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List of Abbreviations

HPLC: high pressure (performance) liquid chromatography

TLC: thin-layer chromatography

R_f: retardation factor

T_g: glass transition temperature

HETP: height equivalent to a theoretical plate

FTIR: fourier transform infrared

ADEPT: distortionless enhancement bypolarization transfer

MS: mass spectrometry

M⁺: molecular ion

C = O: carbon-oxygen double bond

C = C: carbon-carbon double bond

MeOH: methanol

PVA: poly(vinyl alcohol)

EtOAc: ethyl acetate

THF: tetrahydrofuran

AIBN: 2,2'-Azobisisobutyronitrile

DVB: divinylbenzene

t-BOC: t-butyloxycarbonyl

¹H-NMR: proton nuclear magnetic resonance

¹³C-NMR: carbon-13 nuclear magnetic resonance

TGA: thermogravimetric analysis

AQ./ORG.: ratio of aqueous and organic phases

rpm: revolutions per minute

psi: pounds per square inch

ppm: parts per million

wt. %: weight percent

b.p.: boiling point

m²/g: square meters per gram

ml/g: milliliters per gram

g/ml: grams per milliliter

mm of Hg: millimeters of Hg

mg/S: milligrams per second

°C/min: degrees celcius per minute

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Abstract

The development of new enhanced chromatographic media for HPLC applications requires that polymers containing reactive functionalities be prepared in small porous bead form. A study of the suspension copolymerization of a protected vinyl phenol with divinylbenzene was undertaken with the aim of preparing high porosity 10 μm beads with pendant phenolic functionalities. Para-t-butyloxycarbonyloxystyrene was chosen as the protected vinyl phenol monomer due to its ease of preparation and to the variety of procedures which are available for the removal of the t-BOC protecting groups once the copolymers are formed. The suspension polymerization was optimized using large amounts of divinylbenzene to afford polymers with surface areas and pore volumes higher than 220 m^2/g and 1.6 ml/g respectively. Of particular importance was the choice and amount of porogen used in the suspension polymerization, excellent results being obtained using 60 volume % cyclohexanol. Factors which contribute to the control of bead size and size distribution were also optimized. The t-BOC protecting groups can be removed thermolytically as well as with strong acid or strong base. The thermolytic cleavage is useful because it is rapid and allows the product polymer to be isolated without difficulty. Several other new hindered vinyl phenol monomers and bead copolymers have been prepared in a similar fashion to give a series of polymers in which the acidity and steric environment around the phenolic hydroxyl group has been systematically changed. The relationship between the polymer structure and its separation ability in liquid chromatography was explored, with an emphasis on the separation of compounds that can hydrogen bond with the phenolic hydroxyl, such as anilines and pyridines.

1. Introduction

1.1 Silica-based adsorbents

Over the course of the past century, a wide variety of materials have been used as adsorbents in column, thin layer, and, more recently, high performance liquid chromatography (HPLC)¹. The list includes materials such as charcoal, molecular sieves, magnesia, silica and alumina, the latter two being the most frequently used. Alumina, $(\text{Al}_2\text{O}_3)_x$, is a slightly basic, general purpose adsorbent that has a high selectivity for acidic compounds such as carboxylic acids and phenols. The most widely used of all adsorbents is silica, $(\text{SiO}_2)_x$. Chromatographic grade silica is made by the reaction of sodium metasilicate with hydrochloric acid, the product of this reaction being silicic acid². Heating of the silicic acid gives a hard, porous xerogel that is formed by condensation reactions of the silicic acid. The final structure is a porous gel which consists of a three-dimensional array of SiO_4 tetrahedra with silanol ($-\text{SiOH}$) groups at the surface of the pores. It is widely believed that these acidic silanol groups are largely responsible for the unique separation properties of silica gel. Generally, silica adsorbents have a high surface area; a typical commercial silica has a surface area of about $500 \text{ m}^2/\text{g}$. It has been shown that column efficiency increases dramatically as the particle size of the adsorbent decreases because of improved solute mass transfer³. Small particles ($5 \text{ }\mu\text{m}$) with a narrow size distribution became commercially available in the 1970's; the availability of such particles is a major reason for the

popularity of silica adsorbents⁴.

1.1a Physically-coated silica adsorbents

Adsorbents with a wide variety of polarities have been prepared by the physical coating of thin layers of organic liquids onto a silica surface. This thin layer of liquid has excellent mass transfer characteristics and can give columns with very high efficiencies⁵. The most widely used liquid coating is 2-cyanoethylether⁶, which is better known as ODPN. Many other organic liquids, such as formamide, ethylene glycol, and 1,2,3-tris-(2-cyanoethoxy)propane, have also been coated onto a silica surface⁷. The branch of chromatography that uses these types of adsorbents is known as liquid-liquid partition chromatography because solutes are believed to partition between the liquid mobile phase and the liquid phase coated on the silica support⁵. The problem with these phases is that the liquid coating can be stripped from the support by shear forces from the high eluent flow rates and because of the solubility of the liquid coating in the eluent.

1.1b Bonded-phase silica adsorbents

The problem of having the organic phase stripped from the inorganic support has been solved by chemically bonding organic molecules to the silica surface. This is usually done by the reaction of the surface silanol groups with an organochlorosilane or an organomethoxysilane. If the organochlorosilane contains one chlorine group, a monomeric or "brush" bonded phase is formed; if the organochlorosilane contains more than one chlorine group, a thin layer of crosslinked organosiloxane polymer is

formed on the surface of the silica gel⁸. A variety of organic moieties have been bonded to the surface of silica gel in this fashion. The most well-known of these are long-chain alkyl groups (C8 and C18)⁹, alkylamino groups¹⁰, diol groups¹¹, alkyl-nitrile groups¹², and phenyl groups¹³. Chromatography performed with the alkylsilicas is known as reversed-phase chromatography because it employs a non-polar adsorbent and a polar mobile phase (methanol/water), while chromatography performed with silica itself is known as normal-phase chromatography because it employs a polar adsorbent and a non-polar mobile phase (ethyl acetate/hexane)⁸. Recently, it was reported that hexadecyl silica can be prepared by simply heating a mixture of hexadecanol and silica; this resin was used for the immobilization of proteins¹⁴.

Another approach to preparing modified silica adsorbents has been to perform vinyl polymerizations on the surface of silica. For example, a silica with pendant vinyl groups was prepared by the reaction of the silanol groups of silica with 3-(methacryloyloxy)-propyltrimethoxysilane. The "vinyl" silica product was then copolymerized with 4'-vinylbenzo-18-crown-6 to give a poly(crown ether)-immobilized silica that was used as a stationary phase for ion chromatography and reversed-phase chromatography¹⁵. In a recent article, silica was reacted with vinyl tri(t-butylperoxy)silane to give an adsorbent which contained both vinyl and peroxy groups on its surface. When this material was heated in the presence of styrene, decomposition of the peroxy groups occurred and a styrene polymer became grafted onto the surface of the silica by copolymerization with the pendant vinyl groups¹⁶.

1.1c Limitations of silica adsorbents

The major problem with silica is its instability in aqueous media. Silica gradually dissolves in aqueous media even at neutral pH, and this effect is enhanced dramatically by an increase in temperature or by the presence of salts in the aqueous phase. Above pH 7, the silica matrix dissolves rapidly; this dissolution leads to columns with large void volumes and lower efficiencies. In very basic media, silica columns generally have a lifetime of only a few days. The bonded phase columns are more stable because the organic substituents shield the silica surface from attack; however, as these bonded phases rarely cover the entire surface of the silica gel, for steric reasons, these materials also degrade gradually under aqueous or highly basic conditions¹⁷.

1.2 Polymeric adsorbents

Because many separations are done in aqueous and/or basic media, a great deal of research has been carried out in order to produce separation media that are stable under these conditions. Porous organic polymers have generally been found to be suitable for these purposes. There are a number of polymeric separation media which are stable over virtually the entire pH range, and most polymers are completely stable in aqueous media. Also, it is generally believed that polymeric separation media have greater selectivity in separations than silica⁴.

1.2a Polymeric ion-exchange resins

The most well-known polymeric separation media are those

which have been used in ion-exchange chromatography¹⁸. In the late 1800's and early 1900's, all of the ion exchangers used were inorganic materials. In 1935, synthetic organic resins, such as condensation products of formaldehyde with polyhydric phenols or aromatic diamines, were discovered to have ion exchange properties. The most significant development occurred in 1945 when Dow developed bead ion exchangers based on a sulfonated cross-linked polystyrene resin. In fact, the first modern liquid chromatograph, which was an automated amino acid analyzer developed by Spackman, Moore and Stein in 1958¹⁹, used pressurized glass columns containing sulfonated polystyrene beads.

Over the past forty years, a large number of functionalized polystyrene resins that can function as ion exchangers have been produced. The list includes resins containing sulfonate, phosphate, tetraalkylamino, and iminodiacetate groups, as well as copolymers of methacrylic acid and divinylbenzene. A number of ion exchange resins based on chemically modified cellulose and dextran (Sephadex) were produced, and these resins were used in the ion exchange chromatography of proteins and nucleic acids. Also, some ion exchange resins were made by condensation reactions of monomers, such as formaldehyde and phenolsulphonic acid, but such resins have not found widespread use¹⁸.

More recently, a large number of polymeric ion exchangers with unique physical properties and separation abilities have been developed. Rohm and Haas have developed some totally aliphatic acrylic-based ion-exchangers that showed considerably less fouling by organics than polystyrene resins when used in water purification²⁰. In 1981, a review of all the polymeric

materials that act as chelating ion exchangers (highly selective for one ion) was published²¹. Stamberg and Peska have recently described the preparation of porous spherical bead cellulose in a process which closely resembles suspension polymerization; the physical properties of this material make it an ideal adsorbent²². Polymeric crown ethers which can complex alkali metal cations have been synthesized by the condensation of polystyrene-bound catechol and polyglycol dihalides and by other techniques²³. A novel benzoic acid-type ion exchanger has been prepared by sodium chromate oxidation of poly(methylstyrene-divinylbenzene) and poly(chloromethylstyrene-divinylbenzene)²⁴. Although many ion-exchanging functions can readily be bonded to the surface of silica gel, these columns generally have a short lifetime because the silica matrix degrades slowly in the aqueous eluents that are used in ion exchange chromatography⁴.

The early polystyrene-divinylbenzene resins used in ion exchange chromatography were of the gel or microreticular type. For these resins, the porous structure is determined by the amount of crosslinking agent used in the suspension polymerization process, and the pores of these resins are generally considered to be the channels or voids between the chains of the polymer network. Polymers with low amounts of crosslinking are not rigid enough to withstand the high pressures of modern HPLC; polymers with higher amounts of crosslinking are more rigid, but the diffusion of molecules into these resins is very slow because of the small pores present in these resins and the resulting column efficiencies are very low⁴.

A significant development occurred in 1962 when Kunin et al.

reported the synthesis of macroporous ion exchange resins by the suspension polymerization of styrene and divinylbenzene in the presence of a solvent or porogen²⁵, followed by chemical modification of the macroporous resin. In this particular case, the porogen was a solvent for the monomers but a non-solvent for the polymers that were formed. These macroporous beads contained very large pores in addition to the small pores found between the chains of the polymer network. It has been found that macroporous polymers are sufficiently rigid to be used in HPLC because they are usually prepared with a large amount of cross-linking agent. They have a high surface area and their large pores allow molecules to travel more easily in and out of the polymer bead, especially in solvents which do not swell the polymer bead⁴.

1.2b Polystyrene-divinylbenzene adsorbents

It was soon realized that the unmodified polystyrene-divinylbenzene matrix itself could be used as a chromatographic adsorbent. It is very hydrophobic, and it was believed that it might well function as a reverse phase adsorbent, just as the alkylsilicas do. The adsorbent which was tested most in this respect was Amberlite XAD-2, a high surface area ($300 \text{ m}^2/\text{g}$) polystyrene-divinylbenzene copolymer produced by the Rohm and Haas Co. Between 1967 and 1972, a large number of low pressure separations performed with this adsorbent on a variety of organic molecules were reported in the literature. These references are listed in an article published in 1973 by Grieser and Pietrzyk²⁶. In this article, the authors showed several medium pressure sepa-

rations performed with Amberlite XAD-2 and suggested that this adsorbent could be used in high pressure liquid chromatography. In 1974, Chu and Pietrzyk reported performing a number of separations using Amberlite XAD-2 as a high pressure liquid chromatographic adsorbent²⁷. Large particles of crude resin prepared by suspension polymerization were ground and sized and a fraction in the 45-65 μm particle size range was collected. Testing of packings based on Amberlite XAD-1 and Amberlite XAD-4 (each resin having a different surface area) showed that the retention of 4-chloroaniline increases as the surface area of the adsorbent increases. In contrast, this solute showed no retention on a low surface area gel-type polystyrene resin. In the same year, a Japanese group reported that they had prepared a similar polymer with a surface area of 800 m^2/g in the particle size range of 20-30 μm . This product, as well as other similar Japanese products, is known as a Hitachi gel and it was shown to perform a variety of high pressure separations²⁸. In 1980, a solvent elutropic scale, similar in principle to the well-known elutropic scale for silica, was developed for polystyrene-divinylbenzene adsorbents²⁹.

1.2c Novel polymeric adsorbents

Other adsorbents produced by Rohm and Haas include Amberlite XAD-7 and Amberlite XAD-8, which are acrylic polymers³⁰. The Monsanto Research Corporation has developed an open-pore polyurethane adsorbent using a novel technique in which a urethane solution polymerization is performed directly within the HPLC column³¹. Laboratory Instruments of Czechoslovakia has developed

the Spheron series of adsorbents; spheron SE is a copolymer of styrene and ethylene dimethacrylate that has been used in reversed phase chromatography³². Recently, Ageev et al. reported on a number of HPLC separations performed with a bead copolymer of glycidyl methacrylate and ethylene dimethacrylate having an average particle size of 10 μm ³³. Copolymers of 2- and 4-vinylpyridine and divinylbenzene have also been used as adsorbents in HPLC³⁴.

1.2d Recent improvements in polymeric adsorbents

The main problem in the field of polymeric separation media in the 1970's was the lack of availability of spherical porous polymer beads with small sizes (ca. 10 μm) and low dispersity; typically, Amberlite XAD-2 was being sold as rather large spheres (20-50 mesh) which were not useful as HPLC packing materials. In one report, a 3.6-8.4 μm "cut" was obtained from these particles by grinding, sieving, and solvent elutriation; however, this process, which is long and time-consuming, only produces irregular particles rather than the more desirable spherical particles³⁵. Eventually, the suspension polymerization technique was improved and this led to the production of smaller beads. In 1980, the Hamilton Co. began to sell a polystyrene-divinylbenzene copolymer (PRP-1) that consisted of spherical porous beads with an average particle size of 10 μm and a narrow particle size distribution. The efficiencies of columns packed with these materials approached that of the silica-based columns³⁶. Other products were developed from these new materials, such as PRP-X100, a high capacity and high efficiency anion-exchanger

prepared from PRP-1 by chemical modification³⁷. MacBlane et al. have developed a new C18-derivatized polystyrene-divinylbenzene by chemical modification of small, porous polystyrene beads. The aromatic styrene nuclei were functionalized with long-chain alkyl groups that are believed to partially shield the pi electrons of the aromatic rings. This helps to reduce the strong pi-pi interactions that often occur between the aromatic rings of the resin and various aromatic solute molecules. As a result, peak tailing is drastically reduced and separations can be performed much faster³⁸.

1.2e Polymers as adsorbents for gel permeation chromatography

The term gel permeation chromatography (sometimes called gel filtration chromatography) refers to separations performed on the basis of molecular size. Porath and Flodin were the first to effectively demonstrate that molecules could be separated according to size differences³⁹; a lightly crosslinked dextran gel (Sephadex) was used to separate high molecular weight serum proteins from low molecular weight ammonium sulphate using an aqueous mobile phase in a process which was termed gel filtration chromatography. In 1964, Moore performed similar separations using crosslinked polystyrene gels; he called this technique gel permeation chromatography⁴⁰. Macroporous polystyrene-divinylbenzene beads were prepared using high amounts of crosslinking agent and various types and amounts of porogens; this afforded materials with a wide range of pore sizes that were much more rigid than the gels used by Porath and Flodin and could therefore be used at much higher pressures and flow rates. Moore demon-

strated that these columns could be used to separate a number of soluble polystyrenes having a wide range of molecular weights and that this technique could be used in the determination of the molecular weight distributions of high polymers. Recently, more hydrophilic polymers, such as polyvinyl alcohol, have been used as packing materials in gel permeation chromatography because of their compatibility with aqueous eluents⁴¹.

Silica gels have also been used in gel permeation chromatography⁴², mainly because of their mechanical rigidity and their availability in small particle form; however, silica gels are not widely used in this area of chromatography because macroporous polymers generally have a higher percentage porosity than silica, and therefore contain many more pores in which separation by size can occur. Also, the pore size distribution of macroporous polymers can be varied more readily over a much wider range⁴.

1.2f Comparison of silica adsorbents and polymeric adsorbents

Silica gel is still widely used in HPLC applications because of its availability in small particle form and because of its favourable mechanical characteristics. It can easily withstand high pressures and flow rates, and it has good mass transfer characteristics. Macroporous polymers have become very popular in HPLC because of their outstanding chemical stability relative to silica. Macroporous polymers are generally acknowledged to have higher capacities and selectivities than silica, and they are now available with particle size distributions similar to that of the silica-based materials. In fact, about one-quarter of

columns sold for HPLC now contain polymers as packing materials. Current research is focused on producing macroporous polymer beads with increased rigidity and improved mass transfer characteristics⁴.

1.3 The history and development of macroporous resins

The development of macroporous resins can be traced back to the 1950's when Wiley and Schmitt published an article which described the synthesis of a cation exchange resin with unusual properties by suspension polymerization⁴³. The resin was prepared by copolymerization of p-sulfonamidostyrene and di-(p-vinylphenyl)sulfone in a solvent mixture consisting of methanol, dioxane, and dimethylformamide at 100 °C with paraffin oil as the suspending agent. After hydrolysis of the sulfonamide groups, a crosslinked macroporous, sulfonated polystyrene bead polymer was obtained. The authors reported that this material exchanged ions 2-4 times faster than the conventional gel ion exchangers but did not measure the physical characteristics of these beads, such as their surface area and pore volume.

1.3a Macroreticular ion-exchangers

In 1962, Kunin et al. published a paper describing the characteristics of Amberlyst 15, an ion exchanger obtained by the sulfonation of a macroporous styrene-divinylbenzene copolymer⁴⁴. In contrast to conventional gel ion exchangers, which have a surface area of less than 0.1 m²/g, this resin had a surface area of 42.5 m²/g and an average pore diameter of 288 Å. In view of the large difference in physical properties between these two types of resins, the authors called the former a microreticular

ion exchanger and the latter a macroreticular ion exchanger. The microreticular and macroreticular ion exchangers displayed very similar ion exchange kinetics in water because water causes the sulfonated gel to swell; however, in non-polar solvents, which cannot swell the polar sulfonated polymer, the macroreticular ion exchanger displayed far superior ion exchange kinetics. In 1964, Kun and Kunin measured the pore size distributions of several micro- and macroreticular ion exchangers by Hg porosimetry⁴⁵. The pores in the microreticular resins were said to be the distance between polymer chains, while macroreticular resins were said to have a macroporous structure in addition to the normal gel pore structure. These additional pores were described as being channels between small spherical gel particles.

1.3b Systematic studies on porosity formation

Millar et al. were the first to perform systematic studies on macroporous polystyrene resins. In their system, styrene and divinylbenzene were copolymerized in the presence of toluene, a solvating diluent⁴⁶. As the percentage of toluene was increased (at fixed amounts of divinylbenzene), there was a sharp transition from gel to macroporous beads at a certain percentage of toluene. Similarly, as the percentage of divinylbenzene was increased (at fixed amounts of toluene), there was a sharp transition from gel to macroporous beads at a certain percentage of divinylbenzene. The gel resins displayed virtually no uptake of solvents such as hexane and water, but did imbibe a considerable amount of toluene. The macroporous resins imbibed solvents of all polarities, the maximum uptake being observed for toluene.

It was suggested that the latter resins contained macropores that could be filled by any solvent, and that toluene could swell the gel phase in addition to filling the macropores. The authors stated that any copolymer bead of styrene and divinylbenzene which shows an uptake of cyclohexane of greater than 0.1 ml/g should be described as macroporous. In a later publication, the same research group prepared polystyrene-divinylbenzene resins in the presence of heptane, a non-solvating diluent⁴⁷. In this case, partial separation of phases will occur as the monomer is converted into polymer and the diluent mixture becomes increasingly richer in heptane. When solvating diluents such as toluene are used, the polymer chains are fully solvated at all times and no phase separation is believed to occur. These early papers are limited in their contribution to the understanding of the processes which occur in the formation of macroporous resins because the surface areas and pore size distributions of the polymers produced were not measured.

1.3c The first theory of porosity formation

In 1967, Kun and Kunin published a paper in which techniques such as Hg porosimetry and surface area determination by the B.E.T. method were used to fully characterize the porous structure of the Amberlyst series of macroreticular ion exchange resins⁴⁸. In a subsequent article published in 1968, these same authors attempted to explain the mechanism of porosity formation in macroreticular resins⁴⁹. A series of suspension copolymerizations of styrene and divinylbenzene were performed using various concentrations of divinylbenzene in the monomer mixture

(3, 10, and 20 %); t-amyl alcohol was used as the porogen in each case. In each polymerization, aliquots were withdrawn from the polymerization mixture at various time intervals and the porous structure of the insoluble fraction was analyzed by Hg porosimetry, B.E.T., electron microscopy, and IR. From the data, a theory evolved which described how the porous structure was formed as a function of time. The authors recognized that the composition of the diluent mixture (monomer plus porogen) shifts to higher percentages of porogen as the monomer is incorporated into the polymer. When the percentage of precipitating porogen (t-amyl alcohol) becomes high enough, a phase separation into a polymer-rich phase and a diluent rich-phase will occur. Kun and Kunin claimed that the beads are composed of an agglomeration of gel microspheres after phase separation and that the macroreticular structure is formed as the microspheres are bound together by further polymerization of the monomers.

1.3d Additional experimental data

Some other papers were published on this topic at approximately the same time. Tager et al. published a study dealing with the influence of the concentration of heptane on the porosity of polystyrene-divinylbenzene resins⁵⁰; the highest surface area values were obtained at high concentrations of both heptane and divinylbenzene. Wolf and Schaaf performed similar experiments using a number of different hydrocarbon diluents⁵¹, and observed that the pore volume increases as the thermodynamic affinity of the porogen for the polymer decreases because of an increase in the formation of large pores. Sederel and De Jong

have pointed out that there are three different types of macroporous resins which can be prepared⁵². When the porogen is a good solvent for the polymer molecules, a resin with a low pore volume, a very large surface area, and a small average pore diameter is obtained. When the porogen is a poor solvent for the polymer molecules, a resin with a large pore volume, a small internal surface, and a large average pore diameter is obtained. Finally, resins prepared using a linear polymer as porogen generally have a very small internal surface and a large average pore diameter. Sederel and De Jong prepared resins with unique porous properties by using diluents that consisted of various mixtures of the three types of porogens mentioned above (ie. toluene, heptane, and polystyrene). Finally, Seidl et al. published a detailed review article in German on this topic in 1967⁵³.

More recently, Poinescu et al. have studied the effect of cyclohexanol, cyclohexane, and cyclohexanone on the porosity of polystyrene-divinylbenzene copolymers and have found that the solvent-polymer interaction factor plays a large part in determining the porosity of the resins produced⁵⁴. The highest porosity networks were obtained using cyclohexanol as porogen; this porogen could be used to prepare high porosity networks containing a relatively small amount of crosslinking. Also, Svec et al. have published a series of papers dealing with the control of porosity in the glycidyl methacrylate-ethylene dimethacrylate system^{55,56,57}.

1.3e Pore structure collapse during the drying process

Hilgen, De Jong, and Sederel found that the porosity of these resins depends very much on the solvent from which they are dried⁵⁸. This phenomenon was later explained by Wieczorek et al.⁵⁹, who pointed out that polystyrene-divinylbenzene resins are inhomogeneous because the divinyl monomers are incorporated into the polymeric network much more rapidly than the monovinyl monomers. As a result, the final copolymer bead consists of heavily crosslinked "nuclei" joined by relatively loose and flexible polymer chains; the small micropores which contribute to the high surface area of these resins lie between these nuclei. When the porogen used in the polymerization is removed by drying, the flexible polymer chains collapse somewhat, but the rigid and highly crosslinked nuclei do not collapse to any great extent. If the resin is dried from toluene, which is a solvent for the polymer chains, the internuclear chains will be highly swollen by the solvent and will be in a highly flexible or rubber-like state. The chains will collapse to a great extent and many of the small pores between the nuclei will disappear. It is for this reason that polystyrene resins dried from toluene have a very low surface area. The collapse process is completely reversible, as the small pores can be restored by reswelling the polymer in toluene. If the toluene is displaced by methanol in a filtration apparatus and the resin is dried from this solvent, the final product will have a much higher surface area than in the former case. The internuclear polymer chains are not highly swollen by methanol and will be in a more rigid or glassy state. The chains collapse to a much smaller extent in this case and

many of the small pores are preserved. Also, when these polymers are dried at very high temperatures (ie. above the T_g of the internuclear polystyrene chains), the resins are found to have a very low surface area.

1.3f Current theory of porosity formation in macroporous resins

Between 1979 and 1982, Guyot et al. published a series of articles on macroporous polystyrene-divinylbenzene resins. These articles explained why there are differences in porous properties between resins formed with solvating and non-solvating diluents and the mode of formation of the macroporous texture in each case. Resins formed using a solvating diluent (toluene) were studied in great depth⁶⁰. With these resins, there are very sharp boundaries between the gel and macroporous domains. As the percentage of divinylbenzene is increased (while keeping the amount of toluene constant), there is a sharp transition from a gel to a macroporous resin at about 30 % divinylbenzene. Below this threshold value, a gel resin with no measureable surface area is obtained; above this threshold value, a macroporous resin with a high surface area is obtained. Similar trends are observed when the amount of toluene is increased (while keeping the percentage of divinylbenzene constant).

The authors noted that polystyrene-divinylbenzene resins are inhomogeneous because the divinyl monomers are incorporated into the polymeric network much more rapidly than the monovinyl monomers. At low conversions, the resin consists of heavily cross-linked "nuclei" joined by relatively loose and flexible polymer chains. If the amount of toluene present is too low, the nuclei

will be situated very close to one another, and further polymerization will lead to overlap and coalescence of the nuclei; the final product will thus be a gel-like resin swollen by the diluent. When larger amounts of toluene are used, the nuclei will be situated much farther away from each other because of a dilution effect. If enough diluent is present, the nuclei will remain individualized once polymerization is complete and very small pores (about $100 \text{ \AA}$) will be present between the nuclei.

When the amount of divinylbenzene is very low, the nuclei tend to be very large and they can overlap and coalesce very easily. When higher amounts of divinylbenzene are used, the nuclei are much smaller and tighter because of the large amounts of intramolecular crosslinking that occur. If the amount of divinylbenzene is high enough, the nuclei will be small enough and far enough apart that they will remain individualized once polymerization is complete.

Resins formed using solvating diluents such as toluene generally have a very sharp and narrow pore size distribution because they contain only one family of pores, which are the pores that lie between the nuclei. The boundary between the gel and macroporous domains is very sharp, and a very small increase in either the amount of divinylbenzene or the amount of toluene can cause this boundary to be crossed.

The same research group studied the polystyrene-divinylbenzene system using a number of non-solvating diluents. In 1979, a detailed paper was published which described how the porous structure changes as the percentages of divinylbenzene and porogen (ethyl-2-hexanoic acid) are changed⁶¹. As in the pre-

vious case, there is a very sharp boundary between the gel and macroporous domains; however, resins prepared with non-solvating diluents have both small and large pores, and the pore size distributions are very broad. In the previous case, the surface area increased steadily in the macroporous region as the percentage of toluene was increased. In the case of non-solvating diluents, the surface area passes through a maximum and begins to decrease when the percentage of porogen becomes very high. In the same year, this research group published a similar paper using four different non-solvating diluents (benzyl alcohol, ethyl-2-hexanoic acid, heptane, and pentanol)⁶².

Chung, Bartholin and Guyot have explained why different porous structures are obtained when solvating and non-solvating diluents are used as porogens⁶³. In the former case, the situation is fairly simple because the polymer molecules are fully solvated at all times and there is no phase separation. In the latter case, the situation is much more complex. The composition of the diluent mixture (monomer plus precipitating porogen) shifts to higher percentages of porogen as the monomer is incorporated into the polymer. When the percentage of precipitating porogen becomes high enough, a phase separation into a polymer-rich phase and a diluent rich-phase will occur. In this phase separation, the porogen is exuded from the polymer phase, and the volume occupied by the exuded porogen corresponds to the larger pores that are found in resins of this kind. The exudation of the porogen causes the collapse of the loosely crosslinked molecules connecting the heavily crosslinked nuclei. The result is that the space or volume that lies between the

nuclei is reduced. When very large amounts of porogen are used, the phase separation occurs fairly early in the polymerization because the precipitating strength is very high. Further polymerization results in the overlap or coalescence of the nuclei (which are now fairly close together) and the disappearance of the smaller pores which lie between the nuclei. This is the reason that the surface area decreases when the amount of precipitating porogen becomes too high.

In 1982, Guyot and Bartholin published an excellent review article which summarized the observations made in the preceding four papers as well as the work of other authors⁶⁴. In addition, this article discusses the chemistry of the copolymerization and gives conversion-time curves for each of the monomers present in a mixture of styrene and commercial divinylbenzene. The authors also discuss a new experimental technique called thermoporometry that allows the pore size distribution of macroporous resins to be determined in a variety of different solvents, whereas Hg porosimetry gives the pore size distribution in the dry state.

1.4 The history and development of the suspension polymerization technique

Virtually all polymeric separation media used in HPLC are produced by a suspension polymerization process, mainly because this process can be used to produce small, spherical, crosslinked beads that are ideal for chromatography. In a suspension polymerization, mechanical agitation is used to disperse one liquid phase into another in the form of droplets. Generally, one of the liquid phases is aqueous and the other is organic, and

these two phases should have minimal solubility in one another. The organic phase usually consists of one or more polymerizable vinyl monomers (one of these is often a crosslinking divinyl monomer) and a polymerization initiator, while the aqueous phase is usually a dilute solution of a suspension stabilizer. This technique was developed mainly because the high heat capacity of the water in the aqueous phase helps to dissipate the large heat of polymerization that makes bulk polymerizations difficult to control. Also, suspension polymerizations produce granular products that can easily be isolated and purified by filtration, while bulk polymerizations often produce rubbery masses that are difficult to handle⁶⁵.

1.4a Early patent literature

Gottlob was the first to disperse polymerizable monomers as droplets in an aqueous suspension⁶⁶. He polymerized isoprene at 60 °C using aqueous solutions of starch and gelatin as the suspending agents and described his product as having peculiar latex-like properties, but he did not refer to his technique as a suspension polymerization. In 1931, Bauer and Lauth obtained a German patent for a process that was called a pearl polymerization⁶⁷. In this process, acrylic ester monomers were polymerized using water or salt solutions as suspending agents, and the size of the pearl polymers formed was found to depend on the intensity of agitation⁶⁵.

Crawford and McGrath were the first to recognize that successful suspension polymerizations require the presence of a suspension stabilizer in the aqueous phase. Their research

involved the polymerization of alkyl esters of methacrylic acid using dilute solutions (0.2 to 3 %) of organic polymers as suspension stabilizers⁶⁸. The materials that were used as stabilizers included soluble starch, gum tragacanth, gum acacia, gum tragon, water soluble glycol cellulose, sodium alginate, agar agar, glue, and gelatin. The products of these polymerizations were usually obtained in globular form, except when the concentration of suspension stabilizer was too low, in which case a large fused polymeric mass was obtained.

1.4b The importance of the suspension stabilizer

Trommsdorff and Schildknecht have explained the phenomenon discussed above by pointing out that as a suspension polymerization proceeds, monomer droplets become very viscous because of the presence of polymer molecules dissolved in the residual monomer⁶⁵, and the collision of droplets during this "sticky period " can lead to coalescence and agglomeration. In the later stages of polymerization, the monomer droplets become very hard and agglomeration is not a problem. When suspension polymerizations are performed using only water as the aqueous phase, this "sticky period" can lead to the agglomeration of the entire bulk of the organic phase.

The mechanism of the stabilizing action of these organic polymers, which are often referred to as protective colloids, has never been well understood. It has been suggested that these polymers adsorb onto the surface of the droplet to form a protective film that prevents the agglomeration of colliding droplets; however, it has been shown that inorganic salts, such as

ammonium chloride and potassium sulfate, can also act as suspension stabilizers. Even though the technique of suspension polymerization has been known for some time, there is still no theory which relates stabilizer structure to its ability to stabilize a suspension polymerization⁶⁹. Bugada and Rudin have recently investigated the microstructure of a number of commercial samples of poly(vinyl alcohol)⁷⁰, and have found that these samples differ in the amount and kind of branching of the polymer chains, in the mean block lengths of the residual acetate groups, and in the percentage of residual acetate groups. These properties may be very important in determining the performance of these polymers as protective colloids in suspension polymerization and this may explain why only certain grades of poly(vinyl alcohol) result in successful suspension polymerizations.

1.4c Styrene-divinylbenzene copolymers produced by suspension polymerization

In 1945, Hohenstein and Mark published an article which reviewed all of the literature and many of the patents which had been published on this topic up until that time⁷¹; more recent review articles have been published by Trommsdorff^{65,72}. In 1951, Winslow and Matreyek described, in great detail, the influence of the suspension stabilizer in suspension polymerizations of technical divinylbenzene⁷³, using poly(vinyl alcohols) with different degrees of hydrolysis and different molecular weights as the suspending agents (these polymers were prepared by hydrolysis of vinyl acetate polymers). The particle

size was found to decrease as the concentration of the poly(vinyl alcohol) solution was increased and when higher molecular weight grades of poly(vinyl alcohol) were used. Also, a polymer with an 80 % degree of hydrolysis gave smaller particles than the grade of poly(vinyl alcohol) which was 100 % hydrolyzed.

Wolf and Eckert have studied the effect of changing various parameters on the particle size distribution of styrene-divinylbenzene copolymers produced by suspension polymerization^{74,75}. They found that spherical and non-agglomerated beads could only be obtained through the proper design of polymerization reactor and stirrer. The most important factors were the concentration of suspending agent, the stirring speed, and the volume ratio of the aqueous and organic phases. Larger particles were obtained when the ratio of the aqueous phase to the organic phase was reduced because of the increased number of droplet collisions in this case. The percentage of divinylbenzene and the concentration of initiator had no effect on the particle size.

1.4d Methacrylate polymers produced by suspension polymerization

The research group of F. Svec has performed extensive studies on the glycidyl methacrylate-ethylene dimethacrylate system. In this system, the particle size was found to reach a limiting value as the stirring speed was increased⁷⁶. As the concentration of the poly(vinyl alcohol) suspension stabilizer was increased, the mean particle size was reduced because of a large reduction in the interfacial tension between the aqueous and organic phases. Changing the PVA concentration from 0.007 % to 2 % reduced the average particle size from 1500 μm to 7 μm ⁷⁷.

2. Results and discussion

The aim of this research was to study the feasibility of using functionalized polymers containing reactive groups as adsorbents in HPLC. The first task to be accomplished was the choice of the type of chemical functionality to be used as a polymeric adsorbent. Polymers containing a phenol moiety were chosen because this moiety contains an acidic hydrogen atom that can undergo strong hydrogen bonding interactions with basic compounds such as amines and because this bonding mirrors that which occurs between organic molecules and the acidic silanol groups of silica adsorbents. A series of chromatographic adsorbents were prepared in which the acidity of the phenolic hydrogen and the steric environment around the phenolic hydrogen was systematically changed so that we could observe how the separation ability of the phenol moiety changes as its structure is changed. These adsorbents were prepared by suspension copolymerization of the appropriate vinyl monomers and commercial divinylbenzene. The suspension polymerization technique was chosen because it allows the preparation of spherical, crosslinked, macroporous beads which are ideal for HPLC and because bead properties such as particle size, porosity, and mechanical strength can be varied accurately over a wide range by careful control of the polymerization conditions. Compounds containing a basic nitrogen atom that can strongly hydrogen bond to the phenolic hydroxyl, such as aliphatic amines, anilines, and pyridines, were separated.

2.1 Design of the polymeric adsorbents

The synthetic strategy involved in the preparation of the various poly(phenols) shown in Figure 1 is very important. These materials are to be synthesized in the form of small, spherical beads as copolymers with commercial divinylbenzene (this component of the polymer beads is omitted from Figure 1 for the sake of simplicity). We chose to attempt to synthesize the unhindered poly(phenol), and the corresponding dimethyl and diisopropyl substituted polymers. This gives a series of polymers in which the acidity of the hydroxyl group and the steric environment around the hydroxyl group has been systematically changed and varied over a wide range. No attempt was made to synthesize the corresponding di-*t*-butyl derivative because some hydrogen-bonding studies carried out in the past indicate that the 2,6 di-*t*-butyl phenol moiety is so sterically hindered that it does not associate with amines such as pyridine, triethylamine, and dimethylamine, except at high concentrations⁷⁸.

