Solid Phase Peptide Synthesis Using Polymeric Supports
During the last decade innumerable investigations dealing with the quantitative aspects of polymer supported reactions have shown that the insoluble support does have a significant dynamic influence on the reactivity of the bound substrate. An important advantage of polymer supported reagents is the simplification of product work up, easy separation and isolation. The application of functionalised polymers depends on the characteristics of this specific active functional groups and the physicochemical properties of the polymer support. The interdependence of polymer microstructure and reactivity of functional groups in these resins dictates the application of these polymers in a number of areas of chemical, biological and technological interests.¹⁻⁵

In polymer-mediated organic reactions, polymers act as heterogeneous support either as passive or active. In passive supports the polymer functions as a heterogeneous matrix to which a low molecular substrate is covalently bound, allowed to react with various reagents and finally cleaved from the support. Polymers used for synthesis of polypeptides,⁶ and oligonucleotides⁷ belong to this category. In active polymeric supports, the substrate attached to the polymer effects a synthetic or catalytic transformation on a soluble substrate. This include polymer-bound reagents⁸⁻¹⁰ in which active site is consumed during the course of the reaction and the polymer-bound catalysts¹¹,¹² in which the active site catalyses numerous chemical transformations. For example, DVB and TTEGDA-crosslinked polystyrene supported mixed carboxylic dithiocarbamic
anhydrides have been developed as reagents for the acylation of amino
groups, halogen derivatives of poly(acrylamide)s and poly(N-vinyl
pyrrolidone)s are reported as oxidising and brominating agents for alcohols and
carbonyl compounds. Permanganate and chromate species attached on
poly(N-vinyl pyrrolidone) was used as oxidising agents for alcohols. A
number of polymers which contain active sites can function as supports for
immobilisation of enzymes. Poly(acrylamide)s, polystyrenes, and poly(methyl
methacrylate)s were used as supports for enzymes. Study of complexation
behaviour of polymeric ligands has received increased interest in chemical
technology and biology. In polymer supported transition metal catalysts, the
desired metal complex is attached to the functionalised polymer by equilibration
of the polymer with a metal complex having similar or weak ligands.

2.1 Structure and properties of the resins

The use of a functionalised polymer requires a structure which allows easy
diffusion of the substrates to the reactive sites. Similarly the resin should be
stable under the reaction conditions. These properties depend on the degree of
crosslinking of the polymer.

2.1.1 Physical properties

In the case of crosslinked polymers the morphology varies with the nature
and extent of crosslinking. For a linear polymer, it can form a molecular solution
in a suitable solvent and adopts a random coil conformation. Crosslinked
polymers exhibit considerable difference in physical properties depending on the
degree of crosslinking and method of preparation. The important physical
characteristics of crosslinked polymers are its porous structure and chain
flexibility. They can be characterised in terms of their total surface area, total
pore volumes, and average pore diameter. The degree of crosslinking
determines the swelling, pore size, surface area and mechanical stability of the polymer.

(a) Porous structure of the crosslinked polymers

The size and shape of the polymer matrix influence the solvating effect of a good solvent in the swollen state. The crosslinked polymers are classified into gel-type, macroporous, macrorecticular, popcorn and macronet polymers. The gel-type resins have small pore diameter and effective surface area. In the presence of a good solvent, the support swells reversibly to produce a gel, in the thermodynamic sense with significant solvent porosity (Figure 2.1). The high porosity resins has some advantages. It leads to good flow properties and it does not hinder the penetration of substrate molecules. The solvent polymer interaction determines the porous nature of the crosslinked polymers.25

Figure 2.1. (a) Swelling of gel-type resin in good solvents creating solvent porosity and deswelling in a bad solvent; (b) Macroporous resin: (i) highly crosslinked region and (ii) enlargement showing pore structure.
Solvent plays a significant role on physical nature and chemical reactivity of the attached species. In the case of crosslinked resins they absorb a definite amount of suitable solvent and make the functional group easily accessible to reagents in the continuous phase. Swelling of the resin brings the matrix to a state of complete solvation allowing easy penetration of the reagent molecules. The crosslink density is inversely proportional to the swelling. Good solvents enter and solvate the entangled areas of the polymers. The rate of diffusion of the species into the matrix depends on the nature of the polymer support.

