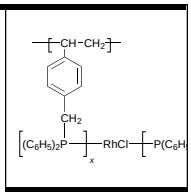
Polymer-supported organic reactions: what takes place in the beads?



CHEMICAL SOCIETY REVIEWS

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The use of polymer-supported reactants in organic synthesis is currently of considerable interest, especially in the context of combinatorial syntheses. To carry out successfully reactions using polymer-supported reactants it is important to be aware of what takes place inside the beads. Examples are presented in this article which show that compared to the analogous homogeneous reaction systems, polymer-supported reactions can show substrate selectivity, be slower or faster, follow a different reaction course, or give a significantly different stereochemical result.

1 Introduction

In 1963 Merrifield first described in the literature his method of 'solid phase' peptide synthesis.[1] In this method the first amino acid residue of the peptide to be synthesised is bound to polystyrene beads through an ester linkage formed using the carboxyl group of the amino acid. As a consequence the peptide subsequently synthesised is attached to the beads *via* the carboxyl terminus. The polystyrene beads are crosslinked and are, therefore, totally insoluble in all organic solvents. Thus, at each stage in the synthesis the supported peptide can be separated cleanly and easily from the other species present. At the end of the synthesis the peptide produced is detached from the polymer support by cleaving the ester linkage. Merrifield first synthesised a tetrapeptide using this approach,[1] but he had soon developed a machine for automated peptide synthesis,[2] and synthesised ribonuclease A[3] an enzyme with 124 amino acid residues. This novel approach so revolutionalised peptide synthesis that Merrifield was awarded the 1984 Nobel Prize for Chemistry.

Also in 1963 Letsinger and Kornet described an alternative 'solid phase' peptide synthesis procedure in which the first amino acid was bound to the polymer support through the amino group.[4] This research work was subsequently developed into a basis for 'solid phase' oligonucleotide synthesis,[5] and this general synthetic approach has proved invaluable for synthesising oligonucleotides for many applications in genetic engineering.

The advantages of the 'solid phase' method are not, however, limited to the synthesis of natural polymers and there are many applications in other areas of organic synthesis. Whilst organic reactions using polymer-supported species had been carried out prior to Merrifield's work, for example, the use of the acid forms of cation-exchange resins as supported acid catalysts for esterifications, his work stimulated other researchers to study a wide range of synthetic organic reactions using polymer-supported substrates, polymer-supported reagents, or polymer-supported catalysts. Over the last 30 years or so more than a thousand papers unconnected with peptide synthesis have been published on these other topics. It is evident from these studies that the polymer support plays an active and crucial role in supported syntheses. With the upsurge in interest in polymer-supported reactions, especially in the context of combinatorial chemistry[6,7] and of the automation of organic syntheses, it is appropriate to briefly review in this article what has been learnt about 'what goes on in the polymer beads', especially as much of this fundamental work has been published other than in the standard organic chemistry journals. Due to space limitations this article cannot in any way be comprehensive. Instead, just a few selected examples are discussed which illustrate some of the complexities of polymer-supported reactions. It is important to appreciate these complexities if, for example, combinatorial syntheses and possibly the screening of the products of such syntheses are to be carried out meaningfully.

'Solid phase' peptide syntheses are, in effect, examples of reactions using supported substrates. More specifically they are examples of reactions involving supported protecting groups. In most 'solid phase' peptide syntheses it is carboxylic acid groups that are protected. Syntheses using supported substrates are also the type of reactions used in combinatorial chemistry. They involve, in sequence, the attachment (linking) of the initial substrate to the support, various polymer-supported synthesis steps, and then the detachment of the final product from the support. Because no separation of the supported species is possible, the supported synthesis reactions must be very clean and high yielding. This requires a very careful choice of reaction conditions, especially as substantial substrate loadings (> 1.5 $mmol^{-1}$ g) are often required in order to obtain useful amounts of the final products. Reactions using polymer-supported reagents are much less demanding since such reagents are used in only one reaction and not every functional site need react. The requirement for high loadings usually remains, however. Polymer-supported catalysts are particularly attractive because not every site needs to react, low loadings are often acceptable, and the recovered catalyst is often available for immediate re-use.

It is tempting to think that the reactions of polymer-supported species will be just the same as those of low-molecular mass analogues. For many reactions carried out under homogeneous conditions this is the case. Indeed, the successful analyses of the kinetics of, for example, free radical polymerisations and

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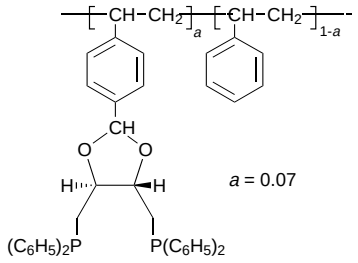
condensation polymerisations are actually based on this assumption. However, the key point with reactions using species bound to insoluble polymer beads is that the reaction systems are heterogeneous. This has far-reaching effects. The polymer behaves as a separate phase. With a uniformly functionalised polymer bead of diameter *ca*. 100 μm, *i.e.* of a size that can be filtered off easily and is therefore commonly used, more than 99% of the functional groups will be within the bead. It is, therefore, clear that with beads of any significant loading reactive species in solution will have to enter into the beads to react and that inside the beads there is often a significantly high concentration of reactive sites.

The major differences between reactions on polymer supports and their low-molecular mass analogues can be grouped loosely into three main types of effect. These are: (*i*) effects resulting from the need for the soluble reactants to gain access to the supported reactants, (*ii*) microenvironmental effects and (*iii*) site–site interactions. These effects are not independent of each other and to complicate matters further the contributions and importance of the various effects can change as a reaction and/or synthesis proceeds. They do, however, provide a convenient framework for the following discussion.

