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SYNTHESIS AND APPLICATIONS OF ORGANIC POLYMERS AS SUPPORTS AND PROTECTING GROUPS

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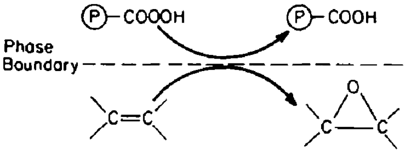
1. INTRODUCTION

Two decades have passed since Merrifield's pioneering work[1] on the solid phase method of synthesis. Although almost all of the early work involving polymer supports was concentrated on repetitive sequential syntheses such as those of polypeptides,[2] nucleosides,[3] and polysaccharides,[4] numerous other applications spanning a wide spectrum of chemistry have been devised and have led to a better understanding of both the advantages and the limitations of polymer-supported species.

Since a number of reviews[5-7] covering different aspects of polymer-supported reactions are available, this report will not attempt to be comprehensive but will examine critically the preparation and the applications of a few selected functional polymers.

In general, the term polymeric reagent describes one-step processes in which the functional polymer itself reacts to transform a low molecular weight substrate to product (Scheme 1),[8] while the term polymeric protecting group is associated with multi-step processes in which the polymer is used to bind a low molecular weight substrate through a given functionality, thus acting as a protecting group for this functionality, while chemical transformations are carried out on other parts of the polymer-bound substrate. Reactions involving polymeric protecting groups will usually include distinct polymer coupling and decoupling steps (Scheme 2).[9]

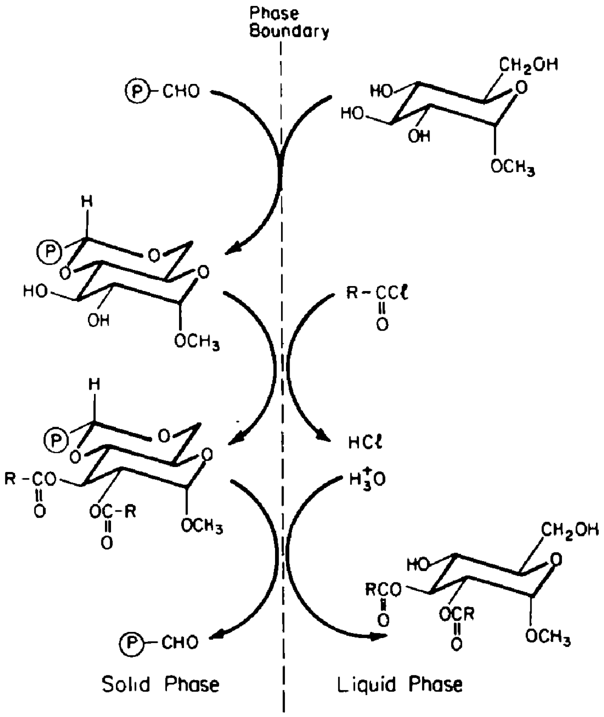


Scheme 1. Polymeric reagent (Ref. 8). Ⓟ = Crosslinked polystyrene

In general the following benefits can be expected when a reaction or a sequence of reactions is carried out with a polymeric reagent or protecting group.

(i) *Ease of processing.* This is usually the most important consideration as work-up and purification of the product of a polymer-supported reaction is often reduced to simple filtrations. This advantage alone is often sufficient to justify the use of a functional polymer.

(ii) *Ability of the polymer to be recovered, regenerated and reused.* This is a critical feature in all but a few instances such as the solid phase synthesis of polypeptides, where the gains associated with the use of the polymer support far outweigh any consideration of its cost. In most cases however, if a functional polymer is to be used in a single step process (polymeric reagent) or in a short reaction sequence (polymeric protecting group), it should be designed in such a way as to allow the spent



Scheme 2. Polymeric protecting group (Ref. 9).

material to be recovered quantitatively and regenerated in as simple a way as possible without appreciable loss of activity.

(iii) *Ease of handling.* Odorless polymers of reduced toxicity can be made containing functionalities which, in low molecular weight compounds, would be associated with significant toxicity or noxious odors.

(iv) *Influence of the polymer backbone and of the local environment within the polymer.* These may modify considerably the reactivity of functional groups attached to a polymer; reactions between species attached to the same polymer backbone may be enhanced or reduced considerably depending on the local environment. Reaction kinetics are also affected.

2. PREPARATION AND CHARACTERIZATION OF FUNCTIONAL POLYMERS

Before looking at some applications of functional polymers in organic synthesis, it is useful to consider the following:

Choice of the physical form of the functional polymer
Reactions which are currently available for the preparation of functional polymers
Means of characterization of polymer-supported species

2.1 *Choice of physical form of the polymer*

Polymers are available as linear chains, which can be dissolved in appropriate solvents, or as crosslinked gels or macroreticular resins which are totally insoluble in all solvents; each type possesses its own distinct advantages and disadvantages. Therefore, in any application of a polymer as a reagent or protecting group, careful consideration must be taken of all the variables involved before choosing the physical form of the polymer in order to maximize the advantages of the polymer system while minimizing any potential problems.

2.1.1 *Linear* vs *crosslinked polymer.* The first choice which has to be made is related to the solubility properties of the polymer. The advantages associated with the use of linear (soluble) polymers include the fact that all the reactions will be carried in solution in an homogeneous medium with few diffusion problems and with equal accessibility to all the functional groups of the polymer. This may be a significant advantage in a reaction which is known to be sluggish or involves substrates which have a large size and may not be able to penetrate all the pores of a crosslinked polymer. In general high conversions will be possible using a soluble polymer but the primary advantage associated with the use of a polymer is at least partially lost, as separation of the polymer from low molecular weight contaminants may be laborious or difficult. Selective and complete precipitation of the polymer may not be easy and obvious pitfalls exist as low molecular weight species may be insoluble in the precipitating medium, and thus complete removal of impurities from the precipitated polymer may not be achieved. There are a few applications for which soluble polymers are ideally suited; perhaps the best example in a single step reaction is the use of N-chloro nylons as halogenating reagents.[10] The difference in solubility between the N-chloro nylons and the unsubstituted nylons is such that the spent reagent (nylon) precipitates out of solution as the reaction proceeds, greatly facilitating the processing of the reaction mixture.

Another potential problem with the use of linear polymers is the possibility of side reactions producing unwanted crosslinks during reaction. This would result in the formation of a gel which may be very difficult to process. In contrast, crosslinked polymers, being insoluble in all solvents, offer the greatest ease of processing as they can be prepared in the form of spherical beads which do not coalesce when placed in a suspending solvent and can be separated from low molecular weight contaminants by simple filtration and washing with various solvents. Yet, insolubility does not mean lack of reactivity. In appropriate solvents, polymer beads with low degrees of crosslinking swell extensively, exposing their inner reactive groups to the soluble reagents. Such swollen beads are highly solvated and react much as if they were in solution. Similarly, more highly crosslinked resins may be prepared with very porous structures which allow solvents and reagents to penetrate the inside of the beads. In both cases, reactions can reasonably be expected to proceed fairly homogeneously throughout the beads, although factors such as rate of diffusion and pore size may restrict the reactions, especially in the case of larger substrates which may only be able to react at some of the more accessible sites located on the surface of the beads or within the larger pores.

2.1.2 *Crosslinked polymers: gels* vs *macroporous*. Crosslinked polymers exhibit considerable differences in properties depending on the degree of crosslinking and the method of preparation. Although numerous variations exist, the two types of crosslinked polymer beads which are most frequently encountered are gel and macroporous resins.

Gel polymers are generally prepared by suspension polymerization using a vinyl monomer suspended in water in the presence of low amounts of a crosslinking agent (typically 0.5–2%). Using this technique the product is obtained in the form of spherical beads which are easily handled and in which the crosslinking sites are essentially randomly distributed.

The pore size in a gel polymer is inversely related to the amount of crosslinking agent used in its preparation; the lower the amount, the larger the pore size. In the dry state the pores of a gel resin are collapsed but on the addition of a good "solvent", extensive solvation of the polymer chains causes the beads to swell extensively and results in the reappearance of pores. It should be emphasized here that the polymer chains are very mobile and the boundaries of the pores are not well defined. However as the degree of crosslinking is increased, the mobility of the polymer chains is reduced.[11a]

When compared with linear polymers, gel polymers are usually found to be slightly less reactive as reactions will be limited by diffusion of the reagent within the resin pores. The reaction yields can be affected by the degree of crosslinking, with lower yields observed for highly crosslinked resins.[11b] These facts would suggest that resins with very low degrees of crosslinking would be the most suitable, as increased swelling would result in higher accessibility through enhanced diffusion properties. However, other problems are encountered when working with very lightly crosslinked resins; if the crosslinking density is very low, the gels will become difficult to handle and may, under some conditions, be degraded to produce soluble linear fragments.

Macroreticular or macroporous resins[12] are also prepared by suspension polymerization, using higher amounts of the crosslinking agent and a solvent. This results in the formation of tiny, highly crosslinked solid particles of polymer which are surrounded by solvent droplets containing some dissolved monomer and crosslinking agent. As the reaction proceeds, the particles grow and incorporate some monomer-depleted solvent droplets in what will become the pores of the final resin beads. Mechanical stability about the pores is obtained through extensive crosslinking. When the solvent is removed once the polymerization has been completed, the pores may collapse partially but this collapsing is reversible and if the polymer is placed again in a good "solvent" the initial macroporous structure is restored.