In the oxidations by bromoderivatives of poly(N-vinyl pyrrolidone)s, the reactivity varies with varying polarity of the polymer support. Conversion of benzoin to benzil using this polymer support was chosen as a model reaction. Depending upon the nature of the crosslinking agent the solvent will vary; e.g., benzene for DVB and dichloromethane for TTEGDA crosslinking agents.

The rates of benzyl aminolysis of dimethyl acrylamide and acrylamide copolymers with p-nitrophenyl isobutyrate in different solvents show that the reaction is sensitive to the medium than the reaction of the polymer. The reaction is less solvent-dependent due to the contribution of chain backbone to the local solvent medium. The introduction of flexible HDODA crosslinking agent into the hydrophobic polystyrene matrix imparts hydrophilicity to the polymer matrix. This polar and flexible nature of the crosslinking agent favour the diffusion of polar solvents and reagents into the reactive sites.

Molecular character and extent of crosslinking

The chemical reactivity of the bound functional groups is governed by their distribution and accessibility on the polymer backbone. The physicochemical properties like swelling, compatibility with different solvents, rigidity and flexibility of these polymers have definite correlation with the variables of macromolecular matrix. The solvation characteristics of the support
and the reactivity of attached functional groups have definite dependence on the molecular character and extent of crosslinking. The rigid and hydrophobic macromolecular environment created by DVB crosslinks cause some disadvantages. Hence more flexible and hydrophilic crosslinking agents have been used to achieve more swelling of the support with high reactivities. The efficiency of crosslinked polystyrene support in peptide synthesis has been illustrated by the solid phase peptide synthesis of a peptide pardaxin on tetraethyleneglycol diacrylate crosslinked polystyrene support.31

The complexation behaviour of the polymeric ligands was found to be significantly influenced by the crosslinking of polymer matrix.32,33 For complexation of poly(acrylamide) supported amines with DVB, NNMBBA and TTEGDA crosslinking agents, the hydrophilic TTEGDA-system has higher complexing ability than other resins. The change in the rate of aminolysis with increase in the extent of crosslinking depends on the nature of the resins. The reactivity decreased in the order: TTEGDA > NNMBBA > DVB-crosslinked amino poly(acrylamide)s. The reactivity increases with increasing flexibility and hydrophilicity of the crosslinking agent.

The swelling characteristics of the crosslinked polymer are affected by the nature of the crosslinking agents. From the water binding studies it was observed that the equilibrium water content (EWC) has been found to be maximum for TTEGDA-crosslinked poly(acrylamide) resin and minimum for DVB-crosslinked resin. This correlates with the relative hydrophilicities of the crosslinked systems.

In the case of polystyrene resins the TTEGDA crosslinking shows maximum reactivity than DVB resins. In these cases the reactivity decreases with increase in crosslinking. In the functionalisation of DVB-crosslinked polystyrene resins with hypochlorite and sulphonamide functions the extent of functionalisation decreases with increase in crosslinking.36
(d) **Microenvironmental effects**

The attachment of a functional group to a polymer backbone does not alter the reactivity of that functional group. The proximity of polymer-bound group in a microenvironment, differs from that existing in solution can lead to a change in the reaction mechanism when they are reacting with the low molecular weight substrate.

The reaction rate of a polymer substituent is sensitive to the polarity of the medium, nature of the polymer backbone which affects the polarity of the polymer environment may have a profound influence on the reactivity. It can be explained by the aminolysis of p-nitrophenyl esters attached to polystyrene poly(methylacrylate) and poly(N,N-dimethylacrylamide) backbone.

The reactivity of crosslinked poly(acrylamide)s was found to be increased with increase in crosslinking. In this polymer the incorporation of crosslinking agent decreased the hydrophilic nature of the monomer, thus making the reactive sites more available for substrates and solvents.

(e) **Site-site interactions**

The most important factors affecting the site-site interactions are the degree of crosslinking, capacity and distribution of functional groups, length of the attached group and the solvent employed for the reaction. Lightly loaded system support the site isolation and heavily crosslinked systems give rise to penetration and diffusion problems. Solvents which swell the resin to a maximum extent should enhance the possibility of site-site interaction. The prospects for site-isolation might be increased by the highly crosslinked and rigid structure of the macroporous resin and the site isolation could be reduced by the higher effective local concentration of surface groups.37
In the acylation of active methylene esters the competing self condensation reactions are reduced by attaching the active ester to a polymer support. Polymers carrying anionic groups bound to the backbone exist with ionic clustering. This leads to restricted mobility of the polymer backbone providing a highly concentrated region of functional groups.

