MAURITIUS RESEARCH COUNCIL

NEW GENERATION POLYMER BEADS FOR SOLID PHASE SYNTHESIS

Final Report

MAURITIUS RESEARCH COUNCIL

Address:

Level 6, Ebène Heights,
34, Cybercity,
Ebène 72201,
Mauritius.

Telephone: (230) 465 1235
Fax: (230) 465 1239
Email: mrc@intnet.mu
Website: www.mrc.org.mu

This report is based on work supported by the Mauritius Research Council under award number MRC/RUN-9810. Any opinions, findings, recommendations and conclusions expressed herein are the author's and do not necessarily reflect those of the Council.

Table Of Contents

1. INTRODUCTION

1.1 INTRODUCTION

The yield and practicality of every reaction in synthesis are limited by the ability to separate and recover the final pure product from the reaction mixture. The desired compound is to be synthesised cheaply, efficiently and safely. The need for new compounds is especially acute in the pursuit of new drugs, catalysts and materials. In response to this need, the emerging disciplines of combinatorial[1-3] synthesis and automated organic synthesis are beginning to provide new compounds at a greatly accelerated pace.

Synthetic organic chemistry has usually been distinguished by the need of several synthetic steps in the preparation of one compound. Along this line, the synthetic chemist has been trained to produce a single target compound with maximum yield and purity. Thus traditional chemistry often makes synthesis a time consuming and expensive activity. On the other hand, in industry where profitability is the most important motive, saving both time and money is vital. To increase productivity, chemists have been trying to innovate their approach to synthesis.

Under these circumstances, combinatorial chemistry has found ample space for development. This emerging sub-discipline has initiated a major rethink of the way chemistry is practised. In particular, combinatorial chemistry has instigated a reappraisal and resurgence in the synthesis and analysis of compounds attached to solid-phase supports. These aspects are changing the way chemistry is performed and will ultimately lead to more rapid and effective research. Combinatorial chemistry augurs to quickly find the sought, though unknown, targets by giving more tries. Chemists have recognised the potential. Research in the development of new solid supports and catalysts, which was stagnant for some time, has now gathered momentum. The rush towards new and better solid supports and catalysts is on.

This project is devoted to the development of new solid supports that are based on styrene and maleic anhydride derivatives (maleimides). The more polar backbone of these polymer beads is expected to be compatible with a wider range of solvents than traditional polystyrene supports.

1.2 COMBINATORIAL CHEMISTRY

1.2.1 OVERVIEW

The conceptual roots of combinatorial chemistry lie in the immune system. In the body, when a new antigen comes in contact with the preexisting large collection of antibodies, the antibody that binds best is selected and is reproduced in large numbers to effect the immune response. In a similar way, combinatorial chemistry involves the synthesis of a large number of compounds, which is then tested for a particular activity or property. Finally the active compound is identified and made in quantity as single compound.

Combinatorial chemistry has its earliest origins in solid-phase peptide synthesis[4], Merrifield's[19] (1963) Nobel Prize winning invention. It depended on the use of consistent and reliable reaction conditions for peptide couplings, and the use of a polymeric support to permit the simple separation of products from reagents. Over the years, solid-phase techniques have been greatly refined. In the mid 1980's, the high efficiency and consistency of the synthetic reactions were recognized. It was also realised that the same conditions could be used to make many peptides simultaneously in the same reaction vessel, thus enhancing productivity and accelerating the discovery of peptides responsible for particular biological activity.

Thus Houghten[5] (1985) used 'tea-bags' as porous containers of beads allowing the same peptide-coupling step to be applied to many beads simultaneously irrespective of the sequence already attached to the bead. Later, Furka[6] (1988) described the mix and split procedure, which was shortly used by Houghten[7] (1991) and Lam[8] (1991) to synthesise huge numbers of peptides in a relatively few number of steps. Combinatorial chemistry was born.

The long-held beliefs that all chemical compounds should be made individually in a fully purified and characterised state have been challenged by combinatorial chemistry, which is based on the efficient, parallel synthesis. High-speed chemistry, both of mixtures and single compounds, has attracted much interest from academics and industrial chemists. The scope of chemistry employed has branched well beyond peptide synthesis to include other key chemical transformations and structural classes.

Compound mixtures can provide a highly effective method for the discovery of compounds with a particular biological activity, provided there is a suitable reporting method to permit the identification of the preferred compound(s) in the mixture. If compounds with specific bulk properties, such as magnetic or semi-conducting properties, are required, it is necessary to test isolated compounds in the pure form. With the increased productivity afforded by these new combinatorial techniques, the challenge has shifted to the efficient screening of all these products. Various solutions have been generated to permit the unambiguous identification of the most active products. Iterative deconvolution[1, 3k, 4h] of mix and split libraries and encoding[1, 2, 3j, 9, 10] methods have been widely used. Encoding methodology involves a simple analysis of a tag molecule that can define the active test compound structure. Encoding methods can be chemical or electronic.

Thus, it can be seen that combinatorial chemistry is not one technique. It embraces a diversity of chemistry techniques: in solution or on solid-phase, making libraries in mixtures or as single compounds, using chemical or electronic encoding methodologies, making compounds manually or with the latest laboratory automation. In addition to revolutionising the way chemistry is now viewed, combinatorial chemistry has also challenged some of science's most inventive minds to generate elegant and practical solutions to real technological problems.

1.2.2 POLYMER SUPPORTED SYNTHESIS

Combinatorial chemistry embraces a wide diversity of different high speed and parallel synthetic techniques. A family of compounds (i.e. compounds with a defined structure) is synthesised in parallel by the use of sets of different building blocks. Thus, instead of targeting one particular compound, combinatorial chemistry aims to provide several related compounds that constitute a 'library'. The production of molecules is accelerated making the whole process more efficient and less expensive. The key to the rapid production of novel molecules is the ability to use separation techniques to effect an easy purification of intermediates and final products. Over the years, mainstream synthetic organic chemistry has tended to divorce synthesis from separation by treating the latter as a technical issue. Combinatorial chemistry has promoted separation from a technical to a strategy-level concern[3g].

Solid-phase[4, 11] and solution-phase[12] synthetic techniques have been employed to

generate libraries. However the solid-phase technique has been the main influence on library methodology. The ability to synthesise compounds on an inert polymeric resin bead, to force the reaction to completion by adding an excess of reagents, and then to remove all unwanted material by a simple filtration and wash is the heart of most library syntheses. Limitations of the solid support technique include reaction-scale restriction (amount of the solid support and its loading capacity) and the need for the validation of heterogeneous reactions.

Solution-phase synthetic techniques have the advantage of non-limiting scale and can be easily manipulated as well. Moreover, organic reactions performed in solution phase decrease the validation time. However, in a solution phase synthesis, isolation or the purification of the reaction products away from the reaction medium may prove to be a difficult task, especially for mixtures of products.

1.2.3 THE DRUG DISCOVERY PROCESS

The outcome of the drug discovery process[1, 6] is the identification of a chemical structure that has the desired potency against a nominated biological target. This structure is ultimately protected through a patent filing. Drug discovery is both a lengthy and expensive business for it takes years from initiating a project to the point where a potential drug is nominated for development and clinical trials.

This lengthy discovery period is often due to the slow synthesis of exploratory compounds. When initiating a drug discovery project, medicinal chemists require a lead: a structure with some degree of affinity for the biological target. With the lead in hand, they can proceed to the identification of a drug development candidate by the stepwise, incremental improvement of the lead's structure. Lead compounds often have their source in literature and natural products: the past success stories of β-lactams, tetracyclines and taxol are well known. However, despite the diversity of natural products, finding activity for a specific biological target is a highly challenging process. Companies usually resort to the screening of compound libraries to find that elusive hint of biological activity.

Lead discovery from combinatorial libraries is primarily a speculative process. Initially there may be no attempt to design an active library. The number and variety of structures that libraries can offer are their main attraction. Often, any structural preconceptions and

affinity for the target protein are ignored in favour of the serendipitous discovery of a novel lead. This does not mean that rational design has no place in combinatorial chemistry, as any knowledge of the receptor or enzyme structure, can be used to design a library of compounds for a specific target.

The new high-speed synthesis is also positively affecting the second phase, which involves the improvement of the biological profile of the lead. The mechanisms by which compounds bind to a particular biological target are often poorly understood. Consequently it is difficult to modify the lead compound in a rational way. Combinatorial chemistry offers a way by which many compounds can be synthesised in parallel to optimise a compound's activity in the absence of any binding model.

Even if medicinal chemists have an understanding of how the lead compound works, combinatorial chemistry provides a way of rapidly exploring structure-activity relationships. For example, if the need for a side chain on the lead is recognised, combinatorial chemistry can be used to make hundreds of analogues to cover the potential range of the substituent. This would allow a more comprehensive investigation and possibly identifying the unexpected active analogue.

Combinatorial methods have made a considerable impact in industrial environments, where there is pressure to discover new, and commercially profitable agents as quickly as possible. Nearly every pharmaceutical company has now established at least one group working in this area. The commercial applications of combinatorial chemistry have spawned new branches of the pharmaceutical and biotechnology industry. However the area is not only useful commercially; it also offers an enormous intellectual challenge for industrialists as well as academics.

1.2.4 COMBINATORIAL SYNTHESIS

The focal point of combinatorial synthesis is the capacity to synthesize many chemical compounds at a high pace. This major advantage has stirred various new applications, utilizing many modifications of the technology. Traditional methods of synthesis, which was characterised by slow, painstaking and steady work, have also been put to question by combinatorial chemistry. For example, all products and intermediates were fully purified and characterised. Combinatorial chemistry has broken many of such presumptions and permitted a high level of productivity. Using reliable chemistry and simple but effective purifications, combinatorial chemistry has allowed great productivity, although at times at the expense of quality.

Formerly chemists used to make one compound at a time, in one reaction at a time. For example, compound A would have been reacted with compound B to give compound AB, which would have been isolated through crystallisation, distillation or chromatography. In contrast to this approach, combinatorial chemistry offers the possibility to make every combination of compound A_1 to A_n with compound B_1 to B_n (Figure 1.1). The diversity of combinatorial techniques would have allowed to make these compounds individually in a parallel fashion or in mixtures, using either solution or solid-phase techniques.

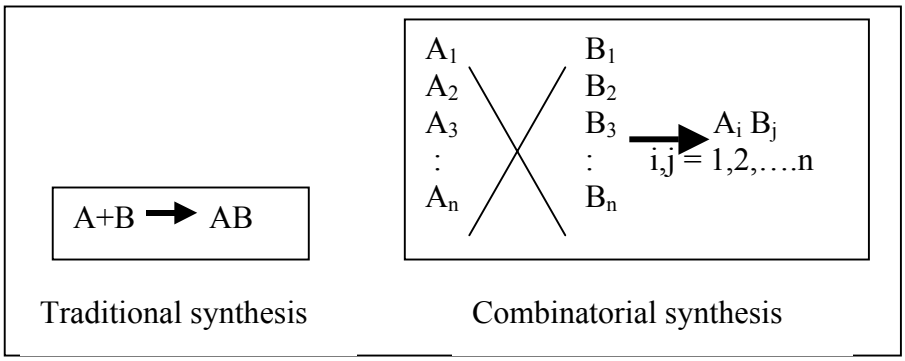


Figure 1.1: Difference between Traditional and Combinatorial Syntheses

Whatever the technique used the bottom line is that productivity has been increased many fold. The types of chemistry employed have been biased towards methods that can be expected to give good yields and purities. There has been reliance on techniques such as solid-phase synthesis that do not require reaction work up and also provide easy and simple purification methods.

1.3 SOLID-PHASE SYNTHESIS

Solid-phase synthesis was the first fundamental strategic alternative to traditional organic synthesis from the standpoint of phase planning[3g]. The techniques for solid-phase synthesis are based extensively on the pioneering work of Merrifield. He introduced chloromethyl groups in some phenyl residues in beads of polystyrene crosslinked with 2% of divinylbenzene. These chloromethyl groups served as anchor for the first amino acid in the synthesis of the tetrapeptide. Techniques for solid-phase synthesis have exploded from their origins to encompass the synthesis of libraries of small molecules.

A small organic molecule is attached to a polymer support (Figure1.2). The substrate and all products (or product intermediates) until detachment are then fixed as solids in any solid-liquid (or solid-gas) separation. Reactions are then conducted at the solid-liquid interface with a large excess of reaction components. The use of these excesses is crucial in solid-phase synthesis since reactions can be more difficult to drive to completion. The purification of reaction mixtures is the essence of simplicity, and generally involves filtration to separate insoluble products from soluble reaction components.

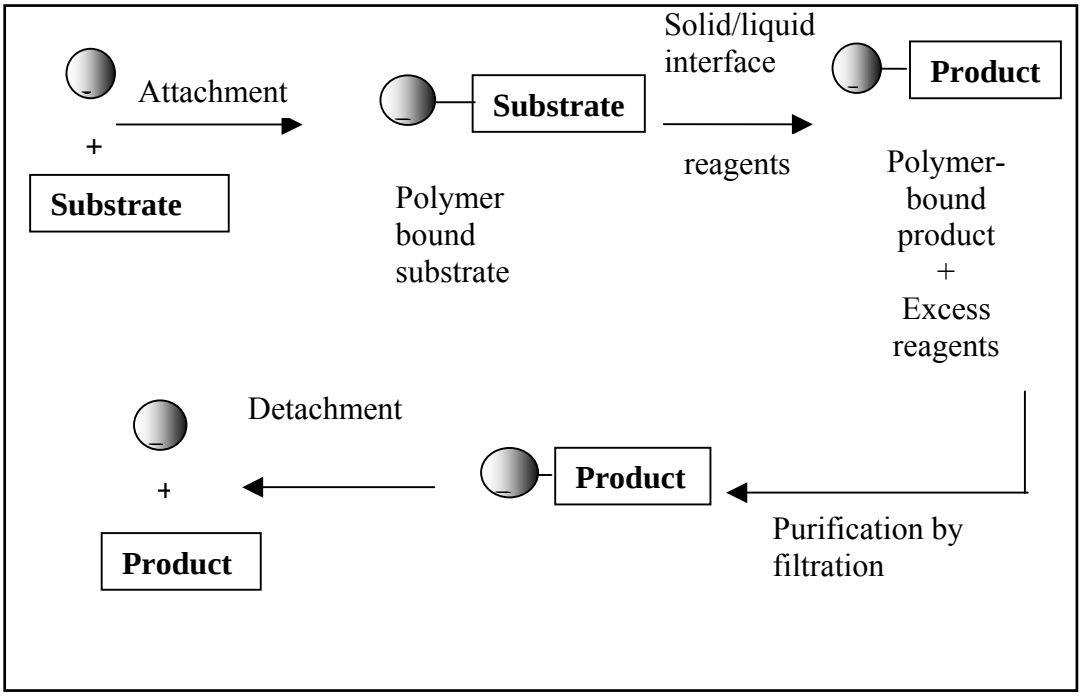


Figure1.2: Schematic Representation of Solid-Phase Synthesis

Purification is thus the overriding strength of solid-phase synthesis. However, problems are encountered at the reaction stage due to inhomogeneity. It is also more difficult to characterize the product at intermediate stages of the synthesis because polymer bound

substrates are mixtures of large macromolecules. Spectroscopic techniques[1-3b, 13] such as IR, NMR or MS can be used to great advantage whereas chromatographic techniques provide no information.

Fourier Transform infrared (FTIR) spectroscopy is a powerful technique for monitoring reactions on solid-phase. By observing the appearance or disappearance of critical diagnostic absorption signals, ensuring that these are not obscured by signals originating from the resin, it is possible to determine whether or not chemical reactions have taken place. In addition, it is also possible to use the intensity of absorption as a marker for the degree of chemical conversion from starting materials to product, allowing kinetic studies of solid-phase reactions to be undertaken.

The majority of NMR work is done on samples in solution, and thus the analysis of compounds whilst attached to resin beads presents new challenges. The limited mobility of the polymers and attached compounds lead to broad and poorly resolved signals. In addition the backbone may give rise to unwanted background signals that may mask important details of the spectra. Gel phase NMR has been developed to study synthetic progress on solid supports. Resin beads are swollen with solvent to maximise compound mobility. However this technique is limited by the very low sensitivity of the small quantities of material on the bead. Larger quantities and higher acquisition time are usually required.

1.3.1 RESIN BEADS

Solid-phase organic synthesis depends on three interrelated requirements:

- A crosslinked, insoluble polymeric material inert to reaction conditions.
- Some way to link the substrate to this solid-phase which would allow the selective cleavage of the product intermediate and final stages.
- A successful procedure compatible with the linker and the solid-phase.

Polymer beads are of two types: microporous (or gel type) and macroporous. Microporous beads have a relatively low degree of crosslinking, usually between 1% and 2%. In the presence of a good solvent, microporous beads swell so that the reactive sites are accessible to reagents and substrates. If a bad solvent is used, little swelling takes place and

the reactive sites are hardly accessible. Macroporous beads have a relatively higher proportion of the crosslinker and exhibit little or no swelling. These beads have permanent pores or channels through which either good or bad solvents can flow. The reactive sites in these channels are accessible to substrates or reagents independent of the solvent used.

Solid-phase resins are usually small spheres (80-200μm). They are produced by suspension polymerisation[14]. Typically two immiscible phases are employed: the continuous phase and the monomer phase. The continuous phase, in which the monomers are insoluble, is used in larger amount. The initiator (radical) should be insoluble in the continuous phase but soluble in the monomer phase. Under vigorous stirring a suspension of the monomer phase is obtained. To prevent coalescence of the monomer droplets, a stabiliser is added. The stabiliser should be insoluble in the monomer phase. Each droplet represents a system of bulk polymerisation and the kinetics of bulk polymerisation usually applies. Stirring has to be maintained to prevent coalescence of the droplets.

There is no heat transfer problem as the suspension medium diffuses the heat evolved during the polymerisation. The polymer is obtained directly as beads at the end of the reaction time. These are insoluble in the continuous phase. Traces of stabiliser, solvents and continuous phase are removed by washing. The most widely used continuous phase is water. A porogen is an inert liquid added to influence the porosity and swelling behaviour of the polymer. For monomers soluble in water, the continuous phase is a hydrophobic liquid.

1.3.1.1 POLYSTYRENE SUPPORTS

Crosslinked polystyrene (Figure 1.3) is a gel type polymer that is widely used in solid-phase synthesis. During polymerization, around 1% divinylbenzene (DVB) is added to the styrene to link the polystyrene chains. This degree of crosslinking is sufficient to give appreciable mechanical strength and allow the polymer to swell in solvents. Polystyrene supports are prone to electrophilic attacks.

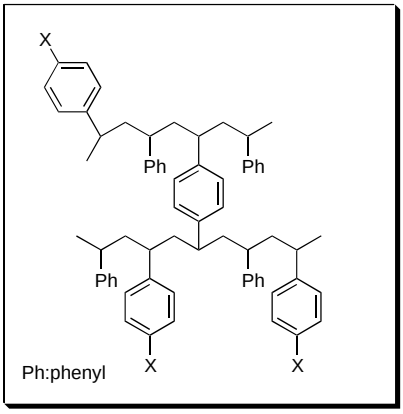


Figure 1.3: Structure of Polystyrene Supports

The groups marked x could be any suitable functionality, which would serve as an anchor group for the substrate, but are generally derived from the chloromethyl group.

The hydrophobic nature of the polystyrene matrix often makes it less compatible with the relatively more polar or hydrophilic solvents i.e. polystyrene based resins swell to a lesser degree. Another concern is the possibility of site-site interactions between molecules in the bead. For example, in solid-phase peptide synthesis, the hydrophilic nature and hydrogen bonding potential of peptides contrast with the hydrophobic nature of the polystyrene backbone. These factors induce chain folding in which the peptide satisfies its own hydrogen bond requirements rather than being solvated. This limits the synthetic access to the exposed end of a growing peptide chain. Moreover solvents that would expand polystyrene would collapse peptides, while solvents that expand peptides have poor polystyrene swelling properties.

Some examples of commercially[28] available polystyrene based resins (derived from the Merrifield resin with a different linker) are given in Table 1.1.

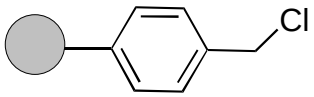
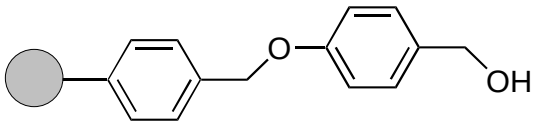
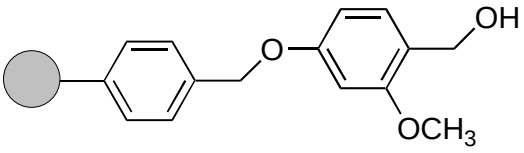
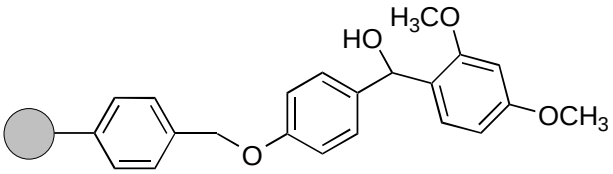
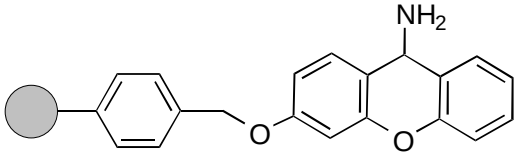
Common Name	Structure	Reference
Merrifield Resin		4(a)
Wang Resin		15
SASRIN Resin		4(b), 16
Rink Acid Resin		17
Sieber Amide Resin		18

Table 1.1: Some Commercially Available Polystyrene Supports

DVB is a rigid crosslinker. DVB crosslinked polystyrene has the necessary mechanical stability but it is less flexible. Renil *et al.*[88] developed a crosslinked polymer support consisting of a hydrophobic polystyrene chain and flexible hydrophilic crosslinker tetraethyleneglycol diacrylate (TEGDA) which showed good stability, and increased swelling and reactivity in solid-phase peptide reaction conditions.

1.3.1.2 TENTAGEL RESINS

To produce a more polar reaction milieu that would enhance compatibility with a wider range of solvents, grafted polymer beads have been prepared. The TentaGel[1, 11o] resin (Figure 1.4) consists of polyethylene glycol chains (PEG) attached to crosslinked polystyrene through a benzyl ether linkage. It combines the benefits of soluble polyethylene glycol with the insolubility, mechanical and handling characteristics of the polystyrene bead.

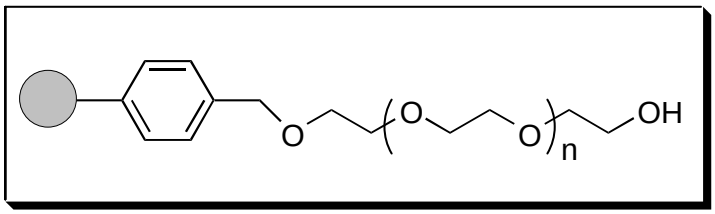


Figure 1.4: Tentagel Resin

It has been postulated that molecules bonded to the end of the PEG chains are in a "solution like"[20] environment relative to sites near the rigid polystyrene backbone. This environment can favourably impact reaction kinetics by allowing rapid diffusion through the swollen gels to sites that are away from the backbone.

