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Polymer-supported Reactions in Organic Synthesis

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A Wiley–Interscience Publication

JOHN WILEY & SONS
Chichester • New York • Brisbane • Toronto

British Library Cataloguing in Publication Data:

Polymer-supported reactions in organic synthesis.
  1. Chemistry, Organic—Synthesis
  2. Polymers and polymerization
  I. Hodge, P II. Sherrington, D C
  547′.2   QD262   79-41482

ISBN 0 471 27712 6

Set in Monophoto Times by
COMPOSITION HOUSE LTD, SALISBURY and printed
in the United States of America

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Preface

The last ten to fifteen years have seen a great increase in the preparation and investigation of chemically active species bound to polymer supports. Studies have been made not only by polymer chemists but also by organic and inorganic chemists and biochemists. In this book those aspects concerned with organic synthesis are gathered together for the first time. Each chapter has been written by a research worker active in the area about which they write. It is hoped that bringing the information together in one place will not only help potential users of these techniques to assess the progress that has been made, but will also help research workers in the field to learn from others who may have been trained in different disciplines. In particular it is hoped to encourage chemists to close the gap between classical organic and classical polymer chemistry.

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August 1979

Editors' Introduction: Why Study Polymer-supported Reactions?

The last ten to fifteen years have seen the rise in popularity of the simple yet far-reaching idea of attaching chemically reactive species to insoluble supports.[1] Applications have been found in organic chemistry, inorganic chemistry, biochemistry, and biology. This book is primarily concerned with polymer-supported reactions in organic synthesis, that is with organic reactions in which either a reagent, a catalyst, or a substrate is attached to a polymer. Reactions using other supports, such as silica, are occasionally included to facilitate comparisons.[2]

The study of reactive polymers is an area which until recently had been largely neglected. Polymer chemists tended to study the preparation and physical properties of polymers and this, of course, led to the growth of the plastics industry. Organic chemists, on the other hand, tended to concentrate on studies of relatively small, well-defined molecules or on studies of natural polymers, and synthetic reactive polymers were hardly studied. This book aims to gather together the recent extensive work in this area that is relevant to organic synthesis.

Chapter 1 is concerned with the preparation of functionalized polymers, their physical properties, and the factors affecting the choice of suitable reaction conditions. Subsequent chapters, therefore, only consider these aspects briefly, but they are nevertheless very important and should be borne in mind. Chapter 2 considers polymer-supported reagents, and this is followed by three chapters which are concerned, respectively, with catalysis by ion-exchange resins, enzyme-like catalysis, and polymer-supported transition metal complex catalysts. Chapters 6, 7, 8, and 9 consider various reactions using polymer-supported substrates. The first of these is concerned with non-repetitive syntheses and the following chapters with the supported synthesis of the three main types of natural polymers, i.e. polypeptides, polysaccharides, and polynucleotides. The final chapter considers, very briefly, the reactions of other polymer-supported species, including some biological applications. A number of polymer syntheses are of considerable value in a wide range of applications and some detailed experimental guidance for readers new to the field is contained in the Appendix.

Having a *reagent* or *substrate* attached to an insoluble support has several practical advantages which include the following:

(i) Reaction work-up is simplified because the supported species are easily separated from the non-supported species by filtration. This may make it possible to avoid exposing the reaction product(s) to water or to avoid a chromatographic separation in the reaction work-up.
(ii) If the use of an excess of a reagent results in a greater reaction yield, then an excess can be used without causing separation problems.
(iii) When a polymer-supported reagent is used, the spent reagent is easily recovered and can possibly be recycled. This is very important economically and can make it worthwhile to prepare complex supported reagents.
(iv) If the reaction proceeds virtually to completion, so that filtration and washing of the polymer are all that is required to work-up the reaction, it becomes feasible to automate the process. This has obvious industrial attractions.
(v) If a reaction proceeds very readily it can possibly be carried out using a column of the supported reagent or substrate and passing the other reactants down the column in turn.
(vi) Since crosslinked polymers are insoluble and non-volatile, they are non-toxic and odourless. Hence carrying out reactions involving, for example, thiols or selenium compounds on polymer supports is a way of making the reactions environmentally more acceptable.

The practical advantages of attaching *catalysts* to insoluble supports are similar to the above and they have long been recognized and industrially exploited. Thus, the reaction products are easily separated from the catalyst and the latter is available for re-use. Catalysts on insoluble supports can be used in flow systems. The vast majority of supported catalysts used commercially employ some sort of ill-defined physical interaction between the catalyst and the support. Indeed the structural nature of the actual catalytic species in these preparations is in many instances unknown. This type of relatively poorly defined physically supported species is not discussed in this book. Instead it is concerned with soluble catalysts which have been 'heterogenized' by being chemically bound to an appropriately functionalized support.

The main reason for using *insoluble* supports is that the supported species are easily separated from the non-supported species by filtration. The ability to make supported species sink or float in a reaction mixture by appropriate adjustment of the density of the medium may also be useful on occasions. *Soluble* polymers have been used as supports but separation is then more difficult. The simplest procedure is to precipitate the polymer by adding the reaction mixture to an appropriate solvent. Failing this, separation may be achieved by the more tedious procedure of membrane filtration.