The main advantage of macroporous resins is their large interior surface area within large pores which allows easy access of the reagents. This large surface area is essential for reactivity as the highly crosslinked beads do not swell appreciably and reactions are carried out on what essentially amounts to a monolayer. This description of macroporous resins is, of course, vastly simplified as the density of crosslinks is far from being uniform throughout the polymer beads and the beads may actually contain a hard, fairly unreactive core of low porosity. Since the reactivity of macroporous resins is not a function of swelling, reactions can often be carried out in a variety of solvents without appreciable changes in reaction rates. This does not mean that reactions of gel polymers cannot also proceed in non-swelling media; it has been shown recently[13] that a very large proportion of the functional groups in a 1 % or 2 % crosslinked gel polymer can be reached even in a non-swelling solvent such as ethanol. However, such a reaction is extremely slow as diffusion within the beads is hindered.

Another advantage of macroporous resins is their dimensional stability which makes them ideally suited for column applications where better solvent flow rates can be achieved than would be the case with gel polymers. Disadvantages may include a lower reactivity in numerous instances, lower capacity, and poor mechanical stability of the beads which tend to break up when handled repeatedly, with formation of fine particles which are extremely difficult to work with. In addition, static electricity often makes the handling of dry beads a difficult and frustrating operation.

2.2 *Preparation of the functional polymers*

Although two approaches exist for the preparation of functional polymers, namely the polymerization or copolymerization of monomers which carry the desired functionality, and the chemical modification of pre-formed polymers, it is mainly the second approach which has been used in the preparation of polymeric reagents or protecting groups. At first glance, the chemical modification approach seems to be simple and straightforward and every would-be solid-phase chemist rightfully expects a polymer containing aromatic rings to be easily modified by an electrophilic aromatic substitution reaction. Obviously this is so, but two major differences exist between reactions carried out on small molecules and reactions on insoluble polymers. The first difference is one of accessibility and reactivity; access to the various reactive sites may be limited and may rest heavily on the proper choice of a swelling or suspending solvent. The reactivity of the various sites can also be expected to be lower than would be the case with low molecular weight soluble species. Thus, more drastic reaction conditions may be required to reach a satisfactory conversion. The second difference is one of purification of the product after modification; while low molecular weight materials can be purified after their reactions by crystallization, distillation, chromotography, etc. crosslinked polymers cannot be purified at all. Since few reactions are either quantitative or free from side-reactions, the final polymer is often one in which a large proportion of the functional groups have been modified but which also contains some unchanged functionalities and the "impurities" resulting from side-reactions. Obviously, the amount of such "impurities" will depend on the specific reactions which are carried out on a given polymer. In some cases very few impurities may be present or the side reactions which do occur may be of such nature that the presence of impurities on the polymer will have no noticeable effect on its end-use. Anyone contemplating the chemical modification of a polymer should, however, keep these potential problems in mind. A critical examination of the fast-growing literature in the field of polymer-supported species suggests that in a number of cases the poor performance of a functional polymer in a given application is not really due to what may be described as "special interactions" or "lack of reactivity" but to a poor choice of reaction conditions, or even more frequently, to a poor preparation of the functional polymer. It is extremely difficult to carry out good chemistry with bad polymer supports.

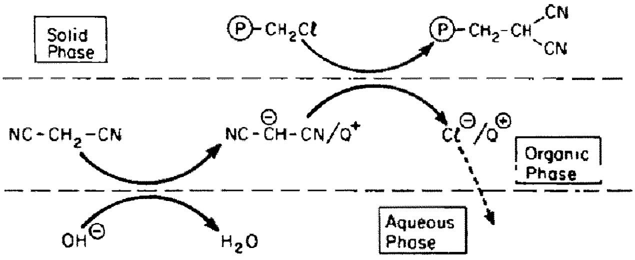
2.2.1 *Chemical modification of polystyrene.* Most of the work involving functional polymers has been carried out on crosslinked polystyrene resins. This choice is by no means coincidental as polystyrene meets many of the requirements of a solid support, a fact which was recognized very early by Merrifield in his pioneering work on the solid phase synthesis of polypeptides.[1] The following are the main advantages of polystyrene resins:

Very pure polystyrene resins in bead form with good mechanical stability and well defined physical characteristics are available commercially.

The aliphatic backbone of the polymer is unreactive and thus the polymer is not overly susceptible to degradative chain scission.

The aromatic rings are very reactive and can be functionalized easily,[14] for example by electrophilic aromatic substitution.

A survey of the literature shows that three intermediates are almost always used in the preparation of new polymeric supports or reagents; these are chloromethylated polystyrene and ring-brominated or ring-lithiated polystyrene. The former resin, often referred to as Merrifield's resin, has been used extensively both as a support, for example in peptide synthesis,[1] and as a precursor to numerous other functional polymers. Its versatility is due to the ease with which its chlorine atoms can be replaced in nucleophilic substitutions. A large number of such reactions have been reviewed earlier[14] while the scope of the reaction has been enlarged recently through the use of phase transfer catalysis[15,16] to afford several otherwise difficultly accessible resins. For example the reaction of malononitrile with chloromethylated polystyrene proceeds smoothly under phase transfer conditions with little side reaction. (Scheme 3.)[15]



Scheme 3.

The fact that such phase transfer reactions involving three distinct phases proceed with relative ease is a further indication of the reactivity of swollen resin beads. Multiphase systems involving one or more polymer phases have been used in ion-exchange technology and, more recently, in elegant mechanistic studies reported earlier in this journal.[17]

Ring-brominated polystyrene is also a very versatile intermediate in the preparation of numerous other polystyrene resins. It is of special importance in the preparation of lithiated or diphenylphosphinated resins. The bromination of polystyrene is best carried out[18] using bromine/carbon tetrachloride in the presence of a *catalytic* amount of a thallium(III) salt. The degree of functionalization can be controlled accurately by regulating the amount of bromine available for the reaction.[18] Satisfactory results can also be obtained with ferric chloride[19] or other catalysts[14] and in all cases the bromination seems to occur exclusively in the *para* position.

Lithiation[18] of the aromatic rings of polystyrene can be achieved in one of two ways:

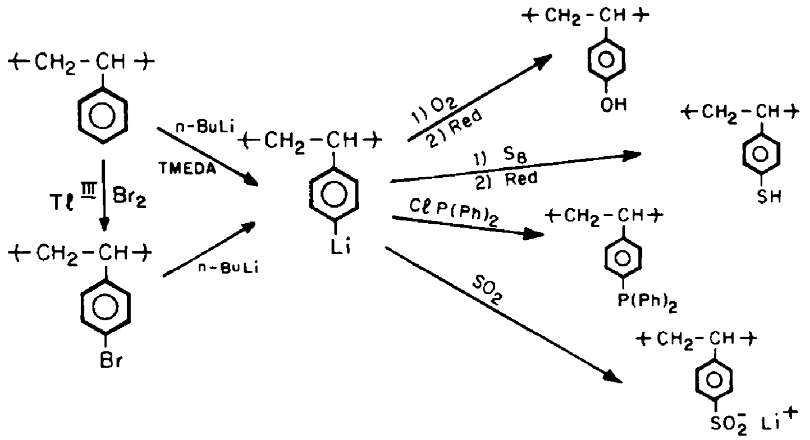
directly, using n-butyllithium--TMEDA complex in cyclohexane;

indirectly, by bromination followed by reaction with n-butyl lithium in benzene.

The first procedure, developed by Chalk[20] for the lithiation of soluble polystyrene, was applied to the lithiation of crosslinked polystyrene by Leznoff and Fyles.[21] The reaction is best carried out in a non-polar solvent such as cyclohexane and results in the lithiation of up to 25 % of the aromatic rings in meta and para positions.[20,22,23] The second procedure,[18,24] although requiring an additional step, is advantageous when a good control of the degree and the position of lithiation is required and is also useful in cases where high loadings are required. Lithiated polystyrene is a useful intermediate in the preparation of numerous other functional polymers. For example, polymeric nucleophiles containing thiophenol or phenol reactive groups can be prepared easily by quenching a lithiated polystyrene resin with elemental sulfur[18,22] or oxygen[22] followed by reduction of the resulting polymer to remove polysulfide or peroxide bonds which may have formed (Scheme 4).[22] Similarly, quenching of the lithiated resin with chlorodiphenylphosphine or SO_2 affords products containing the useful resinodiphenylphosphine[35] or resinosulfinate[36] groups. All of these polymers are versatile intermediates in the preparation of a number of other functional resins.

2.2.2 *Chemical modification of other polymers.* Numerous attempts at using polymers other than polystyrene have been made. These have met with limited success for reasons such as lack of reactivity, degradation of the polymer chain or unsuitable physical properties of the finished polymer. For example, poly-(epichlorohydrin) can be modified by nucleophilic displacement under phase-transfer conditions[25] but the reaction is neither quantitative nor general.[26]

Other reactions on poly-(epichlorohydrin)[27] or poly[oxy(2,2-bis-chloromethyl)trimethylene] gave unsatisfactory results. With polyvinyl chloride an attempted phosphination involving lithium



Scheme 4.

diphenylphosphide[28] was accompanied by extensive breakdown of the carbon backbone. More satisfactory results were obtained[26] in reactions involving polyvinyl bromide and non-basic sulfur nucleophiles, although substitution was usually accompanied by some elimination if base was also present during the reaction. Manecke has successfully modified poly(vinyl alcohol) by reaction with polyfunctional acetals[29] but the low capacity of the polymers and their solubility properties make them only suitable for a very limited number of applications. Although these reactions have not produced very encouraging results, numerous potential supports have yet to be tested and some may prove to be very useful. For example, Daly has recently described[30] the chloromethylation of poly[oxy-2,6-dimethyl-1,4-phenylene], a reaction which yields a film-forming resin of high chemical reactivity.

