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My parents have given me the universe and everything in it. They have fed and housed me during the writing of this Thesis. It is dedicated to them.

God bless you all.

ABSTRACT

Modes of attachment of functional groups to crosslinked polystyrene are discussed. Attention is drawn to the improved stability and activity of polymer-bound reagents and catalysts incorporating a dimethylene or other short spacer between polystyrene aryl and functional group heteroatom, and the simplicity and versatility of their syntheses through high-conversion functional group modifications. Examples are given in polymer-supported dialkylaminopyridines as acylation catalysts, and halopyridinium salts as condensation reagents.

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Part I.

Preparation of Spacer-Containing Functional Polystyrenes

PREPARATION OF SPACER-CONTAINING FUNCTIONAL POLYSTYRENES.

INTRODUCTION

For three decades now,[1,2] crosslinked polystyrenes carrying chemically reactive groups have proliferated in form and application.[3,4] Many of these polymer supports have been adapted or especially designed as photochemical,[5] acylation,[6] and phase-transfer[7-11] catalysts, or as reaction cosolvents,[12,13] or as oxidation,[14-17] reduction,[18,19] dehydrohalogenation,[20] and condensation[21] reagents, or as agents for the sequestering or exchange of both ions[1,22,23] and neutral molecules,[24] or as inducers of molecular asymmetry,[16,19,25,26] or as protecting groups and supports for solid-phase synthesis.[2,27-29] Generally, these solid materials, together with attached products or byproducts, are later easily removed from the reaction mixture by filtration, often considerably simplifying product purification and increasing isolated yields; they can frequently be regenerated for future reuse.

Currently, most such functional or reactive polymers are prepared from (chloromethyl)polystyrene, which itself is easily made by controlled functionalization[1,30,31] of commercially available styrene-divinylbenzene copolymer. Facile nucleophilic displacement of labile[32] benzylic chloride, frequently under phase-transfer conditions,[33,34]

allows appropriate free molecules bearing nucleophilic heteroatoms to become attached to the macromolecular matrix. However, the new carbon-heteroatom bonds formed in these functional group modifications are themselves relatively fragile, since resonance stabilizes the partial charges developed during their rupture.[35,36] Many examples of such benzylic instability are provided by classical (free-molecule) organic chemistry, as well as a few by the smaller and more specialized field of polymer-supported reagents and catalysts. Hence:

- Benzylic quaternary phosphonium and ammonium salts are dealkylated by mild heating and/or nucleophilic anions, particularly thiolates[36] and iodide,[37] but also hydroxide.[38] N-benzyl-pyridinium or quaternary arylammonium compounds are particularly susceptible.[39] Decompositions of this sort have seriously limited the usefulness of solid phase-transfer catalysts derived from (chloromethyl)polystyrene.[10,40]

- Benzyl groups are cleaved from amines heated with inorganic acids,[41] carboxylic anhydrides[42,43] or cyanogen bromide.[39] Acids also catalyze the disproportionation of benzylamine to dibenzylamine and ammonia.[44]

- N-benzyl-sulfonamides are cleaved under "relatively mild conditions" with potassium alkoxide.[45]

- Benzyl ethers are amongst the easiest to cleave by Lewis acids.[46] Significant clipping of such bonds, with consequent loss of functionality, result during attempted HCl-catalyzed

hydrolyses of polystyrene-supported oxazoline intermediates[47,48] and chiral supports.[25,49]

- Additional mechanisms of hydrolysis are available to benzyl-type esters.[50] Their consequent fragility is well-known in polymeric systems.[55-57]

- Acetyl bromide cleaves dibenzyl sulfide, while diethyl or diisopropyl are resistant.[52]

- Benzyl-silanes are sensitive to hydroxide and other nucleophiles.[53,54]

- Benzylic ethers, sulfides, selenides and silanes are cleaved to benzylic carbanions by strong Lewis bases or radical anions. This too is known for polymeric systems.[55-57]

- Benzylic nitrogen, sulfur, and oxygen bonds are rather susceptible to hydrogenolysis, either during catalytic hydrogenation,[58,59] or upon treatment with L-selectride,[60] or even lithium aluminum hydride.[61,62]

Thus, the chemist or chemical engineer may legitimately fear further attack by nuisance nucleophiles on benzylic carbon, as a main or side-reaction during assembly, application or regeneration of any member of this structural class of functional polymer, leading to loss of mobile moieties from the solid phase. As the last step of a solid-phase synthesis, such as that of polypeptides by Merrifield, controlled separation of a pendant from polystyrene support may even be useful[2,28] -- but generally such decomposition of a reactive polymer only serves to deactivate it while introducing

contaminants to both solid and liquid phases. In addition, oxidation[41,63] or alkylation[64-66] may take place at those methylene carbons made particularly acidic by being bound at once to both aryl and electron-withdrawing groups or polarizable second-row elements.

Direct connection of pendant heteroatom to polymer arene is a synthetically more difficult, but often still feasible,[67] alternative. However, though bonds between phenyl groups and many common heteroatoms are relatively strong, resonance activates an arylated atom to leave its other, alkyl, substituents: alkyl-anilium salts[39] and anilines,[68] as well as phenolic esters,[69] are relatively easy to cleave. Electron-rich aryls also make attached nonmetals easier to oxidize. More electropositive elements, such as silicon,[70] are easily displaced from phenyl rings by protons and other Lewis acids through electrophilic aromatic substitution. Furthermore, an antipodal electron-withdrawing group can activate benzyl hydrogen on the polymer backbone for inopportune ionic or radical side-reactions.[5]

On the other hand, inserting even one more methylene group between polymer and pendant would result in a primary bond neither unstable nor destabilizing towards nucleophiles, permitting a chemically more robust functionality while retaining the attractive physical properties of polystyrene resin. Extending a reactive site further from the polymer backbone also improves contact with free substrate in the

liquid phase, for an overall increase in catalytic or other action.[8,71] It is conceivable too that spacers may facilitate cooperation of two or more functional sites in the formation of an active complex, as occurs in solid polar aprotic cosolvents[12,13] or phosphine-containing polymeric ligands for palladium or rhodium,[72,73] and still allow the gel to swell despite this reversible crosslinking. Thus, among both polymers and free molecules containing the "phenethyl" structural feature, it has been observed that:

- N-phenethyl-2-halopyridinium salts are unusually stable compared to their benzyl, and even methyl or ethyl, counterparts;[74-76]

- N-benzyl-N-phenethyl-N,N-dimethylammonium chloride loses benzyl and not phenethyl when heated with thiophenoxide, giving stable N,N-dimethylphenethylamine;[77]

- N,N-dimethylphenethylamine is also inert to further treatment with hot acetic anhydride;[43]

- simple carboxylic acids can be alkylated[51] or photochlorinated,[78] cinnamates treated with BF_3 and photocrosslinked,[79] and t-butylcarbonylated amino acids deprotected by acidolysis,[80] while remaining esterified to polystyrene via dimethylene spacer;

- quaternary phosphonium salts connected through dimethylene spacers are more stable and active phase-transfer catalysts for reaction of cyanide or thiolate with alkyl halides; rates further improve with even longer spacers;[9,81]

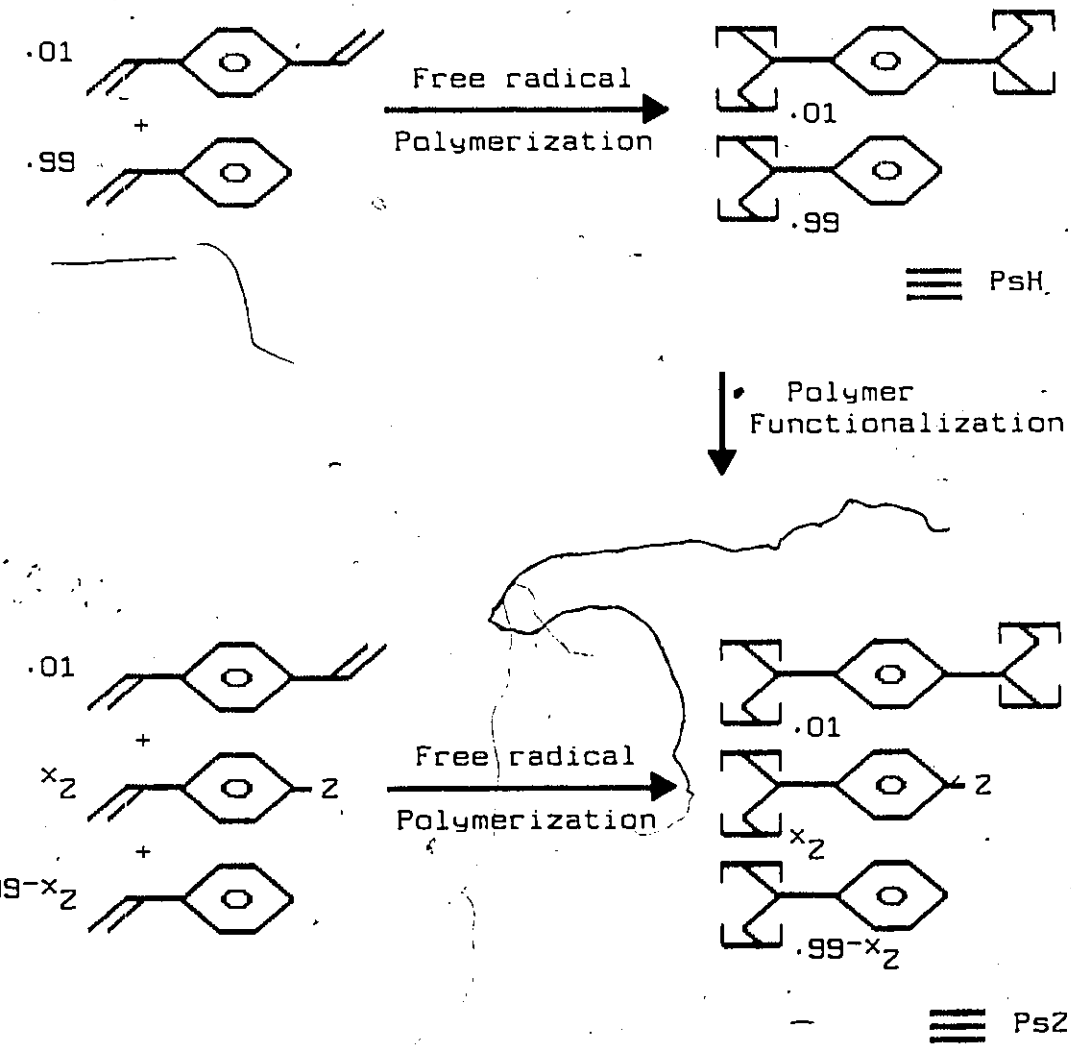
- Polymer-supported phenethyl tartarate, functioning as a stable solid-phase chiral auxiliary for the Sharpless epoxidation of allylic alcohols, gives higher chemical and optical yields than its benzylic analogue.[16]

The promise of polystyrenes incorporating dimethylene spacers, for purer, stabler and more active solid reagents and catalysts, inspired a systematic exploration of simple, general and economical reactions of polymer modification, beginning with commercial resins, and leading towards established and novel members of this structured class of functional polymer.

RESULTS AND DISCUSSION

As with other functionalized polystyrenes (Scheme 1), those containing dimethylene spacers can be prepared from the corresponding specialty monomers, themselves previously made and purified by classical chemical methods before being copolymerized in suspension with styrene and divinylbenzene by appropriate initiators.[51,78,79,82,83] A more versatile strategy is to chemically modify existing polymers, since a single functionalized polymer, once in hand, can act as precursor to any of several others, depending on the reagent and reaction conditions applied. However, each conversion step must be complete and selective, since any unreacted, side-reacted or over-reacted functionalities cannot be removed from the solid product, and may ultimately interfere with its

Scheme 1. Two General Routes to Functionalized Polystyrene: Polymer Functionalization and Functional Monomer Polymerization.



Ps = Polystyrene

Z = Functional Group

x_z = Mole Fraction of Functional Monomer/ Degeee of Functionalization of Polymer

intended application. The purity of a polymer product can be demonstrated by spectroscopic and elemental analyses,[84] and/or inferred by analogy with established reactions of structurally similar free molecules.

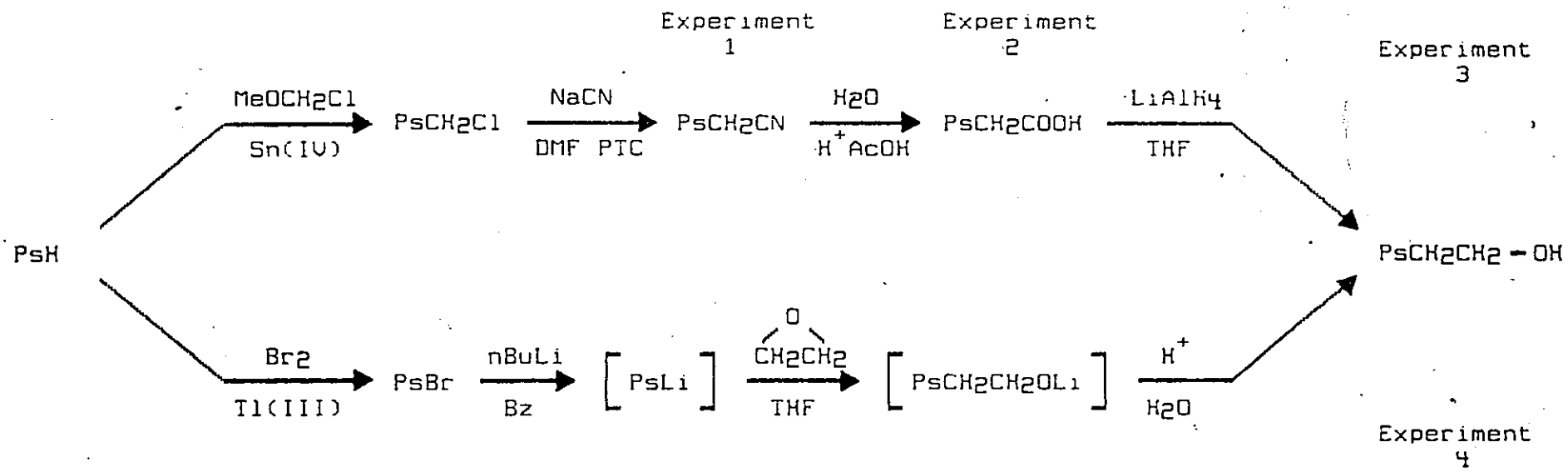
Modification reactions of polymer-bound species can be slower than for the free analogues, when limited by the speed of diffusion of a soluble reagent into the matrix. In good solvents such as benzene or tetrahydrofuran, permeation by liquid phase, visibly manifested by swelling of individual beads, is greatest in resins which are least crosslinked (e.g. initially prepared by suspension copolymerization with only 1-2 mol% divinylbenzene). In contrast, with very poor solvents such as water, the rigid macroporous structure conferred by large amounts (35-40 mol%) of crosslinking agent can maintain an acceptable surface area of contact with liquid phase against considerable hydrophobic forces of collapse -- beads of such macroporous resins have been profitably employed in fixed columns, though in stirred reactors they are easily shattered to very fine particles which clog the fritted glass filters normally used for subsequent separation of phases. Even at best, relatively more forceful conditions of heat and stirring are sometimes necessary to achieve complete functional group modification or other polymeric reaction.[2,10,13,27]

At even moderate degrees of functionalization, local concentrations of reactive sites within a matrix of flexible

polymer chains and spacers can be extremely high, and collisions between them frequent, so that aggregation, cooperation, dimerization or disproportionation between neighbouring functionalities may affect reactions of polymers, for better or worse, in ways or to extents not seen with the analogous free molecules.[85]

A functionalized dimethylene spacer may be obtained by extending available (chloromethyl)polystyrene by one carbon. (Methylsulfinylethyl)polystyrene and (isocyanoethyl)polystyrene have thus been prepared with sodium methylsulfinylmethylide[86] or lithium isocyanomethylide[87] respectively; but common cyanide gives a polymer which is a more versatile intermediate in the synthesis of other spacer-supported functionalities. Several different conditions for preparing (cyanomethyl)polystyrene have previously been reported, but none give an entirely satisfactory product: thus, using dimethylsulfoxide as solvent results in detectable (IR) oxidation to (formyl)polystyrene,[9,86] while hot wet dimethylformamide,[27] or liquid-liquid phase-transfer catalysis in dichloroethane/water[88] turn the polymer brown, possibly due to condensation between deprotonated cyanomethylene product and unreacted chloromethyl precursor groups. However, a combination of dry polar aprotic solvent, and solid-liquid-solid phase-transfer catalysis, results exclusively in nucleophilic substitution of chloride by cyanide anions, according to applied tests on the product (cyanomethyl)polystyrene and its

Scheme 2. Two Methods of Affixing Dimethylene Spacer to Crosslinked Polystyrene.



immediate derivatives (Experiment 1; Scheme 2).

A mixture of sulfuric and acetic acids and water[89] has been used to convert (cyanomethyl)polystyrene into (carboxymethyl)-polystyrene.[9,27,90,91] Lack of nitrogen in the product confirmed completion of the hydrolysis in this study (Experiment 2; Scheme 2), and discounted the possibility[92] of dialkylamino contaminants having been formed earlier by reaction with dimethylformamide solvent. This must be considered the method of choice to prepare (carboxymethyl)-polystyrene; an alternative procedure, where carbon dioxide is added to (lithiomethyl)polystyrene,[57] surely results in a product containing additional crosslinking and some ketone and/or alcohol side-products, as is observed with analogous free molecules[93].

Borane has been used to convert (carboxymethyl)polystyrene into (hydroxyethyl)polystyrene;[9] the more manageable lithium aluminum hydride, commonly used on free molecules such as phenylacetic acid,[94,95] quantitatively performed the same reduction (Experiment 3; Scheme 2). Elemental analysis of this alcohol and its derivatives proved that the polymer conserved its functionality through the entire synthesis via one-carbon extension, without, for example, undergoing decarboxylation[96] during the hydrolysis or reduction steps.

A dimethylene spacer terminated with a versatile hydroxyl handle can be more easily introduced onto commercial cross-linked polystyrene by treating the lithiated polymer,

controllably prepared in two steps via (bromo)polystyrene, with ethylene oxide.[67,78,80,83,97] With free aryllithiums, this reagent gives, after protonation, high isolated yields of primary alcohols without dimerization or rearrangement.[98,99] In contrast to bulkier cations, the intermediate lithium alkoxides, strongly associated even in ethereal solvents, are completely inert towards further addition to excess epoxide, no resulting ethers being recovered from such mixtures even after heating under pressure.[100-104] (Hydroxyethyl)polystyrene prepared by two-carbon addition in this study (Experiment 4; Scheme 2) was unaccompanied by grafted oligoethylene glycol, thus displaying FTIR peak-to-peak correspondence with the same polymer prepared from specialty monomer,[51] or by the one-carbon extension described above.

Prepared either way, via (bromo)polystyrene[105] or (chloromethyl)polystyrene,[31,106] (hydroxyethyl)polystyrene's functionalized spacers are almost exclusively attached <u>para</u> to the alkyl backbone. A slight but detectable reticulation reportedly accompanies similar reactions performed on soluble polystyrene, but this is probably insufficient to noticeably affect physical or chemical behaviour of the already-cross-linked beads used in this study.

Past efforts to attach longer reactive spacers to crosslinked polystyrene, by Friedel-Crafts alkylation with dihalides,[107] or reaction of dihalides[81,108] or cyclic halonium ions[49] with metallated polymer, have generally been

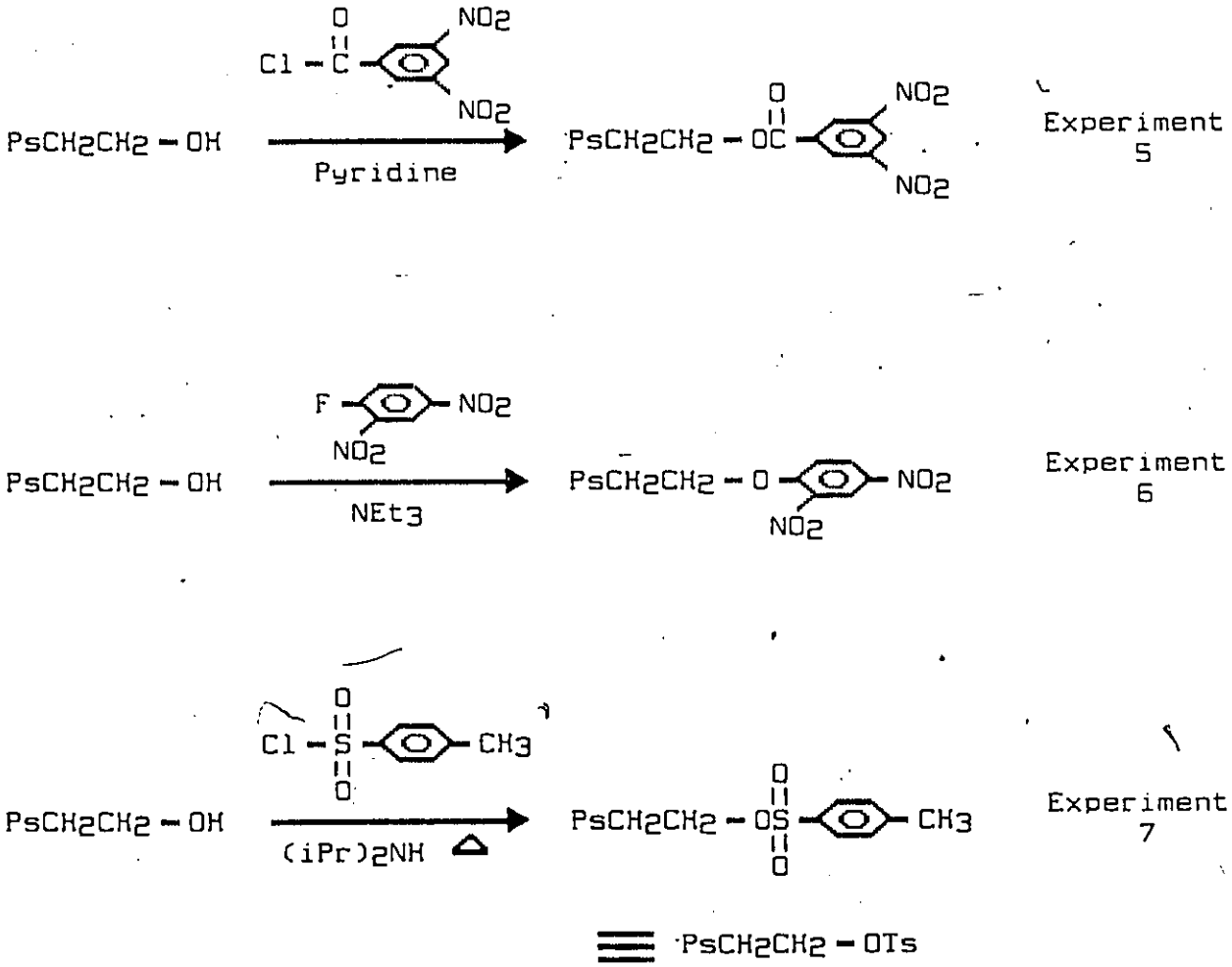
accompanied by excessive additional crosslinking of the polymer network, significantly restricting conversion and reducing later swelling and reactivity. A recent exception is Tomoi et al's[109] alkylation of soluble or crosslinked polystyrene with ω-bromoalkenes and 30 mol% trifluoromethanesulfonic acid catalyst, a promising functionalization which proceeds controllably and without crosslinking of the polymer backbone.

(Hydroxyethyl)polystyrene can be functionalized without breaking the C-O bond. (Diethoxyphosphinoxyethyl)polystyrene results from treatment with chlorodiethoxyphosphine and dimethylaniline in chloroform.[97] The polymeric alcohol has also been acylated by acetic anhydride,[83] by transesterification with methyl tartarate,[16] by carboxylic acids in the presence of dicyclohexylcarbodiimide,[80] and by acyl halides and acid acceptor.[51,67,78]

Derivatization with 3,5-dinitrobenzoyl chloride and a tertiary amine was easily followed by disappearance of the strong C-O-H peaks in a polymer's FTIR spectrum. Subsequent nitrogen analysis provided an indirect method of determining the degree of functionalization of polymeric alcohol precursor which is perhaps more reliable than direct oxygen quantitation, in which traces of air or moisture can obviously interfere (Experiment 5; Scheme 3).

2,4-Dinitrofluorobenzene has often been used to derivatize free amines and alcohols,[110] particularly in peptide

Scheme 3. Functionalization of Dimethylene Spacer. Ester, Ether and Sulfonate.



chemistry. In this study, (hydroxyethyl)polystyrene readily formed a polymeric ether with this reagent in the presence of an acid acceptor (Experiment 6; Scheme 3). Probably this straightforward reaction is also easily accomplished with other alkylating agents.

Treatment with toluenesulfonyl chloride in pyridine is reported to give good isolated yields of sulfonate ester from (hydroxyethyl)benzene.[111,112] However, tosylate anion, unlike carboxylate, is a very good leaving group, and tosylation of the macromolecular alcohol in pyridine must be performed at ice-cold temperatures if formation of quaternary ammonium and other side-products[113,114] is to be entirely suppressed: under these conditions, the reaction takes a week to complete.[115] Elsewhere in this study (Experiment 38), it was observed that tosylated polymer, once formed, is quite inert to futher reaction with even hot diisopropylamine. With this nonnucleophilic[116,117] amine instead of pyridine as acid acceptor, the tosylation mixture could be heated to reflux and still produce, in only a few hours, pure (toluene-sulfonyloxyethyl)polystyrene free of amine, chloride or ether side-products (Experiment 7; Scheme 3). The active reagent is probably the intermediate tertiary dialkylsulfonamide which is formed exothermally upon initial mixing of the reagents.[45,118] This new and very efficient tosylation procedure may prove useful in other important areas of organic synthesis.

For (hydroxyethyl)polystyrene to succeed as a versatile

synthetic intermediate towards useful polymer reagents, techniques must be developed to quantitatively replace oxygen by other atoms which may be more suited to the desired function of final product. Because it increases conjugation in the product, elimination can be an important side-reaction in phenethyl compounds undergoing nucleophilic substitution. Fortunately, this can often be avoided by careful choice of reaction strategy and conditions: for example, by choosing tosylate as leaving group,[111,112] and by working in polar solvents at low or moderate temperatures with strong nucleophiles that are also weak bases.[110,119] With the target functional product, elimination should no longer be a problem, since most final functionalities (amines, etc.) are poor leaving groups under basic conditions.

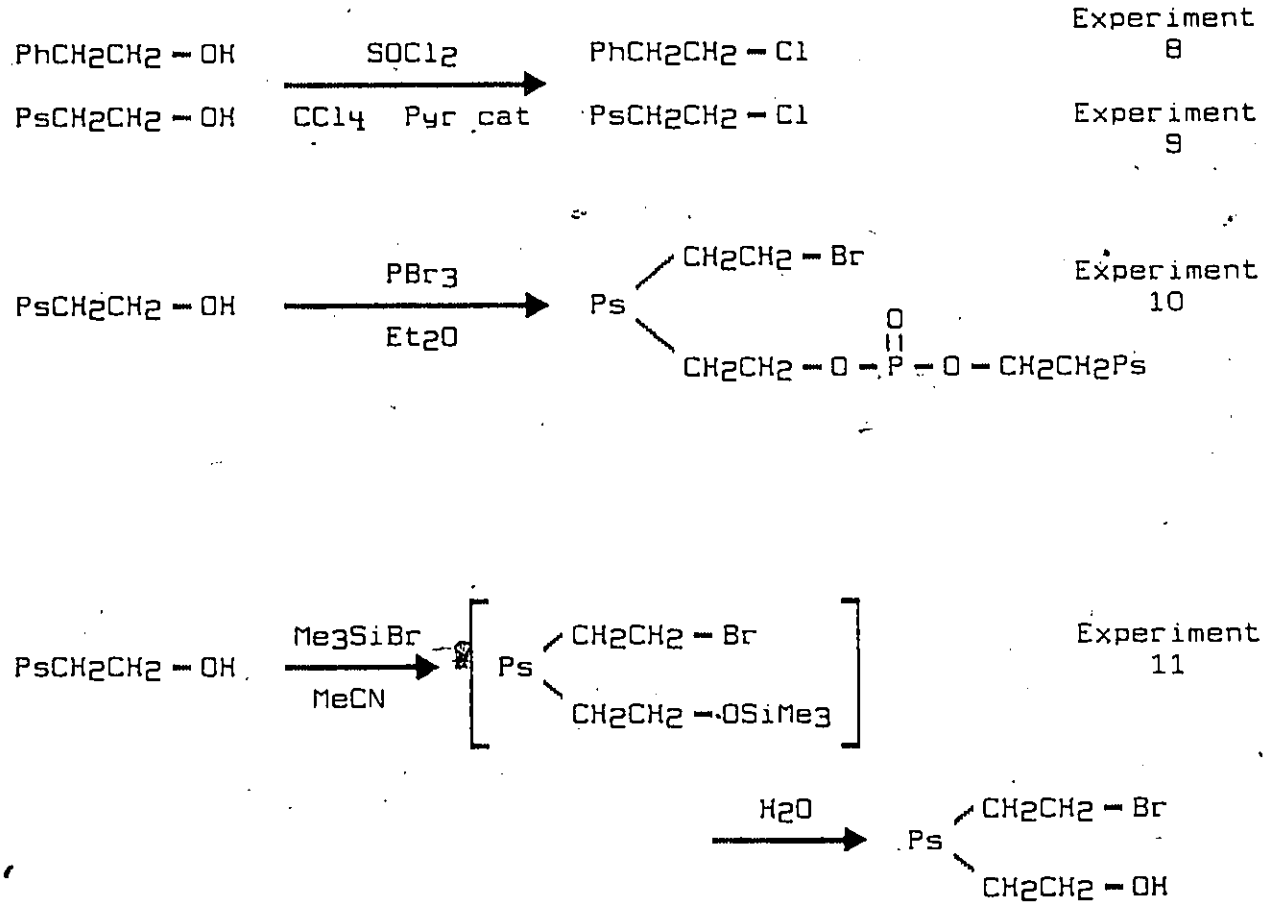
Nucleophilic substitution at a position two carbons distant from an aromatic ring, particularly when conducted on tosic ester in a polar medium with anchimeric assistance by acid (S_N1 conditions), may be accompanied by a curious scrambling of both intervening atoms, giving two distinguishable products from branched or labelled phenethyl substrates, though only one from simple (toluenesulfonyloxyethyl)benzene.[120] This rearrangement is a symptom of the formation of a non-classical trigonal "phenonium" ion intermediate, from which products evolve by attack of nucleophile at either of two positions. Substitutions capable of proceeding by this mechanism, which is further favoured by alkyl or other electron donors at para

on the ring, are faster and cleaner than others in which classical Sn2 operates alone.[121]

A standard method of converting alcohols to alkyl chlorides is to heat them with thionyl chloride and a trace of pyridine: (chloroethyl)benzene is so produced in high yield.[122] In this study, a model showed the reaction to proceed entirely without rearrangement (Experiment 8; Scheme 4). Thionyl chloride swells polystyrene,[27] and so this reagent was able to penetrate to consume all alcohol groups during overnight reflux of (hydroxyethyl)polystyrene in carbon tetrachloride; no (N-pyridiniumethyl)polystyrene contaminates the (chloroethyl)polystyrene product (Experiment 9; Scheme 4).

Tribromophosphine converts free phenethyl alcohols to the bromides in high yields,[99] and it has been reported [9] that (bromoethyl)polystyrene is obtained from polymeric alcohol with this reagent. However, when the reaction was reinvestigated for this study, strange peaks present in the product's FTIR spectrum indicated that phosphite intermediates remained in the resin, not being completely cleaved to alkyl bromide even with further addition of excess HBr (Experiment 10; Scheme 4). Similar bromination of certain bulky free molecules is also easily halted at the dialkylphosphite stage.[123] This is in contrast to the thionyl chloride reaction discussed above, which is pushed to completion by evolution of a gaseous side-product, sulfur dioxide, from the reaction mixture. Use of a trivalent reagent may also have facilitated

Scheme 4. Functionalization of Dimethylene Spacer. Chloride and Bromide.



crosslinking of the polymer network by -O-P-O- bonds, perhaps interfering with the cleavage step or washing out of final phosphonic acid.

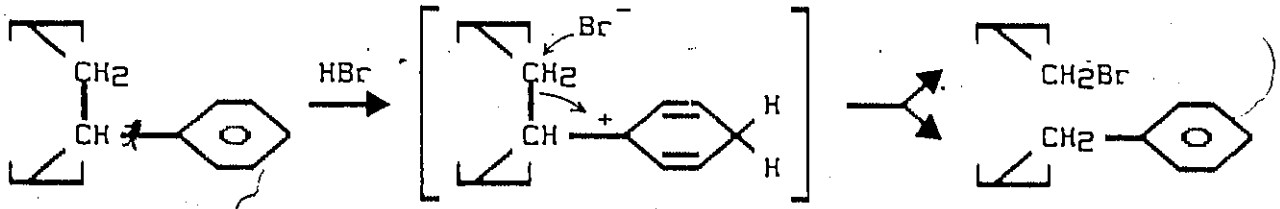
In acetonitrile, lithium bromide/chlorotrimethylsilane is reported to convert free alcohols quantitatively to the corresponding alkyl bromides;[124] the active species is probably a silyl-nitrilium bromide complex.[125] However, spectroscopic and elemental analyses indicated incomplete transformation from (hydroxyethyl)polystyrene; a second identical treatment of the partially-brominated polymer left about the same proportion of remaining hydroxyl still unconsumed (Experiment 11; Scheme 4). In less polar solvents, the preferred product of a halotrimethylsilane with an alcohol is the trimethylsilyl ether,[126,127] which the bromo reagent in particular cannot further cleave.[128] Possibly, even suspended in acetonitrile, the interior of a polystyrene bead is sufficiently apolar[78] to encourage formation of substantial (trimethylsilyloxyethyl)polystyrene, which is hydrolyzed back to starting alcohol in the workup. Similar "polymer solvent effects" may be influencing the rates and outcomes of other kinds of functional group modifications discussed in this thesis.