2.2 Preparation of the monomers

The bead polymers described in Section 2.1 could be synthesized by radical suspension copolymerization of the appropriate hydroxystyrene monomers with commercial divinylbenzene; however, the phenolic hydrogen of these monomers is known to undergo chain transfer reactions in radical polymerizations⁷⁹. For example, a growing polymer chain, represented by P[•] in Figure 2, can react with a hydrogen atom of the phenolic moiety to generate a "dead" polymer chain and a phenoxy radical; this reaction is particularly important for phenols because the resulting phenoxy radical

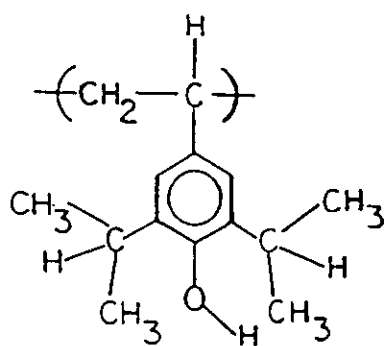
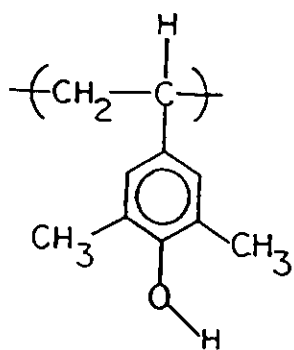
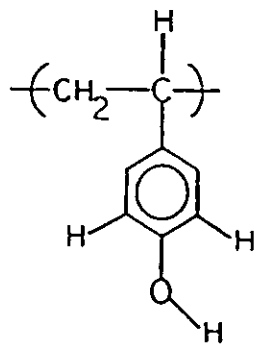


Figure 1 - Structure of the target polymers

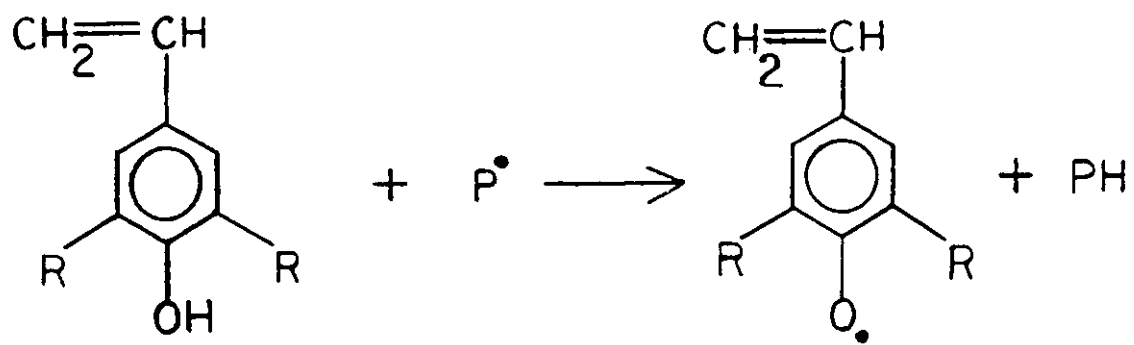
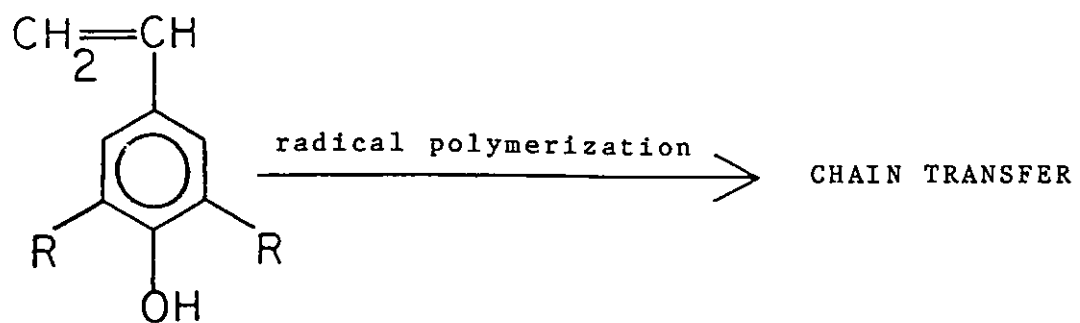


Figure 2 - Chain transfer in the polymerization of vinyl phenols

is resonance stabilized. Hindered phenols, such as the 2,6-di-alkylphenols, are particularly powerful inhibitors, partly because the resulting phenoxy radicals are so sterically hindered that they are not able to undergo further reactions, such as re-initiation of polymerization, and partly because of electronic stabilization of the phenoxy radical by hyperconjugation of the alkyl groups⁸⁰. In addition, the polymers produced by radical polymerization of these hindered vinyl phenol monomers are obtained in lower yield and are of lower molecular weight than polymers prepared by polymerization of blocked hindered phenols⁸¹.

Polymeric materials which are to be used as packing materials in HPLC must have specific physical properties if they are to be effective as polymeric adsorbents. Generally, these materials must have a high degree of crosslinking and mechanical strength because they will be packed and used at high pressures, and they should not swell or shrink very much in the solvents used as mobile phases in HPLC. The chain transfer reactions which occur in the direct polymerization of hindered vinyl phenol monomers may not allow the preparation of polymer beads with sufficient mechanical strength to be used as HPLC adsorbents. In fact, this type of problem was encountered by a research group that attempted to incorporate carbon black into some suspension polymerized copolymers of styrene and n-butyl methacrylate⁸². Carbon black is a known inhibitor of radical polymerization, and only very soft polymer beads were obtained in low yields using peroxy compounds as initiators. The most likely reason for this is that radical termination by the carbon

black additives gives rise to a large fraction of oligomeric material of sufficiently low molecular weight to act as a plasticizer. A "controlled" polymerization using protected phenol groups will probably be required to produce polymer beads which are suitable for HPLC.

Given the above discussion, the target monomers are 3,5-dialkyl-4-hydroxystyrenes containing a protected phenolic group. Any synthesis should begin with starting materials which are commercially available or which can be readily prepared. All of the appropriate alkyl-substituted phenols are available from the Aldrich Chemical Company, and thus all of our syntheses begin with the corresponding phenol. The problem is to find some way to functionalize the phenolic nucleus directly with a functionality, such as an aldehyde group, that can eventually be converted into a vinyl group. Aromatic rings can be functionalized with formyl groups by a variety of synthetic methods. One such method involves a Friedel-Crafts condensation with carbon monoxide and hydrogen chloride catalyzed by aluminum chloride, which is better known as the Gatterman-Koch reaction⁸³. These reactions occur in good yields for most aromatics, but they are very sluggish for phenols because reaction of the -OH group and aluminum chloride gives an adduct which is much less reactive than the phenol itself, mainly because the oxygen electrons are delocalized onto the electron-deficient aluminum⁸⁴. Another approach to the formylation of aromatic rings involves the formation of an aryl lithium reagent, followed by condensation with dialkylformamides and hydrolysis of the resulting adduct⁸⁵; however, the acidic phenolic proton would obviously cause compli-

cations with this reaction.

2.2a Formylation of alkylphenols using the Duff procedure

A direct formylation procedure applicable to phenols involves the Duff reaction, which was first reported in 1934⁸⁶. In this reaction, a mixture of a phenol and hexamethylenetetramine is heated in a large excess of an organic acid, such as acetic acid, which participates in the reaction both as a reagent and as a solvent. There has been a great deal of speculation in the literature concerning the mechanism of this reaction, and a detailed kinetic study published in 1968 helped to elucidate this mechanism, which is shown schematically in Figure 3⁸⁷. Under the action of acid and heat, hexamethylenetetramine is believed to decompose to methylimine, which can undergo an acid catalyzed electrophilic aromatic substitution reaction with the phenol ring to give the aminomethylated phenol. This intermediate is then oxidized by the remaining methylimine to the aromatic imine, and then this intermediate is hydrolyzed to the aldehyde by water. A modification of this reaction uses trifluoroacetic acid as the solvent, and a variety of aromatic compounds can be formylated in good yields using this procedure⁸⁸. The reaction works very well for the direct formylation of phenols; we have obtained a 70 % yield of 3,5-dimethyl-4-hydroxybenzaldehyde when 2,6-dimethylphenol was formylated under these conditions. A similar reaction was performed on 2,6-diisopropylphenol. This particular compound, which can be purchased from Aldrich, is reported to be only 90 % pure. A TLC of this starting material displayed one major component,

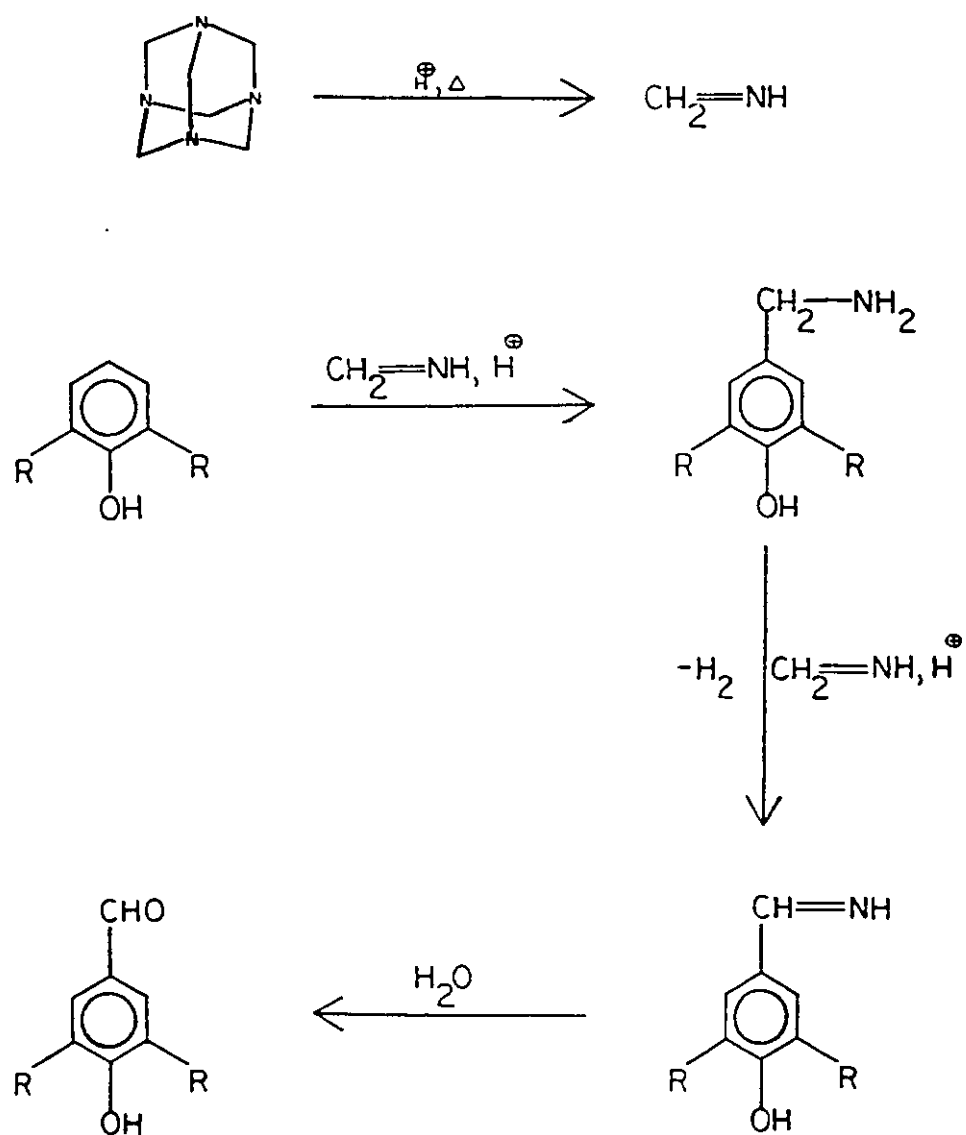


Figure 3 - Mechanism of the formylation reaction

which was the 2,6-diisopropylphenol, and one minor component, which had an R_f identical to that of 2-isopropylphenol. ^{13}C -NMR of this impure starting material shows six large peaks belonging to 2,6-diisopropylphenol, as well as a series of six smaller peaks in the aromatic region belonging to 2-isopropylphenol. The impure commercial material was used in the formylation reaction without any prior purification because of the great difficulty involved in removing this particular impurity. The crude product of the reaction was purified by recrystallization from chloroform/hexane. The yield of 3,5-diisopropyl-4-hydroxybenzaldehyde, based on the total weight of starting material used, was 78 %; the yield based on the actual weight of 2,6-diisopropylphenol present at the start of the reaction was 87 %. The ^{13}C -NMR of the product shows only the peaks corresponding to 3,5-diisopropyl-4-hydroxybenzaldehyde.

The fact that a better yield is obtained for the reaction on diisopropyl phenol than with its dimethyl analog may indicate that fewer side products are formed in the former reaction. In the latter reaction, substitution meta to the hydroxyl groups is a possible side reaction, although these products would certainly not be formed in very large amounts. With diisopropyl phenol, crowding would restrict the possibility of reaction at these positions.

2.2b Protection of phenolic hydroxyls using the t-BOC group

The next step of the synthesis, which is shown in Figure 4, involves protection of the phenolic group as its t-butyl carbonate derivative so that this group will not interfere in the

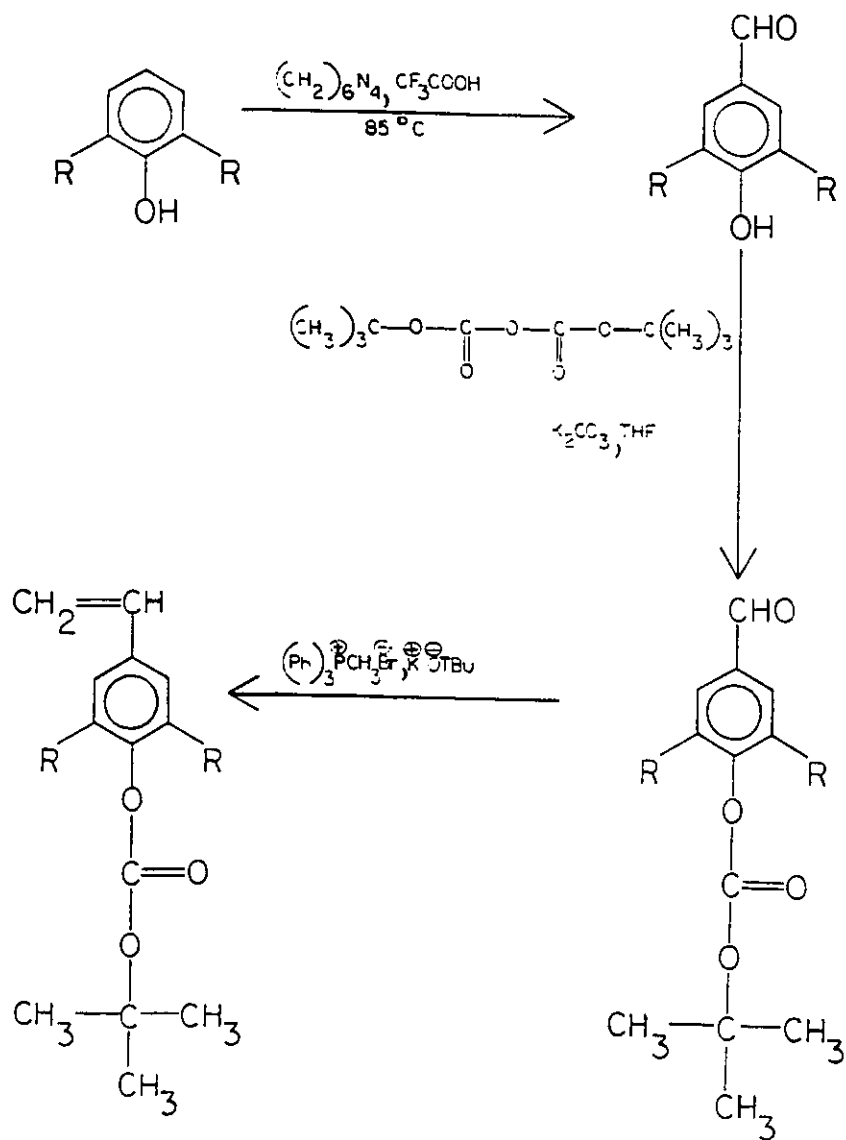


Figure 4 - The synthetic scheme used to prepare the t-BOC derivatives of the desired hindered vinyl phenols

subsequent Wittig reaction. The choice of protecting group is very important, and the reasons for choosing this particular protecting group are discussed fully in Section 2.4b. Experimental conditions which give good yields of t-BOC derivatives of phenols were developed by Houlihan et al⁸⁹. In a model study on the use of the t-BOC functionality as a protecting group for phenols and alcohols, these authors showed that di-t-butyl dicarbonate reacts readily with unhindered phenols in the presence of potassium carbonate and 18-crown-6, but the reaction proceeds only to 10 % conversion with 2,6-di-t-butylphenol, which has a severely hindered phenolic group; the 18-crown-6 catalyst was reported to speed up these reactions but did not improve the yields.

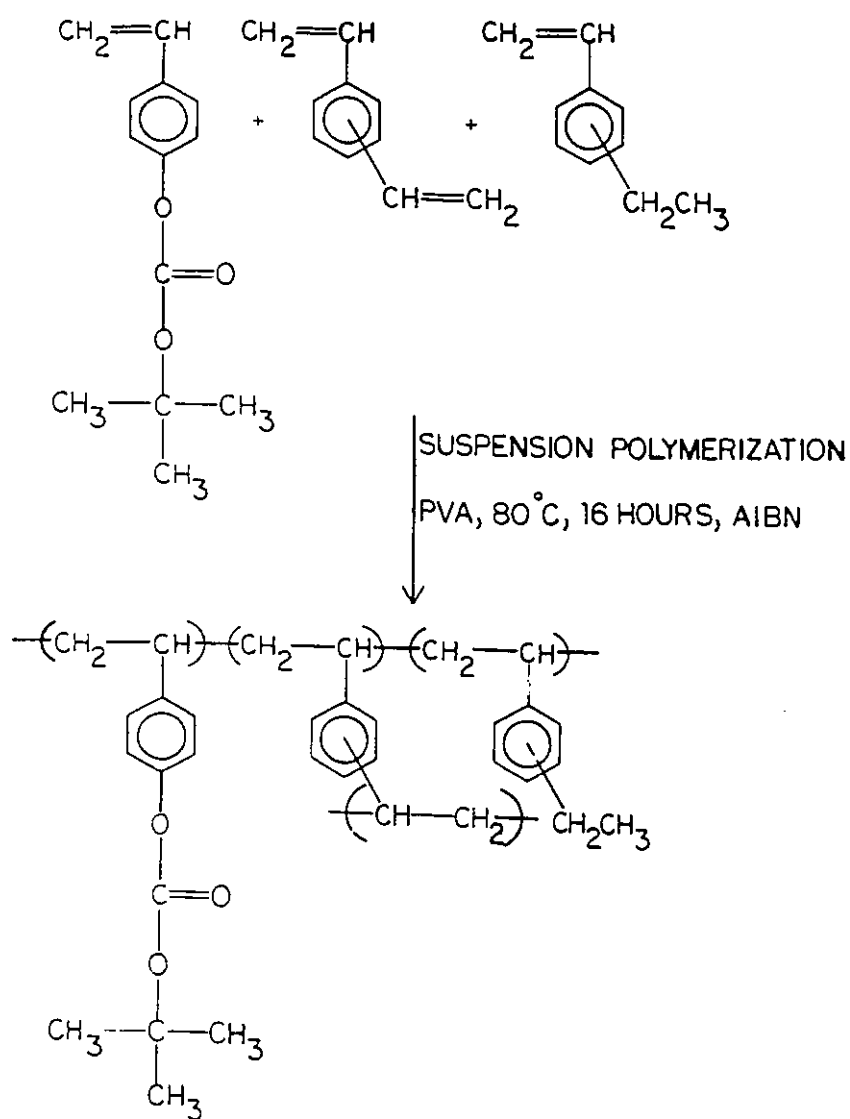
In this research project, this reaction was performed on 3,5-dimethyl-4-hydroxybenzaldehyde and 3,5-diisopropyl-4-hydroxybenzaldehyde; 18-crown-6 was not used in the preparations described herein as its addition is not required for the reaction to proceed and product purification is simpler in its absence. When this reaction was performed on 3,5-dimethyl-4-hydroxybenzaldehyde, a 90 % yield of 3,5-dimethyl-4-t-butyloxycarbonyloxybenzaldehyde was obtained. This reaction was much slower than the reaction with the unhindered phenol, but it was essentially complete after stirring overnight. When a similar reaction was performed on 3,5-diisopropyl-4-hydroxybenzaldehyde, an 87 % yield of 3,5-diisopropyl-4-t-butyloxycarbonyloxybenzaldehyde was obtained. Although these two reactions reach approximately the same conversion, the reaction on the diisopropyl monomer is much slower, requiring 3-4 days to reach completion.

2.2c Wittig reactions

Unlike a simpler acetyl group⁹⁰, the t-BOC protecting group appears to be completely stable under the conditions of the Wittig reaction used in the final step of the synthesis. The Wittig reaction of 3,5-dimethyl-4-t-butyloxycarbonyloxybenzaldehyde gave an 81 % yield of 3,5-dimethyl-4-t-butyloxycarbonyloxy-styrene, while the Wittig reaction of 3,5-diisopropyl-4-t-butyl-oxy carbonyloxybenzaldehyde gave an 86 % yield of 3,5-diiso-propyl-4-t-butyloxycarbonyloxystyrene. The unhindered monomer, 4-t-butyloxycarbonyloxystyrene, which was first prepared by Frechet and coworkers, is now available commercially, and was used as received.

2.3 Development of suspension polymerization techniques for protected vinyl phenols

As outlined above, our goal was to make functionalized, small (10 μ m), polymer beads having a high surface area and porosity. In order to prepare polymer beads having these specific properties, a series of suspension polymerizations was carried out under a variety of experimental conditions; the reactants and experimental conditions are shown in Figure 5. In each experiment, a 2 % solution of poly(vinyl alcohol) was used as the aqueous phase. All the polymerizations were run at 80 °C for 16 hours. The monomer mixture used in each experiment consisted of 50 wt. % of commercial divinylbenzene and 50 wt. % of p-t-BOC-styrene; the latter monomer was chosen to develop polymerization conditions as it is readily available in this laboratory. The composition of commercial divinylbenzene has



CONTROL OF POROSITY AND PARTICLE SIZE

Figure 5 - Experimental conditions and reactants used in the suspension polymerization of protected vinyl phenols

been analyzed and is reported in the literature to consist mainly of a mixture of m-divinylbenzene, p-divinylbenzene, m-ethylstyrene, and p-ethylstyrene⁹¹. The commercial divinylbenzene used in these experiments was purified by distillation prior to polymerization; ¹H-NMR analysis of the distillate indicates that the ratio of the total amount of divinylbenzene isomers to the total amount of ethylstyrene isomers is approximately 1:1. AIBN was used as the initiator in all polymerizations. Each experiment was performed in a Buchi BEP 280 suspension polymerization reactor using a 250 ml glass reaction vessel and a stainless-steel overhead anchor stirrer. The Buchi reactor incorporates a highly regulated transmission system which allows for accurate control of the stirring speed. Porosity was controlled by varying the amount and chemical structure of the porogen used in the polymerization recipe. Particle size was controlled by changing the stirring speed, the ratio of the aqueous and the organic phases, and the porogen.

The porous structure of these materials was characterized by the measurement of their surface area and porosity. Surface areas were determined by measuring the adsorption of nitrogen onto the surface of the polymer samples at liquid nitrogen temperatures⁹²; these measurements were converted into surface area values using the Brunauer-Emmett-Teller (B.E.T.) equation⁹³. Pore volumes were estimated by the solvent regain or centrifugation technique; this method was first reported in 1951 by Pepper⁹⁴. In this procedure, a weighed amount of polymer beads is placed in a filter tube which is immersed in cyclohexane overnight. After a 24 hour immersion period, the sample is centri-

fuged to remove excess cyclohexane and reweighed; the pore volume of the beads can be estimated from the weight of cyclohexane absorbed. Presumably, the solvent is retained in the pores of the polymer by capillary forces. Pore size distributions ($37 \text{ \AA}$ - $37,500 \text{ \AA}$) were determined for several samples using Hg porosimetry. The internal morphology of several samples was studied using scanning electron microscopy.

2.3a Control of porosity

Table 1 lists the surface areas, solvent regains, and % porosities of the polymers obtained in the suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene using a variety of solvents as porogens. Resins with a wide range of porous properties were obtained simply by using five different porogens. Some of the resins have very little surface area ($0\text{-}1 \text{ m}^2/\text{g}$), while others have surface areas near $200 \text{ m}^2/\text{g}$. Obviously, the chemical structure of the porogen plays an important role in determining the porosity of the polymer. Also, the pore volumes, which are estimated by the solvent regain values, vary over a fairly wide range. It is difficult to accurately measure the surface area of a polymer when this value is below $1 \text{ m}^2/\text{g}$. In such instances, the surface area is simply reported as $0\text{-}1 \text{ m}^2/\text{g}$.

2.3a1 Control of porosity by variation of the % of porogen

Table 2 contains the surface areas, solvent regains, and % porosities of the polymers obtained in the suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene using different percentages of n-butanol as porogens. The % porosity

Table 1 Control of surface area and pore volume in the copolymerization of p-t-BOC-styrene and divinylbenzene by variation of the chemical structure of the porogen

<u>Porogen (50 volume %)</u>	<u>Surface Area</u>	<u>Solvent Regain</u>	<u>% Por.</u>
n-butyl acetate	0-1 m ² /g	0.43 ml/g	30 %
n-butanol	4.8 m ² /g	0.60 ml/g	38 %
benzyl alcohol	71 m ² /g	1.33 ml/g	57 %
cyclohexanol	190 m ² /g	0.92 ml/g	48 %
n-heptane	197 m ² /g	1.03 ml/g	51 %

Table 2 Control of surface area and pore volume in the copolymerization of p-t-BOC-styrene and divinylbenzene by variation of the percentage of n-butanol

<u>Porogen (volume %)</u>	<u>Surface Area</u>	<u>Solvent Regain</u>	<u>% Por.</u>
n-butanol (30 %)	0-1 m ² /g	0.12 ml/g	11 %
n-butanol (40 %)	1.3 m ² /g	0.43 ml/g	30 %
n-butanol (50 %)	4.8 m ² /g	0.60 ml/g	38 %
n-butanol (60 %)	143 m ² /g	1.36 ml/g	58 %
n-butanol (70 %)	26 m ² /g	1.85 ml/g	65 %

* For Tables 1-5, % Por. represents the percentage porosity of each sample, which is calculated by the following equation:

$$\% \text{ Por.} = V_s / (V_s + V_p)$$

* V_s is the volume of cyclohexane taken up by 1 g of the polymer, which can be determined from the solvent regain values.

* V_p is the volume of 1 g of polymer beads. This volume is 1 ml in each case because the density of this polymer matrix was determined to be exactly 1 g/ml from the value of its balanced density slurry (see Section 4.11).

increases steadily as the percentage of n-butanol is increased from 30 % to 70 %; this result is expected because the pore volume can generally be related to the amount of porogen used in the polymerization recipe. The surface area, however, increases from 0-1 m²/g with 30 % n-butanol to 143 m²/g with 60 % n-butanol, and then drops drastically to 26 m²/g with 70 % n-butanol.

The data shown in Figure 6 and Figure 7 partially explain the results presented in Table 2. Figure 6 shows the Hg porosimetry curves, in the cumulative form, for the polymers prepared using 50 %, 60 %, and 70 % n-butanol. In this technique, Hg is forced into the pores of a polymer under high pressure; it is forced into progressively smaller pores as the pressure is increased, and the volume of Hg that is forced into the pores is recorded accurately. The pressure-volume data can be transformed into a cumulative pore size distribution curve using the Washburn equation⁹⁵. Cumulative pore volume is plotted on the y-axis in ml/g and the logarithm of the pore radius is plotted on the x-axis. For the sake of clarity, the x-axis is labelled with values of the pore radius rather than the logarithm of the pore radius because of the wide range of pore radii measured. The smallest pore radius that is shown, 37 Å, corresponds to the upper pressure limit of the porosimeter used to make these measurements.

Clearly, the polymer prepared using 50 % n-butanol as porogen has a low surface area because this resin has very few pores, small or large. The polymer prepared using 60 % n-butanol as porogen has a high surface area because most of its porosity is

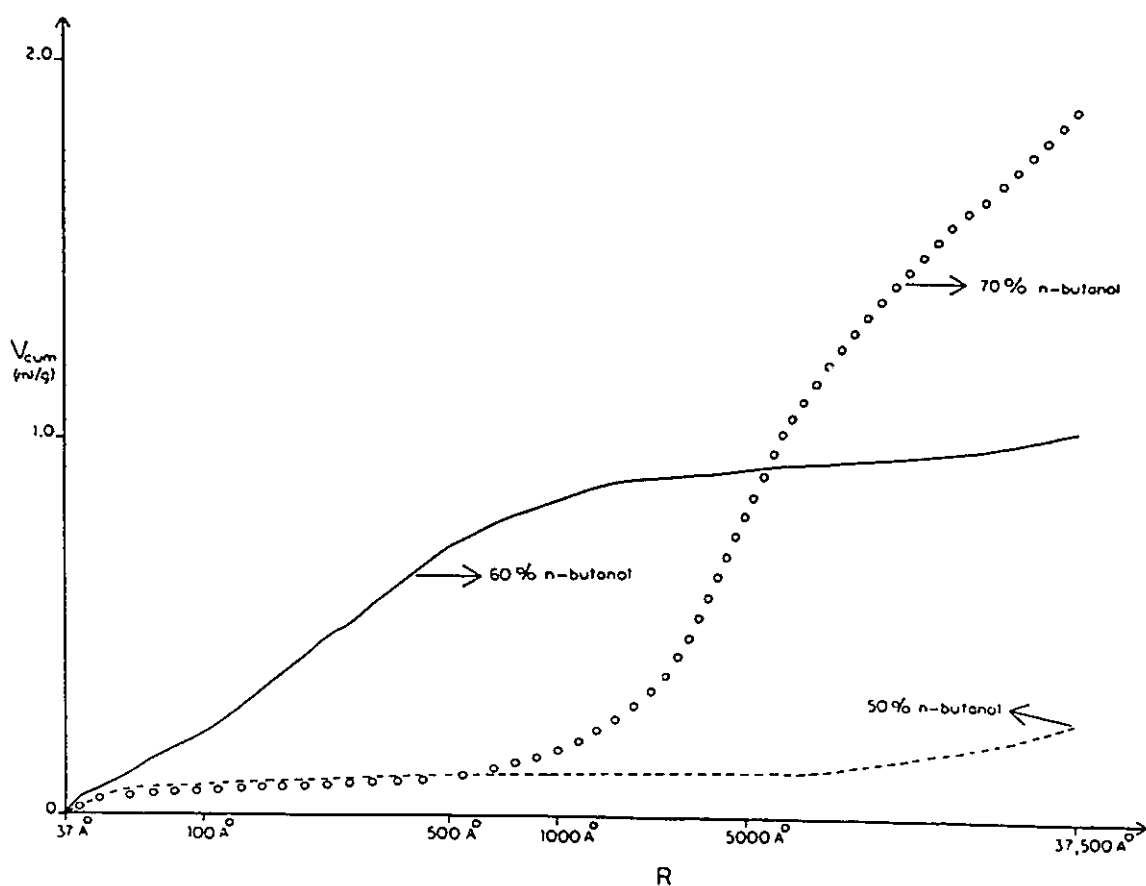


Figure 6 - Cumulative Hg porosimetry curves for the p-t-BOC-styrene-divinylbenzene resins prepared using 50 %, 60 %, and 70 % n-butanol

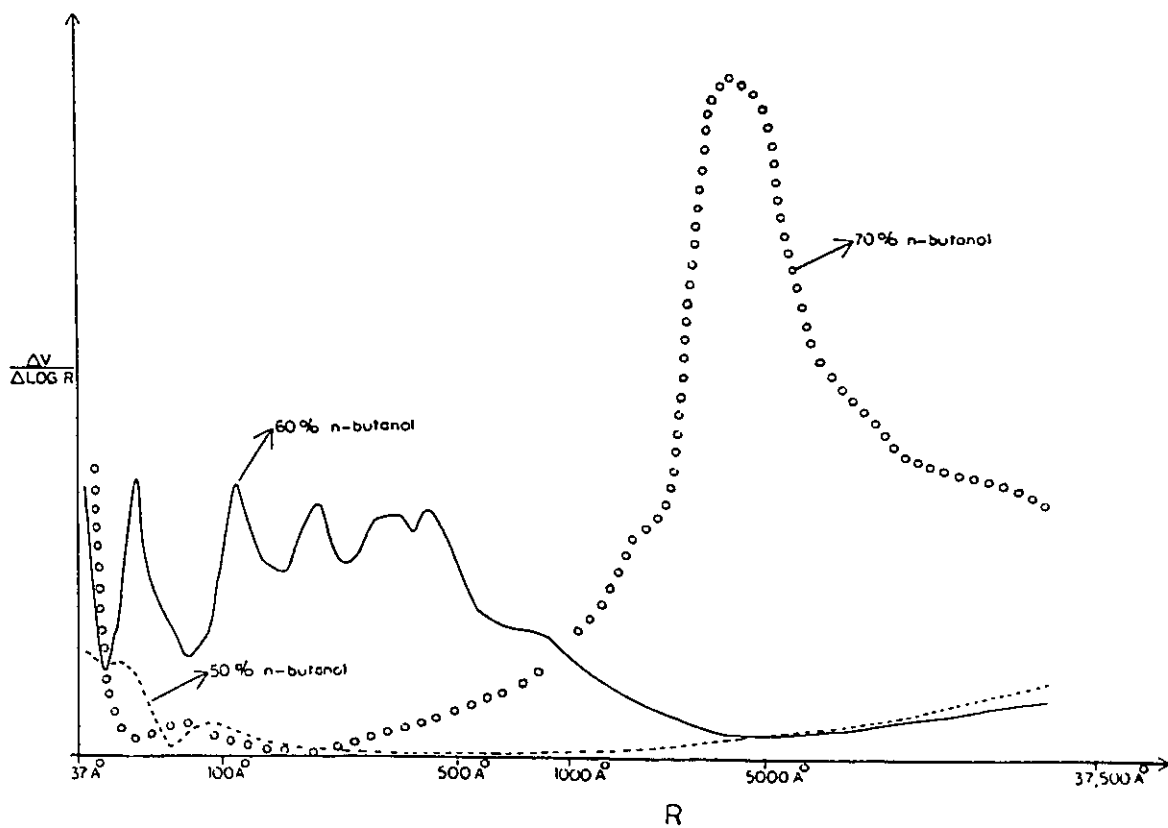


Figure 7 - Differential Hg porosimetry curves for the p-t-BOC-styrene-divinylbenzene resins prepared using 50 %, 60 %, and 70 % n-butanol

contained in pores below $1000 \text{ \AA}$. The surface area drops upon proceeding to 70 % n-butanol because this resin has virtually no small pores; most of its porosity is contained in pores which are larger than $1000 \text{ \AA}$. The "differential" pore size distribution can be calculated from the pore volume-pore radius data⁹⁵; these curves are shown in Figure 7. Both the cumulative and "differential" curves yield the same information, but it is often easier to compare several curves when they are in the latter form.

It is possible to provide an explanation of the above results because the theory of pore formation in macroporous resins has been elegantly developed by the research group of Guyot⁶⁴. This group studied the styrene-divinylbenzene system using both solvents and non-solvents of polystyrene as porogens, and they obtained completely different porous structures in each case. In this dissertation, the system which involves the use of a solvent as porogen will be discussed first.

Resins having a high surface area ($500 \text{ m}^2/\text{g}$) and a moderate pore volume can be made using solvents for the polymers as porogenic agents. These resins generally have a very sharp distribution of small pores ($100 \text{ \AA}$) and virtually no large pores⁶⁰. Figure 8⁶⁴ shows the conditions under which gel resins and macroporous resins can be produced. The percentage of toluene used as porogen is plotted on the y-axis while the percentage of divinylbenzene used in the monomer mixture is plotted on the x-axis. The boundary between the gel and macroporous domains is very sharp; there is a very sharp transition between a resin with no measureable surface area and a resin with a high surface area. Inside the macroporous region, the surface area and pore volume

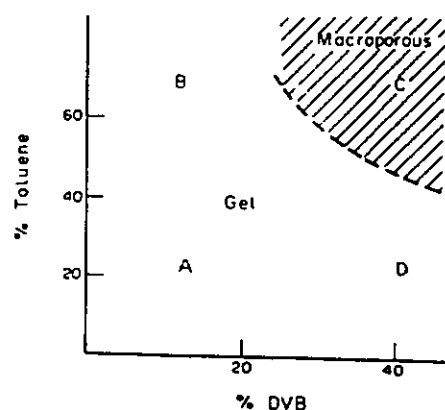


Figure 8 - Regions of gel and macroporosity for poly(styrene-divinylbenzene) resins prepared using toluene as the porogen (taken from reference 64)

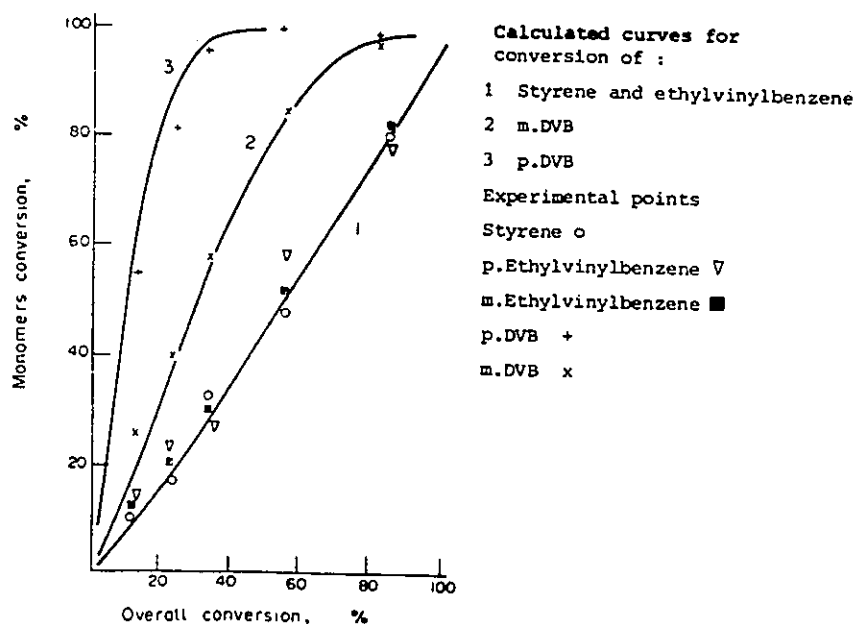


Figure 9 - Conversion curves for the various monomers present in a mixture of styrene and commercial divinylbenzene (taken from reference 64)

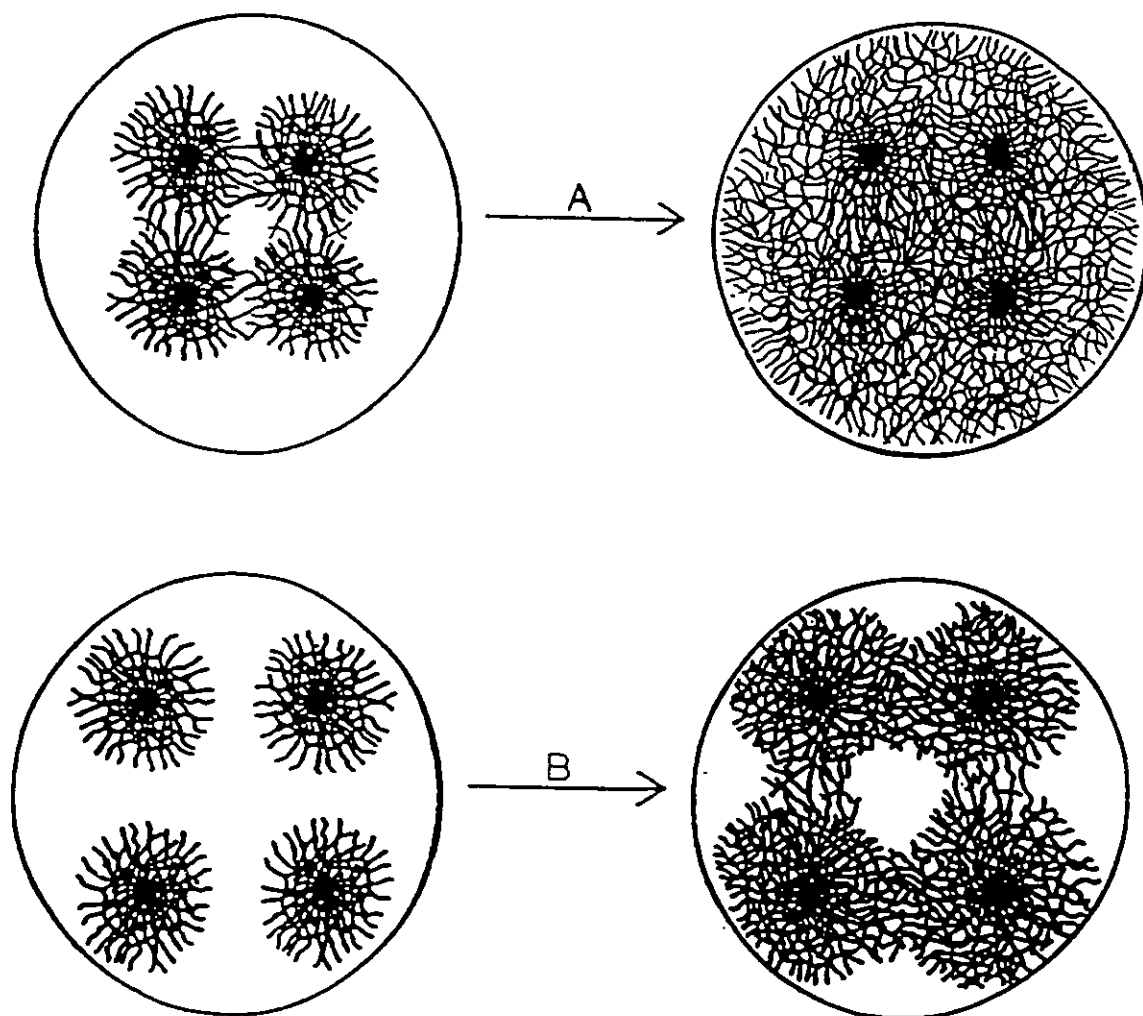


Figure 10 - Formation of the porous texture outside (A) and inside (B) of the macroporous domain

increase steadily as the percentage of toluene increases; the surface area does not decrease at high percentages of porogen when the porogen is a solvent for the polymer molecules⁶⁴.

