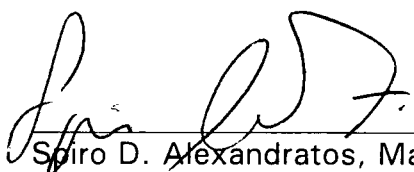
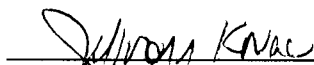


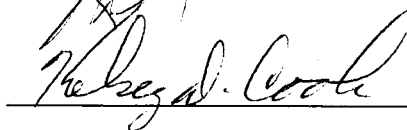
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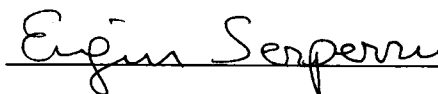
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Associate Vice Chancellor and
Dean of the Graduate School

**MICROENVIRONMENTAL EFFECT
IN POLYMER-SUPPORTED REAGENTS
FOR ORGANIC CHEMISTRY**

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Dorothy Hong Jiang Miller
August 1996

To my husband Brian,
for his love, support, and help,
and

To my father, mother and stepfather,
Chang-fu Jiang, Lan-zheng Li, and Jin-hao Shen
for their love, encouragement and support.

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ABSTRACT

The microenvironment of a polymer-supported reagent consists of the polymer backbone and the neighboring groups surrounding the active moieties. The interactions between the groups are not negligible due to a small confined volume within the macromolecule. The focus of this dissertation is to determine whether polymer-supported reagents can be optimized for a target reaction by tailoring the microenvironment surrounding the active sites to reaction mechanism.

Polymer-supported phosphine resins are synthesized and used to carry out the Mitsunobu reaction of benzyl alcohol with benzoic acid. They are compared with their small molecule analogues to quantify the electronic and microenvironmental effect. It is found that the choice of groups surrounding a ligand can be as important as the choice of the ligand. Increasing the hydrophobicity surrounding the phosphine ligands results in an increase in the reaction rate (at 0.1 h: 41.7, 68.4, 83.7, and 94.5% conversion for polymers with 0, 33, 60, and 82% phenyl groups surrounding the phosphine ligands). Polymers with 60 and 82% phenyl groups give an equilibrium solution that is more pure (97.6% and 97.0%

ester) than that with a comparable soluble reagent (85.3% ester).

Replacing phenyl groups with carbomethoxy groups, or carboxylic acid groups, has a detrimental effect (at 0.1 h: 1.3% conversion with carbomethoxy groups and 0% conversion with carboxylic acid groups). It is proposed that decreasing the polarity of the microenvironment surrounding the active sites increases the reactivity of the intermediate in the rate-determining step, resulting in an increase in the rate of product formation.

Polymer-supported sulfonic acid resins have been synthesized and used to catalyze the aldol condensation. The kinetics for the heterogeneous and homogeneous acid catalyzed reactions are studied and compared.

Macroporous and lightly cross-linked gel resins outperform their small molecule analogues (at 1 h: 35.8, 50.6 and 56.5% conversion for benzenesulfonic acid, fully sulfonated 2% DVB cross-linked gel resin, and fully sulfonated 10% DVB cross-linked MR resin). Introducing phenyl rings as neighboring groups surrounding the sulfonic acid ligands results in an increase in reaction rate (at 1 h: 50.6 and 63.5% conversion for polymers with 0 and 55% phenyl groups). This is attributed to a less polar microenvironment which increases the reactivity of the intermediate

in the rate determining step. Ester groups are found to compete with the reactant for the catalytic ligands. Replacing phenyl groups with carbomethoxy or carbobutoxy groups slows down the reaction (at 1 h: 63.5, 51.3, 49.2% conversions for polymers with phenyl, carbobutoxy, and carbomethoxy groups as neighboring groups).

Polymer-supported sulfonic acid resins have also been used to catalyze the Prins reaction. The kinetics for the heterogeneous and homogeneous acid catalyzed reactions are studied and compared. Macroporous and lightly cross-linked gel resins significantly outperform their small molecule analogues (at 1 h: 8.3, 100, 100% conversion for benzenesulfonic acid, fully sulfonated 2% DVB cross-linked gel resin, and fully sulfonated 10% DVB cross-linked MR resin). Introducing phenyl rings as neighboring groups surrounding the sulfonic acid ligands results in an increase in the reaction rate (rate constant k : 23.1, 44.4, and 53.7 for polymers with 0, 15, and 20% phenyl rings). However, the reaction rate decreases when more than 20% phenyl rings are introduced into the catalyst (k : 53.7, 36.0, 18.6, and 6.4 for polymers with 20, 41, 55, and 80% phenyl rings). Similar behavior has been observed when carbomethoxy and carbobutoxy groups are used as neighboring groups. It is proposed that

the polymeric acid catalyzed reaction rate is favored by the high ligand density and the low polarity surrounding the ligands.

The above results demonstrate that polymer-supported reagents can be tailored to a reaction for maximum reaction rate, and product yield, through the microenvironmental effect. The above studies provide guidelines for designing effective polymer-supported reagents for organic reactions.

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INTRODUCTION

General

Reactive polymers have advanced tremendously since Merrifield introduced solid-phase peptide synthesis.¹ In the scheme which was developed (Figure 1), a terminal amino acid residue of a peptide chain is attached to lightly cross-linked chloromethylated polystyrene. The next residue is protected, activated, and then coupled to the first to form the peptide bond. The process is repeated until the desired peptide sequence is assembled. During each reaction, excess soluble reagents and by-products can be filtered off while the growing peptide chains remain attached to the insoluble polymer. The final peptide can be cleaved from the polymer support by acid. This process gives high yields and allows for automation. Three decades later, peptide synthesis has entered a new stage² by combining solid phase synthesis with photolithography to create up to 250,000 different oligopeptides per square centimeter.³

The widespread application of solid phase synthesis in organic chemistry has led to many studies of the polymer support. Cross-linked beads with diameters $> 50\mu$ are popular due to ease of handling and limited pressure

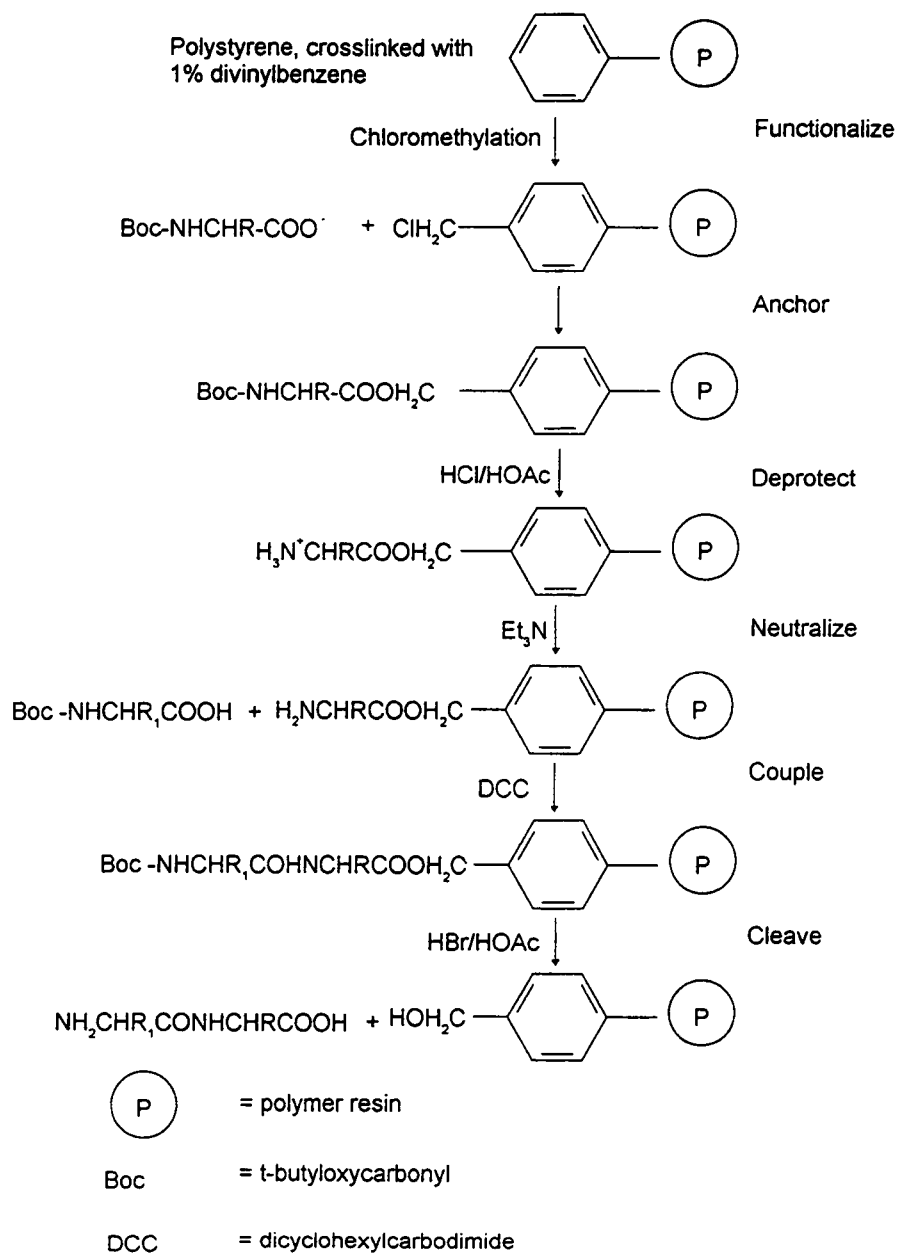


Figure 1. Solid phase peptide synthesis

drops in column applications. Polymer beads are prepared by suspension polymerization wherein an organic phase which consists of vinyl monomer, divinyl cross-linking agent and free radical initiator is mechanically dispersed in an aqueous phase which consists of water and stabilizers. The agglomeration of organic droplets in the aqueous phase is prevented by stabilizers. Polymerization is initiated by homolysis of the initiator, which generates free radicals at a temperature of approximately 80°C. Polymerization occurs within each organic droplet to form hard beads.⁴ Particle size is determined by the stir speed, the reactor shape, the ratio of aqueous to organic phase, and the type of stabilizers used.⁵ Smaller beads are most easily obtained with higher stir speed.

Polystyrene beads, with divinylbenzene (DVB) as the cross-linking agent, are the most often used support due to their physical and chemical versatility. The network structure can be modified by varying the degree of cross-linking and the porosity level. The aromatic rings of the styrene units can be easily transformed, allowing them to form a variety of functional polymers.

There are two main classes of polystyrene-DVB resins that are commonly

used: gel and macroporous resins. The gel-type resins are prepared by suspending styrene/DVB mixtures in aqueous media. During polymerization, growing polymer chains are solvated by non-incorporated monomers. This solvation diminishes as the polymerization approaches completion, causing the polymer chains to slowly collapse into a dense glass-like product with no permanent porosity.⁶

There are a number of ways to create permanent porosity. The addition of a good solvent such as toluene or diethylbenzene to styrene/DVB mixture causes the polymer chains to remain fully solvated even at the end of polymerization. Upon removing the solvent, channels and pores of fine sizes are created (less than 250Å).^{7,8} Larger pores can be generated by the addition of a non-solvent, which is a good solvent for the monomers but not the polymer. During polymerization, phase separation occurs and a polymer with pores several hundred angstroms in diameter is obtained.^{6,7,8} Such polymers are called macroporous (MR) resins.

There are two approaches to introduce a functional group on to a support. One can polymerize a functionalized monomer or chemically modify the copolymer beads. The latter method is preferred because synthesis of an

elaborate monomer and modification of a polymerization process are not required. Standard synthetic methods are used in chemical modification. For example: electrophilic aromatic substitution reactions have been used to introduce a wide variety of functional groups on to polystyrene-DVB supports.⁶ The functionalized polymers can then be used as catalysts and reagents in many organic synthesis.⁶

Phase Transfer Catalysts

Phase transfer catalysts have been used to bring immiscible reactants together by transferring one reactant from one phase to the other.⁹ Figure 2 shows a polymer-supported tetraalkylphosphonium salt transferring cyanide ions from the aqueous to the organic phase. Polymer-supported tetraalkylphosphonium and ammonium salts are effective phase transfer catalysts. They have been used in a number of substitution reactions in which a liquid-liquid-solid triphase system is involved.¹⁰⁻²³ It has been reported that the length of spacer chains between active sites and polymer backbones influences the catalytic activity:¹⁸⁻²³ when n increases from 0 to 4 (Figure 3), the catalytic activity increases by a factor of 2-2.5;^{19,23} when m increases from 0 to 2 (Figure 3), the catalytic activity increase by a factor of 4.3.¹⁸ The high activity of the catalysts with long spacer-chains is

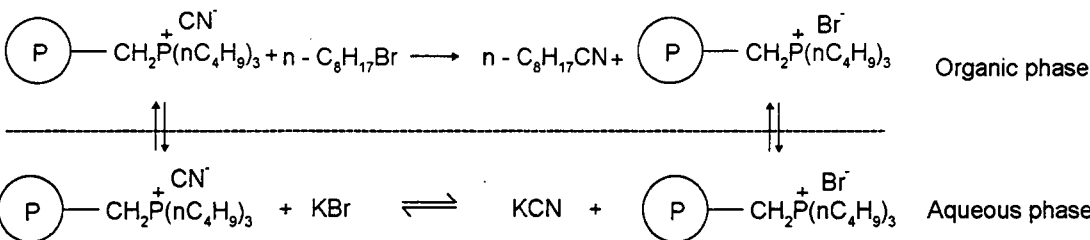


Figure 2. Phase transfer catalysis

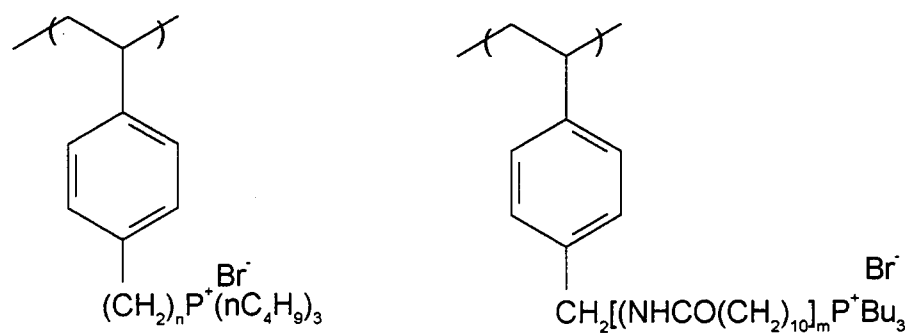


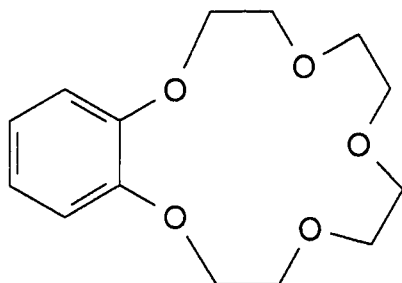
Figure 3. Polymer-supported phase transfer catalysts with spacer chains

attributed to increased lipophilicity of the catalysts, and the ease of ion exchange, which is brought about by an increased distance between active sites and backbone.²²

Polymer-supported crown ethers are usually prepared by the reaction of chloromethylated polystyrene with crown ethers that contain hydroxyl or amino groups.²⁴ Polymer-supported crown ethers have been successfully used as phase transfer catalysts.²⁴⁻²⁸ The polymer-supported crown ether, shown in Figure 4, catalyzes the reaction of n-octylbromide with potassium iodide three times faster than the low molecular weight crown ether.²⁵

Crown ethers with additional donor atoms in the side arms of the macrorings are called lariat crown ethers.²⁸⁻³¹ They can bind alkali metal cations by cooperative coordination of the crown ring donors and the side-chain donors, and therefore, they generally exhibit higher binding ability than that of crown ethers with simple alkyl side-chains.²⁸⁻³¹ Figure 5 shows a polymer-supported lariat crown ether **A**, and a similar crown ether **B**, with simple alkyl side-chains. The reaction of 1-bromooctane with sodium iodide catalyzed by **A** proceeds 2.6 times faster than that catalyzed by **B**.

Low-molecular weight crown ether



Polymer-supported crown ether

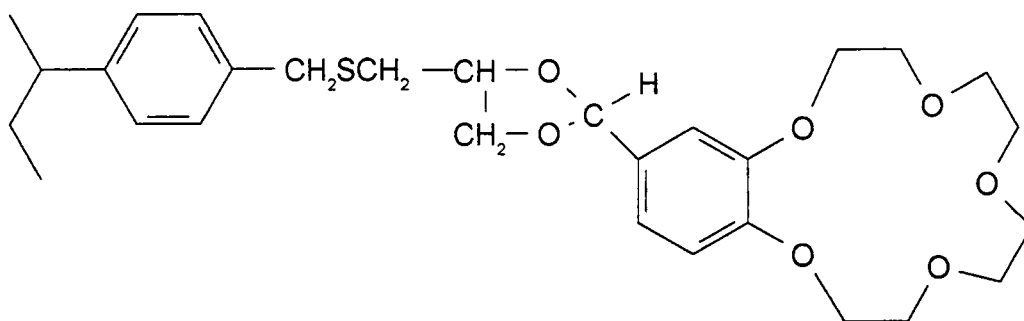
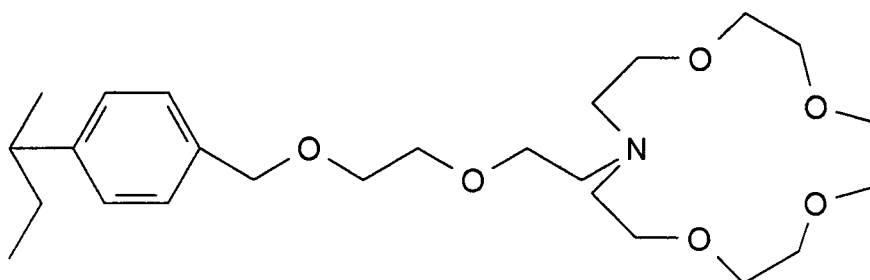


Figure 4. Crown ethers as phase transfer catalysts

Polymer-supported Lariat crown ether A



Polymer-supported crown ether with simple alkyl side-Chain B

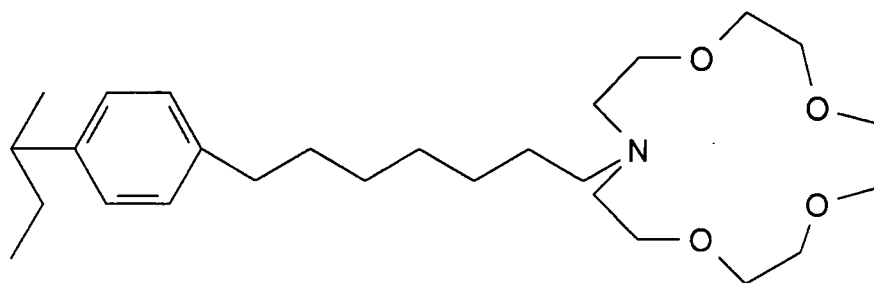


Figure 5. Polymer-supported lariat crown ether and a similar crown ether with a simple alkyl side-chain

A new "drift-type" crown ether, which can be drifted in and out reversibly between a solid phase and a solution by adjusting the experimental conditions, has been synthesized.²⁶ Before the reaction, the drift-type crown ether is adsorbed on a poly(styrene/divinylbenzene)-NR₂ resin (Figure 6). The catalyst is released from the resin during the reaction by adjusting the pH of the reaction solution. It is re-adsorbed on the resin after the reaction by pH readjustment. This type of crown ether can not only be recovered easily, it also has high catalytic activity due to no diffusional limitation.²⁶

Polymer-supported dipolar aprotic species such as dimethylsulfoxide, sulfonane, hexamethylphosphoramide, N,N-dimethylacetamide, N,N-dimethylformamide, and tetramethylurea have been developed and found to be effective phase transfer catalysts, however, their small molecule analogues are practically inactive.³²⁻³⁸ It is believed that the catalytic activity of polymer-supported dipolar aprotic species is due to both cation extraction ability of the polymers, and the activation of anions caused by desolvation in the hydrophobic regions of polymers.³²⁻³⁹

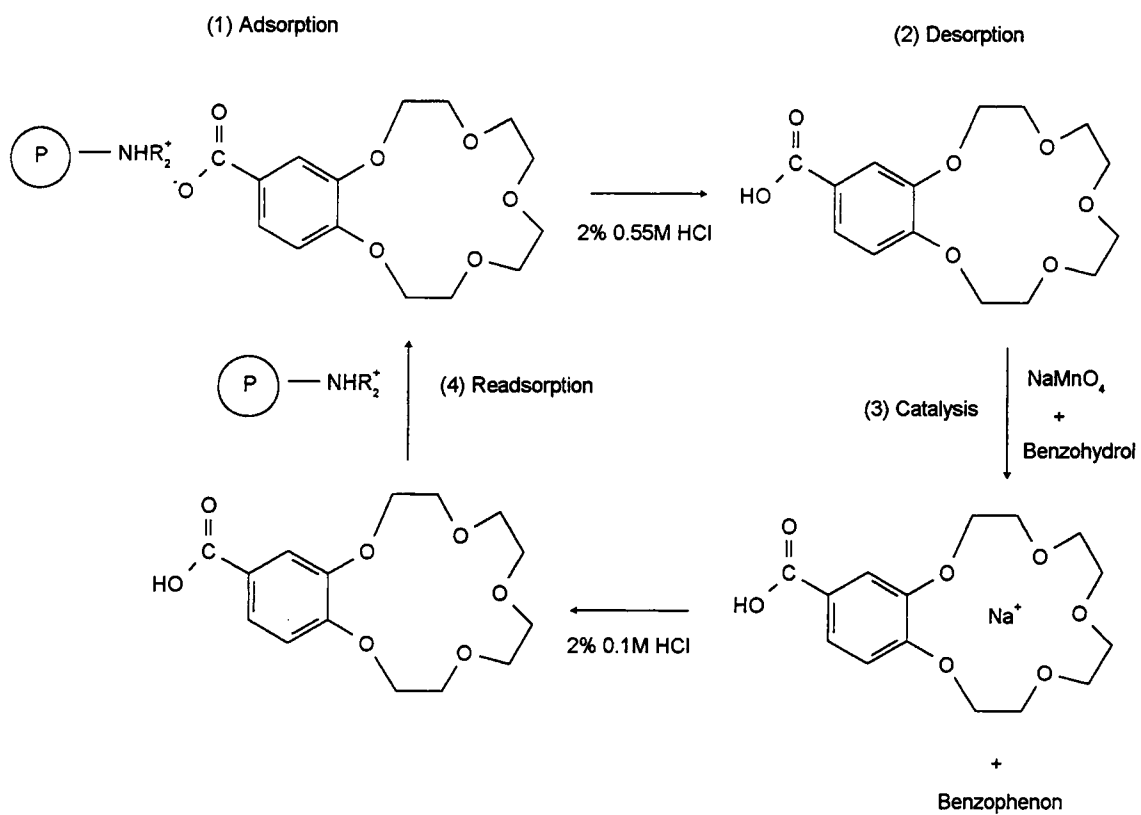


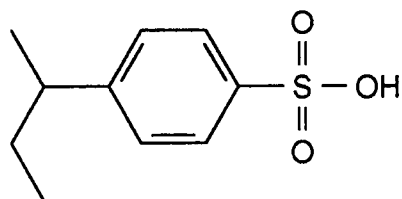
Figure 6. Drift-type crown ether as a phase-transfer catalyst²⁶

Ion Exchange Resins

Ion exchange resins (Figure 7) are the most frequently encountered polymer-supported catalysts. They can carry out virtually all the reactions which are catalyzed by homogeneous acids or bases. Reactions such as sucrose inversion, ⁴⁰⁻⁴⁴ acetal and ketal formation, ⁴⁵⁻⁴⁷ hydrolysis, ⁴⁸⁻⁵³ halogenation, ^{54,55} alkylation, ⁵⁶⁻⁵⁸ etherification, ⁵⁹ hydration, ⁶⁰⁻⁶³ dehydration, ⁶⁴⁻⁶⁷ and condensation⁶⁸⁻⁸² are some of the examples in which ion-exchange resins replace conventional soluble acids and bases as catalysts.

Ion exchange resins have inherent advantages over soluble acids and bases. Removal or neutralization of the catalysts can be done by simple filtration or decantation. Since the acidic and basic groups are immobilized, they are not free to attack metal equipment, and therefore corrosion problems are eliminated. The absence of free strong bases or acids is also beneficial for the preparation of sensitive compounds. It was reported that sensitive fulvene and monosubstituted fulvenes can be prepared by controlling the contact time of reactants with catalysts.⁸³ Simple filtration of catalysts avoids further complicated reactions between diene and carbonyl compound.⁸³ It is known that furfuryl alcohol polymerizes in the presence

Cation exchange resin



Anion exchange resin

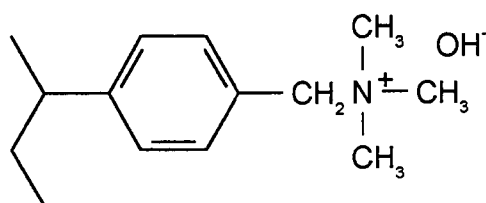


Figure 7. Ion exchange resins

of strong acids; however, with cation exchange resins, furfuryl alcohol can directly react with acetic acid to give a clean esterification product.⁸⁴

Faster reaction rate, better product yield, and selectivity have been obtained with ion exchange resins in place of conventional acids and bases.^{47,48,57,62,74,77,78,80,85} In the acetal formation of butanal and ethylene glycol, the reaction with polymer-supported catalysts is complete in 30 minutes with 99% yield. The reaction with p-toluenesulfonic acid requires 2,880 minutes for 60% yield.⁴⁷ In the hydrolysis of maltose, the polymeric sulfonic acid is 1.5 times faster than sulfuric acid.⁸⁵ In the transesterification of 1,n-diols with esters (Figure 8), the polymeric sulfonic acid is twice as fast as methanesulfonic acid.⁸⁰ The yield of the monoester with the polymeric sulfonic acid (82%) is higher than that with methanesulfonic acid (36%).⁸⁰

Ion exchange resins have also found their applications in pore-size-specific functionalization of porous polymers.⁸⁶ The acetal groups of a macroporous polymer can be hydrolyzed to diols in the presence of an acid catalyst. While sulfuric acid catalyzes hydrolysis of all acetal groups, bulkier poly(styrenesulfonic acid) only causes hydrolysis to occur within pores large enough for them. Therefore two types of functionalities, that

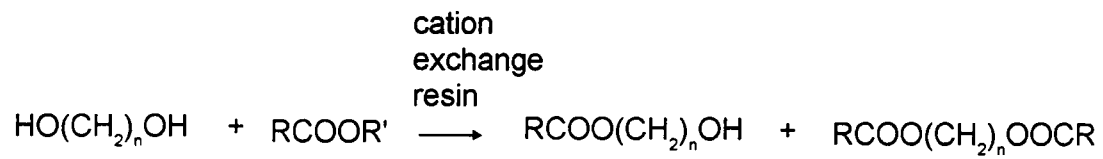


Figure 8. Cation exchange resin catalyzed transesterification⁸⁰

are segregated respectively in pores larger or smaller than the catalysts, coexist in one porous material (Figure 9).⁸⁶ The resulting beads have been successfully used in protein recovery.⁸⁶

Poly(styrene sulfonic acid) is also an effective catalyst for the preparation of novel sol-gel materials.⁸⁷ The polymerization of liquid metal alkoxides to produce chemical glasses is referred to as the sol-gel process. Hybrid organic/inorganic networks prepared by the sol-gel process are called ceramers. Ceramers are monolithic and optically clear. It is found that the mechanical properties of polymeric acid catalyzed ceramers are better than those catalyzed with HCl due to a higher extent of reaction when polymeric acid is used as the catalyst.⁸⁷

Various theoretical models have been proposed to analyze catalysis by ion-exchange resins. Helfferich⁸⁸ divided the catalysis process by ion exchange resins into three parts:

1. Diffusion of the reactants and the products through the liquid film on the catalyst particles.
2. Diffusion of the reactants into the bulk of the catalyst and diffusion of the products into the solution.

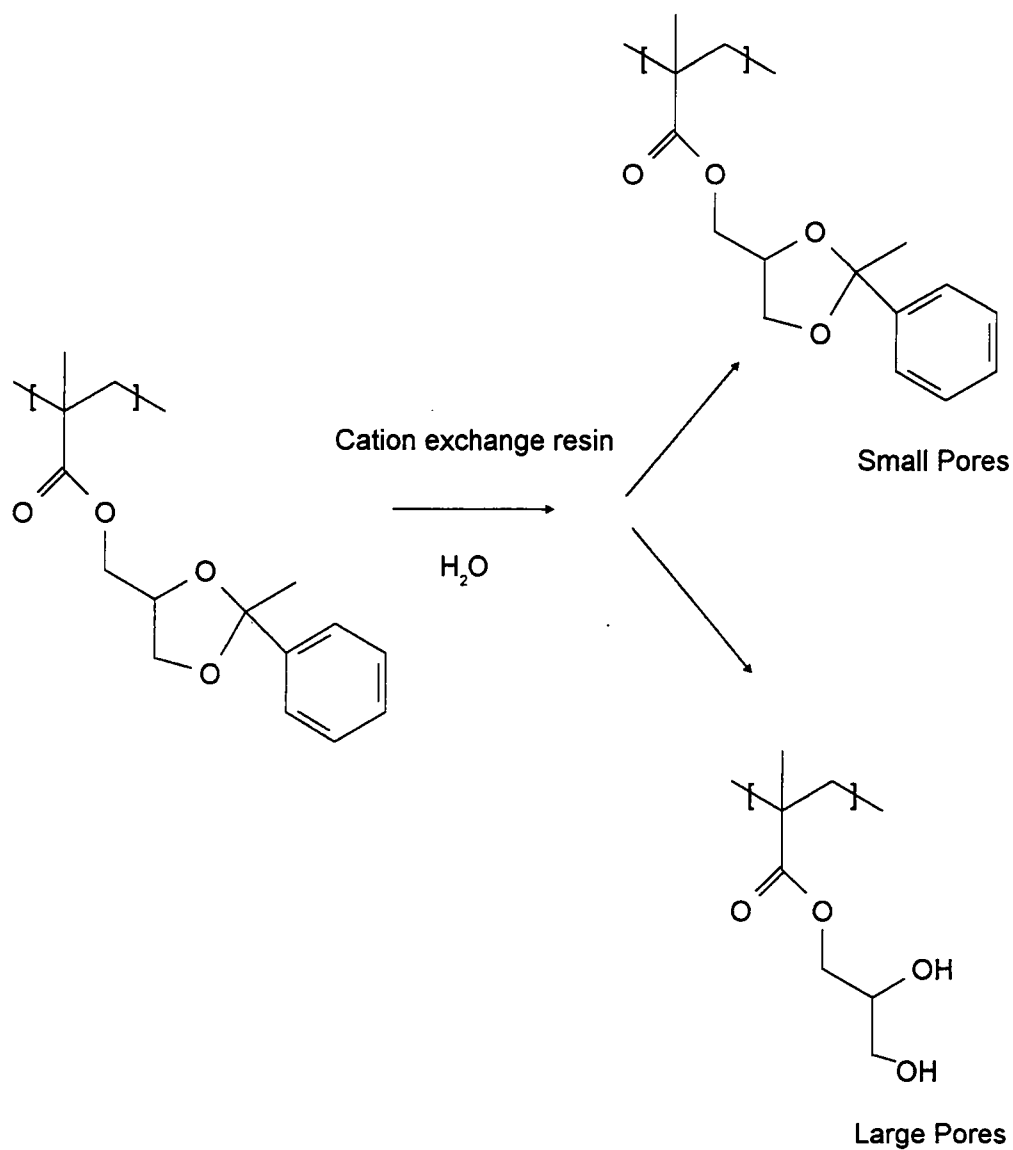


Figure 9. The application of cation exchange resin in pore-size specific functionalization of porous polymers⁸⁶

3. Chemical reaction.

The simplest situation is when the polymer's physical structure (porosity, particle size, and cross-linking level) does not affect the reaction rate. A reasonable assumption is that there is no diffusional limitation and the chemical reaction is the rate determining step. The catalysis can be analyzed as it would be in the homogeneous reaction.⁶

If diffusion through the liquid film is much slower than the chemical reaction, the former will be the rate determining step because all the reactants will react immediately as soon as they reach the surface of the catalyst. This diffusional limitation can usually be avoided by increasing the agitation speed.^{24,74}

If diffusion within the bulk of the catalyst particle is much slower than the chemical reaction, molecules will react before they get into the interior of the catalyst particle. In this case the reaction occurs only on the surface of the particle, and its rate may be determined by the diffusion through the film or by the chemical reaction on the surface. The diffusion within the bulk of the particle may influence the overall reaction rate, but it cannot be the only determining step.⁸⁹

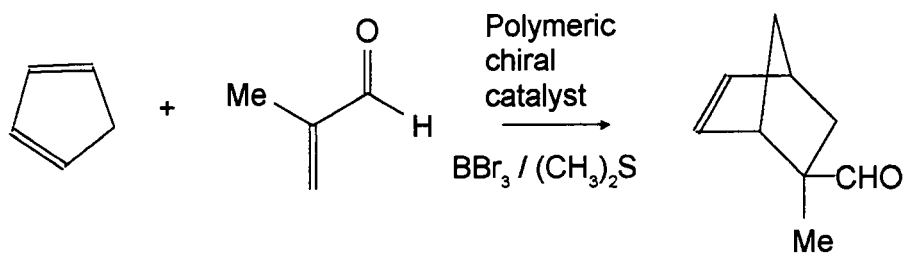
Besides these three extreme cases, there are cases where the rates of the three steps are comparable. Oftentimes, the polymer's physical properties (porosity,^{58,64,72} particle size,^{42,43,55,66} and cross-linking level^{42,58,64-66,72}) have noticeable effects on the rates of reactions. Wheeler⁹⁰ and Thiele⁹¹ have developed a theoretical model for simultaneous diffusion and chemical reaction in porous catalysts. The model was developed for gas-solid systems, however the mathematics can be applied to liquid-solid ion-exchange resin systems.⁹² The model uses an effective diffusivity D to characterize the diffusion of the substrate and assumes D to be a constant value throughout a catalyst particle. The chemical reaction rate constant k_r is also assumed to be constant throughout the resin. The model has been successfully used to analyze data on sucrose inversion catalyzed by an ion-exchange resin.⁴³

In some cases, D and the distribution coefficient (λ) of reactants in the bulk and resin phases may vary as the reaction proceeds. For instance in sulfonic acid resin catalyzed t-butyl alcohol dehydration, acidic resin swells gradually as more and more water forms. A shrinking central core model has been developed⁶⁶ in which D and λ are functions of the extent of reaction. This model fits well with the dehydration reaction data.