TentaGel has a benzylic ether PS-graft linkage, which is known to be unstable to strongly acidic reagents. Gooding *et al.*[11(l)] (1999) prepared PS-PEG graft copolymers (Figure 1.5) centred on improving the acid stability of the polystyrene-graft linkage and increasing the functional group loading per unit weight of resin. The benzylic ether linkage was replaced with an aliphatic ether linkage and increased loading through bifurcation prior to ethylene oxide grafting as indicated in the structure below.

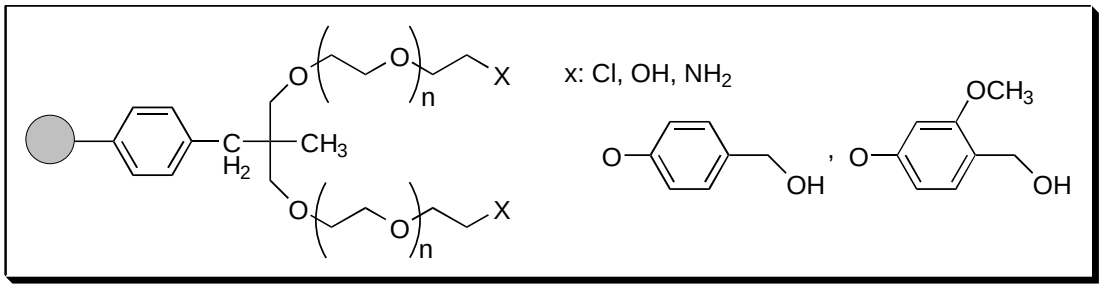


Figure 1.5: More Stable and Higher Loading Tentagel Resins

1.3.1.3 POLYAMIDE RESINS

Polyacrylamide[1, 21] polymers (Figure 1.6) have been prepared to mimic the properties of peptide chains. These polymers have improved solvation properties in polar, aprotic solvents (like DMF) but have limited swellability in less polar solvents (such as DCM).

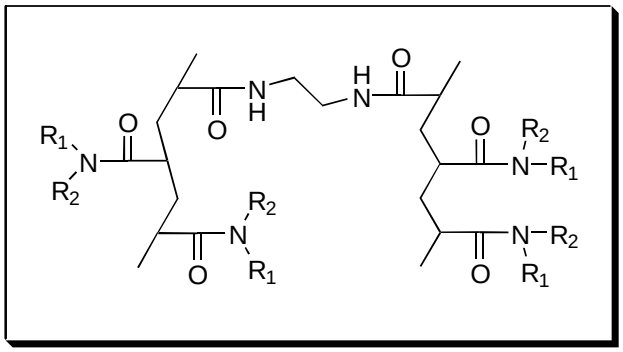


Figure 1.6: Polyacrylamide Resins

1.3.1.4 POLYACRYLATE RESINS

The development of polyacrylate supports[22] (Figure 1.7)is another attempt to enhance the solvent compatibility of the resin by having a more polar polymer backbone.

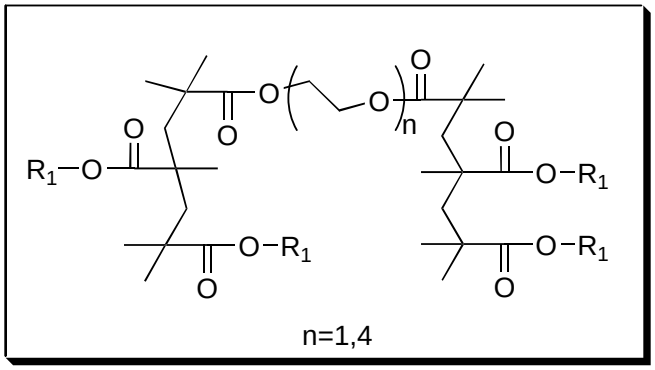


Figure 1.7: Polyacrylate Resins

2-Hydroxyethylmethacrylate (HEMA) is one of the most widely used monomers for the synthesis of spherical gel beads. The preferred crosslinkers associated with polyacrylate resins have been ethyleneglycol dimethacrylate (EGDMA) and tetraethyleneglycol dimethacrylate (TEGDMA). HEMA based microbeads have been investigated in many fields of affinity chromatography, enzyme immobilisation, drug delivery, cell culturing and immunochemistry.

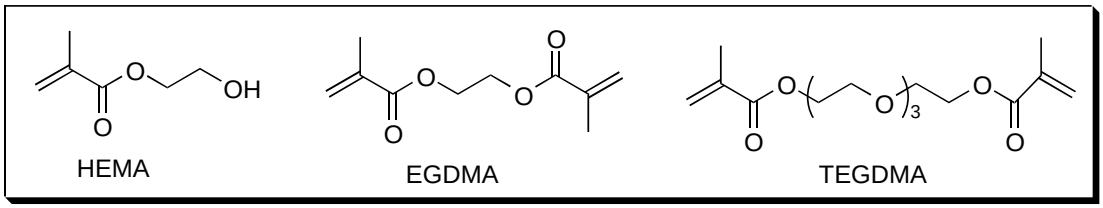


Figure 1.8: HEMA, EGDMA and TEGDMA

Kempe *et al.*[4e] (1996) synthesised a new family of highly crosslinked (≥95% by weight of crosslinker) supports, which showed good swelling properties and performance in batchwise and continuous flow syntheses of peptides. These supports, prepared by radical copolymerisation of the branched crosslinker trimethylolpropane ethoxylate triacrylate (TETA) (Figure 1.9) with other monomers (allylamine, polyethyleneglycol ethyl ether methacrylate, trimethylolpropane trimethacrylate, 2-aminoethyl methacrylate, polyethyleneglycol dimethacrylate), are termed CLEAR, an acronym for **C**ross **L**inked **E**thoxylate **A**crylate **R**esin.

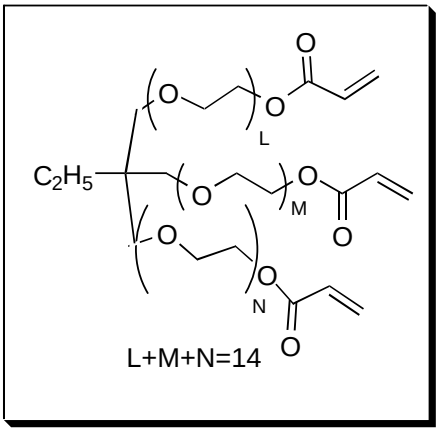


Figure 1.9: TETA

1.3.2 LINKERS

A vital component in any solid-phase synthesis strategy is the linker group[1, 2] that tethers the compound being synthesised to the solid support. The linker is a special protecting group, which will tie up a functional group. It is specially designed to detach under specific conditions. It must not be affected by the chemistry used to modify or extend the attached compound. The cleavage step (ideally the last step) should proceed readily and in good yield with the regeneration of the linker. Some linkers currently used in solid-phase synthesis are discussed in the following sections.

1.3.2.1 CARBOXYLIC ACID LINKERS

The original linking group used for peptide synthesis bears the name of the father of solid-phase peptide synthesis. The attachment of carboxylic acids to Merrifield resins[4a] is usually achieved by the nucleophilic displacement of the chloride with a caesium carboxylate salt in DMF. Cleavage to regenerate the acid is achieved with hydrogen fluoride, trifluoromethyl sulphonic acid or hydrogenolysis. Alcohols can also be linked to Merrifield resins by heating with the corresponding potassium or sodium alkoxide. Cleavage is achieved with acid treatment or hydrogenolysis.

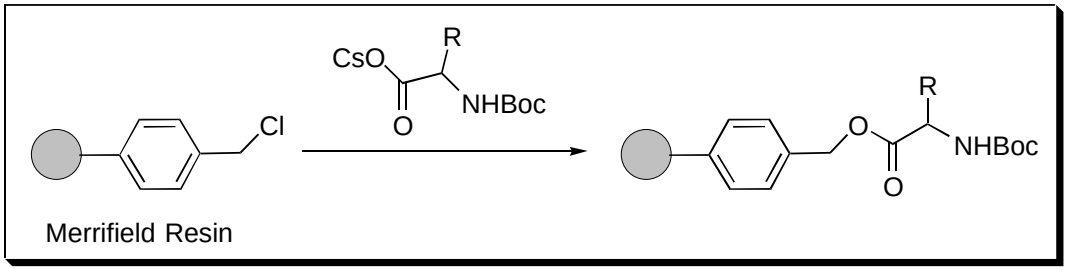


Figure 1.10: Merrifield Linker

The second major class of resin linker for carboxylic acids is the Wang linker[15] (Figure 1.11). It is used for the synthesis of peptide carboxylic acids. The carboxylic acid products are cleaved with TFA.

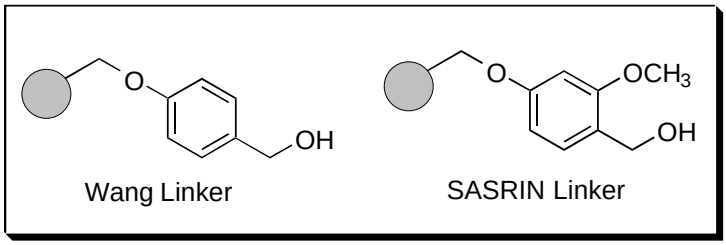


Figure 1.11 :Wang and SASRIN linkers

A more acid-labile form of the Wang linker is the SASRIN linker[4b, 16] (Figure 1.11). It has the same structure as the Wang resin but with the addition of a methoxy group that stabilises the carbonium ion formed during the acid catalysed cleavage. This resin requires only 0.5-1.0% TFA to generate carboxylic acids.

1.3.2.2 CARBOXAMIDE LINKERS

The aminoxanthenyl[1] group had been used as acid labile side chain protection for carboxamides. Sieber[18] (Figure 1.12) was prompted to design a linker based on the same principle. The acid lability of the linker was enhanced by the addition of an electron donating alkoxy substituent, and this very position is used to bind the group to polystyrene solid-phase.

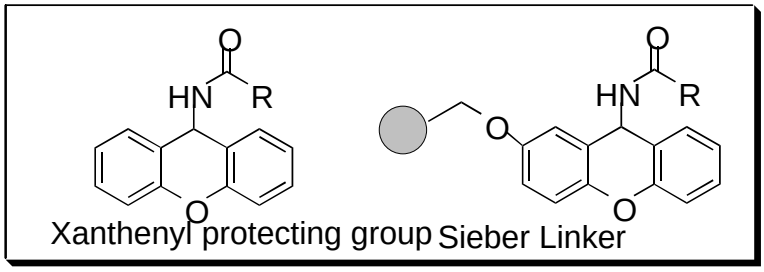


Figure 1.12: Sieber Linker

The Rink linker[17] (Figure 1.13) was developed around the same time as the Sieber linker. The greater acid sensitivity of Rink linkers is a consequence of the two additional electron donating methoxy groups. These groups, combined with ether on the phenyl ring provide considerable stabilisation for the intermediate carbonium ion generated under acidic conditions.

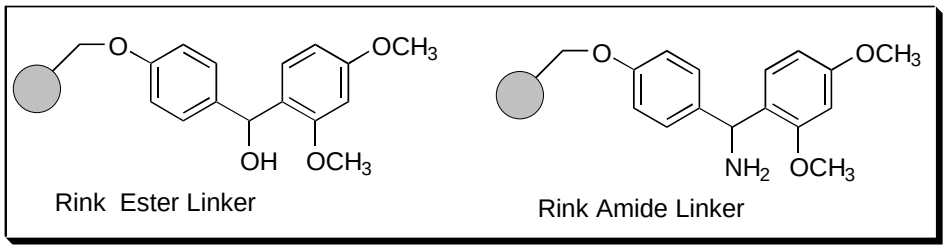


Figure 1.13: Rink Linkers

The p-nitrobenzophenone oxime ester[1] is very vulnerable to attack by nucleophiles, although essentially stable to 25%TFA. Thus it is a good candidate for the C-terminal modification of peptides.

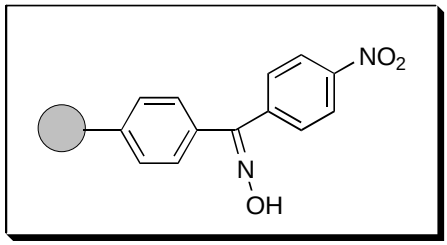


Figure 1.14: Oxime Linker

1.3.2.3 ALCOHOL LINKERS

Tetrahydropyran is a commonly encountered alcohol protecting group. Thomson and Ellman[23] synthesized a hydroxyl linker based on THP protecting group (Figure 1.15). This is stable to strong bases and is easily cleaved with acid (95% TFA in water).

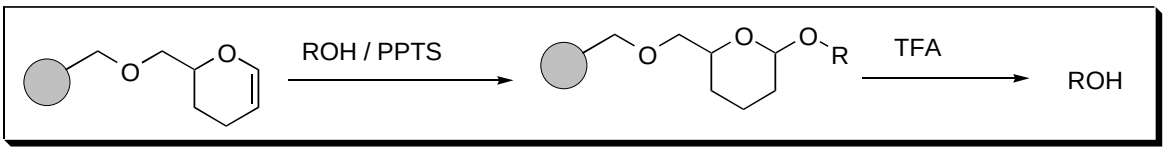


Figure 1.15: THP Linker

The trityl group is well known as an acid labile protecting group for various heteroatoms. Attachment of the trityl group provides a suitable linker for a range of different functionality including alcohols. The 2-chlorotrityl linker[11e, 24] (Figure 1.16) is also commonly used for solid-phase synthesis. The electron withdrawing chloride sufficiently reduces the lability to allow the formation and cleavage of alcohols and carboxylic acids.

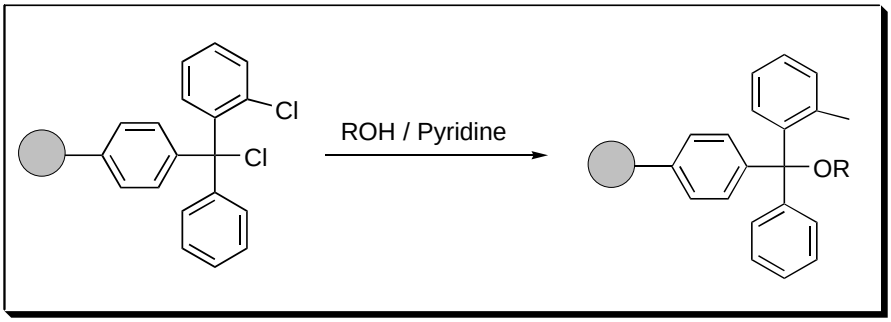


Figure 1.16: 2-Chlorotrityl Linker

1.3.2.4 AMINE LINKERS

Carbamate linkers have been used for the combinatorial synthesis of polyamines. Marsh *et al.*[25] (1996) investigated two linkers (Figure 1.17): one based on hydroxymethylbenzoic acid (A), could be cleaved only with strong acidic conditions (triflic acid/TFA). Modification of the linker by the addition of a p-electron donating group (B) enhanced the reactivity and allowed cleavage with TFA alone.

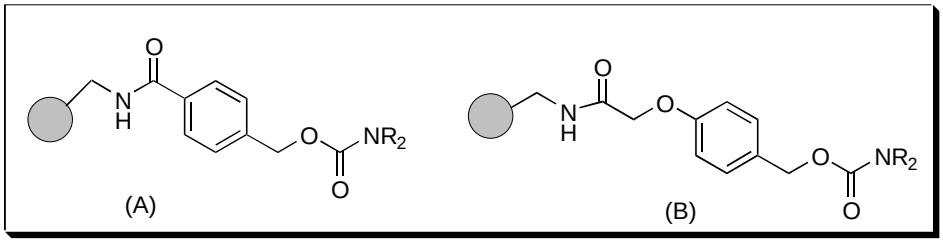


Figure 1.17: Carbamate Linkers

Brown *et al.*[11y] (1997) reported a useful linker for the generation of tertiary amines. Primary and secondary amines are introduced to the linker by Micheal addition to an acrylate attached to hydroxymethyl polystyrene. The amine is alkylated to give a resin bound quaternary ammonium ion. Under mildly basic conditions, this system is set up for a facile Hoffmann elimination to give tertiary amines of high purity. As this approach regenerates the resin bound acrylate and involves a Michael addition, the support has been labeled as REM resin (Figure 1.18).

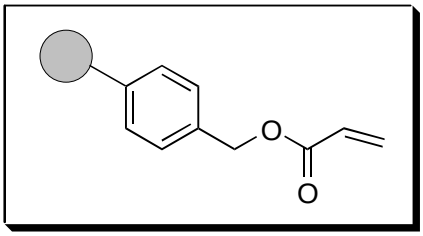


Figure 1.18: REM Linker

1.3.2.5 TRACELESS LINKERS

Traceless linkers[1] are materials that are loaded onto the resin in one form and cleaved in another form. The term 'traceless' is employed because examination of the final compounds reveals no trace of the point of linkage to the solid-phase. Silyl linkers are widely explored as traceless linkers. Silicon attached to a benzene ring can undergo protodesilylation reaction cleaving the silyl-aryl bond when treated with acid. The benzene ring is readily protonated as through hyperconjugation, the silicon stabilizes the formation of a β-carbonium ion. Elimination of the silicon releases the final product and restores aromaticity.

Veber's group[26] (1995) linked their silyl linker to Merrifield resin and demonstrated palldium catalyzed coupling of the aromatic ring before protodesilylation with TFA, caesium fluoride or liquid HF.

Ellman's[27] (1995) use of silyl linker was in the synthesis of a benzodiapinone on polystyrene beads prior to TFA or HF cleavage.

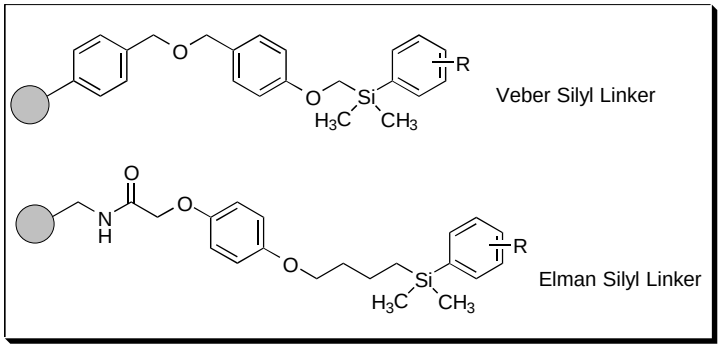
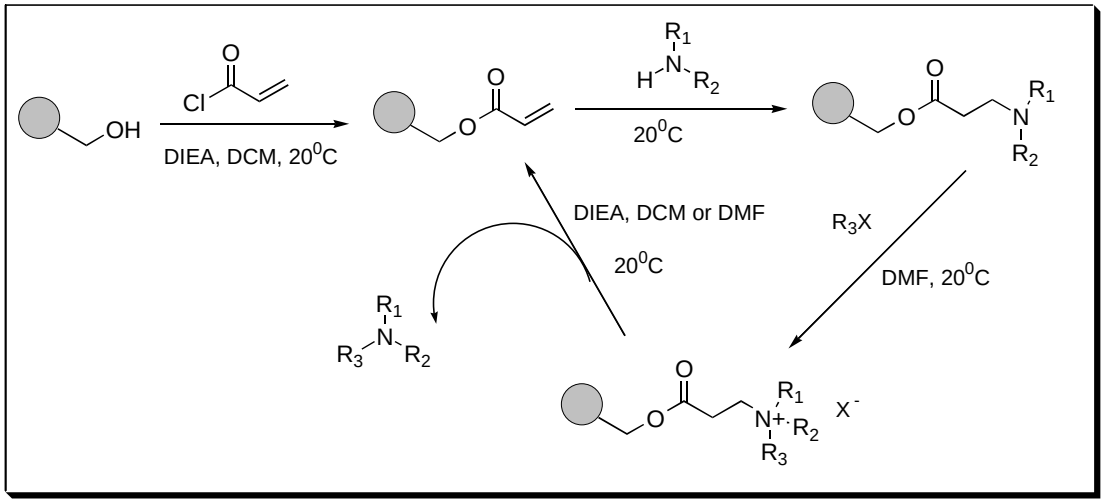


Figure 1.19: Traceless Linkers

1.3.3 EXAMPLES OF COMBINATORIAL SYNTHESES

1.3.3.1 SYNTHESIS OF TERTIARY AMINES

Brown *et al.*[11y] (1997) reported the synthesis of tertiary amines using the REM linker. The synthetic route is outlined in Scheme 1.1.



Scheme 1.1: Synthesis of Tertiary Amines

The resin used was hydroxymethyl polystyrene derivatised as the acrylate ester.

Michael addition of a secondary amine gave a resin bound tertiary amine. Alternatively, a primary amine would give a secondary amine which would be converted into a tertiary amine by reductive alkylation.

Quaternisation of the teriary amine with an alkyl halide activated the linker for a facile Hoffman elimination. Thus DIEA liberated the teriary amine into solution and regenerated the resin. Since the resin is **RE**generated after cleavage of the product and was functionalised through a **M**ichael addition, it was named REM.

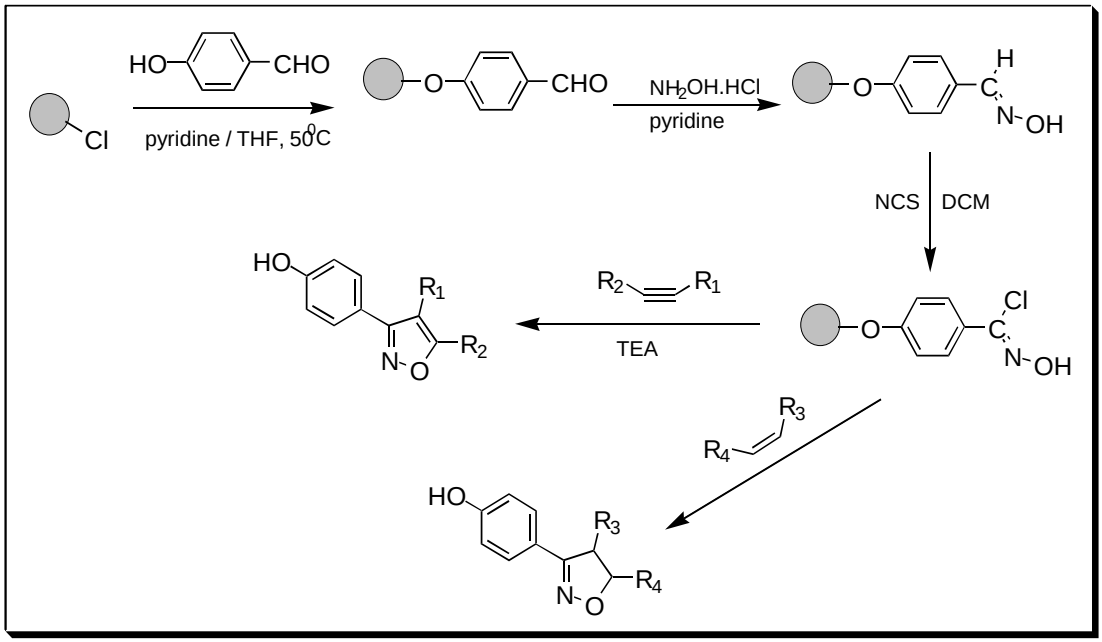
17 amines were thus synthesised, and with the exception of 4 entries, all the yields were above 55%.

