

Preparation, structure and morphology of polymer supports

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The use of polymer resin beads as an aid to synthesis is becoming an increasingly common feature in both academic and industrial synthesis laboratories. The large majority of users employ materials sourced commercially and adopt or adapt procedures already described in the literature without thinking too deeply about the physico-chemical aspects of the support. Success can be immediate, but more often a learning curve needs to be traversed. The present article seeks to describe the chemistry of synthesising supports and to present a user-friendly description of their key physico-chemical properties. A qualitative and pictorial view of how specific morphologies can be generated, and the relevance of these, is also presented. It is hoped that this insight will be of advantage to users in planning and pursuing their chemistry using polymer supports.

Background

Following the discovery and exploitation of ion exchange resins based on suspension polymerised styrene–divinylbenzene (DVB) beads during the 1950s, an enormous amount of effort was directed towards investigating styrene–DVB sulfonic acid resins as potential heterogeneous catalysts. Patenting activity was extensive and throughout the following decades many key large-scale chemical processes have been established employing sulfonic acid resins as the catalyst.^{1,2} These include the manufacture of bisphenol A, isopropyl alcohol, alkylated phenols, branched ethers (petrol organic ‘anti-knocks’) such as methyl *tert*-butyl ether (MTBE), and a variety of alkyl esters including important (meth)acrylate esters. Despite this, there remains a dearth of knowledge amongst synthetic chemists regarding the usefulness of these polymer-based catalysts.

In 1963 Merrifield took the first step towards introducing polymer-supported chemistry to the wider world of synthesis with the publication of his ‘solid phase’ peptide synthesis methodology.³ Notwithstanding this however a more widespread appreciation of the advantages that polymer (and other) supports have to offer to synthesis has only really occurred in the last five years or so, with the explosion in the use of solid

phase combinatorial synthetic methodologies,^{4,5} spurred on by the need for rapid synthesis and screening of potential lead compounds in drug discovery programmes within the pharmaceutical industry. Increasing familiarity with, and confidence in, the use of polymer resins in solid phase synthesis has stimulated even mainstream organic synthetic groups^{6,7} to investigate the prospects of employing polymers as catalyst supports for use, for example, in solution phase combinatorial synthesis. Thus those of us who have been struggling with these systems for many years now find ourselves joined by more illustrious and no doubt more imaginative and skilful colleagues.

Recently the areas of polymer-supported organic reactions^{4,8} and polymer-supported catalysts^{9,10} have been reviewed from the point of view of the solid phase synthetic chemistry which can be carried out on resins and the reactions that have been catalysed by polymer-supported metal complexes *etc.* The main objective of the present article is to focus on the polymer support itself, and to bring a more informed picture of the molecular structure, porous morphology and physico-chemical nature of the support to hard-pressed users and would-be users of these polymers. The hope is that this insight might explain some of the advantages already experienced in the use of supports and, perhaps more importantly, might help overcome some of the disadvantages or downright failures experienced with attempts to use polymer supports.

Linear polymers

Most polymer supports are based on addition polymers typified by polystyrene, the latter conveniently synthesised from styrene *via* a free radical chain propagation reaction (Fig. 1). Since

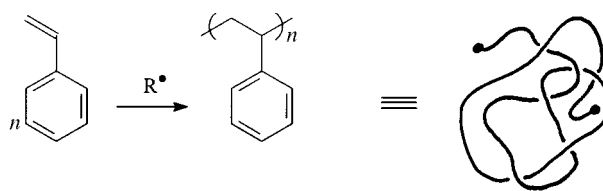


Fig. 1 Polymerisation of styrene to form linear polystyrene, which is a random coil macromolecule.

polystyrene-based supports are particularly widely employed, this is a very convenient model upon which to base a description of the relevant polymer physical chemistry. The principles to be described, however, are widely applicable to other polymer types. Synthetic polymers are generally devoid of any significant secondary or tertiary structure, such as commonly occurs with natural polymers (*e.g.* proteins, DNA), and so individual isolated polymer molecules exist as a random coil typically ~10–20 nm in size, depending upon the molecular weight.¹¹

A collection of chemically similar polymer molecules exist as a mass of interpenetrating random coils—not unlike a bowl of spaghetti. In the case of polystyrene in the solid state, at room temperature, individual polymer chains cannot migrate relative to each other, and indeed even rotation about the bonds in the polymer backbone is very inhibited. Only rotation A (Fig. 2) of

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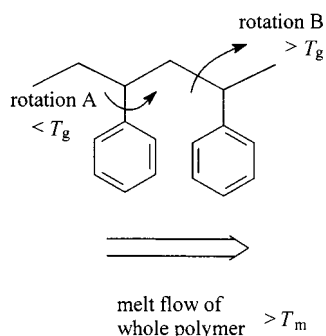


Fig. 2 Molecular motions in polystyrene: T_g = glass transition temperature; T_m = melting point.

the phenyl sidechains occurs freely at room temperature. Overall therefore the polystyrene 'bowl of spaghetti' is essentially frozen at room temperature. Technically the material is said to be below its glass transition temperature, T_g , and the material is amorphous and very glass-like in its general physical nature. The T_g for polystyrene is ~ 100 °C.¹² Above this temperature free rotation B (Fig. 2) about the bonds of the main chain occurs and the polymer becomes pliable or 'plastic'. The analogy now would be a bowl of 'rubbery spaghetti'. Complete movement (translation) of individual polymer chains relative to each is still inhibited until ~ 250 °C. This is the melting point,¹² T_m , above which polymer chains can flow over and through each other and the polymer becomes a viscous liquid or 'melt' (*i.e.* the 'spaghetti' is now hot and mobile and ready to eat). In the glass-like solid state diffusion of even small non-interacting molecules through solid polystyrene is extremely slow.

Solvation behaviour of polymers

The changes described above brought about by an increase in temperature can also be induced at ambient temperatures by the introduction of small interacting organic solvent molecules. Depending upon the relative strength of the interactions of the solvent-solvent, polymer-polymer, and polymer-solvent molecules, an organic solvent may sorb into polystyrene and allow backbone rotation to occur. This is termed 'plasticisation' and the polymer changes from a glass-like solid material into a soft plastic material. A sorbed solvent may interact even more favourably with the polymer chains, heavily solvate them, and allow them to move apart. Such solvents are called thermodynamically 'good' solvents or 'swelling' solvents (see later). This is the onset of the process of dissolution and if enough of such a solvent is added the individual polymer coils will move completely apart to form an isotropic (uniform) solution in the solvent (Fig. 3). Some solvents interact hardly at all with a given

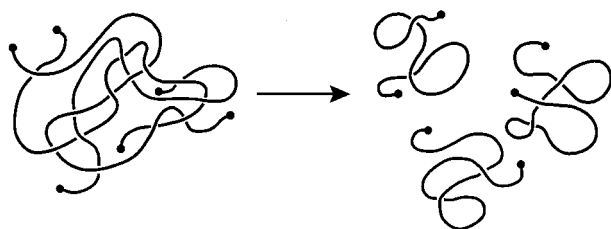


Fig. 3 Dissolution of interpenetrating polymer coils to form independent solvated coils.

polymer and are termed thermodynamically 'bad' solvents, *i.e.* non-solvents, or precipitants. If a polymer is dissolved in a 'good' solvent, and an excess of a 'bad' solvent is added, then the polymer can be precipitated as a solid material. Some typical 'good' solvents and 'bad' solvents for polystyrene are shown in Table 1.

In discussing the compatibility or otherwise of different materials a useful thermodynamic parameter is the solubility

parameter δ . This is a measure of the attractive strength between molecules in a material. A solvent and a polymer are likely to be compatible, *i.e.* the solvent is likely to be a 'good' solvent for the polymer, if they have very similar solubility parameters. If the solubility parameters differ, the solvent is likely to be a 'bad' solvent or precipitant for the polymer. The solubility parameter for polystyrene (and copolymers of styrene and divinylbenzene, see later) is ~ 17 – 18 (MPa)^{0.5}. The corresponding values for a number of 'good' and 'bad' solvents are shown in Table 1.¹³ Note that one group of 'bad' solvents has solubility parameters below that of polystyrene, while the other group has values above that of polystyrene.

Soluble polymer supports

In principle therefore soluble linear polymers seem excellent candidates as reaction and catalyst supports, and indeed they have been well-researched in this context.¹⁴ Dilute solutions of linear polymers should allow rapid unimpeded access of reactants and reagents to functional groups on the support, and the recovery and separation of the polymer might be achieved by addition of a suitable precipitant, by micro- or ultra-filtration, and in some cases by thermal cycling. A major disadvantage of linear polymers as supports is that in general they are useful only with solvents in which they will dissolve. If a solvent is used or required, which will not dissolve the polymer, essentially all the advantages of using a linear polymer as a support are lost. In many instances therefore reagents and catalysts are excluded from use, or possible reaction conditions eliminated, simply because a suitable solvent for the polymer and the reaction cannot be found. Furthermore, in practice micro- and ultra-filtration processes are relatively costly and are not convenient, especially for the hard-pressed laboratory organic synthetic chemist, for laboratory automation, or an industrial chemical manufacturer. While precipitation of many polymers by addition of a suitable non-solvent yields a hard granular product which is readily filtered, linear polymers can selectively sorb a 'good' solvent and be precipitated as a sticky mass, impossible to filter. It is also important to realise that linear polymer coils in solution remain isolated from each other only at concentrations below ~ 1 – 2 wt%. Above this threshold, polymer coils interact and start to interpenetrate, and at more practical synthetic organic chemical concentrations, say > 5 wt%, solutions can become impractically viscous. Bearing in mind that lightly crosslinked polymer networks can be prepared such that they can swell to imbibe > 5 times their own mass of solvent (see shortly) and yet remain in a physical form useful for manipulation, the attractiveness of linear polymers as supports is rather limited.