2.2.3 *Polymerization of functional monomers.* An alternate route to reactive functional polymers is the polymerization or copolymerization of monomers which contain the desired functionality. For example, a chloromethyl polystyrene resin can be prepared by polymerization of vinyl benzyl chloride.[31] The number of reactive ends in the polymer chain can be reduced by addition of a co-monomer and insoluble resins are obtained in the presence of small amounts of a crosslinking difunctional co-monomer. However, problems may arise due to differences in reactivities of the various monomers. This approach has been used very successfully in the preparation of polymers containing pyridine residues[32] and benzaldehyde[33] or phosphine[34,35] units.

2.2.4 *Functionalization of inorganic polymers.* Some of the most promising new supports for polymer supported chemistry are based on porous inorganic oxides such as silica.[37] These can be modified readily through reactions involving the silanol groups at the surface of the silica. Several functionalized inorganic supports based on silica or porous glass have been prepared.[37,38] The main advantages expected from the use of these supports are higher reaction rates, dimensional stability and reduced interaction of reactive sites. However a major drawback in all but catalytic applications is the extremely low capacity of most of the supports prepared to date. Perhaps the highest capacity on a glass-based support was obtained by Anderson and Holick[39] in their approach to the solid phase synthesis of oligosaccharides.

2.3 *Characterization of the polymers and monitoring of polymer-supported reactions*

This is likely the area of polymer-supported chemistry which is most in need of improvement, especially when dealing with insoluble polymers for which the means of analysis are relatively limited. The techniques which are used most often are the following:[40]

Elemental analysis
Gravimetric monitoring of reactions
Titration of reactive functionalities (acid, base, phenol,...)
Infrared spectroscopy[43,89]
Raman spectroscopy
Thermal analysis (DSC, TGA)
Electron microprobe spectrometry[41]
ESCA[42]

Particularly attractive for the monitoring of polymer supported reactions is the use of difference infrared spectroscopy[43] which highlights only the spectral changes observed in a given reaction. Radiolabelling is also a powerful tool which has been used very elegantly by Crowley and Rapoport.[6,43,44] Magic angle NMR spectroscopy can be used to analyze solid polymer samples[45] but, at the time of writing, the instrumentation is not widely accessible. It is expected that this technique will contribute greatly to the characterization of insoluble polymers and the monitoring of polymer-supported reactions.

3. ISOLATION OF THE REACTIVE SITES

An extremely attractive potential feature of polymer supported species would be the ability of the polymer to effectively isolate the reactive sites from one another during reaction. This would be a convenient alternative to the high dilution conditions which are used in solution to prevent interaction of reactive ends. Unfortunately however, the polymer chains of lightly crosslinked resins have a high mobility and, as a result, reactions involving interactions of sites are found to occur quite frequently and to various extents with polymer supported species. A large number of elegant studies have demonstrated the existence of such site interactions[46] and attempted to quantify them[44,46,47] and increase[48] or reduce[47] their frequency of occurrence. Three recent reviews[6,7,49] cover much of the literature on site–site interactions in polymer supported species.

In general, it can be said that while true site isolation is extremely difficult to achieve on a lightly crosslinked polymer, interactions of reactive sites can be reduced and even almost eliminated through an appropriate choice of polymer morphology, degree of functionalization, reactions, and reaction conditions. Another critically important factor is the rate of intrapolymeric reactions. This rate is not limited primarily by diffusion as would be the case in classical systems, but by the restricted conformational motions of the crosslinked polymer chains. Some very elegant measurements of the rates of intrapolymeric reactions have been made.[50] For example, Mazur and Jayalekshmy[50a,b] have prepared a polymer-bound o-benzyne on a crosslinked polystyrene matrix and found that its lifetime was several orders of magnitude larger than that of a comparable aryne which, in solution, dimerizes at an extremely rapid rate. Semi quantitative measurements made by Mazur and Jayalekshmy indicate that, in their experiment, the encounter frequency of reactive substituents in a suspension containing approximately 10^{-2} mole of resin-bound active species per litre of solvent is equivalent to that of a 10^{-11} M solution of similar but non-polymer-bound species. Although these results will vary with reaction conditions, they confirm that intrapolymeric reactions are relatively slow. Thus, it can be expected that if a reaction involving a polymer-bound reactant and a species in solution is much faster than the motions of the polymer chains which would bring two polymer-bound sites in close proximity, *apparent* site isolation can be achieved in a way which would not normally be obtained in solution.

In general, when designing a synthesis which involves a polymer-supported moiety, the following factors which have a direct influence on the extent of site–site interactions should be considered.

—Degree of crosslinking of the support: in general, a higher degree of crosslinking means lower mobility of the polymer chains[11a] and lower interactions of the site.

—Degree of functionalization of the polymer: in general low degrees of functionalization result in fewer site interactions.[51]

—Nature of the solvent:[52] swelling affects the mobility of the polymer chains; the polarity of the solvent may also have an influence.

—Reaction conditions[47] and relative concentration of the reactants.

—Rate of the reaction being contemplated *vs* the rate of movement of the polymer chains.[50]

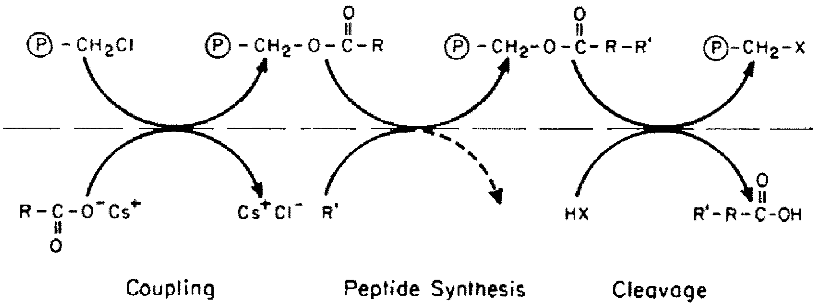
—The presence of charges on the polymer:[53] these may render the support more rigid and thus may decrease the frequency of intersite reactions.

—Other factors which will vary from reaction to reaction.

4. SELECTED APPLICATIONS OF POLYMERS AS PROTECTING GROUPS

4.1 *Carboxylic acids and derivatives*

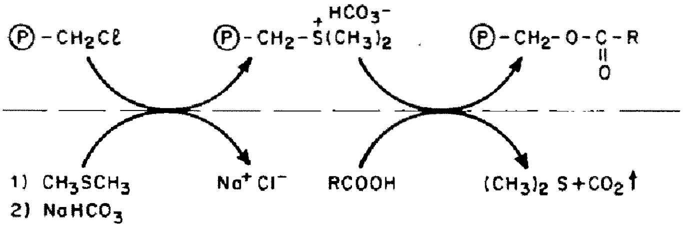
Due to its importance in the solid phase peptide synthesis,[1,2] the protection of carboxyl groups through attachment to functional polymers has received more attention than any other functional group. Indeed, the first polymer support described by Merrifield in 1963, chloromethylated polystyrene, is still used extensively in polymer-supported reactions. In Merrifield's original scheme, the α-carboxyl group of the carboxyl terminal amino-acid was attached to chloromethylated polystyrene to yield a resino-benzyl ester. This type of linkage was selected for two main reasons: the coupling reaction is a simple, high yield nucleophilic displacement by carboxylate, and the resino-benzyl ester is resistant to the conditions of the sequential synthesis while still being susceptible to cleavage once the synthesis is complete (Scheme 5).



Scheme 5.

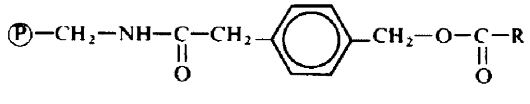
The coupling reaction is best carried out using cesium[54] or tetramethylammonium[55] salts of carboxylic acids although a number of other satisfactory procedures have also been developed.[2]

An interesting variation of this procedure is the conversion of chloromethyl sites into dimethyl resinomethyl sulfonium bicarbonate sites from which dimethyl sulfide can be displaced by reaction with a carboxylic acid to yield a resinobenzyl ester[68] (Scheme 6).



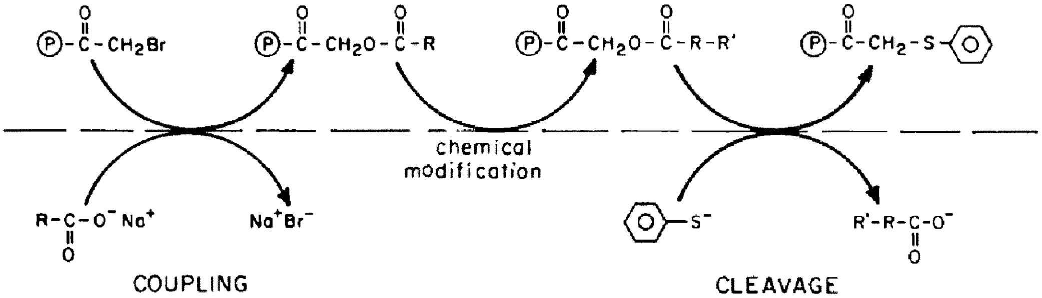
Scheme 6.

