematic view of the observations proving that the deprotected monomer with a chromophore attached bound irreversibly to the column material.

### 2.5.2 – Attempted polymerisation via ammonium salts

After the failed isolation of neutral monomers, polymerisation of the ammonium salts of the monomers was attempted following the precedent of earlier work.[4,5,6,7]

To allow this the hydrochloride and formate salts of the esters were prepared, (Figure 2.26).

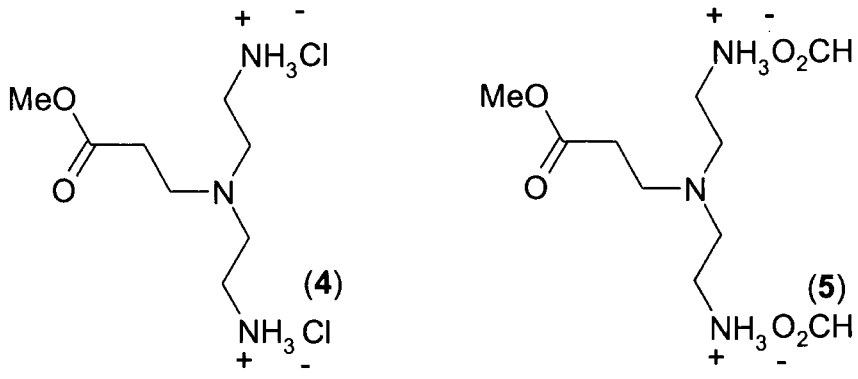



Figure 2.26 – The ammonium salts synthesised.

The salts were heated at a range of temperatures, both using a nitrogen purge and under vacuum. The hydrochloride salts formed intractable black solids under all conditions. Reduction in intensity of the ester peak was seen in the formate salts although only after prolonged heating. This method was not thought to be suitable for condensation polymerisation, which needs good yields to allow polymers of high molecular weight to be obtained and was abandoned without further study.

### 2.5.3 - *In situ* polymerisation via thermal deprotection

An alternative synthesis protocol was provided by the thermal instability of the Boc group. At high temperatures the t-butyloxycarbamate starts to decompose with the release of carbon dioxide and isobutene as in the case of acid deprotection.[27] At this elevated temperature, the amine and ester will undergo an amidation with the alcohol produced being lost by evaporation. This forces the equilibrium to the right hand side and allows the reaction to proceed to high yields, which results in polymer formation. A procedure similar to this has been used previously for the synthesis of polypeptides from N-Boc protected amino acid anhydrides.[28]

By thermogravimetric analysis it was shown that by holding a sample of the protected monomer at 230°C a weight loss equivalent to that for the Boc group decomposition occurs rapidly. A slower loss is then seen which is thought to represent the removal of the alcohol produced by condensation reactions. This result suggested that this approach had potential as a method of polymerisation.

The thermal removal of the Boc groups, followed by *in-situ* amidation in the bulk was investigated as a method of forming hyperbranched polymers. Isolation of the actual monomer is never accomplished in this procedure with protected $AB_2$ monomer undergoing concurrent deprotection and polymerisation in the same vessel. Polymer was formed for both the ethyl and methyl esters, although the t-butyl ester decomposed completely with no formation of polymeric product. Analysis of the materials produced via this method, (Chapter 5), showed that polymer had been successfully produced. The equipment used for this deprotection and polymerisation consisted of a one-piece reaction vessel, equipped with a nitrogen inlet and outlet, the outlet being attached to a cold-trap. Stirring was provided by an overhead mechanical stirrer and temperature controlled by a thermostated oil-bath, (Figure 2.27). Close control and full reproducibility of the polymerisation conditions could be achieved.

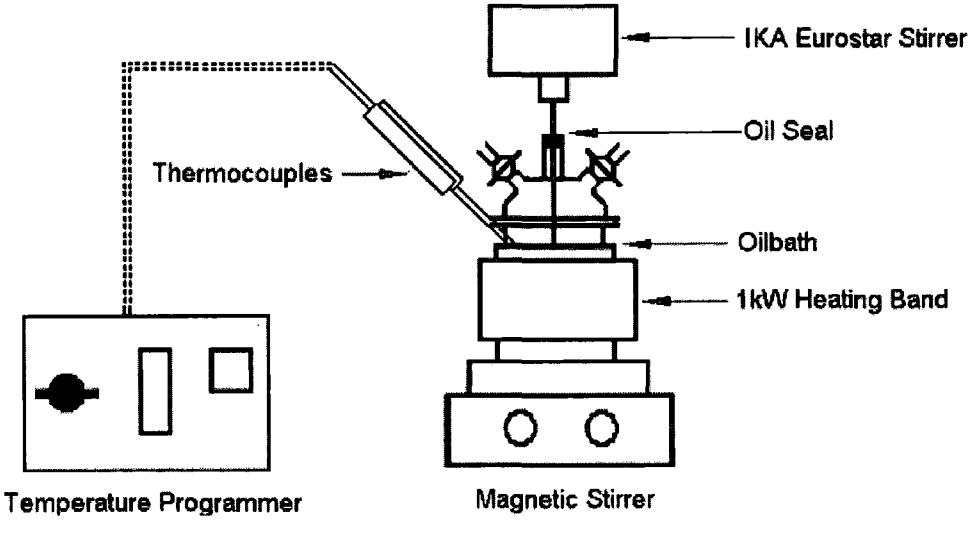



Figure 2.27 – Schematic view of the equipment used for the bulk polymerisations.[29]

The polymers produced were solids, which were fully water-soluble and could be recovered by dissolving in water and subsequent freeze-drying. The polymers were coloured, the intensity varying with the reaction duration from orange/yellow at short reaction times (low molecular weights) to dark brown at long reaction times.

## 2.6 – Strategy for the synthesis of half generation PAMAM analogues

Synthesis of analogues to the half-generations of PAMAM dendrimers requires a different approach. The end groups are esters, (Figure 2.2) and an $AB_2$ monomer with esters as the B groups is needed. To allow the synthesis of such a monomer a diamine was used as the starting material. The first step in the synthesis was to be the addition of a Boc protecting group to one of the two primary amine groups, (Figure 2.28).

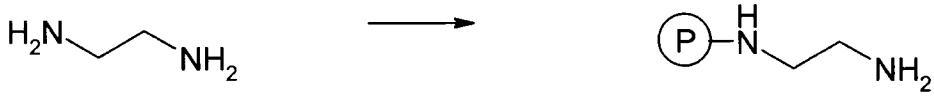



Figure 2.28 – Mono-protection of diamine with a protecting group, (P).

The unprotected primary amine then could undergo a double 1,4 conjugate addition with an acrylate to give the two ester groups for subsequent polyamidation, (Figure 2.29).

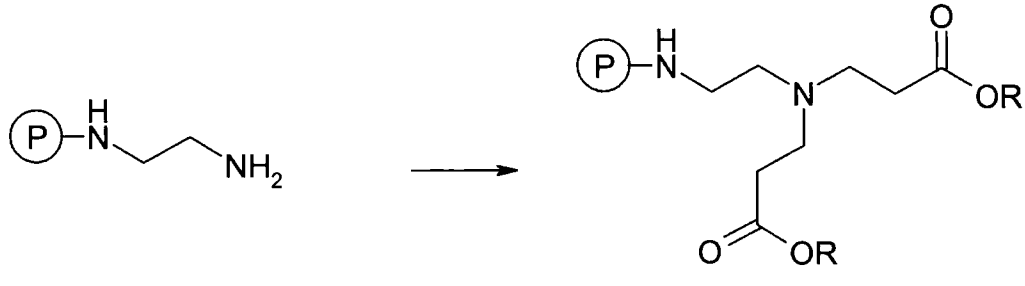



Figure 2.29 – Double 1,4 conjugate addition of a primary amine to an acrylate.

The protecting group was then to be removed, leaving an $AB_2$ monomer with an amine A group, and two ester B groups, (Figure 2.30).

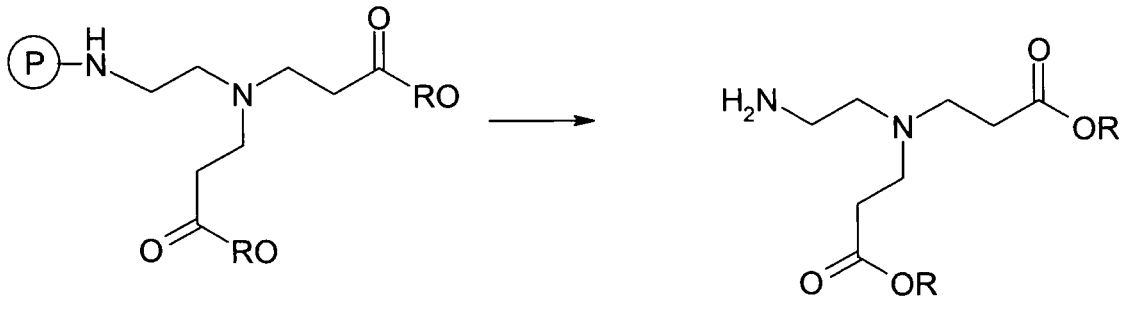



Figure 2.30 – Removal of the Boc protecting group, to give an $AB_2$ monomer.

The deprotected monomer was to be polymerised by amidation, as in the synthesis of the full generation analogues, (Figure 2.31). In this case the amine is the A group and the esters the B groups.

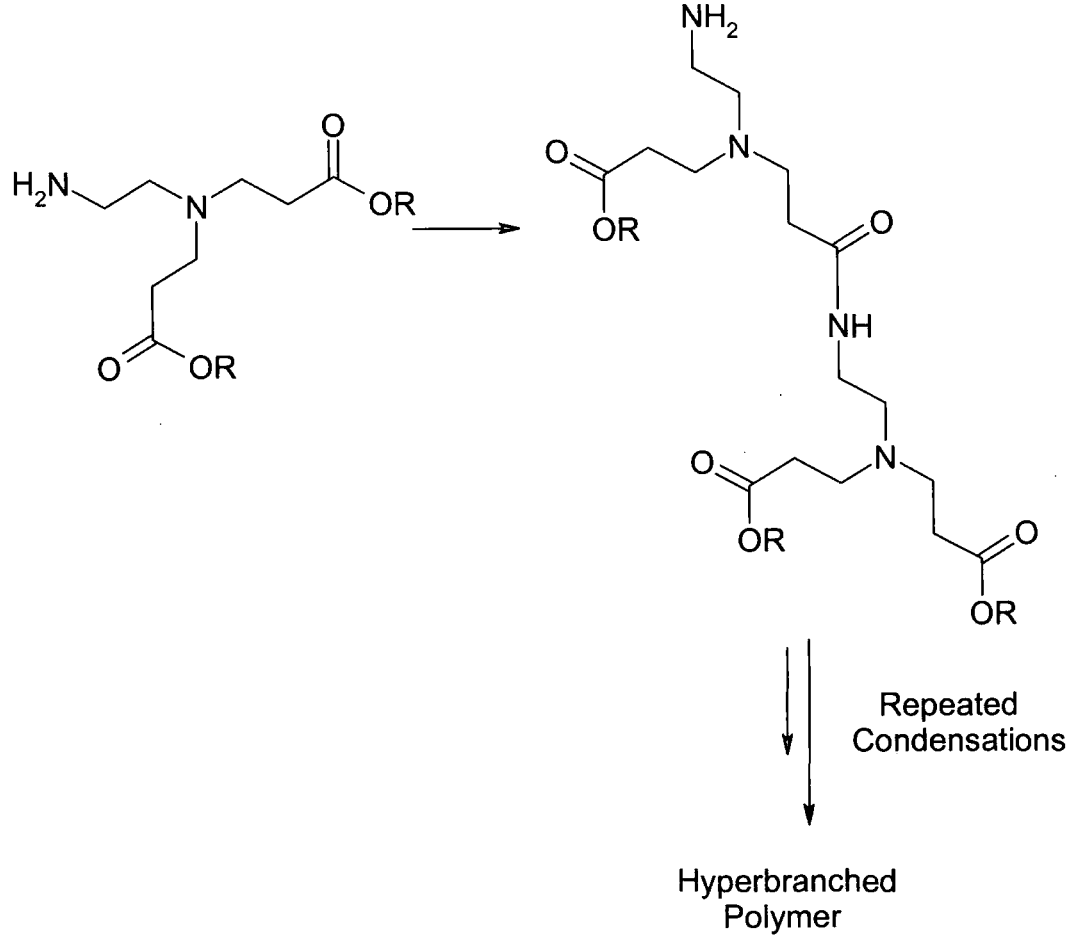



Figure 2.31 – Polymerisation of the $AB_2$ monomers leading to analogues of the half generation PAMAM dendrimers.

## 2.7 – Synthesis of the half-generation analogues

The protection of one amine of a symmetrical diamine requires a different approach to the protection of the two primary amines of a triamine. In this case there is no chance of utilising differential reactivity of the amines as the two amine groups of a symmetrical diamine are identical. Instead a large excess of the diamine was used with a high dilution of the reaction system and slow addition of the reagent needed to introduce the protecting group. Unlike the case of the selective protection using differential reactivity a mixture of the mono and diprotected amine are produced and must be separated. Due to the conditions adopted the amount of monoprotected diamine produced compared to the amount of diprotected diamine is maximised. Rather than using CDI and t-butanol to introduce the Boc protecting group di-tert-butyl dicarbonate was used, (Figure 2.32).[30] A literature precedent exists for use of this reagent[5] to introduce a single Boc group to a diamine. It reacts significantly faster with amines than t-butyl imidazole-N-carboxylate maximising the effect of the slow addition.

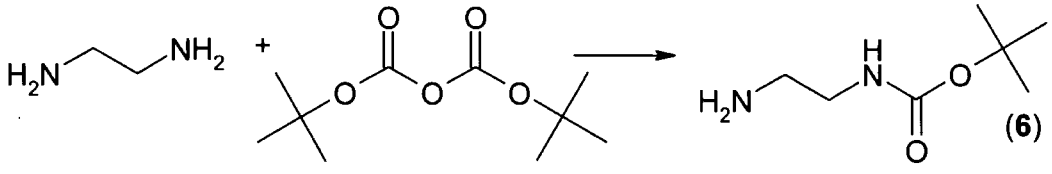



Figure 2.32 – Addition of a single Boc protecting group to ethylenediamine.

To add the two ester B groups a 1,4 conjugate addition similar to that used for production of the monomers for full generation analogues was adopted. Primary amines react in a conjugate addition to form a secondary amine as an intermediate product. The secondary amine is still nucleophilic and if the conjugate acceptor is in excess a second addition is possible forming a tertiary amine, (Figure 2.33).

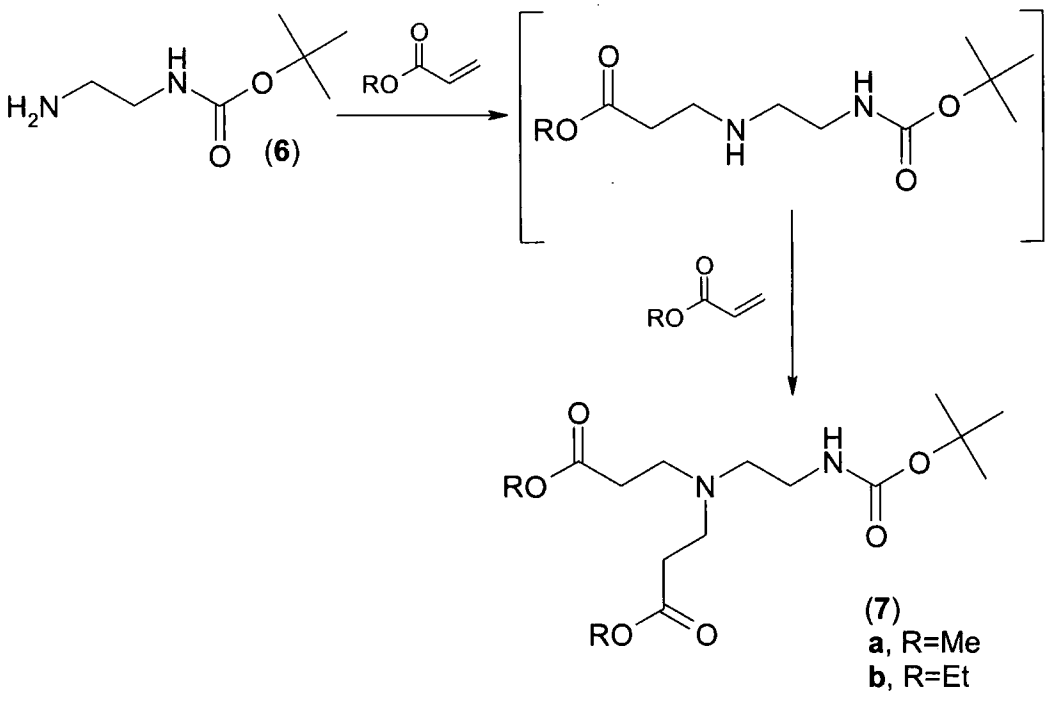



Figure 2.33 – The double 1,4 conjugate addition of a primary amine to an acrylate.

Following the successful synthesis of the full generation analogues via thermal deprotection and *in-situ* polymerisation this method was adopted for the formation of the half generation analogues. The Boc protecting groups were removed thermally to leave a primary amine that could react with the ester in an amidation reaction. The monomers were synthesised with both ethyl and methyl esters. The half-generation analogues produced were soluble in a wider range of solvents than the full generation analogues. In addition to the polar solvents (water, DMSO, DMF and alcohols) in which the full generation analogues are soluble, these materials are also soluble in less polar organic solvents such as chloroform, but insoluble in low polarity solvents such as THF and hydrocarbons.

## 2.8 - Conclusions

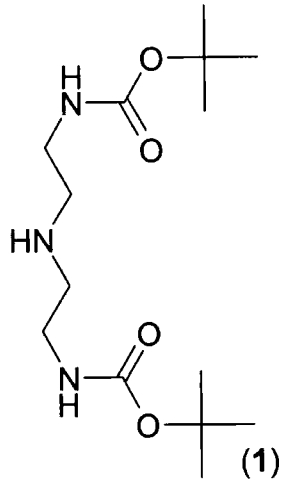
Full generation PAMAM dendrimers have amine end groups and repeat units which contain alternating amide and tertiary amine groups. To allow synthesis of hyperbranched analogues to the full generation dendrimers an $AB_2$ monomer

which has two amine B groups and a single ester A group has been synthesised. The half-generation PAMAM dendrimers have ester termini with alternating amide and tertiary amine groups in the repeat units. $AB_2$ monomers with a single amine A group and two ester B groups have been synthesised to allow production of hyperbranched analogues to the half generation dendrimers.

After difficulties with isolation of the deprotected monomers polymerisation was achieved via the thermal removal of the Boc protecting groups and *in situ* amidation. This allowed production of hyperbranched analogues to both the full and the half generations of the PAMAM dendrimers. The characterisation of these materials is described in chapter 5.

## 2.9 – Experimental

*[2-(2-tert-butoxycarbonylaminoethylamino)ethyl]carbamic acid tert-butyl ester,* (**1**). *(Alternative name – 1,7-bis (tert-butoxycarbonyl)diethylenetriamine)*

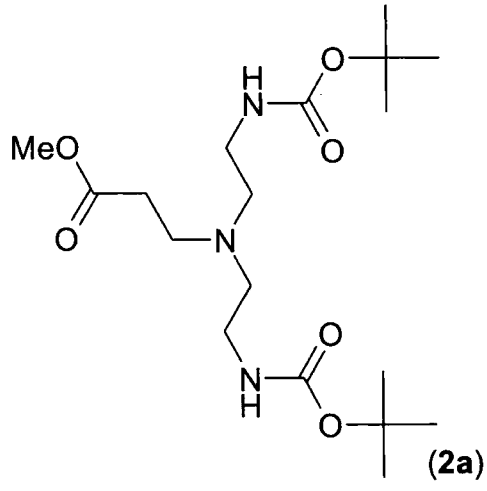



(**1**)

Carbonyl diimidazole (CDI) (72.63g), was added to a one litre three necked round bottomed flask, containing HPLC grade toluene (750mL), this was purged with dry nitrogen and heated to 60°C. To this was added potassium hydroxide (180mg), followed by t-butanol (67.64g). The solution was stirred at 60°C for four hours. After this time diethylenetriamine (DETA) (27.7g) was added, the solution was heated overnight, allowed to cool and the solvent removed *in vacuo*. The resultant oil was dissolved in dichloromethane (250 mL), and washed three

times with 150mL of water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent removed *in vacuo*. The resultant clear oil solidified on standing to give [2-(2-tert-butoxycarbonylaminoethylamino) ethyl]carbamic acid tert-butyl ester (**1**) as a white solid, (49.6g, 73.0%). Found; C, 55.16; H, 9.70; N, 13.55%; M/z (CI) 304 (H). $C_{14}H_{29}N_3O_4$ requires; C, 55.42; H, 9.63; N, 13.85%; M 303. $^1$H NMR: $\delta_H$ (200 MHz; $CDCl_3$) 1.44ppm (s, 18H), 2.72 (t, J=5.8Hz, 4H), 3.19 (m, 4H),[31] 4.94 (bs, 2H).[32] $^{13}$C NMR: $\delta_C$ (63 MHz; $CDCl_3$) 28.48ppm, 40.38, 48.88, 79.23, 156.27.

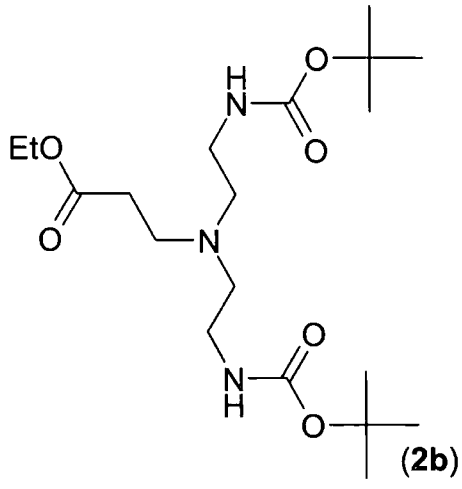
*3-[Bis-(2-tert-butoxycarbonylaminoethyl)amino] propionic acid methyl ester,* (**2a**)




(**2a**)

Compound (**1**), (20.05g) and methyl acrylate (10.52g), were added to a 500mL two necked round bottomed flask, containing methanol (250mL), this was placed in the dark at room temperature and allowed to stand for ten days. After this time the solvent was removed *in vacuo*. The resultant yellow oil was purified by column chromatography, with an eluant of 2:1 ethyl acetate:hexane, to give *3-[bis-(2-tert-butoxycarbonylaminoethyl)amino] propionic acid methyl ester* (**2a**) as a clear colourless oil, (18.7g, 72.6%). Found; C, 54.53; H, 8.96; N 10.57%; M/z (EI) 389. Calculated for $C_{18}H_{35}N_3O_6$: C, 55.51; H, 9.06; N, 10.79%; M 389. $^1$H NMR: $\delta_H$ (200 MHz; $CDCl_3$) 1.44ppm (s, 18H, $CH_3$), 2.44 (t, J=6.6Hz, 2H), 2.48 (t, J=6.0Hz, 4H) 2.74 (t, J=6.6Hz, 2H), 3.14 (m, 4H), 3.72 (s, 3H), 5.03 (bs, 2H). $^{13}$C NMR: $\delta_C$ (100 MHz; $CDCl_3$) 28.54ppm, 32.95, 38.30, 49.44, 51.86, 53.38, 79.18, 156.19, 173.61.

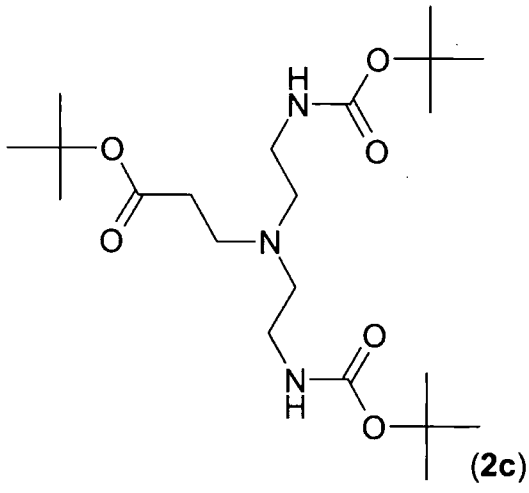
*3-[Bis-(2-tert-butoxycarbonylaminoethyl)amino] propionic acid ethyl ester,* (**2b**)




(**2b**)

Compound (**1**), (90g) and ethyl acrylate (44.5g) were placed into a round bottom flask in 500mL of ethanol. This was placed in the dark at room temperature and allowed to stand for ten days and then the solvent was removed *in vacuo*. The resultant pale yellow oil was purified by column chromatography on silica with an eluant of ethyl acetate, to give *3-[bis-(2-tert-butoxycarbonylaminoethyl)amino] propionic acid ethyl ester* (**2b**) as a clear oil, (91.2g, 76.2%). Found; C, 56.17; H, 9.32; N, 10.28 %; M/z (EI) 403. Calculated for $C_{19}H_{37}N_3O_6$; C, 56.55; H, 9.24; N, 10.41%; M 403. $^1$H NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.27ppm (t, J=7.1Hz, 3H), 1.45 (s, 18H), 2.43 (t, J=6.6Hz, 2H), 2.52 (t, J=5.8Hz, 4H) 2.75 (t, J=6.6Hz, 2H) 3.17 (m, 4H) 4.19 (q, J=7.1Hz, 2H) 5.03 (bs, 2H). $^{13}$C NMR: $\delta_C$ (50 MHz; $CDCl_3$) 14.43ppm, 28.52, 33.10, 38.40, 49.53, 53.55, 60.73, 79.18, 156.19, 173.07.

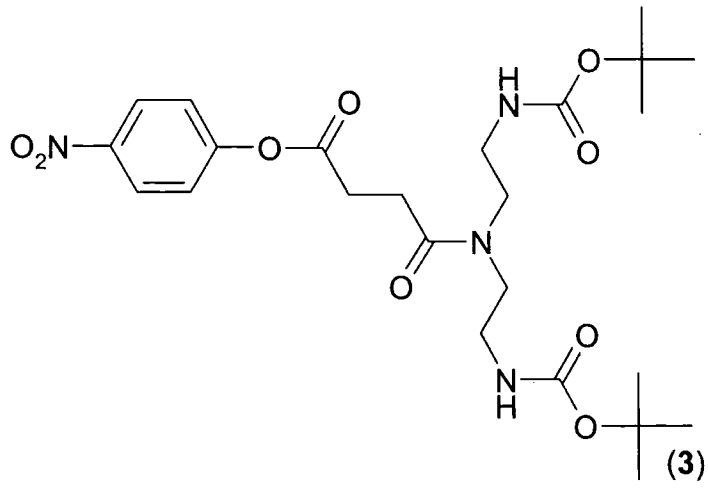
*3-[Bis-(2-tert-butoxycarbonylaminoethyl)amino]propionic acid tert-butyl ester,* (**2c**)




(**2c**)

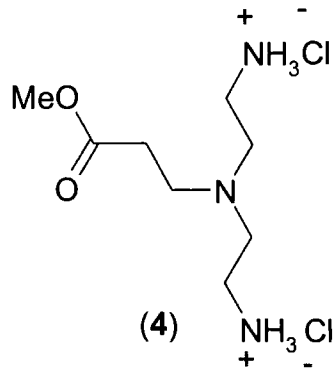
Compound (**1**), (5.05g), was added to a 50mL two necked round bottomed flask, containing HPLC grade methanol (25mL), this was put under a nitrogen atmosphere and heated to 50°C. To this was added t-butyl acrylate (2.73g). The solution was stirred at 50°C for three days. After this time the solvent was removed *in vacuo*. The resultant yellow oil was purified via column chromatography on silica with an eluant of 1:1 ethyl acetate:hexane, to give *3-[bis-(2-tert-butoxycarbonyl aminoethyl)amino]propionic acid tert-butyl ester* (**2c**) as a clear oil, which became a white solid on standing, (4.56g, 63.5%). Found; C, 58.16; H, 9.60; N, 9.46%; M/z (EI) 431. Calculated for $C_{21}H_{41}N_3O_6$; C, 58.44; H, 9.58; N, 9.74%; M 431. $^1$H NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.44ppm (s, 18H), 1.49 (s, 9H), 2.34 (t, J=6.6Hz, 2H), 2.50 (t, J=5.8Hz, 4H), 2.67 (t, J=6.6Hz, 2H), 3.18 (m, 4H), 5.06 (bs, 2H). $^{13}$C NMR: $\delta_C$ (63 MHz; $CDCl_3$) 28.26ppm, 28.52, 33.88, 38.23, 49.27, 53.41, 79.09, 80.28, 156.16, 172.45.

*N,N-Bis-(2-tert-butoxycarbonylaminoethyl)succinamic acid 4-nitrophenyl ester,* (**3**)



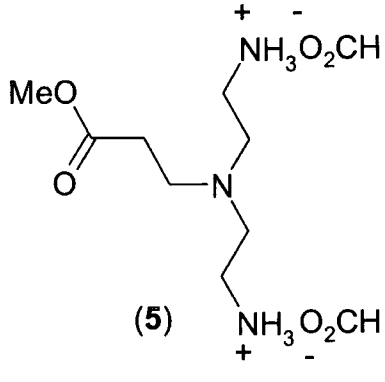

Following the literature procedure[33] compound (**8**), (synthesis described in section 3.7), (8.07g) and p-nitrophenol (2.78g) were dissolved in ethyl acetate (50mL) and cooled in an ice-water bath. Dicyclohexylcarbodiimide (4.09g) was added in a few portions through a powder funnel, which was then rinsed with a small amount of ethyl acetate. After about half an hour the reaction was allowed to warm to room temperature, and stirring was continued for two more hours. The N,N'-dicyclohexylurea by-product was removed by filtration, and washed with ethyl acetate. The filtrate and washings were combined, the solvent removed *in vacuo*, to give *N,N-Bis-(2-tert-butoxycarbonylaminoethyl)succinamic acid 4-nitrophenyl ester* (**3**) as a grey solid, (4.67g, 44.5%). $^1$H NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.43ppm (s, 18H), 2.80 (t, J=6.6Hz, 2H), 2.92 (t, J=6.6Hz, 2H), 3.30 (m, 4H), 3.49 (m, 4H), 5.07 (bs, 2H), 7.31 (d, J=9.3Hz, 2H) 8.26 (d, J=9.3Hz, 2H). This material was required for a simple test and was not purified or characterised further.

*3-[Bis(2-ammonium chloride ethyl)amino] propionic acid methyl ester,* (**4**)




Compound (**2a**), (10g) was placed in a 250mL one-necked round bottomed flask, and dissolved in ethyl acetate (50mL). To this 37% hydrochloric acid (25mL) was added. The solution was stirred at room temperature for three hours, and then the ethyl acetate and acid were removed *in vacuo* to give a light brown solid, which was purified by washing thoroughly with diethyl ether (3x50mL) to give 3-[bis(2-ammonium chloride ethyl)amino] propionic acid methyl ester (**4**) as a white solid, (6.77g, 88.3%). $^{1}$H NMR: $\delta_H$ (200 MHz; $D_2O$) 2.87 (t, J=6.4Hz, 2H), 2.77 (bs, 10H),[34] 3.73 (s, 3H). $^{13}$C NMR: $\delta_C$ (75 MHz; $D_2O$) 29.07ppm, 34.35, 49.67, 50.35, 53.01, 173.78.

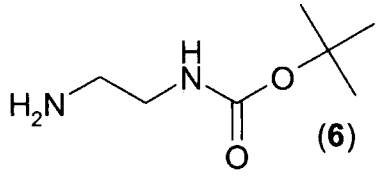
*3-[Bis(2-ammonium formate ethyl)amino] propionic acid methyl ester,* (**5**)




Compound (**2a**), (10g) was placed in a 250mL one-necked round bottomed flask, and formic acid (100mL) was added. The solution was stirred at room temperature for forty-eight hours, and then the formic acid was removed *in vacuo* to leave 3-[bis(2-ammonium formate ethyl)amino] propionic acid methyl ester (**5**) as a brown oil, (5.23g, 72.2%). $^{1}$H NMR: $\delta_H$ (200 MHz; $D_2O$) 2.57 (t, J=6.9Hz, 2H), 2.77 (t, J=6.0Hz, 4H), 2.82 (t, J=6.9Hz, 2H), 3.10 (t, J=6.0Hz, 4H), 3.69 (s,

3H), 8.43 (s, 2H). $^{13}C$ NMR: $\delta_C$ (75 MHz; $D_2O$) 30.71ppm, 36.81, 47.43, 50.08, 52.44, 169.09, 175.80.

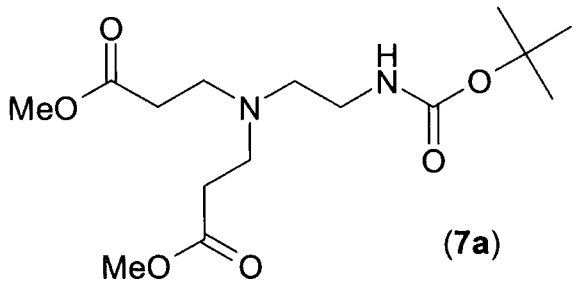
*(2-aminoethyl) carbamic acid tert-butyl ester, (**6**), (Alternative name – N-mono(t-butoxycarbonyl)ethylene diamine)*



(**6**)

Following the published procedure[5] ethylenediamine (75g) was added to a two litre round-bottom flask containing 500mL of dichloromethane and cooled in an ice bath to 0°C. To this was added dropwise a solution of di-tert-butyl dicarbonate (60g) in dichloromethane (250mL) over a period of two hours. The flask was allowed to warm to room temperature and then stirred overnight. The solvent was removed *in vacuo*, and addition of water (250mL) resulted in the precipitation of a white solid that was removed by filtration. The filtrate was saturated with sodium chloride and extracted with ethyl acetate (3x100mL). The organic fraction was collected and the solvent removed *in vacuo* to leave a colourless oil, which was dissolved in chloroform and filtered to remove excess sodium chloride. The solvent was again removed *in vacuo* to give (2-aminoethyl) carbamic acid tert-butyl ester (**6**) as a colourless oil, (27.6g, 62.7%). Found M/z ($ES^+$) 161 (H), 183 (Na). $C_7H_{16}N_2O_2$ requires M 160. $^1H$ NMR: $\delta_H$ (200 MHz; $CDCl_3$) 1.25ppm (s, 2H), 1.44 (s, 9H), 2.79 (t, J=5.8Hz, 2H), 3.17(m, 2H), 4.90 (bs, 1H). $^{13}C$ NMR: $\delta_C$ (75 MHz; $CDCl_3$) 28.39ppm, 41.84, 43.38, 79.04, 156.27. These spectroscopic data were in good agreement with the literature data, the compound is extremely hygroscopic.