Nevertheless there are situations where linear soluble polymers can be extremely useful and a key factor in this is that chemical reactions performed on such polymers can be

Table 1 Polystyrene solvents and non-solvents solubility parameters δ^a

Good solvents	δ (MPa) ^{0.5}	Bad solvents	δ (MPa) ^{0.5}
<i>Aromatic hydrocarbons</i>		Water	47.9
Benzene	18.8	<i>Aliphatic alcohols</i>	
Toluene	18.2	Methanol	29.7
Xylenes	18.0	Ethanol	26.0
<i>Chlorocarbons</i>		2-Ethylhexanol	19.4
1,2-Dichloroethane	20.1	<i>Aliphatic hydrocarbons</i>	
Chloroform	19.0	Hexane	14.9
<i>Cyclic ethers</i>		Dodecane	16.2
Tetrahydrofuran	18.6	<i>Others</i>	
Dioxane	20.5	Diethyl ether	15.1
		Acetic acid	20.7

^a δ for polystyrene and styrene-divinylbenzene copolymers is ~ 17 – 18 (MPa)^{0.5}

monitored by, for example, high resolution solution phase ^1H and ^{13}C NMR spectroscopy.¹⁵ Though the resonances due to backbone protons are usually broadened, signals arising from mobile groups in the sidechain are often as sharp as resonances from analogous low molecular weight groups in isotropic solution. Recently, however, considerable advances have also been made in ^1H and ^{13}C NMR analysis of crosslinked polymers¹⁶ (see later).

Copolymers and copolymerisation

The introduction of functionality onto a polymer support can often be readily achieved simply by treating the polymer as a structural analogue of a low molecular weight species and then utilising identical chemistry to achieve a desired derivatisation or structural elaboration. Thus polystyrene can be treated as isopropyl benzene and, for example, subjected to electrophilic substitution. An enormous amount of chemistry has been developed using this approach.^{1,4,5,17,18} An alternative or complementary approach is to introduce a specific functionality during free radical polymerisation, by utilising a comonomer which already carries the required function, or some precursor group which can subsequently be readily transformed. For example, copolymerisation of styrene and 4-vinylphenyl(diphenyl)phosphine yields polystyrene with pendant triphenylphosphine residues. This approach can be useful in producing a structurally well-defined polymer, for controlling the proportion of functional groups introduced and for providing some information on the distribution of the groups along the polymer chain.

It is important in this context to appreciate that all monomers are not incorporated at the same rate. In a free radical copolymerisation of two vinyl monomers, A and B, the rate at which a given monomer is copolymerised depends on the reactivity of the monomer, the reactivity of the free radical derived from the monomer, and how these two reactivities compare with the corresponding reactivities of the other monomer and its derived radical. These factors are all incorporated in so-called pairs of reactivity ratios, r_A and r_B . Reactivity ratios are determined experimentally and are extensively tabulated¹⁹ for pairs of most common monomers. The values generally fall in the range 0 to 1, but can be much higher in special cases. A low value indicates low reactivity, a high value high reactivity. If two monomers each have a moderate value (~ 0.5) then the copolymer they form will have similar composition to that of the comonomer solution. If both monomers have a low value (~ 0) then copolymerisation will be slow and a rather regular alternating 1:1 copolymer will form, with alternate segments comprised of the different monomer residues. If one reactivity is low (~ 0) and the other high (~ 1), then the initially formed polymer will be essentially a homopolymer of the most reactive monomer, with extremely low incorporation of the less reactive monomer. In all cases the processes are subject to some statistical distribution and, in addition, in a batch copolymerisation, if the monomers are initially incorporated at different rates the more reactive monomer will be depleted from solution more quickly, and this in turn will start to slow its incorporation. The composition of the copolymer formed will therefore alter with time as polymerisation proceeds (composition drift).

A simple kinetic treatment²⁰ shows that the copolymer composition, $A_{\text{pol}}/B_{\text{pol}}$, is given by eqn. (1),

$$A_{\text{pol}}/B_{\text{pol}} = \frac{[A](r_A[A] + [B])}{[B](r_B[B] + [A])} \quad (1)$$

where $[A]$ and $[B]$ are the concentrations of the respective comonomers. Knowledge of the r_A and r_B values also allows computation of the mean sequence lengths, \bar{S}_A and \bar{S}_B , of A monomer and B monomer segments respectively in the copolymer from eqn. (2).

$$\bar{S}_A = \frac{r_A[A]}{[B]} + 1 \quad \text{and} \quad \bar{S}_B = \frac{r_B[B]}{[A]} + 1 \quad (2)$$

Thus the reactivity ratios for 4-vinylphenyl(diphenyl)phosphine and styrene are 1.43 and 0.52 respectively, so that the phosphine monomer is considerably the more reactive. For a comonomer mixture of 1:1 therefore the corresponding copolymer composition $A_{\text{pol}}/B_{\text{pol}}$ will be 1.6, and the values of \bar{S}_A and \bar{S}_B , 2.4 and 1.5 respectively. Hence the copolymer formed initially is enriched in phosphine monomer residues and these occur on average in blocks of 2–3 segments. In contrast the reactivity ratios for 4-vinylpyridine and styrene are very similar (~ 0.55), so that these comonomers polymerise more or less in a random fashion, with the copolymer backbone composition being controlled essentially by the initial composition of the comonomer mixture. These effects are extremely important, for example, in designing functional copolymers where it is desired to ensure that functional groups are remote from each, and essentially ‘site isolated’.²¹

Crosslinked polymers

If styrene is polymerised in a mixture with divinylbenzene (DVB) then the latter becomes a constituent of two polymer chains, effectively linking (crosslinking) the chains together. When all the polymer chains are mutually connected an ‘infinite network’ is formed (Fig. 4). In our ‘bowl of spaghetti’ analogy,

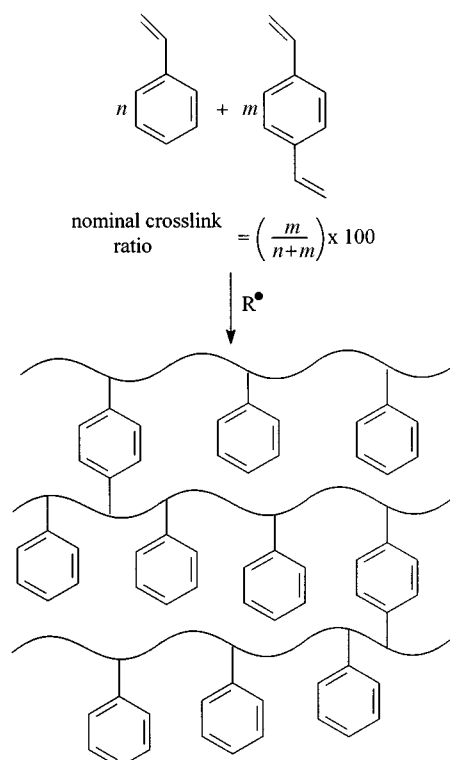


Fig. 4 Polymerisation of styrene and divinylbenzene to form an infinite polymer network.

all the spaghetti strands have been interconnected. Other useful crosslinking monomers are ethylene glycol dimethacrylate (EGDMA) (ethane-1,2-diyl dimethacrylate), trimethylolpropane trimethacrylate (TRIM) [1,1,1-tris(methacryloyloxymethyl)propane] and *N,N*-methylenebisacrylamide (MBA). Note that each TRIM residue effectively links three polymer chains together. DVB has three positional isomers (*o*-, *m*- and *p*-) and there are two routinely available commercial grades of DVB, each of which is a complex mixture. There are four major components, *m*- and *p*-DVB, typically in a ratio of $\sim 2:1$, and *m*- and *p*-ethylstyrene in a similar ratio. In one commercial grade the DVB isomer content is $\sim 50\%$, and in the other

~80%. Care is therefore required in defining or interpreting the DVB content of crosslinked polymers since this might be quoted as a percentage of technical DVB used to make the polymer, or the figure can be adjusted to reflect only the content of *actual* DVB isomers present. Since for convenience the nominal crosslink ratio or degree of crosslinking of a polymer network is often quoted as the mol% of crosslinker used to prepare the network, defining the actual percentage of DVB isomers employed is more informative since this equates with the nominal crosslink ratio (Fig. 4). Bearing in mind that there is no unambiguous method, and certainly no simple and rapid method, for determining the real crosslink ratio in a polymer network, the nominal figure based on the actual DVB feed is a very useful parameter.

Other structural complications also arise which make defining and measuring the real crosslink ratio even more problematical. Although a defined level of crosslinker can be used to synthesise a polymer matrix there is no guarantee that both vinyl groups of *all* crosslinker molecules will react. Indeed, it is well-known that, particularly when higher levels of DVB are used, a significant number of vinyl groups remain unreacted; indeed these can be exploited as sites for further chemical modification. Much effort has been expended in trying to quantify accurately the levels of residual pendant double bonds, and single pulse excitation (SPE) ^{13}C solid state NMR analysis has recently allowed this.²² Rather remarkably a crosslinked resin prepared from 100% *p*-divinylbenzene has ~45% of vinyl groups unreacted, *i.e.* the effective crosslink ratio is ~55%. For a resin prepared with the 80% grade of technical DVB, 45% of initial vinyl groups remain, *i.e.* the effective crosslink ratio is ~45%, while for a resin prepared with the 50% grade of technical DVB, ~32% of initial vinyl groups remain, *i.e.* the effective crosslink ratio is ~35%.

During formation of a crosslinked network it is also possible to produce additional (mobile) crosslinks by virtue of spurious entanglements which cannot disassemble (Fig. 5). Generally

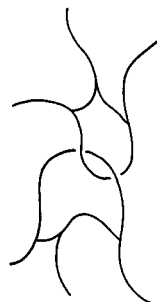


Fig. 5 Permanent entanglement crosslink.