In his excellent manuscript on porosity control in polymeric resins, Guyot states that "At the beginning of the copolymerization, much more divinylbenzene is built into the copolymer than is known to be in accord with the initial composition of the monomeric mixture. Thus, the divinylbenzene constituents, which at first are more tightly embedded into the resin structure, induce the formation of regions of narrow-mesh, highly entangled networks interspaced with long-chain and less highly crosslinked members, which are formed in a later stage of the copolymerization when the major part of the divinylbenzene monomers have been used up⁶⁴." Figure 9⁶⁴ shows the reactivities of the various components of the styrene-divinylbenzene system in a graphical form. Both para- and meta-divinylbenzene are incorporated in the polymer much faster than the mono-vinyl monomers. It is believed that many of the pendant double bonds of the divinylbenzene units participate in intramolecular copolymerization. The process described above is illustrated schematically in Figure 10. The upper half of this Figure depicts the situation outside the macroporous domain at low diluent or porogen contents. The dark black regions indicate the regions of high cross-link density which are formed early in the polymerization. These "nuclei" or "nodules" are connected by the less highly crosslinked molecules formed a little later in the polymerization. The distance between these nodules is not very large because of the small percentage of diluent or porogen present. As the polymerization

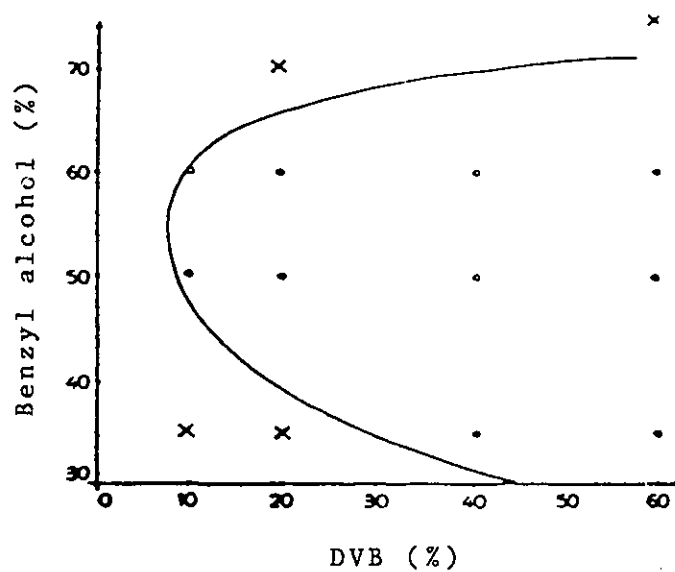
proceeds to its final conversion, as indicated by the arrow in the Figure, the nodules grow in size by addition of monomer molecules to growing chain ends and through the polymerization of the pendant double bonds present in the polystyrene chains. This will eventually lead to complete coalescence or overlap of the nuclei and a gel-like resin with no measurable surface area or pore volume will be produced. The lower half of Figure 10 depicts the situation inside the macroporous domain at high diluent or porogen contents. In this case, there is much more space or available volume in which the nodules or nuclei can grow. If the percentage of diluent is high enough, there will not be a complete coalescence or overlap of the nodules; some empty space or small pores will remain between the nodules at the completion of polymerization. The result of these processes is the production of a resin with a high surface area and a narrow pore size distribution⁶⁴.

It is also known that there is a sharp transition from the gel region (low surface area) to the macroporous region (high surface area) when the percentage of divinylbenzene in the monomer mixture is increased as the volume percent of diluent is held constant. When the percentage of divinylbenzene is high, the nodules or nuclei are small and compact, mainly because of the rapid intramolecular polymerization of the pendant double bonds of the divinylbenzene units. This means that there is a larger available volume in which the nuclei can grow when the percentage of divinylbenzene is high. Above a threshold divinylbenzene value, the nuclei remain individualized upon completion of polymerization; the result is a resin which has many small pores

between the nuclei and a high surface area⁶⁴.

When the porogen is a non-solvent for the polymer molecules being formed, the situation is much more complex. Figure 11⁶³ shows the macroporous domain for the copolymerization of styrene and divinylbenzene in the presence of benzyl alcohol, a non-solvent for polystyrene. This domain is indicated by a parabolic line that has an axis parallel to the abscissa. On the lower side of the macroporous domain (20 % DVB and 35 % diluent), a gel-like resin with very little surface area or pore volume is obtained. Inside the macroporous domain (20 % DVB and 40-65 % diluent), macroporous resins with high surface areas are produced. On the upper side of the macroporous domain (20 % DVB and 70 % diluent), a resin with a small surface area and a large pore volume is obtained. These resins have only very large pores; the smaller pores which contribute most to high surface areas are not present⁶³.

In the early stages of polymerization, the diluent mixture consists of a mixture of the porogen and unreacted monomer. As the polymerization proceeds, the monomer is incorporated into the polymer and the composition of the diluent mixture shifts towards a higher percentage of the porogen, which is a non-solvent for the polymer. When the percentage of porogen in the diluent mixture becomes very large, phase separation or precipitation will occur. In this process, most of the porogen is exuded from the regions between the polymer molecules. Two "phases" are created; one phase contains a high concentration of polymer molecules while the other contains mostly the porogen. The volume occupied by the exuded porogen corresponds to the very large



(x) outside of the macroporous domain
(o) inside of the macroporous domain

Figure 11 - Borderline of the macroporous domain for poly(styrene-divinylbenzene) resins prepared using benzyl alcohol as the porogen (taken from reference 63)

pores seen in the pore size distributions of resins prepared using non-solvents as porogens. When a solvent for the polymer molecules is used as a porogen (e.g.: toluene), the quality of the solvent medium does not change during the polymerization. No phase separation occurs in this case, and so these resins have only a narrow distribution of very small pores⁶⁴.

The discussion presented in the above paragraphs can be used to help to explain the Hg porosimetry curves shown in Figure 7. Also, a schematic representation of the phase separation process is presented in Figure 12. First, consider the case when the porogen is 50 volume % n-butanol, which is a non-solvent for the polymer molecules formed in the p-t-BOC-styrene-divinylbenzene system. The polymer formed in this case contains virtually no small pores or large pores, and the resin obtained has a very low surface area. In this case, there is simply not enough available volume in which the nodules can grow without coalescing because the percentage of diluent is relatively low. Some phase separation may occur, but this would happen very late in the polymerization because of the relatively low amount of n-butanol present. When 70 volume % n-butanol is used as the porogen, a resin with only very large pores is obtained. In this case, phase separation will occur relatively early in the polymerization because of the large amount of non-solvent present. The nodules do not shrink very much when the porogen is exuded from this region because it contains highly crosslinked molecules; however, the molecules connecting adjacent nodules are much less crosslinked, and they do collapse to a large extent upon exudation of the porogen. As a result, the "empty" volume that

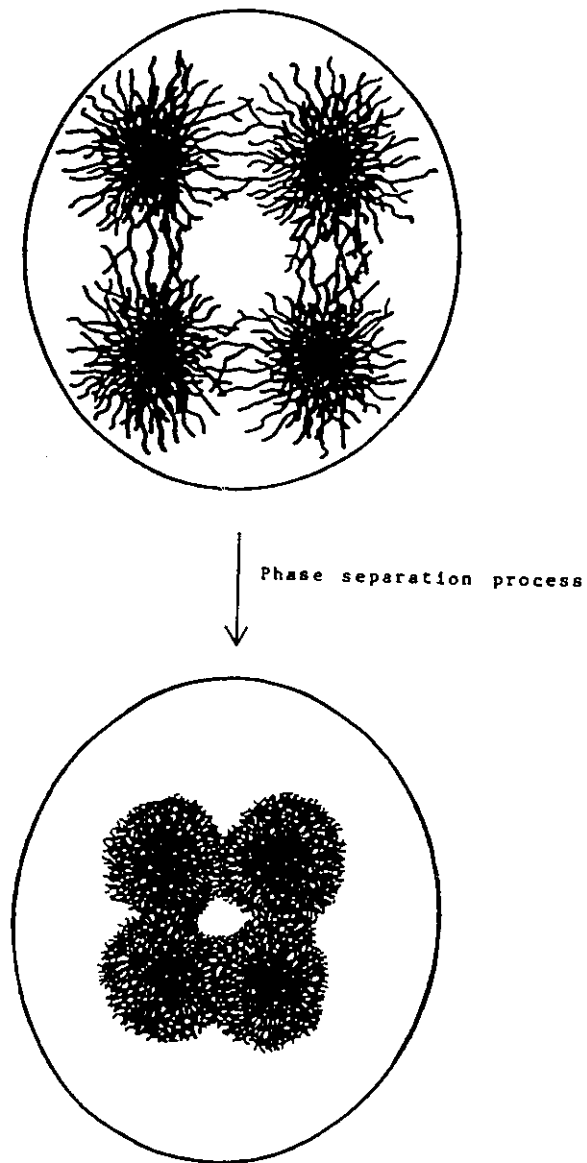


Figure 12 - Changes in resin morphology that occur during the phase separation process

lies between several adjacent nodules is reduced considerably; this is depicted in Figure 12. Because the phase separation occurs very early in the polymerization, the nodules will grow to a considerable extent through polymerization of the remaining monomer and will eventually overlap and coalesce. No small pores remain upon completion of polymerization; only the large pores formed by the exudation of solvent remain. As a result, a resin with a small surface area and a large pore volume is obtained. When 60 volume % of n-butanol is used as the porogen, the phase separation which leads to a concentrated polymer phase occurs much later in the polymerization because there is less non-solvent present in the polymerization mixture. The nodules will still grow after phase separation, but they will not grow as much as in the previous case because a large percentage of the polymerization has occurred before phase separation; therefore, the nuclei will not be completely coalesced upon completion of polymerization and many of the small pores will remain⁶⁴, and the larger pores formed by the exudation of solvent will also be present. As a result, a resin with a large surface area and a large pore volume was obtained.

It must be emphasized that the theory of porosity formation discussed in the preceeding pages is simply a model that was constructed by Guyot based on a large body of experimental data. It is the best model presented to date because it explains why different porous textures are obtained when solvents and non-solvents are used as porogens in copolymerizations involving styrene and divinylbenzene. Our data strongly supports this model.

Table 3 Control of surface area and pore volume in the copolymerization of p-t-BOC-styrene and divinylbenzene by variation of the percentage of cyclohexanol

<u>Porogen (volume %)</u>	<u>Surface Area</u>	<u>Solvent Regain</u>	<u>% Por.</u>
cyclohexanol (40 %)	0-1 m ² /g	0.52 ml/g	34 %
cyclohexanol (50 %)	190 m ² /g	0.92 ml/g	48 %
cyclohexanol (60 %)	227 m ² /g	1.64 ml/g	62 %

Table 4 Control of surface area and pore volume in the copolymerization of p-t-BOC-styrene and divinylbenzene by variation of the molecular weight of the n-alkyl alcohol used as porogen

<u>Porogen (60 volume %)</u>	<u>Surface Area</u>	<u>Solvent Regain</u>	<u>% Por.</u>
n-butanol	143 m ² /g	1.36 ml/g	58 %
n-pentanol	145 m ² /g	1.75 ml/g	64 %
n-heptanol	136 m ² /g	1.91 ml/g	66 %
n-octanol	93 m ² /g	1.95 ml/g	66 %
n-decanol	44 m ² /g	2.10 ml/g	68 %

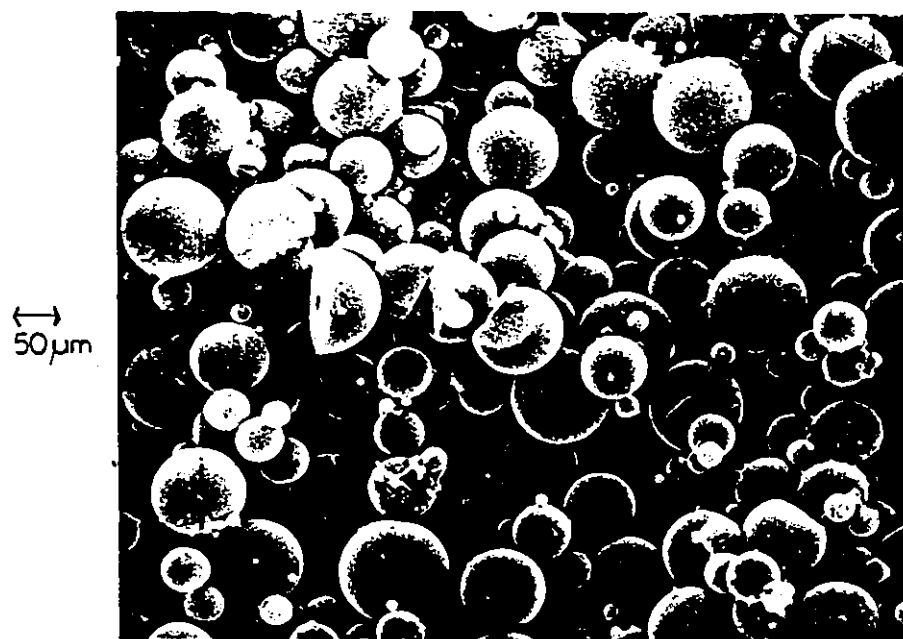
Table 5 Control of surface area and pore volume in the copolymerization of p-t-BOC-styrene and divinylbenzene by using three different isomers of pentanol as porogens

<u>Porogen (60 volume %)</u>	<u>Surface Area</u>	<u>Solvent Regain</u>	<u>% Por.</u>
n-pentanol	145 m ² /g	1.75 ml/g	64 %
3-pentanol	223 m ² /g	1.23 ml/g	55 %
2-methyl-2-butanol	117 m ² /g	1.03 ml/g	51 %

Table 3 contains the surface areas, solvent regains, and % porosities of the polymers obtained in the suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene using different percentages of cyclohexanol as porogens. The sample prepared using 60 % cyclohexanol was analyzed by scanning electron microscopy; the photographs that were obtained are shown in Figures 13a and 13b. Several beads were fractured with a razor blade so that the internal morphology of the resin could be photographed. Picture "A" is a photograph of the polymer sample after it has been chopped up with a razor blade; several fractured particles can be seen in this picture. Picture "B", which is a magnification of picture "A", focuses on one fractured particle. Picture "C", which is a magnification of picture "B", shows the fracture surface. The internal surface of the bead can be seen to the left of this fracture line and the outer surface of the bead can be seen to the right. Picture "D" shows the internal morphology of the bead at a magnification of 20,000.

2.3a2 Control of porosity by variation of the molecular weight of the n-alcohol used as porogen

Table 4 contains the surface areas, solvent regains, and % porosities of the polymers obtained in the suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene using a variety of n-alcohols as porogens. The solvent regains increase over a small range as the porogen is changed. The surface area is high when the lower molecular weight alcohols are used as porogens, but drops drastically when the higher alcohols, such as n-decanol, are used as porogens. The Hg porosimetry curves



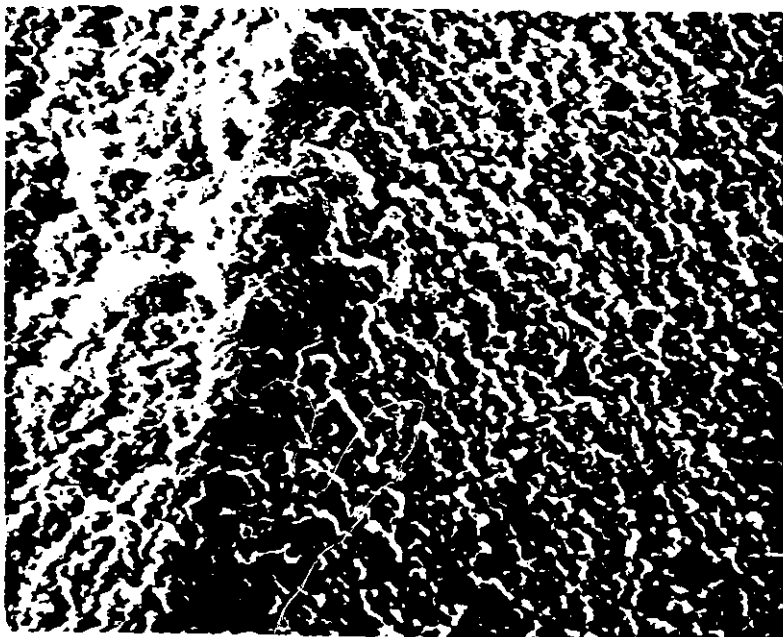
A



B

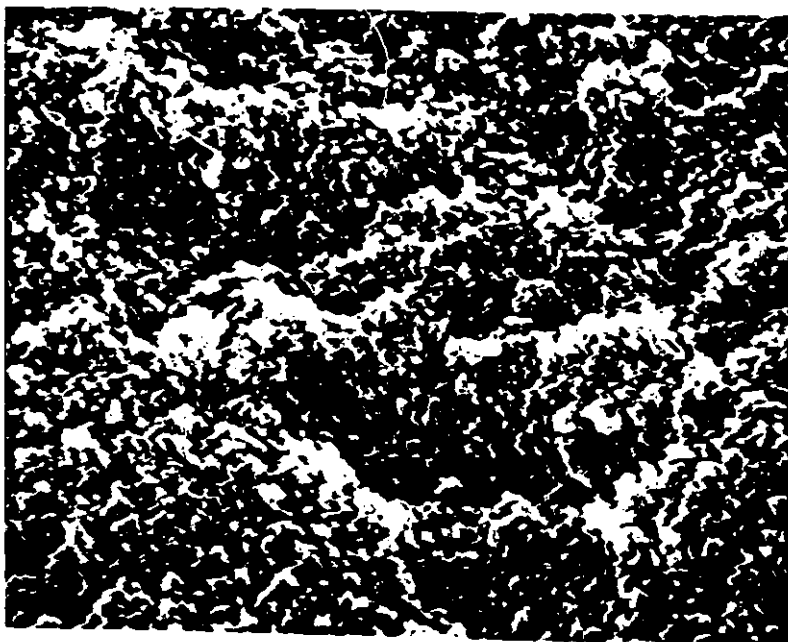
Figure 13a - SEM photographs of the p-t-BOC-styrene-divinylbenzene resin prepared using 60 % cyclohexanol

↔
0.5μm



C

↔
0.5μm



D

Figure 13b - SEM photographs of the p-t-BOC-styrene-divinylbenzene resin prepared using 60 % cyclohexanol

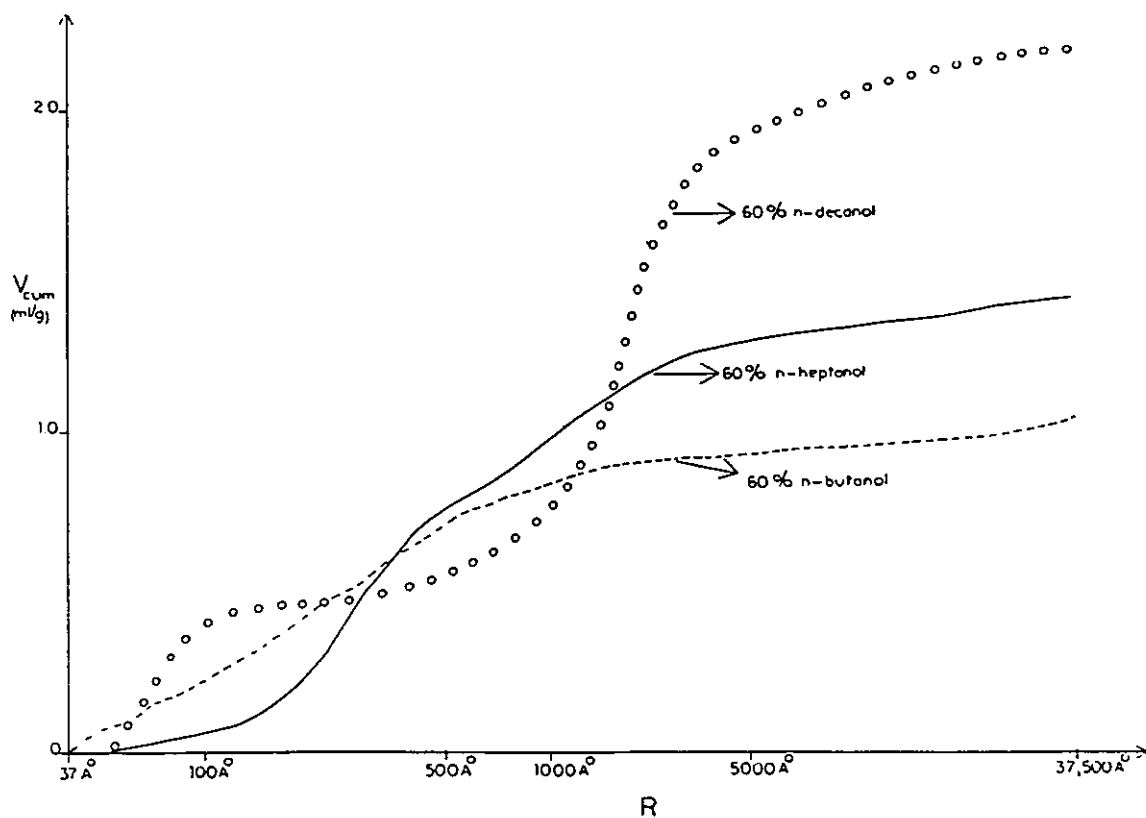


Figure 14 - Cumulative Hg porosimetry curves for the p-t-BOC-styrene-divinylbenzene resins prepared using 60 % n-butanol, 60 % n-heptanol, and 60 % n-decanol

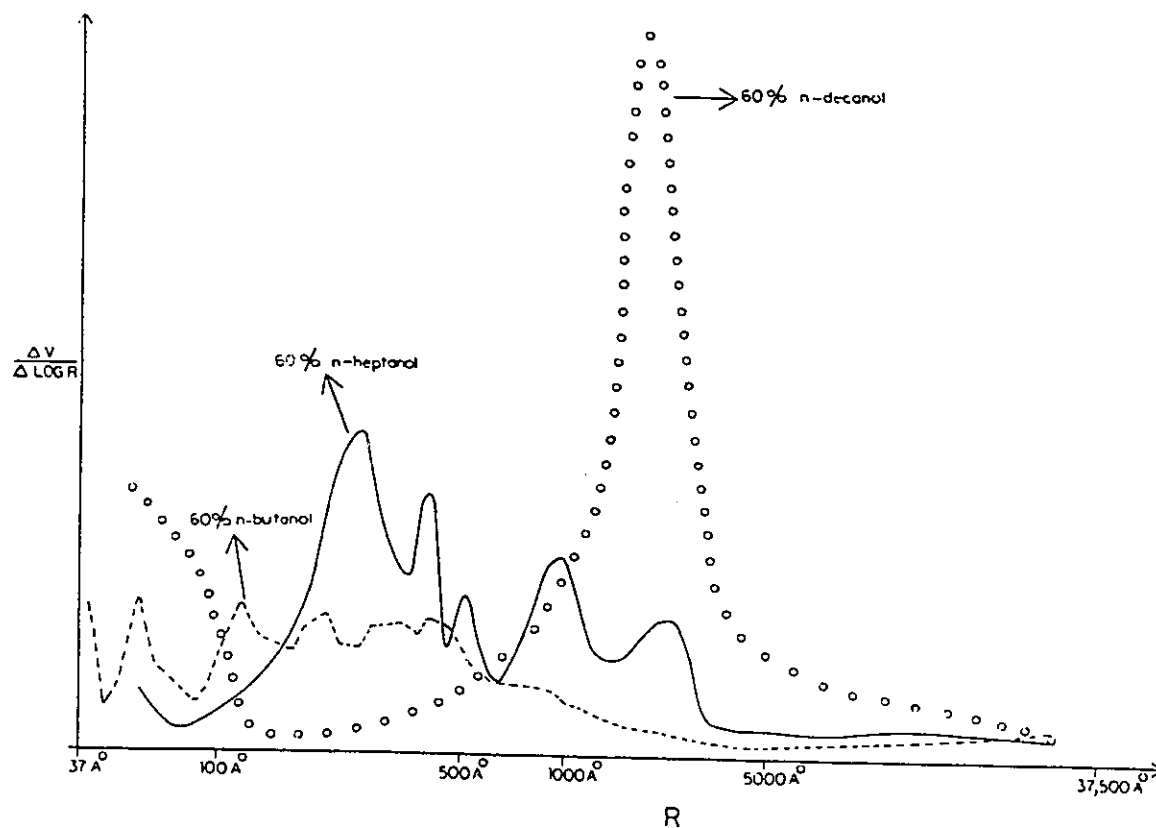


Figure 15 - Differential Hg porosimetry curves for the p-t-BOC-styrene-divinylbenzene resins prepared using 60 % n-butanol, 60 % n-heptanol, and 60 % n-decanol

shown in Figures 14 and 15 help to explain the data given in Table 4. These curves show the pore size distributions for the polymers prepared using 60 % n-butanol, 60 % n-heptanol, and 60 % n-decanol as porogens. For example, the differential pore size distribution curves shown in Figure 15 indicate that there is a drastic change in the pore size distribution as the porogen is changed from n-butanol to n-heptanol to n-decanol. When n-butanol is used as the porogen, the resin that is obtained has a rather broad pore size distribution containing both large and small pores. When n-decanol is used as the porogen, most of the smaller and intermediate size pores disappear; only very large pores ($>1000 \text{ \AA}$) and a few small pores ($<100 \text{ \AA}$) can be seen. The shift in the pore size distribution towards the larger pores accounts for the decrease in surface area and the increase in the pore volume when the higher alcohols are used as porogens. When n-heptanol is used as the porogen, the pore size distribution seems to lie between the distributions obtained with n-butanol and n-decanol.

The shift in the pore size distribution that occurs when the porogen is changed from 60 % n-butanol to 60 % n-decanol is very similar to the shift that is observed when the porogen is changed from 60% n-butanol to 70 % n-butanol. In the latter case, this shift occurred because a mixture of 70 % n-butanol and 30 % monomers has much more precipitating power than a mixture containing 60 % n-butanol and 40 % monomers, and the phase separation which is known to occur in these polymerizations occurs much earlier when the diluent mixture has more precipitating power. In the former case, this shift may occur for a similar reason; n-decanol

may have more precipitating power and may bring about an earlier phase separation than n-butanol. In order to see which of these porogens is a stronger precipitant, a series of "cloud point" titrations were performed using the n-alcohols and a soluble polymer of p-t-BOC-styrene; the results of these titrations are given in Table 6. In these titrations, the alcohol is added dropwise from a buret to a stirred toluene solution of the polymer. The volume of the alcohol that is required to induce turbidity in the polymer solution is reported as V_t in Table 6. Cloud point titrations have been used in the past to construct solubility maps for polymers⁹⁶. The data in Table 6 indicate that the precipitating strength does indeed increase upon passing from n-butanol to n-decanol. A similar trend was observed in the cloud point titrations of polystyrene with a series of n-alcohols⁹⁷.

Figure 16 shows the internal morphology of two polymers at a magnification of 20,000; picture "A" shows the internal morphology of the resin prepared with 60 % n-heptanol and picture "B" shows the internal morphology of the resin prepared with 60 % n-decanol. In picture "A", pores with a wide variety of sizes can clearly be seen; this seems to agree with the pore size distribution curve shown in Figure 15. The resin shown in picture "B" has a much more fused or molten structure. Most of the small and intermediate size pores are not present; only very large pores are visible. Again, this seems to agree with the pore size distribution curve shown in Figure 15.

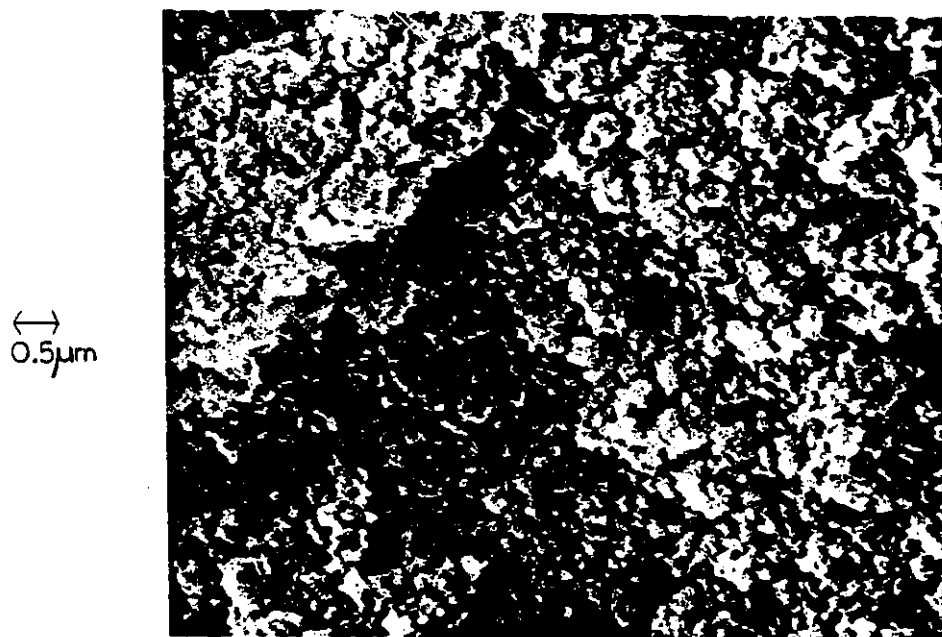
Table 6 Physical properties of solvents used as porogens

<u>Porogen</u>	<u>Water Solubility</u> ^a	<u>V_t</u>
n-butanol	7.9 wt. % (20 °C)	4.2 ml ^b
n-pentanol	2.3 wt. % "	3.8 ml ^b
n-heptanol	0.2 wt. % "	2.7 ml ^b
n-octanol	0.05 wt. % "	2.1 ml ^b
n-decanol	0 wt. % "	1.7 ml ^b
n-pentanol	2.3 wt. % (20 °C)	0.9 ml ^c
3-pentanol	5.6 wt. % "	3.0 ml ^c
2-methyl-2-butanol	12.5 wt. % "	3.4 ml ^c

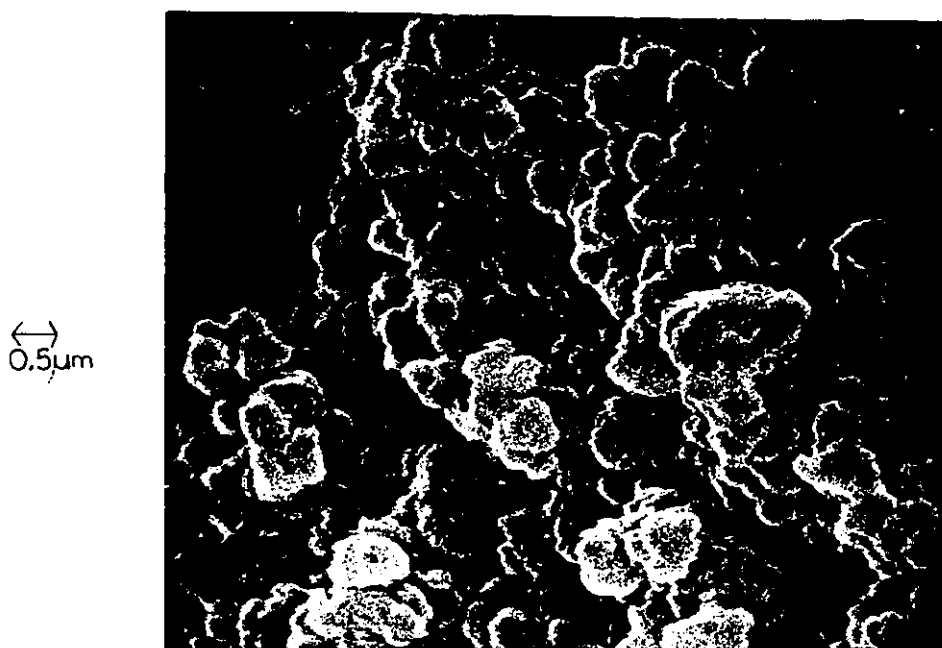
a: "Solubilities of Organic and Inorganic Compounds," H. Stephen and T. Stephen, Editors, Macmillan Co., New York, 1963, and R.T. Morrison and R.N. Boyd; "Organic Chemistry," Allyn and Bacon, Inc., Boston, 1983.

b: V_t is the volume of porogen needed to induce turbidity in a 2.5 % solution of poly(p-t-BOC-styrene) in toluene.

c: V_t is the volume of porogen needed to induce turbidity in a 10 % solution of poly(p-t-BOC-styrene) in toluene.



A



B

Figure 16 - SEM photographs of the p-t-BOC-styrene-divinylbenzene resins prepared using 60 % n-heptanol (A) and 60 % n-decanol (B)

2.3a3 Control of porosity by using three different isomers of pentanol as porogens

Table 5 contains the surface areas, solvent regains, and % porosities of the polymers obtained in the suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene using the primary, secondary, and tertiary isomers of pentanol as porogens; maximum surface area is obtained using the secondary alcohol. The Hg porosimetry curves for the resins obtained using these three porogens are shown in Figures 17 and 18. Figure 17 shows that the largest surface area is obtained using the secondary alcohol as porogen because, in this case, the pore size distribution extends all the way down to $37 \text{ \AA}$. The smallest surface area is obtained using the tertiary alcohol because this resin has the lowest amount of small pores. All three curves are similar and the differences in pore size distribution are certainly not as drastic as was seen in the previous two cases.

2.3a4 Explanation of observed % porosities

For the most part, the % porosities given in Tables 1-5 agree fairly closely with the % of porogen used in the polymerization recipe. For example, Table 2 shows that as the % of n-butanol used in the polymerization recipe is increased, there is a steady increase in the observed % porosity of the final resin. Table 1 shows that an usually low % porosity is obtained (30 %) when n-butyl acetate is used as a porogen, while the other alcohols and alkanes used as porogens give % porosities much closer to the theoretical value of 50 %. It is known that alcohols and alkanes are generally very poor solvents for

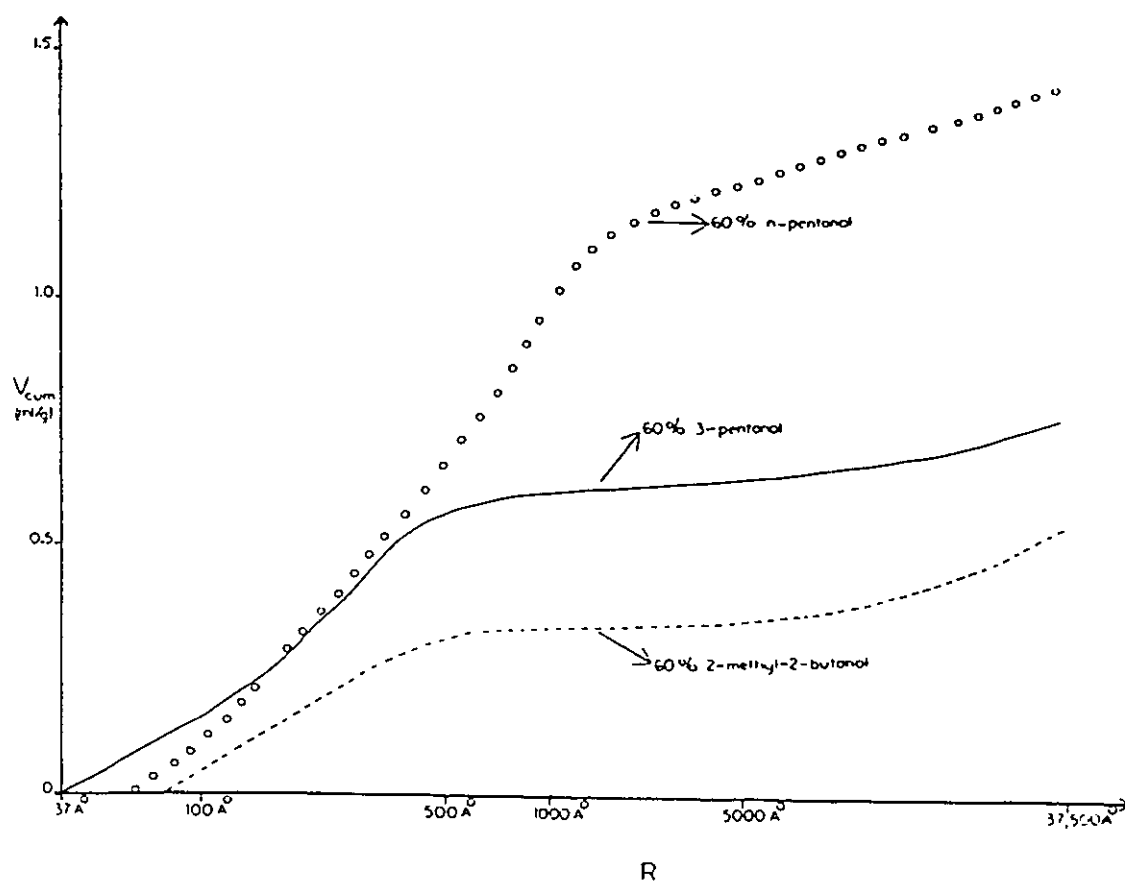


Figure 17 - Cumulative Hg porosimetry curves for the p-t-BOC-styrene-divinylbenzene resins prepared using 60 % n-pentanol, 60 % 3-pentanol, and 60 % 2-methyl-2-butanol

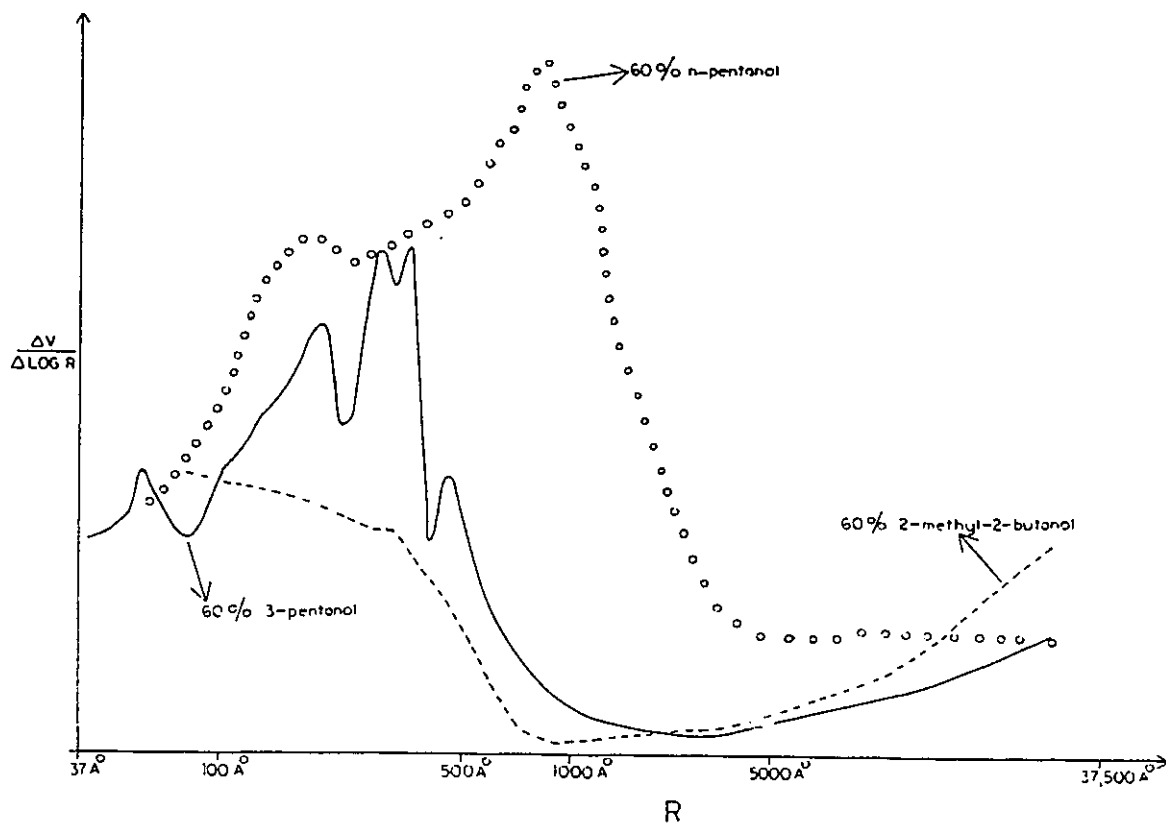


Figure 18 - Differential Hg porosimetry curves for the p-t-BOC-styrene-divinylbenzene resins prepared using 60 % n-pentanol, 60 % 3-pentanol, and 60 % 2-methyl-2-butanol

styrenic polymers, while esters are good solvents for these polymers⁵⁴. Because of this, a solvent such as n-butyl acetate will tend to remain in the polymeric phase where it can solvate the densely packed polymer molecules; very little, if any, of the n-butyl acetate will be exuded into the diluent phase where its presence will contribute to the overall porosity. This accounts for the rather low % porosity obtained when n-butyl acetate is used as a porogen.