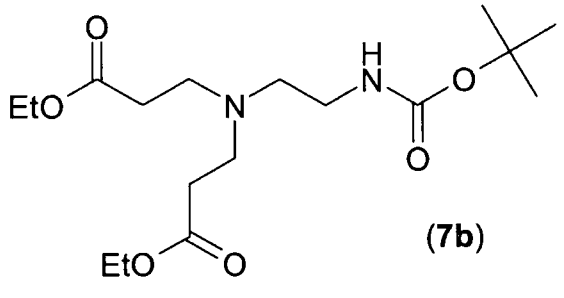
*3-[(2-tert-butoxycarbonylaminoethyl)-(2-methoxycarbonylethyl)amino] propionic acid methyl ester,* (**7a**)




(**7a**)

Compound (**6**), (14.24g) and methyl acrylate (23.2g) were placed in a round bottom flask containing 250mL of methanol. This was placed in the dark at room temperature and allowed to stand for ten days and then the solvent was removed *in vacuo*. The resultant pale yellow oil was purified by column chromatography on silica with an eluant of ethyl acetate to give *3-[(2-tert-butoxycarbonylaminoethyl)-(2-methoxycarbonylethyl)amino] propionic acid methyl ester* (**7a**) as a clear oil, (23.8g, 80.6%). Found; C, 53.90; H, 8.55; N, 8.33%; M/z (EI) 332. Calculated for $C_{15}H_{28}N_2O_6$; C, 54.20; H, 8.49; N, 8.43%; M 332. $^1$H NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.45ppm (s, 9H), 2.43 (t, J=6.6Hz, 4H), 2.50 (t, J=5.7Hz, 2H), 2.74 (t, J=6.6Hz, 4H), 3.17 (m, 2H), 3.68 (s, 6H), 5.10 (bs, 1H). $^{13}$C NMR: $\delta_C$ (50 MHz; $CDCl_3$) 28.56ppm, 32.76, 38.18, 49.29, 51.71, 53.19, 79.00, 156.22, 173.09. At the time of synthesis this was a new compound, however it has since been synthesised as an intermediate in a multi-step synthesis, but no characterisation data was reported.[35]

*3-[(2-tert-butoxycarbonylaminoethyl)-(2-ethoxycarbonylethyl)amino] propionic acid ethyl ester,* (**7b**)




(**7b**)

Compound (**6**), (10.25g) and ethyl acrylate (19.2g) were placed in a round bottom flask containing 250mL of ethanol. This was placed in the dark at room temperature and allowed to stand for ten days and then the solvent was removed *in vacuo*. The resultant pale yellow oil was purified by column chromatography on silica with an eluant of ethyl acetate to give *3-[(2-tert-butoxycarbonylamino ethyl)-(2-ethoxy carbonylethyl)amino] propionic acid ethyl ester* (**7b**) as a clear oil (17.5g, 75.9%). Found; C, 56.10; H, 8.97; N, 7.62%; M/z ($ES^+$) 361(H), 383(Na). Calculated for $C_{17}H_{32}O_6N_2$; C, 56.65; H, 8.95; N 7.77%; M 360. $^1H$ NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.26ppm (t, J=7.2Hz, 6H), 1.44 (s, 9H), 2.43 (t, J=6.6Hz, 4H), 2.52 (t, J=5.7Hz, 2H), 2.75 (t, J=6.6Hz, 4H), 3.17 (m, 2H), 4.14 (q, J=7.2Hz, 4H), 5.08 (bs, 1H). $^{13}C$ NMR: $\delta_C$ (50 MHz; $CDCl_3$) 14.38ppm, 28.56, 32.89, 38.22, 49.26, 53.25, 60.60, 79.00, 156.21, 172.68.

*Bulk polymerisation*

All polymerisations followed the same basic procedure, an example of which is given here. To the polymerisation vessel fitted with an overhead stirrer, an inlet for nitrogen, and an outlet fitted with a cold trap was added (**2a**) (6.24g). The flask was purged with nitrogen, and then heated to 230°C at a ramp of 10°C per minute and this temperature was maintained for 0.5-168 hours in a series of experiments. Throughout the polymerisation a constant stream of nitrogen was passed through the apparatus. After polymerisation the flask was allowed to cool, and the entire contents dissolved in water. The water was removed by freeze-drying to yield the polymer as an orange/brown solid which was stored in a vacuum dessicator.

## 2.10 – References


1 - Tomalia, D. A.; Baker, H., Dewald, J. R.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J. (Tokyo)* **1985**, *17*, 117.

2 - Eichman, J. D.; Bielinska, A. U.; Kukowska-Latallo, J. F.; Baker, Jr., J. R. *Pharm. Sci. Tech. Today* **2000**, *3*, 232.

3 - Esfand, R.; Tomalia, D. A. *Drug Discovery Today* **2001**, *6*, 427.

4 - Hobson, L. J.; Kenwright, A. M.; Feast, W. J. *Chem. Commun.* 1997, 1877.

5 - Hobson, L. J.; Feast, W. J. *Polymer* **1999**, *40*, 1279. (see correction *Polymer* **1999**, *40*, 2873).

6 - Hobson, L. J.; Feast, W. J. *Chem. Commun.* **1997**, 2067.

7 - Hobson, L. J.; Feast, W. J. *J. Mater. Chem.* **2000**, *10*, 609.

8 - Bayoudh, S.; Laschewsky, A.; Wischerhoff, E. *Colloid Poly. Sci.* **1999**, *277*, 519.

9 - Carpino, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 98.

10 - McKay, F. C.; Albertson, N. F. *J. Am. Chem. Soc.* **1957**, *79*, 4686.

11 - Anderson, G. W.; McGregor, A. C. *J. Am. Chem. Soc.* **1957**, *79*, 6180.

12 - Bodansky, M. in *Principles of Peptide Synthesis*, pp. 90-94, Springer-Verlag, Berlin Heidelberg, 1984.

13 - Greene, T.W.; Wuts, P. G. M. in *Protective Groups In Organic Synthesis.* pp. 327-330 John Wiley & Sons Inc. New York, 1991.

14 - Staab, H. A. *Liebigs Ann. Chem.* **1957**, *609*, 75.

15 - Staab, H. A.; Wendel, K. *Chem. Ber.* **1963**, *96*, 3374.

16 - Staab, H. A.; Seel, G. *Liebigs Ann. Chem.* **1958**, *612*, 187.

17 - Klee, W.; Brenner, W. *Helv. Chim. Acta.* **1961**, *44*, 2151.

18 - Rannard, S. P.; Davis, N. J. *Org. Lett.* **2000**, *2*, 2117.

19 - Komnenos, T. *Liebigs Ann. Chem.* **1883**, ***218***, 145.

20 - Michael, A. *J. Prakt. Chem.* **1887**, *3*, 349.

21 - Michael, A. *Am. Chem. J.* **1887**, *9*, 112.

22 - Howton, D. R. *J. Org. Chem.* **1945**, *10*, 277.

23 - Bodansky, M. *Nature* **1955**, *175*, 685.

24 - Pless, J.; Boissonas, R. A. *Helv. Chim. Acta.* **1963**, *46*, 1609.

25 - Anderson, G. W.; Zimmerman, J. E.; Callahan, J. *J. Am. Chem. Soc.* **1963**, *85*, 3039.

26 - For a discussion of the mechanism see Satchell, D. P. N.; Satchell, R. S. in *The Chemistry of Carboxylic Acids and Esters.* Ed. Patai, S. pp.410-425 Wiley: New York, 1969.

27 - Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

28 - Munegumi, T.; Meng, Y-Q.; Harada, K. *Chem. Lett.* **1988**, 1643.

29 - Diagram reproduced with permission from Parker, D. PhD thesis, University of Durham, 2000.

30 - Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Nat. Acad. Sci. (USA)* **1972**, *69*, 730.

31 - In all the species reported here a complex multiplet was seen for a $CH_2$ group adjacent to the amide bond of the Boc protecting group. This could be due to coupling to the amide hydrogen, and/or effects of cis/trans isomerism about the amide bond. Throughout this work, no attempt has been made to report multiplicity or coupling constants for these peaks, and they are reported as multiplets, (m).

32 - The peaks for the amide hydrogen, NH, are seen to be broad signals, which has been indicated by the abbreviation (bs).

33 - Bodansky, M.; Bodansky, A. in *Practice of Peptide Synthesis*, p. 114, Springer-Verlag, Berlin Heidelberg, 1984.

34 - It was observed that five $CH_2$ signals fell at approximately the same frequency, leading to a broad peak being seen.

35 - Martin, I. K.; Twyman, L. J. *Tett. Lett.* **2001**, *42*, 1119.

# Chapter Three

# Synthesis of hyperbranched polyamides

## Chapter Three – Synthesis of hyperbranched polyamides

### 3.1 – An introduction to linear polyamides

Polyamides are a class of polymer where the constituent units of the main polymer chain are held together by amide bonds. They exist both in nature, polypeptides are natural polyamides, and are a well-established synthetic class. Synthetic linear polyamides are most commonly produced by condensation polymerisation, either from a 1:1 mixture of diacids and diamines ($A_2/B_2$ system) or by condensation of a monomer containing both an amine and an acid (an AB monomer). They can also be synthesised by addition polymerisation via the ring-opening of cyclic lactams.

The study of synthetic polyamides (Nylons) began with the work of Carothers[1] and the first commercial synthetic polyamide, Nylon 6,6 (Figure 3.1), went on general sale in 1939, the major application being in hosiery. After the second world war the production and use of synthetic Nylons became widespread with a wide range of different materials possessing different properties being developed.

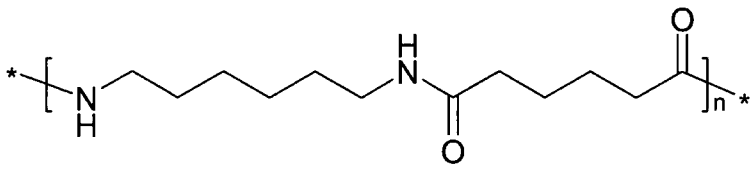


Figure 3.1 – The structure of Nylon 6,6.

The aromatic polyamides were developed after the aliphatic polyamides and are polymers containing amide linkages between two aromatic rings. These polymers cannot be produced by direct condensation of diacids and diamines due to the lower nucleophilicity of aromatic amines. Instead they are produced either by using a coupling reagent[2,3] or by reaction of the diacid chloride and diamine. Due to the unusual properties of aromatic polyamides they have been given the generic term aramids. Depending on the structure of the repeat units these properties often include heat and flame resistance, high tensile strength and resistance to chemicals and to radiation. They are produced commercially, for example Nomex is used in the manufacture of industrial components such as high-temperature filters and protective

clothing and Kevlar, which has a fibre strength greater than steel is used in applications such as bullet-proof vests, (Figure 3.2).

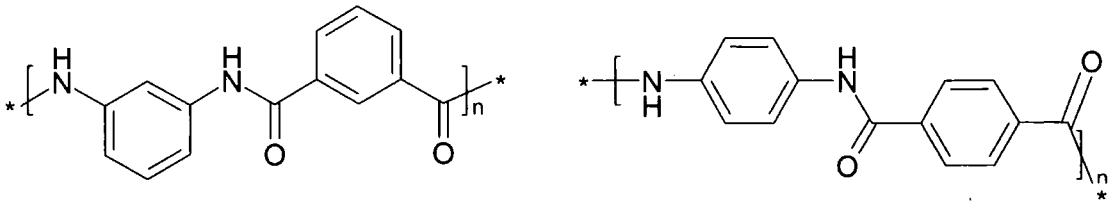


Figure 3.2 – Nomex (left) and Kevlar (right).

### 3.2 - Hyperbranched polyamides

Hyperbranched aramids are very interesting as they retain the excellent heat and flame resistance of the linear homologues coupled with an easier processability due to their higher solubility. This has obvious commercial potential as they may offer an alternative in some applications to the difficult to produce linear aramids that are currently employed. Due to this potential some of the pioneering work in the field of hyperbranched polymers was in the synthesis of hyperbranched aramids. Initially hyperbranched polymers possessing repeat units, (Figure 3.3), that were analogous to those of Kevlar and Nomex were investigated.

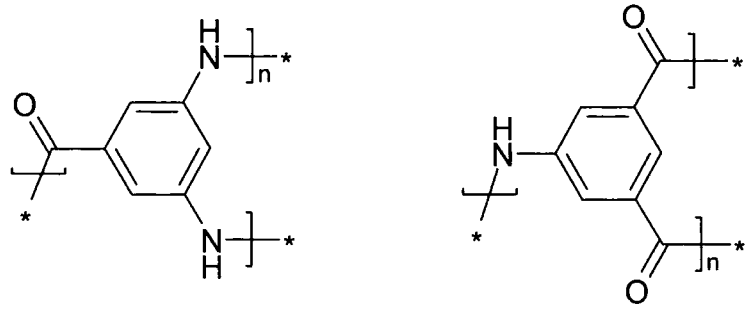


Figure 3.3 - Repeat units of the first hyperbranched aramids that were synthesised.

The first synthesis was from $AB_2$ monomers that were either sulfinyl amino acid chlorides or amino acid hydrochlorides, (Figure 3.4).[4,5,6] These were polymerised to give fully aromatic hyperbranched polyamides with either amine, acid or ester groups

at the surface. The polymers were soluble in amide solvents, whilst the synthesis of the dendrimer equivalents of these hyperbranched polymers had previously proven difficult due to the insolubility of the oligomeric intermediates.[7]

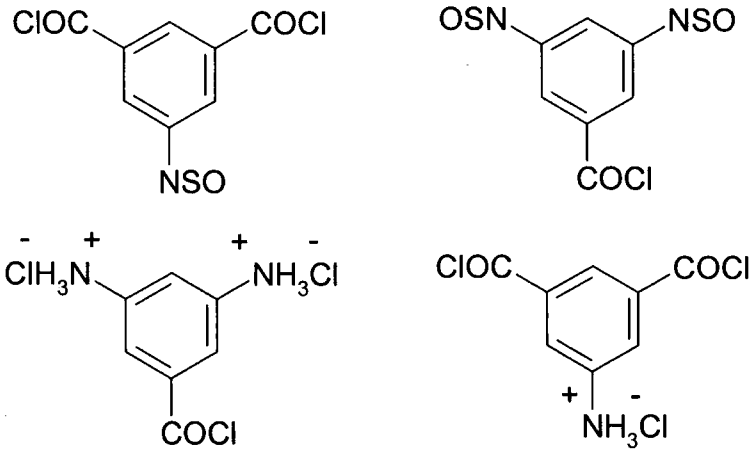



Figure 3.4 – The sulfinyl amino acid chlorides and amino acid hydrochlorides monomers used to produce hyperbranched aramids.

Alternative routes to the same branched aramid structure have since been reported. The palladium catalysed carbonylation of 3,5-dibromoaniline has been used to produce the hyperbranched polymer with bromine (rather than acid or amine) end groups.[8] These polymers were insoluble in all common solvents but solubility in dimethylsulfoxide (DMSO), dimethylformamide (DMF) and dimethylacetamide (DMAc) could be induced by using a core molecule of tetraphenyladamantane. The thermal polymerisation of an amine and an acid to give a hyperbranched polymer is possible with an $AB_2$ monomer with a single acid A group and two amine B groups being polymerised at 235°C under vacuum.[9,10]

To allow synthesis under milder conditions a condensing agent may be employed. 2,3-dihydro-2-thioxo-3-benzoxazolyl phosphonate (DBOP), (Figure 3.5), has been utilised to produce a hyperbranched aramid with an active amide surface,[11] which could be reacted with other amines to introduce different functionalities at the surface.

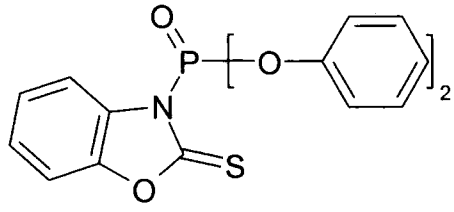


Figure 3.5 – 2,3-Dihydro-2-thioxo-3-benzoxazolyl) phosphonate.

Alternative methods of synthesis using condensing agents have been reported. Activation by triphenyl phosphite and pyridine (a modified Higashi method which had been used previously for the synthesis of linear aramids[12,13]) of 5-(4-aminobenzoylamino) isophthalic acid and 5-(4-aminobenzamido) isophthalic acid, (Figure 3.6), has been used to produce aramids with a slightly different structures.[14,15]

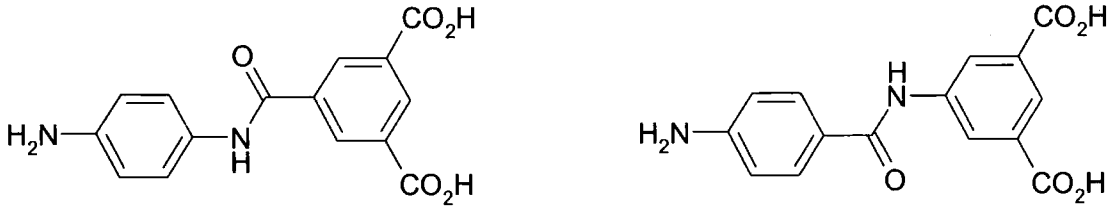


Figure 3.6 – The $AB_2$ monomers used for aramid synthesis by a modified Higashi method.

This method has also been used with the $A_2/B_3$ technique where only the soluble fraction of the material produced is analysed.[16] The materials that were synthesised had their structures characterised in detail using $^1H$ and $^{13}C$ NMR spectroscopy,[17] and the effects of varying the ratio of $A_2$ to $B_3$ were reported.[18] The polymers have been utilised as solid supports for immobilising amylase.[19]

The triphenyl phosphite and pyridine system has been independently investigated elsewhere for the synthesis of hyperbranched aramids. The polymerisation of a mixture of $AB_2$ and AB monomers[20,21] and $AB_4$ and $AB_8$ monomers[22] have been reported in addition to further studies using the $A_2/B_3$ methodology.[23] A comparison between the polymers made by the $AB_2$ and $A_2/B_3$ methods showed highly branched

multifunctional materials had been produced in each case, although the polymers from the $A_2/B_3$ method showed higher inherent viscosities.[24]

In addition to aramids the production of wholly aromatic polyesteramides has also been reported. Silylated monomers were used in the syntheses, avoiding the presence of acids and significantly reducing the risk of acid catalysed side reactions which can cause cross-linking. Two different $AB_2$ monomers[25,26] were investigated, along with an $AB_4$[27] and a congested $AB_3$ monomer.[28]

The synthesis of a series of aliphatic-aromatic polyetheramide hyperbranched polymers by two distinct methods has been reported, (Figure 3.7). In the first the thermal removal of a butyloxycarbonyl protecting group followed by amide formation with methanol liberation was used,[29] a procedure similar to that utilised in the work reported here. Subsequently the synthesis of the same polymers by the ring opening of 2-oxazoline containing monomers has been reported.[30,31,32] The polymers from the ring opening reactions have a phenolic surface, whilst those from the thermal removal of Boc have a methyl ester surface. The major reported advantage of the 2-oxazoline technique was the occurrence of a lower proportion of side reactions.

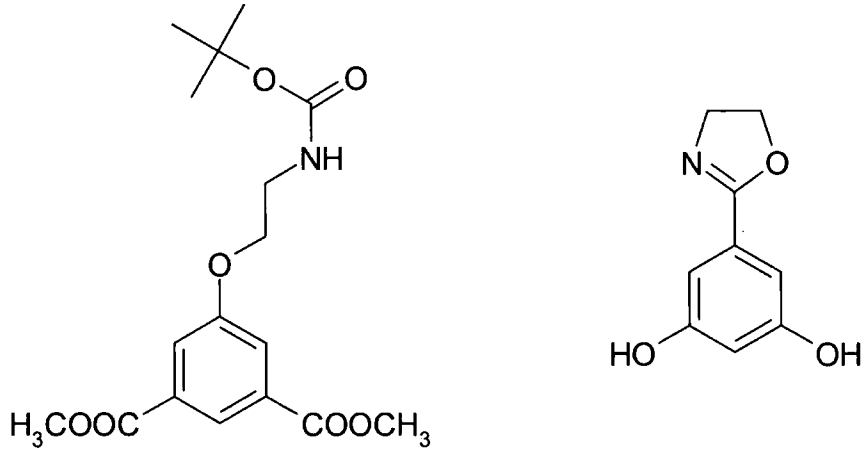



Figure 3.7 – The two alternative monomers used to synthesise aliphatic-aromatic hyperbranched poly(etheramides).

Recently a series of entirely aliphatic hyperbranched poly(esteramides) have been reported.[33] These have been synthesised using a pair of reagents of the type AA' and $BB'_2$, namely a cyclic carboxylic anhydride and diisopropanolamine. The amine from

diisopropanolamine should react selectively in the ring-opening as it is significantly more reactive than both the alcohol groups. This then forms a carboxylic acid equipped with two 2-hydroxypropylamide groups, in what is effectively an *in situ* formation of an $AB_2$ monomer, (Figure 3.8).

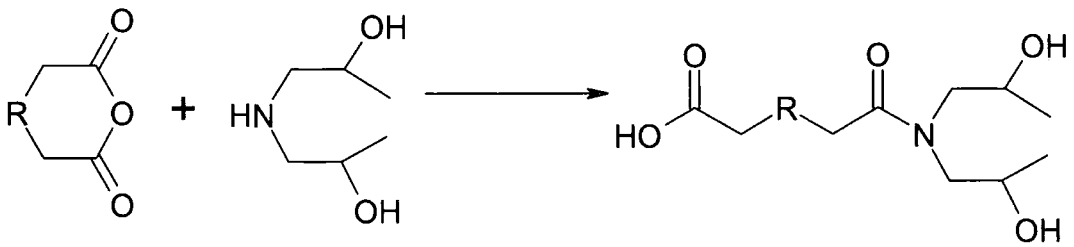



Figure 3.8 – Reaction of cyclic carboxylic anhydride with diisopropanolamine, leading to the *in situ* formation of an $AB_2$ monomer.

The temperature is then raised causing the single acid group and the two alcohol groups to undergo an esterification reaction and form a hyperbranched polymer. The mechanism of this reaction is very different to the normal addition-elimination esterification seen between alcohols and acids, instead it passes through an oxazolinium-carboxylate species, which undergoes a ring opening reaction via the carboxylate to yield the ester, (Figure 3.9).[34] This mechanism leads to a much faster esterification than would normally be expected for an alcohol and acid. The hyperbranched resins formed have been characterised fully by size exclusion chromatography (SEC), small angle neutron scattering (SANS)[35] and matrix assited laser desorption ionisation time of flight mass spectroscopy (MALDI-TOF MS).[36] A mono-carboxylic acid can be added to the polymerisation in different proportions. This is incorporated into the polymers through the esterification reactions and can act either as a chain stopper or as an end-group modifier.[37] In this way functionalised polymers have been formed.

These hyperbranched polyaminoesters are commercially available under the trade name Hybrane[38] and are produced with a variety of different surfaces. It has been suggested by the manufacturers that, with appropriate modification, they may find application in a variety of fields[39] with a number of potential coating applications already having been reported.[40]

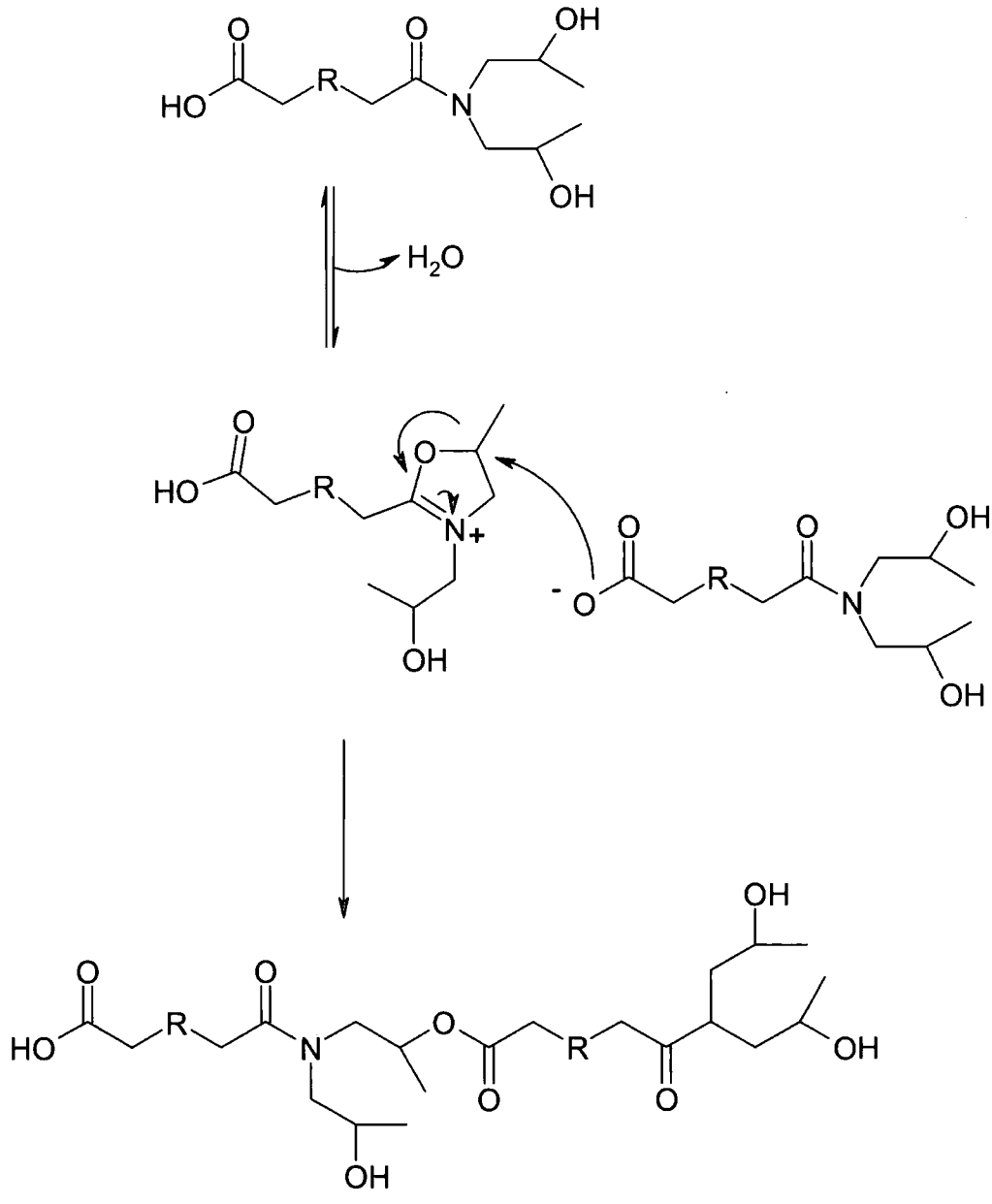



Figure 3.9 – Reaction mechanism for esterification of 2-hydroxyalkylamides.

### 3.3 - Synthetic strategy

It was hoped to develop a method for synthesis of aliphatic hyperbranched polyamides based on our previous method for synthesising aliphatic hyperbranched polyamidoamines, (Section 2.2). The diprotected triamine, (1) could be reacted with an alternative to acrylates, which rather than converting the unprotected secondary amine to a tertiary site eventually giving polyamidoamines, (Figure 3.10, (**a**)) would

form an amide at the secondary amine leading to a polyamide after polymerisation, (Figure 3.10, (**b**)). Two different monomers were investigated, amino acids and amino esters.

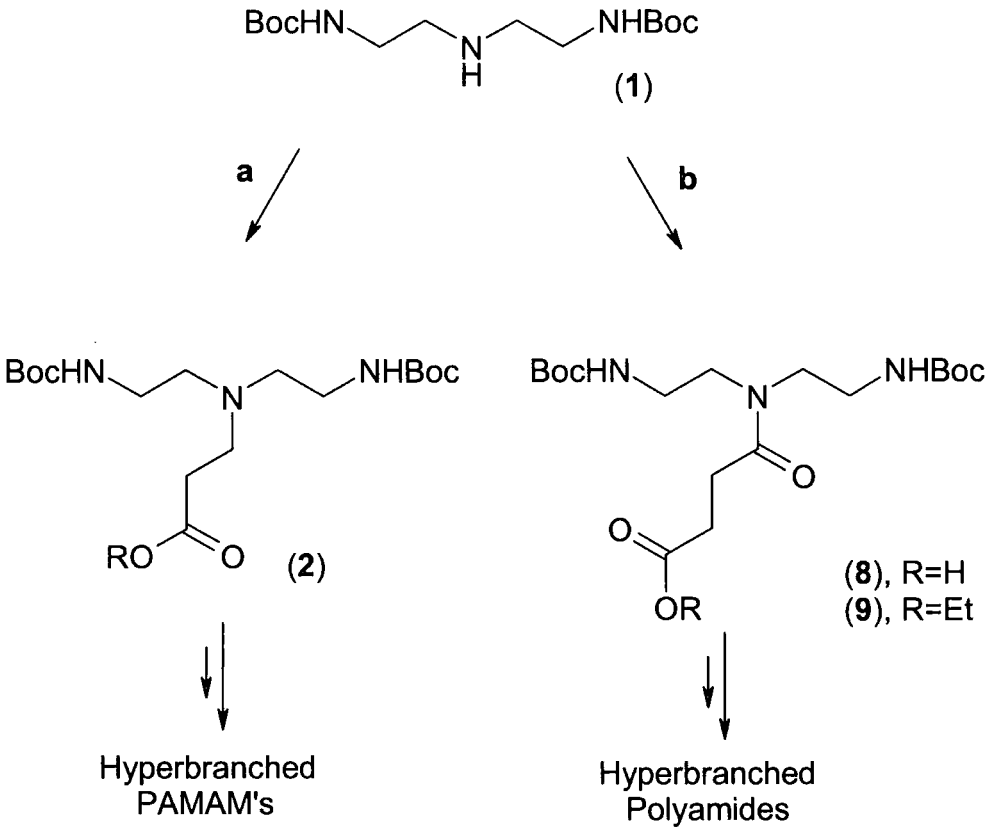



Figure 3.10 – The different monomers synthesised for the production of hyperbranched PAMAMs and for hyperbranched polyamides.

### 3.4 - Synthesis of hyperbranched polyamides from amino acid monomers

Synthesis of a suitable $AB_2$ monomer for the formation of hyperbranched polyamides was achieved through the ring opening of a cyclic anhydride, succinic anhydride. Carboxylic acid anhydrides are useful reagents for the acylation of amines. This reaction is generally considered to proceed through a tetrahedral intermediate, (Figure 3.11), although some evidence exists for the reaction proceeding through a synchronous displacement, as discussed for acylation with esters (Section 2.5).

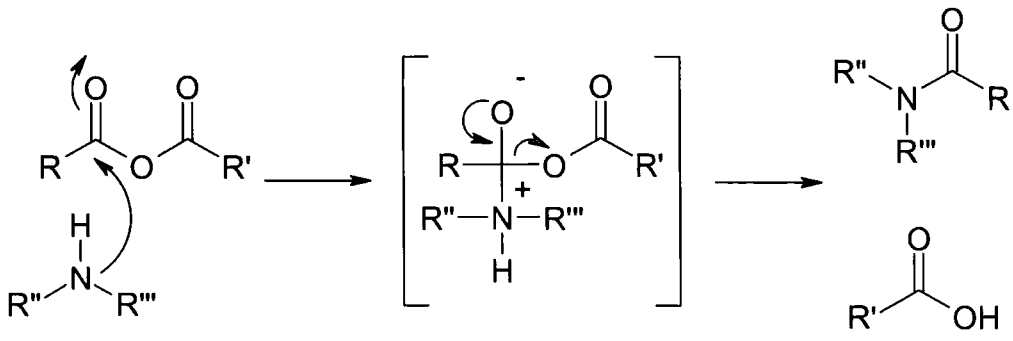


Figure 3.11 – The mechanism of acylation of a secondary amine with an anhydride.

In the case of cyclic carboxylic acid anhydrides, reaction with ammonia or amines forms acid amides, (Figure 3.12), although conditions must be controlled to avoid the cyclisation of the amic acid to form an imide.

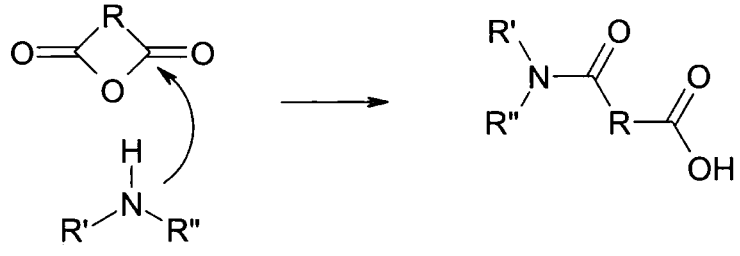
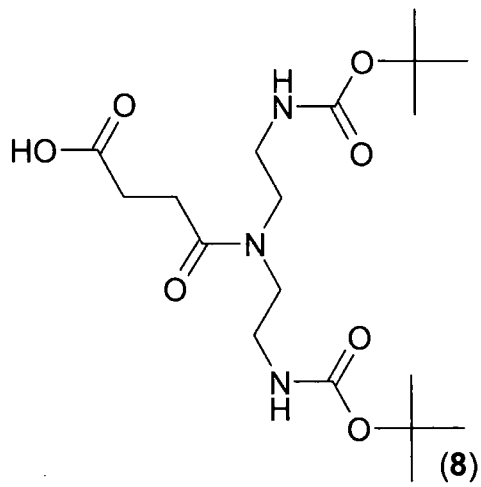


Figure 3.12 – The ring opening of a cyclic anhydride by a secondary amine.

The ring opening of succinic anhydride by the diprotected triamine formed a molecule containing one acid group, and two protected amines, (Figure 3.13). The product could be purified by recrystallisation and no evidence was seen for the formation of imide, which would be a $B_2$ type molecule and could potentially lead to network formation.




(8)

Figure 3.13 – The protected $AB_2$ monomer formed by the ring opening of succinic anhydride.

Attempts to polymerise this material in the bulk led to formation of intractable black solids. An alternative polymerisation in solution was developed using a very high boiling solvent (the deprotection requires a temperature of 230°C). It was necessary to choose a solvent which would dissolve both the unprotected monomer and the polymer. There also needed to be a method to extract the product from the solvent after polymerisation. The solvent chosen was diphenyl sulfone, which boils at 378°C. Aromatic sulfones are used in the synthesis of polyetherether ketone (PEEK) in which a typical procedure involves a polycondensation at 320°C in a diphenyl sulfone solvent.[41] This was thought to be a suitable solvent as despite its highly aromatic nature it is very polar. Syntheses in this solvent produced a series of brown polymers which were extracted from the diphenyl sulfone with water after polymerisation. Production of water soluble polymers was possible by this method but problems existed with practical aspects of the procedure. Diphenyl sulfone is used industrially at temperatures above 230°C, however in laboratory conditions problems occurred with it blocking nitrogen pipes after evaporation from the reaction vessel (it solidifies at 129°C). Every two hours during the reaction polymerisation had to be interrupted while more solvent was added and to allow the pipes to be cleared.

### 3.5 - Synthesis of hyperbranched polyamides from amino ester monomers

Due to the problems encountered with synthesis in a diphenyl sulfone solvent the use of the esters of the amino acids described earlier was investigated. It was hoped that these would prove suitable for bulk polymerisation.

The synthesis of polypeptides is based on the formation of amide bonds between amino acids. To allow these reactions to proceed under mild conditions the acid groups are often esterified prior to amidation. Specialised active esters are commonly used, such as cyanomethyl esters,[42] nitrophenol esters[43] and N-hydroxysucccinimide esters.[44] Formation of these esters is usually achieved using the coupling agent diyclohexylcarbodiimide (DCC). This causes activation of the carboxylic acid by its addition to the C=N double bond of the carbodiimide which can then undergo condensation with an alcohol, (Figure 3.14).[45] DCC mediated coupling can also be used for the direct synthesis of peptides by introducing a 1:1 mixture of carboxylic acid and amine component rather than an alcohol and a carboxylic acid.[46]

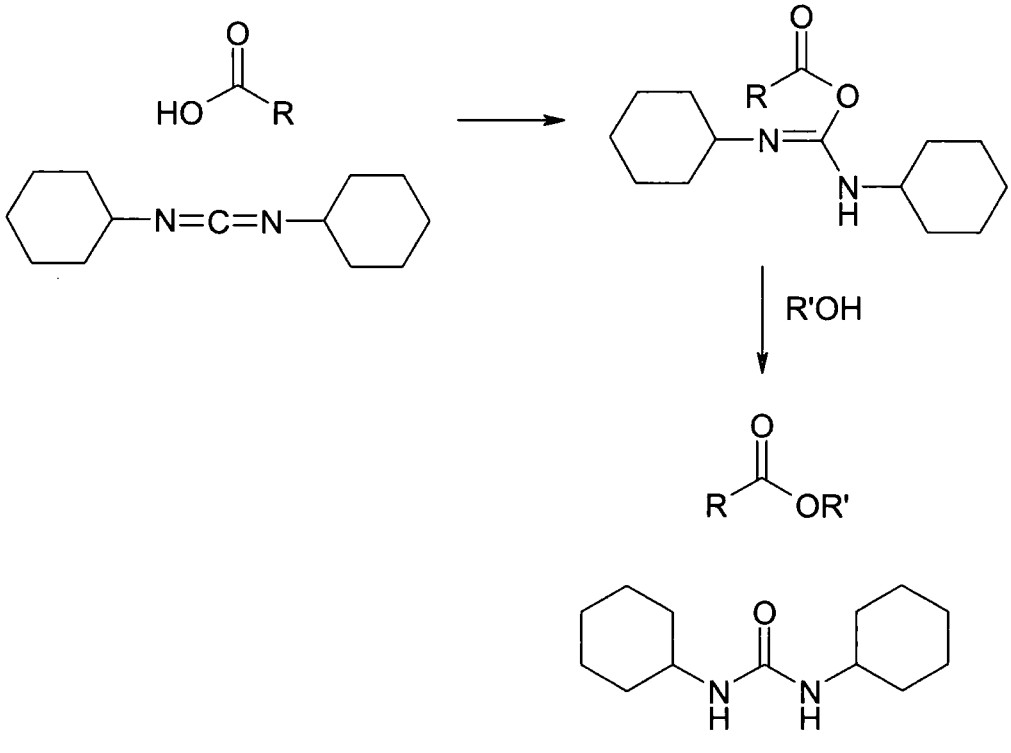



Figure 3.14 – The synthesis of esters by coupling acids and alcohols with dicyclohexylcarbodiimide.