1.3.3.2 SYNTHESIS OF ISOXAZOLINES

Nitrile oxides undergo [3+2] cyclo-addition reactions with olefins and acetylenes to provide isoxazolines and isoxazoles respectively. These products, besides being potential pharmaceutical agents, are also precursors to useful intermediates to other natural products. The major limitation of this chemistry is the propensity of Nitrile oxides to undergo rapid dimerisation to furoxan N-oxide. This problem can be circumvented by generating the nitrile oxide *in situ* underhigh dilution conditions in the presence of multifold excess of the olefinic trap. However purification and isolation of the desired product becomes an issue.

To overcome these limitations,Shankar *et al.*[11u] (1998) successfully employed solid-phase organic chemistry for the synthesis of isoxazolines. A nitrile oxide precursor was anchored on to the solid-phase thereby simulating high dilution by virtue of inherent loading factor, and then generated the reactive species in the presence of excess trap. Washing off all of the surplus reagents followed by cleavage would provide the cycloadducts.

Thus, para-hydroxy benzaldehyde was attached on chlorotrityl resin (Scheme 1.2). The aldehyde functionality was converted to aldoxime by treating with excess hydroxylamine hydrochloride in pyridine at room temperature.



Scheme 1.2: Synthesis of Isoxazolines and Isoxazoles

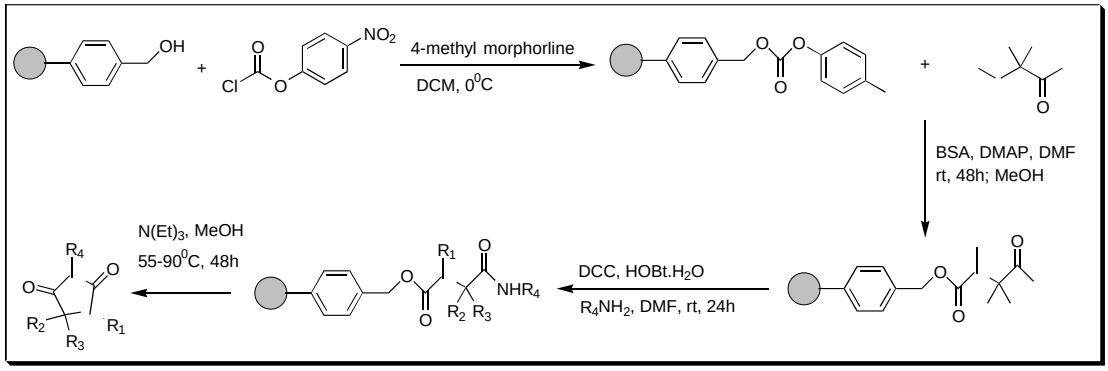
The oxime was chlorinated with 4 equivalent of N-chlorosuccinimide for two hours to provide the chloro oxime, a precursor to the nitrile oxide. To this was added a ten fold excess of dipolaraphile (olefin/acetylene) as a methylene chloride solution before

generating the nitrile oxide by slow addition of triethylamine. The resulting mixture was shaken overnight. The resin was filtered, washed and dried. The cyloadducts were cleaved off the resin with 1% TFA in DCM.

A library of isoxazolines and isoxazoles were thus prepared. The yields were in the range of (60-80%) with purity above 90%.

1.3.3.3 SYNTHESIS OF HYDANTOINS

Dressman *et al.*[11a] (1996) reported the synthesis of hydantoins using a carbamate linker. The general method for the synthesis of hydantoins is shown in Scheme 1.3.



Scheme 1.3: Synthesis of Hydantoins

Hydroxymethyl polystyrene was easily converted to (1) using N-methyl morpholine and p-nitrophenyl chloroformate in nearly quantitative yield. Selected amino acids were dissolved in DMF using N,O-bis(trimethylsilyl)acetamide and then coupled with activated carbonate (1) in the presence of DMAP to obtain free acid resin bound intermediate (2). Amide formation was then carried out using standard carbodiimide coupling conditions with an excess of the primary amine, HOBt.H2O and DCC. Treatment of the resin intermediate with excess triethylamine afforded the hydantoins. Using this methodology, a library of 800 individual hydantoins was synthesised using 20 aminoacids and over 80 primary amine building blocks.

1.4 AIM OF THE PROJECT

The development of polymer supports possessing high stability and loading levels, and yet be compatible with a wide range of solvents will be investigated. Polar monomers, typically maleimides and related structures, will be introduced into the polymer backbone. The polar backbone, obtained either as homopolymers or as copolymers, is expected to show better solvent compatibility than Merrifield resins and be more stable than Tentagel resins.

Electron-rich vinyl monomers, such as styrene and chloromethylstyrene, will be used to synthesise the copolymers. Hence alternating polymerisation (since the C=C bond in maleimides is electron-deficient) will be achieved resulting in a more controllable backbone structure.

Moreover relating properties and chemical behaviour to the backbone architecture will be easier because a random copolymer is more difficult to analyse in detail. As alternation ensures high incorporation of both monomers, high loading levels can be achieved.

The objectives of this project are:

- synthesis and characterisation of monomers
- synthesis and characterisation of linear polymers
- synthesis and characterisation of beads
- swelling studies of beads

- The proposed structures are shown in Figure 1.20.

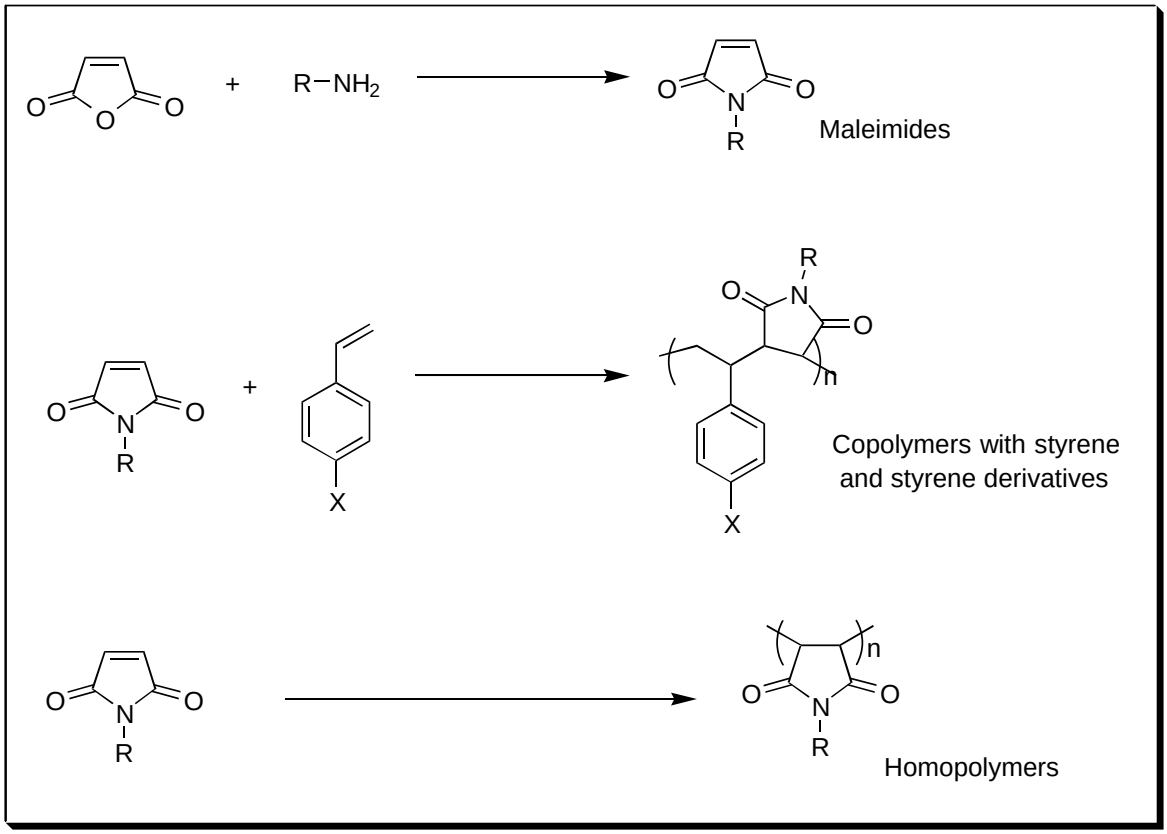


Figure 1.20: Proposed Structures

REFERENCES

1. N. K. Terrett; *Combinatorial Chemistry*, Oxford University Press (1998).

2. S. R. Wilson, A. W. Czarnik; *Combinatorial Chemistry: Synthesis and Application*, John Wiley and Sons, Inc. (1997).

3.

(a) W. J. Haap, T. B. Walk, G. Jung; *Angew. Chem. Int. Ed*., 1998, **37**, No. 23, 3311-3314.

(b) B. Yan; *Acc. Chem. Res*., 1998, **31**, No. 10, 621-630.

(c) P. Conti, D. Demont, J. Cals, H. C. J. Ottenheijm, D. Leysen; *Tetrahedron Letters*, Vol. 38, No. 16, pp 2915-2918, 1997.

(d) N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Steels; *Chem. Eur. J*., 1997, **3**, No. 12, 1917-1920.

(e) J. J. Parlow, D. A. Mischke, S. S. Woodard; *J. Org. Chem.*, 1997, **62**, No. 17, 5908-5919.

(f) B. C. Hamper, D. R. Dukesherer, M. S. South; *Tetrahedron Letters*, Vol.37, No. 21, pp. 3671-3674, 1996.

(g) D. P. Curran; *Agnew. Chem. Int. Ed.,* 1998, **37**, 1174-1196.

(h) R. M. Kim, M. Manna, S. M. Hutchins, P. R. Griffin, N. A. Yates, A. M. Bernick, K. T. Chapman; *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 10012-10017.

(i) K. S. Lam, M. Lebl, V. Krchnak; *Chem. Rev*., 1997, **97**, 411-448

(j) T. R. Boussie, C. Coutard, H. Turner, V. Murphy, T. S. Powers; *Angew. Chem. Int. Ed.,* 1998, **37**, No. 23, 3272-3275.

(k) A. Nefzi, J. M. Ostresh, R. A. Houghten; *Chem. Rev*., 1997, **97**, 449-472.

(l) M. C. Pirrung; *Chem. Rev*.,1997, **97**, No.2.

(m) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating; *Acc. Chem. Res*., 1996, **29**, 123-131.

(n) R. John Booth, J. C. Hodges; *J. Am. Chem. Soc.*, Vol.119, No. 21, 1997

(o) S. J. Shuttleworth, S. A. Mallin, P. K. Sharma; *Synthesis*, Nov. 1997, pp. 1217-1239.

(p) S. J. Shuttleworth, S. A. Mallin, P. K. Sharma; *Synthesis*, Nov. 1997, pp. 1217-1239.

4.

(a) R. B. Merrifield; *J. Am. Chem. Soc.*, **85**, 2149-2154, 1963.

(b) M. Mergler, R. Tanner, J. Gostelli, P. Grogg; *Tet. Lett.*, Vol. 29, No. 32, pp. 4005-4008, 1988.

(c) A. F. Coffey, T. Johnson; *Int. J. Peptide Protein Res*., 1992, **39**, 419-430.

(d) K. C. Pugh, E. J. York, J. M. Stewart; *Int. J. Peptide Protein Res*., 1992, **42**, 208-213.

(e) M. Kempe, G. Barany; *J. Am. Chem. Soc*., 1996, **118**, No. 30, 7083-7093.

(f) B. Blankmeyer-Menge, M. Nimtz, R. Frank; *Tetrahedron Letters*, Vol.31, No.12, pp1701-1704, 1990.

(g) P. W. Small, D. C. Sherrington; *J. Chem. Soc., Chem Commun*., 1989, No. 21, 1589-1591.

(h) R. C. Sheppard, B. J. Williams; *Int. J. Peptide Protein Res.*, **20**, 1982, 451-454.

(i) P. Rivaille, J. P. Gautron, B. Castro, G. Milhaud; *Tetrahedron*, Vol. 36, pp 3413-3419, 1980.

5. R. A. Houghten; *Proc. Natl. Acad. Sci. USA,* **82**, 5131-5135 (1985).

6. Furka, F. Sebestyen, M. Asgedom, G. Digbo; *Abstr. 14th Int. Congr. Biochem. Prague, Czechoslovakia*, Vol. 5, 47, 1988.

7. R. A. Houghten, C. Pinalla, S. E. Blondelle, J. R. Appel, C. T. Dooley, J. H. Cuervo; *Nature (London)*, Vol. 354, 84-86 (1991).

8. K. S. Lam, S. E. Salmon, E. M. Hersch, V. J. Hruby, W. M. Kazmierski, R. J. Knapp; *Nature (London)*, Vol. 354, 82-84 (1991).

9. L. A. Thompson, J. A. Ellman; *Chem. Rev*., 1996, **96**, 555-600

10. W. C. Still; *Acc. Chem. Res*., 1996, **29**, 155-163.

11.

(a) B. A. Dressman, L. A. Spangle, S. W. Kaldor; *Tetrahedron Letters*, Vol. 37, No. 7, pp 937-940, 1996.

(b) L. Gouilleux, J-L. Fehrentz, F. Winternitz, J. Martinez; *Tetrahedron Letters*, Vol. 37, No. 39, pp 7031-7034, 1996.

(c) A. R. Katritzky, L. Xie, G. Zhang, M. Griffith, K. Watson, J. S. Kiely; *Tetrahedron Letters*, Vol. 38, No. 40, pp 7011-7014, 1997.

(d) R. Frenette, R. W. Friesen; *Tetrahedron Letters*, Vol. 35, No. 49, pp 9177-9180, 1994.

(e) W. J. Hoekstra, M. N. Greco, S. C. Yabut, B. L. Hulshizer, B. E. Maryanoff; *Tetrahedron Letters*, Vol. 38, No. 15, pp 2629-2639, 1997.

(f) T. A. Rano, K. T. Chapman; *Tetrahedron Letters*, Vol. 36, No. 22, pp 3789-3792, 1995.

(g) Y. Hu, J. A. Porco Jr.; *Tetrahedron Letters,* **39** (1998), 2711-2714.

(h) D. Sarantakis, J. J. Bicksler; *Tetrahedron Letters*, Vol. 38, No. 42, pp 7325-7328, 1997.

(i) A. M. Fivush, T. M. Willson; *Tetrahedron Letters*, Vol. 38, No. 41, pp7151-7154, 1997.

(j) R. Brown; *Contemporary Organic Synthesis*, 1996, pp. 216-237.

(k) R. Li, X-Y. Xiao, A. W. Czarnik; *Tetrahedron letters,* **39** (1998) 8581-8584.

(l) O. W. Gooding, S. Baudat, T. L. Deegan, K. Heisler, J. W. Labadie, J. A. Porco Jr. , W. S. Newcomb, P. van Eikeren; *J. Comb. Chem.*, 1999, **1**, 113-122.

(m) X. Ouyang, R. W. Armstrong, M. M. Murphy; *J. Org. Chem*., 1998, **63**, No.4, 1027-1032.

(n) A. Florsheimer, B. Riniker; *Peptides*, 1990.

(o) V. Krchnak, Z. Flegelova, A. S. Wiechsel, M. Lebl; *Tetrahedron Letters*, Vol.36, No. 35, pp. 6193-6196, 1995.

(p) K. A. Beaver, A. C. Siegmund, K. L. Spear; *Tetrahedron Letters*, Vol.37, No. 8, pp. 1145-1148, 1996.

(q) M. Meldal, F. I. Auzanneau, O. Hindsgaul, M. M. Palcic*; J. Chem. Soc., Chem Commun.,* 1994, 1849-1850.

(r) K. Lewandowski, P. Murer, F. Svec, J. M. J. Frechet; *Chem. Commun.*, 1998.

(s) S. Booth, P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees; *Tetrahedron*, 1998, **54**, 15385-15443.

(t) K. Dendrinos, J. J. Jeong, W. Huang, A. G. Kalivretenos; *Chem. Commun.,* 1998, 499-500.

(u) B. B. Shankar, D. Y. Yang, S. Girton, A. K. Ganguly; *Tetrahedron Letters*, **39** (1998) 2447-2448.

(v) K. H. Park, E. Abbate, S. Najdi, M. M. Olmstead, M. J. Kurth; *Chem. Commun.,* 1998, 1679-1680.

(w) R. A. Smith, M. A. Bobko, W. Lee; *Bioorg. and Med. Chem. Lett.,* **8** (1998) 2369-2374.

(x) Y. Hamuro, M. A. Scialdone, W. F. Degrado; *J. Am. Chem. Soc*., 1999, **121**, No. 8, 1636-1644.

(y) A. R. Brown, D. C. Rees, Z. Rankovic, J. R. Morphy; *J. Am. Chem. Soc.*, Vol. 119, No. 14, 1997.

(z) H. Han, K. D. Janda; *Angew. Chem. Int. Ed.,* 1998, **36**, No. 16, 1731-1733.

(aa) S. Havez, M. Begtrup, P. Vedso; *J. Org. Chem*., 1998, **63**, 7418-7420.

(ab) E. E. Swayze; *Tetrahedron Letters*, Vol. 38, No. 49, pp 8465-8468, 1997.

12.

(a) J. J. V. Eynde, D. Rutot; *Tetrahedron,* **55** (1999) 2687-2694.

(b) D. E. Bergbreiter, B. L. Case, Y. S. Liu, J. W. Caraway; *Macromolecules*, 1998, **31**, No. 18, 6053-6062.

(c) M. H. Kim, D. Janda; *J. Org. Chem*., 1998, **63**, No. 3, 889-894.

(d) B. Sauvagnat, F. Lamaty, R. Lazaro, J. Martinez; *Tetrahedron Letters*, 1998, **39**, 821-824.

(e) J. Y. Shey, C. M. Sun; *Synlett*, Dec 1998, 1423.

(f) D. J. Gravert, K. D. Janda; *Chem. Rev*.,1997, **97**, 489-509.

13.

(a) K. Kesenci, E. Piskin; *Macromol. Chem. Phys.*, 1998, **199**, 385-391.

(b) N. Ogawa, K. Honmyo, K. Harada, A. Sugii; *Journal of Applied Polymer Science*, 1984, **29**, 2852-2856.

14.

(a) Y-D. Jo, K-S. Park, J-H. Ahn, S-K. Ihm; *Eur. Polym. J.*, Vol. 32, No. 8, pp. 967-972, 1996.

(b) L. Manziek, E. Langenmayr, A. Lamola, M. Gallagher, N. Breese, N. Annan; *Chem. Mater.*, 1998, **10**, 3101-3108.

(c) A. B. Scranton, A. G. Mikos, L. C. Scranton, N. A. Peppas; *J. of App. Pol. Sci.*, Vol. 40, 997-1004 (1990).

(d) O. Okay; *J. of App. Pol. Sci*., Vol.34, 307-317(1987).

(e) D. C. Sherrington; *Chem. Commun*., 1998, 2275-2286.

(f) H. Liang, F. Svec, J. M. J. Frechet; *J. Pol. Sci.:Part A: Polymer Chemistry*, Vol.35, 2631-2643 (1997).

(g) D. Rabelo, F. M. B. Coutinho; *Eur. Polym. J*., 1994, **30**, No. 6, 675-682.

(h) T. Narasimhaswamy, B. S. R. Reddy; *J. of App. Pol. Sci.,* Vol. 43, 1645-1657 (1991).

(i) R. Arshady, A. Ledwith; *Reactive Polymers*, **1** (1983) 159-174.

(j) T. Matynia, B. Gawdzik, E. Chmielewska; *J. of App. Pol. Sci.*, Vol. 60, 1971-1975 (1996).

(k) R. Arshady; *Journal of Chromatography*, **586** (1991) 181-197.

(l) M. R. Jin, Y. X. Wang, X. Zhong, S. C. Wang; *Polymer*, Vol. 36, No. 1, pp. 221-222, 1995.

(m) A. Mathew, P. C. Deb; *Journal of Polymer Science: Part A: Polymer Chemistry*, 1996, **34**, 1605-1607.

(n) H. Deleuze, D. C. Sherrington; *J. Chem. Soc. Perkin Trans*., 1995, **2**, 2217-2221.

15. S. W. Wang, J. Am. Chem. Soc., 1973, **95**, 1328.

16. R. Katritzky, D. Toader, K. Watson, J. S. Kiely; *Tetrahedron Letters*, 1997, **38**, No. 45, 7849-7850.

17. H. Rink; *Tetrahedron Letters*, Vol. 28, pp3787-3790, 1987.

18. P. Sieber, Tetrahedron Letters, Vol. 28, 2107, 1987.

19. Renil, V. N. R. Pillai, *Synthesis, Characterization and Application of Tetraethylene Glycol Diacrylate Crosslinked Polystyrene Support for Gel Phase Peptide Synthesis,* 1585-1594.

20. B. Lehr, H. J. Egelhaaf, H. Fritz, W. Raap, E. Bayer, D. Oelkrug; *Macromolecules*, 1996, 29, 7931-7936.

21.
(a) J. C. Alfred, J. Daunis, R. Jacquier; *Macromol. Chem. Phys*., 197, 389-401(1996).

(b) M. Meldal; *Tetrahedron Letters*, 1992, 33, No. 21, 3077-3080.

22.
(a) D. Horak, F. Lednicky, V. Rehak, F. Svec; *J. of App. Pol. Sci.*, Vol. 49, 2041-2050 (1993).

(b) Tuncel; *Colloid Polym. Sci.,* 278: 1126-1138 (2000).

23. L. A. Thompson, J. A. Ellman; *Tetrahedron Letters*, **35**, 9333-9336, 1994.

24. S. L. Mellor, C. McGuire, W. C. Chan; *Tetrahedron Letters*, Vol. 38, No. 18, pp 3311-3314, 1997.

25. I. R. Marsh, H. Smith, M. Bradley; *Chem. Commun*., 1996, 941.

26. B. Chenera, J. A. Finkelstein, D. F. Veber, *J. Am. Chem. Soc.*, **117**, 1999-2000, 1995.

27. M. J. Plunkett, J. A. Ellman, *J. Org. Chem.*, **60**, 6006-6007.

28. For examples of commercially available resins visit:

(a): http://www.polymerlabs.com, Website of Polymer Laboratories

(b): http://www.argonaut.com, Website of Argonaut Technology

2. RESULTS AND DISCUSSION

2.1 INTRODUCTION

The synthesis of polymer supports having a more polar backbone was undertaken. Maleimides were synthesized by reacting maleic anhydride and amino compounds. Both maleimides and maleic anhydride tend to form alternating[(1)(2)] copolymers with styrene and its derivatives. These polymers are expected to be compatible with a wider range of solvents and have higher loading levels than traditional polystyrene based supports. The ability of maleimides to polymerise yielding linear polymers was studied. Styrene and maleic anhydride polymer beads were synthesised and functionalised. Their swellability in different solvents was investigated.

2.2 SYNTHESIS OF MONOMERS

2.2.1 Synthesis of Maleimides

The synthesis of maleimides is a two-step process: firstly the N-substituted maleamic acid is formed which is then cyclised as shown in Figure 2.1.