Polymer-Supported Catalysts in Asymmetric Synthesis

Many studies have been done on polymer-supported catalysts in asymmetric synthesis.⁹³ Cross-linked polymers having chiral amino alcohol moieties have been used in a variety of reactions, such as an asymmetric Diels-Alder reaction of cyclopentadiene with methacrolein (Figure 10),^{94,95} asymmetric aldol reaction of benzaldehyde with silyl ketene acetal (Figure 11),⁹⁶ and asymmetric carbon-carbon bond formation of aldehyde with dialkylzinc (Figure 12).⁹⁷ Besides the fact that expensive chiral reagents can be recovered easily by simple filtration at the end of the synthesis, polymer-supported reagents often give higher or comparable chemical and optical yields when compared to low molecular weight analogues.^{94,95,97}

Polymer-supported oxazaborolidines are obtained by reacting polymer-supported boronic acid with a β -amino alcohol (Figure 13).⁹⁸⁻¹⁰⁰ They have been used to carry out asymmetric reductions of acetophenone and propiophenone,^{98,99} and asymmetric carbon-carbon bond formation of aldehyde with dialkylzinc.¹⁰⁰ The stereochemical results obtained with polymeric oxazaborolidines are comparable with the non-polymeric analogue in ketone reduction.^{98,99}



Polymeric chiral catalyst :

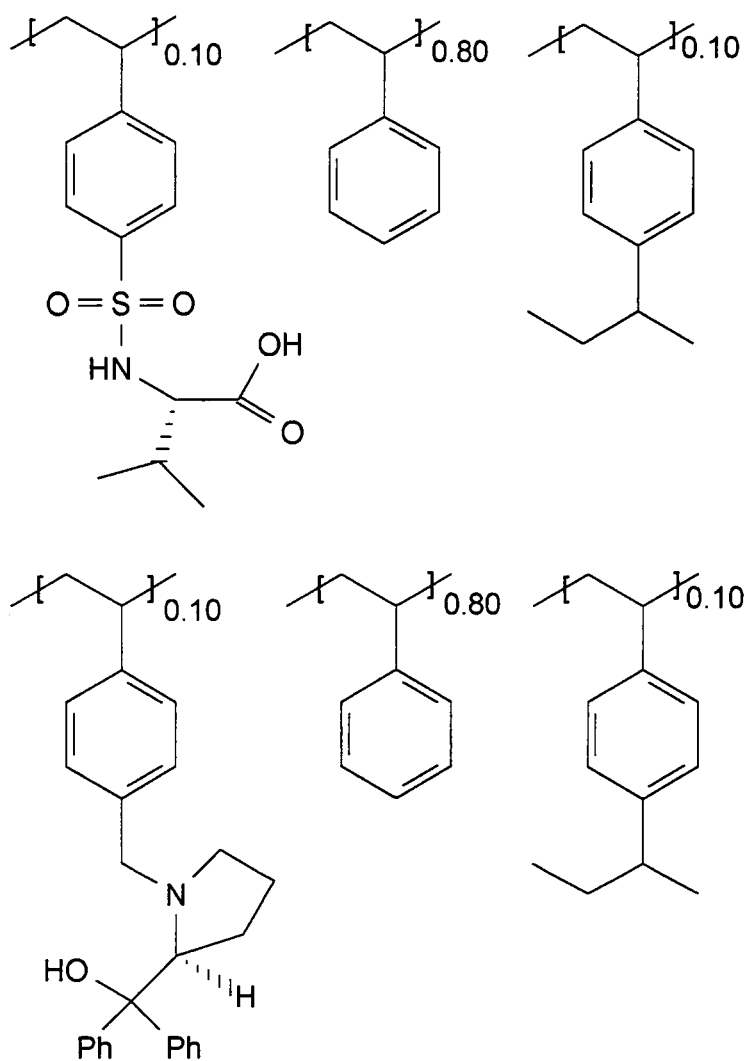
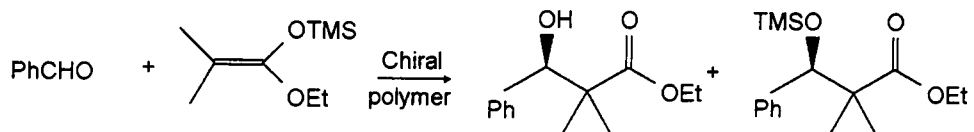


Figure 10: Asymmetric Diels-Alder reaction with polymeric chiral catalyst^{94,95}



TMS = -Si(Me)₃

Polymer-supported chiral catalyst:

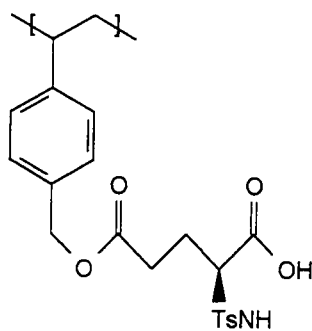
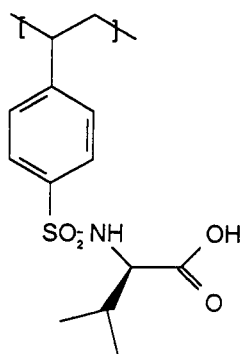
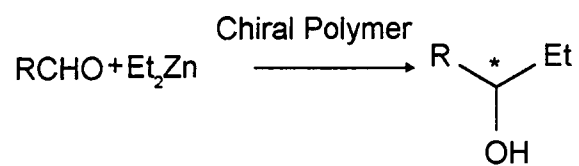


Figure 11. Asymmetric aldol reaction of benzaldehyde with silyl ketene acetal⁹⁶



Chiral polymer:

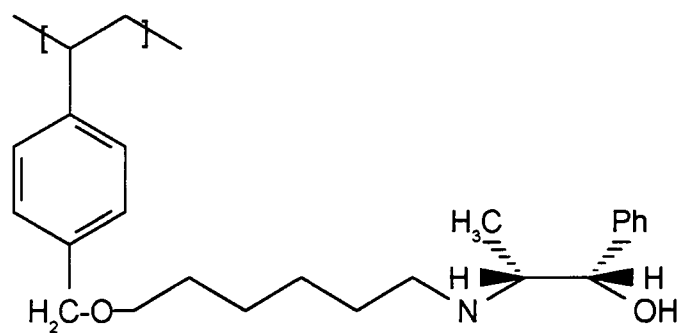


Figure 12. Asymmetric carbon-carbon bond formation in the reaction of an aldehyde with dialkylzinc⁹⁷

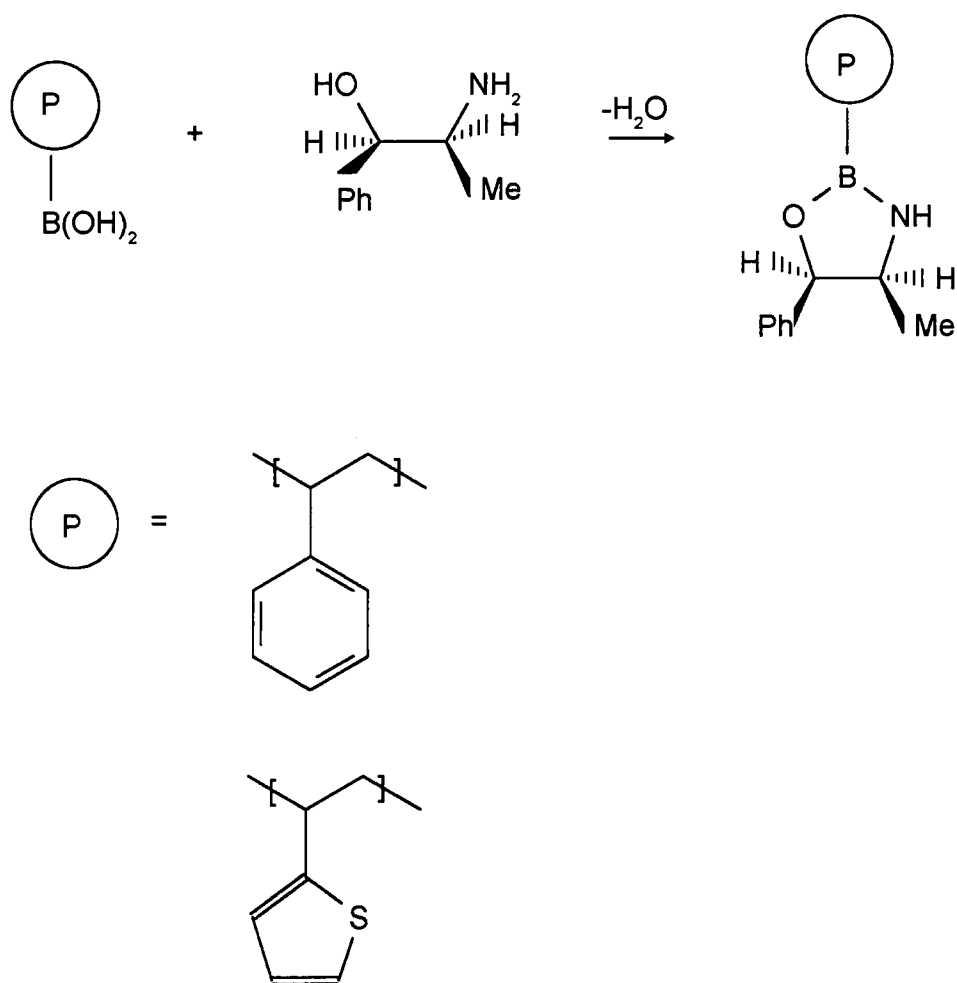


Figure 13. Polymer-supported oxazaborolidines⁹⁸

Polymer-bound cinchona alkaloid derivatives have been used to complex osmium tetroxide in asymmetric dihydroxylation of olefins (Figure 14).^{101,102} The order of optical selectivity is $E > D > C >$ non-polymeric catalysts.^{101,102} The polymers can be recycled at least three times without losing their activities.¹⁰¹

Polymer-supported Reducing Agents

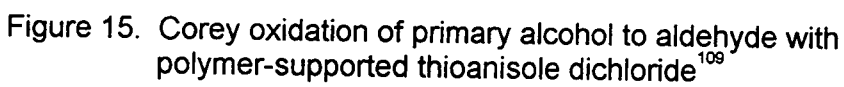
To achieve excellent selectivity in organic synthesis is always a challenge, and polymer-supported reagents have shown strength in this area. Anion exchange resin supported dithionites show exclusive reduction of the C = C system in α - β unsaturated ketones.¹⁰³ Anion exchange resin supported borohydrides have demonstrated their abilities to reduce carbonyl groups without disturbing carbon-carbon double bonds.¹⁰⁴ They can also selectively reduce aldehydes from ketones,¹⁰⁵ aromatic aldehydes from aliphatic aldehydes,¹⁰⁵ aryl acetates from alkyl acetates,¹⁰⁶ and cyclic ketones from open-chain ketones.¹⁰⁵ Aryl azides and aryl sulfonyl azides can be reduced to the corresponding aromatic amines and aryl sulfonamides in excellent yields with borohydride anion exchange resins.¹⁰⁷ It is also reported that polymer-supported amino alcohol-borane complexes have shown exclusive selectivity towards ketones in the presence of esters.¹⁰⁸

Polymer-supported Oxidizing Agents

A number of oxidizing agents have been immobilized onto polymers. Corey oxidation of alcohols to corresponding aldehydes and ketones has been carried out with polymeric thioanisole dichloride, which eliminates toxicity and noxious odor problems associated with the monomeric thio compounds (Figure 15). The mild reaction condition is especially suited to oxidize highly sensitive compounds, such as certain prostaglandin intermediates.¹⁰⁹

Chromic acid has been supported on anion exchange resins.¹¹⁰ The supported reagents are remarkably effective in alcohol oxidizing reactions, giving nearly 100% product yield. They are easier to prepared than polymeric thioanisole dichloride, however, they require higher reaction temperature.¹¹⁰

Polyvinylpyridine and poly(vinylpyridine N-oxide) dichromates are stable and efficient oxidizing catalysts.^{111,112} Polyvinylpyridine supported ferric dichromate has higher reactivity and selectivity than ferric dichromate in the oxidation of benzyl alcohol, p-chlorobenzyl alcohol, benzhydrol, benzoin, furoin, p-hydroquinone, and cinnamyl alcohol.¹¹¹ The monomeric pyridine N-oxide-dichromate is more reactive than the polymeric analogues,



however, it ignites readily when dry, so extreme caution has to be taken in its handling.¹¹² Both monomeric and polymeric dichromates show excellent yield in alcohol oxidation. Polymeric dichromates also show excellent yields in oxidation of thiols, oximes, and amines.¹¹²

Unsymmetrical disulfides are important in diverse biochemical processes.¹¹³ They are prepared by thioalkylation of thiols with thiosulfonates. Polymer-supported thiosulfonates avoid difficult and time consuming separation of the by-product sulfinic acid (Figure 16). A number of mixed disulfides of glutathione and 2-mercaptoethanesulfonic acid has been obtained in excellent yields (>92%) with the polymeric thiosulfonates.¹¹³

Polymer-supported Halogenation Reagents

Polymer-supported reagents have been used to introduce halogen into organic compounds.¹¹⁴⁻¹¹⁸ A triphenyl phosphonium perbromide resin, shown in Figure 17, is a very effective brominating agent. Its reaction with styrene is complete in 15 min with 93% yield; its reaction with β -naphthol is complete in 30 min with 80% yield. The reagent is very stable and odorless. Little loss of activity has been detected after recycling.¹¹⁶

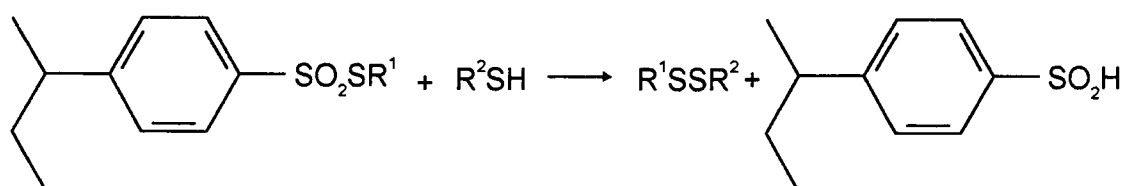
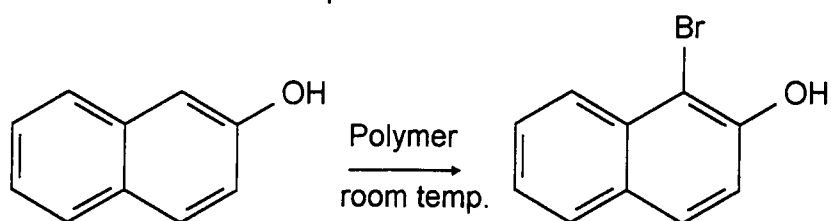
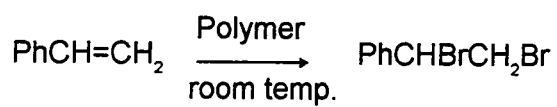


Figure 16. Preparation of unsymmetrical disulfides with polymeric reagents¹¹³



Polymer:

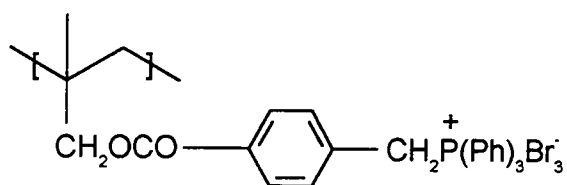


Figure 17. Bromination with polymeric reagents¹¹⁶

Bromination of phenol is carried out with polymer-supported quaternary ammonium perbromide. The reaction is facile and is carried out by passing the reactants through the column packed with the perbromide resin. Excellent product yields are reported.¹¹⁷

Bromochlorination of various trans-phenyl alkenes with poly(styrene-co-4-vinylpyridine) supported reagents (Figure 18) have been studied.¹¹⁴

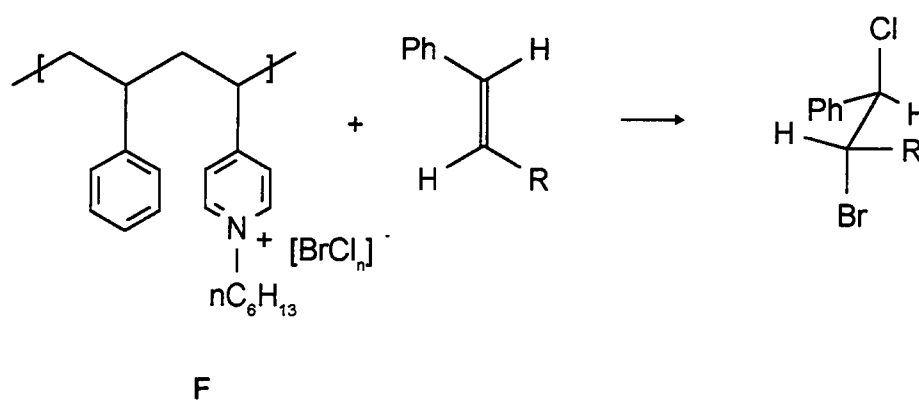
Polymer-supported reagent **F** shows excellent regioselectivity and stereoselectivity (> 93%): when R = Ph or CH₃ the order of both selectivities is **F** $\cong$ (n-C₄H₉)₄NBrCl₂ > BrCl; when R = COOCH₃ the order is **F** > (n-C₄H₉)₄NBrCl₂.

Poly(styrene-co-4-vinylpyridine) supported dichloroiodate is very effective in iodination of a number of substituted aromatic compounds (Figure 19).¹¹⁵

It also reacts with a number of heterocyclic compounds such as dimethyluracil to give high purity products (> 80%) (Figure 19).

Microenvironmental Effect

In many published articles polymer supports are treated as inert spectators to which functional groups are linked by covalent bonds.¹¹⁹ They are usually designated by "P -" and nothing more is said about them.¹¹⁹ It may



R = -Ph

-COOCH₃

-CH₃

Figure 18. Bromochlorination of various trans-phenyl alkenes¹¹⁴

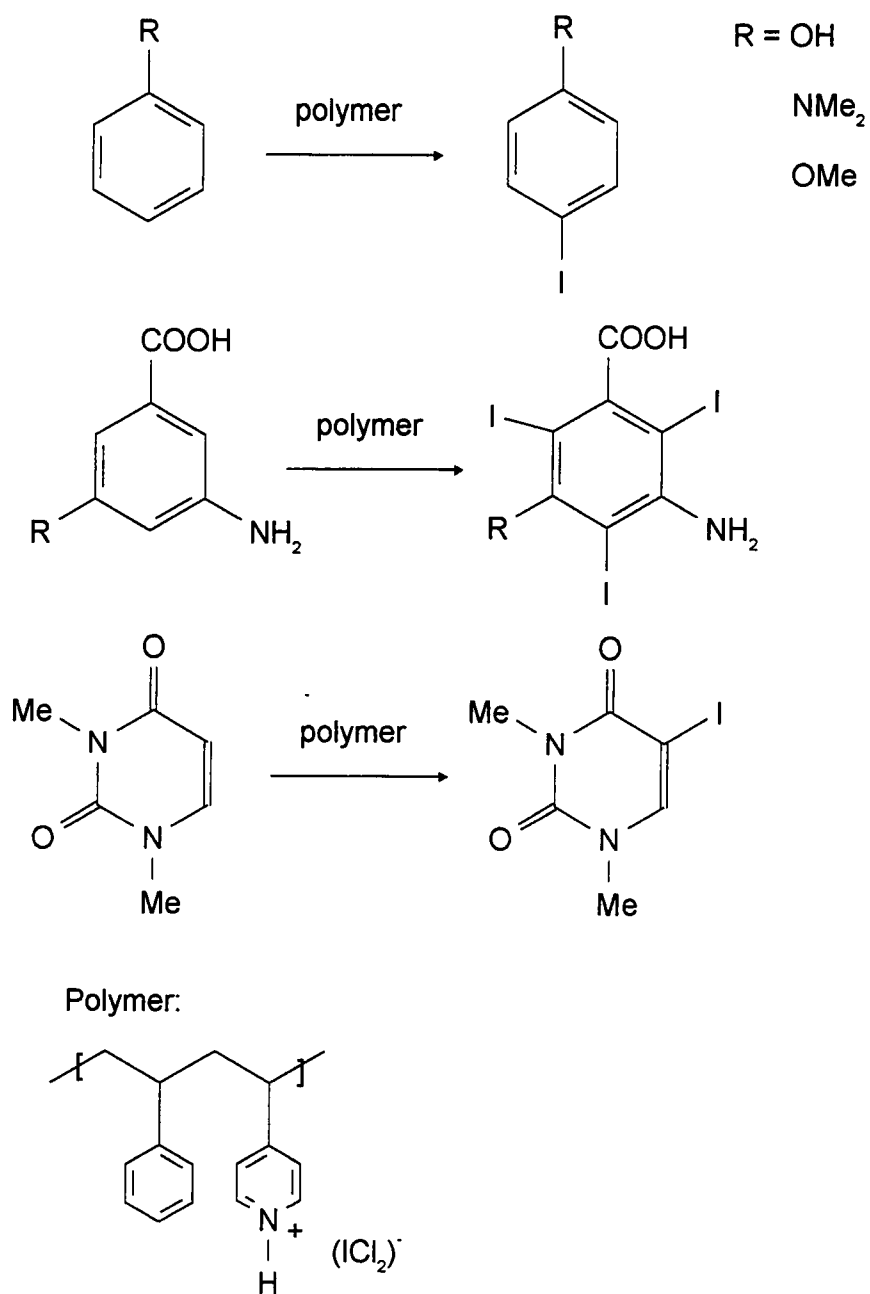


Figure 19. Iodination with polymeric reagent¹¹⁵

be more accurate, however, to note that polymer-supports are not inert spectators and their structures and compatibility with the reaction medium significantly influence the performance of the supported reagents.

Although the intrinsic reactivity of a functional group does not change after it is attached to a macromolecule, the interactions between the groups are greater due to a small confined volume within the macromolecule.⁹³ This microenvironmental effect may be defined as the influence of group A on the strength of the X-Y interaction at the active site (Figure 20), and could arise from changes in polarity affecting the charge stabilization, the hydrophilicity, the lipophilicity, or any such mechanism which does not involve group A in product formation at the active site.¹²⁰

Hydrolysis of polymethacrylamide proceeds quite rapidly until the conversion reaches 70%. This incomplete hydrolysis is believed to be caused by hydrogen bonding between the remaining amide groups and adjacent carboxylate ions, which hinders hydroxide ions from attacking the amide carbonyl groups.¹²¹ When insoluble polystyrenes containing amide moieties are used as phase transfer catalysts in the reaction of n-octyl bromide and potassium thiocyanate, their activities decrease drastically when amide alkyl groups are replaced with hydrogen.³⁷ The low activities

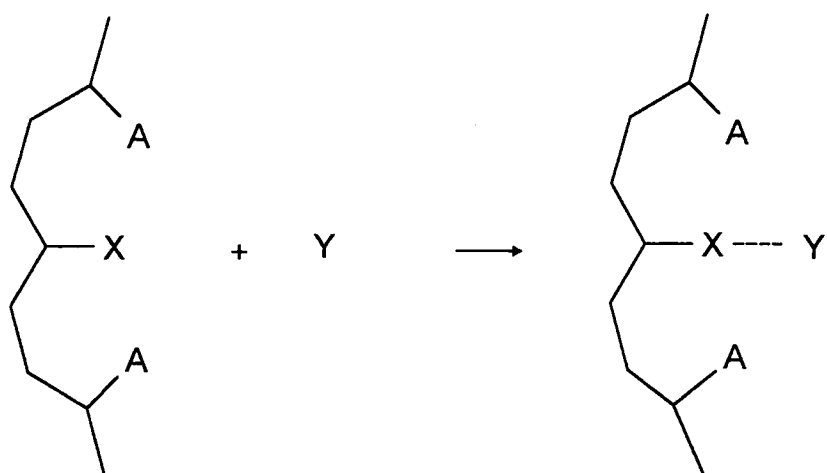


Figure 20. Microenvironmental effect

X: Functional groups
 A: Neighboring groups
 Y: Reactant

are due to the formation of hydrogen bonds, which decreases the metal cation complexing ability of the polymers.³⁷

Hydrophobicity around the active sites can affect the reactivity of the polymeric carriers. When styrene-DVB-(dialkylamino) pyridine is used as a catalyst in the reaction of cyclohexanol and acetic anhydride, better activity has been obtained when the degree of functionalization is less than 50%.^{122,123} This is attributed to the hydrophobic local environment, which provides a favorable reaction medium for nucleophilic attacks.^{122,123} In the hydrolysis of p-nitrophenyl butyrate, a remarkable increase in rate is achieved when long hydrophobic dodecyl groups are incorporated as neighboring groups into the polymeric catalyst.¹²⁴ It is shown that hydrophobic dodecyl groups favor interactions with p-nitrophenyl butyrate, causing an increase in the catalytic activity.¹²⁴ A number of nucleophilic substitution reactions under phase transfer condition shows that the activity of polymer-supported phase transfer catalysts is governed by both the cation extraction ability of the polymers, which is enhanced by high ligand density, and the activation of anions caused by desolvation in the hydrophobic region of polymers, which is favored by low ligand density. A maximum reaction rate can be achieved by carefully balancing the two factors.³⁴⁻³⁷

Studies on the microenvironmental effect have been very limited. This may be due to the complexity of the problem and the difficulty of disentangling the factors affecting overall reactivity. However, if they can be understood, they will provide critical information towards the design and preparation of more active, selective, and efficient polymeric carriers. This dissertation focuses on exploring the microenvironmental effect and how it can be used to optimize product yields and reaction rates. Studies on the application of polymer-supported phosphine reagents on the Mitsunobu reaction show that the choice of neighboring groups surrounding the phosphine ligand is as important as the choice of the ligand. It is found that non-polar neighboring groups enhance the reaction rate and the product yield by decreasing the solvation of charged intermediates in the rate determining step. The studies demonstrate an important principle: polymer-supported reagents can be optimized for a target reaction by tailoring the microenvironment surrounding the active sites to the reaction mechanism. In order to further test the principle, studies on the aldol condensation and the Prins reaction with polymer-supported sulfonic acid catalysts are carried out. The results are in agreement with the principle.

CHAPTER I

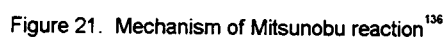
THE APPLICATION OF POLYMER-SUPPORTED PHOSPHINE RESINS IN THE MITSUNOBU REACTION

Introduction

The Mitsunobu reaction has been widely used to synthesize a variety of esters,¹²⁵⁻¹²⁷ phosphinates,¹²⁸ lactones,^{129,130} and natural products.^{131,132}

The reaction is very useful in preparing optically active compounds since it proceeds under mild conditions with inversion of configuration at the alcohol-bearing carbon.¹³³⁻¹³⁵ The reaction mechanism is illustrated in Figure 21.¹³⁶

One of the major difficulties in the Mitsunobu reaction is product isolation from the phosphine oxide and hydrazine. Attempts have been made to immobilize the azodicarboxylate¹³⁷ and the phosphine¹³⁰ on to polystyrene in order to simplify the product recovery process. It has been reported that the hydrazine is the easier of the two by-products to separate.¹³⁰ Immobilized phosphines are the focus of this study. The effect of the microenvironment surrounding covalently-bound phosphorus ligands on product formation rates and yields is investigated.



A series of polymer-supported phosphines (Figure 22) is synthesized to study the microenvironmental effect on reactant conversion and product yield for the esterification of benzoic acid with benzyl alcohol (Figure 23). The results from polymer-supported phosphines and their small molecule analogue are compared.

Synthesis of phosphine resins

2% divinylbenzene (DVB) cross-linked gel resins are synthesized by suspension polymerization, except vinyl benzylchloride (VBC)-methacrylic acid (MAA)-DVB copolymer, which is prepared by bulk polymerization due to the high solubility of MAA in water. The monomer phase compositions for all the copolymers used in this study are listed in Table 1. The nucleophilic substitution reactions of the VBC containing copolymers with lithium diphenylphosphide yields polymer-supported benzyldiphenylphosphine resins (Figure 24). The polystyrene-DVB copolymer is brominated before reacting with lithium diphenylphosphide to form polymer-supported triphenylphosphine (Figure 25). The detailed reaction conditions of immobilizing phosphine ligands are summarized in Table 2. The polymer-supported phosphine resins are characterized in terms of phosphorus capacity and Cl / Br capacity. The excellent

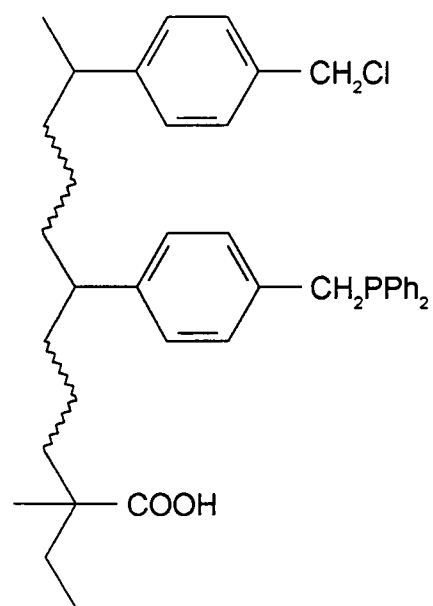
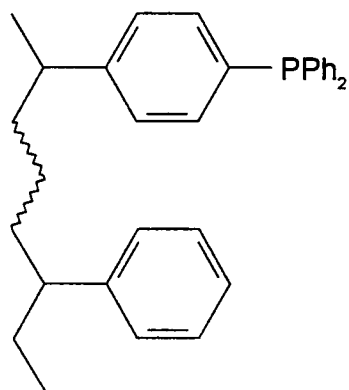
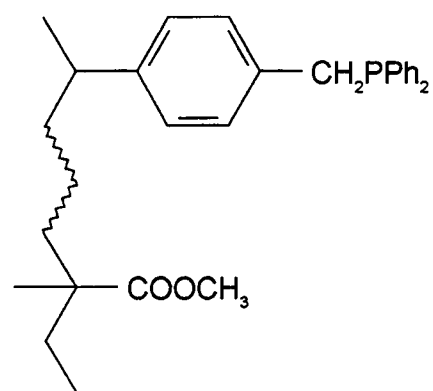
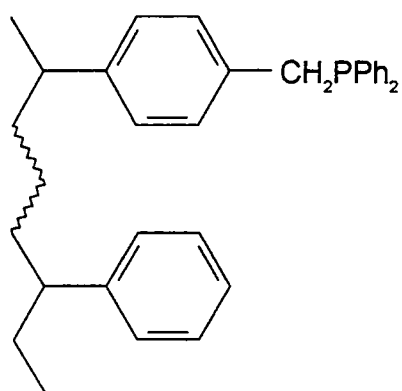


Figure 22. Polymer-supported phosphines

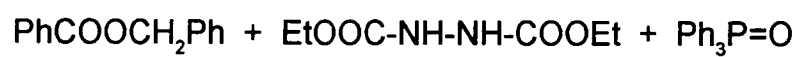


Figure 23. Esterification of benzoic acid with benzyl alcohol under Mitsunobu condition

Table 1. Monomer phase compositions of Copolymers

copolymer	DVB (g)	St ¹ (g)	VBC (g)	MMA (g)	MAA(g)
2 ^a -100V ²	4.33	0	114.47	0	0
2-33S ³ -67V	4.33	28.62	85.85	0	0
2-60S-40V	4.33	57.23	57.23	0	0
2-82S-18V	4.33	85.85	28.63	0	0
2-100S	10.3	286.71	0	0	0
2-82ME ⁴ -18V	4.33	0	29.48	84.99	0
2-82A ⁵ -18V	1.08	0	8.22	0	20.40

¹ St stands for Styrene.

^a Cross-linking level (% of cross-linking agent DVB in a copolymer)

² Percentage of VBC in a copolymer (excluding DVB).

³ Percentage of styrene in a copolymer (excluding DVB).

⁴ Percentage of MMA in a copolymer (excluding DVB).

⁵ Percentage of MAA in a copolymer (excluding DVB).

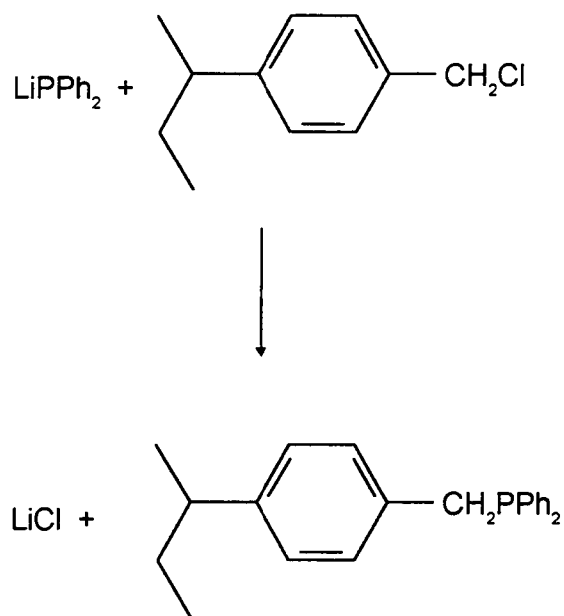


Figure 24. Synthesis of phosphine resins from VBC containing polymers

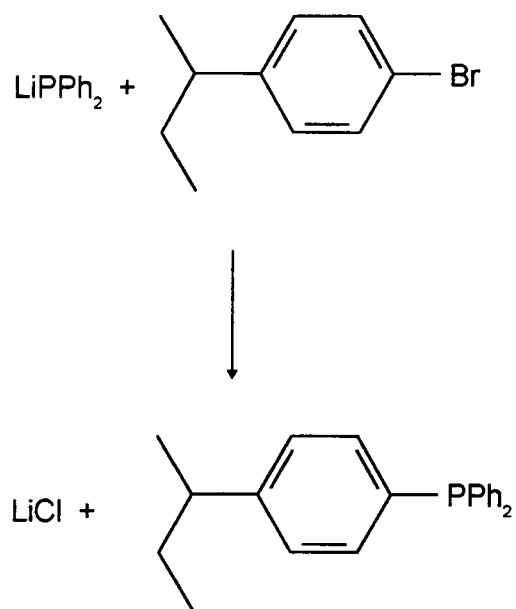
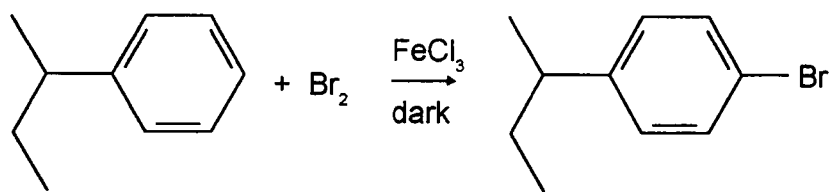


Figure 25. Synthesis of phosphine resins from styrene containing polymers

Table 2. Reaction conditions in phosphine resin synthesis *

resin before funct'nalization	Li (g) / THF (ml)	CIPPh ₂ (g) / THF(ml)	resin (g) / THF (ml)	temperature (°C)	resin after funct'nalization
2-100V	4.98/100	51.94/235	20/150	25	2-100CP ¹
2-33S-67V	5.12/100	50.64/235	25/200	25	2-33S-67CP
2-60S-40V	5.34/103	50.64/235	30/200	25	2-60S-40CP
2-82S-18V	5.17/100	52.45/235	60/400	25	2-82S-18CP
2-60S-40BS ²	4.81/100	51.08/230	30/200	25	2-60S-40P ³
2-82S-18BS	3.76/75	40/172	20/150	25	2-82S-18P-1 ⁴
2-82S-18P-1	3.7/75	40/172	20/150	refluxing	2-82S-18P-2
2-82ME-18V	5.12/100	51.19/220	35/210	25	2-82ME-10V-8CP
2-82ME-18V	5.06/100	53.50/220	35/210	refluxing	2-82ME-18CP
2-82A-18V	1.5/30	16/70	10/80	25	2-78A-12V-10CP-1
2-78A-12V-10CP-1	3.0/60	30/140	10/50	refluxing	2-78A-12V-10CP-2

*Reaction time is 24 hours for all the reactions.