Methyl, ethyl and p-nitrophenol esters were formed by DCC mediated coupling. The methyl and ethyl esters when polymerised in the bulk formed hyperbranched polymers, however the p-nitrophenol ester was less successful possibly due to difficulties of removing the p-nitrophenol condensate. The by-product of DCC esterification, N,N'-dicyclohexylurea is virtually insoluble in most solvents and is removed by filtration. However it generally contaminates the product to some extent. The possibility also exists that an intramolecular rearrangement of the O-acyl isourea derivative can occur to form difficult to remove ureides. Initial successes were seen using this method, however the monomer had to be very carefully purified to avoid contamination, making this procedure difficult to scale up. Due to this alternative syntheses of the same esters were investigated.

Secondary amines react with acid chlorides to form N,N disubstituted amides in a reaction which is one of the most common methods of forming amides. The highly electron withdrawing chlorine group leads to the carbon atom of the carbonyl group being very electrophilic. The reaction is exothermic and is usually controlled by use of an ice-bath. There is less well established mechanistic data about the reaction of acid chlorides with amines than about the reaction between amines and esters, however the evidence that does exist suggests an addition-elimination mechanism as in the amidation with esters, (Figure 3.15).

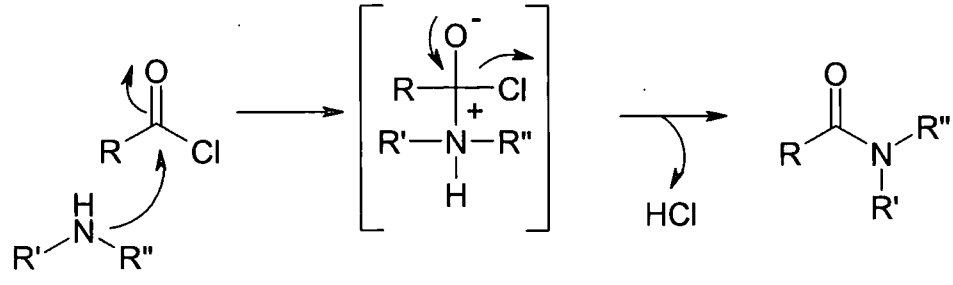



Figure 3.15 – Mechanism of the reaction between a secondary amine and an acid chloride.

A two-fold excess of amine must be used as one equivalent is consumed by a reaction with the hydrogen halide liberated in the acylation. The resultant salts precipitate and are removed by filtration or extraction with water. The maximum available yield with respect to amine is 50%. If the amine is valuable then an alternative method can be

adopted which involves adding a tertiary base to the reaction mixture. In this case the added base reacts with the hydrogen halide produced, preventing it from reacting with the added amine and allowing a theoretical yield of 100% with respect to the amine. The diprotected triamine (**1**) was reacted with ethyl succinyl chloride with triethylamine present as a scavenging base, (Figure 3.16). This caused formation in a one-step reaction of the same amino ester monomers that could be formed by DCC coupling of the amino acids with ethanol.

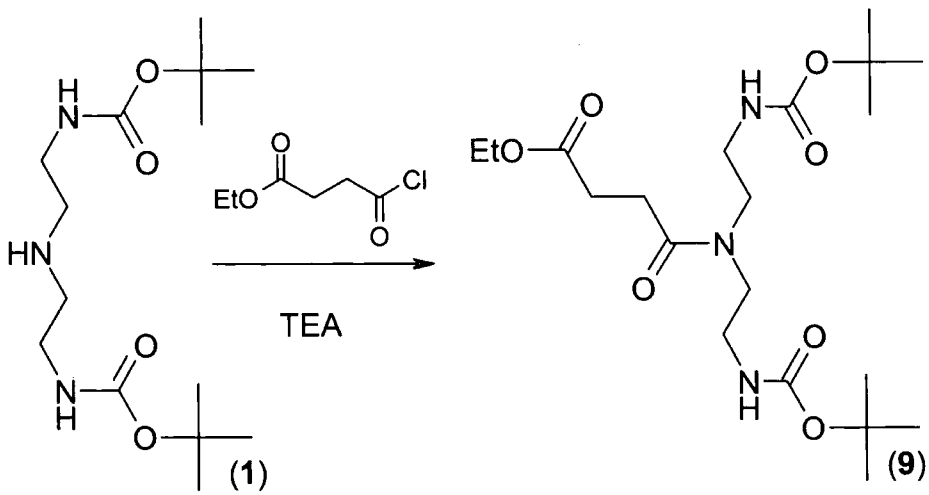



Figure 3.16 – Reaction of the protected triamine with ethyl succinyl chloride to form a protected amino ester monomer.

These monomers could be purified more easily than those from the DCC coupling and were successfully used in bulk thermal polymerisation to form water soluble polymers.

### 3.6 - Conclusions

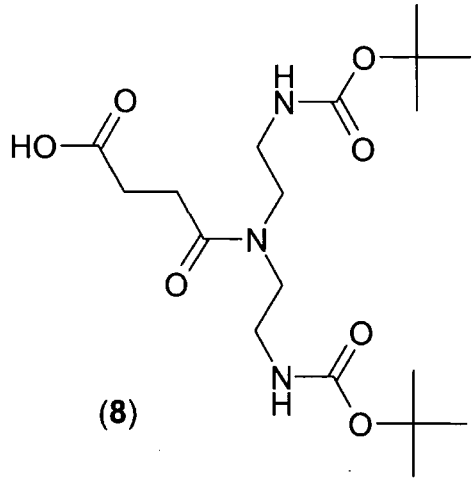
In this chapter the synthesis of hyperbranched polyamides has been reported. These provide the first hyperbranched analogues to the common linear aliphatic polyamides, known in everyday life as the Nylons. These polymers were synthesised from two related $AB_2$ monomers, a protected amino acid and a protected amino ester.

The protected amino acid could not be polymerised successfully in the bulk, instead intractable black solids were produced. In a high boiling solvent, diphenyl sulfone, fully water soluble polymers could be synthesised. There were practical problems with the synthesis in a diphenyl sulfone solvent as despite its high boiling point it evaporated and was precipitated in gas pipes causing their blockage.

Due to these difficulties amino ester monomers were synthesised. These could be produced via the use of DCC as a coupling agent, or in better yields with an easier one-step synthesis via the use of acid chloride esters. These amino ester monomers could be polymerised via the same bulk method reported earlier, (Chapter 2), for the synthesis of the hyperbranched PAMAM analogues. The analysis and characterisation of these materials is described in chapter 5.

### 3.7 - Experimental

*N,N-Bis-(2-tert-butoxycarbonylaminoethyl) succinamic acid,* (**8**)

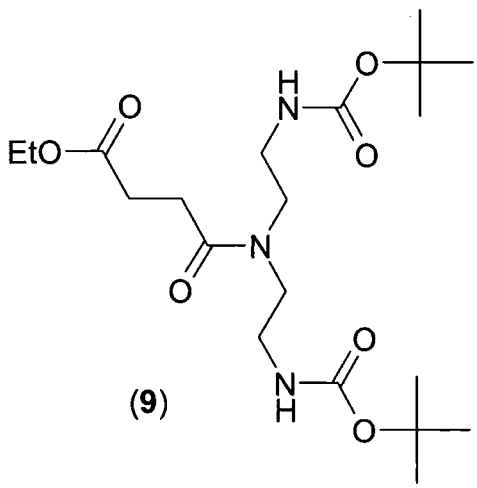



(**8**)

Compound (**2**), (20.01g) was added to a 500mL three necked round-bottomed flask containing HPLC grade toluene (300mL) and was purged with nitrogen and heated to 60°C. To this was added succinic anhydride (8.20g) after which the solution was stirred at 60°C for three hours. After this time the solvent was removed *in vacuo* and the resultant yellow solid was recrystallised from an ethyl acetate/hexane mixture (2:1), to give *N,N-bis-(2-tert-butoxycarbonylaminoethyl) succinamic acid* (**8**) as white solid, (21.94g, 82.5%). Found; C, 53.15; H, 8.21; N, 10.48; M/z (CI): 404 (H).

Calculated for $C_{18}H_{33}N_3O_7$; C, 53.58; H, 8.24; N, 10.41%; M 403. $^1$H NMR: $\delta_H$ (200 MHz; $CDCl_3$) 1.42ppm (s, 18H), 2.66 (s, 4H) 3.28 (m, 4H) 3.46 (m, 4H) 5.23 (bs, 2H). $^{13}$C NMR: $\delta_C$ (100 MHz; $CDCl_3$) 27.99ppm, 28.48, 29.74, 39.11, 46.49/48.52,[47] 78.22, 156.48, 173.49, 176.28.

*N,N-Bis-(2-tert-butoxycarbonylaminoethyl) succinamic acid ethyl ester,* (**9**)




(**9**)

Compound (**2**), (10g) and triethylamine (3.50g) were added to a one litre round bottom flask containing 500mL of dichloromethane which was cooled to -10°C. To this was added a solution of ethyl succinyl chloride (5.70g) in dichlorormethane (250mL) dropwise over the period of one hour. The solution was allowed to warm to room temperature and stirred for a further two hours. After this time the dichloromethane was washed with 1M hydrochloric acid (250mL) and then three times with water (250mL), dried over magnesium sulfate, and the solvent removed *in vacuo*. The yellow oil obtained was purified by column chromatography on silica with an eluant of ethyl acetate to give *N,N-bis-(2-tert-butoxycarbonylaminoethyl) succinamic acid ethyl ester*, (**9**) as a clear oil, (10.27g, 72.2%). Found; C, 55.39; H, 8.70; N, 9.55%; M/z (EI) 431. Calculated for $C_{20}H_{37}N_3O_7$; C, 55.67; H, 8.64; N, 9.74%; M 431. $^1$H NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.26ppm (t, J=7.0Hz, 3H), 1.43 (s, 18H), 2.64 (s, 4H), 3.30 (m, 4H), 3.47(m, 4H), 4.14 (q, J=7.0Hz, 2H), 5.13 (bs, 2H). $^{13}$C NMR: $\delta_C$ (75 MHz; $CDCl_3$) 14.32ppm, 27.85, 28.49, 29.66, 39.32, 46.26/48.43, 60.72, 79.59, 156.13, 156.45, 173.03.

*Polymerisations in diphenyl sulfone solution*

A typical example of a polymerisation in a diphenyl sulfone solvent is outlined here, polymerisations in bulk followed the procedure described earlier, (Section 2.9). Compound (**8**), (4.41g) was ground to a fine powder and mixed with diphenyl sulfone (15.26g). This was put into a flange flask fitted with an overhead stirrer, an inlet for nitrogen, and an outlet fitted with a cold trap. The flask was purged with nitrogen and then heated to 150°C at a ramp of 10°C per minute at which temperature it was held for 15 minutes. The temperature was raised to 230°C at 10°C per minute and this was maintained for 2-24 hours in a series of different experiments. At intervals of about every two hours the polymerisation was interrupted to allow replenishment of solvent and to clear the inlet and outlet pipes. Throughout the polymerisation a constant stream of nitrogen was passed through the apparatus. After the required polymerisation time the flask was allowed to cool and the entire contents dissolved in chloroform. The chloroform solution was then extracted four times with water (50mL), the water layer subsequently being washed four times with chloroform (50mL). The water was then removed *in vacuo* to leave the polymer as a brown solid. The polymer was dissolved in water and decolourising charcoal (10 % by weight) was added. It was refluxed for fifteen minutes, allowed to cool and then filtered thorough cellite filter aid to give the polymer as a yellow solid.

## 3.8 – References


1 - Carothers, W. H. *US Pat. 2 071 250* (**1937**).

2 - Chiriac, C.; Stille, J. K. *Macromolecules* **1977**, *10*, 710.

3 - Higashi, F.; Goto, M.; Hakinoki, H. *J. Polym. Sci. Polym. Chem. Ed.* **1980**, *18*, 1711.

4 - Kim, Y. H. *J. Am. Chem. Soc.* **1992**, *114*, 4947.

5 - Kim, Y. H. *Adv. Mater.* **1992**, *4*, 764.

6 - Kim, Y. H. *Macromol. Symp.* **1994**, *77*, 21.

7 - Miller T. M.; Neenan T. X. *Chem. Mater.* **1990**, *2*, 346.

8 - Reichert, V. R.; Mathias, L. J. *Macromolecules* **1994**, *27*, 7024.

9 - Yang, G.; Jikei, M.; Kakimoto, M. -A. *Macromolecules* **1998**, *31*, 5964.

10 - Yang, G.; Jikei, M.; Kakimoto, M. -A. *Macromolecules* **1999**, *32*, 2215.

11 - Haba, O.; Tajima, H.; Ueda, M.; Nagahata, R. *Chem. Lett.* **1998**, 333.

12 - Mariani, A.; Mazzanti, S. L. E.; Russo, S. *Can. J. Chem.* **1995**, *73*, 1960.

13 - Russo, S. Mariani, A. Mazzanti, S. L. E. *Macromol. Symp.* **1997**, *118*, 73.

14 - Russo, S.; Boulares, A.; Mariani, A. *Macromol. Symp.* **1998**, *128*, 13.

15 - Monticelli, O.; Mendichi, R.; Bisbano, S.; Mariani, A.; Russo, S. *Macromol. Chem. Phys.* **2000**, *201*, 2123.

16 - Russo, S.; Boulares, A.; da Rin, A.; Mariani, A. Cosulich, M. E. *Macromol. Symp.* **1999**, *143*, 309.

17 - Monticelli, O.; Mariani, A.; Voit, B.; Komber, H.; Mendichi, R.; Pitto, V.; Tabuani, D.; Russo, S. *High Perform. Polym.* **2001**, *13*, 545.

18 - Komber, H.; Voit, B.; Monticelli, O.; Russo, S. *Macromolecules* **2001**, *34*, 5487.

19 - Cosulich, M. E.; Russo, S.; Pasquale, S.; Mariani, A. *Polymer* **2000**, *41*, 4951.

20 - Jikei, M.; Fujii, K.; Yang, G.; Kakimoto, M. -A. *Macromolecules* **2000**, *33*, 6228.

21 - Jikei, M.; Fujii, K.; Kakimoto, M. -A. *J. Pol. Sci. A – Polym. Chem.* **2001**, *39*, 3304.

22 - Ishida, Y.; Sun, A. C. F.; Jikei, M.; Kakimoto, M-. A. *Macromolecules* **2000**, *33*, 2832.

23 - Jikei, M.; Chon, S-H.; Kakimoto, M-. A.; Kawauchi, S.; Imase, T.; Watanebe, J. *Macromolecules* **1999**, *32*, 2061.

24 - Jikei, M.; Kakimoto, M. -A. *High Perform. Polym.* **2001**, *13*, S33.

25 - Kricheldorf, H. R.; Löhden, G. *J. M. S. – Pure Appl. Chem.* **1995**, *A32*, 1915.

26 - Kricheldorf, H. R.; Löhden, G. *Macromol. Chem. Phys.* **1995**, *196*, 1839.

27 - Kricheldorf, H. R.; Bolender, O.; Stukenbrock, T. *Macromol. Chem. Phys.* **1997**, *198*, 2651.

28 - Kricheldorf, H. R.; Bolender, O. *J. M. S. – Pure Appl. Chem.* **1998**, *A35*, 903.

29 - Brenner, A. R.; Schmaljohann, D.; Voit, B. I.; Wolf, D. *Macromol. Symp.* **1997**, *122*, 217.

30 - Huber, T.; Voit, B.; Wolf, D. *Macromol. Symp.* **1999**, *142*, 133.

31 - Huber, T.; Böhme, F.; Komber, H.; Kronek, J.; Luston, J.; Voigt, D.; Voit, B. *Macromol. Chem. Phys.* **1999**, *200*, 126.

32 - Böhme, F.; Clausnitzer, C.; Gruber, F.; Grutke, S.; Huber, T.; Pötschke, P.; Voit, B. *High Perform. Polym.* **2001**, *13*, S21.

33 - Van Benthem, R. A. T. M. *Progr. Org. Coat.* **2000**, *40*, 203.

34 - Stanssens, D.; Hermanns, R.; Wories, H. *Prog. Org. Coat.* **1993**, *22*, 379.

35 - Geladé, E. T. F.; Goderis, B.; de Koster, C. G.; Meijerink, N.; van Benthem, R. A. T. M. *Macromolecules* **2001**, *34*, 3552.

36 - Muscat, D.; Henderickx, H.; Kwakkenbos, G.; van Benthem, R.; de Koster, C.; Fokkens, R.; Nibbering, N. M. M. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 218.

37 - van Benthem, R. A. T. M.; Meijerink, N.; Geladé, E.; de Koster, C. G.; Muscat, D.; Froehling, P. E.; Hendriks, P. H. M.; Vermeulen, C. J. A. A.; Zwartkruis, T. J. G. *Macromolecules* **2001**, *34*, 3559.

38 - http://www.dsm.com/hybrane/

39 - http://www.dsm.com/hybrane/applications/

40 - Muscat, D.; van Benthem, R. A. T. M. *Top. Curr. Chem.* **2001**, *212*, 41.

41 - Rose, J.; Staniland, P. *US Pat. 4 320 224* **(1982)**.

42 - Schwyzer, R.; Iselin, B.; Feurer, M. *Helv. Chim. Acta.* **1955**, *38*, 69.

43 - Bodansky, M. *Nature* **1955**, *175*, 685,

44 - Anderson, G. W.; Zimmermann, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 3039.

45 - Rothe, M.; Kunitz, F. W. *Liebigs. Ann. Chem.* **1957**, *609*, 88.

46 - Sheehan, J. C.; Hess, C. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.

47 - Two signals are seen for the $CH_2$ group adjacent to the middle nitrogen when it is part of an amide group. After consultation with Dr. A. M. Kenwright these have been ascribed to a large cis/trans effect across this amide bond due to restricted rotation. A cis/trans effect is seen in other carbon signals but is smaller and an average value has been given in these cases.

# Chapter Four

# The control of molecular weight, degree of branching and end group functionality in hyperbranched polymers

## Chapter Four – The control of molecular weight, degree of branching and end group functionality in hyperbranched polymers

When a hyperbranched polymer is synthesised from an $AB_2$ monomer in a bulk step-growth polymerisation the product is predicted to display a statistical distribution of structure and size.[1] The key features which define the polymer, the molecular weight, polydispersity, terminal functionality and degree of branching are all determined by the statistics of the polymerisation and the structure of the monomers, generally with little control over these features being in the hands of the synthesist. There has been a drive to control these features and the structures of the product polymer molecules to allow the chemist to define better the types of molecule produced. In this chapter the author presents an overview of the literature of this area and reports the new syntheses that have been conducted in the current work.

### 4.1 – Control of molecular weight of hyperbranched polymers by termination with a polyfunctional core

If a molecule $B_f$ which has f functional groups B is co-polymerised in a one-step reaction with an $AB_x$ monomer then the $B_f$ component acts as a growth terminator. In principle this leads to a measure of control over the molecular weight, (Figure 4.1). By altering the ratio of the $B_f$ core molecule to the $AB_x$ monomer a theoretical number average molecular weight, ($\overline{M}_{n(th)}$) for the product polymers can be calculated. This is only true if all molecules are joined to a central core, which requires complete conversion of A groups and an absence of cyclisation but does not require the reaction of all the B groups in $B_f$. If these conditions are met then the theoretical number average molecular weight of the product polymer molecules is defined by the equation below.

$$\overline{M}_{n(th)} = x(M_r) + M_c$$

Where x is the mole ratio of monomer to core, $M_r$ is the molar mass of the repeat unit and $M_c$ is the molar mass of the $B_f$ core residue.

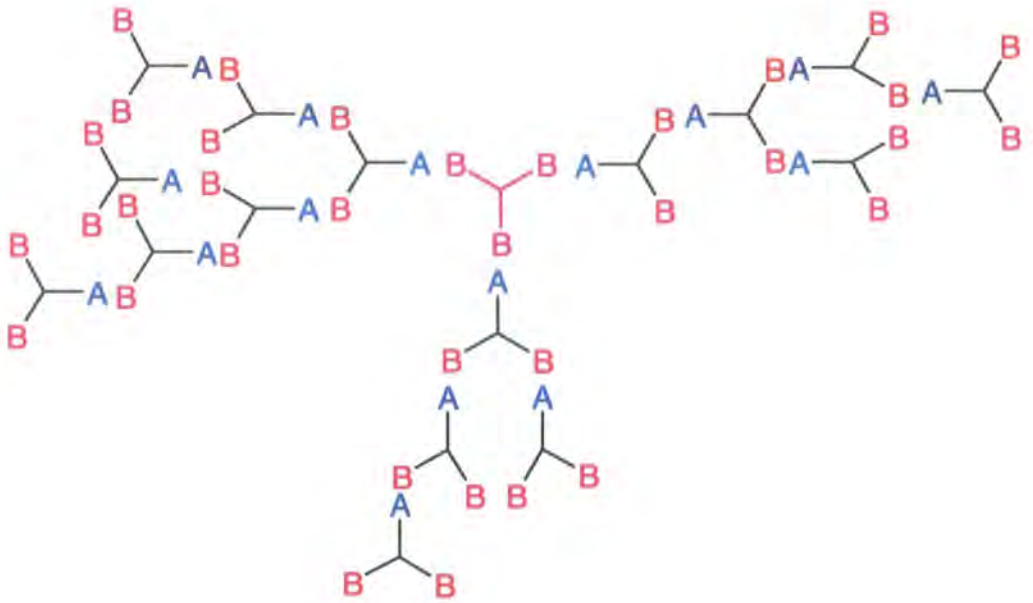


Figure 4.1 – A schematic example of a polymer molecule produced by co-polymerisation of a $B_3$ core (purple) with an $AB_2$ monomer in the ratio 16:1, (the real product having a distribution of size and structure).

In addition to allowing control over the molecular weight of the resultant polymers the use of cores in hyperbranched polymer syntheses has other benefits, for example it causes a reduction in the polydispersity of the samples produced, the higher the functionality of the core the narrower the molecular weight distribution of the final polymer.[2] However when the core and monomer are introduced together at the start of the reaction there is no effect on the degree of branching of the polymer.[3]

The first examples of core-linked hyperbranched polymers were low molecular weight polyesters which were linked to a core carrying four alcohol groups.[4] The $AB_2$ monomer 2,2-bis(hydroxymethyl)propionic acid was co-polymerised with the $B_4$ core 3,3,7,7-tetra(hydroxymethyl)-5-oxa-nonane, (di-tri-methylolpropane), (Figure 4.2). It was shown that as the ratio of core to $AB_2$ monomer increased the molecular weight of the resultant polymers decreased. An increase in the degree of branching in these polymers was seen, which was subsequently explained[5] as being due to the monomer only slowly being solubilised in the melt, and hence the

kinetics seen for slow addition applying. (Section 4.2.1) Since this work many examples of similar core-linked hyperbranched polymers have been reported.

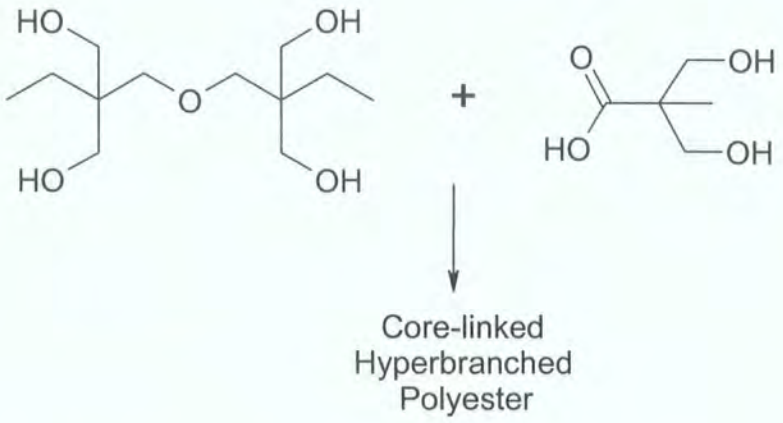



Figure 4.2 – The synthesis of core-linked hyperbranched polyesters.

A reduction in polydispersity in polymers synthesised with a core present has been observed experimentally and it has also been shown that at high core to monomer ratios a bimodal distribution may be produced. By using a chromophoric core it could be seen that the core appeared predominantly at the high molecular weight end of the distribution, which is consistent with the production of core-linked polymers competing with $AB_2$ homopolymerisation.[6]

A change in the properties of core-terminated co-polymers compared to non core-linked hyperbranched polymers has been observed. It has been reported that when hyperbranched polyesters from 2,2-bis(hydroxymethyl)propionic acid were core-terminated with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP) the solubility of the resultant polymer increased.[7] In the case of hyperbranched polyelectrolyte PAMAM polymers a clear difference was seen between the properties of the core terminated polymers and those which were not core terminated. In the core terminated polymers from this system a maximum was seen in a graph of intrinsic viscosity versus molecular weight which was reminiscent of dendrimers, whilst the non-core terminated polymers followed the Mark-Houwink-Sakurada relationship.[8]

Attempts have been made to control the molecular weight of the polymers produced in this study using a $B_f$ core. The monomer selected was the $AB_2$ monomer, (**9**), which possesses a single ester A group and two protected amine B groups. A $B_f$ core with amine B groups was sought. As it was intended to use the core in a copolymerisation in the bulk at 230°C it was necessary that the core was neither volatile nor unstable at this temperature. A generation one dendrimer with six protected amine terminal groups was chosen as a suitable core. This was synthesised by coupling (**1**) to 1,3,5-benzenetricarbonyl trichloride. A reaction occurs between the secondary amine and the acid chloride producing a molecule (**10**) with six butyloxycarbonyl protected amines at the surface, (Figure 4.3). Since the Boc group is labile at the reaction temperature this molecule is a potential $B_6$ core. This core was then co-polymerised in different ratios with the monomer, to produce polymers of different theoretical number average molecular weights ($\overline{M}_{n(th)}$).

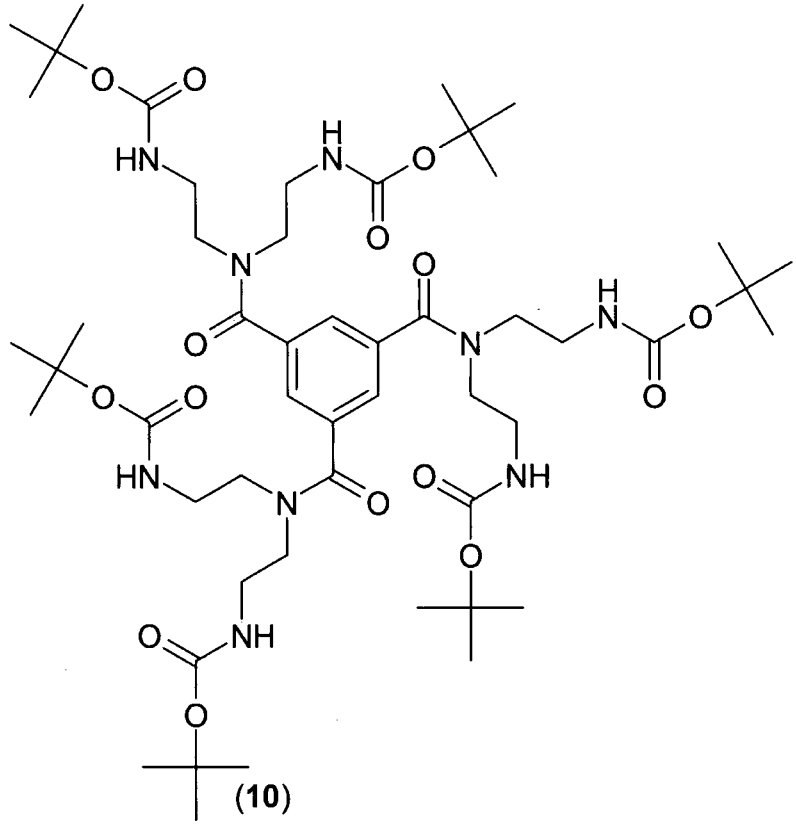



Figure 4.3 – The dendrimer synthesised for use as a $B_6$ core.

The commercially available bis amine capped polyethylene glycol has been used as an alternative core, (Figure 4.4). The two amine end groups can react as B

groups and this polymer can act as a $B_2$ core. It was shown to be stable to the reaction conditions by thermogravimetry (TG), a weight loss of about 2.5% being seen after two hours at 230°C, this probably being due to loss of adsorbed water. By using this core at a variety of different ratios with the $AB_2$ monomer, polymers of different theoretical number average molecular weights were again synthesised.

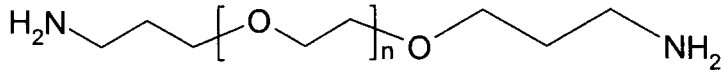



Figure 4.4 – Bis amine capped polyethylene glycol, where $\bar{n} = 34$.

The polymer which would be produced by using the bis amine capped polyethylene glycol as a core can alternatively be described as an ABA triblock co-polymer of the type [hyperbranched polymer-linear PEG-hyperbranched polymer], (Figure 4.5).

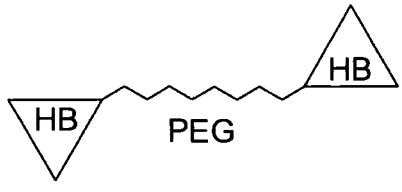



Figure 4.5 - ABA triblock co-polymer of the type [hyperbranched polymer-linear PEG-hyperbranched polymer].

Block copolymers of linear polymers and dendritic polymers have been reported previously, although most of the previous work has been on the synthesis of dendron-linear copolymers or dendrimer-linear co-polymers rather than hyperbranched-linear co-polymers. Preformed convergent dendrons have been coupled to the chain ends of linear polymers to make AB and ABA co-polymers[9,10] or to well defined functional groups in their backbones in a 'coupling to' approach.[11] Linear polymers with suitable end groups have been used as a core from which divergent dendrimers can be grown.[12,13,14] Convergent dendrons with suitable functionality at their focal point have been used as initiators for polymerisation of monomers to form dendron-linear diblocks[15,16] and triblocks[17]

and dendrimers[18] and hyperbranched polymers[19] with functionalities at their surfaces have been used as multifunctional initiators for the formation of linear grafts from the termini of the polymers. The analysis of the products produced in this study of synthesis of core-linked polymers is discussed later, (Section 5.1.4.6).

## 4.2 – Controlling the degree of branching in hyperbranched polymers

After molecular weight, the degree of branching receives most attention in the characterisation of hyperbranched polymers. Within the limitations discussed earlier, this parameter gives some idea of the architecture of the polymer. For statistical homopolymerisations of $AB_2$ molecules a degree of branching of 0.5 is expected, (Section 1.7) but many attempts have been made to produce polymers with different degrees of branching by changing the monomer structure, reaction conditions or by modification of the polymers after their synthesis.

### 4.2.1 – Increasing the degree of branching

Much effort has been expended in trying to increase the degree of branching of hyperbranched polymers above the statistical value of 0.5. The simplest method conceptually is to choose a monomer in which a large substitution effect occurs. In the case of hyperbranched polymer synthesis this requires a difference in reactivity between the terminal and linear B groups. The first reaction of an $AB_2$ monomer gives a dimer with two terminal and one linear B groups and the requirement is that the reactivity of the linear B groups is greater than that of the terminal B groups, (Figure 4.6). This means that linear groups will react preferentially and will produce a polymer with a higher degree of branching than would otherwise be expected.

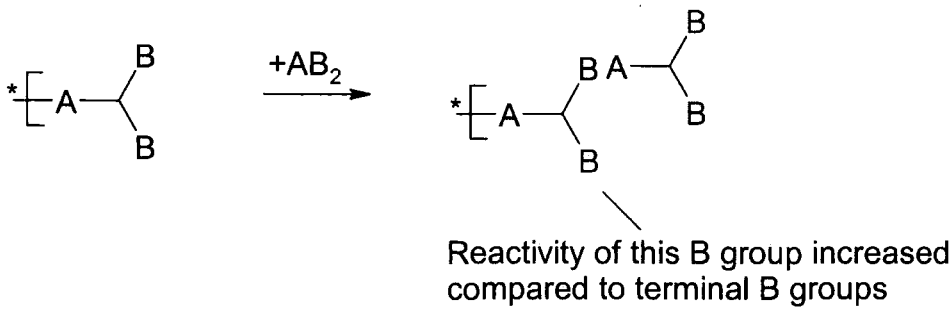



Figure 4.6 – A reaction of the $AB_2$ monomer causing the B group attached to the linear units (green) to be more reactive than those on the terminal units (purple).

This situation has been studied theoretically and it has been shown that for a DB of 0.8 to be produced the second B group must be five times more reactive than the first.[20] Kinetic modelling of the reaction of an $AB_2$ monomer explored the consequences of different substitution effects including an examination of how changes in the reactivity ratio changes the degree of branching at different conversions.[21] The effect of changing the reactivity of the terminal and linear units on the structure has also been studied by simulation, allowing steric effects to be properly analysed.[22] Examples of systems in which a substitution effect is known to cause a DB of greater than 0.5 have been reported experimentally, these often occur in systems in which the A and both the B groups are attached to the same benzene ring,[23] however, in most cases of hyperbranched polymer synthesis a negative substitution effect is seen, the first reaction at the $AB_2$ monomer causes the second group to be somewhat sterically shielded and thus the terminal groups are more reactive than the linear and a polymer with a lower degree of branching than 0.5 is produced.

Degree of branching can also be increased through the slow addition of the $AB_2$ monomer to a core. The ideal case in which the $AB_2$ monomers are added so slowly that each monomer is added sequentially has been studied theoretically. It is assumed that the coupling reaction is complete and that no steric hindrance occurs during the growth of the hyperbranched polymer (i.e. all B groups have equal chance of reacting). Only reactions between monomer and growing polymer were allowed with reactions between all other species being excluded. These studies suggested that for an $AB_2$ monomer reacting with a $B_f$ core the

maximum value of the degree of branching to be expected from slow addition is 0.67.[20] Both computer simulations of slow addition to a core[24] and experimental results[25] have been shown to reproduce theoretical predictions, with significant increases of DB seen. It has also been shown that cyclisation is suppressed by this technique,[6,26] as the number of A groups present at any time is minimised reducing the probability of intramolecular cyclisation. If stoichiometric amounts of $AB_x$ monomer equivalent to each generation of the analogous dendrimer are successively added to a core 'pseduo-dendrimers' are produced, that is hyperbranched polymers which are linked to a core and show a higher degree of branching and lower polydispersity than a statistical process and possess molecular weights close to the analogous dendrimers.[7]

The degree of branching of hyperbranched polymers can also be increased by using preformed dendrons as monomers. This method is a hybrid between dendrimer synthesis and hyperbranched polymer synthesis, as the preformed dendron monomers are obtained by the same route as dendrimers. When polymerised these perfectly branched segments are retained within the structure and hence the degree of branching of the product is increased.

