Polymer Bound Reagents: A Review

2.1 Introduction

The use of functionalised polymers as stoichiometric reagents and catalysts is widespread and opens up a field of growing progress\(^73-85\). Functionalised polymers are macromolecules to which functional groups are either physically adsorbed or chemically attached. They have the physical properties of the macromolecule and chemical properties of the bound function. The interest in the field of solid phase reactions with polymer supported reagents is being enhanced by the possibility of creating systems that combine the unique properties of conventional active moieties and those of high molecular weight polymers\(^86-88\). A polymer bound reagent is the functional polymer, which itself reacts to transform a low molecular weight substrate to product.

\[
P \xrightarrow{\text{Reagent + Substrate}} P + \text{Product}
\]
The use of polymeric reagent in organic chemistry has continued to receive steadfast attention\textsuperscript{89-90}. The major thrust behind the use of polymer supported reagents is due to the simplicity of use, performance and product isolation. The polymer supported reagents offer simplified reaction procedure, which eliminates the tedious chromatographic separation methods, which are usually employed in organic reactions. This enables the use of excess polymeric reagent to obtain high yields of the product. Regeneration and reusability are some other important advantages of the polymeric reagents. Polymer supported reagents are used in oxidation\textsuperscript{91-93}, reduction\textsuperscript{94-95}, halogenation\textsuperscript{96,97}, peptide condensation\textsuperscript{98-100} and a number of other specific reactions. The more widespread appreciation of the use of polymer supports has occurred with the explosion in the use of solid phase combinatorial methodologies\textsuperscript{101-103}. Since the present work is focussed on the development of a polymeric reagent for reduction, the review describes the existing literature of such reagents only.

The polymeric reagents differ in reactivity from the low molecular weight counterparts due to the effects of the macromolecular matrix. Originally, it was thought that the polymer support had no influence on the reactivity of the attached functional groups. But later studies reveal that the macromolecular matrix has a definite influence on the reactions of bound species. A thorough knowledge of these influences is important not only in designing new efficient and specific polymeric reagents but also in understanding the fundamental nature of these reactions. The ease of chemical modification and it's adaptability in different
reaction conditions depend on the microstructure of polymers. The use of a functional polymer whether reagent or catalyst, demands a structure, which permits adequate diffusion of reagents to the reactive sites which in turn is dependent on the extent of solvation, effective pore size and volume. The review gives an account of the characteristic features of the polymer supported reactions and various structural parameters which influence these reactions.

2.2 Nature of Polymer Support

The use of a functional polymer depends on the physical properties and chemical constitution of the polymer support. The reactivity and selectivity of the supported reagents or catalysts may be seriously changed from the low molecular weight reagents by the so called ‘polymer effects’. The polymer should be chemically and mechanically stable under the reaction conditions. The nature and extent of crosslinking, mode of preparation and hydrophilic-hydrophobic character of the polymer govern the reactivity and utility of a polymer bound reagent.

2.2.1 Physical form of the polymer

In polymer supported reactions the polymer may be linear or crosslinked. Depending on the utilisation each type has its own advantages and disadvantages.
2.2.1a Linear polymers

A linear polymer is a long chain species in which the monomeric units have been linked together in one continuous length. In the solid state the linear polymers have thread like shape. These polymers can be made soluble by suitable solvent. In solution the linear polymer adopts a random coil conformation. The soluble polymers are excellent candidates as reaction supports and catalysts\textsuperscript{108}. The use of functionalised linear polymer is of growing interest because there is no diffusional limitation due to the homogenous nature of linear polymers. Molecular engineering using linear polymers are recently reported\textsuperscript{109}. Linear polymers are useful in the reactions where separation of the polymer after application is not of much importance. The use of N-chloronylon as a halogenating agent is an application, where soluble polymers are most suited\textsuperscript{109,111}. The difference in solubility between N-chloronylons and nylons is such that the spent reagent precipitates out of solution as the reaction proceeds.

Higher conversions are obtained in the reactions of linear polymers because of the homogeneity of the reaction medium. The functional groups of the linear polymers are equally available. Easier characterisations are possible at various stages of functionalisation of linear polymers. But the primary advantage associated with the use of polymer is usually lost in the case of linear polymer because the separation of the soluble polymer from low molecular weight contaminants is difficult. The recovery of the polymer by ultrafiltration, dialysis or precipitation methods are not quantitative. D.E. Bregbreiter et al. have made studies
to improve the efficiency of separation methods of linear polymers\textsuperscript{112}. Low molecular weight species may be insoluble in the precipitating medium, which cannot be completely separated from the polymer. Another problem associated with the use of linear polymer is the possibility of side reactions, producing unwanted crosslinks during reaction, resulting in the formation of gel, which may be very difficult to process.

2.2.1b Crosslinked polymer

If a difunctional reagent is added during the preparation of a polymer support, the polymer chains get interconnected to form an infinite network, which is insoluble in all solvents. The insolubility of the crosslinked polymer simplifies the separation procedures and hence ensures easy reaction work up. The properties of crosslinked polymers differ on varying the degree of crosslinking and the method of preparation\textsuperscript{113}. Crosslinked polymers can be prepared in the form of spherical beads by suspension polymerisation, which do not coalesce when placed in a solvent. In the suspension polymerisation technique, the monomer is suspended in excess of an immiscible solvent. Hydrophobic monomers such as styrene were suspended in water and the suspension was stabilised by polyvinyl alcohol. The polymer beads obtained are chemically and mechanically stable and do not coalesce when placed in a solvent.