'entanglement crosslinks' increase when the rate or speed of polymerisation is increased. This in turn can be induced by increasing the free radical flux in the polymerisation by increasing the temperature of the reaction and/or the quantity of free radical initiator used. Entanglement crosslinking is also high in a non-agitated polymerisation system, whereas vigorous agitation tends to minimise entanglements. Detecting and quantifying the level of entanglement crosslinking is very difficult.

Further uncertainty in the real level of crosslinking can arise following chemical modification of a polymer network. Some reactions, for example, chloromethylation and sulfonation of polystyrenes, are well known to be accompanied by intramolecular side-reactions which introduce additional crosslinks (Fig. 6) depending upon the conditions used. Again much investigative work has been carried out to try and quantify these reactions and SPE ^{13}C solid state NMR has proved very valuable in the case of the methylene bridging which accompanies chloromethylation.²³ Using the typical conditions to secure essentially quantitative chloromethylation of aromatic

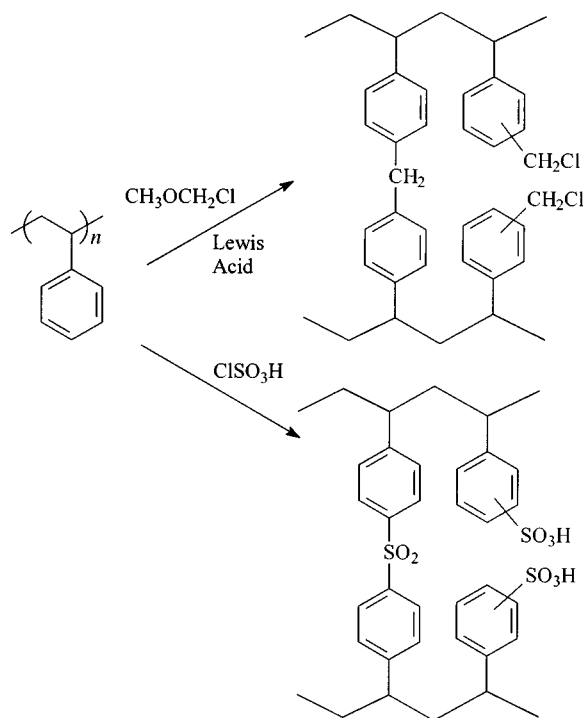


Fig. 6 Secondary crosslinking reactions.

groups in polystyrene resins simultaneously induces ~50% of the aromatic groups to become methylene bridged. While industrial manufacturers of anion exchange resins have learnt to live with, indeed exploit, the methylene bridging side reaction, the discovery of such high levels of these structural units came as a surprise.

Returning to the styrene-DVB copolymerisation, the r_A , r_B values quoted¹⁹ for styrene and *m*-DVB are 0.58 and 0.58, and for styrene and *p*-DVB are 0.26 and 1.2, where the DVB figure refers to the first double bond in the molecule. After this first vinyl group is reacted the now pendant second double bond will assume a reactivity close to that of styrene. In the case of styrene-DVB mixtures these data predict (or imply) that initially the *p*-DVB isomer is incorporated into the copolymer significantly more quickly than styrene (and the *m*-DVB isomer) and that the initially so-formed copolymer is enriched in *p*-DVB residues relative to the composition of the solution phase. The latter becomes progressively more depleted in *p*-DVB and hence its rate of incorporation into the copolymer also falls. These reactivity data therefore predict a copolymer primary structure relatively rich in DVB residues at the start of a chain and somewhat depleted at high chain lengths. The situation however is complex and extensive unpublished data from industrial sources²⁴ suggest that overall there seems to be a strong tendency for styrene and DVB residues to be incorporated more or less evenly initially to produce a rather regular structure along the backbone tending towards a 1:1 alternating relationship; to some extent this occurs irrespective of the initial styrene-DVB composition of the comonomer solution.

As pointed out earlier, with a divinyl comonomer the polymer formed becomes crosslinked as the second pendant double bond is reacted. Initially this is a local phenomenon with the formation of small volumes of microgel (microgelation) (Fig. 7). Eventually however the mass of growing polymer molecules dissolved in solution becomes crosslinked into one infinite network; the system reaches its 'gel-point'. At the point of macrogelation the comonomer swollen crosslinked polymer mass becomes a monolith soft gel filling the containing vessel (Fig. 7). At this point macroscopic diffusion of molecular compounds in the gel starts to become impaired, with the problem growing more acute as crosslinking increases. Further

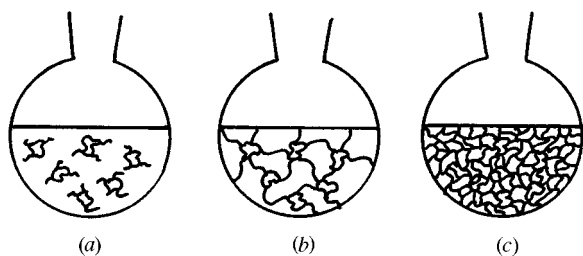


Fig. 7 Polymerisation of a monomer and crosslinker to undergo initially (a) microgelation, then (b) macrogelation, and finally (c) forming a solid glass.

incorporation of comonomers into the crosslinked copolymer becomes less controlled by solution reactivity parameters and more controlled by the composition of the comonomers in the swollen gel, *i.e.* the composition of the copolymer formed tends towards the composition of the comonomers in solution at the gel-point, with formation of a structurally fairly uniform copolymer. If polymerisation is allowed to continue, the liquid comonomers are gradually consumed, the polymer mass becomes increasingly desolvated and finally an amorphous crosslinked glassy monolith is formed in the shape of the containing vessel (Fig. 7). The monolith can be recovered, crushed, solvent extracted and dried to form crosslinked polymer particles or powder with irregular size and shape.

Suspension polymerisation

In practice the size, shape, and often the uniformity of crosslinked polymer particles is vital in most applications. For example, irregularly shaped particles are much more susceptible to mechanical attrition and breakdown to 'fines'. One of the major advantages in using crosslinked polymers as supports is the ease of handling, and robust spherical particles of an appropriate size and size distribution are essential in most applications. The technique of suspension polymerisation allows such particles to be produced fairly readily and highly reproducibly. The methodology is used widely on a laboratory scale but it is also a major large-scale industrial technology as well. Typically a styrene and DVB liquid mixture is dispersed as spherical liquid droplets (the dispersed or non-continuous phase) in a excess of an immiscible water phase (the continuous phase). The styrene-DVB mixture also contains a source of free radicals, the polymerisation initiator, and the aqueous phase generally contains a low level of some dissolved 'suspension stabiliser', a surface active species, often a water-soluble polymer, which helps to maintain the organic monomer droplets separate from each other. The suspension is maintained stable by continuous stirring and the reaction typically heated to $\sim 80^\circ\text{C}$ for 12 h. During this period the spherical liquid monomer droplets are converted into hard glassy polymer particles, still retaining the spherical symmetry of the original liquid droplets (Fig. 8). The rather attractive 'beads' or 'pearls'

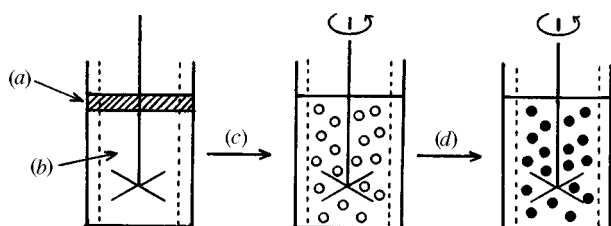


Fig. 8 Schematic representation of suspension polymerisation: (a) organic comonomer mixture (with porogen) containing dissolved initiator; (b) aqueous continuous phase containing dissolved polymeric suspension stabiliser; (c) shearing to form comonomer liquid droplets; (d) thermal polymerisation to form solid polymer resin beads.

are referred to as 'resins' (Fig. 9). In the laboratory, when the reaction is complete the resin particles can be collected by

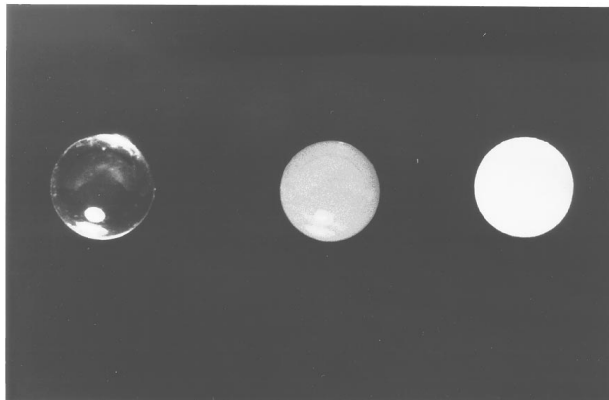


Fig. 9 Optical photograph of (left) gel-type bead, (right) macroporous bead, and (centre) mixed morphology.

filtration and traces of unreacted monomer, initiator and other organic fragments removed by solvent extraction in a Soxhlet, and finally the particles are vacuum dried. Fig. 10 shows the



Fig. 10 Suspension polymerisation reactor, internal volume 1 l, used in the author's laboratory.

type of suspension polymerisation reactor used in the author's laboratory. Further extensive details of suspension polymerisations are available in the literature.^{25,26}

Resin morphology

Gel-type resins

When the comonomer mixture in a suspension polymerisation consists only of styrene and DVB (plus the polymerisation initiator) the product generally consists of hard glassy transparent resin beads (see left-hand sample Fig. 9). The percentage

of DVB can be varied in principle from 0–100% but typically for most resin applications the range 0.5–20% is more usual and for combinatorial synthesis resins, 0.5–2%. As described earlier such materials are composed of an amorphous crosslinked infinite network of interpenetrating polymer chains without any fine structure. The polymer chains are in molecular contact with each other, and the resins have very low surface area in the dry state when measured by, for example, N_2 sorption and application of the BET theory, typically less than $10 \text{ m}^2 \text{ g}^{-1}$ of dry resin. The diffusion of even small molecules through this polymeric glass is very slow indeed. These materials will, however, swell in a ‘good’ solvent, *e.g.* toluene (*i.e.* a solvent with a solubility parameter similar to that of the polymer), with the percentage swelling typically being inversely related to the DVB content or nominal crosslink ratio. Swelling creates space or ‘solvent porosity’ within the resin and allows ready access by small molecules to the polymer network. The swelling process itself occurs largely ‘from the outside to the interior’ and this behaviour has been treated quantitatively using the so-called ‘shrinking core’ model. In this the polymer network on the geometric exterior of resin beads becomes swollen first, forming an expanded pellicular layer and leaving a central unswollen glassy core. As time goes on the thickness of the swollen layer increases and the central core gradually shrinks and finally disappears (Fig. 11).