Though reaction with hydrochloric acid is too slow, and hydriodic acid tends to overreact, concentrated hydrobromic acid is a standard and economical reagent for the conversion of alcohols to haloalkanes;[129] in particular, excellent

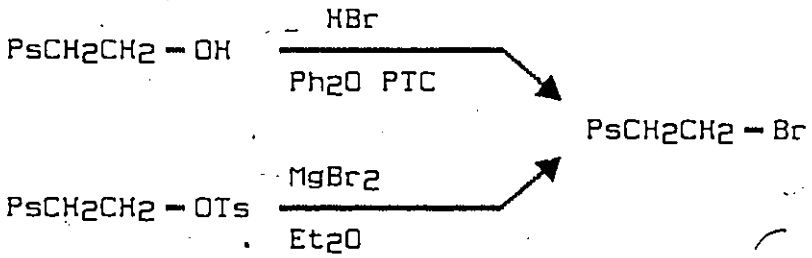
isolated yields have been reported from (hydroxyethyl)-benzene.[120,130] This was confirmed for this study by a model reaction (Experiment 12; Scheme 4), in which the alcohol, diluted in aromatic organic solvent to simulate a swollen polymer environment, was rapidly stirred with hot HBr/H_2O, together with a heat-stable onium catalyst capable of transporting hydrohalide into a hydrophobic medium by hydrogen-bonding.[131-133] With the polymer (Experiment 13; Scheme 5), this quaternary phosphonium salt also functionned as a surfactant, dispersing the organic solid which otherwise formed lumps impermeable to the aqueous phase. Nevertheless, conversion past 90% of polymeric hydroxyls in toluene was very slow, and was accompanied by physical degradation of the polymer beads resulting from chain scission. Additives or solvents such as chlorobenzene, octanoic acid, toluenesulfonic acid, pyridine or tetramethylene sulfone failed to improve the reaction. However, substituting diphenyl ether as solvent, which permitted a higher reaction temperature while leveling the Lewis acidity of HBr, allowed complete conversion in a reasonable time without disintegration of the polymer matrix (Experiment 14; Scheme 5).

Satisfactory synthesis of (bromoethyl)polystyrene was also achieved via available (toluenesulfonyloxyethyl)polystyrene (Experiment 15; Scheme 5). Finklestein-like metathesis of phenethyl and other tosylates to the bromides has been achieved with excess LiBr/acetone,[111] NaBr/dimethylsulfo-

Scheme 5. Functionalization of Dimethylene Spacer. Bromide and Iodide.

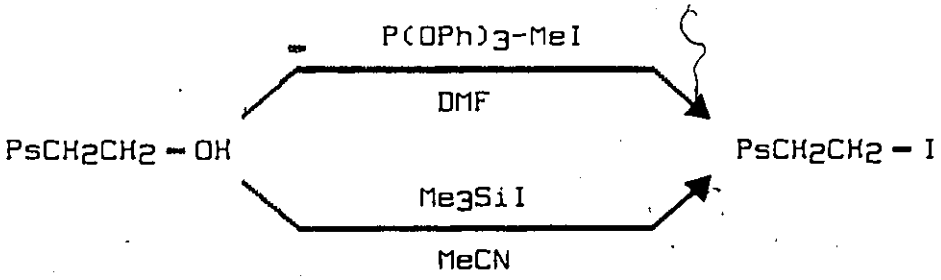


Experiment 13



Experiment 14

Experiment 15



Experiment 16

Experiment 17

xide,[134] and $CaBr_2$/dimethylformamide,[135] but best yields are reported with $MgBr_2$/ether,[136] with which equilibrium is shifted to products by hard-hard ion adhesion between magnesium cation and tosylate anion. Anhydrous magnesium bromide etherate is very easily made by adding 1,2-dibromoethane to magnesium metal, a vigorous reaction often used to help Grignard formation.

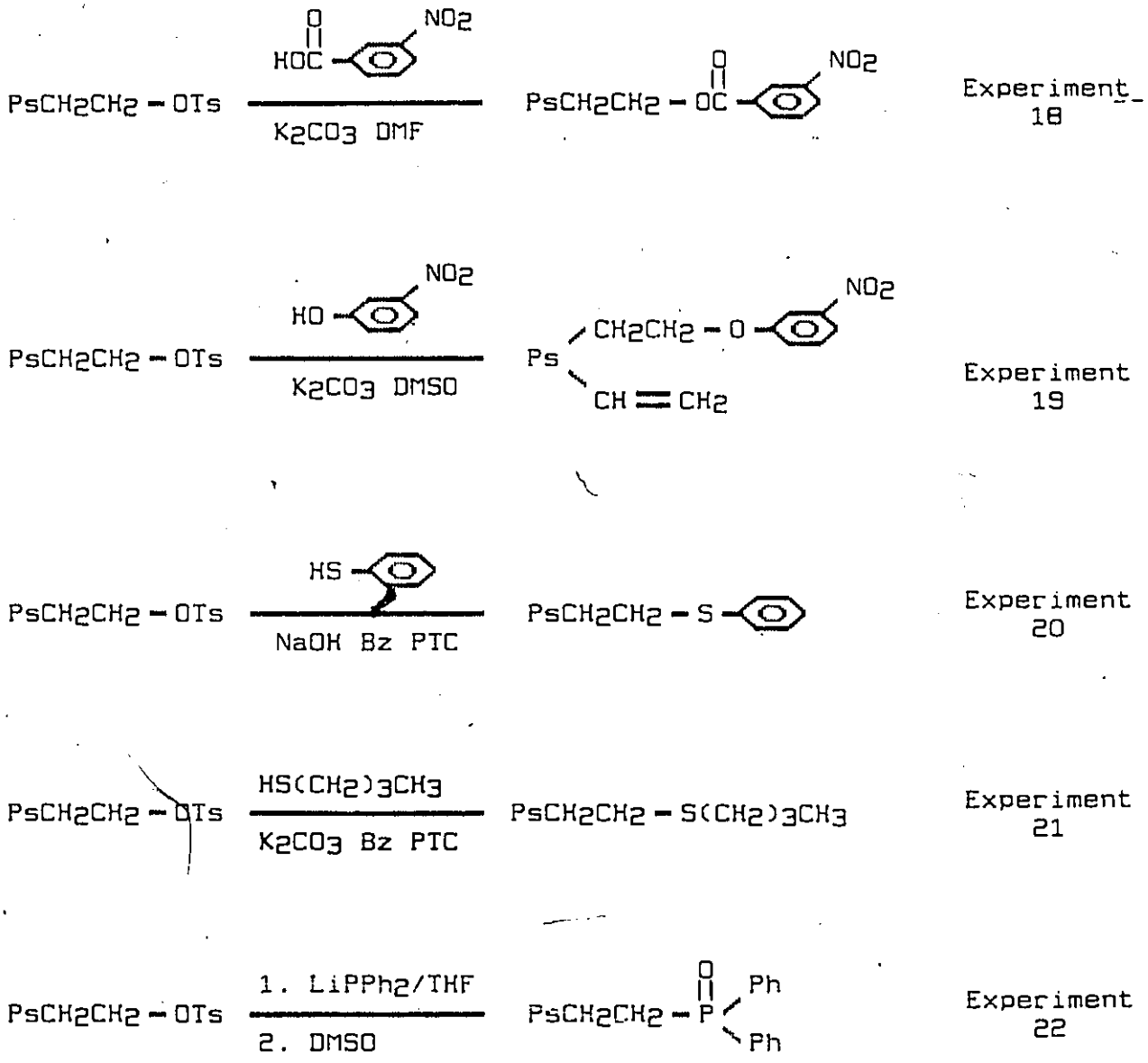
Iodomethane/triphenyl phosphite/dimethylformamide converts free phenethyl alcohol to (iodoethyl)benzene in excellent isolated yield without rearrangement.[137] Reaction of the polymeric alcohol (Experiment 16; Scheme 5) also proceeded smoothly to completion without trace of the phosphite residue seen earlier (Experiment 10; Scheme 4) with PBr_3. The recently developed sodium iodide/chlorotrimethylsilane/acetonitrile reagent[125] is as effective (Experiment 17; Scheme 5), more convenient and less wasteful than the nineteen-carbon phosphorous species (Experiment 16; Scheme 5). In contrast to the bromo compound (Experiment 11; Scheme 4), iodotrimethylsilane is quite strong enough[125] to further cleave any trimethylsilyl ethers[127] which might have been formed in the course of the reaction.

Displacement of a good leaving group by carboxylate is an alternative method of forming an ester. Phase-transfer catalysis, often used for reactions with (chloromethyl)polystyrene, is not helpful with (toluenesulfonyloxyethyl)-polystyrene because of catalyst poisoning by released

lipophilic tosylate.[33,34,138,139] Fortunately, the reaction proceeds well without onium salts or crown ethers if polar aprotic solvents are employed; hexamethylphosphoramide notably solvates alkali metal cation, freeing carboxylate anion for nucleophilic instead of basic action.[140-142] For example, m-nitrobenzoic acid, whose nitrogen functionality makes its presence easy to quantitate on insoluble polymer, was readily attached to dimethylene spacer with little or no elimination, using potassium carbonate in a mixture of dimethylsulfoxide and hexamethylphosphoramide (Experiment 18; Scheme 6). Cesium fluoride in dimethylformamide, also able to generate very "free" anions,[143,144] was effective too.

Even with tert-butoxide, phenethyl tosylate prefers nucleophilic substitution to elimination in polar aprotic solvent;[119,145] it can be hoped that less hindered or basic alcohols[111] may produce polymeric phenethyl-type ethers in acceptable conversions under similar conditions. Nevertheless, in this study, reaction with nitrophenolate still resulted in a small but detectable loss of polymer functionality, according to elemental analysis of the product, probably through competing elimination of tosylate (Experiment 19; Scheme 6). Other reactions with primary alkoxides gave significant IR peaks for alkene, proving that these modifications had fallen even further short of the required 100% functional yield. Continued exploration of conditions, perhaps employing cations capable of promoting substitution by

Scheme 6. Functionalization of Dimethylene Spacer. Oxygen, Sulfur and Phosphorus.



anchimeric assistance of leaving group,[46,136,146,147] may yet enable efficient immobilization of useful functionalities through the ether linkage.

Thiolates are stronger nucleophiles and weaker bases than the corresponding alkoxides, and give little or no elimination in reactions with primary alkylating agents,[148] even with (toluenesulfonyloxyethyl)benzene as substrate.[111] Being themselves very soft and lipophilic anions, they can successfully compete with others such as iodide or tosylate for transport by onium salts, which are otherwise poisoned by these leaving groups during phase-transfer catalysis.[148-150] Overnight stirring at room temperature of (toluenesulfonyloxyethyl)polystyrene with thiophenolate and tricaprylmethylammonium chloride in benzene gave complete replacement of tosylate with thiophenyl peaks in the polymer's FTIR spectrum (Experiment 20; Scheme 6). At a somewhat higher temperature, requiring a heat-resistant[148,151] phosphonium phase-transfer catalyst, butanethiol was also immobilized in complete or near-complete conversion (Experiment 21; Scheme 6).

Polymeric phosphines have found wide application as supports for hydrogenation and other catalysts;[72,73,152] sulfoxides[153] oxidize them to the more stable phosphine oxides, which are also useful as regenerable reagents for making acyl chlorides from carboxylic acids.[21] However, synthesis[21,73] from (chloromethyl)polystyrene and lithium diphenylphosphide (frequently generated in situ with lithium

metal[72]) is accompanied by overalkylation with the reactive benzylic alkylant, as testified by a persistent residue of ionic chloride.[154] Since metal phosphide also gives high yields of free tertiary phosphine ligands from primary alkyl tosylates,[155] (toluenesulfonyloxyethyl)polystyrene ought to be a good or even better alternative solid substrate, except that "one-pot" conditions using elemental lithium might result here in reduction of released tosylate to products that might contaminate the polymer resin. Treatment with pre-formed phosphide, followed by dimethylsulfoxide or exposure to air, gave a polymer-bound tertiary phosphine oxide in a single step without quaternization or elimination, according to FTIR spectroscopy (Experiment 22; Scheme 6). Phosphorus analyses of the benzylic polymers are elsewhere reported "usually high and nonreproducible",[21] as they were found here, possibly due to traces of only slightly soluble diphenylphosphine or phosphinate remaining in the polymer even after solvent wash.

(Tributylphosphoniumethyl)polystyrene bromide has been obtained from (bromoethyl)polystyrene by heating with tributylphosphine; similarly, heating with tributylamine gives (tributylammoniumethyl)polystyrene bromide.[9] Free alkyl tosylates--including (toluenesulfonyloxyethyl)benzene[111]--are also quaternized by heating with tertiary amine; N-alkylpyridinium salts have been made this way.[35,156-159] Heating (toluenesulfonyloxyethyl)polystyrene with pyridine in organic solvent gave, according to FTIR spectroscopy, quantitative

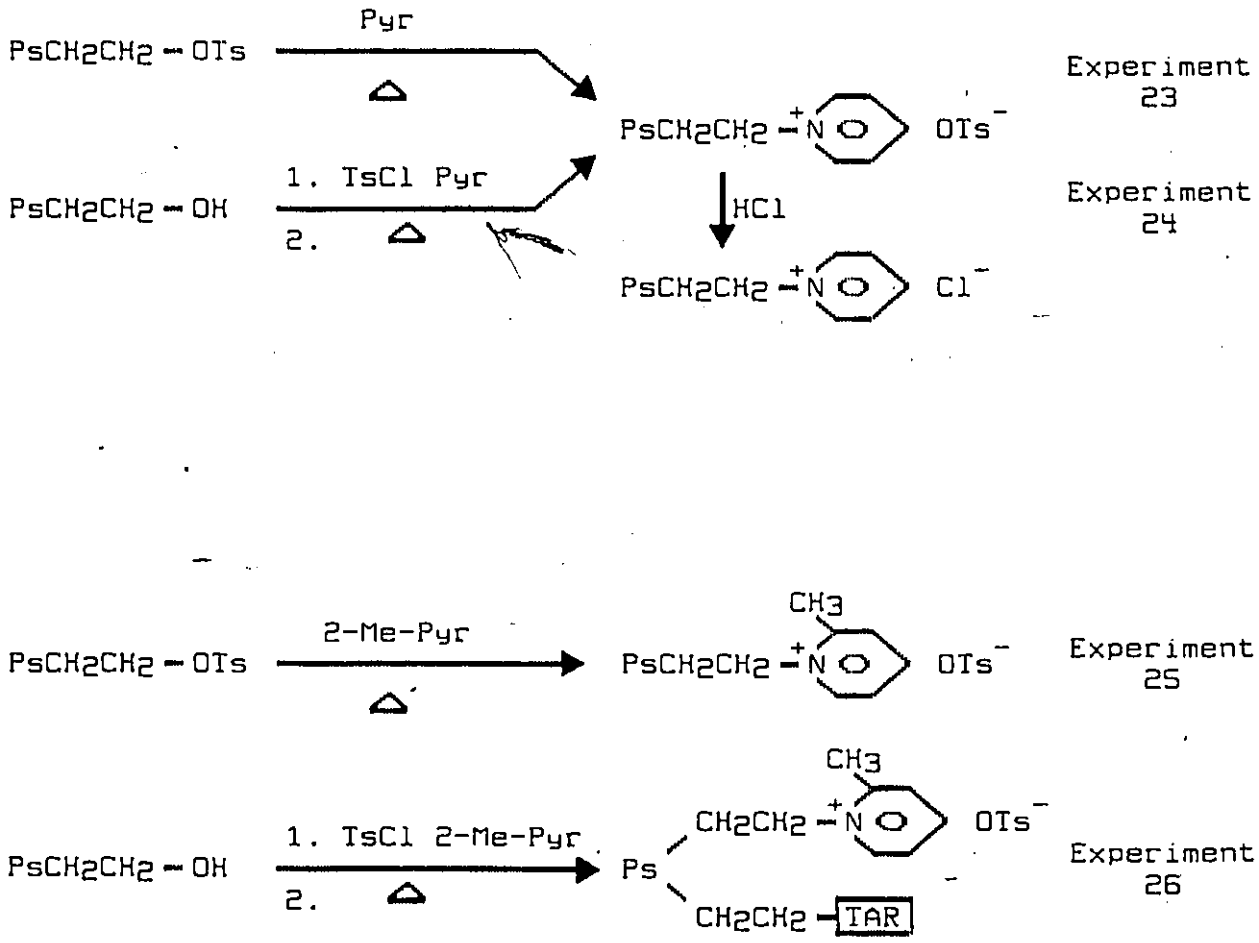
conversion to quaternary ammonium tosylate (Experiment 23; Scheme 7).

Heating with tosyl chloride and an excess of tertiary amine is a good way of converting an alcohol to a quaternary ammonium salt in a single step.[160] (Hydroxyethyl)polystyrene treated in this way (Experiment 24; Scheme 7) gave exactly the same product as from (toluenesulfonyloxyethyl)polystyrene heated in pyridine (Experiment 23; scheme 7). The stronger hydrochloric acid protonated toluenesulfonate and forced metathesis to the quaternary ammonium chloride.

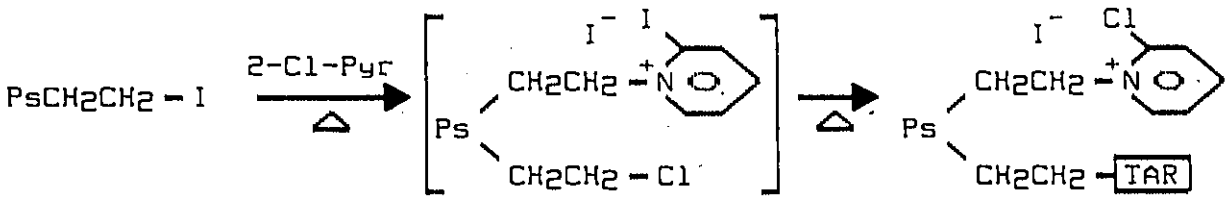
Pyridines with sterically hindered nitrogen and/or electron-withdrawing groups are more difficult to alkylate.[157,161] Heating in a large excess of pure nucleophile as solvent was necessary for 2-methylpyridine to completely displace primary tosylate from polystyrene (Experiment 25). With 2-alkylpyridine the "single-pot" method from alcohol gave a very dark product, probably due to partial sulfonylation of the acidic methyl by excess tosyl chloride to give a coloured methide impurity (Experiment 26; Scheme 7).

Free alkyl halides such as iodomethane[162-164] or, much less reversibly, [165,166] (bromoethyl)benzene,[167] can alkylate the nuclear nitrogen of 2-chloropyridine, despite steric and electronic inhibition by its ortho-chlorine, to give 2-chloro-N-alkylpyridinium halides in good to excellent yield. Nevertheless, in hot halopyridine as solvent, reaction with (iodoethyl)polystyrene proved difficult (Experiment 27; Scheme

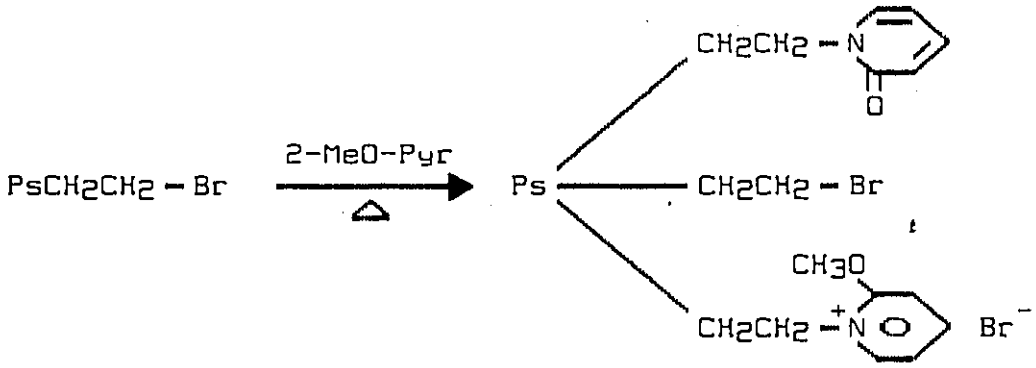
Scheme 7. Functionalization of Dimethylene Spacer. Pyridinium salts.



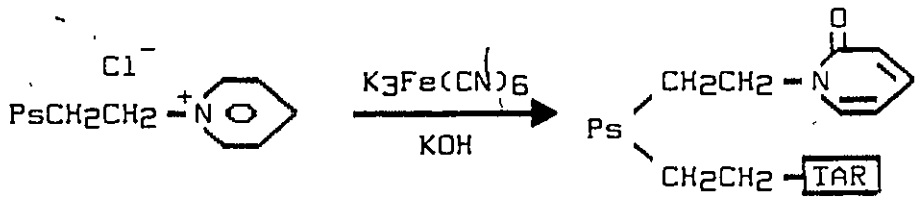
Scheme 8. Functionalization of Dimethylene Spacer. 2-Halopyridinium and Pyridinone.



Experiment 27



Experiment 28



Experiment 29

Table 1. Results of Alkylation of (iodoethyl)-polystyrene with 2-chloropyridine.

Degree of Functionalization	Temp. °C	Time (days)	Conv. %	Anal. %N[a]	Anal. %Cl[a]	Anal. %I[a]	Tot.X meq/g[a]
.25	61[b]	1	0	0.00 (0.00)			1.75 (1.68)
.29	90	2	50	1.23 (1.23)			2.56 (2.63)
.29	90	4	66	1.54 (1.56)			2.85 (2.81)
.25	100	3	84	1.78 (1.76)			
.21	100	5	100	1.83 (1.76)	5.00 (4.64)	16.60 (17.00)	2.68 (2.62)

Notes:

[a] Numbers in parentheses were calculated from estimated conversions. [b] Solvent was 10% 2-chloropyridine/$CHCl_3$; others in pure 2-chloropyridine.

8; Table 1): conditions required to force the reaction to completion resulted in darkening of the polymer, possibly due to self-polymerization[161] and/or ring-opening[168] reactions of neutral or quaternized nitrogen heterocycles. A reluctance to push past 50% conversion may be attributed to exchange of mobile chloride for nearby unreacted alkyl iodide, as has frequently been observed of free halopyridinium salts in warm organic solvents,[162,163,169,170] giving a 1:1 mixture of (2-iodopyridinium-N-ethyl)polystyrene and relatively inert (chloroethyl)polystyrene functionalities, both clearly evident by FTIR spectroscopy. Morevover, since halopyridinium salts precipitate in many solvents,[163,167,171] their formation may lead to shrinkage of polymer gel with exclusion of remaining groups from further reactions.

2-Alkoxypyridines are known to react with (bromoethyl)benzene to give (2-pyridinon-N-ethyl)benzene after workup.[76] Application of this reaction towards an alternative synthesis of polystyrene-supported 2-substituted pyridine functionality again proved difficult: though the product was not so strongly coloured by ring-opening impurities, elemental analyses indicated that both formation of polymer-bound alkoxypyridinium salt and its subsequent cleavage to pyridinone had been incomplete (Experiment 28; Scheme 8). This again may be due to a relatively apolar and hydrophobic environment within the polystyrene matrix. Undoubtedly as well a certain amount of reagent is lost from the reaction mixture

at high temperatures by rearrangement to N-alkyl-pyridinone through an O-to-N alkyl migration, via either intermolecular free-radical or ionic mechanisms, the latter catalyzed by alkyl halides and other Lewis acids.[172-174]

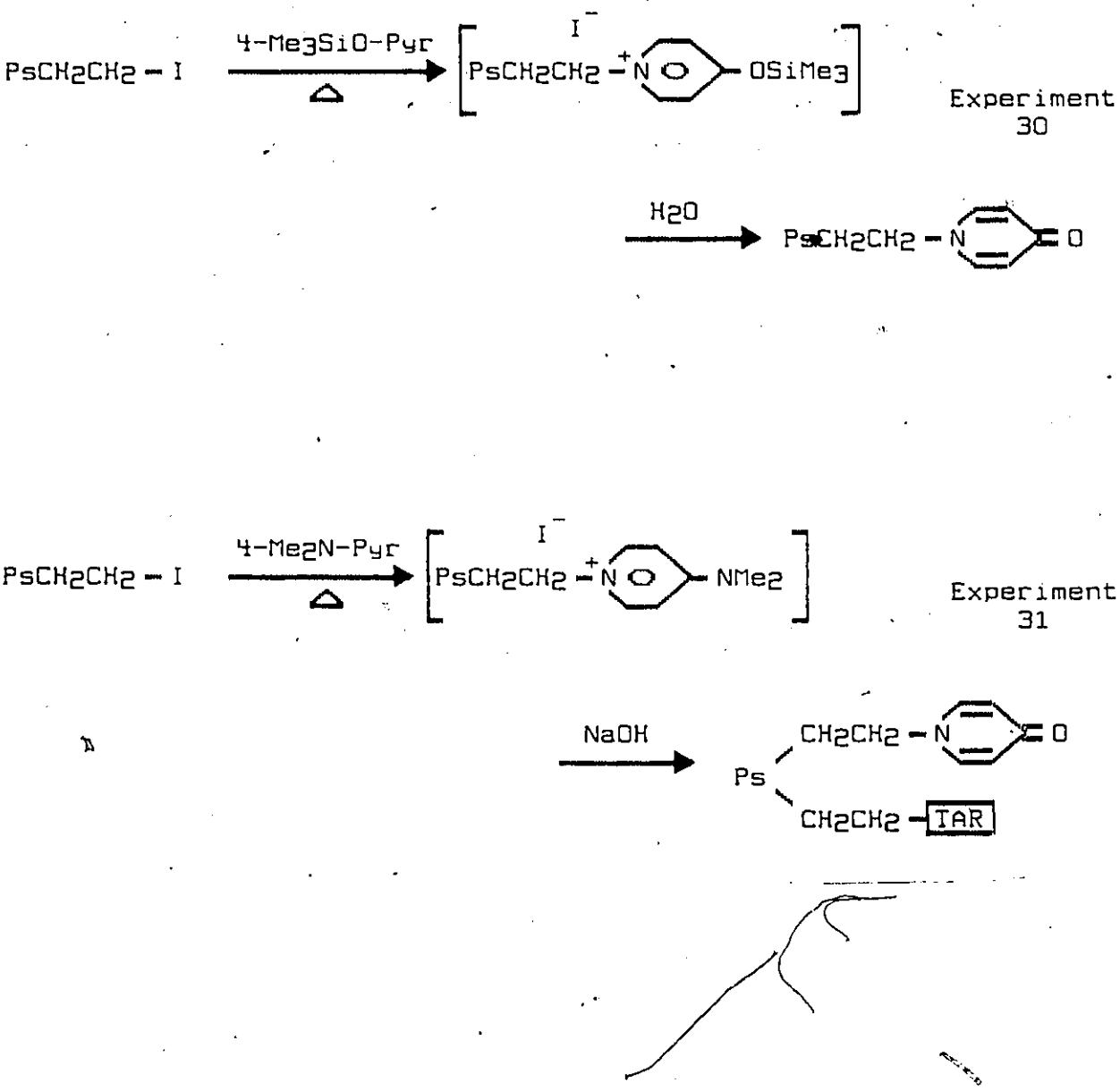
A standard route towards free N-alkyl-2-pyridinones involves the oxidation, by ferricyanide,[175] of the pseudo-base formed from hydroxide and N-alkylpyridinium salts.[176,177] This reaction works well with (pyridinium-N-ethyl)benzene, giving none of the 4-keto isomer.[178-180] With the polymer analogue, the only solvent in which pyridinium precursor was completely consumed was dimethylsulfoxide, presumably because of its ability to swell or dissolve all the species involved (Experiment 29; Scheme 8). However, the polymer became very dark, because of ring-opening[168] of some of the intermediate pseudo-base groups before they could be oxidized, giving conjugated aminals which further disproportionate or polymerize to coloured side-products. A clean synthesis of polymer-bound pyridinones must be sought elsewhere.

Gamma trimethylsilyloxypyridine is easily prepared from the economical hydroxypyridine; it is somewhat more reactive than the ortho isomer.[44,181] In general, siloxypyridines are easily N-alkylated, then the silyl ether hydrolyzed to give the corresponding pyridinones, without the ring-opening, rearrangement or self-polymerization side-reactions produced by the more severe conditions required with other substituents.[181-183] Indeed, with (iodoethyl)polystyrene,

either isolated, or generated in situ from other polymers by halide exchange, the reaction appeared swift and complete, yielding, after workup, (4-pyridinon-N-ethyl)polystyrene of acceptable weight, colour, FTIR spectrum and nitrogen content (Experiment 30; Scheme 9).

Electrophiles react with N,N-dialkyl-4-aminopyridines exclusively at ring nitrogen, being attracted to this position by its enhanced electron density;[162,184,185] with the 2-isomers, the more electronegative site is sterically hindered by the side-chain, so that alkylation at peripheral nitrogen may become important and even predominant.[186] Quaternization of pyridine generally activates tertiary amino substituents at the 2 or 4 position for nucleophilic aromatic substitution by hydroxide, but not fluoride, cyanide, alkoxides or thiolates, for which N-alkyl-dimethylaminopyridinium salts are exceptionally stable phase-transfer catalysts in anhydrous media.[184,187] Under neutral conditions, alkylations of primary or secondary pyridinamines occur at either nitrogen; pyridonimines, arising from the ring alkylation, are also hydrolyzable to pyridinones.[188-190] Alkylation of available and easily-handled 4-dimethylaminopyridine went well with functionalized polystyrenes, but subsequent hydrolysis could not be accomplished without severe darkening by the ubiquitous ring-opening reactions of N-alkylpyridinium compounds in aqueous base (Experiment 31; Scheme 9).

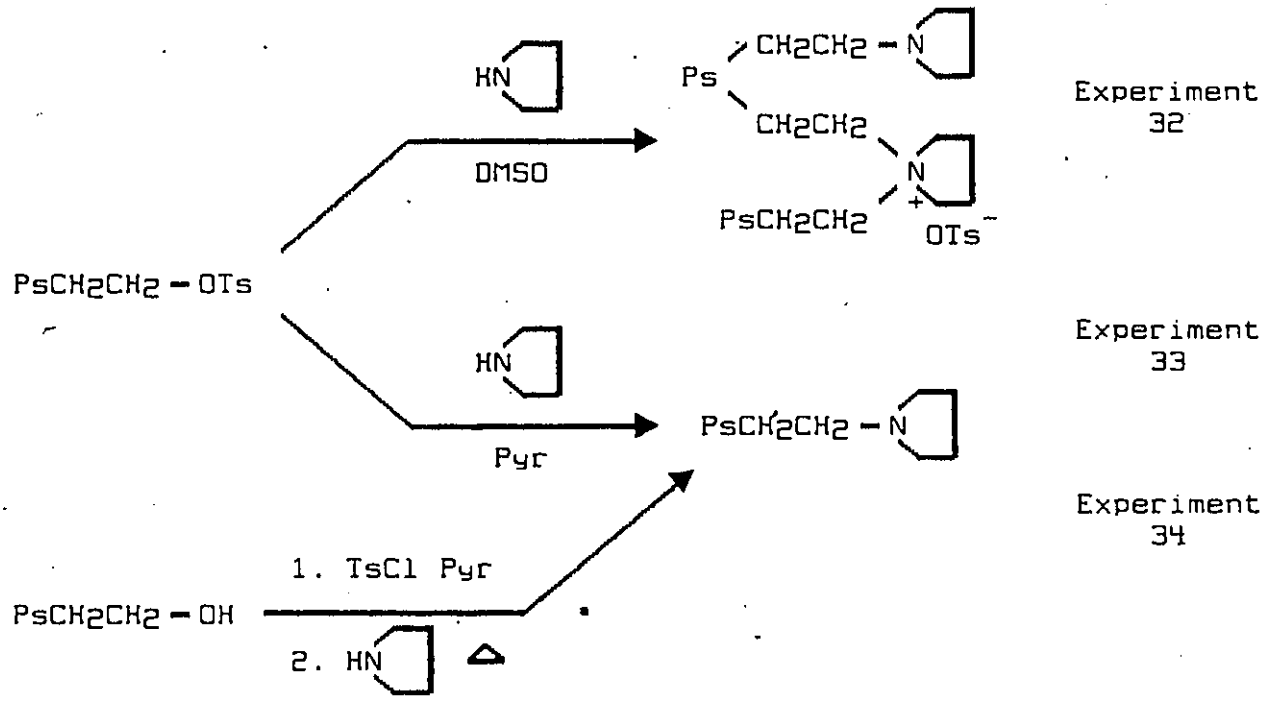
Scheme 9. Functionalization of Dimethylene Spacer. 4-Pyridinone.

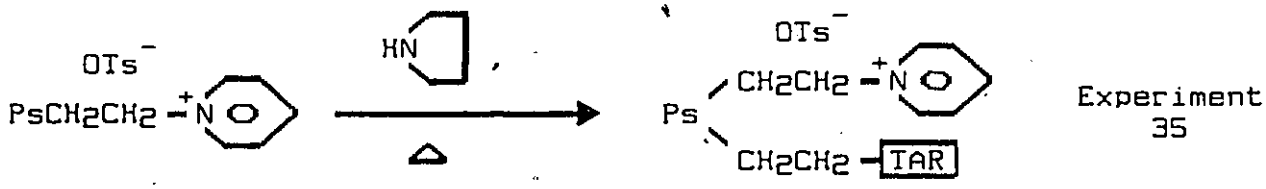


Many secondary amines are monoalkylated by sizeable tosylates,[113,158] such as (toluenesulfonyloxyethyl)-benzene),[111] in high isolated yields without side-reaction. In this study, (toluenesulfonyloxyethyl)polystyrene treated with stochiometric pyrrolidine and acid acceptor in polar aprotic solvent gave a polymer of nitrogen content slightly lower than expected for complete conversion to tertiary amine; small irregularities in the FTIR spectra suggested formation of traces of tosylate anions and carbon-carbon double bonds (Experiment 32; Scheme 10). An extremely polar solvent like dimethylsulfoxide or dimethylformamide may encourage competitive quaternization[156,157] (often seen with the very reactive (chloromethyl)polystyrene)[191] by tosic ester of polymer-bound tertiary amine rather than alkylation of absorbed free secondary amine, particularly when local concentrations of the former and latter are respectively very high and very low towards the end of a reaction; subsequent and/or simultaneous elimination by solvated inorganic base is also conceivable under these conditions.

Use of pyridine, a solvent of somewhat lower polarity, resulted in complete functional group modification of tosic ester to tertiary amine without quaternization, either of polymer-bound functionalities or free solvent (Experiment 33; Scheme 10). With pyridine as solvent, tertiary amines could even be prepared directly from (hydroxyethyl)polystyrene in a one-pot reaction using an excess of nucleophile over toluene-

Scheme 10. Functionalization of Dimethylene Spacer. Pyrrolidine.





sulfonyl chloride (Experiment 33; Scheme 10). Tosylation in situ must be complete before addition of secondary amine because, unlike diisopropylamine (Experiment 7; Scheme 3), the toluenesulphonamides of unhindered amines such as pyrrolidine appear to be too stable to transform alcohols to alkyl tosylates.

