Polymeric Reagents and Catalysts

EDITED BY

Warren T. Ford

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Polymeric Reagents and Catalysts

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FOREWORD

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the Series parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that, in order to save time, the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. Papers are reviewed under the supervision of the Editors with the assistance of the Series Advisory Board and are selected to maintain the integrity of the symposia; however, verbatim reproductions of previously published papers are not accepted. Both reviews and reports of research are acceptable, because symposia may embrace both types of presentation.

PREFACE

POLYMERIC REAGENTS AND CATALYSTS are of interest to organic chemists whose research could profit from their use. The purpose of this book is to bring this subject to their attention. Unlike most volumes in the ACS Symposium Series, this one contains no research papers, but only invited authoritative reviews.

Many synthetic chemists are reluctant to use polymeric reagents and catalysts because they do not understand polymers, or because they have been educated to believe that polymer chemistry is not pure. The development of polymer chemistry does lag behind that of organic chemistry. But after all, the concept of the macromolecule was generally accepted only around 1930, whereas urea was synthesized first in 1828. Its relative youth helps make polymer chemistry an exciting field of research, wide open for further exploration. For the benefit of readers who lack a fundamental background in polymer chemistry, the overview chapter includes a short section of basic terminology and concepts that should help in understanding the up-to-date reviews of research that follow.

A comprehensive work on polymeric reagents and catalysts would include coverage of immobilized enzymes, solid-phase peptide and nucleotide synthesis, and reagents and catalysts on inorganic supports. That work would also require several volumes. This single volume deliberately concentrates on ideas for the synthetic chemist working on new compounds, synthetic methods, or industrial chemical processes. At present, the organic chemical applications of polymeric reagents and catalysts are less well developed than immobilized enzymes and solid-phase peptide synthesis. The recent shift of research emphasis in industry from commodity chemicals to higher markup fine chemicals could change that situation. This recent shift presents opportunities for invention and use of many new polymeric reagents and catalysts and should lead to a rapid growth of the field.

I warmly thank the authors for their fine contributions that make this volume possible. The ACS Divisions of Organic and Polymer Chemistry, The Petroleum Research Fund, and the Rohm & Haas Company provided generous support for the original symposium. The reviewers and my colleague Erich Blossey contributed constructive suggestions that improved many of the chapters. Kris Shabestari did an excellent job of typing my own

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Polymeric Reagents and Catalysts

An Overview

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R. Bruce Merrifield was honored with the Nobel Prize in Chemistry in 1984 for invention of peptide synthesis in polymer supports. Merrifield peptide synthesis is now used in scores of laboratories to produce natural peptides and, perhaps more importantly, analogs of natural peptides that are vital for the correlation of structures of peptides with their biological activity.

The basic concept of peptide synthesis in a support seems simple in retrospect, causing many of us to say "Why didn't I think of that?" Merrifield did, and the concept was clearly described in his research notebook (1) and dated 5/26/59, four years before his first paper on the subject in the Journal of the American Chemical Society (2).

> There is a need for a rapid, quantitative, automatic method for synthesis of long chain peptides. A possible approach may be the use of chromatographic columns where the peptide is attached to the polymeric packing and added to by an activated amino acid, followed by removal of the protecting group & with repetition of the process until the desired peptide is built up. Finally the peptide must be removed from the supporting medium.

Merrifield succeeded in doing exactly what he described. The basic steps are in Scheme 1 (3): 1) An N-protected amino acid is attached as an ester to a cross-linked polystyrene support. 2) The protecting group is removed. 3) An N-protected, activated amino acid is coupled to the amino group of the polymer-bound amino acid. Steps 2 and 3 are repeated with different amino acids to produce the desired peptide sequence. 4) The completed peptide is cleaved from the polymer, deprotected, and purified.

Within three years of the first publication Merrifield built a machine to automate the synthesis, and in six years he had synthesized ribonuclease A, an enzyme with 124 amino acid residues, having partial activity of the naturally isolated enzyme. The key features of the Merrifield method that have led to its widespread use are: 1) At each stage of the synthesis the polymer-bound peptide can be separated from all other components of the reaction mixture by filtration. This makes possible the use of a large excess of the soluble N-protected amino acid to drive each coupling step to high conversion. 2) The method can be automated.