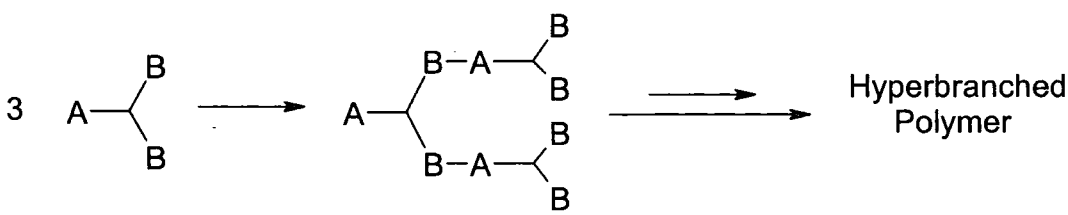



Figure 4.7 – The polymerisation of perfect dendron monomers to make hyperbranched polymers with an enhanced degree of branching.

Theoretical treatments of this situation have been carried out[20] and show that for a hyperbranched polymer synthesised from perfectly branched $AB_w$ monomers made up of $AB_m$ sub-units the degree of branching is given by the equation below.

$$DB = \left(\frac{w-1}{w}\right)^{m-1}$$

Thus, an $AB_4$ monomer made up of two terminal and one dendritic $AB_2$ subunits, (Figure 4.7), can be polymerised to yield a maximum degree of branching of 0.75. Experimental results have confirmed these theoretical suggestions with one study reporting the synthesis of hyperbranched polyetherketones from an $AB_2$ monomer and $AB_4$ monomer in which a dendritic unit is incorporated, (Figure 4.8), with degrees of branching for the two cases being 0.49 and 0.71 respectively.[27]

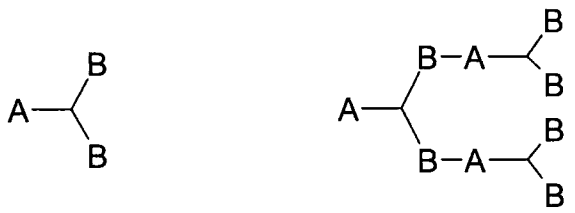



Figure 4.8 – A schematic view of the structure of an $AB_2$ monomer and an $AB_4$ monomer in which a dendritic unit is incorporated.

The influence of monomer multiplicity on the degree of branching[28] has been studied by the synthesis of $AB_4$ and $AB_8$ monomers equivalent to 3,5-diaminobenzoic acid. These monomers were polymerised and it was found that the degree of branching could be increased from a value of 0.32 found for the $AB_2$ case, to a value of 0.84 for the $AB_8$ case, and that by copolymerising the $AB_2$, $AB_4$ and $AB_8$ monomers the degree of branching of the resulting polymers could be controlled over this range.

An interesting and general method of increasing the degree of branching of hyperbranched polymers has been reported recently. In this a post synthesis modification is used in which all of the B groups are reacted with a protected $AB_n$ monomer. Subsequent deprotection of the terminal B groups leads to a hyperbranched polymer without linear units. This means that hyperbranched polymers with a DB of (close to) 1 are produced, although these will still be imperfectly branched.[29] This method has subsequently been used on different systems including a series of hyperbranched polyimides in which all linear units could be removed by end-capping, producing a polymer which is shown by NMR to have a DB of 1.0.[30]

### 4.2.2 - Decreasing the degree of branching

Much effort has been invested in creating polymers with branching between 0.5 and 1.0. There has been less work to create polymers with a degree of branching between 0 and 0.5, although some results have been reported. A control over the degree of branching in this range would allow polymers to be tailored to give particular properties.

One method of decreasing the degree of branching below 0.5 is to change the multiplicity of the monomers so that in an $AB_x$ system x is greater than two. With the exception of the special case of preformed dendrons (in which degree of branching is increased due to the perfect branching fixed into the system, (Section 4.2.1)) an increase in x causes a reduction of the degree of branching. A theoretical analysis for these systems[20] shows that a general expression for the degree of branching and its dependence on x and $p_A$, the conversion of A groups is given by,

$$DB = \frac{\left(1-\frac{1}{x}p_A\right)^x + p_A - 1}{\left(\frac{x-1}{x}\right)p_A}$$

at full conversion ($p_A$=1) this simplifies to the following equation.

$$DB = \left(\frac{x-1}{x}\right)^{x-1}$$

Thus, at complete conversion of A groups the degree for branching of an $AB_4$ polymer has a maximum value of 0.42 and, as x tends to infinity, DB tends to 0.37 (1/e).

Two $AB_4$ monomers were synthesised and studied in this work. It was expected that the degree of branching of the resultant polymers would be reduced below

0.5. The first of these was produced from the selectively protected triamine, (**2**). This molecule was reacted with acryloyl chloride to form a potential $AB_4$ monomer with two protected primary amines and a double bond, (Figure 4.9).

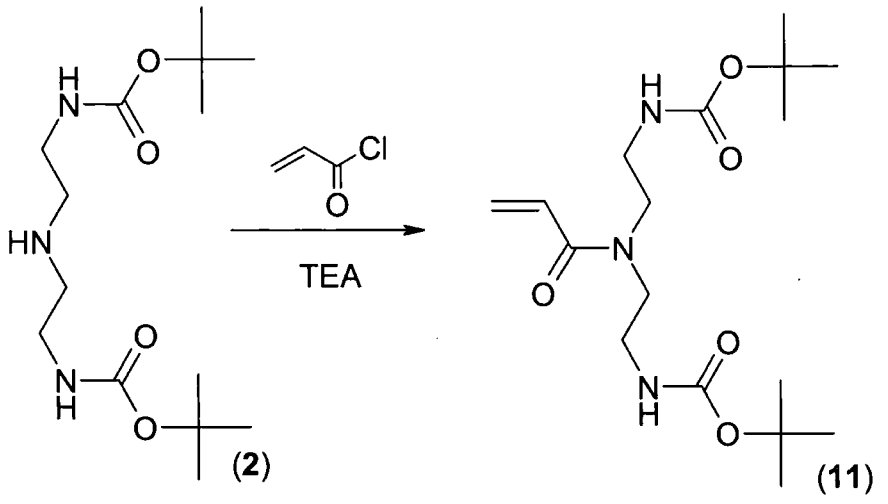



Figure 4.9 – The $AB_4$ monomer formed by reaction between the diprotected triamine and acryloyl chloride.

This is a potential $AB_4$ molecule in which the A group is the double bond and the B groups are the N-H bonds of the amines. Polymerisation would involve a conjugate addition between the amines and the double bond. After the primary amine undergoes an addition a secondary amine is formed, which is capable of undergoing a second addition, hence this molecule is an $AB_4$ monomer, not an $AB_2$ monomer, (Figure 4.10). It is possible that the polymerisation will show a substitution effect as the secondary amine will be more nucleophilic than the primary, however, the extra steric crowding at the secondary amine will act in the opposite sense to decrease the degree of branching and the overall effect of these conflicting forces could not be predicted.

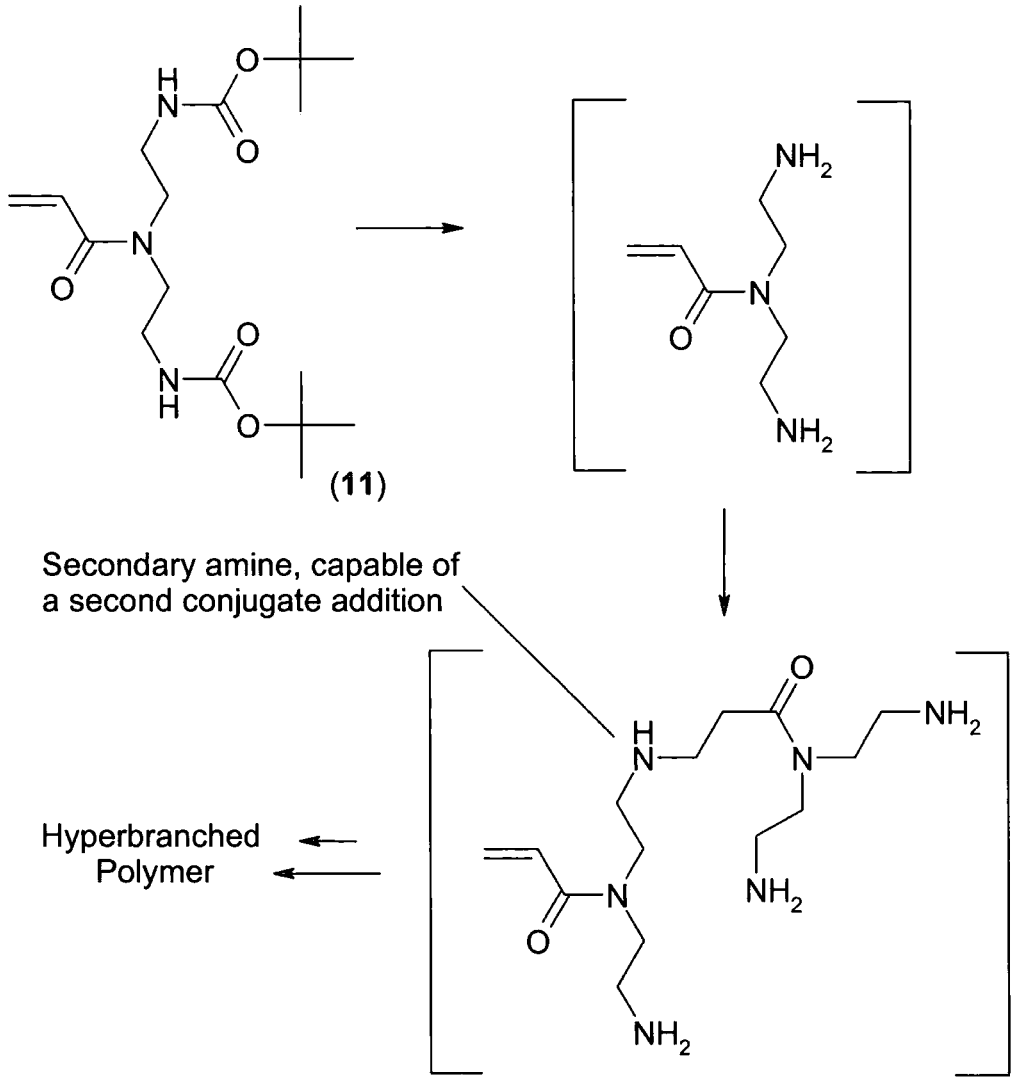



Figure 4.10 – The two primary amines cause (**11**) to react as an $AB_4$ monomer.

The *in situ* deprotection was used in an attempted polymerisation of this monomer. A white material was produced which was insoluble in all common solvents, including trifluoroacetic acid and dichloroacetic acid, which are commonly used to dissolve heavily hydrogen bonded polymers.

The synthesis of the second $AB_4$ monomer used in this work, began with the mono-protection of the symmetrical triamine, tris-(2-aminoethyl)amine with di-tert-butyldicarbonate, using a high dilution method. After purification by column chromatography it was possible to isolate the mono-protected amine (**12**). This underwent exhaustive conjugate addition at the two unprotected amines to introduce four ester groups, (Figure 4.11).

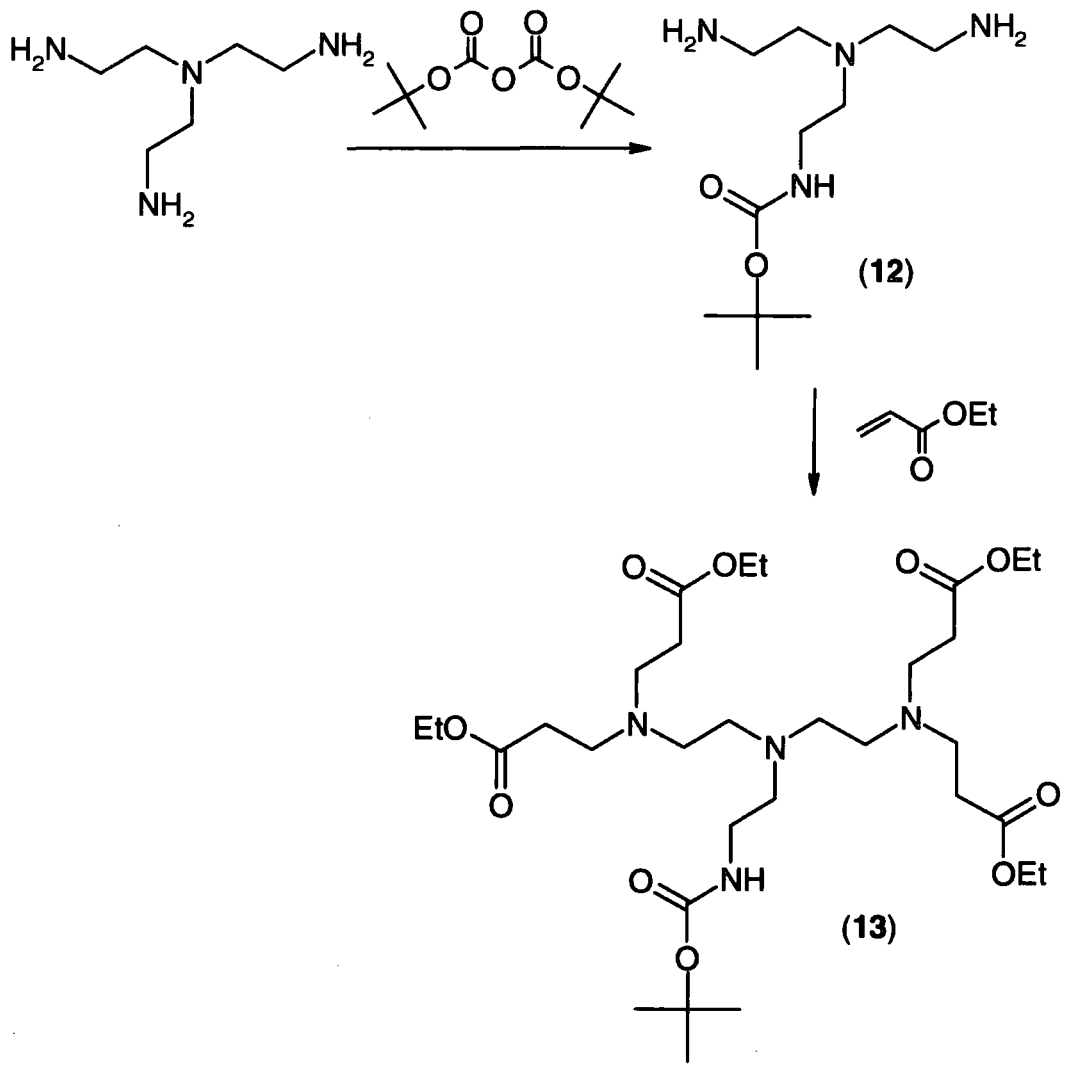



Figure 4.11 – Synthesis of an $AB_4$ monomer starting from tris-(2-aminoethyl)amine.

This is a potential $AB_4$ monomer as the protected primary amine provides (after deprotection) an A group and the four ester groups can act as B groups. This was polymerised in the same manner as described earlier using thermal deprotection and *in situ* amidation. The product was an orange powder, which was shown to be insoluble in all common solvents including dichloroacetic acid and trifluoroacetic acid.

Another method of controlling the degree of branching between 0 and 0.5 is the addition of AB monomers to an $AB_2$ polymerisation. The highly branched polycondensates, amylopectin and glycogen, in which energy is stored in living cells, have the structure of polymers formed by the co-polymerisation of $AB_2$ and

AB monomers (although they are not synthesised in this manner *in vivo*, but by a redistribution of linear chains).[31]

The concept of copolymerising AB with $AB_x$ monomers was examined by Flory.[1] The structural similarity of these polymers to amylopectin and glycogen was discussed and expressions calculated for the weight fraction of species with a given number of linear and branched units. The use of a simpler 'complexity-distribution' was suggested which is the weight fraction of all species with a given number of branched units independent of the number of linear units, a function which parallels the actual size distribution of the molecules. A more recent theoretical treatment of the co-polymerisation of $AB_2$ and AB polymers identified five types of unit in the polymers built up from the co-polymerisation of $AB_2$ and AB monomers,[32] (Figure 4.12). In addition to the dendritic (D, red), linear (L, blue) and terminal (T, purple) units seen in the homopolymerisation of an $AB_2$ monomer, the AB monomer can either be incorporated as a linear unit in the polymer ($L_l$, green) or at a terminal location ($T_l$, orange),

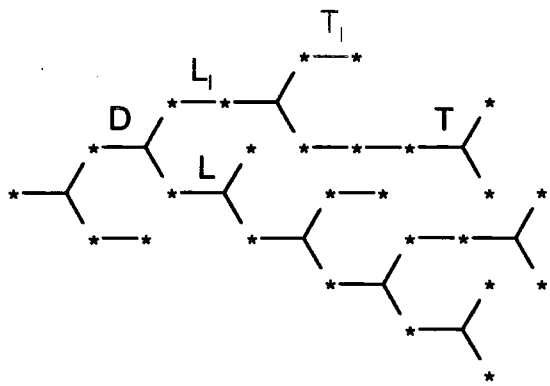



Figure 4.12 – The units produced by co-polymerising $AB_2$ and AB monomers.

To obtain an equation for the degree of branching of these systems it has been assumed that there is no difference between an AB monomer incorporated into a polymer as a linear unit and an $AB_2$ incorporated linearly. An expression for the degree of branching can be obtained by substituting the expression for the total number of linear units ($L_{CO} = L+L_l$) into the expression used to define degree of branching for homopolymerisations of $AB_2$ monomers.[3] This gives the expression shown below.

$$DB = \frac{2D}{2D + L_{CO}}$$

To calculate the expected degree of branching it is assumed that all B groups possess the same reactivity (whether they are from an AB or an $AB_2$ group and regardless of whether in a monomer, oligomer, or is part of a polymer) and that the reaction proceeds as a one-pot random co-polymerisation with no cyclisation. If these assumptions are correct then the degree of branching can be shown to obey the equation shown below.

$$DB = 2P_A\left(\frac{r+1}{(r+2)^2}\right)$$

Where $P_A$ is the conversion and r is the ratio of monomers in the feed, $[AB]/[AB_2]$.

The degree of branching at complete conversion ($P_A$=1) for various ratios of monomer feed can be calculated. With an equimolar amount of AB and $AB_2$ the degree of branching is 0.44 and to achieve a reduction in the degree of branching to below 0.25 the molar fraction of AB must be greater than 0.8, (Figure 4.13). This shows that introduction of a relatively small amount of $AB_2$ monomer to the polymerisation of an AB monomer causes a significant degree of branching.

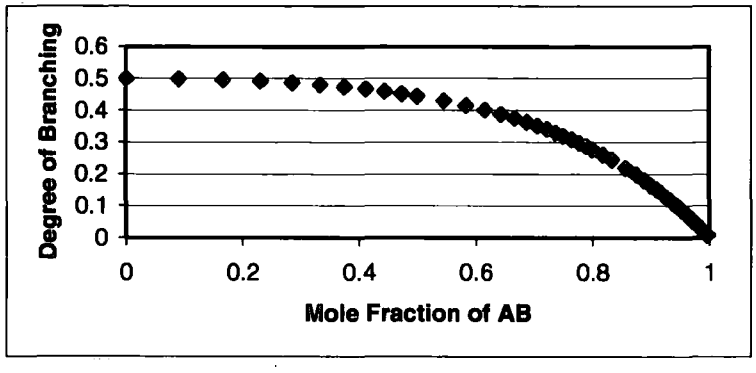



Figure 4.13 – An illustration of how the degree of branching of a hyperbranched polymer falls as the proportion of AB monomer increases.

Theoretical work predicts that the composition of the polymers varies with $P_A$, and that it is only at high conversions that the copolymer composition matches that of the feed ratio.

The concept of introducing branching into a synthetic linear polymer by using co-polymerisation of an $AB_2$ monomer with an AB monomer, predates this detailed theoretical work. A synthesis of branched poly(3-hydroxybenzoates) was reported via the bulk condensation of 3-(trimethylsiloxy)benzoyl chloride and 3,5-bis(trimethylsiloxy)benzoyl chloride, (Figure 4.14).[33] Highly branched aromatic polyesters were produced, which were soluble in polar solvents.

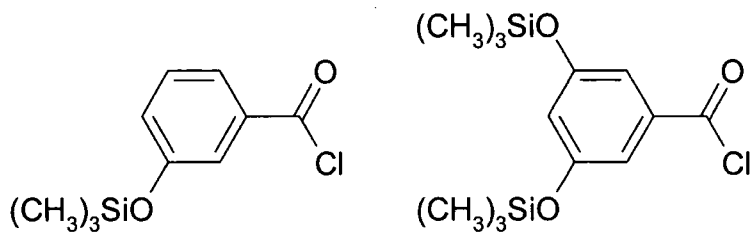



Figure 4.14 - 3-(trimethylsiloxy)benzoyl chloride and 3,5-bis(trimethylsiloxy) benzoyl chloride used to produce $AB_2$/AB co-polymers.

In recent years more studies of the co-polymerisation of $AB_2$ and AB monomers have been reported, including a reinvestigation of the synthesis of branched poly(3-hydroxybenzoate)s[34] and an investigation of the effect of introduction of branching into polyethyleneterphalate (PET).[35,36]

The co-polymerisation of $AB_2$ and AB monomers to form highly branched aromatic polyetheramides has been reported.[37,38] 3,5-Bis-(4-aminophenoxy) benzoic acid ($AB_2$) and 3-(4-aminophenoxy)benzoic acid (AB) were polycondensed together with pyridine and triphenyl phosphite as a condensing agent, (Figure 4.15).

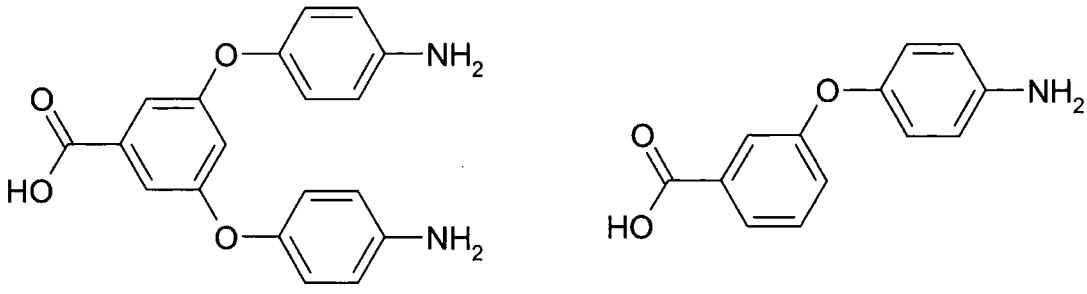



Figure 4.15 – 3,5-Bis-(4-aminophenoxy)benzoic acid and 3-(4-aminophenoxy) benzoic acid , copolymerised to form highly branched aromatic polyetheramides.

The content of the $AB_2$ units in the polymer was shown by infra-red spectroscopy to be higher in the early stages of polymerisation, as suggested by theory,[32] and the solubility of the AB homopolymer (which is only partially soluble in NMP) was improved significantly by the introduction of the $AB_2$ monomer, with introduction of 0.125 mol % of the $AB_2$ unit conferring solubility in aprotic polar solvents such as NMP, DMF and DMSO. The architecture of the final polymers could be altered by either carrying out the reaction in a one-step procedure, or by using stepwise addition of the $AB_2$ and AB monomers, i.e. starting with a homopolymerisation of one of the monomers and subsequently adding the second. An increase in solubility of a hyperbranched polymer by adding AB monomer is also known. For example, investigations into a congested $AB_3$ monomer failed to lead to soluble hyperbranched polymers whilst if they were copolymerised with an AB monomer it was possible to produce soluble randomly branched copolymers.[39]

The $AB_2$ monomer (**9**) used in the work reported earlier for the synthesis of hyperbranched polyamides (Section 3.2) possesses one ester A group and two (protected) amine B groups. A molecule with a single ester A group, and a single protected amine B group was needed as an AB equivalent, (Figure 4.16). This monomer can be synthesised from the addition of ethyl succinyl chloride to the mono-protected diamine, (**6**).

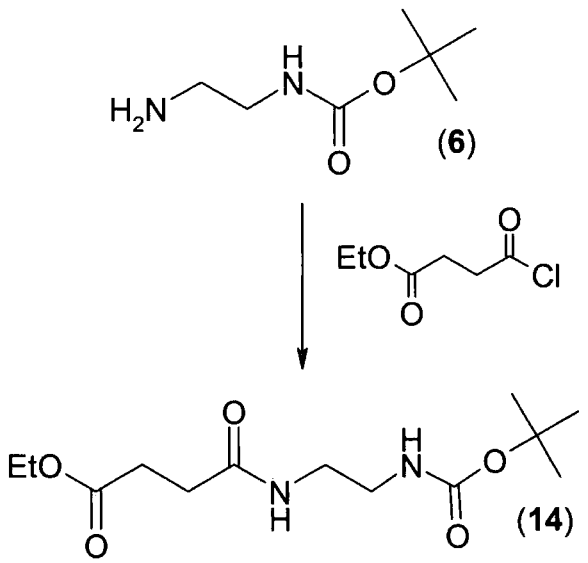



Figure 4.16 – The synthesis of an AB monomer for the production of highly branched polyamides.

Homopolymerisation of this AB monomer leads to production of Nylon 2,4, (Figure 4.17). Nylon 2,4 is a known linear polymer which has been previously synthesised by co-polymerisation of ethylenimine and succinimide,[40] by a polyaddition of N,N'-ethylenedisuccinimide and ethylenediamine[41] or more recently by interfacial and solution phase polycondensation of ethylenediamine and succinyl dichloride.[42]

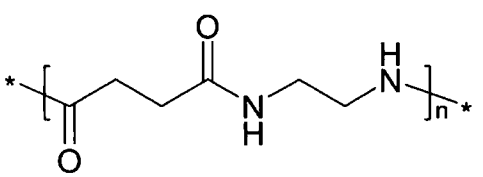



Figure 4.17 – Nylon 2,4.

Nylon 2,4 has an amide content which is much higher than the common commercial Nylons. It is highly insoluble in most common solvents with full solubility only being reported in dichloroacetic acid and trifluoroacetic acid. Even m-cresol, a solvent which is commonly used to dissolve hydrogen bonded polymers (including many commercial Nylons) will not dissolve Nylon 2,4. Homopolymerisation of the AB monomer produced in the current study gave a

sample of orange material believed to be Nylon 2,4. It was shown to be insoluble in all common solvents but was fully soluble in dichloroacetic acid and trifluoroacetic acid, as previously reported for these materials. The copolymerisation of this AB monomer with the $AB_2$ monomer used in the synthesis of hyperbranched polyamides was attempted as a means of introducing branching into the polymers, (Figure 4.18). This allowed the solubility of the linear polymer to be increased and a soluble sample of branched Nylon 2,4 was produced, the characterisation of which is described later, (Section 5.1.4.5).

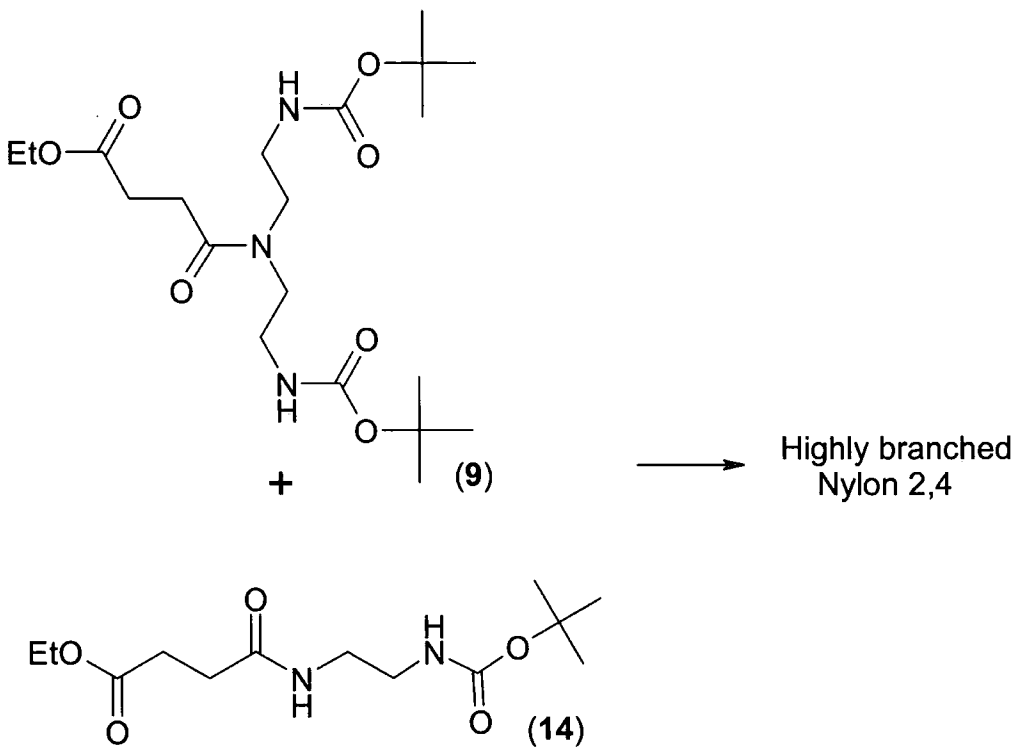



Figure 4.18 – Copolymerisation of an $AB_2$ and an AB monomer to form highly branched Nylon 2,4.

### 4.3 - Control of terminal groups in hyperbranched polymers

The control of the functionalities at the termini of dendritic polymers is an important consideration as properties are known to be affected by the identity of these groups. In convergent dendrimer synthesis the identity of the end-groups can be exactly controlled by the choice of the groups used to synthesise the first

generation dendron. If reaction conditions are carefully selected it is possible to control both the number and placement of end groups and even to define a solitary end-group on the dendrimer.[43] Such control is not possible in divergent dendrimer synthesis, but the surface groups can be altered by a post-synthesis modification. Stoichiometric amounts of metal hydroxides have been added to the half generation PAMAM dendrimers, to alter their ester surfaces to metal carboxylates so as to give good electron scattering and improved contrast in electron microscopy, allowing single dendrimer molecules to be observed.[44]

In hyperbranched polymers derived from condensation polymerisations the end groups are defined by the B groups of the $AB_2$ monomer. The identity of these end groups can be altered by modification reactions upon the hyperbranched polymer, which allows a broad variation of the chemical and physical properties without any variation of the polymer backbone or significant change in molecular weight. The first examples of end-group modification reactions on hyperbranched polymers were reported on hyperbranched polyphenylenes, in which the terminal groups of a bromo-terminated polymer were changed by lithiation and reaction with carbon dioxide to induce water solubility, (Figure 4.19).[45] The lithiated polymers were later reacted with a variety of different electrophiles to produce polymers with different solubilities and glass transition temperatures.[46] Many examples of changing the end groups of hyperbranched polymers have now been reported. Such end group modification reactions can be used to introduce species with specific utility at the termini of a hyperbranched polymer, for example initiators for free radical polymerisation have been introduced[19] and allyl ether maleate functionalised polymers have been synthesised to give thermally curable systems in which the curing rate and final hardness were shown to increase with an increase in functionality.[4]

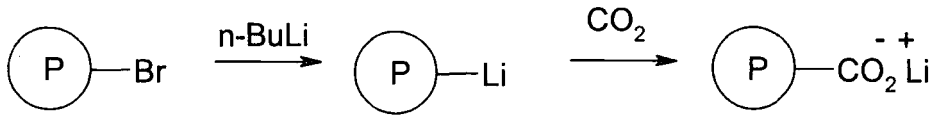



Figure 4.19 – Changing the end groups of a bromoterminated hyperbranched polymer to give a carboxyl terminated hyperbranched polymer, where the circle represents the hyperbranched polymer, and the Br, all of the many bromine groups which would be present as the polymer end groups.

An alternative method to control surface functionality in a hyperbranched polymer is to use a capping agent. This has the advantage of eliminating the need for two separate steps. The terminating agents generally possess the A functionality of the $AB_2$ monomer, but lack the B functionality and are incorporated into the polymer via the same reactions used to produce it. The functionalities which are to be introduced in this manner must be stable to the polymerisation conditions. This method was first used when an alcohol was introduced at the beginning of an $AB_2$ polymerisation in which the B groups were blocked isocyanates and the A groups were alcohols.[47] The end-capping occurred during the polymerisation and led to a reduction in the molecular weight of the product polyurethanes as the number of B groups available for reaction was reduced.

When carrying out a post-synthesis surface modification of a hyperbranched polymer certain criteria must be considered. It is necessary for the reaction to proceed in a very good yield, as separation of fully and partially modified polymers will be difficult if not impossible. Ideally the modifying agent, unmodified and modified polymer should all have a common solvent. It is often necessary to be able to use an excess of the modifying agent, as it is uncertain exactly how many terminal groups exist on the polymer. Excess starting material and any by-products of the reactions have to be easy to remove.

### 4.3.1 - Model reactions for end group modification

In the work reported here amine termini were modified to change the nature of the end groups. Model compounds were prepared to prove that the substitution

reactions proceeded in good yields and were free from side reactions. Unlike the end-capped polymers the reaction products from the model systems could be fully characterised. Ethylenediamine was selected as a suitable model for the amine terminated hyperbranched materials.

For the model systems it was necessary that the conditions that were used met the necessary criteria for the modification of the polymers. The modifications had to be carried out using a solvent for the polymer ( i.e. DMSO, DMF, alcohols or water) and the only purification techniques used were those that could be utilised for the polymers. Three surfaces were highlighted by the sponsors of this work as being particularly interesting; t-butyl, which would produce large hydrophobic terminal groups; dimethylated amines, which were expected to have interesting materials properties and acid termini which should lead to zwitterionic hyperbranched polymers, (Figure 4.20).

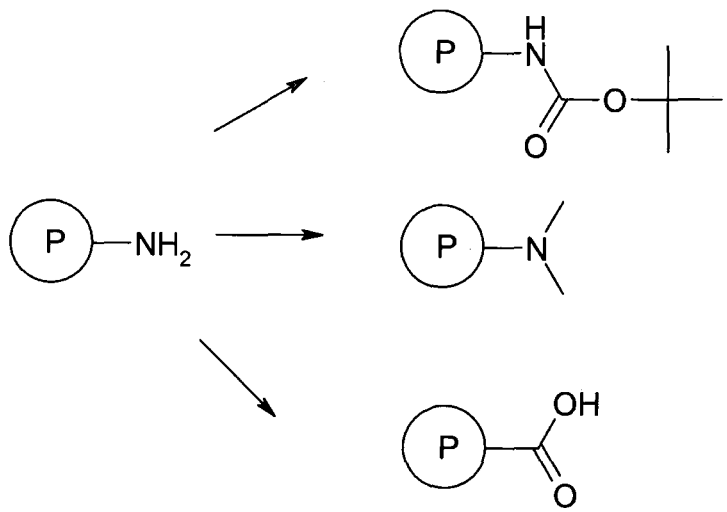



Figure 4.20 – The three end group modification reactions which were to be carried out on the polymers.

For the production of the polymers with the t-butyl end groups the agent di-tert-butyl dicarbonate was used, (Figure 4.21). DMSO was found to be a suitable solvent, and excess di-tert-butyl dicarbonate could be removed by adding water, which caused rapid decomposition of excess reagent into volatile by-products. Ethylenediamine was easily converted into the bis t-butyl derivative and under

these experimental conditions, analytically pure samples were obtained without recourse to further purification.