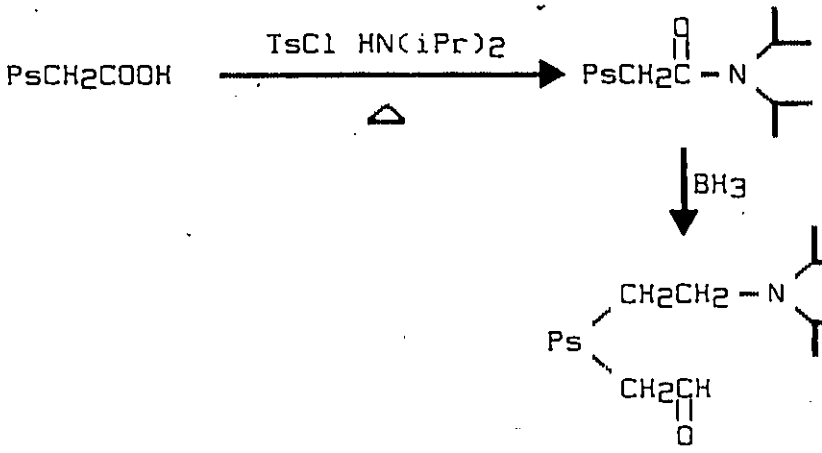
It might be suggested that this reaction (and possibly other nucleophilic substitutions employing pyridine as solvent) proceeds via a quaternary ammonium functionality, quickly formed by attack of pyridine onto (toluenesulfonyloxyethyl)polystyrene, then slowly cleaved by secondary amine to give tertiary amine product. However, a test reaction between preformed polymeric pyridinium tosylate and pyrrolidine was incomplete even after overnight reflux (Experiment 35; Scheme 10); whatever pyrrolidyl that became bound did so by attack onto the pyridinium ring, giving conspicuous dark dyestuff, rather than by displacement and expulsion of heterocycle from polymer support. Therefore, the synthesis of (pyrrolidin-N-ethyl)polystyrene in pyridine demonstrates successful competition for alkylant by secondary over tertiary amine in a nucleophilic substitution under kinetic control.

In contrast to pyrrolidine, diisopropylamine seemed at first glance difficult or impossible to alkylate with (toluenesulfonyloxyethyl)polystyrene (see above); its anion, notorious as a nonnucleophilic base,[192] would be an even more unsuitable substrate. Nevertheless, (diisopropylaminoethyl)-

polystyrene would be of interest as a stable, recyclable version of the non-nucleophilic base diisopropylethylamine, much used for tricky alkylations and eliminations.[193] An unequivocal synthesis was conducted via polymeric carboxamide, which was prepared from (carboxymethyl)polystyrene using (toluenesulfonyl)chloride as condensing agent (Experiment 36; Scheme 11). Isolation of tosic-carboxylic anhydride intermediate[194,195] was not necessary: in a one-pot reaction, it was in situ both generated by tertiary sulfonamide then, unlike the tosic ester prepared in a similar way (Experiment 7; Scheme 3), aminated by excess secondary amine. This procedure avoids the polymeric acid chloride,[27] whose preparation and reactions may be accompanied by acylation of acidic methylene carbon, a well-known side-reaction of the free analogue.[196]. Elemental analysis indicated that the subsequent borane[197] reduction of polymeric carboxamide to tertiary amine (Experiment 37; Scheme 11) was accompanied by a slight loss of nitrogen, probably due to a side-reaction known for hindered amides in general,[198] in which hemiaminal reduction intermediate decomposes to aldehyde (usually further reduced to the alcohol) and free amine.

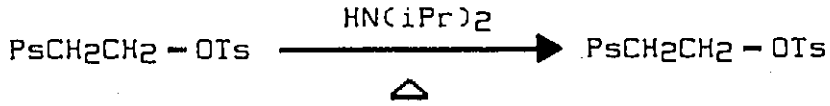
The target polymer was now in hand, but it had been obtained via a lengthy and specialized synthetic route; moreover, it was less than 100% pure. So, further efforts were made to discover conditions for obtaining (N,N-diisopropyl-aminoethyl)polystyrene directly from versatile and available

Scheme 11. Functionalization of Dimethylene Spacer. Other amines.

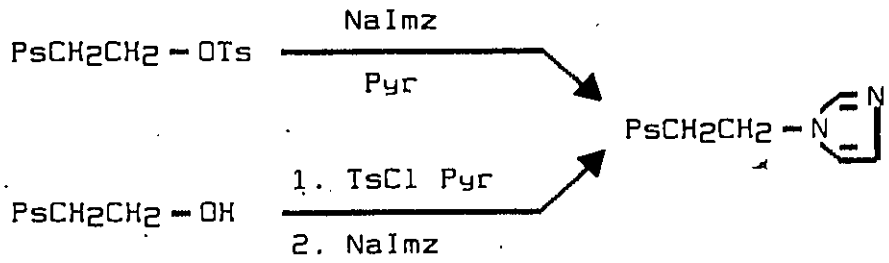


Experiment 36

Experiment 37



Experiment 38



Experiment 39

Experiment 40

(toluenesulfonyloxyethyl)polystyrene. Using the FTIR peak for isopropyl C-H (2694 cm^{-1}) as a yardstick, it was ascertained that the tosic ester was indeed inert to diisopropylamine in refluxing carbon tetrachloride or pure amine, as well as in tetramethylenesulphone polar aprotic solvent at a similar temperature (85°C)(Experiment 38; Scheme 11). In N-methylpyrrolidinone, diisopropylamination was only barely detectable, and was accompanied by products of elimination and possibly of attack by amide solvent. Acid catalysts led to more serious decomposition of the solvent, but a fortuitous application of chlorotrimethylsilane, during an unsuccessful synthesis of (2-pyridinon-N-ethyl)polystyrene, seemed to result in functionalization, not by pyridinone, but by the diisopropylamine which was also present as an acid acceptor (as well as by chloride anion). This slight improvement may possibly be due either to anchimeric assistance of tosylate departure by silicon, or to improved reactivity or persistence of silylated derivative above the boiling point of the free amine. These experiments suggest new avenues of approach; nevertheless, to date, not one of the conditions so far explored was entirely satisfactory for even bench-scale manufacture of this potentially useful polymer.

An amide anion will prefer substitution over elimination if its basicity is sufficiently lowered by resonance, and can be useful where uncharged nitrogen is unreactive or otherwise unsuitable. Even free N-alkylimidazoles are exceptionally

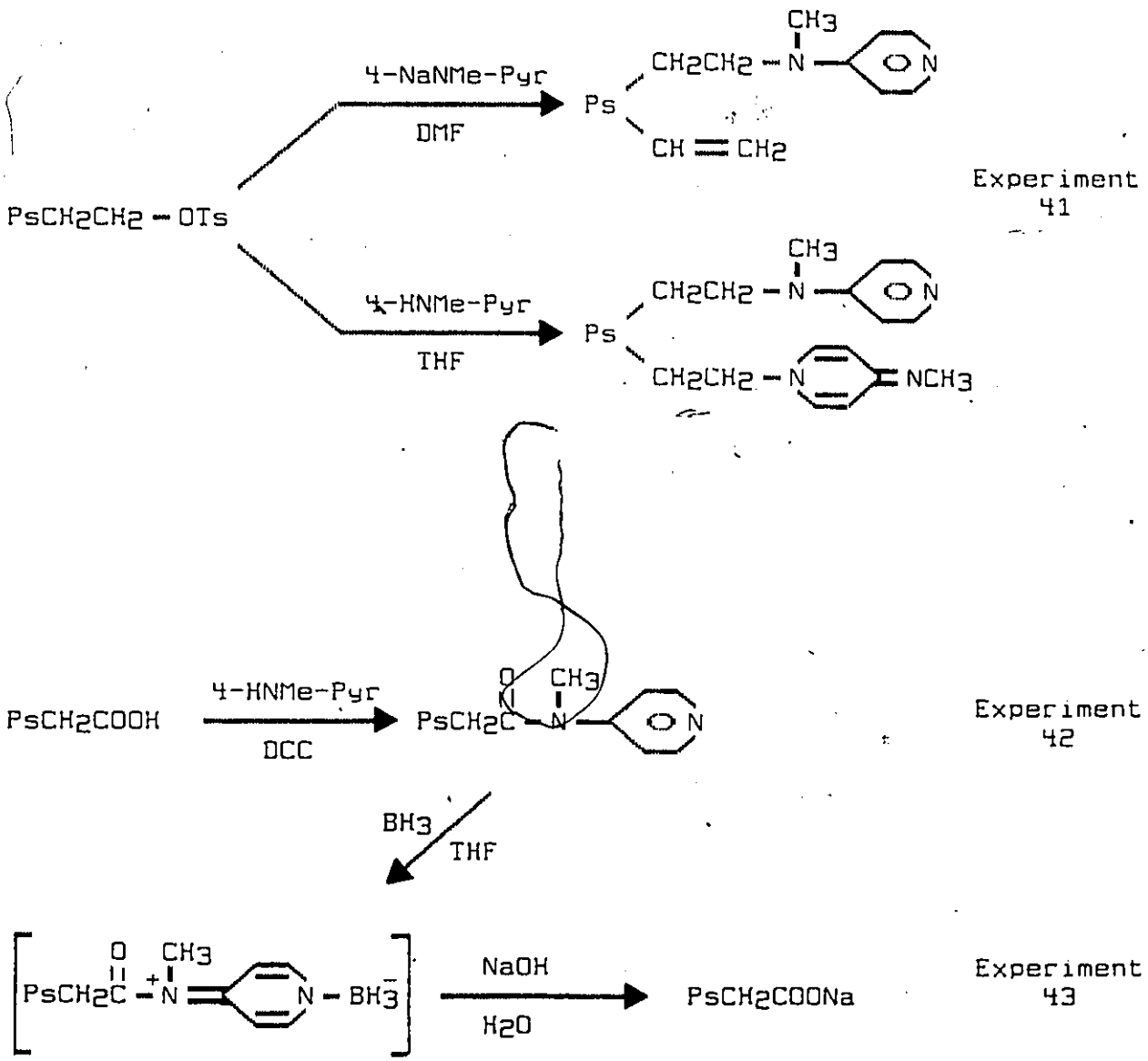
susceptible to over-alkylation during their preparation in neutral media; however, the imidazolide anion, being a much stronger nucleophile though still a weak base, can be selectively monoalkylated under controlled conditions.[199,200] With (toluenesulfonyloxyethyl)polystyrene in cold organic solvent, pre-formed sodium imidazolide gave (N-imidazolethyl)-polystyrene, potentially useful as a catalyst support, without crosslinking through quaternization (Experiment 39; Scheme 11). A one-pot procedure for polymer-supported imidazole, starting from polymeric alcohol, and using a large excess of imidazolide over toluenesulfonyl chloride, also proved successful by FTIR and elemental analysis, though a slightly darker colour may indicate traces of quaternization/ring-opening side-products (Experiment 40; Scheme 11).

Under neutral conditions, N-alkyl and unsubstituted 4-aminopyridines are alkylated partly at ring nitrogen, to give N-alkyl-4-pyridonimines which are easily hydrolyzed to the corresponding 4-pyridinones; however, once deprotonated with a strong base, their conjugated anions react with iodomethane and other electrophiles predominantly or exclusively at the side-chain.[188,189] This suggested the reaction of metallated N-methylaminopyridine with (toluene-sulfonyloxyethyl)polystyrene as a possible route towards polymer-bound N,N-dialkylaminopyridines, which are of interest as solid-phase acylation catalysts (see Part III). However, analysis of the product (Experiment 41; Scheme 12) revealed

elimination to have been the major reaction, probably because, at pKa = 22 (much higher than for imidazolide, whose negative charge is stabilized by aromaticity),[201] the metal amide is too powerful a base for phenethyl-type substrates. Nucleophilic substitution proved more successful for both shorter and longer spacers (see below), in which elimination was either impossible, or, at least, not favoured by the formation of a conjugated product.

Unlike alkyl electrophiles, activated acyls become permanently attached exclusively to the side-chain nitrogen of 2- and 4-aminopyridines, giving high isolated yields for product from phenylacetic acid.[202] Amination/reduction of (carboxymethyl)polystyrene, the strategy attempted with fair success for making (N,N-diisopropylaminoethyl)polystyrene when direct alkylation had failed (see Experiment 37), was thus repeated in an alternative synthesis of supported dialkyaminopyridine. However, toluenesulfonyl chloride now proved to be an ineffectual condensing agent, while thionyl chloride[90] gave coloured C-alkylation side-products; best results were finally achieved with dicyclohexylcarbodiimide in tetrahydrofuran with dimethylaminopyridine as catalyst, which after a day's reaction gave a product adequate to test the rest of the procedure (Experiment 42; Scheme 12). This pyridinyl amide polymer resisted reduction (Experiment 43; Scheme 12) far more than the earlier hindered aliphatic one (Experiment 37; Scheme 11), perhaps because complexation of

Scheme 12. Functionalization of Dimethylene Spacer. Aminopyridines.



aminopyridyl with borane reagent deactivated the conjugated carbonyl towards hydride addition. Thus, by FTIR spectroscopy, the dominant product in the end was merely the polymeric sodium carboxylate, produced during workup with aqueous base normally meant to dissolve the borate side-products. Since a parallel synthesis had just yielded an effective acylation catalyst supported through trimethylene spacer (see Part II), further efforts with polymers containing dimethylene spacers were abandoned for the time being.

Electron withdrawal by carbonyl deactivates the nitrogen of a secondary amide for nucleophilic attack, resulting in alkylation at oxygen, or no alkylation at all, on treatment with a carbon electrophile under neutral conditions.[198] However, the conjugate base, obtainable by deprotonation with alkali metal hydroxide, readily attacks alkyl halides such as (bromoethyl)benzene from the less electronegative heteroatom; substitution often predominates, particularly with pyrrolidinone in polar aprotic solvent.[203-205] The polymer-bound versions of functionalities such as tertiary amides show catalytic activities sometimes superior to the corresponding free polar aprotic solvents, because of positive cooperativity effects which are enhanced by a higher local concentration;[12,13] support of such groups on short spacers may even further increase their mobilities, and consequently their abilities to cooperatively complex positive centres, leading to better solid catalysts or chelating agents. A

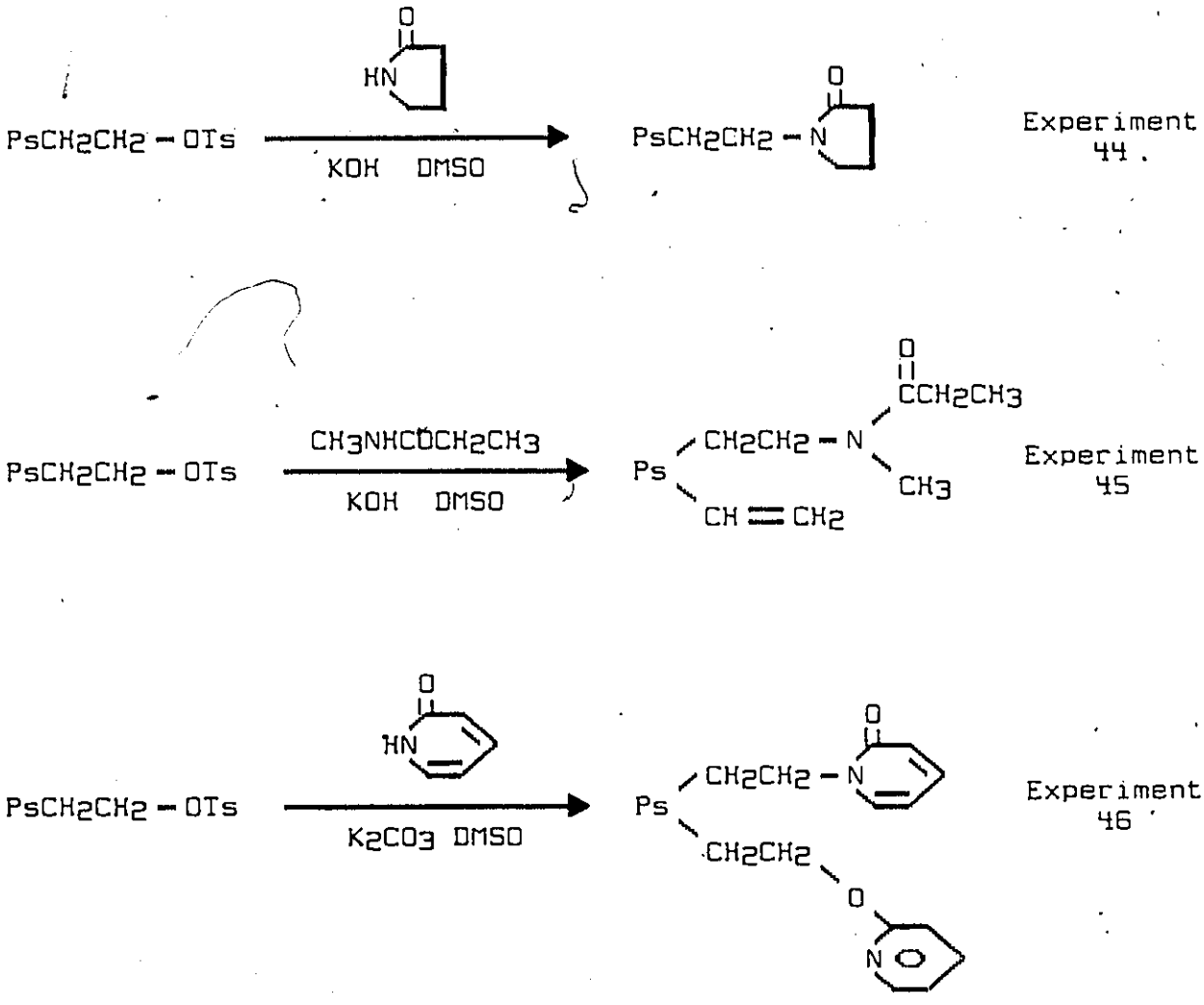
spacer-supported polymeric tertiary amide was readily made from (toluenesulfonyloxyethyl)polystyrene and the secondary cyclic amide with little or no side-reactions, using solid potassium hydroxide in anhydrous dimethylsulfoxide (Experiment 44; Scheme 13). In the absence of base, alcohol groups were produced, probably from O-alkylation of the amide followed by hydrolysis during workup.

In the same reaction, acyclic secondary amides such as N-methylpropionamide gave significant and even predominant elimination (Experiment 45; Scheme 13). The superior nucleophilicity demonstrated by the lactam (Experiment 44; Scheme 13) may perhaps be explained by a greater concentration of negative charge on its nitrogen, since ring strain would disfavour the "imino" resonance form in both the neutral carboxamide (resulting in the observed upward shift of the carbonyl peak in the FTIR spectrum) and its conjugated anion.

—2-Pyridinolate is a strong nucleophile, but a notoriously ambident one; N-alkylation is reported to be favoured by polar aprotic solvents and cations which don't complex with the leaving group.[206-208] Nevertheless, no conditions could be found from (toluenesulfonyloxyethyl)polystyrene for a product uncontaminated by O-alkylated heterocycles (Experiment 46; Scheme 13), and alternative syntheses of polymer-bound pyridinones were sought elsewhere (Experiment 31; Scheme 8).

Sulfonyl being a very strong electron-withdrawing group, secondary sulfonamides are far more acidic than the

Scheme 13. Functionalization of Dimethylene Spacer. Carboxamides.

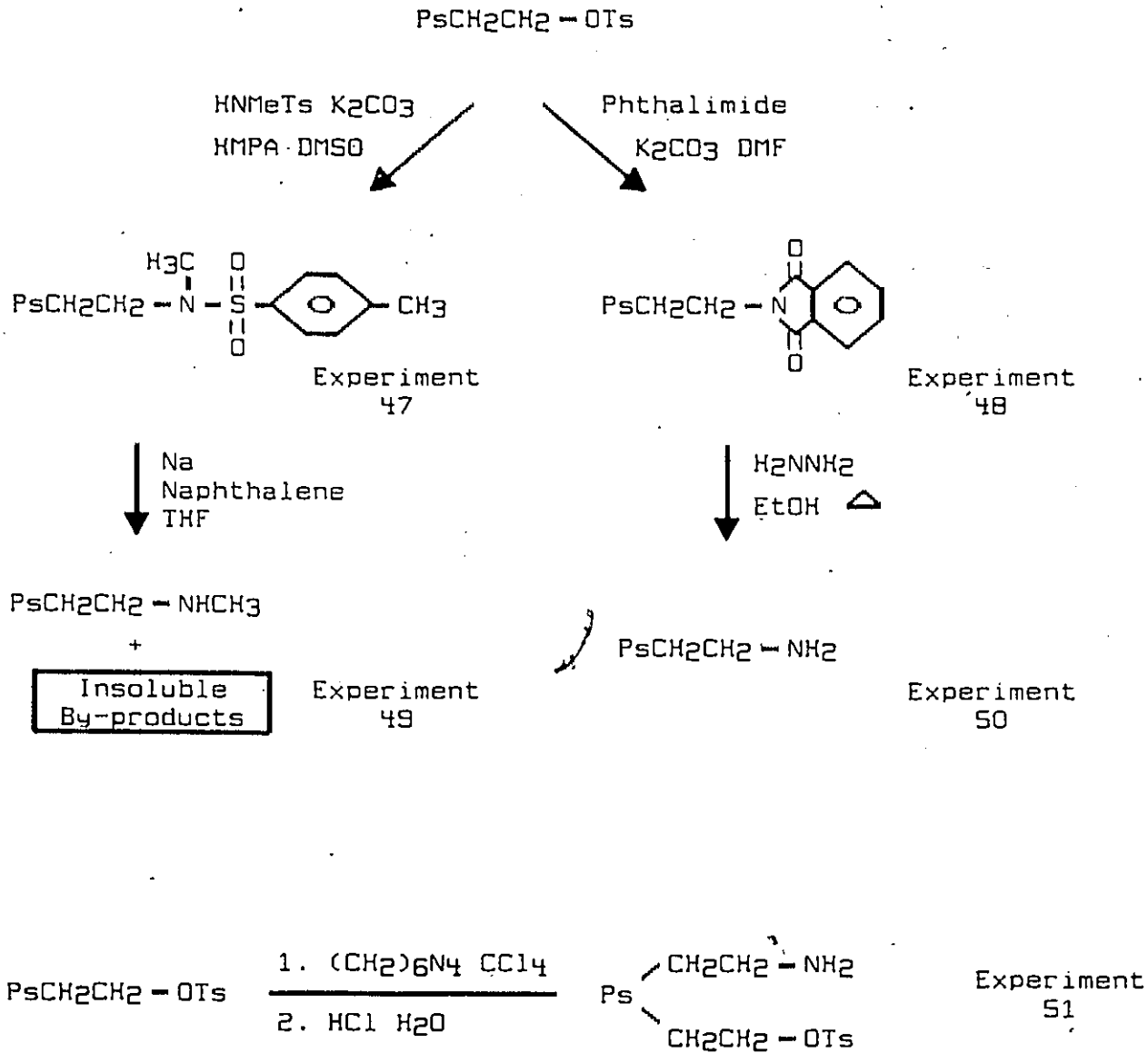


corresponding carboxamides, and thus even the acyclic ones are easily alkylated at nitrogen in the presence of mild base.[209] In warm polar aprotic solvent, with potassium carbonate as base, N-methyl-toluenesulfonamide readily gave tertiary toluenesulfonamide from (toluenesulfonyloxyethyl)polystyrene (Experiment 47; Scheme 14).

Like pyrrolidinone, phthalimide is also cyclic, and the basicity of its anion is further decreased by delocalization to a second carbonyl. Its alkylation by free electrophiles including alkyl tosylates is well-known; (chloromethyl)polystyrene also reacts with it to give a benzylic tertiary imide.[210-212] Analysis of its isolated product with (toluenesulfonyloxyethyl)polystyrene showed that the expected straightforward nucleophilic substitution had taken place without significant side-reactions (Experiment 48; Scheme 14).

Generally, secondary amines are themselves too nucleophilic to be prepared by alkylation of primary, whether with tosic esters or other agents, without some formation of trialkyl side-product.[158,159] For example, the amount of nitrogen in the product of a reaction between (toluenesulfonyloxyethyl)-polystyrene and methylamine is significantly lower than expected for complete conversion to pure (methylaminoethyl)-polystyrene, being in fact consistent with 47% overalkylation of polymer-bound dialkylamines to crosslinking tertiary functionalities.[115] Several indirect approaches generally circumvent the problem by employing amine derivatives capable

Scheme 14. Functionalization of Dimethylene Spacer. Other Nitrogen Compounds.



only of monoalkylation, their protecting groups such as carboxyl or sulfonyl then being replaced by hydrogen through hydrolysis or reduction.[59,213] Toluenesulfonamides are generally acknowledged rather difficult to cleave, recommended methods including hydrolysis with hot HCl,[45] or reductive cleavage by such reagents as HBr/phenol,[45] sodium naphthalenide,[214,215] lithium di-t-butyl-biphenylide[216] or potassium/alcohol.[217] However, to date, polymeric dimethylene-supported tertiary acyclic carboxamides have not become readily available (Experiment 45; Scheme 13), and the N-methyltoluenesulfonamide either resisted cleavage (with HCl or Li/di-t-butylbiphenyl or K/ROH), or gave considerable amounts of coloured (HBr/phenol) or insoluble and sulfurated (Na/Naphthalene) byproducts (Experiment 49; Scheme 14).

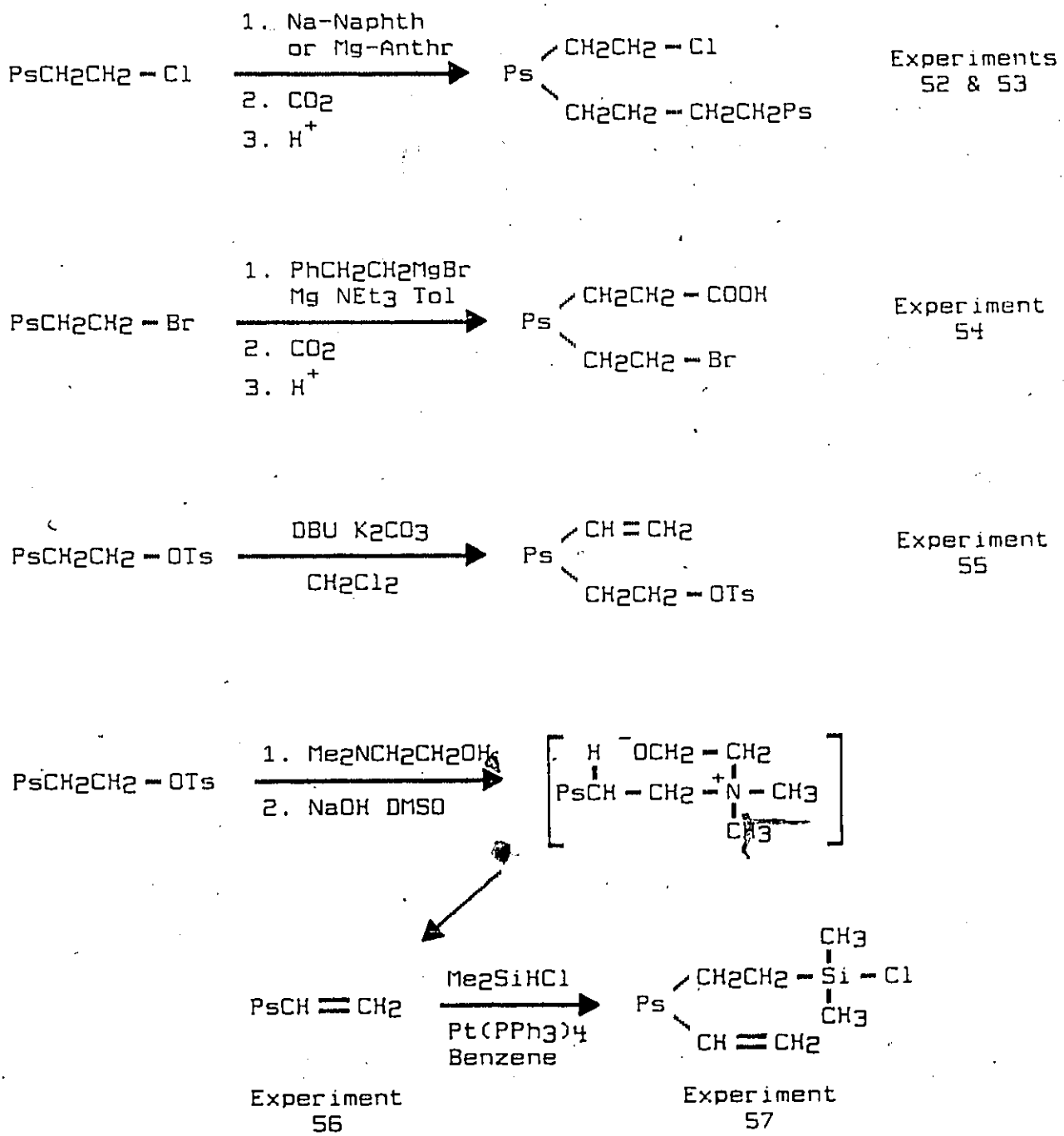
For the same reasons, producing polymeric primary amine by alkylation of ammonia is out of the question. Reaction of (cyanomethyl)polystyrene with lithium aluminum hydride/aluminum chloride has been reported to give a product containing significantly less nitrogen than expected for pure (aminoethyl)polystyrene; the low figure can be accounted for by about 32% transamination of primary to crosslinking secondary amino functionalities in the course of the reduction.[115] Primary amino groups, including (aminomethyl)-polystyrene, are produced in excellent yields from cleavage of tertiary phthalimides in the second step of the classic Gabriel synthesis.[210,212,218] A small sample of

(N-phthalimidoethyl)polystyrene (Experiment 48; Scheme 14) was indeed smoothly hydrazinolyzed to (aminoethyl)polystyrene in this way, as shown by the disappearance of carbonyl in its FTIR spectrum. The Delépine reaction,[219] which has been proven effective for (chloromethyl)polystyrene,[220] was also briefly explored as a means of generating primary amine from (toluenesulfonyloxyethyl)polystyrene in fewer steps. By FTIR spectroscopy, heating with hexamethylenetetramine, followed by ethanolic HCl in a one-pot procedure, resulted in transformation of most tosic ester groups to primary amine (Experiment 51; Scheme 14). The reaction has not yet been optimized; but use of a more polar solvent for the amination step would probably suffice to make it quantitative.

In most of the functional group modifications so far discussed, nucleophilic atoms within free molecules couple to the partially-positive carbons of tosylated or halogenated dimethylene spacers scattered over a solid network of crosslinked polystyrene. Were these same spacers to be terminated instead with negatively charged carbons, other free molecules containing electrophilic centres such as acyl carbon or halo-silicon could then be similarly immobilized, giving rise to whole new classes of stable and reactive functional polymers largely unattainable by other routes. The synthesis of polymer-supported primary carbanions was therefore briefly explored.

Though lithium or magnesium turnings reduce (bromoethyl)-

Scheme 15. Functionalization of Dimethylene Spacer. Metallation. Elimination. Hydrosilylation.



benzene to phenethyl carbanion in excellent yields,[221,222] this is generally a heterogenous reaction only made possible by direct contact between liquid-phase alkyl halide and solid-phase metal, and would naturally not be expected to work with solid halogenated polystyrene; even free molecules become difficult to metallate in this manner above a modest molecular weight.[223] However, it has recently been discovered that, in ethereal solvents, magnesium[224,225] and lithium,[216] can reversibly form complexes with anthracene and di-t-butylbiphenyl respectively, giving homogenous solutions of radical anions. These are then able to rapidly convert dissolved alkyl halides to metal alkyls[226,227] while regenerating the polycyclic moieties, which therefore can sometimes be employed in less than stochiometric amounts in these reactions as solid-liquid phase-transfer catalysts.[228] Unfortunately, these reagents proved surprisingly disappointing with (bromoethyl)polystyrene and (chloroethyl)polystyrene (Experiments 52 & 53; Scheme 15). It is possible that these radical anions, which are reported to precipitate and disproportionate back to neutral hydrocarbon and solid metal in media less polar than pure ether,[224,229] penetrated the largely aromatic interior of the polystyrene matrix only very slowly or not at all. Under these conditions, metallation would be unable to compete with crosslinking side-reactions, such as between freshly-formed carbanions and nearby unconsumed halides,[216] or between free radical intermediates[230,231] which would be generated in

relatively high local concentrations along the reaction front within the solid phase. Phenylalkylsulfides also give high yields of alkyllithium with lithium naphthalenide, and are less susceptible than alkyl halides to cross-coupling with organometallic reagents;[232] further work with these or other substrates or conditions may yet result in a practical metallation reaction using radical anions.

Organic halides may also trade halogen for metal with pre-formed organolithium or, to a lesser extent,[233] organomagnesium compounds. This exchange is generally useful as a synthetic step only when quickly forced to completion, such as by the formation of a stabler and less soluble carbanion in the reaction of butyl-lithium with (bromo)benzene[234] or, for that matter, with (bromo)polystyrene;[67] persistent contact of alkyl halide with reactive organometallic eventually consumes both through elimination or cross-coupling side-reactions, which are particularly rapid in ether solvents.[235,236] Thus, at equilibrium, the metallated product from primary (bromoethyl)polystyrene treated with a five-fold excess of n-butyl lithium contains sufficient residual bromine to become crosslinked and precipitate; reaction with even a ten-fold excess is still incomplete.[237] In general, the solid polymers investigated in this study fared even worse, carbanions either not being generated or being consumed by nearby halide groups faster than they were formed. Various conditions were tried in attempts to improve

the reaction: adding elemental lithium or magnesium, sometimes with sonication,[238] to consume free halide byproduct and regenerate the metallation reagent; using even more basic secondary or tertiary alkyl metals, whose halides then rapidly decompose after exchange;[235,239] or by using coordinating solvents such as ethers or amines, which reportedly improve organometallic reactivities by breaking up oligomeric aggregates such as may be hindering reagent penetration of polymer matrix, but which also increase the rates of covalent cross-coupling and other side-reactions.[235,236] Only with (bromoethyl)polystyrene, in the presence of clean magnesium metal, with dry toluene as solvent, catalytic phenethylmagnesium bromide as metal-"shuttle", and a minimum of triethylamine as ligand, was a polymeric carbanion even partly formed and functionalized with added electrophile, and even here much room for optimization still remains (Experiment 54; Scheme 15).