2.3a5 Other factors that may influence porosity

Although the precipitating strength of the porogen plays a large part in determining the porosity of the final resin, other factors must also be considered. For example, Dusek⁹⁸ states that "phase separation is promoted by increasing concentration of the divinyl monomer and reactivity of its vinyls, by increasing dilution, molar volume of the diluent, and polymer-solvent interaction parameters." Also, Table 6 shows that the porogens used in these experiments have a wide range of solubilities in water; n-decanol is insoluble in water, while n-butanol has a significant water solubility. It is possible that some of the n-butanol could be extracted from the organic phase into the aqueous phase during the polymerization. This would mean that there might be less than 60 volume % of n-butanol present in the organic phase. It should be noted that the porogens are pre-dissolved in large volumes of the monomers, which are not water soluble, and so virtually all of the porogen should remain in the monomer phase⁵⁴.

The pore volumes of the polymers can be read from the Hg

porosimetry curves and compared with those determined by the solvent regain method. Both sets of data show the same trends, but the pore volumes determined by the solvent regain method are consistently higher than those determined by Hg porosimetry. Although the solvent regain method measures the amount of solvent retained by the pores of the polymer through capillary action, it is possible that some solvent will be retained by these same forces in the channels between the polymer particles⁹⁹. In fact, close observation of the cumulative Hg porosimetry curves shows that, in most cases, there is a rise in the cumulative curve above 5000 Å; this rise represents the filling of the interparticle volume by Hg¹⁰⁰.

2.3b Control of particle size

Tables 7 and 8 give details of the experiments that were performed in order to determine the conditions that are necessary to produce small beads which are suitable for HPLC. High stirring speeds and high concentrations of suspension stabilizer were used in these experiments because these conditions⁷² favor the formation of small beads.

2.3b1 Control of particle size by variation of the chemical structure of the porogen

Table 7 shows the experimental conditions for three suspension copolymerizations of p-t-BOC-styrene and commercial divinylbenzene; n-butanol, benzyl alcohol, and n-butyl acetate were used as porogens. The particle size distribution curves for these three polymers are given in Figures 19, 20, and 21. These distributions were determined using a Coulter Counter TA II

Table 7 Control of particle size in the copolymerization of p-t-BOC-styrene and divinylbenzene by variation of the chemical structure of the porogen

<u>Porogen (volume %)</u>	<u>RPM</u>	<u>AQ./ORG.</u>	<u>Mean Particle Size (Standard Deviation)</u>
n-butanol (40 %)	712	3/1	7.54 μm (2.68)
benzyl alcohol (50 %)	800	4/1	8.70 μm (2.71)
n-butyl acetate (50 %)	800	3/1	29.37 μm (11.19)

Table 8 Control of particle size in the copolymerization of p-t-BOC-styrene and divinylbenzene by variation of the stirring speed and the aqueous/organic ratio

<u>Porogen (volume %)</u>	<u>RPM</u>	<u>AQ./ORG.</u>	<u>Mean Particle Size (Standard Deviation)</u>
cyclohexanol (60 %)	725	4/1	13.77 μm (5.81)
cyclohexanol (60 %)	800	4/1	10.18 μm (4.42)
cyclohexanol (60 %)	850	4/1	8.25 μm (3.43)
cyclohexanol (60 %)	925	4/1	6.81 μm (3.13)
cyclohexanol/ dodecanol(9:1) (60 %)	700	3/2	51.76 μm (31.37)

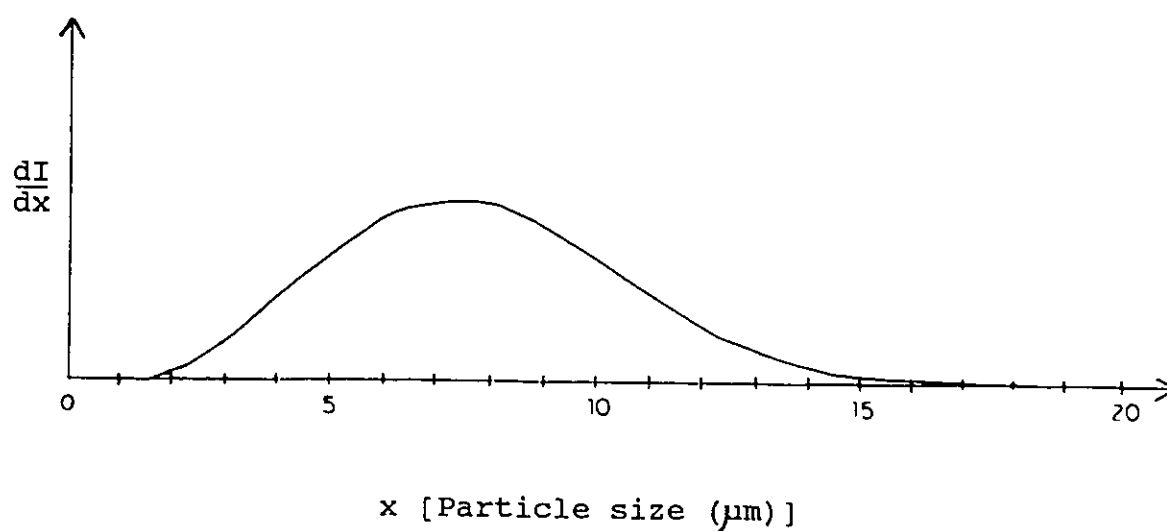


Figure 19 - Particle size distribution curve for the p-t-BOC-styrene-divinylbenzene resin prepared using n-butanol as the porogen

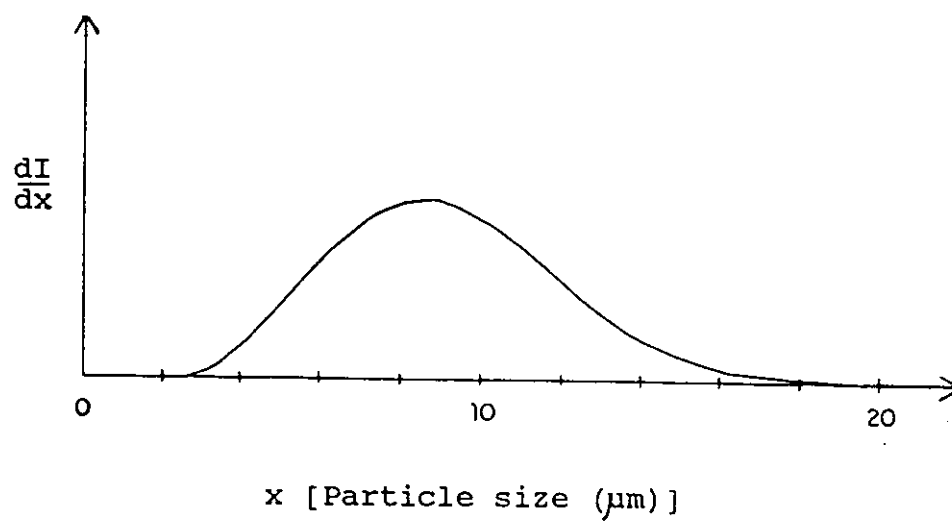


Figure 20 - Particle size distribution curve for the p-t-BOC-styrene-divinylbenzene resin prepared using benzyl alcohol as the porogen

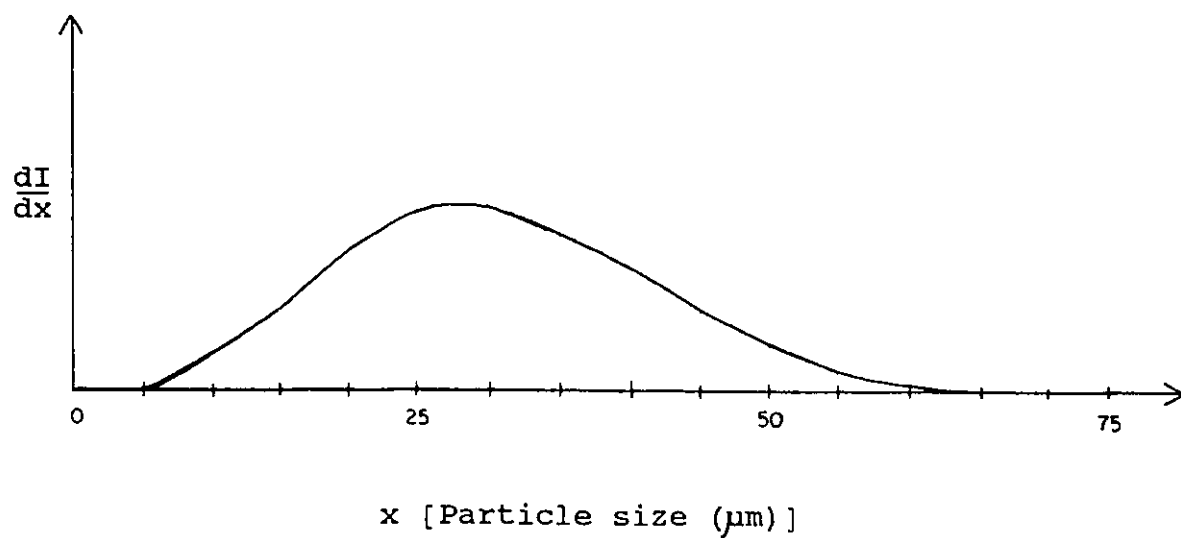
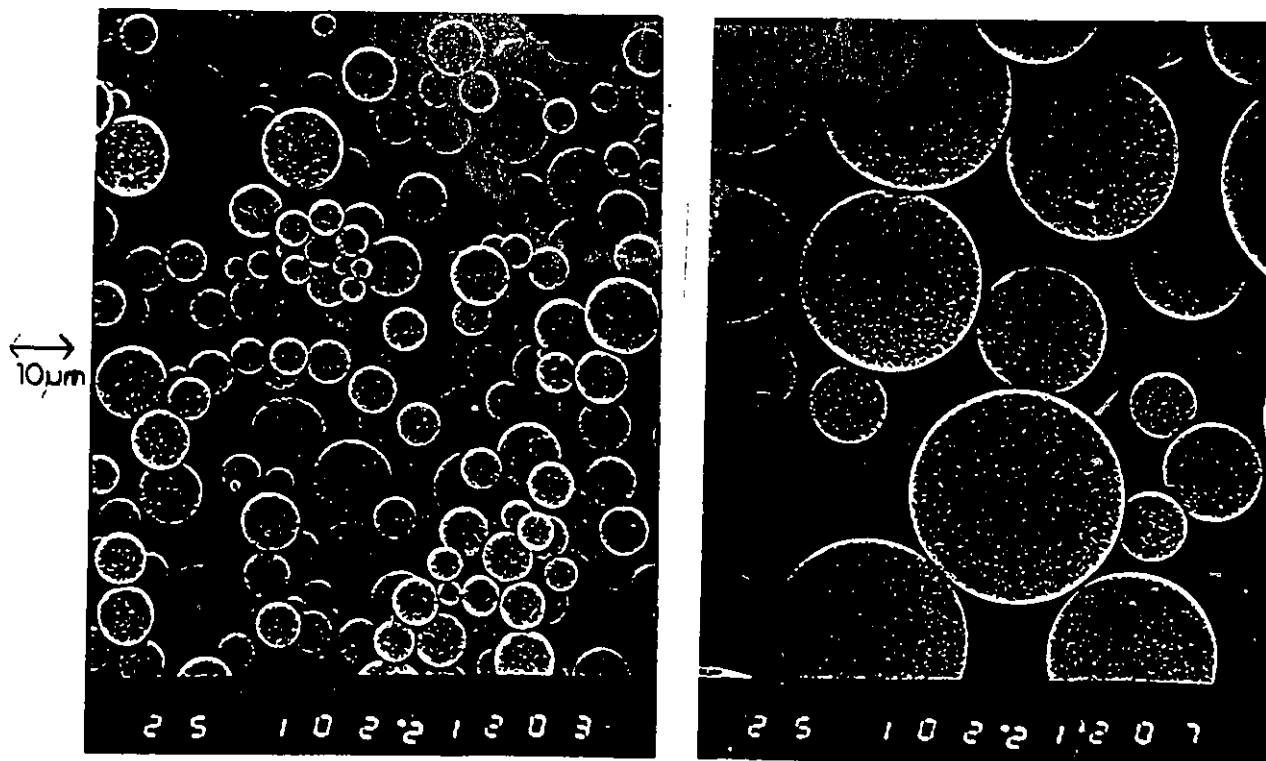


Figure 21 - Particle size distribution curve for the p-t-BOC-styrene-divinylbenzene resin prepared using n-butyl acetate as the porogen

apparatus. The raw data from the Coulter Counter, in the form of the volume percent distribution, was transformed into a particle size distribution curve using a model distribution function that can be expressed in both the integral $[I(x)]$ and differential form dI/dx ¹²². The mean particle sizes and standard deviations of the distributions are given in Table 7. Under similar experimental conditions, the two alcohols give very small beads while the ester gives beads which are much larger. Figure 22 shows scanning electron micrographs of the polymers prepared using n-butanol and n-butyl acetate as porogens at a magnification of 1400. Although the beads prepared using n-butyl acetate are very large, they are individual spheres and are not agglomerated in any way.

The only significant difference between the alcohols and the ester is their solubility for the polymer molecules being formed in the polymerization. Generally, alcohols are very poor solvents for styrenic polymers, while esters and ketones are good solvents for these polymers⁵⁴. A search of the literature revealed that a similar observation has been made by Schutten et al.¹⁰¹ They used various mixtures of n-butanol, a non-solvent for polystyrene, and toluene, a solvent for polystyrene, as porogens in the copolymerization of styrene and divinylbenzene; the results of their experiments are shown in Figure 23¹⁰¹. When toluene was used as the porogen, a polymer with a large mean particle size and a broad particle size distribution was produced. As the percentage of n-butanol in the porogenic mixture was increased, the particle size distribution became narrower and the mean particle size decreased. This phenomenon, which was



A

B

Figure 22 - SEM photographs of the p-t-BOC-styrene-divinylbenzene resins prepared using n-butanol (A) and n-butyl acetate (B) as the porogens

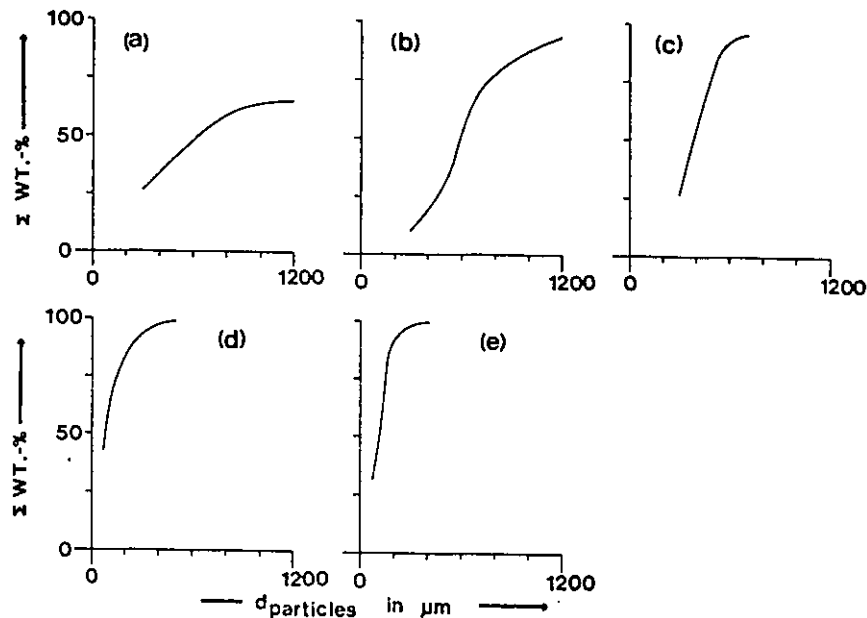


Figure 23 - Cumulative particle size distributions obtained from sieve analysis of St-DVB copolymers (prepared by suspension polymerization of 10 wt.-% St and 90 wt.-% commercial DVB). The composition of the inert phase applied during preparation was varied: a 100/0; b 75/25; c 50/50; d 25/75; e 0/100 (v/v) toluene/n-butanol (taken from reference 101)

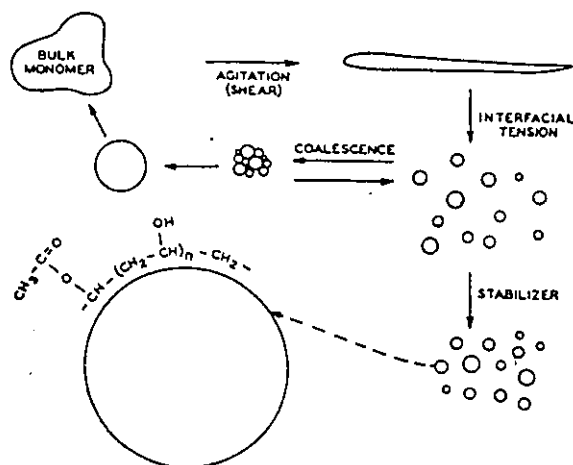


Figure 24 - Representation of the suspension polymerization process (taken from reference 73)

not explained by Schutten et al., will be explained in the next few paragraphs of this dissertation.

In order to provide some explanation of the results given in Table 7, it is necessary to understand the processes which are occurring in a typical suspension polymerization; these processes are presented schematically⁷³ in Figure 24. Mechanical agitation and shear forces cause the organic phase (monomers plus diluent) to be dispersed into spherical droplets⁷³. "The suspended droplets collide with each other, coalesce into larger ones, and are rapidly redivided into smaller ones again. Under these conditions the system is in a state of dynamic equilibrium and remains apparently stable upon continued mixing¹⁰²." As polymerization proceeds, the droplets become increasingly viscous, and it becomes more and more difficult for the larger particles to be redivided into smaller ones by shear forces. If no suspension stabilizer is present, the entire organic phase would eventually agglomerate into one large fused mass. Suspension stabilizers help to reduce the amount of agglomeration that occurs when droplets collide, presumably by forming a thin, protective film around the bead or droplet surface¹⁰².

When polymerizations are carried out in the presence of diluents which are solvents for the polymer molecules, "the polymer is unfolded, obtaining to the maximum extent the more favorable polymer-solvent interactions¹⁰³" (and therefore the greatest viscosity), and when polymerizations are carried out in the presence of diluents which are poor solvents for the polymer, "the polymer molecule remains folded because of its more favorable intramolecular interactions¹⁰³." This could mean that

suspension polymerizations which use good solvents for the polymer as porogens produce more viscous droplets than those which use poor solvents as porogens. Redivision of the larger droplets should be more difficult in the former case than in the latter case; therefore, larger bead particles should be produced when good solvents for the polymer molecules are used as porogens. N-butyl acetate produced a resin with a rather large mean particle size because esters are good solvent for styrenic polymers, while alcohols are rather poor solvents for these polymers⁵⁴.

2.3b2 Control of particle size by variation of the stirring speed

The data in Table 8 show how the particle size distribution changes as the stirring speed is increased. For these experiments, cyclohexanol (60 volume %) was used as the porogen because this solvent is known to give beads with a high surface area and porosity. The particle size distributions for these four polymers are shown in Figure 25. As the stirring speed is increased, the average particle size decreases along with the width of the particle size distribution. Mikos et al. have tried to explain this phenomenon by developing a reaction engineering model for suspension polymerizations which produce cross-linked polystyrene beads¹⁰⁴. This model was used to calculate the particle size distribution curve, from which the mean particle size and the standard deviation were derived. They found that "both quantities scale to the stable droplet mass of the initial dispersion of the organic phase into the aqueous one, which is a function of the agitation rate and the surface

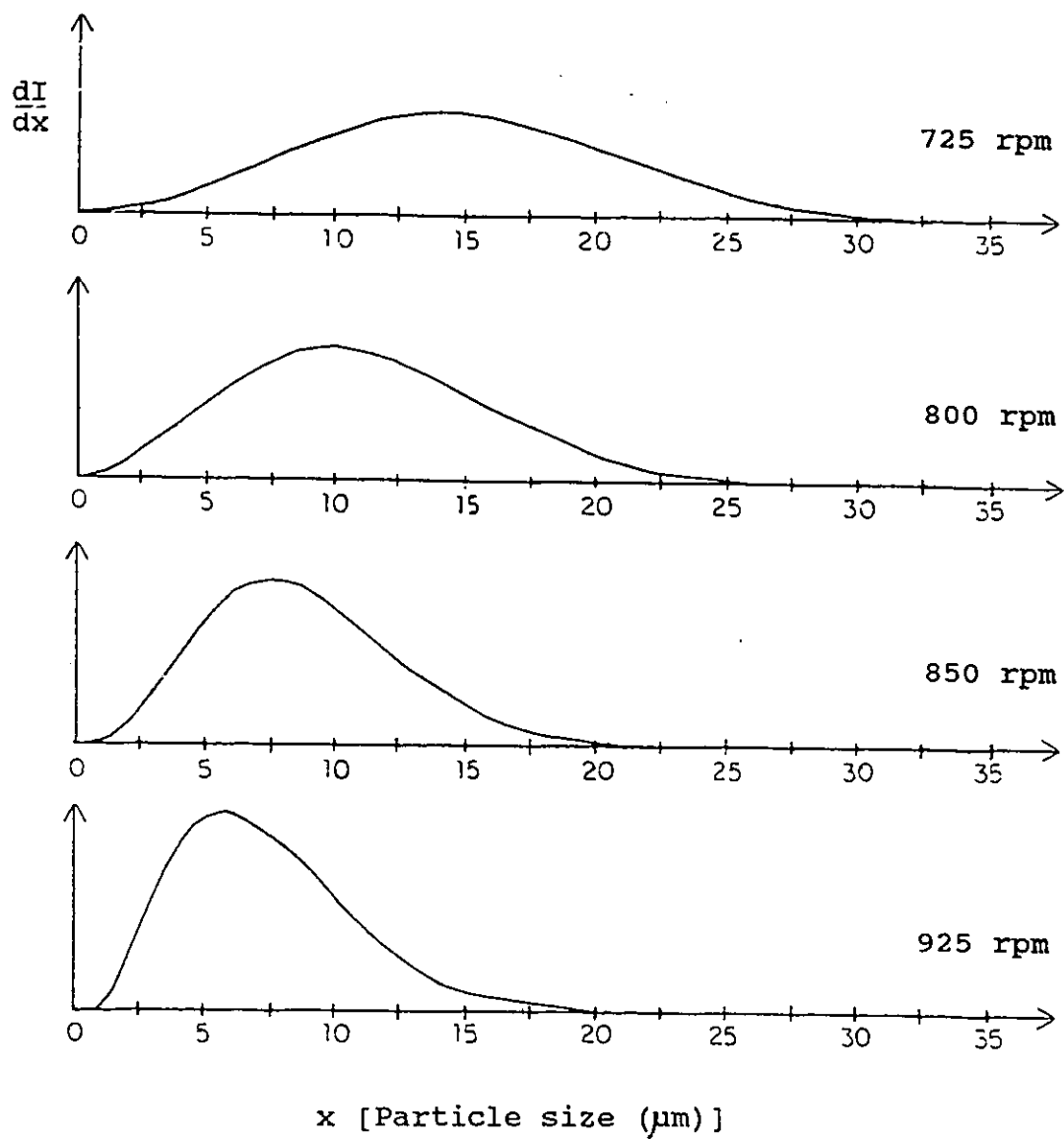


Figure 25 - Variation of particle size with stirring speed for p-t-BOC-styrene-divinylbenzene polymerizations

tension¹⁰⁴." In other words, any factor that changes the mean particle size will bring about a similar change in the width of the particle size distribution; therefore, it is possible to make very small beads with a narrow particle size distribution, but it is impossible to make very large beads with a narrow particle size distribution.

2.3b3 Control of particle size by variation of the aqueous/organic ratio

The last entry in Table 8 gives the mean particle size for an earlier polymerization performed under similar experimental conditions. This polymerization was performed using an aqueous:organic ratio of 3:2 rather than 4:1. Figure 26 shows that much larger particles with a broad particle size distribution were produced, while Figure 27 shows some photographs of these particles taken by scanning electron microscopy. The photographs show that the polymer consists mostly of agglomerates of polymer beads. When the amount of aqueous phase is reduced, the probability of droplet collision is increased, and the result can be the production of an agglomerated polymer¹⁰⁵.

2.4 Preparation of a series of vinyl phenol polymers in the form of 10 μ m, macroporous, spherical beads

Having optimized the surface area, porosity, and particle size of our resins, we turned our attention to the synthesis of a series of small (10 μ m), porous beads containing phenolic moieties with different acidities and steric environments; these experiments are outlined schematically in Figure 28. An attempt was made to produce polymer beads with an average size of about

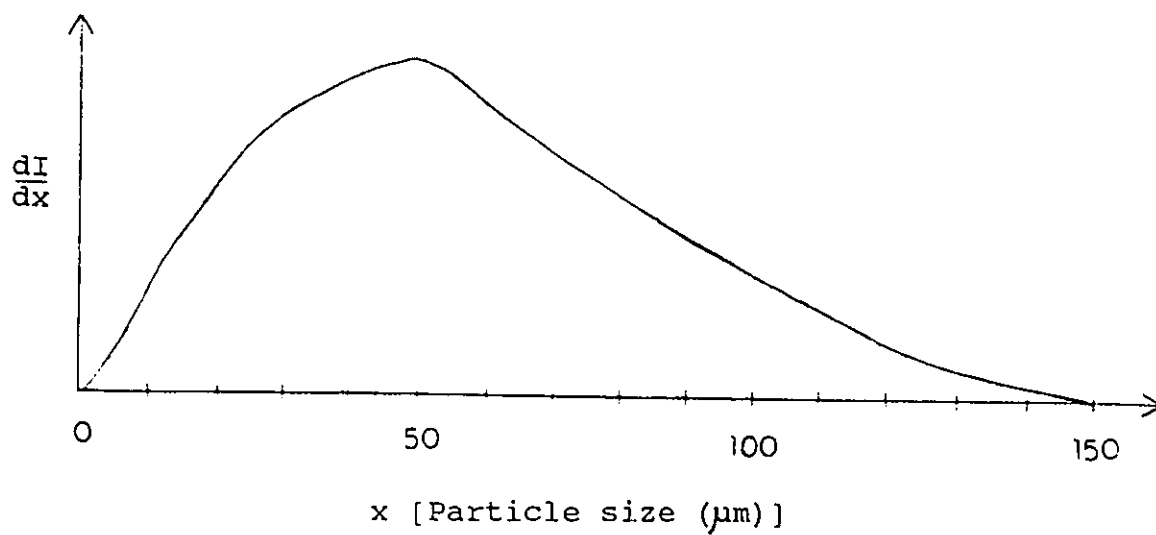


Figure 26 - Particle size distribution for a p-t-BOC-styrene-divinylbenzene resin prepared using an aqueous:organic ratio of 3:2

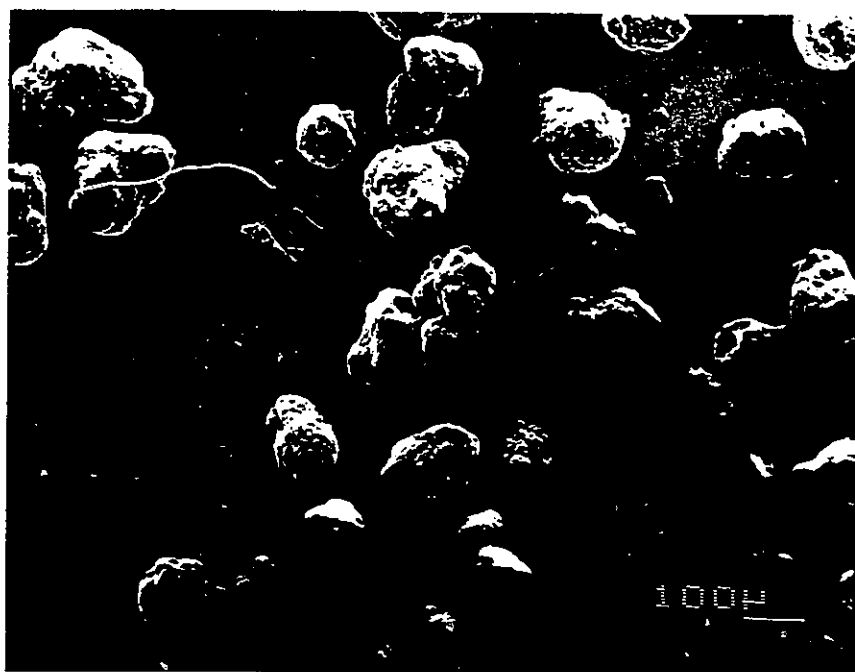


Figure 27 - SEM photographs of a p-t-BOC-styrene-divinylbenzene resin prepared using an aqueous:organic ratio of 3:2

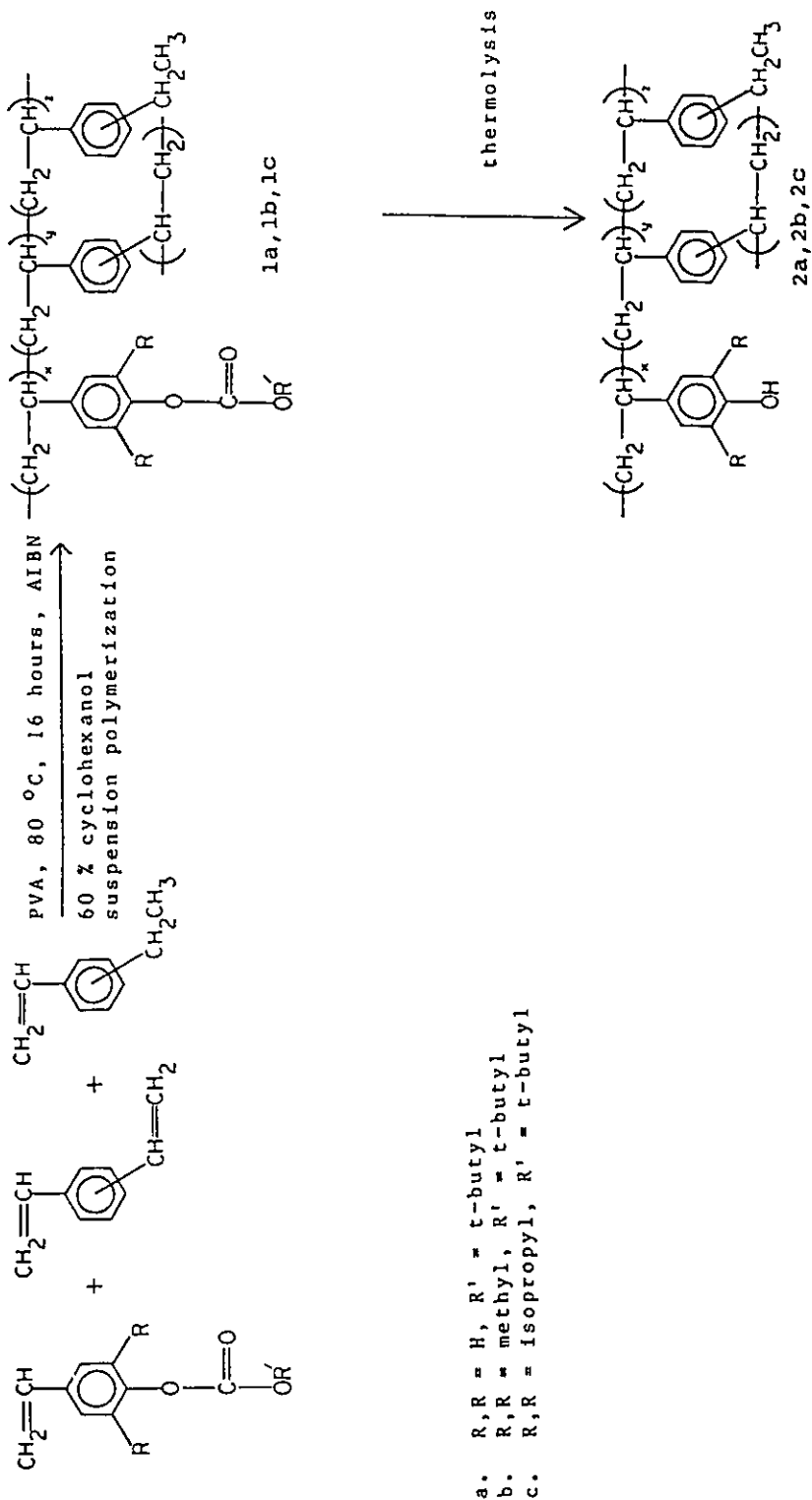


Figure 28 - Experimental conditions and reactants used in the preparation of a series of vinyl phenol bead polymers to be used as HPLC separation media

10 μm . Beads with a smaller average particle size could have been used, but these materials presented some practical problems in HPLC column packing experiments; these problems will be discussed more fully in Section 2.5. Each experiment involved the suspension copolymerization of commercial divinylbenzene and one of the three monomers described in Section 2.2. All of the polymerizations were run for 16 hours at 80 °C. AIBN was used as the initiator and a 2 % solution of poly(vinyl alcohol) was used as the aqueous phase; the volume ratio of the aqueous phase to the organic phase was 4:1. The polymerizations were run at 800 rpm and 60 volume % of cyclohexanol was used as the porogen. The weights of the monomers used in each of the three polymerizations were adjusted so that each of the three polymerization recipes would contain the same mole fraction of protected vinyl phenol monomer. All of the polymerizations were performed under the same conditions (with respect to amount and type of porogen, stirring speed, temperature, etc.) so that each of the three polymers produced would have approximately the same porosity and particle size. All of the relevant physical data concerning these polymers is shown in Table 9 and the Figures that follow.