¹ Percentage of -CH₂(PPh)₂ in a copolymer (excluding DVB).

² Percentage of bromostyrene units in a copolymer (excluding DVB).

³ Percentage of -(PPh)₂ in a copolymer (excluding DVB).

⁴ Batch number to differentiate resins with the same composition.

agreement between the experimental and theoretical capacity in most functionalized polymers indicates a clean functionalization reaction (Table 3).

Effect of washing

The surface of the beads contains contaminants from surfactants and stabilizers that are used in the suspension polymerization. Their reactions with organometallic reagents lead to the formation of ions on the surface of the beads, which prevent further penetration of the reagents into the beads.¹³⁸ Table 4 shows that the resin with surface impurities gives very low phosphorus capacity, while the resin without surface contamination reaches full phosphine functionality. The detailed washing procedure is described in Chapter V.

Effect of temperature

About 50% of the $-\text{CH}_2\text{Cl}$ groups in 2-18V-82ME are functionalized to phosphine after reacting with lithium diphenylphosphide for 24 hours at room temperature (Table 3 #8). Increasing the reaction temperature increases the degree of functionalization to 100% (Table 3 #9). Similar behavior has been reported with the 8% DVB cross-linked

Table 3. Characterization of phosphine resins

	Resins	Capacities (mequiv/g)			
		P	Cl / Br	Acid	theoretical P
1	2-100CP	3.117	0	N/A	3.232
2	2-33S-67CP	2.678	0	N/A	2.757
3	2-60S-40CP	2.284	0	N/A	2.131
4	2-82S-18CP	1.171	0	N/A	1.268
5	2-60S-40P	2.098	0	N/A	2.190
6	2-82S-18P-1	1.451	0	N/A	1.266
7	2-82S-18P-2	1.356	0	N/A	1.266
8	2-82ME-10V-8CP	0.644	0.732	N/A	1.311
9	2-82ME-18CP	1.134	0	N/A	1.311
10	2-78A-12V-10CP-1	0.815	1.02	6.46	1.416
11	2-78A-12V-10CP-1	0.820	0.960	6.46	1.416

Table 4. The effect of washing on the degree of functionalization

surface impurities	<u>P capacities (mequiv/g)</u>	
	experimental	theoretical
yes	0.236	1.266
no	1.451	1.266

bromopolystyrene gel resin: a higher phosphorus capacity is obtained at reflux than at room temperature.¹³⁹

The MAA-containing copolymers are not sensitive to reaction temperature. After reacting 2-18V-82A, (detected MAA capacity = 8.19 mequiv/g; theoretical MAA capacity = 7.90 mequiv/g), with lithium diphenylphosphide for 24 hours at room temperature, the resulting copolymer has a phosphorus capacity of 0.815 mequiv/g (Table 3 #10). Further reacting with lithium diphenylphosphide at reflux does not improve the degree of functionalization (Table 3 #11). This is probably due to the strong solvation of lithium diphenylphosphide provided by carboxylic acid moieties, decreasing the nucleophilicity of the phosphide anion.

The copolymer mass balance value provides a measure of the extent of any otherwise undetected side reactions. The concept is that the measured capacities of a given resin should account for all possible mass in the sample. For example, consider a resin thought to contain only phosphine ligands, unreacted benzyl chloride, and carboxylic acid moieties. If the measured capacities (P, Cl and acid as mequiv/g) are converted into masses, then the sum of these masses should equal 1.00. The presence of cross-linking lowers this value since, in general, the DVB

sites will not undergo functionalization. Thus one gram of 2% cross-linked resin made with 55.4% technical grade DVB would contain 0.9639 g of functionalizable material. If only the phosphine ligands (MW of repeat unit = 0.302 g/mequiv), benzyl chloride (MW of repeat unit = 0.153 g/mequiv), and carboxylic acid moieties (MW of repeat unit = 0.086 g/mequiv) are present, then the quantity

$$\frac{(P \text{ capacity}) \times (0.302) + (Cl \text{ capacity}) \times (0.153) + (Acid \text{ capacity}) \times 0.086}{0.9639}$$

should equal 1.00. A lower g/g value indicates the presence of side reactions, which are forming undetected products. The mass balance of 2-10V-80ME-8CP, 2-12V-78A-10CP-1, and 2-12V-78A-10CP-2 calculates to exactly 1, indicating no unexpected side reactions at room temperature, or at reflux.

The esterification reaction experimental

The reactions were carried out in tetrahydrofuran (THF) at 25°C. Microliter samples of the reaction mixture were taken and analyzed by GC with THF used as the internal standard. The concentration of each component in a microliter sample is calculated as follows:

$$W_n/W_s = \alpha A_n/A_s$$

where A_s = internal standard peak area

A_n = component n peak area

W_s = weight of internal standard

W_n = weight of component n

α = constant

A calibration curve can be obtained by plotting W_n/W_s against A_n/A_s . The calibration curve for benzyl alcohol is illustrated in Figure 26. The detailed experimental procedures are described in Chapter V.

The electronic effect

Yields and conversion data with soluble reagents in a given solvent establish the baseline electronic effect against which the behavior of polymer-supported reagents can be understood. A comprehensive mechanistic study of the Mitsunobu reaction has shown that S_N2 displacement on the oxyphosphonium cation by the carboxylate anion is the rate determining step when the pK_a of the acid is similar to acetic acid, and the concentration ratio of the acid to its conjugate base is equal to or less than 1.¹⁴⁰ The reaction rate can be increased by decreasing the solvation of the carboxylate anion. Figure 27 illustrates the decrease in $PhCH_2OH$ concentration as a function of time in the presence of PPh_3 , and each of the polymeric reagents shown in Figure 22. Table 5 gives the percent conversion of benzyl alcohol at different times as well as the

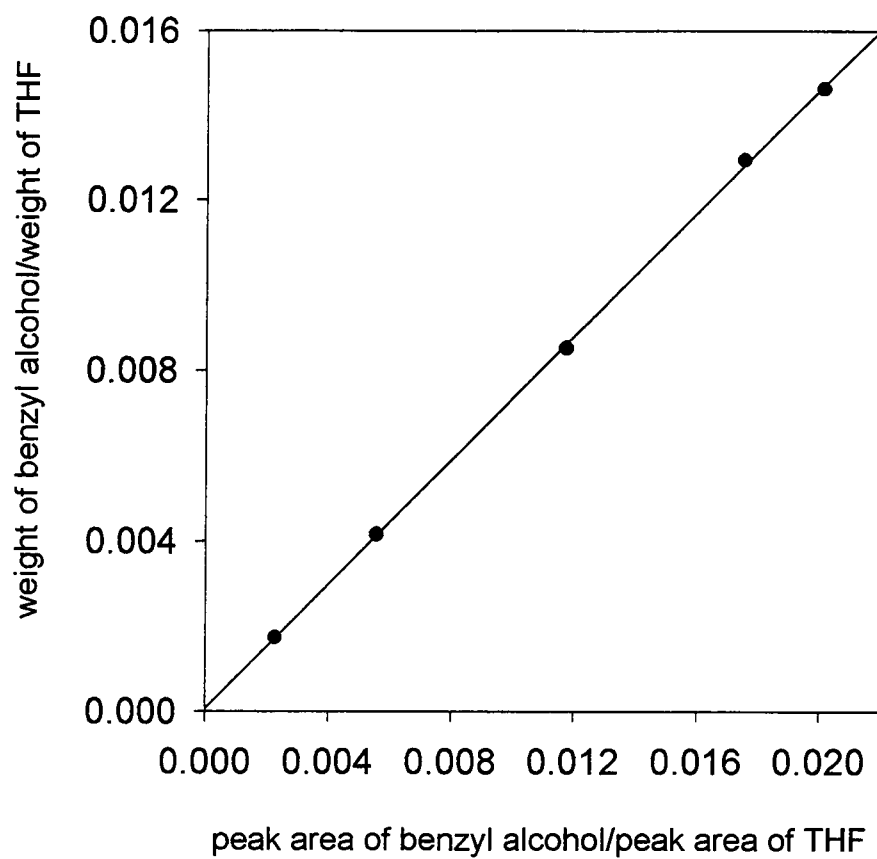


Figure 26. Calibration curve for the determination of the amount of benzyl alcohol in a mixture. Internal standard: THF.

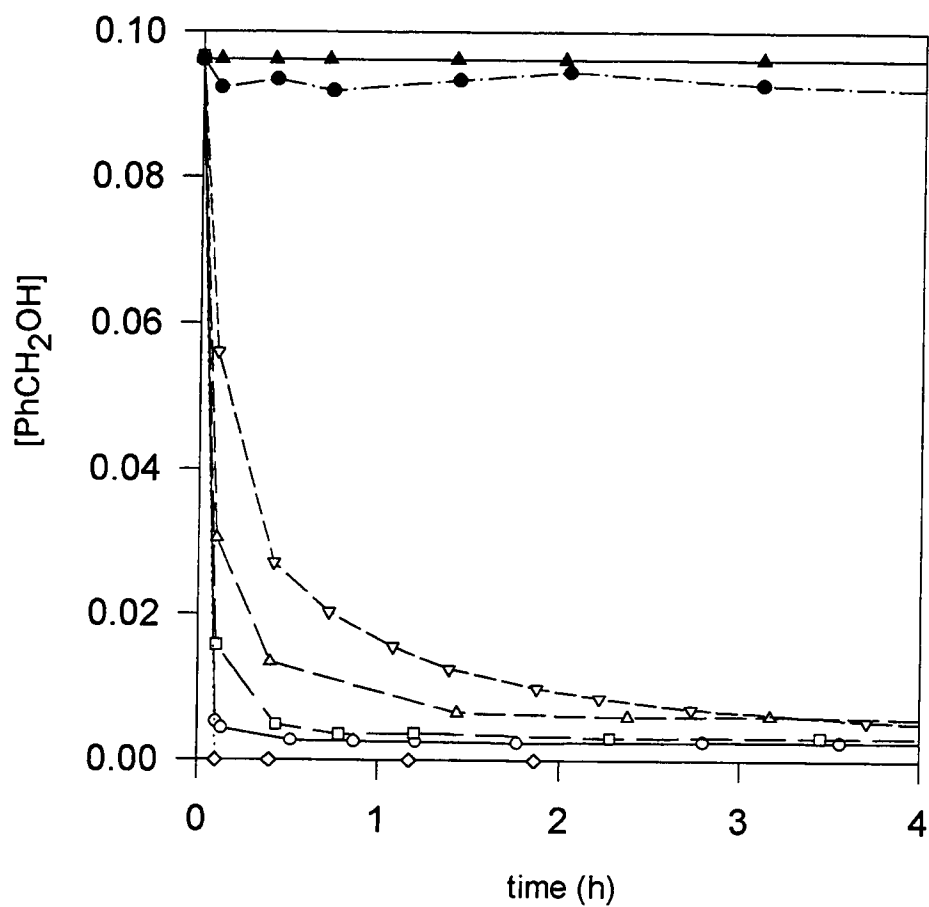


Figure 27. The Mitsunobu reaction with triphenylphosphine and polymer-supported phosphine resins

- ◇ Triphenylphosphine, 2-60S-40P and 2-82S-18P.
- ▽ 2-100CP △ 2-33S-67CP □ 2-60S-40CP
- 2-82S-18CP ● 2-82ME-18CP ▲ 2-82A-18CP

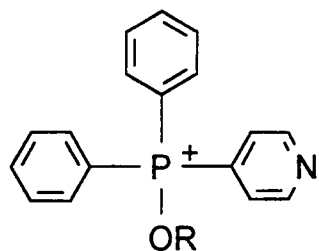
Table 5. Percent conversions of benzyl alcohol and percent yields of benzyl benzoate at equilibrium

	PPh ₃	2- 100CP	2-33S- 67CP	2-60S- 40CP	2-82S- 18CP	2- 82ME- 18CP	2-60S- 40P	2-82S- 18P	2-78A- 12V- 10CP-2
%conv at 0.1hr	100	41.7	68.4	83.7	94.2	1.3	100	100	0
%conv at 0.4hr	100	71.9	86.1	95.0	97.2	2.7	100	100	0
%conv at equil.	100	96.6	94.2	97.0	97.6	56.3	100	100	0
Time to equil.(hr)	<0. 1	8.5	6.0	2.3	0.5	80	<0.1	<0.1	93
%yield at equil.	85.3	79.8	77.8	96.0	95.1	29.8	84.6	86.0	0

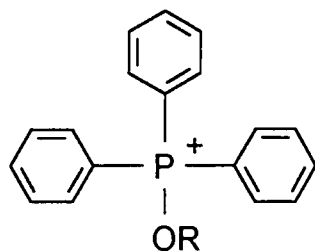
percent yield of benzyl benzoate when reactions reach equilibrium.

Addition of the soluble reagent, PPh_3 , to the reactant solution leads to a very rapid approach to equilibrium (< 0.1 h) with 100% benzyl alcohol conversion, and 85.3% yield of ester. The fully functionalized poly(vinylbenzyl diphenylphosphine), 2-100CP, is not a direct analogue of PPh_3 , but it is worth studying because it can be synthesized as a well-characterized reagent from VBC copolymer beads. It does, however, give a significantly slower rate of ester formation, with 41.7% alcohol in 0.1 h, and 96.6% conversion requiring 8.5 hours; the ester yield is lower than with the soluble PPh_3 . The results with 2-100CP quantify the electronic effect of the polymeric ligand on the reaction. It has been found that the electrophilicity decreases in the order oxypyridyldiphenylphosphonium cation $>$ oxytriphenylphosphonium cation $>$ oxytributylphosphonium cation (Figure 28), due to the decreasing electronegativity of the substituent groups on the phosphorus.^{141,142,143} It is thus reasonable to postulate that benzyldiphenylphosphonium cation is not as electrophilic as triphenylphosphonium cation, which slows down the rate determining step.

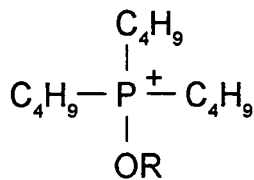
The kinetic performance of polymeric phosphines can be improved by using poly(styryldiphenylphosphine). Though it was not possible to



oxypyridyldiphenylphosphonium
cation



oxytriphenylphosphonium
cation



oxytributylphosphonium
cation

Figure 28. Phosphonium cation structures

synthesize fully functionalized poly(styryldiphenylphosphine), partially functionalized polymers (2-60S-40P and 2-82S-18P) have been synthesized. 2-60S-40P and 2-82S-18P are structurally identical to 2-60S-40CP and 2-82S-18CP respectively, except for the absence of the methylene spacer between the aromatic ring and diphenylphosphine moiety (Figure 22). 2-60S-40P and 2-82S-18P behave in a manner identical to the soluble PPh_3 , and give faster kinetic results than 2-60S-40CP and 2-82S-18CP (Figure 27). The accessibility of the reactants into the polymer matrix is not a variable: all resins used in this study swell at least two-fold in the dry THF solvent (Table 6); additionally, the particle size of 2-100CP does not affect the reaction rate (Figure 29).

The microenvironmental effect

The results in Figure 27 indicate that whereas the electronic effect of the ligand at the active site is an important influence on the rate and extent of product formation, it is not the sole influence: keeping the ligand type constant but decreasing the degree of substitution, (degree of substitution: 2-100CP > 2-33S-67CP > 2-60S-40CP > 2-82S-18CP), results in a significant increase in both reactant conversion and product yield (Table 5). 2-82S-18CP, with only 18 mol% $-\text{CH}_2\text{PPh}_2$, is superior to

Table 6. Swelling ratios of phosphine resins in dry THF

resin	swelling ratio
2-100CP	2.0
2-33S-67CP	2.2
2-60S-40CP	2.6
2-82S-18CP	2.8
2-82ME-18CP	2.0
2-60S-40P	3.1
2-82S-18P	2.7
2-78A-12V-10CP-2	2.0

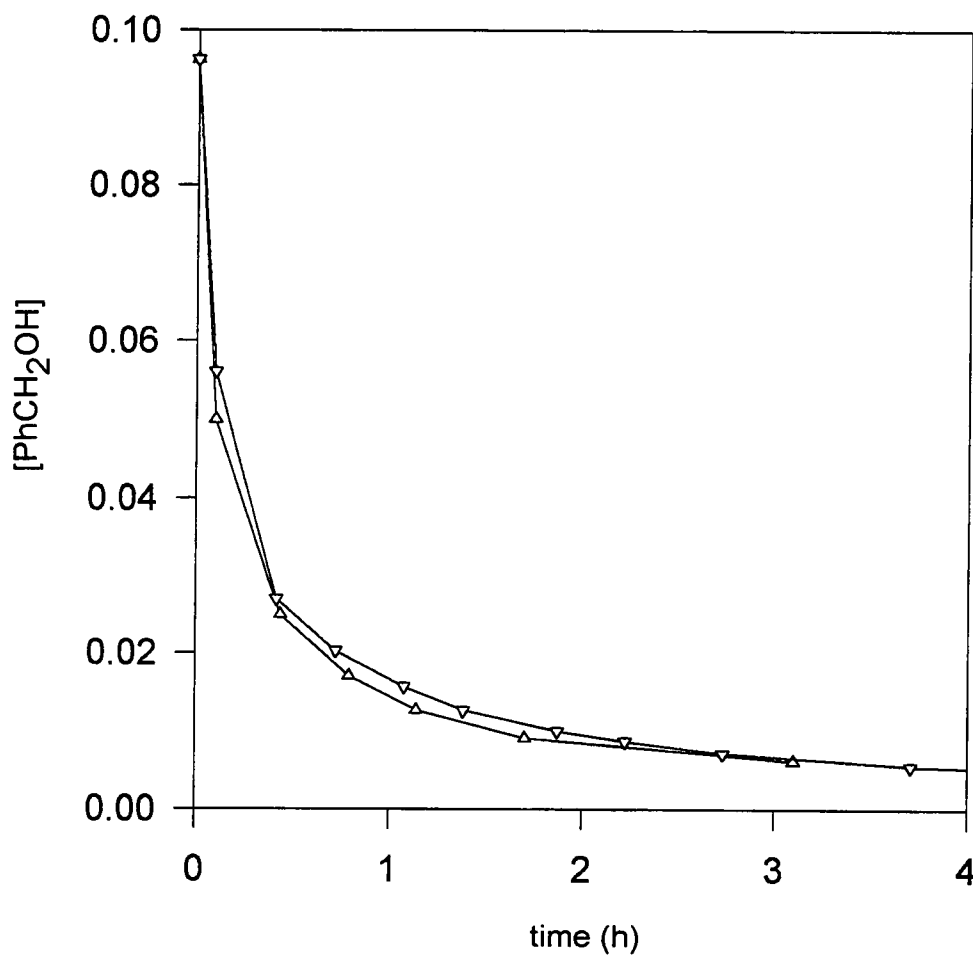


Figure 29. Dependence of reaction rate on the particle size of 2-100CP

- ▽ 2-100CP (14.92 meq H⁺, -40+60 mesh size)
- △ 2-100CP (15.02 meq H⁺, -100+200 mesh size)

the soluble reagent, given that alcohol conversion is almost as rapid, and ester formation is greater due to an apparently cleaner reaction.

The influence of neighboring groups on the reaction rate is further explored with methylmethacrylate and methacrylic acid moieties surrounding the phosphine ligands. Resin 2-82ME-18CP has the same degree of substitution as 2-82S-18CP but with the phenyl rings replaced by ester groups. The ester groups would not be expected to be directly involved in the Mitsunobu reaction but, by being more polar than the phenyl rings, could influence the microenvironment surrounding the active sites. The increase in polarity is shown by the fact that 2-82ME-18CP has a swelling ratio in acetonitrile (dielectric constant = 37.5) of 1.7 and in toluene (dielectric constant = 2.379) of 1.1, whereas 2-82S-18CP has swelling ratios of 1.3 and 2.6 respectively. The results show that ester groups have a detrimental effect on the conversion and yield (Figure 27 and Table 5): conversion reaches only 56.3% after 80 hours, and the ester yield is merely 29.8%. Resin 2-12V-78A-10CP-2 has strongly hydrogen bonding carboxylic acid groups instead of ester groups surrounding the phosphine ligands. The mole ratio of phosphine to total (i.e., phosphine, acid and VBC) sites is 0.10, which is less than the targeted 0.18 but still sufficiently high to determine reagent reactivity.

Addition of 2-12V-78A-10CP-2 to the reactant solution leads to absolutely no reaction, even after 93 hours.

Given the mechanism of the Mitsunobu reaction, it is proposed that decreasing the degree of $-\text{CH}_2\text{PPh}_2$ substitution while concomitantly increasing the number of unsubstituted phenyl rings results in a decrease of polarity in the microenvironment surrounding the active sites in the order $2-100\text{CP} > 2-33\text{S}-67\text{CP} > 2-60\text{S}-40\text{CP} > 2-82\text{S}-18\text{CP}$. This in turn, increases the reactivity of the benzoate /oxyphosphonium ion pair which results in an increase in the rate of product formation, with $2-82\text{S}-18\text{CP} > 2-60\text{S}-40\text{CP} > 2-33\text{S}-67\text{CP} > 2-100\text{CP}$. This hypothesis is supported by results with 2-82ME-18CP and 2-12V-78A-10CP-2. In the presence of 2-82ME-18CP, the reactivity of the benzoate/phosphonium ion pair is lowered through greater solvation by ester groups than by phenyl groups, which results in a reduction of reaction rate. The presence of $-\text{COOH}$ groups in 2-12V-78A-10CP-2 eliminates the nucleophilicity of the benzoate anion through hydrogen bonding (Figure 30) and decreases the kinetics more than 2-82ME-18CP. This observation is in agreement with results from the mechanistic study with soluble reagents.¹⁴⁰ 2-82S-18CP, with no hydrogen bonding interactions stabilizing the benzoate/phosphonium ion pair and with the most non-

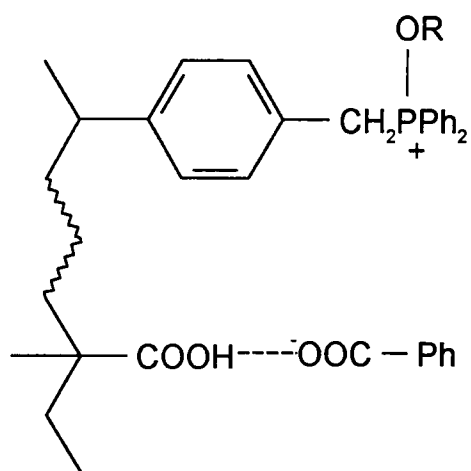


Figure 30. Hydrogen bonding eliminates the nucleophilicity of the benzoate anion

polar microenvironment to enhance the reactivity of the ion pair, is the preferred polymer-supported reagent for the Mitsunobu reaction. The microenvironmental effect thus superimposed on the electronic effect, results in the synthesis of an efficient polymer-supported reagent for a targeted reaction.

Conclusion

Polymer-supported reagents can be optimized for a given reaction by tailoring the microenvironment surrounding the active sites to the reaction mechanism. This study also demonstrates that if the rate determining step involves ionic intermediates, a non-polar microenvironment can be used to enhance the intermediate's reactivity, the product selectivity, and the reaction rate.

CHAPTER II

POLYMER-SUPPORTED SULFONIC ACID RESINS

Introduction

Sulfonic acid resins have been studied as substitutes for homogeneous catalysts in many organic reactions that require acid catalysts.^{6,93} The use of sulfonic acid resins exhibits numerous advantages including ease of handling, elimination of corrosion and waste generation, and the flexibility of continuous or batch processes. A few successful applications are: the esterification of palmitic acid with isobutyl alcohol,¹⁴⁴ the dimerization of α -methylstyrene,¹⁴⁵ the transesterification of ethylene carbonate,⁷⁸ and the monoacylation of 1,n-diols.⁸⁰ The sulfonic acid resins have also been used in a number of petrochemical reactions such as synthesis of aldyphenols,¹⁴⁶ bisphenol A,⁷² and methyl t-butyl ether (MTBE).¹⁴⁷

This chapter focuses on the synthesis and the characterization of sulfonic acid resins and the incorporation of neighboring groups surrounding the sulfonic acid ligands. Their application as catalysts in aldol condensation of propionaldehyde and the Prins reaction of formaldehyde with styrene will be presented in later chapters.

Synthesis and Characterization of Sulfonic Acid Resins

The divinylbenzene (DVB) cross-linked polystyrene supports are synthesized by suspension polymerization. Sulfonic acid ligands are attached to the supports by electrophilic aromatic substitution on the copolymers with sulfuric acid (Figure 31). The beads are swelled in ethylene dichloride at room temperature for one hour before reacting with sulfuric acid at 85°C. The sulfonic acid resins are characterized by their acid capacities and percent solids. The acid capacity of a resin is the number of acid groups in one gram (dry weight) of resin (mequiv/g). The percent solids indicates the amount of water in Buchner-dried resin. Hydrophilic resins have low percent solids. The characterization of two sulfonic acid resins is listed in Table 7.

The beads are sulfonated from the external surface towards the central core.^{148,149} The swelling solvent, such as ethylene dichloride, facilitates the mass transport. The concentration profile of sulfur, measured with an electron microprobe, shows that in the absence of ethylene dichloride the sulfonic acid ligands are concentrated on the surface of the beads;^{148,149} however, in the presence of ethylene dichloride, the sulfonic acid ligands are distributed throughout the particle.¹⁴⁹ Table 8 shows that the

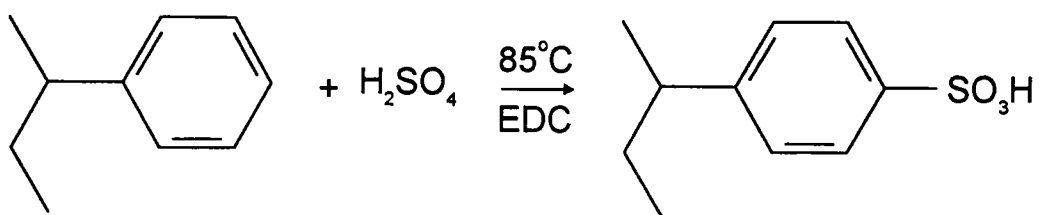


Figure 31. Sulfonation with sulfuric acid

Table 7. Characterization of sulfonic acid resins

resin	%solids	acid capacities (mequiv/g)		temperature
		experimental	theoretical	
2-100H ¹ -G ² -SA ³	20.76	5.26	5.29	85°C
10-100H-G-SA	50.67	5.01	4.80	85°C

¹ Percentage of -SO₃H in a copolymer (excluding DVB).

² Gel resin.

³ Functionalized with sulfuric acid.

Table 8. The effect of swelling solvent on the sulfonation reaction

swelling solvent	reaction temperature	acid capacity (mequiv/g)
EDC	85°C	5.01
none	100°C	0.493

sulfonation reaction proceeds to a very limited extent without ethylene dichloride, but completely with ethylene dichloride.

Reaction temperature affects the degree of sulfonation. Low reaction temperature results in low degree of functionalization.¹⁴⁸ Table 9 shows that at 85°C, full sulfonation is achieved, whereas at 40°C, sulfonation barely proceeds.

Water is added during the quenching process, which causes the beads to crack due to large osmotic pressure generated inside the beads. In order to reduce the osmotic pressure, a series of aqueous sulfuric acid solutions (10M, 8M, 6M, 4M, 2M) are used in decreasing concentration order to allow for a gentler quench. Cracked beads cannot be used in the catalysis study because the mass transport rate is affected by the cracks, which are difficult to measure and vary from batch to batch.

A much milder sulfonation can be achieved by reacting the DVB cross-linked polystyrene copolymers with chlorosulfonic acid (Figure 32). After the beads are swelled in ethylene dichloride at room temperature for one hour, chlorosulfonic acid is added slowly at 0°C. The cooling bath is then removed and the reaction temperature is raised to room temperature

Table 9. The effect of temperature on the sulfonation reaction

reaction temperature	acid capacity (mequiv/g)	%solids
85°C	5.01	50.67
40°C	0.320	80.66

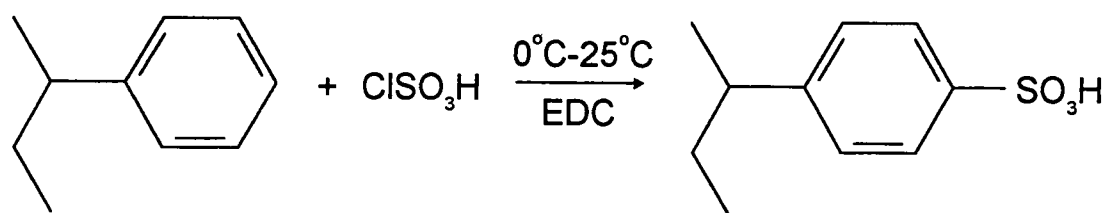


Figure 32. Sulfonation with chlorosulfonic acid

to ensure uniformity of substitution. The mixture is stirred for 24 hours at room temperature. The beads are washed with EDC, 1,4-dioxane, 1,4-dioxane/water solution, and water successively. The resulting beads are free of cracks, and therefore can be used in the catalysis studies.

Partial sulfonation can be achieved by using a stoichiometric amount of chlorosulfonic acid. For example: a 2% DVB cross-linked resin with 45% (mol %) functionality can be synthesized by reacting 100g of 2% DVB cross-linked polystyrene (0.917 mol phenyl rings) with 0.413 mol of chlorosulfonic acid. The resulting resin has an expected acid capacity of 3.10 mequiv/g and an experimental value of 3.07 mequiv/g. The sulfonic acid groups are distributed throughout the beads because under the microscope the water swollen beads appear uniformly transparent.

When a DVB cross-linked styrene-alkyl methacrylate copolymer reacts with chlorosulfonic acid, the phenyl groups are sulfonated and the ester groups remain unchanged. IR spectra of the DVB cross-linked styrene-methyl methacrylate (MMA) copolymer and the corresponding functionalized polymer show that the carbonyl group is unaffected by sulfonation as indicated by the strong peak at 1720cm^{-1} (Figure 33). IR spectra of the DVB cross-linked styrene-butyl methacrylate (BMA)

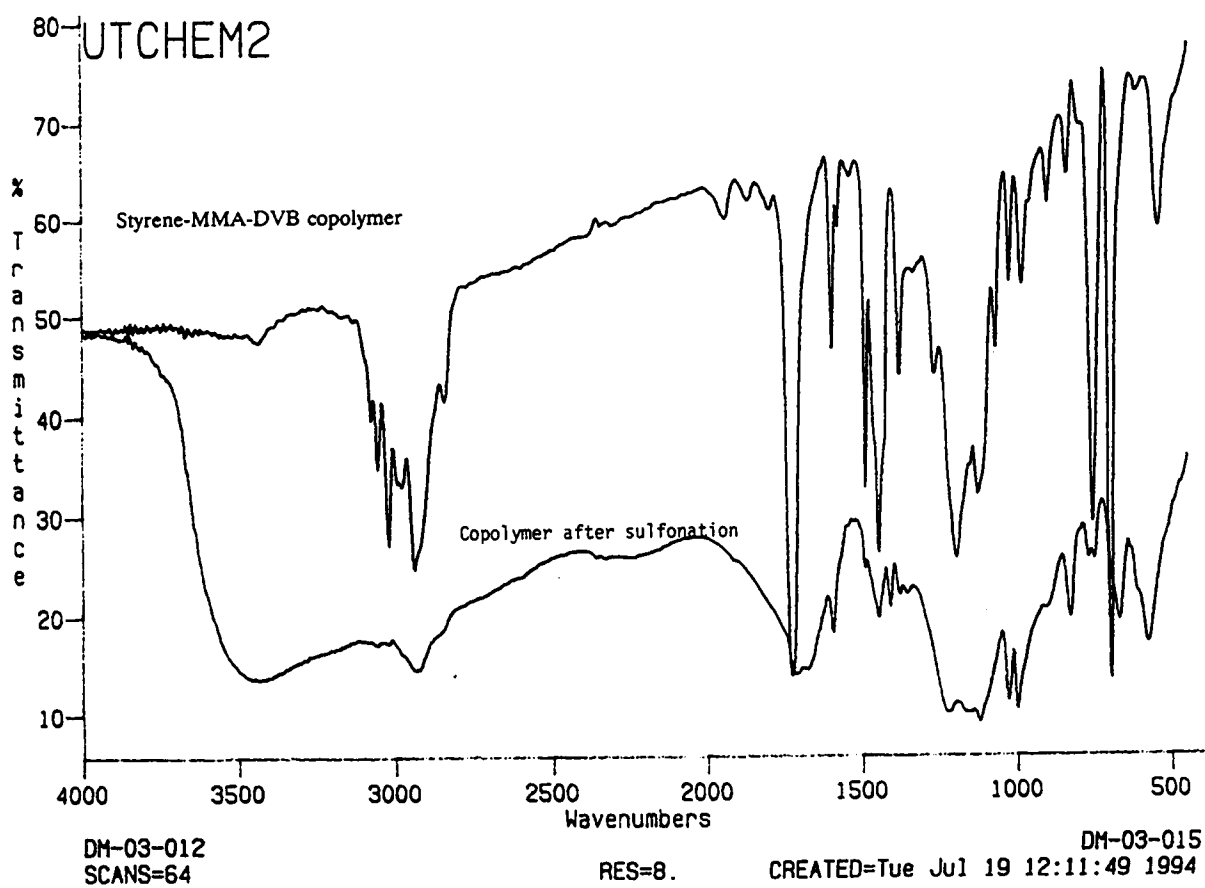


Figure 33. FTIR spectrum of Styrene-MMA-DVB copolymer and
FTIR spectrum of the copolymer after sulfonation.

copolymer and the corresponding functionalized polymer also show that the carbonyl group is unaffected by sulfonation (Figure 34). The agreement between the measured acid capacity and theoretical capacity, which is based solely on the number phenyl rings, further confirms that sulfonation only occurs on the phenyl rings (Table 10).