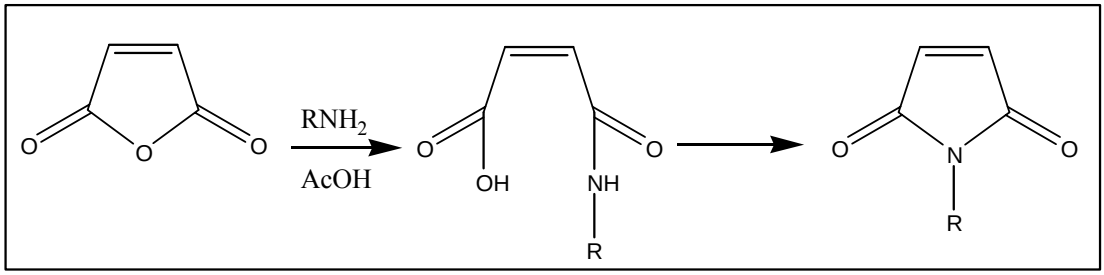


Figure 2.1: Synthesis of maleimides

Most of the reported methods rely on the use of acidic conditions[(3)]. Apparently under these conditions, competitive Michael addition in the first step is suppressed. The ring closure can then be achieved using either acidic or basic conditions. Yields are moderate.

2.2.1.1 Synthesis of Maleimides under Acidic Conditions

After carrying out the initial ring-opening step in acetic acid, two methods for ring closure were attempted:

(a) by refluxing in acetic acid

(b) by refluxing in toluene in the presence of catalytic amount of p-toluene sulphonic acid (PTSA)

The results are shown in Figure 2.2.

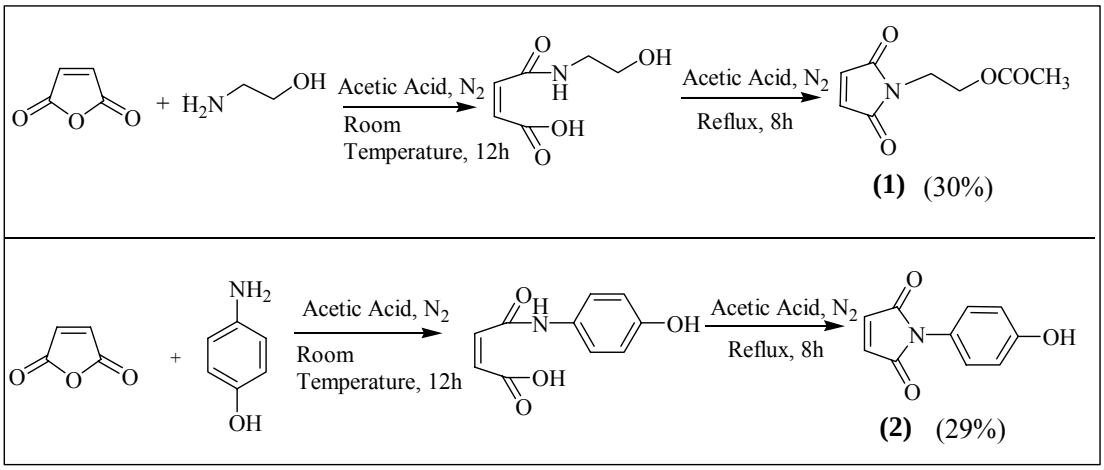


Figure 2.2: Synthesis of maleimides under acidic conditions

(1) was obtained as colourless crystals whereas **(2)** was obtained as a yellow crystalline solid.

The absence of peaks in the region of 3400 cm^{-1} in the IR spectrum suggested that the OH group in ethanolamine had undergone a change. The presence of a singlet at δ = 2.02 ppm (intensity = 3H) in the ^{1}HNMR spectrum and a peak at δ=20.5 ppm in the ^{13}CNMR confirmed the conversion of the alcohol moiety into an acetate group.

However in the case of 4-amino phenol, the phenolic group in **(2)** was not acetylated. No peak in the region around δ = 2 ppm in the ^{1}HNMR spectrum and below δ = 60 ppm in the ^{13}CNMR spectrum was obtained. The presence of a peak at 3450 cm^{-1} in the IR spectrum was noted. However, no peak, relating to the phenol group was obtained in the region of δ = 9 ppm in the ^{1}HNMR spectrum when acetone was used as solvent. Nevertheless, this peak was observed (^{1}HNMR in $CDCl_3$) when **(2)** was

homopolymerised as described under section 2.3.1. The phenolic group was not acetylated probably due to the involvement of the lone pairs of electron on the phenolic oxygen atom in resonance with the benzene ring.

When the cyclisation was attempted in toluene in the presence of PTSA, hard and insoluble solids were obtained in both cases. This may be due to the condensation of the hydroxyl group with the carboxylic acid moiety of another molecule yielding polymer like products.

2.2.1.2 Synthesis of Maleimides under Basic Conditions

The cyclisation of the maleamic acids under basic conditions was also investigated. The use of tri-ethylamine (TEA) or anhydrous sodium acetate in the presence of acetic anhydride has been reported[(3)]. This is especially suitable for aromatic maleimides, for which relatively high yields have been obtained. The results are shown in Figure 2.3.

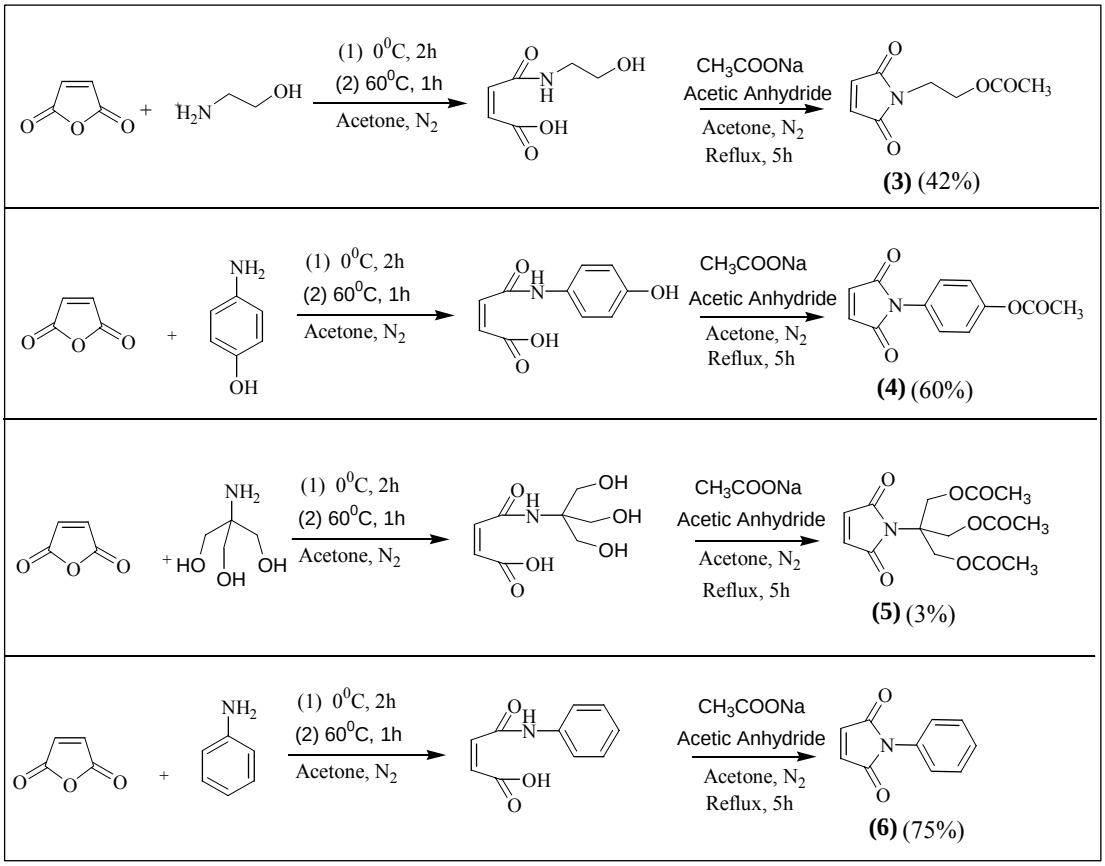


Figure 2.3: Synthesis of maleimides under basic conditions

(3) and **(5)** were obtained as colourless crystals, **(4)** was obtained as a brown solid and **(6)** was obtained as yellow crystals.

Under the reaction conditions, all the hydroxyl groups are acetylated. No peak was obtained in the region 3400 cm^{-1} in the IR spectrum. The NMR spectra of **(3)** was identical to the maleimide **(1)** obtained under acidic conditions.

Unlike in the case of **(2)**, the phenolic group in **(4)** was acetylated. There was an absence of peaks in the region around 3400 cm^{-1}. Compared to the ^{1}HNMR spectra of **(2)**, there was an additional singlet at δ = 2.09 ppm with an intensity of 3 protons. Moreover, there were two more peaks in the ^{13}CNMR of **(4)**: one at 169.2 ppm (C=O of acetate) and one at 25.6 ppm (CH_3). As expected, the ^{1}HNMR spectra of **(5)** constituted of 3 singlets. The singlet at δ = 2.05 ppm with an intensity of 3 protons marked the acetylation of the alcohol group. The melting point of **(6)** (91°C) was as reported in literature[(4)].

The yield of **(3)** was higher when carried out under basic conditions. Moreover, better yields were obtained when aromatic amines were used. The yield of **(5)** was poor probably due to a marked influence of steric hindrance. The use of excess acetic anhydride and sodium acetate had no effect on the yield.

2.2.2 Synthesis of Maleimido Crosslinkers

Bis-maleimido crosslinkers were synthesised using diamino compounds and maleic anhydride. Because of the overall better yield that was obtained under basic conditions, the cyclisation was attempted under basic conditions, in the presence of sodium acetate and acetic anhydride. Ethylene diamine, propylene diamine and 1,4-diamino benzene were the diamino compounds used. The results are shown in Figure 2.4.

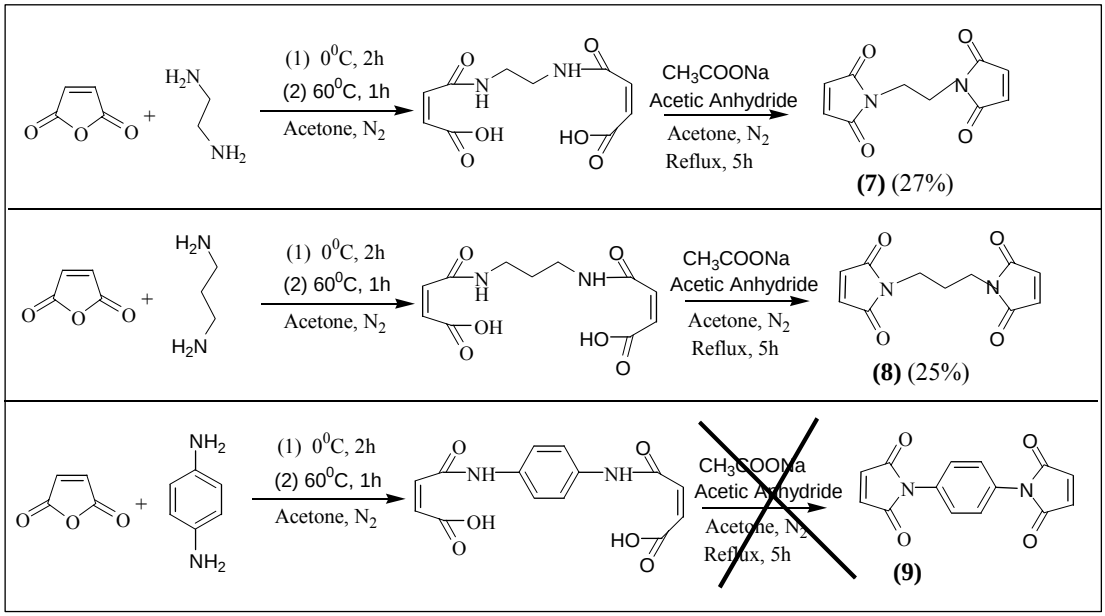


Figure 2.4: Synthesis of maleimido crosslinkers

The yields of **(7)** and **(8)** are similar. Both were obtained as colourless crystals.
As expected the ^{1}HNMR spectrum of **(7)** shows only two singlets (δ = 6.69 ppm (C=O??) and δ = 3.74 ppm (-CH_2-) of equal intensity. Because of symmetry, no coupling between adjacent protons was observed. The ^{13}CNMR exposes only three different carbon environment (δ = 170.5 ppm (C=O), δ = 134.2 (C=C), δ = 36.5 (-CH_2-)).

In the case of **(8)**, there is an additional peak in the ^{13}CNMR at δ = 27.4 ppm due to the innermost –CH_2- group. The latter gives rise to a quintet at δ =1.96 ppm (J=7.5 Hz) in the ^{1}HNMR. A triplet at δ = 3.53 ppm (J=7.5 Hz) (-CH_2- closer to the

maleimide ring, 4H) and a singlet at $\delta = 6.78$ ppm due to maleimide ring protons were also obtained.

With 1,4-diamino benzene the anticipated bismaleimide was not obtained. This might be because 1,4-diamino benzene is a highly conjugated system. The lone pair of electron on the nitrogen atom is less readily available. This is not the case with the aliphatic counterparts, where the electron pair is more readily available.

2.2.3 Synthesis of Styryl Monomers

The aim was to transform chloromethylstyrene into more hydrophilic and polar monomer by attaching polyhydroxyl compounds at the benzyl position. The resulting monomer could be used to synthesize Tentagel type polymers where the bulky polyethylene glycol (PEG) chains have been replaced with a hydrophilic group of lower molar mass. The polyhydroxyl group would also have a relatively higher loading. 1,2-di-O-isopropylidene glycerol[(4)] and tris(hydroxy methyl) methyl amine (THMMA) were used. The results are shown in Figure 2.5.

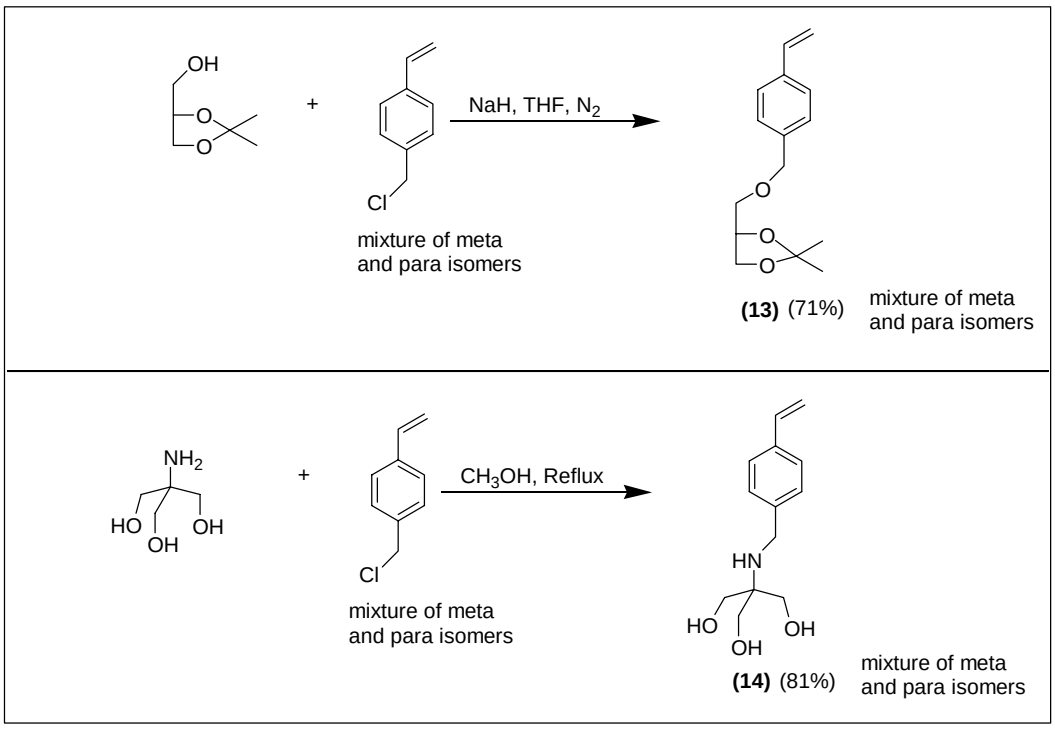


Figure 2.5: Synthesis of styryl monomers

Good yields were obtained. **(13)** was obtained as viscous yellow liquid while **(14)** was obtained as a white solid. **(13)** was a mixture of meta and para isomers. The NMR spectra, which was a little scrambled, showed a good correlation between the aromatic and aliphatic counterparts. The band corresponding to the OH group in the sugar moiety in the IR spectrum disappeared. The goal was to polymerise **(13)** and then remove the protecting acetal group. This would expose the more hydrophilic hydroxyl groups, which could be potential anchor groups for linkers and other substrates.

The NMR spectrum of **(14)** was taken in deuteriated water (D_2O). It was insoluble in chloroform and acetone. Peaks due to the benzene ring were clearly visible. This monomer looks very promising because it is easy to synthesize, stable (does not polymerise spontaneously) and hydrophilic.

2.3 SYNTHESIS OF LINEAR POLYMERS

The C=C bond in maleic anhydride is flanked by two carbonyl groups. Due to the presence of these electron withdrawing groups and as a result of conjugation, there is less electron density at the C=C bond. Thus, maleic anhydride does not homopolymerise under free radical conditions. But it forms alternating copolymers with electron-rich monomers such as styrene. Because of the high similarity in their structure, the reactivity of maleimides with respect to free radical polymerisation is expected to be similar to that of maleic anhydride.

The behaviour of the maleimides prepared in this study during polymerisation, under free radical conditions, was investigated by homopolymerising and copolymerising the monomer (with styrene and chloromethylstyrene). The polymers were characterised by NMR. These would serve as a reference.

2.3.1 Polymerisation of Maleimides

Homopolymers derived from N-(phenyl) maleimide **(6)**, N-(4-hydroxy phenyl) maleimide **(2)**, N-(2-acetoxyethyl)maleimide **(3)** and N-(4-acetoxy phenyl) maleimide **(4)** were synthesised under the same conditions. The results are shown in Figure 2.6.

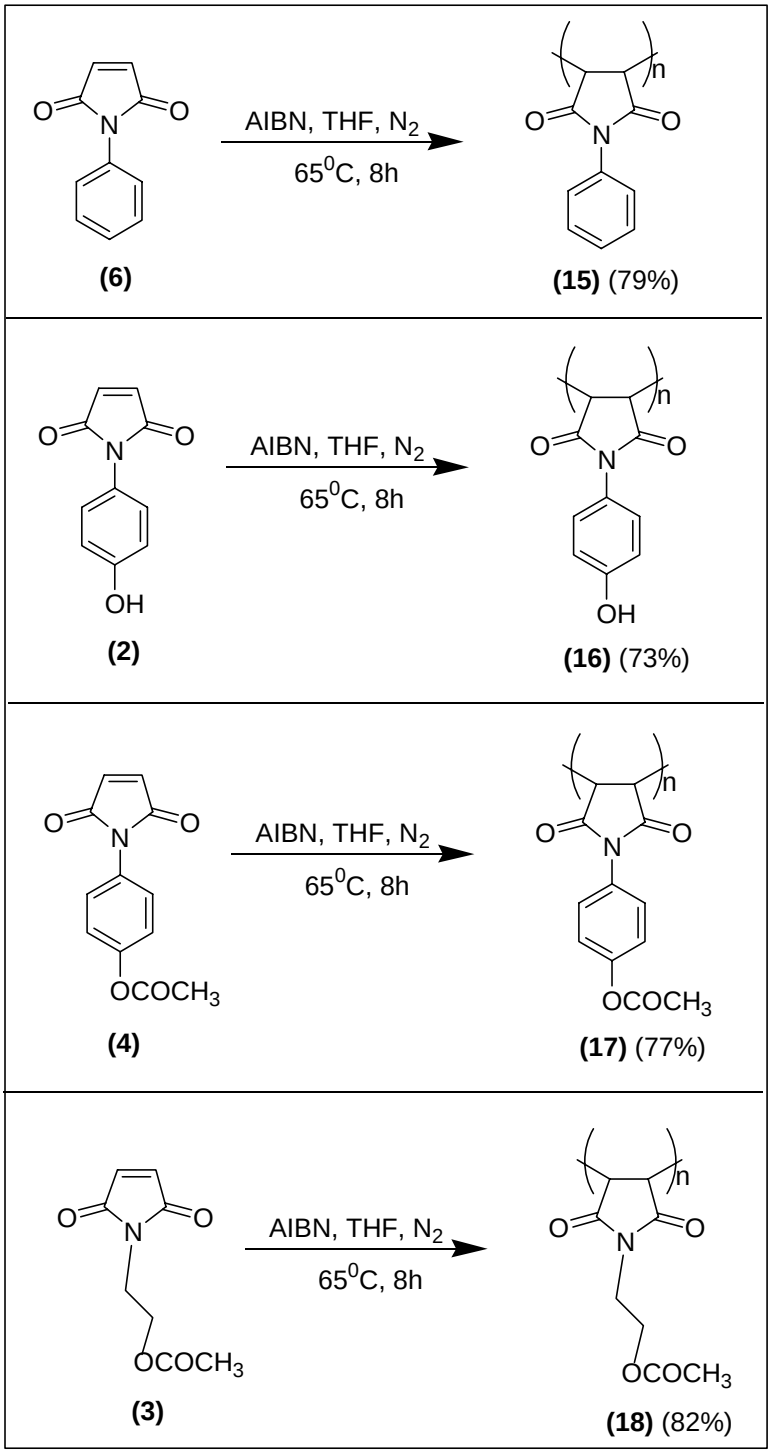


Figure 2.6: Homopolymerisation of maleimides

All the polymers were obtained as white powdery solids. The NMR spectra of all the polymers typically contained broad peaks. Moreover, the peak due to the H-C=C-H protons disappeared and gave rise to broad peaks which were more upfield (δ = 2.5-4.5 ppm). In the case of the ^{13}CNMR spectra of all the polymers, the peak due to the C=C bond (around δ = 134 ppm) in the maleimide was no longer obtained.

Unlike maleic anhydride, these monomers homopolymerised despite being relatively electron-deficient at the C=C bond. This may be due to the higher electron density at the C=C bond, as a consequence of resonance between the lone pair of electrons on the nitrogen atom and the carbonyl groups. The C=C bond would be less involved in conjugation with the carbonyl groups and thus be more "available".

However, the rate of polymerisation of maleimides is expected to be lower than the rate of polymerisation of electron-rich monomers like styrene. An electron-deficient free radical is less stabilised than an electron-rich one. A growing polymer chain would be 'reluctant' to add to another electron-deficient reaction centre. This could mean higher reaction times for complete conversion and lower mass of polymers. Although it is common practice to determine the molecular mass of new polymers, this could not be established due to the lack of equipment at our laboratory.

Poly(N-(phenyl)maleimide) and polystyrene have analogous structures (Figure 2.7). Poly(N-(phenyl)maleimide) is more polar than poly(styrene) due to the presence of the succinimide moiety. Poly(N-(phenyl)maleimide) is likely to be compatible with a wider range of solvents than poly(styrene).