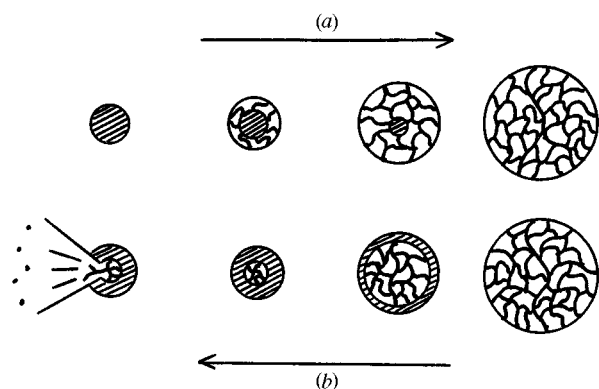


Fig. 11 Solvent response of gel-type resins: (a) shrinking glassy core to form an expanded gel in a good solvent; (b) contraction of swollen gel on addition to a bad solvent with bursting of resin due to osmotic shock.

Unlike linear polymers (see earlier) even a very ‘good’ solvent cannot make the individual polymer chains migrate apart because each chain is connected to at least one other by a crosslink—the polymer chains are part of a continuous infinite network. With a very ‘good’ solvent, the network will swell to its elastic limit, where further expansion is limited by the crosslinks. Note that no swelling occurs with ‘bad’ solvents for the network, and gel-type resins cannot be exploited in such solvents.

Providing the degree of crosslinking is low, sufficient swelling occurs in appropriate solvents to allow all the network to be penetrated and exploited in chemical reactions. The resultant resin particles, typically $\sim 0.1\text{--}1 \text{ mm}$ in diameter, have a molecular structure analogous to a ball of rubbery spaghetti, with all spaghetti strands interconnected and the network saturated with free flowing ‘sauce’. Very low levels of crosslinker ($< 1\%$) however yield mechanically weak swollen resin networks, easily damaged by shear. On the other hand, highly crosslinked gel-type resin networks, although mechanically stronger, may swell too little even in a very ‘good’ solvent to allow all the network to be penetrated and exploited.

If a gel-type resin is fully swollen in a ‘good’ solvent and then introduced into an excess of ‘bad’ solvent, the solvent types will exchange and the resin starts to shrink. This is the reverse of the swelling process, but again shrinking takes place ‘from the outside to the interior’. This can cause very high levels of stress

in the resin and if there are any microscopic flaws, *e.g.* cracks, the resin particles can fracture or burst (Fig. 11). The effect is known as osmotic shock, and gel-type resins are only useful if the matrix is able to undergo many cycles of swelling and deswelling without mechanical damage.

With regard to the stepwise synthesis of a complex structure on a gel-type resin, especially when the synthesis is performed under high load conditions (*i.e.* a large proportion of polymer segments are derivatised) it is important to realise that the swelling behaviour of the resin can change enormously as each modification to the resin is made. A very simple example is a chloromethylated polystyrene resin which is highly swollen in toluene and completely collapsed in water. On reaction with trimethylamine to form benzyltrimethylammonium chloride residues the resultant resin is collapsed in toluene yet swollen in water. Such dramatic changes can, for example, give rise to sudden attenuation of reaction and hence low conversion, or can result in the trapping of reagents or by-products. Careful assessment of such possibilities before reaction and an appropriate choice of a (compromise?) solvent or solvent mixtures can be invaluable.

Generally highly swollen gel-type resins are soft and compressible and this can restrict their use in packed columns, particularly on a large scale, when large back pressures can build-up as the resin particles compress into the restricted geometric shape available to them. Many of the above shortcomings can be overcome by the use of macroporous resins.

Macroporous resins

The term ‘macroporous’ resin is somewhat misleading because its use is not intended to convey anything about the size of pores in a resin. Instead the expression is used simply to indicate a class of resins which have a permanent well-developed porous structure even in the dry state.

If a suspension polymerisation of a styrene–DVB mixture is carried out with the comonomer mixture also containing an appropriate organic solvent (diluent or porogen) at some appropriate level then the internal structure (morphology) of the product resin beads can be very different to that of a gel-type resin. In particular, removal of the solvent or porogen at the end of the polymerisation can leave resin beads which are hard but opaque and with a rough surface which might be visible even with a good optical microscope (see right hand sample, Fig. 9). The polymer matrix is rather heterogeneous or non-uniform. Some areas consist of impenetrable crosslinked and entangled polymer chains, other areas are devoid of polymer. Most importantly, these materials can have much higher surface areas in the dry state (again measured by N_2 BET) than gel-type resins, typically ranging from ~ 50 to $\sim 1000 \text{ m}^2 \text{ g}^{-1}$. Unlike gel-type resins these materials do not need to swell in a solvent to allow access to the interior because they possess a permanent porous structure, *i.e.* a permanent network of pores whose dimensions can be manipulated by the precise conditions used in polymerisation. Such materials are called ‘macroporous’ resins. Providing the surface of the pores is wetted with a compatible solvent, the pore structure can be accessed by essentially all solvents whether categorised as ‘good’ or ‘bad’, *e.g.* even water can penetrate macroporous styrene–DVB resins. When a ‘good’ solvent is contacted with a macroporous resin then as well as filling the pore volume, the solvent may also swell the polymer matrix (*i.e.* the microgel particles—see next section) to some extent. This swelling often occurs rather rapidly because the permanent pore structure gives rapid access to the solvent throughout the whole resin. The swelling (and deswelling) is not restricted in direction ‘from the outside to the interior’ as with gel-type resins, and no ‘shrinking core’ effect is manifest. Consequently macroporous resins show much better resistance to osmotic shock.

There is no universally accepted definition of a macroporous resin but in the case of styrene–DVB resins Millar *et al.*²⁷ suggested that ‘The criterion of macroporosity ... is that the uptake of cyclohexane in 16 h should not be less than 0.1 m² g⁻¹ dry polymer’ with cyclohexane falling into the category of a ‘bad’ solvent for this resin. Recently²⁸ Millar has suggested the use of *n*-heptane in place of cyclohexane since the latter has a low but finite tendency to sorb into styrene–DVB glassy matrices.

For many years there has been confusion in the literature over the terms ‘macroreticular’ resins and ‘macroporous’ resins. A recent patent settlement now allows a clearer definition: a macroreticular resin being one produced in a suspension copolymerisation in which the presence of an appropriate porogen or inert diluent at an appropriate level in the comonomer phase gives rise to phase separation or precipitation of the crosslinked polymer. The resultant isolated dried resin is permanently porous, *i.e.* macroporous, having been produced in this ‘macroreticulation process’. The description therefore distinguishes these macroporous species from others where the porosity is created by a different mechanism, *e.g.* gas blowing. The term ‘macroreticular’ was coined by scientists from Rohm and Haas Co.,²⁹ although other groups were reporting similar resins around the same time.^{27,28,30} In principle, in a suspension polymerisation it is possible to employ a porogen or inert diluent with an appropriate solubility parameter with a particular comonomer composition which does not induce phase separation, or to employ sufficiently low levels of porogen that phase separation does not occur.

Macroporous resins are therefore formed when a porogen is present in the comonomer mixture which causes phase separation of the polymer matrix. At full conversion each polymer bead is composed of a crosslinked polymer phase and a discrete porogen phase, the latter acting as a template for the permanent porous structure of the resin (Fig. 12). Removal of the porogen and drying yields rigid opaque permanently porous beads (see right hand sample, Fig. 9). The point at which phase separation occurs depends upon the nature of the porogen, its compatibility with the incipient polymer matrix and the level at which it is used. These are the key factors that control the fine detail of the resin porous morphology and are discussed in detail in the next section.

In practice the level of crosslinker employed also influences the onset of phase separation and for some commercially produced styrene–DVB resins, the DVB level is adjusted upwards such that even with toluene, a thermodynamically good solvent (for polystyrene) as a porogen, phase separation occurs eventually, since pure poly(DVB) is less compatible with toluene than is polystyrene itself. Thus a matrix prepared from ~25% DVB and ~75% styrene requires ~70% phase volume toluene for phase separation, whereas a mixture with ~80% DVB and ~20% styrene requires only ~30% phase volume of toluene for phase separation as a result of the reduced compatibility arising from the higher DVB level.²⁴

It is also worth emphasising that gel-type resins can be made in the presence of a porogen providing the latter is present at a level which does not cause precipitation of the growing polymer. Generally this also requires a low level of crosslinking

and the network is formed in a solvent expanded form relative to a normal gel-type species. Hence, for example, a resin prepared with ~5% DVB and ~95% styrene with ~65% phase volume of toluene shows very similar physical characteristics to a normal gel-type resin prepared with ~2% DVB and no toluene present.³¹ To some extent therefore the presence of the solvating toluene compensates for the higher level of DVB.