Conclusion

Sulfonic acid resins can be synthesized by electrophilic aromatic substitution. A swelling solvent must be used during the reaction to allow internal functionalization. Both sulfuric acid and chlorosulfonic acid are effective sulfonating agents. The reaction conditions are milder with chlorosulfonic acid than with sulfuric acid. The beads, functionalized with chlorosulfonic acid, are free of cracks and can be used in catalysis studies.

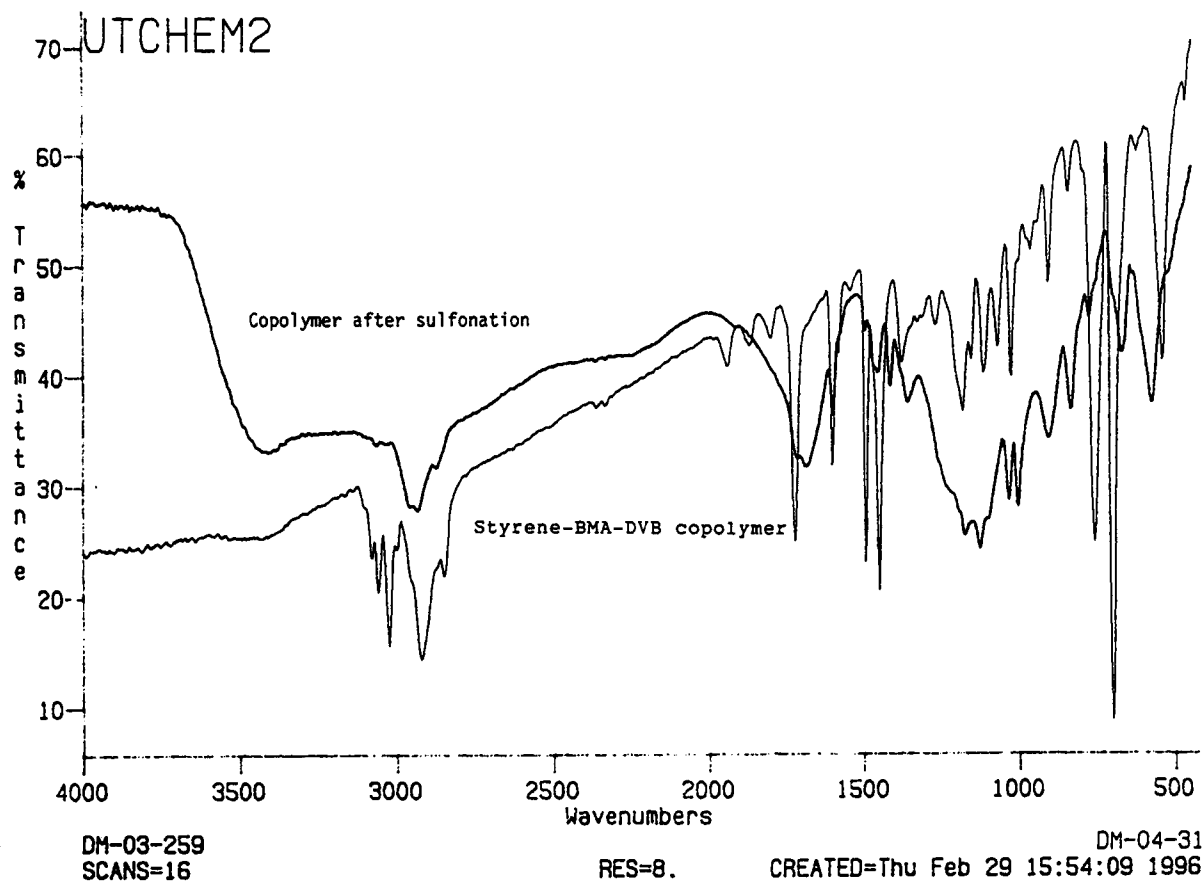


Figure 34. FTIR spectrum of Styrene-BMA-DVB copolymer and
FTIR spectrum of the copolymer after sulfonation.

Table 10. Characterization of sulfonic acid resins with ester moieties as neighboring groups

acid capacities (mequiv/g)		ester moieties
experimental	theoretical	
3.88	3.85	MMA
1.39	1.59	BMA

CHAPTER III

THE APPLICATION OF POLYMERIC SULFONIC ACIDS AS CATALYSTS IN THE ALDOL CONDENSATION OF PROPIONALDEHYDE

Introduction

The aldol condensation is a well-established reaction¹⁵⁰ that continues to be applied in modern organic chemistry.¹⁵¹ Recent studies include its use in the synthesis of monosaccharides,¹⁵² enynes,¹⁵³ 3-hydroxycarboxylic acids¹⁵⁴ and carbohydrates.¹⁵⁵

The current chapter focuses on polystyrene-bound sulfonic acids as catalysts in the aldol condensation of propionaldehyde (Figure 35). The aldol condensation of several aldehydes using a commercially available sulfonic acid resin has been studied at equilibrium.^{68,156} Sulfonic acid polymers are now utilized where the synthesis parameters are controlled. The effect on the reaction rate is determined as the catalyst particle size, the cross-linking level, the porosity, and the microenvironment surrounding the acid ligands are varied. The kinetics for the heterogeneous and homogeneous acid catalyzed reactions are

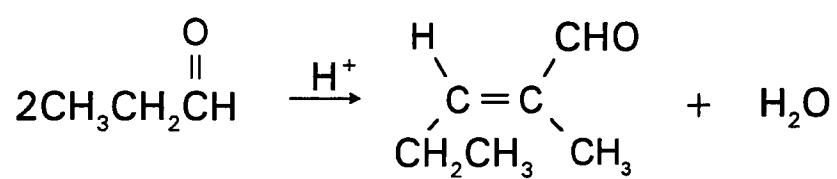


Figure 35. The aldol condensation of propionaldehyde

studied and compared.

Aldol condensation study

1. Experiment

The reactions were carried out in 1,4-dioxane at 75°C. Microliter samples were taken and analyzed by GC with dioxane used as the internal standard. Calibration curves (Figures 36 and 37) were used to calculate the concentration of reactant and product. The dehydration product, trans-2-methyl-2-pentenal, was obtained and its structure was confirmed with ^1H and ^{13}C NMR, FTIR and GC mass spectra. The detailed procedures are described in Chapter V.

2. Homogeneous catalyst kinetics

A linear correlation of $[\text{EtCHO}]^{-1}$ vs time indicates that the reaction is second order in propionaldehyde (Figure 38). Slopes and intercepts are determined by linear least-squares analysis, with all correlation coefficients greater than 0.9950. The slopes are equal to the observed rate constants. The acid catalyzed self-condensation of acetaldehyde has been found to be second order in acetaldehyde.¹⁵⁷ The reaction rate is proportional to the initial acid concentration (Figure 39), and the rate constant can be calculated from the slope and $[\text{H}^+]_0$ (Table 11).

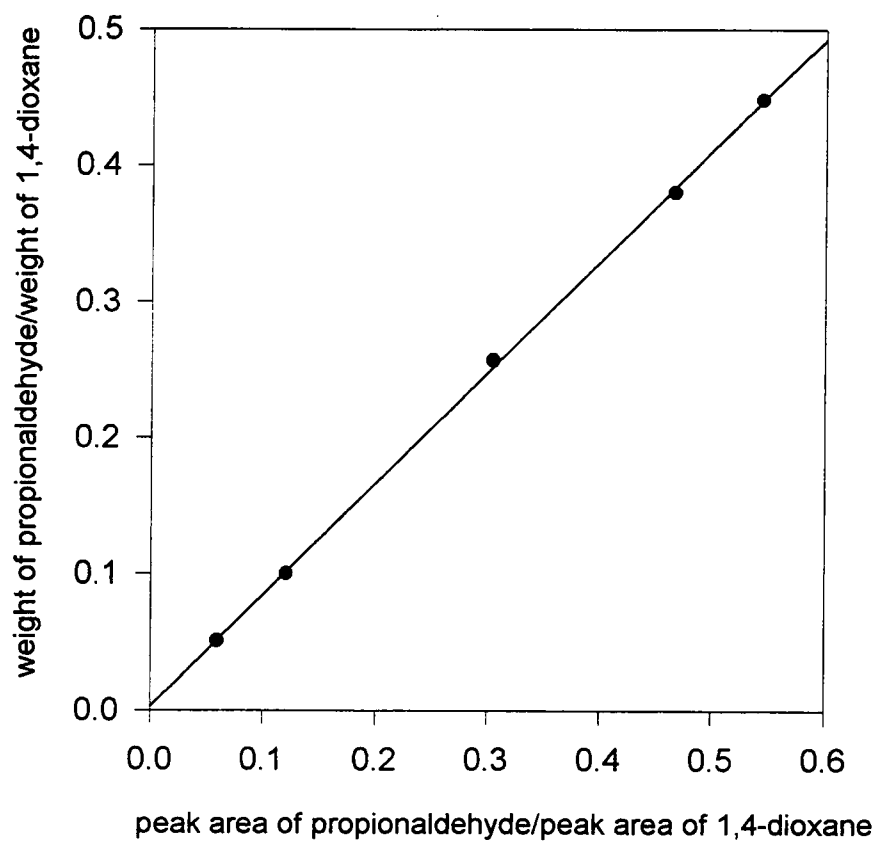


Figure 36. Calibration curve for the determination of the amount of propionaldehyde in a mixture. Internal standard: 1,4-dioxane

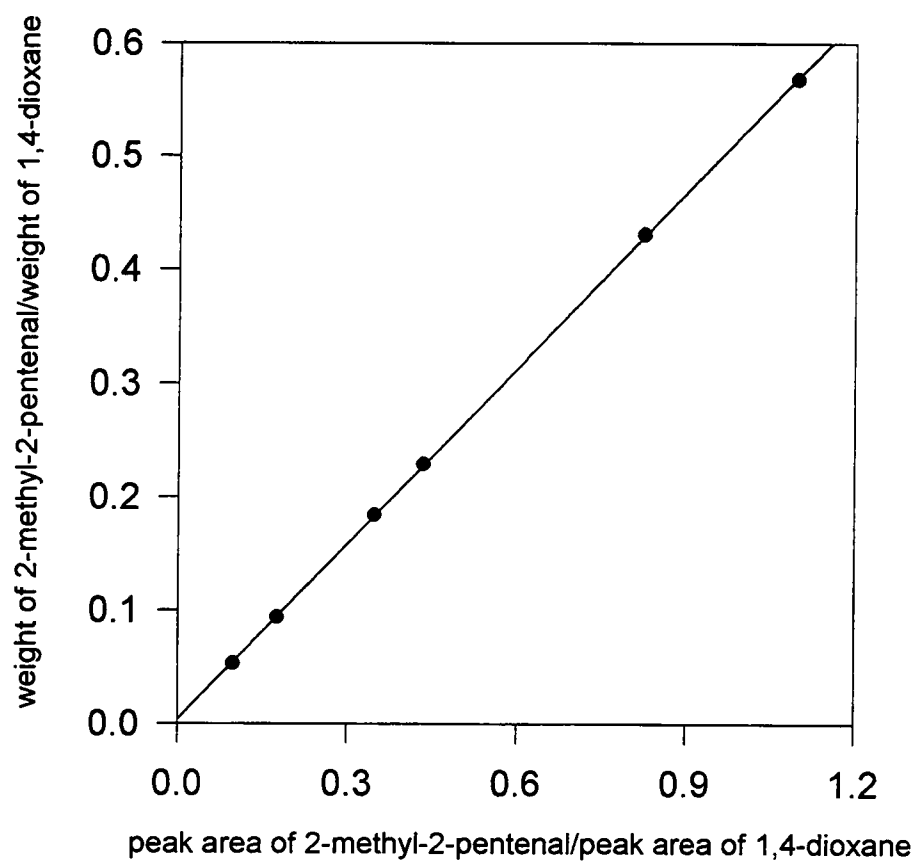


Figure 37. Calibration curve for the determination of the amount of 2-methyl-2-pentenal in a mixture. Internal standard: 1,4-dioxane

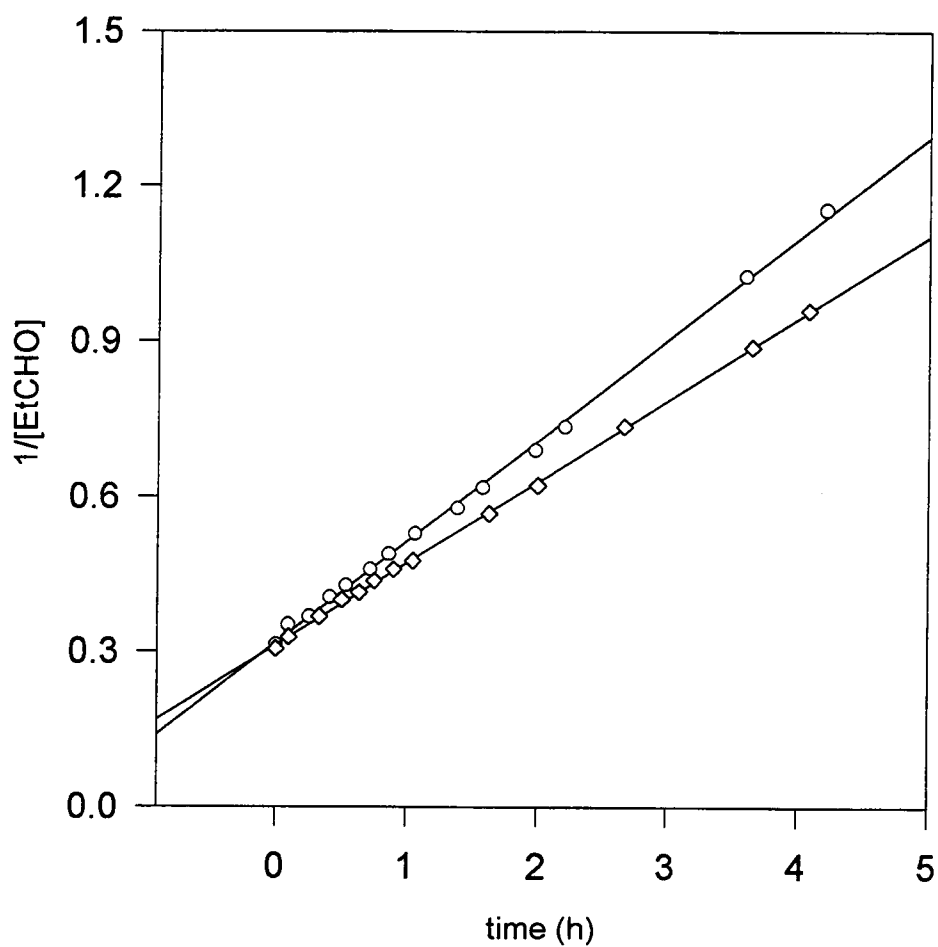


Figure 38. Second order rate equation in the aldol condensation of propionaldehyde with homogeneous acid catalysts

- 6.35 mmol H₂SO₄ as catalyst, [EtCHO]₀=3.0M.
- ◇ 6.35 mmol PhSO₃H as catalyst, [EtCHO]₀=3.0M.

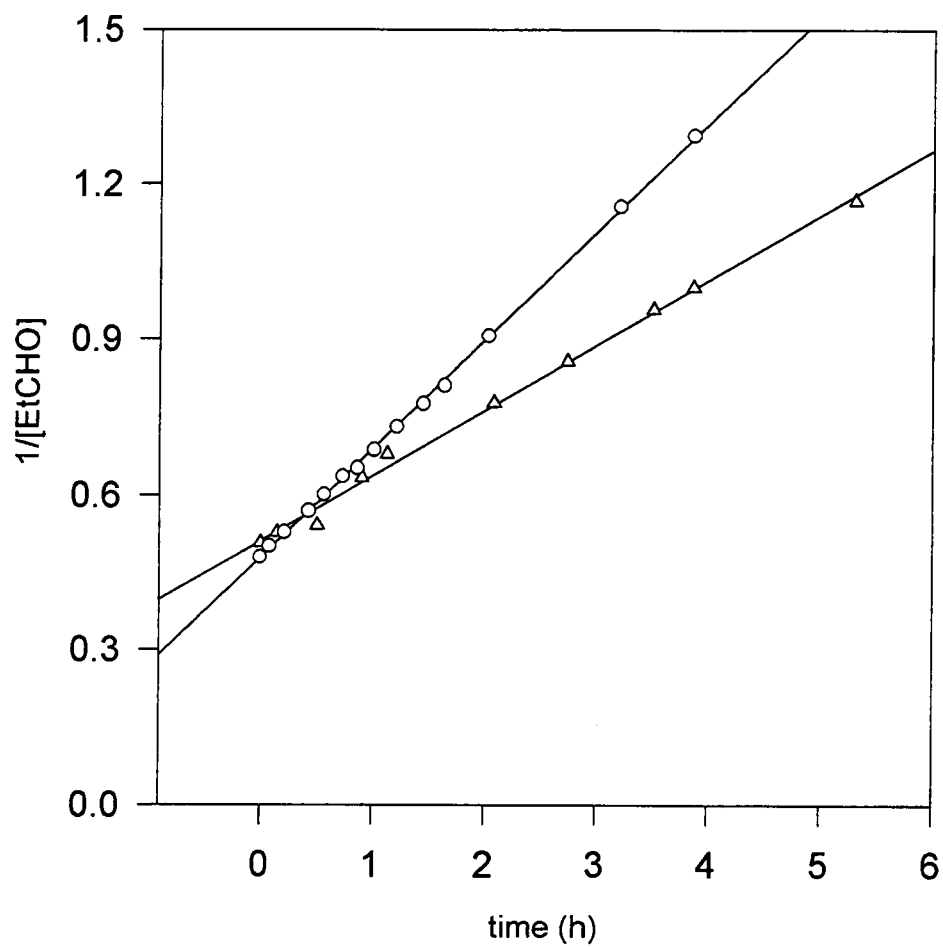


Figure 39. Observed rate constants as a function of H_2SO_4 concentration

- 6.17 mmol H_2SO_4 as catalyst, $[\text{EtCHO}]_0 = 2.0\text{M}$.
- △ 3.00 mmol H_2SO_4 , $[\text{EtCHO}]_0 = 2.0\text{M}$.

Table 11. Homogeneous acid catalyzed aldol
condensation of propionaldehyde

[EtCHO] ₀ ^a	Catalyst (mmol)	%conv. ^b	% yield ^b	k ^c
2.0	6.17 H ₂ SO ₄	93.1	61.7	3.06
3.0	6.35 H ₂ SO ₄	94.3	62.2	2.82
2.0	3.00 H ₂ SO ₄	85.3	62.5	3.05
2.0	8.28 PhSO ₃ H	94.7	62.6	2.47
3.0	6.35 PhSO ₃ H	93.9	60.5	2.23

^aInitial concentration of EtCHO

^bAt equilibrium

^cSecond-order rate constant, L²mol⁻²h⁻¹

The conversion and yield data are equilibrium values, all at a reaction time of 24 hours. The rate expression for the aldol condensation of propionaldehyde with homogeneous acid catalysts may be summarized by equation 1, in agreement with the proposed rate determining step (Figure 40).^{158,159}

$$d[\text{EtCHO}]/dt = -k_{\text{obs}}[\text{EtCHO}]^2 = -k[\text{EtCHO}]^2[\text{H}^+] \quad (1)$$

3. Heterogeneous catalyst kinetics

The structures of polymer-supported sulfonic acid resins used in this study are illustrated in Figure 41. Their properties are summarized in Table 12. Each polymer is dried thoroughly before being used to catalyze reactions.

A non-linear correlation of $[\text{EtCHO}]^{-1}$ vs time indicates that the reaction is not second order in propionaldehyde (Figure 42). Figure 43 shows that straight lines are obtained by plotting $[\text{EtCHO}]^{-2}$ vs time. The slope is proportional to the initial acid sites present per volume of solution and allows for the observed rate constant to be calculated (Figure 44). The rate expression for the aldol condensation catalyzed by the polymer-supported sulfonic acids may be summarized by equation 2.

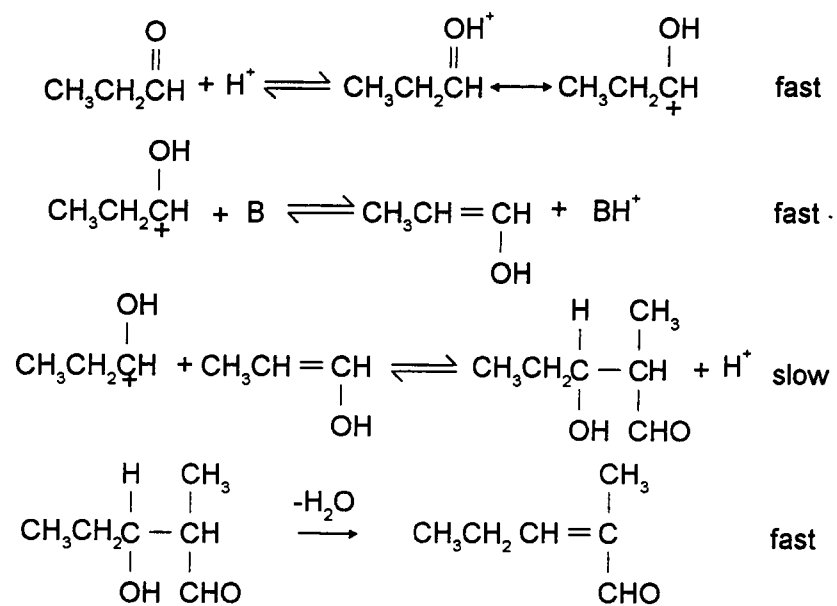


Figure 40. The mechanism of the acid catalyzed aldol condensation

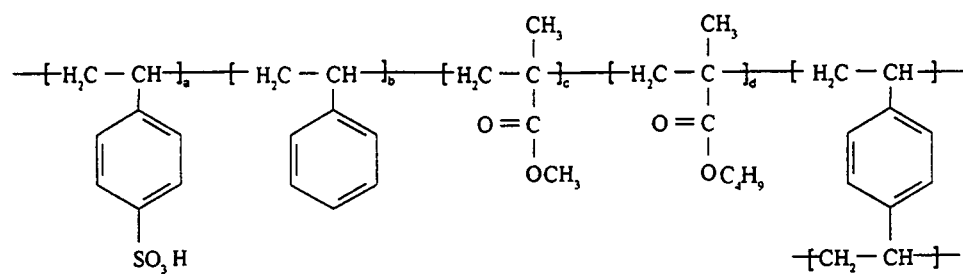


Figure 41. The structure of polymer-supported sulfonic acid resins

Table 12. Polymer-supported sulfonic acid catalysts used in aldol study

Polymer	<u>Acid capacity (mequiv/g)</u>	
	experimental	theoretical
10-100H-50MR ¹	4.93	4.80
2-100H-G	5.18	5.29
2-55S-45H-G	3.07	3.10
2-55BE ² -45H-G	2.73	2.66
2-55ME-45H-G	2.97	3.10
2-33BE-67H-G	4.09	3.82
2-41ME-59H-G	3.88	3.85
10-100H-G	5.01	4.80
10-100G-20MR	5.02	4.80

¹ Percentage of porosity in a MR resin.

² Percentage of BMA in a copolymer (excluding DVB).

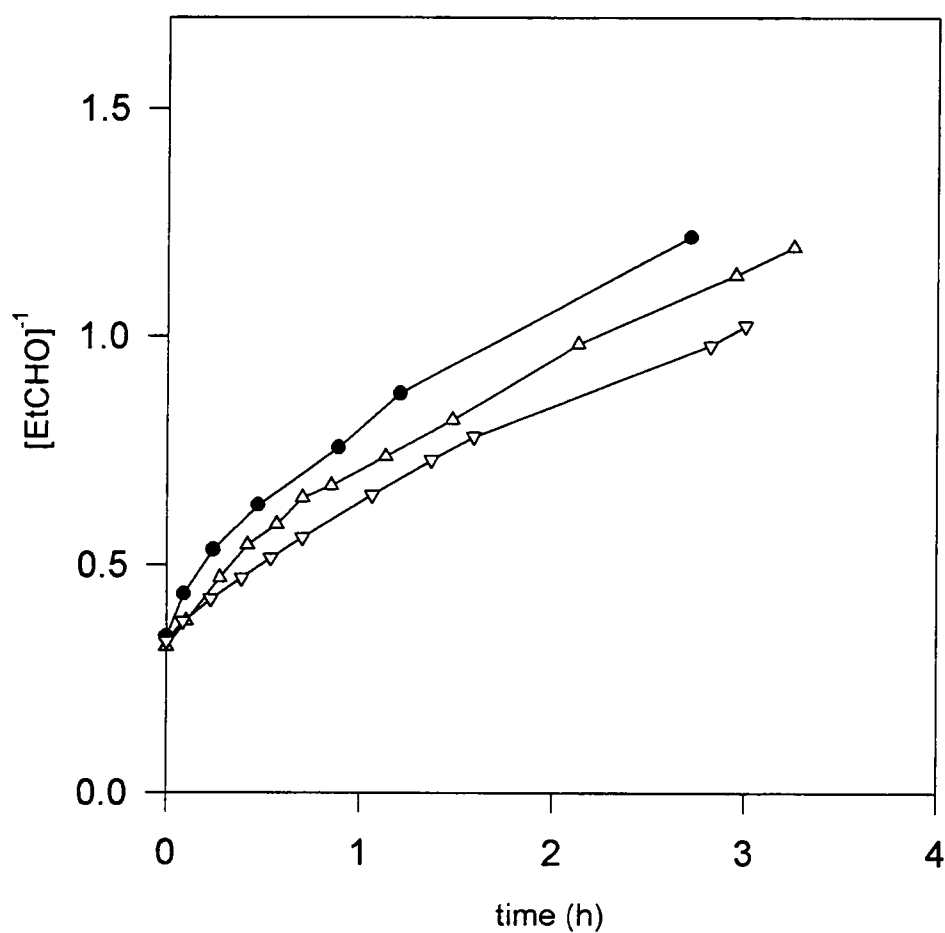


Figure 42. Second order rate equation in the aldol condensation of

propionaldehyde with polymer-supported acid catalysts

- △ 6.34 mmol 2-100H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- 6.43 mmol 2-33BE-67H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- ▽ 6.39 mmol 2-55ME-45H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.

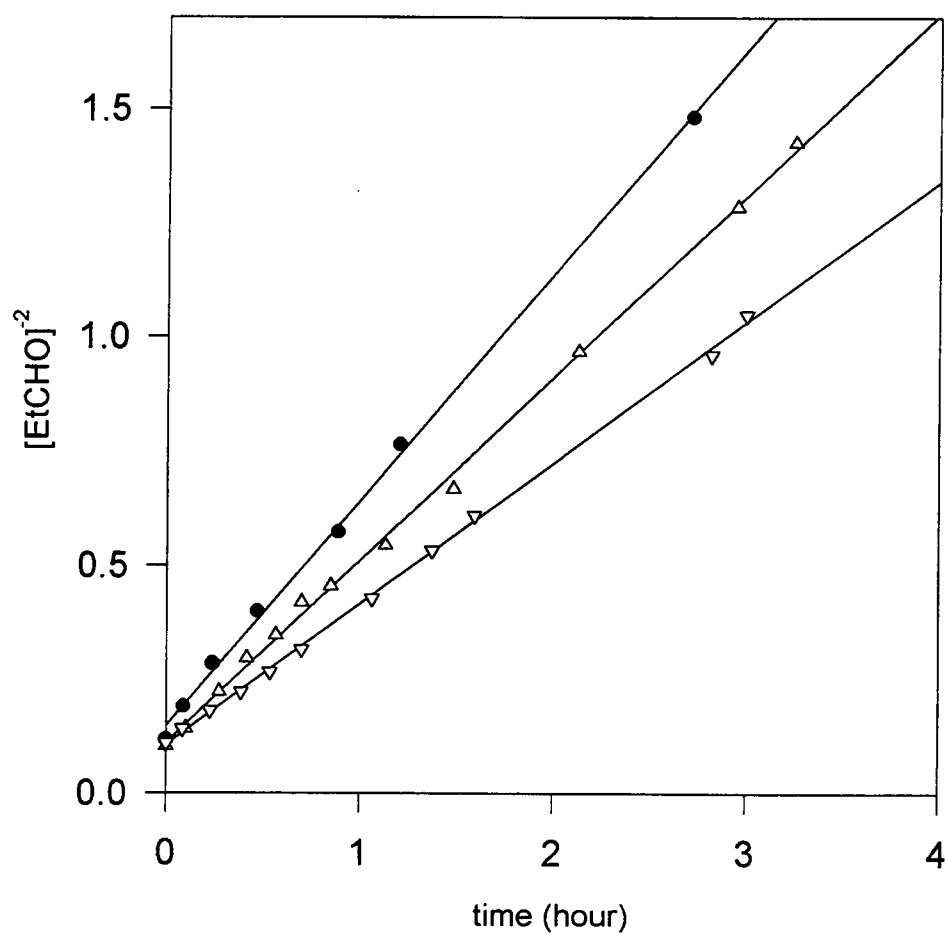


Figure 43. Third order rate equation in the aldol condensation of propionaldehyde with polymer-supported acid catalysts

- △ 6.34 mmol 2-100H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- 6.43 mmol 2-33BE-67H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- ▽ 6.39 mmol 2-55ME-45H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.

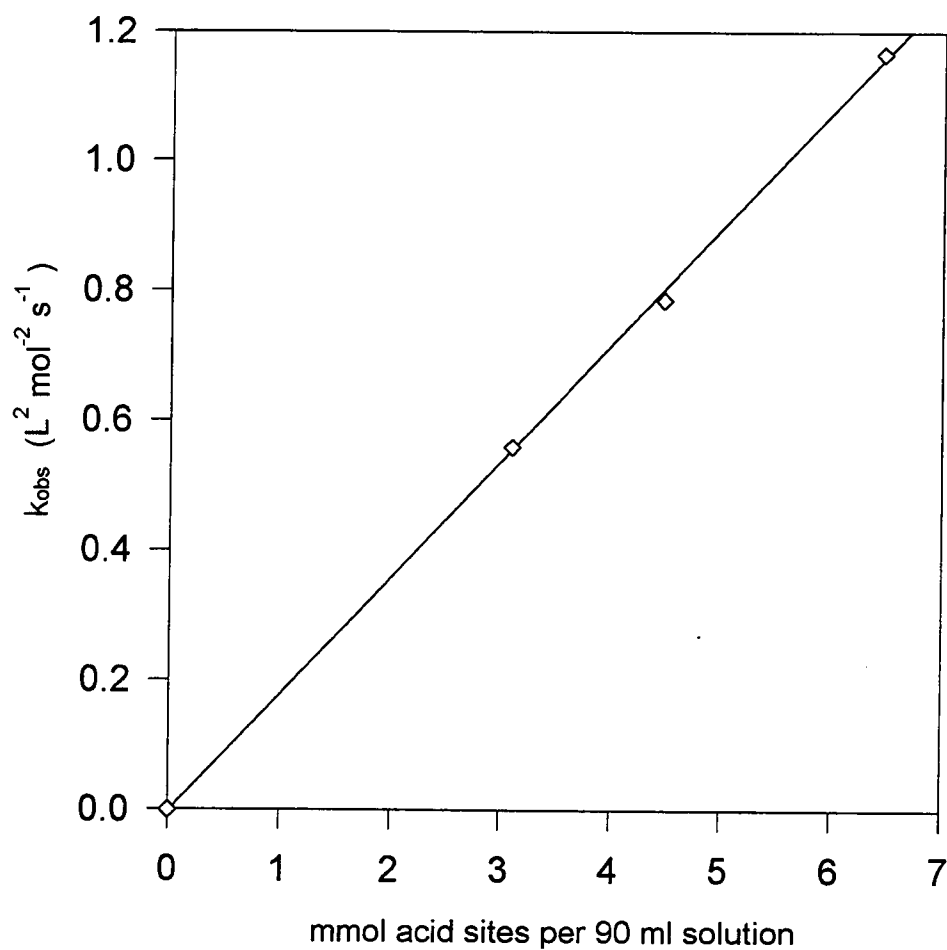


Figure 44. Dependence of k_{obs} on the acid sites per volume solution.

$[\text{EtCHO}]_0 = 2.0\text{M}$; 10-100H-50MR (0.25-0.42 mm diameter) as catalyst.

$$d[\text{EtCHO}]/dt = -k_{\text{obs}}[\text{EtCHO}]^3 = -k[\text{EtCHO}]^3[\text{mmolH}^+/\text{ml}] \quad (2)$$

The rate constant is independent of initial propionaldehyde concentration when sulfuric acid and benzenesulfonic acid are used as catalysts (Table 11). This is not the case with the polymeric acid catalysts where the rate constant is dependent on the initial reactant concentration (Figure 45).

Similar behavior has been observed in the hydrolysis of ethyl acetate with polymer-supported sulfonic acid catalysts.^{51,53} It has been postulated that this behavior is due to the fact that a change in solution concentration of a given substrate does not necessarily result in the same change in the polymer phase:⁵¹ a Freundlich adsorption isotherm of organic acids on ion exchange resins ($x/m = AC^{1/n}$, where x/m is the mmol adsorbed per g resin, C is the solution concentration, A and n are constants) yields values of n that are greater than unity,¹⁶⁰ indicating that the change in organic acid concentration is greater in the solution phase than in the polymer phase.