Since the success of a solid phase synthesis usually depends, in part, on the ability to carry out reactions in the solid phase without affecting the polymer to substrate bond and on the ability to cleave this bond selectively once the reaction sequence is complete, several seemingly minor, yet important, modifications of the standard chloromethylated polystyrene have been studied. Thus, an important step in solid phase peptide synthesis is the removal of the α-amino acid protecting group (t-butyloxycarbonyl) by treatment with acid. This reaction is accompanied by approximately 1% cleavage of the resino-benzyl ester which reduces the overall yield of final product and may cause side reactions at later stages of the synthesis. To improve the resistance of the resino-benzyl ester link to acids and avoid this premature cleavage, chloromethylated resins have been subjected to aromatic bromination or nitration.[1] More recently, Merrifield *et al.*[56] have developed a new resin containing an electron withdrawing acetamidomethyl spacer group shown below, which confers on the resino-benzyl ester group a 100-fold greater stability toward acidolysis.



In contrast, introduction of an electron donating spacer increases the acid liability of the resino-benzyl ester group.[57]

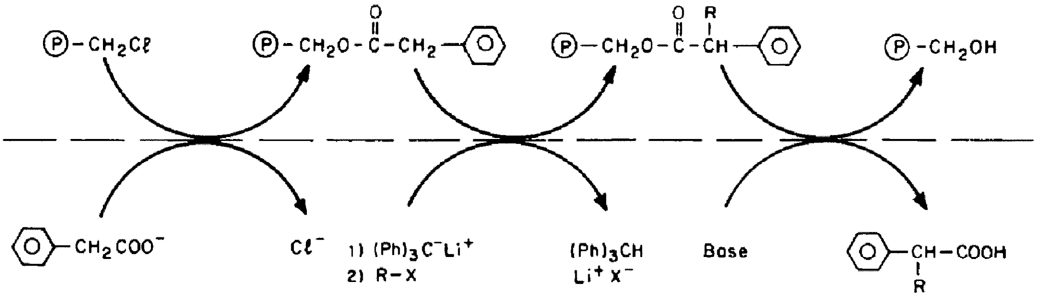
Another somewhat similar carboxyl protecting group which has also been used in solid phase peptide synthesis can be prepared by Friedel–Crafts acylation of polystyrene with bromoacetyl chloride. The bromoacetyl resin can be esterified readily by nucleophilic displacement of bromide using a carboxylate.[58] Once a synthesis using this support is complete, the resino-phenacyl ester linkage can be cleaved with a variety of nucleophilic reagents including sodium thiophenoxide, ammonia, etc. (Scheme 7).



Scheme 7.

Numerous other, very imaginative schemes have been used in the protection of carboxylic acid ends for the solid phase synthesis of polypeptides; these are reviewed more thoroughly elsewhere.[2,59]

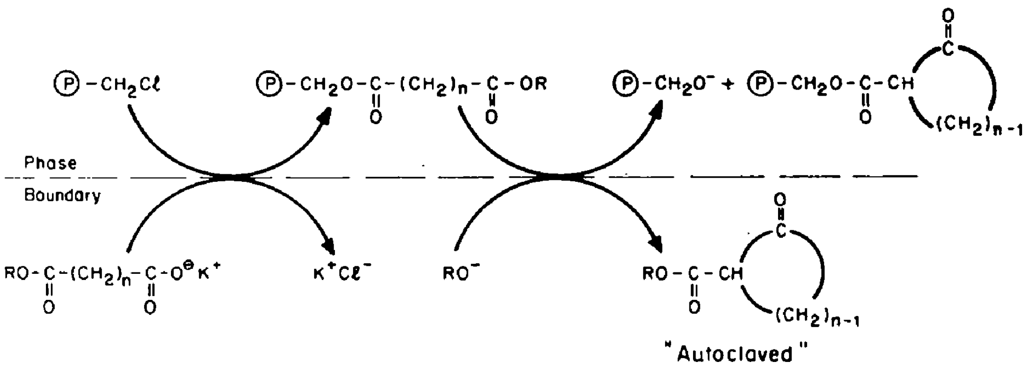
In non-peptide chemistry, several of the first applications of chloromethylated polystyrene were designed to take advantage of the expected ability of the polymer to isolate reactive sites. For example, while the monoacylation of esters in solution is always accompanied by intermolecular Claisen condensations and polyacylations, Patchornik *et al.*[60] were able to find conditions under which polymer-bound esters could be monoacylated. Using polymers of low capacity (0.1–0.2 mmole/g) at low temperature, with rapid quenching of the polymer-bound enolates, intersite Claisen condensations or polyacylations were drastically reduced or eliminated (Scheme 8). Similarly, a single product could be obtained in alkylation or carbonation reactions under similar reaction conditions. A different support was also used successfully in the monoalkylation of polymer-bound esters by Camps *et al.*[61]



Scheme 8.

An obvious drawback in this approach is that since apparent site isolation can only be obtained with polymers of low capacity, the synthesis is ill-suited for applications on a practical scale due to the large amounts of polymer which would be required. No attempts at regenerating the starting polymers have been made.

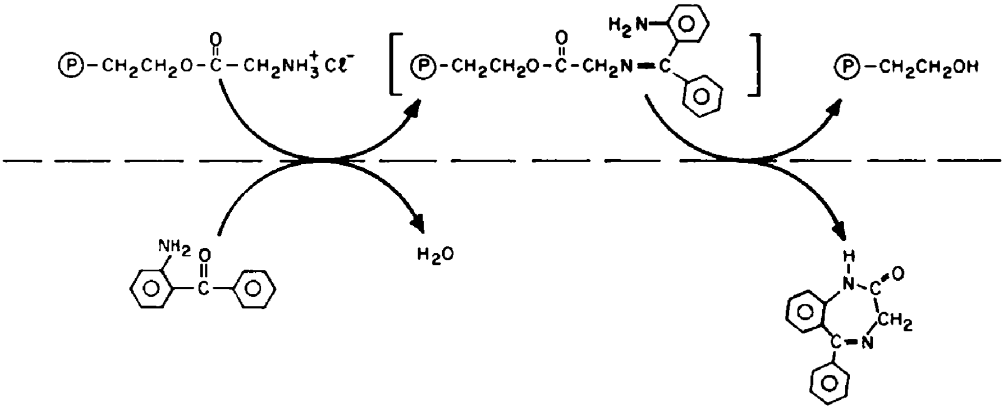
A second study, also designed to take advantage of the site isolation which was foreseen for polymer supported reactions, was the intramolecular Dieckmann cyclization of polymer-bound diesters. This reaction was expected to provide a good route to medium and large size cyclic condensation products. Diesters in which one ester alkoxy group was attached to a crosslinked polymer were prepared from potassium salts of alkanedioic monoesters and chloromethyl polystyrene.[43,44] Dieckmann cyclization in the presence of alkoxide occurred in both directions yielding a polymer-bound β-keto ester and an "autocleaved" condensation product. This reaction was very successful for the



Scheme 9.

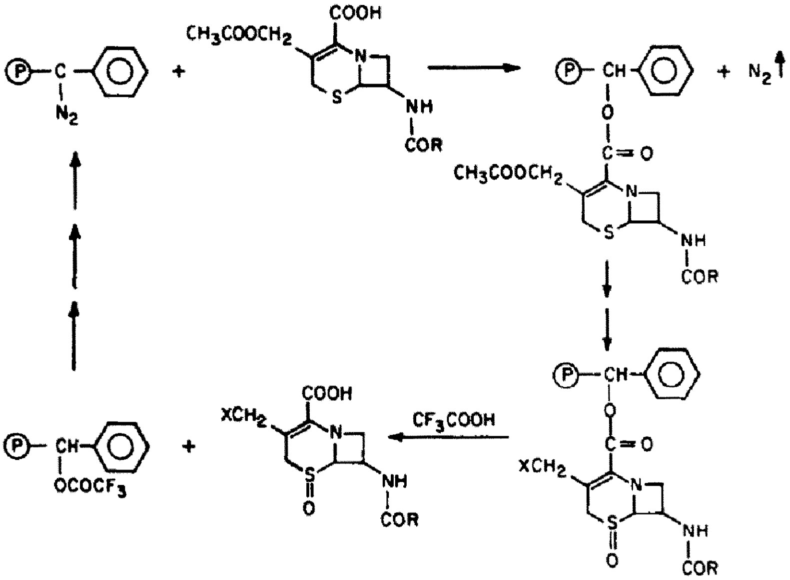
preparation of substituted cyclohexanones (Scheme 9) but only produced very low yields of cyclononanone products. Crowley and Rapoport attributed this result to the fact that the desired cyclization to yield the cyclononanone product is much slower than intraresin site–site interactions. This study was one of the first to point out that site–site interactions were indeed very common in polymer-supported reactions and that their influence would be felt more strongly in cases involving slow reactions.

A third synthetic scheme[63] designed to take advantage of the elusive site isolation phenomenon turned out to be quite successful due to the ease with which the key step in the reaction sequence takes place. The aim of the synthesis was to prepare a benzodiazepinone from Boc-glycine using a polymer to protect the carboxyl end of the amino acid. The polymer chosen for this synthesis was a cross-linked poly (p-2-hydroxyethyl styrene) and loading of the amino acid was achieved through the use of N,N′-carbonyldiimidazole as coupling agent.[63] After removal of the amino protecting group, condensation with 2-aminobenzophenone gave the desired benzodiazepinone in a single step with a yield of 60%. The intermediate condensation product shown in Scheme 10 could not actually be isolated. The fact that products resulting from intermolecular dimerizations were not produced in significant amounts confirms that the intramolecular dimerization of the intermediate must be a very fast reaction and this is the key to the success of the process. The polymer support used in this reaction sequence was regenerated in the final step and could be reused in subsequent reactions.