Polymer beads with low degree of crosslinking swell extensively in good solvents, exposing their inner reactive groups to the soluble reagents. Highly swollen polymer beads react as if they were in solution. One of the
defects associated with crosslinked polymers is that the reactive sites within the polymer beads and near the crosslinks are not chemically and kinetically equivalent, which makes quantitative conversion almost impossible. The heterogeneous nature of the reaction medium, which causes problem of restricted diffusion of substrates and reagents into the polymer beads results in lesser accessibility of the inner reactive sites of the polymer. The characterisation of the structural changes is very difficult due to the insoluble nature of crosslinked polymer. The crosslinked polymer can be classified into microporous or gel type resin, macroporous and macroreticular, popcorn and macronet polymers depending on the polymerisation conditions and swelling behaviours.

i) Microporous or gel type resins

Microporous or gel type resins are prepared by suspension polymerisation of vinyl monomers and small amounts of crosslinking agents\textsuperscript{14,15}. The monomer itself acts as the solvating medium for the growing polymer chain; but as higher conversions are reached, the solvation decreases and finally disappears. The polymer formed is a glass like material in the form of spherical beads, which can be easily handled. The gel type polymers have many advantages over non-swellable polymers. They are less sensitive to sudden shock and they can be more easily functionalised. The crosslinks are randomly distributed in the polymer. The pore size in a gel polymer is inversely related to the amount of crosslinking agent used during the preparation of the polymer. In the dry state the pores are collapsed and the polymer chains are held together by solid state
intermolecular forces. On contact with a suitable solvent, the polymer chains uncoil and form soft gel network with generation of considerable porosity, depending on the extent of crosslinking. As the degree of crosslinking increases, the mobility of the polymer chains is restricted\textsuperscript{116}.

Microporous resins with less than 1% crosslinking, generally have low mechanical stability and will readily fragment even under careful handling. Resins with higher crosslinking are mechanically stable but more rigid and the bound functional groups are not easily available, resulting in slow and incomplete reactions, due to limitation in diffusion of soluble molecules into the matrix. Practically, resins of \~2% crosslinking provide a satisfactory compromise allowing more easy penetration of the soluble reagents and also retains sufficient mechanical stability. 2% crosslinked polystyrene resins have been used successfully in peptide synthesis\textsuperscript{117} and polymer supported reactions\textsuperscript{118}.

\textbf{ii) Macroporous and Macroreticular resins}

Macroporous and macroreticular resins are prepared by suspension polymerisation, using higher amounts of the crosslinking agent and a solvent\textsuperscript{119-121}. The product obtained is in the form of tiny, highly crosslinked solid particles of polymer, surrounded by solvent droplets containing some dissolved monomer and crosslinking agent. Removal of solvent causes reversible collapse of the resins. Macroporous resins prepared are of high crosslink density. 20% crosslinking is common among macroporous resins. They have sufficient mechanical stability in the solvated state and large volume of solvent is retained. The main advantage of
Macroporous resins is their large interior surface area with large pores which allows easy access of reagents. The macroporous and macroreticular resins are used in industrial applications where resins with enhanced mechanical properties are required.

Macroreticular resins are prepared by copolymerisation of monomers in the presence of a solvent, which solvates the monomers, but precipitates the polymer formed\textsuperscript{122,123}. The method adopted for the synthesis of macroreticular resins is the usual solution phase process modified by inclusion of a non-solvent for the expected polymer. Macroreticular resins are highly porous and rigid material, which retains the shape and porosity even after the solvent is removed. They are non-swelling, having permanent and large pore volume and reactive groups are located in the interior regions. The macroreticular resins are not susceptible to changes in the nature of the surrounding medium. They are resistant to high pressure in column process. The dimensional stability of the macroreticular resins makes them most suitable for column applications where better solvent rates can be achieved than would be the case with gel polymer.

**iii) Popcorn polymers**

Popcorn polymers\textsuperscript{124-128} are prepared by warming a mixture of vinyl monomer and a small amount of crosslinking agent 0.1%-0.5% in the absence of initiators and solvent. Popcorn polymer is a white glassy opaque granular material, fully insoluble and porous with a low density. It does not swell in most solvents, but is easily penetrated by small molecules. Popcorn polymers have reactivity comparable with that of solvent swollen beads, but they are more difficult to handle.
iv) Macronet polymers

Macronet Polymers\textsuperscript{129,130} are three dimensional crosslinked networks in which linear polymer chains are interconnected by a separate chemical reaction following polymerisation. Macronet polymers have poor mechanical stability.

2.3 Methods of Functionalisation of Polymer

Active functional groups may be incorporated into the polymer chain by

1) Polymerisation or copolymerisation of the monomers which carry desired functional groups.

2) Chemical modification of the preformed polymers.

The vinyl type\textsuperscript{131-133} polymers can be produced by both of these methods. But polysaccharide based resins\textsuperscript{134} can be obtained by the functionalisation of the preformed polymer. The first method gives a polymer with uniform functional group distribution and capacity, but the polymerisation reaction needs considerable manipulation to ensure good yield of product and also to get good physical form. The second method gives functional polymers with characteristic physical form, but the degree of functionalisation may not be reasonable and functional group distribution is non-uniform.

2.3.1 Copolymerisation of functional monomer

This method involves the polymerisation or copolymerisation of the functionalised monomers with suitable substituents. Monomers with desired functional groups can be synthesised or purchased commercially. In the
polymerisation method a mixture of water insoluble polymers are suspended in aqueous medium in presence of suspending agents.

\[ CH_2=CH \rightarrow CH_2=CH \]

\[ \text{Scheme 2.1: Polymerisation of functionalised monomer} \]

2.3.2 Chemical modification of preformed polymer

The application of chemical modification of polymers enables to create new classes of polymers, which cannot be prepared by direct polymerisation of monomers due to their instability or unreactivity. Chemical modification is used extensively in both industrial and academic fields to modify the properties of polymers for various technological applications and to prepare chemically reactive polymers\textsuperscript{135-138}. The method also helps to modify the structure and physical properties of the commercial polymers for specific applications. The ease of chemical modification of a resin and its applications depend ultimately on the physical properties of the resin. Polystyrene resin is the most widely used support because of the ease of functionalisation, availability and mechanical stability.