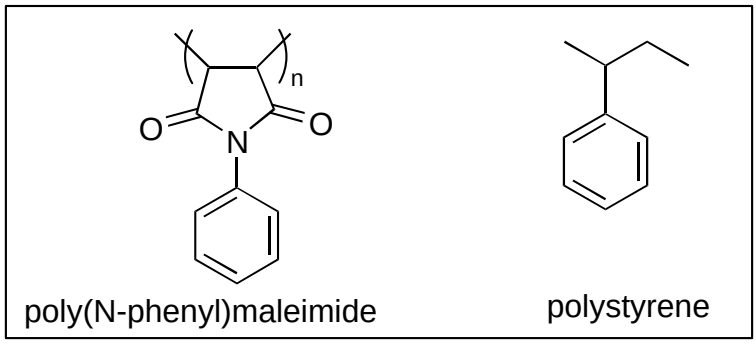


Figure 2.7: poly(N-phenyl)maleimide and polystyrene

However, in the presence of strong nucleophiles, the succinimide ring is quite susceptible to open up. This is not a concern in the case of poly(styrene), where the backbone is inert and hence more stable. Functionalised poly(styrene) is a widely used support in solid phase synthesis. For example, in chloromethylated poly(styrene) (for example, the Merrifield resin), the chloromethyl moiety serves as an anchor for linkers or substrates. Functionalisation of poly(N-(phenyl)maleimide) with appropriate groups would yield similar supports, but with a more polar backbone.

Poly(N-(4-hydroxyphenyl)maleimide) does not require functionalisation. The phenolic group can directly be used as an anchor for substrates or linkers. The presence of the phenolic group makes the polymer more polar than poly(N-(phenyl)maleimide). Theoretically, this polymer has a loading of 5 mmol/g, which is a relatively high value.

However, both in poly(N-(phenyl)maleimide) and poly(N-(4-hydroxyphenyl) maleimide), there may be significant steric hindrance due to the bulky phenyl groups and the rigid planar structure of the monomer. Steric hindrance does not seem to be such an important matter in the case of poly(N-(2-acetoxyethyl)maleimide). The aliphatic acetoxyethyl moiety is more flexible and less bulky.

Removing the acetate group would expose the more reactive and useful hydroxyl group. This can then be used as an anchor.

2.3.2 Polymerisation of Styrene Derivatives

Chloromethylstyrene is very similar to styrene in terms of reactivity and structure. Upon polymerisation, it yields polymers with the same backbone as polystyrene, but with a more versatile chloromethyl group, which can be used as an anchor.

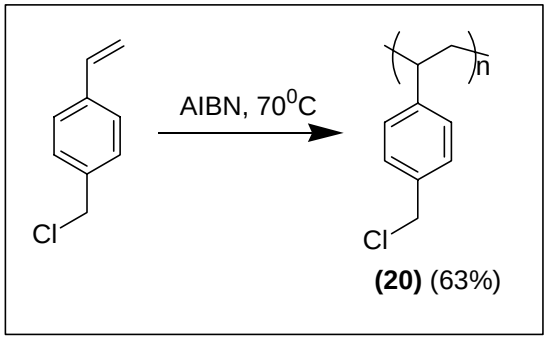


Figure 2.8: Polymerisation of chloromethyl styrene

Poly(chloromethylstyrene) **(20)** has a higher loading than chloromethylated poly(styrene), as in the latter case not all of the phenyl groups are functionalised.

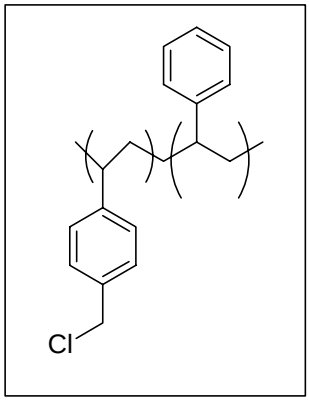


Figure 2.9: Chloromethylated polystyrene

The monomer **(14)** is very attractive as regards to hydrophilicity. It is soluble in water and has three hydroxyl groups that can be used as sites for chemical interaction. However it did not homopolymerise in DMF (AIBN as initiator) or in water (azobis (-2-amidinopropane)dihydrochloride) as initiator). The desired polymer **(22)** was synthesised by reacting THMMA with poly(chloromethylstyrene) **(20)** in DMF as shown in Figure 2.10.

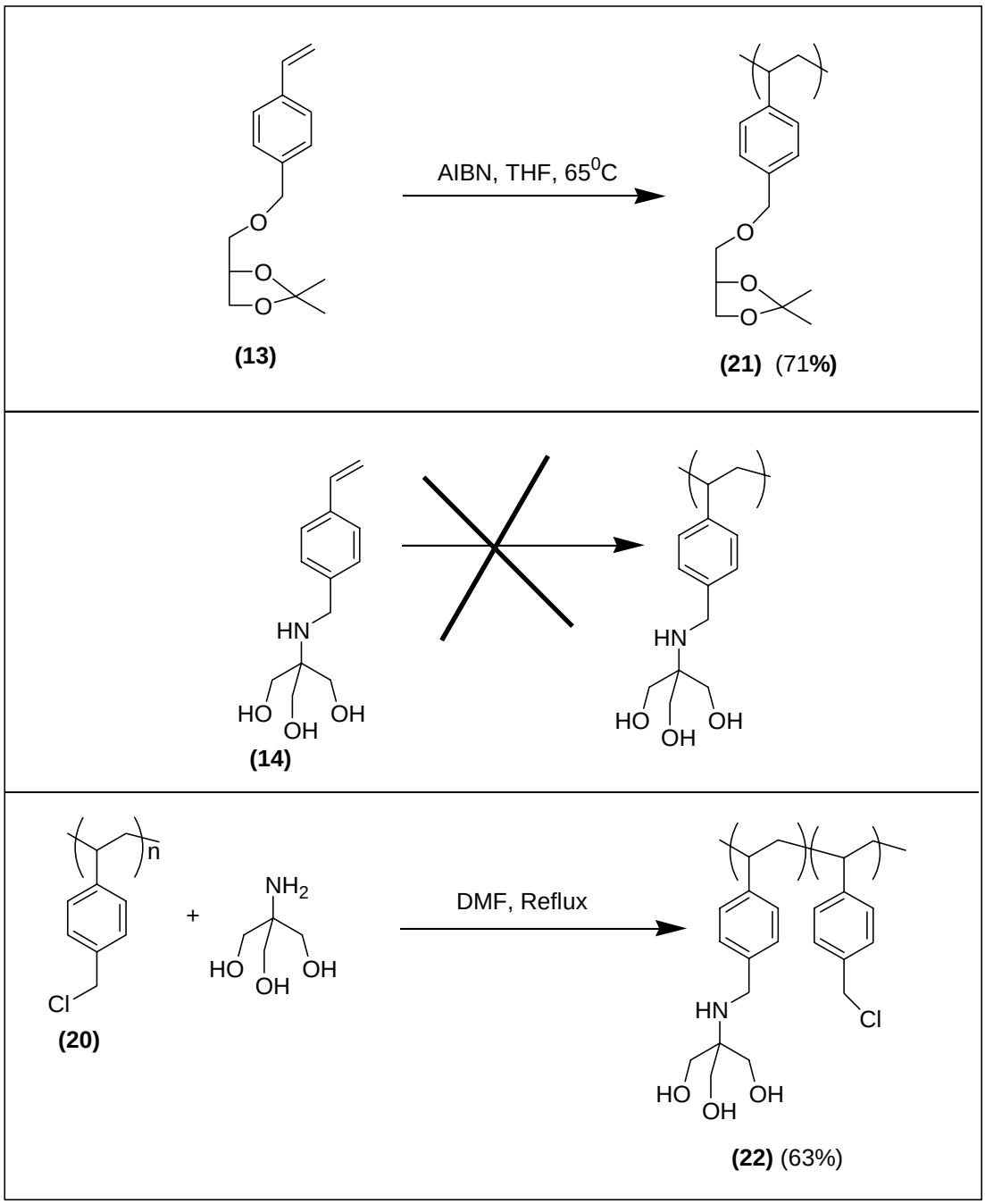


Figure 2.10

No such problem was encountered with monomer **(13)**. It homopolymerised in THF to give the anticipated polymer **(21)**. The NMR spectra of **(21)** and **(22)** contained broad overlapping peaks.

The NMR spectra of **(21)** and especially **(22)** were scrambled because the chloromethylstyrene used was a mixture of meta and para isomers.

2.3.3 Synthesis of Copolymers

Styrene and chloromethylstyrene were copolymerised with maleic anhydride, **(2)**, **(3), (4)** and **(6)**. The results are shown in Figure 2.11 and Figure 2.12.

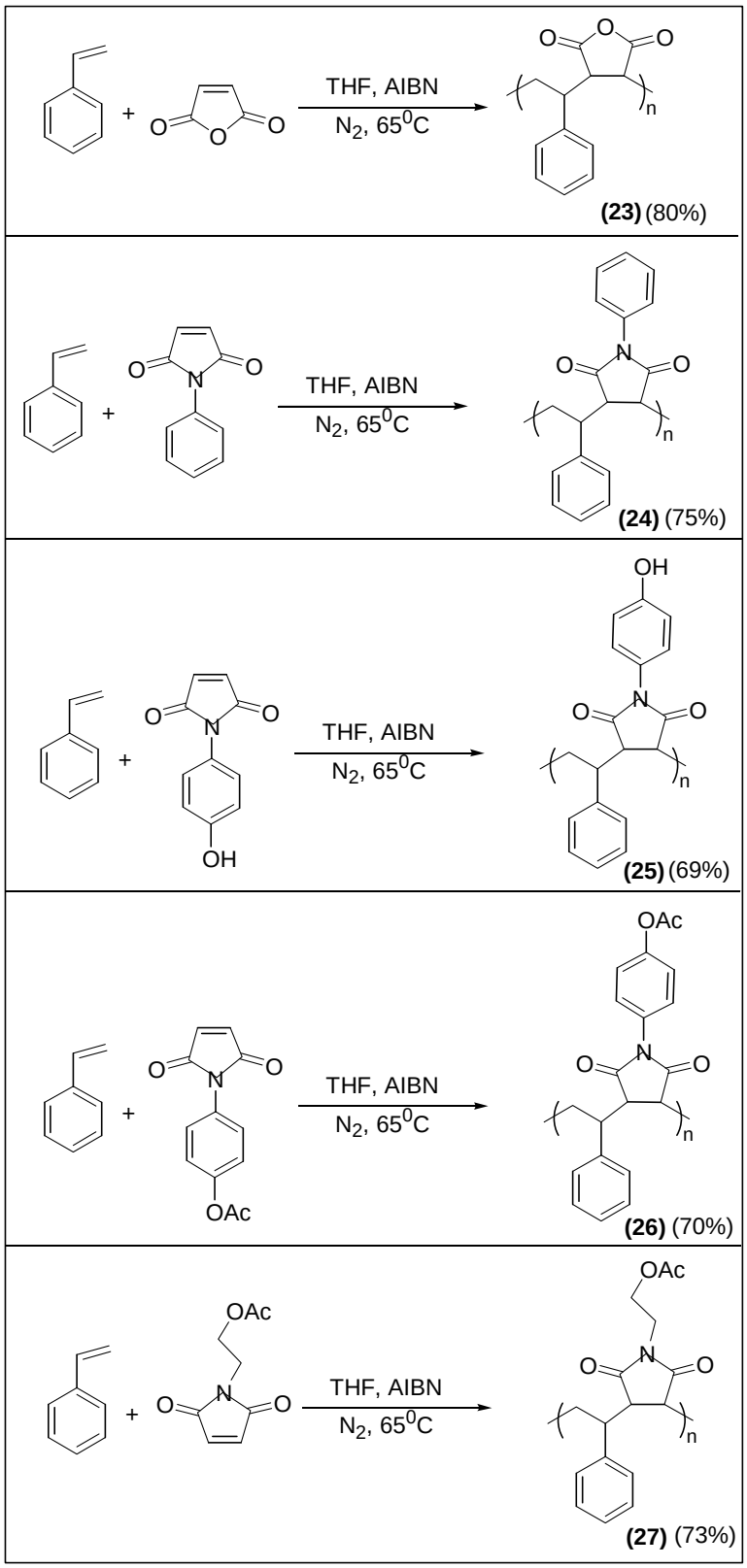


Figure 2.11: Copolymers of styrene

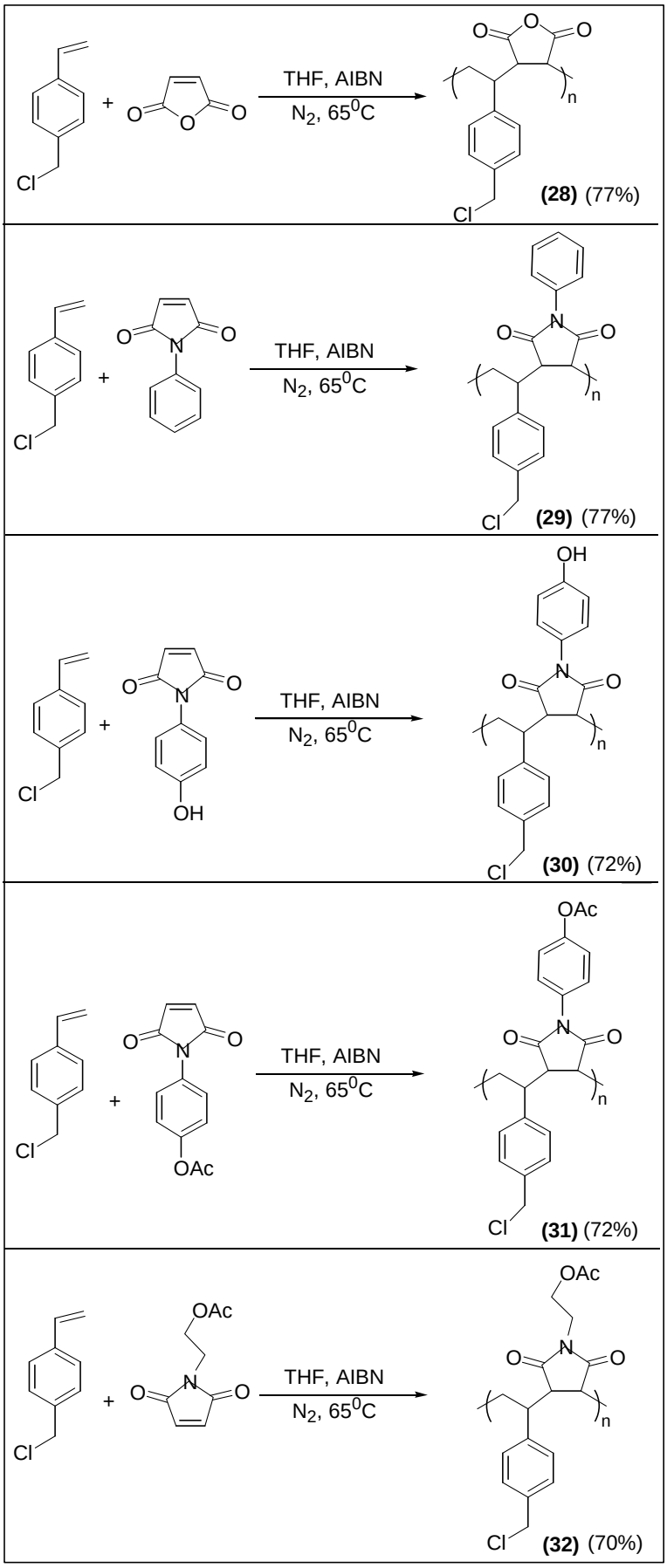


Figure 2.12: Copolymers of CMS

All the polymers were white solids. Styrene and CMS are electron rich monomers whereas the maleimides, as well as maleic anhydride, are electron deficient at the C=C bond. Copolymers of styrene (or CMS) and maleimides are expected to be alternating. NMR data confirms this anticipation. In all the cases, a good correlation of styrene to maleimide was obtained. As stated earlier, the molar mass of the polymers were not determined due to the lack of equipment at our laboratory.

2.4 SYNTHESIS OF POLYMER BEADS

2.4.1 DVB as Crosslinker

Polymer beads, with 1% to 2% divinylbenzene (DVB) as crosslinker, were synthesised. All the co-polymer beads were prepared in glycerol. Poly(chloromethylstyrene) beads was synthesised in water. All the beads were prepared under a nitrogen atmosphere. The product constituted of beaded and non-beaded products. The swellability of the beads was determined.

The results are shown in Figure 2.13, Figure 2.14 and Figure 2.15.

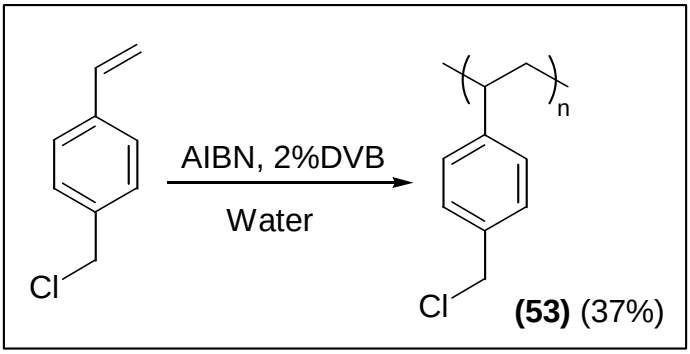


Figure 2.13: Synthesis of poly(CMS) beads

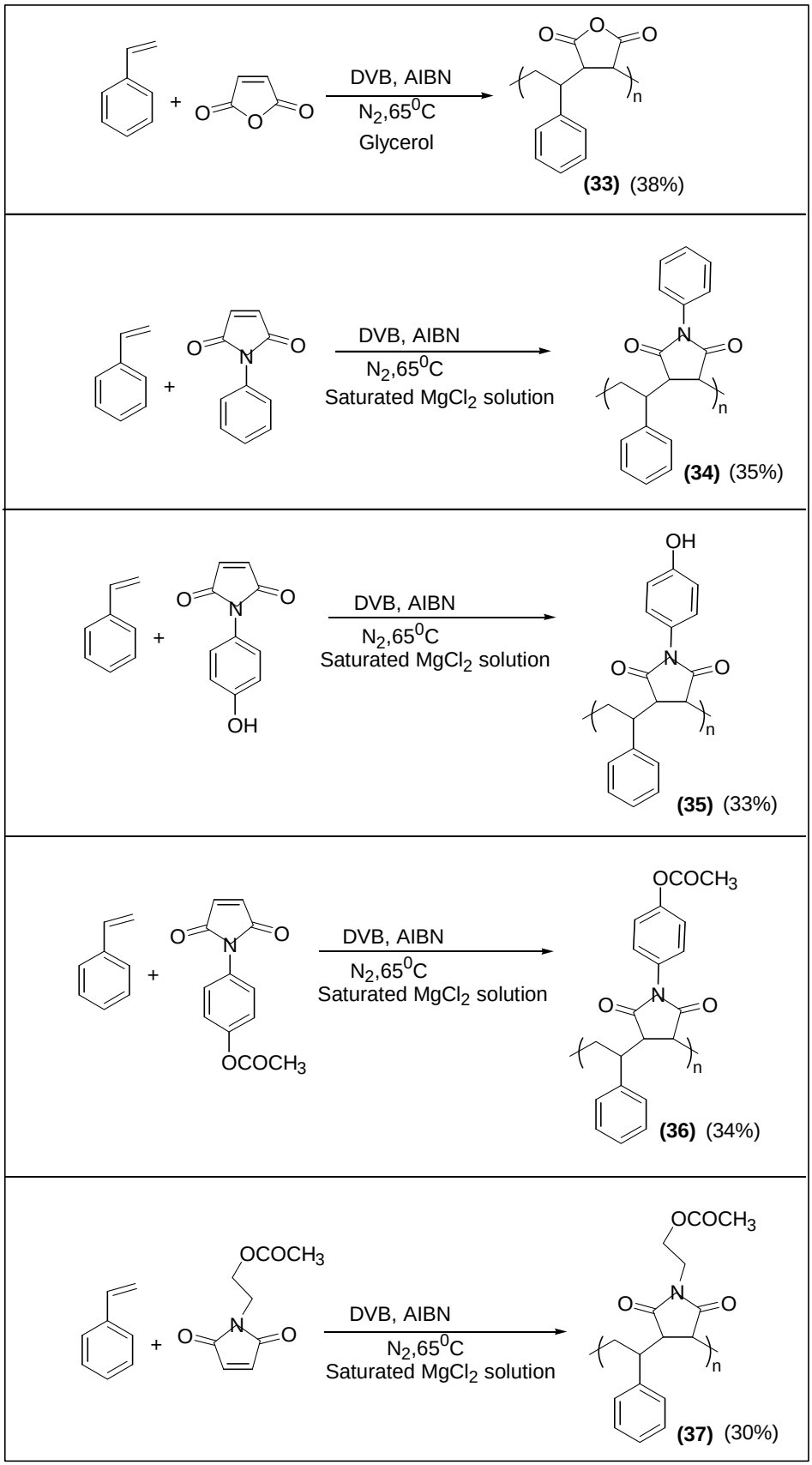


Figure 2.14: Copolymer beads of styrene

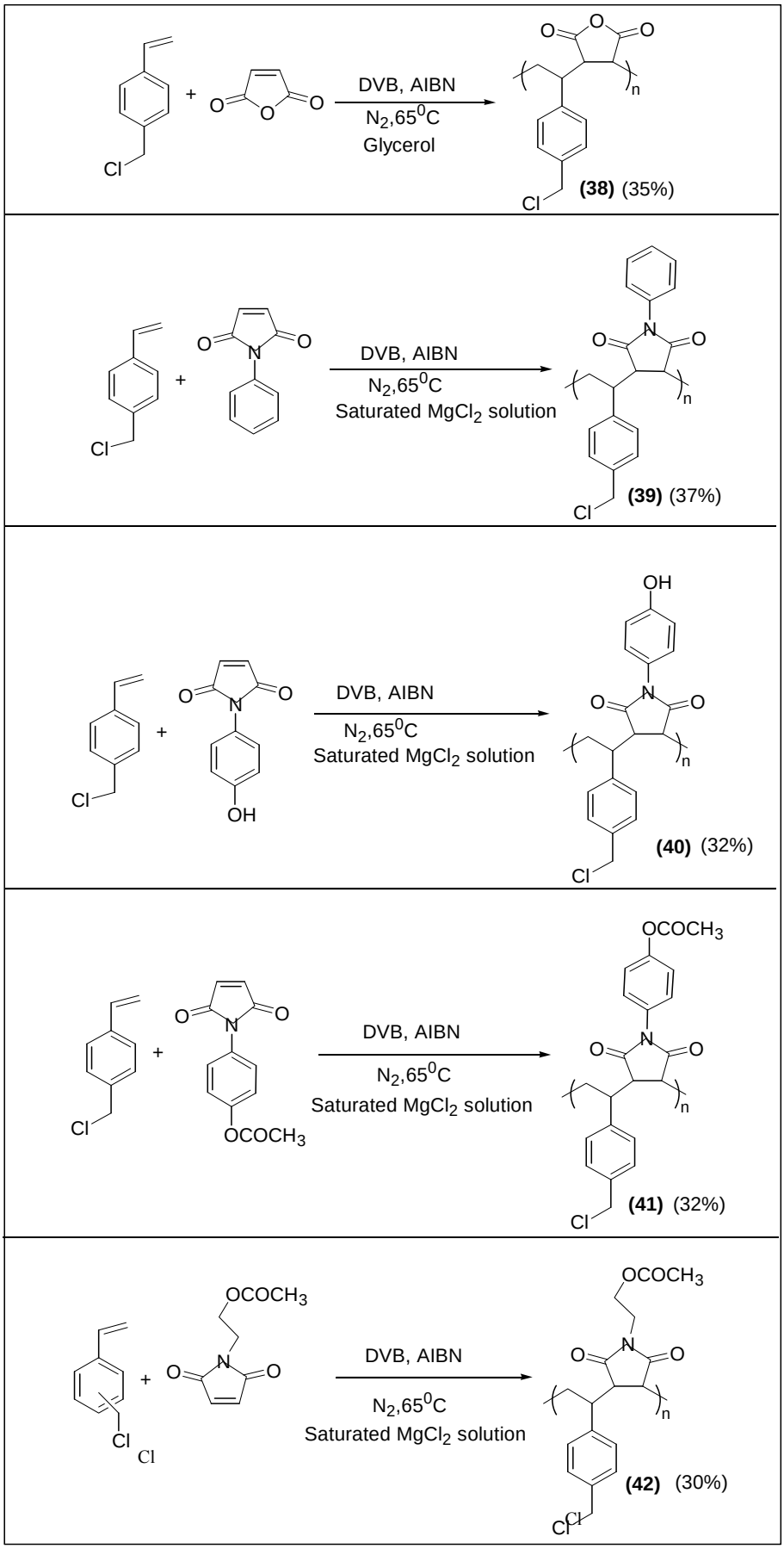


Figure 2.15: Copolymer beads of CMS

All the polymer beads were insoluble white solids. The finer ones were translucent. The yields are between 30% and 40%. The beads were characterised by IR spectrum. The NMR spectrum of the beads could not be obtained.