2 Access of soluble reactants to supported reactants

The supports which have been used most extensively for polymer-supported organic syntheses are microporous polystyrene beads crosslinked with 1 or 2% of divinylbenzene. For reactive species in solution to gain access to the reactive sites in the beads, these beads must be swollen by the reaction solvent. To a first approximation the solvents which will swell the beads best are those that would dissolve the corresponding linear polymers. Indeed swelling represents an attempt by the polymer chains to dissolve. The extent of swelling decreases markedly as the percentage of crosslinking increases and a 1% crosslinked bead swells significantly more than a 2% crosslinked bead. If the percentage crosslinking is much less than 1%, however, polystyrene beads tend to become physically fragile and, unless they are handled very carefully, they can disintegrate. It is important to stress here that the functionalities attached to the beads can significantly affect the swelling properties, especially with highly functionalised beads, and that during chemical reactions the swelling properties may change considerably as one functionality is transformed into another. The choice of reaction solvent is therefore crucial in polymer-supported reactions and the optimum solvent may not be the same one as that commonly used in the analogous reaction using low-molecular mass reactants. It should be noted that the reactions in the swollen beads take place in a gel phase and not, as commonly described, a 'solid phase'. Reactions in the solid state are very different from polymer-supported reactions.

Reaction systems which serve to illustrate the importance of the choice of swelling solvent come from early studies of supported transition metal complex catalysts. Kagan's research group prepared 2% crosslinked polystyrene beads containing 0.5 mmol g^{-1} of 2,3-*O*-benzylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane residues **1**.[8] Rhodium(I) complexes prepared from these beads could be used successfully to catalyse the reactions between dihydrosilanes and prochiral ketones in benzene at 20 °C: see Scheme 1. The chemical yields were high and the percentage enantiomeric excesses (% ee) achieved were very similar to those obtained (≤58% ee) in the analogous low-molecular mass reactions. The same polymer-supported catalyst also catalysed the hydrogenations (see Scheme 2) of α-methylstyrene, 2-ethylhex-1-ene, α-ethylstyrene **3** and methyl α-phenylacrylate **4** in benzene at 20 °C but in the last two cases the % ee values achieved were even lower than in the corresponding low-molecular mass reactions (≤2.5% ee *vs.* ≤15% ee). α-Acetamidoacrylic acid **5** is practically insoluble in pure benzene and attempts to hydrogenate it in benzene–ethanol mixtures failed as did



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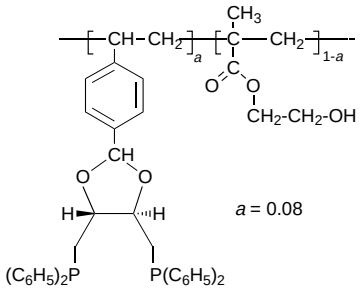
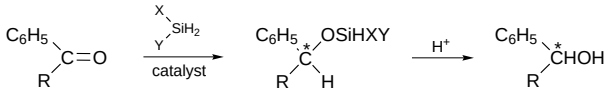


2

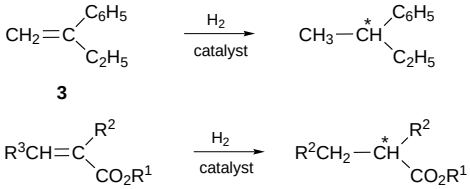
attempts to hydrogenate α-methylstyrene and 2-ethylhex-1-ene under these conditions. The reactions failed because ethanol did not swell the crosslinked polystyrene matrix. The use of ethanol as a solvent is, however, highly desirable as the % ee obtained in such hydrogenations are often higher with this solvent. Stille and his group[9] overcame the problem by incorporating the same catalytic groups (8% of repeat units) into a lightly crosslinked poly(2-hydroxyethyl methacrylate) **2**. The hydroxyethyl moieties interact well with ethanol and the matrix swells well in this solvent. The derived rhodium(I) complexes successfully catalysed the hydrogenations of α-acetamidoacrylic acid **5**, its β-phenyl derivatives **6**, and α-phenylacrylic acid **7** in benzene–ethanol (1 vol : 5 vol) and gave the desired products in essentially the same ee (52–60% *vs.* 73%; 86% *vs.* 81%; 58–64% *vs.* 63% respectively) as those obtained with the analogous low-molecular mass catalyst. The dominant configurations were the same in both reaction systems.

Even when reactions using polymer-supported reagents or catalysts do proceed smoothly, if diffusion of the soluble substrate into the active sites in the beads is rate limiting, and it often is, this can result in the supported reactant displaying a significant size selectivity. This is illustrated by some work of



R = alkyl ; X = aryl ; Y = alkyl or aryl

Scheme 1 Asymmetric hydrosilylation of prochiral ketones



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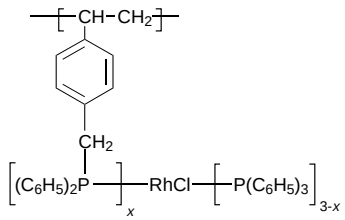
4 $R^1 = CH_3$; $R^2 = C_6H_5$; $R^3 = H$
5 $R^1 = H$; $R^2 = —NHCOCH_3$; $R^3 = H$
6 $R^1 = H$; $R^2 = —NHCOCH_3$; $R^3 = C_6H_5$
7 $R^1 = H$; $R^2 = C_6H_5$; $R^3 = H$