Polystyrene, chloromethylated polystyrene and ring lithiated polystyrene are used in the chemical modification of styrene resins for the preparation of new functional polymers because they provide a facile method for the preparation of a variety of nucleophilic and electrophilic species\textsuperscript{90}.
Scheme 2.2: Chemical Modification of Polystyrene

The polymers prepared by the chemical modification method will not have every repeat unit, functionalised. Due to the difference in the chemical environment of the functional groups on the polymer matrix, their chemical reactivity also vary. The major drawback of chemical modification is that polymers cannot be purified after modification. Every undesirable group that is formed by a side reaction will become part of the polymer chain. The functionalisation reactions used must be free from side reactions.

2.4 Effect of Solvent

The solvent has a dominant influence on the physical nature and chemical reactivity of a functionalised polymer. The effectiveness with which a functional polymer can act as an alternative to the low molecular weight analogue, depends on the accessibility and reactivity of the functional groups anchored on it. In the case of linear polymers, the limited diffusion of reacting
species is not a severe problem because they can dissolve in an appropriate solvent. In solution the polymer chain exists as a random coil, which may be tightly contracted or highly expanded depending on the thermodynamics of the polymer-solvent interactions. A highly compatible or good solvent favours polymer-solvent interactions and will give rise to an expanded coil conformation. As the solvating medium is progressively made poorer, the coil contracts and consequently precipitation takes place. The extent of solvation of polymer due to a given solvent depends on the chemical nature of polymer backbone, the molecular weight, the nature of the solvent and the polymer-solvent interactions and temperature. In the case of crosslinked polymers the sufficiently large intermolecular force hinder the solubility of the polymers. By absorbing considerable amount of a suitable solvent, the crosslinked polymeric network can expand greatly and become porous forming a pseudo-gel. Swelling of resin beads is very important because it brings the polymer to a state of complete solvation and thus allows easy penetration of the polymer network by molecules of the soluble reagents. The extent of crosslinking of the polymer controls the behaviour of a resin in contact with a solvent and is inversely related to the degree of swelling. When a good solvent is added to a crosslinked polymeric network, solvent molecules interact with the polymer resulting in swelling and the resin becomes highly expanded and extremely porous. The polymer–solvent interaction determines the porous structure of the polymer network. At low crosslink density (2%), the solvated polymer may resemble a homogenous solution, that the gel network consists largely of the solvent with only a small
fraction of the total mass being the polymer. But with the increase in crosslink density, the tendency of the polymer backbone to expand in a good solvent is hindered by the crosslinks and penetration of the reagents into the interior may become impaired. At higher concentration of the crosslinking agent in addition to crosslinking, chain entanglement also occurs during polymerisation. This reduces the extent of swelling even in the presence of good solvents. The compatibility of the solvent with the polymer support can be adjusted by incorporating appropriate monomeric units in the polymeric chain during copolymerisation. In the dissolution or swelling of a polymer, the driving force is due to normal entropy and enthalpy changes associated with the mixing of solvent and solute molecules added with configurational entropy resulting from dilution of flexible chain molecules. In the case of crosslinked polymers, the decreased configurational entropy of the polymer chains held between the crosslink points oppose the tendency to disperse. Thus highly crosslinked polymers are less solvated due to restricted mobility of the polymer chain. For the successful completion of a reaction with linear or crosslinked polymers, the polymers must not only be swollen initially by the reaction solvent, but must remain swollen throughout the reaction, as the reactive species are transformed into other groups which may have a very different polarity. The most effective solvent for a polymer supported reaction may differ from that commonly used for analogous low molecular weight reactions. The rate of aminolysis of active esters by polymeric amines based on crosslinked polyacrylamides was found to be affected by the composition of the solvent system. The reactivity was found to be maximum in the solvent mixture.
dioxane/water. In the quaternization reaction of DVB-crosslinked poly(styrene-co-4-vinylpyridine) the reaction rate was found to be higher in the solvent toluene than in heptane. The solvation of the polymer is much better in toluene than in heptane.

The solvent dependence of polymer supported reactions is directly related to the solvation of the polymer. The degree of swelling of a polymer can be determined from the measured density of the dry resin and the weight of the imbibed solvent using the centrifugation technique.

2.5 Molecular Character and Extent of Crosslinking

The reactivity of a group, attached to a polymer backbone is governed by the characteristic structural features of the polymer support like the polarity, nature and extent of crosslinking and the solvation of the support and bound species. Thus the hydrophobic/hydrophilic character and flexible/rigid nature of the crosslinking agent and the extent of crosslinking have decisive role in determining the porosity, polarity and inter-chain interactions of crosslinked polymer supports. So the affinity of a crosslinked polymer towards solvents and low molecular weight reagents and the steric constraints within the pores of the crosslinked matrix are determined to a large extent by the nature and extent of the crosslinking. As a result, the solvation characteristics of the support and the reactivity of attached functional groups have a definite dependence on the molecular character and extent of crosslinking. It is reported that in the solvolysis
of p-nitrophenyl acetate by poly(N-2-acrylamidopyridine), the reaction rate is increased up to a certain crosslink density and then decreased\textsuperscript{151}.