The beads were of irregular size and shape. However, upon gradation, the beads were separated into distinct groups according to their size. The styrene-maleimide copolymer beads were more difficult to obtain compared to their maleic anhydride counterparts. In general, the maleimides were less soluble in moderately polar solvents such as dioxane.

Several suspension systems were tried. The glycerol-sodium chloride system, which was relatively successfully applied to the synthesis of styrene-maleic anhydride beads, was somewhat inefficient. The suspension tended to coalesce, even when different stabilising agents were used. Moreover, the polymer beads obtained were of poor quality in terms of size and shape.

Saturated sodium chloride and saturated magnesium chloride solution were tried as continuous phase. The saturated sodium chloride system was more efficient than the glycerol-sodium chloride system. The quality of the beads showed a slight improvement. Yet, the best results were obtained when saturated magnesium chloride was used as the continuous phase. The beads were more regular in size and shape. The yield also showed a slight improvement.

The IR spectra of all the beads match those of their linear counterparts.

2.4.2 (7) and (8) as Crosslinker

The synthesis of copolymer polymer beads, where compounds **(7)** and **(8)** were used as crosslinker, were synthesised. In all cases, one of the monomers was styrene and the other co-monomer was maleic anhydride or one of the synthesised maleimides.
The saturated magnesium chloride system was used. 2% by mole of the crosslinker was used in all the cases. The results are shown in Figure 2.16 (**(7)** as crosslinker) and Figure 2.17 (**(8)** as crosslinker).

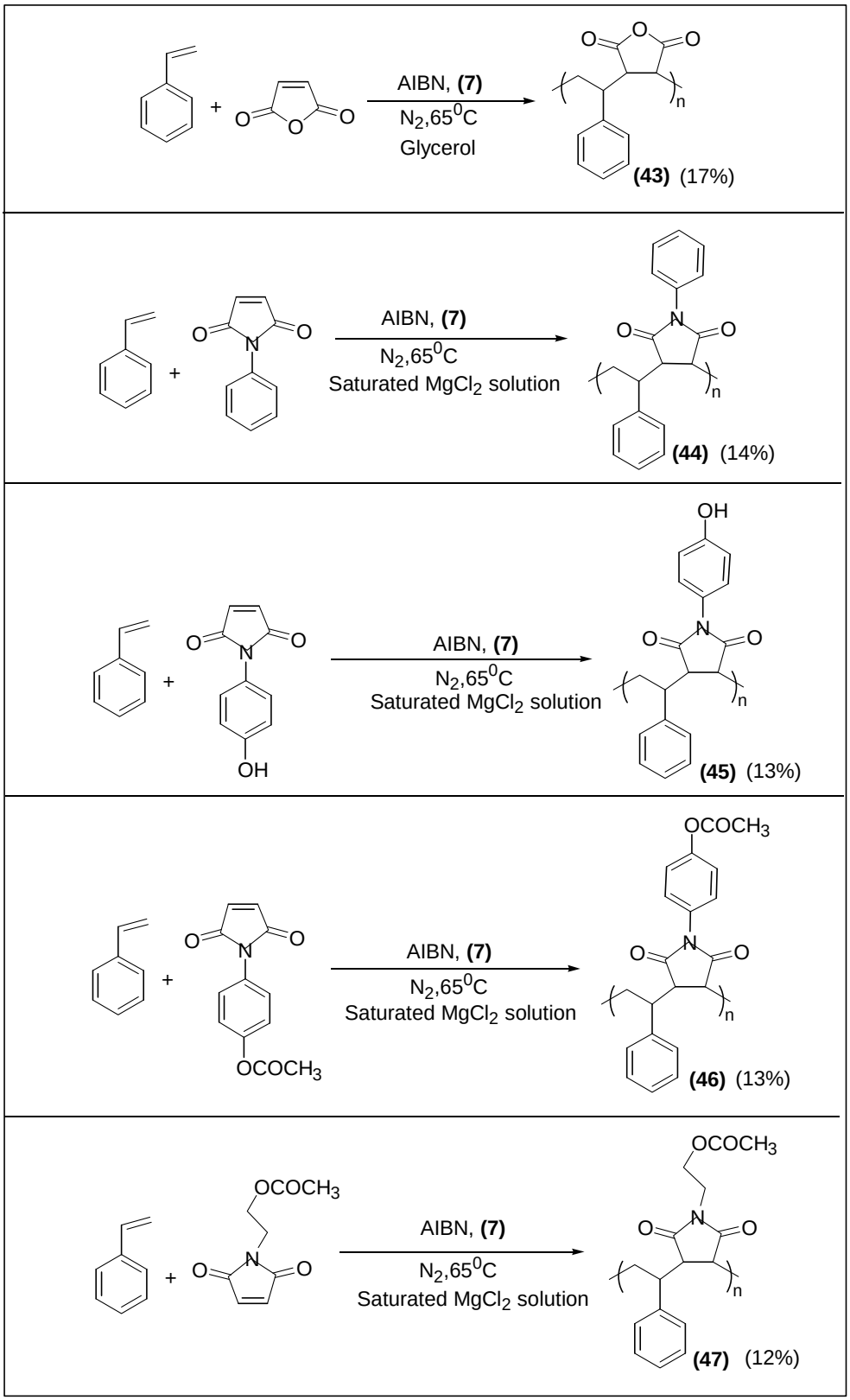


Figure 2.16: Copolymer beads with bismaleimide **(7)** as crosslinker

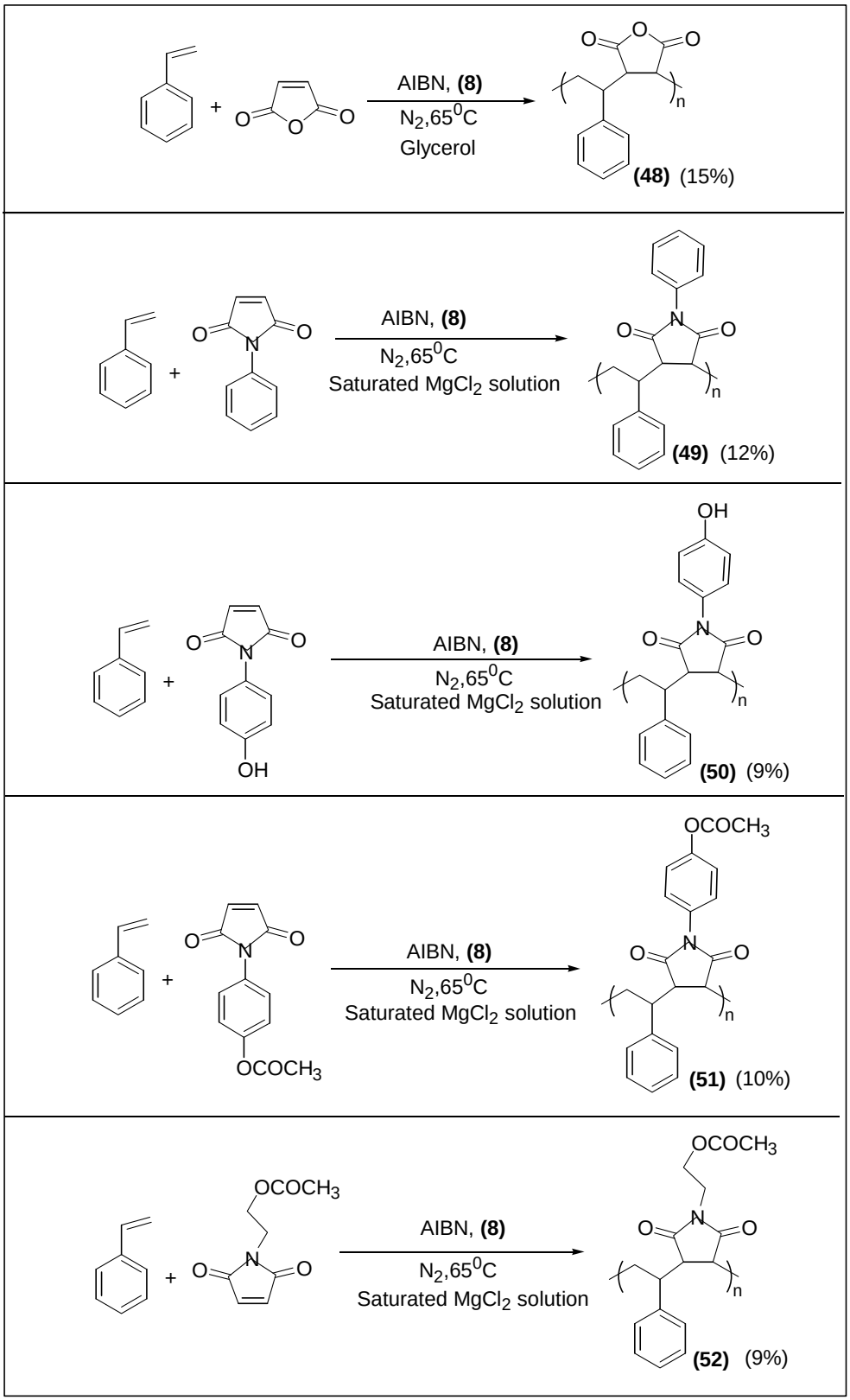


Figure 2.17: Copolymer beads with bismaleimide **(8)** as crosslinker

Because of the relative success of the saturated magnesium chloride solution to generate styrene-maleimide beads, it was again applied when **(7)** and **(8)** were used as crosslinkers. In general, the yield of the beads were lower compared when DVB was used as crosslinker. All the beads were insoluble and white and their IR spectra matched those of their linear counterparts. The beads were of irregular size and shape.

2.5 FUNCTIONALISATION OF THE BEADS

(43) was hydrolysed to convert the anhydride to the acid. **(53)** was refluxed with THMMA, so that the latter could displace the benzilic chlorine atom. The results are shown in Figure 2.18.

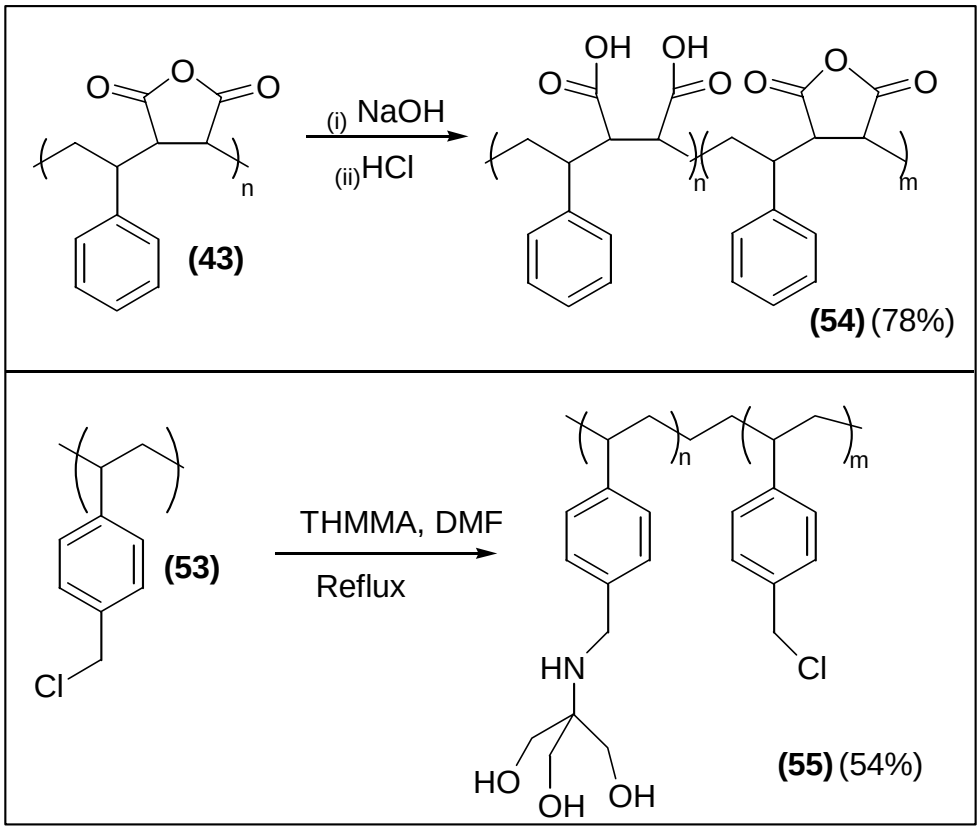


Figure 2.18: Functionalisation of beads

Compared to **(43)**, the IR spectrum of **(54)** showed a marked increase in the area of the peak at 3455cm^{-1}. Compared to **(53)**, the IR spectrum of **(55)** had a peak at 3468 cm^{-1}. This indicated the presence of the OH and NH groups.

2.6 SYNTHESIS OF GELS

Gels were synthesised from linear polymers **(20)** and **(23)**. Both were crosslinked with tetraethylene glycol (TEG). The TEG chain was expected to give these gels a more flexible structure compared to beads synthesised with DVB or the maleimido crosslinkers **(7)** and **(8)**.

The results are shown in Figure 2.19 and Figure 2.20.

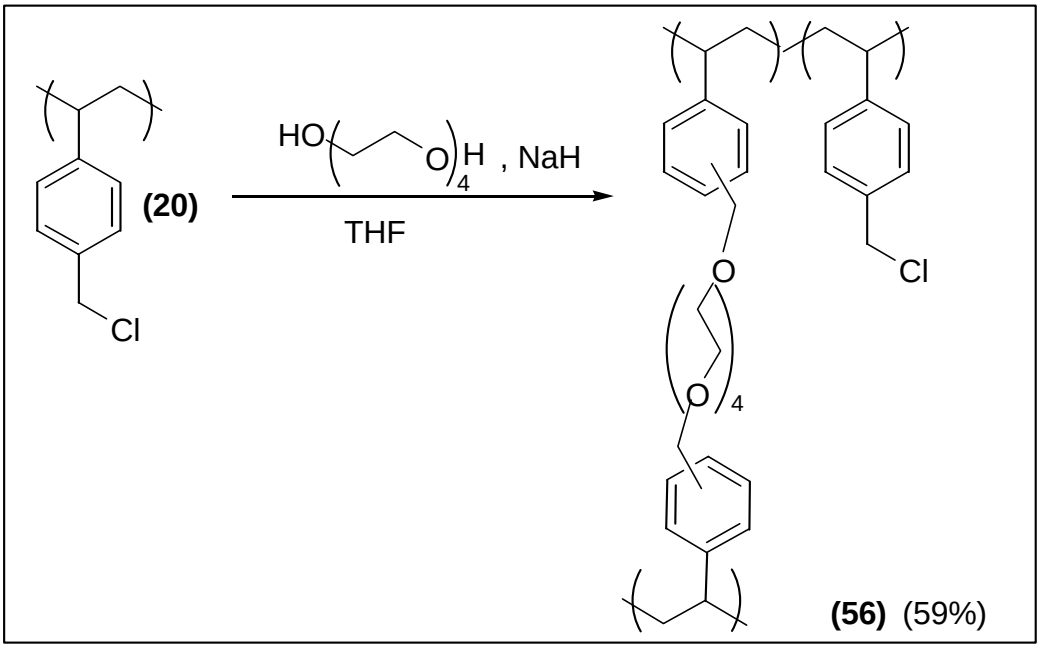


Figure 2.19: Synthesis of gel from (20)

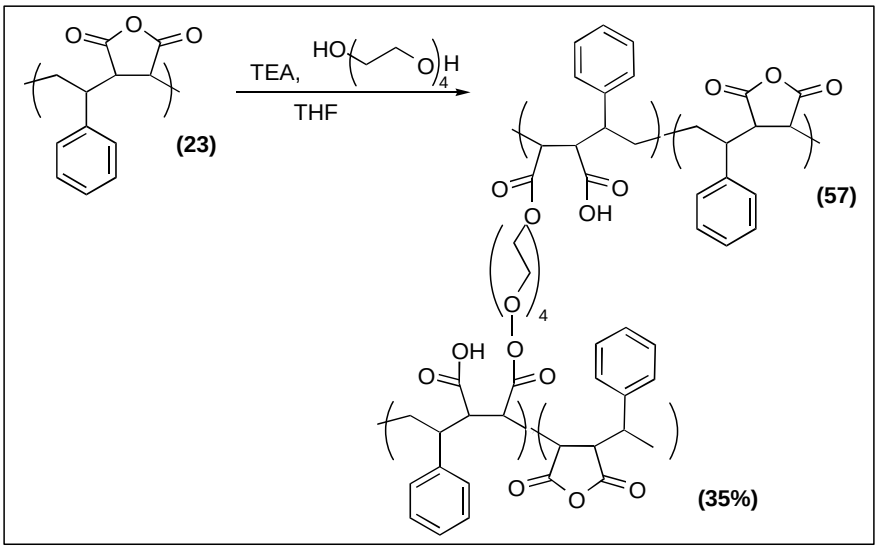


Figure 2.20: Synthesis of gel from (23)

(56) was obtained as a cream coloured solid while **(57)** was white. Both were insoluble due to the crosslinking. They swelled in solvents to different extents. In the case of **(56)**, some of the TEG hydroxyl groups did not react as indicated by the peak in the IR spectrum at 3491 cm^{-1}.

2.7 SWELLABILITY STUDIES

The swellability (ml/g) of the beads and gels synthesised in this study were determined. The swellability is an indication of the interaction of the polymer chains with solvent molecules. One of the limitations of polymer supports is that they are not compatible with a wide range of solvents. The aim of this study was to synthesise beads that would show higher compatibility with a wide range of solvents. These were then compared to the swellabilities of two of the commonly available supports in the market, namely poly(chloromethyl styrene) and poly(styrene-co-maleic anhydride).
The swellability of polymer supports is affected by:

(a) the polarity of the solvent

(b) the nature of the polymer backbone

(c) the amount of crosslinking in the support

(d) the type of crosslinker used.

The results are shown in Table 2.1.

Bead / Gel	Solvent									
	$CHCl_3$	Acetone	CH_3CN	MeOH	ETOH	ETOAc	DMF	DMSO	THF	Water
(33)	4.5	3.3	2.2	2.1	1.9	2.7	3.5	3.8	4.6	0.2
(34)	4.7	3.2	1.3	0.8	0.5	2.6	3.4	3.8	4.5	0.1
(35)	1.4	3.9	1.9	1.1	1.1	2.8	5.0	6.3	5.0	0.0
(36)	3.7	3.2	2.1	0.7	0.4	3.0	4.9	5.1	5.2	0.0
(37)	7.6	2.9	3.0	0.6	0.4	3.3	5.1	4.5	4.5	0.1
(38)	4.4	3.2	2.3	1.9	1.8	2.5	3.4	4.0	4.5	0.1
(39)	4.5	3.0	1.1	0.9	0.4	2.3	3.3	3.9	4.7	0.0
(40)	1.0	4.0	1.9	0.8	0.8	3.3	7.6	8.1	4.9	0.0
(41)	3.5	3.0	2.3	0.9	0.5	2.8	4.7	5.0	5.0	0.0
(42)	7.4	3.0	3.0	0.6	0.5	3.2	4.9	4.4	4.6	0.0
(43)	5.0	3.7	2.8	2.7	2.6	3.5	4.2	5.0	5.3	0.4
(44)	5.2	3.9	1.6	1.5	1.3	3.4	4.1	4.5	5.0	0.3
(45)	1.8	4.5	2.4	1.6	1.4	3.2	5.3	6.9	5.8	0.1
(46)	4.0	3.5	2.7	1.0	0.8	3.5	5.3	5.6	5.9	0.0
(47)	8.0	3.5	3.5	0.9	0.7	3.6	5.6	5.1	5.3	0.2
(48)	5.2	3.9	3.0	3.0	3.0	3.9	4.6	5.3	5.5	0.5
(49)	5.3	4.3	1.9	1.6	1.5	3.8	4.5	4.8	5.9	0.4
(50)	2.0	4.8	2.8	1.8	1.6	3.5	5.6	7.2	7.0	0.1
(51)	4.2	3.5	3.0	1.2	1.2	3.8	5.5	5.9	6.3	0.0
(52)	8.3	3.8	3.7	1.0	1.0	3.9	6.0	5.5	5.6	0.2
(53)	6.7	2.9	0.8	1.1	0.8	1.5	2.8	3.2	3.9	0.0
(54)	3.0	3.5	1.4	1.8	1.3	3.1	3.6	4.3	3.6	0.0
(55)	3.1	3.2	1.2	1.8	1.7	3.0	3.8	4.5	2.5	0.1
(56)	9.7	9.5	1.8	2.1	1.9	13.8	16.2	17.1	15.3	0.9
(57)	8.2	5.6	3.6	3.5	3.2	10.2	16.1	17.4	15.7	0.8

Table 2.1: Swellabilities of polymer supports

The swellabilities of copolymer supports of styrene and chloromethyl styrene are similar because the polymer backbone in both cases is analogous.

Compared to **(53)**, the styrene-maleimide beads and CMS-maleimide beads, which have DVB as crosslinker, show slightly better overall compatibility with the solvents. This may be due to the presence of the maleimide moiety, which adds to the polarity of the polymer backbone.

However compared to **(33)**, the styrene-maleimide beads and CMS-maleimide beads, which have DVB as crosslinker, show slightly lower overall swellability. Most of the maleimides synthesised have aromatic rings. These polymers have a higher proportion of hydrocarbon relative to **(33)**. In effect, **(33)** seems to be more polar than the styrene-maleimide and CMS maleimide systems.

In general the polymer beads show better overall swellability in chloroform, acetone, DMF, DMSO and THF. These solvate the polymer chains better than methanol, ethanol and acetonitrile. Methanol and ethanol are polar hydrophilic solvents, which have intermolecular hydrogen bonding. They have lower affinity for the more hydrocarbon-like polymers. In the same line, all the polymers showed poor swellability in water. Most of the polymers synthesised have a marked hydrophobic character, but enhanced polarity.

The beads having DVB as crosslinker exhibited lower swellability than those having **(7)**, **(8)** or TEG as crosslinker. DVB is planar and has a fairly rigid structure. It holds the polymer chains closer. During solvation, the polymer chains cannot get as far apart as possible. Hence the swellability is lower. On the other hand, **(7)** and **(8)** have more flexible structures. During solvation, the polymer chains can get further apart. Beads having **(8)** as crosslinker show higher swellabilities than those having **(7)** as crosslinker. **(8)** is one carbon atom longer then **(7)**.