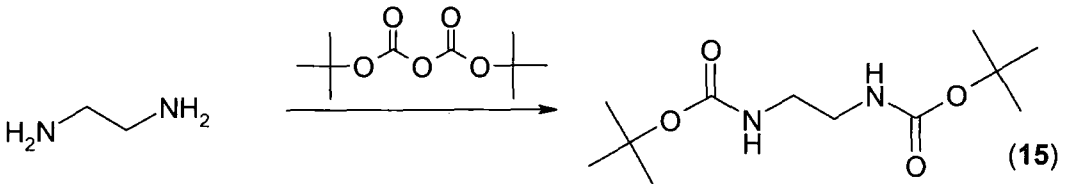



Figure 4.21 – The model reaction used to study the conversion of amine groups to t-butyl groups.

To produce polymers with an acid surface, the ring-opening of succinic anhydride was employed, (Figure 4.22), DMSO again proving to be the best solvent. The excess succinic anhydride could be extracted from the product by three extractions with hot toluene and three with hot acetone, a procedure which could easily be utilised for the polymer. Removal of all the excess succinic anhydride was confirmed by the absence of the distinctive resonance at 2.90 ppm in the $^{1}H$ NMR spectrum.

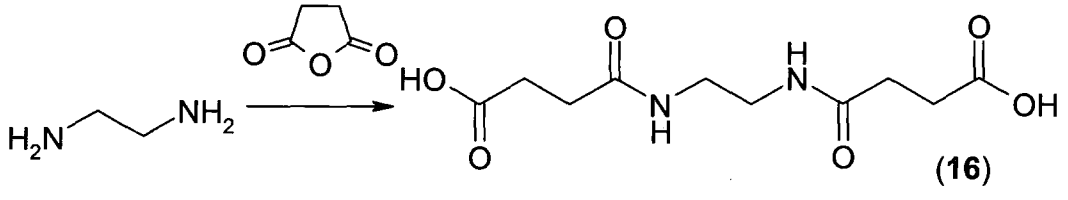



Figure 4.22 - The model reaction used to study the conversion of amine groups to carboxylic acid groups.

The development of a system to produce polymers with a dimethylated amine surface proved to be more difficult. Attempts were made to directly dimethylate a diamine using the Borch method, (Figure 4.23)[48] however it proved impossible to separate the product from the inorganic by-products using methods which could be adapted to the polymer. Attempts to couple 4-dimethylaminobenzoic acid to a diamine, (Figure 4.23), via DCC or CDI mediated coupling were unsuccessful as it proved impossible to remove excess 4-dimethylaminobenzoic acid.

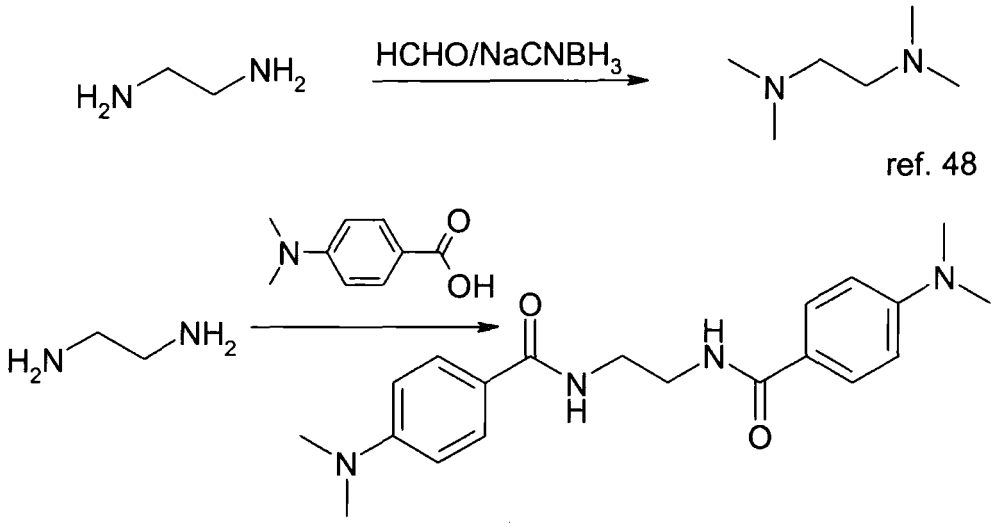



Figure 4.23 – The unsuccessful attempts to form dimethylated amine surface groups on an ethylenediamine model system.

Conjugate addition of 2-(dimethylamino)ethyl acrylate in a N,N-dimethylethanolamine solvent allowed successful production of a dimethylated amine, (**17**), (Figure 4.24).

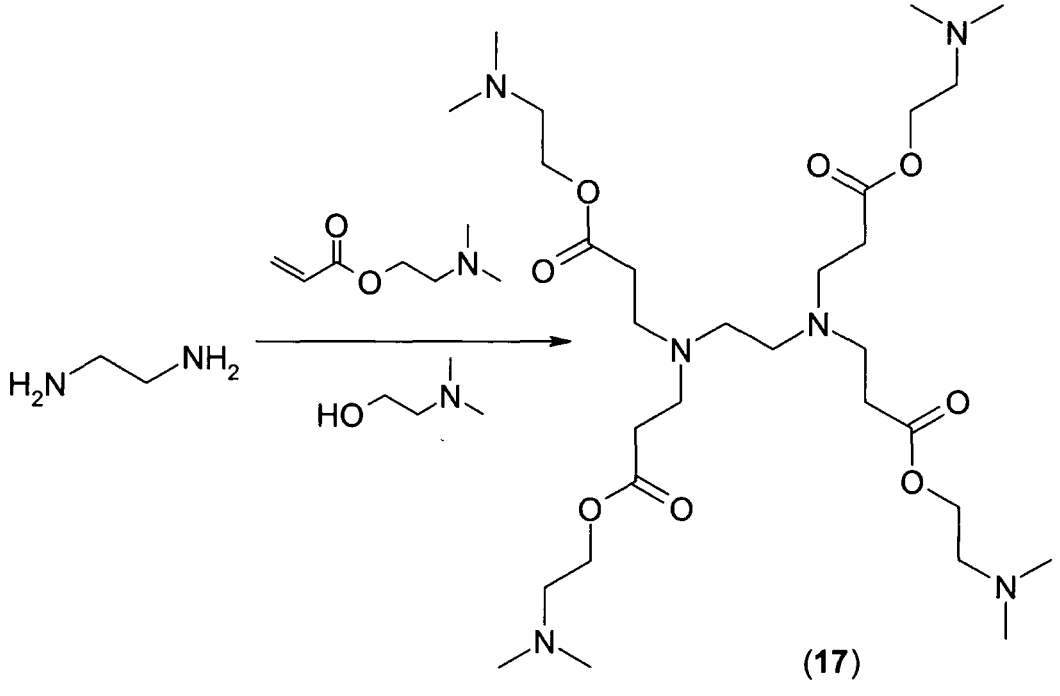



Figure 4.24 - The model for formation of dimethylated amine surface groups.

### 4.3.2 - Modifications of the end groups of hyperbranched polymers

The two step method was used to perform end group modifications in this work, with the amine terminated polymers being isolated and then subsequently reacted to introduce a chosen functionality on the surface. The reactions described above for the model compound were completed on the hyperbranched polymers to give products which could be expected to have the required end groups. It is difficult to directly quantify what groups are on the surfaces of each polymer, but hopefully due to the success of the model reactions and the differences in the properties of the resultant polymers from the starting materials it can be believed that the majority of the end groups have been converted to give the three required end-modified polymers. The samples which have been prepared will be tested in the sponsors laboratory in due course.

## 4.4 – Controlling the rate of polymerisation

It was established that the polymerisation to form the full generation analogues of the PAMAM dendrimers proceeded at a much slower rate than that to produce the polyamides and half-generation analogues, (Section 5.1.4.4). Attempts were made to allow the synthesis of the full generation analogues of the PAMAM dendrimers on a more convenient time scale.

The polymers in this work are all formed by the amidation reaction between deprotected primary amines and esters, which was discussed at length earlier, (Section 2.5). Amidation reactions with esters are known to be catalysed by base,[49] however the effect of base catalysis is greatly dependent on the structure of the reactants. When there is a good leaving group the formation of the tetrahedral intermediate can become rate limiting, a process which is aided by the presence of a proton donor in the material. It has been seen previously that ammonium salts added to an aminolysis reaction may in some instances serve to increase the rate of the amidation,[50,51] and the existence of both an acid and base catalysed pathway has been suggested,[52] although others have suggested that the observed rate increase may be due to a salt effect.[53]

Attempts were made to enhance the rate of polymerisation by introducing ammonium ion to the reaction mixture, (Figure 4.25). Ammonium trifluoroacetate (**18**) was added, which decomposes at the reaction temperature to release ammonia and trifluoroacetic acid. It was expected that at the elevated temperatures used for the reactions the trifluoroacetic acid produced would be lost over time, and the structure of the final polymer would not be affected. As the Boc protecting group is also acid labile the rate of removal of this group may be increased by the evolved trifluoroacetic acid. The analysis of the effects of this beneficial modification of the reaction protocol will be discussed later (Section 5.1.4.4).

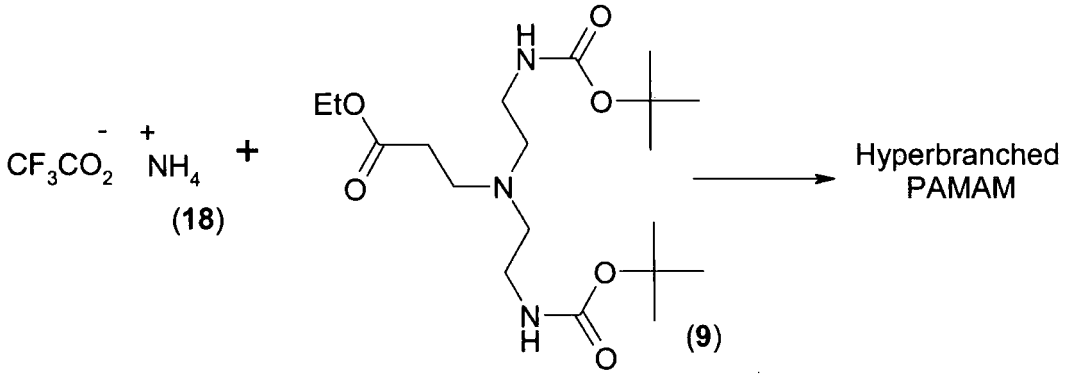



Figure 4.25 – The addition of trifluoroacetate to the production of hyperbranched PAMAMs in an effort to increase rate.

## 4.5 - Conclusions

Methods to control the degree of branching, molecular weight and surface functionality of hyperbranched polymers have been discussed. Through these methods it was hoped to control the features of the product polymers more precisely than a standard bulk step-growth polymerisation would allow.

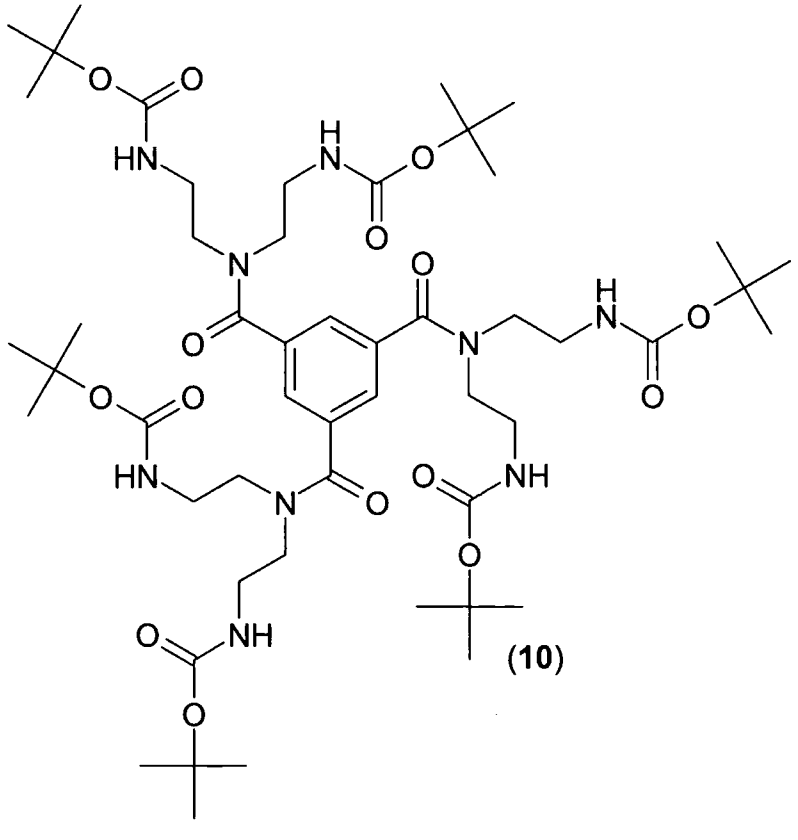
Attempts to control the molecular weight of the hyperbranched polymers were made through the use of $B_f$ functional cores. Two separate cores, one a low generation dendrimer and the second a bis amine capped polyethylene glycol were used in this study. In an attempt to reduce the degree of branching of the polymers, monomers with different functionalities were used. Two $AB_4$

monomers were synthesised and attempts to polymerise these were made, however the products of each of these reactions proved to be insoluble and difficult to characterise. An $AB_2$ and an AB monomer have been copolymerised to produce a branched soluble Nylon 2,4. End group modification reactions were used to allow control of the functionalities present at the termini of the product polymers. These reactions were first modelled using ethylenediamine, as the products from these model reactions were easier to analyse than the modified polymers themselves. Attempts have also been made to increase the rate of the polymerisation by adding ammonium trifluoroacetate to allow faster production of high molecular weight polymers.

## 4.6 - Experimental

### 4.6.1 – Synthesis of multifunctional cores

*{2-[{3,5-Bis-[bis-(2-tert-butoxycarbonylaminoethyl)carbamoyl]benzoyl}(2-tert-butoxycarbonylaminoethyl)amino]ethyl}carbamic acid tert-butyl ester,* **(10)**

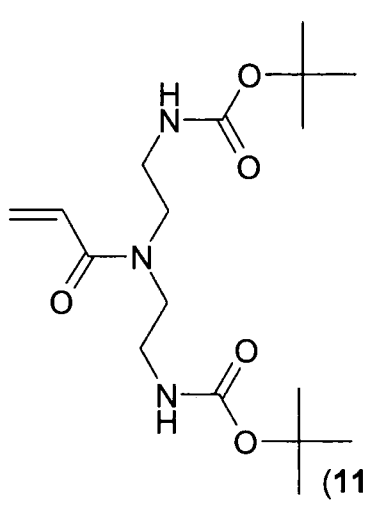


**(10)**

1,3,5-Benzenetricarbonyl trichloride (0.5g) was added to a 100mL litre two necked round-bottomed flask containing HPLC grade dichloromethane (50mL), this was put under a nitrogen atmosphere and cooled to 0°C. To this was added a solution of compound (**1**), (1.77g) and triethylamine (0.59g) in HPLC grade dichloromethane (25mL) dropwise over one hour. The solution was allowed to warm to room temperature and stirred for a further two hours. After this time the solvent was removed *in vacuo*. The resultant yellow solid was purified by recrystallisation from a 1:1 ethyl acetate:hexane mixture to give *{2-[{3,5-Bis-[bis-(2-tert-butoxycarbonylaminoethyl) carbamoyl] benzoyl} (2-tert-butoxycarbonyl aminoethyl)amino]ethyl}carbamic acid tert-butyl ester*, (**10**), as a white solid, (1.37g, 68.2%). Found; C, 56.76; H, 8.06; N, 11.47%; M/z (MALDI-TOF MS, 2,5 dihydroxybenzoic acid matrix) 1088 (Na) 1104 (K), ($ES^+$) 1066 (H) 1088 (Na). Calculated for $C_{51}H_{87}N_9O_{15}$; C, 57.45; H, 8.22; N, 11.82%; M 1065. $^1H$ NMR: $\delta_H$ (200 MHz; $CDCl_3$) 1.38 (s, 54H), 3.20 (s, 6H), 3.41 (s, 12H), 3.64 (s, 6H), 5.30 (bs, 6H), 7.51 (s, 3H). $^{13}C$ NMR: $\delta_C$ (100MHz; $CDCl_3$) 28.54ppm, 38.96, 46.10/50.08,[54] 79.67, 126.51, 137.02, 156.34, 170.92.

### 4.6.2 – Synthesis of $AB_4$ monomers

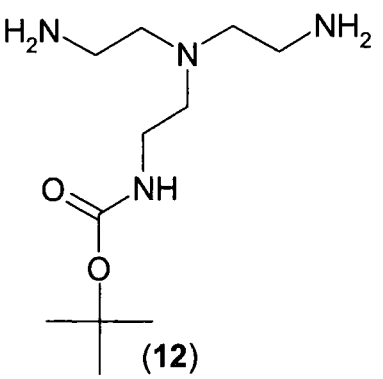
*{2-[Acryloyl-(2-tert-butoxycarbonylaminoethyl)amino]ethyl} carbamic acid tert-butyl ester,* (**11**)




(**11**)

Acroyl chloride (6.57g) was added to a one litre three necked round-bottomed flask, containing HPLC grade dichloromethane (500mL), this was put under a nitrogen atmosphere and cooled to O°C. To this was added a solution of compound (**1**) (20.06g) and triethylamine (9.2mL) in HPLC grade dichloromethane (200mL) dropwise over one hour. The solution was allowed to warm to room temperature and stirred for a further two hours. After this time the solvent was removed *in vacuo*. The resultant white solid was recrystallised from an ethyl acetate/hexane mixture (1:2), to give *{2-[Acryloyl-(2-tert-butoxycarbonylaminoethyl)amino] ethyl} carbamic acid tert-butyl ester*, (**11**) as white crystals, (14.71g, 62.2%). Found; C, 57.12; H, 8.84; N, 11.82; M/z (EI) 357. Calculated for $C_{17}H_{31}N_3O_5$; C, 57.12; H, 8.74; N, 11.76%; M 357. $^1H$ NMR: $\delta_H$ (200 MHz; $CDCl_3$) 1.42ppm (s, 18H), 3.28 (m, 4H), 3.52 (t, J=6Hz, 4H), 5.07 (bs, 2H), 5.68 (dd, J=2.1Hz, 10.5Hz, 1H), 6.36 (dd, J=2.1Hz, 16.8Hz, 1H), 6.63 (dd, J=10.5Hz, 16.8Hz, 1H). $^{13}C$ NMR: $\delta_C$ (100 MHz; $CDCl_3$) 28.46ppm, 39.47, 46.67/48.26, 79.50, 127.37, 128.73, 156.35, 167.61.

*[2-{Bis-(2-aminoethyl)amino}ethyl] carbamic acid tert-butyl ester,* (**12**)

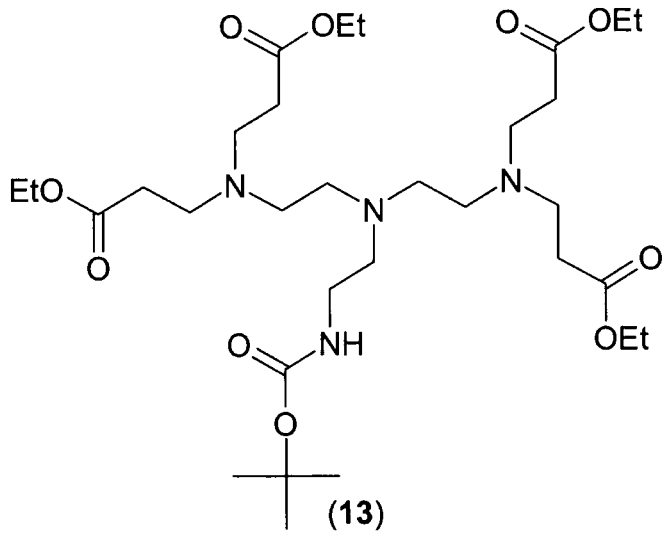



**(12)**

Following the literature procedure[55] tris-2-aminoethylamine (14.6g) was added to a 1 litre round bottom flask containing 500mL of dichloromethane. The flask was cooled to –78°C and to this was added a di-tert-butyldicarbonate (4.4g) solution in dichloromethane (250mL) dropwise over two hours. When the addition was completed the solution was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo* and then purified by column chromatography on silica with an eluant of chloroform:methanol:aqueous

ammonia (10:4:1) to give [2-{Bis-(2-aminoethyl) amino}ethyl] carbamic acid tert-butyl ester (**12**) as a yellow oil, (3.54g, 70.3%). $^{1}$H NMR: $\delta_H$ (300 MHz; $CD_3OD$) 1.48ppm (s, 9H), 2.53 (t, J=5.4Hz, 2H), 2.57 (t, J=6Hz, 4H), 2.73 (t, J=6Hz, 2H), 3.16 (m, 4H).[56] $^{13}$C NMR: $\delta_C$ (75 MHz; $CD_3OD$) 28.81, 39.66, 40.12, 55.54, 57.88, 79.71, 158.54.

*3-[{2-[{2-[Bis-(2-methoxycarbonylethyl)amino]ethyl}-(2-tert-butoxycarbonyl aminoethyl)amino]ethyl}—(2-ethoxycarbonylethyl)amino] propionic acid ethyl ester,* (**13**)

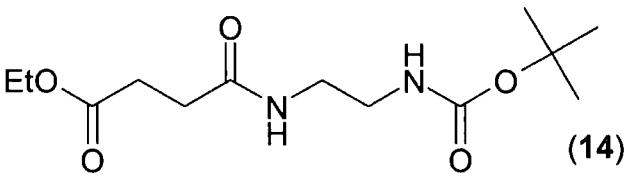



(**13**)

Compound (**12**), (3.29g) was added to a one-necked 250mL round bottomed flask containing ethanol (100mL). To this was added ethyl acrylate (8.22g). This was placed in the dark for two weeks and then the solvent removed *in vacuo*. The resultant pale yellow oil was purified by column chromatography on silica with an eluant of ethyl acetate to give *3-[{2-[{2-[Bis-(2-methoxycarbonylethyl) amino] ethyl} - (2-tert-butoxycarbonylaminoethyl) aminoethyl} - (2-ethoxycarbonylethyl) amino] propionic acid ethyl ester*, (**13**), as a colourless oil, (7.53g, 64.9%). Found; C, 57.11; H, 9.08; N, 8.53; M/z ($ES^+$) 647 (H), 669 (Na). Calculated for $C_{31}H_{58}N_4O_{10}$; C, 57.56; H, 9.04; N, 8.66%; M 646. $^{1}$H NMR $\delta_H$ (300 MHz; $CDCl_3$) 1.24ppm (t, J=7.2 Hz, 12H), 1.44 (s, 9H), 2.50 (m, 18H),[57] 2.77 (t, J=7.2Hz, 8H), 3.10 (q, J=5.7Hz, 2H), 4.11 (q, J=7.2Hz, 8H), 6.08 (bs, 1H). $^{13}$C NMR: $\delta_C$ (75 MHz; $CDCl_3$) 14.27ppm, 28.51, 32.39, 38.99, 49.47, 52.04, 52.59, 52.86, 60.39, 78.65, 156.23, 172.51.

### 4.6.3 – Synthesis of $AB_2$/AB co-polymers

*N-(2-tert-butyoxycarbonylaminoethyl)succinamic acid ethyl ester,* (**14**)

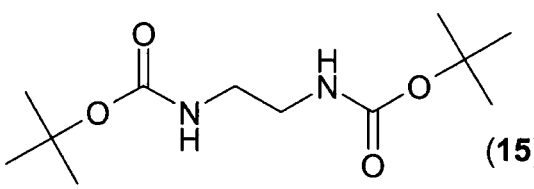



**(14)**

Compound (**6**), (20g) and triethylamine (13.89g) were added to a 500mL round bottom flask containing 250mL of dichloromethane which was cooled to -10°C. To this was added a solution of ethyl succinyl chloride (22.60g) in dichloromethane (250mL) dropwise over a period of one hour. The solution was allowed to warm to room temperature and stirred for a further two hours. After this time the solvent was removed *in vacuo* and the yellow solid produced was recrystallised twice from a mixture of 10:1 ethyl acetate:hexane to give *N-(2-tert-butyoxycarbonylaminoethyl) succinamic acid ethyl ester*, (**14**), as a white crystalline powder, (24.5g, 67.9%). Found; C, 54.00; H, 8.44; N, 9.65%; M/z ($CI^+$) 289 (H). Calculated for $C_{13}H_{24}N_2O_5$; C, 54.15; H, 8.39; N, 9.72%; M 288. $^1H$ NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.24ppm (t, J=6.9Hz, 3H), 1.42 (s, 9H), 2.45 (t, J=6.9Hz, 2H), 2.64 (t, J=6.9Hz, 2H), 3.23 (t, J=5.4Hz, 2H), 3.32 (m, 2H), 4.13 (q, J=6.9Hz, 2H), 5.10 (bs, 1H), 6.44 (bs, 1H). $^{13}C$ NMR: $\delta_C$ (50 MHz; $CDCl_3$) 14.28ppm, 28.47, 29.68, 31.06, 40.34, 40.63, 60.80, 79.64, 156.87, 172.24, 173.12.

### 4.6.4 – Surface modification reactions

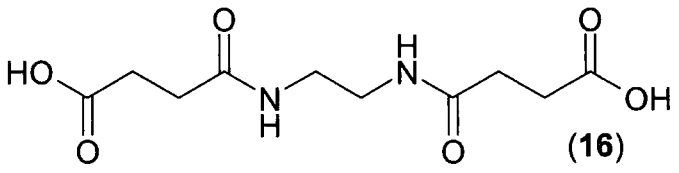
*Model of t-butylation of surface groups*




**(15)**

Ethylenediamine (0.5g) was added to a 50mL round bottom flask containing dimethyl sulfoxide (25mL). Di-tert-butyl dicarbonate (5.45g) was added slowly and the reaction left to stir at room temperature for 18 hours. After this time 10mL of water was added and the solvent removed *in vacuo* to leave (2-tert-butoxycarbonylaminoethyl) carbamic acid tert-butyl ester, (**15**), as a white solid upon which no further purification was attempted, (2.13g, 98.3%). Found; C, 55.31; H, 9.38; N 10.62%; M/z ($ES^+$) 283 (Na). $C_{12}H_{24}O_4N_2$ requires; C, 55.36; H, 9.29; N, 10.76%; M 260. $^1H$ NMR: $\delta_H$ (300 MHz; $CDCl_3$) 1.43 ppm (s, 18H), 3.21 (s, 4H), 4.92 (bs, 2H). $^{13}C$ NMR: $\delta_C$ (50MHz; $CDCl_3$) 28.51ppm, 40.93, 79.53, 156.48.

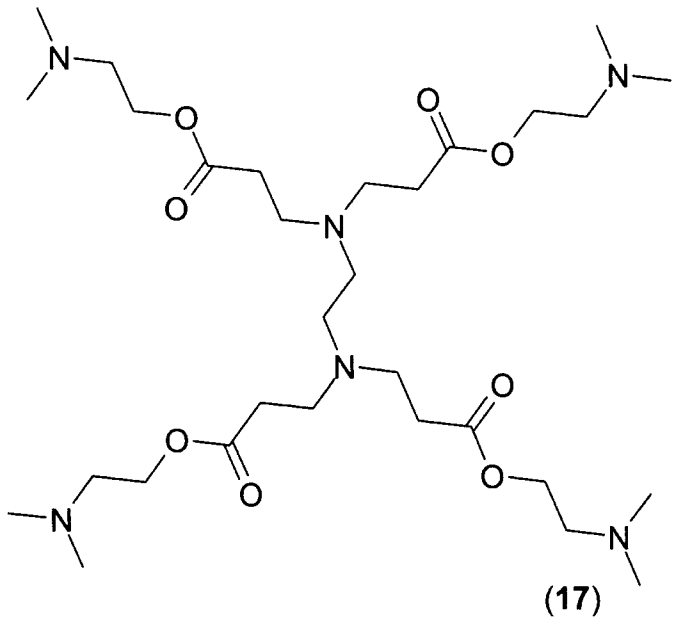
*Model of conversion of surface groups to carboxylic acids*




**(16)**

Ethylenediamine (1g) was added to a 50mL round bottom flask containing 25mL of dimethyl sulfoxide which was heated to 60°C. Succinic anhydride (5.00g) was added slowly and the reaction mixture heated for 18 hours. After this time the solvent was removed *in vacuo* to leave the target compound as a white solid. Toluene (25mL) was added to the flask and the mixture heated to reflux and stirred for three hours. The toluene was then decanted off and the process repeated three times; this procedure was subsequently repeated using acetone, to give *N-[2-(3-carboxypropionyl amino) ethyl] succinamic acid*, (**16**), as a white solid, (3.87g, 88.7%). Found C, 46.10; H, 6.21; N, 10.62 %; MS, no parent ion seen. $C_{10}H_{16}N_2O_6$ requires; C, 46.15; H, 6.20; N, 10.76% ; M 260. $^1H$ NMR: $\delta_H$ (200 MHz; DMSO) 2.26 ppm (t, J=6.6Hz, 4H) 2.38 (t, J=6.6Hz, 4H) 3.02 (s, 4H) 7.83 (bs, 2H). $^{13}C$ NMR: $\delta_C$ (100MHz; DMSO) 29.17ppm, 30.07, 38.38, 171.18, 173.96.

*Model of conversion of surface groups to dimethylated amines*



**(17)**

Ethylenediamine (0.5g) was added to a 50mL round bottom flask containing N,N-dimethylethanolamine (25mL). 2-(Dimethylamino)ethyl acrylate (7.15g) was added slowly and the reaction left in the dark for fourteen days. After this time the solvent was removed *in vacuo* to give *3-{(2-{bis-[2-(2-dimethylaminoethoxycarbonyl) ethyl] amino} ethyl) - [2- (2-dimethylaminoethoxy carbonyl)-ethyl]-amino} propionic acid 2-dimethylamino ethyl ester*, **(17)** as a yellow/orange oil (4.87g, 92.5%). Found; C, 56.08; H, 9.24; N, 12.09%;[58] MS (ES) 633 (H), 655 (Na). Calculated for $C_{30}H_{60}N_6O_8$; C, 56.94; H, 9.56; N, 13.28%; M 632. $^1$H NMR: $\delta_H$ (300MHz; $CDCl_3$) 2.20ppm (s, 12H) 2.34 (t, J=7.2Hz, 4H) 2.41 (s, 2H) 2.48 (t, J=6.0Hz, 4H) 2.69 (t, J=7.2Hz, 4H) 4.08 (t, J=6.0Hz, 4H). $^{13}$C NMR: $\delta_C$ (50MHz; $CDCl_3$) 32.67ppm, 45.81, 49.71, 52.30, 57.86, 62.23, 172.56.

### 4.6.5 – Synthesis of ammonium salts

*Synthesis of ammonium trifluoroacetate, (18)*

$$CF_3CO_2^- \quad NH_4^+$$

Ammonia (33% aqueous solution) (10mL) was added to a 50mL round bottom flask containing 25mL of water. Trifluoroacetic acid (2.28g) was added dropwise with stirring and then the solvent was removed *in vacuo* to leave ammonium trifluoroacetate as a white solid, (2.44g, 93.1%). Found; C, 18.29; H, 3.07; N, 10.60; $C_2H_4NF_3O_2$ requires C, 18.33; H, 3.08; N, 10.69. $^{13}C$ NMR: $\delta_C$ (100MHz; $D_2O$) 116.48 ppm (d, J=291Hz),[59] 163.09 (d, J=3.5Hz). $^{19}F$ NMR: $\delta_F$ (188MHz; $D_2O$) –76.21ppm.

### 4.6.6 - Synthesis of polymers

The synthesis of all polymers in this chapter broadly followed the procedure outlined earlier, (Chapter 2.9). As an example the synthesis of an $AB_2$/AB copolymer with a content of 0.5 mole fraction $AB_2$ and 0.5 mole fraction AB is described here. To the polymerisation vessel fitted with an overhead stirrer, an inlet for nitrogen, and an outlet fitted with a cold trap was added (**9**), (4.06g) and (**14**) (1.36g). The flask was purged with nitrogen, and then heated to 230°C at a ramp of 10°C per minute and this temperature was maintained for 0.5-24 hours in a series of experiments. Throughout the polymerisation a constant stream of nitrogen was passed through the apparatus. After polymerisation the flask was allowed to cool, and the entire contents dissolved in water. The water was removed by freeze-drying to yield the polymer as an orange/brown solid which was stored in a vacuum desiccator.

## 4.7 – References


1 - Flory, P. J. in *Principles of Polymer Chemistry*, chapter. 9. Cornell University Press, Ithaca, New York, **1953**.

2 - Yan, D.; Zhou, Z. *Macromolecules* **1999**, *32*, 819.

3 - Hölter, D.; Burgath, A.; Frey, H. *Acta Polym.* **1997**, *48*, 30.

4 - Johansson, M.; Malmström, E.; Hult, A. *J. Polym. Sci.: Part A: Polym. Chem.* **1993**, *31*, 619.

5 - Malmström, E.; Hult, A. *Macromolecules* **1996**, *29*, 1222.

6 - Bharathi, P.; Moore, J. S. *Macromolecules* **2000**, *33*, 3212.

7 - Malmström, E.; Johansson, M.; Hult, A. *Macromolecules* **1995**, *28*, 1698.

8 - Hobson, L. J.; Feast, W. J. *Chem. Commun.* **1997**, 2067.

9 - Gitsov, I.; Fréchet, J. M. J. *Macromolecules* **1994**, *27*, 7309.

10 - Gitsov, I.; Wooley, K. L.; Hawker, C. J.; Ivanova, P. T.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 5321.

11 - Desai, A.; Atkinson, N.; Rivera Jr., F.; Devonport, W.; Rees, I.; Branz, S. E.; Hawker, C. J. *J. Pol.Sci. Part A: Polym. Chem.* **2000**, *38*, 1033.

12 - Iyer, J.; Fleming, K.; Hammond, P. T. *Macromolecules* **1998**, *31*, 8757.

13 - Aoi, K.; Motoda, A.; Okada, M.; Imae, T. *Macromol. Rapid Comm.* **1997**, *18*, 945.

14 - van Hest, J. C. M.; Delnoye, P. A. P.; Baars, M. W. P. L.; van Genderen, M. H. P., Meijer, E. W. *Science* **1995**, *268*, 1592.

15 - Leduc, M. R.; Hawker, C. J.; Dao, J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 11111.

16 - Mecerreyes, D.; Dubois, Ph.; Jérôme, R.; Hedrick, J. L.; Hawker, C. J. *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 1923.

17 - Emrick, T.; Hayes, W.; Fréchet, J. M. J. *J. Polym. Sci. Part A: Polym. Chem.* **1999**, *37*, 3755.

18 - Carlmark, A.; Vestberg, R.; Malmström Jonsson, E. *Polymer* **2002**, *43*, 4237.

19 - Brenner, A. R.; Voit, B. I.; Massa, D. J.; Turner, S. R. *Macromol.Symp.* **1996**, *102*, 47.

20 - Hölter, D.; Frey, H. *Acta Polymer.* **1997**, *48*, 298.

21 - Galina, H.; Lechowicz, J.B.; Walczak, M. *Macromolecules* **2002**, *35*, 3253.

22 - Jo, W. H.; Lee, Y. U. *Macromol. Theory Simul.* **2001**, *10*, 225.

23 - Hawker, C. J.; Lee, R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4583.

24 - Hanselmann, R.; Hölter, D.; Frey, H. *Macromolecules* **1998**, *31*, 3790.

25 - Möck, A.; Burgath, A.; Hanselmann, R.; Frey, H. *Macromolecules* **2001**, *34*, 7692.

26 - Sunder, A.; Hanselmann, R.; Frey, H.; Mülhaupt, R. *Macromolecules* **1999**, *32*, 4240.

27 - Hawker, C. J.; Chu, F. *Macromolecules* **1996**, *29*, 4370.

28 - Ishida, Y.; Sun, A. C. F.; Jikei, M.; Kakimoto, M. -A. *Macromolecules* **2000**, *33*, 2832.

29 - Lach, C.; Frey, H. *Macromolecules* **1998**, *31*, 2381

30 - Yamanaka, K.; Jikei, M.; Kakimoto, M. -A. *Macromolecules* **2001**, *34* , 3910.