2.4a Comparison of the physical properties of the different vinyl phenol polymers

Table 9 shows that all three of these polymers have a small particle size and a large surface area. Figures 29-31 show the particle size distribution curves for these three polymers; Figures 32-34 show the Hg porosimetry curves for these three

Table 9 Physical Data for Polymers 1a, 1b, and 1c

<u>Polymer</u>	<u>1a</u>	<u>1b</u>	<u>1c</u>
Mean Particle Size (Standard Deviation)	10.18 μm (4.42)	10.42 μm (4.34)	12.00 μm (5.75)
Surface Area	232 m^2/g	313 m^2/g	262 m^2/g
Thermolysis Temp.	190.8 $^{\circ}\text{C}$	210.8 $^{\circ}\text{C}$	215.8 $^{\circ}\text{C}$
% Weight Loss	23.4 %	23.6 %	21.6 %
Mole Fraction of x units in the polymer	0.39	0.43	0.45

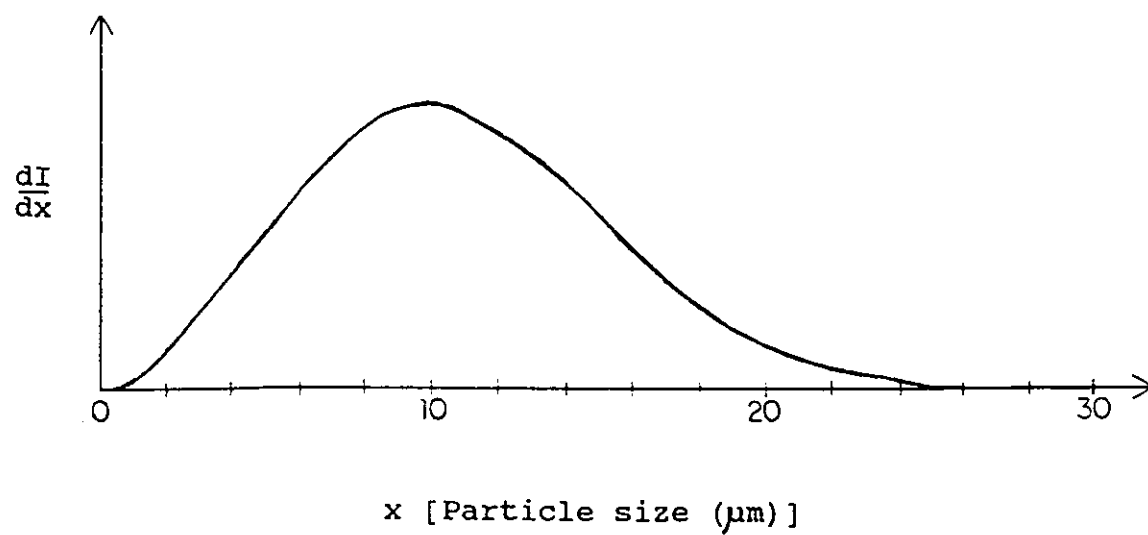


Figure 29 - Particle size distribution curve for 1a (800 rpm)

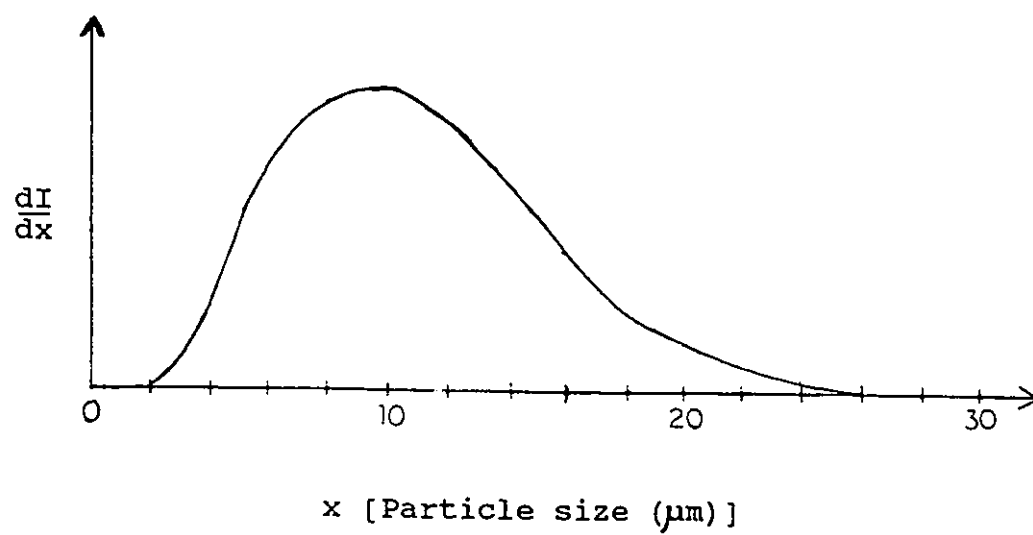


Figure 30 - Particle size distribution curve for 1b (800 rpm)

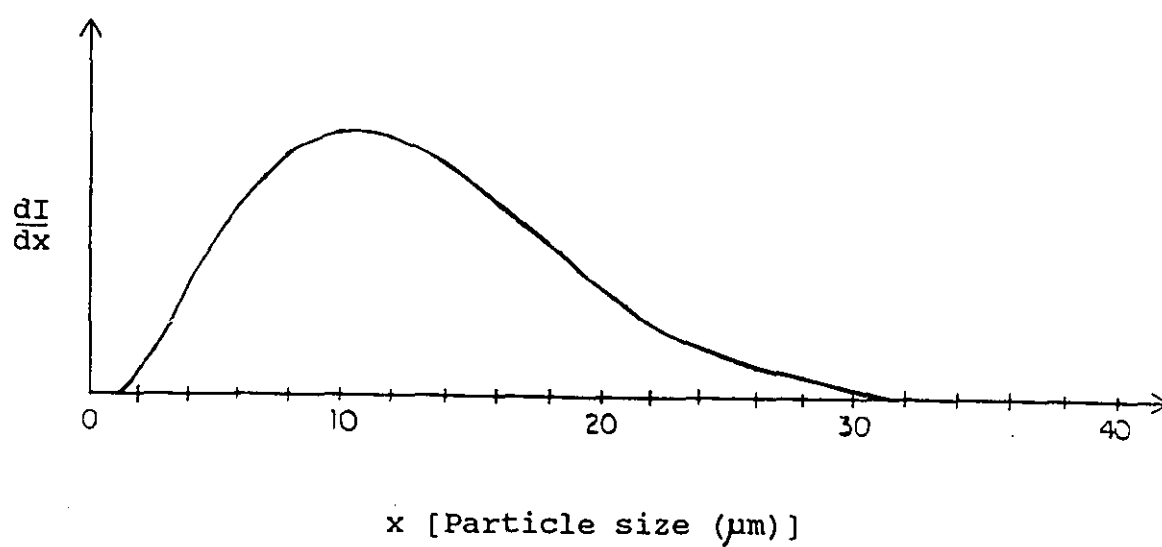


Figure 31 - Particle size distribution curve for 1c (800 rpm)

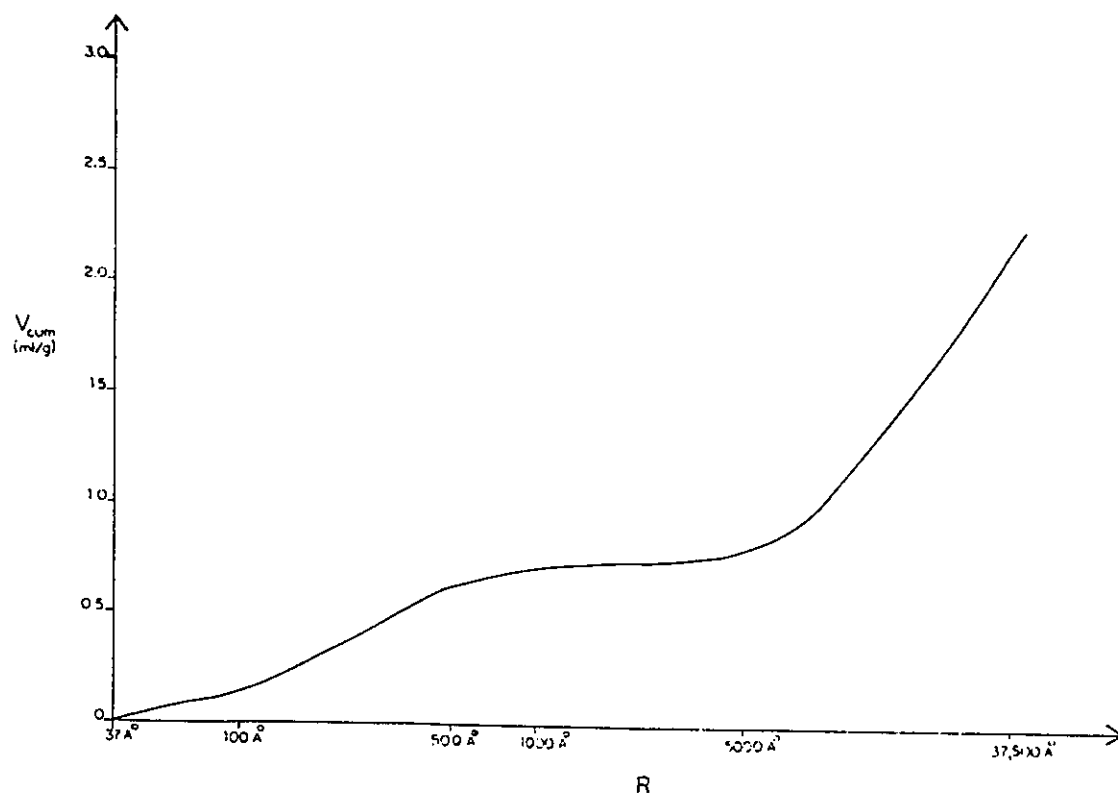


Figure 32 - Cumulative Hg porosimetry curve for 1a

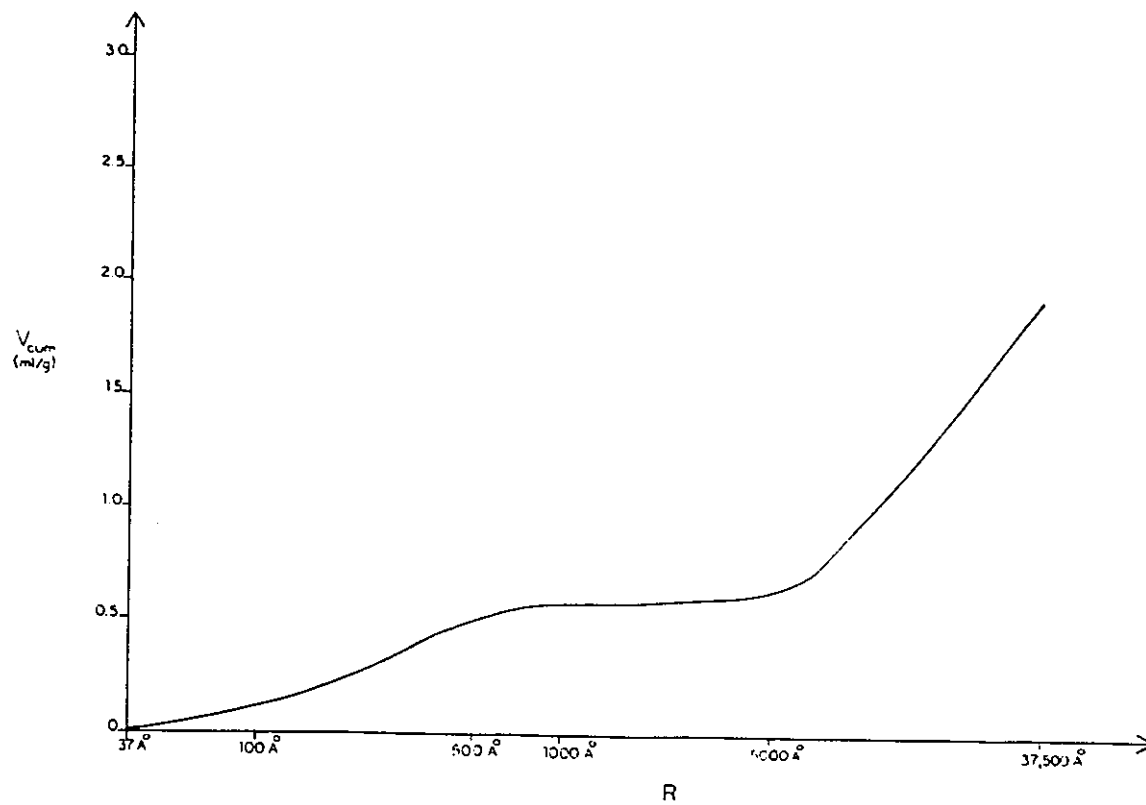


Figure 33 - Cumulative Hg porosimetry curve for 1b

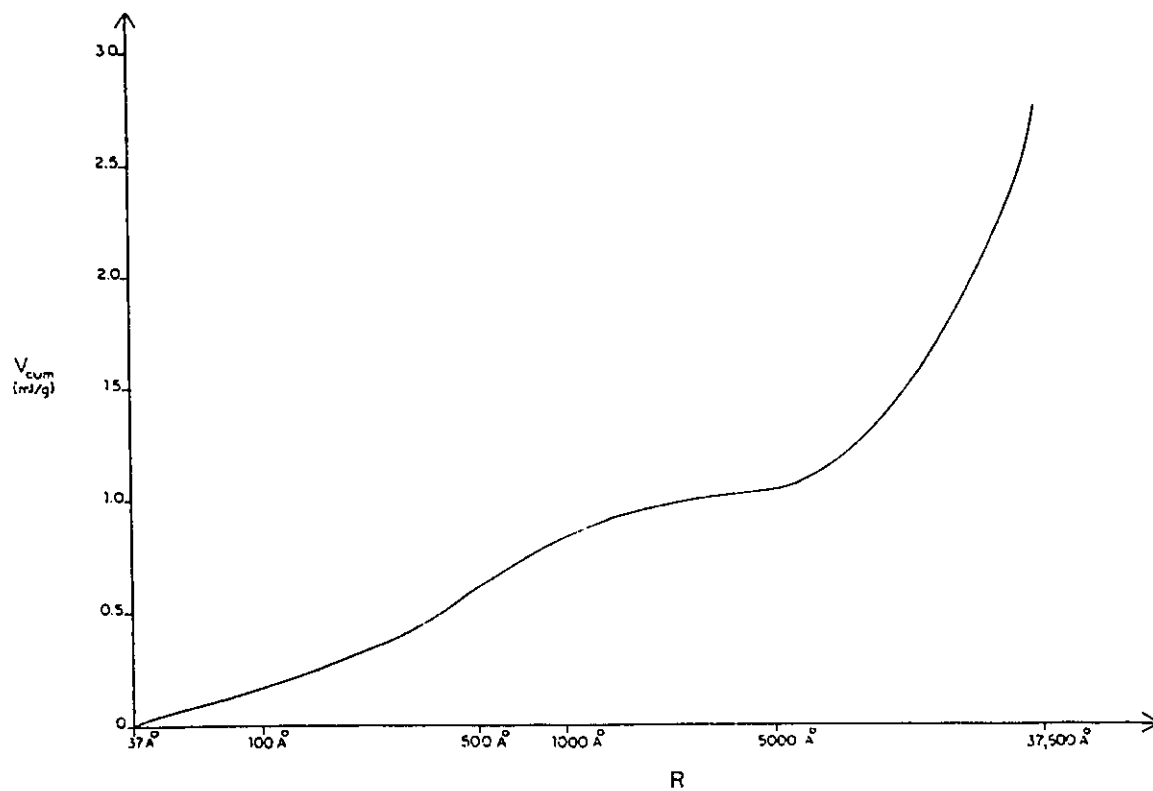


Figure 34 - Cumulative Hg porosimetry curve for 1c

polymers from 37 Å-37,500 Å. Two regions of porosity are indicated in each figure. Each of the three resins has pores in the 37 Å-1000 Å range and each also shows some porosity in the 5000 Å-37,500 Å range, the latter of which corresponds to the filling of the interparticle voids by Hg. Table 9 shows that all three samples are composed of small, high surface area beads. This Table also shows the thermolysis temperature for the t-BOC group of each polymer and the % weight loss of the polymer upon heating from 50 °C to 300 °C. From these weight losses, the mole fraction of protected phenolic units in each sample was calculated.

2.4b Cleavage of the t-BOC protecting groups

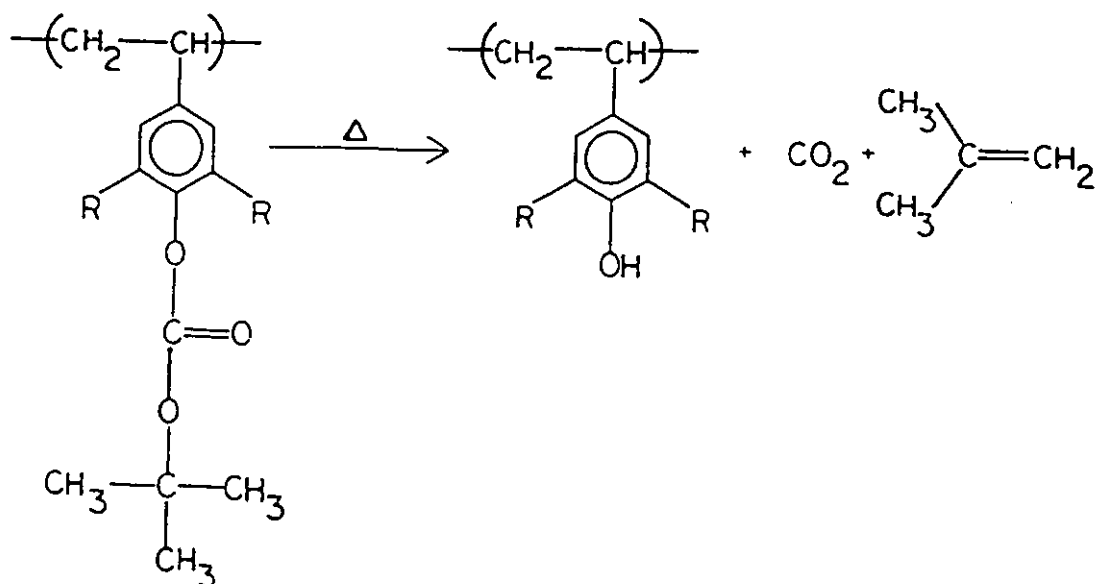
Cleavage of protecting groups on very small polymer beads can be done fairly simply with chemical reagents, but the physical form of the polymer beads presents a special problem. Excess reagents, solvents, and reaction by-products are usually removed from insoluble polymer beads by filtration; however, filtrations done with very small polymer beads are quite difficult because these small particles can easily clog filtration media, and this leads to extremely long filtration times. To avoid filtration problems, these types of particles can be washed through a series of decantations with the appropriate solvents; however, this is a lengthy procedure that can typically take up to 4 weeks because one must allow time for the solvent to fully penetrate the beads and for the impurities to diffuse out of the beads.

2.4b1 Ease of processing of the bead products resulting from the thermal cleavage of the t-BOC groups

The t-BOC protecting group was used in this project because it is easily and cleanly removed by thermolysis in a process which affords only gaseous by-products; therefore, it can be removed in a solid-state reaction that does not require any tedious washing procedures to isolate the polymer beads. In a typical procedure, the small polymer beads containing the t-BOC protected phenolic group are placed in a round-bottom flask and heated to the appropriate temperature under a flow of inert gas or under a high vacuum. The by-products of this reaction are carbon dioxide and isobutylene¹⁰⁶, which are gases at the temperatures used for the cleavage of these protecting groups and which are easily removed by the vacuum or a flow of inert gas. Once the cleavage reaction is complete, the polymer beads are ready to be packed into HPLC columns. No reaction workup is necessary, and the long washing times that are associated with chemical cleavage are avoided.

2.4b2 Mechanism of the thermal cleavage of the t-BOC groups

The mechanism of the thermolysis of the t-BOC group is shown in Figure 35, which is a general mechanism¹⁰⁷ for esters or carbonates having a hydrogen atom on carbon C_β. In our case, X represents the polymeric phenoxy group. The thermolysis is a cis elimination and is believed to be a semi-concerted process. The reactivity of the ester, as well as the polarity of the transition state, increases drastically as the alkyl group is changed from a 1° group to a 3° group; therefore, methyl carbonates are



Polymer

Thermolysis temperature

R,R = H

191 °C

R,R = Methyl

211 °C

R,R = Isopropyl

216 °C

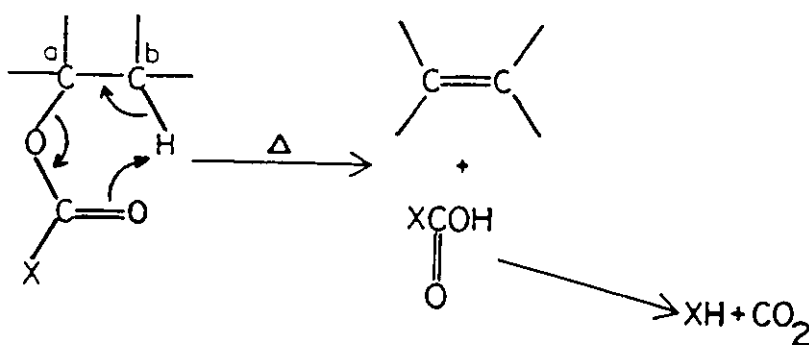


Figure 35 - Mechanism of carbonate thermolysis (taken from reference 107)

more stable thermally than t-butyl carbonates. The 3° esters thermolyze by the most E1-like transition state, while the 1° esters thermolyze by the most E_i-like transition state. Partial formation of a carbocation is believed to occur at C_a, especially when the ester is tertiary. The inductive effect of X is believed to have a large influence on the reactivity of the ester. As X becomes more electron withdrawing, as is the case for carbonates, the rate of elimination is increased because of increased polarization of the C_a-O bond¹⁰⁷.

2.4b3 The effect of steric hindrance on the thermolysis of the phenolic t-BOC groups

The data for the thermolysis of polymers 1a-1c are shown in Figures 36-38. The thermolysis temperatures are 191 °C for 1a, 211 °C for 1b, and 216 °C for 1c; therefore, the least reactive polymer is the one containing two isopropyl groups ortho to the t-butyloxycarbonyloxy group, and the most reactive polymer is the one containing two hydrogen atoms ortho to the t-butyloxycarbonyloxy group. The most likely explanation is that inductive electron donation by the two isopropyl groups decreases the polarization of the C_a-O bond by the phenoxy group. It is known that alkyl groups attached to unsaturated carbon atoms are electron donating relative to hydrogen and that secondary alkyl groups are more electron donating than primary alkyl groups¹⁰⁸; therefore, the inductive electron donation by two methyl groups will be less than that of two isopropyl groups but more than that of two hydrogen atoms.

Figure 39 shows the FTIR spectrum of 1a before and after

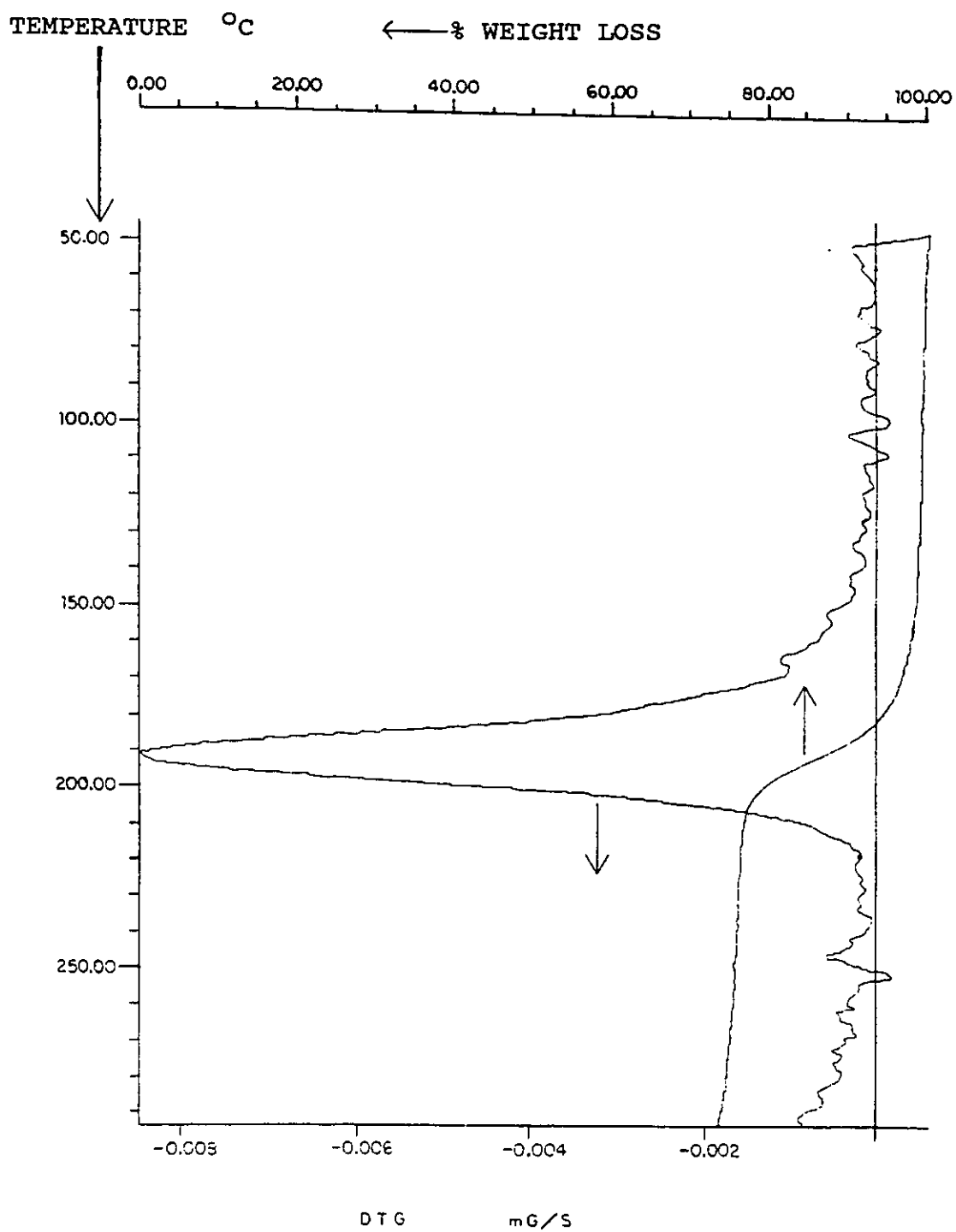


Figure 36 - TGA of 1a

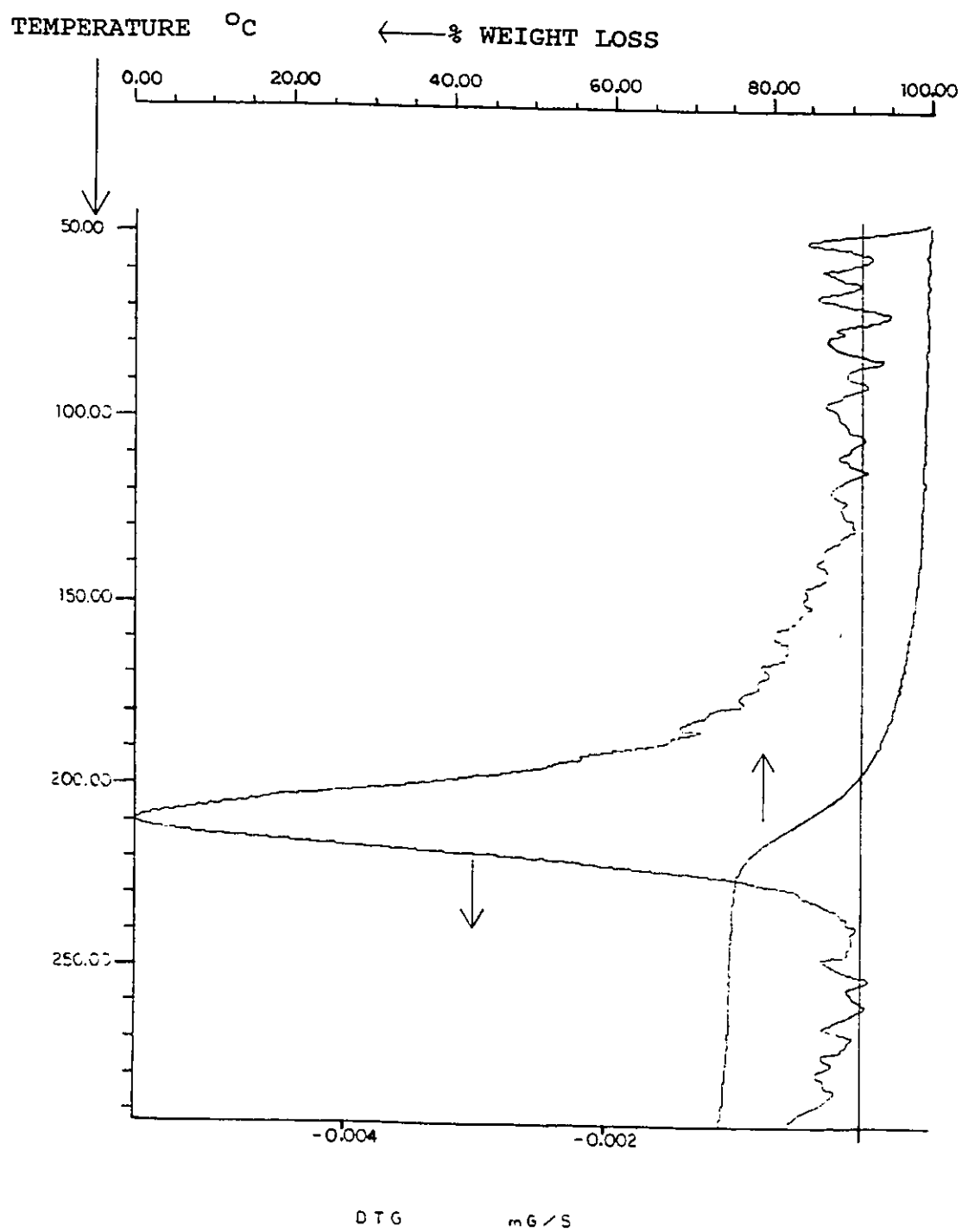


Figure 37 - TGA of 1b

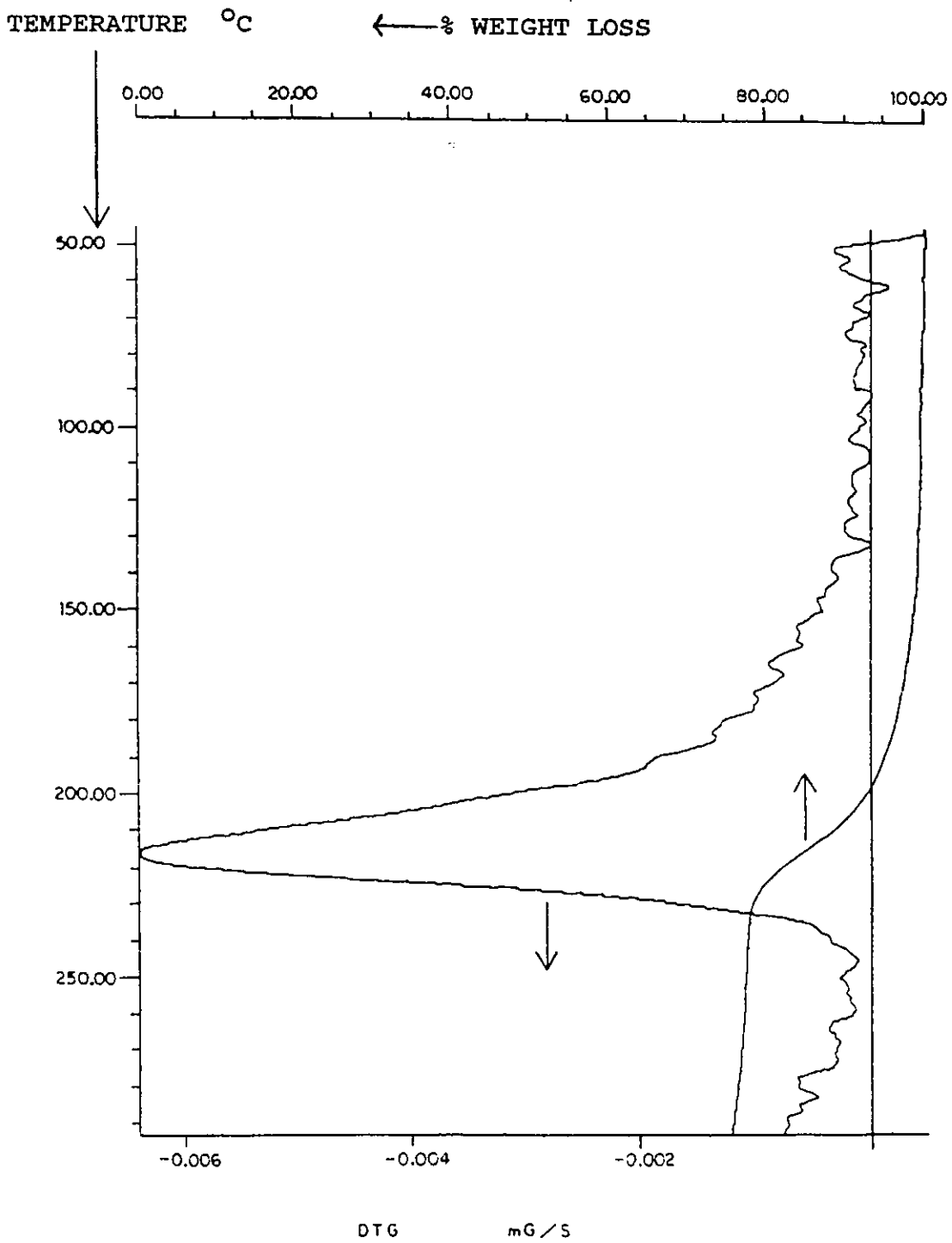


Figure 38 - TGA of 1c

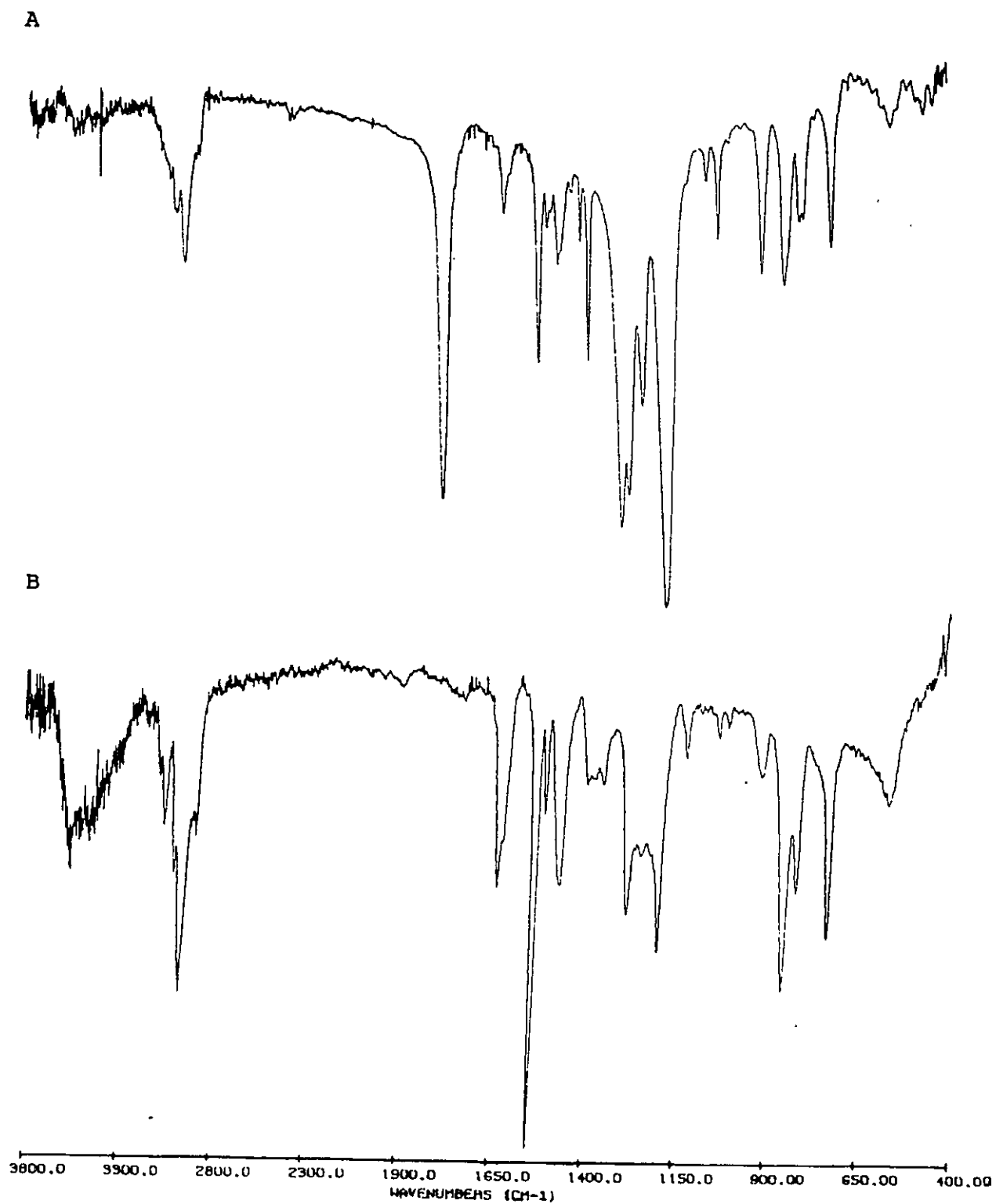


Figure 39 - FTIR spectra before (A) and after (B)
thermolysis of 1a

thermolytic cleavage under high vacuum at 220 °C. Thermolysis under vacuum results in complete cleavage of the t-BOC group (this is indicated by the disappearance of the t-BOC absorption at 1752 cm⁻¹) and gives polymer beads that are pure-white in color; this indicates that no oxidation of the polymer has occurred. Also, no oxidation peaks (from 1650-1730 cm⁻¹ resulting from ketonic and quinoid species) can be seen in the spectrum. The FTIR spectra of 2a-2c are shown in Figure 40. Polymer 2c, which contains the diisopropylphenol moiety, has a fairly sharp hydroxyl band because the bulky ortho isopropyl groups hinder the intermolecular hydrogen bonding of the hydroxyl groups¹⁰⁹.