Divinylbenzene (DVB) has been the most extensively used crosslinking agent because of the exceptionally high stability of the crosslinks. Polystyrene crosslinked with DVB has been successfully used in SPPS\textsuperscript{152-154}. However, the rigid, hydrophobic, DVB crosslinks impart many disadvantages to the crosslinked polymer support. The low solvent compatibility of the resin makes it inefficient in many applications\textsuperscript{155-157}. Systematic studies on polymer supported reactions have shown that the use of a flexible polymer support enhances the reactivity of the immobilized reagent due to the enhanced solvation characteristics of the polymer support\textsuperscript{158-160}. The use of polystyrene resin crosslinked with polar 1,6-hexanediol diacrylate (HDODA) has been reported in solid phase reactions\textsuperscript{161}. The HDODA crosslinked polystyrene resin was found to be superior to DVB crosslinked polystyrene resin due to the high solvation of HDODA-PS resin which imparts smooth diffusion of soluble reagents throughout the polymer matrix. The use of butanediol dimethacrylate crosslinked polystyrene resin was found to be a more effective support in solid phase peptide syntheses\textsuperscript{162-165}.

The effect of the molecular character and extent of crosslinking on the performance of polymeric reagents in oxidation reactions have been studied\textsuperscript{166-169}. In oxidation reactions using DVB-crosslinked polystyrene bound t-butyl hypochlorite, the capacity and reactivity of the reagents were found to decrease with increase in the extent of crosslinking\textsuperscript{166}. In the oxidation reactions using N-bromo derivatives of
polyacrylamides crosslinked with N,N'-methylene-bis-acrylamide (NNMBA),
tetraethyleneglycol diacrylate (TEGDA) and divinylbenzene (DVB), the capacity
and reactivity were found to be least in the case of DVB crosslinked resins. The
reactivity of the DVB crosslinked resin decreases with increase in crosslinking. In
the cases of NNMBA and TEGDA crosslinked resins maximum reactivities were
observed at 10% and 15% crosslinking respectively.

The effect of degree of crosslinking on the reactivity of polystyrene
supported t-butyl chromate in the oxidation of alcohol was studied. It was
reported that the reagents derived from 2% crosslinked polystyrene resins were
most efficient in terms of reaction period and product yield. In the oxidation of
benzoin to benzil, the t-butyl chromate prepared from 20% crosslinked
polystyrene gave only less than 30% conversion whereas the reagent prepared
from 2% crosslinked polystyrene gave 80% conversion.

Dependence of the functional group capacity and reactivity of the polymer
bound reagents on the nature and extent of crosslinking was observed in the
oxidation reactions with bromo-derivatives of poly(N-vinylpyrrolidones). PVP
resins crosslinked with NNMBA, DVB and TEGDMA were used for the
reaction. The capacity decreases with increasing NNMBA content. With
TEGDMA crosslinked system, the reactivity first decreased for the 5% and then
increased for 10 and 15% and decreased thereafter. With increase in the degree
of DVB crosslinking, the reactivity is decreasing. Among the three crosslinking
agents, NNMBA and TEGDMA are hydrophilic and DVB is hydrophobic.
Thus, with TEGDMA and NN MBA crosslinked reagents the flexibility of the polymer support is higher which accounts for their increased reactivity.

In the transamidation of linear and crosslinked polyacrylamides with ethylenediamine for application as reagents and chelating agents, the extent of transamidation depends on the polarity and the extent of the crosslinking in the polymer support.\textsuperscript{172,173} With increase in crosslink density the rigidity of the polar polyacrylamide backbone increases and the penetration of the solvent and substrate molecules into the active sites of the reagent become difficult. The DVB crosslinked resins have low amino capacities and NN MBA crosslinked resins have higher amino capacities. The amino capacities were found to decrease with increase in crosslinking.

The complexation behaviour of polymer ligands were found to be significantly influenced by the crosslinking of the polymer matrix.\textsuperscript{174,175} In the complexation of polyacrylamide-supported amine and dithiocarbamates with DVB, NN MBA and TTEGDA crosslinks, the hydrophilic TTEGDA crosslinked system has higher complexing ability than DVB and NN MBA crosslinked systems. The complexing ability of a polymer ligand depends on the hydrophilic nature of the macromolecular support. The swelling of these systems in water decreases with increase in the hydrophobicity of the crosslinking agent. The co-ordination structure of the polymer metal complexes\textsuperscript{176}, the kinetics of metal ion complexation\textsuperscript{177,178} and the thermal decomposition behaviour of polymer metal complexes\textsuperscript{179} were found to depend on the molecular character and extent of
crosslinking. The water binding properties of crosslinked polyacrylamides were found to depend on the molecular character and extent of crosslinking\(^\text{180,181}\). Among DVB, TTEGDA and NN MBA crosslinked polyacrylamides, the equilibrium water content has been found to be the least for the DVB-crosslinked resin and it decreases with the extent of crosslinking.

The influence of the nature and extent of crosslinking on the porous structure of crosslinked matrices has been observed in the encapsulation and benzil-benzilic acid rearrangement of benzil encapsulated in the cavities of crosslinked matrices\(^\text{182}\). Benzil could be encapsulated and subjected to rearrangement in the cavities of 2,3 and 4% DVB crosslinked polystyrene matrices having higher amount of crosslinker. In the case of polystyrene resins crosslinked with more flexible crosslinking agents like ethyleneglycol dimethacrylate (EGDMA) and butanediol dimethacrylate (BDDMA) a slow release of encapsulated molecules was observed as compared to that in the case of DVB crosslinked polystyrene resins.

The studies of the immobilization of enzymes on synthetic polymeric supports showed that, the efficiency of immobilization and the retention of the enzymic activity in the immobilization process depends on the nature and extent of crosslinking in the polymer support\(^\text{183,184}\). In the immobilization of papain, on DVB-polystyrene resins of varying crosslink densities (1,2,4 and 20\%), the immobilization yield and enzyme activity were found to decrease with increase in crosslink density.
The nature and extent of crosslinking of the polymer support influence even the functionalisation of the polymer. It has been found that in the functionalisation of DVB crosslinked polystyrene with hypochlorite and sulphonamide functions, the extent of functionalisation decreases considerably with increase in the degree of DVB crosslinking\textsuperscript{166,185}. This is explained as due to poor interaction of the low molecular weight reagents with the rigid DVB crosslinked system. With polystyrene supported peroxyacids, a 1% crosslinked resin gave better results than the 2% crosslinked polystyrene during the oxidation of alkenes\textsuperscript{186}. Evidently, the reactivity of a crosslinked polymer is highly influenced by the nature and extent of crosslinking.