31 - Bolker, H. I. in *Natural and Synthetic Polymers, An Introduction*, Marcel Dekker Inc. New York, **1974** p324-331.

32 - Frey, H.; Hölter, D. *Acta Polym.* **1999**, *50*, 67.

33 - Kricheldorf, H. R.; Zang, Q. -Z.; Schwarz, G. *Polymer* **1982**, *23*, 1821.

34 - Kricheldorf, H. R.; Stöber, O.; Lübbers, D. *Marcomol. Chem. Phys.* **1995**, *196*, 3549.

35 - Jayakannan, M.; Ramakrishnan, S. *J. Polym. Sci. Part A: Polym. Chem.* **1998**, *36*, 309.

36 - Jayakannan, M.; Ramakrishnan, S. *J. Appl. Polym. Sci.* **1999**, *74*, 59.

37 - Jikei, M.; Fujii, K.; Yang, G.; Kakimoto, M. –A. *Macromolecules* **2000**, *33*, 6228.

38 - Jikei, M.; Fujii, K.; Kakimoto, M. -A. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 3304.

39 - Kricheldorf, H. R.; Bolender, O. *J. M. S. – Pure Appl. Chem.* **1998**, *A35*, 903.

40 - Kagiya, T.; Narisawa, S.; Manabe, K.; Kobata, M.; Fukui, K. *J. Pol. Sci. A-1*, **1966**, *4*, 2081.

41 - Kagiya, T.; Izu, M.; Matsuda, T.; Fukui, K. *J. Pol. Sci. A-1* **1967**, *5*, 15.

42 - Wang, Q.; Shao, Z.; Yu, T. *Polym. Bull.* **1996**, *36*, 659.

43 - Wooley, K.L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, *5*, 1509.

44 - Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, J.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466.

45 - Kim, Y. H.; Webster, O. W. *J. Am. Chem. Soc.* **1990**, *112*, 4592.

46 - Kim, Y. H.; Webster, O. W. *Macromolecules* **1992**, *25*, 5561.

47 - Spindler, R.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 4809.

48 - Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.

49 - Bunnett, J. F.; Davis, G. T. *J. Am. Chem. Soc.* **1960**, *82*, 665.

50 - Glasoe, P. K.; Kleinberg, J.; Audrieth, L. F. *J. Am. Chem. Soc.* **1939**, *61*, 2387.

51 - Jung, S. L.; Miller, J. G.; Day, A. R. *J. Am. Chem. Soc.* **1953**, *75*, 4664.

52 - Hawkins, P. J.; Piscalnikow, I. *J. Am. Chem. Soc.* **1955**, *77*, 2771.

53 - Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 675.

54 - Experimentally two signals for the $CH_2$ group adjacent to the middle nitrogen are seen when it is part of an amide group. After consultation with Dr. A. Kenwright these have been ascribed to be due a large cis/trans effect across this amide bond due to restricted rotation. A cis/trans effect is seen in other carbon signals but is smaller and an average value in these cases has been given.

55 - Tecilla, P.; Tonellato, U.; Veronese, A.; Felluga, F.; Scrimin, P. *J. Org. Chem.* **1997**, *62*, 7621.

56 - The amine and amide protons are not observed in $CD_3OD$.

57 - This resonance with intensity equivalent to eighteen protons is believed to be composed of four separate overlapping resonances, a triplet with intensity two, a triplet and a quartet with intensity four and a triplet with intensity eight. Due to their overlapping it is thought that they appear as one large multiplet centred at 2.50ppm.

58 - It was noted by the analyst that the sample was gaining weight. This could be explained by the sample being hydroscopic and gaining water. This would explain the observed deficiency in nitrogen and carbon.

59 - Coupling in this spectrum is between the carbon atoms and the fluorine atoms as the spectra have been acquired with hydrogen decoupled.

# Chapter Five
# Characterisation of hyperbranched polymers

## Chapter Five – Characterisation of hyperbranched polymers

The characterisation of the hyperbranched polymers synthesised in this work has concentrated on two features of their structure, molecular weight and degree of branching. These are the most commonly measured properties of hyperbranched polymers and quantification of these two features is the first step in the characterisation of such materials.

Most methods of molecular characterisation of polymers involve the study of polymers in dilute solution. The hyperbranched polymers studied here were soluble only in water, DMSO, DMF and alcohols which has complicated the characterisation of these materials.

### 5.1 – Molecular weight distribution

The properties of macromolecules are fundamentally linked to their size, which is normally quantified by referring to the molecular mass, more commonly called the molecular weight. This is, in turn, intimately related to the degree of polymerisation of the polymer. With the notable exception of dendrimers, a polymer sample consists of an assembly of macromolecules with a range of molar masses. This distribution of molecular masses is often characterised in terms of molar mass averages, the two most common being the number average molar mass ($\overline{M}_n$) and the weight average molar mass ($\overline{M}_w$).

The number average molar mass is defined by the equation below.

$$\overline{M}_n = \frac{\sum N_i M_i}{\sum N_i}$$

Where $N_i$ equals the number of molecules i with mass $M_i$.

The weight average molar mass is defined by the equation below.

$$\overline{M}_w = \frac{\sum N_i M_i^2}{\sum N_i M_i}$$

Often the polydispersity index is quoted as a measure of the breadth of the molar mass distribution. This quantity is simply the ratio of the weight average and number average molecular masses, $\overline{M}_w / \overline{M}_n$.

Theoretical work on the expected molecular weight distribution for hyperbranched polymers has been discussed previously (Section 1.2.5). The discussion here is confined to the methods of measuring this distribution. Much work has been completed to quantify the molecular weight distribution for hyperbranched polymers. The commonly used methods include size exclusion chromatography (SEC), vapour pressure osmometry (VPO), nuclear magnetic resonance spectroscopy (NMR) and matrix assisted laser desorption time of flight mass spectrometry (MALDI-TOF-MS).[1]

### 5.1.1 – Size exclusion chromatography of polyamidoamine hyperbranched polymers with amine terminal groups using linear standards

Size exclusion chromatography (SEC) (also known as gel permeation chromatography, GPC) is the most common method employed for finding molecular weight data on a routine basis in a polymer synthesis laboratory. An SEC set up consists of a pump, a column where the separation takes place and a detector monitoring the composition of the effluent from the column. The column contains a gel most commonly made from polystyrene beads synthesised by cross-linking styrene in different ratios with divinyl benzene. In the solvent swollen gel there are a range of cavity sizes.

As the injected polymer molecules pass along the column the molecules diffuse into those pores which are sufficiently large and reside there for a time before diffusing back into the flowing stream, consequently the smaller molecules are

delayed longer. The separation is on the basis of hydrodynamic volume and is a purely entropic process independent of adsorption or partition between two phases.

Traditionally the SEC technique depended on calibration using monodisperse standards (usually polystyrene) whose molecular weights had been determined by an absolute technique, e.g. osmometry or light scattering. It is found that a plot of elution time versus the logarithm of the molecular weight is approximately linear over several orders of magnitude. It must be remembered when considering the SEC results for non-linear polymers that separation is on the basis of molecular volume rather than molecular weight. A branched polymer is more compact than a linear one of an identical molecular weight and will take longer to elute. This means that the simple correlation of elution time compared to linear standards will not yield an accurate molecular weight value for a branched polymer. Many of the literature reports of hyperbranched polymer synthesis involve calibration against linear standards, despite the underestimation of molecular weight inherent in this technique. The determination of molecular weights for polymers of unusual topology is an active area of research and debate at present.

Many solvents are used in SEC systems, the two most common being tetrahydrofuran (THF) and chloroform. In an attempt to solubilise the hyperbranched polyamidoamine polymers in THF or chloroform the amine end groups of the polymers were modified to t-butyl termini (Section 4.3). The resultant polymers were soluble in chloroform, although not in THF. The chloroform soluble samples obtained were analysed by SEC using TRI-SEC detection equipment and software with a chloroform eluant, with the resultant traces being multi-modal with a long tail due to adsorption. It proved impossible to extract any meaningful molecular weight data from these traces. There is a literature precedent for hyperbranched polyamides producing multi-modal SEC traces.[2] In that case the observation was explained in terms of aggregate formation in the solutions as when the SEC solvent was altered to prevent aggregation mono-modal distributions were produced. It is possible that aggregates are forming in the samples investigated here and that these caused the

observed SEC results, unfortunately there was no possibility of altering the eluant to replicate the previously reported conditions.

The majority of SEC analysis is still based on organic solvents although the range of columns for use with more polar solvents has increased in recent years. The solvents and columns available for SEC now cover the range of polarities from hexane to water, the largest challenge for aqueous SEC, and for SEC in other polar solvents, being to avoid the adsorption of polymers onto the column material, which occurs frequently to the detriment of the column and the validity of the analysis.

The SEC traces for the polymer samples in this study were recorded using an aqueous SEC system in the sponsors laboratory the eluant consisting of 95% water and 5% acetic acid. The acetic acid prevents the aggregation of the polymers by giving them a positively charged surface, which should also prevent their interaction with the column walls. In initial studies a series of six monodisperse Shodex Pullulan polysaccharide standards having molecular weights of 504 (triose), 12200, 23700, 100000, 380000 and 853000 were used as calibrants. These provided a good straight line calibration against which the molecular weight data for the hyperbranched PAMAM samples was correlated. The elution volumes for the hyperbranched polyamidoamines were compared with these standards using a refractive index (RI) detector. The data produced, (Figure 5.1), showed an increase in molecular weight with time. It was appreciated that this data would not be precise, due to calibration against linear standards, but it was expected to provide a reasonable qualitative measure. In view of the fact that highly branched materials were being measured using linear standards the true molecular weights were expected to be somewhat higher than the observed values. The data used for the construction of figure 5.1 (and all other SEC traces contained within this work) was taken from duplicate runs, which generally agreed within 5%, with the maximum observed error being 15%. Because of limited instrument time it was not possible to complete further runs to establish a reliable estimate of errors and hence throughout this work no error bars are recorded on graphs of results from SEC.

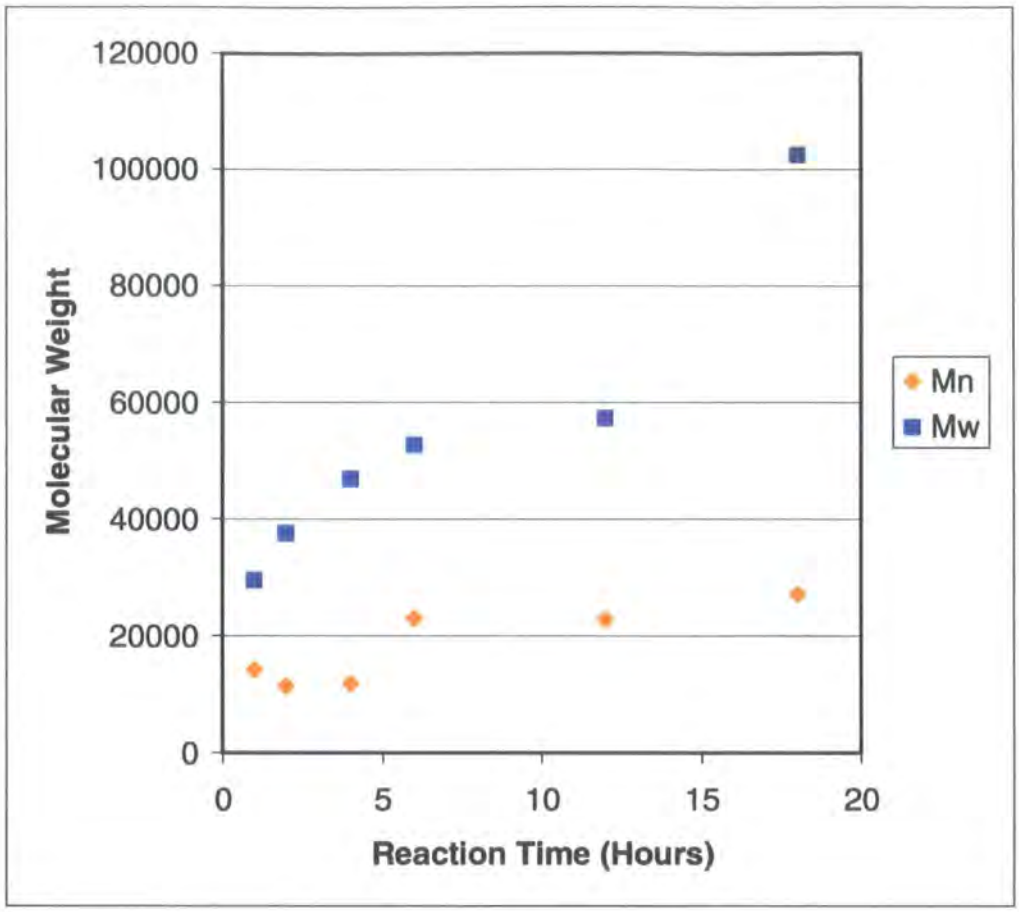



Figure 5.1 – The molecular weights of the hyperbranched polyamidoamines from aqueous SEC using calibration against a series of linear standards.

As will emerge later, (Section 5.1.4), these apparently encouraging results, indicating the anticipated increases in molecular weight and polydispersity with reaction time are not reliable.

### 5.1.2 – Light scattering

An absolute method for determining the molecular weight of the polymers was sought and the static light scattering of these molecules was investigated. The light which is elastically scattered from a polymer can be analysed and the data obtained related to the weight average molecular weight ($\overline{M}_w$). Using such techniques it was hoped to obtain some absolute data for the molecular weight of the polymers produced in this study.

Scattering of light results from the interaction of molecules with the oscillating electric field of the radiation, which forces the electrons to move in one direction and the nuclei to move in the opposite direction. The oscillating dipole is a source of electromagnetic radiation and the molecules emit scattered light in all directions. The majority of the scattered light is scattered elastically (Rayleigh scattering) although some is scattered inelastically (Raman scattering); the latter containing information about bond vibrations. Elastically scattered light from dilute polymer solutions enables $\overline{M}_w$ and values for the Flory-Huggins interaction parameter and the radius of gyration to be calculated. In the study of dilute polymer solutions only the scattering due to polymer molecules is wanted and thus the ratio of the intensity of the scattered light ($I_s$) to the intensity of the incident light ($I_0$) is measured at a given angle and is defined as the excess Rayleigh ratio ($R_\theta$). The scattering intensity is dependent on a number of solvent and particle parameters, the relationship commonly being written in the form shown below.

$$\frac{Kc}{R_\theta} = \frac{1}{M}\left(1 + \frac{16\pi^2 R_g^{\,2}}{3\lambda_o^{\,2}}\sin^2\left(\frac{\theta}{2}\right)\right)$$

Where c is the weight concentration, M is the weight average molecular weight, $A_2$ is the second virial coefficient (indicative of solute-solvent interactions), $R_g$ is the radius of gyration, $\theta$ is the scattering angle, $\lambda_0$ is the vacuum wavelength of the incident radiation and K is the optical constant.

The term K is a compound construction which is given by the expression below.

$$K = \frac{4\pi^2 n_o^{\,2}}{\lambda_o^{\,4} N_A}\left(\frac{dn}{dc}\right)^2$$

Where $N_A$ is Avogadro's number, $n_0$ is the solvent refractive index and (dn/dc) is the analyte specific refractive index increment.

Once (dn/dc) has been determined, (Section 5.1.3), then the optical constant has a fixed value for the system in question. The angular dependence of the term used to describe the excess Rayleigh ratio arises from interference effects due to multiple scattering from a single particle. These must be accounted for in polymers as the molecules cannot always be assumed to be point scatterers. The equation derived describes a three dimensional surface, but it is usual to reduce this to two dimensions by plotting $Kc/R_\theta$ against $\sin^2(\theta/2)+k'c$, where k' is an arbitrary constant chosen such that $\sin^2(\theta/2) \approx k'c$.

A grid-like graph (referred to as a Zimm plot) is obtained, consisting of two sets of lines, one connecting points of constant c, the other connecting points of constant $\theta$. The two sets of lines have a common intercept of $1/M_w$ when $\theta = 0^\circ$. Other information such as radius of gyration and Flory-Huggins parameters can be obtained from the gradients of the lines and the shape of the graph.

The hyperbranched polymers described here were analysed using a multi-angle static light scattering array to try to obtain information about the molecular weight. This data was processed to produce a Zimm plot, (Figure 5.2).

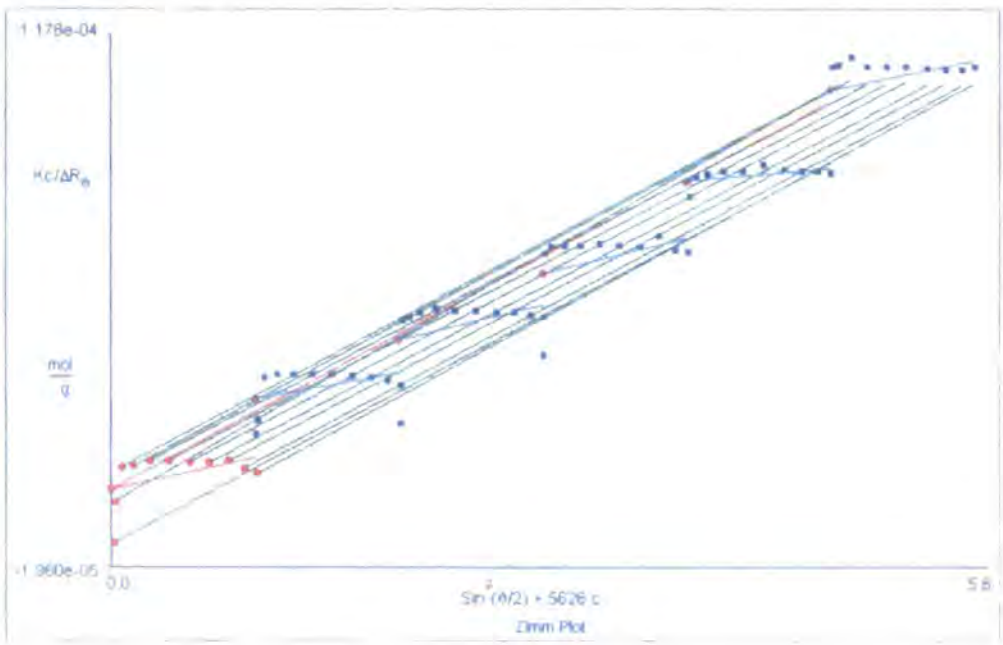



Figure 5.2 – An example of a Zimm plot produced for a hyperbranched polyamide prepared using a polymerisation time of 5 hours.

When the data is plotted and extrapolated the results indicate that the polymer has a molecular weight ($\overline{M}_w$) of 3 010 000. This was a surprising and probably spurious result. It was explained by observing the interaction of the polymer solution with the laser beam. The light leaving the sample cell was red whilst the incident light was green, and by measuring the absorption spectrum of the polymer solution it could be seen that it was absorbing light at the wavelength of the source (532 nm), (Figure 5.3). The polymer shows a strong absorption maximum in the ultra-violet region of the spectrum with the shoulder of this band still being significant at 532nm. This prevents use of this wavelength for light scattering measurements. Meaningful molecular weight data could not be obtained by this technique without using a laser of a different wavelength which was not accessible to the author, so this approach was abandoned without further work.

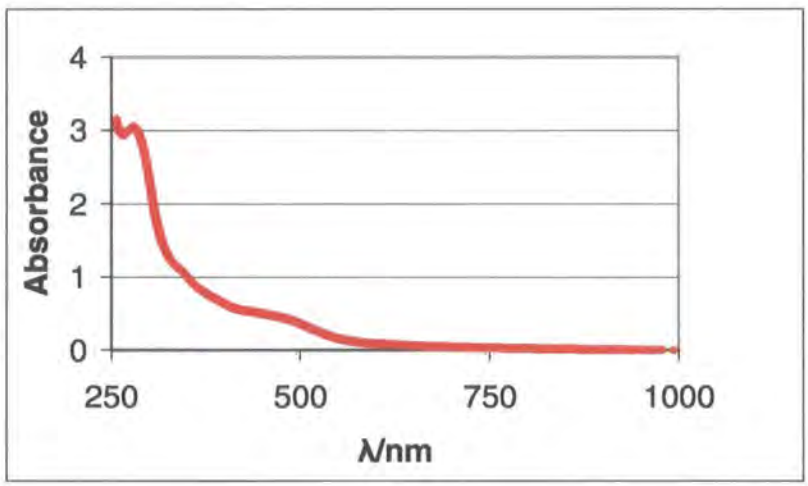



Figure 5.3 – The absorbance spectrum of a hyperbranched polyamide prepared with a polymerisation time of 5 hours in a solution of 95% water, 5% acetic acid.

### 5.1.3 - Refractive index increment determination

The refractive index increment (dn/dc) of a given polymer/solvent pairing shows how the refractive index of a dilute solution of the polymer changes with concentration. The determination of this quantity is necessary to obtain molecular weight information for the polymer from light scattering, either static light

scattering, (Section 5.1.2), or from a SEC system with a light scattering detector, (Section 5.1.4). It is necessary for an accurate value of this quantity to be known so that the optical constant K (Section 5.1.2) can be calculated. A measurement of (dn/dc) was performed upon the hyperbranched polymers in a 95% water/5% acetic acid solution.

The difference in refractive index between a solution and its solvent ($\Delta n$) was measured for a series of different solution concentrations. This was achieved by using a differential refractometer containing a cell with two compartments, one for the solvent and one for the solution. The cell used had a square cross section which was split into two compartments by a partition allowing both compartments to act as triangular prisms, (Figure 5.4). A monochromatic light beam is introduced perpendicular to the cell wall and if both compartments are filled with solvent it passes through undeflected (apart from a small shift due to the partition). Once the second compartment is filled with the polymer solution the beam is refracted as it passes through. The magnitude of the deflection of the beam can be measured using a microscope, and the difference in the refractive index of the liquids in both cell compartments can be calculated, as the deflection of the image of the slit is proportional to $\Delta n$.

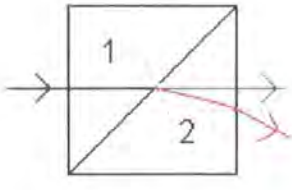



Figure 5.4 – Schematic view of the cell used in a differential refractometer, showing the deflection of a beam (red) if compartment two is filled with solution, compared to an undeflected beam (blue) if compartment two is filled with the same pure solvent as compartment one.

The refractive index was measured for a selection of hyperbranched polymers at a variety of different concentrations and wavelengths, (Figure 5.5). From the

gradients of these graphs the (dn/dc) for each polymer/solvent combination at a temperature of 25°C could be calculated.

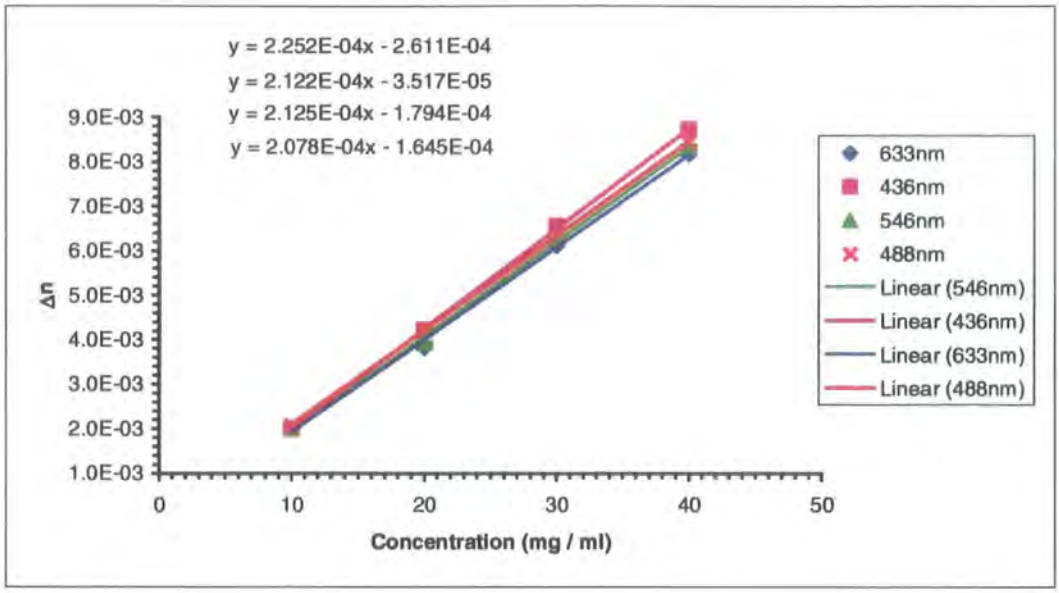



Figure 5.5 – An example of the concentration dependence of the refractive index of a hyperbranched polyamide prepared with a polymerisation time of 5 hours in a 95% water/5% acetic acid solution.

This data shows the behaviour of the refractive index with concentration at four different wavelengths. The difference in the refractive index between the solution and the solvent ($\Delta n$) can be seen to increase linearly with concentration and from the gradient of these lines the refractive index increment (dn/dc) at each wavelength can be calculated.

The refractive index is wavelength dependent and can be shown to be proportional to $\lambda^{-2}$. If measurements are to be made at a different wavelength to those available in the differential refractometer it is normal to carry out measurements at the wavelengths available and to extrapolate to the wavelength required. Experiments were carried out at four different wavelengths, (Figure 5.6) and the wavelength dependence of dn/dc was established. The data shown here is representative of that seen for all of the samples studied, differences occurring as a result of structural or molecular weight variations being minimal.

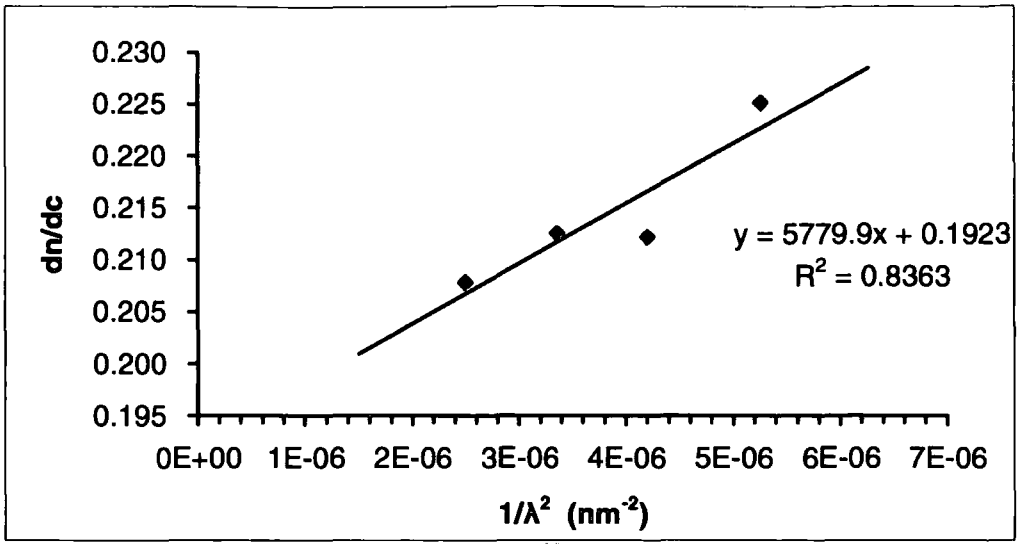



Figure 5.6 – The variation of dn/dc with wavelength for the hyperbranched polyamide prepared using a polymerisation time of 5 hours.

A value for the (dn/dc) was established, this being used to calculate the molecular weight in the static light scattering and the SEC-MALLS experiments.

### 5.1.4 – Size exclusion chromatography, using a multi-angle laser light scattering detector (SEC-MALLS)

A major limitation of conventional SEC using only a concentration detector such as a refractometer, is that it is unable to distinguish between the effects of molecular weight and structural effects which change molecular size. This causes problems in the analysis of non-linear polymers as an increase in molecular weight may not be accompanied by an equivalent increase in molecular size. Furthermore the analysis is based on the assumption that there is no interaction between the individual polymer molecules or between the polymer molecules and the column and that separation is solely on the basis of molecular size in solution, the hydrodynamic volume. In recent years there has been a drive to acquire more information from SEC, motivated in part by the need to characterise an ever increasingly complex array of new polymers. It has become common to use a laser light scattering detector in conjunction with SEC separation to give a measure of molecular weight which is independent of molecular structure. The

absolute molecular weight data from a light scattering detector can be used in conjunction with the chromatographic separation from the SEC column. Often a refractometer and a viscometry detector are also used and if the polymers are separated only on the basis of a size exclusion mechanism universal calibration can be applied giving a wealth of other information about the polymers, including true molecular weight distribution, intrinsic viscosity distribution and size distribution.

When a MALLS detector is coupled in series with a refractometer and the (dn/dc) of the polymer solution is known (Section 5.1.2), then the absolute $\overline{M}_w$ and $\overline{M}_n$ values can, in theory, be determined for any polymer. For SEC-MALLS the retention time of the slice of the distribution analysed is not required, only the refractometer and MALLS responses are needed for each slice; these can then be combined to give the molecular weight averages using the standard formulae. The refractometer signal is proportional to the refractive index increment and the concentration, and the light scattering response is proportional to the concentration and the molecular weight. By combination of these two responses the amount of material in each slice of the distribution and the molecular weight of that slice can be calculated. The light scattering detector measures the weight average molecular weight of the material within a slice, however if these segments of the distribution are small enough that only polymer molecules of one molecular weight elute in that slice then for this segment of the distribution $\overline{M}_w$ is equal to M, the absolute molecular weight. If this is the case then the number and weight average molecular weights for the polymer can be calculated by summation of the values for each slice across the whole SEC trace.

Limitations exist in SEC-MALLS analyses which may affect the accuracy of the results. If adsorption occurs then the separation by SEC may not be on a solely size exclusion basis and each slice cannot be assumed to contain molecules of one size. The molecular weight distribution of polydisperse samples is artificially lowered by the inability of the light scattering detector to observe molecules of low molecular weight. This means that small molecules are excluded from the analysis, which has the effect of artificially increasing the $\overline{M}_n$ compared to the

$\overline{M}_w$ as the small molecules have a larger effect on this average. For step growth polymers, where even at high degrees of conversion monomers and small oligomers are present, this has a great effect on the molecular weight distribution which is observed. The hyperbranched polymers synthesised in this study were analysed using aqueous SEC with a multi-angle laser light scattering detector (SEC-MALLS). This was intended to further confirm the results obtained earlier and hopefully to provide absolute values of the molecular weight for the polymers. In the present study the values for the $\overline{M}_n$ given by the instrument software were indeed very high and close to the $\overline{M}_w$ values. This is undoubtedly due to the problems discussed above with calculating $\overline{M}_n$ values for step growth polymers by SEC-MALLS, consequently only the reliable $\overline{M}_w$ values, which come directly from the light scattering detector, are reported.

#### 5.1.4.1 – Analysis of polyamidoamines with amine surfaces

The hyperbranched PAMAMs with amine surfaces whose analysis by conventional SEC against linear standards was discussed earlier, (Section 5.1.1), were subsequently re-analysed using SEC-MALLS. This work, (Figure 5.7), showed that the polymers were of far lower molecular weight than the analysis using calibration with linear standards had indicated. This result is surprising because as SEC separates on the basis of size rather than molecular weight it usually underestimates the molecular weight of branched polymers as they have a smaller hydrodynamic radius than equivalent linear polymers. In this work a polymer which had been measured as having a $\overline{M}_w$ of over 100000 by SEC using linear standards was shown to have an $\overline{M}_w$ of under 1000 by SEC-MALLS. This suggested that the branched polymers must be retarded on the SEC column relative to the linear polymers, an observation which can be most easily explained by interaction between the polymers and the column material a phenomenon which has been previously reported.[3] These observations suggested that the polymers previously produced were of a significantly lower molecular weight than had been expected and in an attempt to produce polymers of a higher

molecular weight syntheses employing longer reaction times were undertaken. This was successful and SEC-MALLS showed that after a reaction time of 125 hours a $\overline{M}_w$ of 20 000 is produced, (Figure 5.7).

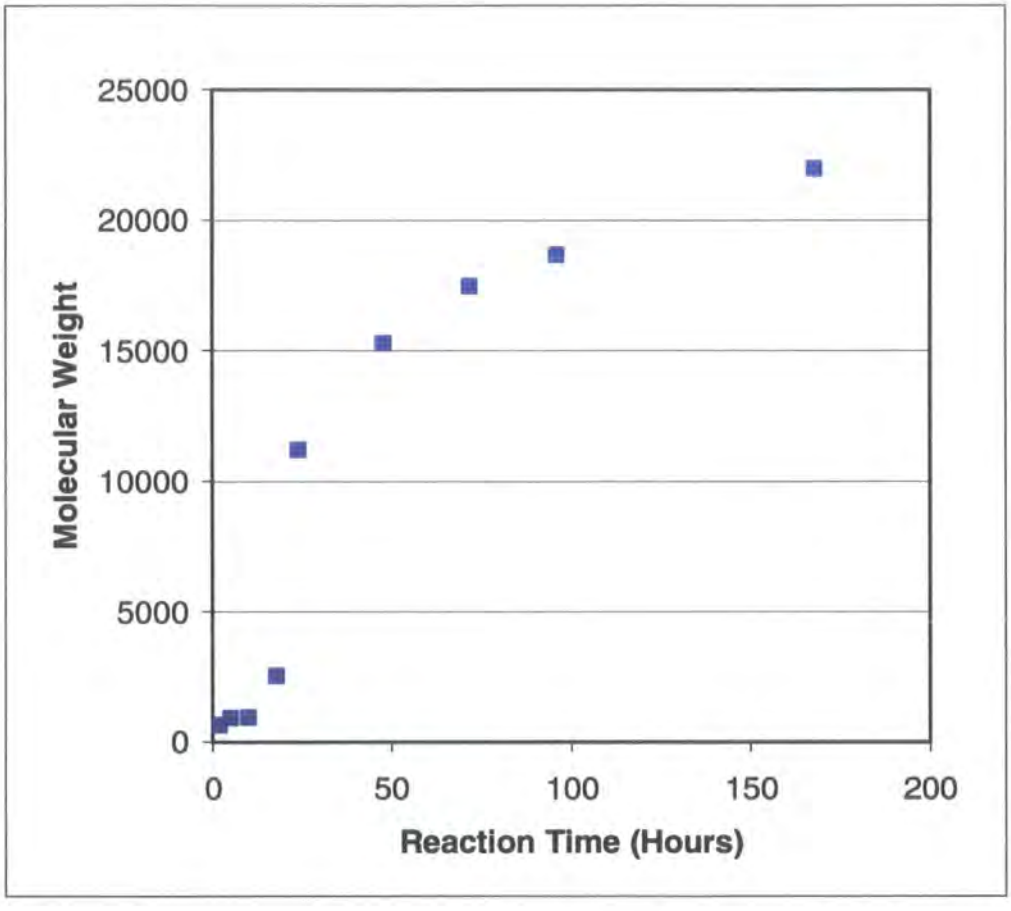



Figure 5.7 – The evolution of molecular weight ($\overline{M}_w$) with time in the formation of the hyperbranched polyamidoamines with an amine surface.

### 5.1.4.2 – Analysis of hyperbranched polyamidoamines with ester surfaces

The hyperbranched polyamidoamines with an ester surface (half generation analogues), (Section 2.7), were also analysed by SEC-MALLS. In these polymers the molecular weight increases with reaction time and after a period of 168 hours polymers with a $\overline{M}_w$ of 45 000 were produced, (Figure 5.8).