Scheme 2 Catalytic hydrogenations carried out with polymer-supported chiral catalysts

Grubbs and Kroll on the hydrogenation of olefins.[10] A catalyst **8** was prepared by equilibrating 2% crosslinked polystyrene beads in which 8% of the repeat units were benzyldiphenyl-



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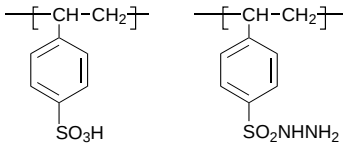
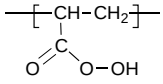


9 **10**

phosphine residues with a twofold excess of tris(triphenylphosphine)-chlororhodium(I). When used as a catalyst with benzene as the solvent at 25 °C under 1 atm of hydrogen the relative rates of hydrogen uptake, with hex-1-ene arbitrarily set to be 100, were octadecene (mixture of isomers) 19; cyclohexene 39; cyclooctene 15; cyclododecene (*cis*- and *trans*-mixture) 8.8; and Δ^2-cholestene 1.2. With a similar soluble catalyst the relative rates of hydrogen uptake, again relative to hex-1-ene arbitrarily set to be 100, were all in the range 71–100. Thus with the supported catalyst the rate of reduction depended greatly on the molecular size of the olefin. Going from an acyclic to a cyclic olefin or increasing the ring size of a cyclic olefin decreased the rate of reduction. The large rigid Δ^2-cholestene showed the most dramatic decrease in reduction rate. These differences arise because the more bulky a molecule the more slowly it diffuses to the reactive sites in the beads. The effects are particularly pronounced in the present case probably because most of the catalyst sites will involve two or more polymer-supported phosphine ligands. These sites will, therefore, serve as extra crosslinks. This makes diffusion through the matrix more difficult than it otherwise would be. It also means that many of the active sites will actually be on crosslinks. The latter are clearly regions which are particularly crowded. In most other reaction systems access to the active sites is less of a problem and bulky molecules such as steroids, for example, can react without difficulty.[11]

Reaction solvent restrictions may sometimes be overcome by using macroporous or macroreticular polymers. Usually these are 20–40% crosslinked polystyrene beads prepared by suspension polymerisation in the presence of a porogen. Various types of internal structure are possible depending on the amount and type of porogen used. Such beads have a rigid porous structure that scarcely swells in most solvents. The open texture allows a wide variety of solvents to enter the pores but not necessarily the highly crosslinked near-rigid framework of the bead. Some commercial polymer beads including certain anion-exchange resins are specially prepared for use in organic solvents. They can provide a convenient means of making various anions available for reaction in non-aqueous solvents. For example, the periodate form of such resins containing 1.3–2.0 mmol of oxidant per g can be used successfully to cleave 1,2-diols in ethanol, chloroform, dichloromethane, diethyl ether or benzene as well as water.[12] However, in other cases a substantial fraction of the reactive groups are located in highly crosslinked regions and are often not readily available for chemical reaction. Evidence for such effects was found by Emerson *et al.*[13] They converted a commercial macroreticular cation-exchange resin containing more than 5.2 mmol g^{-1} of residues **9** into various polymer-supported benzenesulfonylhydrazides **10**. These were then reacted with a range of aldehydes and ketones, presumably to give hydrazones. Starting with a polymer containing 2.8 mmol g^{-1} of residues **10**, acetone in benzene reacted with virtually every site (2.7 mmol g^{-1}), but pentan-2-one and cyclopentanone only reacted respectively with 1.9 and 1.8 mmol g^{-1} of the groups even when a substantial excess of ketone was used or when more highly loaded starting polymers were used. Starting with polymers containing 4.2 and 4.8 mmol g^{-1} of residues **10**, 1.2 and 1.7 mmol g^{-1} reacted respectively with cyclohexanone and cyclohex-2-enone. When these polymers were first treated with an excess of glucose in water to remove the more accessible residues **10**, only 0.4 mmol g^{-1} reacted with these six-ring ketones. These results suggest that as far as the present reactions are concerned only *ca.* 1.0 mmol g^{-1} of the residues **10** are in the more accessible parts of the macroporous beads: the rest are in the highly crosslinked regions.

An effect relating to access arises if the polarity of the microenvironment within the beads differs significantly from that of the solvent outside the beads. The difference can either encourage or discourage low-molecular mass reactants from diffusing into the beads. If the diffusion barriers are not too high equilibria may be set up between the soluble reactants in the beads and the soluble reactants outside the beads. Takagi converted crosslinked poly(acrylic acid)s into supported peroxyacids **11** and carried out detailed studies of their reactivity.[14]



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In this connection he studied the distribution of benzene and cyclohexane, as models for cyclohexene, between various peroxyacid resins and solvents. With several resins changing the solvent from dioxane to *tert*-butyl alcohol, for example, approximately doubled the concentrations of the model compounds in the resins. He observed that in epoxidation reactions conversion to epoxides was very poor when the solvent was less polar than the resin since then the olefin tended to stay in the solvent outside the beads.

Sometimes it is desirable to be able to react non-polar functional groups in polystyrene beads with salts and it might be expected that this could cause some difficulties. However, often an excellent practical solution is to use phase transfer catalysis. Well known examples are the chemical modification of chloromethylated polystyrenes by reaction with cyanide, carboxylates, phenoxides, or thiolates.[15,16] Such reactions are a convenient means to introduce desired functionalities into polystyrenes.