Up to now, conditions have been sought to promote nucleophilic substitution and prevent elimination in reactions of spacer-containing polymers with Lewis bases. However, (vinyl)polystyrene is also interesting as a functional polymer itself or as a precursor to others.[64,240] Its production directly from (toluenesulfonyloxyethyl)polystyrene or (haloethyl)polystyrene was attempted using several reagents recommended by the literature for such reactions, such as diazabicycloundecene, or alkali metal hydroxide or alkoxide,

with or without polar aprotic solvents or phase-transfer catalysts,[111,241-243] but reactions were generally sluggish, and conditions required for complete conversion often gave products which were visibly coloured and/or which displayed additional peaks in their infrared spectra. Elimination was much faster and cleaner when polymers were first treated with a tertiary alkanolamine prior to addition of base. In neutral polar solvents at mild temperatures, N,N-dimethylaminoethanol rapidly reacts with alkyl halides or tosylates exclusively at nitrogen to give the corresponding onium salts; these are generally stable to the conditions of their formation, though they can subsequently be demethylated in situ by heating over to 120°C with excess amino alcohol.[30,244,245] Methyl and benzyl alkylants give quaternary ammonium alcohols which, again unless strongly heated, are further stable towards even concentrated caustic. Indeed, "Dowex 2", an ion-exchange resin easily and quantitatively prepared from N,N-dimethylaminoethanol and (chloromethyl)polystyrene of intermediate degree of functionalization, is a common and useful strong-base anion exchange resin which is regenerable by saturated solutions of sodium hydroxide.[23,245,246] With polymers containing longer β spacers, beta-hydrogens are available and elimination becomes possible; its relative rapidity, observed in this study (Experiment 55; Scheme 15), may be attributed to fast permeation of the polymer by base due to good solvation by its polar functional functional

groups, as well as to a favourable mechanism which probably involves initial deprotonation of hydroxy functionality to give a zwitterionic intermediate which then rapidly decomposes in cyclic fashion to generate olefin and regenerate free N,N-dimethylaminoethanol. This entirely new procedure for elimination avoids the possibility of formation of alcohol, ether and aldehyde (with dimethylsulfoxide solvent) side-products, and would probably work as well on soluble polymers and free molecules without crosslinking or dimerization.

Hydrosilylation of the new (vinyl)polystyrene was briefly investigated, with the object of synthesizing a stable and recyclable trialkylhalosilyl support for solid-phase synthesis. The addition of silicon hydride across a carbon-carbon double bond is generally catalyzed by many transition metal complexes, the rates and selectivities of attack varying with alkene, silane, solvent, temperature and catalyst.[58,247] Speier's catalyst, $H(C_3H_6)PtCl_3$,[248] is commonly used but suffers from low reactivity and poor solubility in aromatic solvents, as well as often giving mixtures of products from unsymmetrical olefins like styrene.[247,249] With tetrakis(triphenylphosphine)platinum(0) instead, reaction of halosilane with styrene is milder, faster and 97% selective, thus producing a single primary organosilicon species in excellent yield after the benzylic minor product has been converted to alkane by hot caustic

alcohol.[249] Kinetics of the hydrosilylation display an induction period during which the initially neutral noble metal is transformed to active Pt(II).[250,251]

After several days with chlorodimethylsilane and this catalyst, FTIR spectroscopy of the reacting polymer showed significant peaks characteristic of both precursor vinyl and product chlorotrialkylsilyl functionalities (Experiment 56; Scheme 15). The reluctance of the reaction to proceed to completion may be due to decomposition of part of the active catalyst to insoluble material and free triphenylphosphine which poisons the rest; this process is known to occur in environments rich in silane but deficient in olefin, such as must exist in the bulk of the solvent outside the polymer beads.[247,251] The problem may possibly be alleviated by including free olefin as stabilizer, by adding silane dropwise to the other reagents, by carefully admitting air into the vessel,[252] or by using an even better catalyst such as one of the bridged complexes $(Pt(SiR_3)H(PR_3))_2$[253] or $[PtCl_2(2,4,6\text{-trimethylpyridine})]_2$.[254]

Good preparative methods now exist for a tremendous variety of functional groups to be bound through short spacers to polystyrene. Later in this thesis it will be shown how even short spacers may significantly improve the performance of a useful functional polymer over its benzylic analogue.

CALCULATIONS

Consider 1 mol of a chosen repeating unit i, containing x_i^J moles of each element J, of which one mole would weigh m^J, for a total weight m_i.

m^J = mass of 1 mol of element J

x_i^J = # mol of element J in 1 mole of repeating unit i

m_i = mass of 1 mole of the repeating unit i

$$= \sum_J x_i^J m^J$$

Now consider a polymer consisting of several species i of repeating unit, each numbering x_i, 1 mole of which would weigh m_i, for a total weight m.

x_i = # mol unit i in 1 mol of all polymer units.

Thus:

$$1 = \sum_i x_i$$

m = mass of 1 mol of all polymer units

$$= \sum_i x_i m_i$$

$$= \sum_i x_i \sum_J x_i^J m^J$$

$$= \sum_J m^J \sum_i x_i x_i^J$$

The concentration of an element may be expressed as either weight-percent (w^J) or molar capacity (c^J) for that element. Elemental analysis furnishes these values, or they can be calculated from a given polymer composition:

ω^j = mass of element j in 1 gram polymer

$$= \left[m^j \sum_i x_i x_i^j\right]/m$$

Thus:

$$1 = \sum_j \omega^j$$

c^j = # mol of element j in 1 gram polymer

$$= \left[\sum_i x_i x_i^j\right]/m$$

Thus:

$$\omega^j = m^j c^j$$

Molar capacity c_i can also be defined for a functional group i:

c_i = # mol of unit i in 1 gram of polymer

$$= x_i/m$$

Thus:

$$c^j = \sum_i x_i^j x_i/m$$

$$= \sum_i x_i^j c_i$$

Many functionalized polymers consist of x_0 moles of crosslinking agent (in the absence of later reticulation side-reactions, x_0 is the "percent crosslinking" which determines polymer swelling and access to reactive sites), x_1 mole of unsubstituted monomer, and x_2 mole (the "degree of

functionalization") of functionalized repeating units that often contain an element J (nitrogen, halogen, sulfur) not present in other unit species, so that the result w^J of an elemental analysis can give c_2 directly.

x_0 = # mol of crosslinked units in 1 mole of all units

x_1 = # mol of unfunctionalized units in 1 mol

x_2 = # mol of functionalized units in 1 mol

m_0 = mass of 1 mol of crosslinked units

m_1 = mass of 1 mol of unfunctionalized units

m_2 = mass of 1 mol of functionalized units

c^J = # mol element J in 1 gram polymer

$$= \sum_i x_i^J c_i$$

But, $x_i^J = 0$ for all i except i=2. Thus:

$$c^J = x_2^J c_2$$

And:

$$c_2 = c^J / x_2^J$$

$$= w^J / m^J x_2^J$$

x_2 can be derived from c_2 as follows:

$$c_2 = x_2 / m$$

$$= x_2 / \sum_i x_i m_i$$

$$= x_2 / (x_0 m_0 + x_1 m_1 + x_2 m_2)$$

Now x_0 is known, and:

$$x_1 = 1 - x_0 - x_2$$

So:

$$c_2 = x_2/(x_0m_0 + (1 - x_0 - x_2)m_1 + x_2m_2)$$

$$= x_2 / (x_0(m_0 - m_1) + m_1 + x_2(m_2 - m_1))$$

Inverting both sides,

$$1/c_2 = (x_0(m_0 - m_1) + m_1)/x_2 + m_2 - m_1$$

Isolating x_2,

$$x_2 = (x_0(m_0 - m_1) + m_1)/(1/c_2 + m_1 - m_2)$$

For the lightly-crosslinked gels employed in this study, an approximation can be made based on:

$$m_1 >> x_0(m_0 - m_1)$$

So, in these polymers, degree of functionalization is related to functional capacity by:

$$x_2 = m_1/(1/c_2 + m_1 - m_2)$$

In a typical functional group modification reaction, part of x_I mole of species i = I in a mole of mixed polymer units weighing m is transformed into a new species i = I+1, which numbers x_{I+1} and weighs m_{I+1} per mole. All other species i=0 to i=I-1 remain unaffected. The conversion or functional yield of the reaction is y_{I+1}. x' mol of I remains, and the new total mass is m'.

x_I = old # mol of old unit in 1 mol of all units

x_{I+1} = new # mol of new unit in 1 mol of all units

y_{I+1} = conversion or functional yield

$$= x_{I+1} / x_I$$

x'_I = new # mol of old unit in 1 mol of all units

$$= x_I - x_{I+1}$$

m' = new mass of 1 mol of all units

$$= \sum_{i=0}^{I-1} x_i m_i + x'_I m_I + x_{I+1} m_{I+1}$$

$$= \sum_{i=0}^{I-1} x_i m_i + x_I m_I - x_{I+1} m_I + x_{I+1} m_{I+1}$$

$$= m - x_{I+1} m_I + x_{I+1} m_{I+1}$$

$$= m + x_{I+1}(m_{I+1} - m_I)$$

The measured relative weight change d_{I+1} can convey useful information on the success of the reaction. For 1 mol

d_{I+1} = relative change in total mass in reaction

$$= (m' - m)/m$$

$$= (m + x_{I+1}(m_{I+1} - m_I) - m)/m$$

$$= x_{I+1}(m_{I+1} - m_I)/m$$

Thus:

$$x_{I+1} = m d_{I+1}/(m_{I+1} - m_I)$$

And:

$$y_{I+1} = m d_{I+1}/(m_{I+1} - m_I) x_I$$

Functional yield, functional capacity and degree of functionalization can also be derived for these simple polymers from the results of elemental analysis using equations previously described. More complex situations, involving the generation of more than 1 new species of repeating unit and/or the presence of the same element on several species, may still be amenable to the same general treatment, though requiring additional assumptions (often verifiable by FTIR spectroscopy) and extra algebraic manipulation.

EXPERIMENTAL

Materials.

Where specified, organic reaction solvents and liquid reagents were dried by distillation from sodium-benzophenone ketyl (ethers) or calcium hydride or carbide (amines, hydrocarbons, acetonitrile, dimethylformamide), or by distilling onto or standing over molecular sieves (dimethylsulfoxide, others). Otherwise, technical grade solvents for polymer wash, and reagent grade solid reagents, were used as received. The starting material for all the following preparations was "SX-1 Bio-Beads", 200-400 mesh, a copolymer of 1% divinylbenzene (and possibly 1% ethylstyrene contaminant, which was ignored in all calculations) and styrene. As a general rule, the minimum solvent needed for a stirrable suspension was used in all polymer reactions. Reactions under inert atmosphere were performed in oven-dried glassware under bubblers and/or using Firestone valves.

Infrared spectra of KBr pellets were measured on a Nicolet 10-DX FTIR spectrometer. Polymer halogen content was measured by Volhard titration of 200-300 mg samples ignited in a Parr peroxide bomb; other quantitative analyses were performed by MHW Laboratories (Phoenix, AZ). Laboratory notebook pages are in angular brackets.

Experiment 1. (Cyanomethyl)polystyrene. From (chloromethyl)-polystyrene.

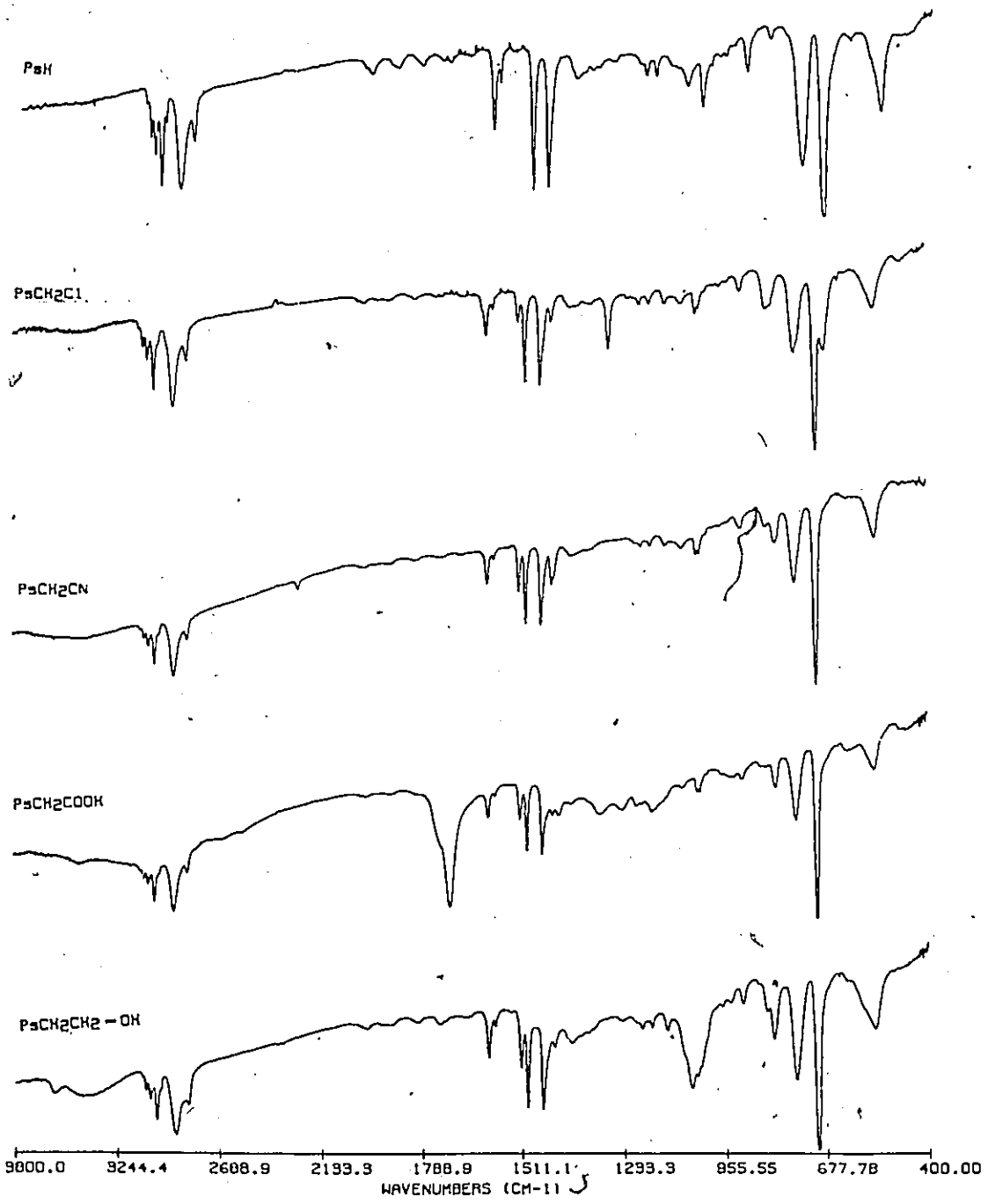
(Chloromethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_9H_9Cl)_{.31}$ had been prepared from washed commercial 1%-crosslinked polystyrene and characterized by published procedures[31]. This white powder (59.1 g, 151 meq Cl) was stirred with sodium cyanide pellets (12.0 g, 245 meq) and tetrabutylammonium chloride crystals (1.0 g, 3.6 meq) in 600 ml dry DMF under a nitrogen atmosphere at 80°C for 16 hours. The pale orange suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 56.3 g of a very pale beige powder. IR (KBr) peak absent at 1265 cm^{-1} for chloride precursor; peak present at 2250 cm^{-1} (w, CN) for cyano product (Figure 1). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_{10}H_9N)_{.31}$ (100% conversion): N, 3.73; Cl, 0. Found N, 3.85; Cl, 0.

<D846>.

Experiment 2. (Carboxymethyl)polystyrene. From (cyanomethyl)-polystyrene.

(Cyanomethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_{10}H_9N)_{.31}$ (55.2 g, 152 meq), water (30 ml, 1700 meq), 300 ml glacial acetic acid, then 30 ml concentrated sulfuric acid, were mixed and refluxed with stirring under nitrogen for 19 hours. The pale suspension was filtered, and the residue washed H_2O (3X),

Figure 1. FTIR spectra of intermediates towards (hydroxyethyl)polystyrene by 1-carbon extension.



MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 58.5 g of a pale beige-yellow powder: IR (KBr) peak absent at 2250 cm^{-1} for nitrile precursor; peaks present at 3000 (br, COO-H), 1710 (s, C=O) and 1294 cm^{-1} (m, CO-O) for carboxyl product (Figure 1). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_{10}H_{10}O_2)_{.31}$ (100% conversion): N, 0.0. Found: N, <0.2.

<D848>.

Experiment 3. (Hydroxyethyl)polystyrene. From (carboxymethyl)-polystyrene.

(Carboxymethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_{10}H_{10}O_2)_{.31}$ (50.0 g, 127 meq) was suspended in 500 ml dry THF under nitrogen, to which was added in portions $LiAlH_4$ powder (7.1 g, 748 meq H) with some fizzing, then the whole was refluxed for 12 hours. Upon cooling were added by drops to the gray suspension 7 ml H_2O, 7 ml 15% NaOH/H_2O, then 21 ml H_2O, giving a yellow suspension which was easily filtered, the residue then being washed with 3N HCl/H_2O (2X), 12N HCl/H_2O (1X), H_2O (3X), THF (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 48.8 g of a very pale beige powder: IR (KBr) peaks absent at 3000, 1710 and cm^{-1} 1294 for carboxy precursor; peaks present at 3400 (br, CH_2O-H) and 1046 cm^{-1} (s, CH_2-O). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_{10}H_{12}O)_{.31}$ (100% conversion): C, 87.90; H, 7.90; N, 0. Found: C, 87.03; H, 7.61; N 0. A sample was derivatized with 3,5-dinitrobenzoyl

chloride (Experiment 5). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}$-$(C_{17}H_{14}N_2O_6)_{.31}$ (100% conversion): N, 4.87. Found: N, 4.87. <D851>.

Experiment 4. (Hydroxyethyl)polystyrene. From (bromo)polystyrene.

(Bromo)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.57}(C_8H_7Br)_{.42}$ (20.00 g, 60 meq) had been prepared and characterized from washed commercial 1% crosslinked polystyrene resin.[67] The pale beige powder (20.00 g, 60 meq) was suspended in 500 ml dry benzene under nitrogen, then 2.2M n-butyl lithium/hexane (60 ml, 132 meq) was injected, and the whole was stirred at 60°C for 3 hours. The liquid phase was then removed by filtration, and the beige residue, still under nitrogen, was resuspended in 200 ml dry tetrahydrofuran, and cooled to -50°C, before receiving condensed ethylene oxide by injection (9.5 ml, 190 meq), and being stirred under a CO_2-cooled condenser for a further 18 hours while gradually warming to room temperature. The pale orange-yellow suspension was then filtered, and the residue washed with THF:H_2O 3:1 (1X), THF:H_2O:conc HCl/H_2O 8:2:1 (1X), H_2O (3X), THF (1X), CH_3OH (2X), Et_2O (1X), then dried under vacuum overnight, to yied 18.4 g of pale yellow powder: IR (KBr) peaks absent at 1487, 1408, 1073, 1010, and 718 cm^{-1} for aryl bromide precursor, and at 1150-1060 cm^{-1} for ether side-products;[100] peaks present at 3400 (br, CH_2O-H) and 1046 cm^{-1} (s, CH_2-O) for hydroxy product (Figure 2). Anal.

Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.57}(C_{10}H_{12}O)_{.42}$ (100% conversion): C, 86.58; H, 7.96; O, 5.47; Br, 0. Found: C, 86.51; H, 8.05; O, 5.51; Br, 0. A sample was derivatized with 3,5-dinitrobenzoyl chloride (Experiment 5). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.57}(C_{17}H_{14}N_2O_6)_{.42}$ (100% conversion): N, 5.76. Found: N, 5.66.

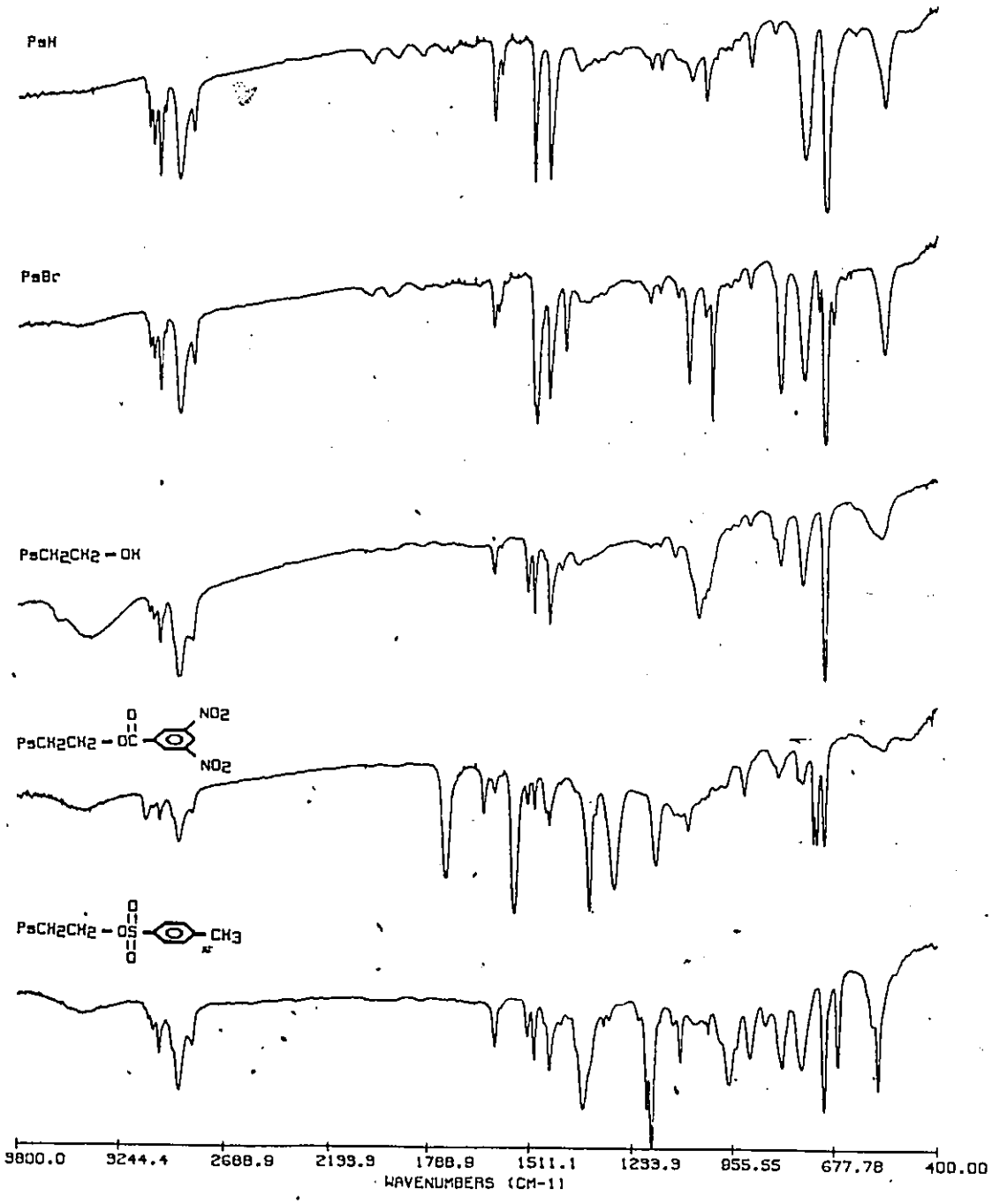
<D734>

Experiment 5. (3,5-dinitrobenzoxyethyl)polystyrene. From (hydroxyethyl)polystyrene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.57}(C_{10}H_{12}O)_{.42}$ (0.13 g, 0.44 meq) was heated with 3,5-dinitrobenzoyl chloride (0.13 g, 0.55 meq) in 2 ml dry pyridine at 100°C under nitrogen for 2 hours, then the yellow-green suspension was filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.20 g of a pale yellow-beige powder: IR (KBr) peaks absent at 3400 and 1046 cm^{-1} for alcohol precursor; peaks present at 3098 (w, Ar-H), 1733 (s, C=O), 1547 (s, Ar-NO_2), 1344 (s, Ar-NO_2), 1277 (s, CO-O), 1164 (m, CO-O), 721 cm^{-1} (m, Ar-NO_2) for ester product (Figure 2). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.57}(C_{17}H_{14}N_2O_6)_{.42}$ (100% conversion): N, 5.76. Found: N, 5.66.

<D964>.

Figure 2. FTIR spectra of intermediates towards (hydroxyethyl)polystyrene by 2-carbon addition. Products of acylation and tosylation.



Experiment 6. (2,4-Dinitrophenoxyethyl)polystyrene. From (hydroxyethyl)polystyrene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.57}(C_{10}H_{12}O)_{.42}$ (0.51 g, 1.7 meq) was heated with 2,4-dinitrofluorobenzene (0,30 ml, 2.4 meq) and triethylamine (0.30 ml, 2.2 meq) in 2 ml dry toluene at 88°C for 40 hours. The dark red suspension was then filtered, and the residue washed with acetone (3X) until filtrate was colourless, H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.74g of bright yellow powder: IR (KBr) peaks absent at 3400 and 1046 cm^{-1} for alcohol precursor; peaks present at 1609 (s, Ar-NO_2), 1536 (s, Ar-NO_2), 1344 (s, Ar-NO_2), 1287 (s, Ar-NO_2), 1152 (m, CH_2-OAr), 1087 (m, CH_2-OAr), 833 cm^{-1} (m, Ar-H) for complete conversion to aryl ether product.

<D934>.

Experiment 7. (Toluenesulfonyloxyethyl)polystyrene. From (hydroxyethyl)polystyrene using diisopropylamine.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{12}O)_{.29}$ (10.35 g, 35 meq), toluenesulfonyl chloride (8.4 g, 44 meq), and dry diisopropylamine (10 ml, 71 meq), were stirred together in 70 ml carbon tetrachloride under nitrogen at room temperature, then heated to reflux for 6 hours. The pale yellow suspension was filtered, and the residue washed with acetone (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), Et_2O (2X), then

dried under vacuum overnight to yield 14.28 g of a very pale yellow-beige powder: IR (KBr) peaks absent at 3400 and 1046 cm^{-1} for alcohol precursor, and at 2694 cm^{-1} for amino side-product; peaks present at 1363 (s, SO-OC), 1180 (doublet, s, SO-OC), 1098 (m, C-O), 964 (s, S-O-C), 905 (m, S-O-C), 815 (m, S-O-C), 760 (m, S-O-C), 664 (m, Ar-SO_3) and 555 cm_{-1} cm^{-1} (s, Ar-SO_3) for tosic ester product (Figure 2). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{17}H_{18}SO_3)_{.29}$: S, 5.74; N, 0. Found: S, 5.73; N, 0. Similar results were obtained using pure diisopropylamine as solvent.

<D981>.

Experiment 8. (Chloroethyl)benzene. From (hydroxyethyl)benzene with thionyl chloride.

Dry (hydroxyethyl)benzene (0.50 ml, 4.2 meq), clear and colourless thionyl chloride freshly distilled from limonene[255] (0.50 ml, 6.9 meq) and dry pyridine (0.05 ml, 0.6 meq) were mixed with 10 ml dry carbon tetrachloride at 0°C, then refluxed under nitrogen for 24 hours. Gas chromatography (SE-30 90°C) of the reaction mixture showed only a single peak which matched that from a commercial sample of (2-chloroethyl)benzene.

<D762>.

Experiment 9. (Chloroethyl)polystyrene. From (hydroxyethyl)-polystyrene with thionyl chloride.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{12}O)_{.24}$ (3.03 g, 6.3 meq), purified thionyl chloride (1.5 ml, 21 meq) and dry pyridine (0.1 ml, 1 meq) were suspended in 30 ml dry CCl_4 under nitrogen, and stirred at reflux for 16 hours. The orange suspension was filtered, and the residue washed with H_2O (1X), MEK (1X), H_2O (3X), THF:conc HCl/H_2O 1:1 (1X), THF (1X), CH_2Cl_2 (1X), CH_3OH (1X), and dried under vacuum overnight, yielding 3.15 g of a pale peach powder: IR (KBr) peaks absent at 3400 and 1046 cm^{-1} for alcohol precursor; peaks present at 1245 (w, CH_2Cl), 657 cm^{-1} (w, C-Cl). Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{11}Cl)_{.24}$ (100% conversion): Cl, 7.13. Found: Cl, 7.09.

<D812>.

Experiment 10. (Bromoethyl)polystyrene. Attempt from (hydroxy-ethyl)polystyrene with tribromophosphine.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.68}(C_{10}H_{12}O)_{.31}$ (5.01 g, 13 meq) and phosphorous tribromide (0.50 ml, 5.3 meq) were stirred together in 50 ml dry ether for 18 hours at 0°C under nitrogen. The yellow suspension was quenched with methanol (fumes), then filtered and the residue washed CH_3OH (2X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, to yield 5.68 g of white powder: IR

(KBr) peaks absent at 1046 cm^{-1} for alcohol precursor; peaks present at 1263 (m, CH_2Br) and 647 cm^{-1} (w, C-Br) for bromo product, but also at 1220 (m, P=O), 1068 (m, P-O) and 978 cm^{-1} (m, P-O) for phosphite side-product. Another reaction using 1.3 meq (hydroxyethyl)polystyrene and 13 meq PBr_3 gave identical results. After further stirring with concentrated hydrobromic acid at room temperature for 12 hours and again washing and drying, the spectrum remained unchanged. <D942, D943, D952>.

Experiment 11. (Bromoethyl)polystyrene. Attempt from (hydroxyethyl)polystyrene with lithium bromide/chlorotrimethylsilane.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.58}(C_{10}H_{12}O)_{.41}$ (10.00 g, 33 meq) and lithium bromide dried at 100°C under vacuum for 2 days[256] (6.96 g, 80 meq) were stirred together in 50 ml dry acetonitrile at room temperature while slowly injecting chlorotrimethylsilane (13.0 ml, 102 meq), then the mixture was refluxed under nitrogen for 26 hours. The green-brown suspension was filtered, and the residue washed with THF (1X), H_2O (4X), CH_3OH (1X), CH_2Cl_2 (1X), Et_2O (2X), and dried under vacuum overnight, yielding 10.74 g of pale beige powder: IR (KBr) peaks present at 1046 cm^{-1} (s, C-O) for significant residual alcohol precursor, and at 1262 (m, CH_2-Br) and 647 (w, C-Br) for bromo product. Anal. Calcd. for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.58}(C_{10}H_{12}O)_{.23}(C_{10}H_{11}Br)_{.18}$ (44% conversion): Br, 10.75. Found: Br, 10.71. 10.49 g of this polymer was subjected

to a second treatment with brominating agent, giving 10.99 g of product whose IR spectrum shows weaker -OH and stronger CH_2Br peaks. Anal. Calcd. for $(C_{10}H_{10})_{.01}(C_8H_8)_{.58}$-$(C_{10}H_{12}O)_{.14}(C_{10}H_{11}Br)_{.27}$ (39% conversion from previous polymer; 66% conversion from original polymeric alcohol): Br, 15.47. Found: Br, 15.66.

<D713, D714>.

Experiment 12. (Bromoethyl)benzene. From (hydroxyethyl)benzene with hydrobromic acid.

(Hydroxyethyl)benzene (0.39 g, 3.2 meq), hexadecyltributyl-phosphonium bromide[151] (0.10 g, 0.20 meq), and colourless concentrated hydrobromic acid freshly distilled from stannous chloride[252] were rapidly stirred in 10 ml refluxing toluene under nitrogen. The reaction, followed by GLC (SE-30 90°C), had progressed 50% in 2 hours, and was complete within 12. Even after 3 days further heating, (2-bromoethyl)benzene was the only product.

<D729>.

Experiment 13. (Bromoethyl)polystyrene. Attempt from (hydroxy-ethyl)polystyrene with hydrobromic acid in toluene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{12}O)_{.24}$ (4.00 g, 8.4 meq), hexadecyltributyl phosphonium bromide (0.33 g, 0.7 meq), and colourless 48% HBr/H_2O freshly distilled from stannous chloride[257] (10.0 ml, 90 meq) were vigorously stirred

with 40 ml toluene at slow reflux under nitrogen for 45 hours. The sticky suspension was then filtered with difficulty, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), Et_2O (1X), and dried under vacuum overnight, yielding 4.46 g of pale yellow powder: IR (KBr) peaks absent at 1046 cm^{-1} for alcohol precursor, as well as at 1220, 1068 and 978 cm^{-1} for phosphite side-products seen with PBr_3 reagent (Experiment 10); peaks present at 1263 (m, CH_2Br) and 647 cm^{-1} (w, C-Br) for bromo product. Anal. Calcd. for $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}$-$(C_{10}H_{11}Br)_{.24}$: Br, 14.74. Found: Br, 13.82.

<D807>.

Experiment 14. (Bromoethyl)polystyrene. From (hydroxyethyl)-polystyrene with hydrobromic acid in diphenyl ether.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{10}H_{12}O)_{.25}$ (0.51 g, 1.1 meq), hexadecyltributylphosphonium bromide (0.050 g, 0.1 meq), and colourless concentrated hydrobromic acid (1.0 ml, 9 meq) were rapidly stirred in 7 ml diphenyl ether at 135°C for 48 hours. The yellow suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (1X), and dried under vacuum overnight, yielding 0.58 g of pale beige-yellow powder: IR (KBr) peaks absent at 1046 cm^{-1} for alcohol precursor; peaks present at 1263 (m, CH_2Br) and 647 cm^{-1} (w, C-Br) for bromo product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{10}H_{11}Br)_{.25}$ (100% conversion): Br, 15.23. Found: Br, 16.06.

<D902>.

Experiment 15. (Bromoethyl)polystyrene. From (toluenesulfonyloxyethyl)polystyrene.

Magnesium turnings (1.2 g, 50 meq) and 1,2-dibromoethane (2.2 ml, 25 meq) were mixed under nitrogen in 50 ml anhydrous ether. After the vigorous reaction had subsided, the supernatant solution of magnesium bromide etherate was decanted through a double-ended needle onto (toluenesulfonyloxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{17}H_{18}SO_3)_{.29}$ (5.00 g, 9.0 meq), and the mixture was stirred at gentle reflux under argon for 17 hours. The pale brown suspension was then filtered, and the residue washed with acetone (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 4.21 g of a very pale beige powder: IR (KBr) peaks absent at 1363, 1180, 1098, 964, 905, 815, 760, 664 and 555 cm^{-1} for tosic ester precursor; peaks present due to CH_2Br, identical to product of the previous procedure (Experiment 14). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{11}Br)_{.29}$ (100% conversion): Br, 17.11. Found: Br, 17.18.