4. The effect of particle size

The particle size of the macroporous polymer, (10-100H-50MR), does not affect the reaction rate because its large pore volume allows the reactant molecules access to the catalytically active sites without diffusional

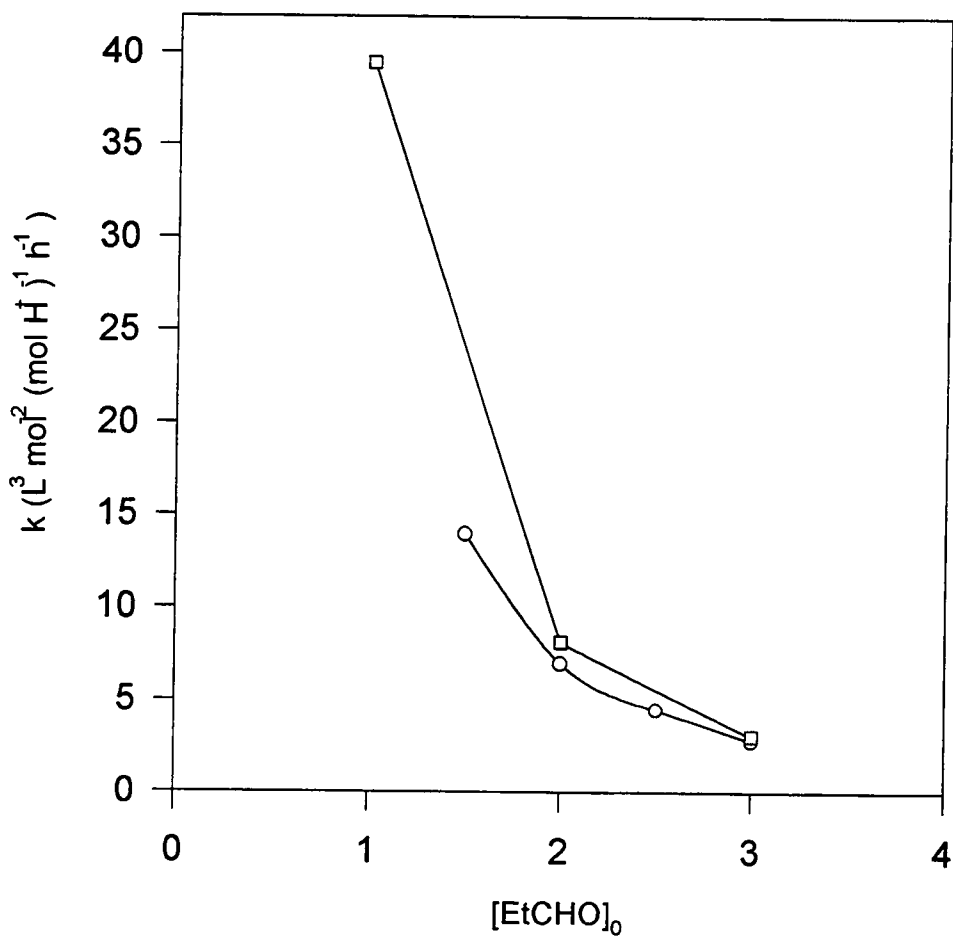


Figure 45. The rate constant is dependent on $[\text{EtCHO}]_0$ in the polymeric acid catalyzed aldol condensation reactions.

- 6.35 mmol 2-100H-G as catalyst.
- 6.35 mmol 10-100H-50MR as catalyst.

limitations (Figure 46). The particle size of the microporous resin, (2-100H-G), however, does affect the reaction rate (Figure 46). As the average particle size decreases from 0.5 mm to 0.06 mm, the rate constant increases 1.45 fold. This is caused by the increased surface area of smaller beads.

5. The effect of matrix rigidity and porosity

When the cross-linking level of gel resins is increased from 2% to 10% DVB, the rate constant decreases from 2.78 to 0.342 (Table 13, Runs 1 and 2). This indicates that the diffusional limitation is enhanced with a higher level of cross-linking.

The performance of 10-100H-G can be improved by increasing its porosity. 10-100H-50MR is approximately 50% macroporous with 500-1000Å macrochannels.¹⁶¹ The macroporous structure allows rapid access to the catalytic sites which leads to a highly efficient reaction (Table 13, Runs 2 and 4).

Porous matrices form when the levels of diluent and DVB exceed a critical value (see the Introduction of this dissertation).⁸ Because of its low diluent content (20% 4-methyl-2-pentanol) when initially prepared, the

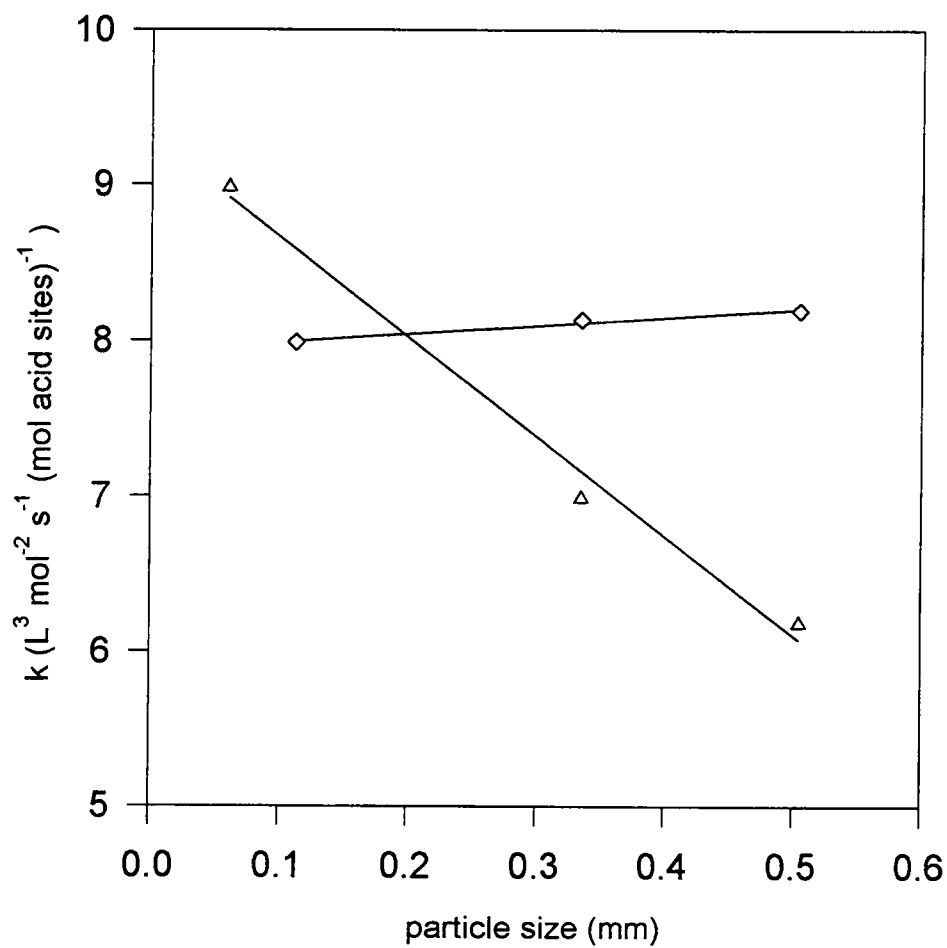


Figure 46. Dependence of rate constant on particle size

- ◇ Polymer 10-100H-50MR; $[\text{EtCHO}]_0 = 2.0\text{M}$.
- △ Polymer 2-100H-G; $[\text{EtCHO}]_0 = 2.0\text{M}$.

Table 13. Matrix rigidity effect and porosity effect in polymeric sulfonic acid catalyzed aldol condensation reactions

Run	[EtCHO] ₀	catalyst (mmol)	%conv.	%yield	k ¹
1	3.0	6.34 2-100H-G	93.0	71.0	2.78
2	3.0	6.22 10-100H-G	61.6	41.3	0.34
3	3.0	6.44 10-100H-20MR	81.0	54.6	0.44
4	3.0	6.37 10-100H-50MR	91.0	78.6	3.04

*The particle size of polymeric acid in all the runs is mesh 40-60 size (0.25-0.42 mm).

¹ Third order rate constant, L³mol⁻²(mol H⁺)⁻¹h⁻¹. The experimental error is within 5%.

macroporous structure of 10-100H-20MR develops to only a limited extent. 10-100H-20MR thus has a catalytic activity similar to 10-100H-G (Table 13, Runs 2 and 3).

6. The effect of microenvironment surrounding the sulfonic acid ligands

The microenvironment surrounding the acid sites is modified by incorporating styrene, butyl methacrylate (BMA) or methyl methacrylate (MMA) as the neighboring groups. The higher activity of 2-55S-45H-G than 2-100H-G, (Table 14, Runs 1 and 5), may be caused by the lower polarity around the catalytic sites in the former, which increases the reactivity of the carbocation in the rate determining step.

The hypothesis is supported by the results with 2-55BE-45H-G and 2-55ME-45H-G. Both polymers have the same degree of functionalization as 2-55S-45H-G but with the phenyl groups replaced by ester groups. The ester groups stabilize the carbocation better than phenyl groups; as a result, reactions catalyzed with 2-55BE-45H-G and 2-55ME-45H-G are slower than those catalyzed by 2-55S-45H-G (Table 14, Runs 5, 6, and 7). Furthermore, butyl methacrylate is less polar than methyl methacrylate and, therefore, 2-55BE-45H-G slightly outperforms 2-55ME-45H-G (Table 14, Runs 5 and 6).

Table 14. Microenvironmental effect in polymeric acid
catalyzed aldol condensation reactions

Run	[EtCHO] ₀	catalyst (mmol)	%conv.	%yield	k ¹
1	3.0	6.34 2-100H-G	93.0	71.0	2.78
5	3.0	6.34 2-55S-45H-G	95.9	64.9	4.11
6	3.0	6.55 2-55BE-45H-G	95.9	62.0	2.43
7	3.0	6.39 2-55ME-45H-G	95.2	64.6	2.14
8	3.0	6.43 2-33BE-67H-G	95.6	68.3	3.95
9	3.0	6.46 2-41ME-59H-G	93.5	63.9	2.68

*The particle size of polymeric acid in all the runs is mesh 40-60
size (0.25-0.42 mm).

¹ Third order rate constant, L³mol⁻²(mol H⁺)⁻¹h⁻¹. The experimental error is
within 5%.

As the number of ester groups increases, the reaction rate decreases (Table 14, Runs 7 and 9 for resins with MMA groups; Runs 6 and 8 for resins with BMA groups). This indicates a competition between ester groups and propionaldehyde molecules for the catalytic sites. Similar behavior has been observed in the polymeric sulfonic acid catalyzed dehydration of t-butyl alcohol, in which the reaction rate decreases when polar molecules, such as water, are introduced into the polymer matrix.^{66,162,163}

7. Comparison between homogeneous and heterogeneous acid catalysts

Since the order of the reactions with the homogeneous and polymeric acid catalysts are different, the two types of rate constants cannot be compared. However, the loss of propionaldehyde is significantly slower with the homogeneous catalysts than with the polymeric catalysts (Figures 47 and 48). This can be attributed to a much higher concentration of H^+ within the beads,^{42,164-166} where the reaction occurs, than in the solutions used in the homogeneous reactions.

The reactant conversion and product yield data in Tables 11, 13 and 14 show the presence of side reactions. It is known that acid catalysts can

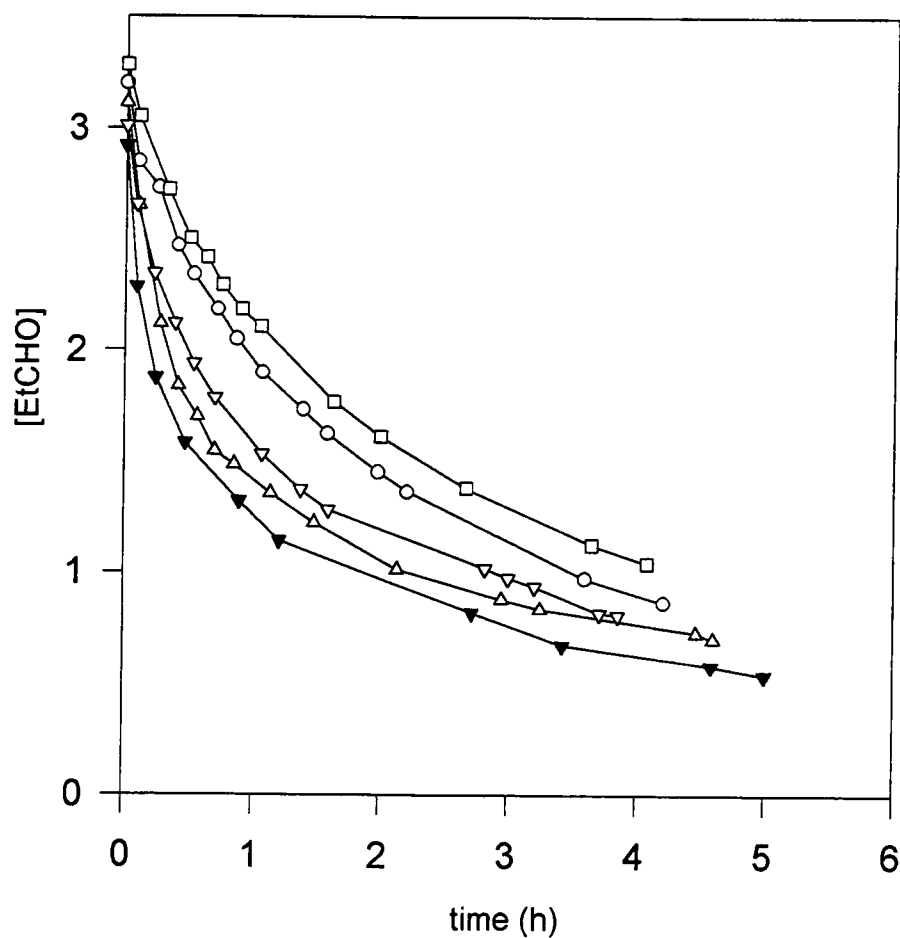


Figure 47. Comparison of propionaldehyde disappearing rate for 2-100H-G, 2-55ME-45H-G, 2-33BE-67H-G and homogeneous catalysts

- 6.35 mmol H₂SO₄ as catalyst, [EtCHO]₀=3.0M.
- 6.35 mmol PhSO₃H as catalyst, [EtCHO]₀=3.0M.
- △ 6.34 mmol 2-100H-G as catalyst, [EtCHO]₀=3.0M.
- ▽ 6.39 mmol 2-55ME-45H-G as catalyst, [EtCHO]₀=3.0M.
- ▼ 6.43 mmol 2-33BE-67H-G as catalyst, [EtCHO]₀=3.0M.

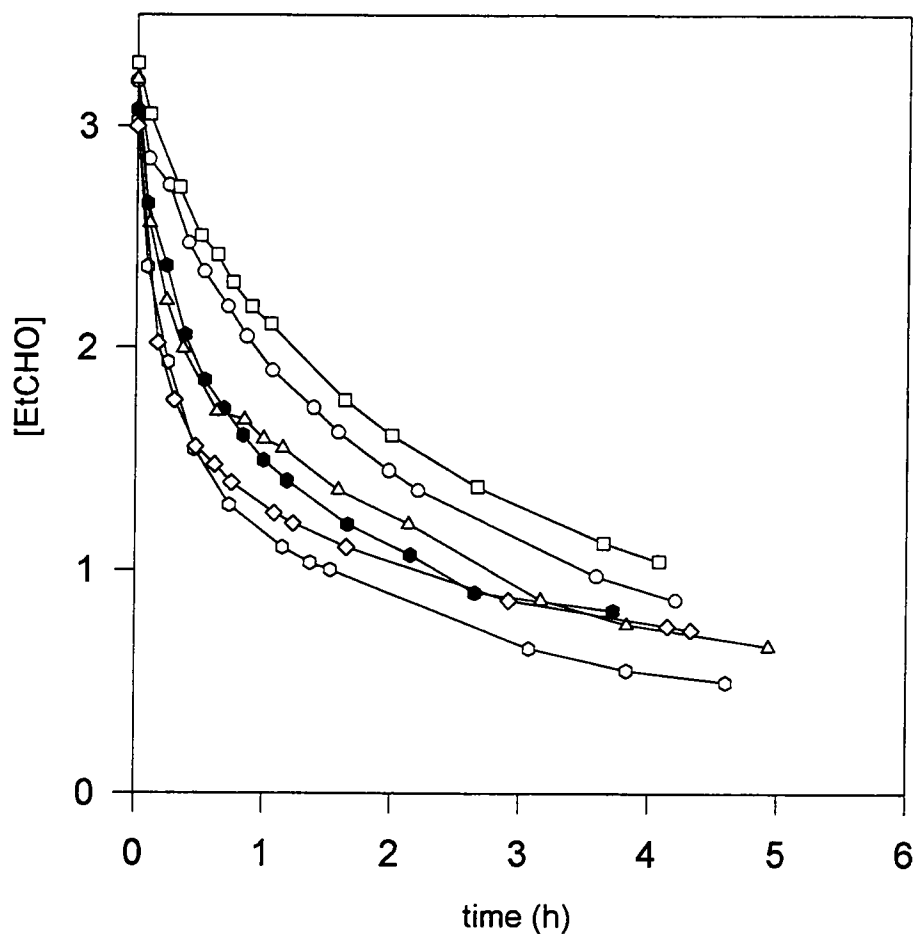


Figure 48. Comparison of propionaldehyde disappearing rate for 2-55S-45H-G, 2-55BE-45H-G, 2-41ME-59H-G, 10-100H-50MR and homogeneous catalysts

- 6.35 mmol H_2SO_4 as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- 6.35 mmol PhSO_3H as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- ◇ 6.34 mmol 2-55S-45H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- 6.55 mmol 2-55BE-45H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- △ 6.46 mmol 2-41ME-59H-G as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.
- ◇ 6.37 mmol 10-100H-50MR as catalyst, $[\text{EtCHO}]_0 = 3.0\text{M}$.

lead to by-products in aldehyde condensation reactions.¹⁵⁰ The polymer-supported acid catalysts, however, display an important advantage over their homogeneous counterparts: contact time with the polymeric catalysts can be minimized due to their greater catalytic activity. The different catalysts are compared under identical initial conditions after 1 hour contact (Table 15). Conversions are favorable for the polymers, except 10-100H-G and 10-100H-20MR, when compared to the homogeneous catalysts. The yield/conversion ratio quantifies the extent of side reactions: 10-100H-50MR, 2-100H-G, 2-33BE-67H-G, and 2-41ME-59H-G outperform sulfuric acid; all polymeric catalysts have better results than benzenesulfonic acid.

Conclusion

The polymeric catalysts outperform their small molecule analogues. Catalytic activity is influenced by matrix rigidity, porosity, particle size, and the microenvironment surrounding acid ligands. Catalyst activity of the sulfonic acid ligand is enhanced when non-polar groups, such as phenyl rings, are incorporated into the network.

Table 15. Comparison of reactant conversion and product yield for homogeneous and polymeric catalysts at a 1h reaction time*

Catalyst	% conv.	%yield	yield/conv.
H ₂ SO ₄	40.2	23.7	0.582
PhSO ₃ H	35.8	15.2	0.424
2-100H-G	50.6	32.7	0.656
2-55S-45H-G	63.5	36.9	0.581
2-55BE-45H-G	51.3	27.2	0.530
2-55ME-45H-G	49.2	25.0	0.508
2-33BE-67H-G	58.4	34.7	0.593
2-41ME-59H-G	50.5	30.9	0.612
10-100H-G	18.2	8.39	0.461
10-100H-50MR	56.5	36.5	0.646
10-100H-20MR	22.4	10.7	0.480

*All reactions are carried out under the same condition:

[EtCHO]₀ = 3.0M, T = 75°C, mmol catalyst = 6.50 .

CHAPTER IV

THE APPLICATION OF POLYMERIC SULFONIC ACID AS CATALYSTS IN THE PRINS REACTIONS

Introduction

The acid catalyzed condensation of aldehydes with olefins is called the Prins reaction. It is a valuable method of forming 1,3-diols, 1,3-dioxanes or unsaturated alcohols.^{167, 168} The reaction is extremely versatile due to the wide variety of commercially available olefins and aldehydes.¹⁶⁷

Recent studies include its use in the synthesis of natural prostaglandins,¹⁶⁸ ($\pm$)- β -isocomene,¹⁶⁹ polyether antibiotics,¹⁷⁰ and nucleosides.¹⁷¹

The current chapter focuses on an acid catalyzed reaction of styrene with 1,3,5-trioxane (Figure 49). The Prins reaction, using commercially available sulfonic acid resins, has been studied at equilibrium.¹⁷²⁻¹⁷⁵

Significant improvement of the product yield has been observed: The condensation of paraformaldehyde with 4-methoxystyrene in the presence of sulfuric acid gives a product yield of 61% after 6 h, whereas the reaction gives a product yield of 97% with Lewatit SP 120 after 0.5

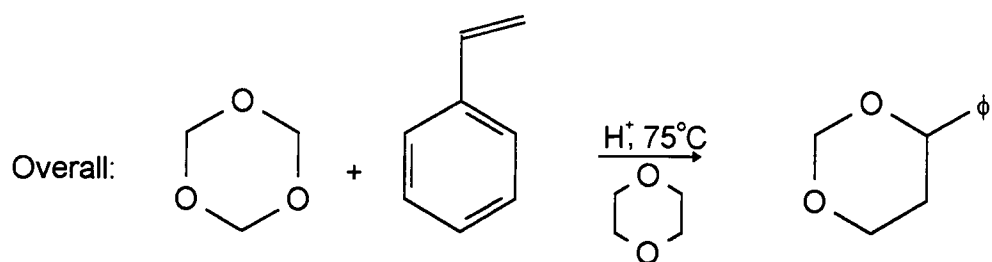
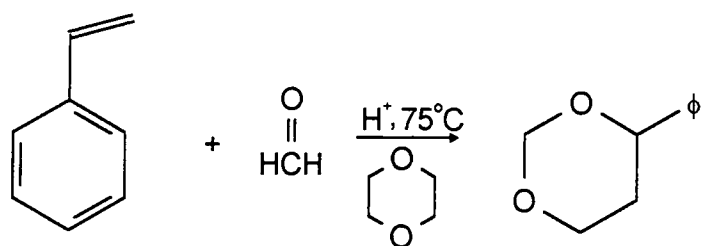
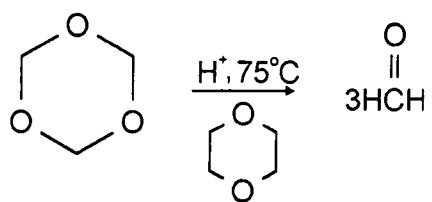


Figure 49. The Prins reaction of styrene with 1,3,5-trioxane

h.¹⁷³ Sulfonic acid polymers are now utilized where the synthesis parameters are controlled. The effect on the reaction rate is determined as the catalyst particle size, cross-linking level, porosity, and microenvironment surrounding the acid ligands are varied. The kinetics for the heterogeneous and homogeneous acid catalyzed reactions are studied and compared.

Prins reaction study

1. Experiment

The reactions were carried out in 1,4-dioxane at 75°C. Under acidic conditions, 1,3,5-trioxane decomposed to form formaldehyde, which then reacted with styrene to produce 4-phenyl-1,3-dioxane. The structure of the final product was confirmed with ¹H NMR. Microliter samples of reaction mixture were taken and analyzed by GC with dioxane used as the internal standard. Calibration curves (Figures 50 and 51) were used to calculate the concentration of styrene and 4-phenyl-1,3-dioxane. The detailed procedures are described in Chapter V.

2. Homogeneous catalyst kinetics

A linear correlation of [styrene] vs time indicates that the reaction is

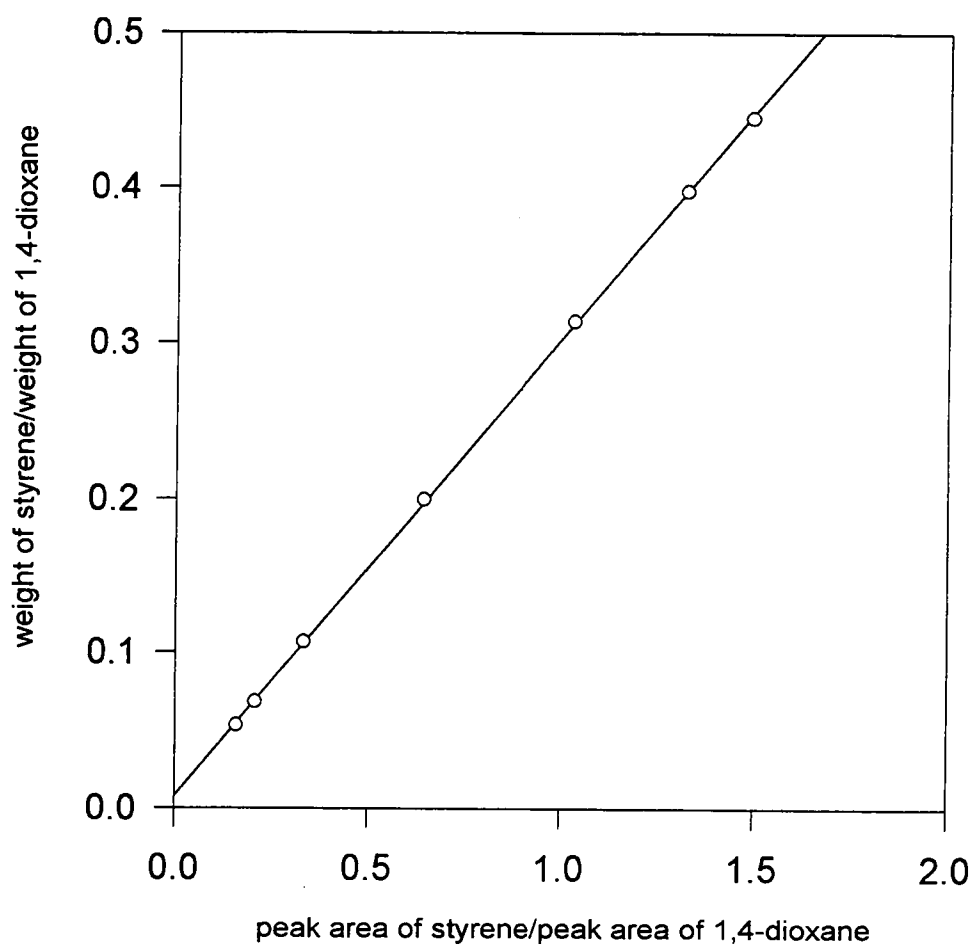


Figure 50. Calibration curve for the determination of the amount of styrene in a mixture. Internal standard: 1,4-dioxane

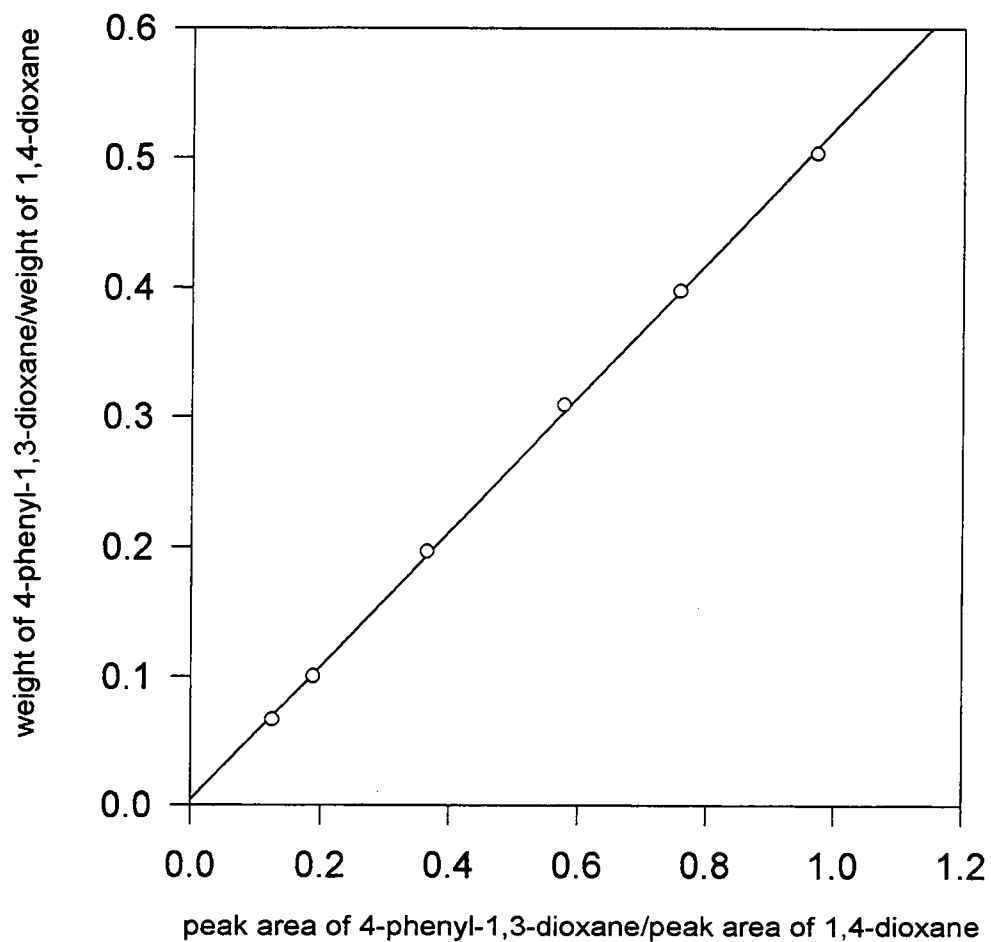


Figure 51. Calibration curve for the determination of the amount of

4-phenyl-1,3-dioxane in a mixture. Internal standard: 1,4-dioxane

zero order in styrene (Figure 52). The slope of the line is equal to the observed rate constant. A set of runs were made in which the acid concentration was varied and all other concentrations were held constant, the logarithm of the observed rate constant is plotted against $\log[H^+]$, the slope of the plot, 1.75, is taken as the order in the catalyst (Figure 53). By using the same method, the order in 1,3,5-trioxane is found to be 1.75 (Figure 54). Slopes and intercepts in all the plots are determined by linear least-squares analysis, with all correlation coefficients greater than 0.9920. The rate expression for the Prins reaction of styrene and 1,3,5-trioxane with homogeneous acid catalysts may be summarized by equation 1.

$$\text{Rate} = -k [\text{styrene}]^0 [1,3,5\text{-trioxane}]^{1.75} [H^+]^{1.75} \quad (1)$$

The rate constant values have been calculated based on equation 1 and listed in Table 16 and 17. The validity of equation 1 is demonstrated by the constant k values at different concentrations.

3. Heterogeneous catalyst kinetics

The structures of the polymer-supported sulfonic acid resins used in this study are illustrated in Figure 41. Their characterizations are summarized in Table 18. Each polymer is dried thoroughly before being used to catalyze reactions.

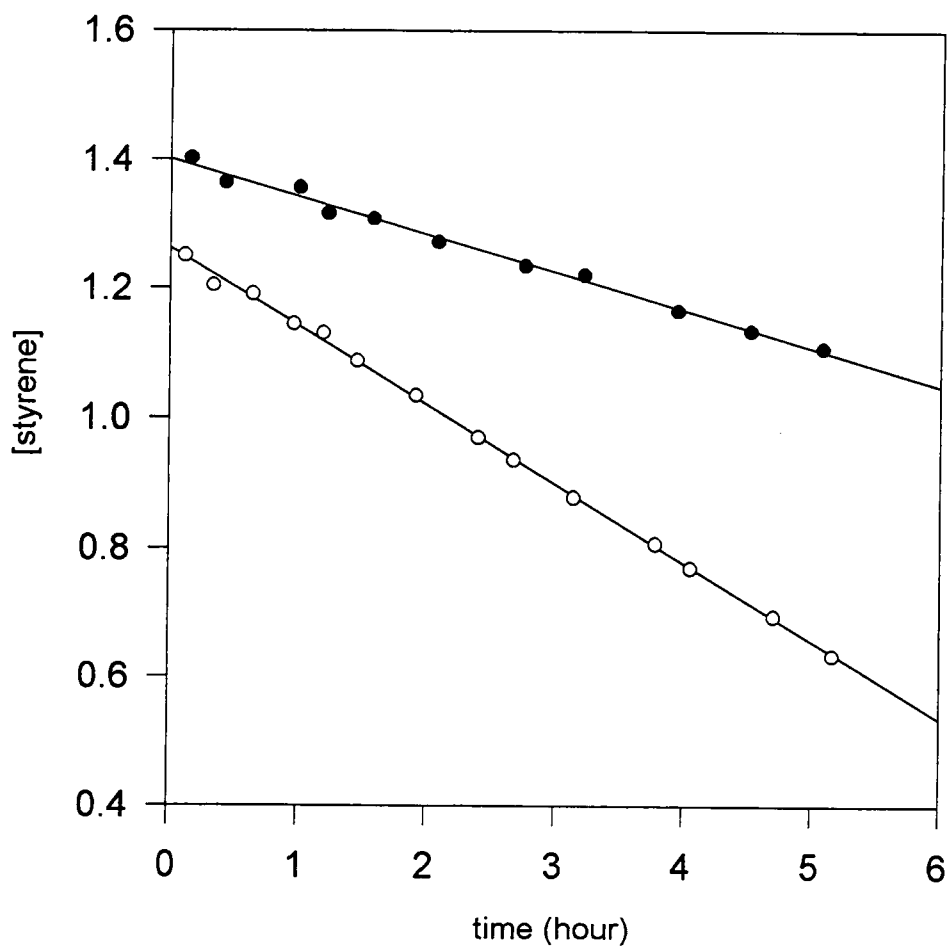


Figure 52. Zero order dependence on [styrene] in the Prins reaction catalyzed by homogeneous acid catalysts.

○ 12.52 mmol H₂SO₄ as catalyst, [styrene]₀=1.56M, [1,3,5-trioxane]₀=2.08M.

● 12.14 mmol PhSO₃H as catalyst, [styrene]₀=1.56M, [1,3,5-trioxane]₀=2.08M.

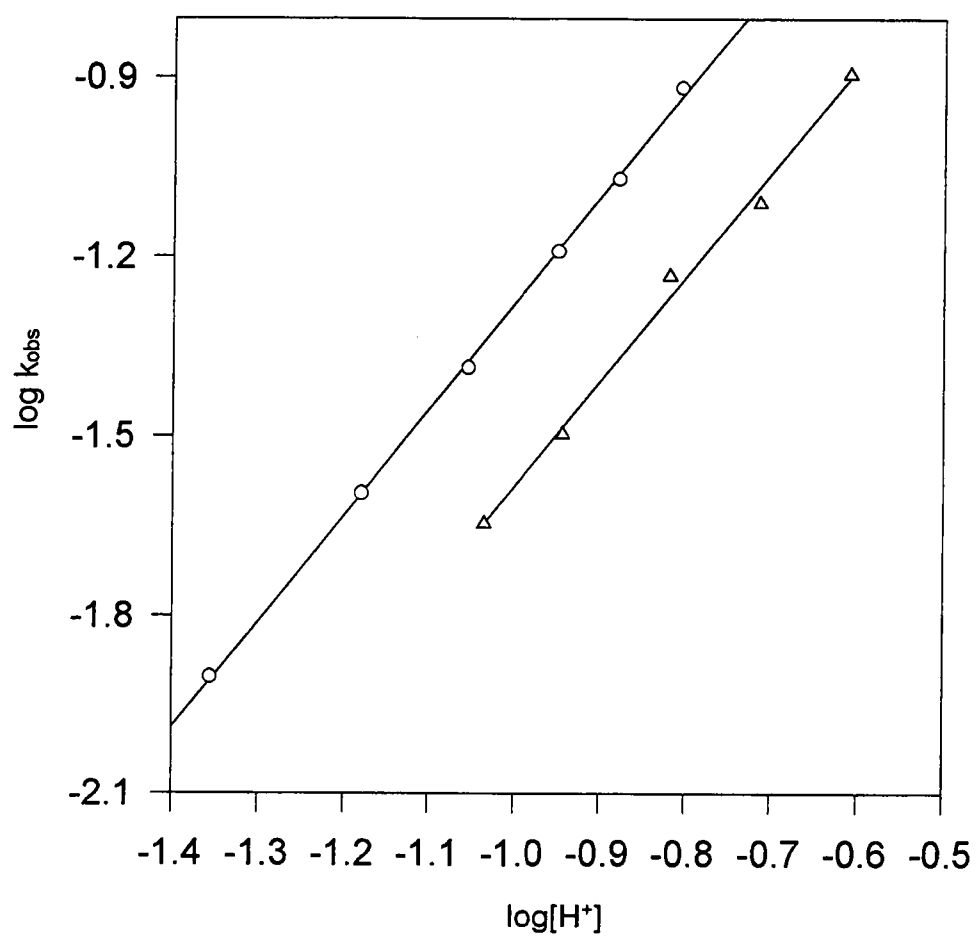


Figure 53. 1.75 order dependence on $[H^+]$ in homogeneous acid catalyzed Prins reaction.