2.6 Diffusional and Molecular Sieving Effects

In the case of linear polymers, the proper choice of reaction solvent and concentrations of polymer species make compensation for the limitations offered by the macromolecular matrix. But with crosslinked polymers, such limitations always remain as a real possibility. In a crosslinked functional polymer, many of the reaction sites are present in the inner side of the polymer matrix. The rate of diffusion of soluble reagents into the polymer matrix depends on particle size and pore volume\textsuperscript{187}. In several cases there exists a significant pore volume and interior surface which makes the reactive groups of the polymer surface readily accessible to substrate molecules. By increasing the pore volume of a resin support by the incorporation of diluents during polymerisation, considerable rate enhancements can be achieved in diffusion controlled reactions. Sherrington et al.
have quantified diffusional limitation and the molecular sieving of substrates in a series of quaternisation reactions of crosslinked styrene/4-vinylpyridine copolymers with alkyl halides having varying molecular bulk. A wide range of copolymers of varying crosslink ratio and pyridine content were prepared in bead form by suspension copolymerisation. As the crosslink ratio of the support is changed from ~5 to 37 percent, the rates of reaction of various halides decrease. The reactivity of the copolymer was increased by factors favouring diffusion such as decrease in the extent of crosslinking, decrease in the size of alkyl halides, decreased size of the polymer beads, the presence of solvents and enhanced porosity of the crosslinked polymer matrix. Many polymer bound transition metal catalysts show decreased reaction rate with molecules of large size. In the hydrogenation of olefins of varying sizes, using 1.8% DVB-crosslinked polystyrene bound Wilkinson catalyst, the reduction rates were found to decrease with increase in the size of olefins. In many cases, the diffusion controlled reactions exhibit deviation from simple kinetics. Thus the aminolysis of N-benzoyl glycine-4-nitrophenyl ester by crosslinked polyacrylamide based polymeric amines does not follow the expected second order kinetics, probably because the aminolysis is diffusion controlled.

2.7 Steric Effects and Spacer Effects

Polymer supported heterogeneous reactions are very slow compared to homogeneous reactions. The decreased reaction rate in the functional group conversion is one of the serious demerits of the polymeric reagents. One of the
reasons for the low reaction rate is the steric effect caused by the close proximity of the polymer backbone. Such effects are more prominent in the case of crosslinked polymers where the active functional groups are either flanked by the crosslinks or buried in the interior of the polymer matrix. The rate of aminolysis of p-nitrophenyl ester group of copolymers of styrene and methylacrylate was found to be less than the rates of reactions of their low molecular weight analogues\(^{191}\). The reason was attributed to the steric effect imposed by the polymer matrix.

Stereoselectivity is another consequence of steric effect. A series of crosslinked polystyrene bound oximes were prepared and subjected to Beckmann rearrangement. The polymeric group was found to migrate in all cases indicating the exclusive formation of oximes with the polymeric group in the anti position to the hydroxyl group due to steric reasons\(^{192}\).

It has been observed that the reactivity of functional groups could be considerably increased, if the active site is effectively separated from the macromolecular matrix\(^{193}\). The increased reactivity of functional groups are reported, where they are separated from the polymer backbone by a flexible spacer arm\(^{194}\). In most cases, a few methylene or ethylene oxide groups will serve the purpose of the spacer arm, which makes the functional groups project from the polymer matrix into the solution phase where they are more accessible to low molecular weight species and solvents. Methacrylates with long normal aliphatic ester groups showed increase in the rate of polymerisation, when the aliphatic chain of the alcohol of the methacrylate has a certain length\(^{195}\).
DVB crosslinked polystyrene supported analogue of t-butyl hypochlorite was reported as an oxidising agents for alcohols to carbonyl compounds. The oxidising efficiency of the polymeric reagent containing trimethylene spacer between the polymer matrix and t-butyl hypochlorite function was found to be significantly greater than those of the reagents containing only one spacer or no spacer between the reagent function and the polymer support.

The extent of immobilization of enzymes depends on the length of spacer arm. As the length of the spacer arm in the DVB-PS resin increases, the extent of immobilization increases. The separation between the carboxyl group and polymer backbone permits easy binding of enzyme to the polymeric ligand. The immobilization of papain on polymer supports with different spacer arms was reported. The extent of immobilization and activity of immobilized enzymes were found to increase with increase in the length of spacer arm. When a long flexible and hydrophilic PEG spacer was introduced between polystyrene backbone and the functional group used for immobilization, the extent of coupling and enzyme activity were found to be increased. The increased length of the spacer arm decreases the steric effect imposed by the crosslinked polymer backbone.

2.8 Microenvironmental Effects

The microenvironment within the vicinity of the polymer bound reactive site is very similar to that in the vicinity of a low molecular weight analogue of the reagent in the same reaction medium. The local concentration of reagent groups within a definite volume of a polymer is greater than that in a
homogeneous reaction media involving groups surrounding the active sites which influence the product formation.