Size of the reagents

Size of the reagent molecule becomes important when we consider the case of diffusion process. Because in a crosslinked functionalised polymer, the reactive sites are buried in the interior of the matrix. So reactions with low molecular weight reagents can occur only if it diffuses into the interior of the polymer support. In the case of gel-type resins reaction rates would be expected to display inverse relationship with the size of the reactant and particle size of the resin. When the reactant becomes very large, even reaction with groups bound on the surfaces of the macropores may be inhibited. The movement of reactant through the resin would be diffusion through the macroscopic pores rather than through the molecular size matrix. It involves long range co-operative motion of the polymer support chains and not just local motion which can be characterised by a quite different diffusion constant.

2.1.2 Reactivity of functionalised polymers

The success of a solid phase reaction which involves the reaction of a low molecular weight amino acid derivative to a polymer-bound amino group depends on whether the reaction of a polymer-bound functional group with the reagents in solution will go to completion or not. The reactivity of a functional group attached to a polymer support may have quite different reactivity from the analogous group on a small molecule because of the macromolecular environment. The sluggishness in the rate of reaction has been shown to be due to the kinetic non-equivalence of functional groups in the polymer domain.38,39
The anomalous behaviour of the reaction rates of bound functional groups are due to the following factors.\textsuperscript{40}

(a) Energetic interactions between a polymer and a low molecular weight reagent may either concentrate or deplete the small molecules in the polymer domain and this affect their reaction rate with the functional groups appended to the polymer.

(b) If a group attached to a polymer is to react with the bulky reagent easily accessible analogous do not properly simulate, the steric restraint due to the chain backbone.

(c) Since the polymer backbone makes a contribution to the effective solvent medium in its immediate neighbourhood, this medium may be different from the pure solvent. If a reaction rate is sensitive to solvation, the polymeric reagent will then behave different by from the low molecular weight analog.

For designing a new reactive polymer the following factors should be considered. The nature of the solvents and reagents to which the polymer must be subjected during the course of its functionalisation or subsequent reaction and chemical behaviour of the support which depends on its physical form.

Since the functional groups on the support are not free to move the low molecular weight substrate must diffuse to the fixed reactive sites in the gel-structure. The main function of the solvent is to swell the matrix to a greater extent and it is important in the chemical reactivity of immobilised molecules. Resins with low degree of crosslinking shows increased swelling and this results in higher accessibility through the diffusion properties. The capacity of a polymer support is also important in the case of reactivity. Above all the reaction rate of the functional group depends on the nature of the functional group, polarity of the medium, the diffusion rate of low molecular weight species, pore size and pore volume, and temperature of the reaction. Morawetz \textit{et al.}\textsuperscript{41} observed that
polymer reactivity is governed by the local effect which is dependent on the nature of polymer backbone.

The foregoing investigations point out that the functional group in the crosslinked polymer is in an environment quite different from the analogous low molecular weight reagent. The kinetic non equivalence of the chemically bound groups can cause many problems in the use of these functionalized polymers. It can be minimised by the selection of proper polymer support.

2.2 Solid phase peptide synthesis

The solid phase peptide synthesis introduced by R. B. Merrifield has revolutionised the field of organic synthesis. In recognition of these contributions Merrifield was honoured the 1984 Nobel prize in Chemistry. The fundamental idea of solid phase peptide synthesis was to employ insoluble and filterable polymeric support which function at the same time as the carboxy protecting group for the C-terminal amino acid. The N\textsuperscript{α}-protected amino acid is attached to the polymer support as shown in Scheme 2.1. The process was repeated until the desired peptide is assembled on the support. After completing the desired sequence, a reagent was used to cleave the crude peptide from the resin and separate peptide chain into the solution. Finally the peptide was purified and characterised to ensure that the desired structure is indeed the one obtained.

The advantage of this procedure is that a large excess of coupling components and additive reagents can be employed and it will be easily separated from the polymer-bound peptide by simple filtration. The entire synthesis was carried out in a single reaction vessel and this avoids the loss involved in repeated transfer of materials. Similarly the expensive materials can be retained and they can be recycled many times.
Scheme 2.1. Outline of solid phase peptide synthesis.
2.3 Problems in the synthesis of peptides

Research in many laboratories during the past two decades has shed light on many problems that existed in the classic Merrifield system and has suggested means for overcoming these difficulties. These improvements have been mainly in the nature of the polymeric support.