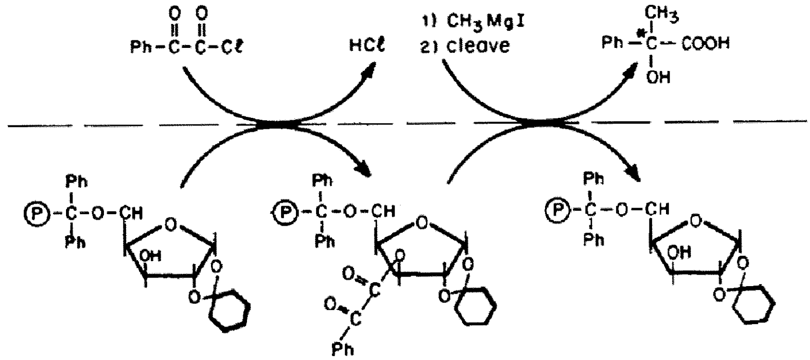
Scheme 10.

A very effective polymeric protecting group, better suited for synthetic applications on a practical laboratory scale, is a diazomethylene polymer used by Chapman and Walker[64] for the protection of the free carboxylic acid end-groups of some penicillins and cephalosporins. The polymer was prepared easily by benzoylation of a polystyrene resin followed by reaction with excess hydrazine and oxidation of the hydrazone polymer with a peracid in the presence of iodine. Both the hydrazone formation and the subsequent oxidation were almost quantitative and a reactive, high capacity (approx. 3 mmoles/g) polymer was obtained. Both the diazomethylene and its hydrazone precursor could be used to protect the free carboxylic acid group of penicillin G-1(S)-oxide. The polymer-bound penicillin could be efficiently transformed into the corresponding cephalosporin by a simple thermal rearrangement in the solid phase. In a similar reaction, a cephalosporin was attached to the polymer and was then subjected to a series of transformations involving reactions such as oxidations and nucleophilic substitutions (Scheme 11). After cleavage with trifluoroacetic acid the polymer, recovered as a trifluoroacetate, could be regenerated. However it is unlikely that the regeneration procedure, which required more than four steps, would be of great practical value. The diazomethylene polymer is nonetheless notable for its high reactivity and for the high yields of coupling it can deliver in its reactions with carboxylic acids.



Scheme 11.

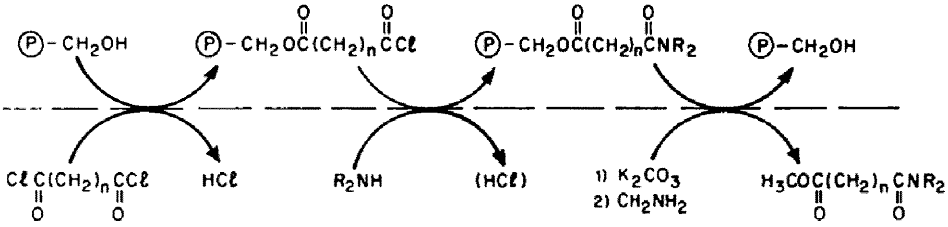
The concept of using polymers containing chiral groups in asymmetric synthesis is a particularly attractive one as the polymer can serve the dual purpose of support, with the resulting enhanced purification benefit, and of asymmetric "inducer" in the modification reaction of the achiral polymer-bound substrate. An interesting feature of such a chiral polymer is that, if properly designed, its chiral centers should remain unaffected by the asymmetric synthesis and thus the polymer should be easily recycled. Kawana and Emoto[65] have applied this concept to the preparation of optically active atrolactic acid from phenylglyoxyl chloride (Scheme 12). The support they selected was a polymer-bound xylofuranose derivative in which all but one of the hydroxyls were substituted. The free



Scheme 12.

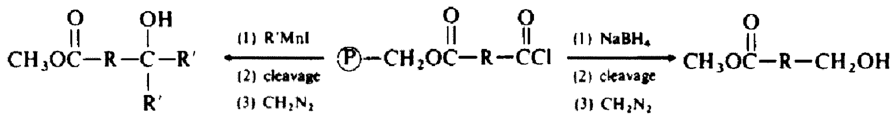
hydroxyl was used to esterify phenylglyoxyl chloride and asymmetric introduction of a methyl group to the ketone carbonyl of the polymer-bound keto ester was accomplished by a Grignard reaction. After cleavage from the polymer, the desired atrolactic acid was obtained in higher chemical and optical yield than was possible with a similar reaction performed in solution. The recovered polymer could be used again but was slightly less effective in a second reaction cycle. It is likely that this slight degradation of the polymer would not occur if the substituents on the sugar moiety, including the polymer, were less sensitive to hydrolysis.

Another area in which polymeric protecting groups can make a useful contribution is the monoprotection of symmetrical difunctional molecules. Most of the work in this area has been done by Leznoff *et al.*[7] Obviously the usefulness of the method rests on the premise that the symmetrical difunctional molecules will become attached to the polymer through one end only. As was discussed earlier in Section 3 of this report, true site isolation is unlikely to be obtained with most functional polymers; yet apparent site isolation, which would result in single attachment of the bifunctional molecule, can be obtained using various techniques if a fast reaction is involved. An excellent illustration of this principle is afforded by Leznoff's approach to the monofunctionalization of symmetrical diacid chlorides[66] using a simple hydroxymethyl polystyrene resin. After attachment of a symmetrical diacid chloride (Scheme 13) and amidation of the remaining free acyl chloride in the solid phase, base cleavage followed by esterification afforded a monoester monoamide in high yield. No diesters, which might have resulted from initial reaction of the diacid chloride with two sites of the polymer, were detected indicating that apparent site isolation on the polymer matrix had been achieved.



Scheme 13.

Other applications[66] of the polymer-bound acid chloride included its elaboration into the monoester-monoalcohol by reduction on the solid phase followed by cleavage and esterification, or into a tertiary hydroxyester by reaction with an organomanganese iodide as shown below.

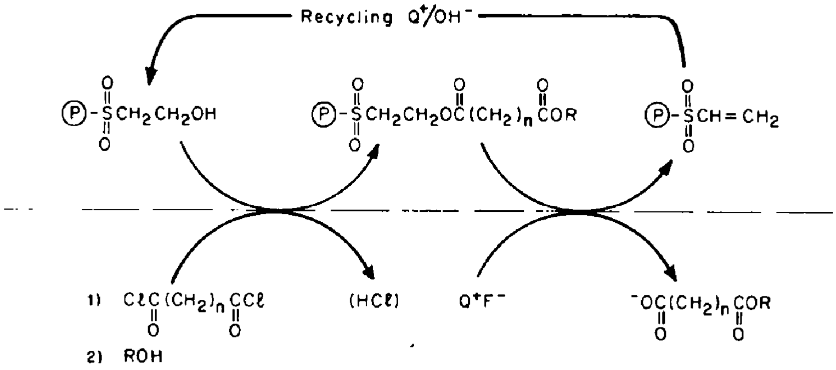


$$\mathrm{CH_3O\overset{\overset{O}{\|}}{C}-R-\underset{\underset{R'}{|}}{\overset{\overset{OH}{|}}{C}}-R'} \xleftarrow[\substack{(2)\ \text{cleavage}\\ (3)\ \mathrm{CH_2N_2}}]{(1)\ \mathrm{R'MnI}} Ⓟ\mathrm{-CH_2O\overset{\overset{O}{\|}}{C}-R-\overset{\overset{O}{\|}}{C}Cl} \xrightarrow[\substack{(2)\ \text{cleavage}\\ (3)\ \mathrm{CH_2N_2}}]{(1)\ \mathrm{NaBH_4}} \mathrm{CH_3O\overset{\overset{O}{\|}}{C}-R-CH_2OH}$$

Perhaps the most obvious drawback of this approach is that only low loadings of diacid chlorides on the polymer (0.4–0.6 mmole/g) were used, which makes the method somewhat impractical to prepare larger amounts of the unsymmetrical derivatives. Although higher loadings might have led to site interactions, it would have been interesting to see how much apparent site isolation would have been retained using polymers of higher capacities, perhaps in the range of 2–3 mmoles/g.

A somewhat similar approach was used by Fréchet and Brazeau[67] to prepare the monoester or monoamide derivative of a symmetrical diacid chloride using a resin containing sulfonyl ethanol functionalities (Scheme 14).

The main interest of this approach does not lie in its practical applications since once again the polymer has a low capacity (< 1 mmole/g); however, the polymer-bound diester has two ester groups of different reactivity. Cleavage of the ester link to the polymer can be achieved by β-elimination under conditions which do not affect the second ester group. Current efforts on this approach include the development of a more reactive, high capacity support.



Scheme 14.