Morphology generation and control

Within each comonomer droplet many polymer molecules begin to grow *via* free radical chain propagation, and indeed with a styrene–DVB mixture these start to crosslink. Initially microgelation occurs but eventually macrogelation of each droplet ensues. In the presence of a porogen sooner or later precipitation of the polymer occurs and this can be before or after macrogelation. Irrespective of this, eventually a well-developed system of microgel particles or microspheres can be detected within each resin bead. These are of approximate spherical symmetry since this represents the form of lowest surface energy. Thus macroporous resin beads (~50–500 μm diameter) are composed of a mass of microgel particles (typically ~1000 Å in diameter) and the molecular structure of an individual microgel particle is very similar to that of a whole gel-type resin bead. To a good approximation therefore a macroporous resin particle can be regarded as comprised of a mass of tiny gel-type particles between which is a complex pore structure or labyrinth of channels (Figs. 13 and 14). The microgel particles are referred to as the ‘gel-phase’ and the pore structure as the ‘pore-phase’. In reality the manner in which the porous morphology develops is very complex, and indeed difficult to study. Further details are available in references 32 and 33, and the references cited therein.

From a practical point of view macroporous resins can be prepared with a wide range of porous structures. These can vary from species with rather low surface area (~50 m² g⁻¹ determined by N₂ sorption and application of the BET theory) and a large proportion of macropores (IUPAC definition: micropores < 20 Å; mesopores 20–500 Å; macropores > 500 Å) to species with a very high surface area (~800 m² g⁻¹) with a large proportion of micropores. Control of the fine detail of this morphology is exercised by choice of the nature and proportion of the porogen, and the level of crosslinker employed. In particular, controlling the point during polymerisation when phase separation of the polymer network occurs is crucial.

Thus, when a porogen with good compatibility with the polymer network is utilised the network remains fully solvated up to high conversion of monomers into polymer. When phase separation finally occurs the microgel particles are small and discrete, and are swollen with residual monomer and crosslinker. Likewise the separate porogen phase contains unreacted monomer and crosslinker. Further polymerisation in the porogen phase creates additional polymer which acts to fuse microgel particles together; however, relatively low levels of polymer are formed in this way since the conversion of monomer to polymer at the point of phase separation is already rather high. The microgel particles therefore tend to retain their

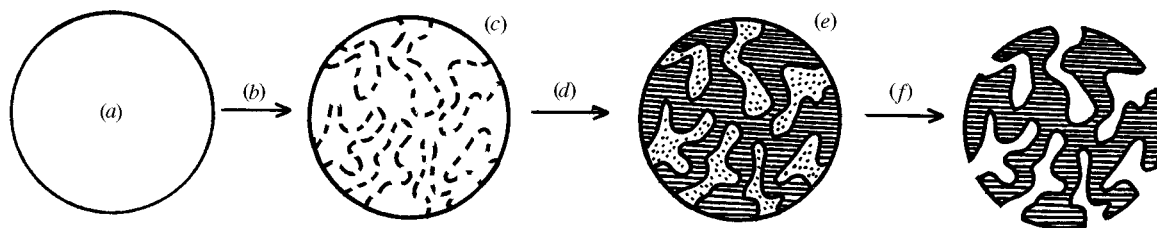


Fig. 12 Action of porogen in forming porous morphology in a macroporous resin: (a) monomer, crosslinker and porogen isotropic solution; (b) polymerisation; (c) polymer network forming; (d) porogen and network start to phase separate; (e) porogen phase acts as pore template; (f) porogen phase removed to yield pores (hatched area = crosslinked polymer; dots = porogen phase).

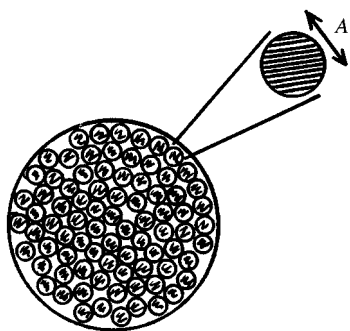


Fig. 13 Enlarged macroporous resin bead showing individual microgel particles ($A = 1000 \text{ \AA}$).

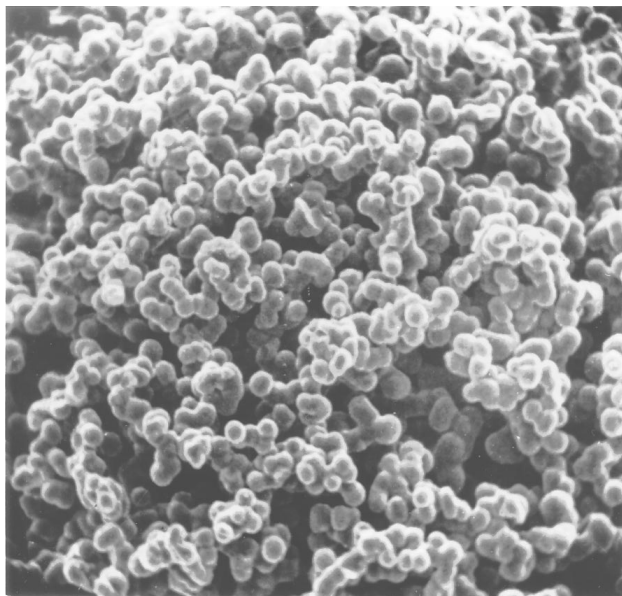


Fig. 14 Scanning electron micrograph of a macroporous resin fracture section (magnification = $5000\times$).

individual identity and the network of micro- and meso-pores, generated between the microgel particles when first formed, is essentially retained [Fig. 15(a)]. Such resins therefore have high

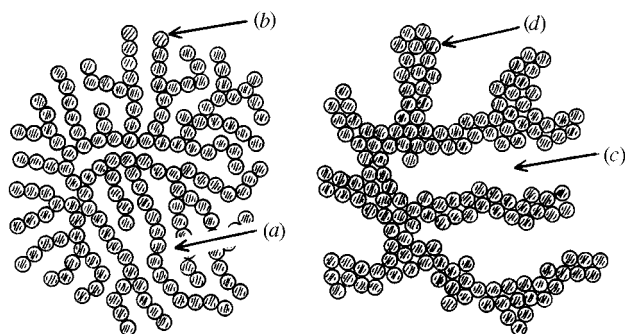


Fig. 15 Connectivity of microgel particles showing formation of small pores (a) from a network of interconnecting individual microgel particles (b) and large pores (c) from a network of fused or aggregated microgel particles (d).

surface area and a pore size distribution with a maximum in the micropore/mesopore region. Typically, for styrene–DVB mixtures, porogens such as toluene and xylene are useful in this respect but they must be used with relatively high levels of DVB ($> 50\%$) in order to achieve satisfactory phase separation.

When a porogen is used which induces polymer network phase separation at much lower conversion, then again microgel

particles are formed, now swollen with a high level of monomer and crosslinker, and likewise the separate porogen phase contains significant levels of monomer and crosslinker. A great deal more copolymer is therefore formed in the porogen phase after the phase separation process, and this has the effect not only of fusing the microgel particles together, but also causing significant in-filling of small pores between the microgel particles. In an extreme case the individual microgel particles can lose their identity and in scanning electron micrographs large fused *aggregates* of microgel particles can be seen interconnecting to form a labyrinth mainly of macropores, all the micropores having long since been in-filled [Fig. 15(b)]. Typically, for styrene–DVB mixtures porogens such as aliphatic hydrocarbons or higher alcohols (e.g. 2-ethylhexanol) are useful in this context. Phase separation of styrene-based networks with formation of stable microgel particles occurs readily even with DVB levels down to $\sim 12\%$ and resins are formed with a surface area typically $\sim 50 \text{ m}^2 \text{ g}^{-1}$ and a pore size distribution skewed towards the macropore region. Note that generally the total pore volume is controlled largely by the amount of porogen employed and is less influenced by the nature of the porogen.

Appearance of resin beads

Dry gel-type resin beads appear clear and transparent (or translucent) because the system is an amorphous glassy solid with no discontinuities to allow interaction with visible light and hence scattering and opacity. Various mechanisms can arise giving rise to light scattering. However, for strong scattering some particulate or porous structure is required where the discontinuous features of differing refractive indices have dimensions similar to the dimensions of the wavelength of visible light. The arrays of aggregated microgel particles described above generally are of this size and so macroporous resins prepared with thermodynamically bad porogens are particularly opaque. The microgel particles themselves are usually individually much smaller than the wavelength of light, and so cannot scatter strongly by this mechanism. They can scatter by a less efficient process and so those macroporous species with microgel particles which retain substantially their individual identity (*i.e.* those formed with good porogens and not aggregated) are often less opaque and can even be quite translucent. Depending on the refractive index of the solvent employed all macroporous resins tend to become much less opaque when imbibed with solvent.