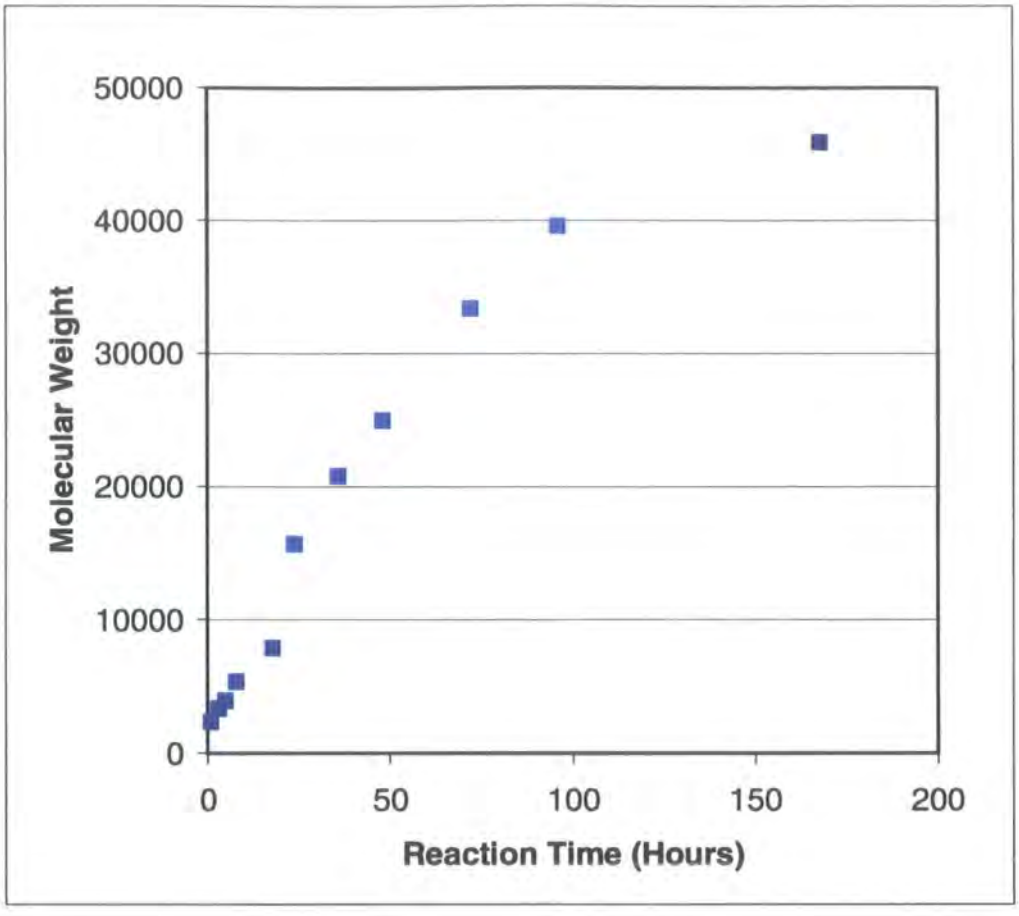



Figure 5.8– The evolution of molecular weight ($\overline{M}_w$) with time in the formation of the hyperbranched polyaminoamides with ester surfaces (half generation analogues).

### 5.1.4.3 – Analysis of polyamides

Hyperbranched polyamides (Chapter 3) have also been analysed by SEC-MALLS, (Figure 5.9). These show a much faster increase of molecular weight, with a $\overline{M}_w$ of 80 000 being achieved in 12 hours. No further increases in molecular weight were seen with more extended reaction times.

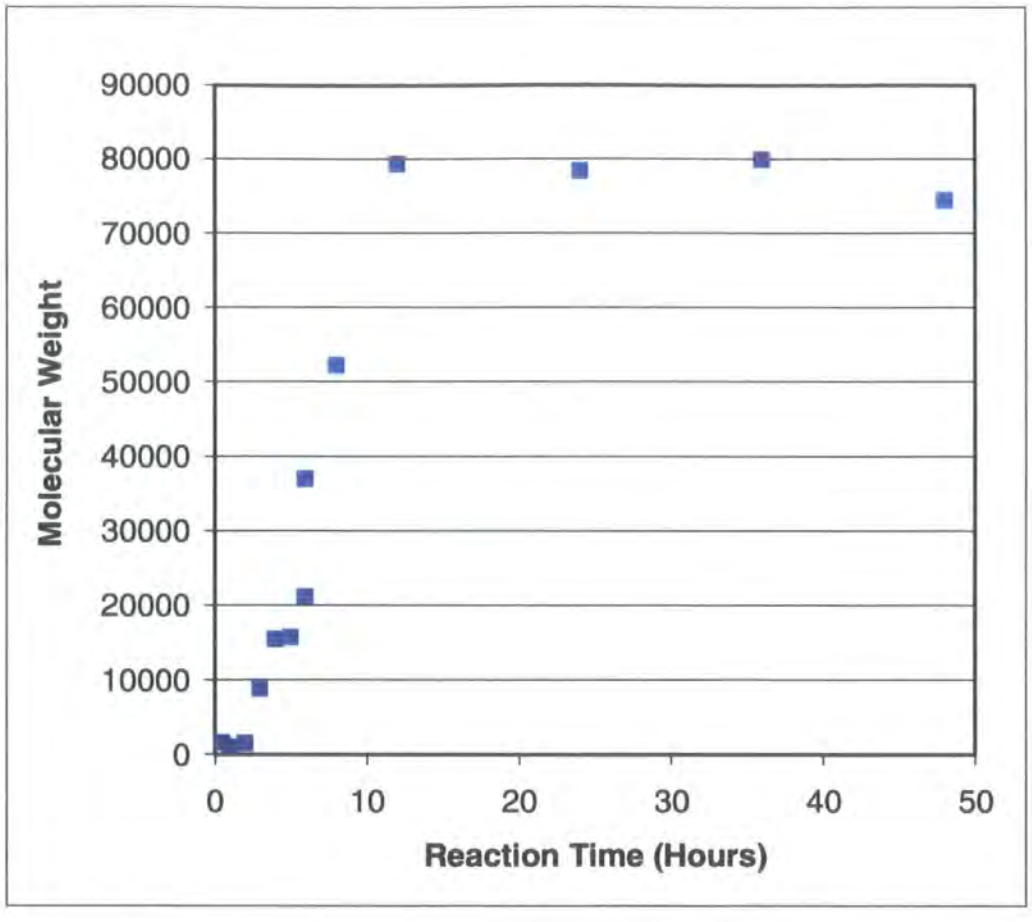



Figure 5.9 – The evolution of molecular weight ($\overline{M}_w$) with time in the formation of the hyperbranched polyamides.

### 5.1.4.4 – Comparison of rates of polymerisation seen in the different hyperbranched polymer systems

The three different hyperbranched polymer systems discussed show very different rates of polymerisation. After 12 hours of polymerisation, the polyamide has reached a molecular weight ($\overline{M}_w$) of 80000, the polyamidoamine with an ester surface 12000 whilst the polyamidoamine with an amine surface has a molecular weight of only 1000 at this time, (Figure 5.10)

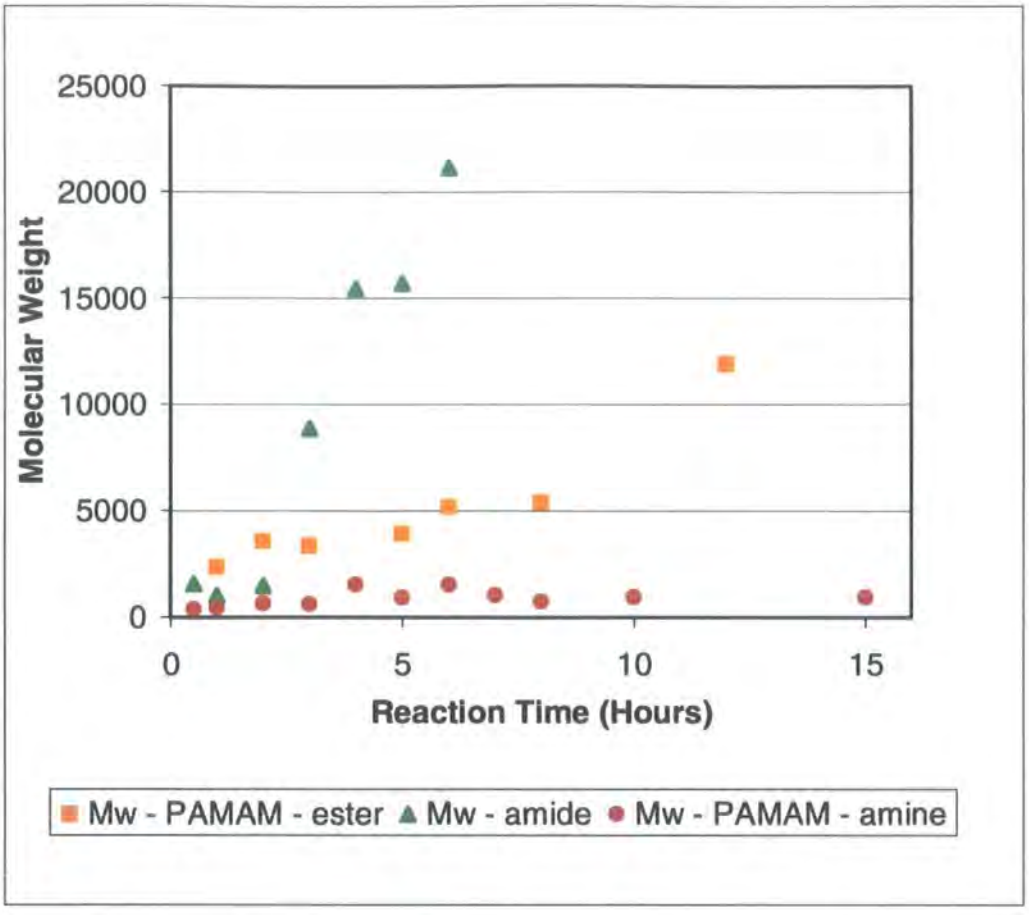



Figure 5.10 – The evolution of molecular weight with time in the formation of the different hyperbranched polymers investigated in this study, where PAMAM-ester are the ester terminated hyperbranched polymers (the half generation analogues), PAMAM-amine are the amine terminated hyperbranched polymers (the full generation analogues) and amide are the hyperbranched polyamides. Mw in the legend refers to the weight average molecular weight $\overline{M}_w$.

The reason for this huge difference in rate in the polymerisation of the three different polymer types is not immediately obvious. The answer may lie in the structure of the deprotected monomers, (Figure 5.11), however no direct evidence for these species has been seen, and NMR suggests alcohol is lost from the A group at a faster rate than SEC-MALLS shows polymers are being formed, (Section 5.1.5). If the reaction proceeds through these three species, the reason for the slow rate of polymerisation leading to the polyamidoamines compared to that of the process leading to polyamides could be due to the presence of the

tertiary amines in the structures, which is the main difference between the two monomers. As the NMR evidence suggests that a different mechanism may be needed to explain the disparity between the rate of alcohol loss and the rate of polymerisation, a convincing explanation for the observed differences is hard to construct based on our current level of understanding. One alternative hypothesis might be that there is initial intramolecular ring closing in the monomer which is followed by ring opening polymerisation. However, the details of the mechanism remain an open question and so explanations of differences in rate are difficult.

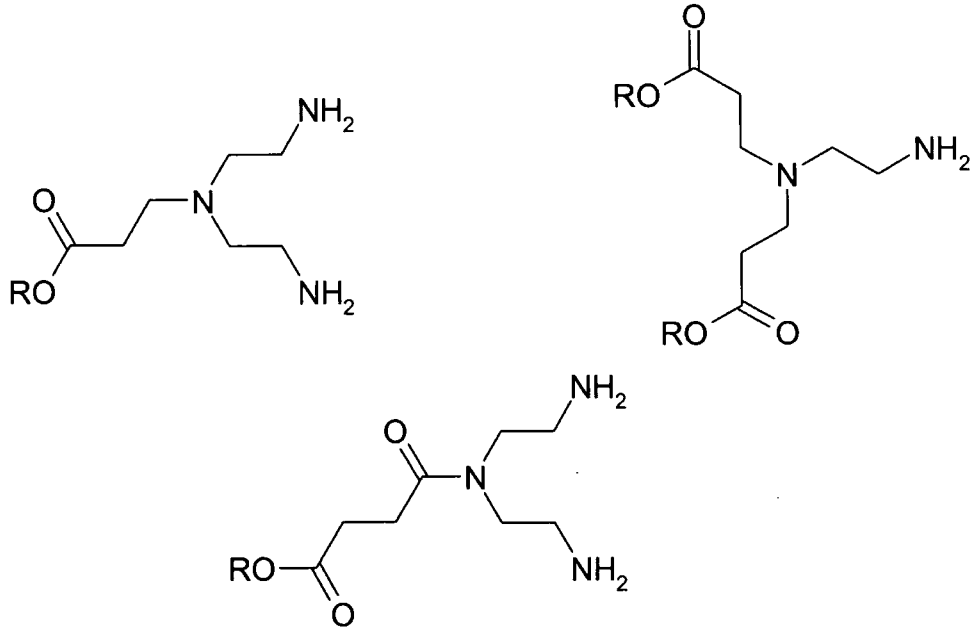



Figure 5.11 – The structure of the three deprotected monomers, through which polymerisation is presumed to occur.

The slow rate of the formation of the polyamidoamines with amine terminal groups posed practical difficulties for the formation of high molecular weight polymers as extremely long reaction times were needed. Attempts were made to increase the rate of polymerisation by addition of ammonium salts (Section 4.4). This proved successful with polymers with a $\overline{M}_w$ of 16 000 being produced in 24 hours, (Figure 5.12), compared to 1 000 when not promoted by ammonium salts (Section 5.1.4.1).

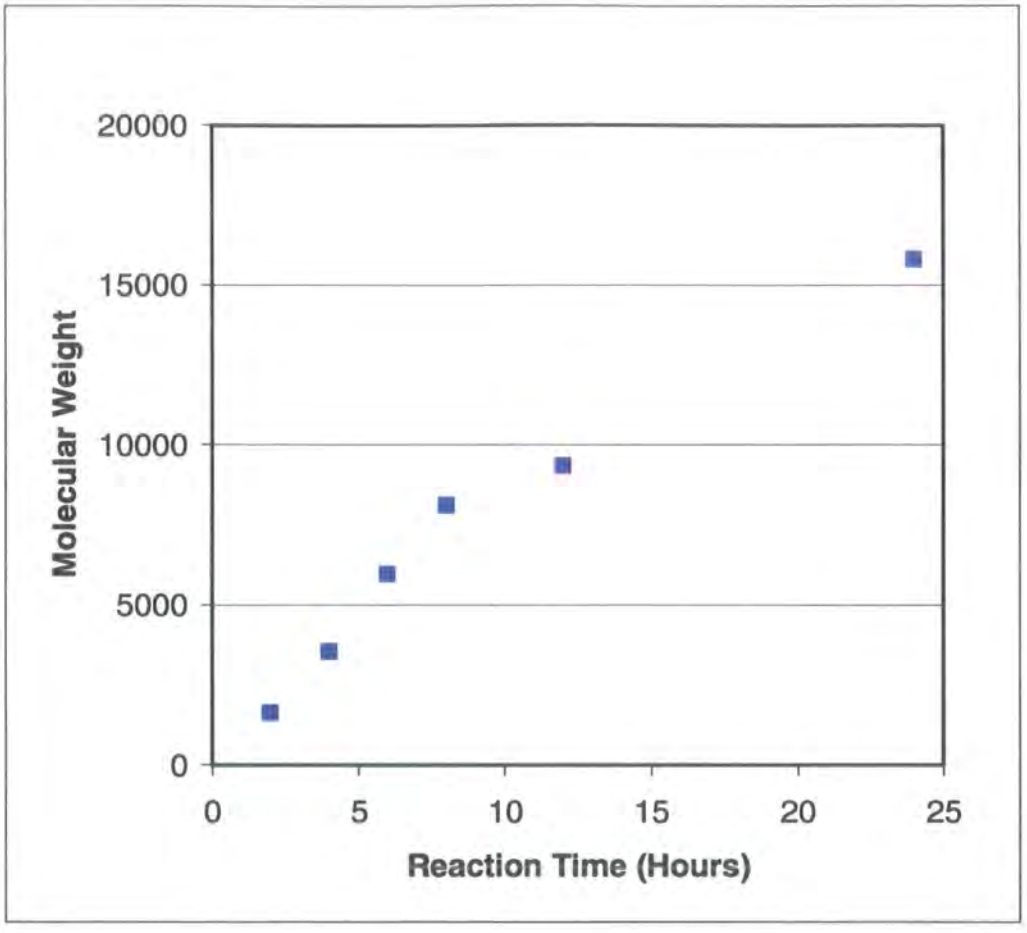



Figure 5.12 – The growth of molecular weight ($\overline{M}_w$) with time when synthesis of hyperbranched polyamidoamines with an amine surface is promoted with ammonium trifluoroacetate.

This methodology offered a method for producing hyperbranched polymers at a faster rate than in the unpromoted case, allowing high molecular weight polymers to be produced on a shorter time scale. The polymers from the ammonium ion promoted synthesis were indistinguishable from those produced without the addition of ammonium salt, showing no residual fluorine and an identical pH in aqueous solution.

### 5.1.4.5 – Analysis of branched Nylon 2,4

The hyperbranched polyamides produced by copolymerising the branched and linear monomers, (Section 4.2.2), showed similar behaviour with respect to

growth of molecular weight to that observed for the synthesis of hyperbranched polyamides, (Figure 5.13).

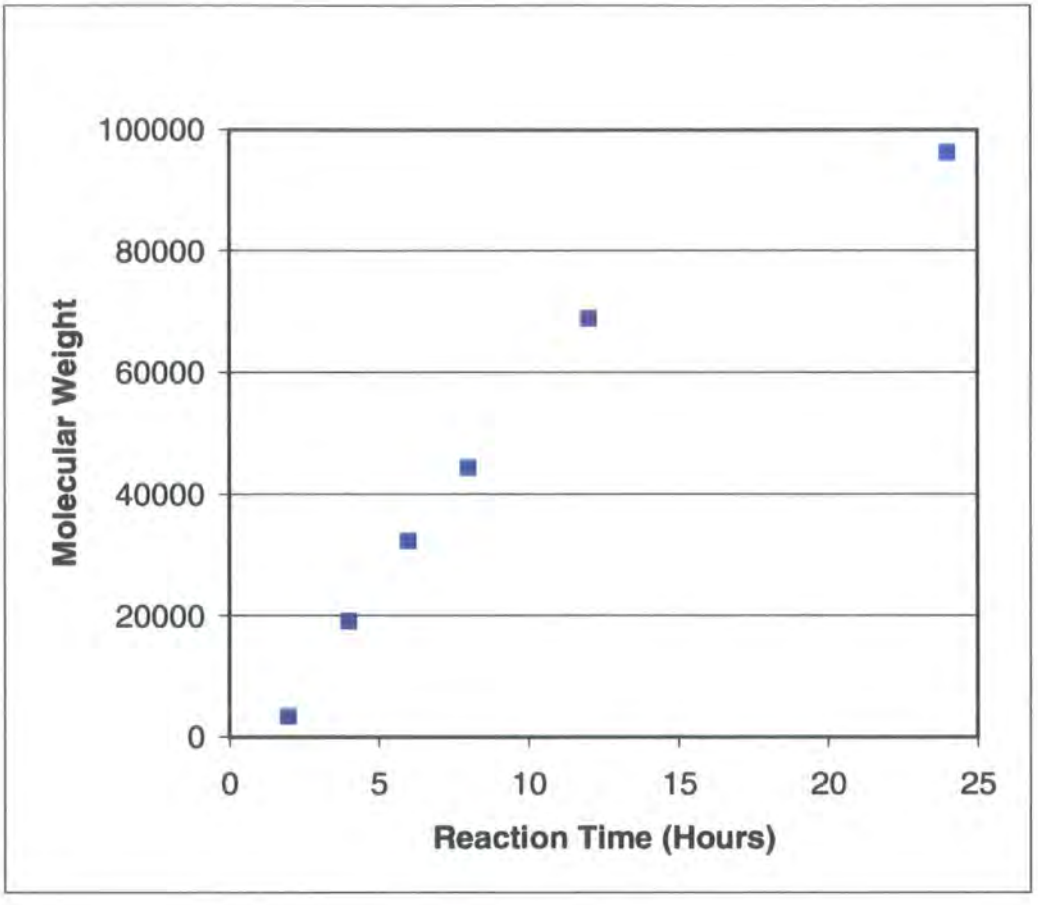



Figure 5.13 – The evolution of molecular weight ($\overline{M}_w$) with time in the formation of a branched-linear polyamide copolymer (0.33 mole fraction linear shown as a representative example).

The results were similar at all degrees of branching, a range of polymers varying from 0.05 to 0.95 mole fraction of linear have been produced. Below 0.75 mole fraction of linear monomer the polymers are fully water soluble, whilst at or above 0.75 mole fraction of linear monomer some of the product polymer is insoluble. The proportion of insoluble material increases with increasing proportion of linear monomer from 5% of the total mass for 0.75, to 25% for 0.90 mole fraction of linear monomer. This insoluble material will not dissolve, even in a large volume of water, and it is not case of lower solubility of the polymer as

a whole, but a distinctive insoluble fraction of material. The insoluble fraction presumably contains large fragments of linear structure. Increasing the mole fraction of linear monomer in the feed increases the proportion of polymer molecules containing sufficient linear units to cause the polymer to become insoluble.

### 5.1.4.6 – Control of molecular weight using amine functionalised cores

Attempts were made to control molecular weight of the polymers by introducing a hexafunctional core (**10**) at various ratios, (Section 4.1). The polymers produced were analysed by SEC-MALLS and the molecular weights of the polymers compared to the theoretical molecular weights of the polymers, based on the $B_6/AB_2$ ratio, (Figure 5.14).

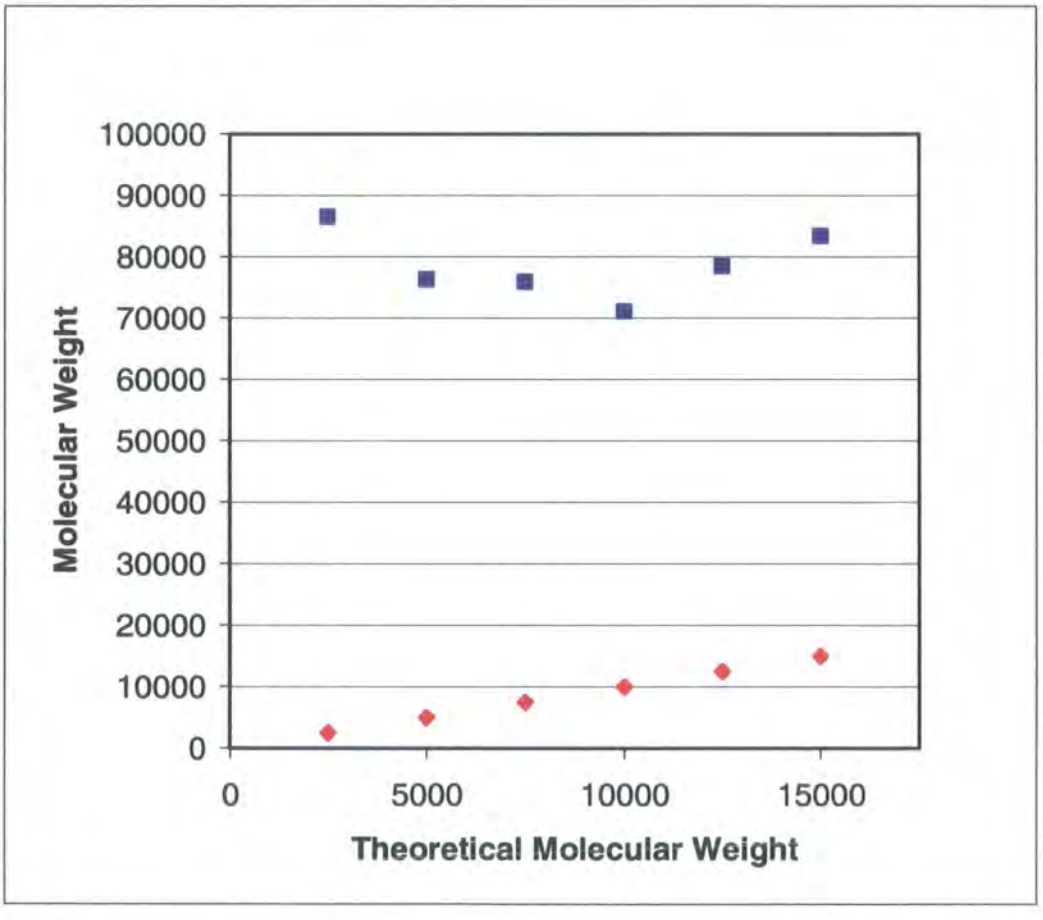



Figure 5.14 – The molecular weights of hyperbranched polymers (blue) compared to the theoretical values (red) based on the amount of core introduced.

It can be seen that there is no relationship between the molecular weight of the polymers produced and the theoretical molecular weights of the samples, with all the polymers having approximately the same molecular weight, which is the same as that for the hyperbranched polyamide without a core at the same reaction time. A commercially available polyethylene glycol with two amine terminal groups was used as an alternative core, (Figure 4.4). SEC-MALLS again showed no relationship between the theoretical and observed molecular weights in this system, (Figure 5.15).

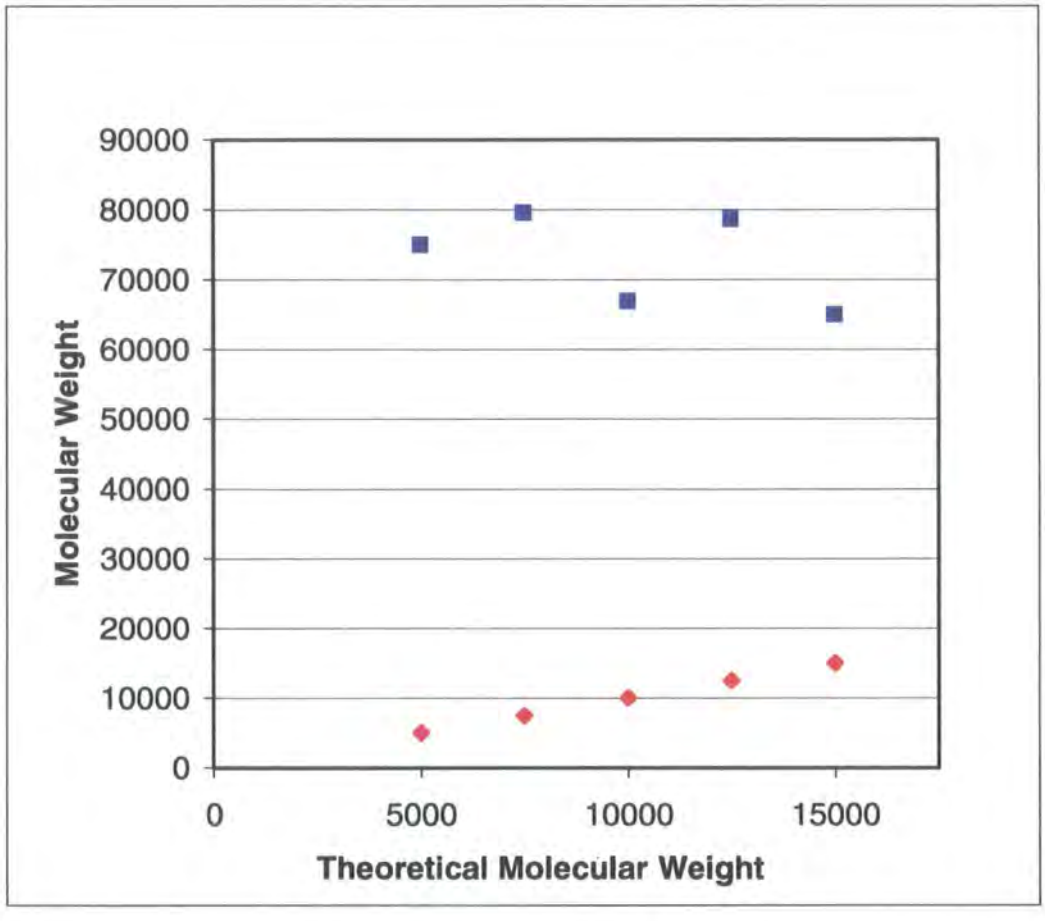



Figure 5.15 –The molecular weights of hyperbranched polymers (blue) compared to the theoretical values (red) based on the amount of core introduced.

The introduction of these cores at various ratios had no effect on the molecular weight of the samples produced. The reason for this is not understood as both the $B_6$ core produced from the thermal deprotection of the protected core (**10**), and the polyethylene glycol $B_2$ core were shown by thermogravimetry not to be volatile at

the reaction temperature. It could be shown by NMR that resonances expected for the cores were seen in the sample of polymer, e.g. in the aromatic region for the $B_6$ core, although NMR could offer no evidence regarding whether or not they were incorporated into the hyperbranched polymers. It appears that in the presence of both these core terminator molecules no modification of the established $AB_2$ polymerisation occurs. The simplest rationalisation of this disappointing result would be that the two reagents were incompatible, although other explanations may be required.

### 5.1.5 – Determination of molecular weight by nuclear magnetic resonance spectroscopy

The use of nuclear magnetic resonance (NMR) to determine the molecular weight of hyperbranched polymers relies upon the assumption that all polymers contain a single A group at the focal point. This assumption is only true if there are no side reactions which remove the A group. If intramolecular cyclisation occurs in the polymers then this relationship does not hold and the number of A groups is reduced causing this method to overestimate molecular weight. To use end group analysis to quantify molecular weight a distinctive resonance for the A group is chosen, and then the integration for this peak is compared to that for a resonance in the polymer. The ratio of the two signals allows quantification of the degree of polymerisation and hence the molecular weight ($\overline{M}_n$). There is clearly a limit to the size of molecule which can be characterised by this procedure.

In the polymerisation of monomer **(2b),** it was intended to compare the signal from the $CH_3$ of the ethyl group of the ester present on the A group, to those for $CH_2$ groups contained within the repeat units of the polymer. These two peaks could be easily distinguished, and it was thought that they could be used to produce an estimate of the molecular weight of the polymers. The intensity of the methyl resonance diminished very quickly. A polymer that was shown by SEC-MALLS to have a $\overline{M}_w$ of only 1000 was shown to have a very small residual resonance for the A group, (Figure 5.16). This would suggest a molecular weight by end-group analysis several orders of magnitude higher than that seen in SEC-

MALLS. This faster disappearance of the A group than would be expected compared to the increase in molecular weight suggests that the polymerisation may not proceed via a simple amidation between a deprotected amine and an ester. Side reactions must occur which cause removal of the ester, but leave a group which can proceed in a subsequent reaction produce polymers, in practice the majority of the increase in molecular weight occurs after the resonance for the A group has entirely vanished from the NMR spectrum. The obvious possibility for such reactions would be hydrolysis with growth then occurring through condensations between the resultant acid groups and the primary amines. An alternative might be intramolecular cyclisation followed by ring opening polymerisation as discussed earlier, (Section 5.1.4.4).

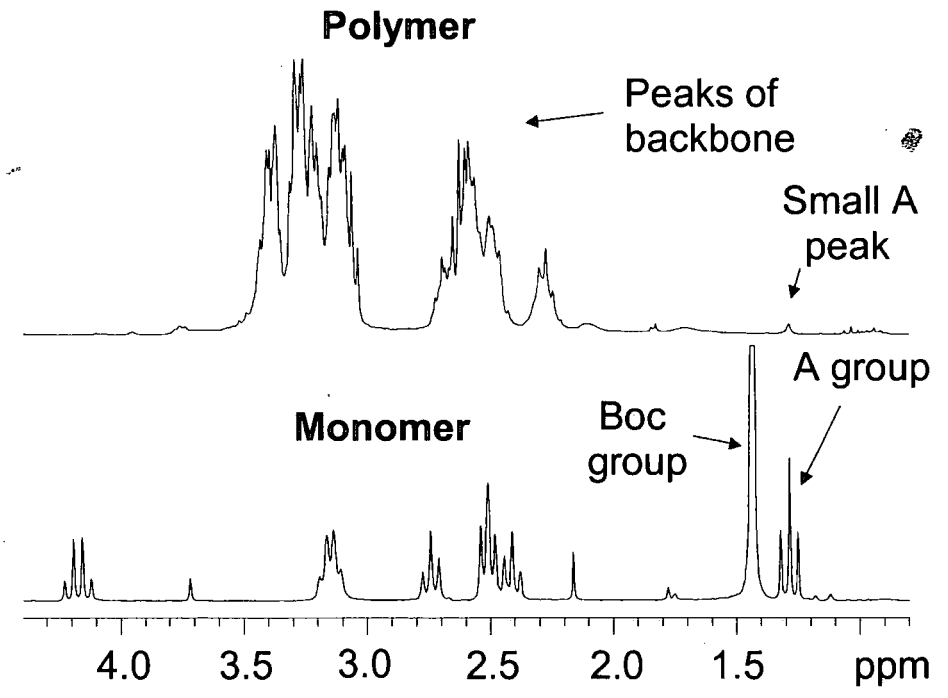



Figure 5.16 – A $^{1}$H NMR spectrum of a polymer which from SEC-MALLS is suggested to have a $\overline{M}_w$ of 1000, compared to the spectrum of the monomer used to produce it.

## 5.2 – Degree of branching studies

In addition to molecular weight the other major factor which defines the structure of a hyperbranched polymer is the degree of branching. The theory of the degree of branching has been considered earlier, (Section 1.2.5), and the analysis here is restricted to how degree of branching can be measured and the work on quantifying it for the hyperbranched polymers from this work. The measurement of degree of branching relies on the differentiation of the different units which make up the polymer. For the Fréchet definition the ratios of all the different units, terminal, linear and branched is needed, whilst for the Frey definition it is not necessary to find the number of terminal groups explicitly. The method of finding the ratios of the different units varies depending on the structure of the polymer in question. The simplest and the most widely used method is to identify a resonance in the NMR spectrum of the particular polymer that is different for each of the three units and allows the relative proportions of each type of unit to be determined.[4]

In the case when it proves impossible to quantify the number of branched units, one alternative is to use the fact that at all degrees of polymerisation the number of terminal units is equal to the number of branched units plus one (T=B+1), so that at high degrees of polymerisation the number of branched units is effectively equal to the number of terminal units. This means that if there is some distinguishable feature in the terminal groups that can be quantified the degree of branching can be obtained. This was first demonstrated in a system of hyperbranched poly(ether ketone)s which had a fluorine group attached to the terminal groups, (Figure 5.17).[5] The ratio of linear and terminal units was measured and the number of branched units assumed to be equal to the number of terminal.

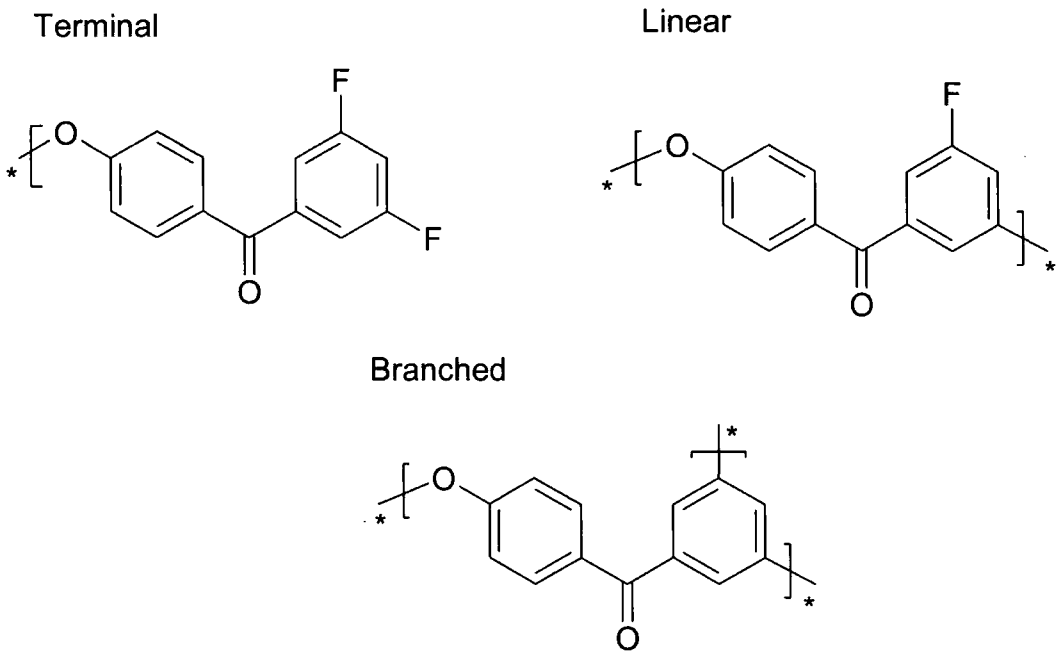



Figure 5.17 – The three types of unit present in the hyperbranched poly(ether ketone).