The microenvironmental effect may be defined as the influence of groups A on the X-Y interactions and it arises from changes in polarity affecting the charge stabilization, hydrophilicity, lipophilicity and any such mechanism which does not involve group A in product formation at the active site\textsuperscript{108}. The binding constants of soluble molecules interacting with polymer supported reagents are also influenced by the microenvironmental effects\textsuperscript{199}. It was reported that in the Mitsunobu reaction, the microenvironmental effects could be used to maximise reaction rates and product yields\textsuperscript{200}. The Mitsunobu reactions are used for the syntheses of different esters\textsuperscript{201}, phosphinates\textsuperscript{202}, lactones\textsuperscript{203} and natural products\textsuperscript{204}.

\[
\text{RCOOH} + \text{ROH} + \text{EtOOC} = N = \text{NCOOE} + P \text{Ph}_3
\]

\[
\text{RCOOR} + \text{EtOOCNH} = \text{NHCOOEt} + \text{Ph}_2 \text{P} = O
\]

\textbf{Scheme 2.3:} Mitsunobu reaction
Crosslinked copolymers of poly(vinylbenzyl chloride) substituted with diphenyl phosphine ligands are used in the Mitsunobu reaction of esterification of benzoic acid with benzyl alcohol\textsuperscript{200}. The microenvironmental effect on reactant conversion and product yield in the esterification reactions was studied using a series of polymer supported phosphines. The decrease in substitution within the polymer matrix decreases the polarity and increases the reactant conversion and yield. It is suggested that decrease in the polarity of the microenvironment surrounding the active sites increases the reactivity. The significance of stereochemical and conformational factors in the rate enhancement or retardation of polymer supported reactions can be evident in the hydrolysis of polymethacrylic ester\textsuperscript{205}. In the case of syndiotactic and isotactic polymers a retardation in rate was observed. This was explained as due to the electrostatic repulsion of hydroxyl ions. The alkali hydrolysis of stereo regular methacrylic polymers in pyridine-water medium is accelerated by the carboxyl groups in the neighbourhood of ester groups. Here a ten fold increase in the rate of hydrolysis was noted which can be explained as a nucleophilic mechanism involving anionic assistance. PEG grafted polystyrene acts as a solid phase co-solvent\textsuperscript{206}. It acts as a phase transfer catalyst in a three phase reaction. The polymeric microenvironment is capable of dissolving both the hydrophobic and hydrophilic reagents implying that it brings together the substrate and reactant which are present in organic and aqueous phases respectively. It was observed that the reaction of cumene with poly(N-bromomaleimide) differed considerably depending upon whether the homopolymer or poly(N-bromomaleimide)-styrene copolymer was
used. The polarity of the polymer when succinimide moieties were adjacent to each other favours dehydrobromination of the expected product\(^{207}\). The efficiency of (dialkylamino)pyridine ligands covalently bound to a polystyrene support as an acylation catalyst was found to be greater when the degree of functionalisation was less than 50% due to a more hydrophobic environment around each ligand\(^{208}\).

### 2.9 Site-Site Interactions and Site Isolation

The ability to effectively isolate the reactive sites from one another during a reaction is an important factor regarding a functionalised polymer. When a functional group is immobilized on a polymer matrix, its interaction is limited substantially. The polymer chains of lightly crosslinked resins have high mobility. Thus the reactions involving interactions of sites are found to occur frequently to various extents with polymer supports. The important factors which govern these site-site interactions are the degree of crosslinking, functional group capacity, distribution of functional groups, distance between the polymer matrix and the attached group and the solvent used for the reaction\(^{90}\). Low degree of crosslinking and high capacity favours uniform distribution of functional groups along the polymer backbone. In the presence of good solvents, which solvate the polymer to a pseudo-gel, mutual interaction between functional groups is large\(^{209}\). Systems with low capacity of functional groups favour site isolation\(^{110}\). When the loading is above 1 mmol/g, the possibility of intra-resin reaction increases. Increasing the crosslink density of the support decreases the
chain flexibility and discourages the site-site interactions, as the crosslink points are closer. In good solvents, which solvates the polymer matrix effectively, the possibility of site-site interactions can be minimised by the use of highly crosslinked, rigid, macroporous resin. But the higher effective local concentration of functional groups on the surface may reduce the possibility of site isolation.

In the acylation of active methylene esters, the competing self-condensation reaction is reduced by attaching the active ester onto polymer supports due to site isolation. Higher reaction rate and product yield are obtained as the reaction was carried out on polymer supports, due to site isolation. Many species are stable to exist on polymer supports, which under homogeneous solution conditions would be destroyed by mutual intermolecular reactions. This property has been exploited in the preparation of cyclic peptides, in the preparation and use of polymer bound transition metal catalysts, and in the trapping of reaction intermediates. Benzyne intermediate generated on a crosslinked polystyrene matrix has been found to be stable for minutes, due to site isolation.

Many observations illustrate the facility of site-site interactions. One of such reactions is the conversion of aldehydes into dichloro and dibromo olefins by treating with polymer-supported phosphine and carbontetrachloride. A key step in these reactions is the intra polymeric reaction between phosphine residues and
trihalomethyl phosphonium salt residue to give triarylphosphine dihalide residues and dihalomethylated groups.

\[
\begin{align*}
\text{Scheme 2.4: Intra polymeric interaction between phosphine residues} \\
\text{and trihalomethyl phosphonium salt residues}
\end{align*}
\]

2.10 Neighbouring Group Effect

The interaction of specific neighbouring groups modifies the reactivity of a functional group bound to a polymer support. The ionization of carboxylic acid groups in polyacrylic acid illustrates the influence of neighbouring groups on the reactivity. The ease ionization will decrease as the degree of ionization increase because the polymeric backbone becomes more and more negatively charged \(^{22}\). The neighbouring groups need not be of the same type. The acidity of a carboxylic acid group and phenol residue can be mutually influenced by hydrogen bond formation between the two \(^{224}\).
Scheme 2.5: Neighbouring group effect on the acidity of carboxylic acid and phenol residue

Similar phenomenon was observed in the base catalysed hydrolysis of polymethacrylamide. All of the amide groups are not readily cleaved, residual functions flanked by the two carboxylate groups become inactive as a result of the local electrostatic repulsion of hydroxide ions. In the protonation and alkylation of poly(vinylpyridine), similar neighbouring group effects are noted.