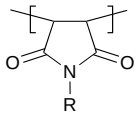
It is evident from the above discussion that the polymer supports used for other than peptide or nucleotide synthesis are at present far from ideal in several respects and that there is considerable scope to prepare improved supports. This is likely to be a very active area of research in the future. Already numerous attempts have been made.[17–19] It is, however, not a trivial matter to identify new supports that are easy to prepare, that have a satisfactory physical form that permits agitation during reactions and filtrations without problems, that have a reasonably high capacity (> 1.0 mmol g^{-1}), and that contain repeat units that, unless required to do so, will not react with the diverse range of reagents involved in, say, a multistage combinatorial synthesis. Many of the supports used for peptide or nucleotide synthesis are simply lightly crosslinked microporous polystyrenes with novel linker groups which allow the easy detachment of the products when required. They generally

have relatively low capacities, and some of them, for example glass beads, have exceedingly low capacities. A significantly different type of support are those (TentaGels) where the hydrophobic properties of crosslinked polystyrenes have been substantially offset by carrying out a graft polymerisations of ethylene oxide inside the beads.[20] In other cases poly(*N*,*N*-dimethylacrylamide)s are used and the poor physical properties of these polymers overcome by depositing them inside rigid supports.[21,22] One way forward is to investigate beads prepared using longer more flexible crosslinking agents than divinylbenzene. Such networks are likely to be superior to the common polystyrene beads.[23]

3 Microenvironmental effects

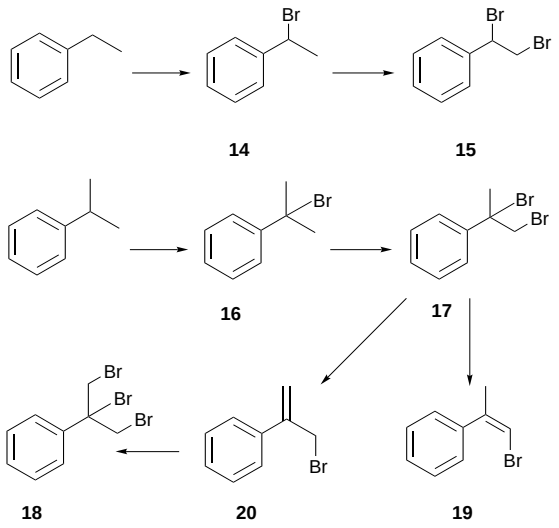
It has already been noted that the microenvironment in a bead may alter the concentrations of low-molecular mass reactants present relative to those in the surrounding solution. The present section is concerned with cases where the microenvironment in a polymer bead can result in a change in the direction or the rate of a particular polymer-supported reaction.

One of the earliest reported examples of a significant microenvironmental effect involves the reactions of several alkylbenzenes with a crosslinked poly(maleimide) **12** in which 70% of the repeat units were *N*-brominated to give residues **13**.[24] Although *N*-bromosuccinimide reacts with ethylbenzene



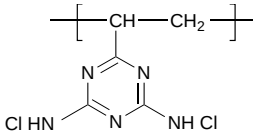
12 R = H
13 R = Br

in carbon tetrachloride in the presence of benzoyl peroxide to give a high yield of the α-bromo derivative **14**, with the polymer-supported reagent **13** a significant amount of the dibromide **15** was also produced. Cumene reacts with *N*-bromosuccinimide under similar conditions to give high yields of bromide **16** or dibromide **17**, depending on the amount of reagent used. In contrast cumene gave a mixture of the tribromide **18** (48%), monobromide **19** (15%), and monobromide **20** (13%) when 2.3 equiv. of the supported reagent **13** were used and an 85% yield of tribromide **18** when 3.7 equiv. were used. *p*-Cymene and *p*-bromocumene behaved similarly. The authors suggest that the differences between the results obtained with *N*-bromosuccinimide and supported reagent **13** arise because the microenvironment within the polymer beads is relatively polar and this favours dehydrobromination reactions. Thus, dehydrobromination of the initial product **16** from cumene would afford α-methylstyrene, and this would then react with bromine, formed by reaction of the supported reagent **13** with the hydrogen bromide liberated by dehydrobromination, to give dibromide **17**. Repetition of these dehydrobromination and bromination reactions leads to the other products. Several further results support this interpretation. For example, treatment of dibromide **17** with the unbrominated crosslinked polymaleimide **12** resulted in dehydrobromination to give bromides **19** and **20**, and *N*-bromosuccinimide reacted with cumene in acetonitrile, a more polar solvent, to give tribromide **18**.



14 **15** **16** **17** **18** **20** **19**

A closely related system to that just discussed has recently been studied by Kondo *et al*.[25] They prepared a polymer by copolymerising 2,4-diamino-6-vinyl-1,3,5-triazine with 5 mol% of divinylbenzene and then reacted the product with *tert*-butyl hypochlorite in methylene dichloride to give polymer beads containing 4.6 mmol g^{-1} of residues **21**. This supported



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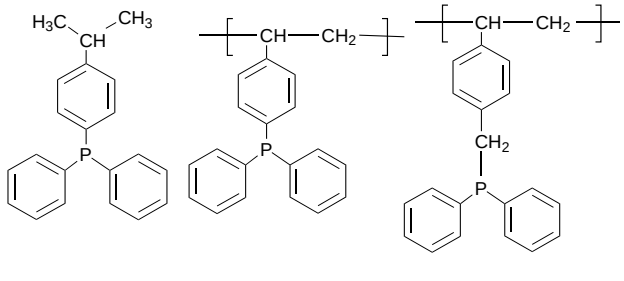
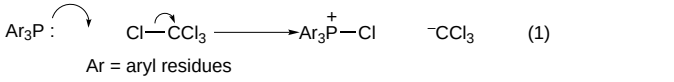
reagent reacted smoothly with cyclohexanol in methylene dichloride at room temperature to give cyclohexanone in 98% yield and with butane-1,4-diol to give γ-butyrolactone in 76% yield. However, the analogous low-molecular mass reagent failed to react with the same substrates under similar conditions. The authors suggested that this was a microenvironmental effect. The polarity of the microenvironment in the beads may be significantly higher than that in the analogous reaction in solution and this may favour the oxidation reaction.