2.3.1 Incompatibility of the supports

Due to the steric hindrance at the various functional sites on the heterogeneous polymer matrix the rate of coupling of amino acids has been found to decrease with increase in chain length. The influence of solid support on synthetic applications were governed by the physicochemical compatibility of the polymer matrix with the growing peptide chain. While selecting a polymer as support for solid phase peptide synthesis the following factors must be considered.

- The support should be totally insoluble in common solvents to avoid losses and to facilitate handling and purification.
- The support must be inert towards the reagent and not impart steric restriction to the circulation of the reagent and of the product near the active sites.
- It should be capable of functionalisation to a high degree and functional groups should be accessible to reagents and solvents.
- The crosslinked support must be swellable in suitable solvents and should be physicochemically compatible with the bound substrate, reagents and solvents used for the reactions.

In solid phase peptide synthesis the peptidyl resin was considered as a graft co-polymer in which the matrix and the peptide chain have different polarities. In polar solvents the hydrophobic polymer backbone collapse and entangling the smaller peptide chains in it. As the polymer backbone collapses
they hindered the approach of reagents and solvents. In non-polar medium the extended peptide chain collapse while the polystyrene backbone remains largely extended.\textsuperscript{51} Polystyrene bound peptides in different environments can be represented in Figure 2.2. An ideal situation for efficient coupling would be that, where both the polymer and peptide chain are extended Figure 2.2.

![Figure 2.2. Hypothetical models of polystyrene bound peptides in (a) non-polar solvent, (b) polar solvent and (c) ideal situation of polystyrene bound peptide.](image)

The swelling characteristics within the polymer matrix are important. Polystyrene is a hydrophobic matrix and therefore not the best choice for the hydrophilic peptides. The solvation properties of the support and the peptide chain are different and this make it difficult to attain a fully expanded structure for easy penetration of solvent and reactant molecules. The polymer support exerts a profound influence on the coupling efficiency of the functional groups attached on it.\textsuperscript{52}

By a judicious choice of the monomers and their presence in definite proportions can help in designing the macromolecular support with predetermined characteristics and coupling efficiency.
2.3.2 Incomplete coupling and deprotection reactions

The formation of truncated failure sequences remains the major problem for the Merrifield’s peptide synthesis. The by-products formed by racemization, rearrangement and cyclization reactions can then react further and remain together with the growing peptide chain on the support until the end of the synthesis. These error peptides arise if the polymer-bound peptide no longer reacts in a synthetic step. Because of the conformational changes, an end group which was not reacted in one or other coupling steps can become accessible at a later stage. Therefore as the peptide grows, a binomially increasing number of failure sequences will be produced. It is very difficult to purify these sequences, because they are chemically related to the desired sequence. The formation of error peptides can be minimised by making the coupling rates quantitative in every step and also by capping the residual amino groups after the first coupling by acylation with acetic anhydride.

2.3.3 Non equivalence of reactive sites

Chemically equivalent groups attached to crosslinked polymer backbone are not uniformly reactive and this is the major cause of difficulty in the solid phase peptide synthesis. The varied reactivity of functional sites in crosslinked polystyrene has been reported. Morawetz and co-workers reported that the insertion of crosslinking agent into a polymer leads to changes in the local polarity of the network. There is strong relation between the physical characteristics of the polymers and the coupling yields and it was investigated towards the optimisation of the polymeric support.

Recent improvements in the solid phase peptide synthesis and in associated chemistry have extended the usefulness of the solid phase peptide synthesis to the preparation of short and long peptides. By this method synthetic peptides are readily available to biological researchers and has changed the way in which many problems are approached.
2.4 Different supports for peptide synthesis

2.4.1 Poly(acrylamide)s

Poly(acrylamide)s were introduced as polymeric supports in peptide synthesis by Atherton and Sehppard et al., which are more hydrophilic than the conventional polystyrene supports. N,N-dimethyl acrylamide has a polarity similar to peptides and their swelling characteristics are much better in the solvents commonly used in solid phase peptide synthesis. Maximum solvation of the polymer backbone is necessary for the free access of the functional group in the polymer. These supports minimise the aggregation of the peptides within the support.