(56) and **(57)** exhibited the highest swellabilities. TEG, which are used as crosslinker in these gels, is relatively longer and more flexible than DVB, **(7)** and **(8)**. The polymer backbone chains can get even further apart. There is a significant increased

in the swellability, especially in DMF, DMSO, THF and ethyl acetate. The influence of the crosslinker is very apparent in this case.

References

1.

(a) N. Ogawa, K. Honmyo, K. Harada, A. Sugii; *J. of App. Pol. Sci.*, 29, 2852-2856 (1984)

(b) O. Okay; *J. of App. Pol. Sci*., Vol.34, 307-317(1987).

(c) J. R. Ebdon, C. R. Towns, K. Dodgson; *JMS-REV. Macromol. Chem. Phys.*, C26(4), 523-550 (1986)

(d) N. T. H. Ha, K. Fujimori, I. E. Craven; *Macromol. Chem. Phys.,* 198, 3507-3516 (1997)

(e) M. Talukder, C. U. Pittman; *J. of Pol. Sci.: Part A: Pol. Chem.,* Vol. 33, 2375-2383 (1995)

2.

(a) T. Matynia, B. Gawdzik, E. Chmielewska; *J. of App. Pol. Sci.*, Vol. 60, 1971-1975 (1996)

(b) T.Iijima, N. Suzuki, W. Fukuda, M. Tomoi; *Eur. Pol. J.,* Vol. 31, No. 8, 775-783 (1995)

(c) G-Q. Chen, Z-Q. Wu, J-R. Wu, Z-C. Li, F-M. Li; *Macromol.,* 33, 232-234 (2000)

(d) G. D. Merfeld, K. Chan, D. R. Paul; *Macromol. ,* 32, 429-439 (1999)

(e) L. Shi, S. Chen, J. Huang; *Eur. Pol. J.,* 36, 236-372 (2000)

(f) K. Kagawa, T. Oishi, K. Matsuaki, M. Fujimori; *Pol.,* Vol. 36, No. 5, 941-948 (1998)

(g) R. Bharel, V. Choudhary, I. K. Varma; *J. of App. Pol. Sci.*, Vol. 49, 31-38, (1993)

3.

(a) T. Oishi, M. Fujimoto; *J. Pol. Sci.: Chem. Ed.*, 22, 2789 (1984)

(b) T. Oishi, M. Fujimoto; *J. Pol. Sci.: Part A: Pol. Chem.*, 30, 1821 (1992)

(c) T. Oishi, K. Sase; *Polymer*, 36, 3935 (1995)

(d) K. Kagawa, T. Oishi, K. Matsuaki, M. Fujimoto; *Polymer*, 36, 941 (1995)

(e) S. Amou, S. Nishimara, A. Takahashi, T. Hagiwara, H. Hamana, T. Narita; *J. Pol. Sci.: part A: Pol. Chem.,* 37, 341 (1999)

(f) R. Bharel, V. Choudhary, I. K. Varma; *J. of App. Pol. Sci.*, Vol. 49, 31-38 (1993)

4. *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, 572

3. EXPERIMENTAL

3.1 REAGENTS AND APPARATUS

Reagents and solvents were obtained commercially from Aldrich, BDH, Fluka, Acros, Avocado and Merck. They were used as received unless stated otherwise. DCM and THF were refluxed over calcium hydride for 4 hours and distilled under nitrogen. Ethyl acetate and hexane were distilled before use. Column chromatography was performed on silica gel (70-230 mesh). Styrene and CMS were washed with 2 Molar sodium hydroxide solution, dried over anhydrous magnesium sulphate and filtered through silica gel. NMR spectra were recorded on a Brucker 250 (250 MHz) FTNMR apparatus. Chemical shifts were noted as δ in ppm relative to TMS. IR spectra were recorded on an ATi Unicam Mattson 1000 FTIR apparatus on potassium bromide pellets unless stated otherwise. The wavenumbers were noted in cm^{-1}. Melting points were measured using an Electrothermal 9100 apparatus.

3.2 SYNTHESIS OF MALEIMIDES

3.2.1 Synthesis of N-(2-Acetoxy Ethyl) Maleimide (1) and N-(4-Hydroxy Phenyl) Maleimide (2) under Acidic Conditions

Maleic anhydride (0.50 g, 5 mmol) and the amine (5 mmol) were stirred in acetic acid (20 ml) under nitrogen at room temperature for 12 hours. The mixture was then refluxed for 8 hours. Acetic acid was evaporated under reduced pressure. The residue was equilibrated between ethyl acetate (25 ml) and saturated aqueous sodium hydrogen carbonate solution. The product was extracted with ethyl acetate (3*20 ml). The combined organic extracts was washed with saturated aqueous sodium hydrogen carbonate solution (15 ml), distilled water (20 ml) and dried over anhydrous sodium sulphate. Ethyl acetate was evaporated under reduced pressure to yield a viscous liquid which crystallised on standing.

(i) N-(2-Acetoxy Ethyl) Maleimide (1)

N-(2-acetoxy ethyl) maleimide was extracted with boiling hexane as colourless crystals.

Yield: 30%

Melting point: 72˚C -73˚C

IR (cm^{-1}): 3153, 3097 (Olefinic *C-H*), 2957 (Aliphatic *C-H*), 1752,1706 (*C=O*), 1610 (*C=C*), 1330 (*C-N*), 1258 (*C-O*)

^{1}H NMR ($CDCl_3$) δ (ppm): 6.74(s, 2H, OC-C*H*=C*H*-CO), 4.25(t, 2H, N-CH_2-, J=5.5 Hz), 3.80(t, 2H, O-CH_2, J=5.5 Hz), 2.02 (s, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ (ppm): 173.2 (HC-*C*=O), 170.7 (CH_3-*C*=O), 134.0 (*C=C*), 61.2 (N-*C*H_2), 36.7 (*C*H_2-O), 20.5 (*C*H_3)

Elemental analysis: Calculated: C (52.46%), H (4.92%), N (7.65%)

Found: C (52.31%), H (4.85%), N(7.72%)

(ii) N-(2-Hydroxy Phenyl) Maleimide (2)

N-(2-hydroxy phenyl) maleimide was purified by column chromatography (silica gel, 1:3 ethyl acetate/hexane). Yellow crystals were obtained.

Yield: 29%

Melting point: 185˚C

IR (cm^{-1}): 3450 (Ar-*OH*), 3110 (Ar-H), 1702 (*C*=*O*), 1616, 1521 (*C*=*C*)

^{1}H NMR (Acetone-D6) δ (ppm): 7.13(m, 2H, Ar-*H*), 6.89(m, 2H, Ar-*H*), 6.85(s, 2H, OC-C*H*=C*H*-CO)

^{13}C NMR (Acetone-D6) δ (ppm): 169.8 (*C*=*O*), 155.3 (Aromatic *C*=*C*), 134.0 (Olefinic *C*=*C*), 127.9, 123.5, 116.0 (Aromatic *C*=*C*)

Elemental Analysis: Calculated: C(63.49%) H(3.70%) N(7.41%)

Found: C(63.77%) H(3.89%) N(7.56%)

3.2.2 Synthesis of N-(2-Acetoxy Ethyl) Maleimide (3)

To an ice cold solution of maleic anhydride (1.00 g, 10 mmol) in acetone under nitrogen, the amine (10 mmol) was added in small portions. The ice bath was removed and the mixture stirred for 2 hours at room temperature under nitrogen. The medium was heated to 60˚C and stirred for a further 1 hour. Acetic anhydride (5 ml) and anhydrous sodium acetate (0.84 g) were added and the mixture was refluxed for 5 hours. Acetic anhydride, acetone and acetic acid formed were distilled under reduced pressure. The residue was equilibrated between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The aqueous medium was extracted with ethyl acetate (3 * 20 ml). The combined organic extracts was washed with saturated aqueous sodium hydrogen carbonate solution (20 ml), distilled water (20 ml) and dried over anhydrous sodium sulphate. Ethyl acetate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 1:3 ethyl acetate/hexane). Colourles crystals were obtained.

Yield: 42%

Melting point: 72˚C -73˚C

IR (cm^{-1}): 3160, 3091 (Olefinic C-H), 2954 (Aliphatic C-H), 1748,1710 (C=O), 1612 (C=C), 1333 (C-N), 1259 (C-O)

^{1}H NMR ($CDCl_3$) δ (ppm): 6.74(s, 2H, OC-C*H*=C*H*-CO), 4.29(t, 2H, N-CH_2-, J=5.5 Hz), 3.82(t, 2H, O-CH_2, J=5.5 Hz), 2.05 (s, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ (ppm): 173.0 (HC-*C*=O), 170.6 (CH_3-*C*=O), 134.0 (*C*=*C*), 61.2 (N-*C*H_2), 36.7 (*C*H_2-O), 20.4 (*C*H_3)

Elemental analysis: Calculated: C(52.46%), H(4.92%), N(7.65%)

Found: C(52.52%), H(4.91%), N(7.73%)

3.2.3 Synthesis of N-(2-Acetoxy Phenyl) Maleimide (4)

To an ice cold solution of maleic anhydride (1.00 g, 10 mmol) in acetone, the amine (10 mmol) was added in small portions and the mixture stirred for 2 hours at room temperature under nitrogen. The medium was heated to 60˚C and stirred for a further 1 hour. Acetic anhydride (5 ml) and anhydrous sodium acetate (0.84 g) were added and the mixture was refluxed for 5 hours. The reaction mixed was poured in ice. The resulting brown precipitate was filtered by suction. It was washed thoroughly with cold water. The product was purified by column chromatography (3:1 hexane/ethyl acetate)

Yield: 60%

Melting point: 157˚C

IR (cm^{-1}): 3115 (Ar-H), 1712 (C=O), 1615, 1521 (C=C), 2940 (Aliphatic C-H)

^{1}H NMR ($CDCl_3$) δ (ppm): 7.16(m, 2H, Ar-*H*), 6.93(m, 2H, Ar-*H*), 6.74(s, 2H, OC-C*H*=C*H*-CO), 2.09 (s, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (CH-*C*=O), 169.2 (CH_3*C*=O), 152.3 (Aromatic *C*=*C*), 134.0 (Olefinic *C*=*C*), 127.9, 123.5, 116.0 (Aromatic *C*=*C*), 25.6 (CH_3)

Elemental analysis: Calculated: C(62.34%) H(3.90%) N(6.06%)

Found: C(62.58%), H(3.78%), N(5.99%)

3.2.4 Synthesis of N-tris(Acetoxymethyl) Methyl Maleimide (5)

To an ice cold solution of maleic anhydride (1.00 g, 10 mmol) in acetone, the amine (10 mmol) was added in small portions and the mixture stirred for 2 hours at room temperature under nitrogen. The medium was heated to 60˚C and stirred for a further 1 hour. Acetic anhydride (5 ml) and anhydrous sodium acetate (0.84 g) were added and the mixture was refluxed for 5 hours. Acetone, acetic anhydride and acetic acid formed were distilled under reduced pressure. The remaining solid was equilibrated between saturated sodium hydrogen carbonate solution and ethyl acetate. It was extracted with ethyl acetate (5 * 25 ml). The combined organic extracts was washed with water and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure. The resulting white solid was purified by column chromatography (DCM, silica gel).

Yield: 3%

Melting point: 88˚C

IR (cm^{-1}): 3158 (Olefinic C-H), 2941 (Aliphatic C-H), 1716 (C=O), 1612 (C=C), 1277 (C-O)

^{1}H NMR ($CDCl_3$) δ (ppm): 6.64(s, 2H, OC-C*H*=C*H*-CO), 4.67(s, 6H, CH_2), 2.05(s, 9H, CH_3)

^{13}C NMR ($CDCl_3$) δ (ppm): 171.0 (CH-*C*=O), 169.9 (CH_3*C*=O), 134.1 (*C*=*C*), 63.1 (CH_2-O), 60.4 (N-*C*-$(CH_2)_3$), 20.5 (CH_3)

Elemental Analysis: Calculated: C(51.38%), H(5.20%), N(4.28%)
Found: C(51.45%), H(5.29%), N(4.25%)

3.2.5 Synthesis of N-Phenyl Maleimide (6)[(1)]

Yield: 75%

Melting point: 91˚C (*Literature: 91˚C*)

^{1}H NMR (CDCl3) δ (ppm): 6.9-7.4 (m, 5H, Ar*H*), 6.73 (s, 2H, (CO-C*H*=C*H*-CO)

^{13}C NMR (CDCl3) δ (ppm): 170.2 (C=O), 134.9 (CO-*C*H=*C*H-CO), 131.8, 129.2, 128.0, 127.1 (Aromatic C=C)

Elemental analysis: Calculated: C(69.36%) H(4.29%) N(7.85%)
Found: C(69.77%) H(4.04%) N(8.09%)

3.2.6 N,N'-(Ethylene) Bismaleimide (7) and N,N'-(Propylene) Bismaleimide (8)

To an ice cold solution of maleic anhydride (1.00 g, 10 mmol) in acetone, the diamine (5 mmol) was added in small portions and the mixture stirred for 2 hours at room temperature under nitrogen. The medium was heated to 60˚C and stirred for a further 1 hour. Acetic anhydride (5 ml) and anhydrous sodium acetate (0.84 g) were added and the mixture was refluxed for 5 hours. Acetone, acetic anhydride and acetic acid formed during the reaction were distilled under reduced pressure. The remaining solid was equilibrated between saturated sodium hydroxide carbonate solution and ethyl acetate (30ml). It was extracted with ethyl acetate (5*25ml). The combined organic extracts was washed with water and dried over sodium sulphate. The solvent was removed under reduced pressure. The resulting white solid was purified by column chromatography (1:4 ethyl acetate/hexane).

(i) N,N'-ethylene bismaleimide (7)

Yield: 27%

Melting point: 193˚C

IR (cm^{-1}):): 3155 (Olefinic C-H), 2939 (Aliphatic C-H), 1705 (C=O), 1615 (C=C), 1280 (C-O)

^{1}H NMR ($CDCl_3$) δ (ppm): 6.69(s, 4H, *H*-C=C-*H*), 3.74(s, 4H, CH_2)

^{13}C NMR ($CDCl_3$) δ (ppm): 170.5 (C=O), 134.2 (*C*=*C*), 36.5 (*C*H_2)

Elemental analysis: Calculated: C(56.41%), H(4.27%), N(11.97%)

Found: C(56.71%), H(4.68%), N(11.63%)

(ii) N,N'-propylene bismaleimide (8)

Yield: 25%

Melting point: 167˚C

IR (cm^{-1}):): 3160 (Olefinic C-H), 2947 (Aliphatic C-H), 1720(C=O), 1616 (C=C), 1252 (C-O)

^{1}H NMR ($CDCl_3$) δ (ppm): 6.70(s, 4H, *H*-C=C-*H*), 3.50(t, 4H, N-CH_2, J=7.5 Hz), 1.93(q, 2H, C-CH_2-C, J=7.5 Hz)

^{13}C NMR ($CDCl_3$) δ (ppm): 170.6 (*C*=O), 134.2 (*C*=*C*), 35.3 (N-*C*H_2), 27.4 (C-*C*H_2-C)

Elemental Analysis: Calculated: C(54.54%), H(3.64%), N(12.73%)
Found: C(54.67%), H(3.64%), N(12.81%)

3.3 SYNTHESIS OF STYRYL MONOMERS

3.3.1 Synthesis of (13)

Sodium hydride (0.09 g, 3.7 mmol) was added to a solution of 1,2-di-O-isopropylideneglycerol **(3)** (0.47 g, 3.5 mmol) in dry THF (15 ml) under nitrogen. The solution was stirred for 15 minutes. Chloromethylstyrene (0.5 ml, 3.5 mmol) was added and the mixture refluxed for 5 hours. Water (20 ml) was added and **(13)** was extracted with diethylether (3*15 ml). The combined organic extract was washed with 2 molar aqueous sodium hydroxide solution (20 ml), water (20 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish a yellow oil, which was purified by column chromatography (6:1 hexane/ethyl acetate).

Yield: 71%

^{1}H NMR($CDCl_3$) δ (ppm): 1.36 (s, 3H, CH_3), 1.42(s, 3H, CH_3), 3.44 (m, 2H, Ar-CH_2-O-C*H*$_2$), 3.73 (m, 2H, Ar-O-CH_2-CH-C*H*$_2$), 4.02 (m, 1H, O-CH_2-C*H*-CH_2), 4.54 (s, 2H, Ar-CH_2), 5.22 (m, 1H, Ar-CH=C*H*), 5.72 (m, 1H, Ar-CH=C*H*), 6.64 (m, 1H, Ar-C*H*=C), 7.20 (m, 4H, Ar-H)

3.3.2 Synthesis of (14)

CMS (1.0 ml, 7 mmol) was added to a hot solution of tris(hydroxy methyl) methyl amine (THMMA) (2.0 g, 16.5 mmol) in methanol (20 ml) and the mixture refluxed for 5 hours. After cooling, the reaction mixture was placed in the refrigerator overnight at 0˚C. The white precipitated solid was filtered and washed with cold methanol. The solvent was evaporated from the filtrate to yield a white solid, which was washed thoroughly with chloroform to remove any unreacted CMS. The product was dried in vacuum.

Yield: 81%

Melting point: 274˚C

^{1}H NMR (D_2O) δ (ppm): 7.05-7.26(m, 4H, Ar-*H*), 6.51(m, 1H, Ar-C*H*=C), 5.56(m, 1H, Ar-CH=C*H*), 5.08(m, 1H, Ar-CH=C*H*), 3.69(s, 2H, Ar-CH_2), 3.45(s, 6H, CH_2-OH)

^{13}C NMR (D_2O) δ (ppm): 137.7, 132.2, 129.1, 128.3, 127.8, 126.3 (Aromatic *C*=*C*), 114.5, 112.3 (Olefinic *C*=*C*), 61.2 (Ar-*C*H_2), 48.7 (*C*H_2OH), 16.6 (N-*C*($CH_2OH)_3$)

Calculated: C(65.82%), H(5.91%), N(8.01%)

Found: C(65.59%), H(5.74%), N(8.05%)

3.4 SYNTHESIS OF LINEAR POLYMERS

3.4.1 Synthesis of (15), (16), (17) and (18)

A solution of the maleimide (0.5 g) and AIBN (2% mol) in THF (10 ml) was purged with nitrogen for 15 minutes. The reaction flask was placed in an oil bath at 65˚C for 8 hours. The polymer was precipitated in isopropyl ether and filtered. It was dissolved in acetone and precipitated in isopropyl ether (repeated twice). The polymer was filtered and dried in vacuum for 24 hours.

(i) (15)

Yield: 79%

IR (cm^{-1}): 3123 (Ar-H), 2934 (Aliphatic C-H), 1710(C=O), 1616 (Aromatic C=C)

^{1}H NMR ($CDCl_3$) δ (ppm): 7.172 (bs, 5H, Ar-*H*), 4.05 (bs, 2H, C*H*-C=O)

^{13}C NMR ($CDCl_3$) δ (ppm): 176.0 (*C*=O), 130.7, 128.9, 126.4, 124.5 (Aromatic *C*=*C*), 40.6 (*C*H-C=O)

(ii) (16)

Yield: 73%

IR (cm^{-1}): 3441 (Ar-*OH*), 3121 (Ar-H), 1715 (*C*=*O*), 1613 (Aromatic C=C)

^{1}H NMR ($CDCl_3$) δ (ppm): 9.75(bs, 1H, O*H*), 6.83(bs, 4H, Ar-*H*), 4.00(bs, 2H, C*H*-C=O)

^{13}C NMR ($CDCl_3$) δ (ppm): 175.5 (*C*=O), 132.7, 128.4, 126.6, 124.9 (Aromatic *C*=*C*), 41.1 (*C*H-C=O)

(iii) (17)

Yield: 77%

IR (cm^{-1}): 3123 (Ar-H), 1712 (*C*=*O*), 1615 (Aromatic *C*=*C*)

^{1}H NMR ($CDCl_3$) δ (ppm): 6.83(bs, 4H, Ar-*H*), 4.09(bs, 2H, C*H*-C=O), 3.09 (bs, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ (ppm): 175.7 (*C*=O), 138.5, 129.3, 126.5, 124.7 (Aromatic *C*=*C*), 42.1 (*C*H-C=O), 26.4 (CH_3)

(iv) (18)

Yield: 82%

IR (cm^{-1}): 2954 (Aliphatic C-H), 1712 (C=O)

^{1}H NMR ($CDCl_3$) δ (ppm): 4.16 (bs, 2H, C*H* C=O), 3.75 (bs, 4H, N-CH_2-CH_2-O), 2.02 (bs, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ (ppm): 176.3 (N-*C*=O), 170.7 (CH_3*C*=O), 60.3 (N-CO-*C*H), 44.5 (N-*C*H_2), 38.0 (COO*C*H_2), 20.5 (*C*H_3)

3.4.2 Poly(Chloromethylstyrene) (20)

A mixture of chloromethyl styrene (2.0 ml, 14 mmol) and AIBN (2% mol) was degassed with nitrogen for 15 minutes and placed in an oil bath at 70˚C for 2h. The viscous solution was poured into methanol(50 ml). The precipitate polymer was dissolved in minimum amount of chloroform and precipitated in methanol. This process was repeated twice.

The white solid was dried in vacuum at 45˚C for 24 hours.

Yield: 63%

IR (cm^{-1}): 3129 (Ar-H), 2954 (Aliphatic C-H)

^{1}H NMR: 7.09(bs, 2H, Ar-H), 6.53(bs, 2H, Ar-H), 4.54(bs, 2H, CH_2-Cl), 1.73(bs, 1H, Ar-C*H*-CH_2), 1.45(bs, 2H,Ar-CH-CH_2)

^{13}C NMR: 145.4, 136.7,134.9, 127.8, 126.0 (Benzene ring), 46.2, 43.5, 40.5, 36.5 (Aliphatic C)

Calculated: C(70.81%), H(5.90%), N(0.00%)

Found: C(71.23%), H(6.42%), N(0.00%)

3.4.4 Synthesis of (21)

A mixture of **(13)** (0.5 g, 2 mmol) and AIBN (0.01g, 2% mol) was degassed with nitrogen for 15 minutes and placed in an oil bath at 70˚C for 2 hours. The viscous solution was poured into methanol(50 ml). The precipitate polymer was dissolved in minimum amount of chloroform and precipitated in methanol. This process was repeated twice.

The white solid was dried in vacuum at 45˚C for 24 hours.

Yield: 63%

IR (cm^{-1}): 3129 (Ar-H), 2954 (Aliphatic C-H)

^{1}H NMR: 7.09(bs, 2H, Ar-H), 6.53(bs, 2H, Ar-H), 4.54(bs, 2H, CH_2-Cl), 1.73(bs, 1H, Ar-CH-CH_2), 1.45(bs, 2H,Ar-CH-CH_2)

^{13}C NMR: 145.4, 136.7,134.9, 127.8, 126.0 (Benzene ring), 46.2, 43.5, 40.5, 36.5 (Aliphatic C)

Calculated: C(70.81%), H(5.90%), N(0.00%)

Found: C(71.23%), H(6.42%), N(0.00%)

3.4.4 Functionalisation of Poly(Chloromethylstyrene) with THMMA (22)

A solution of THMMA (4.0 g, 33 mmol) and poly(chloromethylstyrene) (20) (1.5 g, 10 mmol) in dry DMF (30 ml) was refluxed for 8 hours. The polymer was precipitated in 2-propanol (500 ml) and filtered. It was dissolved in the minimum amount of methanol, filtered (to remove unreacted THMMA) and precipitated in 2-propanol. This process was repeated twice. The polymer was washed with chloroform to remove unreacted poly(chloromethylstyrene). The product was dried in vacuum. It was hygroscopic and kept under nitrogen. A good NMR spectrum could not be obtained in DMSO, the only solvent suitable to dissolve the polymer.