Another example of a microenvironmental effect, in this case one which leads to an increase in reaction rate, concerns the conversion of *n*-alcohols into *n*-alkyl chlorides.[11] Reaction of octan-1-ol with carbon tetrachloride and 4-diphenylphosphinylisopropylbenzene **22** or polymers containing residues **23** produces 1-chlorooctane. When a linear polymer containing residues **23** is used the rate of the reaction is about two times



22 **23** **24**

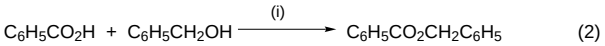
faster than when phosphine **22** is used. With a lightly crosslinked polymer containing residues **23** the same effect is observed except that now the reaction is about 5 times faster. The rationalisation proposed depends on the fact that as the reactions proceed phosphonium salts are formed. In the reactions using the phosphine **22** these salts are either dispersed throughout the reaction medium or they precipitate out and thus play no further part in the reaction. With the polymers, however, the salt residues remain in the vicinity of the unreacted phosphines and they provide a favourable polar microenvironment for reaction of the latter with carbon tetrachloride. This last reaction (see Reaction 1) is the rate-limiting step in the whole process and is favoured by a polar environment. The



Ar = aryl residues

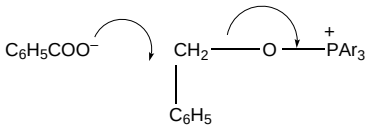
crosslinked polymer probably produces a greater effect than the linear polymer because with the latter the polar interactions can to some extent be reduced by the chains uncoiling. The crosslinks restrict the extent to which this can happen. It should be noted in this reaction system that as the polarity in the crosslinked beads increases they would be expected to swell less thus making the microenvironment within them even more polar, and that as the polarity in the beads increases the alcohol substrate will tend to accumulate there rather than remain in the non-polar carbon tetrachloride solution outside. Also it should be noted that the reaction involving the phosphine **22** takes place more rapidly than that involving simply triphenylphosphine. This reminds us of the need to use good low-molecular mass models when studying polymer effects.

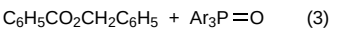
Alexandratos and Miller have taken the study of microenvironmental effects a step further and have actually sought to tailor the microenvironment in 2% crosslinked polymers containing phosphine residues **24** for carrying out the Mitsunobu reaction of benzoic acid with benzyl alcohol (Reaction 2).[26] The rate-determining step in the Mitsunobu reaction is the reaction shown in Reaction 3. In proceeding to the transition



(2)

(i) phosphine and diethyl azodicarboxylate

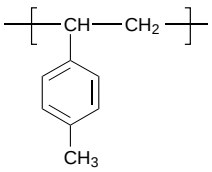




(3)

state this S_N2 reaction involves charge dispersal and is, therefore, expected to be favoured by a non-polar environment. Alexandratos and Miller found that for a range of polymers suspended in tetrahydrofuran at 25 °C the percentage conversion of benzyl alcohol after 6 min was greatest (94%) with a crosslinked polystyrene in which 18% of the repeat units were residues **24**. As the loadings of residues **24** increased, *i.e.* as fewer unsubstituted phenyl residues were present, the percentage conversion under standard conditions dropped. For example, with a polymer in which 100% of the repeat units not involved in crosslinking were residues **24** the percentage conversion was only 42% after 6 min. When phenyl residues were replaced by the more polar residues derived from either methyl methacrylate or from methacrylic acid percentage conversions dropped drastically (⩽2%). In most of these reaction systems high yields of ester were obtained given sufficiently long reaction times.

The microenvironment in the vicinity of the polymer backbone can be expected to be sterically crowded. This is, for example, the reason why reactions at the phenyl residues of polystyrene occur mainly at the *meta*- and *para*-positions and not the *ortho*-positions. It is also the reason why chlorination of polymers containing residues **25** occurs mainly at the side chain position rather than the backbone position. This reaction forms



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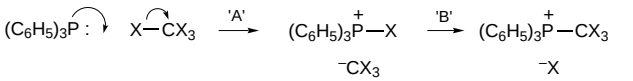
a convenient route for the preparation of chloromethylated polystyrenes.[27] In general steric effects will be greatest when a reactive functional group is directly attached to the polymer backbone, but as the functional groups are separated from the backbone by 'spacer groups', steric effects would be expected to disappear rapidly and functional group accessibility and mobility to increase.[19] Most polymer-supported reactants are prepared from polystyrenes and here the benzene ring itself will act as a small rigid spacer group.

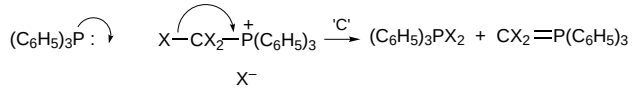
The support might be expected to influence the course of reactions greatly if polarities are such that a substrate moiety bound to a polymer support prefers to interact with the support itself rather than with the solvent. Extreme examples of this situation occur when a hydrophobic substrate is simply adsorbed to a support and then undergoes reaction with aqueous reagents. When prochiral ketones adsorbed onto cellulose triacetate are reduced with aqueous potassium borohydride or prochiral enones adsorbed onto cellulose triacetate are epoxidized with alkaline hydrogen peroxide the chiral support clearly influences the course of the reactions as modest levels of asymmetric synthesis occur.[28] Other examples of such effects are given in the next section.