4.2 *Hydroxyls*

Next to the use of polymers in the protection of carboxylic acids with its implications in the peptide field, the development of polymeric protecting groups for the protection of hydroxyls has received the most attention. Applications are found mainly in carbohydrate chemistry and in the synthesis of insect sex attractants. Early work on sugar derivatives was aimed at the solid phase synthesis of oligosaccharides[39,40,68–70] using approaches in which the anomeric centers of various sugar derivatives were first activated by formation of glycosyl halides, then attached to a polymer through a simple glycosylation reaction. The polymers used incorporated features which allowed their cleavage from the completed oligosaccharide under reaction conditions which did not affect the glycosidic linkages between sugar units. For example, these included a resino-allyl alcohol support which could be cleaved by ozonolysis, or a light sensitive resino-orthonitrobenzyl alcohol support. These polymers were designed specifically for oligosaccharide syntheses and have not been used in other applications. Since this type of solid phase synthesis is still plagued by many unresolved problems and is unlikely to be the object of much research in the near future, it will not be discussed any further in this report; a recent review is available elsewhere.[40]

Other, less ambitious, applications of polymer protecting groups in carbohydrate chemistry have centered on short reaction sequences in which the enhanced purification advantage and other useful features of polymer supports could be exploited to their maximum. Typical applications involve the use of a polymeric trityl chloride as a protecting group for the C-6 primary OH group of various sugars[71] in simple reactions or in somewhat more complex schemes involving the synthesis of oligonucleotides. Polymers with high capacities can be used in these reactions and the polymeric by-product obtained after cleavage of the sugar can be regenerated easily and repeatedly without loss of activity. Another simple polymer containing resino-benzaldehyde units was also useful for the protection of diol groupings in various carbohydrates[9] (Scheme 2 in part 1).

A much more interesting and versatile diol protecting group, polystyrylboronic acid, has been studied extensively by Fréchet *et al.*[72–75] The polymer is obtained easily by chemical modification of polystyrene via the following sequence: bromination, lithiation, reaction with trimethyl borate, and hydrolysis.[18] In most applications it is desirable to use a high capacity polymer (> 2–3 mequiv/g). The most interesting features of this polymeric protecting group are the following:

—Coupling of a diol to the polymer to form a boronate can be accomplished in high yield under extremely mild conditions, typically, azeotropic removal of water.

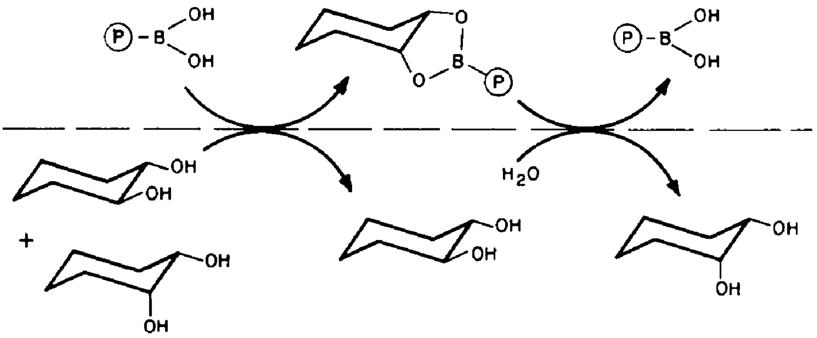
—The boronate esters are stable to a variety of reaction conditions such as those required in the preparation of esters and trityl or tetrahydropyranyl ethers.

—Cleavage of the boronate can be carried out under extremely mild conditions in neutral medium by addition of water or a low molecular weight alcohol.

—The polymer is extremely *selective* in its reactions with cyclic diols such as cyclohexanediols or carbohydrate derivatives.

—The polymer is regenerated in the cleavage step and can be reused repeatedly without requiring a regeneration step and without loss of activity.

The selectivity of the polystyrylboronic acid is illustrated by its reaction with a 1:1 mixture of *cis*- and *trans*- 1,2-cyclohexanediols.[72] A boronate is formed exclusively with the *cis*-diol which can be removed later from the polymer by addition of a moist solvent or of a solvent containing some

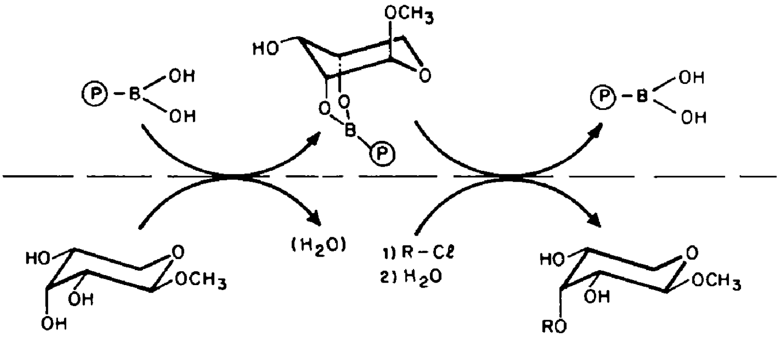


Scheme 15.

methanol (Scheme 15). Similar results have been obtained in column separations of *cis*- and *trans*- 1,3-cyclohexanediols and even 1,4-cyclohexanediols over a polystyrylboronic acid resin. In the latter case the *cis*-diol is not bound firmly but is retarded enough to allow its separation from the *trans*-diol which passes through the column unhindered. Other chromatographic applications of the resin have been reported.[73]

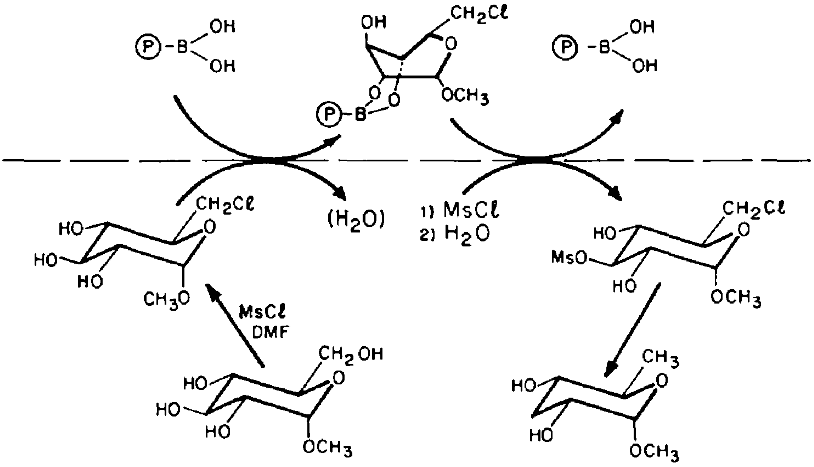
This marked preference for *cis*-diols can be fully exploited in the selective protection of carbohydrate derivatives. Studies with a variety of simple sugars possessing different stereochemical arrangements of their OH groups[74] have shown that in all cases the more stable boronate was formed. For example, the reaction of polystyrylboronic acid with methyl β-D-ribopyranoside could conceivably lead to three different boronates: two 5-membered ring boronates by reaction with the OH's in positions 2 and 3 or 3 and 4, and a 6-membered ring boronate involving the OH's in positions 2 and 4.

Only the 6-membered ring boronate was obtained and thus the polymer is extremely efficient in the high yield selective protection of this 2,4-diol (Scheme 16). It should be noted here that a classical diol protecting group such as the isopropylidene group would not be suitable for this reaction as its use would result in ring contraction to a furanose form and would lead to the formation of several products.[75]



Scheme 16.

Another interesting application of polystyrylboronic acid for the preparation of otherwise inaccessible protected diols such as the *cis*-2,4 diol grouping of D-glucopyranosides has led to a rapid method of preparation of several deoxy-sugars of biological importance.[67] Thus, methyl 3,6-dideoxy-α-D-ribo-hexopyranoside and its β anomer can be prepared from the corresponding methyl D-glucopyranosides in excellent yields with isolation of only one intermediate (Scheme 17). The key step in this synthesis is the protection of the 2,4-diol grouping after halogenation of the C-6 primary OH. In fact, the polymer serves the dual purpose of a protecting group for the 2,4-diol and of a hook to "fish out" the sugar from the halogenation mixture. After mesylation of the remaining C-3 OH, the sugar is split off from the polymer. All of these steps can be carried out in excellent yield in one pot with sequential additions of reagents and filtrations but with no isolation of intermediates. The last step is

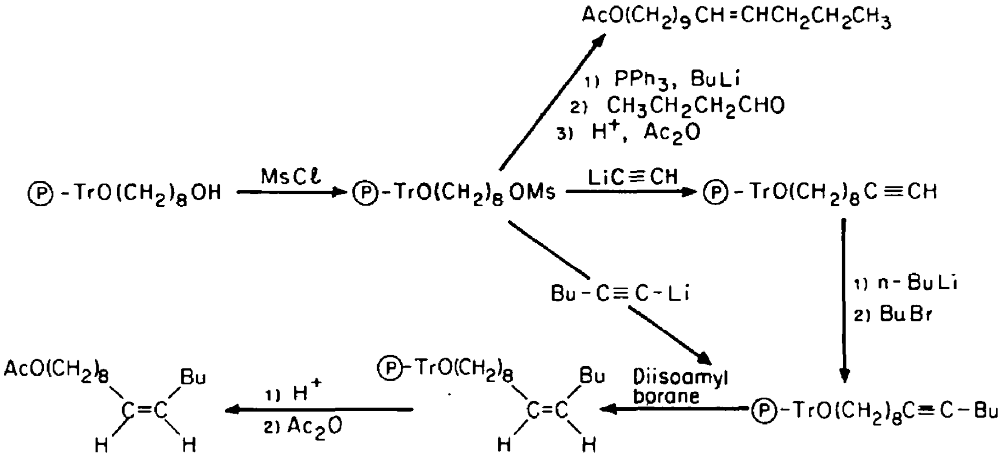


Scheme 17.

the removal of both the 3-O-mesyl and the 6-chloro substituents, a reaction which can be easily accomplished using one of several reagents, for example cyanoborohydride. Other applications of the polystyrylboronic acid as a diol protecting group include the preparation of selectively functionalized derivatives of prostaglandin intermediates[67] or of acyclic polyols.[76] Another very interesting use of a crosslinked resin containing styrylboronic acid units will be described in the last section of this report.