Morphology diagram

Putting all the available experimental data together it is possible to generate an idealised morphology or pseudo-phase diagram^{27,28,33} defining resin systems in terms of the morphology anticipated from a given type and level of porogen, coupled with the level of crosslinker (Fig. 16). This has been developed for styrene–DVB resins but extensive data now exists for methacrylate resins crosslinked with trimethylolpropane trimethacrylate, and a similar treatment seems possible for this system as well.^{34,35} In any event the principles embodied here are more widely applicable. Compositions of polymerising mixtures falling within the macroporous domain yield porous resins whereas those compositions outside this domain yield essentially gel-type or related resins. Thus, for a DVB content of $X\%$, porogen levels below $A\%$ do not cause phase separation of the polymer matrix and the network formed is a lightly solvated gel-type which collapses to form a glassy amorphous gel-type resin on drying. For porogen levels between A and $B\%$, phase separation of the polymer network does occur and the dried resins are macroporous types. The total pore volume of the resins increase in going from A to $B\%$ and phase separation occurs more quickly as the porogen content increases from $A\%$. The surface area of the so-formed resin therefore falls while the

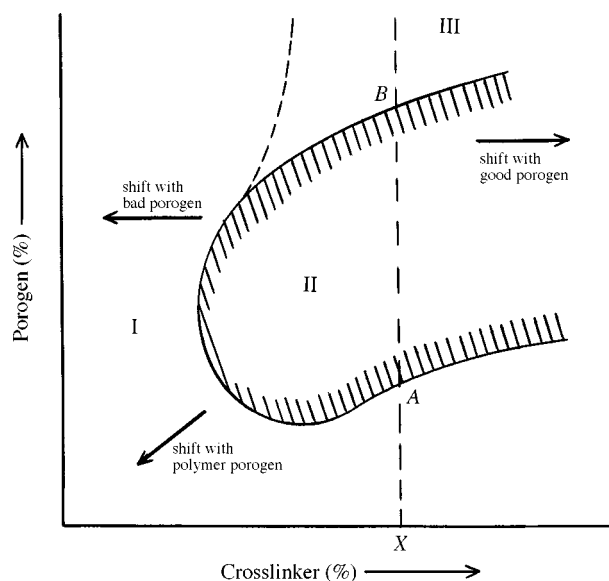


Fig. 16 Resin pseudo-phase diagram: I = gel-type resins; II = macroporous resins; III = microgel powder.

average pore diameter rises. On approaching $B\%$ porogen the total concentration of polymer formed can become too low for stable beads to be formed (*i.e.* the microgel particles are not well-fused) and above $B\%$ porogen the microgel particles appear as a fine powder.

Those porogens falling into the category of thermodynamically good solvents push the macroporous domain towards higher crosslink ratios, whereas thermodynamically poor porogens shift the macroporous domain to lower crosslink ratios. A rather interesting and much less studied class of porogens are oligomers or polymers.^{28,33} Different polymer types tend to be very incompatible and so rather low levels of a polymer can be employed as a porogen to induce phase separation in polymerisation, with or without a solvent coporogen. The overall trend is to cause phase separation at much lower levels of porogen and at much lower levels of crosslinker. In addition, polymeric porogens tend to create large pores in keeping with the idea that earlier phase separation allows more aggregation of microgel particles and in-filling of small pores.

Bearing in mind that the quantity of initiator, polymerisation temperature and degree of agitation are additional variables that can influence morphology generation, albeit in a less dramatic manner, it is quite clear that these systems are very complex in physico-chemical terms. Not surprisingly therefore the boundary between the formation of a macroporous and an essentially gel-type resin is by no means as sharp as that indicated in Fig. 16. A particularly intriguing regime for styrene-DVB resins is that $\sim 7\text{--}12\%$ DVB. Within this range there are polymerisation compositions that can be employed which generate a well-defined macroporous morphology, but the latter is apparently lost on removal of the porogen phase, *i.e.* the pore structure collapses (reversibly) resulting in the formation of a clear glassy amorphous bead.^{26,36–38} However, these species are not conventional gel-types since on addition of a suitable solvent the resin re-swells and reforms its macroporous morphology. The transparent glassy beads can indeed swell and become opaque, depending on the refractive index of the solvent used. Whether such resins fold and collapse on drying, and the extent to which the pore structure is lost, depends also on the solvent from which drying is undertaken. Though superficially such resins seem to embody the weaknesses of both gel-types and macroporous species, they do offer macroporous morphologies in the swollen state with rather low levels of crosslinker in the microgel particles, and there are applications where this might be a significant advantage.

Composite resin supports

With regard to performing stepwise synthesis of oligopeptides on a support, Merrifield³⁹ and others settled for very simple gel-type lightly crosslinked polystyrene-DVB beads as optimum. Later, Atherton and Sheppard⁴⁰ introduced a more polar *N,N*-dimethylacrylamide-based resin, together with an orthogonal protecting group strategy, but again the resin was a gel-type. Rigid macroporous resin beads more suitable for automated use in packed columns, and having greater versatility in terms of use of solvents, gave problems associated with omission of peptide residues, and truncation of peptide growth, probably arising from chemistry taking place in the heavily crosslinked microgel particles. In an attempt to overcome these difficulties two composite supports were developed and commercialised. One employs Kieselguhr as a rigid inorganic primary support, within which is deposited a soft highly swollen polyamide gel and upon which peptide synthesis is performed.⁴¹ The other employs rigid particles of polystyrene in the form of a PolyHIPE®.⁴² The latter is a low density ($\sim 0.1\text{ g ml}^{-1}$) macrocellular ($\sim 5\text{--}10\text{ }\mu\text{m}$ cell diameter) material which allows incorporation of a high level of a soft highly swollen polyamide gel, again the locus for the assembly of peptides. The latter composite functions well in a packed column and offers loading capacities up to $\sim 5\text{ mmol g}^{-1}$.

More recently those involved in solid phase combinatorial synthesis⁵ initiated their work using lightly crosslinked (0.5–2%) gel-type resins developed typically for use with peptide chemistry. These however have been quickly shown to have considerable limitations in terms of both the organic synthetic chemistry that can be carried out on them, and the maximum capacity available. A major limitation in terms of the chemistry is the range of solvents which are capable of swelling styrene-DVB gel-type resins, to the extent that reactions in aliphatic hydrocarbons, alcohols and water are not applicable. A major step forward in this context has been the polystyrene-poly(ethylene glycol) (PEG) composite resin beads developed by Bayer and Rapp^{43,44} which form the basis of the TentaGel® range of supports available from Rapp Polymere (Tübingen, Germany) and known also as the 'Rapp resin'. These have a 1–2% crosslinked styrene-DVB resin as their basis, but grafted onto this are long PEG sidechains or 'tentacles' (Fig. 17), the

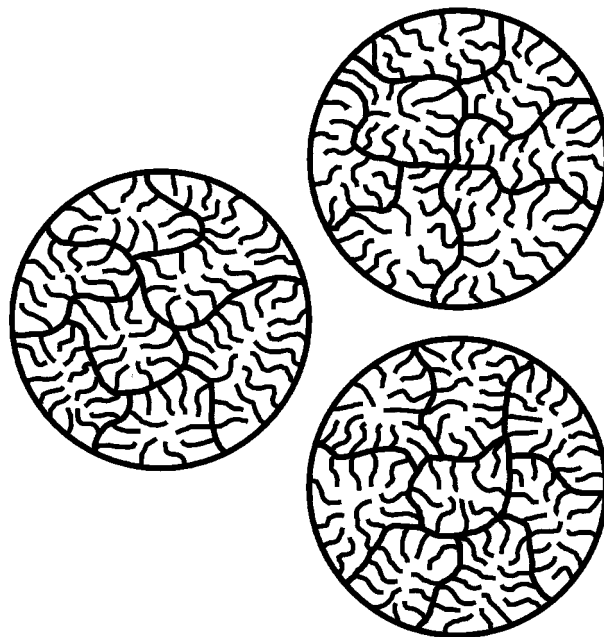


Fig. 17 TentaGel® or Rapp resin showing PEG chains grafted onto gel-type polystyrene-DVB resin; the PEG chains form separate microdomains.

free termini of which are the sites for solid phase synthesis.⁴⁵ The materials are unusual and very versatile because of the

broad solvent compatibility range they offer, and also for the high flexibility and accessibility of the functional endgroups. Typically these composites swell 2–4 times in water, alcohols and ether, and 5 times in CH_2Cl_2 and toluene. The PEG chains have a molecular weight of ~ 3000 , and typically the composite comprises ~ 70 wt% PEG and ~ 30 wt% crosslinked poly(styrene–DVB).⁴³ Such high levels of PEG are needed to generate the advantageous broad solvation properties, and unfortunately brings with it some limitations. The composite can therefore be very sticky and difficult to dry; the capacity of the endgroups is necessarily low and so the synthetic capacity of the resin is likewise low. A specific chemical limitation is the benzyl ether linkage between the PEG chains and the polystyrene backbone which can be readily cleaved yielding PEG contamination of products. Some of these problems have been addressed by second generation analogues produced in the USA;⁴⁶ in particular it is claimed that the capacity has been improved, and the cleavage problem much reduced. The simple model that synthesis occurs on a long PEG spacer arm from polystyrene is too naive. Undoubtedly in polymer physical chemistry terms these composites represent microphase-separated systems (Fig. 17) in which solid phase synthesis occurs in the microdomains of PEG rather than polystyrene, and both the solvation effects in synthesis and the gel-phase ^{13}C NMR spectroscopy of bound species tend to confirm this.⁴⁷

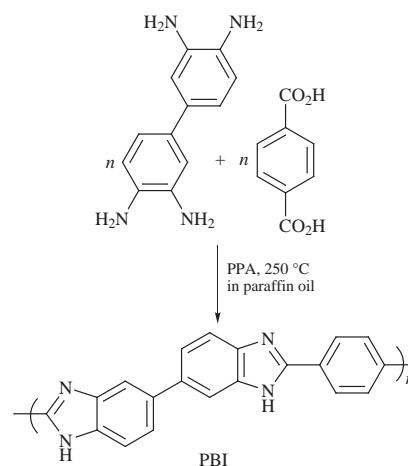
Thermo-oxidatively stable supports

Polymer supports based on vinyl-type monomers (styrene, methacrylates and acrylamides) have found wide applicability, but a serious limitation is their restricted thermo-oxidative stability. Typically the maximum temperature at which these supports can be operated continuously is currently ~ 120 °C, although under highly reductive conditions more extreme regimes may be tolerable. Many potentially useful hydrocarbon oxidation catalysts function optimally at higher temperatures under highly oxidative conditions, and there is therefore an opportunity for the development and exploitation of much more thermally stable polymer supports than those routinely available. In this context the use of polyacrylonitrile, polyamides, polysulfones, polyaniline and polysiloxanes has been reported, but these materials have not been produced in the spherical porous particulate form so useful for application in both batch and continuous catalytic processes.