2.4b4 Other advantages in the use of the t-BOC protecting group

The use of the t-BOC protecting group is useful with this system for another reason. For example, the t-BOC protecting group of 1a can be cleaved easily by heating the polymer beads overnight in a 5 % solution of NaOH/MeOH at 65 °C. Figure 41 shows the FTIR spectrum of 2a produced in this way; complete removal of the t-BOC group occurs under these conditions. In contrast, the t-BOC group of 1c is more difficult to cleave under these conditions because the bulky isopropyl groups shield the carbonate group from attack by chemical reagents. Even after 7 days of heating 1c at 65 °C in a 5 % of solution of NaOH/MeOH, a significant amount of the t-BOC group remains; this can be seen in Figure 41. As was noted earlier, the t-BOC group of 1c can be removed thermolytically in a few minutes by heating 1c at 230 °C. Accessibility of reactive sites is not a factor with the thermolysis reaction. Also, cleavage reactions performed with

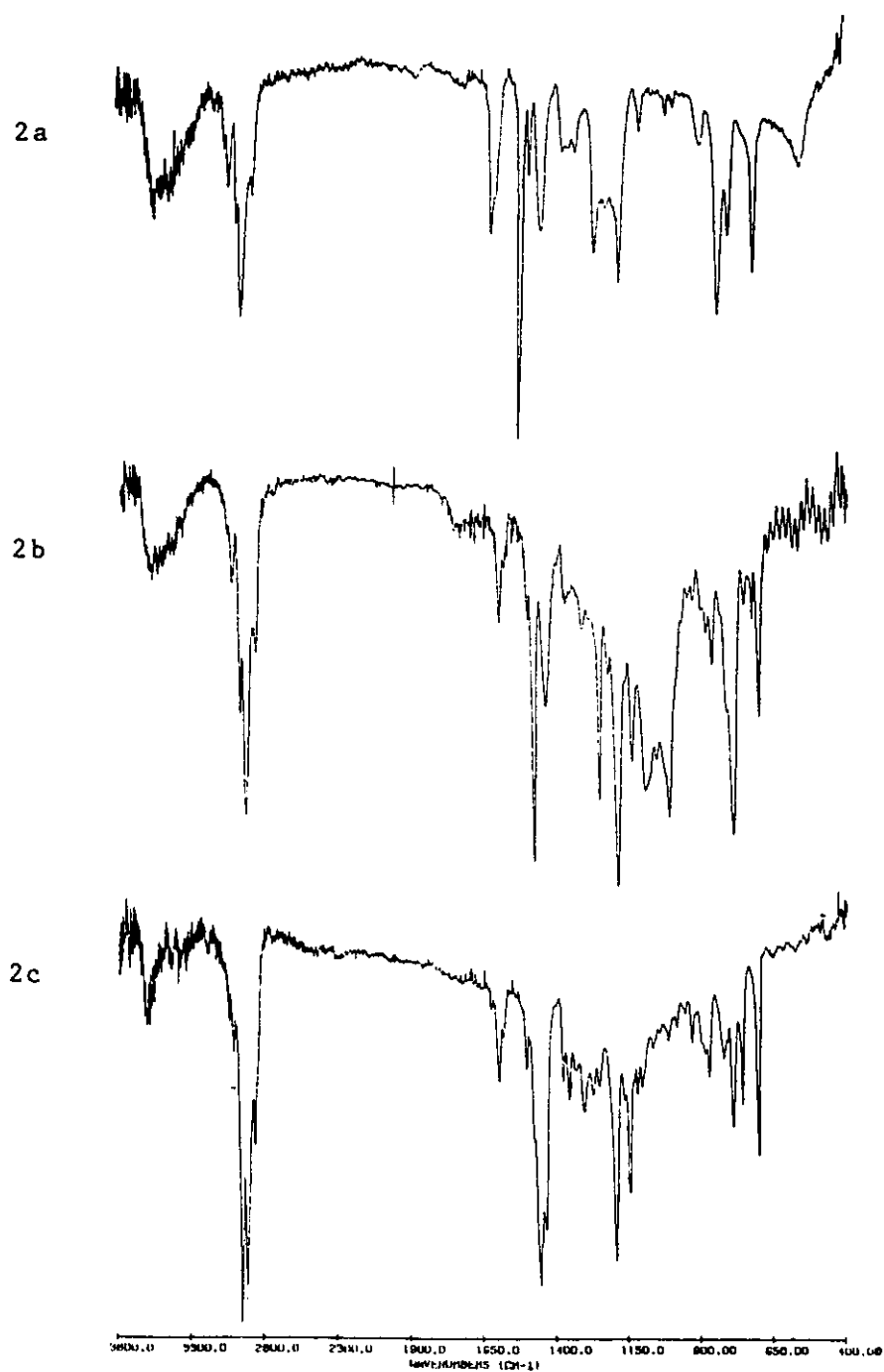


Figure 40 - FTIR spectra of 2a, 2b, and 2c

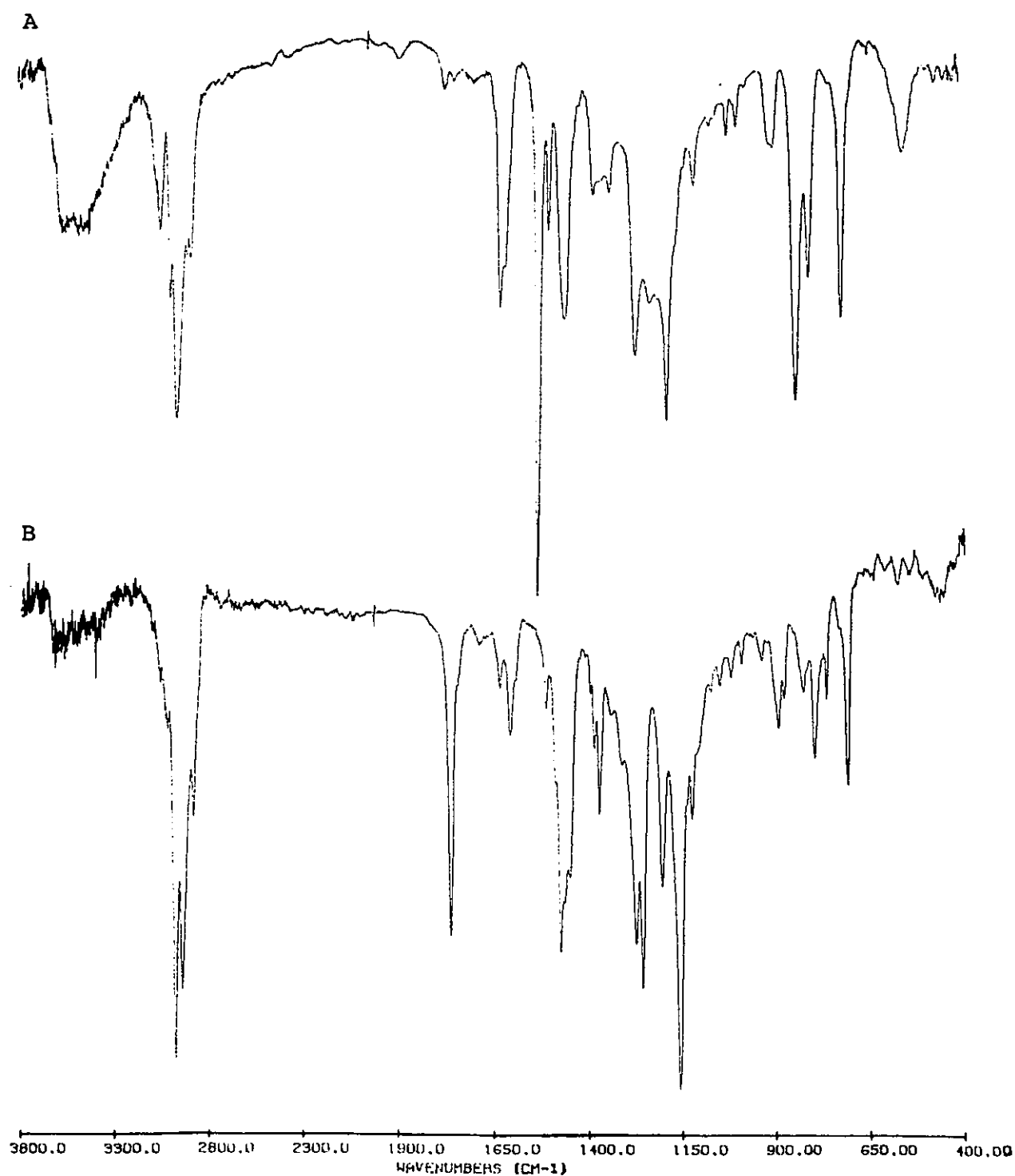


Figure 41 - FTIR spectra after:
(A) Cleavage of 1a in 5 % NaOH/MeOH (1 day)
(B) Cleavage of 1c in 5 % NaOH/MeOH (7 days)

chemical reagents are often time consuming because the reagent must diffuse through the very small pores of the material to the active site. Once again, this is not a factor with the thermolysis reaction.

2.5 Packing of the polymer beads into HPLC columns

The polymer beads synthesized in this project were packed by the balanced density slurry technique¹¹⁰ under 3000 psi of solvent pressure into 15 cm stainless steel columns. In each case, the slurry solvent consisted of a mixture of MeOH and CCl₄ and the packing solvent was MeOH. Similar experiments were attempted using hexane in place of MeOH, but these experiments were unsuccessful because the polymer beads could not be properly dispersed into mixtures of hexane and CCl₄. Once these columns had been packed in MeOH, it was possible to change to a more non-polar mobile phase by passing mixtures of solvents through the column. For example, the mobile phase in a column can be changed from MeOH to hexane by passage of 100 ml of each of the following solvent mixtures through a column: 75/25 MeOH/EtOAc, 50/50 MeOH/EtOAc, 25/75 MeOH/EtOAc, EtOAc, 75/25 EtOAc/hexane, 50/50 EtOAc/hexane, and 25/75 EtOAc/hexane (the ratios indicated are volume ratios). Ethyl acetate was used as an intermediate because of the poor miscibility of methanol and hexane. The columns do not lose any of their efficiency during the change of solvents, and the process can be repeated as many times as is necessary; therefore, chromatography can be performed with mobile phases having a wide range of polarities.

2.5a Packing of polymer 2a with an average particle size of 6.81 μm

The first packing experiment was performed with the sample of polymer 2a having an average particle size of 6.81 μm . During the packing experiment, the solvent passed through the column very slowly. When the column was connected to the analytical HPLC and MeOH was pumped through at a flow rate of 0.5 ml/min, the backpressure rose steadily to over 5000 psi. This pressure is too close to the upper pressure limit of the pump for this polymer to be useful as an HPLC packing material. High backpressure usually results from clogged frits, and this is probably caused by the large fraction of particles in this sample which have a diameter of less than 4 μm . It would be difficult to size this polymer to any significant extent because only about 6-7 g of polymer was produced in each polymerization.

2.5b Packing of polymer 2a with an average particle size of 8.25 μm

The sample of polymer 2a having an average particle size of 8.25 μm was then packed under the same experimental conditions. When this column was connected to the analytical HPLC and MeOH was pumped through at a flow rate of 0.5 ml/min, the backpressure was steady at about 1800 psi; however, the backpressure rose uncontrollably when viscous solvent mixtures such as 80 % MeOH/20 % H_2O were used. Also, the backpressure began to rise uncontrollably when the flow rate was increased.

2.5c Packing of polymer 2a with an average particle size of 10.18 μm

Next, the sample of polymer 2a having an average particle size of 10.18 μm was packed into an HPLC column. When this column was connected to the analytical HPLC and MeOH was pumped through at a flow rate of 0.5 ml/min, the backpressure was only about 600 psi. Even with such viscous solvent mixtures as 70 % MeOH/30 % H_2O , the backpressure did not rise above 1200 psi. The HETP was determined to be 55.6 μm , which is very good for an unsized polymer sample. This particular sample of polymer 2a is ideal for our purposes because it can be packed efficiently into HPLC columns and because it can be used conveniently with even very viscous mobile phases. This latter fact implies that our systems can be studied using a wide variety of mobile phases. Also, the backpressure of this column did not rise uncontrollably when the flow rates were increased.

2.5d Packing of polymers 2b and 2c

Polymerizations of all other monomers were carried out with the intention of producing beads with an average particle size of about 10 μm . Polymers 2b and 2c were packed into HPLC columns under similar experimental conditions to those described above, and the HETP's for these columns were found to be 53.5 μm and 97.0 μm respectively. The data used to calculate these values is given in Table 10.

2.6 Choice of mobile phase

It is important to determine which mobile phase is best suited to study the interactions between the hindered and unhin-

Table 10 Calculation of HETP for HPLC columns

<u>Polymer</u>	<u>T_r</u>	<u>W_{1/2}</u>	<u>N</u>	<u>N/meter</u>	<u>HETP</u>
2a	4.85	0.220	2695	17,967	55.6 μm
2b	5.06	0.225	2804	18,693	53.5 μm
2c	5.51	0.330	1546	10,307	97.0 μm

$$N = (T_r/W_{1/2})^2 \times 5.545$$

$$\text{HETP} = L/N$$

where N = number of plates

T_r = retention time for pentane (minutes)

W_{1/2} = width of pentane peak at half-height (minutes)

L = length of HPLC column (150 millimeters)

HETP measured by injection of 6 μl a 2 % solution of pentane in MeOH using 0.5 ml/min of MeOH as the mobile phase.

dered phenol polymers and the compounds that are to be separated. We have chosen to separate compounds which can hydrogen bond with the phenolic hydroxyl, such as anilines, pyridines and aliphatic amines. The well-known eluotropic solvent series for alumina shows that solvents such as hexane and carbon tetrachloride are at one end of the polarity spectrum, while solvents such as methanol and ethanol are at the other end of the polarity spectrum¹¹¹. When methanol was used as the mobile phase with the column containing polymer 2a, compounds such as aniline showed very little retention. In fact, aniline and pentane had almost the same retention time in a methanol mobile phase. This could occur because aniline is very soluble in methanol or because the interactions between the nitrogen atom of aniline and the phenolic hydroxyl are not very strong in methanol; there is evidence in the literature to suggest that polar solvents can disrupt hydrogen bonding between solute molecules¹¹².

When hexane was used as the mobile phase, aniline showed very strong retention. In fact, it was not possible to elute aniline from the column using hexane. Carbon tetrachloride, which is more polar than hexane, was also tested as a mobile phase. Figure 42 shows the chromatograms that were obtained when a variety of compounds were injected onto the column using carbon tetrachloride as the mobile phase. Both toluene (1 % solution) and 2,4,6-tri-*t*-butylaniline (1 % solution) showed very little retention on the column, the latter compound eluting essentially with the column dead volume. Toluene would be expected to show very little retention because it cannot hydrogen bond to the phenolic hydroxyl, while the hindered aniline shows

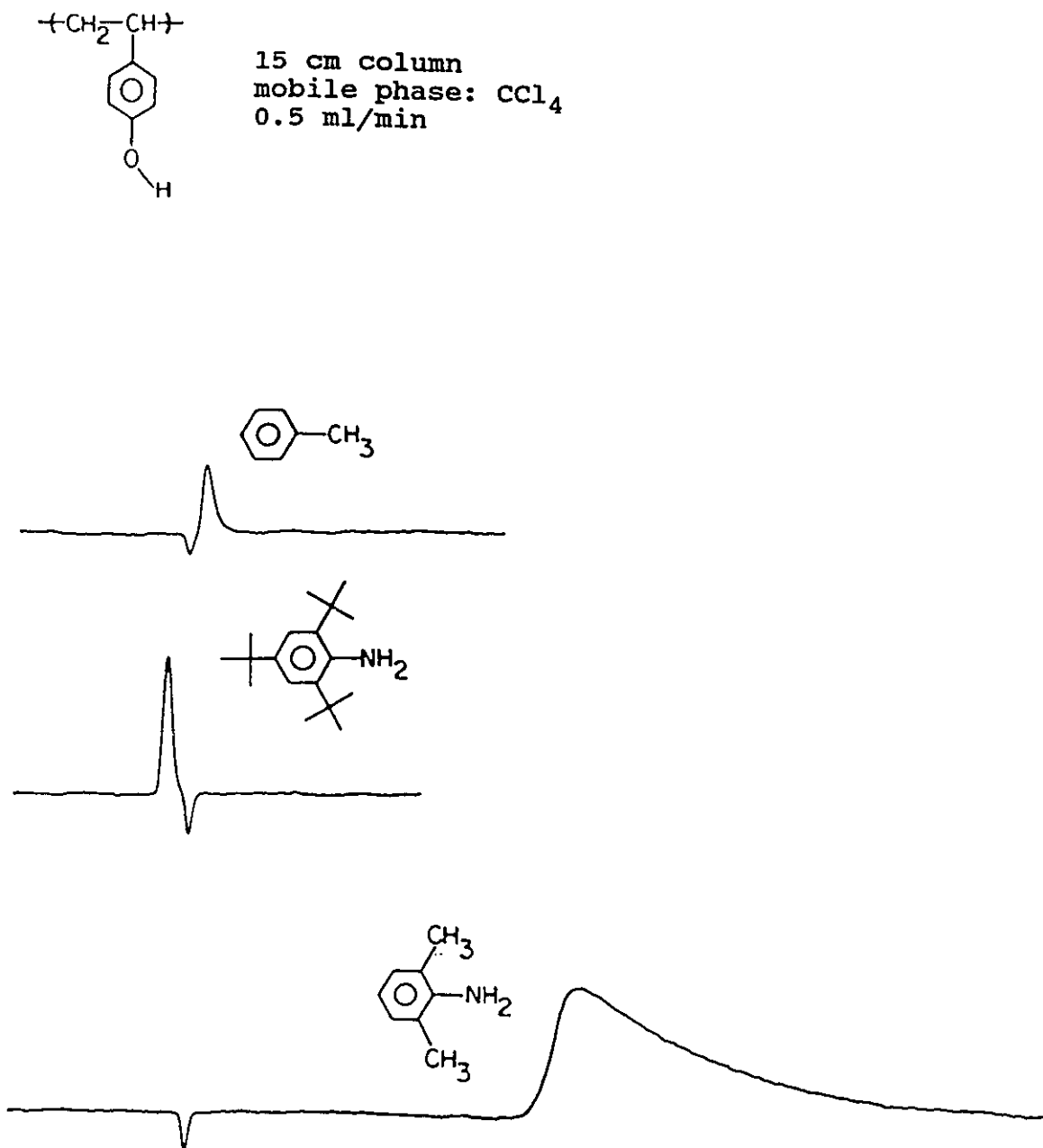


Figure 42 - Retention of toluene, 2,4,6-tri-t-butylaniline, and 2,6-dimethylaniline using 2a

very little retention because it is too hindered to hydrogen bond to the phenolic hydroxyl. When a 1 % solution of 2,6-dimethylaniline was injected, a very broad peak which virtually disappeared in the baseline was observed. Figure 42 shows the peak obtained when a 10 % solution of 2,6-dimethylaniline was injected. This relatively unhindered amine, which can easily hydrogen bond to the phenolic hydroxyl, gives rise to a peak that shows a considerable amount of tailing due to very strong adsorption. Aniline itself was so strongly adsorbed to the resin that it was not possible to observe its elution.

We have found that mixtures of polar and non-polar solvents give the best results with these systems. Most of the aromatic amines were separated using 10 % EtOAc/hexane as the mobile phase at a flow rate of 0.5 ml/min. These amines still show considerable retention with this solvent mixture, but the severe peak tailing that was present when carbon tetrachloride was used as the mobile phase is now absent. For the separation of pyridines, which are approximately five times more basic than anilines¹¹³, a more polar mobile phase was required to achieve similar retention times. Most of the pyridines were separated using 90 % EtOAc/hexane as the mobile phase at a flow rate of 0.5 ml/min.

2.7 Determination of the dead volume time, t_0

The dead volume time, t_0 , is the time required for a solute which has no interaction with the stationary phase to pass through the column. It has been measured in many ways for silica columns, and each method gives a different value for

Table 11 Chromatographic data for separations done with 2a

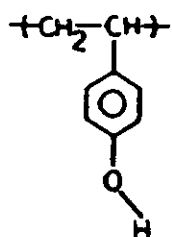
<u>Compound</u>	<u>t_r</u>	<u>t₀</u>	<u>k'</u>	<u>α</u>
2,4,6-tri-t-butylaniline	3.91	3.52	0.11	---
2,6-diisopropylaniline	6.58	3.52	0.87	7.91
2,6-diethylaniline	8.34	3.52	1.37	12.45
2,6-dimethylaniline	11.19	3.52	2.18	19.82
aniline	18.89	3.52	4.37	39.73
triphenylamine	5.89	3.52	0.67	---
diphenylamine	9.83	3.52	1.79	2.67
aniline	19.00	3.52	4.40	6.57
N-ethylaniline	8.21	3.52	1.33	---
N-methylaniline	10.32	3.52	1.93	1.45
N,N-dimethylaniline	6.42	3.52	0.82	---
N-methylaniline	10.30	3.52	1.93	2.35
aniline	19.02	3.52	4.40	5.37
2,6-dimethylaniline	11.30	3.52	2.21	---
2,4-dimethylaniline	14.28	3.52	3.06	1.38
2-methylaniline	14.77	3.52	3.20	---
4-methylaniline	18.65	3.52	4.30	1.34
2-methylpyridine	12.12	3.52	2.44	---
4-methylpyridine	14.70	3.52	3.18	1.30
2,6-dimethylpyridine	10.86	3.52	2.09	---
2,5-dimethylpyridine	13.57	3.52	2.86	1.37
2,4-dimethylpyridine	15.61	3.52	3.43	1.64
1-aminonaphthalene	23.74	3.52	5.74	---
2-aminonaphthalene	29.45	3.52	7.37	1.28
2-aminobiphenyl	13.55	3.52	2.85	---
4-aminobiphenyl	28.52	3.52	7.10	2.49

where $k' = (t_r - t_0)/t_0$

t_0 = retention time of an unretained component (heptane)

$\alpha = k'_2/k'_1$

Both t_r and t_0 are in units of minutes.



15 cm column
mobile phase: 10 % EtOAc/90 % Hexane
0.5 ml/min

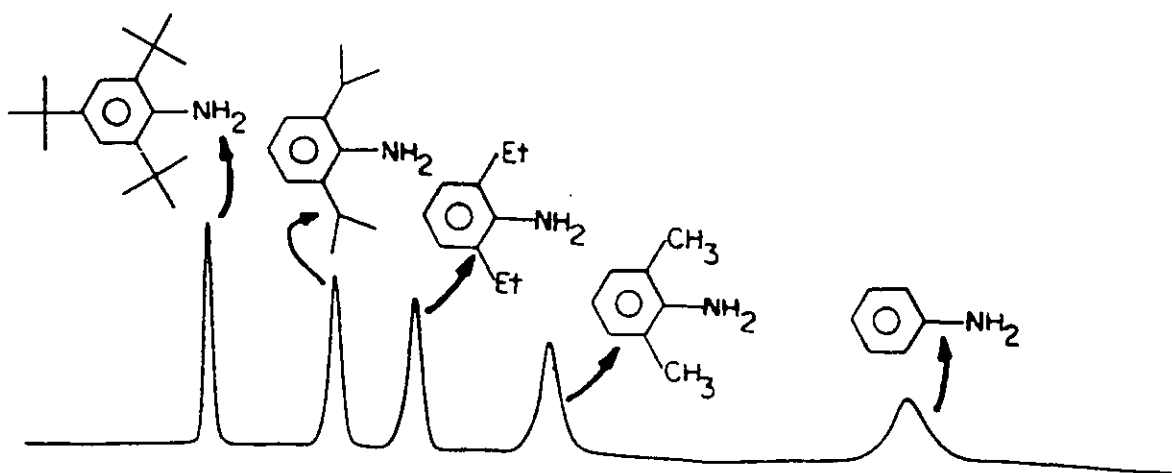
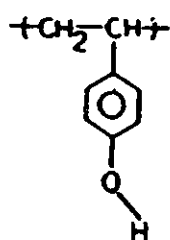


Figure 43 - Separation of aniline, 2,6-dimethylaniline, 2,6-diethylaniline, 2,6-diisopropylaniline, and 2,4,6-tri-*t*-butylaniline using 2a



15 cm column
mobile phase: 10 % EtOAc/90 % Hexane
0.5 ml/min

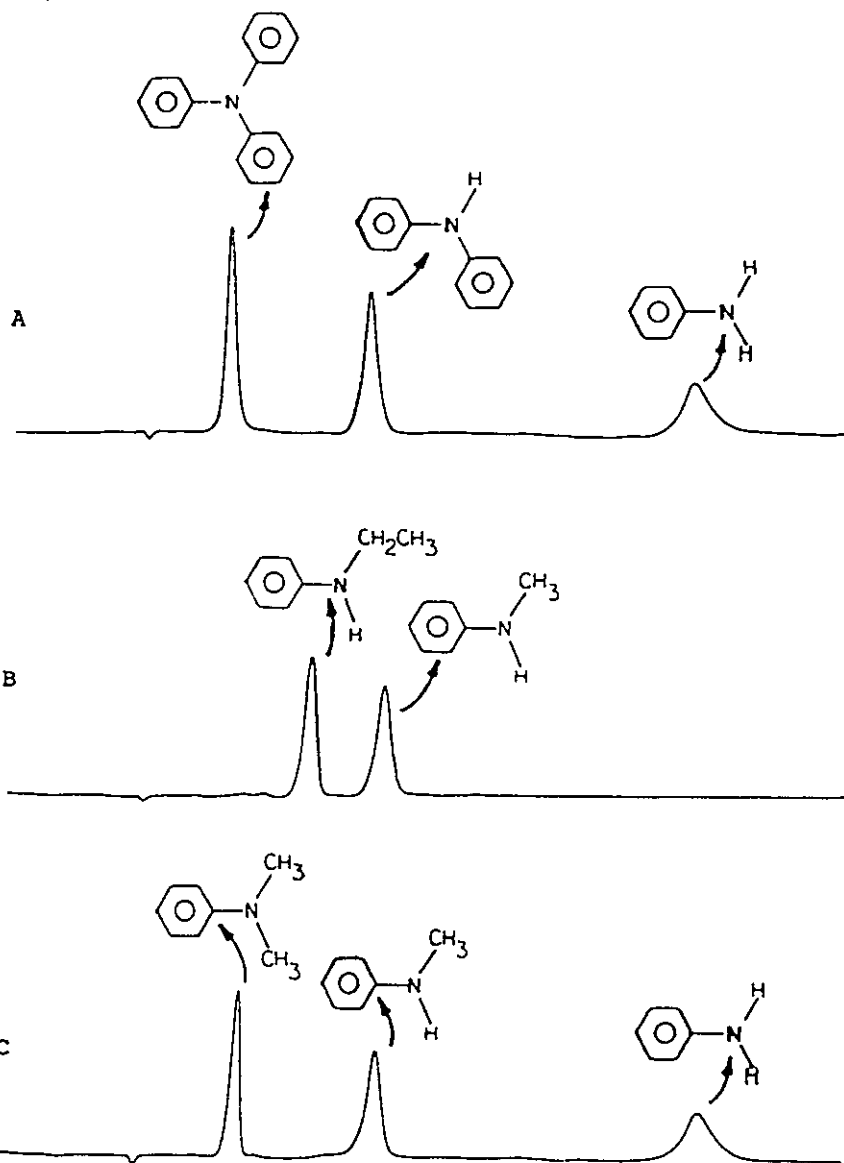
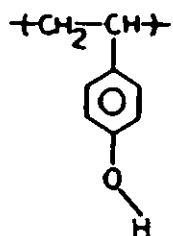


Figure 44 - Separation of (A) aniline, diphenylamine, and triphenylamine, (B) N-methylaniline and N-ethylaniline, and (C) aniline, N-methylaniline, and N,N-dimethylaniline using 2a



15 cm column
mobile phase: 10 % EtOAc/90 % Hexane
0.5 ml/min

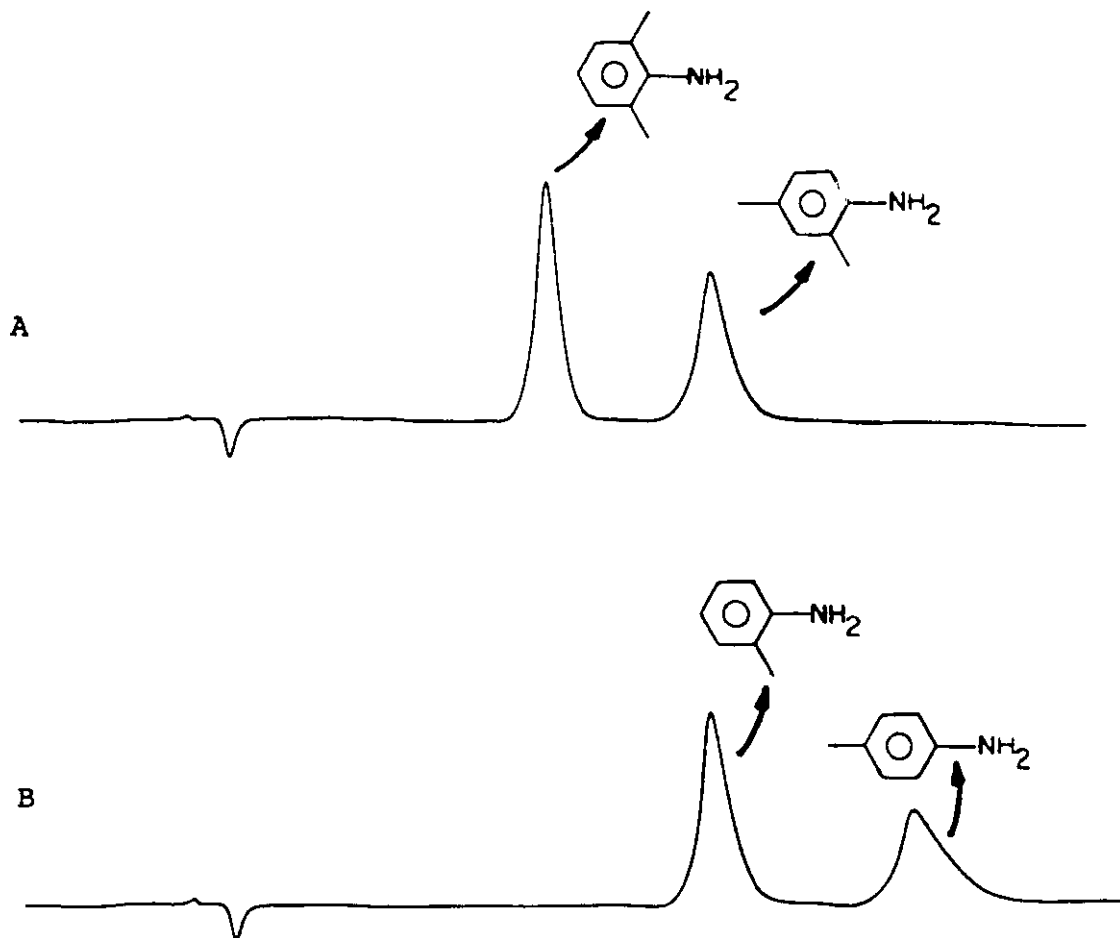


Figure 45 - Separation of (A) 2,6-dimethylaniline and 2,4-dimethylaniline and (B) 2-methylaniline and 4-methylaniline using 2a

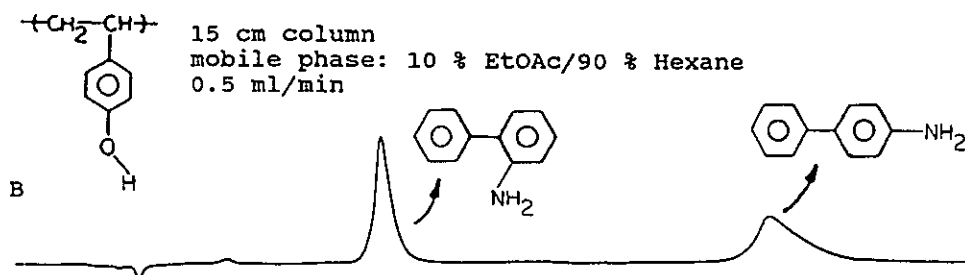
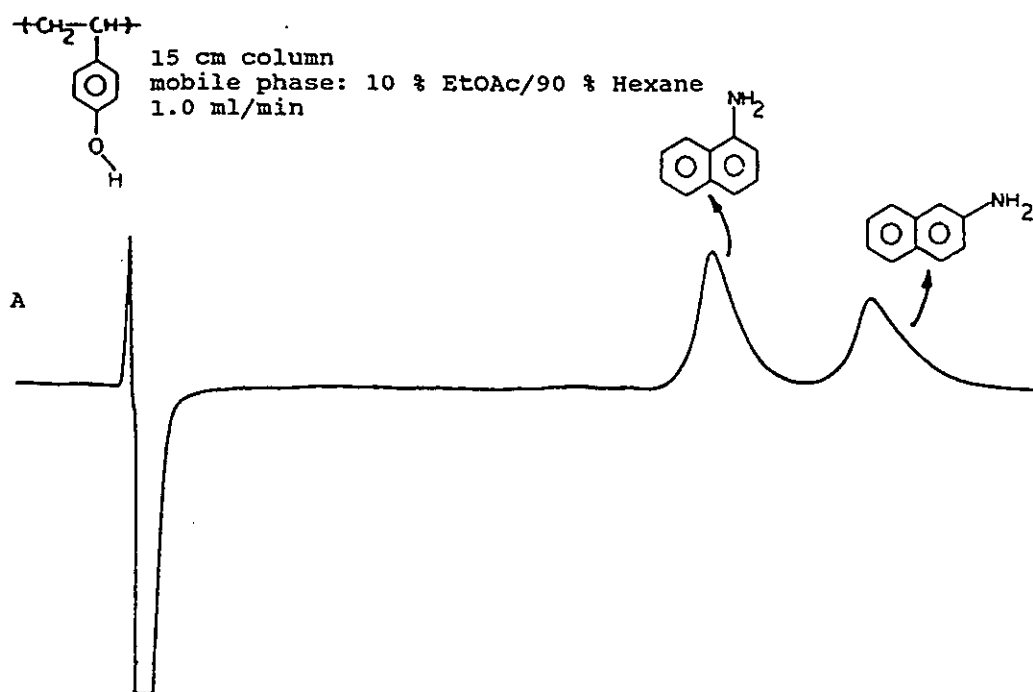
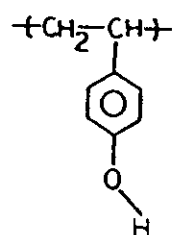


Figure 46 - Separation of (A) 1-aminonaphthalene and 2-aminonaphthalene and (B) 2-aminobiphenyl and 4-aminobiphenyl using 2a



15 cm column
mobile phase: 90 % EtOAc/10 % Hexane
0.5 ml/min

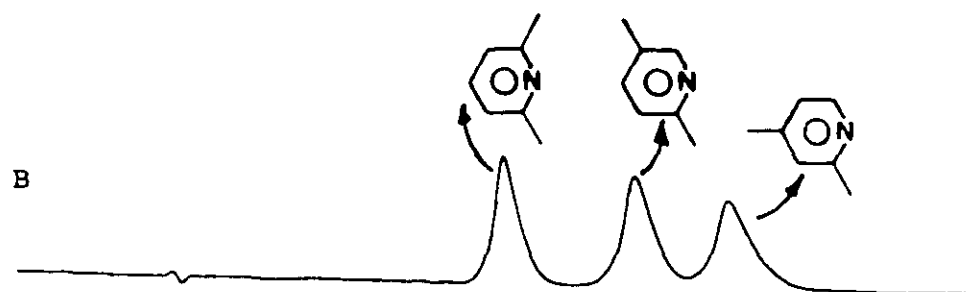
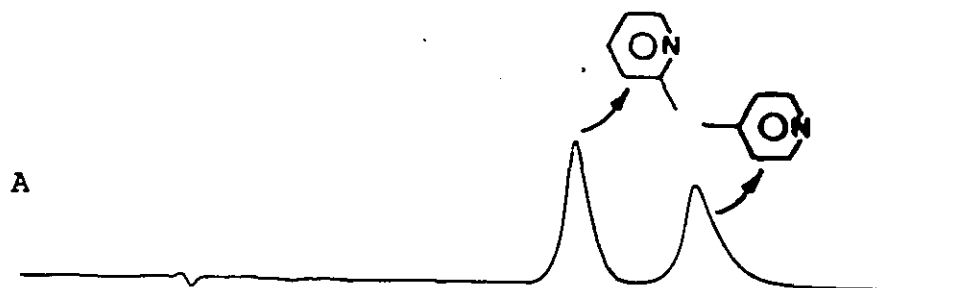


Figure 47 - Separation of (A) 2-methylpyridine and 4-methylpyridine and (B) 2,6-dimethylpyridine, 2,5-dimethylpyridine, and 2,4-dimethylpyridine using 2a

t_0^{114} . The dead volume times in this work were measured by injection of 6 μ l of a 2 % solution of heptane onto each column using 10 % EtOAc/hexane as the mobile phase; this technique is often used with silica columns. The "stronger" solvent, ethyl acetate, saturates the surface of the sorbent and the "weaker" solvent, heptane, passes through the column with little or no retention or adsorption.

2.8 Separations performed with polymer 2a

Table 11 gives the chromatographic data for some compounds separated using polymer 2a; the corresponding chromatograms are given in Figures 43-47. The unhindered phenolic polymer gives good separations for a variety of nitrogen-containing compounds. For example, aniline, 2,6-dimethylaniline, 2,6-diethylaniline, 2,6-diisopropylaniline, and 2,4,6-tri-t-butylaniline are all easily separated from one another by this column. The most hindered molecule, 2,4,6-tri-t-butylaniline, shows very little retention on the column because it is too hindered to hydrogen bond to the phenol. The least hindered phenol, aniline, shows the most retention because it can most easily hydrogen bond with the phenol. Also, it is important to keep in mind that the solubility of a particular molecule in the mobile phase plays an important part in determining its retention. For example, 2,4,6-tri-t-butylaniline is less polar than aniline and should be much more soluble in the relatively non-polar mobile phase, 10 % EtOAc/hexane; this should also contribute to the lower retention times for the more hindered monomers.

Figure 44 shows that this column can easily separate pri-

mary, secondary, and tertiary amines. Again, the more hindered tertiary amines show the least retention while the unhindered primary amines show the most retention. This Figure also shows that it is possible to separate two secondary amines of similar structure, N-ethylaniline and N-methylaniline. Figure 45 shows some excellent separations of some alkyylaniline isomers. The more hindered anilines show lower retention on the column, probably because they would not be able to hydrogen bond to the phenol moiety as strongly as the unhindered isomers. A similar result can be seen in Figure 47 for some alkylpyridine isomers. Finally, Figure 46 shows good separations of 1- and 2-amino-naphthalene and 2- and 4-aminobiphenyl.

The term k' is known as the capacity factor of the solute and indicates how strongly a particular solute is bound to the column. α is the relative retention of one solute to another and is obtained by dividing the capacity factors of the solutes; the larger the value of α , the better the separation¹¹⁵. In Table 11, all of the values of α are determined relative to the first component of each mixture.

We thought that there might be some general correlation between the basicity of the aniline or pyridine and its retention on the column, but this correlation does not exist. For example, aniline (pKa of conjugate acid = 4.60)¹¹⁶ is more basic than triphenylamine (pKa of conjugate acid = -5)¹¹⁶ and is held more strongly on the column; however, aniline is held more strongly on the column than N,N-dimethylaniline (pKa of conjugate acid = 5.06)¹¹⁶, which is more basic than aniline. This correlation probably does not exist because pKa values are deter-

mined in acidic aqueous media and our mobile phases usually consist of mixtures of ethyl acetate and hexane. It is known that solvation of the conjugate acid of a base largely determines the stability of the conjugate acid and thus the basicity of the amine¹¹⁶. Basicities determined in organic solvent media and in the gas phase are usually much different than basicities determined in aqueous solution, and the order of basicities is often reversed when the solvent medium is changed¹¹⁷. The results in Table 11 do show, in every case, that those amines which are sterically hindered have less retention than those which are relatively unhindered.