In certain cases, the neighbouring groups have been shown to co-operate producing a pronounced increase in the reactivity of bound functional groups. In the dehydration of alcohol catalysed by sulfonic acid polymers the rate of the reaction can be increased by 4 or 5 times at high acid loadings.

2.11 Characterisation of Functionalised Polymers

The adequate characterisation of chemical changes carried out on polymer supports is one of the most serious problems encountered with polymer supported reactions. Since the loadings of polymer involved are small, the
simple dilution factor makes many conventional techniques totally insensitive. With linear, soluble macromolecular supports the ranges of analyses that can be applied is more or less the same as applicable to small molecular chemistry. However, with insoluble crosslinked resins many techniques which rely on the preparation of homogeneous solutions are no longer of use.

The two most useful techniques of analysis, which are readily applicable are elemental microanalysis and infrared absorption spectroscopy. Elemental microanalysis is a much used technique and carbon, hydrogen, halogen, nitrogen, sulphur and phosphorus analyses have been performed widely. Much of the interpretation in literature depends heavily on this quantitative measurement. IR spectroscopy is a very informative technique in the case of functionalised polymers. The presence or absence of characteristic band of functional group in the IR spectrum is very useful in polymer supported reactions.

Valuable confirmatory evidence for a particular transformation can be obtained by performing reactions with a reasonable degree of gravimetric accuracy. The increase in weight of a fixed mass of support on the introduction of significant amounts of a heavy element or a large functional group is readily measured.

Some of the functional groups can be readily quantified by titration. For the acidic and basic moieties, attached to a polymer support, conventional titrations can be quite accurate, providing the polymer matrix allows the penetration of reagents. It is more advantageous to react on bound group with
excess of acid or base allowing a long period of time for complete reaction of bound function and then to carry out a back titration. When an aqueous solution of reagent will not penetrate into the polymer matrix, instead of aqueous solution, an organic solution of appropriate acid or base can be employed for the initial neutralisation, then the back titration is to be carried out in two immiscible liquid phases.

Polymer bound oxidising agents such as peracids can be estimated iodimetrically. Many functionalisation reactions involve the displacement of species, which can be readily estimated. Typical example is the estimation of chlorine capacity of chloromethyl polystyrene resin by Volhard’s titration. Quantitative conversion in polymer supported reaction can be studied by UV spectrophotometric analysis. One example is the estimation of immobilized primary and secondary amino groups by Gisin’s picric acid method.

Resins can also be characterised by swelling index or solvent imbibition measurement using a simple centrifugation technique. Generally, functionalisation of a polymer support leads to decrease in the volume of a given solvent, which the material can absorb. The volume uptake per gram of resin can be determined before and after modifications.

B. Altava et al. have reported the application of FT-Raman Spectroscopy for the qualitative and semi-quantitative characterisation of functional polymers being used for the preparation of resin supported reagents and catalysts. The technique enables the analysis of polar functional groups such as chloromethyl
groups. Simplicity in the sampling for the analysis enable this method for the characterisation of functional polymers.

Despite the many successful investigations, which have been performed, the need for a more detailed structural analysis of polymer bound groups still remains. The successful application of modern methods in NMR spectroscopy, the solid state $^{13}$C NMR magic angle technique is very useful for a polymer chemist.

2.12 Polymer Supported Reducing Agents

A number of synthetically important polymeric reagents have been reported so far, of which polymer bound reducing agents have a significant contribution, even though they are less in number as compared to the polymer bound oxidising agents. Polymer supported tin hydride$^{232}$, polyvinylpyridineborane$^{233}$ and polypropylene sulfide-borane$^{234}$ are a few examples of polymer bound reducing agents. These polymeric reducing agents have many advantages over the low molecular weight reactive species. A functional group when anchored to a polymer support, behave differently because of the effect of macromolecular matrix. The polymer bound reagent exhibits combined properties of the macromolecular support and the reactive residue. The low molecular weight reducing agents lithium aluminium hydride, sodium borohydride, tin hydride, diborane, borane-THF, amine-borane, borane-dimethyl sulfide and borane-amino alcohol are well known reducing agents used in synthetic organic chemistry. But in the case of certain low molecular weight reagents, the volatility, instability and high reactivity of the reagents cause problems in
preparation and handling. By anchoring to a polymer support the volatility and toxicity of the reagents can be reduced. The use of polymer bound reducing agents in the place of low molecular weight reagents can simplify the reaction work up. The usual tedious chromatographic separation procedures used in organic synthesis can be minimised by the use of polymeric reagents. Use of reagents on crosslinked polymer supports enables separation by simple filtration. The polymer supported reducing agents have increased stability and selectivity with respect to their low molecular weight reagents.

Polymer supported amino alcohol-borane reagent\textsuperscript{72} and polypropylene sulfide-borane reagents\textsuperscript{234} were reported to have increased chemoselectivity than the low molecular weight amino alcohol-borane and borane-dimethyl sulfide. They are found to be chemoselective in the reduction of aldehydes in the presence of ketones. Another significance of these reagents is the regenerability of the reducing functional group. The regenerated polymeric reagent could be reused several times. Few selected examples of polymer bound reducing agents are listed below.

2.12.1 Polyvinylpyridine-borane reagent

Hallensleben have prepared polyvinylpyridine-borane (1) and have reported its use as a reducing agent for carbonyl compounds\textsuperscript{233}. The reagent was prepared by the reaction of polyvinylpyridine hydrochloride and sodium borohydride at room temperature.
When the linear polyvinylpyridine was used in dry benzene as a reducing agent, only moderate yields of the alcohol are obtained. Macroporous gels of polyvinylpyridine-borane were prepared and used as the reagent in the column. The substrate carbonyl compound in benzene was passed down the column at 70°C. The carbonyl compounds were reduced to the respective alcohols. But the yields of alcohols obtained were low. At reflux temperature in dry benzene, 14% reduction of benzaldehyde was reported after 4 h. The polyvinylpyridine-borane could be regenerated and reused after reaction. The schematic representation of the reactions was given in Scheme 2.7.