As was seen in the previous section, polymer protecting groups offer an attractive solution to the problem of the monoprotection of symmetrical difunctional molecules. Many of the early studies in this area were concerned with the monoprotection of diols; some approaches were very successful, others much less so. This type of application requires a careful selection of the polymer support and of reaction conditions to minimize site interactions which would lead to attachment of the diols to the polymer through both of their OH's. In addition, the polymer should have a capacity sufficiently high to allow syntheses on a practical scale. The first polymer to be described by Leznoff and Wong[77] was a polystyrene resin containing phenacetyl chloride units. It gave good results in the monoprotection of long chain aliphatic diols but suffered from a very low capacity and a lack of regenerability. A more useful polymeric protecting group which can serve the same purpose is the polymeric trityl chloride[71] which had been described earlier and had found use in the protection of the primary OH's of sugar derivatives. This polymer is particularly attractive due to its relatively high capacity ($\leqslant 2$ mmoles/g), high reactivity, and excellent regenerability. Although there are somewhat conflicting reports[78,79] on the extent of site interactions in simple reactions between this polymer and diols such as 1,4-butanediol, reactions involving this polymer usually gave products for which analysis indicated up to 31% double-binding[7] of the diol depending on reaction conditions. In fact an accurate evaluation of the extent of double-binding is not available but, in most applications, some free diol was released during cleavage of the modified substrate from the polymer. This may be due mainly to site interactions but also could arise because of incomplete reactions or side reactions on the solid phase or during cleavage. It is worthwhile noting that more highly crosslinked polymers in which the trityl chloride functionalities were located at crosslinks[79] provided apparently *complete* site isolation in their reactions with symmetrical diols.[79] This is likely due to the reduced conformational mobility of the reactive sites which favors apparent site isolation. Unfortunately however, the capacity of these polymers is too low (0.2–0.3 mmole/g) to be of practical value.

The most extensive and thorough study of the use of a polymeric protecting group to date is the preparation of insect sex attractants[80] using a polymeric trityl chloride as support. The key step in this type of synthesis is the binding of one extremity of a long chain diol to the polymer. This is followed by the chemical modification of the remaining alcohol functionality in the solid phase, taking advantage of the enhanced purification feature of polymer supported reactions. Leznoff, Fyles and Weatherston[80] have studied at least six different routes involving the polymer-protected diol; three of these are presented in Scheme 18. Particularly noteworthy in these reaction schemes is the vast array of reactions of different types which have been used and optimized on polymer supports.



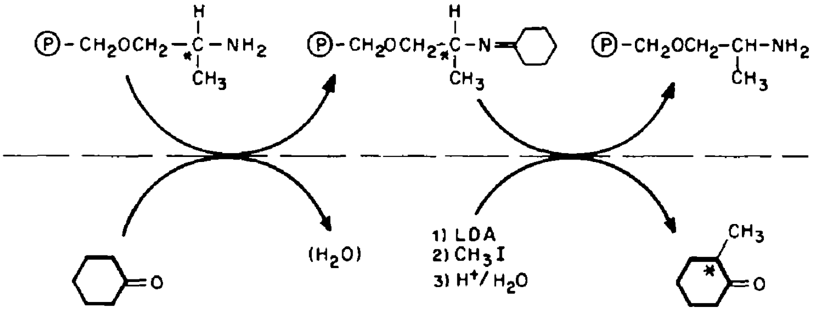
Scheme 18.

In addition to the purification advantage which is common to all solid phase syntheses, other specific advantages were apparent over conventional solution methods. For example, in the reverse-Wittig route[80] (Scheme 18) a high stereoselectivity was observed, resulting in a high proportion of the *cis*-isomer in the final product. In the alkyne route[80] (Scheme 18) the borane reduction was greatly facilitated and did not require an oxidation step, which in turn translated into a higher yield of product. This approach has been used to prepare gram quantities of insect sex attractants.[80] A recent review covering these and other solid phase syntheses is available.[7]

4.3 *Carbonyls*

Several polymers containing 1,2- or 1,3-diol functional groups have been prepared[81] and used in the protection of symmetrical dialdehydes. However it is unlikely that these polymers, in their present form, would find much application as they can only be used with aromatic or conjugated dialdehydes, have fairly low capacities of 0.2–0.4 mmole/g, and in most cases are non-recyclable.

A potentially much more interesting polymer containing a chiral primary alkoxy-amine was used successfully in the asymmetric synthesis of 2-alkylcyclohexanones.[87] The chiral functionalities were introduced by chemical modification of crosslinked chloromethyl polystyrene using the potassium salt of (*S*)-2-phthalimido-1-propanol in the presence of 18-crown-6, with hydrazinolysis of the resulting resino-phthalimido derivative. The asymmetric synthesis shown in Scheme 19 gave (*S*)-2-methylcyclohexanone in 95 % optical yield. Unfortunately the polymer could not be reused and this approach will only become worthwhile when fully recyclable polymers are available. This type of application is nevertheless very attractive and it is likely that much attention will be devoted to the use of chiral polymeric protecting groups in the next few years.

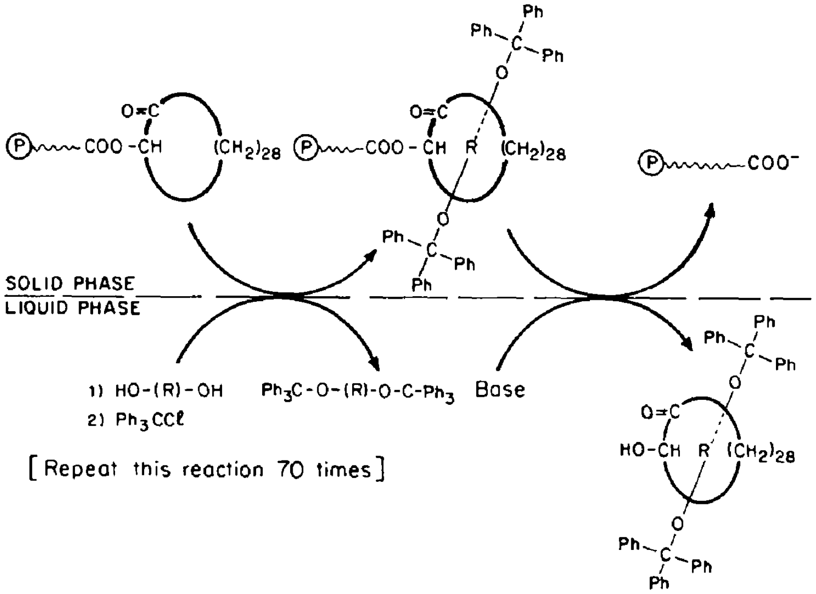


Scheme 19.

5. OTHER SELECTED APPLICATIONS OF POLYMER SUPPORTS

5.1 *Use of polymers to "extract" minor components from complex mixtures*

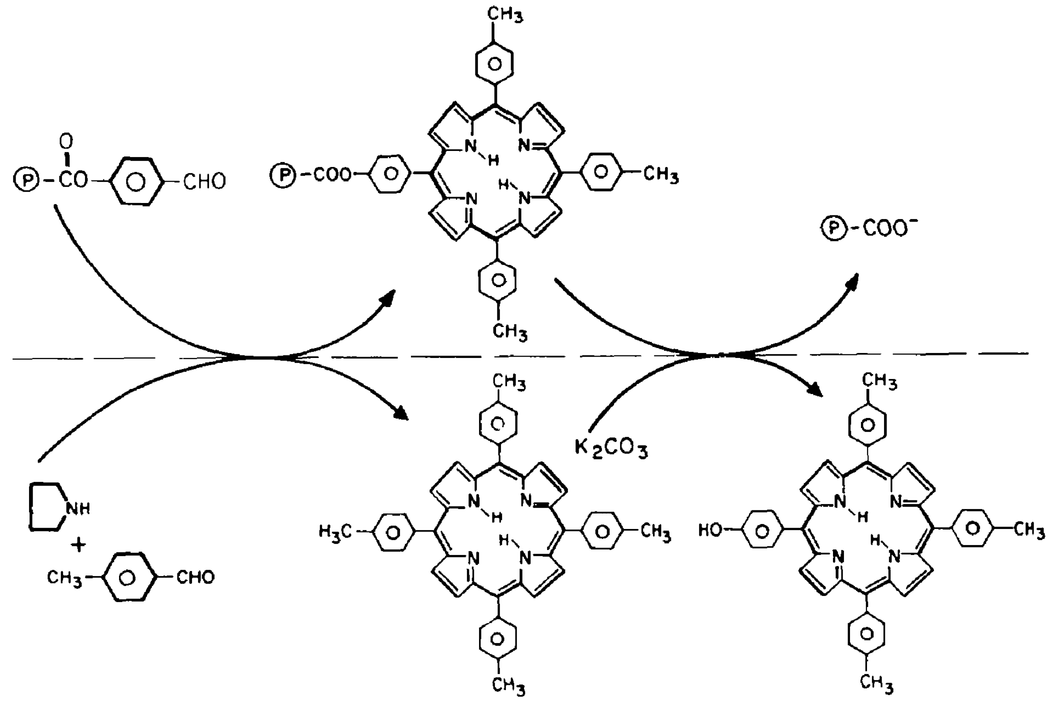
As was discussed earlier in Section 4.2, a functional polymer such as polystyrylboronic acid can be used to effectively "fish out" a reactive component such as a *cis*-diol from a relatively complex reaction mixture. Similarly, attachment of a reactant to a polymer may greatly facilitate the isolation of what would normally be a minor product. A very fine example of this principle is the preparation of a threaded macrocycle by Harrison and Harrison (Scheme 20).[82] The strategy which was used was the following: a macrocyclic compound was attached to an insoluble polymer through an appropriate side group; after addition of an excess of a long chain diol and equilibration of the mixture, an excess of trityl chloride in pyridine was added. The main product of this reaction was the ditritylated derivative of the diol. However, the tritylation reaction also trapped the few diol molecules which were threaded through the macrocycle. Thus the reaction also produced an infinitesimal amount of the polymer-bound threaded macrocycle which could be separated from the rest of the reaction mixture by a simple filtration. This process of diol addition, capping reaction, and filtration could be repeated over and over, resulting in a steady accumulation of the threaded molecule on the polymer. After 70 such reaction cycles, the threaded macrocycle was cleaved from its support and obtained in an unprecedented 6% yield.