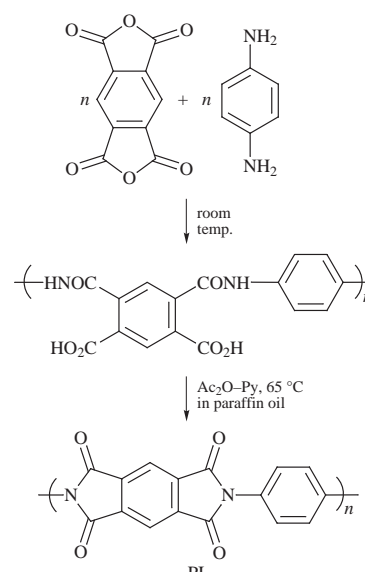
Recently the preparation of spherical particulate forms of polybenzimidazoles,⁴⁸ polyimides⁴⁹ and polysiloxanes⁵⁰ have been reported, and their successful exploitation as supports for alkene transition metal complex oxidation catalysts demonstrated.^{51,52} In each case paraffin oil is used as the continuous medium within which droplets of the appropriate polymerisation phase are dispersed using the principles of suspension polymerisation.

For polybenzimidazole (PBI) it is necessary to condense an aromatic tetraamine with an aromatic dicarboxylic acid (Scheme 1) usually in the presence of polyphosphoric acid at ~ 250 °C.⁴⁸ The reaction is difficult to control and reproduce in the laboratory, but samples are now available from a commercial source.⁵³ Typically the surface area of the dry beads is rather low (~ 10 m² g⁻¹) but remarkably they will sorb ~ 1 ml of toluene per gram of resin to allow catalyst preparation and exploitation.

The polyimide (PI) species are prepared by condensation of an aromatic dianhydride and an aromatic diamine in a two step process (Scheme 2). Initially polyamide formation occurs at ambient temperature in a solvent such as dimethylacetamide, then imidisation can be induced very conveniently by treatment with acetic anhydride and pyridine at ~ 65 °C. This dispersion polycondensation is conveniently carried out in the laboratory, and functional groups can be introduced by utilising appropriately derivatised diamines into the polymerisation. Using



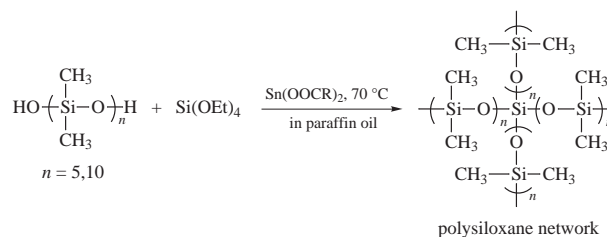
Scheme 1



Scheme 2

also a tetraamine as a crosslinker some of the methodology of macroporous resin preparation has been exploited to prepare species with surface area up to ~ 80 m² g⁻¹.⁴⁹

Most recently a similar dispersion methodology has been exploited in producing spherical particulate polysiloxanes.⁵⁰ Typically an oligomeric silanol is dispersed with a tetraalkoxysilane and a Sn^{II} catalyst (Scheme 3) in paraffin oil, and the



Scheme 3

polycondensation performed at ~ 70 °C. The highly elastomeric spherical particulate products are most unusual, have essentially no surface area in the dry state, but swell readily in non-polar solvents. While their potential for exploitation is still being explored, the value of PBI and PI particulates as metal complex catalyst supports has already been well-demonstrated. In particular, PBI has been shown to offer highly active, long-lived

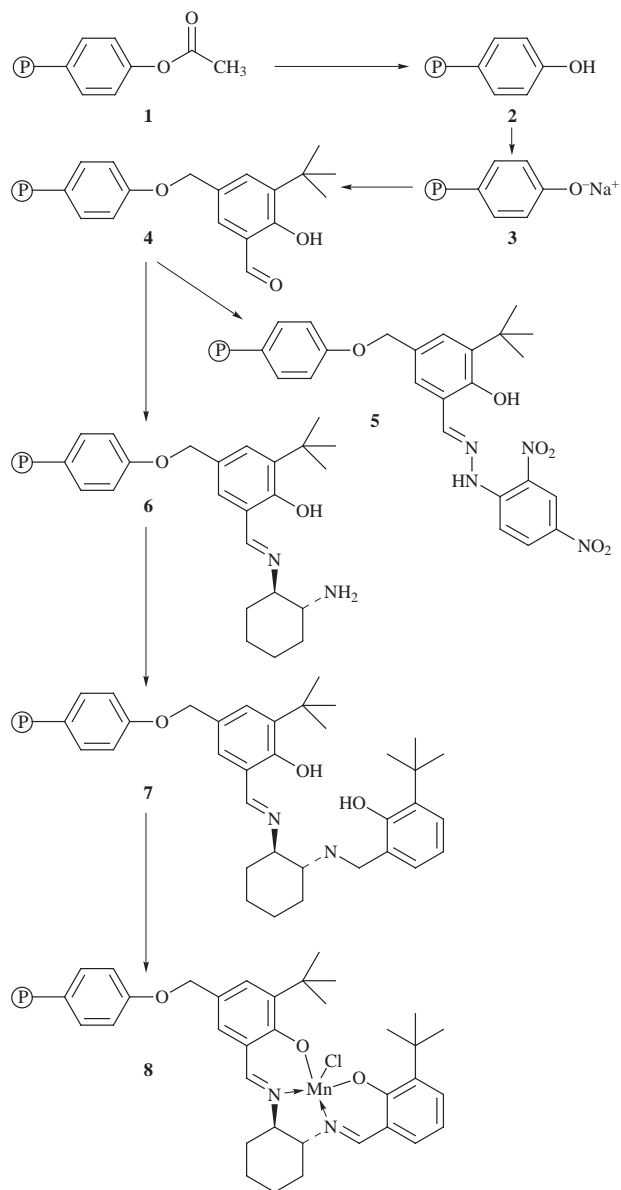
and thermo-oxidatively stable Mo-based alkene epoxidation catalysts, perhaps limited only by cost factors. Overall however all of these support species live up to expectation in terms of their thermo-oxidative stability, with thermogravimetric analytical data typically showing little evidence for decomposition in these resins in air below 400 °C.

Technological prospects for polymer supports in synthesis

The two main areas where technological application already exists, and further growth will undoubtedly occur, are polymer-supported catalysts and solid phase combinatorial synthesis and related methodologies. Polystyrene sulfonic acid resins are important industrial catalysts,^{1,2} and polymer-supported transition metal complex catalysts are poised to make an important contribution in both the commodity chemicals and speciality fields. A partially Pd²⁺-exchanged sulfonic acid resin is already used in the B.P. Chemicals Etherol Process⁵⁴ in which a mixed C₄ alkane/alkene/diene feedstream is converted in the presence of H₂ and methanol into a mixture of alkanes and branched ethers for direct use in the blending of unleaded petrol. A recently announced methanol carbonylation technology for the production of acetic acid utilises a poly(4-vinylpyridine) resin to immobilise the active Rh catalyst.⁵⁵ If ultimately commercialised this will add considerable impetus to the further use of polymer-supported metal complex catalysts. Until recently most polymer-heterogenised versions of asymmetric catalysts have performed rather poorly and, in particular, have given levels of asymmetric induction significantly lower than their homogeneous counterparts.^{9,10} We have, however, developed an insoluble branched poly(tartrate ester)⁵⁶ with technological potential, since this acts as a very efficient heterogeneous asymmetric ligand in the Sharpless epoxidation of allylic alcohols using Ti(OR)₄-*tert*-butylhydroperoxide. Seebach *et al.*⁶ have also reported the synthesis of a number of polymer-supported TADDOL ligands and use of these to generate, for example, asymmetric Ti-based Lewis acids. The latter have been shown to function as enantioselective reagents and catalysts in a number of reactions with, in many instances, activity and selectivity very comparable to their homogeneous analogues. Recently also we have developed a number of polymer-supported analogues of Jacobsen's asymmetric alkene epoxidation catalyst with emphasis on ensuring site isolation of the catalyst and pendant attachment of the chiral salen ligand.⁵⁷ Scheme 4 shows a typical route we have adopted and in this case the steps in the synthesis can be monitored qualitatively by the obvious colour changes that occur in the resin at each stage (1, white; 2, cream; 3, pale pink; 4, sandy yellow; 5 orange; 6, yellow; 7, yellow; 8 dark red-brown).[‡] The resin catalyst performance compares favourably with the soluble catalyst but is very substrate dependent.

In solid phase combinatorial chemistry primarily gel-type resins have been used as the support, based on experience from solid phase peptide synthesis. However, the more diverse chemistry that must be achieved on supports nowadays is encouraging the use of a broader range of resin morphological variants, and commercial sources of these are becoming available.^{46,58}

Automation is also a key factor in combinatorial synthetic methodology, and so scope exists for ingenious development of supports with novel formats to facilitate automation. In this context there is the important concept of inverting the whole solid phase strategy, and carrying out all the combinatorial assembly in solution, by employing an array of supported reagents, catalysts and protecting groups (inverse solid phase combinatorial synthesis). This approach overcomes the major weakness of the normal solid phase method, *i.e.* the limitation in achieving precise molecular structural characterisation at each step of a synthesis. Though magic angle spinning ¹³C and ¹H



Scheme 4

gel-phase NMR¹⁶ and single bead FTIR, Raman and mass spectral techniques have impinged significantly on this problem, very often the analytical capability still falls far short of that which is achievable with soluble molecules. Interestingly therefore the areas of (inverse) solid phase combinatorial synthesis and polymer-supported catalysts and reagents seem destined to converge and there may be much to be gained by practitioners combing the early literature in this area.^{59,60}

Whenever separation problems arise in synthesis, polymer-supported species may have something very positive to offer. These need not involve complex species, *e.g.* poly(4-vinylpyridine)-based resins are useful scavengers of HCl and can avoid the need for aqueous/organic liquid-liquid extractions. The resin is also readily regenerated with aqueous NaOH. At the other extreme, if there is a requirement to trap a particular metal ion from a mixture of ions, then synthesis of a selective chelating ion exchange resin may provide the way forward. A number of groups are also synthesising small libraries of compounds for various applications, and then using a resin-bound specific binding group to 'fish-out' any compound showing a particularly high binding constant.