The polar polyacrylamide support (4) was prepared by emulsion copolymerisation of a mixture of dimethyl acrylamide (2), ethylene bis acrylamide (1) and acryloyl sarcosine methyl ester (3) initiated by ammonium per sulphate.

\[
\begin{align*}
\text{CH}_2=\text{CH-} & \text{C-NH-CH}_2 & \text{CH}_2=\text{CH-C-N(\text{CH}_3)_2} \\
\text{O} & & \text{O} \\
\text{CH}_2=\text{CH-C-HN-CH}_2 & & \text{CH}_2=\text{CH-C-N-CH}_2\text{COOMe} \\
\text{O} & & \text{O Me} \\
\text{(1)} & & \text{(2)}\end{align*}
\]

\[
\begin{align*}
\text{CONMe}_2 & & \text{CON(\text{Me})CH}_2\text{-COOMe} & \text{CONMe}_2 \\
\text{CONMe}_2 & & \text{CONH-CH}_2 & \text{CONMe}_2 \\
\text{CONMe}_2 & & \text{CONH-CH}_2 & \text{CONMe}_2 \\
\text{CONMe}_2 & & \text{CON(\text{Me})CH}_2\text{-COOMe} & \text{CONMe}_2 \\
\text{CONMe}_2 & & \text{CONH-CH}_2 & \text{CONMe}_2
\end{align*}
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\begin{align*}
\text{(4)}
\end{align*}
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After that instead of (3) another functionalising substituent (5) i.e., N-acryloyl-N'-(butyloxy carbonyl-β-alanyl) hexamethylene diamine was used. By using these supports a number of peptides like acyl carrier protein, 69 substance P, 70 and human-β-endorphin 71 were synthesised in high yield than polystyrene resins. Terpolymers of acrylamide, NNMBa and dimethylacrylamide were prepared for preventing the intermolecular H-bonding during the polymerisation of acrylamides. The modified polymers have almost same efficiency as that the acrylamide support. 72, 73

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\text{CH}_2=\text{CH}-\text{C}-\text{N-}-(\text{CH}_2\text{e}NH-\text{C}-\text{CH}_2\text{CH}_2\text{NH-Boc}
\]

(Carino and Han introduced the use of the fluorenylmethoxy carbonyl (Fmoc) group for protection of the amino end. It can be cleaved with bases such as piperidine and can therefore be used in conjunction with the acid labile protecting groups. Fmoc group furnishes decisive improvements than Boc group in its UV absorption. The peptide synthesis can be monitored UV-spectroscopically. Treatment with bases is preferred to acid due to the corrosion of the automated peptide synthesisers in the latter.

### 2.4.2 Poly(ethyleneglycol)s

Poly(ethyleneglycol) (PEG) was shown to be a valuable support for liquid phase peptide synthesis. The main problem was the separation of the bound
peptide from the reagents in the homogenous medium. This difficulty was solved by immobilising long chain PEGs on a polymeric support to get the combined advantages of solid phase peptide synthesis and liquid phase method.

The mobility of the polymer chains can be restricted by the crosslinking of the linear PEG which was grafted on the support. The immobilisation can be done by coupling one of the hydroxyl groups of PEG to chloromethylated polystyrene. There exists a tendency for both the hydroxy groups to react with chloromethyl group and the polystyrene gets again crosslinked. Hence the number of hydroxy groups will be reduced with concomitant lowering of the capacity of the graft copolymer for binding to peptides. By means of anionic polymerisation of ethylene oxide, PEG chains of unlimited size can be immobilised on crosslinked polystyrene beads containing hydroxy functional groups. For peptide synthesis graft copolymers based on the porous polystyrene are used. These copolymers contain 70% linear PEG and 30% crosslinked polystyrene matrix. They swell in all solvents which dissolve PEG and have high mobility of the PEG chains and the peptide bound on the support. These polymers can be used in continuous flow peptide synthesis because of their swelling characteristics. The mobility of the PEG chain of the graft copolymer is same as that of the mobility of free PEGs. These polymers behave like a homogenous phase in the solvated state. These tentacle polymers are suitable hydrophilic supports for peptide synthesis.