4 Site–site interactions

The ease with which polymer-supported reactive groups can react together has long been an intriguing topic. In the 1960s and early 1970s organic chemists tended to assume that the fact species were attached to a polymer automatically resulted in substantial site isolation, but detailed studies carried out since then have clearly shown that this is not the case.[29] In this connection it should be remembered that in most of the polymer-supported reaction systems studied the overall concentration of the reactive groups in the beads is reasonably high. For example, with a loading of reactive functional groups of 1.0 mmol g^{-1} on a lightly crosslinked gel that swells in the reaction solvent by a factor of 3, the concentration of reactive groups is 0.33 mol dm^{-3}. With a loading of reactive groups of 0.5 mmol g^{-1} on a highly crosslinked macroporous support which swells only modestly in the reaction solvent, the overall concentration of reactive groups will be *ca*. 0.5 mol dm^{-3}, but if the functional groups were introduced by chemical modification of preformed beads they will be located mainly in the pores and there the local concentration will probably be in excess of 1.0 mol dm^{-3}.

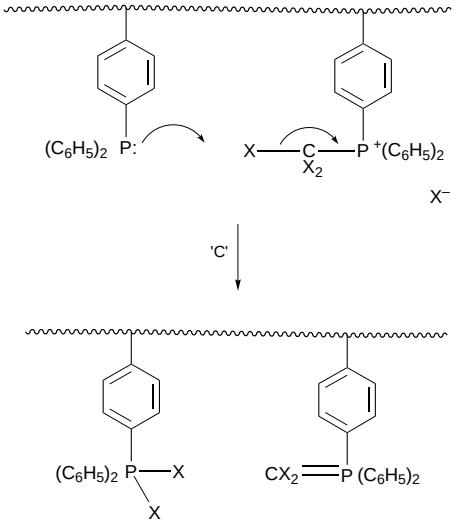
An example of a reaction system which clearly demonstrates that in many circumstances a high proportion of polymer-supported reactive groups can reach each other easily comes from studies of Wittig reactions involving one of the less common ways of generating ylides.[30] Consider first the reactions that occur when triphenylphosphine reacts with carbon tetrabromide in methylene dichloride or with carbon tetrachloride. These are summarised in Scheme 3. Here





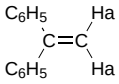
Scheme 3 Reactions occurring when carbon tetrabromide or carbon tetrachloride are treated with triphenylphosphine. X = Br or Cl

Reaction 'C' involves two phosphorus-containing species reacting together and it generates the dihalomethylene ylide. When, starting with polymers containing triphenylphosphine moieties **23**, the analogous reactions occur, the analog of Reaction 'C' involves two supported species reacting together: see Scheme 4. Moreover, this particular reaction has to compete with that of the phosphine residues **23** directly with the carbon



Scheme 4 Site–site reactions occurring when polymer-supported phosphines (**23**) are treated with carbon tetrabromide or carbon tetrachloride. The reaction is the polymer-supported analogue of reaction 'C' in Scheme 3. X = Br or Cl.

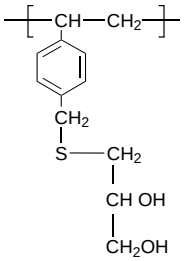
tetrahalide, *i.e.* the analogue of Reaction 'A' in Scheme 3. When the polymer-supported reactions are carried out in the presence of suitable aldehydes or ketones Wittig reactions will occur and dihalo-olefins with result. The yields of these olefins will be an indication of the extent of site–site interactions in these systems. In practice when a 1% crosslinked polystyrene containing 2.5 mmol g^{-1} of phosphine residues **23** was reacted with 0.6 mol dm^{-3} equivalents of carbon tetrabromide and 0.4 equiv. of benzophenone in chloroform, the 1,1-dibromo-olefin **26** could be isolated as crystals in 89% yield. In the analogous reaction with carbon tetrachloride, as both reactant and solvent, the 1,1-dichloro-olefin **27** was isolated in 87% yield. These figures



26 Ha = Br
27 Ha = Cl

indicate that at least 70% of residues **23** reacted together. Clearly increasing the percentage of crosslinking would be expected to reduce chain mobility and thus be a major factor in decreasing the ease of site–site interactions. This proved to be the case in the present reaction system. Thus as the percentage crosslinking increased successively from 2 to 4 to 8 to 15 and to 37% the minimum number of sites reacting together decreased respectively from 47 to 41 to 14 to 2 and to 0%. Changes in the loading of reactive sites are expected to have a significant but less dramatic effect.