2.9 Comparison of polymers 2a, 2b and 2c

The compounds in Table 11 were then separated using polymers 2b and 2c so that we could observe how the separation ability of the phenol moiety changed as the acidity and steric environment around the phenolic hydroxyl group was systematically changed; Figure 48 shows a typical example. It appears that for these three isomers, the unhindered phenol gives the best separation. Baseline resolution of 2,6-dimethylpyridine, 2,5-dimethylpyridine, and 2,4-dimethylpyridine can be achieved using 2a. The separation becomes worse as the steric hindrance around the hydroxyl group is increased. All of the other groups of compounds in Table 11 were tested in a similar fashion, and they all displayed the same effect shown in Figure 48. For these groups of compounds, the unhindered phenol gives the best separation. It is not surprising to see that the anilines and pyridines have less retention on the hindered phenol columns than on the unhin-

15 cm columns
 mobile phase: 90 % EtOAc/10 % Hexane
 0.5 ml/min

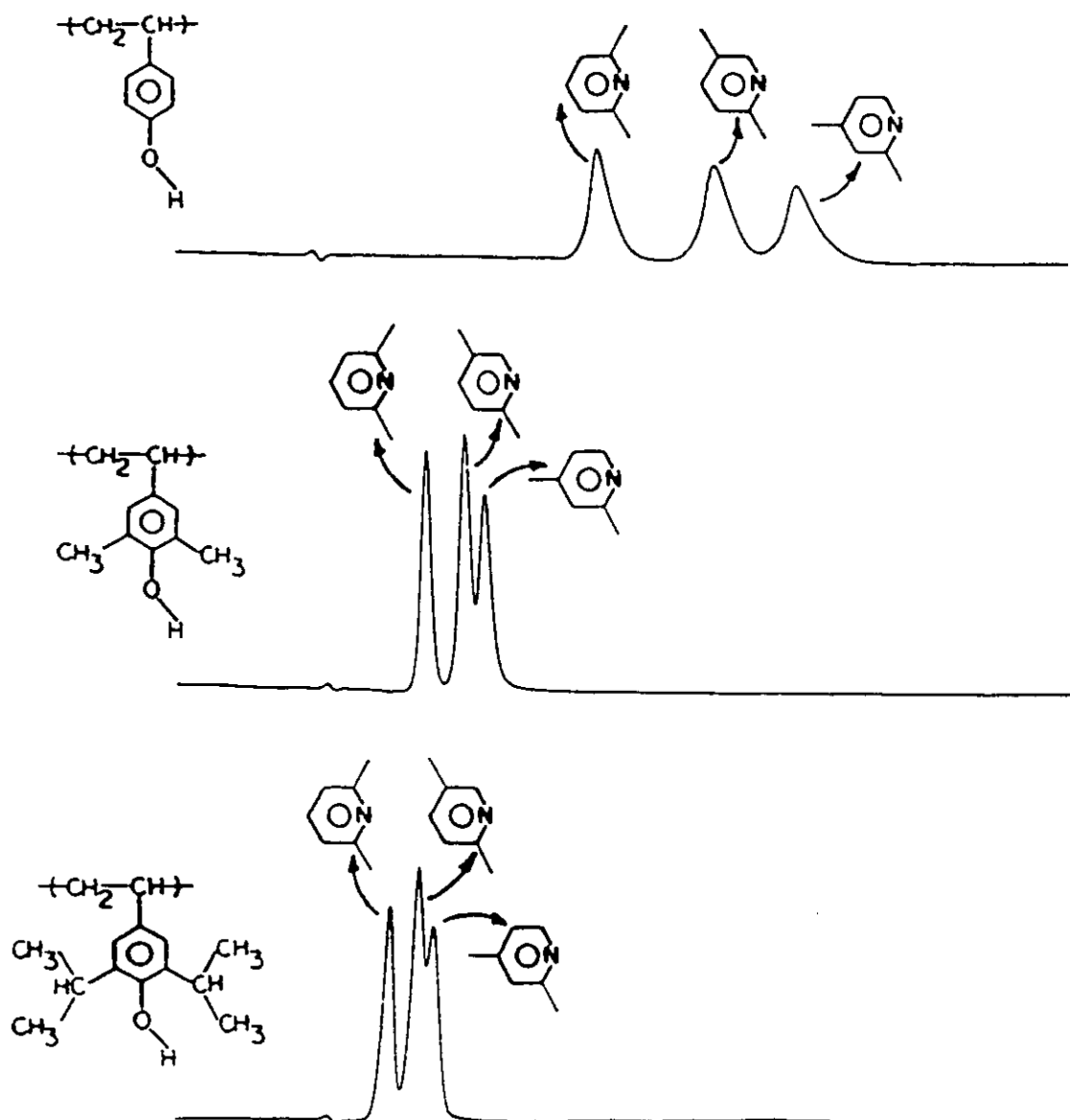


Figure 48 - Separation of 2,6-dimethylpyridine, 2,5-dimethylpyridine, and 2,4-dimethylpyridine using 2a, 2b, and 2c

15 cm columns
mobile phase: 90 % EtOAc/10 % Hexane
0.5 ml/min

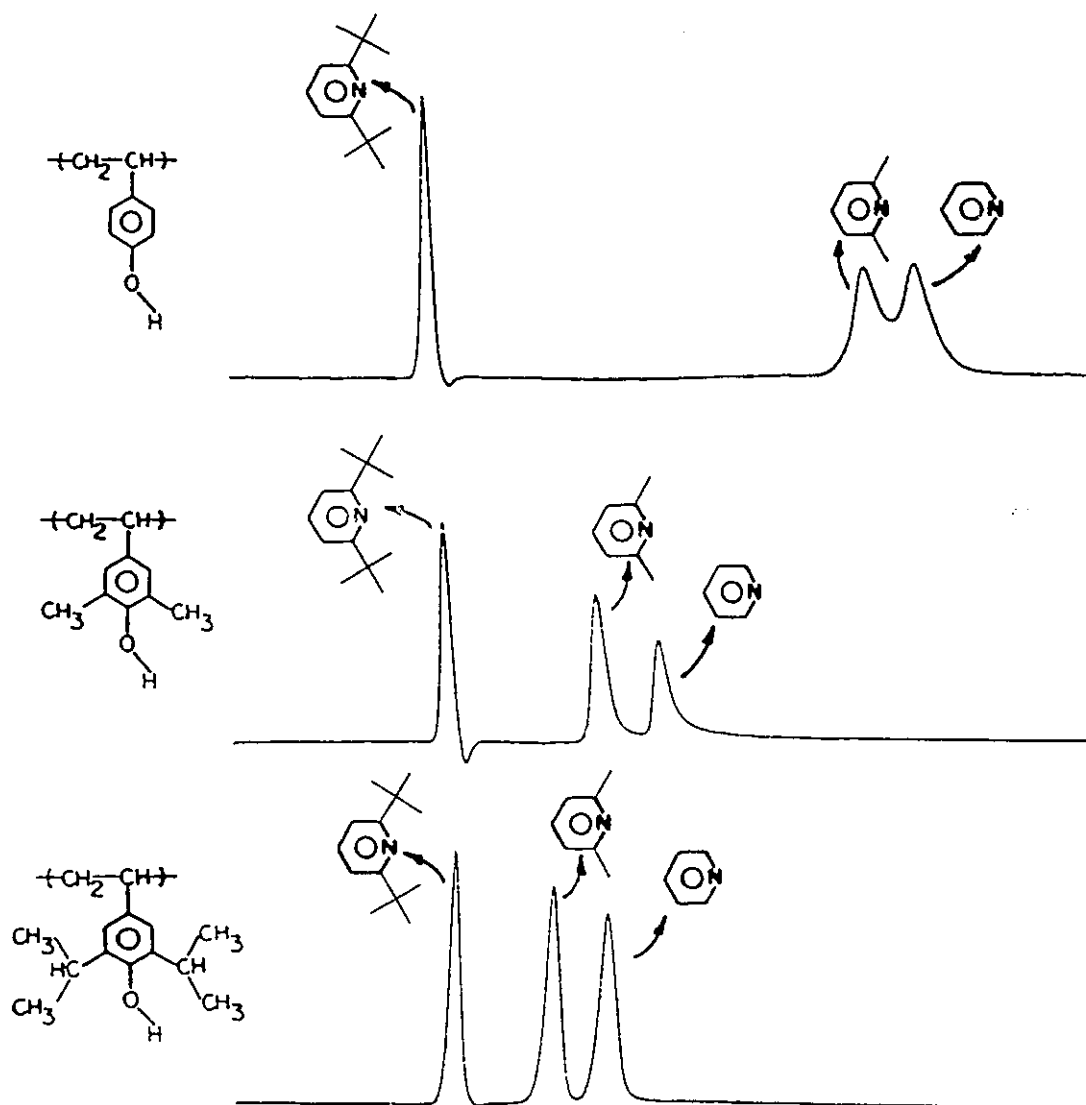


Figure 49 - Separation of pyridine, 2,6-dimethylpyridine, and 2,6-di-t-butylpyridine using 2a, 2b, and 2c

dered phenol column because the hindered phenols are less acidic than the unhindered phenol and would be expected to form weaker hydrogen bonds with nitrogen-containing compounds. In these cases, the decreased acidity and steric hindrance of the phenolic hydroxyl group in the hindered phenol polymers does not help to improve the selectivity of the separations.

A few cases have been found where the hindered phenol polymers separate compounds which cannot be distinguished by polymer 2a. For example, Figure 49 shows that 2a cannot resolve pyridine and 2,6-dimethylpyridine, but the hindered polymers, 2b and 2c, resolve these compounds quite nicely. Severe steric interactions between the methyl groups of 2,6-dimethylpyridine and the alkyl groups of the hindered phenol polymers may allow these polymers to resolve the hindered pyridine from pyridine itself, which is relatively unhindered. These steric interactions would be absent when chromatographing these compounds on polymer 2a. The severely hindered pyridine, 2,6-di-t-butylpyridine, elutes essentially as t_0 on each column. Table 12 shows the relevant chromatographic data for the separations discussed above. The separation factor, α , is only 1.12 for polymer 2a, but increases to 1.39 and 1.51 for polymers 2b and 2c respectively. Also, a better separation can be achieved in a much shorter amount of time using the hindered polymers.

Another potential application of these hindered phenol polymers lies in the separation of aliphatic amines, which are much more basic than pyridines and anilines. It is virtually impossible to achieve any meaningful separation of aliphatic amines using polymer 2a. The phenol moiety has a pK_a of 10 (in aqueous

Table 12 Comparison of polymers 2a, 2b, and 2c in the separation of pyridine and 2,6-dimethylpyridine

<u>Polymer 2a</u>	<u>t_r</u>	<u>t_o</u>	<u>k'</u>	<u>α</u>
2,6-dimethylpyridine	10.74	3.52	2.05	---
pyridine	11.62	3.52	2.30	1.12
 <u>Polymer 2b</u>				
2,6-dimethylpyridine	6.12	3.49	0.75	---
pyridine	7.12	3.49	1.04	1.39
 <u>Polymer 2c</u>				
2,6-dimethylpyridine	5.30	3.76	0.41	---
pyridine	6.10	3.76	0.62	1.51

Both t_r and t_o are in units of minutes.

15 cm columns
mobile phase: MeOH
0.5 ml/min

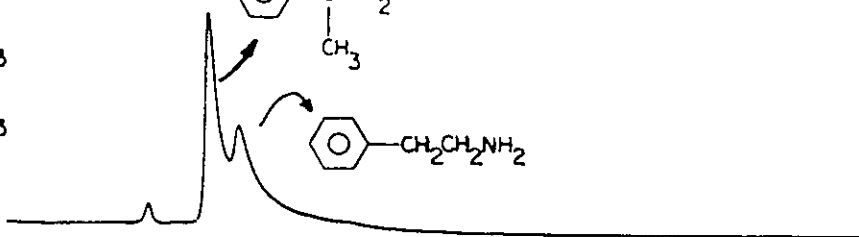
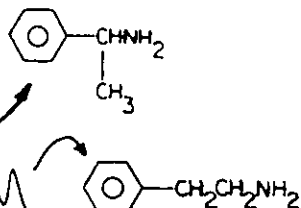
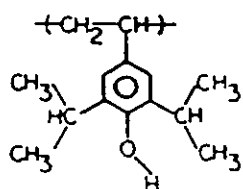
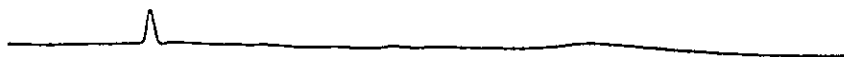
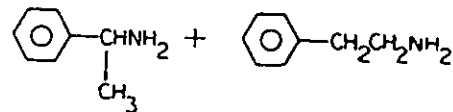
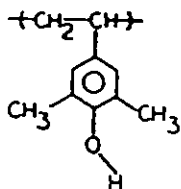
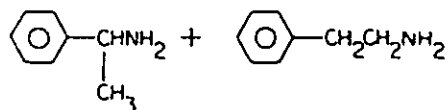
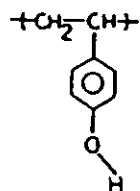
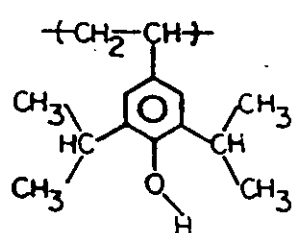


Figure 50 - Separation of 1-phenylethylamine and 2-phenylethylamine using 2a, 2b, and 2c

solution) and a p-substituted phenol has a pKa of 10.3¹¹⁸; the pKa of the conjugate acid of most aliphatic amines lies between 9 and 10. In this region of pKa values, proton exchange can occur between a phenol and an amine as well as very strong hydrogen bonding. Figure 50 shows an attempted separation of 1-phenylethylamine and 2-phenylethylamine using polymer 2a. This separation was attempted using methanol as the mobile phase because methanol has been shown to be a very "strong" solvent with this system (aniline had virtually no retention on this column in a methanol mobile phase). These two compounds adsorb very strongly onto this column, and the resulting chromatographic peaks are so broad that they virtually disappear in the baseline. The pKa's of the conjugate acids of 1-phenylethylamine and 2-phenylethylamine are 9.35 and 9.88 respectively¹¹³. These compounds can hydrogen bond very strongly to a phenolic moiety, and this accounts for the broad and badly tailing peaks seen in Figure 50.

2,6-Dimethylphenol and 2,6-diisopropylphenol are reported to have pKa's of 10.6 and 11.1 respectively¹¹⁸. This means that they are much less acidic than the phenol moiety and should form weaker hydrogen bonds with the aliphatic amines. Figure 50 shows the attempted separation of 1-phenylethylamine and 2-phenylethylamine using polymer 2b. Again, only very broad peaks which virtually disappear in the baseline can be seen. It is only with polymer 2c that "normal" chromatographic peaks can be obtained, although these peaks still show some tailing. One reason for the reduced tailing is the weaker hydrogen bonds formed by the less acidic proton of the phenol moiety of 2c. Also, it has been shown that hindered phenols form longer and



15 cm column
mobile phase: 80 % MeOH/20 % H₂O
0.5 ml/min

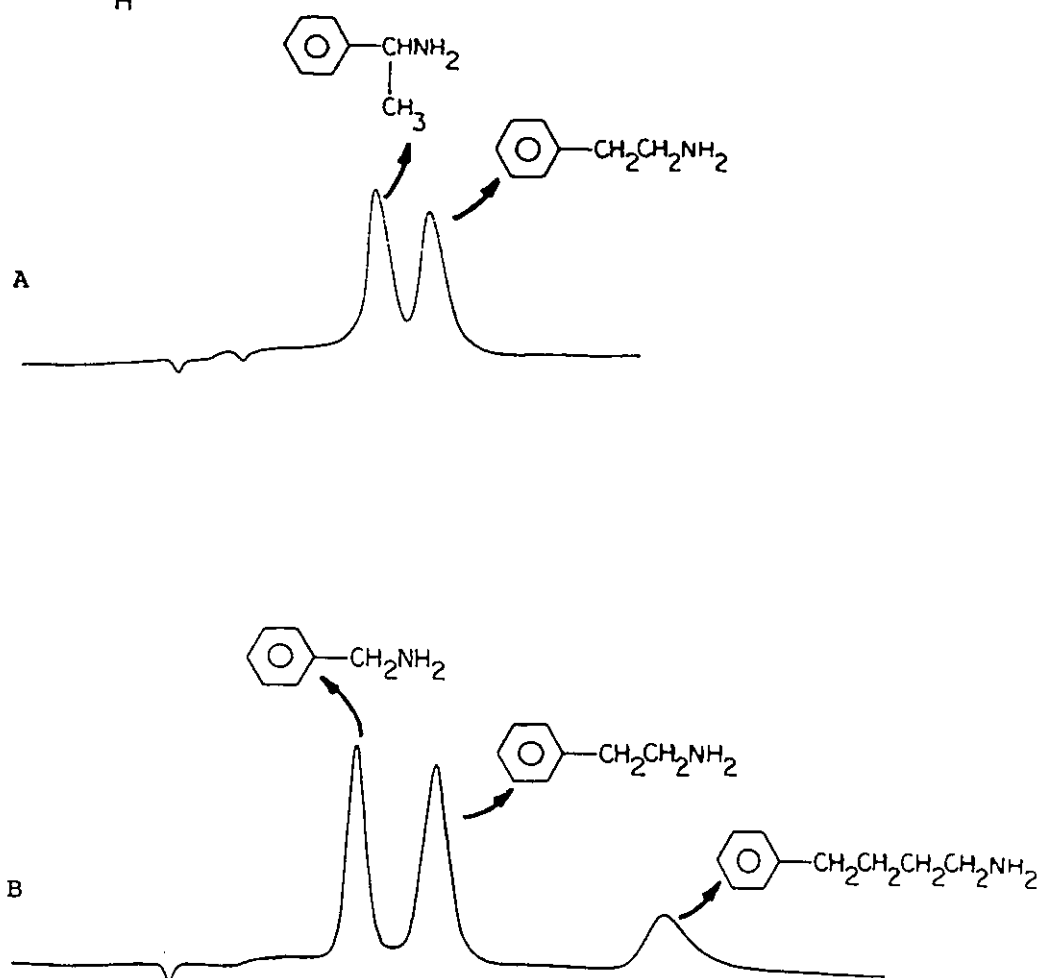


Figure 51 - Separation of (A) 1-phenylethylamine and 2-phenylethylamine and (B) benzylamine, 2-phenylethylamine and 4-phenylbutylamine using 2c

weaker hydrogen bonds with other molecules than unhindered phenols because of steric interference between the alkyl groups of the hindered phenol and the substituents of the molecule to which the phenol is hydrogen bonding¹¹⁹. Both of these factors could lead to the formation of a relatively weak hydrogen bond between the aliphatic amines and the 2,6-diisopropyl moiety; this explains the greatly reduced tailing observed in this case. Figure 51 shows that the separation of these two compounds can be improved by using 80 % MeOH/20 % H₂O as the mobile phase. This Figure also shows a good separation of benzylamine, 2-phenylethylamine, and 4-phenylbutylamine using 2c.

The ability of 2c to separate aliphatic amines has important practical applications. Silica is not suitable for the separation of these compounds because they show badly tailing peaks on silica gel. Even the bonded phase silicas show these badly tailing peaks because of interactions between aliphatic amine groups and residual silanol groups on the silica surface. In one paper, procainamide, which contains a tertiary aliphatic amine group, showed very bad tailing on an octadecyl silica gel¹²⁰. The chromatogram that was shown resembles the chromatogram shown in the upper half of Figure 51. In fact, the pK_a of the silanol groups of silica has been determined to lie between 9.5 and 9.8¹²¹, and this is very close to the pK_a of the unhindered phenol. Also, the columns prepared in this work can operate with aqueous or non-aqueous mobile phases, while silica columns are very unstable in aqueous mobile phases, especially when the pH of the mobile phase is above 7.

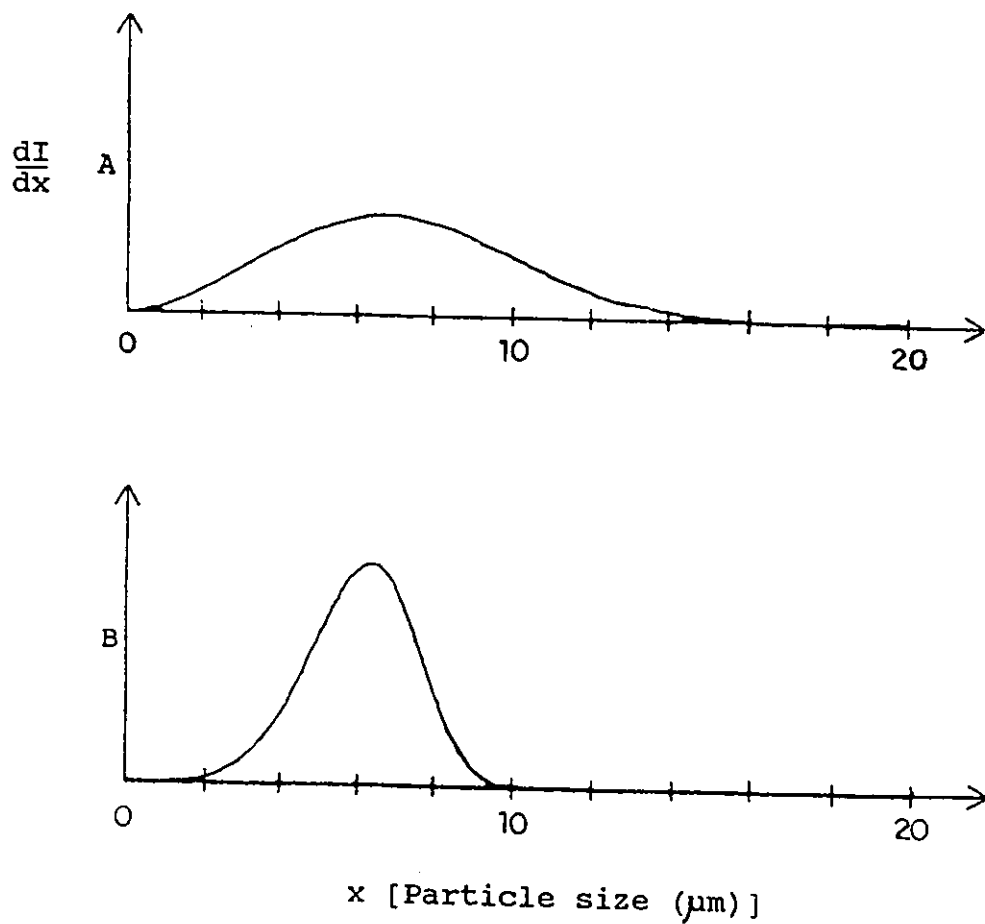
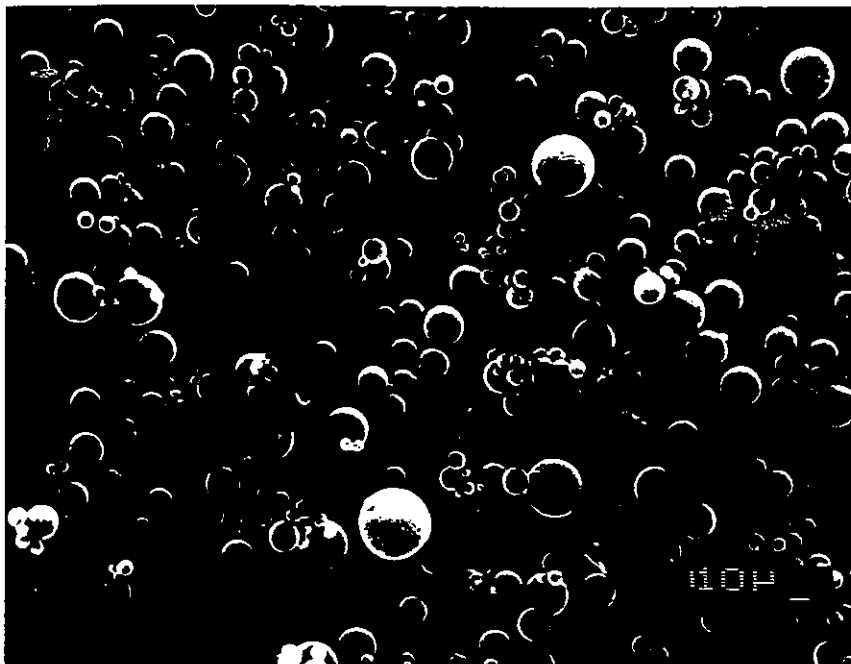


Figure 52 - Particle size distribution curves for 1a produced on a large scale before (A) and after (B) sizing

A



B

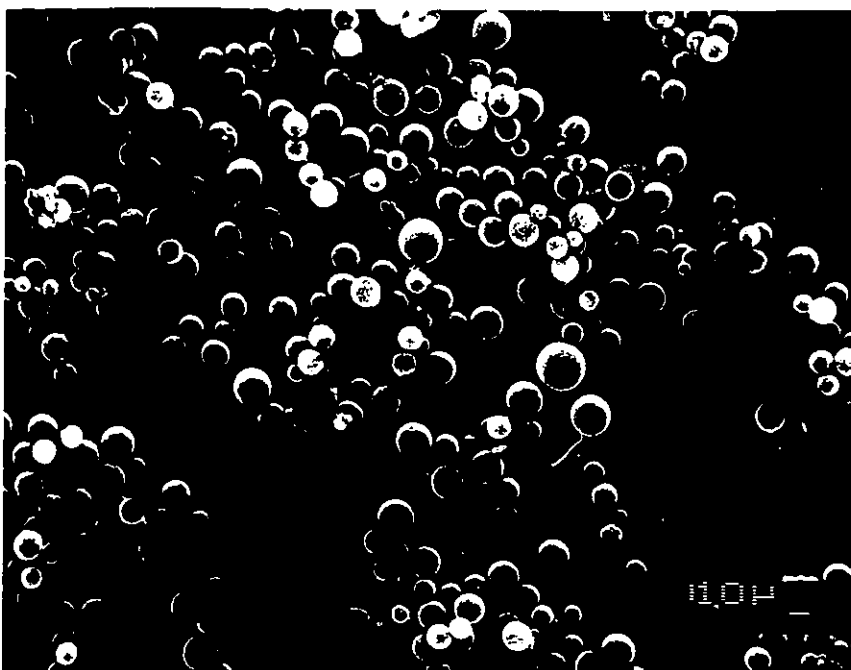


Figure 53 - SEM photographs of 1a produced on a large scale before (A) and after (B) sizing

2.10 Production of 1a on a large scale

The experiment that produced 1a was scaled up by doing the same polymerization in a 1-litre reactor five times and combining the reaction products; about 125 g of polymer beads were produced. This sample had a mean particle size of 7.11 μm with a standard deviation of 2.95. The beads were sized into three fractions with an Alpine air-classifier at the Institute of Macromolecular Chemistry in Prague, Czechoslovakia. The middle fraction had a mean particle size of 6.04 μm and a standard deviation of 1.29 μm . The corresponding Coulter Counter particle size distribution curves are shown in Figure 52, and some electron micrographs are shown in Figure 53. After thermolysis of the t-BOC groups, this middle fraction was packed into an HPLC column under the same conditions as 2a, but there was no improvement in column efficiency. In fact, the column efficiency was worse in this case, giving an HETP of 120 μm . This column showed high backpressure, which is an indication that the frits are clogged somewhat. This high backpressure may prevent the particles from packing very closely together, and this would account for the poor efficiency. If this large-scale polymerization were performed at a slower stirring speed and then sized, perhaps a narrow fraction with an average particle size of 10 μm could be obtained. This column would have almost no backpressure and might show some improved efficiency relative to the unsized sample of 1a with an average particle size of 10 μm .

3. Conclusions

Our research has shown that both 3,5-dimethyl-4-t-butyloxy-carbonyloxystyrene and 3,5-diisopropyl-4-t-butyloxy-carbonyloxystyrene can be prepared in good yields in a simple and efficient three-step synthesis that begins with the corresponding 2,6-di-alkylphenol. These monomers, along with the commercially available 4-t-butyloxy-carbonyloxystyrene, can be copolymerized with commercial divinylbenzene in a suspension polymerization system to give 10 μm , macroporous, spherical, protected vinyl phenol resins. Surface area and pore volume can be controlled accurately by variation of the volume % of the porogen in the suspension polymerization recipe or by variation of the thermodynamic quality of the porogen. Particle size and particle size distribution can be controlled accurately by variation of the thermodynamic quality of the porogen, the stirring speed, and the ratio of the aqueous to organic phases. The t-BOC protecting groups can be removed easily by briefly heating the bead polymers under a vacuum or a flow of inert gas. This solid-state thermolysis step is unique because it is complete within a few minutes and requires no processing of the product polymer, whereas chemical cleavage reactions performed on polymer beads often require long and laborious processing steps. In addition, it is very difficult for chemical reagents to cleave a t-BOC group that is shielded by two isopropyl groups, whereas accessibility of reactive sites is not a factor in the thermolysis reaction.

These vinyl phenol bead polymers have enough mechanical stability to be packed into 15 cm HPLC columns at 3000 psi of

solvent pressure without crushing to any significant extent. Our data shows that polymer beads with an average particle size of 10 μm are ideal for packing into HPLC columns. Beads with an average particle size of less than 10 μm can be used, but the frits of these columns become clogged very easily because of the high percentage of small particles found in these samples. These columns have efficiencies ranging from 10,000 to 18,000 plates per meter and can be used with a variety of mobile phases.

The resin containing the unhindered phenol moiety, polymer 2a, was found to give the best separations of a variety of mixtures of pyridines and anilines. Polymers 2b and 2c, containing the dimethylphenol and diisopropylphenol moieties respectively, were found to give inferior separations of these compounds in most cases. For the separation of mixtures of aliphatic amines, polymer 2c was found to be of the greatest utility. The separation of aliphatic amines on 2a and 2b was impossible because of tailing effects due to strong hydrogen bonding. Good separations of these compounds with drastically reduced tailing was possible with resin 2c because the phenolic moiety of this polymer has a very weakly acidic hydroxyl group that is shielded by two bulky isopropyl groups. These acidic and steric factors result in the formation of very weak hydrogen bonds between the hydroxyl group of 2c and aliphatic amines, which allows these amines to be chromatographed much more effectively with resin 2c. In practical terms, this is important because aliphatic amines are very difficult to separate on silica-based separation media due to strong hydrogen bonding interactions between the amine groups and the surface silanol

groups of silica. Also, silica-based separation media are unstable in aqueous media, especially above pH 7, whereas these vinyl phenol resins are compatible with a variety of mobile phases, including aqueous media.

4. Experimental

The monomer p-t-butoxycarbonyloxystyrene and AIBN are commercial products that were purchased from the Kodak Co. and were used as received. Divinylbenzene was purchased from Poly-science Inc.; prior to polymerization, it was washed three times with 5 % NaOH and three times with water, dried over CaCl_2 , filtered, and then distilled at 50 °C at a pressure of 0.5 mm of Hg. Poly(vinyl alcohol) was purchased from Wacker Chemie; the code number of this sample was Polyviol 25/140. It has a molecular weight of 80,000, a degree of polymerization of 1600, and a degree of hydrolysis of 86-89 %. All of the solvents used in HPLC were obtained from Fisher Scientific and were distilled prior to their use. All of the compounds that were separated by the columns prepared in this work were purchased from the Aldrich Chemical Co. 2,6-dimethylphenol, 2,6-diisopropylphenol, trifluoroacetic acid, and potassium t-butoxide were purchased from the Aldrich Chemical Co. and were used as received. Cyclohexanol and potassium carbonate (anhydrous and granular grade) were obtained from the J. T. Baker Chemical Co. Before being used, potassium carbonate was ground to a fine powder using a mortar and pestle in a nitrogen atmosphere. Hexamethylenetetramine was obtained from Matheson, Coleman, and Bell. Di-t-butyl pyrocarbonate was purchased from Sigma Chemicals. Methyltriphenyl phosphonium bromide was obtained from Sigma Chemicals. B & J brand tetrahydrofuran was purchased from American Scientific Products.

All suspension copolymerizations were performed in a Büchi

BEP 280 suspension polymerization reactor purchased from Büchi AG, Uster (Switzerland). This reactor has a motor which provides overhead stirring, a semi-cylindrical round bottom glass reaction vessel, a stainless-steel anchor-type stirrer, and a circular water-cooled condensor. The anchor stirrers, both small and large versions, were a gift of Dr. Frantisek Svec of the Institute of Macromolecular Chemistry in Prague, Czechoslovakia. The glass reaction vessel has an outer water-jacket which is used to provide heat for the polymerization; a 250 ml vessel was used in most experiments, while a 1000 ml vessel was used for one larger scale experiment along with a larger stirrer. The speed of rotation of the stirrer can be varied from 0 to 2000 rpm; a Cole-Parmer 8204-00 Digital Tachometer was used to calibrate the instrument.

Polymer beads were packed into HPLC columns with a Chromatem Slurry Packing Machine for HPLC columns purchased from Touzart and Matignon; a drawing of this instrument is presented in Figure 54. This apparatus consists of a Haskell piston pump which operates on nitrogen gas pressure, a solvent reservoir, a stainless-steel coil for solvent delivery, a stop-valve, a semi-cylindrical slurry reservoir, and a 5 cm stainless-steel pre-column. The analytical HPLC equipment used included a Perkin-Elmer Sigma 15 Chromatography Data Station, a Perkin-Elmer Series 10 Liquid Chromatograph, a Perkin-Elmer LC-25 Refractive Index Detector, and a Rheodyne 7125 Sample Injector equipped with a 6 μ l sample loop. Stainless-steel columns (15 cm x 4.6 mm internal diameter) were purchased from Mandel Scientific, and all stainless-steel frits were purchased from P.M. Instruments

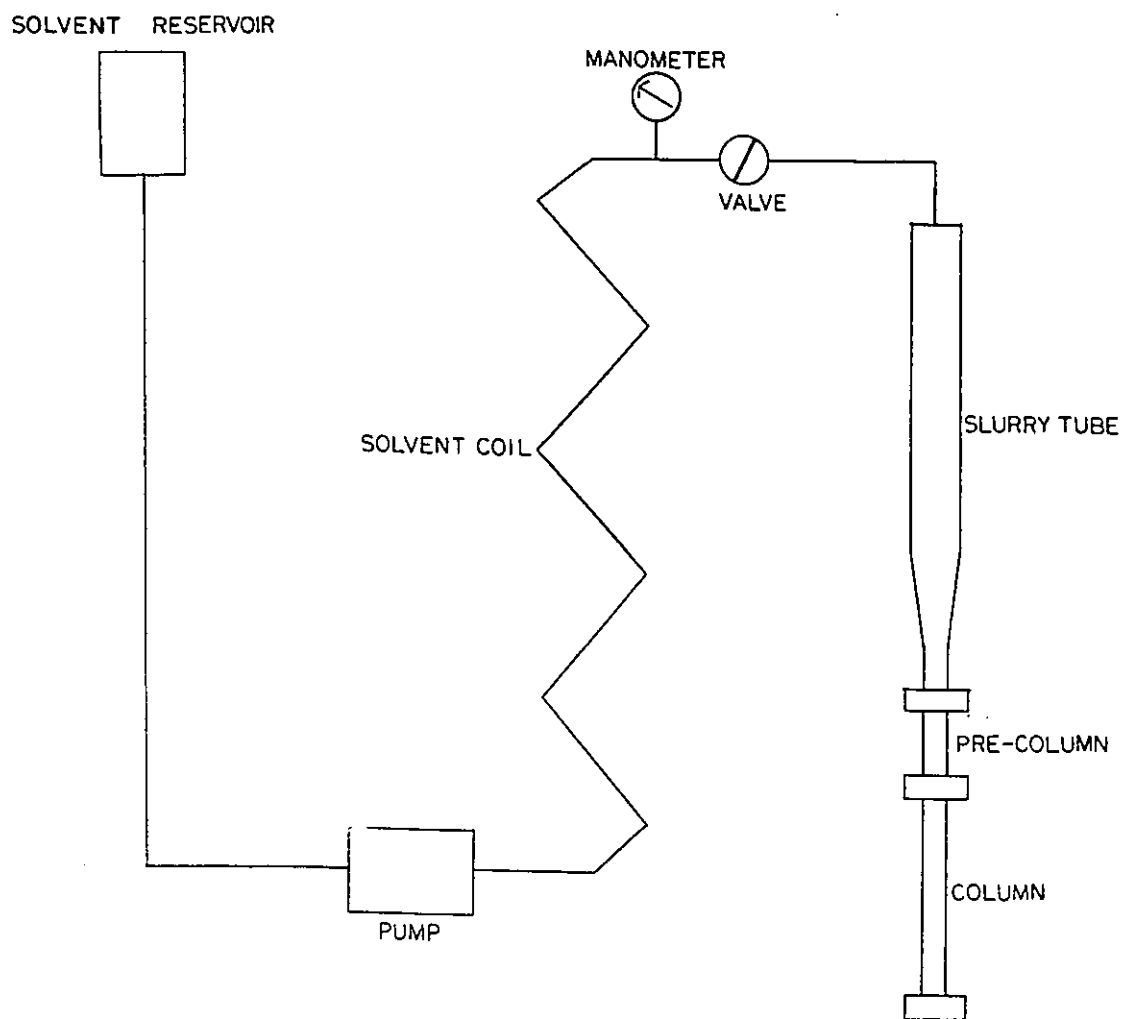


Figure 54 - Column packing apparatus (taken from reference 110)

(Toronto). A Cole-Parmer ultrasonic cleaner was used to help prepare chromatographic slurries.

A sixteen-channel particle size analyzer, a Coulter Counter Model TA II of Coulter Electronics, Luton, England, was used to measure particle size distributions of bead samples. Calibration was performed with standard poly(styrene-divinylbenzene) latexes; a 1 % NaCl solution served as the electrolyte. The orifice tube used had an aperture of 70 μm . The numerical results, in the form of the volume distribution, were fed into a Wang 2200 desk programmable computer. The data were numerically treated using a distribution function which produced the mean and standard deviation of the distribution¹²². All of the measurements of particle size and all of the calculations of the mean and standard deviation were performed at the Institute of Macromolecular Chemistry, Prague, Czechoslovakia.

Optical photographs of polymer beads were taken with a system consisting of an Olympus BH-2 Microscope and a PM-10-A Camera accessory. The internal morphology of several samples of polymer beads was examined by scanning electron microscopy; the polymer beads were fixed onto aluminum supports with colloidal silver using an adhesive and then cut using a razor blade. After coating with gold using a Balzer's sputtering device, the beads were photographed with a JSM-35 (JEOL, Tokyo, Japan) scanning electron microscope in the mode of secondary electrons. These photographs were taken at the Institute of Macromolecular Chemistry in Prague, Czechoslovakia. Some similar experiments were performed at the University of Ottawa using a Semco Nanolab 7 scanning electron microscope.

Specific surface areas were obtained by the method of dynamic desorption of nitrogen using a Quantasorb Sorption System; the data was transformed into specific surface areas by way of the B.E.T theory. Hg porosimetry measurements were made with a Carlo Erba Model 225 Hg porosimeter (Carlo Erba Strumentazione, Italy) at the Institute of Macromolecular Chemistry in Prague, Czechoslovakia. Solvent regains were measured by the centrifugation technique using disposable Centrex centrifugal microfilters purchased from Mandel Scientific.

A Nicolet 10-DX FTIR spectrometer was used to obtain infrared spectra. Solid samples were run as KBr pellets; liquids were run by spreading a thin film of the liquid on top of a KBr pellet. Nuclear magnetic resonance spectra were obtained on Varian EM-360A, CFT-80, and XL-300 spectrometers. CDCl_3 was used as the solvent and tetramethylsilane was used as the reference. Mass spectra were obtained on a VG 7070E double-focusing mass spectrometer in both the electron impact (EI) and chemical ionization (CI) modes. Thermogravimetric analyses were done with a Mettler TA 3000 at a heating rate of $10^\circ\text{C}/\text{min}$ and in a nitrogen atmosphere.

For ^1H -NMR:

s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet
Values are reported in ppm.

For ^{13}C -NMR:

Values are reported in ppm.

Assignments are given in Figure 55 and Figure 56.

ADEPT was used to help make the assignments.

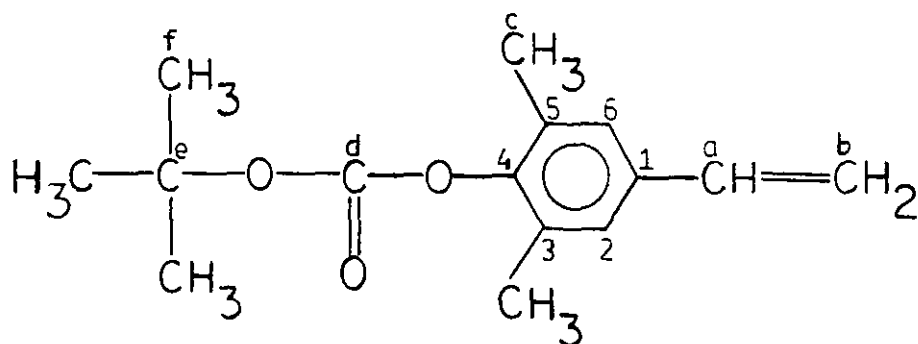
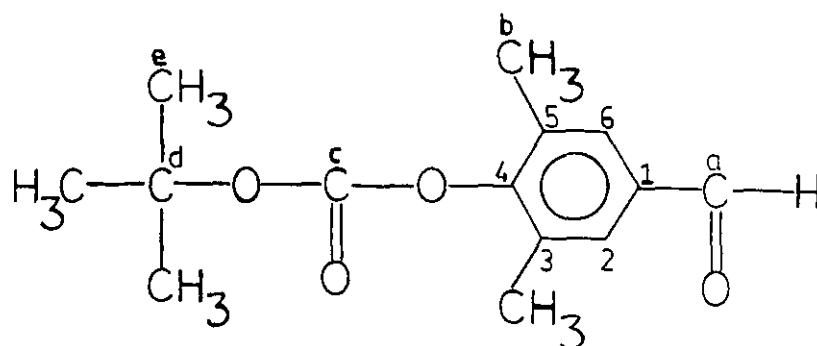
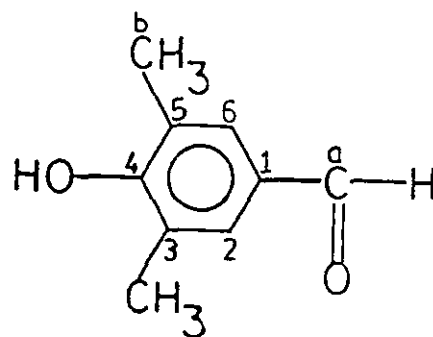


Figure 55 - Assignments for ^{13}C -NMR

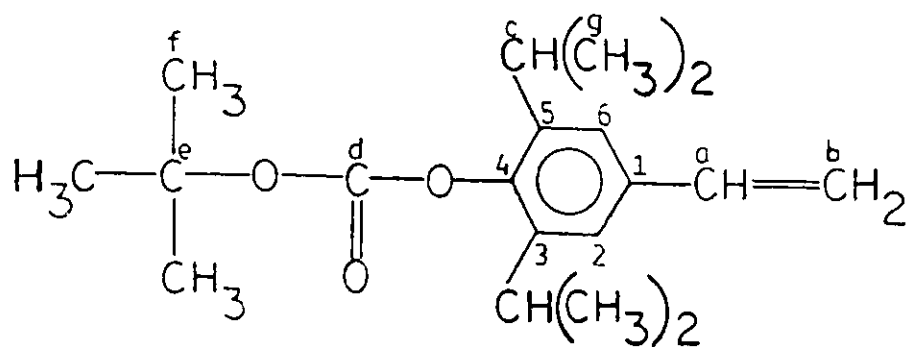
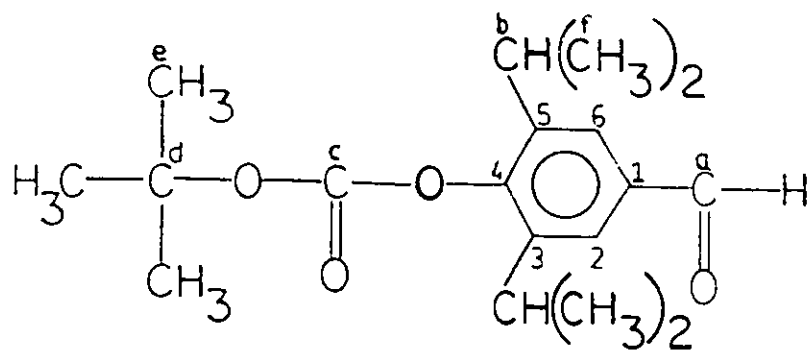
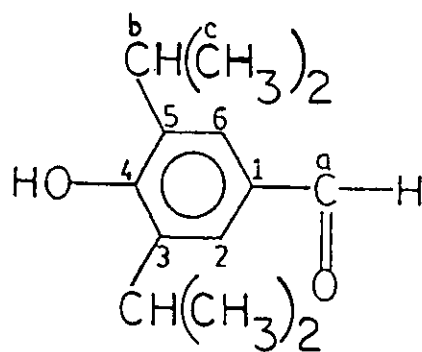


Figure 56 - Assignments for ^{13}C -NMR

For FTIR:

Values are reported in reciprocal centimeters.