Direct analysis of the polymers by NMR cannot be used to determine degree of branching in cases when the resonances for the different units are not distinct. A more versatile two step technique has been developed, which can be employed in this case.[6] This consists of an initial modification of the chain ends of the polymer followed by chemical degradation of the polymeric linkages. The three different species produced from the degradation, which should represent linear, terminal and branched units are then analysed. The modification chemistry must achieve complete conversion of the terminal groups and the chemistry used for the degradation must result in complete conversion to elementary sub-units, whilst not affecting the modified chain ends or causing any side reactions. This method was first used on a series of hyperbranched polyesters in which it had proven impossible to distinguish between the different units, (Figure 5.18), of the polymer spectroscopically.

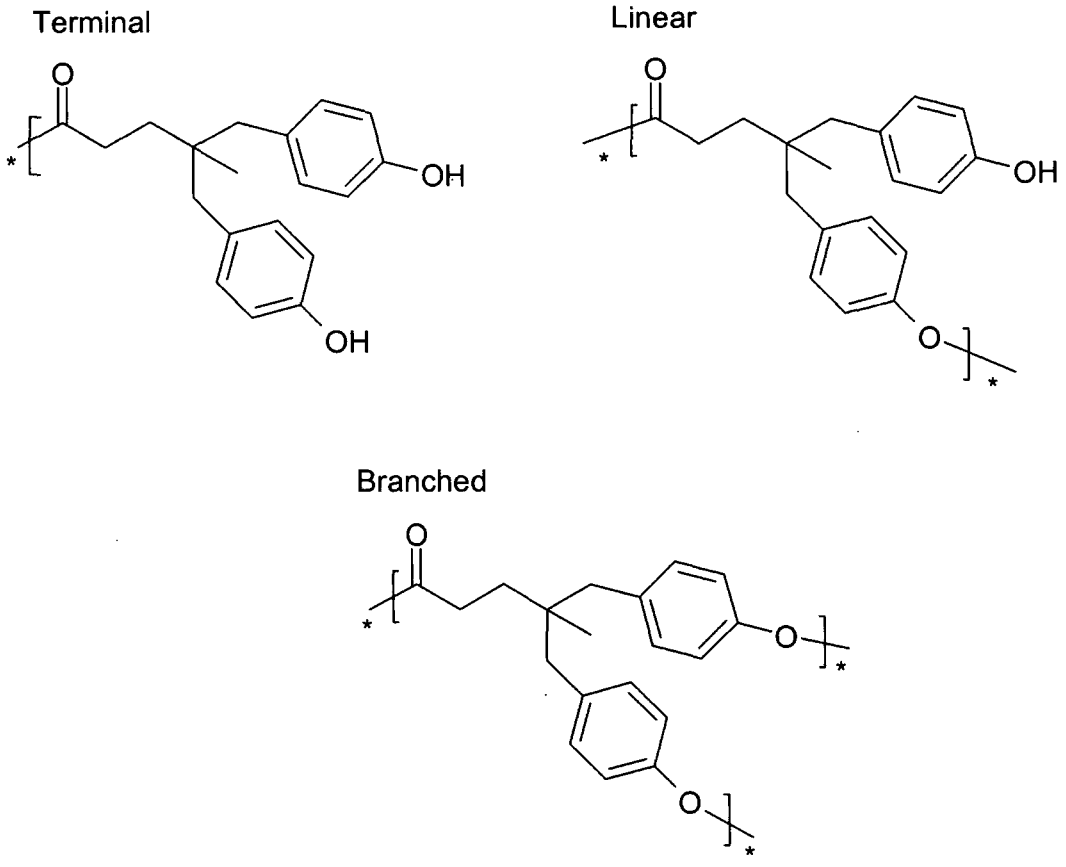



Figure 5.18 – The three different types of unit found in the hyperbranched polyester in which it proved impossible to distinguish the units from NMR spectroscopy.

The polymer possessed phenol terminal groups, which could be converted to methyl ether groups by reaction with a mixture of silver oxide and methyl iodide These modified hyperbranched polymers could then be decomposed by hydrolysis with base and capillary gas chromatography showed only three signals, one for each of the repeat units, which were unambiguously identified, (Figure 5.19). By integrating the intensity of these signals a degree of branching of 0.49 was demonstrated.

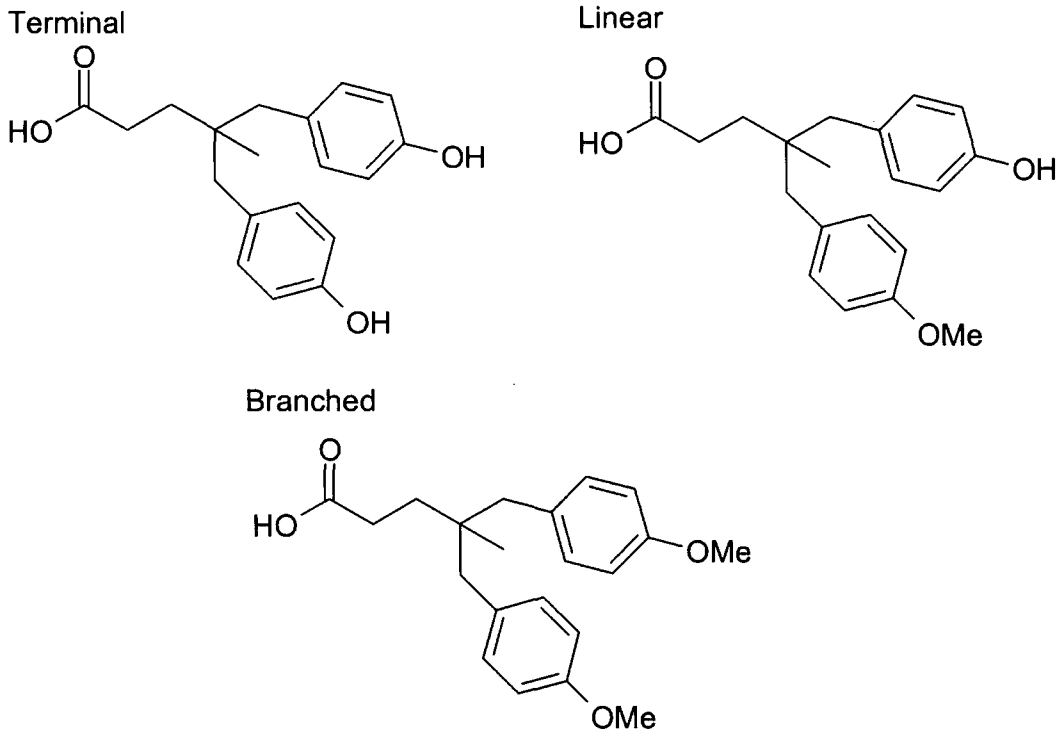



Figure 5.19 – The three different species produced by modification with silver oxide and methyl iodide, followed by hydrolysis.

In the case of the polymers studied here the method of using a distinctive resonance to determine the ratios of the three units proved impossible, as the spectrum contained many overlapping resonances, and no clear signals could be assigned to the three units in any of the $^{1}H$, $^{15}N$ or $^{13}C$ NMR spectra.

An alternative method of finding the degree of branching was considered. If all of the terminal units of the polymer could be reacted to produce a species capped with a better group for the analysis then two distinctive capped species should be produced, one for the capped terminal end groups and one for the capped linear end groups, (Figure 5.20). This could then be used to calculate the ratio of linear to terminal groups, and thus assuming a significant degree of polymerisation the ratio of linear to branched groups and the degree of branching following the Frey formula.[7]

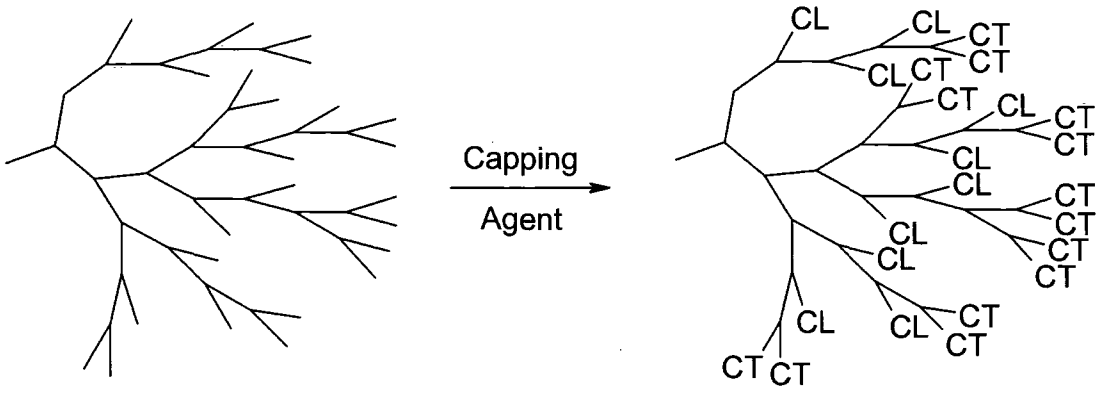



Figure 5.20 – By complete reaction with a capping agent two different end groups are produced, capped terminal units (CT) and capped linear units (CL).

For the hyperbranched PAMAMs a reaction was needed that would convert the amine terminal groups in a 100% yield to give a species that could be more easily observed spectroscopically. The fluorine nucleus was thought to be a good candidate as it is easily seen in NMR spectroscopy, in which it shows a wide distribution of chemical shifts and a successful introduction of fluorine into the polymers, which hitherto possessed no fluorine groups should produce a simple spectrum with only the two peaks for the two different capped end-groups. A reaction was sought which would convert the terminal amine groups into fluorine containing species. Two potential reactions were investigated the reaction of the amines with an isocyanate, 3,5-bis(trifluoromethyl) phenyl isocyanate, and the reaction with ethyl trifluoroacetate, (Figure 5.21).

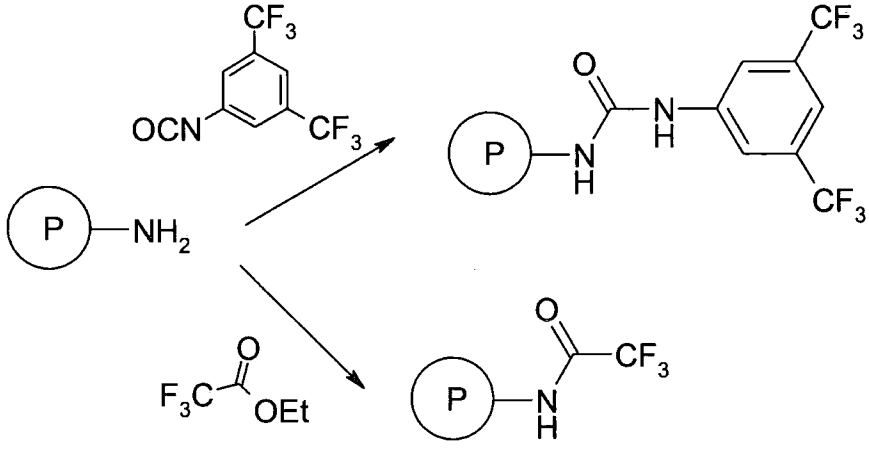



Figure 5.21 – Two potential routes studied for conversion of the terminal groups.

### 5.2.1- Model reactions for the conversion of terminal groups

Before the capping reactions were attempted on the polymers, model reactions were completed. This allowed suitable reaction conditions for conversion of the terminal groups to be established, (Section 4.3.1), the yields of the reactions could be shown to be high enough to assume complete conversion of terminal groups and also would provide models of the terminal and the linear units so that the different resonances seen in the fluorine spectrum of the modified polymer could be assigned by comparison with the chemical shifts of the models.

Tris(2-aminoethyl)amine provided a good model of the hyperbranched polyamidoamines with amine end groups and the tris fluorinated analogue of this would also provide a good model for the terminal units of the polymer. The reaction with the isocyanate was carried out in a variety of solvents, however no solvent which dissolved the model, the polymer and the product could be found. Due to the large aromatic groups, a precipitate forms when the tris-2-aminoethylamine is reacted with the isocyanate in a polar solvent, this appearing to be a mixture of the mono, di and tri functionalised material. The same change in solubility could be expected for the polymer, a factor which would prevent the complete reaction of all the amine groups. The reaction with ethyl trifluoroacetate, (Figure 5.22), was more successful as the reagents and the product were soluble in ethanol, which is known to be a good solvent for all of the polymers studied here.

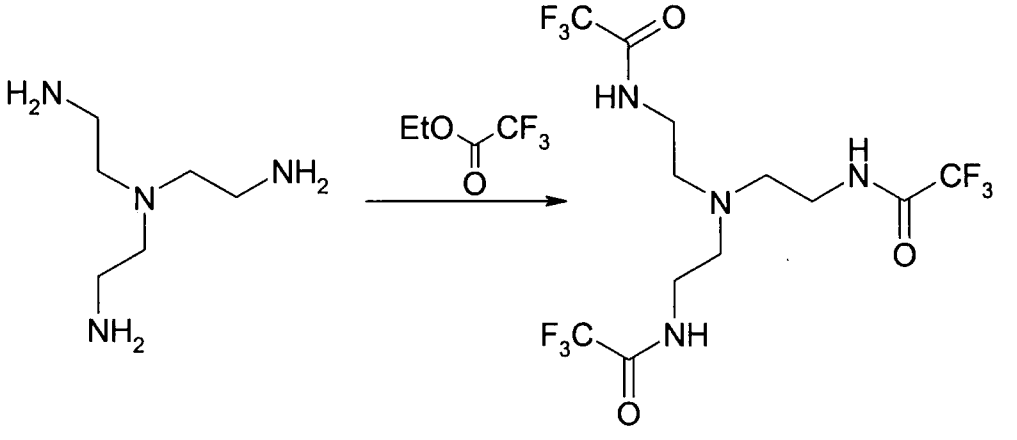



Figure 5.22 – The reaction of tris(2-aminoethyl)amine with ethyl trifluoroacetate.

The trifluorinated tris-2-aminoethylamine was considered to be a good model to aid the assignment of the resonances expected from the reaction of the terminal units with ethyl trifluoroacetate, the relevant structures are compared below, (Figure 5.23).

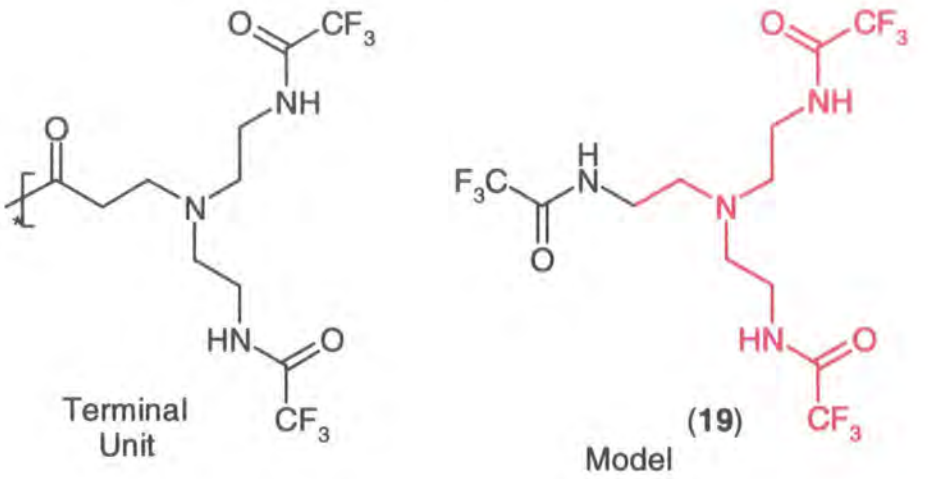



Figure 5.23 – Comparison of the repeat unit of the terminal groups of the polymer and the trifluorinated model. Areas of exact equivalence between the two structures are highlighted in red.

The model of the linear unit was harder to conceive and synthesise. The method that was chosen was the reaction of a vast excess of tris(2-aminoethyl)amine with ethyl trifluoroacetate, and subsequent exhaustive reaction with propionic anhydride to form a mixture of the mono-fluorinated species (minor product) and the unfluorinated material from reaction of excess triamine exclusively with the anhydride (major product). These two species were then separated by careful silica gel chromatography. The relevant structures are compared below, (Figure 5.24).

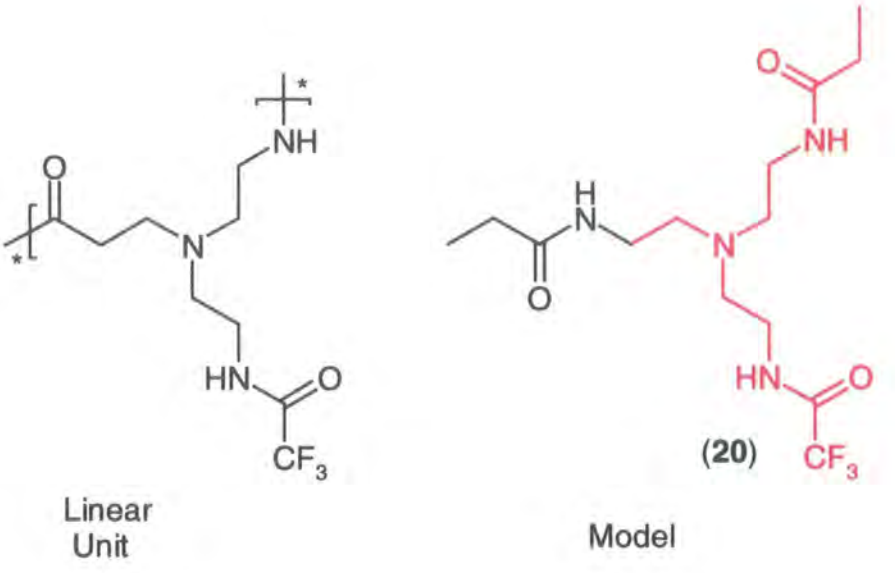



Figure 5.24 - Comparison of the repeat unit of the linear groups of the polymer and the model, exact equivalence to the polymer being highlighted in red.

### 5.2.2 – Introduction of fluorine at the surface groups of the hyperbranched polyamidoamines

A sample of the hyperbranched polyamidoamine was reacted with ethyl trifluoroacetate to fluorinate the terminal groups. The NMR spectrum of this modified polymer contains two distinct peaks, (Figure 5.25), one at –77.15ppm and a second at –77.80ppm. These can be assigned to be the linear and terminal units respectively by comparison to the resonances seen in model compounds, -77.60 ppm for the linear model, (**20**) and –77.76ppm for the terminal model, (**19**). Although an exact match in the resonances is not seen for the model of the linear unit and the peak assigned to the linear unit of the polymer it can be clearly seen to be upfield of the peak of the branched model, and as such the peaks can be assigned with reasonable confidence.

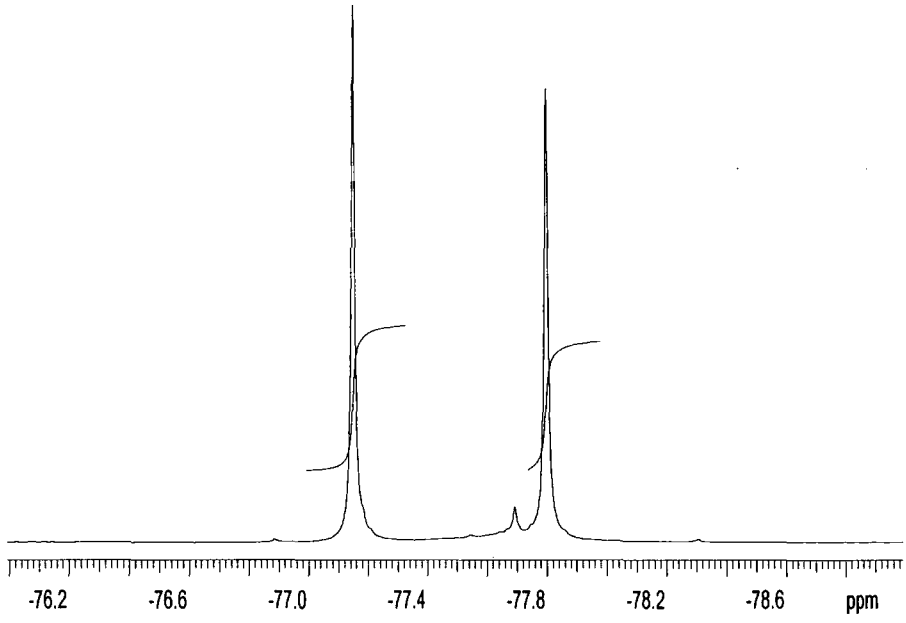



Figure 5.25 – The $^{19}F$ NMR spectrum of the fluorinated hyperbranched polyamidoamines.

By using the approximation that the number of branched units is equal to the number of terminal, the integrations of these peaks, which are in a ratio of 1.17:1 for the linear and terminal units respectively, can be used to calculate a value for the ratio of branched and linear units. The intensity of the peak for the terminal units must be halved as there are two primary amine groups on each terminal unit, compared to one on each linear unit. These values can be substituted into the Frey equation (Section 1.2.5), to give a value for the degree of branching of 0.46.

## 5.3 – Differential scanning calorimetry

Polymers are usually characterised by thermal analysis, however in the polymers studied here the differential scanning calorimetry traces were featureless.

## 5.4 - Conclusions

The characterisation of the polymers produced in this work has concentrated on two main features of their structures, namely the molecular weight and the degree

of branching. These two features are the most fundamental aspects of the structure of a hyperbranched polymer as they allow definition of both the size and architecture of the molecules which have been produced.

Initial analysis of the molecular weight distribution relied on the comparison of elution times in size exclusion chromatography (SEC) to those seen for a series of linear polysaccharides. This was expected to give a qualitative view of the molecular weight which would underestimate the true molecular weight as the branched molecules could be expected to have a smaller hydrodynamic volume in solution than a linear molecule of the same molecular weight. However, a SEC system with a light scattering detector (SEC-MALLS) showed that the molecular weights were overestimated by this technique, probably due to an interaction between the polymers and the column material, which retards the polymers and causes them to elute from the column at a larger volume than would occur if separation was due solely to size exclusion. The SEC-MALLS results allowed quantification of the weight average molecular weights $\overline{M}_w$ of the polymers and showed that hyperbranched polyamidoamines with both amine and ester surfaces and hyperbranched polyamides had been successfully produced. It also showed that the attempts to control the molecular weights of the polyamides using a series of multifunctional cores was unsuccessful with no control being achieved.

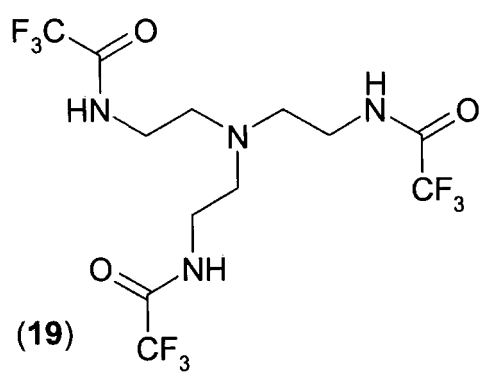
Attempts to further quantify the molecular weight distributions of the polymers using static light scattering and end group analysis by NMR proved less successful. The light scattering work produced no useful results as the polymer solutions absorbed light at the frequency of the laser source (532nm) leading to an anomalously high $\overline{M}_w$. The NMR also appeared to overestimate the molecular weight as the resonances representing the A group disappeared much faster than the SEC-MALLS showed that the polymer was produced, suggesting that a different mechanism to the simple amidation of the esters by primary amines was occurring.

Initial attempts to quantify the degree of branching using direct measurements from NMR proved impossible due to there being no clearly separated resonances.

An indirect technique was developed in which the primary amine terminal groups of the polymer were reacted with ethyl trifluoroacetate and the $^{19}F$ NMR of these modified polymers was studied. This showed two clear resonances for the polymers, which were assigned as the linear and terminal units by comparison with models. When the intensities of these peaks were substituted into the Frey equation (using the approximation that the number of terminal units is equal to the number of branched) then a value for the degree of branching of 0.46 was calculated.

## 5.5 - Experimental

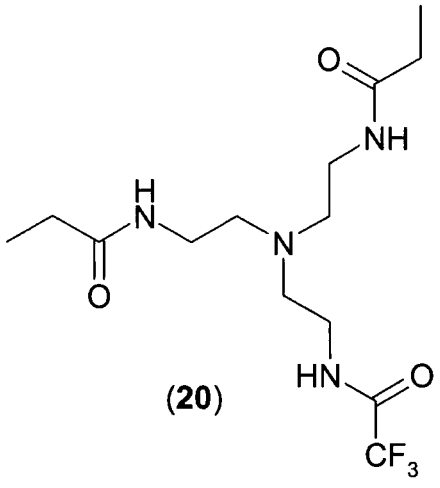
*N-(2-{Bis-[2-(2,2,2-trifluoroacetylamino)ethyl]2,2,2-trifluoroacetamide,* (**19**)




(**19**)

Tris(2-aminoethylamine) (73mg) was added to a 25mL round bottomed flask containing dry ethanol (10mL).[8] To this was added ethyl trifluoroacetate (266mg) and the solution was allowed to stir at room temperature for 18 hours. The solvent and excess reagent were removed *in vacuo*, to give *N-(2-{Bis-[2-(2,2,2-trifluoroacetylamino)ethyl]2,2,2-trifluoroacetamide*, (**19**), as a white solid, (203mg, 93.6%). Found; C, 33.15; H, 3.54; N, 12.91; F, 37.32;[9] (M/z) ($ES^+$) 435 (H) 457 (Na). Calculated for $C_{12}H_{15}F_9O_3N_4$; C, 33.19; H, 3.48; N, 12.90; F, 39.37%. M 434. $^1H$ NMR: $\delta_H$ (400 MHz; $CD_3OD$) 3.35ppm (t, J=6.4Hz, 4H), 2.70 (t, J=6.4Hz, 4H).[10] $^{13}C$ NMR: $\delta_C$ (100 MHz; $CD_3OD$)[11] 38.81ppm, 53.71, 117.49 (q, J=284.8Hz), 159.19 (q, J=37.0Hz). $^{19}F$ NMR: $\delta_F$ (376 MHz; $CD_3OD$) –77.76ppm.

*N-(2-{(2-Propionylaminoethyl)[2-(2,2,2-trifluoroaetylamino)ethyl]propionamide,* **(20)**



**(20)**

Tris-(2-aminoethyl)amine (731mg) was added to a 50ml round bottomed flask containing dry ethanol (25mL). To this was added ethyl trifluoroacetate (71mg) dropwise and the solution was left to stir at room temperature for eighteen hours. Propionic anhydride (1.95g) was then added and the solution left to stir for a further eighteen hours. The solvent was removed *in vacuo* and the product mixture was then purified by column chromatography on silica with an eluant of ethyl acetate:methanol (7.5:1) to give *N-(2-{(2-Propionylaminoethyl)[2-(2,2,2-trifluoroaetylamino)ethyl]propionamide*, **(20)**, as a yellow oil (92mg, 76.0%). Found; C, 46.70; H, 7.01; N, 15.56%; M/z ($ES^+$) 355 (H), 377 (Na). Calculated for $C_{14}H_{25}N_4O_3F_3$; C, 47.45; H, 7.11; N, 15.81; M 354. $^1H$ NMR: $\delta_H$ (400 MHz; $CD_3OD$) 1.12ppm (t, J=7.6Hz, 4H) 2.22 (q, J=7.6Hz, 4H), 2.62 (t, J=6.4Hz, 4H), 2.67 (t, J=6.4Hz, 2H), 3.23 (t, J=6.4Hz, 4H), 3.34 (t, J=6.4Hz, 2H). $^{13}C$ NMR: $\delta_C$ (50 MHz; $CD_3OD$) 10.49ppm, 30.15, 57, 54.36, 54.43, 117.56 (q, J=284.7Hz), 159.18 (q, J=36.2Hz), 177.26. $^{19}F$ NMR δF (376MHz; $CD_3OD$) –77.60ppm.

*Fluorination of amine terminal groups of the hyperbranched polyamidoamine*

Dried hyperbranched polyamidoamine with an amine surface (110mg) was added to a 25mL round bottom flask containing dry ethanol (10mL). This was stirred to dissolve the polymer, and then ethyl trifluoroacetate (300mg) was added. Stirring

was continued at room temperature overnight, and the solvent and excess reagent was removed *in vacuo*, to leave the product as a brown solid. $^{19}F$ NMR: $\delta_F$ (376 MHz; $CD_3OD$) –77.15ppm, -77.80 in a relative intensity of 1.17 to 1.

*Analysis Conditions*

SEC-MALLS was carried out with an eluant of 95% water and 5% acetic acid. The separation was achieved using a Jordi Gel Polar Pac WAX mixed bed column and detection was accomplished using a DAWN EOS MALLS detector with a laser source at 690nm. The results were normalised using a sample of poly(2-vinyl N-methyl pyridinium iodide) with Mn = 56 000 obtained from Polymer Source Inc.

Static light scattering was achieved using a Brookhaven BI-200SM goniometer fitted with a Brookhaven BI-9000AT digital auto-correlator. The laser source was a Quantum Nd-YAG solid state laser with $\lambda_0 = 532$nm.

The refractive index increment measurements were made on a Brice-Phoenix Archive XLe differential refractometer.

## 5.6 – References


1 - Sunder, A.; Hanselmann, R.; Frey, H.; Mülhaupt, R. *Macromolecules* **1999**, *32*, 4240.

2 - Kim, Y. H. *J. Am. Chem. Soc.* **1992**, *114*, 4947.

3 - Bozanko, A.; Carswell, W. D.; Hutchings, L. R.; Richards, R. W. *Polymer* **2000**, *41*, 8175.

4 - Hawker, C. J.; Lee, R.; Frèchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4583.

5 - Hawker, C. J.; Chu, F. *Macromolecules* **1996**, *29*, 4370.

6 - Kambouris, P.; Hawker, C. J. *J. Chem. Soc. Perkins Trans. 1* **1993**, *22*, 2717.

7 - Hölter, D.; Burgarth, A.; Frey, H. *Acta Polymer.* **1997**, *48*, 30.

8 - Lund, H.; Bjerrum, J. *Ber.* **1931**, *64B*, 210.

9 - The analyst at Durham has noted previously that in samples with a high fluorine content, a relatively large discrepancy in the fluorine analysis is often observed due to difficulties in calibration.

10 - The amide peak is not seen in $CD_3OD$.

11 - Coupling in this spectrum is between the carbon atoms and the fluorine atoms as the spectra have been acquired with hydrogen decoupled.

# Chapter Six

# Overall conclusions and suggestions for future work

## Chapter Six – Overall conclusions and suggestions for future work

### 6.1 - Conclusions

The production of a series of hyperbranched polymers has been described. Hyperbranched analogues of the polyamidoamine (PAMAM) dendrimers have been synthesised and these offer a substantially easier route to the production of such highly branched structures. The route developed to produce these polymers has been extended to allow production of analogues to the half generations of the PAMAM dendrimers and also a related series of polyamide hyperbranched polymers. It has proved impossible to isolate and purify the monomers due to experimental difficulties, however an alternative technique of synthesising the polymers *in situ* after a thermal deprotection of the amine groups was successful. This allowed production of a series of polymers from the protected monomers in a one step procedure. The production of hyperbranched PAMAMs with amine end groups was shown to be a slow process, however the rate was successfully increased by incorporating ammonium trifluoroacetate into the reaction mixture as a 'promoter'.

The polymers obtained are fully water soluble and their molecular weights have been analysed using size exclusion chromatography (SEC) with a multi-angle laser light scattering detector (MALLS). Initial attempts to use aqueous SEC with calibration against linear standards led to a significant over-estimation of molecular weight contrary to the normal under-estimation seen when analysing branched polymers in this fashion. Attempts to use static light scattering to obtain weight average molecular weight data failed because the polymers absorbed at the wavelength of light source, other wavelengths were not available for use in this study.

It proved impossible to measure the degree of branching by direct NMR measurements due to overlapping resonances, however by reacting the amine termini of the hyperbranched PAMAMs and applying the approximation that at significant degrees of polymerisation the number of terminal and branched units are equal it was possible to measure the degree of branching in these polymers.

This work suggested a degree of branching of 0.46, slightly lower than that which would be expected for a purely statistical polymerisation.

Surface group modifications were possible, allowing the amine terminal groups of these polymers to be changed giving a variety of different end group functionalities. This allowed the solubility of the polymers to be altered, and also potentially offers a route into their use in a variety of different applications.

A related series of hyperbranched polyamides have been synthesised. These are a branched variant of Nylon 2,4 and were used to introduce a degree of branching into this polymer. This rendered the Nylon 2,4 soluble in a variety of different solvents including water, whilst linear Nylon 2,4 is soluble only in very polar solvents such as dichloroacetic acid and trifluoroacetic acid.

Attempts were made to control the molecular weights of the polymers using multifunctional cores. Neither the use of a generation one dendrimer with six terminal amine groups as a $B_6$ core, nor the use of a bis amine terminated polyethylene glycol as a $B_2$ core was successful, with no relationship between the theoretical molecular weights and those measured by SEC-MALLS being observed. The reasons for the failure of this technique to control molecular weight is not understood.

Two different $AB_4$ monomers were used in an attempt to produce hyperbranched polymers, however the products of these reactions were insoluble in all solvents, probably due to a large degree of hydrogen bonding in the structures. This inhibited the analysis of these compounds.

### 6.2 - Suggestions for future work

The analysis of the polymers synthesised in this work is somewhat limited at present. The molecular weight analysis is restricted to an analysis of $\overline{M}_w$ from aqueous SEC-MALLS. An accurate measurement of $\overline{M}_n$ would be useful to allow the polydispersity of the samples to be measured. The degree of branching

studies via the indirect methodology developed have only been completed for the hyperbranched PAMAM polymers with amine termini, it would be useful to extend this work to a study of the degree of branching of the hyperbranched polyamides, and also to develop a similar method for measuring the degree of branching of the ester terminated PAMAMs. A possible method for achieving the fluorination of the ester end groups would be to leave a sample of polymer in trifluoroethanol with a small amount of base for an extended period of time to allow exhaustive ester interchange to occur and convert the ethyl ester termini into trifluoroethyl ester termini. This should allow a similar indirect measurement of degree of branching to be carried out on these polymers.

The lack of success in controlling the molecular weight with cores remains unexplained, and further work could be attempted in this area. The development of ester functionalised cores for use with the production of the half generation analogues offers a potential route to control molecular weight in this class of polymers. It would also be interesting to investigate the co-polymerisation of the AB and $AB_4$ monomers in an attempt to produce soluble materials. The mechanism of the polymerisation remains uncertain with the NMR results suggesting that the ester groups are lost at a faster rate than the polymerisation proceeds. This would suggest that the reaction does not proceed by simple amidation of the esters by the primary amines. No work has been attempted to unravel the complexities of this mechanism and this would provide a better understanding of the processes occurring.

These materials have the potential to be inexpensive alternatives to the much vaunted PAMAM dendrimers and the author hopes that they are tested for activity in some of the applications suggested for the dendrimers. The samples made in the period of this work have been passed over to the sponsors for study in applications in household products at their laboratories, and samples have been sent to a collaborator at the University of California at San Francisco (Prof. F. Szoka) for study as potential gene transfer agents. The author believes that these materials potentially offer an alternative to PAMAM dendrimers for use in some of the applications suggested that do not require the mono-dispersity and perfection offered (at a huge cost) by the dendrimeric equivalents.