Merrifield was not the only one to conceive independently syntheses with polymer supports. Also in 1963 Letsinger and Kornet (4) reported a peptide synthesis

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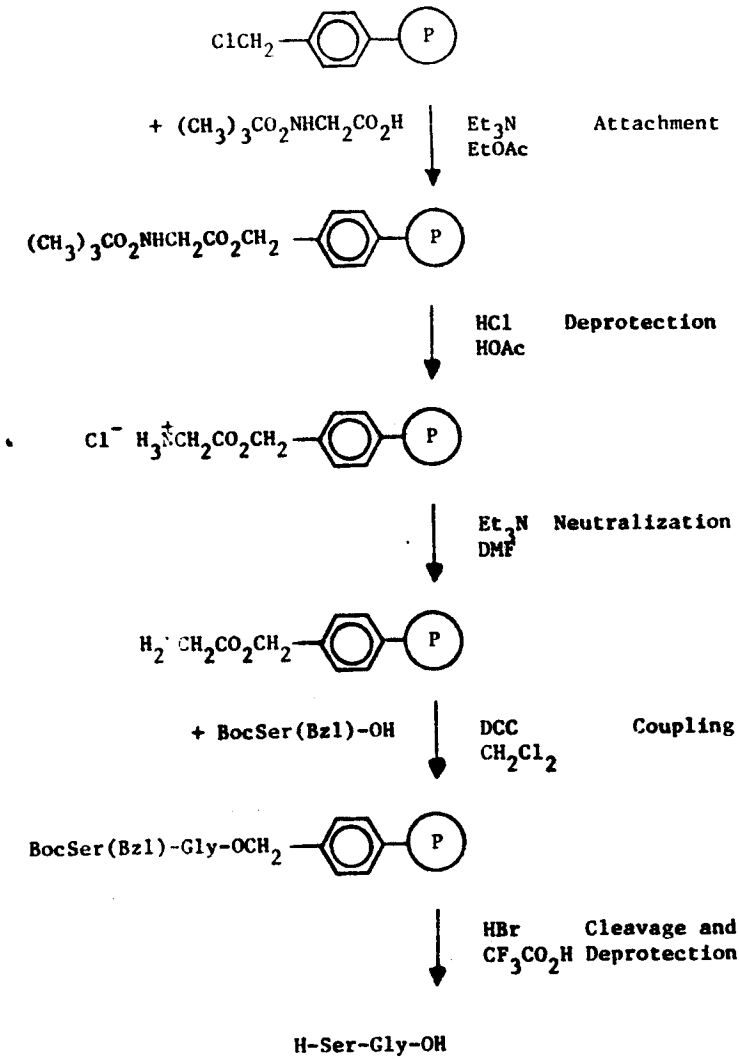
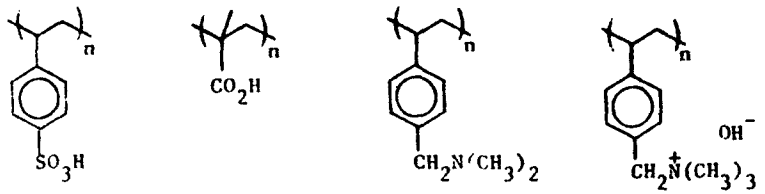
Scheme 1


ClCH2
P
+ (CH3)3CO2NHCH2CO2H
Et3N
EtOAc
Attachment
(CH3)3CO2NHCH2CO2CH2
HCl
HOAc
Deprotection
Cl⁻ H3N⁺CH2CO2CH2
Et3N
DMF
Neutralization
H2 CH2CO2CH2
+ BocSer(Bzl)-OH
DCC
CH2Cl2
Coupling
BocSer(Bzl)-Gly-OCH2
HBr
CF3CO2H
Cleavage and Deprotection
H-Ser-Gly-OH