<D982>.

Experiment 16. (Iodoethyl)polystyrene. From (hydroxyethyl)-polystyrene with methyl iodide/triphenyl phosphite.

A mixture of triphenyl phosphite (17.5 ml, 67 meq) and iodomethane (4.5 ml, 72 meq) was slowly warmed under nitrogen reflux, then heated at 140°C for 18 hours. The resulting dark brown mass was washed under nitrogen with dry ether, then dry ethyl acetate, then quickly sucked dry to a yellow powder, which was then dissolved in 110 ml dry dimethylformamide. To this was added (hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_{88})_{.70}$-$(C_{10}H_{12}O)_{.29}$ (16.22 g, 40 meq), and the mixture was stirred at room temperature under nitrogen for 18 hours. The yellow suspension was filtered and the residue washed with DMF (3X), DMF:H_2O 1:1 (1X), H_2O (3X), THF (1X), CH_3OH (2X), Et_2O (1X), and dried under vacuum overnight, yielding 20.67 g of a pale yellow powder: IR (KBr) peaks absent at 3400 and 1046 cm^{-1} for alcohol precursor, and at 1220, 1068 and 978 cm^{-1} for phosphite intermediate (Experiment 10); peaks present at 1236 (m, CH_2-I) and 1168 cm^{-1} (m, CH_2-I) for iodo product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{11}I)_{.29}$ (100% conversion): I, 24.69. Found: I, 24.49.

<D381>.

Experiment 17. (Iodoethyl)polystyrene. From (hydroxyethyl)-polystyrene with sodium iodide/chlorotrimethylsilane.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{12}O)_{.29}$ (0.504 g, 1.24 meq), sodium iodide dried at 100°C under vacuum for 2 days[256] (0.412 g, 2.75 meq), chlorotrimethylsilane (0.35 ml, 2.8 meq) and 4 ml dry acetonitrile were stirred under nitrogen at slow reflux for 8 hours. The red suspension was filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.654 g of a very pale beige-yellow powder: IR (KBr) identical to that from the other method. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{11}I)_{.29}$ (100% conversion): I, 24.69. Found: I, 24.87.

<D1004>.

Experiment 18. (3-Nitrobenzoxyethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.794}$-$(C_{17}H_{18}SO_3)_{.196}$ (0.41 g, 0.55 meq), m-nitrobenzoic acid (0.14 g, 0.83 meq) and anhydrous potassium carbonate (0.17 g, 1.2 meq) were rapidly stirred in a mixture of 4 ml dimethyl-sulfoxide and 0.5 ml hexamethylphosphoramide under nitrogen at room temperature, then warmed to 60°C for 22 hours. The pale brown suspension was filtered and washed acetone (1X), H_2O (3X rapidly), MEK (1X), CH_2Cl_2 (1X), 1 X Et_2O, and dried under

vacuum overnight, yielding 0.41 g of yellow-beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1046 cm^{-1} for hydrolysis side-product; peaks present at 1727 (s, C=O), 1617 (w, Ar), 1535 (s, Ar-NO_2), 1351 (s, Ar-NO_2), 1263 (m, CO-O), 1134 (m, CO-O) and 720 cm^{-1} (m, Ar-H) for product ester. Anal. Calcd for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.794}(C_{17}H_{15}NO_4)_{.196}$ (100% conversion): N, 1.93. Found: N, 1.87. A similar reaction was performed using anhydrous CsF as base, in dry dimethylformamide slowly heated to 100°C to give a polymer which was identical by FTIR.

<D1054, D1080>.

Experiment 19. (3-Nitrophenoxyethyl)polystyrene. Attempt from (Toluenesulfonyloxyethyl)polystyrene.

(Toluenesulfonyloxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}$-$(C_{17}H_{18}SO_3)_{.29}$ (0.51 g, 0.91 meq), m-nitrophenol (0.25 g, 1.8 meq) and anhydrous potassium carbonate (0.28 g, 2.0 meq) were stirred in 5 ml dry dimethylformamide under nitrogen at 66°C for 16 hours. The red suspension was filtered, and the residue washed with acetone (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight to give a pale yellow powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor; peaks present at 1531 (s, Ar-NO_2), 1351 (s, Ar-NO_2), 1245 (m, CH_2-OAr), 1029 (m, CH_2-OAr) and 738 cm^{-1} (m, Ar-H) ether product. Calcd for $(C_{10}H_{10})_{.04}(C_8H_8)_{.70}$-$(C_{16}H_{15}NO_3)_{.26}$ (90% conversion to ether, 10% to olefin): N,

2.46. Found: N, 2.45.

<D987>.

Experiment 20. (Benzenethioethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{17}H_{18}SO_3)_{.25}$ (0.9490 g, 1.54 meq), thiophenol colourless liquid (0.40 ml, 3.9 meq), sodium hydroxide (0.55 g, 14 meq), tricaprylmethylammonium chloride (0.04 g, 0.1 meq), 0.5 ml water and 10 ml benzene were rapidly stirred together under nitrogen at room temperature for 24 hours. The mephitic beige suspension was then filtered, and the residue washed with H_2O (3X), acetone (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight to yield 0.8583 g of odourless pale beige-yellow powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1630 cm^{-1} for vinyl side-product; new peaks present at 1590 (w, Ar), 1262 (m, CH_2-S) and 737 cm^{-1} (w, C-S) for sulfide product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{16}H_{16}S)_{.25}$ (100% conversion): weight change, -10.07%. Found: weight change, -9.56%.

<D1174>.

Experiment 21. (Butanethioethyl)polystyrene. From (toluene-sulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}$-$(C_{17}H_{18}SO_3)_{.25}$ (0.50 g, 0.81 meq), anhydrous potassium carbonate (0.33 g, 2.4 meq), hexadecyltributylphosphonium bromide (0.077 g, 0.15 meq) and butanethiol (0.22 ml, 2.1 meq) were rapidly stirred in 5 ml toluene under nitrogen at reflux for 30 hours. The mephitic white suspension was then filtered, and the residue washed H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight to yield 0.44 g of odourless white powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1630 cm^{-1} for vinyl side-product; new peak present at 2853 cm^{-1} (w, alkyl C-H) for sulfide product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}$-$(C_{14}H_{20}S)_{.25}$ (100% conversion): S, 6.01%. Found: S, 5.76%. <D904>.

Experiment 22. (Oxydiphenylphosphinethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

Chlorodiphenylphosphine pale yellow liquid (0.40 ml, 2.2 meq) and 25% lithium powder in mineral oil (0.092 g, 3.3 meq) were stirred in 5 ml anhydrous tetrahydrofuran until the vigorous reaction had subsided. The red solution was then decanted through a double-ended needle onto (toluene-sulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}(C_{17}H_{18}SO_3)_{.20}$

(0.50 g, 0.69 meq), and the mixture stirred under argon at room temperature for 15 hours, then at 60°C for one hour before receiving anhydrous dimethylsulfoxide (0.5 ml, 7.0 meq). After further stirring for 30 hours the red suspension was cooled, quenched with ethanol and filtered, and the residue washed with acetone (1X), H_2O (3X), MEK (1X), benzene (1X), CH_3OH (3X), and dried under vacuum overnight, yielding 0.51 g of pale beige powder: IR (KBr) peaks absent at 1363 cm^{-1} for tosic ester precursor, and at 569 ($ArSO_3^-$) and 1630 cm^{-1} (C=C) for quaternization and elimination side-products respectively; peaks present at 1585 (w, Ar), 1435 (m, P-Ar) and 1188 cm^{-1} (P=O) for pyridinium tosylate product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}(C_{22}H_{21}PO)_{.20}$ (100% conversion): P, 4.13%. Found: P, 5.24%. Repeating the reaction at room temperature in hexamethylphosphoramide/THF under argon for 8 hours, followed by air for 8 hours, gave a polymer with identical IR spectrum.

<D1046, D1060>.

Experiment 23. (N-pyridinium)polystyrene tosylate. From (toluenesulfoxyethyl)polystyrene.

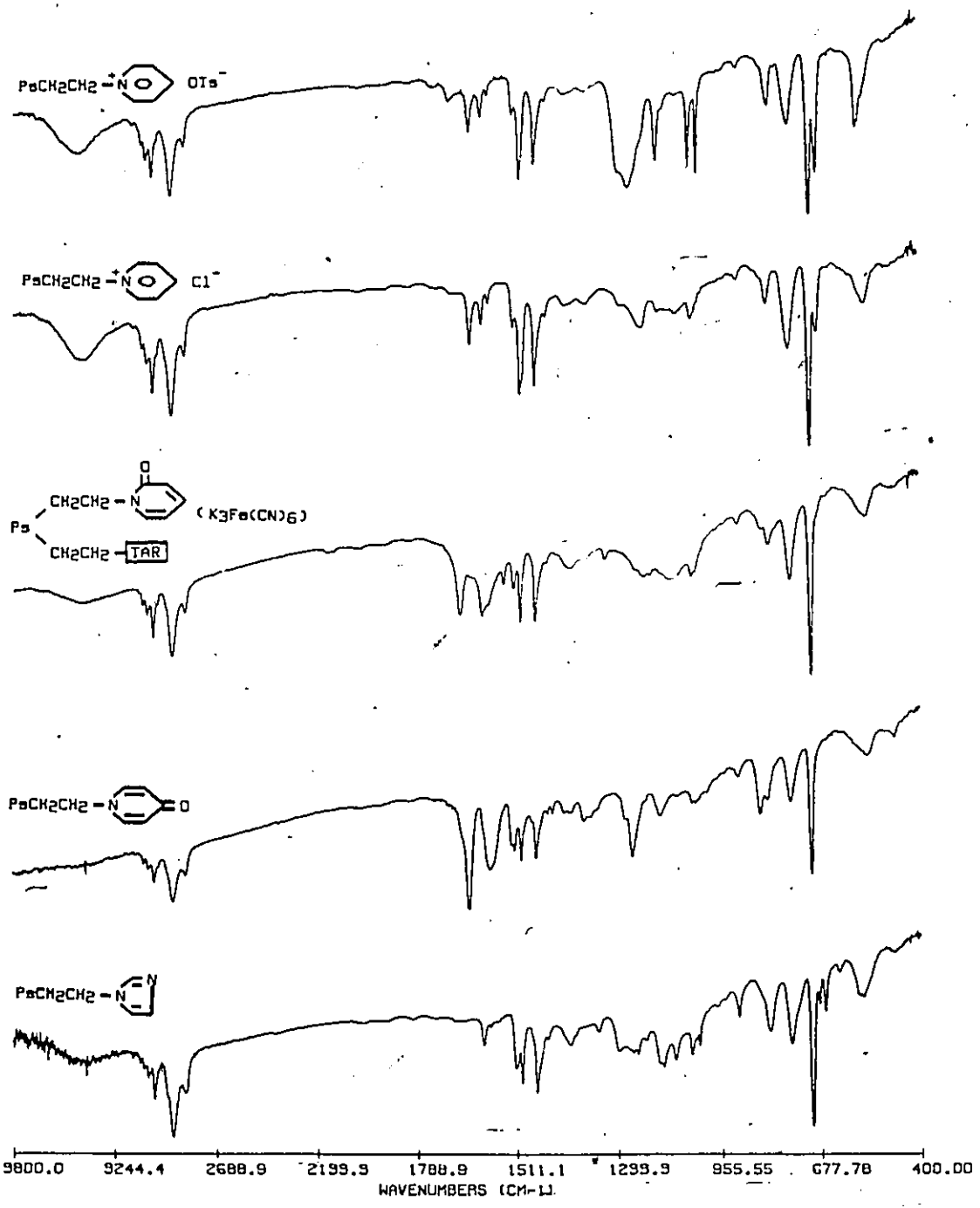
(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}$-$(C_{17}H_{18}SO_3)_{.24}$ (0.51 g, 0.83 meq) and dry pyridine (2.0 ml, 25 meq) were refluxed in 7 ml toluene under nitrogen for 14 hours. The beige suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and

dried under vacuum overnight, yielding 0.58 g of yellow-beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor; peaks present at 1633 (m, pyr), 1582 (w, pyr), 1196 (s, SO_3^-), 1012 (s, SO_3^-), 682 (m, pyr^+) and 569 cm^{-1} (m, $ArSO_3^-$) for pyridinium tosylate product (Figure 3). <D916>.

Experiment 24. (N-pyridinium)polystyrene tosylate, chloride. From (hydroxyethyl)polystyrene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{12}O)_{.24}$ (4.99 g, 10.4 meq) and toluenesulfonyl chloride (5.0 g, 26 meq) were suspended in dry pyridine (60 ml, 700 meq) chilled in an ice bath to 0°C under nitrogen. The mixture was allowed to warm to room temperature over 4 hours, then refluxed for 2 hours, then cooled and filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (1X), Et_2O (1X), and dried under vacuum overnight, yielding 6.72 g of a peach-coloured powder: IR (KBr) peaks absent at 1046 cm^{-1} for alcohol precursor, at 1363 and 1176 cm^{-1} for tosyl ester intermediate, and at 1245 and 657 cm^{-1} for chloro side-product; peaks present at 1633 (m, pyr), 1582 (w, pyr^+), 1196 (s, SO_3^-), 1123 (s, SO_3^-), 1034 (s, SO_3^-), 1012 (s, SO_3^-), 682 (m, pyr^+) and 569 cm^{-1} (m, $ArSO_3^-$) for pyridinium tosylate product (Figure 3). The product was then washed with 12N HCl/H_2O (1X), HCl/H_2O:THF 1:1 (1X), HCl/H_2O:THF 1:4 (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (1X), Et_2O (1X), hexane

Figure 3. FTIR spectra of polymer-bound heterocycles.



(3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (1X), Et_2O (1X), hexane (1X), and dried under vacuum overnight, yielding 5.99 g of beige powder: IR (KBr) peaks absent at 1196, 1123, 1034, 1012 and 569 cm^{-1} for tosylate anion; peaks still present at 1633, 1582 and 682 cm^{-1} for pyridinium nucleus (Figure 3). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{15}H_{16}NCl)_{.24}$ (for 100% conversion): Cl, 6.15. Found: Cl, 6.19.

<D833, D834>.

Experiment 25. (2-Methylpyridinium-N-ethyl)polystyrene tosylate. From (toluenesulfonyloxyethyl)polystyrene.

(Toluenesulfoxethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}(C_{10}H_{12}O)_{.20}$ (0.46 g, 0.63 meq) was suspended in pure 2-methylpyridine (5 ml, 50 meq), and stirred under nitrogen at 90°C for 14 hours. The brown suspension was filtered and washed acetone (2X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.50 g of pale brown powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor; peaks present at 1651 (m, Me-pyr), 1581 (w, pyr^+), 1199 (s, SO_3^-), 1120 (s, SO_3^-), 1034 (s, SO_3^-), 1012 (s, SO_3^-), 680 (m, pyr^+) and 570 cm_{-1}(m, $ArSO_3^-$) for pyridinium tosylate product.

<D1072>.

Experiment 26. (2-Methylpyridinium-N-ethyl)polystyrene tosylate. Attempt from (hydroxyethyl)polystyrene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}(C_{10}H_{12}O)_{.20}$ (0.51 g, 0.90 meq) and toluenesulfonyl chloride (0.94 g, 4.9 meq) were stirred together in pure 2-methylpyridine (5 ml, 50 meq) under nitrogen at 90°C for 14 hours. The black suspension was then filtered, and the residue washed with acetone (3X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.76 g of black powder: IR (KBr) spectrum similar to that from Experiment 25, but with an extra small peak at 1155 cm^{-1} (SO_2).

<D1070>.

Experiment 27. (2-Chloropyridinium-N-ethyl)polystyrene iodide. Attempts from (iodoethyl)polystyrene.

(Iodoethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{11}I)_{.29}$ (14.4 g, 28 meq) was stirred in dry 2-chloropyridine (150 ml, 1.6 mol) under nitrogen at 95°C for 48 hours. The golden brown suspension was then filtered (2-chloropyridine was recovered by distilling the filtrate), and the residue washed with dry benzene (3X), then dry ether (2X), and dried under vacuum overnight to yield 16.0 g of brown powder: IR (KBr) peaks absent at 1245 and 1168 cm^{-1} for iodo precursor; peaks present at 1659 (m, pyr^+), 1539 (w, pyr^+), 1159 (m, CH_2-N) and 690 cm^{-1} (w, pyr^+) for pyridinium product, but also at 1245 (w,

CH_2-Cl) and 657 cm^{-1} (w, C-Cl) for chloro side-product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{15}H_{15}NI_2)_{.145}(C_{10}H_{11}Cl)_{.145}$ (50% conversion to iodopyridinium iodide, and the remainder to chloro) N, 1.23; total halogen, 2.63 meq/g; weight change, +11.05%. Found: N, 1.23; total halogen, 2.56 meq/g; weight change, +11.11%. The reaction was repeated for longer periods (see Table 1), eventually giving, on a 7 g scale of Df=.21 starting polymer, a very dark brown powder without $-CH_2Cl$ peaks in its FTIR spectrum. Anal. Calcd for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.78}(C_{15}H_{15}NICl)_{.21}$: N, 1.83; total halogen, 2.62 meq/g. Found: N, 1.76; total halogen, 2.68 meq/g.

<D353, D699, D394, D357, D369>.

Experiment 28. (2-pyridinon-N-ethyl)polystyrene. Attempts from (bromoethyl)polystyrene with 2-alkoxypyridines.

(Bromoethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.73}(C_{10}H_{11}Br)_{.26}$ (0.76 g, 1.5 meq) was suspended in an excess of dry 2-methoxypyridine (5 ml, 50 meq) and gently stirred under nitrogen at 120°C for 15 hours. The red-brown suspension was filtered, and the residue washed 3 X CH_2Cl_2, H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and vacuum-dried overnight, yielding 0.82 g of beige powder: IR (KBr) peak still present at 1263 cm^{-1} for starting bromide; new peaks at 1663 (s, pyr=O) and 1593 cm^{-1} (m, pyr) for product pyridinone (N-methyl-2-pyridinone (Nujol) reported 1665 and 1595 cm^{-1};[180] a medium peak at 1538 cm^{-1} shrank with more washing of polymer

in aqueous base, and can thus be at least partly attributed to 2-methoxypyridinium imtermediate. Anal. Calcd for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.73}(C_{10}H_{11}Br)_{.05}(C_{16}H_{18}NOBr)_{.15}(C_{15}H_{15}NO)_{.06}$ (81% quaternization, followed by 40% hydrolysis): N, 1.97; Br, 10.69. Found: N, 1.98; Br, 10.47. Another reaction of Df=.25 polymer, with 10% 2-ethoxypyridine in tetramethylenesulfone at 120°C for 16 hours, gave a product with similar IR. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{10}H_{11}Br)_{.17}(C_{16}H_{18}NOBr)_{.02}$-$(C_{15}H_{15}NO)_{.06}$ (32% quaternization, followed by 75% hydrolysis): N, 0.83; Br, 11.29. Found: N, 0.85; Br, 11.26. <D873, D1024>.

Experiment 29. (2-pyridinon-N-ethyl)polystyrene. Attempt from (pyridinium-N-ethyl)polystyrene chloride.

To a bright yellow suspension of (pyridinium-N-ethyl)polystyrene chloride $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{15}H_{16}NCl)_{.24}$ (0.50 g, 0.86 meq) and potassium ferricyanide (0.50 g, 1.52 meq) in a mixture of 3.4 ml water and 6 ml dimethylsulfoxide was added, dropwise over 3 hours while stirring under nitrogen at 0°C, a solution of 50% NaOH/H_2O (1 ml, 20 meq). After stirring at 0°C for a further 16 hours, the dark brown suspension (with white precipitate) was filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.47 g of red-brown powder: IR (KBr) peaks absent at 1633, 1582 and 682 cm^{-1} for pyridinium precursor, and at 2050 for cyano intermediate and byproduct;

peaks present at 1662 (C=O) and 1593 (m, pyr) for product; the remainder of the spectrum displayed some small irregularities not seen in polymer prepared by the previous method (Figure 3). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{15}H_{15}NO)_{.24}$ (100% conversion): N, 2.52. Found: N, 2.34. Similar reactions in water, methanol, or benzene (with & without phase-transfer catalyst) gave (by FTIR) little or no pyridinone product. Darkening was no less with potassium carbonate or fluoride as base.

<D790, D860>.

Experiment 30. (4-pyridinon-N-ethyl)polystyrene. From (haloethyl)polystyrene with 4-trimethylsiloxypyridine.

(Chloroethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{10}H_{11}Cl)_{.25}$ (2.034 g, 3.05 meq) and anhydrous sodium iodide (1.01 g, 6.7 meq) were suspended in 15 ml dry N-methyl-pyrrolidinone, then freshly-prepared[44] clear and colourless trimethylsiloxypyridine (1.0 ml, 6 meq) was injected, and the mixture heated to 105°C and stirred for 20 hours under nitrogen. The red-brown suspension was then filtered, and the residue washed H_2O (3X), H_2O:pyridine 4:1 (1X), H_2O (3X), acetone (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 2.282 g of pale brown powder: IR (KBr) peaks absent at 1245 and 1236 cm^{-1} for alkyl chloride or iodide precursor; peaks present at 1639 (s, pyr), 1582 (m, pyr=O) and 1189 cm^{-1} (m, C-N) for 4-pyridinone product (figure 3). Anal. Calcd for $(C_{10}H_{10})_{.01}$-

$(C_8H_8)_{.74}(C_{15}H_{15}NO)_{.25}$ (100% conversion to pyridinone): N, 2.60; weight change, +2.59%. Found: N, 2.37; weight change, +2.59.

<D1140>.

Experiment 31. (4-pyridinon-N-ethyl)polystyrene. Attempt from (haloethyl)polystyrene with 4-dimethylaminopyridine.

(Chloroethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}(C_{10}H_{11}Cl)_{.20}$ (0.27 g, 0.46 meq), anhydrous sodium iodide (0.12 g, 0.80 meq) and 4-dimethylaminopyridine white crystals (0.080 g, 0.65 meq) were stirred in a mixture of 2 ml dry toluene and 1 ml N-methylpyrrolidinone at 110°C under nitrogen for 24 hours. The red-brown suspension was then filtered, and the residue washed with acetone (3X), water (3X), acetone (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.38 g of beige powder: IR (KBr) peaks absent at 1245 and 1236 cm^{-1} for chloro precursor or iodo active intermediate; peaks present at 1650 (s, pyr), 1567 (m, pyr-N) and 1170 cm^{-1} for aminopyridinium product. A qualitative halogen test with silver nitrate showed presence of much ionic halide. The same reaction without sodium iodide gave recovered starting polymer. Another compound, prepared from (toluene-sulfoxyethyl)polystyrene, showed strong peaks at 1196, 1012 and 569 cm^{-1} for tosylate anion. Treatment of this polymer with 50% $NaOH/H_2O$ at 100°C for 8 hours gave an extremely dark brown powder of FTIR spectrum with very weak peaks or

shoulders at 1653, 1012 and 569 cm^{-1} for residual pyridinium tosylate precursor; otherwise similar to that of (4-pyridinon-N-ethyl)polystyrene from the previous experiment, with peaks present at 1640 (s, pyr), 1582 (m, pyr=O) and 1189 cm^{-1} (m, C-N) for product. The darkening was no less upon hydrolysis at lower temperatures, or with the addition of acetate, benzoate, methanol, diisopropylamine, or phase-transfer catalyst to the reaction mixture.

<D1122, D1116, D1111>.

Experiment 32. (Pyrrolidin-N-ethyl)polystyrene. Attempts from (toluenesulfoxyethyl)polystyrene in dimethylsulfoxide and dimethylformamide.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}$-$(C_{17}H_{18}SO_3)_{.25}$ (0.19 g, 0.32 meq), dry pyrrolidine (0.050 ml, 0.60 meq), and potassium phosphate tribasic (0.10 g, 0.47 meq) and dibasic (0.053 g, 0.30 meq) were suspended in 2 ml dimethylsulfoxide and stirred under nitrogen at room temperature for 16 hours, then at 40°C for 24 hours. The beige suspension was then filtered, and the residue washed acetone (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), 1 X CH_3OH, and dried under vacuum overnight, yielding 0.17 g of pale beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor; faint peaks or shoulders present, not seen by other procedures (Experiment 33 & 34), present at 1632 (C=C), 1201 (w, SO_3^-) and 552 cm^{-1} (w, SO_3^-) for traces of quaternization

and elimination side-products; peak present at 2784 (m, CH_2-N) and 1154 (w, C-N) for product amine. Anal. Calcd for $(C_{10}H_{10})_{.03}(C_8H_8)_{.74}(C_{14}H_{19}N)_{.23}$ (92% conversion to tertiary amine, 8% to olefin): N, 2.53. Found: N, 2.55. The reaction was repeated with potassium carbonate in dimethylformamide on a polymer of Df=0.29, giving a product of similar FTIR, but with impurities less pronounced. Anal. Calcd for $(C_{10}H_{10})_{.03}$-$(C_8H_8)_{.70}(C_{14}H_{19}N)_{.27}$ (93% conversion to tertiary amine, 7% to olefin): N, 2.88. Found: N, 2.85.

<D968, D995>.

Experiment 33. (Pyrrolidin-N-ethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene in pyridine.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}$-$(C_{17}H_{18}SO_3)_{.29}$ (0.19 g, 0.34 meq), dry pyrrolidine (0.032 ml, 0.38 meq) and anhydrous potassium carbonate (0.050 g, 0.36 meq) were stirred in 2 ml dry pyridine under nitrogen at room temperature for 2 hours, then slowly warmed to reflux over 5 hours. The red-orange suspension was filtered, and the residue washed H_2O (3X), MEK (1X), CH_2Cl_2 (1X), 1 X Et_2O, and dried under vacuum overnight to yield 0.17 g of yellow-beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1633, 1582 and 682 cm^{-1} for pyridinium, 1196, 1123, 1034, 1012, 682 and 569 cm^{-1} for tosylate, and 1632 cm^{-1} for olefin side-products; peak present at 2784 cm^{-1} (CH_2-N) for product. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}$-

$(C_{14}H_{19}N)_{.29}$: N, 3.06. Found: N, 2.98.

<D992>.

Experiment 34. (Pyrrolidin-N-ethyl)polystyrene. From (hydroxyethyl)polystyrene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{12}O)_{.24}$ (1.01 g, 2.1 meq) and toluenesulfonyl chloride (1.00 g, 5.2 meq) were stirred in dry pyridine (10 ml, 120 meq) under nitrogen at 0°C for 23 hours. Dry pyrrolidine (2.00 ml, 24 meq) was then added, and the red-orange suspension was stirred for a further 45 hours, then slowly heated and refluxed for 4 hours. The mixture was then filtered, and the residue washed with MEK (1X), CH_3OH (1X), H_2O (3X), 20% $^1NaOH/H_2O$:ethanol 1:5 (1X), H_2O (3X), EtOH (1X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, yielding 1.12 g pale beige powder: IR (KBr) identical to that from previous experiment, including peak absent at 1046 cm^{-1} for alcohol precursor. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{14}H_{19}O)_{.24}$ (100% conversion to amine): N, 2.63. Found: N, 2.69. In another experiment, in which the pyridine-toluenesulfonyl chloride mixture was stirred for only 4 hours before receiving pyrrolidine, FTIR indicated a small remnant of hydroxy functional groups. Another experiment, performed in excess pyrrolidine as solvent, showed no reaction whatsoever by FTIR even after reflux (no peak at 2784 cm^{-1}).

<D825, D824, D818>.

Experiment 35. (Pyrrolidin-N-ethyl)polystyrene. Attempt from (pyridinium-N-ethyl)polystyrene tosylate.

(Pyridinium-N-ethyl)polystyrene tosylate $(C_{10}H_{10})_{.01}(C_8H_8)_{.65}(C_{22}H_{23}NSO_3)_{.34}$ (0.50 g, 0.86 meq) and dry pyrrolidine (0.48 g, 6.7 meq) were stirred in 5 ml dry pyridine at 115°C under nitrogen reflux for 24 hours. The initially bright yellow suspension quickly turned dark red-brown, then eventually black; it was filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.41 g of very dark chocolate-brown powder: IR (KBr) peaks still present at 1633, 1582 and 682 cm^{-1} for pyridinium, and 1196, 1033, 1012 and 568 cm^{-1} for tosylate; strange weak to medium peaks present at 1649, 1624, 1351 and 1220 cm^{-1} for ring-opening & decomposition side-products; peak at 2794 cm^{-1} (w, CH_2-N) due to pyrrolidinyl, but not attached in the same way as in the previous experiment.

<D1041>.

Experiment 36. (N,N-Diisopropylcarbamomethyl)polystyrene. From (carboxymethyl)polystyrene.

(Carboxymethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{10}O_2)_{.29}$ (0.46 g, 1.1 meq) and toluenesulfonyl chloride (0.68 g, 3.6 meq) were suspended in an excess of dry diisopropylamine (5 ml, 36 meq). After the initial exothermic reaction, the

suspension was heated to 105°C, and stirred under nitrogen reflux for 18 hours. The pale brown suspension was filtered, and the residue washed 2 X acetone, H_2O (3X), MEK (1X), CH_2Cl_2 (1X), 1 X CH_3OH, and dried under vacuum overnight, yielding 0.55 g of pale brown powder: IR (KBr) peak absent at 1160 and 1294 cm^{-1} for carboxyl precursor, and at 664 and 555 cm^{-1} for tosic anhydride intermediate; peaks present at 2964 (w, CH_3), 1641 (s, C=O), 1370 (m, CH_3), 1336 (m, CH_3) and 1127 cm^{-1} (w, C-N) for product amide. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}$-$(C_{16}H_{23}NO)_{.29}$ (100% conversion to amide): N, 2.79. Found: N, 2.72.

<D893>.

Experiment 37. (N,N-Diisopropylaminoethyl)polystyrene. Attempt from (N,N-Diisopropylcarbamomethyl)polystyrene.

(N,N-Diisopropylcarbamomethyl)polystyrene $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.70}(C_{16}H_{23}NO)_{.29}$ (0.50 g, 0.99 meq) and 10M borane/dimethylsulfide (0.30 ml, 3 meq BH_3) were gently refluxed in anhydrous THF under nitrogen for 30 hours. The pale yellow-green suspension was filtered, and the residue washed with 10% NaOH/H_2O (1X), H_2O (2X), acetone (1X), H_2O (1X), 10% NaOH/H_2O (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (1X), and dried under vacuum overnight, yielding 0.48 g of pale beige powder: IR (KBr) peak absent at 1641 cm^{-1} for starting amide, and at 1730 cm^{-1} for aldehyde side-product; peak present at 1046 cm^{-1} (w, CH_2-OH) for alcohol side-

product, and at 2964 (w, CH_3), 1382 (m, CH_3) and 1118 cm^{-1} (s, CH_2-N) for product amine. Anal. Calcd for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.70}(C_{10}H_{12}O)_{.04}(C_{16}H_{25}N)_{.25}$ (86% conversion to tertiary amine, 14% to alcohol): N, 2.54. Found: N, 2.54. <D896>.

Experiment 38. (N,N-Diisopropylaminoethyl)polystyrene. Attempts from (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.73}$-, $(C_{17}H_{18}SO_3)_{.26}$ (0.49 g, 0.79 meq) and dry diisopropylamine (0.5 ml, 4 meq) were heated together in dry tetramethylene-sulphone at 85°C for 30 hours. The pale orange-brown suspension was then filtered, and the residue washed with H_2O (3X), acetone (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.48 g of pale beige powder: IR (KBr) peaks present at 1363 and 1176 cm^{-1} for tosic ester precursor; peaks absent at 2965 and 1118 cm^{-1} for amine product. The same reaction was performed in N-methylpyrrolidinone at 85°C for 40 hours: IR (KBr) peaks much smaller at 1363 and 1176 cm^{-1} for tosic ester precursor; very weak peaks present at 2965 and 1118 cm^{-1} for amine product, but also at 1620 (w, C=C) and 1736 cm^{-1} (m, C=O) for elimination and solvent alkylation respectively. The same reaction with toluenesulfonic acid added (0.05 g, 0.3 meq) gave a product with very strong FTIR peak at 1700 cm^{-1} for -COOH of alkylated solvent, and none at 2965 cm^{-1} for diisopropylamine product. A

reaction of tosylated polymer (0.28 g, 0.39 meq) with 2-pyridinone (0.068 g, 0.72 meq), chlorotrimethylsilane (0.10 ml, 0.79 meq), and diisopropylamine (0.20 ml, 1.4 meq) in N-methylpyrrolidinone at 110°C for 26 hours showed FTIR peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor; peaks present at 2965 and 1118 cm^{-1} stronger than reaction in N-methylpyrrolidinone alone, but peaks also present at 1621 (w, C=C) and 1245 cm^{-1} (w, CH_2-Cl) for for elimination and chlorination side-products respectively.

<D1159, D1147, D1135, D1090>.

Experiment 39. (Imidazol-N-ethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

Sodium hydride (0.23 g, 10 meq) was suspended in 15 ml dry dimethylformamide at 10°C under nitrogen, then anhydrous crystalline imidazole (0.72 g, 11 meq) in 5 ml dry DMF was added by drops over 20 minutes. After effervescence had subsided, (toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.70}(C_{17}H_{18}SO_3)_{.29}$ (1.898 g, 3.4 meq) was added by powder dropping funnel over 15 minutes, then the mixture was gently stirred at 10°C under nitrogen for 16 hours. The pale red-brown suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, yielding 1.546 g of pale beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, at 1630 cm^{-1} for elimination and at 1375

(R_2Imz^+),[258] 1196, 1123, 1034, 1012 and 569 cm^{-1} for quaternization side-products; peaks present at 3105 (w, Imz-H), 1508 (m, Imz), 1284 (m, Imz-H), 1231 (m, Imz), 1108 (m, Imz-H), 1076 (m, Imz), 905 (m, Imz), 663 (s, Imz) and 624 (w, Imz) for imidazole[259] product (Figure 3). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{13}H_{14}N_2)_{.29}$ (100% conversion): N, 6.17; weight change, -18.66. Found: N, 5.87; weight change, -18.51. In another experiment, sodium imidazolide was formed with sodium metal in tetrahydrofuran, and reacted with (toluenesulfoxyethyl)polystyrene in cold pyridine, to give a product with identical IR (Figure 3). Attempts (with sodium hydride or potassium hydroxide) to form imidazolide in situ with tosylated polymer resulted in detectable (FTIR) elimination. <D983, D1075, D948, D1058>.