The above reaction system is relatively simple in that the supported residues come together, react and then separate. No new crosslinks are formed. Some systems are more complex and site–site interactions introduce new crosslinks which would be expected to reduce the ability of the beads to swell in the reaction solvent. An example of such a system involves acetal/ketal formation with the polymer-supported diol **28**.[16] When 1% crosslinked polystyrene beads containing 3.15 mmol g^{-1} residues **28** were reacted with terephthaldehyde, some molecules of the latter bound at just one aldehyde group, some bound at both. To determine the proportions, the free aldehyde groups in the 'singly bound' molecules were fully reduced (as monitored by FT-IR spectroscopy) with sodium borohydride, then the bound molecules were released and the mixture of recovered aldehydes analysed. Molecules which had been 'singly bound' were now present as 4-hydroxymethylbenzaldehyde. Those that had been 'doubly bound' were recovered unchanged, *i.e.* as terephthaldehyde. It was found that approximately equal amounts of terephthaldehyde were 'singly bound' and 'doubly bound'. More extensive studies of this same type were carried out using 5α-androstane-3,17-dione **29**. This



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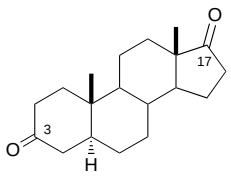

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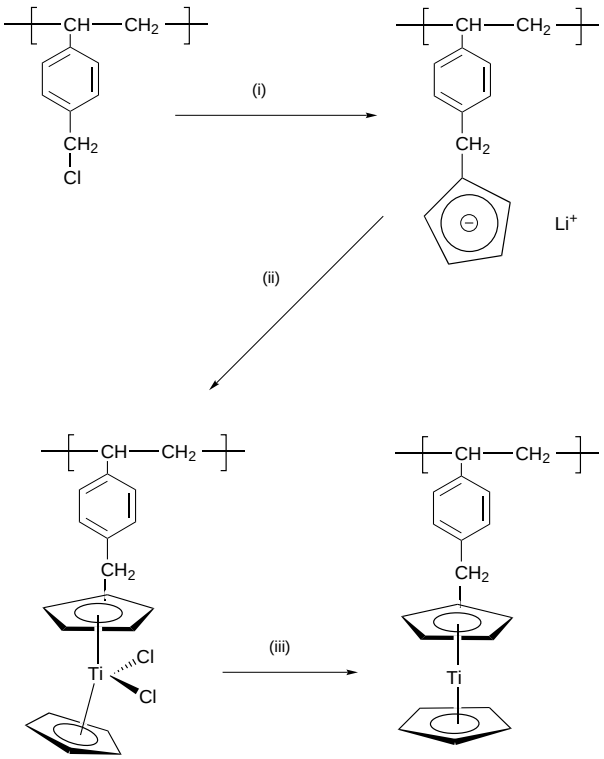
substrate is almost rigid and the 3-keto group is significantly more reactive to ketal formation than the 17-keto group. These features should significantly favour 'single binding' (*via* the 3-position). Indeed, when the dione **29** was bound to various resins the only ketone band in the FT-IR spectrum was that at 1745 cm^{-1} due to a ketone group in a five-membered ring, *i.e.* the 17-ketone. After reduction of these keto groups, detachment of the steroids from the support, and analysis the proportions of 'single binding' and 'double binding' could be estimated. Several factors were investigated which were expected to favour greater 'single binding' than was achieved with terephthaldehyde. These were (*i*) the use of larger excesses of diketone; (*ii*) the use of polymer with lower loadings of diol groups per g; (*iii*) the use of a 20% crosslinked macroporous polymer; and (*iv*) the use of a shorter attachment time in the expectation that the 3-keto groups would react more rapidly. However, in no case was useful 'single binding' achieved; the 'double binding' in all cases was in the range 23–48%.

It is evident from the two examples discussed above, and from numerous other reaction systems studied in recent years,[29] that site–site interactions are possible between a large fraction of the reactive sites on both lightly crosslinked polystyrene beads and macroporous polystyrene beads. This is not surprising as with a linear polymer in solution there is no reason why, given time, all sites should not encounter others. Whilst crosslinking will reduce mobility it will need to be very extensive to achieve permanent site isolation. Although macroporous beads have high crosslinking, the ability to reduce site–site interactions is significantly offset because, as noted above, if prepared by chemical modifications the more accessible reactive sites tend to be concentrated in the pores. It should also be noted that in many cases the supported substrate molecule will itself serve as a 'spacer group' and facilitate site–site interactions. This could completely negate any reduction in site–site interactions the polymer itself may achieve.

In the first of the two examples discussed above, in a competitive situation almost all the phosphine residues **23** in the 15 and 37% crosslinked supports reacted with the carbon tetrahalides in solution (the analogue of Reaction 'A' in Scheme 3) rather than with the other phosphorus-containing residues (Reaction 'C'). It is very likely that with highly crosslinked supports a degree of permanent site isolation is achieved. Support for this view comes from some early work on polymer-supported catalysts by Grubbs *et al.*[31,32] They found that a catalyst prepared from 20% crosslinked macroporous polystyrene beads and containing 1.0 mmol g^{-1} of PS 'titanocene' residues **30**, prepared as outlined in Scheme 5, was 25–120 times more active for the hydrogenation of the hex-1-ene in hexane than the corresponding soluble catalyst. The higher activity of the supported catalyst was attributed to permanent site isolation which allowed a catalytically significant amount of an active monomeric titanium species, presumably residue **30**, to survive. Only a dimeric titanium species was found in



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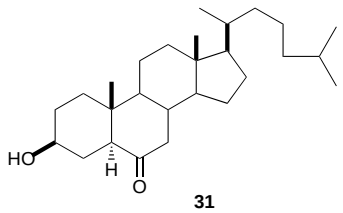
Scheme 5 Synthesis of a polymer-supported titanocene catalyst. (*i*) $Na^+C_5H_5^-$; (*ii*) $CpTiCl_3$; (*iii*) Bu^nLi.

solution. The variation in catalytic activity as a function of the loading of the beads reached a maximum at 0.14 mmol of Ti per gram.[33] These results suggest that permanent site isolation is only achieved at very low loadings on highly crosslinked supports and will, therefore, only be useful in the context of polymer-supported catalysts.