Scheme 2



strongly acidic | weakly acidic | weakly basic | strongly basic

with the amino terminus bound to the polymer. Fridkin, Patchornik, and Katchalski (5) used insoluble polymeric active esters of amino acids to acylate the N-termini of peptides in solution. Soon the concept was applied also to the syntheses of polynucleotides (6) and of polysaccharides (7). Many of the key papers in the development of polymer-supported syntheses of peptides, polynucleotides, and polysaccharides have been collected in a volume of reprints (8). Now in 1985, peptide synthesis in polymer supports is widely used (3), and polynucleotides are synthesized with silica gel as the support (9,10), but there has been much less development in synthesis of polysaccharides.

Merrifield peptide synthesis is the most highly developed method of synthesis with solid supports. Every step of the synthesis is carried out in the same polymer. Polymer-supported species also have been used as reagents and catalysts for single step synthetic transformations. Useful single step syntheses should be much easier to achieve than multi-step syntheses in polymer supports because they do not require >99% yield to be valuable. This book emphasizes one step processes in the synthesis of low molecular weight organic compounds carried out with polymer-supported reagents and catalysts.

The use of ion exchange resins as catalysts preceeds Merrifield peptide synthesis by more than a decade (11,12). These resins are most often functionalized, cross-linked polystyrenes. The primary commercial uses are water softening and deionization. For *fundamentals of their chemistry see* ref. (11). The common functional groups in ion exchange resins are strong and weak acids, tertiary amines, and quaternary ammonium salts (Scheme 2). (The latter are called "strongly basic", because they are used frequently with hydroxide as the counter ion. The quaternary ammonium ion is not a base.) The sulfonic acid resins are used as heterogeneous alternatives to soluble acid catalysts such as sulfuric acid or *p*-toluenesulfonic acid. The polymeric catalyst can be filtered out of a reaction mixture or used in a continuous flow process. The largest volume application at present is in the manufacture of the gasoline additive methyl *tert*-butyl ether by the addition of methanol to isobutylene catalyzed by a macroporous sulfonic acid resin (13). Chapter 3 by Waller describes catalytic uses of the much stronger acid Nafion, an insoluble polymeric perfluoroalkanesulfonic acid. The tertiary amine resins are heterogeneous alternatives to the common soluble tertiary amines used catalytically as weak bases and stoichiometrically as traps for strong acids liberated in reactions. The quaternary ammonium ion resins can be used with almost any desired counter ion as a reagent or catalyst, serving as sites for reactions of not only hydroxide ion, but also cyanide, halides, carboxylic acid anions, and carbanions.

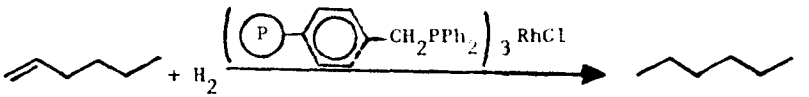
The common ion exchange resins were developed in the 1950's, and Merrifield peptide synthesis was developed in the 1960's. Following a surge of research in transition metal-organic chemistry, in the 1970's heterogeneous analogs of a large number of homogeneous transition metal complexes were prepared by binding them to polymers and to silica gel. The aim was to create easily recovered catalysts with the high activity and selectivity of homogeneous catalysts for certain hydrogenation, hydroformylation, coupling, and oxidation reactions (Scheme 3) (14,15). Recovery is especially important because precious metals such as platinum, palladium, and rhodium often provide the best catalysts. The polymers used to bind transition metal species most often contain ligands such as phosphines or pyridines, or ion exchange sites to bind ionic metal complexes. The great initial hopes for such polymer-bound transition metal catalysts have not yet led to any commercial processes of which this author is aware. One problem is that the transition metals are not bound irreversibly, and their complexes are not as stable as they were once thought to be. Chapter 5 by Garrou analyzes the "leaching" of metals from and the chemical degradation of polymer-bound transition metal complexes.