Alcohols obtained from the reducing reaction are freed from the boron esters by acid hydrolysis. Polyvinylpyridine hydrochloride sites are formed from the hydrolysis, which can again be transformed into polyvinylpyridine–borane units by the reaction with sodium borohydride.
Polymer bound reagents: A Review

Scheme 2.7: Reduction of aldehyde using polyvinylpyridine-borane

2.12.2 Polymer bound borohydride

Polymer supported borohydride (2) was developed by Gibson et al. for use in a number of reduction processes. The resin supported borohydride was used in ethanol to reduce benzaldehyde to benzyl alcohol. The reaction was much slower than that using sodium borohydride. Kabalka reported the successful utilisation of this reagent for the reduction of arylazides and arylsulfonyl azides.

Recently, crosslinked chitosan supported borohydride was developed and it was found to be effective in the reduction of aldehydes and ketones to the corresponding alcohols.
2.12.3 Polymer supported tin hydrides

Polymer supported tin hydrides were used extensively to reduce aldehydes and ketones\(^3\). The reagent (3) was prepared from a crosslinked macroporous styrene\(^2\). In order to limit or avoid residual tin contamination, organotin hydride anchored to insoluble polymer supports have been prepared and used\(^238-240\). The advantage of the reagent over low molecular weight analogue is it’s non-toxicity. The yields of alcohols obtained were very high in the reduction using polymer supported tin hydrides.

![Scheme 2.9: Preparation of polystyrene supported tin hydride](image)

\[ \text{Scheme 2.9: Preparation of polystyrene supported tin hydride} \]

Dumartin has developed a series of polymer supported organotin hydrides \textit{in situ} from polymer supported organotin halides and sodium borohydride\(^240\). A
series of organotin hydrides was examined in the reduction of 1-bromoadamantane. Polymer supported organotin hydrides were developed using different polymer supported tin halides such as P(CH2)2SnBu2Cl and P(CH2)4SnBu2I. The P(CH2)4SnBu2I/NaBH4 system, was found most efficient due to higher reduction yield and less pollution. The optimum reagent with respect to maximum yield and purity of the product was (4).

![Chemical Reaction](attachment:reaction.png)

**Scheme 2.10:** *in situ* generation of polymer supported tin hydride from polymer supported tin halide

The organotin halides could be recovered after reduction and reused without significant loss of reactivity.

### 2.12.4 Polypropylene sulfide-borane and haloborane reagents

Domb, A. and Avny, Y. have reported borane complexes of polypropylene sulfide grafted on crosslinked polystyrene. They have prepared graft polymer bound borane by the reaction of the polymer with borane-tetrahydrofuran and also with diborane. The polymer bound reagent was used for the reduction of carbonyl compounds. The reactivities of the polypropylene sulfide-boranes derived from graft and homo polymer supports were similar to that of borane-methylsulfide. Aldehydes, ketones, carboxylic acids and esters were reduced to the corresponding alcohols. Reduction of cyclohexanone with polypropylene
sulfide-borane was compared with the reaction of borane-methylsulfide (BMS). The polymeric reagent was found to be as reactive as its low molecular weight analogue. The polystyrene grafted polypropylene sulfide-borane reagent was found to be chemoselective in the reduction of aldehydes in presence of ketones and the reagent also shows selectivity in the reduction of ketones. Cyclohexanone was preferentially reduced in the presence of other ketones.

\[
\begin{align*}
(P) &\rightarrow BH_3 + 3RCOR^1 \\
&\rightarrow P + B(OH)R^1_3 \\
&\rightarrow H^+/CH_3OH \\
&\rightarrow RR^1CHOH + H_3BO_3
\end{align*}
\]

**Scheme 2.11**: Reduction of ketone using polypropylene sulfide-borane

**2.12.5 Polymer supported amino alcohol-borane**

Polymer supported amino alcohol-borane reagent was prepared by S. Itsuno et al. by the reaction of polymer bound amino alcohol with borane in THF\(^2\). Initially the reaction mixture was kept at -78\(^{\circ}\)C and the temperature was gradually elevated to 30\(^{\circ}\)C by warming. The unreacted borane was evaporated under reduced pressure (13Pa). They have prepared polymer bound amino alcohol-borane reagent on DVB crosslinked polystyrene resins of different degrees of crosslinking. The polymer bound amino alcohol-borane reagent was found to reduce aldehydes selectively in the presence of ketones.
The polymer bound amino alcohol-borane reagent derived from 1% crosslinked polystyrene reduces benzaldehyde within 1 h. The reagent derived from 2% crosslinked polystyrene was found to reduce aldehyde within 3 h and acetophenone within 50 h, completely. The reagents derived from secondary and tertiary amino alcohols were reported to have lower reactivities than that prepared from primary amino alcohol.

2.13 Conclusion

The reagents supported on insoluble polymers have acquired high popularity and have already found wide applications in various fields. Many reactions in organic syntheses can be carried out cleanly, rapidly and in high yields under mild reaction conditions using polymer supported reagents. In the attempts to carry out some reactions with usual procedures, either the reagents frequently fail or involve difficult separation procedures. The products obtained in polymer supported reactions are less contaminated. Isolation of organic products simply involves decanting or filtration to remove the spent polymer from the product obtained, followed by evaporation of the solvent. The reactivity of the polymeric reagent is very much influenced by the macromolecular characteristics of the polymer support. The nature and structure of the polymer backbone and crosslink density, effect of solvent, nature of active species and its environment, all these factors govern the reactivity of a polymer bound reagent. Due to the increased stability and selectivity the polymer supported reagents have an important role in organic syntheses.