PEGA polymeric supports were used for high capacity continuous flow solid phase peptide synthesis. By the inverse suspension copolymerisation of acryloyl sacrosin ethyl ester (1) with N, N-dimethyl acrylamide (2) and bis-2-acrylamide prop-1-yl-PEG1900 (3) resulted in a PEGA polymer (4) with high loading capacity (Scheme 2.2). The new support has similar physical and mechanical properties of PEGA supports and both the functional ester and the subsequently formed amino groups had sufficiently high reactivities for solid phase peptide synthesis.
Scheme 2.2. Synthesis of high capacity PEGA resin

Inverse suspension polymerise in CCl₄
Heptane, SPAN-20, 70°C
NH₄⁺, "O₃SOOSO₃"⁻, NH₄⁺
(CH₃)₂NCH₂CH₂N(CH₃)₂
NH₂ CH₂ CH₂ NH₂

R = CON(CH₃)₂
2.5 Recent trends in solid phase peptide synthesis

Marrifield's original technique for solid phase peptide synthesis had undergone a series of modifications and improvements. The tactics of every aspect of peptide synthesis have been reviewed and novel improved supports were introduced. "Rink" resin, \textsuperscript{81} "TSK-Blank"\textsuperscript{82} and "RINK AMIDE" resin, Bis 2-acrylamido prop-1-yl poly(ethylene glycol) crosslinked dimethyl acrylamide (PEGA) supports, \textsuperscript{80} "Boc-Aca-oxime" resin (Boc-\(\epsilon\)-amino caproic acid) for cyclic peptide mixtures, \textsuperscript{83} p-nitro benzophenone oxime\textsuperscript{84} and carboxy amide terminal (CAT)\textsuperscript{85} resin offers new promises in the synthesis of free peptide and peptide derivatives. 2-Hydroxy 4-methoxy benzyl (Hmb)\textsuperscript{86} was used as a backbone protecting group for Fmoc \(\text{tBu}\) strategies. Methods for N-t-butoxy carbonyl protection of sterically hindered amino acids, 2-adamantyloxy carbonyl (2-Adoc)\textsuperscript{87} and a new \(\epsilon\)-amino protecting group in combination with \(N^2\)-Fmoc protection are the new base amino protecting groups similar to 9-fluorenyl methyloxy carbonyl (Fmoc) group. New Cys-S-Sulfonate derivatives i.e., Boc-Cys(SO\textsubscript{3}Na)-ONa and Fmoc-Cys-(SO\textsubscript{3}Na)-ONa\textsuperscript{88} and 2,4-dimethyl-3-pentyl ester protecting group\textsuperscript{89} for aspartic acid that prevents base catalysed aspartimide formation, were introduced as side chain protecting groups.

Allyl carbamate was introduced as linkages\textsuperscript{90} and which is stable to both bases and anhydrous acids. It can be cleaved by palladium catalysed allyl transfer reaction. New coupling reagents like 2,6-di-tert-butyl-4-(dimethyl amino) pyridine\textsuperscript{91} and Bis [4-(2,2-dimethyl-1, 3-dioxoaryl)methyl] carbodiimide (BDDC)\textsuperscript{92} have been introduced.

A new deprotecting agent for Boc-group was iodo trichlorosilane\textsuperscript{93} and a new reductive acidolysis final deprotection strategy in solid phase peptide synthesis was developed using safety catch linkers. High speed peptide synthesis\textsuperscript{94} and convergent solid phase peptide synthesis\textsuperscript{95} for larger peptides. A number of methods have been applied to the simultaneous multiple peptide

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synthesis e.g., tea bag, multipin, spot synthesis and photolithographic techniques.

With the help of sophisticated analytical techniques purification and characterisation of the peptides became easier. HPLC using reverse phase column, amino acid analysis using fast atom bombardment (FAB) and mass spectrometry were used for purification.

The systematic studies of the interdependence of the various factors and support characteristics have contributed very much for the improvement in the design of the original Merrifield resins and also for the evolution of a number of related strategies for polymer-bound peptide synthesis. A more general approach to solve the problem would be the development of supports which are structurally similar to the backbone structure of the peptide. This can overcome the dynamic changes in the solvation of the polymer and the bound substrate. In our laboratory attempts have been made to synthesise some polymeric supports for solid phase peptide synthesis. The aim of the thesis is to direct the studies towards the optimisation of the support for solid phase peptide synthesis.
References