Another development of the 1970's was the use of polymeric reagents in general organic synthesis (16,17,18). In principle, a polymeric analog can be devised for any useful soluble reagent. In practice, there is no reason to develop the polymeric reagent unless there are distinct advantages to be gained with the polymeric species, such as ease of separation of a by-product from a reaction mixture, use of the reagent in a continuous flow process instead of a batch process, the substitution of an odorous or toxic reagent with an analog that has no vapor pressure, or achievement of a chemical specificity not possible in solution. Chapter 8 on Wittig reagents by Ford and chapter 7 by Taylor on oxidizing agents concern some of the most common reagents in organic synthesis whose by-products are easier to separate from reaction mixtures when they are in insoluble, polymer-bound form. Chapter 6 by Neckers details the advantages of immobilization of the photosensitizer Rose Bengal. Polymer-supported reagents are potentially adaptable to continuous flow processes, although they have seldom been used that way in academic laboratories. Chapter 10 by Patchornik and co-workers describes a laboratory scale flow reactor for acyl transfer reactions. The problem of altering chemical reactivity by "isolation" of polymeric species from one another in a polymer support or by forcing them into "cooperation" in a polymer support are discussed in chapter 11 by Ford on site isolation syntheses. The concepts of isolation and cooperation of functional groups in polymer supports have not been easy to reduce to practice. The state of the art of specific binding of organic compounds by templates in polymer networks is reported in chapter 9 by Wulff.

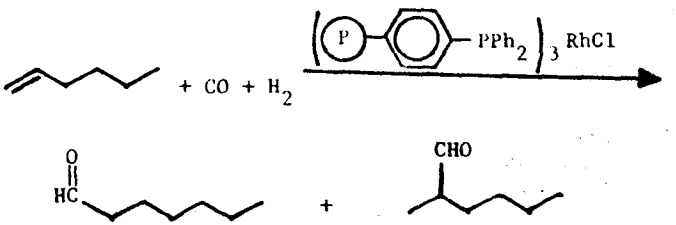
A new version of catalysis by ion exchange resins appeared in the late 1970's. Insoluble polymers with much lower degrees of quaternary ammonium and phosphonium ion functionalization than the conventional ion exchange resins are active catalysts for reactions of anions with nonpolar organic compounds in triphase solid/liquid/liquid and solid/solid/liquid mixtures (Scheme 4). The organic reactant (and solvent if used) is one liquid phase, the polymeric catalyst is a solid (actually a gel) phase, and the inorganic reagent is used as either an insoluble solid or an aqueous solution. Polymer-bound chelating agents of metal ions such as crown ethers, cryptands, and polyethers show similar activity. The processes have been called "triphase catalysis" (19) and polymer-supported phase transfer catalysis (20). The latter term stresses the analogy to catalysis of reactions between hydrophilic anions and nonpolar organic molecules by lipophilic quaternary onium ions and crown ethers in liquid/liquid and solid/liquid mixtures. Subsequent kinetic analyses of polymer-supported phase transfer catalysis have shown that the reactions behave as normal heterogeneous catalysis in the sense that often there are diffusional limitations to catalytic activity.