Experiment 40. (Imidazol-N-ethyl)polystyrene. From (hydroxyethyl)polystyrene.

(Hydroxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{12}O)_{.24}$ (0.97 g, 2.0 meq) and toluenesulfonyl chloride (1.00 g, 5.2 meq) were stirred in 10 ml dry pyridine under nitrogen at 0°C for 16 hours. A white suspension of excess sodium imidazolide, prepared by stirring anhydrous crystalline imidazole (1.50 g, 22 meq) with sodium metal (0.39 g, 17 meq) in anhydrous tetrahydrofuran for 18 hours, was then decanted from unreacted sodium (about 0.10 g, 4 meq) onto the red-orange polymer suspension, which became yellow. After stirring for a further

2 hours at room temperature, the mixture was warmed over 1 hour to reflux, then cooled, and the green-brown suspension was filtered and washed with H_2O (1X), 20%NaOH/H_2O:EtOH 1:2 (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), and CH_3OH (2X), then dried under vacuum overnight to yield 1.09 g of pale brown powder: IR (KBr) spectrum identical to that from previous experiment. Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{13}H_{14}N_2)_{.24}$ (100% conversion): N, 5.29. Found: N, 5.15.

<D823>.

Experiment 41. (N-(4-pyridin)-N-methyl-aminoethyl)polystyrene. Attempts from (toluenesulfoxyethyl)polystyrene and others.

N-Methylaminopyridine (1.08 g, 10 meq) was suspended with sodium hydride (0.23 g, 9.6 meq) in 15 ml dry dimethylformamide at 7°C under nitrogen. After stirring for 17 hours, slow effervescence had completely subsided, and (toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{17}H_{18}SO_3)_{.29}$ (1.936 g, 3.5 meq) was then added from a powderdropping funnel. After stirring for a further 20 hours, the dark red-brown suspension was filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, yielding 1.361 g of pale yellow-white powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1663 cm^{-1} for pyridinone side-product; peaks very weak or absent at 1230 and 800 cm^{-1} (see Part III) for dialkylaminopyridine functional group, but substantial at

1629 cm^{-1} (C=C) for vinyl side-product. Anal. Calcd for $(C_{10}H_{10})_{.28}(C_8H_8)_{.70}(C_{16}H_{18}N_2)_{.02}$ (7% conversion to dialkylaminopyridine, 93% to olefin): weight change, -29.51. Found: -29.67. Other reactions with (chloroethyl)polystyrene and (iodoethyl)polystyrene gave similar results, confirmed by very low or negligible nitrogen content. Reactions in THF, in benzene/H_2O with phase-transfer catalyst, or in the absence of base, gave significant FTIR absorbtion at 1665 cm^{-1} for ring-alkylated products.

<D984>.

Experiment 42. (N-(4-pyridin)-N-methyl-carbamomethyl)polystyrene. From (carboxymethyl)polystyrene.

(Carboxymethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{10}O_2)_{.29}$ (0.51 g, 1.2 meq), N-methylaminopyridine (0.22 g, 2.0 meq), dicyclohexylcarbodiimide (0.46 g, 2.2 meq) and dimethylaminopyridine (0.02 g, 0.2 meq) were stirred in 5 ml dry THF under nitrogen at room temperature for 26 hours. The very pale yellow beige suspension was filtered, and the residue washed wih MEK (1X), CH_2Cl_2 (1X), methanol (2X) and dry ether (2X), then dried under vacuum overnight: IR (KBr) very small shoulder remains at 1710 cm^{-1} for carboxy precursor; peak present at 1671 (s, C=O) and 1587 cm^{-1} (s, pyr) for amide product. Similar reactions with toluenesulfonyl chloride were incomplete after 130 hours reflux; treatment with thionyl chloride followed by N-methylaminopyridine gave a black solid.

<D990>.

Experiment 43. (N-(4-pyridin)-N-methyl-aminoethyl)polystyrene. Attempt from (N-(4-pyridin)-N-methyl-carbamomethyl)polystyrene.

(N-(4-Pyridin)-N-methyl-carbamomethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{16}H_{16}N_2O)_{.29}$ (0.49 g, 0.97 meq) was suspended in 5 ml anhydrous THF under nitrogen, then 10M BH_3/dimethylsulfide (0.50 ml, 5.0 meq) was slowly injected, and the mixture refluxed for 25 hours. The white suspension was then quenched with methanol and filtered, and the residue washed with 10% NaOH/H_2O (1X), H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight to yield 0.48 g of white powder: IR (KBr) peaks absent at 1671 and 1587 cm^{-1} for amide precursor, and at 1730 and 1046 cm^{-1} for aldehyde and alcohol side-products, but also at 1595 cm^{-1} for dialkylaminopyridine product (see Part III); peaks present at 1636 cm^{-1} (s, C=O) and 1399 cm^{-1} (w, C-O) for carboxylate side-product. ≤D991, DN39B>.

Experiment 44. (Pyrrolidinon-N-ethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.794}(C_{17}H_{18}SO_3)_{.196}$ (0.31 g, 0.42 meq), powdered potassium hydroxide (0.11 g, 2.0 meq) and dry pyrrolidinone (0.050 ml, 0.66 meq) were stirred in 4 ml dry dimethylsulfoxide under

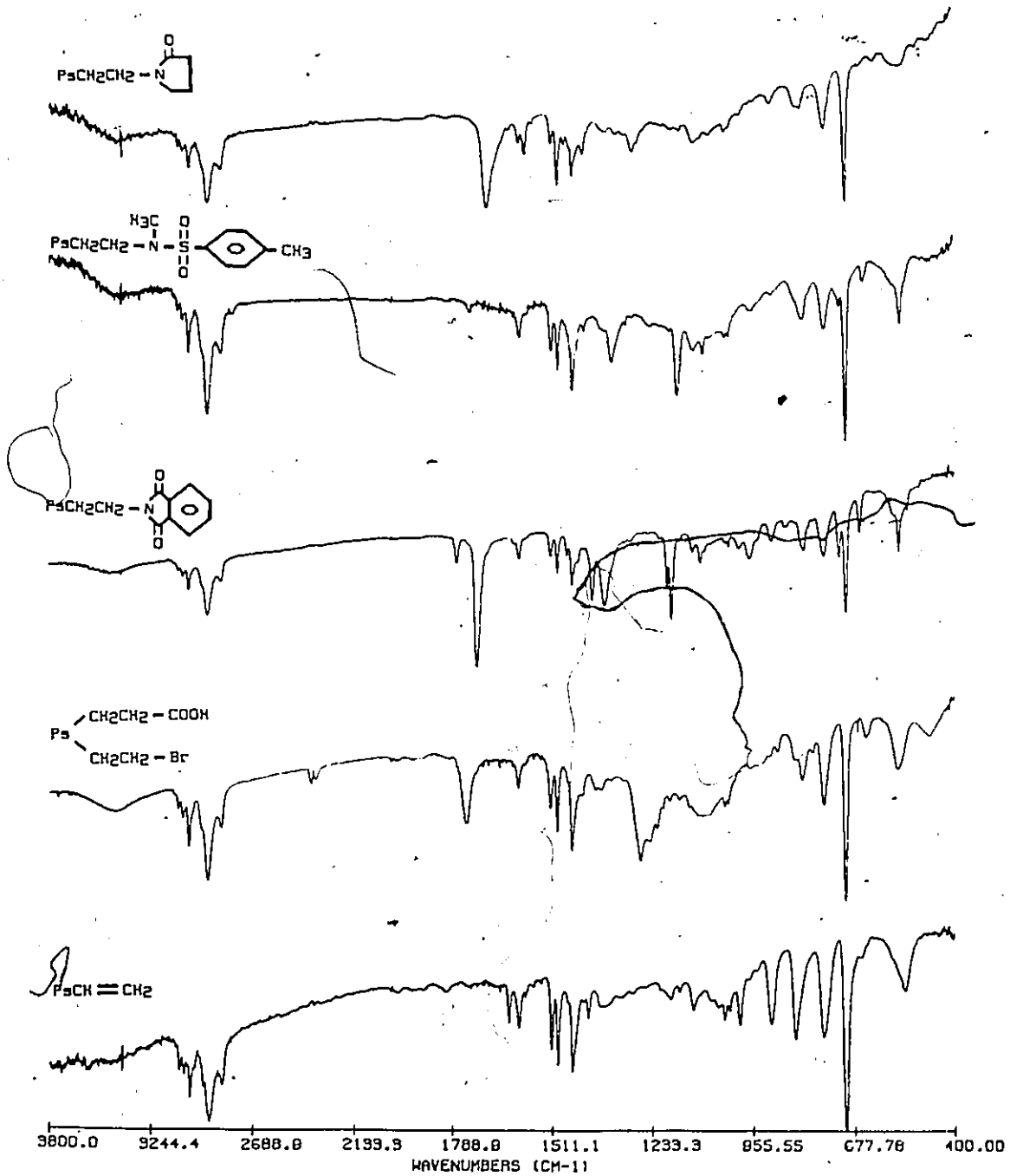
nitrogen at room temperature for 3 hours, then at 60°C for 23 hours. The beige-brown suspension was then washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight to give 0.26 g of pale yellow-beige powder: IR (KBr) peak absent at 1176 cm^{-1} for tosic ester precursor, and at 1636 cm^{-1} for ring-opened carboxylate side-product; peak present at 1691 cm^{-1} (s, C=O) for cyclic tertiary amide product (Figure 4). Anal. Calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.794}$-$(C_{14}H_{17}NO)_{0.196}$ (100% conversion to amide): N, 2.18. Found: N, 2.06. A similar experiment was performed without potassium hydroxide: IR (KBr) peak present at 1046 cm^{-1} for alcohol side-product.

<D1062, D1071>.

Experiment 45. (N-methyl-propionamidoethyl)polystyrene. Attempt from (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}$-$(C_{17}H_{18}SO_3)_{.25}$ (0.3347 g, 0.53 meq), dry N-methyl-propionamide (0.34 g, 4.7 meq), and powdered potassium hydroxide (0.45 g, 8 meq) were stirred in a mixture of 3 ml dry dimethylsulfoxide and 0.5 ml hexamethylphosporamide under nitrogen at room temperature for 17 hours, then at 50°C for 5 hours. The yellow-brown suspension was then filtered, and the residue washed with water (3X), acetone (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, yielding 0.2492 g of yellow powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic

Figure 4. FTIR spectra of polymer-bound carboxamide, sulfonamide, imide, carboxyl (via metallation) and vinyl functionalities.



ester precursor; peaks present at 1653 cm^{-1} (w, C=O) for only small amounts of amide product, and at 1629 cm^{-1} (w, C=C) for substantial olefin side-product. Anal. Calcd for $(C_{10}H_{10})_{.22}(C_8H_8)_{.74}(C_{14}H_{19}NO)_{.04}$ (16% conversion to amide, 84% to olefin): weight change, -25.70. Found: -25.55. Other reactions using dimethylformamide as solvent, or sodium hydride or cesium fluoride as base, or with N-methylformamide, N-methylacetamide or N-methyl-o-toluamide as secondary amide substrates, gave comparable results.

<D1137, D1006, D1134, D1141>.

Experiment 46. (2-pyridinon-N-ethyl)polystyrene. Attempts from (toluenesulfoxyethyl)polystyrene with 2-pyridinolate.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}(C_{17}H_{18}SO_3)_{.20}$ (0.32 g, 0.44 meq), 2-pyridinone beige crystals (0.068 g, 0.72 meq) and anhydrous potassium carbonate (0.23 g, 1.7 meq) were stirred in dry dimethylsulfoxide under nitrogen at room temperature for 2 hours, then at 60°C for 23 hours. The beige-brown suspension was then filtered, and the residue washed with water (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight to yield 0.30 g of beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1629 cm^{-1} for elimination side-product; peaks present at 1662 (s, C=O) and 1593 cm^{-1} (m, pyr) for 2-pyridinone product, but also at 1432 (m, pyr), 1463 (w, pyr), 1474 (w, pyr), 1570 (w, pyr) and 1540 cm^{-1} (m, pyr-OR),

not seen in polymeric 2-pyridinone prepared by ferricyanide oxidation (Experiment 29), for pyridyl ether side-product. Similar reactions using cesium fluoride or barium oxide as base also gave products containing these anomalous peaks. Large tosic ester peaks remained in polymer heated with 2-pyridinone in the absence of base.

<D1055, D1081, D1089>.

Experiment 47. (N-methyl-toluenesulfonamidoethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.79}$-$(C_{17}H_{18}SO_3)_{.20}$ (0.39 g, 0.53 meq), N-methyl-toluenesulfonamide (0.14 g, 0.74 meq) and potassium carbonate (0.21 g, 1.5 meq) were stirred in a mixture of 4 ml dry dimethylsulfoxide and 0.5 ml hexamethylphosphoramide under nitrogen at 60°C for 22 hours. The pale brown suspension was then filtered, and the residue washed with acetone (1X), H_2O (2X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, yielding 0.39 g of beige-white powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and 1630 cm^{-1} for elimination side-product; peaks present at 1344 (s, SO_2-N), 1161 (s, SO_2-N), 653 (m, $ArSO_2$) and 549 cm^{-1} (m, $ArSO_2$) for sulfonamide product (Figure 4). Anal. Calcd for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.79}(C_{18}H_{21}NSO_2)_{.20}$ (100% conversion): N, 1.91; S, 4.37. Found: N, 1.98; S, 4.80.

<D1056>.

Experiment 48. (N-Phthalimido-ethyl)polystyrene. From (toluenesulfoxyethyl)polystyrene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{17}H_{18}SO_3)_{.29}$ (0.200 g, 0.36 meq), phthalimide (0.062 g, 0.42 meq), and anhydrous potassium carbonate (0.057 g, 0.41 meq) were stirred in 2 ml dry dimethylformamide under nitrogen at room temperature for 27 hours, then at 60°C for 18 hours. The yellow-green suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight, yielding 0.199 g of pale yellow-beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, and at 1629 cm^{-1} for olefin side-product; peaks present at 1774 (w, C=O), 1716 (s, C=O) and 719 cm^{-1} (m, Ar-CO) for phthalimide product (Figure 4). Anal. Calcd for $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{18}H_{15}NO_2)_{.29}$ (100% conversion): N, 2.63. Found: N, 2.54.

<D1000>.

Experiment 49. (N-methylaminoethyl)polystyrene. Attempts from (N-methyl-toluenesulfonamidoethyl)polystyrene.

(N-methyl-toluenesulfonamidoethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{18}H_{21}NSO_2)_{.29}$ (0.378 g, 0.65 meq) was added in portions to a blue mixture of naphthalene (0.63 g, 4.9 g) and sodium metal (0.094 g, 4.1 meq) in 4 ml anhydrous dimethoxyethane under argon, and the mixture was then stirred at room

temperature for 30 hours. The brown suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight to yield 0.348 g pof pale yellow-green powder: IR (KBr) peaks absent at 1344 and 1161 for sulfonamide precursor; peak present at 2790 cm^{-1} (w, N-CH_3) for amine product. Anal. Calcd for 75 wt% $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{11}H_{15}N)_{.29}$ (100% conversion to secondary amine) + 25 wt% other insoluble material: N, 2.52; S, 0; weight change, -5.30. Found: N, 2.43; S, 1.05; weight change, -7.91. Similar reactions were conducted with Li/di-t-butyl-biphenyl/THF and K/isopropanol: FTIR showed cleavage to be incomplete. Sulfonamide peaks disappeared with refluxing HBr/phenol/H_2O/CH_3COOH, but the product was dark brown. Refluxing HCl/H_2O/CH_3COOH had no effect.

<D989, D1154, D1056, D1005, D1181>.

Experiment 50. (2-Aminoethyl)polystyrene. From (phthalimidoethyl)polystyrene.

(Phthalimidoethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{18}H_{15}NO_2)_{.29}$ (0.14 g, 0.26 meq) and 0.1 ml 40% hydrazine/H_2O (1.2 meq) were refluxed together in 2 ml ethanol under nitrogen for 5 hours. The white suspension was then filtered, and the residue washed with acetone (1X), H_2O (3X), 5% NaOH/EtOH (1X), H_2O (3X), EtOH (1X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, yielding 0.11 g of white powder: IR (KBr) peaks absent at 1774 and 1716 cm^{-1} for phthalimide

precursor:

<D1003>.

Experiment 51. (Aminoethyl)polystyrene. Attempt from (toluenesulfoxyethyl)polystyrene with hexamethylenetetramine/hydrolysis.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{17}H_{18}SO_3)_{.25}$ (0.51 g, 0.83 meq) and hexamethylenetetramine white crystals (0.25 g, 1.8 meq) were refluxed together in 6 ml carbon tetrachloride under nitrogen for 22 hours, then concentrated HCl/H_2O (1 ml, 1.2 meq) in 3 ml ethanol was added and reflux continued for a further 2 hours. The bright yellow suspension was then filtered, and the residue washed with EtOH (2X), H_2O (3X), 5% NaOH/EtOH (1X fast), H_2O (3X), EtOH (1X), CH_2Cl_2 (1X), CH_3OH (1X), Et_2O (1X), then dried under vacuum overnight to yield 0.46 g yellow powder: IR (KBr) peaks present but less than half the intensity at 1363 and 1176 cm^{-1} for tosic ester precursor; spectrum otherwise similar that from the other route (Experiment 50).

<D1182>.

Experiment 52. (Lithium-ethyl)polystyrene. Attempt from (chloroethyl)polystyrene with lithium di-t-butylbiphenylide.

Di-t-butylbiphenyl was prepared, purified and characterized as described in the literature.[260] A 0.2 M solution of lithium di-t-butylbiphenylide [216] was prepared by

stirring a mixture of di-t-butylbiphenyl (1.69 g, 6.3 meq), fresh-cut lithium metal (0.0406 g, 5.9 meq) and 30 ml anhydrous tetrahydrofuran with a glass-coated magnet under argon at 0°C for 3.5 hours. The dark blue solution was then cooled to -78°C, and (chloroethyl)polystyrene $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.74}(C_{10}H_{11}Cl)_{.25}$ (0.848 g, 1.8 meq) was added in portions from a powder dropping funnel under argon over 1 hour. Stirring was continued for an additional hour before the blue solution was warmed to room temperature and quenched with chlorotrimethylsilane (1.5 ml, 12 meq). After a further 12 hours, the resulting pale orange suspension was filtered, and the residue washed with acetone (2X), H_2O (3X), acetone (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight to yield 0.823 g of pale beige-brown powder: IR (KBr) spectrum was identical to that of starting material. Similar absence of reaction was noted with radical anion generated in situ from lithium and a catalytic amount of di-t-butylbiphenyl. <D1158>.

Experiment 53. (Chloromagnesium-ethyl)polystyrene. Attempt from (chloroethyl)polystyrene with magnesium anthracenide.

Anthracene was recrystallized twice from hot ethanol and dried under vacuum. A suspension of magnesium anthracenide[231] was prepared by stirring a mixture of these white crystals (1.2 g, 6.7 meq), magnesium turnings (0.60 g, 25 meq), iodomethane (0.37 g, 2.6 meq) and 15 ml anhydrous tetra-

hydrofuran with a glass-coated magnet under argon at room temperature for 5 days. The thick orange suspension was decanted from unconsumed magnesium, filtered under argon and vacuum-dried to yield 0.7164 g of orange powder (1.71 meq of Mg.Anthr.3THF). This was resuspended in 5 ml anhydrous THF and rapidly transferred under argon to a flask containing (chloroethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.75}(C_{10}H_{11}Cl)_{.24}$ (0.379 g, 0.76 meq). After stirring a further 18 hours with a glass-coated magnet at room temperature under argon, the yellow-beige polymer was allowed to settle, and the cloudy yellow supernatant was decanted through a double-ended syringe. Chlorotrimethylsilane (2.0 ml, 16 meq) in 15 ml anhydrous tetrahydrofuran was then added and the mixture was stirred under argon at 50°C for a further 24 hours before being filtered, and the residue washed with CH_2Cl_2 (2X), THF (2X), acetone (1X), then dried under vacuum overnight to yield a pale beige-brown powder: IR (KBr) spectrum was identical to that of starting material. Similar absence of reaction was observed using (bromoethyl)polystyrene as substrate, or generating radical anion in situ with a catalytic amount of anthracene, or quenching with dry ice.

<T455>.

Experiment 54. (Bromomagnesium-ethyl)polystyrene. Attempt from (bromoethyl)polystyrene with phenethyl Grignard.

(Bromoethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.65}(C_{10}H_{11}Br)_{.34}$ (0.265 g, 0.74 meq), magnesium metal (0.103 g, 4.2 meq), (bromoethyl)benzene (0.01 ml, .07 meq), and triethylamine (0.11 ml, 0.79 meq) in 8 ml anhydrous toluene were stirred with a glass-coated magnet under nitrogen at 45°C for 24 hours, then the gray suspension was cooled to -78°C and dry ice (about 10 g, 200 meq) was added in portions. After warming to room temperature, the gray suspension was filtered and the residue washed with 6N H_2SO_4/H_2O:THF 1:1 (1X) to dissolve residual Mg, then with H_2O (3X), H_2O:THF 1:1 (1X), THF (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight to yield 0.170 g of pale beige-yellow powder: IR (KBr) peaks still present at 1263 cm^{-1} for bromo precursor, but new peak also present at 1747 cm^{-1} (m, C=O) for product from carbanion (Figure 4); qualitative analysis of a sodium fusion sample indicated substantial residual bromine. FTIR spectroscopy showed that a similar reaction after 48 hours gave much less carboxylated product, and none at all with a toluene-ether mixture as solvent, or with methyl, isopropyl or t-butyl shuttle, or with lithium or no added metal at all.

<D941, D967, T422, D960, D965, T417, T419>.

Experiment 55. (Vinyl)polystyrene. Attempts from (toluenesulfoxyethyl)polystyrene with diazabicycloundecene.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{17}H_{18}SO_3)_{.29}$ (2.00 g, 3.6 meq), anhydrous potassium carbonate (0.70 g, 5.1 meq) and catalytic diazabicycloundecene (0.12 g, 0.79 meq) were stirred together in 15 ml dry dichloromethane under nitrogen at room temperature for 6 hours. The beige-brown suspension was filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight, giving a pale brown powder: IR (KBr) shows large peaks remaining at 1176 and 1363 cm^{-1} for tosic ester precursor, and only a very small peak at 1629 cm^{-1} for vinyl product. The same reaction in dimethylsulfoxide at 100°C was still incomplete after 2 hours; moreover, the FTIR spectrum showed an extra peak at 1734 cm^{-1} (w, CHO).

<T424, T426, T429>.

Experiment 56. (Vinyl)polystyrene. From (toluenesulfoxyethyl)-polystyrene with N,N-dimethylaminoethanol.

(Toluenesulfoxyethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}$-$(C_{17}H_{18}SO_3)_{.29}$ (0.98 g, 1.8 meq) and N,N-dimethylaminoethanol (0.49 g, 5.5 meq) were stirred together in 4 ml dry dimethylsulfoxide at room temperature under nitrogen for 2 hours, then sodium hydroxide (1.0 g, 25 meq) was added and stirring was continued an additional 3 hours. The beige suspension was then filtered, and the residue washed with H_2O (3X), MEK (1X), CH_2Cl_2 (1X), CH_3OH (2X), then dried under vacuum overnight to yield 0.83 g of pale beige powder: IR (KBr) peaks absent at 1363 and 1176 cm^{-1} for tosic ester precursor, at 1046 cm^{-1} for hydroxyalkyl intermediate, and at 1730 cm^{-1} for aldehyde side-product; peak present at 1629 cm^{-1} (m, C=C) for vinyl product (Figure 4). Similar results were obtained upon substituting (chloroethyl)polystyrene as substrate, N,N-dimethylephedrine as reagent, or hexamethyl-phosphoramide as solvent.

<T427, T428, T429>.

Experiment 57. (Chlorodimethylsilylethyl)polystyrene. Attempt from (vinyl)polystyrene.

Tetrakis(triphenylphosphine)platinum(0) was prepared, purified and characterized as described in the literature.[261, 262] This pale yellow powder (0.014 g, 0.012 meq) was stirred with

(vinyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{10}H_{10})_{.29}$ (0.161 g, 0.42 meq), chlorodimethylsilane (2.0 ml, 18 meq) and 2 ml anhydrous benzene under nitrogen at room temperature for 95 hours, then a small portion of the beige suspension was rapidly rinsed with anhydrous toluene (3X) and dried under vacuum at 45°C: IR (KBr) peak still present at 1629 cm^{-1} for vinyl precursor, but new peak also present at 1262 (m, $Si-CH_3$) for silane product. Vinyl peak had not disappeared after heating at 40°C for a further 120 hours.

<T447>.

Part II.

Application of Spacer-Containing Functional Polystyrenes

APPLICATION OF SPACER-CONTAINING FUNCTIONAL POLYSTYRENES.

A. POLYMER-BOUND DIALKYLAMINOPYRIDINES.

INTRODUCTION

Though simple acylation reactions using acid chlorides or anhydrides and pyridine have been known since the turn of the century,[232] their remarkable acceleration in the presence of 4-(N,N-dimethylamino)pyridine only became noticed approximately fifteen years ago.[263,264] Since then, a number of other catalytically active dialkylaminopyridines have been developed,[92,265] and these reagents have taken their place on the shelves of chemists for a variety of applications from the laboratory bench to the production reactor.

"DMAP" and related compounds catalyze many reactions, including various acylations, alkylations, silylations, and condensations[92,265,266,267]. In some, such as the acetylation of certain hindered alcohols or amines used in pharmaceutical formulations, it is particularly necessary to ensure that all traces of the catalyst be removed from the product mixture after the reaction. This requirement, and the general advantage of being able to recover and recycle a relatively costly chemical, warrant the development of solid-phase versions of known acylation catalysts; that is, insoluble polymer matrices[2] to which are attached functional groups similar to 4-(N,N-dimethylamino)pyridine (DMAP), 4-(1-pyrrolidino)pyridine, 4-(1-piperidino)pyridine, and others which are reported

active in the chemical literature.[92,265,268]

Tomoi and coworkers[6] have previously incorporated 4-(N-benzyl-N-methylamino)pyridine moieties into crosslinked polystyrene beads by treating the sodium salt of 4-(N-methylamino)pyridine either directly with Merrifield resin[2] or with (chloromethyl)styrene which was later polymerized. Tomoi's method was also used by Menger and McCann[269] to modify linear (chloromethyl)polystyrene to give a soluble but easily precipitable reagent. Reaction of the same anion with polystyrenes bearing much longer haloalkyl[270] functionalized spacers gave somewhat more reactive and stable catalysts. 4-(N-Alkyl-N-methylamino)pyridine moieties have also been linked to polystyrene through amide bonds,[13] but these risk being cleaved during reaction or regeneration of the polymer catalyst. Finally, other polymers incorporating interesting dialkylaminopyridine structures in their backbones have recently been made,[271,272] but these lack the attractive physical and/or chemical properties of reticulated polystyrene beads.

The present study examines the syntheses and acylating abilities of several other novel, readily-attainable polymers containing aminopyridine moieties supported through short spacers, in order to discover and optimize factors which afford effective functional polymers in general, and efficient solid-phase acylation catalysts in particular.

RESULTS AND DISCUSSION

A plausible[92,265,268] mechanism for dialkylaminopyridine-catalyzed acylations (Scheme 16) passes through a soluble and stable acylpyridinium complex ($PyrAc^+ OAc^-$), which exists in equilibrium with anhydride reagent (Ac_2O) and free dialkylaminopyridine (Pyr):

$$(PyrAc^+ OAc^-) \underset{K_d}{\rightleftharpoons} Pyr + Ac_2O$$

This equilibrium is defined by a dissociation constant K_d, such that:

$$K_d = [Pyr][Ac_2O]/[(PyrAc^+ OAc^-)]$$

The total of catalyst in all forms (Pyr_T) remains constant:

$$[Pyr_T] = [(PyrAc^+ OAc^-)] + [Pyr]$$

Substituting and rearranging,

$$[(PyrAc^+ OAc^-)] = [Pyr_T][Ac_2O]/(K_d + [Ac_2O])$$

Attack of alcohol (ROH) decomposes this charged complex to neutral products, namely the ester (ROAc), regenerated catalyst (Pyr) and free acid (HOAc), which is later consumed by an added acid acceptor to prevent protonation and consequent deactivation of the basic catalyst.

$$(PyrAc^+ OAc^-) + ROH \underset{k_2}{\longrightarrow} Pyr + HOAc + ROAc$$

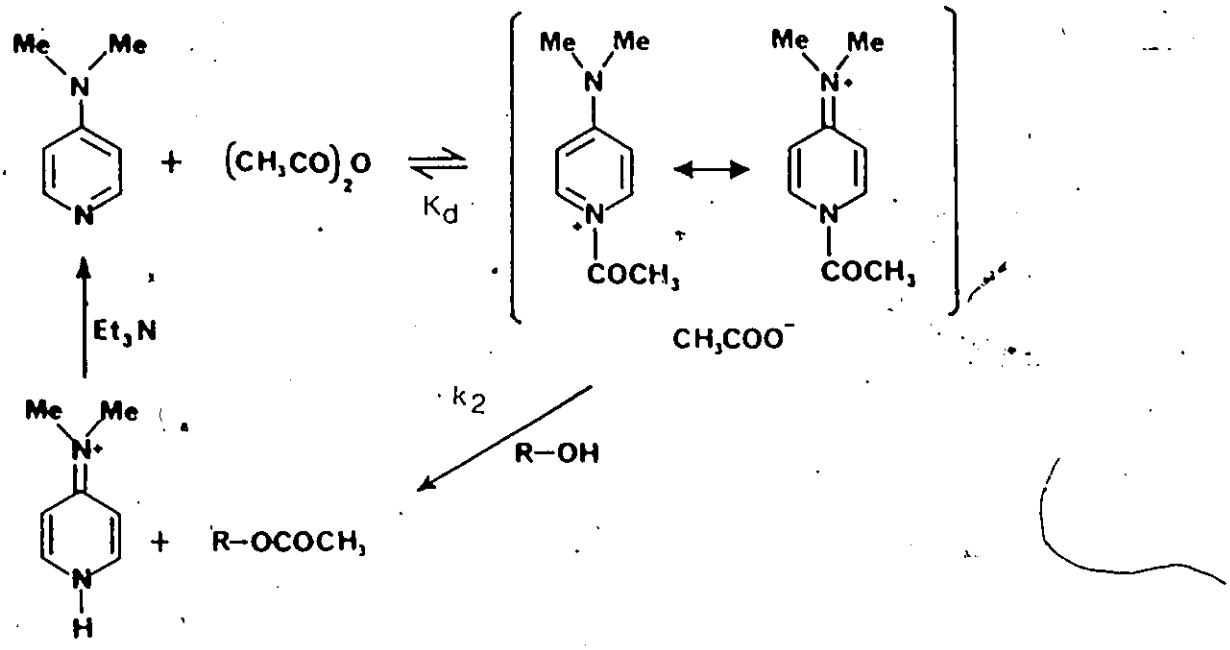
The rate of this step is a function of a second-order rate constant k_2, so that:

$$d[ROAc]/dt = k_2[(PyrAc^+ OAc^-)][ROH]$$

Substituting the earlier equation gives a complete expression for the reaction rate:

$$d[ROAc]/dt = k_2[Pyr_T][Ac_2O][ROH]/(K_d + [Ac_2O])$$

Scheme 16: Catalysis of Alcohol Acetylation by Dialkylaminopyridine.



For conditions in which the complexed form of the catalyst is the minor species ($K_d >> [Ac_2O]$), this simplifies to:

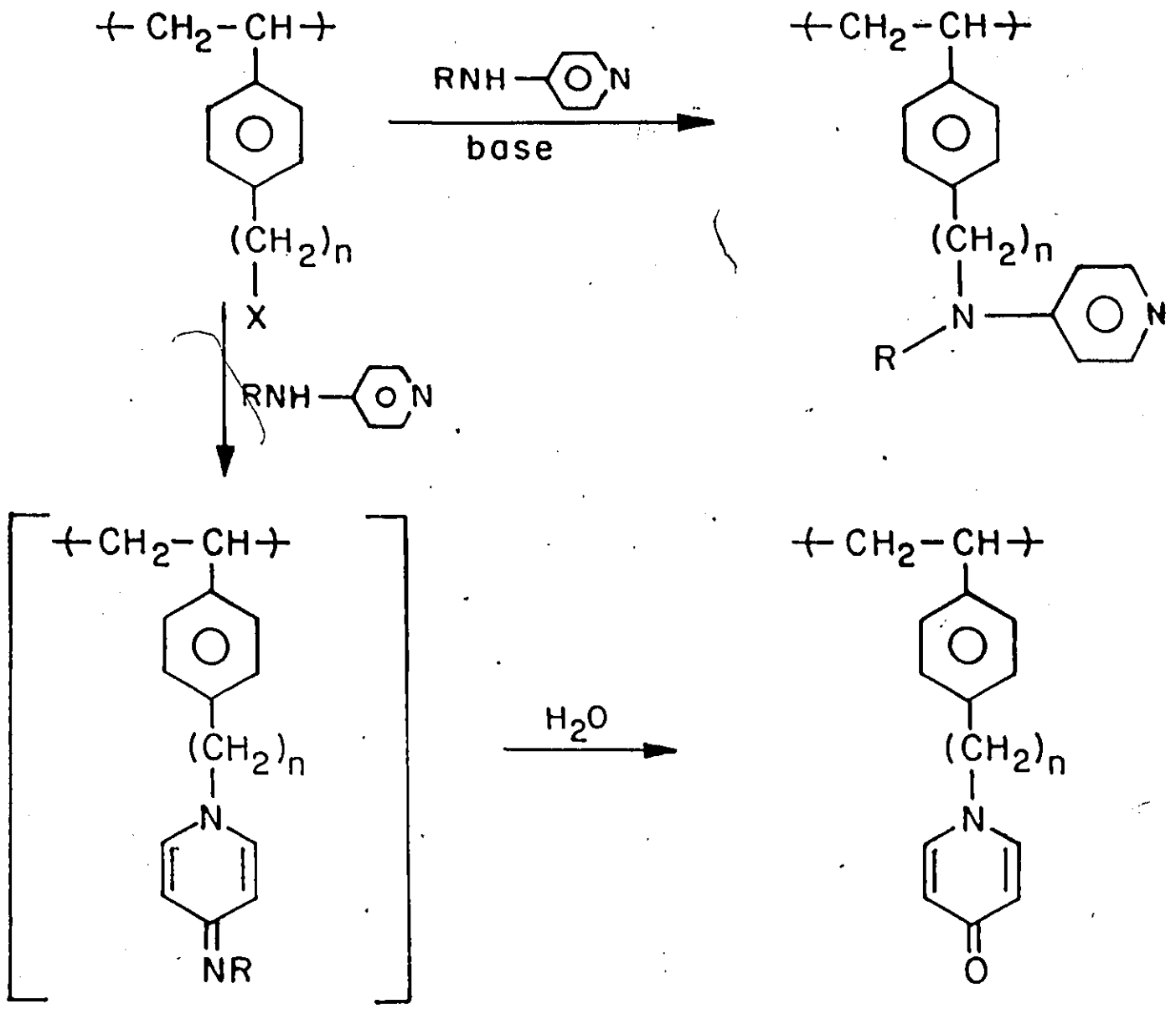
$$d[ROAc]/dt = k_2[Pyr_T][Ac_2O][ROH]/K_d$$

Since the second step is essentially irreversible, and since as much acetate would be released as consumed in a reaction with the intermediate acylpyridinium acetate complex, this mechanism precludes direct inhibition by acetate or any other product.