4.1 Formylation of 2,6-dimethylphenol

The reaction was done in a 1-litre round-bottom flask equipped with a water-cooled condensor and a nitrogen bubbler. For a typical experiment, 480 ml of trifluoroacetic acid was placed in the flask and 44.8 g (0.319 moles) of hexamethylene-tetramine was added to this, followed by 39.04 g (0.319 moles) of 2,6-dimethylphenol. This mixture was stirred overnight at 85 °C for 13 hours; a TLC taken at this time indicated that there was no starting material remaining. Most of the trifluoroacetic acid was removed and collected by evaporation and condensation on a rotavapor instrument equipped with a cold finger; a mixture of ethylene glycol and dry ice gave a cold finger temperature of -15 °C. The crude product was poured into 500 ml of ice water and stirred for five minutes; this mixture was made slightly basic by gradual addition of a 5 % solution of sodium carbonate, which neutralizes the remaining trifluoroacetic acid. This aqueous phase was then extracted three times with 500 ml portions of diethyl ether, and then most of the ether was removed on a rotavapor. At this point, the product has a dark brown color which can be removed by shaking three times with 200 ml of 1N HCL. The acid may protonate some nitrogen containing byproducts and extract them into the aqueous phase. The clear, red ether solution was then washed three times with 300 ml portions of water, dried over magnesium sulfate and evaporated to dryness. At this point, the product is not pure enough for the next stage

of the synthesis, and must be purified by recrystallization. This product can be recrystallized very easily by dissolving it in the minimum amount of hot chloroform, followed by dropwise addition of hexane until the warm mixture just begins to show some turbidity. Chloroform is then added dropwise until the warm solution becomes clear, and then the solution is allowed to cool down slowly to room temperature. Tiny orange crystals begin to form within an hour, and the solution is then placed in the refrigerator overnight to help crystal formation. The mother liquor is then filtered off and the orange crystals are dried in a vacuum oven. The product was isolated in 70 % yield after recrystallization and its spectral data confirm that the compound is 3,5-dimethyl-4-hydroxybenzaldehyde.

Melting Point:

101-103 °C

Purity:

HPLC (15 cm silica column; 50 % EtOAC/hexane) shows no impurities

Elemental analysis:

found (C:71.77, H:6.65); calculated (C:71.98, H:6.71).

¹H-NMR:

9.73 (s, 1H, H-aldehyde); 7.47 (s, 2H, H-aromatic); 6.35 (broad absorption, 1H, OH); 2.30 (s, 6H, H-methyl).

¹³C-NMR:

192.082 (aldehyde, C_a); 158.952 (aromatic, C₄); 131.204 (aromatic, C_{2,6}); 128.840 (aromatic, C₁); 124.257 (aromatic,

C_{3,5}); 15.976 (methyl, C_b).

MS (EI):

150 (M⁺); 149 (M⁺-1, base peak, characteristic of aromatic aldehydes); 121 (M⁺-29, loss of CHO).

FTIR:

3234 (relatively sharp OH stretch); 2838 (aldehyde CH stretch); 1664 (aldehyde C = O stretch); 1595 (aromatic C = C stretch).

4.2 Formylation of 2,6-diisopropylphenol

The general experimental procedure for the formylation of 2,6-diisopropylphenol is the same as that for 2,6-dimethylphenol and can be found in Section 4.1. Recrystallization of the crude product was performed by dissolving the crude product in the minimum amount of hot chloroform, followed by dropwise addition of hexane to the warm mixture. In this case, addition of hexane did not cause the solution to become turbid, probably because this monomer is somewhat non-polar (relative to the dimethyl analogue) and thus has a slightly higher (though small) solubility in hexane. After addition of a large excess of hexane, the solution was allowed to cool to room temperature and was then placed in the refrigerator overnight. The desired product crystallized out very nicely and the yellowish crystals were isolated by filtration and dried overnight in a vacuum oven. The first crop of crystals was obtained in 78 % yield and all the spectral data confirm that the compound is 3,5-diisopropyl-4-hydroxybenzaldehyde.

Melting Point:

97-99 °C

Purity:

HPLC (15 cm silica column; 20 % EtOAC/heptane) shows that the crystals are very pure.

Elemental Analysis:

found (C:75.43, H:8.82); calculated (C:75.69, H:8.79).

¹H-NMR:

9.83 (s, 1H, H-aldehyde); 7.57 (s, 2H, H-aromatic); 5.82 (broad absorption, 1H, OH); 3.19 (m, 2H, CH-isopropyl); 1.30 (d, 12H, CH₃-isopropyl).

¹³C-NMR:

192.240 (aldehyde, C_a); 156.676 (aromatic, C₄); 134.825 (aromatic, C_{3,5}); 129.218 (aromatic, C₁); 126.312 (aromatic, C_{2,6}); 26.840 (isopropyl, C_b); 22.490 (isopropyl, C_c).

MS (EI):

206 (M⁺); 191 (M⁺-15, base peak, loss of methyl); 177 (M⁺-29, weak, loss of CHO).

FTIR:

3243 (relatively sharp OH stretch); 1665 (aldehyde C = O stretch); 1605, 1580 (doublet, aromatic C = C stretch).

4.3 Protection of the phenolic group of 3,5-dimethyl-4-hydroxy-benzaldehyde as its t-BOC derivative

The reaction was done in a 1-liter 3-necked flask equipped

with overhead mechanical stirring and a nitrogen bubbler. For a typical experiment, 15 g (0.1 moles) of 3,5-dimethyl-4-hydroxybenzaldehyde and 27.64 g (0.2 moles) of potassium carbonate were placed in the flask and covered with 400 ml of dry THF; granular potassium carbonate was ground to a fine powder with a mortar and pestle in a nitrogen-flushed glove bag directly before its use in this reaction. This suspension was cooled to 5 °C using an ice bath and then a solution of 21.83 g (0.1 moles) of di-*t*-butyl dicarbonate in 50 ml of THF was added to this suspension. This mixture was stirred at 5 °C for one hour and then at room temperature for 48 hours. A TLC taken at this time indicates that there is very little starting material remaining. The solid phase was filtered off and the material in the filter was washed twice with EtOAC. The solvents were evaporated on a rotavapor and the resulting viscous, orange liquid was dried overnight in a vacuum oven; any unreacted di-*t*-butyl dicarbonate can be removed rapidly by raising the temperature in the vacuum oven to 60 °C for a few hours. The product of this reaction could be used as is for the next step of the synthesis, but it is usually chromatographed by preparative HPLC (on a Waters prep LC) using 10 % EtOAC/hexane. The weight of pure 3,5-dimethyl-4-*t*-butyloxycarbonyloxybenzaldehyde obtained after HPLC is 22.37 g (89.5 % yield). An attempt was made to purify this material by high-vacuum distillation rather than HPLC, but the material does not have enough vapor pressure for distillation at temperatures below the decomposition temperature of the *t*-BOC group.

Purity:

analytical HPLC (15 cm silica column; 10 % EtOAC/hexane) shows no impurities.

Elemental Analysis:

found (C:66.99, H:7.31); calculated (C:67.18, H:7.24).

^1H -NMR:

9.93 (s, 1H, H-aldehyde); 7.60 (s, 2H, H-aromatic); 2.27 (s, 6H, H-methyl); 1.57 (s, 9H, H-t-butylcarbonate).

^{13}C -NMR:

191.161 (aldehyde, C_a); 152.781 (carbonate, C_c); 150.256 (aromatic, C_4); 133.806 (aromatic, C_1); 131.484 (aromatic, C_3 , C_5); 129.974 (aromatic, $\text{C}_{2,6}$); 83.620 (quaternary, C_d); 27.325 (t-butyl, C_e); 15.868 (methyl, C_b).

MS (EI):

250 (M^+ , not observed); 150 (strong, loss of CO_2 and isobutylene from the molecular ion); 57 (t-butyl); 29 (CHO).

MS (CI/ether):

251 (MH^+ , strong).

FTIR:

2725 (aldehyde CH stretch); 1757 (carbonate $\text{C}=\text{O}$ stretch); 1698 (aldehyde $\text{C}=\text{O}$ stretch); 1600 (aromatic $\text{C}=\text{C}$ stretch).

4.4 Protection of the phenolic group of 3,5-diisopropyl-4-hydroxy benzaldehyde as its t-BOC derivative

The experimental procedure for the protection of the

phenolic group of 3,5-diisopropyl-4-hydroxy benzaldehyde is the same as that for the protection of the phenolic group of 3,5-dimethyl-4-hydroxy benzaldehyde and can be found in Section 4.3. The product of this reaction, 3,5-diisopropyl-4-*t*-butyloxy-carbonyloxybenzaldehyde, was obtained in 87 % yield.

Purity:

analytical HPLC (15 cm silica column; 5 % EtOAC/hexane) shows no impurities.

Elemental Analysis:

found (C:70.46, H:8.56); calculated (C:70.56, H:8.55).

¹H-NMR:

9.98 (s, 1H, H-aldehyde); 7.71 (s, 2H, H-aromatic); 3.13 (m, 2H, CH-isopropyl); 1.57 (s, 9H, H-*t*-butylcarbonate); 1.29 (d, 12H, CH₃-isopropyl).

¹³C-NMR:

191.591 (aldehyde, C_a); 151.318 (carbonate, C_c); 150.443 (aromatic, C₄); 142.085 (aromatic, C_{3,5}); 134.653 (aromatic, C₁); 125.865 (aromatic, C_{2,6}); 83.709 (quaternary, C_d); 27.464 (*t*-butyl, C_e); 27.365 (isopropyl, C_b); 23.022 (isopropyl, C_f).

MS (EI):

306 (M⁺, not observed); 206 (strong, loss of CO₂ and isobutylene from the molecular ion); 191 (base peak, additional loss of methyl); 57 (*t*-butyl); 29 (CHO).

MS (CI/ether):

307 (MH⁺).

FTIR:

2715 (aldehyde CH stretch); 1758 (carbonate C = O stretch); 1698 (aldehyde C = O stretch); 1586 (aromatic C = C stretch).

4.5 Wittig reaction of 3,5-dimethyl-4-t-butyloxy-carbonyloxy-benzaldehyde

The reaction was done in a 1-litre 3-necked flask equipped with a nitrogen bubbler and magnetic stirring. The flask was immersed in an ice bath and then 31.31 g (0.087 moles) of methyl-triphenylphosphonium bromide was placed in the flask, covered with dry THF and stirred; 9.84 g (0.087 moles) of potassium t-butoxide was added to the flask and the suspension was stirred for 20 minutes during which time the bright yellow-colored ylide formed. A solution of 19.92 g (0.080 moles) of 3,5-dimethyl-4-t-butyloxy-carbonyloxybenzaldehyde in 50 ml of THF was added dropwise from a dropping funnel, the ice bath was removed, and the resulting mixture was allowed to stir at room temperature for 5 hours. The crude product was poured into 500 ml of ice water and this aqueous phase was then extracted 3 times with 500 ml of ethyl acetate. Some of the ethyl acetate was removed on a rotavapor, and then the ethyl acetate layer was backwashed 3 times with 500 ml of water, dried over magnesium sulfate, and evaporated to dryness. It is very important to precipitate out the triphenylphosphine oxide formed in the reaction before isolating the desired product by HPLC; if it is not removed beforehand, it will precipitate out in the injection port of the HPLC instrument when pressure is applied to the injection syringe. In order to remove this byproduct, a small amount of ethyl acetate was added

to the crude product (just enough to make it flow) followed by a large volume (500 ml) of hexane; this mixture was placed in the refrigerator overnight to help the precipitation of the triphenylphosphine oxide. The solid precipitate was then removed by filtration and the excess solvent was removed by evaporation. This process may have to be repeated in order to remove all of the triphenylphosphine oxide. The crude product was then purified by HPLC using 3.5 % EtOAc/hexane which gives 15.91 g (80.5 % yield) of a white solid which is shown to be 3,5-dimethyl-4-t-butyloxycarbonyloxystyrene by the relevant spectral data. It is possible to distill the crude product rather than chromatograph it (b.p. 104 °C at 1 mm Hg), but the distillate does not seem to be of sufficient purity for suspension polymerization (see Section 2.1 for further details).

Purity:

HPLC (15 cm silica column; 3.5 % EtOAc/hexane) shows no impurities.

Elemental Analysis:

found (C:72.72, H:8.21); calculated (C:72.55, H:8.11).

¹H-NMR:

7.07 (s, 2H, H-aromatic); vinyl group with characteristic ABX pattern and insufficient resolution to observe J_{AB} (J_{AX} = 18Hz, J_{BX} = 11Hz); 2.18 (s, 6H, H-methyl); 1.56 (s, 9H, H-t-butyloxycarbonate).

¹³C-NMR:

151.219 (carbonate, C_q); 148.029 (aromatic, C₄); 136.211 (vinyl,

C_a); 135.210 (aromatic, C₁); 130.310 (aromatic, C_{3,5}); 126.494 (aromatic, C_{2,6}); 113.507 (vinyl, C_b); 83.058 (quaternary, C_e); 27.620 (t-butyl, C_f); 16.139 (methyl, C_c).

MS (EI):

248 (M⁺, very weak); 148 (base peak, loss of CO₂ and isobutylene from the molecular ion); 57 (t-butyl).

MS (CI/ether):

249 (MH⁺).

FTIR:

3083 (vinylic CH stretch); 1755 (carbonate C = O stretch); 1633 (vinylic C = C stretch); 1601 (aromatic C = C stretch).

4.6 Wittig reaction of 3,5-diisopropyl-4-t-butyloxycarbonyloxybenzaldehyde

The experimental procedure for the Wittig reaction of 3,5-diisopropyl-4-t-butyloxycarbonyloxybenzaldehyde is the same as that for the Wittig reaction of 3,5-dimethyl-4-t-butyloxy-carbonyloxybenzaldehyde and can be found in Section 4.5. The product of this reaction, 3,5-diisopropyl-4-t-butyloxycarbonyloxy-styrene, was obtained in 86 % yield.

Purity:

analytical HPLC (15 cm silica column; 1 % EtOAC/hexane) shows no impurities.

Elemental Analysis:

found (C:74.91, H:9.37); calculated (C:74.96, H:9.27).

^1H -NMR:

7.10 (s, 2H, H-aromatic); vinyl group with characteristic ABX pattern with insufficient resolution to observe J_{AB} ($J_{AX} = 18$ Hz, $J_{BX} = 11$ Hz); 3.00 (m, 2H, CH-isopropyl); 1.53 (s, 9H, H-t-butylcarbonate); 1.22 (d, 12H, CH_3 -isopropyl).

^{13}C -NMR:

152.086 (carbonate, C_d); 145.424 (aromatic, C_4); 140.670 (aromatic, $\text{C}_{3,5}$); 136.778 (vinyl, C_a); 135.719 (aromatic, C_1); 121.990 (aromatic, $\text{C}_{2,6}$); 113.331 (vinyl, C_b); 83.043 (quaternary, C_e); 27.607 (t-butyl, C_f); 27.340 (isopropyl, C_c); 23.255 (isopropyl, C_g).

MS (EI):

304 (M^+ , not observable); 204 (strong, loss of CO_2 and isobutylene from the molecular ion); 189 (strong, loss of CH_3 from 204 ion); 57 (base peak, t-butyl).

MS (CI/ether):

305 (MH^+).

FTIR:

3086 (vinylic CH stretch); 1751 (carbonate $\text{C}=\text{O}$ stretch); 1633 (vinylic CH stretch); 1599, 1589 (doublet, aromatic $\text{C}=\text{C}$ stretch).

4.7 Suspension copolymerization of p-t-BOC-styrene (or its substituted analogs) with commercial divinylbenzene : control of porosity and particle size

In a typical experiment, a 2 % solution of poly(vinyl

alcohol) was poured into the suspension polymerization reactor through a long-stemmed funnel and nitrogen was bubbled through this solution for 15 minutes. Nitrogen was bubbled through the organic phase for 10 minutes, and it was then poured into the reactor on top of the aqueous phase. The reactor was flushed with nitrogen and sealed, and then the suspension was stirred at room temperature for 25 minutes at the appropriate stirring speed. The suspension was then heated with stirring at 80 °C for 16 hours, and then the heat was removed and the suspension was allowed to stir at room temperature for an additional 30 minutes. For experiments which produced larger beads, the particles were taken into 500 ml of water and filtered through cloth. The polymer beads were then washed 10 times with 1000 ml of water, 10 times with 200 ml of methanol, 10 times with 100 ml of toluene, and 10 times with 200 ml of methanol, followed by drying overnight in a vacuum oven at 40 °C. For experiments which produced smaller beads (<15 μ m), the milky-white suspension was poured into a 2000 ml beaker and diluted to a volume of 1000 ml with water. The beaker was placed in an ultrasonic bath and sonicated for 30 minutes. This is a very important step because the ultrasonic vibrations break up the aggregates of the polymer beads that have formed by electrostatic interactions; this separates the "fines" from the larger particles and allows the fines (which have a tendency to clog the frits in HPLC columns) to be removed in the decantation procedure. The beaker was removed from the ultrasonic bath and the particles were allowed to settle overnight. After 24 hours, the supernatant was removed by siphoning with a thin piece of rubber tubing, and

another 1000 ml of water was added; this sonication and siphoning procedure was carried out 5 more times with 1000 ml portions of water. This procedure was used because of the great difficulties involved in the filtration of tiny particles; also, the long settling times allow the excess poly(vinyl alcohol) to diffuse out of beads and into the aqueous phase, where it can be removed along with the "fines" by siphoning. The particles were then washed as above with five 500 ml portions of methanol, five 200 ml portions of toluene, and five 200 ml portions of methanol. The beads were then dried overnight in a vacuum oven at 40 °C. The relevant experimental data is given in Tables 13-15.

4.8 Large-scale suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene using 60 % cyclohexanol as porogen with high speed stirring

For this experiment, a 1-liter suspension polymerization vessel was used; a 250 ml vessel was used in all other experiments described in this thesis. A 2 % solution (300 ml) of poly(vinyl alcohol) was poured into the suspension polymerization reactor through a long-stemmed funnel and nitrogen was bubbled through this solution for 15 minutes. The monomer phase was prepared by weighing out 15.00 g of divinylbenzene and then dissolving 15.00 g of p-t-BOC-styrene in this. 0.558 g of AIBN was added to this mixture and dissolved in it with the aid of a spatula; nitrogen was then bubbled through this mixture for 10 minutes. 30 ml of this monomer phase was combined with 45 ml of cyclohexanol, and then this organic phase was poured into the reactor on top of the aqueous phase through a long-stemmed glass

Table 13 Suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene: Experimental conditions for control of porosity

<u>Porogen</u>	<u>Monomers</u>	<u>Yield</u>	<u>S.A.</u>	<u>S.R.</u>
n-butanol (5.1 ml)	11.9 ml	74 %	0 m ² /g	0.12 ml/g
n-butanol (6.8 ml)	10.2 ml	76 %	1.3 m ² /g	0.43 ml/g
n-butanol (8.5 ml)	8.5 ml	78 %	4.8 m ² /g	0.60 ml/g
n-butanol (10.2 ml)	6.8 ml	80 %	142.6 m ² /g	1.36 ml/g
n-butanol (11.9 ml)	5.1 ml	76 %	26.1 m ² /g	1.85 ml/g
cyclohexanol (10.2 ml)	6.8 ml	66 %	226.9 m ² /g	1.64 ml/g
cyclohexanol (8.5 ml)	8.5 ml	76 %	189.5 m ² /g	0.92 ml/g
cyclohexanol (6.8 ml)	10.2 ml	73 %	0 m ² /g	0.52 ml/g
n-pentanol (10.2 ml)	6.8 ml	80 %	145.1 m ² /g	1.75 ml/g
3-pentanol (10.2 ml)	6.8 ml	83 %	222.5 m ² /g	1.23 ml/g
2-methyl-2-butanol (10.2 ml)	6.8 ml	84 %	117.4 m ² /g	1.03 ml/g
n-heptanol (10.2 ml)	6.8 ml	87 %	136.3 m ² /g	1.91 ml/g
n-octanol (10.2 ml)	6.8 ml	82 %	93.4 m ² /g	1.95 ml/g
n-decanol (10.2 ml)	6.8 ml	81 %	44.0 m ² /g	2.10 ml/g
n-heptane (8.5 ml)	8.5 ml	88 %	196.9 m ² /g	1.03 ml/g

Aqueous phase: 60 ml of a 2 % solution of poly(vinyl alcohol).

Monomers: Equal weights of p-t-BOC-styrene and divinylbenzene were weighed out and mixed together. To this was added 1.86 weight % of AIBN (based on the combined weight of the two monomers). In each case, enough of the monomers was weighed out to give a volume of monomers that was slightly higher than required. The appropriate volume of monomers was mixed with the appropriate volume of porogen to give the organic phase (the few drops of monomers left over were discarded).

Stirring speed: 350 rpm

S.A.: Surface area; S.R.: Solvent regain

Table 14 Suspension copolymerization of p-t-BOC-styrene and commercial divinylbenzene: Experimental conditions for control of particle size

<u>Porogen</u>	<u>n-Butanol</u>	<u>Benzyl Alcohol</u>	<u>n-Butyl Acetate</u>
Volume of 2 % PVA	51 ml	76 ml	60 ml
Volume of Porogen	6.8 ml	9.5 ml	10 ml
Weight of Monomer	5.0 g	5.0 g	5.0 g
Weight of DVB	5.0 g	5.0 g	5.0 g
Weight of AIBN	0.186 g	0.186 g	0.186 g
Total Volume of Monomers Used	10.2 ml	9.5 ml	10 ml
Stirring Speed	712 rpm	800 rpm	800 rpm
Yield	64 %	67 %	79 %
Mean Particle Size (Standard Deviation)	7.54 μ m (2.68)	8.70 μ m (2.71)	29.37 μ m (11.19)

Monomers: Equal weights of p-t-BOC-styrene and divinylbenzene were weighed out and mixed together. To this was added 1.86 weight % of AIBN (based on the combined weight of the two monomers). In each case, enough of the monomers was weighed out to give a volume of monomers that was slightly higher than required. The appropriate volume of monomers was mixed with the appropriate volume of porogen to give the organic phase (the few drops of monomers left over were discarded).

Table 15 Experimental conditions for the suspension
copolymerization of p-t-BOC-styrene and its
substituted analogs with commercial divinylbenzene

<u>Monomer</u>	<u>A</u>	<u>B</u>	<u>C</u>
Volume of 2 % PVA	90 ml	90 ml	90 ml
Weight of Monomer	4.50 g	4.82 g	5.00 g
Weight of DVB	4.50 g	4.28 g	3.62 g
Weight of AIBN	0.167 g	0.159 g	0.135 g
Total Volume of Monomers Used	9.0 ml	9.0 ml	9.0 ml
Volume of Cyclohexanol	13.5 ml	13.5 ml	13.5 ml
Stirring Speed	800 rpm	800 rpm	800 rpm
Yield	86 %	79 %	80 %
Mean Particle Size (Standard Deviation)	10.18 μm (4.42)	10.42 μm (4.34)	12.00 μm (5.75)
Surface Area	232 m^2/g	313 m^2/g	262 m^2/g
Elemental Analysis (Calculated-from TGA)	C:83.55 H:8.01	C:83.43 H:8.31	C:84.05 H:8.82
(Found)	C:81.19 H:7.80	C:83.21 H:8.27	C:81.64 H:8.77

A: p-t-BOC-styrene

B: 3,5-dimethyl-4-t-butyloxycarbonyloxystyrene

C: 3,5-diisopropyl-4-t-butyloxycarbonyloxystyrene

The experiment with p-t-BOC-styrene was also done at stirring speeds of 725 rpm, 850 rpm, and 925 rpm. The yields were 89 %, 84 %, and 87 % respectively, while the mean particle sizes (and standard deviations) were 13.77 μm (5.81), 8.25 μm (3.43), and 6.81 μm (3.13) respectively.

funnel. The reactor was flushed with nitrogen and sealed, and then the suspension was stirred at room temperature for 25 minutes at a stirring speed of 700 rpm. The suspension was heated with stirring at 80 °C for 16 hours, and then the heat was removed and the suspension allowed to stir at room temperature for an additional 30 minutes. This experiment was repeated 4 times and the products of all 5 polymerizations were poured into a 4000 ml beaker and diluted to a volume of 3800 ml with water; the mixture was stirred, and the particles were allowed to settle overnight. After 24 hours, the supernatant was removed by siphoning with a thin piece of rubber tubing, and another 3800 ml of water was added; this siphoning procedure was carried out 5 more times with 3800 ml portions of water. The particles were then washed as above with five 1000 ml portions of methanol, five 500 ml portions of benzene, and five 1000 ml portions of methanol. The beads were then dried overnight in a vacuum oven at 40 °C; 124.25 g of pure-white, small polymer beads were obtained (88 % yield).

Mean Particle Size (Standard Deviation)

7.11 μm (2.95) (Before sizing)

6.04 μm (1.29) (After sizing, middle fraction)

4.9 Thermal cleavage of the t-BOC groups of 1a, 1b, and 1c

These reactions were done in 100 ml round-bottom flasks equipped with adapters which connect the flasks to a high vacuum pump. For a typical experiment, the polymer beads were placed in a flask that was connected to a high-vacuum pump operating at 0.2 mm of Hg. The flask was then immersed in an oil bath preheated

at 220 °C-230 °C and the polymer was heated in this temperature range for 90 minutes. Some time is required for the heat to be transferred from the outside of the flask to the middle of the sample when large samples (2-3 g of polymer) are used; smaller samples require less heating time. The product polymers were pure-white in color, which indicates that no oxidation occurred, and this was confirmed by the absence of oxidation peaks in the FTIR. The FTIR spectra showed complete removal of the t-BOC groups in each case. The yields were a little less than quantitative in each case because a little bit of the polymer is sucked out of the flask when the vacuum is initially applied to the system. When similar experiments were attempted under a flow of nitrogen, the product polymers were brown and displayed some oxidation peaks in the FTIR.

Elemental Analysis: (Calculated from weight loss in TGA)

(2a) Calculated (C:87.07, H:7.77); Found (C:84.84, H:7.88)

(2b) Calculated (C:87.06, H:8.32); Found (C:85.48, H:8.27)

(2c) Calculated (C:87.38, H:9.08); Found (C:85.27, H:8.82)

4.10 Cleavage of the t-BOC groups of 1a, 1b, and 1c using chemical reagents

The t-BOC group of these polymers was cleaved using chemical reagents so that the efficiency and convenience of chemical cleavage and thermolysis could be compared. All of these reactions were done in 50 ml 3-necked flasks equipped with water-cooled condensors; one of the necks of each flask was fitted with a rubber septum that was punctured with a metal syringe needle connected by rubber tubing to an argon cylinder. The tip of the

syringe needle was placed at the bottom of the flask. For a typical experiment, about 100 mg of polymer beads was placed in the flask and covered with 30 ml of a 5 % NaOH/MeOH solution or 30 ml of a 5 % HCL/MeOH solution, and then the suspension was heated at temperatures ranging from 65 to 100 °C while argon was bubbled through the solution. At various time intervals, a small amount of polymer beads was extracted from the suspension and isolated by filtration on Whatman GF/F 0.2 μ m glass microfibre filter paper (these filter papers are not suitable for filtration of large amounts of polymer beads because they are fragile and tend to tear very easily). The beads were washed on the filter paper with methanol (a 1 % HCL/MeOH wash was added where appropriate), dried overnight in a vacuum oven at 40 °C, and analyzed for protecting group removal by FTIR.

4.11 Determination of the balanced density slurry

Beads used in HPLC columns are usually packed by pouring a slurry of the polymer beads into a column-packing apparatus, followed by pumping solvents through the apparatus at high pressures and high flow rates. The column packing apparatus used in these experiments is shown in Figure 54. The slurry solvent is normally a mixture of two solvents, one of which has a higher density than the polymer beads, while the other solvent usually has a lower density than the polymer beads. The quantities of the two solvents are adjusted so that the density of the solvent mixture exactly matches that of the polymer beads; thus, the beads do not rise or fall in the slurry solvent mixture. This helps to give a more homogeneously packed column because, for

example, the larger and heavier polymer beads will not settle out to the bottom of the column while the slurry is sitting in the column packing apparatus. In order to determine the balanced density slurry, a small amount of polymer beads (enough to fit on the tip of a spatula) is placed in a 10 ml vial and 2 ml of CCl_4 (density = 1.594 g/ml) is added to this; the polymer beads float up to the top of the vial in this solvent. Methanol (density = 0.791 g/ml) is then added to the vial from a buret in 0.1 ml increments, and the direction of travel of the polymer beads is observed after the addition of each increment. The addition of methanol is stopped when the particles begin to sink to the bottom of the vial because the balanced density slurry has been reached at this point. The relevant experimental data for the polymers packed in this work can be found in Table 16.

4.12 Packing of bead polymers into 15 cm HPLC columns

For a typical packing experiment, 1.5 g of polymer beads was placed in a 25 ml erlenmeyer flask and 15 ml of slurry solvent mixture was added to this; the composition of the slurry solvent mixture was the same as that of the balanced density slurry for each polymer. The flask was stoppered and sonicated for 15 minutes, and then the contents were poured into the slurry reservoir using a funnel. The reservoir was filled to the top with methanol and connected to the high pressure pump of the packing instrument; 150 ml of methanol was pumped through at about 3000 psi of solvent pressure. The 15 cm column was then disconnected from the rest of the packing apparatus and immediately fitted at the top with a column end fitting containing a 0.5 μm stainless

Table 16 Experimental conditions for the packing of HPLC columns

<u>Polymer</u>	<u>Balanced Density Slurry</u>	<u>Backpressure</u>
2a (6.81 μm)	1.2 ml MeOH/1.0 ml CCl_4	>5000 psi (MeOH)
2a (8.25 μm)	1.2 ml MeOH/1.0 ml CCl_4	1800 psi (MeOH) >5000 psi (MeOH/H ₂ O)
2a (10.18 μm)	1.2 ml MeOH/1.0 ml CCl_4	600 psi (MeOH) 1200 psi (MeOH/H ₂ O)
2b (10.42 μm)	1.2 ml MeOH/1.0 ml CCl_4	600 psi (MeOH)
2c (12.00 μm)	1.4 ml MeOH/1.0 ml CCl_4	1200 psi (MeOH)
2a (6.04 μm) (middle fraction from large scale polymerization)	1.2 ml MeOH/1.0 ml CCl_4	1800 psi (MeOH)

steel frit (an identical frit was used in the end fitting at the bottom of the column). The column was then connected to the analytical HPLC and methanol was pumped through at a flow rate of 0.5 ml/min. The relevant experimental data can be found in Table 16.

For the sample of polymer 2a with an average particle size of 6.81 μm , the backpressure in the column at 0.5 ml/min of methanol rose steadily to over 5000 psi because this sample has too many small particles which are capable of clogging the frits used in HPLC columns. A similar result was observed for the sample of polymer 2a with an average particle size of 8.25 μm . Although the backpressure in this column at 0.5 ml/min of methanol was only 1800 psi, the backpressure rose steadily to over 5000 psi when more viscous solvents were used, such as mixtures of methanol and H_2O . These high backpressures make these samples unsuitable for use as HPLC adsorbents.

The sample of polymer 2a with an average particle size of 10.18 μm was found to be ideal for use as an HPLC adsorbent. A column packed with this adsorbent had a very low backpressure, even with viscous methanol- H_2O mixtures. In addition, this column could be run at higher flow rates without any significant increase in column backpressure. Optical microscope examination of the beads after packing revealed that no crushing of the beads had occurred during the packing procedure.

An attempt was made to pack this polymer using a CCl_4 /hexane slurry and a hexane mobile phase, but it was very difficult to disperse the polymer in this slurry because these solvents are relatively non-polar and the polymer contains a hydrophilic OH

group. Fortunately, once the polymer has been packed into a column using MeOH as the mobile phase, a change to a more non-polar mobile phase can be made by passing a series of solvent mixtures of decreasing polarity through the column. No loss of column efficiency was observed upon changing mobile phases, and the process could be reversed without any difficulty; therefore, these columns can be used with mobile phases having a wide range of polarities. Similar results were obtained with polymer 2b (10.42 μm) and polymer 2c (12.00 μm). The HETP's were 55.6 μm for 2a, 53.5 μm for 2b, and 97.0 μm for 2c. All of the relevant experimental data can be found in Table 10 and Table 16.

The product from the large scale polymerization of 1a was sized into three fractions. The middle fraction (6.04 μm) was thermolyzed and packed into a 15 cm HPLC column. For this column, the backpressure was about 1800 psi at 0.5 ml/min of methanol and the HETP was 120 μm .

4.13 Determination of pore volume by the solvent regain method

Centrex disposable centrifugal microfilters were used for the determination of solvent regains; a drawing of one such filter is presented in Figure 57. This apparatus consists of three pieces: a rubber cap, a plastic receiver tube which collects centrifuged solvent, and a plastic filter tube which is fitted with a Nylon membrane (0.2 μm pore size). In a typical experiment, the weight of the empty filter tube was recorded, a small amount of polymer beads was added (200 mg), and the filter tube was then reweighed. Four ml of cyclohexane was added and the tube was sealed with a rubber cap. The filter tube was then

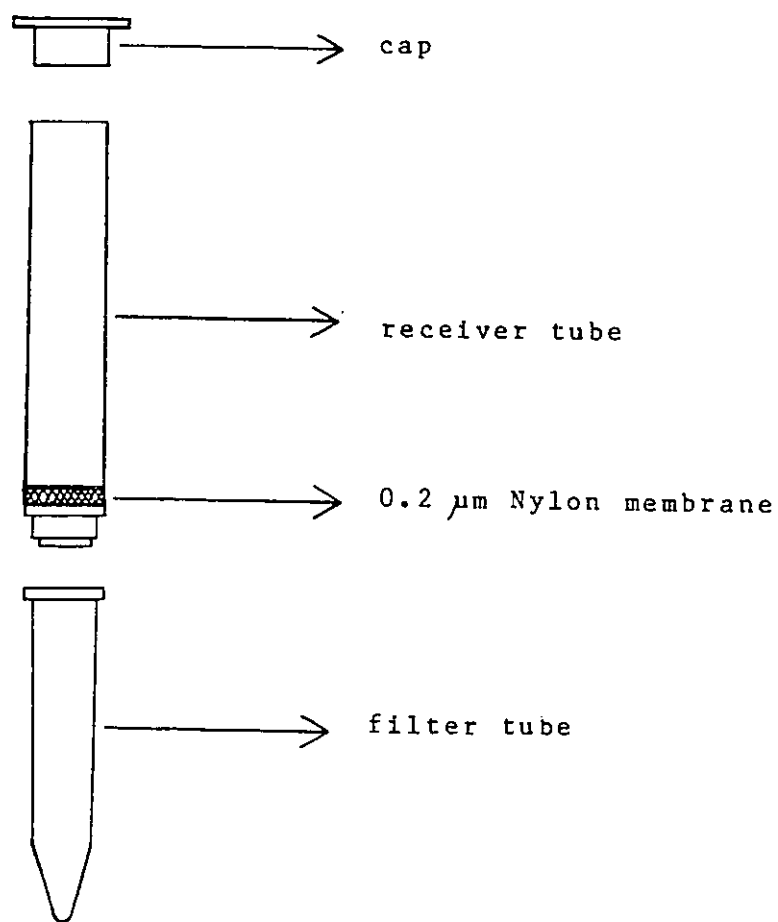


Figure 57 - Solvent regain apparatus

placed in a large beaker of cyclohexane for 24 hours; this step prevents the cyclohexane from draining through the membrane overnight. After the 24 hour equilibration period had elapsed, the receiver tube was connected to the filter tube and the excess cyclohexane was removed by centrifugation (without the rubber cap) at high speeds for 5 minutes; the filter tube was then weighed quickly. The amount of cyclohexane absorbed by the sample, (a), was calculated from the increase in weight of the filter tube. In each experiment, an empty filter tube was also filled with cyclohexane and centrifuged. The weight of cyclohexane retained by the membrane, (b), was calculated from the increase in weight of this tube. The solvent regain of the polymer was then calculated using the following equation:

$$R_s = [(a-b)d]/w \quad [\text{ml/g}]$$

where d = density of cyclohexane (0.78 ml/g)
w = weight of polymer used in the experiment

5. Statement of Original Research

- Synthesis of some novel alkyl-substituted p-t-BOC-styrene monomers.
- Development of suspension polymerization techniques for p-t-BOC-styrene-divinylbenzene resins that produce beads with a large surface area and porosity.
- Development of suspension polymerization techniques for p-t-BOC-styrene-divinylbenzene resins that produce beads with a small mean particle size and a narrow particle size distribution.
- Synthesis of a series of 10 μ m, macroporous, alkyl-substituted vinyl phenol bead polymers containing hydroxyl groups with a wide range of acidities and steric environments.
- Development of techniques for packing 10 μ m vinyl phenol bead polymers into HPLC columns with high plate counts.
- Synthesis of a series of vinyl phenol bead polymers that show good HPLC separations of organic bases and that can function effectively with a variety of mobile phases.
- Synthesis of a sterically hindered vinyl phenol bead polymer that shows excellent HPLC separations of aliphatic amines with drastically reduced tailing effects that cannot be obtained with any silica-based column currently available.

6. Statement of Future Possible Extensions of the Work

- An in-depth study of the mechanism of porosity formation through analysis of the porous structure of the resins as a function of polymerization time.
- Synthesis of a series of alkyl-substituted vinyl pyridine bead polymers that could be used in the separation of organic acids.
- Synthesis of a series of alkyl-substituted vinyl benzoic acid bead polymers that could be used to study the effects of steric hindrance in cation-exchange chromatography.

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