Scheme 20.

A somewhat similar technique was used by Leznoff and Svirskaya[83] in the synthesis of an unsymmetrical tetraarylporphyrin (Scheme 21). In this preparation a substituted aldehyde such as 4-hydroxybenzaldehyde is attached to a polymer through an ester linkage. Treatment of the polymer with an excess of *p*-tolualdehyde and pyrrole in hot propionic acid yields two different types of porphyrins; the one formed in the soluble phase is a tetratolylporphyrin, while the other, formed through the pendant aldehyde group of the polymer, contains only three tolyl groups. After filtration to remove the soluble porphyrin and all other impurities, cleavage with base affords a 4.5% yield of the 5-(4-hydroxyphenyl)-10,14,20-tritolylporphyrin. A similar yield can be obtained using classical methods, but the preparation requires a more involved work-up to separate the desired unsymmetrical porphyrin from the reaction mixture.

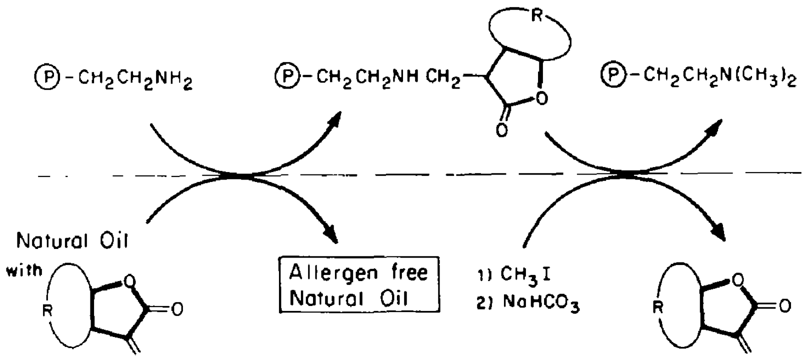
A third example of the use of a polymer in the recovery of a minor component from a complex mixture is illustrated by the removal of allergenic substances which are often found in natural oils. Some of these allergens have been identified as sesquiterpene α-methylene-γ-butyrolactones. Their removal from the natural oils is desirable to produce allergen-free preparations which can be used in the perfume and cosmetics industry, and also to fully characterize the lactones and study their allergenic properties. As α-methylene-γ-butyrolactones are very prone to nucleophilic Michael-type



Scheme 21.

additions, they can be removed from a natural oil such as Costus oil by reaction with various polymer-bound nucleophiles (Scheme 22).[84] Filtration affords an allergen-free Costus oil while cleavage of the bound lactone from its support affords enough material for a full characterization and further study.

These are only three examples of the very varied types of applications in which a reactive polymer can simplify an otherwise complex purification process through its ability to "fish out" a minor component of a mixture.

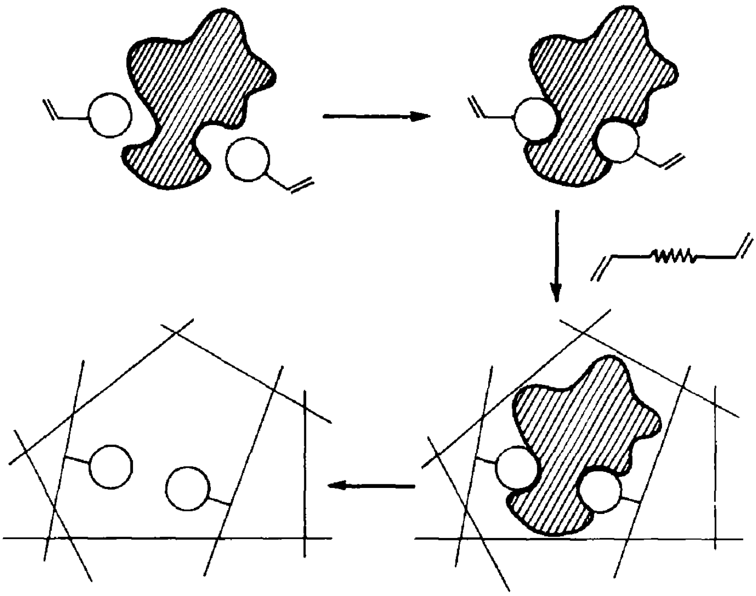


Scheme 22.

5.2 *Template synthesis*

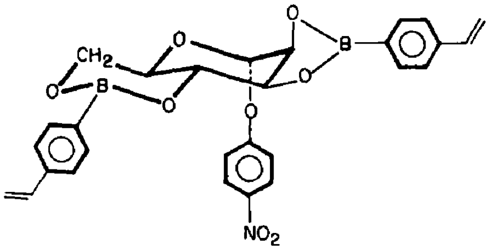
A highly original and novel application of polymer supports has been developed in recent years by Wulff *et al.*[85] Using chiral templates temporarily bound to polymerizable groups, Wulff was able to prepare rigid polymers containing microcavities of specific shape with pendant reactive groups of well defined stereochemistry which can be used as reagents in binding or catalytic processes.

In a typical preparation (Scheme 23) a template molecule is modified to incorporate two or more polymerizable functionalities. The resulting moiety is then copolymerized with a large amount of a crosslinking monomer to yield a rigid three dimensional polymer network which incorporates the template molecules. After removal of the latter by action of an appropriate reagent, a cavity possessing the shape of the template is obtained. This cavity also includes the functional groups which were



Scheme 23.

originally responsible for the binding of the template molecule and these are held in a well defined spacial relationship. For example, Wulff used the di-*p*-vinylphenylboronic ester of *p*-nitrophenyl-α-D-mannopyranoside (Structure 24) as the polymerizable template in a copolymerization with a large amount of divinylbenzene in an inert solvent. This procedure afforded a macroporous polymer with a rigid pore structure. The *p*-nitrophenyl-α-D-mannopyranoside template was then removed by hydrolysis of the boronate linkages, leaving chiral cavities with pendant boronic acid functionalities.



Structure 24.

The polymer could be used in the resolution of a racemic mixture of the original template using a batch technique followed by filtration. Monitoring of the filtrate showed that it was enriched in the L-compound while some of the D-isomer was retained by the polymer. Using this batch technique an optical enrichment of 2–10 % was obtained. The efficiency of the batch procedure corresponds to one theoretical plate in chromatography, and by use of column chromatography as a multiplicative procedure, good separation can be achieved. Using a careful combination of reaction conditions (solvent, pumping velocity, temperature, etc.) a large improvement in number of theoretical plates could be achieved with up to 87 % overall optical yield. Wulff and coworkers noticed that the separation improved at lower flow rates, due to the constant competition between the two enantiomers for the boronic acid sites. Both interact somewhat but the D-enantioner is the only one which can become attached, albeit temporarily, to the two boronic acid residues which form the site. The lack of complete specificity may be due to some isolated boronic acid sites which resulted from polymerization of the original diboronate through one end only or to the drifting apart of functional groups due to shrinking or swelling in the solvent used for the chromatography.

This problem of swelling is of critical importance as the specificity of the polymer could be destroyed completely and irreversibly by heating it in dioxane. The shape of the cavities could not be restored after removal of the swelling agent. Two factors may contribute to the asymmetric shape of the cavity; one is asymmetric crosslinking during polymerization around the template, and the other is the induction of chirality in some parts of the polymer chains owing to the presence of the chiral template in the vicinity of the polymerizing groups.

Another template synthesis has been reported recently by Shea *et al.*[86] who attempted the controlled introduction of two benzyl alcohol sites into a highly crosslinked polymer network using a chiral diacid template. After removal of the template, the benzyl alcohol sites were used to bind fumaryl dichloride in the expectation that their local asymmetry could assist in the chiral methylenation of the bound substrate. Unfortunately, essentially no chiral induction was obtained; obviously, further improvements in the method are required before significant results can be obtained.[88] Nevertheless, it is certain that this very imaginative approach to the use of polymers for the transfer of stereochemical information will receive much attention once the factors which influence stereochemical control in template syntheses are better understood.

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