Scheme 3

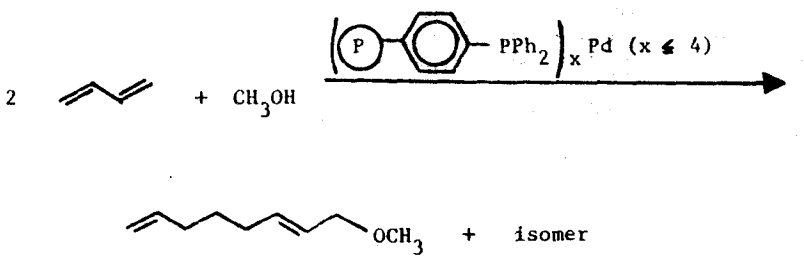
Hydrogenation



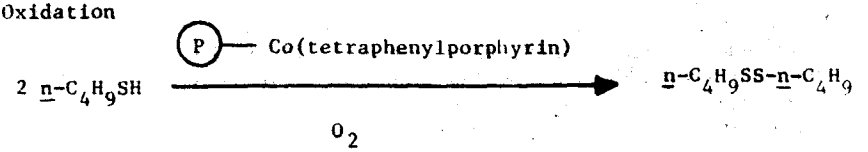
Hydroformylation



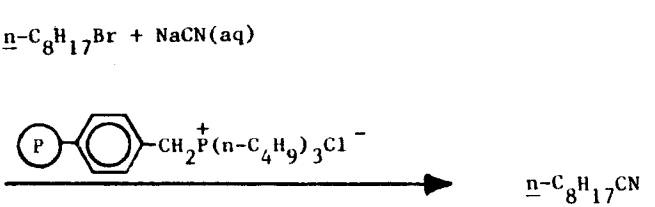
Coupling



Oxidation



Scheme 4



The state of polymer-supported reactions in organic chemistry at the end of the 1970's is described well in two books which the reader may wish to consult as further background for this volume (21,22).

Basic Polymer Chemistry

Far too often the organic chemist's concept of a polymer is a residue from a distillation. A polymer is considered by many non-polymer chemists to be an intractible mixture of compounds, difficultly soluble at best, and completely uncharacterizable. Although there are elements of truth in this concept, it is largely based on ignorance due to the failure of chemistry professors to teach students and experienced chemists to teach themselves a few basic principles about the nature of synthetic macromolecular materials. Readers who have not studied basic polymer chemistry are encouraged to consult and study one of the basic textbooks in the references (23,24,25,26). For principles of polymerization reactions the book by Odian (27) is especially recommended, but it lacks coverage of basic physical principles of macromolecules found in the other textbooks. A few fundamental definitions are covered in the following paragraphs to refresh some readers' memories. Anyone familiar with polymers should skip this section.

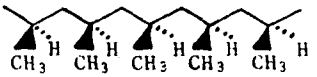
Polymer Structures and Properties. Synthetic polymers are mixtures of compounds composed of the same repeating structural units but differing in molecular weight. Thus polystyrene has the *repeat unit* structure

$$(CH_2\,CH)_n$$
$$\quad\;|$$
$$\quad C_6H_5$$

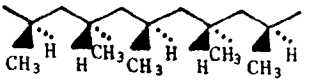
where n is the number average *degree of polymerization*, the average number of repeat units per molecule. A polymer is made by polymerization of *monomer*, a small molecule that reacts in regular, repeating fashion. The *number average molecular weight*, $\bar{M}_n$, is n times the formula weight of the repeat unit. When n exceeds some lower limiting value (which depends on the structure of the polymer and usually corresponds to $\bar{M}_n$ of 20,000 or more), the polymeric material has the desirable physical characteristics needed to produce a plastic, fiber, or elastomer. A material with regular repeating structure but too low an $\bar{M}_n$ to achieve these properties is usually called an *oligomer*.

A polymer having pseudochiral carbon atoms in its main chain is *isotactic* if adjacent centers are related as in a meso compound, *syndiotactic* if adjacent centers

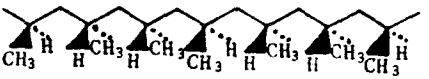
are related as in a (d,l) compound, and *atactic* if stereochemically random. Seldom is a polymer completely isotactic or completely syndiotactic. Most polymers made by free radical polymerization of vinyl monomers are atactic.



isotactic



syndiotactic



atactic

The structures of the *end groups* of the polymer chains are usually not specified because they have no effect on the bulk properties of the polymer, and often they are not known.

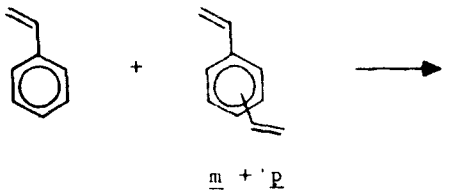
A *copolymer* is comprised of more than one kind of repeat unit and is synthesized from two or more monomers. Those repeat units, A and B, may be arranged in *alternating*, *block*, or *random* fashion.