Yield: 63%

IR (cm^{-1}): 3553 (OH), 3315 (NH), 3135 (Ar-H), 2954 (Aliphatic C-H), 1614 (Aromatic C=C), 1285 (C-O), 1190 (C-N)

3.4.5 Poly(styrene-co-maleic anhydride) (23) and Poly(chloromethylstyrene-co-maleic anhydride) (28)

Styrene (3.9 ml, 34 mmol), maleic anhydride (3.31 g, 34 mmol) and benzoyl peroxide (40 mg, 0.16 mmol) were dissolved in toluene (20 ml) and the solution was purged with nitrogen for 15 minutes. The mixture was refluxed under nitrogen. The white solid was filtered by suction and dissolved in THF. It was precipitated in methanol. The precipitation process was repeated twice. The filtered solid was dried in vacuum.

(i) (23)

Yield: 80%

IR (cm^{-1}): 3135 (Ar-H), 2954 (Aliphatic C-H), 1714 (C=O), 1614 (Aromatic C=C)

^{1}H NMR (Acetone-D_6): 7.26(bs, 5H, Ar-*H*), 3.29(bs, 2H, CO-C*H*), 2.32(bs, 3H, ArCH-CH_2)

^{13}C NMR: 170.6 (C=O), 145.4, 136.7, 127.8, 126.0 (Aromatic C), 50.1, 46.5, 42.5, 37.8, 35.7 (Aliphatic C)

(ii) (28)

Yield: 77%

IR (cm^{-1}): 3143 (Ar-H), 2965 (Aliphatic C-H), 1717 (C=O), 1609 (Aromatic C=C)

^{1}H NMR (Acetone-D_6): 7.12 (bm, 4H, Ar-*H*), 4.09 (bs, 2H, Cl-CH_2), 3.19 (bs, 2H, CO-C*H*), 2.28 (bs, 3H, ArC*H*-CH_2)

^{13}C NMR: 170.6 (C=O), 145.4, 136.7, 133.4, 127.8, 126.0 (Aromatic C), 50.1, 49.5, 46.5, 42.5, 41.2, 37.8, 35.7 (Aliphatic C)

3.4.5 Syntheses of (24), (25), (26), (27)

A solution of styrene (2.0 ml, 17 mmol), the maleimide (17 mmol) and AIBN (0.06 g, 1% mol) in THF (15 ml) was purged with nitrogen for 15 minutes and placed in an oil bath at 60˚C for 4 hours. The polymer precipitated in methanol. It was dissolved in acetone and precipitated in methanol. This process was repeated twice. The filtered polymer dried in vacuum.

(i) (24)

Yield: 75%

IR (cm^{-1}): 3129 (Ar-H), 2943 (Aliphatic C-H), 1708(C=O), 1613 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 7.23 (bs, 10H, Ar-*H*), 3.33 (bs, 2H, CO-C*H*), 2.29 (bm, 3H, ArC*H*-CH_2)

^{13}C NMR: 170.6 (C=O), 145.4, 136.7, 133.4, 130.7, 129.1, 128.5, 127.8, 126.0 (Aromatic C), 50.1, 46.5, 42.5, 37.8 (Aliphatic C)

(ii) (25)

Yield: 69%

IR (cm^{-1}): 3553 (OH), 3109 (Ar-H), 2935 (Aliphatic C-H), 1707(C=O), 1619 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 9.43 (bs, 1H, O*H*), 7.17(bm, 9H, Ar-*H*), 3.29(bs, 2H, CO-C*H*), 2.32(bm, 3H, ArC*H*-CH_2)

^{13}C NMR: 171.3 (C=O), 151.4, 146.2, 136.7, 133.2, 129.4, 128.5, 127.8, 126.0 (Aromatic C), 46.5, 42.5, 37.8, 35.7 (Aliphatic C)

(iii) (26)

Yield: 70%

IR (cm^{-1}): 3125 (Ar-H), 2937 (Aliphatic C-H), 1707 (C=O), 1615 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 7.19 (bs, 9H, Ar-*H*), 3.30 (bs, 2H, CO-C*H*), 2.29 (bm, 3H, ArC*H*-CH_2), 2.01 (bs, 3H, CH_3)

^{13}C NMR: 170.6, 169.2 (C=O), 149.5, 132.1, 130.4, 129.1, 128.4, 127.6, 126.1 (Aromatic C), 50.1, 46.5, 42.5, 37.8, 25.3 (Aliphatic C)

(iv) (27)

Yield: 73%

IR (cm^{-1}): 3125 (Ar-H), 2959 (Aliphatic C-H), 1717 (C=O), 1613 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 7.22 (bs, 5H, Ar-*H*), 3.78 (bm, 4H, N-C*H*$_2$-C*H*$_2$-O), 3.23(bs, 2H, CO-C*H*), 2.27(bm, 3H, ArC*H*-C*H*$_2$), 1.92 (bs, 3H, CH_3)

^{13}C NMR: 170.6, 169.9 (C=O), 145.1, 136.3, 127.7, 126.5 (Aromatic C), 60.4, 45.5, 42.7, 38.8, 35.8, 20.4 (Aliphatic C)

3.4.6 Syntheses of (29, (30), (31), (32)

A solution of chloromethylstyrene (2.5 ml, 17 mmol), the maleimide (17 mmol) and AIBN (1% mol) in THF (15 ml) was purged with nitrogen for 15 minutes and placed in an oil bath at 60˚C for 4 hours. The polymer precipitated in methanol. It was dissolved in acetone and precipitated in methanol. This process was repeated twice. The filtered polymer dried in vacuum.

(i) (29)

Yield: 77%

IR (cm^{-1}): 3133 (Ar-H), 2952 (Aliphatic C-H), 1712 (C=O), 1614 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 7.25 (bs, 9H, Ar-*H*), 4.13 (bm, 2H, C*H*$_2$-Cl), 3.33 (bs, 2H, CO-C*H*), 2.31 (bm, 3H, ArC*H*-C*H*$_2$)

^{13}C NMR: 172.2 (C=O), 146.7, 145.3, 141.6, 134.4, 133.7, 130.7, 129.1, 128.5, 127.8, 126.0, 125.5 (Aromatic C), 51.5, 49.7, 44.5, 42.2, 40.9, 37.8 (Aliphatic C)

(ii) (30)

Yield: 72%

IR (cm^{-1}): 3530 (OH), 3127 (Ar-H), 2952 (Aliphatic C-H), 1711(C=O), 1620 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 9.51 (bs, 1H, O*H*), 7.23 (bm, 8H, Ar-*H*), 4.22 (bm, 2H, C*H*$_2$-Cl), 3.16 (bs, 2H, CO-C*H*), 2.37 (bm, 3H, ArC*H*-C*H*$_2$)

^{13}C NMR: 172.2 (C=O), 153.1, 144.7, 141.2, 134.6, 133.1, 130.5, 129.9, 129.0, 125.1, 124.3, 123.9 (Aromatic C), 52.1, 49.9, 44.7, 43.4, 41.4, 39.2 (Aliphatic C)

(iii) (31)

Yield: 72%

IR (cm^{-1}): 3133 (Ar-H), 2948 (Aliphatic C-H), 1722 (C=O), 1621 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 7.13 (bs, 8H, Ar-*H*), 4.09 (bm, 2H, C*H*$_2$-Cl), 3.29 (bs, 2H, CO-C*H*), 2.35 (bm, 3H, ArC*H*-C*H*$_2$), 1.95 (bs, 3H, CH_3)

^{13}C NMR: 175.6, 171.8 (C=O), 154.2, 145.7, 143.4, 137.1, 134.3, 131.7, 129.8, 129.2, 127.7, 126.4, 125.2 (Aromatic C), 53.0, 49.5, 44.4, 42.9, 41.5, 39.5 (Aliphatic C)

(iv) (32)

Yield: 70%

IR (cm^{-1}): 3145 (Ar-H), 2915 (Aliphatic C-H), 1708 (C=O), 1616 (Aromatic C=C)

^{1}H NMR ($CDCl_3$): 7.15 (bs, 4H, Ar-*H*), 4.12 (bm, 2H, C*H*$_2$-Cl), 3.69 (bm, 4H, N-C*H*$_2$-C*H*$_2$-O), 3.12 (bs, 2H, CO-C*H*), 2.24 (bm, 3H, ArC*H*-C*H*$_2$), 1.89 (bs, 3H, CH_3)

^{13}C NMR: 172.1, 170.5 (C=O), 149.2, 145.6, 137.4, 129.9, 125.5 (Aromatic C), 61.6, 51.2, 47.4, 43.8, 37.1, 35.3, 21.2 (Aliphatic C)

3.5 POLYMER BEADS

3.5.1 Synthesis of poly(CMS) beads (53)

A mixture of AIBN (0.06 g, 2% mol), divinyl benzene (DVB) (0.12 ml, 0.41 mmol) and chloromethylstyrene (3.0 ml, 20 mmol) was flushed with nitrogen for 15 minutes. PVA (0.12g) and calcium sulphate (0.24 g) were stirred in distilled water (120ml) at 600 rpm under nitrogen in a three-neck 250ml RB (previously flushed with nitrogen for 15 minutes), placed in an oil bath at room temperature, for 20 minutes. The monomer mixture was added to the suspension medium over a period of 5 minutes. The temperature of the oil bath was slowly raised to 70˚C and polymerisation allowed to proceed for 4 hours. The reaction mixture was then allowed to cool and poured in water (300ml) and stirred overnight. The solid was filtered by suction and washed with water, methanol, acetone, chloroform, acetone, chloroform, acetone and methanol. The product was dried *in vacuum* for 48 hours. It constituted of beads of non-uniform size and shape.

Yield: 37%

IR (cm^{-1}): 3056 (Ar-H), 2925 (Aliphatic C-H), 1604 (Aromatic C=C)

3.5.2 Synthesis of poly(styrene-co-maleic anhydride-co-DVB) beads (33) and poly(chloromethylstyrene-co-maleic anhydride-co-DVB) beads (38)

Styrene (5.0g, 48mmol), maleic anhydride (4.7g, 48mmol), AIBN (0.19g) and DVB (0.2ml) were dissolved in a mixture of toluene (4.0ml) and dioxane (4.0ml). The monomer mixture was flushed with nitrogen for 15 minutes. A mixture of sodium chloride (5.1g) and glycerol (100ml) was stirred under nitrogen for 30 minutes in a three-neck 250ml RB (previously flushed with nitrogen for 20 minutes). The monomer mixture was added and the RB was placed in an oil bath at 70˚C for 2hrs. The resulting milky solution was poured in water (300ml) and stirred overnight. The solid was filtered by suction, washed with water, THF, acetone, DCM, DMF, water, THF, acetone, DCM and diethyl ether and dried *in vacuum* at 40˚C for 48hrs. The product constituted of beaded polymers and non-beaded polymers. The beads were of non-uniform size and shape.

(i) (33)

Yield: 37%

IR (cm^{-1}): 3440 (Hydrolysed anhydride), 3056 (Aromatic C-H), 2923 (Aliphatic C-H), 1761 (C=O), 1635, 1454 (C=C), 1220, 1079 (C-O)

(ii) (38)

Yield: 35%

IR (cm^{-1}): 3462 (Hydrolysed anhydride), 3048 (Aromatic C-H), 2917 (Aliphatic C-H), 1779 (C=O), 1637 (C-O)

3.5.3 Synthesis of (34), (35), (36) and (37)

A dry three necked 500 ml round bottom flask, fitted with an overhead stirrer and two condensers, was placed in a water bath at room temperature and flushed with nitrogen for 10 minutes. Saturated magnesium chloride solution (180 ml) was added and the overhead stirrer switched on to rotate at 600 rpm, with the stream of nitrogen still flowing. A solution of styrene (1.0 ml, 8.8 mmol), the maleimide (8.8 mmol), divinylbenzene (0.1 ml, 0.18 mmol) and AIBN (0.05 g, 2% mol) in dioxane (7 ml) was purged with nitrogen for 20 minutes. The monomer mixture was slowly added to the well stirred suspension medium and allowed to stabilise for 15 minutes at room temperature. The temperature of the bath was slowly raised to 65°C and the reaction allowed to proceed for 5 hours. The reaction mixture was allowed to cool and poured into 250 ml of distilled water and stirred gently. The solid was then filtered and washed thoroughly with water, methanol, ethanol, chloroform, acetone, ethanol and methanol. It was dried in vacuum.

(i) (34)

Yield: 35%

IR (cm^{-1}): 3128 (Ar-H), 2951 (Aliphatic C-H), 1716 (C=O), 1616 (Aromatic C=C)

(ii) (35)

Yield: 33%

IR (cm^{-1}):3459 (OH), 3133 (Ar-H), 2955 (Aliphatic C-H), 1709 (C=O), 1610 (Aromatic C=C)

(iii) (36)

Yield: 34%

IR (cm^{-1}): 3139 (Ar-H), 2953 (Aliphatic C-H), 1718 (C=O), 1611 (Aromatic C=C)

(iv) (37)

Yield: 30%

IR (cm^{-1}): 3125 (Ar-H), 2941 (Aliphatic C-H), 1709 (C=O), 1623 (Aromatic C=C)

3.5.4 Synthesis of (39), (40), (41) and (42)

A dry three necked 500 ml round bottom flask, fitted with an overhead stirrer and two condensers, was placed in a water bath at room temperature and flushed with nitrogen for 10 minutes. Saturated magnesium chloride solution (180 ml) was added and the overhead stirrer switched on to rotate at 600 rpm, with the stream of nitrogen still flowing. A solution of chloromethylstyrene (1.3 ml, 8.8 mmol), the maleimide (8.8 mmol), divinylbenzene (0.1 ml, 0.18 mmol) and AIBN (0.05 g, 2% mol) in dioxane (7 ml) was purged with nitrogen for 20 minutes. The monomer mixture was slowly added to the well stirred suspension medium and allowed to stabilise for 15 minutes at room temperature. The temperature of the bath was slowly raised to 65°C and the reaction allowed to proceed for 5 hours. The reaction mixture was allowed to cool and poured into 250 ml of distilled water and stirred gently. The solid was then filtered and washed thoroughly with water, methanol, ethanol, chloroform, acetone, ethanol and methanol. It was dried in vacuum.

(i) (39)

Yield: 37%

IR (cm^{-1}): 3125 (Ar-H), 2933 (Aliphatic C-H), 1718(C=O), 1603 (Aromatic C=C)

(ii) (40)

Yield: 32%

IR (cm^{-1}): 3466 (OH), 3129 (Ar-H), 2949 (Aliphatic C-H), 1715 (C=O), 1613 (Aromatic C=C)

(iii) (41)

Yield: 32%

IR (cm^{-1}): 3134 (Ar-H), 2950 (Aliphatic C-H), 1711 (C=O), 1620 (Aromatic C=C)

(iv) (42)

Yield: 30%

IR (cm^{-1}): 3120 (Ar-H), 2943 (Aliphatic C-H), 1708 (C=O), 1625 (Aromatic C=C)

3.5.5 Synthesis of (44), (45), (46) and (47)

Styrene (5.0g, 48 mmol), maleic anhydride (4.7g, 48 mmol), AIBN (0.19g, 1.1 mmol) and DVB (0.2 ml) were dissolved in a mixture of toluene (4.0 ml) and dioxane (4.0 ml). The monomer mixture was flushed with nitrogen for 15 minutes. A mixture of sodium chloride (5.1g) and glycerol (100 ml) was stirred under nitrogen for 30 minutes in a three-neck 250ml RB (previously flushed with nitrogen for 20 minutes). The monomer mixture was added and the RB was placed in an oil bath at 70˚C for 2hrs. The resulting milky solution was poured in water (300 ml) and stirred overnight. The solid was filtered by suction, washed with water, THF, acetone, DCM, DMF, water, THF, acetone, DCM and diethyl ether and dried *in vacuum* at 40˚C for 48 hours. The product constituted of beaded polymers and non-beaded polymers. The beads were of non-uniform size and shape.

(i) (44)

Yield: 14%

IR (cm^{-1}): 3135 (Ar-H), 2923 (Aliphatic C-H), 1716 (C=O), 1612 (Aromatic C=C)

(ii) (45)

Yield: 13%

IR (cm^{-1}): 3466 (OH), 3129 (Ar-H), 2949 (Aliphatic C-H), 1715 (C=O), 1613 (Aromatic C=C)

(iii) (46)

Yield: 13%

IR (cm^{-1}): 3134 (Ar-H), 2950 (Aliphatic C-H), 1711 (C=O), 1620 (Aromatic C=C)

(iv) (47)

Yield: 12%

IR (cm^{-1}): 3120 (Ar-H), 2943 (Aliphatic C-H), 1708 (C=O), 1625 (Aromatic C=C)

3.5.6 Synthesis of (43) and (48)

Styrene (5.0 g, 48 mmol), maleic anhydride (4.7g, 48 mmol), AIBN (0.19g) and **(7)** (2% mol) were dissolved in a mixture of toluene (2.0 ml) and dioxane (6.0 ml). The monomer mixture was flushed with nitrogen for 15 minutes. A mixture of sodium chloride (5.1 g) and glycerol (100 ml) was stirred under nitrogen for 30 minutes in a three-neck 250ml round bottom flask (previously flushed with nitrogen for 20 minutes). The monomer mixture was added and the flask was placed in an oil bath at 70˚C for 2hrs. The resulting milky solution was poured in water (300 ml) and stirred overnight. The solid was filtered by suction, washed with water, THF, acetone, DCM, DMF, water, THF, acetone, DCM and diethyl ether and dried *in vacuum* at 40˚C for 48 hours. The product constituted of beaded polymers and non-beaded polymers. The beads were of non-uniform size and shape.

(i) (43)

Yield: 17%

IR (cm^{-1}): 3425 (Hydrolysed anhydride), 3137 (Ar-H), 2922 (Aliphatic C-H), 1717 (C=O), 1615 (Aromatic C=C)

(ii) (48)

Yield: 15%

IR (cm^{-1}): 3451 (Hydrolysed anhydride), 3125 (Ar-H), 2917 (Aliphatic C-H), 1708 (C=O), 1613 (Aromatic C=C)

3.5.7 Synthesis of (49), (50), (51) and (52)

A dry three necked 500 ml round bottom flask, fitted with an overhead stirrer and two condensers, was placed in a water bath at room temperature and flushed with nitrogen for 10 minutes. Saturated magnesium chloride solution (180 ml) was added and the overhead stirrer switched on to rotate at 600 rpm, with the stream of nitrogen still flowing. A solution of chloromethylstyrene (1.3 ml, 8.8 mmol), the maleimide (8.8 mmol), **(8)** (2% mmol) and AIBN (,2% mol) in dioxane (6 ml) was purged with nitrogen for 20 minutes. The monomer mixture was slowly added to the well stirred suspension medium and allowed to stabilise for 15 minutes at room temperature. The temperature of the bath was slowly raised to 65°C and the reaction allowed to proceed for 5 hours. The reaction mixture was allowed to cool and poured into 250 ml of distilled water and stirred gently. The solid was then filtered and washed thoroughly with water, methanol, ethanol, chloroform, acetone, ethanol and methanol. It was dried in vacuum.

(i) (49)

Yield: 12%

IR (cm^{-1}): 3137 (Ar-H), 2922 (Aliphatic C-H), 1717 (C=O), 1615 (Aromatic C=C)

(ii) (50)

Yield: 9%

IR (cm^{-1}): 3471 (OH), 3127 (Ar-H), 2927 (Aliphatic C-H), 1713 (C=O), 1613 (Aromatic C=C)

(iii) (51)

Yield: 10%

IR (cm^{-1}): 3127 (Ar-H), 2941 (Aliphatic C-H), 1712 (C=O), 1620 (Aromatic C=C)

(iv) (52)

Yield: 9%

IR (cm^{-1}): 3119 (Ar-H), 2945 (Aliphatic C-H), 1718 (C=O), 1614 (Aromatic C=C)

3.5.8 Synthesis of (54)

(43) (3.0 g, 14.8 mmol) was refluxed in 2M sodium hydroxide solution (40 ml) for 5 hours. After cooling, most of the sodium hydroxide solution was decanted. 2M hydrochloric acid (40 ml) was added to the remaining solid and refluxed for 3 hours. The beads were filtered and washed thoroughly with water, dilute hydrochloric acid, water, acetone and methanol. It was dried in vacuum.

Yield: 78%

IR (cm^{-1}): 3455 (COOH), 3031 (Ar-H), 2925 (Aliphatic C-H), 1706 (C=O), 1612 (C=C)

3.5.9 Synthesis of (55)

(53) (2.0 g, 13 mmol) was stirred in DMF (30 ml) under nitrogen for 1 hour. A solution of THMMA (3.0 g, 2.5 mmol) in DMF (10 ml) was added. The system was refluxed for 4 hours. After cooling the beads were filtered and washed thoroughly. The beads were suspended in water and refluxed for 2 hours. They were filtered and washed successively with acetone and methanol. The beads were dried in vacuum.

Yield: 54%

IR (cm^{-1}): 3468 (OH), 3021 (Ar-H), 2944 (Aliphatic C-H), 1612 (C=C)

3.6 SYNTHESIS OF GELS

3.6.1 Poly(Chloromethylstyrene) Gel (56)

Sodium hydride (0.08 g, 3 mmol) was added to a solution of TEG (0.43 ml, 5% mol) in THF (10 ml) under nitrogen and the mixture stirred for 2 hours at 50˚C. To this, a solution of poly(chloromethylstyrene) (7.75 g, 0.05 mol) in THF (40 ml) was added under vigorous stirring. A brown solid was obtained after a few minutes. Isopropyl alcohol was cautiously added to kill any unreacted sodium hydride. The product was then poured into methanol (100 ml) and filtered. It was washed thoroughly with DMF, chloroform, methanol, acetone, THF, methanol, DMF chloroform, methanol. An off-white solid was obtained.

Yield: 59%.

IR (cm^{-1}): 3491 (OH), 3141 (Ar-H), 2937 (Aliphatic C-H), 1613 (Aromatic C=C), 1204 (C-O)

3.6.2 Poly(Styrene-Co-Maleic anhydride) Crosslinked With TEG (57)

Poly(styrene-co-maleic anhydride) (2.0 g, 9.9 mmol) was dissolved in acetone. TEG was added and stirred for about 15 minutes. Then TEA was added dropwise. A white precipitate was obtained. This was allowed to stir for 5 hours under nitrogen atmosphere. Acetone was removed by decantation. The solid was repeatedly (3 times) allowed to swell in DMF and poured into chloroform. Then it was repeatedly (3 times) swollen in acetone and washed thoroughly with chloroform.

Yield: 35%

IR (cm^{-1}): 3492 (OH), 3144 (Ar-H), 2933 (Aliphatic C-H), 1721 (C=O), 1614 (Aromatic C=C), 1293 (C-O)

References

1. R. Bharel, V. Choudhary, I. K. Varma, *J. of App. Pol. Sci.*, 49, 31-38 (1993)