- sulfuric acid as catalyst, $[1,3,5\text{-trioxane}]_0 = 2.08\text{M}$, $[\text{styrene}]_0 = 1.56\text{M}$.
- △ benzenesulfonic acid as catalyst, $[1,3,5\text{-trioxane}]_0 = 2.08\text{M}$, $[\text{styrene}]_0 = 1.56\text{M}$.

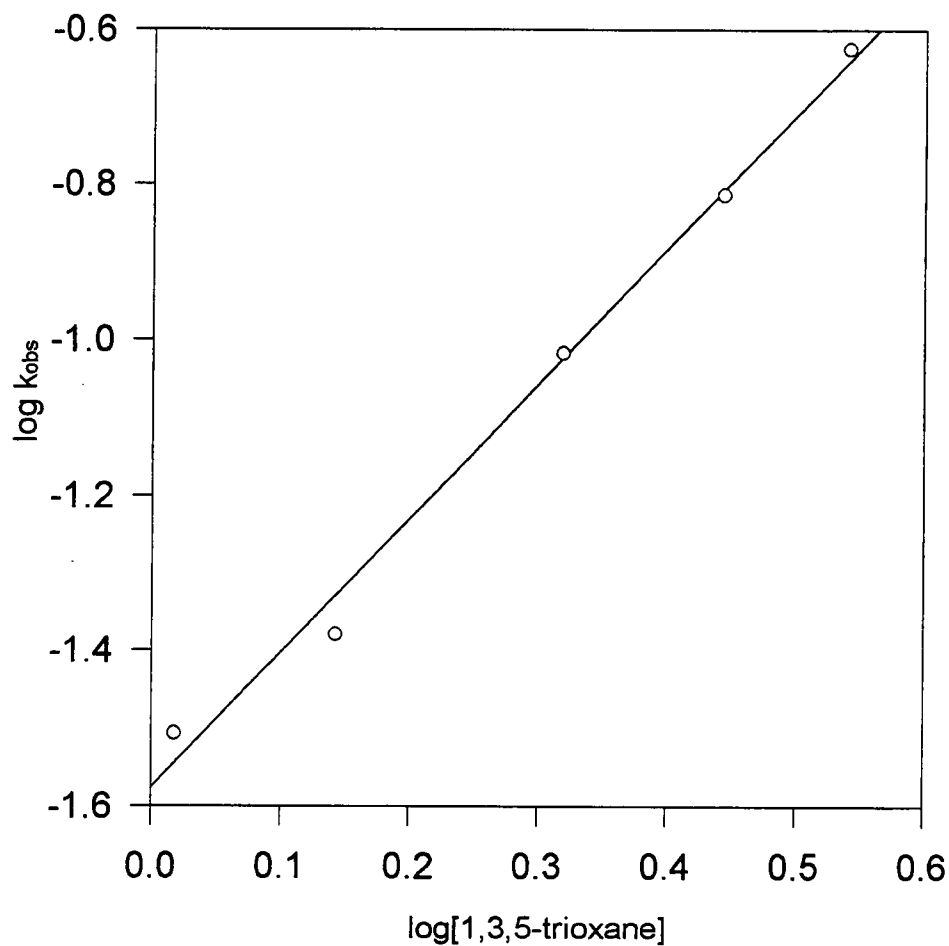


Figure 54. 1.75 order dependence on [1,3,5-trioxane] in homogeneous acid catalyzed Prins reaction.

Reaction condition: 10.65 mmol H_2SO_4 as catalyst
[styrene] $_0$ =1.56M

Table 16. Sulfuric acid catalyzed Prins reaction of
styrene¹ and 1,3,5-trioxane

[trioxane]	<u>mmol H⁺</u> 80 ml	%conv.	%yield	k*	equil. time (hour)
2.08	3.53	81.0	64.5	0.82	120
2.08	5.29	99.3	80.5	0.79	95
2.08	7.05	100	84.1	0.80	48
2.08	8.99	99.5	81.7	0.82	40
2.08	10.66	99.1	82.2	0.87	24
2.08	12.52	99.0	75.6	0.85	15
1.04	10.58	100	70.2	0.87	70
1.39	10.85	99.3	84.7	0.81	40
2.78	10.40	100	75.0	0.88	20
3.47	10.74	99.4	84.2	0.83	10

¹[styrene] = 1.56M in all the reactions.

* L^{2.5} mol^{-2.5} s⁻¹.

Table 17. Benzenesulfonic acid catalyzed Prins reaction of
styrene¹ and 1,3,5-trioxane

[trioxane]	<u>mmol H⁺</u> 80 ml	%conv.	%yield	k*	equil.time (hour)
2.08	7.37	100	49.8	0.41	120
2.08	9.11	95.0	46.0	0.40	65
2.08	12.14	96.8	50.5	0.44	50
2.08	15.46	99.4	56.1	0.38	30
2.08	19.62	98.9	54.8	0.41	24

¹[styrene] = 1.56M in all reactions.

*L^{2.5}mol^{-2.5}s⁻¹.

Table 18. Polymeric sulfonic acid catalysts used in the Prins reactions

Polymer	Acid capacity (mequiv/g)	
	experimental	theoretical
10-100H-50MR	4.93	4.80
2-100H-G	5.18	5.29
2-15S-85H-G	4.76	4.80
2-20S-80H-G	4.56	4.62
2-41S-69H-G	3.81	3.78
2-55S-45H-G	3.07	3.07
2-80S-20H-G	1.55	1.60
2-92S-8H-G	0.65	0.69
2-10ME-90H-G	4.83	4.97
2-20ME-80H-G	4.59	4.65
2-41ME-59H-G	3.88	3.85
2-55ME-45H-G	2.97	3.10
2-75ME-25H-G	2.21	1.94
2-8BE-92H-G	4.83	4.95
2-15BE-85H-G	4.85	4.64
2-20BE-80H-G	4.21	4.42
2-33BE-67H-G	4.09	3.82
2-58BE-42H-G	2.84	2.64
2-65BE-35H-G	1.90	2.13
2-75BE-25H-G	1.39	1.60
10-100H-G	5.01	4.80

2-55S-45H-G is used to study the heterogeneous catalyst kinetics. The linear correlation of [styrene] vs time indicates the reaction is zero order in styrene (Figure 55). The unity slope, obtained by plotting $\log k_{\text{obs}}$ vs $\log[1,3,5\text{-trioxane}]$ (Figure 56), indicates the reaction is first order in 1,3,5-trioxane. By using the same method, the first order dependence on mmol acid sites present per volume of solution is observed (Figure 57). The rate expression for the Prins reaction of styrene and 1,3,5-trioxane with polymeric acid catalysts may be summarized by equation 2.

$$\text{Rate} = -k [\text{styrene}]^0 [\text{trioxane}]^1 [\text{mmolH}^+/\text{ml}]^1 \quad (2)$$

Table 19 shows that the value of rate constant k , calculated based on the equation 2, stays constant at different concentrations. This proves that equation 2 is valid for polymeric acid catalyzed reactions.

The Prins reactions with polymeric acid catalysts appear to follow different kinetics than those with homogeneous acid catalysts. It is possible that in homogeneous acid catalyzed reactions, the rate of trioxane decomposition and the rate of subsequent styrene and formaldehyde condensation are comparable. This hypothesis can be rationalized as follows:

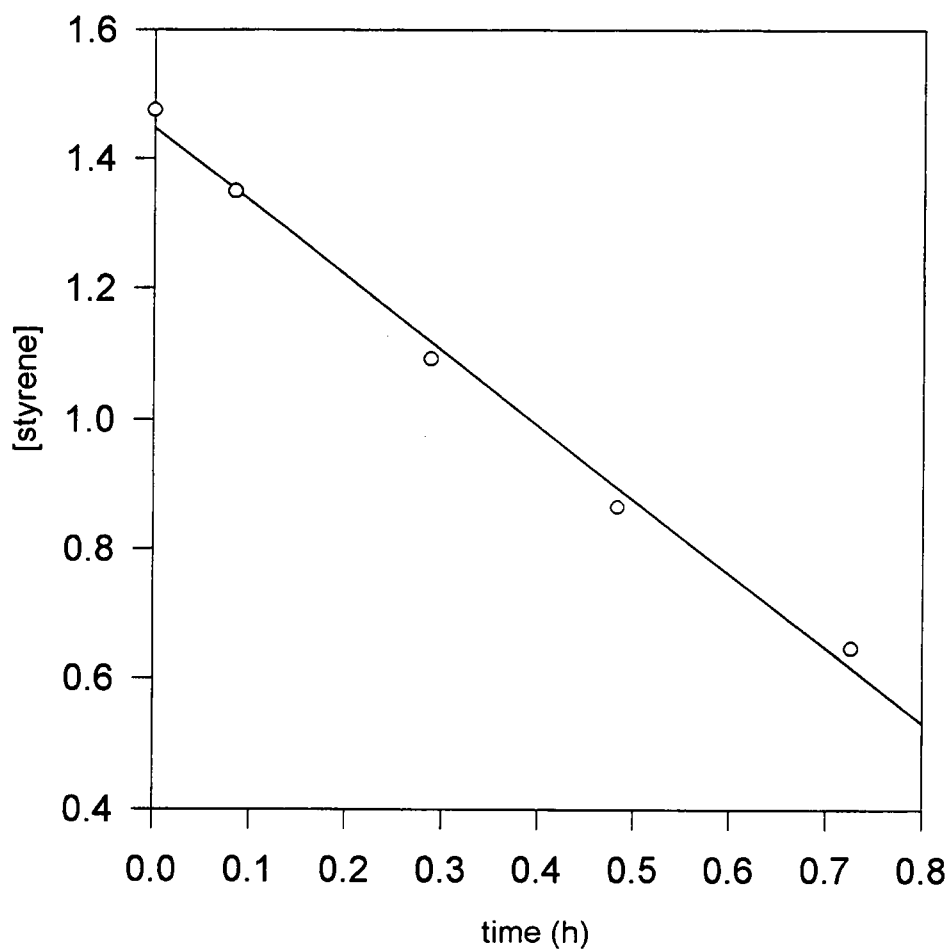


Figure 55. Zero order dependence on [styrene] in the Prins reaction catalyzed by 2-55S-45H-G.

Reaction condition: 3.57 mmol catalyst

[styrene]₀=1.56M

[1,3,5-trioxane]₀=1.39M

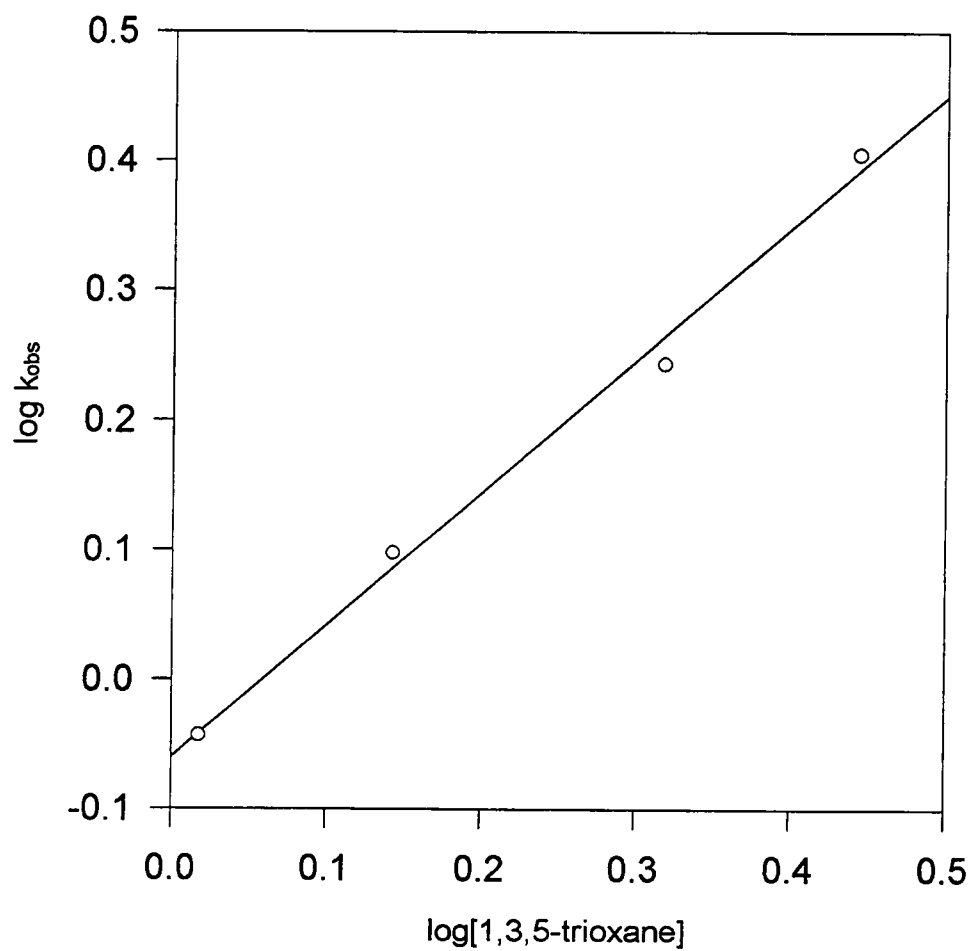


Figure 56. First order dependence on [1,3,5-trioxane] in the Prins reaction catalyzed by 2-55S-45H.

Reaction condition: 3.54 mmol catalyst
[styrene]₀ = 1.56M

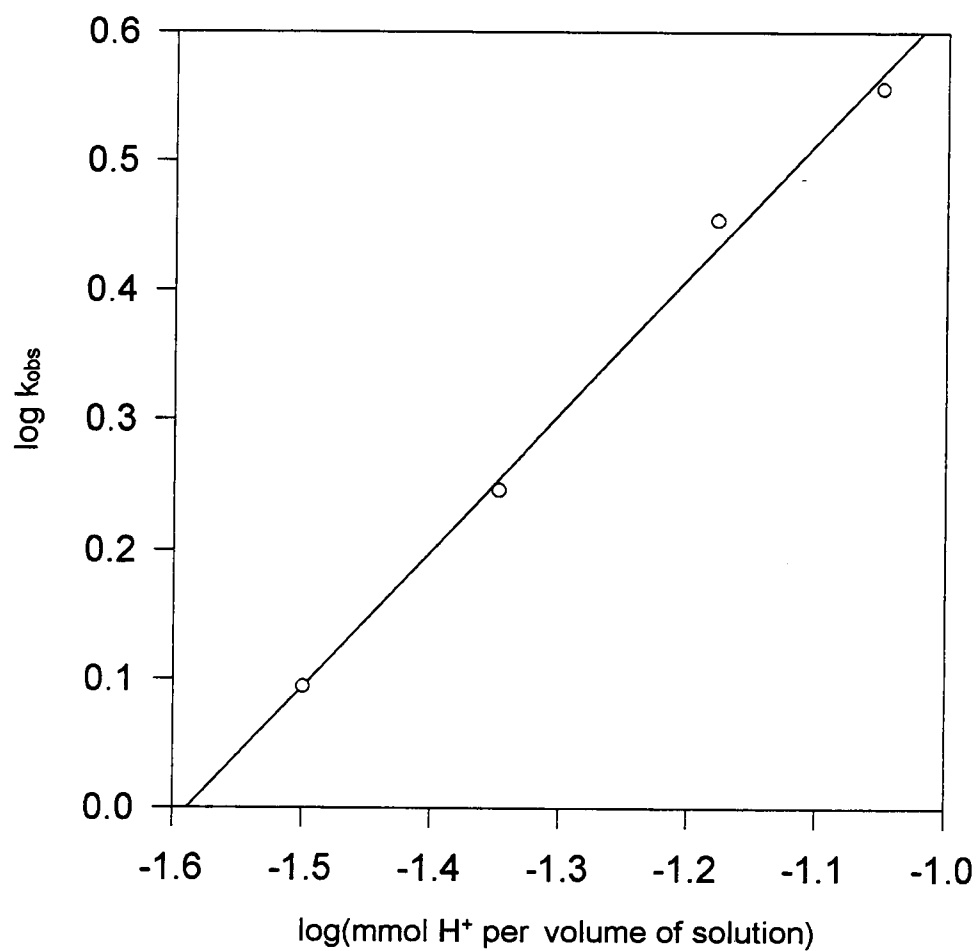


Figure 57. First order dependence on mmol H^+ present per volume of solution in the Prins reaction catalyzed by 2-55S-45H.

Reaction condition: $[1,3,5\text{-trioxane}]_0 = 2.08\text{M}$, $[\text{styrene}]_0 = 1.56\text{M}$.

Table 19. 2-55S-45H-G¹ catalyzed Prins reaction of
styrene² and 1,3,5-trioxane

[trioxane]	$\frac{\text{mmol H}^+}{80 \text{ ml}}$	%conv.	%yield	k*	equil. time (hour)
1.04	3.40	100	67.7	20.3	5.0
2.78	3.58	100	77.3	20.5	2.5
1.39	3.57	100	71.1	20.2	3.5
2.08	3.59	100	82.1	18.8	3.0
2.08	2.53	100	72.0	20.4	4.6
2.08	5.31	100	75.1	20.6	1.6
2.08	7.13	100	80.5	18.6	1.4

¹The resin particle size is 0.25-0.42 mm in all reactions.

²[styrene] = 1.56M in all reactions.

*L¹mol⁻¹s⁻¹.

1. The condensation of styrene and formaldehyde is subject to general acid catalysis^{176,179} and the reaction proceeds through the formation of an acid formaldehyde carbocation (Figure 58).^{167,179} If this is the slow step, there should be no trioxane left at the end of the reaction, however, GC detects the trioxane even after all the styrene is consumed.
2. The trioxane decomposition is known to have first order dependence on both 1,3,5-trioxane and the homogeneous acid catalyst.¹⁷⁷ If this is the rate determining step, the overall reaction should be second order, however, this is not the case.

In polymeric acid catalyzed reactions, as soon as the formaldehyde molecules are formed, they are protonated by the acid groups in close vicinity due to the high acid ligand concentration.^{164,165} The overall reaction kinetics is represented by the polymeric acid catalyzed trioxane decomposition, which is second order,¹⁷⁸ in agreement with equation 2.

4. The effect of particle size

Table 20 shows that the particle size of both the gel and the macroporous resins affect the reaction rate. The rate constant increases as the particle

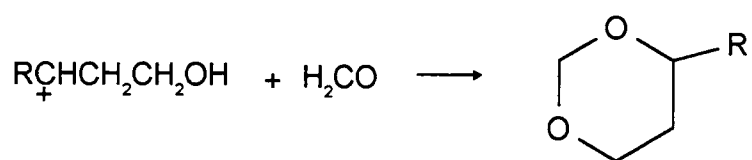
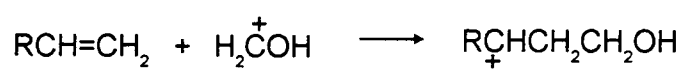
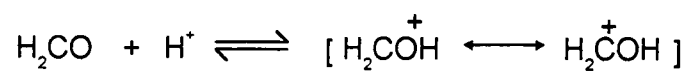


Figure 58. The mechanism of the Prins reaction

Table 20. The effect of particle size on the rate of the Prins reaction

catalyst	particle size (mm)	k (Lmol ⁻¹ h ⁻¹)
2-100H-G	0.25-0.42	23.1
2-100H-G	0.42-0.60	18.5
10-100H-50MR	0.25-0.42	196
10-100H-50MR	0.42-0.60	154

size decreases, indicating the diffusional limitation. Higher reaction rate can be achieved by using smaller size resins.

5. The effect of matrix rigidity and porosity

The reaction goes to completion in one hour with excellent yield when 2%DVB cross-linked gel, 2-100H-G, is used, however, there is almost no reaction with 10% DVB cross-linked gel, 10-100H-G (Table 21, Runs 2 and 21). This indicates that the diffusional limitation is enhanced with a higher level of cross-linking.

The performance of 10% DVB gel can be improved by increasing its porosity. 10-100H-50MR is approximately 50% macroporous with 500-1000Å macrochannels.¹⁶¹ The macroporous structure allows rapid access to the catalytic sites which leads to a highly efficient reaction (Table 21, Runs 1 and 21). The fact that the MR resin outperforms the lightly cross-linked gel resin (Table 21, Runs 1 and 2) demonstrates that the high cross-linking level of the MR resin is compensated by its high porosity and surface area.

6. The effect of microenvironment surrounding the sulfonic acid ligands

Table 21. Polymeric acid¹ (7.20 mmol) catalyzed Prins
reaction of styrene² and 1,3,5-trioxane³

Run	polymeric catalyst	%conv.	%yield	k*	equil. time (hour)
1	10-100H-50MR	100	82.8	196	0.1
2	2-100H-G	100	83.2	23.1	1.0
3	2-15S-85H-G	100	81.9	44.4	0.55
4	2-20S-80H-G	100	77.9	53.7	0.40
5	2-41S-69H-G	100	75.2	36.0	0.85
6	2-55S-45H-g	100	80.5	18.6	1.60
7	2-80S-20H-G	99.7	82.9	6.40	2.50
8	2-92S-8H-G	100	73.6	3.35	6.0
9	2-10ME-90H-G	100	75.2	43.8	0.60
10	2-20ME-80H-G	100	79.8	37.5	0.80
11	2-41ME-59H-G	100	73.6	18.2	1.6
12	2-55ME-45H-G	99.9	67.4	3.17	7.0
13	2-75ME-25H-G	99.9	67.4	0.30	85
14	2-8BE-92H-G	100	86.2	41.4	0.75
15	2-15BE-85H-G	100	84.8	42.0	0.75
16	2-20BE-80H-G	100	83.4	41.1	0.65
17	2-33BE-67H-G	100	74.1	34.6	0.90
18	2-58BE-42H-G	100	72.2	7.76	2.8
19	2-65BE-35H-G	100	60.3	0.72	36
20	2-75BE-25H-G	99.7	63.2	0.42	80
21	10-100H-G	15.0	4.00	~0	25

¹The resin particle size is 0.25-0.42 mm in all the reactions.

²[styrene] = 1.56M in all reactions.

³[trioxane] = 2.08M in all reactions.

*L¹mol⁻¹s⁻¹.

The microenvironment surrounding the acid sites is modified by incorporating styrene, butyl methacrylate or methyl methacrylate as the neighboring groups. The relationship between the activity and the copolymer composition has been investigated. Figure 59 shows that when the mole ratio of phenyl units to total (i.e., phenyl and sulfonic acid) sites increases from 0 to 0.2, the rate constant increases from 23.1 to 53.7. This means that over the range of this composition, the catalytic activity is inversely related to the acid ligand concentration. When the ratio is above 0.2, the catalytic activity decreases with decreasing ligand concentration. Similar behavior has been observed: in the acid catalyzed hydrolysis of benzophenone azine to hydrazine, the maximum reaction rate is reached as the mole ratio of styrene units to total sites increases from 0 to 0.8;¹⁴⁸ In the polymeric sulfoxide catalyzed reaction of 1-bromooctane with sodium iodide, the reaction rate increases almost 50-fold to reach the maximum when the mole ratio of styrene to total sites increases from 0 to 0.5.³⁶ This finding strongly suggests that not only the catalytic ligand concentration inside the beads, but also the hydrophobicity of the microenvironment around the active sites affect the reaction rate. A less ionic environment is more compatible with the reactant molecules and favors the product formation, however, it also has a lower acid ligand concentration, which tends to slow down the reaction.

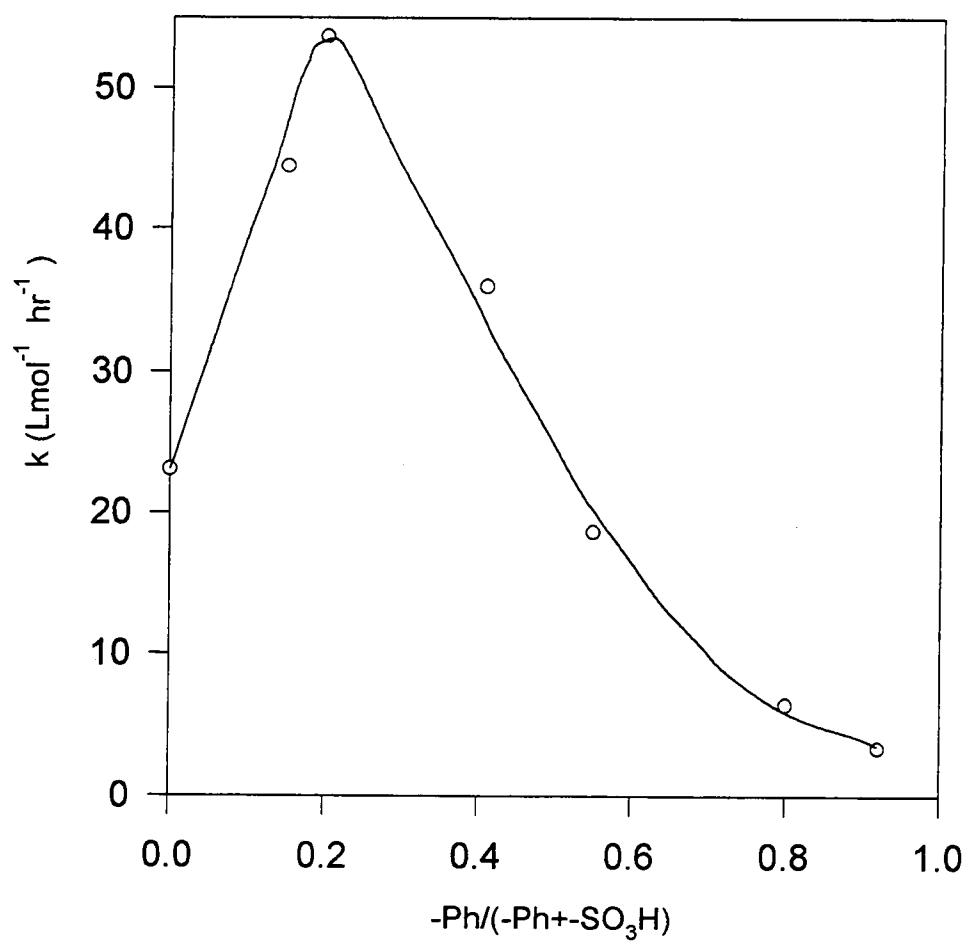


Figure 59. Microenvironmental effect on the reaction rate when phenyl units are the neighboring groups surrounding the acid ligands.

A maximum reaction rate is achieved when the mole ratio of neighboring units to total sites reaches a critical value. The critical values are 0.20, 0.10 and 0.15 for phenyl, MMA and BMA neighboring groups respectively (Figures 59, 60, and 61). The competition between ester groups and formaldehyde molecules for the catalytic sites lowers the critical values. This is more pronounced with neighboring MMA groups than BMA groups due to the fact that MMA groups are less bulky than BMA groups. The competition between ester groups and formaldehyde molecules for the catalytic sites also affects the reaction rate. Figure 62 shows that the maximum reaction rate decreases when phenyl groups are changed to ester groups. It also shows that when the ratio of neighboring units to total sites increases from 0.20 to 0.55, the rate constant decreases about 3 fold with styrene units, 5.5 fold with BMA units, and 12 fold with MMA units. The rate constants approach zero when the ratio is 0.75 with MMA or BMA units (Table 21, Runs 13 and 20), however, the rate constant is 3.35 even at a ratio of 0.92 with styrene units (Table 21, Run 8).

7. Comparison between homogeneous and heterogeneous acid catalysts

Since the order of the reactions with the homogeneous and polymeric acid catalysts is different, the two types of rate constants can not be

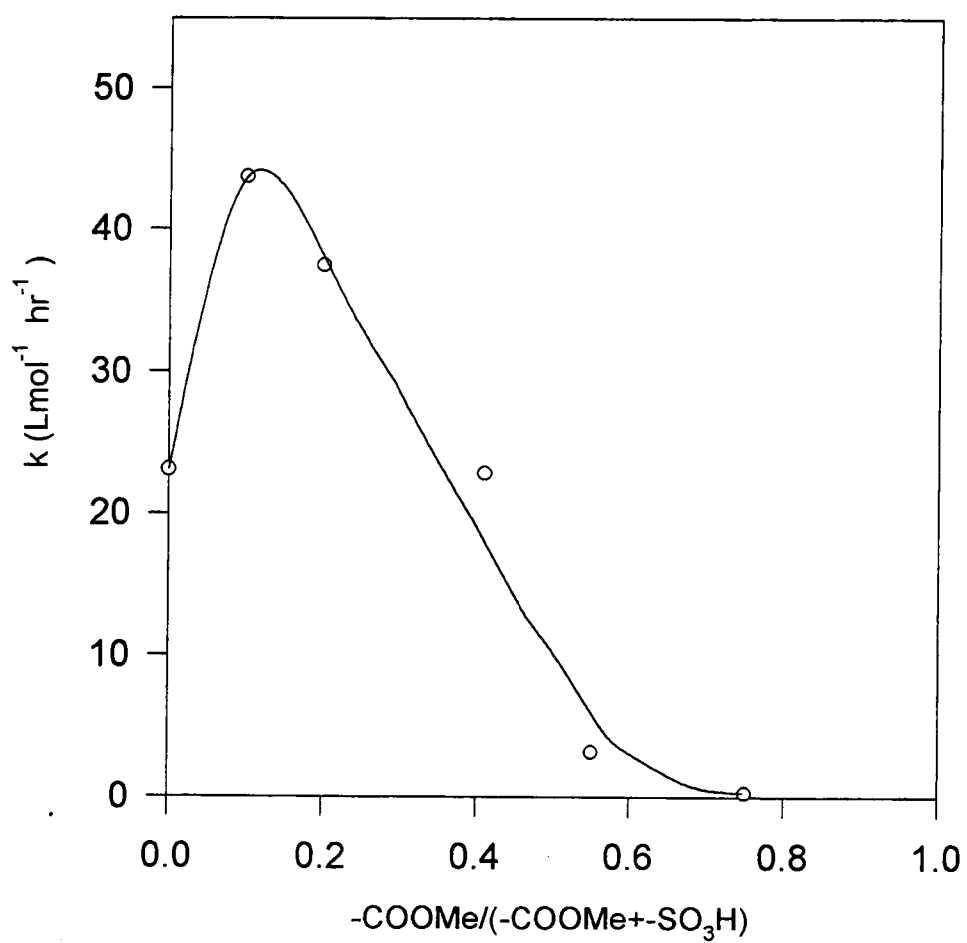


Figure 60. Microenvironmental effect on the reaction rate when MMA units are the neighboring groups surrounding the acid ligands.

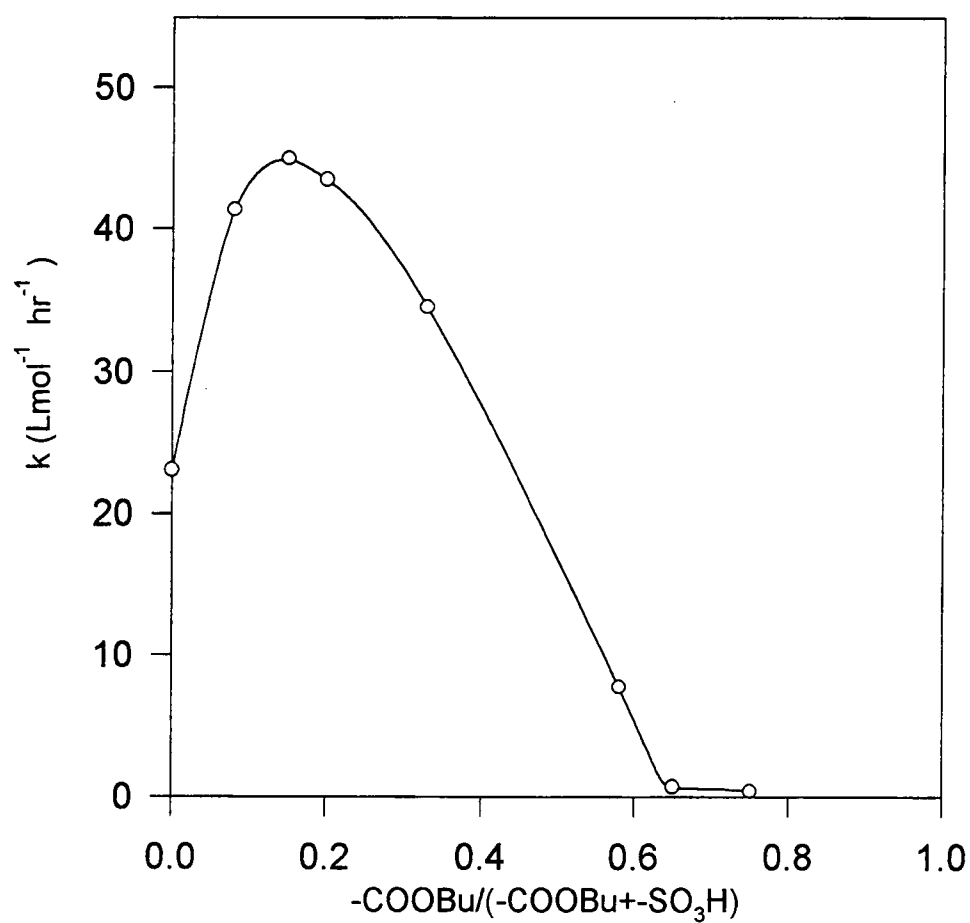


Figure 61. Microenvironmental effect on the reaction rate when BMA units are the neighboring groups surrounding the acid ligands.