If it is desired to allow low-molecular mass species in solution reacting with a polymer-supported site to compete effectively with reactions between supported sites then one way to achieve this would be to use modestly loaded lightly crosslinked polymer supports which swell extensively in the reaction solvent, so reducing the concentration of the supported sites and making it relatively easy for the species in solution to diffuse into the beads, and where the polarities of the reactive species in solution, the reaction solvent and the microenvironment in the beads encourage the low-molecular mass reactive species to concentrate in the beads.

A simple novel polymer-supported system where significant site isolation is probably achieved relatively easily and which results in a major change in the stereochemical course of a reaction comes from work of the author's group.[34] This involves the reductions of 6-keto 5α-steroids, such as 3β-hydroxy-5α-cholestan-6-one **31**, whilst adsorbed to the



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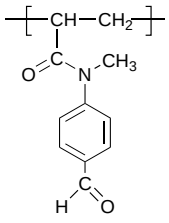
inner surfaces of Amberlite XAD-4, a type of macroporous crosslinked polystyrene beads which have internal surfaces of *ca*. 750 $m^2\ g^{-1}$. The reduction was achieved by aqueous potassium borohydride with the assistance of phase transfer catalysts. Under these reaction conditions, in the presence of the aqueous medium, the lipophilic steroid remained adsorbed to the polystyrene support. At the end of the reaction period the steroidal products were easily recovered by washing the beads with an appropriate organic solvent. Reductions of 6-ketosteroids with borohydride in solution or with the steroid as a suspension in aqueous borohydride generally afford *ca*. 80% of the 6β-alcohol, which is axial, and *ca*. 20% of the 6α-alcohol, which is equatorial. This is in contrast to most other borohydride reductions of cyclic ketones which give mainly the equatorial alcohol ('product development control'). The difference arises because to give the 6α-alcohol the incoming reagent has to pass the 19-methyl group and for steric reasons this is difficult. The reagent, therefore, approaches from the less hindered α-face and the product is now mainly the axial 6β-alcohol ('steric approach control'). In the reductions of the 6-ketosteroids adsorbed on the Amberlite XAD-4 the 6α-alcohol was found to be the main product and it formed up to 90% of the alcohol fraction. This reversal of the normal ratio was attributed to the difficulty of one adsorbed species reacting with another. Thus, in solution the initial reduction is brought about by $^-BH_4$; subsequent reductions are brought about by the various alkoxyborohydrides produced: see Scheme 3. The latter are both more reactive and more sterically demanding. In the supported system the reductions with alkoxyborohydrides involve two adsorbed steroid molecules reacting together and they can only do so with difficulty, if at all. As a consequence, in the supported system most of the reduction is brought about by $^-BH_4$ itself. This reductant is not, apparently, subject to 'steric approach control' and the product formed is that expected from 'product development control'. It should be noted that this type of reaction system involves the simplest possible way of attaching and detaching substrates to a polymer support and it could find applications with other reactions.

Finally in this section and still on the subject of the stereochemical course of polymer-supported reactions, Daunis *et al*. have achieved substantial asymmetric synthesis in a supported reaction system that depends totally on helpful site–site interactions.[35] Recognising that many enolate anion reactions systems involve aggregates including solvent, Daunis *et al*. prepared a series of crosslinked polyacrylates in which *ca*. 1.0 mmol g^{-1} of residues **32** were surrounded on average by three or four chiral pendant groups. Best results were obtained when the latter were residues **33** derived from (*S*)-prolinol. The residues **32** were condensed with glycine *tert*-butyl ester then the enolate **34** was generated by treatment with lithium di-



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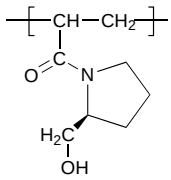

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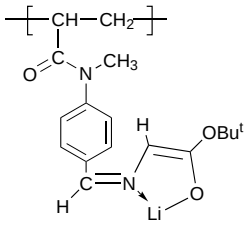

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isopropylamide in tetrahydrofuran. Due to the chiral residues **33** the prochiral lithium enolate **34** was present in a chiral environment. The enolate was alkylated at 20 °C with methyl

iodide and the product cleaved off the support by treatment with hydrochloric acid. Conversion of the alanine hydrochloride into free alanine gave the latter in 85% overall yield with an 82% ee of the (*S*)-enantiomer. A similar experiment where the alkylating agent was isopropyl iodide gave valine in 84% yield with an 84% ee of the (*S*)-enantiomer. The recovered polymer could be re-used successfully. A minor but useful point to note in these experiments is that since polyacrylates have a more flexible backbone than polystyrenes, to achieve a supported reactant with good physical properties 10% of the crosslinking agent *N*,*N*′-dimethylethylenebisacrylamide was needed.

5 Conclusions

In this article some of the various effects that can occur when reactions are carried out using polymer-supported species have been considered. Some of the effects result from the need for the low-molecular mass reactants to gain access to the supported reactive sites, other effects can result if the microenvironment in the beads differs from that in solution, and others can result from the presence or absence of site–site interactions. Examples have been quoted which show that compared to the analogous reaction systems in solution, polymer-supported reactions can show substrate selectivity, be slower or faster, follow a different course or give a different stereochemical result. What is absolutely clear is that it is unwise to assume that a polymer-supported reaction proceeds in just the same way as the analogous reaction in solution.

6 Acknowledgement

The author thanks Monbusho for a Visiting Professorship at Tokyo Institute of Technology during which time this article was written.

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Received, 27th June 1997
Accepted, 5th August 1997