Not always obvious to the bench/batch chemist are the processing and operational advantages that supported systems can offer. Indeed the option to operate a process under particularly favourably physico-chemical conditions, not acces-

sible when using soluble catalysts, may prove an important driver in the successful application of supported systems. Interestingly, detecting such advantages is not always readily possible until industrial process conditions are probed. So, for those of us committed to this area, a further period of patience and dedication may be required but there is no doubt that the future for polymer-supported synthesis has never been so optimistic.

Acknowledgements

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Notes and references

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‡ A photograph of the samples is available on the RSC's web server, <http://www.rsc.org/suppdata/cc/1988/2275/>, and also forms part of the cover picture of this journal issue.

- 1 D. C. Sherrington, in *Polymer-supported Reactions in Organic Synthesis*, ed. P. Hodge and D. C. Sherrington, Wiley, Chichester, UK, 1980, ch. 3, p. 157 and references cited therein.
- 2 H. Widdecke, in *Synthesis and Separations Using Functional Polymers*, ed. D. C. Sherrington and P. Hodge, Wiley, Chichester, UK, 1988, ch. 4, p. 149 and references cited therein.
- 3 R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149.
- 4 F. Balkenhopl, C. von dem Bussche-Hünnefeld, A. Lansky and C. Zechel, *Angew. Chem., Int. Edn., Engl.*, 1996, **35**, 2288.
- 5 *Combinatorial Peptide and Non-peptide Libraries*, ed. G. Jung, VCH, Weinheim, Germany, 1996.
- 6 D. Seebach, R. E. Marti and T. Hintermann, *Helv. Chim. Acta*, 1996, **79**, 1710.
- 7 B. Hinzen and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1907; 1988, 1.
- 8 P. Hodge, *Chem. Soc. Rev.*, 1997, **26**, 417.
- 9 S. J. Shuttleworth, S. M. Allin and P. K. Sharma, *Synthesis*, 1997, 1217.
- 10 C. Bolm and A. Gerlach, *Eur. Org. Chem.*, 1998, 21.
- 11 M. Kurata and Y. Tsunashima, in *Polymer Handbook*, ed. J. Brandrup and E. H. Immergut, Wiley, New York, 3rd edn., 1989, section VII, p. 38.
- 12 J. F. Rudd, see ref. 11, section V, p. 81.
- 13 R. A. Orwoll, see ref. 11, section VII, p. 526.
- 14 D. J. Gravert and K. D. Janda, *Chem. Rev.*, 1997, **97**, 489.
- 15 H. C. Henderson, D. C. Sherrington and A. Gough, *Polymer*, 1994, **35**, 2867.
- 16 R. V. Law and D. C. Sherrington, in *Solid State NMR of Polymers*, ed. I. Ando and T. Asakura, Elsevier, The Netherlands, 1998, ch. 15, p. 509.
- 17 P. Hodge, see ref. 2, ch. 2, p. 43.
- 18 P. H. H. Hermkens, H. C. J. Ottenheijm and D. Rees, *Tetrahedron*, 1996, **52**, 4527.
- 19 R. Z. Greenley, see ref. 11, section II, p. 153.
- 20 M. P. Stevens, *Polymer Chemistry—An Introduction*, 2nd edn., Oxford University Press, Oxford, UK, 1990, ch. 6, p. 221.
- 21 W. T. Ford, in *Polymeric Reagents and Catalysts*, ed. W. T. Ford, ACS Symp. Ser. No. 308, Washington DC, 1986, ch. 11, p. 155.
- 22 R. V. Law, D. C. Sherrington and C. E. Snape, *Macromolecules*, 1997, **30**, 2868.
- 23 R. V. Law, D. C. Sherrington, C. E. Snape, I. Ando and H. Korosu, *Ind. Eng. Chem. Res.*, 1995, **35**, 2740.
- 24 R. L. Albright, personal communication.
- 25 D. C. Sherrington, see ref. 1, Appendix, p. 469.
- 26 E. A. Gulke, in *Encyclopedia of Polymer Science and Engineering*, ed. H.F. Mark, N. M. Bikales, C. G. Overberger, G. Menges and J. I. Kroschwitz, 2nd edn., Wiley, New York, vol. 16, 1989, p. 443.
- 27 J. R. Millar, D. G. Smith, W. E. Marr and T. R. E. Kressman, *J. Chem. Soc.*, 1996, 218.
- 28 I. M. Abrams and J. R. Millar, *React. Funct. Polym.*, 1997, **35**, 7.
- 29 R. Kunin, E. Meitzner and N. Bortnick, *J. Am. Chem. Soc.*, 1962, **84**, 305; K. A. Kun and R. Kurin, *J. Polym. Sci., Polym. Lett.*, 1964, **2**, 587; K. A. Kun and R. Kunin, *J. Polym. Sci., Pt I*, 1968, **6**, 2689.
- 30 J. R. Millar, D. G. Smith and T. R. E. Kressman, *J. Chem. Soc.*, 1965, 304.
- 31 M. Morrison and D. C. Sherrington, unpublished results.
- 32 R. L. Albright, *React. Polym.*, 1986, **4**, 155.
- 33 A. Guyot, see ref. 2, ch. 1, p. 1.
- 34 J. E. Rosenberg and P. Flodin, *Macromolecules*, 1986, **19**, 1543; 1987, **20**, 1518; 1987, **20**, 1522; A. Schmid and P. Flodin, *Makromol. Chem.*, 1992, **193**, 1579.
- 35 P. D. Verweij and D. C. Sherrington, *J. Mater. Chem.*, 1991, **1**, 371.
- 36 J. Gimenez, J. Costa and S. Cervera-March, *Appl. Catal.*, 1987, **31**, 221.
- 37 Z. Prokop and K. Setinek, *Collect. Czech. Chem. Commun.*, 1974, **79**, 1256.
- 38 W. Neier, in *Ion Exchange Technology*, ed. D. Naden and M. Streat, Ellis Horwood, Chichester, UK, 1984, p. 361.
- 39 R. B. Merrifield, *Life During a Golden Age of Peptide Chemistry*, ACS, Washington DC, USA, 1993.
- 40 E. Atherton and R. C. Sheppard, *Peptides 1974*, ed. Y. Wolman, Halsted Press, NY, 1975, p. 123.
- 41 E. Atherton, R. C. Sheppard and A. J. Rosevar, *J. Chem. Soc., Chem. Commun.*, 1981, 1151.
- 42 P. W. Small and D. C. Sherrington, *J. Chem. Soc., Chem. Commun.*, 1989, 1589.
- 43 E. Bayer, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 113.
- 44 E. Bayer and W. Rapp, GP DE-A3714258 (1988).
- 45 W. Rapp, see ref. 5, p. 425.
- 46 Argonaut Technologies Inc., San Carlos, CA 94070, USA - ArgoGel® and ArgoPore® Resins.
- 47 E. Bayer, K. Albert, H. Willis, W. Rapp and B. Hemmasi, *Macromolecules*, 1990, **23**, 1937.
- 48 T. Brock and D. C. Sherrington, *Polymer*, 1992, **33**, 1773.
- 49 T. Brock, D. C. Sherrington and J. Swindell, *J. Mater. Chem.*, 1994, **4**, 229.
- 50 K. Alder and D. C. Sherrington, *J. Chem. Soc., Chem. Commun.*, 1998, 131.
- 51 D. C. Sherrington and M. Miller, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2091.
- 52 J.-H. Ahn and D. C. Sherrington, *J. Chem. Soc., Chem. Commun.*, 1996, 643; *Macromolecules*, 1996, **29**, 4164.
- 53 Hoechst-Celanese PBI Aurorez Microporous Beads, Charlotte, NC 28232-2414, USA.
- 54 B.P. Etherol Process—see *New Catalyst Resins and their Applications*, ed. W. Strüver and R. Wagner, Bayer AG, D-5090 Leverkusen, Germany.
- 55 See announcement by UOP and Chiyoda, *Eur. Chem. News*, 1997, 26 May–1 June, p. 25.
- 56 L. Canali, J. K. Kaarjalainen, O. E. O. Hormi and D. C. Sherrington, *J. Chem. Soc., Chem. Commun.*, 1997, 123; J. K. Kaarjalainen, O. E. O. Hormi and D. C. Sherrington, *Tetrahedron: Asymmetry.*, 1998, **9**, 1563.
- 57 L. Canali, H. Deleuze and D. C. Sherrington, *React. Funct. Polym.*, 1998, in the press; L. Canali, Ph.D. Thesis, University of Strathclyde, Glasgow, 1998, in preparation.
- 58 Polymer Laboratories Ltd., Church Stretton, SY6 6AX, UK; PL-CMS Resins.
- 59 A. Akelah and D. C. Sherrington, *Chem. Rev.*, 1981, **81**, 557; *Polymer*, 1983, **24**, 1369.
- 60 D. C. Bailey and S. H. Langer, *Chem. Rev.*, 1981, **81**, 109.

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