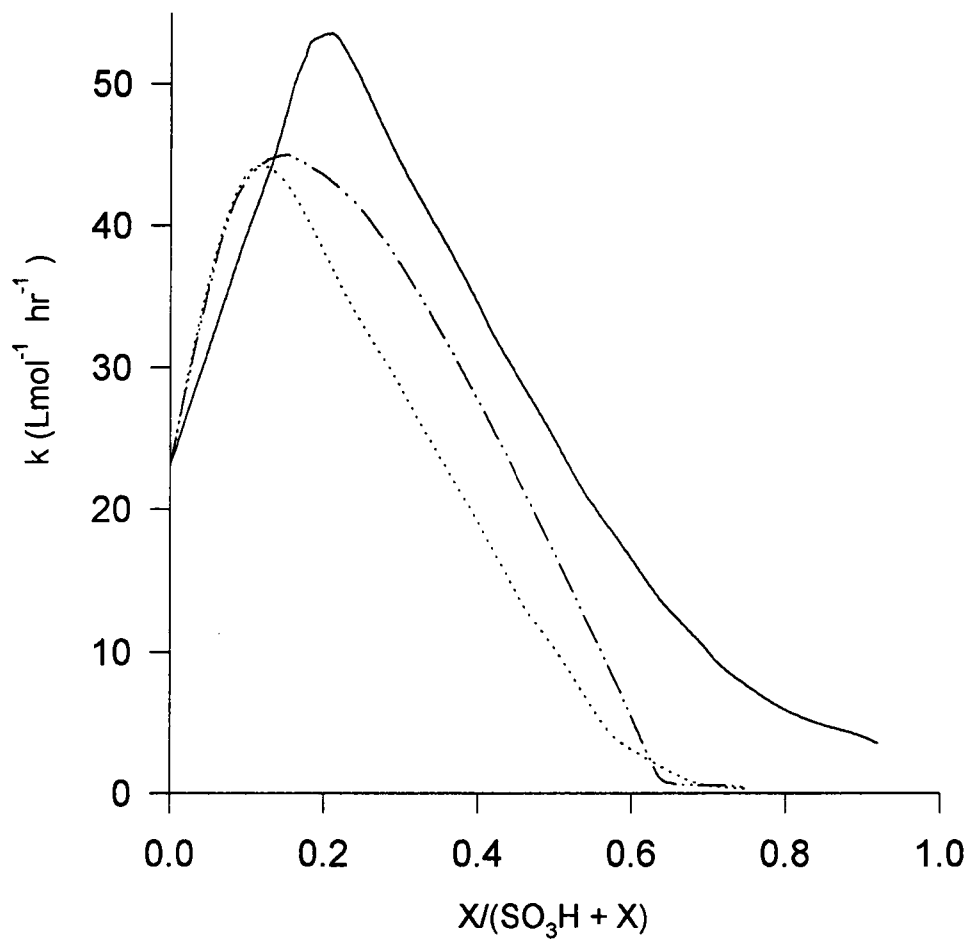


Figure 62. Microenvironmental effect on the reaction rate by varying the neighboring groups and copolymer compositions.

- Ph/(SO₃H + Ph)
- · - COOBu/(SO₃H + COOBu)
- COOCH₃/(SO₃H + COOCH₃)

compared. However, the reaction times with polymeric catalysts are significantly shorter than those with homogeneous catalysts (Tables 16, 17, and 21). For example, under identical reaction conditions and reaching 100% styrene conversion, the reaction times are 120 hour, 48 hour, and 0.1 hour with benzenesulfonic acid, sulfuric acid, and 10-100H-50MR respectively. The superior performance of polymeric catalysts is due to a much higher acid ligand concentration. Most polymeric catalysts also show better product selectivity than homogeneous catalysts (Tables 16, 17 and 21).

Conclusion

Polymeric sulfonic acid catalysts significantly outperform their small molecule analogues in the Prins reaction of styrene with 1,3,5-trioxane. Their catalytic activities are influenced by the matrix rigidity, the porosity, the particle size, and the microenvironment surrounding the acid ligands. The macroporous resin, 10-100H-50MR, catalyzes the reaction to completion 1200 times faster than its small molecule analogue, benzenesulfonic acid.

CHAPTER V

EXPERIMENTAL

Copolymer Synthesis

A suspension polymerization technique was employed to prepare the divinylbenzene cross-linked polystyrene and poly(vinylbenzyl chloride) (VBC) beads. The polymerization apparatus consisted of a three-neck round-bottom flask equipped with a condenser, a thermometer, and an overhead stirrer. Oxygen was excluded from the system by a nitrogen purge which was continued throughout the polymerization. The aqueous phase was composed of 0.96 g gelatin dissolved in 100.1 g H₂O at 50°C, 11.90 g poly(diallyldimethylammonium chloride) (Calgon Corp.), 6.33 g boric acid and 216.5 g H₂O. The pH of the aqueous phase is then adjusted to 10 by the addition of 50% NaOH. After adding the aqueous phase to the reaction flask the stir motor was adjusted to the appropriate speed to obtain the desired bead size. For the preparation of a 2% cross-linked gel polymer, the organic phase consisted of 286.7 g styrene (Aldrich Chemical Company) or vinylbenzyl chloride (Dow Chemical Company), 10.83 g divinylbenzene (Dow; contained 44.6% ethylstyrene

as impurity) and 3.00 g benzoyl peroxide initiator. The aqueous and organic phases were mixed for 2 min and then allowed to separate for 1 min (repeated three times). The polymerization mixture was then heated to 80°C over a 2 h period and held at this temperature for 10 h. To ensure complete polymerization, the reaction mixture was heated for an additional 2 h at 100°C. After cooling to room temperature, the copolymer beads were washed with pH 4 water, (adjusted with HCl), and then with distilled water. The beads were dried at room temperature and extracted with toluene for 17 h to remove unreacted monomers. The beads were then placed in a drying dish and allowed to air dry.

To obtain macroporous (MR) polymer, half of the monomer mixture was replaced with a non-solvent. For example, a 10% cross-linked MR polymer was prepared using the aqueous phase described above and an organic phase composed of 121.42 g styrene or vinylbenzyl chloride, 27.08 g DVB, 150 g 4-methyl-2-pentanol (Aldrich) and 1.5 g benzoyl peroxide. The 2 h hold at 100°C employed in the gel synthesis was replaced for the MR beads by a 6-h steam distillation to remove the alcohol.

Washing of Cross-Linked Polystyrene and Poly(vinyl benzylchloride) Resins

The resins were washed to remove surface impurities⁹⁴. The following solutions were used at 70°C unless otherwise noted with, in each case, a contact time of 30 min with the resin: 1 N NaOH at 70°C for polystyrene and 25°C for VBC containing resins, 1 N HCl, 2 N NaOH-dioxane (1:2) at 70°C for polystyrene and 25°C for VBC-containing resins, 2 N HCl-dioxane (1:2), H₂O, dimethylformamide. The resins were then washed at room temperature with the following: 2 N HCl in methanol, H₂O, methanol, methanol-dichloromethane (1:3), methanol-dichloromethane (1:10). The resins were then dried at 60°C under vacuum for 24 h.

Bromination of polystyrene beads⁹⁴

Cross-linked polystyrene beads (24.85 g) were swelled in 250 ml CCl₄ at room temperature for 1 h and anhydrous FeCl₃ (4.1 g) was added. The mixture was stirred in the dark while a solution of 6.5 ml Br₂ in 25 ml CCl₄ was slowly added. The reaction mixture was then stirred overnight at room temperature. The resulting mixture, which still contained free bromine, was filtered and the resin was washed repeatedly with acetone until all the bromine coloration had disappeared. Further washings were

made with dioxane-water (2:1), and methyl ethyl ketone. The resin was then dried at 65°C under vacuum for 18 h.

Phosphine Resin Synthesis

A solution of 52.5 g chlorodiphenylphosphine in 235 ml tetrahydrofuran (THF) was slowly added through an addition funnel to a stirred mixture of 5.1 g lithium metal in 100 ml THF under argon. Stirring was continued for 24 h. The resulting lithium diphenylphosphine was contacted with poly(vinylbenzyl chloride) beads (20 g, preswollen in 200 ml THF for 1 h at room temperature). Reaction continued at room temperature for 24 h under argon. The beads were recovered by filtration and washed with THF, diethyl ether, 2:1 (v/v) THF:water, water, THF, toluene and methanol, each with 30 min stir times, followed by drying under vacuum at 60°C for 44 h.

Sulfonic Acid Resin Synthesis (using chlorosulfonic acid)

1. Synthesis of fully functionalized resin: Cross-linked polystyrene beads (50 g) were placed in a 500 ml round-bottom flask equipped with an overhead stirrer. The beads were swelled in 400 ml ethylene dichloride (EDC) at room temperature for 1 h, then cooled to 0°C.

Chlorosulfonic acid (113.51 g) in 60 ml EDC was added dropwise through an addition funnel. The mixture was stirred for 24 h, during which time cooling was removed and the temperature increased to 25°C. The beads were washed twice with EDC, dioxane, and a 4:1 (v/v) dioxane/water solution, each with 15 min stir times, and with water until neutral. They were then placed in a glass frit funnel and eluted with 1 L H₂O, 1N NaOH, H₂O, 1N HCl, and H₂O, each with a 1 h elution time. A final elution with 500 ml ethanol, acetone and isooctane, then drying at 70°C under vacuum for 48 h, yielded the polymeric catalyst in its final form.

2. Synthesis of partially functionalized resin: Partial sulfonation can be achieved by using a stoichiometric amount of chlorosulfonic acid. For example: a 2% DVB cross-linked resin with 45% (mol%) functionality can be synthesized by reacting 100 g of 2% DVB cross-linked polystyrene (0.917 mol phenyl rings) with 0.413 mol of chlorosulfonic acid. The synthesis procedure was the same as described above for the fully functionalized resin.

Sulfonic Acid Resin Synthesis (using 96% sulfuric acid)

Cross-linked polystyrene beads (40 g) were placed in a 500 ml round-bottom flask equipped with a condenser, a thermometer, and an overhead stirrer. The beads were swelled in 300 ml ethylene dichloride at room temperature for 1 h and 360 g sulfuric acid was added. The reaction mixture was heated to reflux (85°C) over a period of 1 h and held at reflux for 3 h. After cooling to room temperature, the reaction was quenched by either of the two following methods: in method 1 the beads were washed with H₂O until neutral; in method 2 the beads were washed in sequence with aqueous 10M H₂SO₄, 8M H₂SO₄, 6M H₂SO₄, 4M H₂SO₄, and 2M H₂SO₄, each with 15 min stir times, and then with water until neutral. They were then placed in a glass frit funnel and eluted with 1 L H₂O, 1N NaOH, H₂O, 1N HCl, and H₂O, each with a 1 h elution time.

Amine Resin Synthesis

Cross-linked poly(vinyl benzylchloride) MR beads (40 g) were placed in a 1 L round-bottom flask equipped with a thermometer, condenser, and overhead stirrer. The beads were swelled in 750 ml 25 wt% aqueous dimethylamine (Aldrich) at room temperature for 24 h. The mixture was heated to reflux over a period of 1 h and held at reflux for 17 h. After

cooling to room temperature, the beads were washed with water until neutral. They were then placed in a glass frit funnel and eluted with 1 L H₂O, 1N NaOH, H₂O, 1N HCl, H₂O, each with a 1 h elution time.

Determination of % Solids

The resin was aspirated for 5 min at 720 mm Hg. A weighed sample of the suction-dried resin (1-1.5 g) was dried at 110°C for 16 h to remove all water from the resin pores. After drying was complete, the sample was reweighed and the % solids was calculated as follows:

$$\% \text{ solids} = (\text{wt. of oven-dried resin} / \text{wt. of suction-dried resin}) \times 100\%$$

Determination of Resin Acid Capacity

A weighed sample of suction-dried resin (approximately 0.5-1.0 g dry weight) was placed in a 250 ml ground glass Erlenmeyer flask and stirred for 17 h with 200 ml standard 0.1 N NaOH in 5 wt% NaCl. A 50 ml aliquot was then removed and titrated with 0.1 N H₂SO₄ using a phenolphthalein indicator. The acid capacity (in units of mequiv/g) was calculated as follows:

$$\text{acid capacity} = [(\text{ml NaOH})(\text{N NaOH}) - 4(\text{ml H}_2\text{SO}_4)(\text{N H}_2\text{SO}_4)] / \text{g dry resin}$$

The NaOH solution was standardized against primary standard potassium hydrogen phthalate and was then used to determine the concentration of the sulfuric acid solution.

The acid capacity of samples with low aqueous reagent accessibility was determined using a standard solution of KOH in 81% aqueous 1,4-dioxane. The titration was performed exactly as described above for aqueous NaOH.

Phosphorus Elemental Analysis Method I

An oven-dried resin (~ 20 mg) was placed in a 125 ml Erlenmeyer flask with 10 ml 70-72% HClO_4 and 5 ml concentrated HNO_3 . The mixture was heated until the beads were digested and the solution became clear. After cooling to room temperature, the solution was diluted to 100 ml with water. To a 5 ml aliquot of this solution was added (in the following order) 3.5 ml 72% HClO_4 , 4.5 ml freshly prepared amidol reagent (1 g recrystallized 2,4-diaminophenol dihydrochloride (Aldrich), 10 g Na_2SO_3 , 2.7 g concentrated H_2SO_4 and 90 g H_2O) and 3.5 ml ammonium molybdate solution (4.4 g in 50 ml H_2O). After diluting to 50 ml with water, the solution was allowed to develop for 30 min. A blank solution

containing all reagents except the phosphorus solution was prepared and used to zero the spectrometer. The absorbance of the solution was measured at 700 nm on a Bausch and Lomb Spectronic 21. The amount of phosphorus present in the sample was determined from a Beer's Law plot (slope = 131.70 ml/mg) using a series of K_2HPO_4 standards. The phosphorus capacity was calculated (in units of mequiv/g) from the following equation:

$$\text{Phosphorus capacity} = \frac{(\text{absorbance})(1000 \text{ ml})}{(\text{g resin})(30.974 \text{ mg/mequiv})(131.7 \text{ ml/mg})}$$

Phosphorus Elemental Analysis Method II

An Oven-dried resin (~ 20 mg) was placed in a 125 ml Erlenmeyer flask with 400 μL 0.5 M copper sulfate and 10 ml concentrated sulfuric acid. The mixture was heated for 2 h. After cooling to room temperature, aqueous potassium persulfate solution (2g potassium persulfate in 75 ml H_2O) was added. The mixture was then heated for 2 hours. The resulting clear pale blue solution was cooled to room temperature and 50 wt% NaOH was added until it turned slightly cloudy. A dilute sulfuric acid solution (2 wt %) was then added until the solution turned back to clear. The solution was diluted to 100 ml with water. To a 25 ml aliquot was added 10 ml Vanadate-Molybdate solution (25.0 g ammonium

molybdate tetrahydrate, 1.28 g ammonium metavanadate, 330 ml 36.5 wt% HCl and enough water to make 1 L solution). After diluting to 50 ml with water, the solution was allowed to develop for 30 min. A blank solution containing only Vanadate-Molybdate solution was prepared and used to zero the spectrometer. The absorbance of the solution was measured at 470 nm on a Bausch and Lomb Spectronic 21. The phosphorus capacity was calculated (in units of mequiv/g) as follows:

$$\text{Phosphorus capacity} = [4(\text{absorbance})] / [(\text{slope})(\text{g resin})(30.974)]$$

The usage of dangerous perchloric acid was avoided in this method. Discrepancies in phosphorus capacity values between the two methods were not found.

Chlorine Elemental Analysis Method I

Sodium metal (~ 0.5 g) and xylene (~ 3 ml) were placed in a pyrex 15 x 160 test tube. The tube was clamped to a ring stand and the sodium was melted using a Bunsen burner. A second test tube, also clamped to a ring stand, was charged with accurately weighed oven-dried resin, (0.3 g to 0.4 g), 2 g sodium metal and 1 ml xylene. The two test tubes were connected with a U-shaped glass transfer tube equipped with a rubber

stopper at one end. One end of the transfer tube was immersed into the molten sodium of the first test tube and the end with the stopper was tightly connected to the second test tube. While continuing to heat the first test tube, the sodium in the second test tube was slowly melted using a second Bunsen burner. After the sodium was melted, the second test tube was intensely heated for 2-4 min to decompose the beads. The chlorine gas, produced by the sodium fusion of the resin, passed through the transfer tube and was bubbled through the molten sodium of the first test tube. Both tubes were intensely heated for 15 min. After cooling to room temperature, the two test tubes and transfer tube were broken into a 250 ml beaker containing 100 ml methanol. The methanol was evaporated and the resulting solid was dissolved with water. The solution was quantitatively transferred with filtering into a 250 ml volumetric flask. A 50 ml aliquot of this solution was acidified with concentrated HNO_3 to a methyl orange endpoint (red), and was then neutralized with 0.3 M NaOH to a yellow endpoint. A Mohr titration was employed to determine the amount of chloride in the sample using standard 0.05 M AgNO_3 as the titrant, and 5 wt% $\text{K}_2\text{Cr}_2\text{O}_4$ (2ml) as the indicator. The chlorine capacity (in mequiv/g) was calculated as follows:

$$\text{chlorine capacity} = [5(\text{ml AgNO}_3)(N \text{ AgNO}_3)] / (\text{g resin})$$

The fusion solution was boiled, when nitrogen was present in the sample, for 15 min after acidification to remove CN^- which was found to interfere with the Mohr titration.

Chlorine Elemental Analysis Method II

An oven-dried resin (0.2 g) and mineral oil (0.6 g) were placed in the capsule of the Parr bomb. The capsule was placed securely in the holder. A 10 cm nickel alloy fuse wire was threaded through the bomb stem holes and was allowed to barely dip into the oil. After its inner surface was wet with 5ml 5% Na_2CO_3 , the Parr bomb was closed and purged with oxygen gas twice. The bomb was then charged with 30 atm oxygen gas and placed into a cold water bath. After no gas leakage was detected, the ignition button was pressed. The red light came on indicating combustion was complete. The bomb was removed from the water bath and the pressure inside was slowly released by gently opening the bleeder. The combusted solution was quantitatively transferred with filtering into a 250 ml volumetric flask. A 25 ml aliquot of this solution was acidified with 3 ml 2N HNO_3 and 10 ml 0.05 N AgNO_3 was added. The solution was then boiled for 2 min. After cooling to room

temperature, the boiled solution was quantitatively filtered into a clean 125 ml Erlenmeyer flask, and titrated with 0.05N NH_4SCN using a $\text{FeNH}_4(\text{SO}_4)_2$ indicator. A blank solution containing only 5 ml of AgNO_3 was used to standardize the NH_4SCN solution. The chlorine capacity (in mequiv/g) can be calculated as follows:

$$\text{Chlorine capacity} = \frac{10[(N \text{ AgNO}_3)(\text{ml AgNO}_3) - (N \text{ NH}_4\text{SCN})(\text{ml NH}_4\text{SCN})]}{\text{g resin}}$$

Method II was more efficient than Method I. Furthermore, in method I the aliquot to be titrated was light to dark brown, causing difficulties in end point determination, which did not exist in method II because the aliquot to be titrated was clear and colorless.

Nitrogen Elemental Analysis

An oven-dried resin (0.2 g) was placed in a 500 ml 3-neck round-bottom flask with 0.25 g CuSO_4 , 10 g K_2SO_4 , and 25 ml of concentrated H_2SO_4 . The mixture was heated until the beads were digested and the solution became clear. 100 ml of distilled water was carefully added to the flask. A distillation apparatus, with one end in one joint of the flask and the other end connected to a funnel, was set up. The funnel was then

placed in a beaker containing 50 ml of standardized 0.1N HCl solution. 150 ml of 6 N NaOH was slowly added to the flask through an addition funnel over a period of 5 min. The ammonia gas produced was then distilled and captured by HCl. When the liquid volume in the beaker reached approximately 200 ml, the distillation was stopped, and the solution in the beaker was quantitatively transferred to a 250 ml volumetric flask. A 50 ml aliquot of this solution was titrated with a standardized 0.1 N NaOH solution using a bromocresol green indicator. The nitrogen capacity (in mequiv/g) was calculated as follows:

$$\text{nitrogen capacity} = 5[50 (\text{N HCl}) - (\text{ml NaOH})(\text{N NaOH})] / \text{g resin}$$

Use of Gas Chromatography in Studying the Organic Reactions

GC is an essential instrument in studying organic reaction kinetics. The GC used was a Hewlett-Packard model 5890 with a injection port, a flame ionization detector and a 15 m x 0.53 mm x 1.5 μ dimethylpolysiloxane capillary column. Recording and integration of peaks was performed by Hewlett-Packard model 3353A recording integrator. The injection port temperature was set at 275°C, the detector temperature was set at 325°C, the flow rate was set to a head pressure of 70 kpasal, and the oven was set to increase 15°C per minute from

35°C. Sample injection was accomplished with a Hamilton 7000 series 1 μ l positive displacement syringe, with 0.1 μ l injections of solutions. The data was treated with the internal standard method. The principal advantages of this method are that the exact knowledge, or the reproducibility, of the sample volumes is unimportant, and calibration curves can easily be established by plotting the peak area ratios of the component to the internal standard against their weight ratios. The weight of the component can be calculated as follows:

$$W_n = \alpha (A_n/A_s) W_s$$

(A_s is the peak area of the internal standard, A_n is the peak area of the component, W_s is the weight of the internal standard, W_n is the weight of the component, and α is a constant which can be obtained from the slope of the calibration curve).

The Mitsunobu Reaction of Benzyl Alcohol and Benzoic Acid

To a 100 ml three-necked round-bottom flask, 7.5 mmol benzoic acid, 15 mmol phosphine reagent, 65 ml anhydrous THF, and 7.5 mmol dry benzyl alcohol in 10 ml THF, was added, in that order, under an argon atmosphere. The solution was stirred at 252 rpm with an overhead stirrer. The flask was placed in a water bath held at 25°C and 2 ml (12.7

mmol) diethylazodicarboxylate added. Microliter samples were taken and analyzed by GC with THF used as the internal standard. Percent conversion was calculated from the decrease in the benzyl alcohol peak and percent yield from the increase in the benzyl benzoate peak.

The Aldol Condensation of Acid Catalyzed Propionaldehyde

Exactly 90 ml of a 3M 1,4-dioxane solution of propionaldehyde was added to a 100 ml three-necked round-bottom flask equipped with an overhead stirrer, a thermometer, and a condenser. The solution was stirred at 252 rpm, heated to 75°C and the zero-time sample taken just prior to the addition of 1.03 g benzenesulfonic acid (6.30 mmol) or other type of catalyst. Constant temperature was maintained with a therm-o-watch (Instruments for Research and Industry, Cheltenham, PA).

Microliter samples were taken at given intervals (eight during the first hour, one every 30 min for six hours, then two on the second day) and analyzed by GC with 1,4-dioxane used as the internal standard. The calibration curves for propionaldehyde and 2-methyl-2-pentenal were established. Percent conversion was calculated from the decrease in the propionaldehyde peak and percent yield from the increase in the product peak.

The Prins Reaction of Formaldehyde and Styrene

Styrene(13.00 g) and 1,3,5-trioxane (15.00 g) were dissolved in 1,4-dioxane (55.00 g). The solution was added to a 100 ml three-necked round-bottom flask equipped with an overhead stirrer, a thermometer, and a condenser. The solution was stirred at 252 rpm, heated to 75°C and the zero-time sample taken just prior to the addition of the catalyst. Constant temperature was maintained with a therm-o-watch. Microliter samples were taken and analyzed by GC with 1,4-dioxane used as the internal standard. The calibration curves were established for styrene and 4-phenyl-1,3-dioxane. Percent conversion was calculated from the decrease in the styrene peak and percent yield from the increase in the product peak.

The Claisen-Schmidt Reaction of Propionaldehyde with Benzaldehyde and Its Derivatives

A 1,4-dioxane solution of 0.6M propionaldehyde and 6M benzaldehyde or its derivatives was prepared in a 100 ml volumetric flask. Exactly 90 ml was transferred into a 100 ml three-necked round-bottom flask equipped with an overhead stirrer, a thermometer, and a condenser. The solution

was stirred at 252 rpm, heated to 75°C and the zero-time sample taken just prior to the addition of the catalyst. Constant temperature was maintained with a therm-o-watch. Microliter samples were taken at given intervals (four during the first hour, one every 30 min for six hours, then two on the second day) and analyzed by GC with 1,4-dioxane used as the internal standard. The calibration curves for propionaldehyde and the condensation products were established. Percent conversion was calculated from the decrease in the propionaldehyde peak and percent yield from the increase in the product peak.

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APPENDIX

APPENDIX A

APPLICATION OF POLYMERIC SULFONIC ACIDS AS CATALYSTS IN THE CLAISEN-SCHMIDT REACTION OF PROPIOANLDEHYDE WITH BENZALDEHYDE AND ITS DERIVATIVES

Introduction

The purpose of the present investigation is to extend work on the aldol condensation of propionaldehyde. Acid catalyzed reactions of propionaldehyde with benzaldehyde, and its derivatives, are chosen as the model reaction (Figure 63). The substituent effect on the rate of reaction is studied. The results for the polymeric catalysts are compared to their small molecule analogues.

Experimental

The concentration of benzaldehyde, or its derivative, was 10 times higher than that of propionaldehyde in order to suppress the self-condensation reaction of propionaldehyde. The reactions were carried out in 1,4-dioxane at 75°C. Microliter samples were taken and analyzed by GC with dioxane used as the internal standard. Calibration curves (Figures 36, 64, 65, and 66) were used to calculate the concentration of reactants

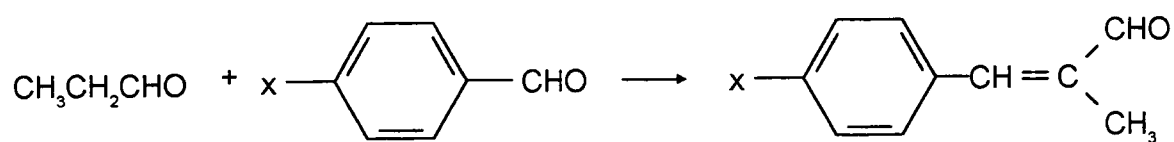


Figure 63. Model reaction of the Claisen-Schmidt reaction

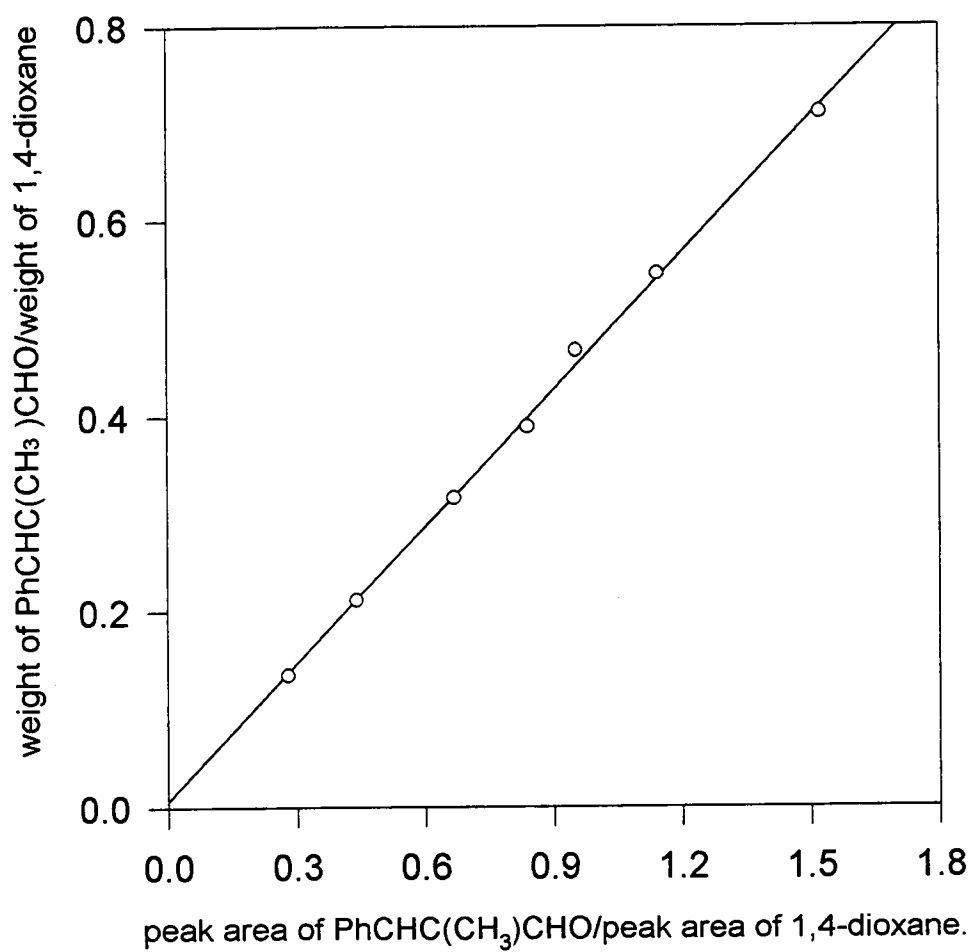


Figure 64. Calibration curve for the determination of the amount of PhCHC(CH₃)CHO in a mixture. Internal standard: 1,4-dioxane

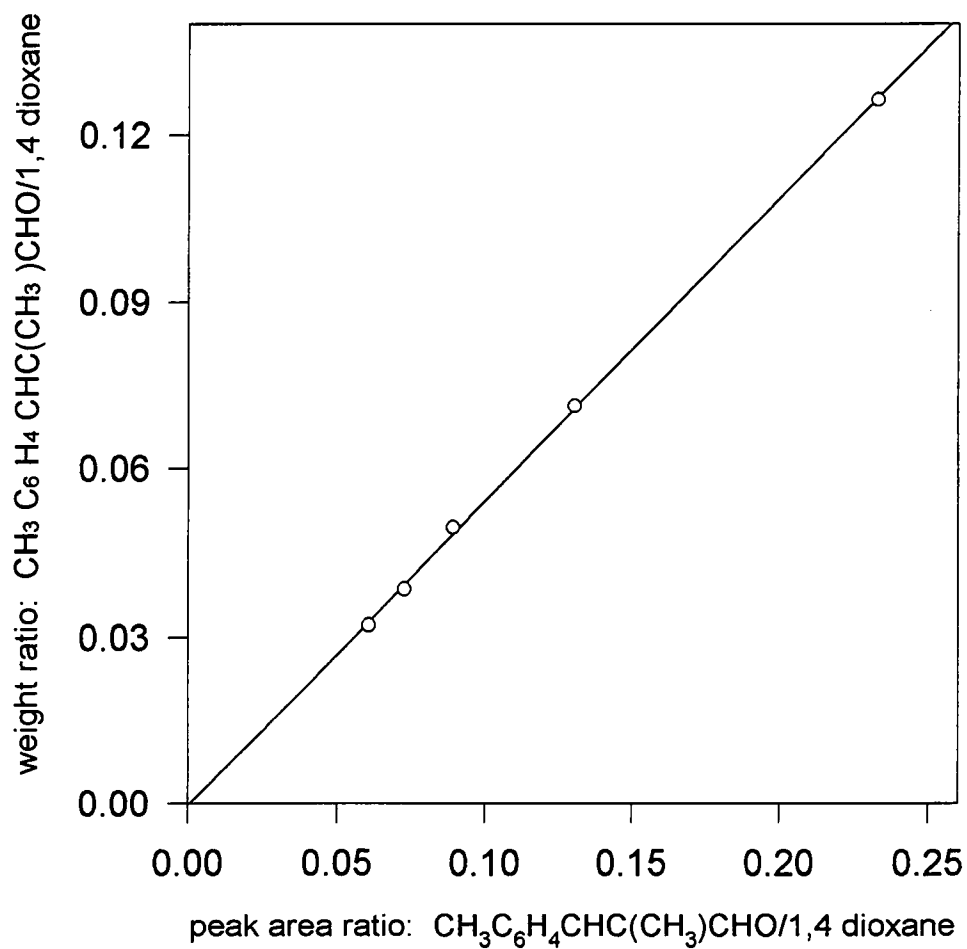


Figure 65. Calibration curve for the determination of the amount of $\text{CH}_3\text{C}_6\text{H}_4\text{CHC}(\text{CH}_3)\text{CHO}$ in a mixture. Internal Std.: 1,4-dioxane

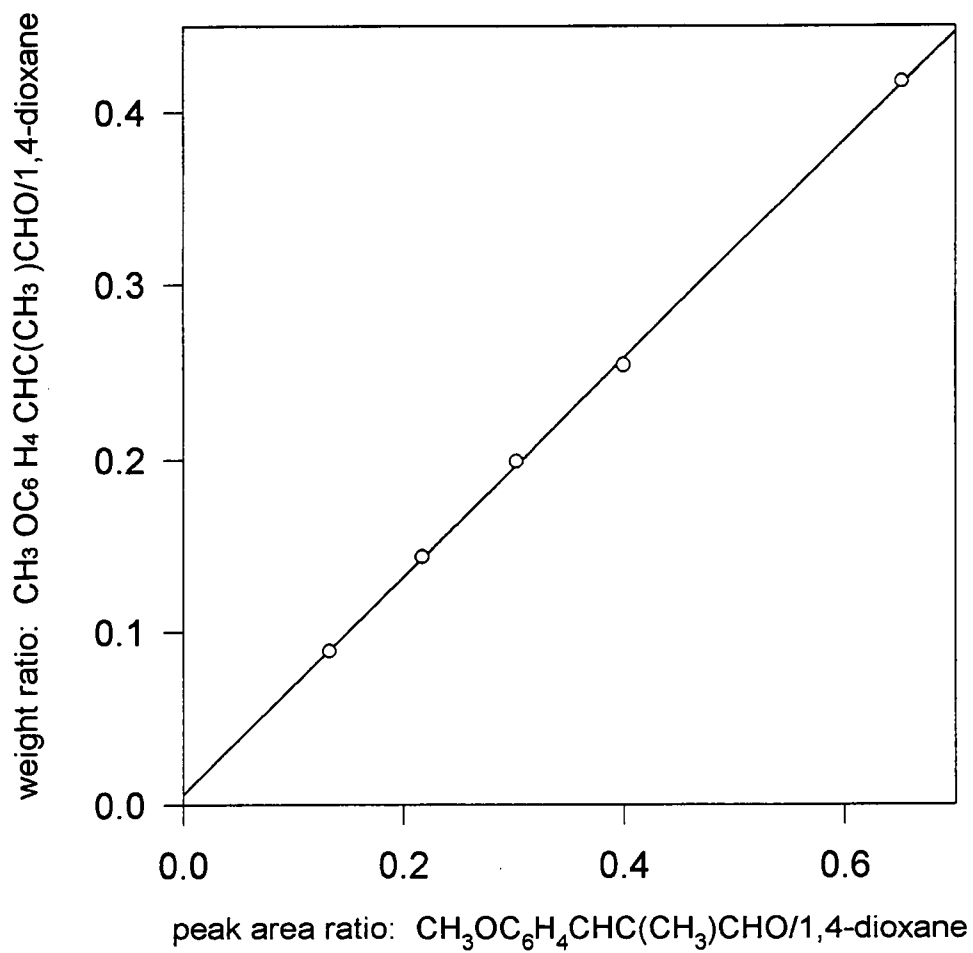


Figure 66. Calibration curve for the determination of the amount of $\text{CH}_3\text{OC}_6\text{H}_4\text{CHC}(\text{CH}_3)\text{CHO}$ in a mixture. Internal Std.: 1,4-dioxane.

and products. Dehydration products were obtained and their structures were confirmed with ^1H NMR.