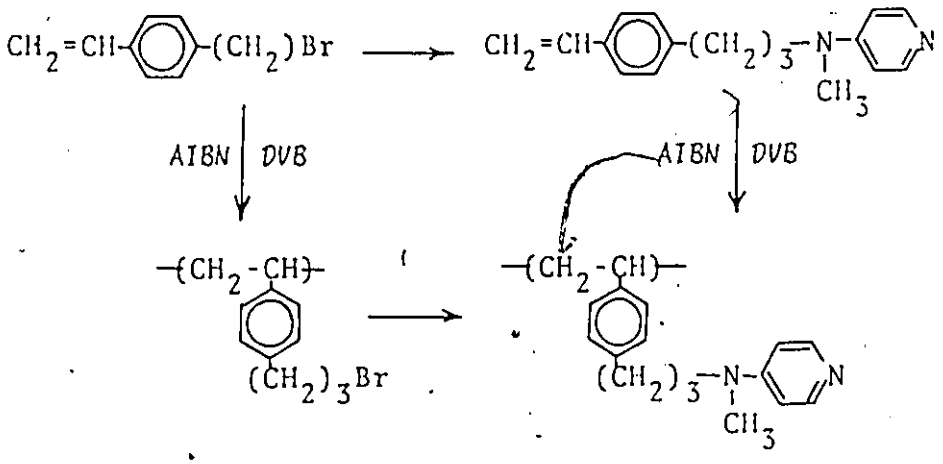
Free models of proposed polymeric catalysts were made from reaction of sodium 4-pyridin-N-methylamide with the appropriate (haloalkyl)benzenes in dimethylformamide; all were purified by vacuum distillation. The latter reagent also transformed 2%-crosslinked (chloromethyl)polystyrene and (bromopropyl)polystyrene to the corresponding polymer-supported dialkylaminopyridines in satisfactory conversion (Scheme 17). However, unacceptable levels of unremovable side-products were encountered on attempted reaction at higher temperatures, in tetrahydrofuran, under phase-transfer catalysis or with (haloethyl)polystyrene (Part I). Other resins possessing nonstandard copolymers or degrees of cross-linking or functionalization were made by copolymerization of dialkylaminopyridine-containing monomer with divinylbenzene and styrene or vinylpyridine (Scheme 18).

The acetylation of 1-methylcyclohexanol has been used to assay the catalytic activities of many dialkylaminopyri-

Scheme 17. Functional Group Modification with N-Methylaminopyridine.



Scheme 18. (N-(4-Pyridin)-methylamino-propyl)polystyrene by Functional Group Modification or Functional Monomer Polymerization.



dines.[265,273] This hindered tertiary alcohol is easily made from cyclohexanone and methylmagnesium bromide,[274] and recycled from its acetate with hot aqueous base.[275] All acetylations in this study were performed at 60°C under nitrogen, with identical quantities of alcohol (2.00 mL, 16.1 meq), acetic anhydride (3.00 mL, 31.7 meq), triethylamine (3.00 mL; 21.5 meq) and dialkylaminopyridine moieties (0.819 meq), and sufficient additional toluene and/or other organic solvent to make up a total volume of either 18.0 or 28.0 mL. Progress was monitored by periodic removal of small liquid samples for immediate analysis by GLC. Results for identical reactions were reproducible to about 2%.

The mixtures were all stirred at about 4 revolutions per second, though lowering the speed to 1 revolution per second had no significant effect on reaction rates with free or 2%-crosslinked solid catalysts. Such dialkylaminopyridine-containing polymers were all in the form of spherical beads of 80-140 micron size, which maintained their shape through repeated reaction and recycling; deliberate crushing to 4-9 micron particles was only achieved with difficulty, and did not significantly improve catalytic activity. Resin beads were swollen in the medium for 15 minutes before addition of acetic anhydride to initiate reaction; further overnight pre-soaking made no difference. Thus, with catalysts in the form of free molecules or polymer gels, the kinetics of the acetylation reactions were not controlled by mass-transfer effects.

Under these mild conditions, the fastest reaction (with free DMAP) required 6 hours for 66% completion; no side-reactions arising from acetic anhydride self-condensation, or from decomposition of even the benzylic catalysts, were detected. The polymeric catalysts could be recycled at least 10 times without loss of activity. No acetylated products could be detected in the absence of dialkylaminopyridine moieties, even if the mixture had been supplemented with (imidazol-N-ethyl)polystyrene (Part I) or unfunctionalized polystyrene or polyvinylpyridine resins.

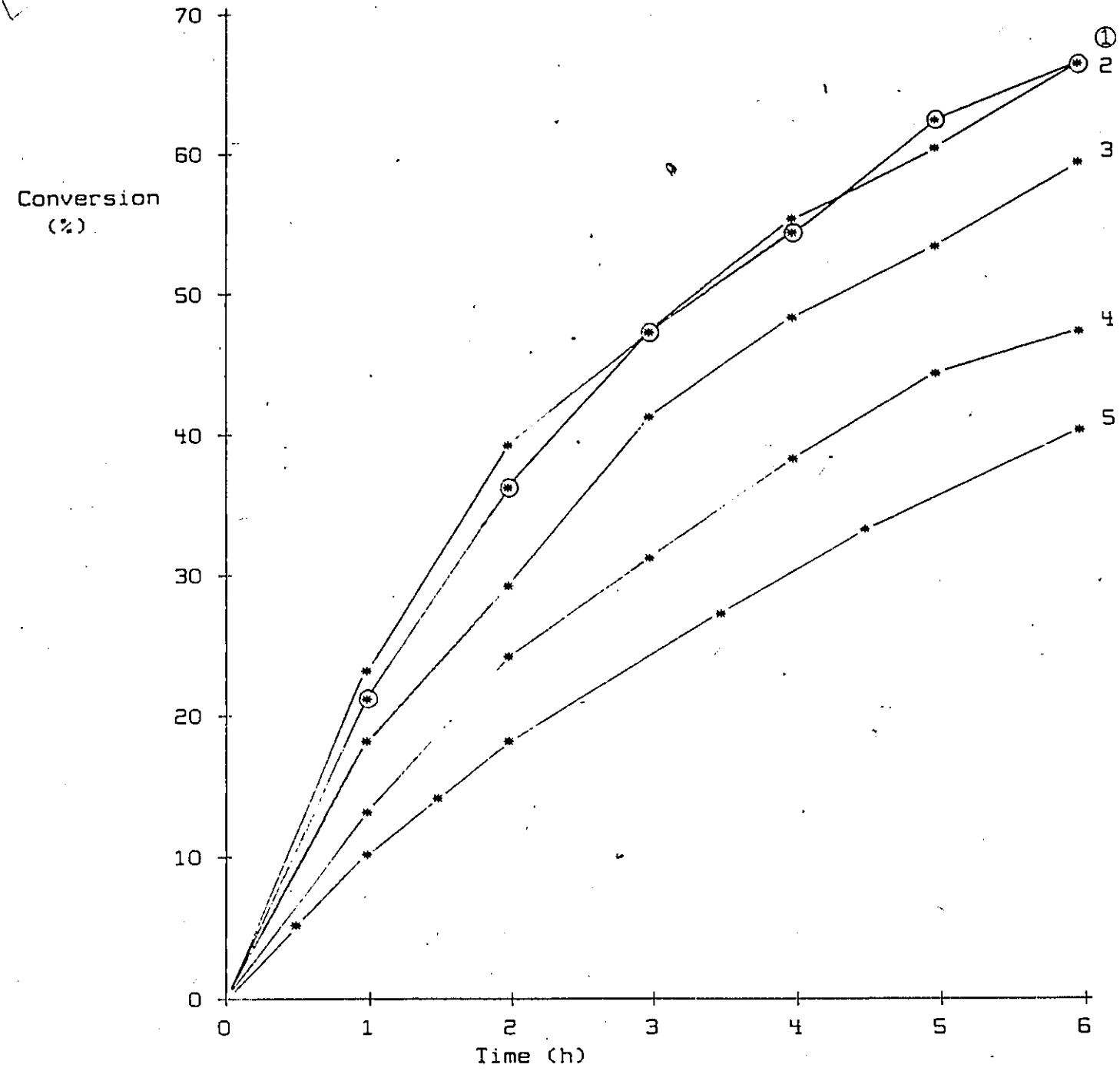
The intrinsic activities of various dialkylaminopyridine moieties were evaluated using free molecules (Table 2; Figure 5). In these experiments, the proposed functionalities compared favourably with commercially-available dimethylamino-pyridine as catalytic sites: in particular, catalytic activity was seen to increase with the length of alkyl spacer between phenyl and pyridine rings, abruptly from (N-(4-pyridin)-methylamino-methyl)benzene, which was relatively inept, to (N-(4-pyridin)-methylamino-ethyl)benzene, then slightly more to (N-(4-pyridin)-methylamino-propyl)benzene, which was as efficient as DMAP itself. Still longer spacers, such as advocated by Tomoi[270], would probably have given no better activity, merely supplementing the inert bulk in a polymeric reagent. These findings were in accord with the theory of dialkylaminopyridine action described above: thus, a nearby phenyl group is unable to rotate into the plane of the pyri-

Table 2. Relative catalytic activities of (N-(4-pyridin)-N-methyl-amino$(CH_2)_n$)benzenes in the acetylation of 1-methylcyclohexanol[a].

n	Relative Yield (%)[b]	^{1}HMR Shift (ppm)[c]
1	83	6.52
2	95	6.45
3	100	6.38

[a]0.82 meq catalyst, 2.00 mL 1-methylcyclohexanol, 3.00 mL Ac_2O, 3.00 mL Et_3N, 60°C, toluene to total 18.0 mL. [b]With respect to performance of DMAP under the same conditions after 6 hours (82% conversion to ester). [c]In $CDCl_3$, of pyridine beta hydrogen.

Figure 5. Graph of 1-methylcyclohexanol acetylation vs time vs dialkylaminopyridine catalyst.



1 - Dimethylaminopyridine
2 - (4-Pyridin-N-methyl-amino-propyl)benzene
3 - (4-Pyridin-N-methyl-amino-propyl)polystyrene
4 - (4-Pyridin-N-methyl-amino-methyl)benzene
5 - (4-Pyridin-N-methyl-amino-methyl)polystyrene

dine ring, which would be required if electrons are to be supplied from side-chain nitrogen towards stabilization of the intermediate acylpyridinium complex. Besides raising K_d, the electronic impoverishment brought on by this apparently remote steric hindrance is also manifested in the compound's NMR spectrum by a shift in the peak corresponding to the beta nuclear hydrogens (Table 2).[269,273]

The catalyzed reaction can also be affected by manipulating k_2. In the second step of the proposed mechanism, a charged complex is transformed to uncharged products, decreasing electron dispersal in the transition state. Reactions of this type[69] are slowed by an increase in the dielectric constant of the local microenvironment such as would be induced by the proximity of other polar functionalities, which at even moderate degrees of functionalization would be locally more concentrated within a polymer matrix than the corresponding free molecules dispersed in a homogenous reaction medium. This negative cooperativity effect may account for the slight drop, mole for mole, in catalytic activity with respect to free model, which was observed (Figure 5; Table 3) for dialkylaminopyridine moieties affixed to 15-25% of the repeating units of 2%-crosslinked polystyrene resin. The magnitude of this inhibition was similar whether monomethylene or trimethylene spacer lay between nitrogen and phenyl, or whether the solid catalyst had been made via polymerization of aminated monomer or modification of halogenated polystyrene,

Table 3. Relative catalytic activities of (N-(4-pyridin)-N-methyl-amino$(CH_2)_n$)polystyrenes in the acetylation of 1-methylcyclohexanol[a].

n	Preparation	Cross-link (%)	Degree of Functionalization	Nitrogen Content (wt %)	Relative Inhibition (%)[b]
1	Polymer	2	.16	3.71	6
3	Polymer	2	.16	3.37	5
3	Monomer	2	.22	4.58	6
3	Monomer	2	.96	10.73	23
1	Monomer/Butanol	34	.08	1.72	44
1	Monomer/Heptane	33	.09	1.83	60

[a]0.82 meq catalyst, 2.00 mL 1-methylcyclohexanol, 3.00 mL Ac_2O, 3.00 mL Et_3N, 60°C, toluene to total 18.0 mL. [b]With respect to performance of corresponding model compound after 6 hours under the same conditions.

but was much larger in the "homopolymer" lacking styrene apolar diluent. In macroreticular resins, rates did become limited by access to the catalytic sites, which was worse for beads copolymerized in the presence of heptane rather than butanol as porogen.

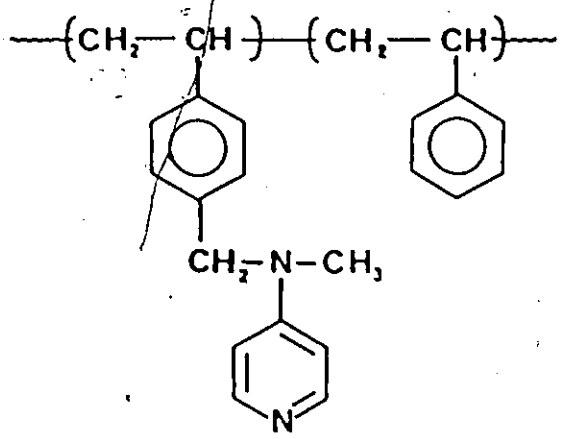
Since the immediate acid acceptor in the second step is the acetate counterion (the complexes formed with acetyl chloride, whose anions are far less basic, are correspondingly more difficult to alcoholyze)[92], adding amine beyond the stochiometric amount would contribute no additional general base catalysis. Indeed, pyridine, unable to contribute much nucleophilic catalysis either, actually inhibited this acetylation (Table 4) by increasing the polarity of the medium, whether it was present in the liquid medium or as part of the polymer backbone (Scheme 19). Taking into account negative effects consequent from immobilization alone, inhibition of the polystyrene-bound catalysts by pyridine cosolvent was less than expected, particularly with trimethylene spacer. This was probably because apolar styrene moieties were able to "shield" the catalytic sites by simply displacing polar solvent molecules from the surrounding micro-environment. On the other hand, the polarity within polyvinyl-pyridine swollen in pyridine apparently exceeded the greatest which was possible in the homogenous phase alone, since the dielectric constant of the latter must necessarily fall upon addition of less polar reagents required in the acetylation.

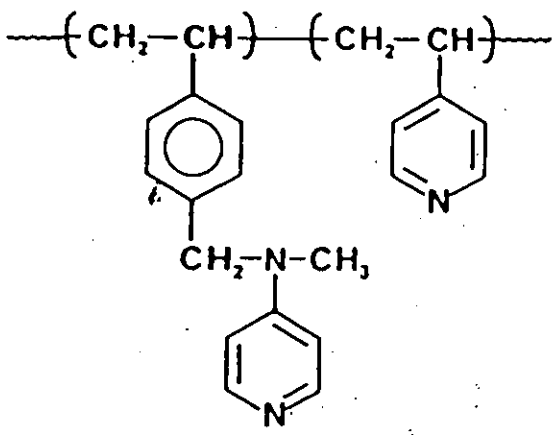
Table 4: Relative catalytic activities of (N-(4-pyridin)-N-methyl-amino$(CH_2)_n$)-R in the acetylation of 1-methylcyclohexanol in the presence of pyridine[a].

n	R	Degree of Functionalization	Nitrogen Content (wt %)	pyridine Conc. (vol %)	Relative Inhibition (%)[b]
1	Benzene	-	-	0	0
				24	23
				71	47
3	Benzene	-	-	0	0
				71	47
1	Poly-styrene	.16	3.71	0	15
				69	49
3	Poly-styrene	.16	3.37	0	11
				69	42
1	Polyvinyl-pyridine	.08	12.04	0	38
				67	74

[a]0.82 meq catalyst as free model or bound to 2%-crosslinked polymer matrix, 2.00 mL 1-methylcyclohexanol, 3.00 mL Ac_2O, 3.00 mL Et_3N, 60oC, toluene and/or pyridine to total 28.0 mL. [b]With respect to performance of corresponding model, without pyridine, after 6 hours.

Scheme 19. (N-(4-Pyridin)-methylamino-methyl)polystyrene and (N-(4-Pyridin)-methylamino-methyl)poly(styrene-co-vinylpyridine).





The introduction of even very short spacers can therefore significantly improve the performance of a polymer-bound functional group. Under certain conditions, polymer-bound dialkylaminopyridines may catalyze difficult acylations better than the analogous free molecules in the same liquid medium.

EXPERIMENTAL

Materials

Styrene, 4-vinylpyridine and 1-methylcyclohexanol (Aldrich) were distilled prior to use. Divinylbenzene (polysciences) containing about 45% ethylbenzene and used without further purification, as were other chemicals (Aldrich). (Chloromethyl)polystyrene had been prepared by chemical modification of washed 1%-crosslinked polystyrene Bio-beads SX-1 (Bio-Rad Laboratories)[31], and (bromopropyl)polystyrene from the functionalized monomer[26]. 4-dimethylaminopyridine (DMAP) and 4-methylaminopyridine were gifts of Reilly Tar and Chemical Company. Infrared spectra were measured on a Nicolet 10-DX FT-IR, NMR spectra were recorded in $CDCl_3$ + TMS using Varian EM 360, CFT-80 or XL-300 spectrometers while mass spectra were obtained on a VG-7070E double focusing mass spectrometer using chemical ionization where appropriate.

Free model catalysts. (N-(4-pyridin)-methylamino-propyl)-benzene.

Sodium hydride (0.65 g, 28 meq) was stirred with N-methyl-aminopyridine (2.7 g, 25 meq) in 12 mL anhydrous dimethyl-formamide at room temperature under nitrogen for 1 hour. When fizzing had subsided, (bromopropyl)benzene (5.0 g, 25 meq) was added in 5 mL more DMF, and the solution was stirred at room temperature for 20 hours. After filtering to remove sodium bromide, solvent was flash evaporated, and the residual oil redissolved in CH_2Cl_2 and thrice extracted with water, then dried over $MgSO_4$ and distilled under vacuum, yielding 3.2 g (57%) of a thick yellow liquid: bp 151-152°C (0.1 mm); MS m/e 226 (M^+), 121; ^1H NMR ($CDCl_3$) : 1.90 (m, 2H), 2.63 (t, 2H), 2.92 (s, 3H), 3.22 (t, 2H), 6.38 and 8.14 (2d, 4H, pyridyl), 7.15-7.28 (m, 5H, phenyl); IR (KBr) 1595 cm^{-1} (pyr, s). Anal. Cal for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.37. Found: C, 79.36; H, 7.89; N, 12.48.

<AL064>

(N-(4-pyridin)-methylamino-ethyl)benzene.

Bp 147-149°C (0.1 mm); MS m/e 212 (M^+), 121; ^1H NMR ($CDCl_3$) 2.84 (m, 5H), 3.56 (t, 2H), 6.45 and 8.18 (2d, 4H, pyridyl), 7.14-7.30 (m, 5H, phenyl); IR (KBr) 1595 cm^{-1} (s, pyr). Anal. Calc for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.10; H, 7.58; N, 13.45.

<AL091>

(N-(4-pyridin)-methylamino-methyl)benzene.

Bp 148-150 (0.1 mm); MS m/e 198 (M+), 121, 91; ^{1}H NMR ($CDCl_3$) 3.05 (s, 3H), 4.56(s, 2H), 6.54 and 8.18 (2d, 4H, pyridyl), 7.15-7.30 (m, 5H, phenyl); IR (KBr) 1595 cm^{-1} (s, pyr). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.63; H, 6.96; N, 14.00.

<AL038>

Polymer-bound catalysts by polymer modification. (N-(4-pyridin)-methylamino-propyl)polystyrene.

Sodium hydride (0.18 g, 7.5 meq) was stirred with N-methyl-aminopyridine (0.70 g, 6.5 meq) in 10 mL anhydrous dimethyl-formamide at room temperature under nitrogen for 3 hours. When fizzing had subsided, (bromopropyl)polystyrene $(C_{10}H_{10})_{.02}$-$(C_8H_8)_{.82}(C_{11}H_{13}Br)_{.16}$ (2.5 g, 3.3 meq) was added in 15 mL more DMF, and the solution was stirred at room temperature for 96 hours. The suspension was then filtered and washed with DMF (1X), CH_3OH (1X), H_2O (3X), CH_3OH (1X), CH_2Cl_2 (1X), CH_3OH (2X), and dried under vacuum overnight to give a pale beige powder: IR (KBr) peaks absent at 1263 cm^{-1} for bromo precursor, and at 1663 cm^{-1} for pyridinone and 1629 cm^{-1} for vinyl side-products; peak present at 1595 cm^{-1} (s, pyr) for aminopyridine product (Figure 6). Anal. Calcd for $(C_{10}H_{10})_{.02}$-$(C_8H_8)_{.82}(C_{17}H_{20}N_2)_{.16}$ (100% conversion): C, 88.68; H, 7.76; N, 3.48; Br, 0. Found: C, 84.77; H, 7.74; N, 3.37; Br, 0.

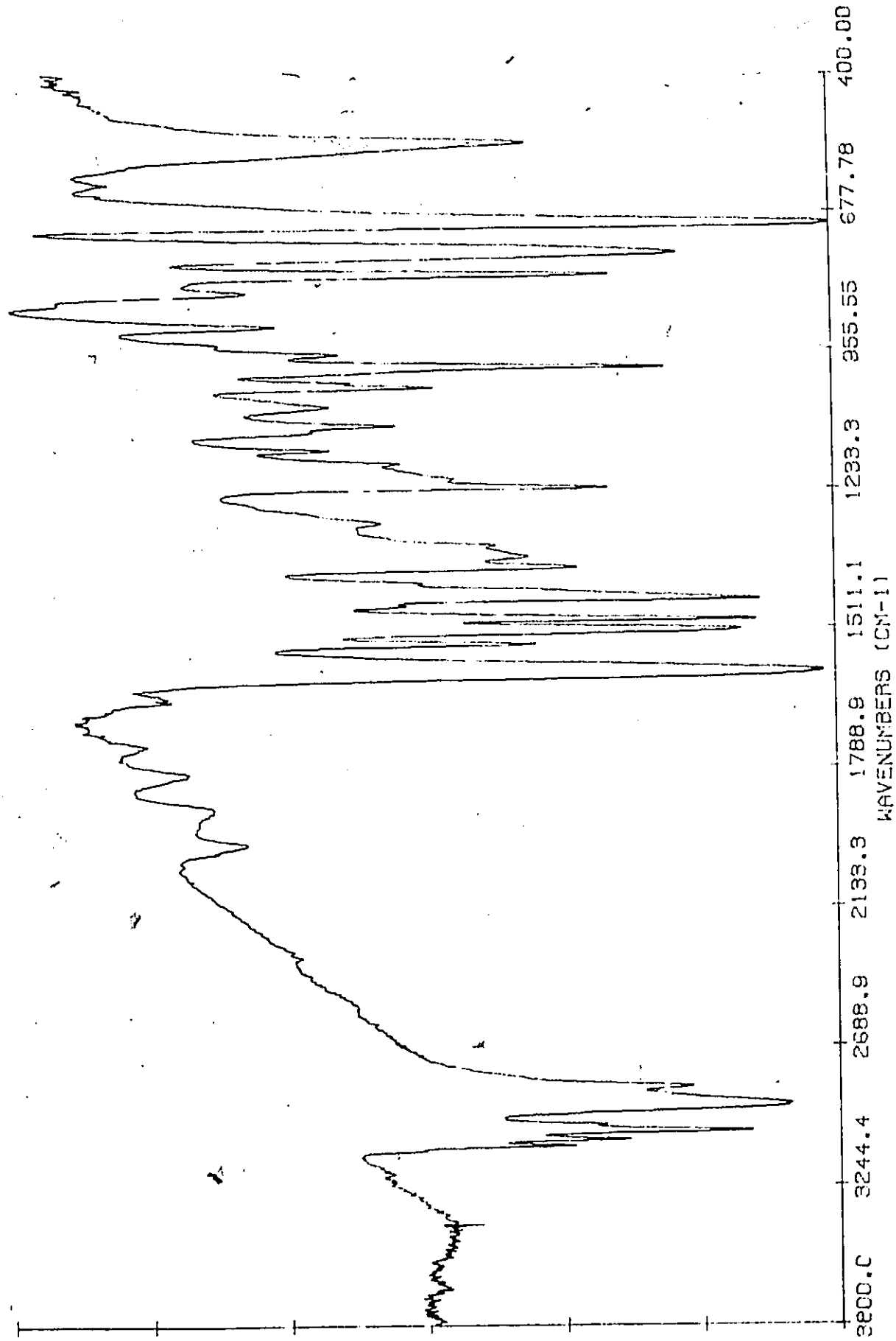


Figure 6. FTIR spectrum of (N-(4-pyridin)-methylamino-propyl)polystyrene.

<AL090>.

(N-(4-pyridin)-methylamino-methyl)polystyrene.

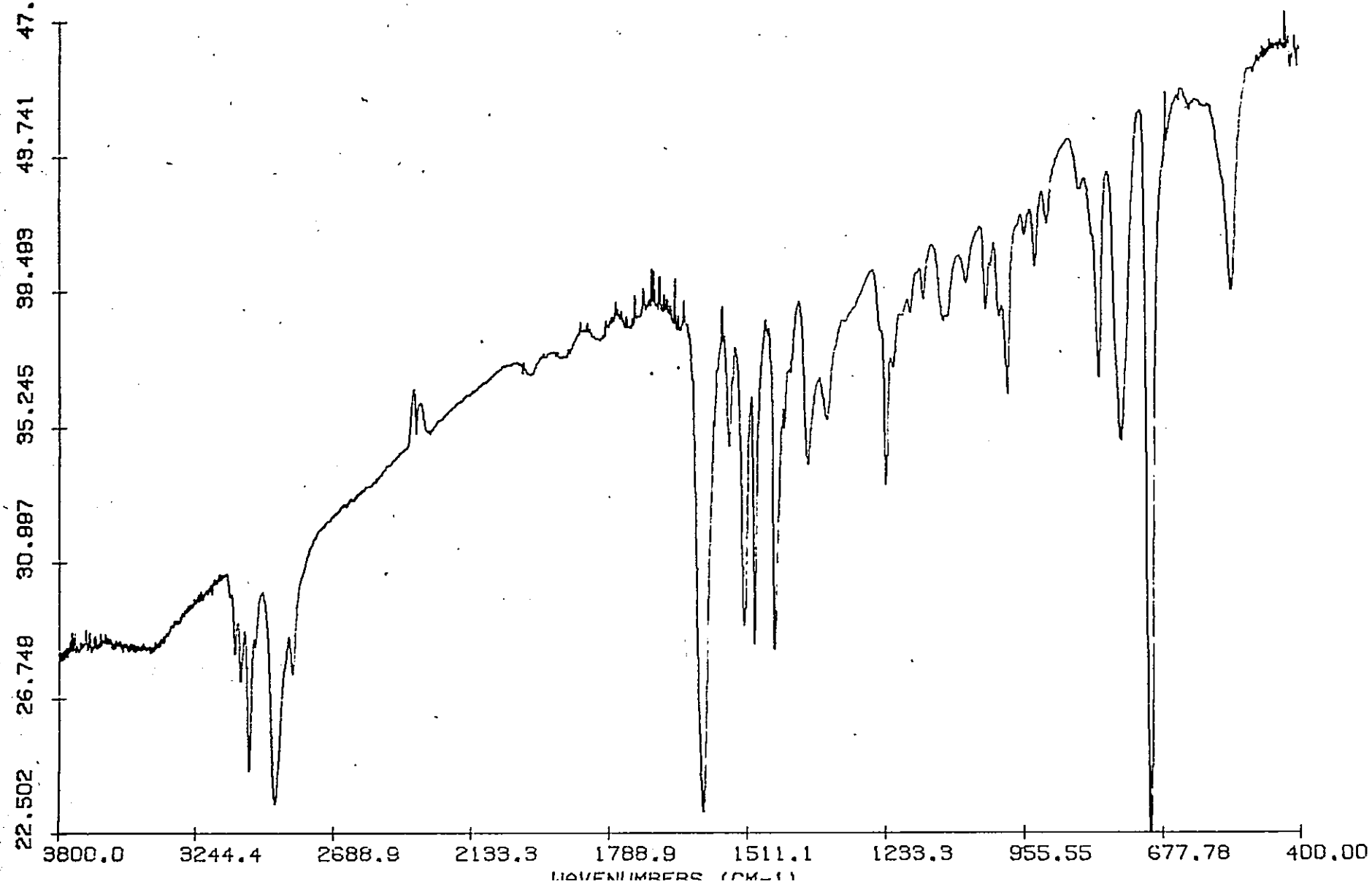
A product was obtained from (chloromethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.83}(C_9H_9Cl)_{.16}$; IR (KBr) peaks absent at 1263 cm^{-1} for bromo precursor, and at 1663 cm^{-1} for pyridinone side-product; peak present at 1595 cm^{-1} (s, pyr) for aminopyridine product (Figure 7). Anal. Calc for $(C_{10}H_{10})_{.01}$-$(C_8H_8)_{.83}(C_{15}H_{16}N_2)_{.16}$ (100% conversion): N, 3.63 ; Cl, 0. Found: N, 3.71; Cl, 0.

<DN022)

Catalyst monomers. (N-(4-pyridin)-methylamino-propyl)styrene.

Sodium hydride (1.3 g, 54 meq) was stirred with N-methyl-aminopyridine (5.4 g, 50 meq) in 25 mL anhydrous dimethyl-formamide at room temperature under nitrogen for 1 hour. When fizzing had subsided, the mixture was chilled to 0°C and (bromopropyl)styrene (11.25 g, 50 meq) was added in 10 mL more DMF, then the solution was stirred at room temperature for 20 hours. After filtering to remove sodium bromide, solvent was flash evaporated, and the residual oil redissolved in CH_2Cl_2 and thrice extracted with water, then dried over $MgSO_4$ to yield 17.4 g of brown oil. A portion (3.06 g) was chromatographed on silica gel (EtOAc:MeOH 1:1) and recrystallized (ether:petrolem ether 1:1) to yield 0.61 g pale yellow crystals (27% overall):mp 50-51°C; MS m/e 252 (M+),

Figure 7. FTIR spectrum of (N-(4-pyridin)-methylamino-methyl)polystyrene.



121; ^{1}H NMR 1.88 (m, 2H), 2.59 (t, 2H), 2.90 (s, 3H), 3.30 (t, 2H), 5.16, 5.66 and 6.64 (2d + m, 3H, vinyl), 6.36 and 8.11 (2d, 4H, pyridyl),7.08 and 7.28 (2d, 4H, phenyl); IR (KBr) 1629 (m, C=C), 1595 cm^{-1} (s, pyr). Anal. Calc for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.60; H, 7.99; N, 11.12.

<AL111>.

N-(4-pyridin)-methylamino-methyl)styrene.

^{1}H NMR ($CDCl_3$) 3.05 (s, 3H), 4.50 (s, 2H), 5.31, 5.54 and 6.90 (2d + m, 3H, vinyl), 6.52 and 8.20 (2d, 4H, pyridyl), 7.17 and 7.27 (2d, 4H, phenyl); IR (KBr) 1629 (m, C=C) and 1595 cm^{-1} (s, pyr).

<DN035>.

Polymer-bound catalysts by polymerization of catalyst monomers. (N-(4-pyridín)-methylamino-propyl)polystyrene.

(N-(4-pyridin)-methylamino-propyl)styrene (2.70 g, 10.7 meq) was dissolved in 16 mL toluene and filtered, then mixed with styrene (5.2 g, 49.9 meq), 55% divinylbenzene (0.33 g, 2.5 meq monomer) and azo-bis-isobutyronitrile (0.2 g, 1.2 meq), then added to 74 mL of degassed 1.5% poly-vinylalcohol/H_2O ("polyviol W25/140", Wacker Chemie) in a Buchi BEP 280 stirred autoclave using a 250 mL thermostatted vessel fitted with overhead anchor-type stirrer. After further bubbling of nitrogen for a further 10 minutes, the mixture was stirred at 330 rpm under nitrogen, at room temperature for 10

minutes, then at 75°C for 8 hours, then at room temperature for 16 hours. The supernatant was decanted from the beads of polymer precipitate, which were then resuspended in water and the process repeated (5X) until the supernatant was clear. The product was washed again with methanol (3X), toluene (2X), methanol (2X), then dried under vacuum overnight to yield 2.33 g (28%) white powder: IR (KBr) identical to that of same polymer made by modification). Anal. Calc for $(C_{10}H_{10})_{.02}$-$(C_{10}H_{12})_{.02}(C_8H_8)_{.74}(C_{17}H_{20}N_2)_{.22}$ (5% more catalyst than the monomer ratio): N, 4.47. Found: 4.58.

<AL120>.

(N-(4-pyridin)-methylamino-propyl)polystyrene. Homopolymer.