ABABABABABABABAB	alternating
AAAAAAAABBBBBBBB	block
ABAAABBABABBBABA	random

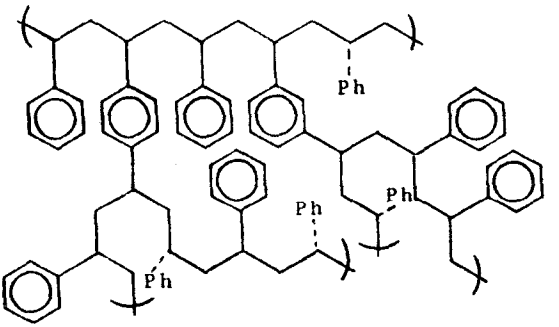
Polymers are less soluble than low molecular weight materials because of the smaller entropy of mixing. They are totally insoluble when they are *cross-linked* by bonding the primary macromolecular chains into a *network*. Copolymerization of styrene with divinylbenzene provides the cross-linked polymers most often used for polymer-supported reagents and catalysts (Scheme 5). The insolubility makes them easy to separate from a reaction mixture but complicates their analysis. Their molecular weights are effectively infinite. A solvent that dissolves a homopolymer only swells a cross-linked polymer. Some swelling of a polymeric reagent is usually necessary to permit transport of the reagents to the reactive sites within the polymer network. A polymer swollen but not dissolved by solvent is a *gel*, a state of matter that as a solid does not exhibit macroscopic flow, but has properties of a liquid at a molecular level.

A *thermoplastic* may have either a partly crystalline or a completely amorphous structure in the solid state. An amorphous glassy solid is converted to a rubbery liquid upon heating above its *glass transition temperature*, T_g. A semicrystalline polymer has thermoplastic properties when it is above the T_g of its amorphous regions but still below its crystalline *melting temperature*, T_m. Upon heating above T_m a semicrystalline polymer becomes a viscous liquid. Network polymers are usually completely amorphous. The heating of a polymer network to above its T_g leads to an *elastomer* that can be deformed but does not flow. The presence of a low molecular weight solvent in a network markedly reduces its T_g, and under most conditions of use of polymeric reagents and catalysts, the solvent-swollen polymer gel is in an elastomeric state.

Scheme 5



m + p

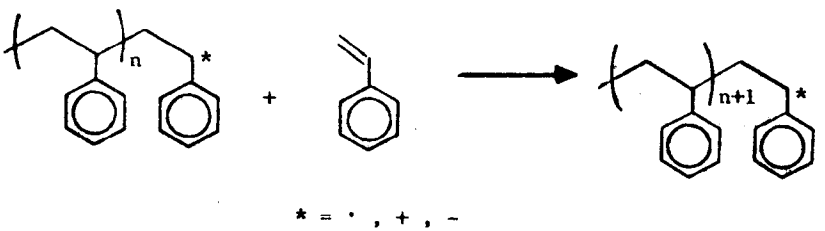


The term *resin* may refer to particles of any plastic or elastomeric polymer, as an ion exchange resin.

Polymer Synthesis. Polymer synthesis could be as varied as all of synthetic organic chemistry, but it is not, because the conditions required for successful production of macromolecules are far more exacting than for most micromolecules. In a polymerization the chain-forming step must occur 100 times for every termination step to achieve a degree of polymerization of 100. Not many organic reactions proceed in >99% yield.

Most polymerization reactions fall into two large classes, *chain growth* (Scheme 6) and *step growth* (Scheme 7) polymerizations. In a chain growth process a macromolecule is formed rapidly from monomer via a highly reactive intermediate such as a free radical, a carbanion, a carbenium ion, or a transition metal alkyl complex. After partial conversion of monomer in a free radical polymerization, the reacting mixture contains monomer and high molecular weight polymer. A step growth polymerization involves slow reactions of two monomers to form dimer, dimer and monomer to form trimer, two dimers to form tetramer, and so on in all possible combinations until macromolecules are formed. High molecular weight is achieved only after high conversion of monomer. After partial conversion the reacting mixture contains a broad distribution of monomers and oligomers.

Scheme 6



Scheme 7