Homogeneous catalyst kinetics

A linear correlation of $\ln [\text{EtCHO}]$ vs time indicates that the reaction is first order in propionaldehyde (Figure 67). Slopes and intercepts are determined by linear least-squares analysis, with all correlation coefficients greater than 0.9970. The slopes equal the observed rate constants and are proportional to the initial acid concentration (Table 22). The rate constants can be calculated from the slope and $[\text{H}^+]$ (Table 22). The conversion and yield data are equilibrium values, all at a reaction time of 24 hours. The rate expression for the Claisen-Schmidt reaction may be summarized by equation 1:

$$d[\text{EtCHO}] / dt = -k_{\text{obs}} [\text{EtCHO}] = -k [\text{EtCHO}][\text{H}^+] \quad (1)$$

Considering that the concentration of benzaldehyde, or its derivative, is 10 times higher than that of propionaldehyde, the reaction is pseudo 2nd order. It has been found that the acid catalyzed condensation of benzaldehyde with acetophenone follows the same kinetics.^{83,180}

The substituent effect on the rate of condensation is quite small. The change from benzaldehyde to anisaldehyde results in a rate change by a

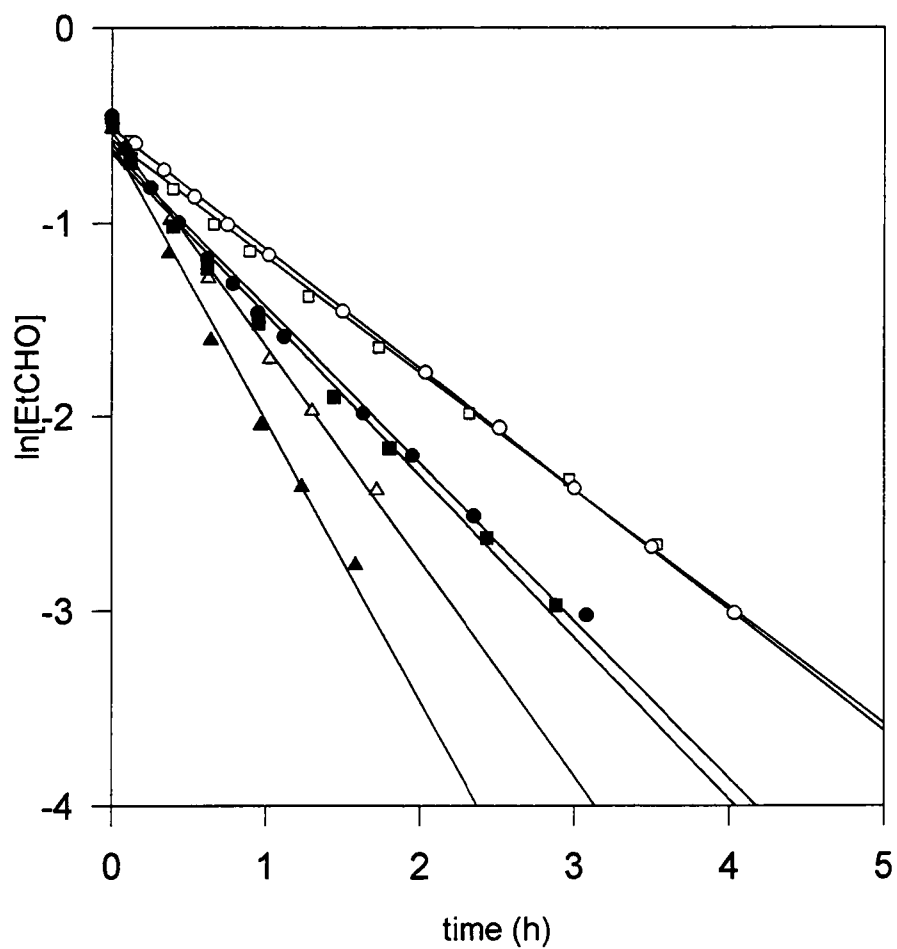


Figure 67. First order dependence on propionaldehyde in Claisen-Schmidt reactions with homogeneous catalysts.

- △ 0.072M PhSO_3H , 0.6M PA, 6M AA.
- 0.069M PhSO_3H , 0.6M PA, 0.6M TA.
- 0.070M PhSO_3H , 0.6M PA, 6M BA.
- ▲ 0.072M H_2SO_4 , 0.6M PA, 6M AA.
- 0.072M H_2SO_4 , 0.6M PA, 6M TA.
- 0.071M H_2SO_4 , 0.6M PA, 6M BA.

Table 22. Homogeneous acid catalyzed condensation of propionaldehyde with benzaldehyde and its derivatives at equilibrium*

run	[reactant]	[H ⁺]	k _{obs}	k ^a	%yield
1	0.6M PA ¹ 6M BA ²	0.0355M H ₂ SO ₄	0.395	11.13	88.3
2	0.6MPA 6M BA	0.0709M H ₂ SO ₄	0.809	11.41	82.8
3	0.6M PA 6M BA	0.07011M PhSO ₃ H	0.620	8.85	83.4
4	0.6M PA 6M BA	0.0372M PhSO ₃ H	0.338	9.09	67.8
5	0.6M PA 6M TA ³	0.0691M PhSO ₃ H	0.585	8.47	88.7
6	0.6M PA 6M TA	0.0355M PhSO ₃ H	0.301	8.48	78.2
7	0.6M PA 6M TA	0.0721M H ₂ SO ₄	0.831	11.53	76.9
8	0.6M PA 6M AA ⁴	0.0721M H ₂ SO ₄	1.449	20.10	31.8
9	0.6M PA 6M AA	0.0361M H ₂ SO ₄	0.755	20.91	29.0
10	0.6M PA 6M AA	0.0720M PhSO ₃ H	1.106	15.36	38.8
11	0.6M PA 6M AA	0.0379M PhSO ₃ H	0.561	14.80	31.7

*All reactions have 100% conversion of propionaldehyde

¹ PA stands for propionaldehyde

² BA stands for benzaldehyde

³ TA stands for tolualdehyde

⁴ AA stands for anisaldehyde

^a Lmol⁻¹h⁻¹. The experimental error is within 5%.

factor of 1.68 with benzenesulfonic acid. The factor is 1.819 with sulfuric acid. The rate constant stays almost unchanged when benzaldehyde changes to tolualdehyde. Similar behavior has been observed in the condensation of substituted benzaldehydes with acetophenone and is postulated to result from two opposing factors.⁷⁶ The first factor is the effect of the substituent on the basicity of the aldehyde. Anisaldehyde and tolualdehyde are more basic than benzaldehyde, and the concentration of the aldehydic oxonium cation will be higher for anisaldehyde and tolualdehyde than for benzaldehyde at a given acidity. Such a contributing factor accelerates the rate determining step, which involves the aldehydic oxonium cation and the enol (Figure 68). The second opposing factor is the decreasing electrophilicity of the aldehydic oxonium cation caused by electron donating methoxy and methyl groups.

The substituent effect with the polymer-supported catalysts

The qualitative substituent effect with polymeric catalysts is illustrated in Figure 69, 70, and 71. The propionaldehyde disappearing rate increases when benzaldehyde is replaced with anisaldehyde and stays almost constant when benzaldehyde is replaced with tolualdehyde. This is similar to the substituent effect with the homogeneous catalysts,

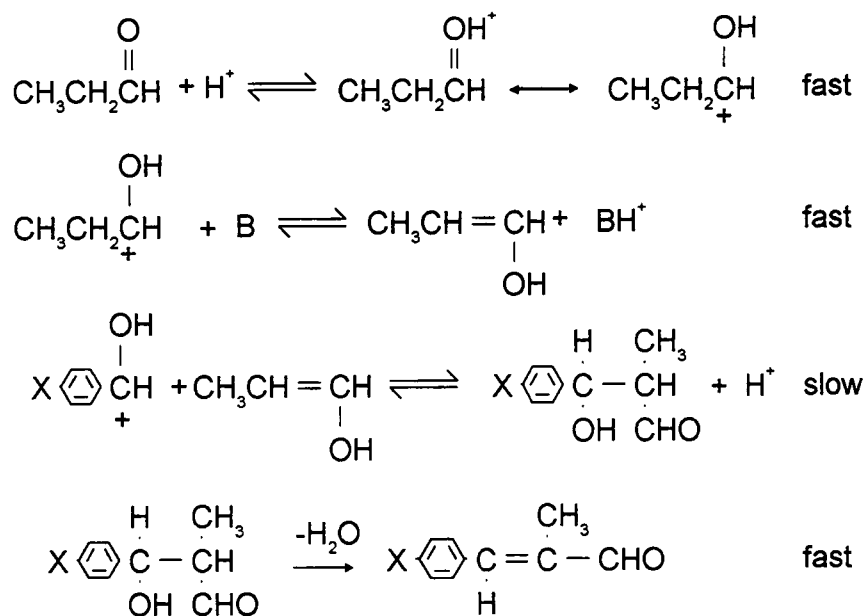


Figure 68. The mechanism of the acid catalyzed Claisen-Schmidt condensation

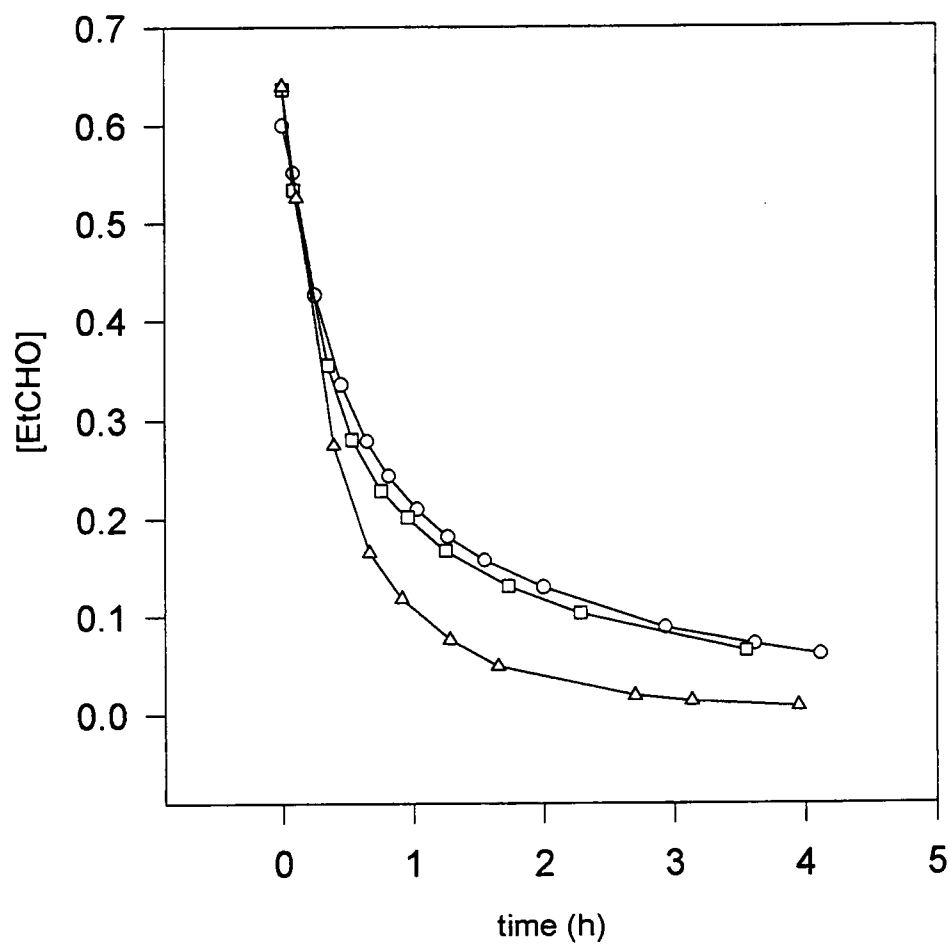


Figure 69. The substituent effect on the Claisen-Schmidt reaction with 2-100H-G as catalyst.

- 7.10 mmol catalyst, 0.6M PA, 6M BA.
- 7.76 mmol catalyst, 0.6M PA, 6M TA.
- △ 7.16 mmol catalyst, 0.6M PA, 6M AA.

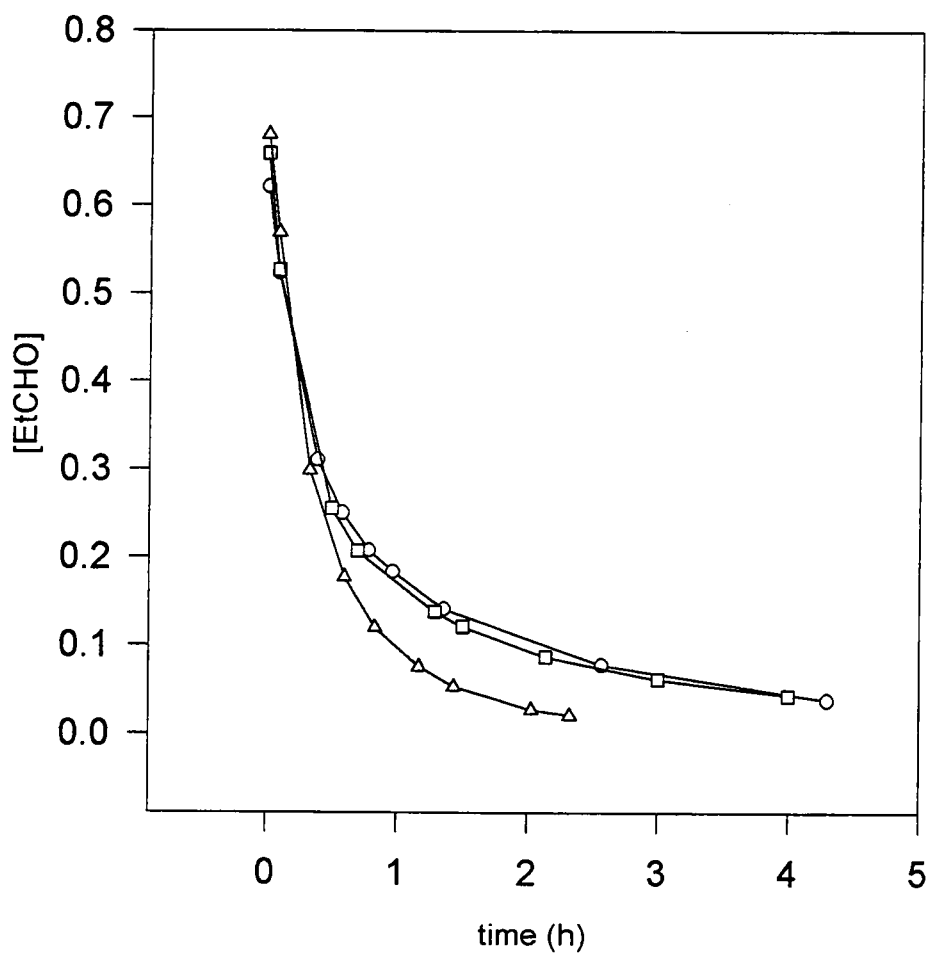


Figure 70. The substituent effect on the Claisen-Schmidt reaction with 2-41ME-59H-G as catalyst.

- 7.33mmol catalyst, 0.6M PA, 6M BA.
- 7.69mmol catalyst, 0.6M PA, 6M BA.
- △ 7.56mmol catalyst, 0.6M PA, 6M AA.

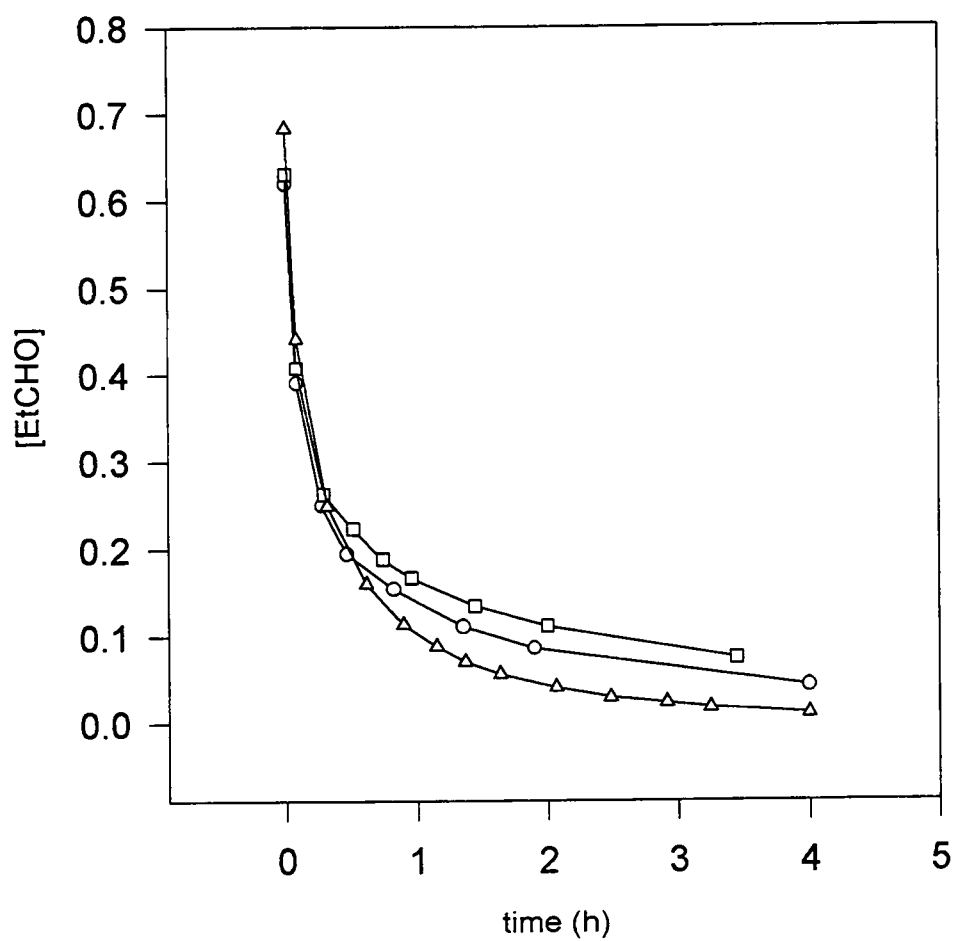


Figure 71. The substituent effect on the Claisen-Schmidt reaction with 10-100H-50MR as catalyst.

- 7.16mmol catalyst, 0.6M PA, 6M BA.
- 7.49mmol catalyst, 0.6M PA, 6M TA.
- △ 7.12mmol catalyst, 0.6M PA, 6M AA.

suggesting that the substituent effect with the polymeric catalysts is also the result of two opposing factors.

Comparison between homogeneous and heterogeneous acid catalysts

The loss of propionaldehyde with the polymeric catalysts is slightly faster than that with benzenesulfonic acid, and similar to that with sulfuric acid (Figure 72, 73 and 74). The side reactions, such as the self-condensation of propionaldehyde, are observed. The ratio of cross-condensation product to self-condensation product measures the selectivity of the catalyst. In the reactions of propionaldehyde with benzaldehyde, or tolualdehyde, the homogeneous catalysts have better selectivity than the polymeric catalysts (Table 23, runs 2, 3, 12, 13, and 14; runs 5, 7, 15, 16, and 17), however, in the reactions with anisaldehyde better selectivity is observed with polymeric catalysts (Table 23 Runs 8, 10, 18, 19, and 20). Similar product yields are obtained at equilibrium with both homogeneous and heterogeneous catalysts (Tables 22 and 24). The advantage of a shorter contact time with the polymeric catalysts, which has been demonstrated in the aldol condensation of propionaldehyde, is not obvious in this case as the yield/conversion ratios with polymeric catalysts are similar to, or less than, those with homogeneous catalysts (Table 25).

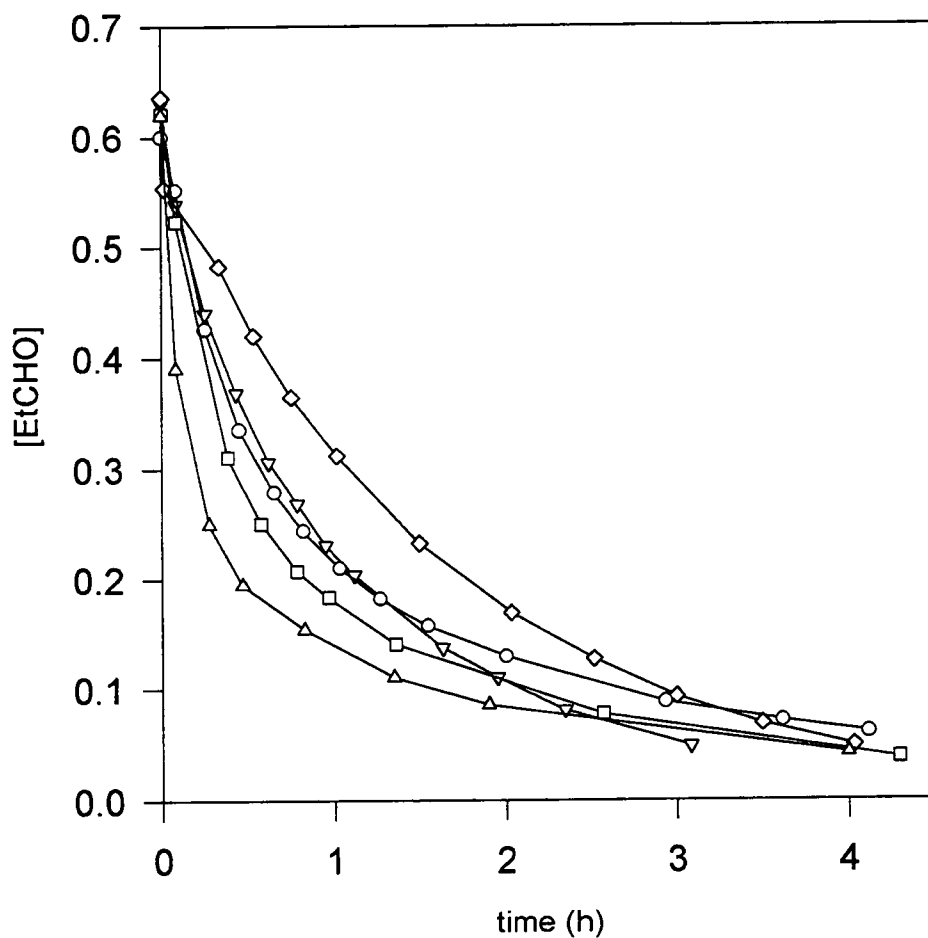


Figure 72. Rate comparison of propionaldehyde loss between homogeneous and heterogeneous catalysts (I).

- ▽ 7.09mmol H₂SO₄, 0.6M PA, 6M BA.
- ◇ 7.01mmol PhSO₃H, 0.6M PA, 6M BA.
- 7.10mmol 2-100H-G, 0.6M PA, 6M BA.
- 7.33mmol 2-41ME-59H, 0.6M PA, 6M BA.
- △ 7.16mmol 10-100H-50MR, 0.6M PA, 6M BA.

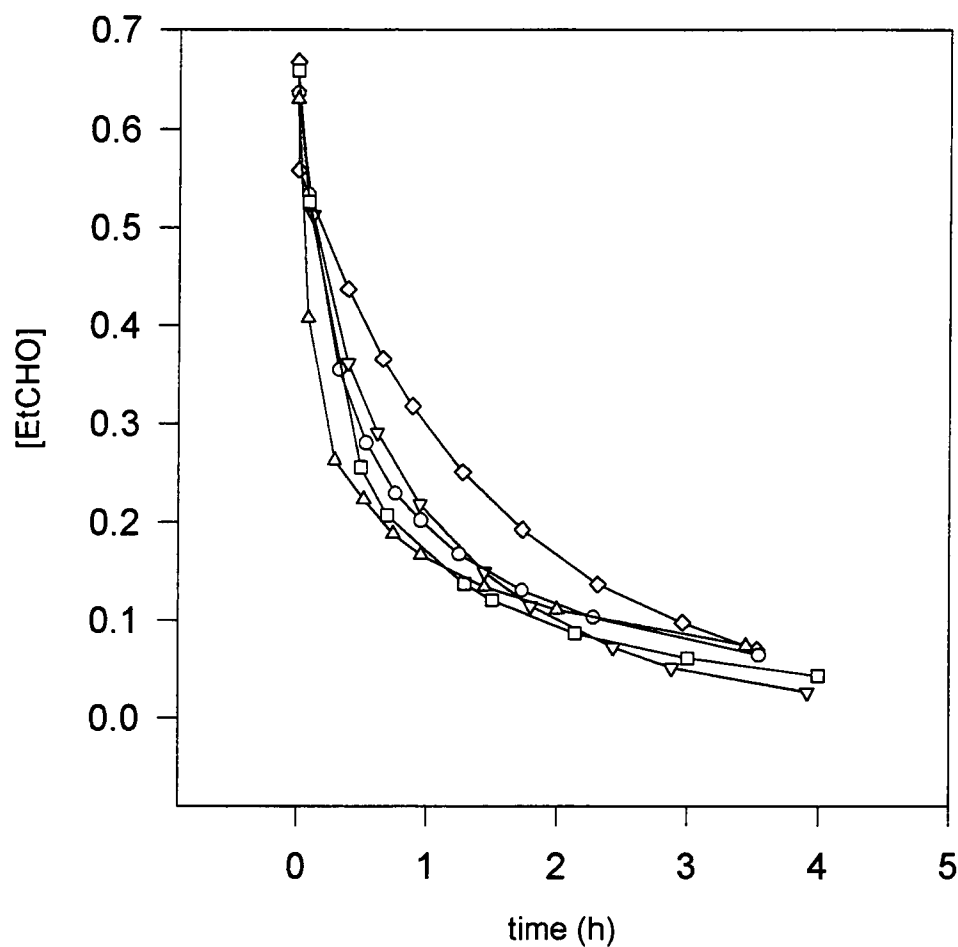


Figure 73. Rate comparison of propionaldehyde loss between homogeneous and heterogeneous catalysts (II).

- ▽ 7.21mmol H₂SO₄, 0.6M PA, 6M TA.
- ◇ 6.91mmol PhSO₃H, 0.6M PA, 6M TA.
- 7.76mmol 2-100H-G, 0.6M PA, 6M TA.
- 7.69mmol 2-41ME-59H-G, 0.6M PA, 6M TA.
- △ 7.49mmol 10-100H-50MR, 0.6M PA, 6M TA.

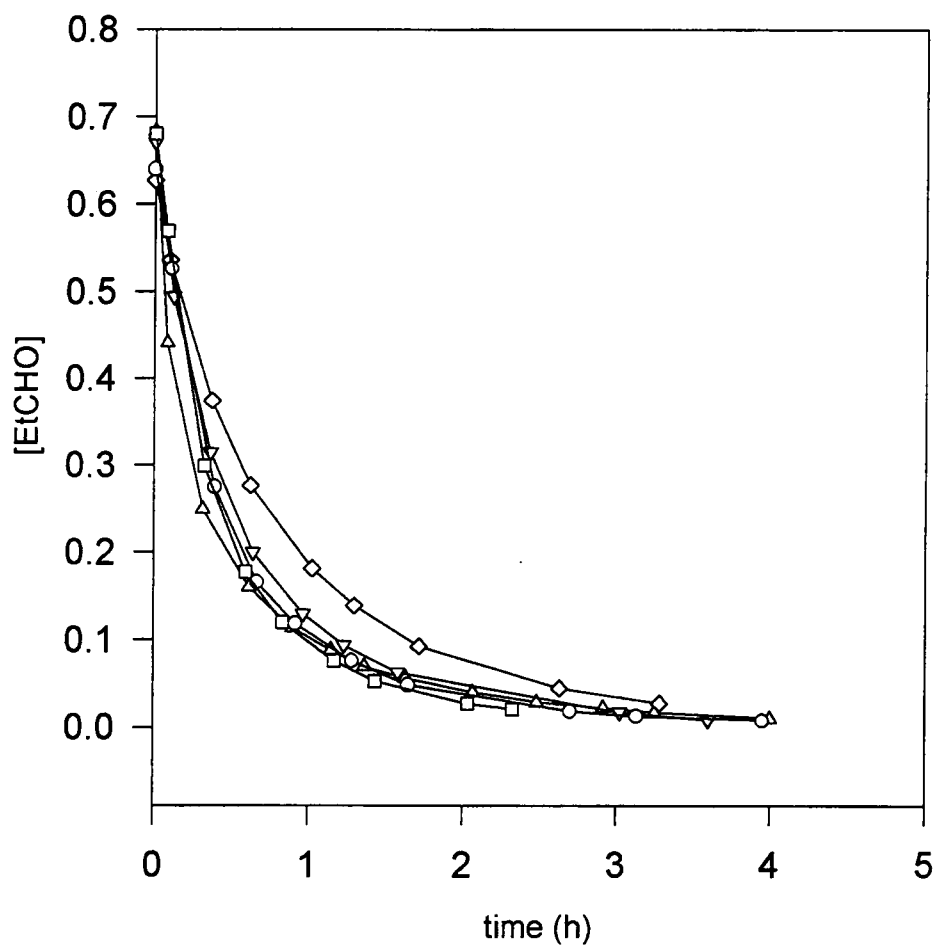


Figure 74. Rate comparison of propionaldehyde loss between homogeneous and heterogeneous catalysts (III).

- ▽ 7.21mmol H₂SO₄, 0.6M PA, 6M AA.
- ◇ 7.20mmol PhSO₃H, 0.6M PA, 6M AA.
- 7.16mmol 2-100H-G, 0.6M PA, 6M AA.
- 7.56mmol 2-41ME-59H-G, 0.6M PA, 6M AA.
- △ 7.12mmol 10-100H-50MR, 0.6M PA, 6M AA.

Table 23. Comparison of product selectivity for homogeneous and polymeric catalysts at equilibrium

run	[cross]/[self] *
2	38.5
3	27.3
5	25.8
7	59.6
8	54.7
10	24.6
12	25.8
13	22.2
14	15.3
15	19.4
16	23.1
17	6.52
18	∞
19	∞
20	44.2

*ratio of cross-condensation product to self-condensation product.

Table 24. Polymeric acid catalyzed condensation of propionaldehyde with benzaldehyde and its derivatives at equilibrium*

Run	[reactant]	mmolH ⁺ /100ml		%yield
12	0.6M PA 6M BA	7.10	2-100H-G	80.0
13	0.6M PA 6M BA	7.33	2-41ME-59H-G	79.9
14	0.6M PA 6M BA	7.16	10-100H-50MR	76.9
15	0.6M PA 6M TA	7.76	2-100H-G	76.8
16	0.6M PA 6M TA	7.69	2-41ME-59H-G	85.4
17	0.6M PA 6M TA	7.49	10-100H-50MR	53.4
18	0.6M PA 6M AA	7.16	2-100H-G	42.2
19	0.6M PA 6M AA	7.56	2-41ME-59H-G	32.9
20	0.6M PA 6M AA	7.12	10-100H-50MR	35.0

*All reactions have 100% conversion of propionaldehyde

Table 25. Comparison of reactant conversion and product yield for homogeneous and polymeric catalysts at a 1h reaction time

run	% conv.	%yield	yield/conv.
2	63.4	43.4	0.684
3	51.0	33.3	0.653
5	53.8	28.8	0.535
7	65.7	50.9	0.775
8	80.7	20.6	0.255
10	71.1	24.7	0.347
12	65.0	34.2	0.525
13	70.5	43.1	0.611
14	71.8	39.2	0.546
15	68.3	38.3	0.560
16	75.3	23.7	0.315
17	73.5	19.9	0.271
18	84.4	23.5	0.278
19	85.6	24.3	0.291
20	85.3	29.9	0.351

Conclusion

Both the polymeric and the homogeneous acid catalyzed reactions show similar substituent effect. It is the results of two opposing factors: the basicity of the aldehyde and the electrophilicity of the aldehydic oxonium cation. Reactions with polymeric acids proceed slightly faster than those with homogeneous catalysts, however, the polymeric catalysts do not give superior product selectivity and yield.

APPENDIX B

Abbreviation of polymer-supported reagents used
in this dissertation and in the research note books

Abbreviation in the dissertation	Abbreviation in the note books
2-100V	DM-3-109
2-33S-67V	DM-3-108
2-60S-40V	DM-3-100
2-82S-18V	DM-3-104
2-100S	DM-3-106
2-82ME-18V	DM-3-118
2-82A-18V	DM-4-094
2-60S-40BS	DM-3-128
2-82S-18BS	DM-4-098
2-82S-18P-1	DM-4-104
2-82S-18P-2	DM-4-107
2-82ME-10V-8CP	DM-3-125
2-82ME-18CP	DM-3-127
2-78A-12V-10CP-1	DM-4-105
2-78A-12V-10CP-2	DM-4-108

Abbreviation in the dissertation	Abbreviation in the note books
2-100CP	DM-3-115
2-33S-67CP	DM-3-113
2-60S-40CP	DM-3-107
2-82S-18CP	DM-3-111
2-60S-40P	DM-3-129
2-100H-G-SA	DM-1-140
10-100H-G-SA	DM-1-203
10-100H-50MR	DM-2-129
2-100H-G	DM-2-101
2-15S-85H-G	DM-4-097
2-20S-80H-G	DM-4-049
2-41S-59H-G	DM-4-096
2-55S-45H-G	DM-3-136
2-80S-20H-G	DM-3-141
2-92S-8H-G	DM-4-029
2-10ME-90H-G	DM-4-036
2-20ME-80H-G	DM-4-014
2-41ME-59H-G	DM-3-015
2-55ME-45H-G	DM-4-038

Abbreviation in the dissertation	Abbreviation in the note books
2-75ME-25H-G	DM-4-024
2-8BE-92H-G	DM-4-035
2-15BE-85H-G	DM-3-284
2-20BE-80H-G	DM-4-059
2-33BE-67H-G	DM-3-259
2-58BE-42H-G	DM-4-023
2-65BE-35H-G	DM-4-039
2-75BE-25H-G	DM-3-285
10-100H-G	DM-2-100
10-100H-20MR	DM-2-128

VITA

Dorothy Hong Jiang Miller was born in China on August 6, 1966. She graduated from Shanghai High School in 1984. She received her Bachelor of science degree in Chemical Physics from East China University of Chemical Engineering and Technology in July 1988. She worked as an assistant engineer in Zhong-hua Pharmaceutical Plant before coming to the United States. In August 1991 she accepted a teaching and research assistantship from the Chemistry Department at the University of Tennessee. In August of 1996, she received her Ph.D. degree.