The procedure was repeated with 9.0 g of (N-(4-pyridin)-methylamino-propyl)styrene, 0.19 g of 55% divinylbenzene, and no styrene. Product was isolated in 75% yield: IR (KBr) similar to that of same polymer made by modification, but peaks at 1595 cm^{-1} and elesewhere for pyridine are more intense. Anal. Calc for $(C_{10}H_{10})_{.02}(C_{10}H_{12})_{.02}(C_{17}H_{20}N_2)_{.96}$ (equal to the monomer ratio): N, 10.87. Found: 10.73.

<AL166>.

(N-(4-pyridin)-methylamino-methyl)polystyrene. Macroreticular, using butanol.

The procedure was repeated with 1.60 g (N-(4-pyridin)-methylamino-methyl)styrene, 6.75 g of 55% divinylbenzene, 2.73 g of styrene, and butanol instead of toluene. Product was isolated in 89% yield: IR (KBr) similar to other polymer-bound dialkylaminopyridines. Calc for $(C_{10}H_{10})_{.34}(C_{10}H_{12})_{.27}(C_8H_8)_{.31}(C_{15}H_{16}N_2)_{.08}$ (equal to the monomer ratio): N, 1.72.

<DN036>

(N-(4-pyridin)-methylamino-methyl)polystyrene. Macroreticular, using heptane.

The procedure was repeated with 1.78 g (N-(4-pyridin)-methylamino-methyl)styrene, 6.75 g of 55% divinylbenzene, 2.73 g of styrene, and heptane instead of toluene. Product was isolated in 72% yield: IR (KBr) similar to other polymer-bound dialkylaminopyridines. Calc for $(C_{10}H_{10})_{.33}(C_{10}H_{12})_{.27}(C_8H_8)_{.31}(C_{15}H_{16}N_2)_{.09}$ (equal to the monomer ratio): N, 1.92. Found: N, 1.83.

<DN025>

(N-(4-pyridin)-methylamino-methyl)polyvinylpyridine.

The procedure was repeated with 1.60 g (N-(4-pyridin)-methylamino-methyl)styrene, 0.69 g of 55% divinylbenzene and 7.77 g of of 4-vinylpyridine instead of styrene. Product was isolated in 66% yield: IR (KBr) peak present at 1595 cm^{-1} as with other polymers, but polystyrene peaks missing at 699 cm^{-1} and elsewhere, while polyvinylpyridine peaks at 1415 and 819 cm^{-1} are very strong. $(C_{10}H_{10})_{.03}(C_{10}H_{12})_{.03}(C_7H_7N)_{.86}$-$(C_{15}H_{16}N_2)_{.08}$ (equal to the monomer ratio): N, 12.29. Found: N, 12.04.

<DN020>

Evaluation of the catalysts. General procedure.

A mixture of 1-methylcyclohexanol (2.00 mL, 16.2 mmol), dialkylaminopyridine (0.81 mmol, 5 mole %) and triethylamine (3.00 mL, 21.6 mmol), in toluene to total 18.0 or 28.0 mL solution, was placed in jacketed cell whose temperature was regulated at 60.0°C. After stirring under nitrogen for 15 min., acetic anhydride (3.00 mL, 31.6 mmol) was added while stirring continued. Progress of the reaction was monitored by timely withdrawal of 10 uL aliquots for chromatographic analysis (10% SE-30 on Chromosorb G).

<AL 20, 28, 30, 31, 34, 57, 99, 106, 123, 155, 157, 181; D 1094, 1095, 1099, 1100, 1102, 1107, 1108>

APPLICATION OF SPACER-CONTAINING FUNCTIONAL POLYSTYRENES.

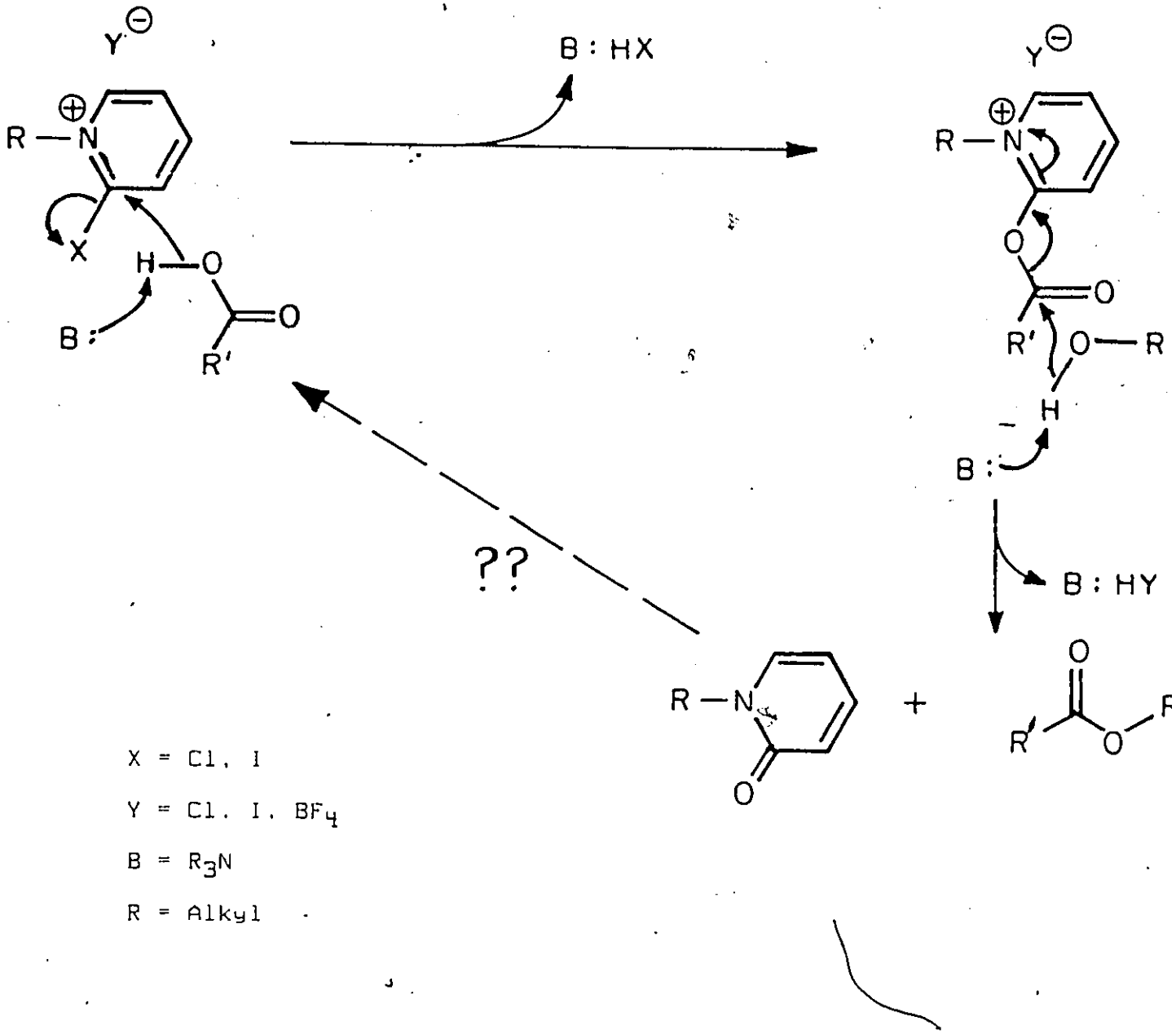
B. POLYMER-BOUND HALOPYRIDINIUM SALTS.

INTRODUCTION

In 1964, Sutherland and Widdowson[170] first reported the use of 2-iodo-N-methyl-pyridinium iodide, made by the reaction of hot 2-halopyridine with an excess of iodomethane,[163] to acylate nucleophiles with carboxylic acids. 2-Chloro-N-methyl-pyridinium iodide, from the same alkylation conducted at lower temperatures,[167,169,170] was later employed by Mukaiyama and coworkers towards one-pot syntheses of esters, amides and many other compounds from carboxylic acids in excellent yields and under mild conditions; N-phenyl-2-chloropyridinium tetrafluoroborate and N-methyl-2-fluoropyridinium tosylate were also effective.[164,171] In general, the reaction starts (Scheme 20) with carboxylate displacing halide from the pyridinium ring by nucleophilic aromatic substitution, which is then followed by attack of nucleophile onto the activated acyl to form a condensed product and N-alkyl-2-pyridinone side-product; a tertiary amine acts as basic catalyst, and accepts hydrogen halide released in the course of the reaction[164].

Partial dealkylation of labile methyl, ethyl or benzyl substituents from halopyridine has been observed during some of these condensations,[165] as well as during attempted regenerations from the corresponding N-alkyl-pyridinones with

Scheme 20. Condensation of Alcohol with Carboxylic Acid Using N-Alkyl-2-Halopyridinium Salt.



X = Cl, I

Y = Cl, I, BF_4

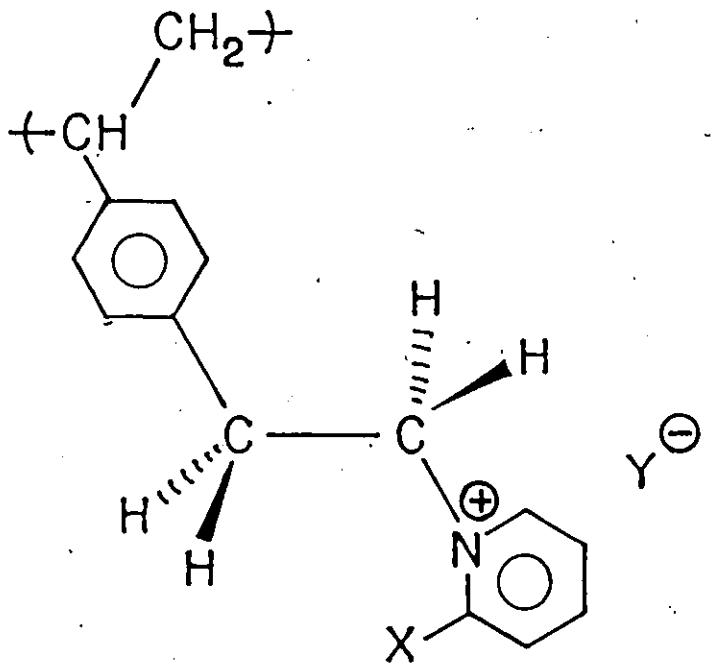
B = R_3N

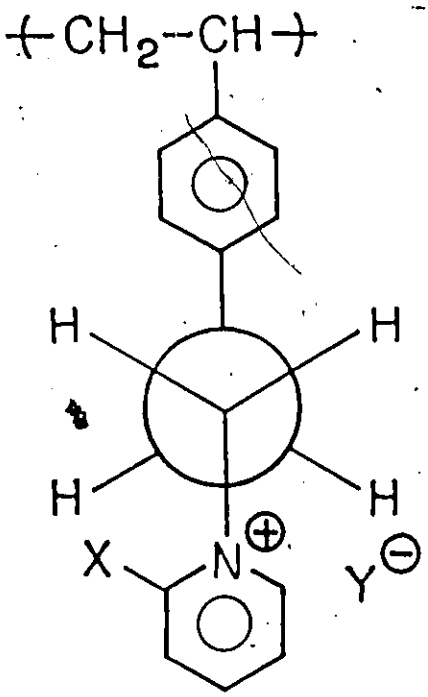
R = Alkyl

phosphoryl chloride, thionyl chloride, phosgene or other reagents commonly employed to convert amides to Vilsmeyer reagent or other iminium salts.[74,276] However, numerous workers have noticed that 2-phenethyl substituents resist such decomposition even under severe conditions,[75,76] possibly because steric hindrance in the preferred anti conformation prevents nucleophilic attack by counterion onto aminated carbon (Scheme 21). Phenethyl pyridinone is also stable towards aqueous base.[277] Thus, an expensive halopyridinium salt, if connected to aryl through a dimethylene spacer, after assisting in the preparation of an equimolar quantity of ester or amide, need not be discarded but can be regenerated with inexpensive chemicals for multiple reuse, provided that the recovery of heterocyclic moiety from the reaction mixture is clean and efficient. This final requirement for a useful recyclable reagent is easily fulfilled by simple filtration if the phenethyl substituent is incorporated in a solid phase, such as an insoluble matrix of crosslinked polystyrene.

Scheme 21. N-Phenethyl-2-Halopyridinium Salt.

Stablest Conformation.





X = Cl, I

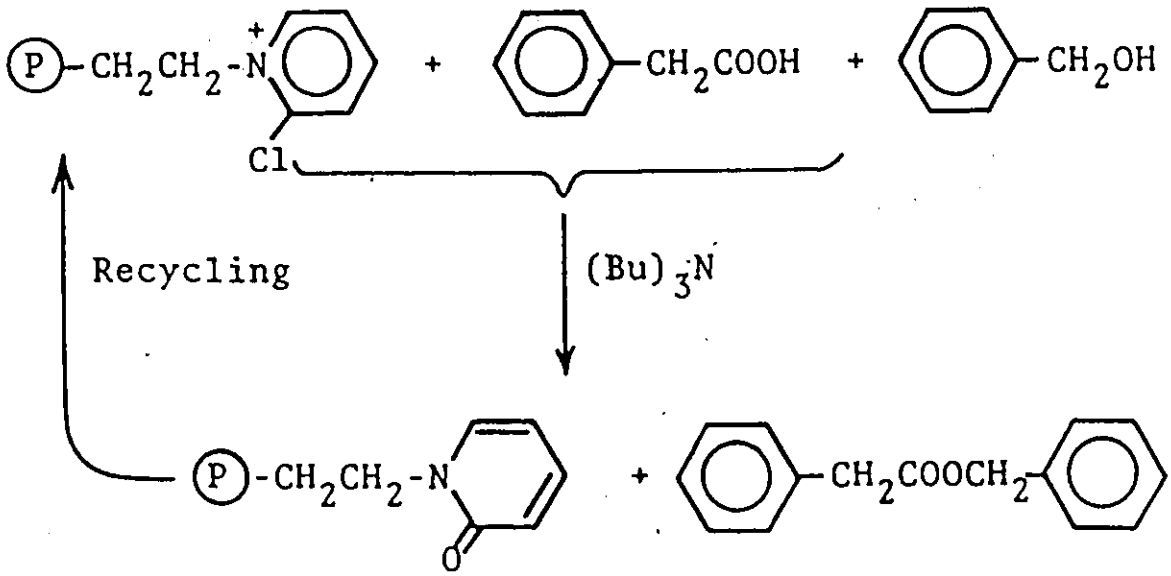
Y = Cl, I, BF_4

RESULTS AND DISCUSSION:

The acylation of benzyl alcohol with phenylacetic acid in the presence of tertiary amine (Scheme 22) has been used to measure the condensing abilities of free halopyridinium salts.[164] In a preliminary reaction, an excess of (2-iodopyridinium-N-ethyl)polystyrene iodide, previously prepared from (iodoethyl)polystyrene and 2-chloropyridine and quantitated by elemental analysis (Part I: Experiment 27), though admittedly impure, was nevertheless able to produce the standard ester in quantitative yield, under conditions comparable to those necessary for the free analogue. However, regeneration of the polymeric 2-pyridinone (Scheme 23) proved unexpectedly difficult, requiring prolonged reflux with thionyl chloride in the presence of dimethylformamide catalyst for conversion to be judged complete by FTIR spectroscopy. Even then, the resulting 2-chloropyridinium chloride was much less active than the original iodide in promoting the same esterification (30% yield of benzyl phenylacetate).

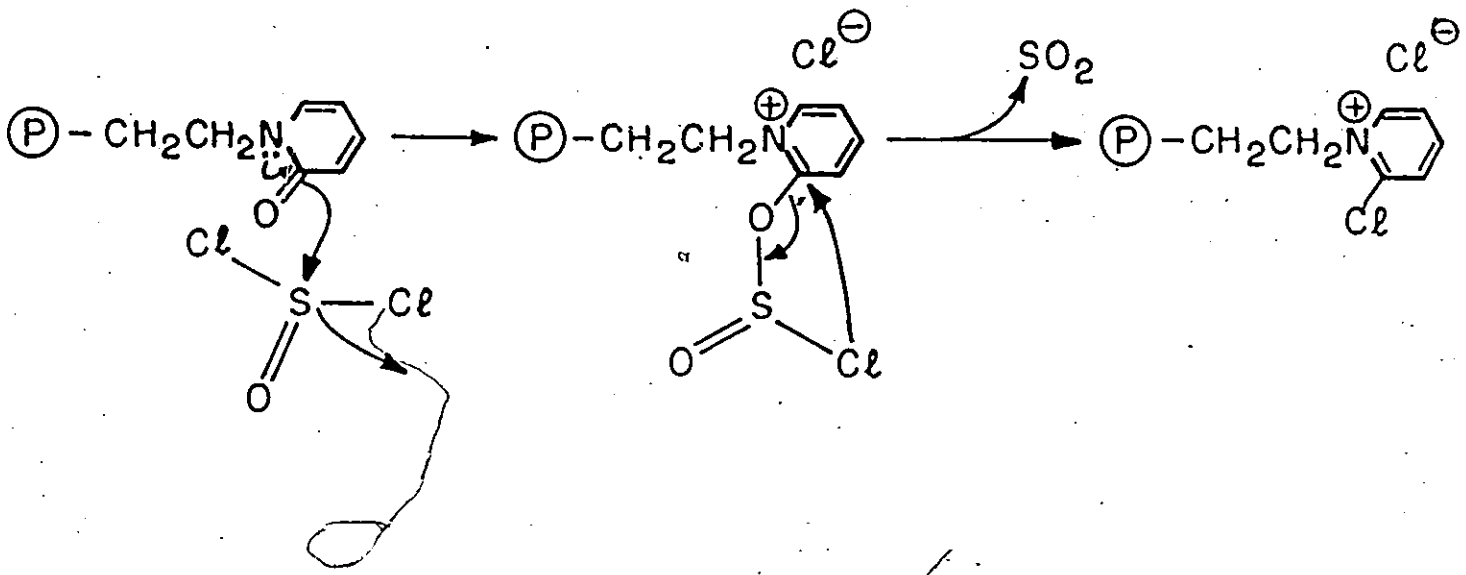
(4-Pyridinon-N-ethyl)polystyrene was also available, through a much cleaner and higher-yielding synthesis (Part I: Experiment 30). 4-Pyridinones and halopyridinium salts are reported to be even more reactive than the 2-isomers, the reactive centre being less sterically hindered by nitrogen alkylant.[161,163,169] Thus, far milder conditions (e.g. $COCl_2$ at room temperature for 2 hours without catalyst) were

Scheme 22. A Standard Esterification Used to Test the Polymer Reagents.



(P) = Polystyrene

Scheme 23. Regeneration of (2-Halopyridinium-N-Ethyl)Polystyrene Salt from (2-Pyridinon-N-Ethyl)Polystyrene with $SOCl_2$.



required to eliminate pyridinone peaks in the FTIR spectrum of the 4-isomer. However, like the 2-isomer, 4-chloropyridinium chloride also gave only poor (8%) yields of ester from alcohol and acid. Fortunately, this reluctance was greatly offset by the addition of a softer anion, such as iodide (57%) or tetrafluoroborate (62%), to the reaction medium. In general, condensations employing only catalytic trialkylamine, and excess dipotassium phosphate, gave comparable results to others using stochiometric organic base alone, while simplifying workup and isolation of the desired ester.

Iminium halides, including halopyridinium salts, are not very soluble in apolar organic solvents such as benzene.[171,276] However, lipophilic iodides and tetrafluoroborates are probably somewhat less subject to aggregation and precipitation while concentrated inside an aromatic polymer matrix than the chlorides from which they can be derived by metathesis.[279,280] It is also possible that the polymer-bound chloro-pyridinium chlorides were relatively more inhibited by complexation or covalent reaction with polar trialkylamine, or even with nearby N-alkylpyridinone groups as these were formed during esterification. Finally, during regeneration, some of the 4-pyridinone functionalities may merely have been protonated by hydrogen chloride, either endogenous to the activating reagent or generated in situ by traces of moisture, to give 4-hydroxypyridinium moieties difficult to distinguish from halo groups by FTIR spectroscopy -- addition of pyridine

at this time may have been of some benefit in preventing this, but the resulting hydrochloride precipitate would still be capable of interfering with later condensations through proton transfer to trialkylamine needed as base.

Thus, it has been demonstrated that a polymer-bound version of Mukaiyama's reagent is capable of promoting acyl condensations in excellent yields. However, regeneration remains to be optimized, probably by taking greater pains to replace chloride with a more lipophilic counterion, and to remove interfering protons from the reaction environment.

EXPERIMENTAL

Materials.

Phenylacetic acid and sodium iodide crystals were dried in a warm vacuum oven. Reagent-grade benzyl alcohol and acetonitrile were distilled onto molecular sieves. Pyridine, triethylamine, , and tributylamine were distilled from and stored over calcium carbide. 1M $COCl_2/CHCl_3$ was prepared from phosgene gas and ethanol-free chloroform; $SOCl_2$ was purified by distillation from limonene[255]. All polymers were originally prepared from "SX-1 Bio-Beads", 200-400 mesh particles of polystyrene crosslinked with 1% divinylbenzene (Part I). Infrared spectra of KBr pellets were measured on a Nicolet 10-DX FT-IR Spectrometer, and NMR spectra were recorded in $CDCl_3$ + TMS using Varian EM 360, CFT-80 or XL-300 spectrometers.

Benzyl phenylacetate. With (2-iodopyridinium-N-ethyl)polystyrene iodide.

Previously-prepared (Part I: Experiment 27) (2-iodopyridinium-N-ethyl)polystyrene iodide-(chloroethyl)polystyrene copolymer $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{15}H_{15}NI_2)_{.145}(C_{10}H_{11}Cl)_{.145}$ (1.80 g, 1.58 meq) was stirred with phenylacetic acid (0.136 g, 1.00 meq), benzyl alcohol (0.108 g, 1.00 meq) and triethylamine (.245 g, 2.42 meq) in 12 ml CH_2Cl_2 under nitrogen reflux at 40°C for 1.5 hours. The brown suspension was filtered and the residue washed with ethyl acetate and water, then the

filtrate was separated, dried over Na_2SO_4, flash-evaporated, and subjected to thin-layer chromatography, to give 0.225 g (100%) of clear and colourless liquid: ^1H NMR ($CDCl_3$) 7.27 (s, 10H), 5.02 (s, 2H), 3.56 (s, 2H). A similar experiment using only 5% excess halopyridinium salt gave 74% yield of isolated ester. After further washing with aqueous base, the pale brown residue was dried under vacuum: IR (KBr) peaks absent at 1640-1659 for 2-halopyridinium salts; strong peaks present at 1663, 1582 and 1539 cm^{-1} for 2-pyridinone product, and a shoulder at 1245 cm^{-1} for original chloro impurity. <C719, C722, C720>.

Benzyl phenylacetate. Attempts with regenerated (2-chloro-pyridinium-N-ethyl)polystyrene chloride.

(2-Pyridinon-N-ethyl)polystyrene-(chloroethyl)polystyrene copolymer $(C_{10}H_{10})_{.01}(C_8H_8)_{.78}(C_{15}H_{15}NO)_{.145}(C_{10}H_{11}Cl)_{.145}$ (1.0 g, 1.1 meq), thionyl chloride (1.5 ml, 21 meq) and dimethylformamide (0.5 ml, 6.5 meq) in 10 ml benzene were stirred under nitrogen reflux at 80°C for 36 hours. The brown suspension was then filtered under nitrogen, and washed with dry methylene chloride (3X), then dried under vacuum: IR (KBr) peaks absent at 1663, 1582 and 1539 cm^{-1} for pyridinone precursor; peak present at 1646 cm^{-1} (m, pyr^+) for 2-halo-pyridinium product. This chloropyridinium chloride $(C_{10}H_{10})_{.01}(C_8H_8)_{.70}(C_{15}H_{15}NCl_2)_{.145}(C_{10}H_{11}Cl)_{.145}$ (1.0 g, 1.1 meq) was then stirred with phenylacetic acid (.136 g, 1.00

meq), benzyl alcohol (.108 g, 1.00 meq) and triethylamine (.122 g, 1.21 meq) in 12 ml CH_2Cl_2 under nitrogen reflux at 40°C for 3 hours. The brown suspension was filtered and the residue washed with ethyl acetate and water, then the filtrate was separated, dried over Na_2SO_4, flash-evaporated, and subjected to thin-layer chromatography, to give 0.037 g (16%) of clear and colourless liquid: ^1H NMR ($CDCl_3$) 7.27 (s, 10H), 5.02 (s, 2H), 3.56 (s, 2H). In another experiment, a larger (120%) excess of another polymer bearing the same species $(C_{10}H_{10})_{.01}(C_8H_8)_{.73}(C_{15}H_{15}NO)_{.21}(C_{10}H_{11}Cl)_{.05}$ (0.77 g, 1.1 meq) was stirred with phenylacetic acid (0.50 meq), benzyl alcohol (0.50 meq) and triethylamine (1.20 meq) in refluxing CH_2Cl_2 for 1.5 hours; a conversion of 30% was estimated by comparing the areas under the $PhCH_2O$ singlet peaks for alcohol precursor and ester product, which were easily distinguishable from all others in the NMR spectrum of the organic filtrate after flash-evaporation. After further washing with aqueous base, the pale brown residue was dried under vacuum: IR (KBr) peaks absent at 1640-1659 for 2-halopyridinium salts; strong peaks present at 1663, 1582 and 1539 cm^{-1} for 2-pyridinone product, and a shoulder at 1245 cm^{-1} for original chloro impurity.

Alternatively, treatment of polymeric pyridinone with phosphoryl chloride gave a product whose FTIR spectrum showed no pyridinone peak at 1663 cm^{-1}, but very large peaks at 1018 and 1240 cm^{-1} were present due to phosphate or halophosphoryl.

Thionyl chloride without heat or DMF, or other reagents such as carbonyl chloride, oxalyl chloride or chlorotrimethylsilane, with or without catalytic or stochiometric tertiary amines, gave polymers whose IR spectra displayed no change from their 2-pyridinone precursors, and which gave 0% yields of benzyl phenylacetate from benzyl alcohol and phenylacetic acid.

<C726, 730, 735; D1024, 1026-1032, 1032>

Benzyl phenylacetate. Attempts with (4-chloropyridinium-N-ethyl)polystyrene chloride.

Previously-prepared (Part I; Experiment 30) (4-Pyridinon-N-ethyl)polystyrene $(C_{10}H_{10})_{.01}(C_8H_8)_{.74}(C_{15}H_{15}NO)_{.25}$ (0.40 g, 0.75 meq) was stirred with $COCl_2$ (4 meq) in 4 ml $CHCl_3$ at room temperature under nitrogen for 16 hours. The brown suspension was then filtered under nitrogen, and the residue washed with dry CH_2Cl_2 (2X), and dried in a stream of nitrogen: IR (KBr) peak absent at 1582 cm^{-1} (m, C=O) for pyridinone precursor; peaks present at 1637 (smaller, m, pyr) and 1522 (m, pyr^+) for halopyridinium product, or hydroxypyridinium side-product (the two spectra were very similar)[280]. The polymer (0.75 meq) was then resuspended in 5 ml dry CH_2Cl_2 with phenylacetic acid (0.40 meq), benzyl alcohol (0.40 meq), and diazabicycloundecene (0.17 ml, 1.4 meq), with stirring at room temperature under nitrogen for 24 hours: NMR of the concentrated filtrate indicated 8% conversion to ester; after washing with aqueous

base and drying, FTIR spectrum of the polymer was identical to starting 4-pyridinone.

<D1169>

Benzyl phenylacetate. Attempts with (4-chloropyridinium-N-ethyl)polystyrene iodide.

The same phosgene-treated polymer (0.65 meq), after washing with dichloromethane and drying, was resuspended under nitrogen in 5 ml dry acetonitrile with phenylacetic acid (0.30 meq), benzyl alcohol (0.30 meq) and tributylamine (0.72 meq). Dry sodium iodide (0.05 g, 0.3 meq) was added, forming a clear yellow solution from which rapidly formed a white microcrystalline precipitate. Stirring was continued at 70°C for 17 hours: NMR of the concentrated filtrate indicated 26% conversion to ester; after washing with aqueous base and drying, FTIR spectrum of the polymer was identical to the starting 4-pyridinone. In another experiment, the polymeric 4-pyridinone (1.21 g, 2.24 meq) was first treated with a mixture of $COCl_2$ (20 meq) and $SOCl_2$ (1.0 ml, 14 meq) under nitrogen at room temperature for 2 hours. After washing with dry CH_2Cl_2 (3X) and drying, sodium iodide (0.15 g, 1.0 meq), phenylacetic acid (0.139 g, 1.02 meq), benzyl alcohol (0.111 g, 1.02 meq) and 12 ml dry CH_2Cl_2 were added, then triethylamine (0.34 ml, 2.4 meq) in 3 portions 30 minutes apart. After stirring under nitrogen at 40°C for a total of 6 hours, the brown suspension was filtered and the filtrate evaporated: NMR

of the concentrated filtrate indicated 57% conversion to the ester; after washing with aqueous base and drying, FTIR spectrum was identical to the starting pyridinone.

Phosphate in a polymer which had been treated with $POCl_3$ was not displaced by washing[75] with concentrated KI/H_2O. An attempt to introduce iodide during the regeneration step ($COCl_2$) led to a clear purple solution due to the liberation of elemental iodine.

<D1139, D1163, D1169, D1183>.

Benzyl phenylacetate. Attempts with (4-chloropyridinium-N-ethyl)polystyrene tetrafluoroborate.

The polymeric 4-pyridinone (1.15 g, 2.1 meq) was first combined with $COCl_2$ (10 meq) and $SOCl_2$ (1 ml, 14 meq) to which was also added anhydrous sodium tetrafluoroborate (0.30 g, 2.7 meq) and pyridine (2.0 ml, 25 meq). After stirring under nitrogen at room temperature for 24 hours, the brown suspension was filtered, and the residue washed with dry CH_2Cl_2 (3X), and dried in a stream of nitrogen: IR (KBr) peak absent at 1663 cm^{-1} for pyridinone; several very strong peaks present near 1000-1100 cm^{-1} for both organic and inorganic tetrafluoroborate salts[280]. The polymer (2.1 meq) was resuspended in 10 ml dry CH_2Cl_2 with phenylacetic acid (1.0 meq), benzyl alcohol (1.0 meq), and tributylamine (0.55 ml, 2.3 meq), and stirred under nitrogen at room temperature for 18 hours: NMR of the concentrated filtrate indicated 62%

conversion to the ester; after washing with aqueous base and drying, FTIR spectrum was identical to the starting pyridinone.

Substituting methanesulfonyl chloride, tributylamine or potassium tetrafluoroborate for, respectively, thionyl/carbonyl chloride, pyridine or sodium tetrafluoroborate in this recipe for halopyridinium regeneration gave polymers only able to promote 10-30% esterification. Use of dimethylaniline instead of pyridine with phosgene during the regeneration step produced a coloured solution due to the formation[171] of crystal violet. Neither dimethylaminopyridine nor tricaprylmethylammonium chloride catalysts, nor dipotassium phosphate acid acceptor, seemed to affect the outcome of the esterification.

<D1139, 1142, 1143, 1146, 1157, 1160, 1170-1173, 1175, 1177, 1180, 1183>.

CLAIMS TO ORIGINAL RESEARCH

- Preparation of crosslinked polystyrenes containing dimethylene spacers bearing various leaving groups, as versatile intermediates towards other functional polymers.
- A new method for the clean tosylation of alcohols, employing diisopropylamine as a nonnucleophilic acid acceptor.
- Preparation, by quantitative polymer modification, of illustrative or useful oxygen, nitrogen, sulfur or phosphorus functionalities supported on polystyrene through dimethylene spacer. General conditions to minimize common side-reactions.
- Discovery of several new examples of "polymer effect", in which functional groups immobilized within the special microenvironment provided by a polymer matrix behaved eccentrically compared to the analogous free molecules.
- Metallation at insoluble primary carbon.
- A new and probably general method for the clean formation of alkenes from alkyl halides and tosylates, involving treatment with N,N-dimethylaminoethanol, then mild base; its application towards crosslinked (vinyl)polystyrene.
- New polymer-supported dialkylaminopyridine acylation catalysts whose activities, improved by spacers, approached or equalled those of the best free molecules available.
- A new polymer-bound reagent for the acylation of nucleophiles. Its partial regeneration by inexpensive chemicals.

SUGGESTIONS FOR FUTURE RESEARCH

- The two new synthetic methods discovered during this work, for tosylation and for elimination, can be tested on a selection of free molecules to determine their usefulness to the general organic chemist. A one-pot procedure employing them both is easily envisaged for the conversion of alcohols to olefins. A recyclable, polymer-bound beta-aminoalcohol, perhaps prepared from lithiated polystyrene and epichlorohydrin, would further simplify workup and purification of the desired olefin product.
- Elimination might be more or less suppressed in the synthesis of (alkoxy-ethyl)polystyrenes from alkoxides if a positive counterion were employed capable of anchimerically assisting departure of leaving group, such as mercury or thallium with polymeric halide, or magnesium with tosylate. Perhaps even diisopropylamine might be immobilized in this manner.
- The synthesis of (diisopropylaminoethyl)polystyrene can also be attempted through a new, entirely different route employing diisopropylaminoethyl chloride or tosylate and polystyrene copper or magnesium, derived from the lithiated polymer by metal exchange. Some illustrative applications of the new non-nucleophilic polymer base would then be in order.
- Certain other photochemical, basic and/or reductive

procedures have yet to be attempted for the clean cleavage of polymeric tosylamide to secondary amine. Failing this, the more labile but expensive triflamide may be more suitable.

- Conditions for the metallation of insoluble polystyrene alkyl can probably be improved... if not, the reasons may also be interesting for the understanding of metallation reactions and polymer chain dynamics. Hydroboration of vinylpolystyrene would be a step towards many other interesting derivatives.
- Nuclear magnetic resonance spectroscopy would greatly help in the analysis of functionalized reticulated polystyrenes. Since polystyrene gels are swollen by common NMR solvents, advanced hardware accessories usually required for solid samples may not be necessary.
- The effect of spacers on cooperativity phenomena can perhaps be tested with polystyrene-supported tertiary pyrrolidinone.
- Metal complexes with spacer-supported phosphine, imidazole and quaternary ammonium groups may be particularly potent and stable catalysts. Here, too, cooperativity may play a role.
- (Hydroxypropyl)polystyrene may be accessible from commercial crosslinked polystyrene by coupling the metallated polymer with allyl halide, followed by hydroboration-oxidation. Further functional modifications would be the same as for the dimethylene spacer.
- Complete optimization of the regeneration of active polymer-bound halopyridinium reagent may be only one experiment away...

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