Virtually all reactions occurring in animals and plants are catalysed by enzymes and the latter can be considered as a particular type of functionalized polymer. There is, therefore, a resemblance between polymer-supported reactions and enzymic reactions. Effects have been observed which are common to both. The insolubility of crosslinked polymers makes the study of such effects difficult and in many cases they are best studied using soluble linear polymers.

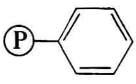
TERMINOLOGY

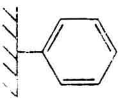
The description *supported* refers to the situation where structurally well-defined molecules are attached by specific covalent or ionic bonds to polymeric or inorganic oxide supports. Alternative expressions such as *anchored* and *attached* are used consistently by some authors, and these terms may be regarded as synonymous with the definition of *supported* given above. The term *immobilized* is most commonly used in a biological or biochemical context. The *immobilized* species may be very specifically chemically bound or they may be simply physically trapped or encapsulated within a support matrix.

The description of a synthesis as employing the *solid-phase* technique is common and was originally introduced by Merrifield. The term does not provide an accurate molecular picture of the process employed, but it has become a common way of indicating the use of an essentially insoluble polymeric or inorganic oxide support.

In polymer chemistry the term *resin* is usually used to describe all solid or semi-solid polymers whether or not the polymers are crosslinked. However, in the context of polymer-supported reactions *resin* is usually used as a convenient term to describe polymers which have a three-dimensional network and are, therefore, insoluble.

In order to simplify chemical equations a number of shorthand notations have been used. Two particularly common ones are shown here. The first





indicates an organic macromolecular or polymeric support with the most important pendant group displayed. The second indicates a support which may be organic or inorganic. Neither symbol should be taken to indicate any further details about the nature of the support; reference to the text will be required for this.

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1

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1.1 INTRODUCTION

A considerable number of polymeric and inorganic materials have been investigated as support matrices. While many of these are conveniently available only from commercial sources, others lend themselves readily to synthesis in the laboratory. Indeed the latter approach is more likely to provide a knowledge of the structure of the support, and equally importantly its likely contaminants. The previous history of a support can be vital with regard to the success or failure of a particular chemical transformation and materials from commercial sources should be treated with some recommended washing sequence.[1,2] Even this careful attention to detail can occasionally be ineffective since some supports can retain traces of both organic and inorganic fragments quite tenaciously.

Linear and crosslinked organic macromolecular species have found wide application in more recent years, the latter in particular being experimentally very attractive because of their ease of filtration and purification. Inorganic oxides and glasses have been employed more widely in large-scale applications, particularly in plants operating high-temperature catalytic processes. However, there have also been some attempts to reproduce the elegant syntheses of structurally well-defined, polymer-supported reagents employing various inorganic supports.[3–5]

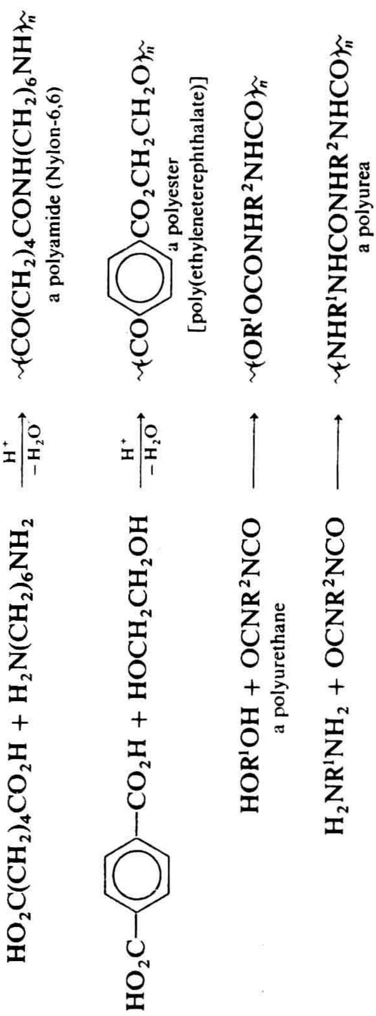
This chapter will review the various methods of preparing the main types of support and their functionalization. It will also deal with the structure and physical properties of supports, and discuss the various matrix and micro-environmental effects which can arise in reactions employing supported species.

1.2 PREPARATION, STRUCTURE AND PROPERTIES OF SUPPORTS

1.2.1 Synthesis of Linear Polymers

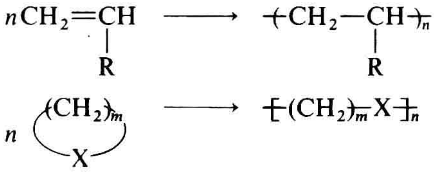
Synthetic linear macromolecules fall into two groups, those formed by polycondensation and those made by addition polymerization.

Polycondensation[6] involves the repetition of a simple condensation process to form a long-chain species, e.g. the reaction of a diol with a diacid to form a polyester, or a diamine with a diacid to form a polyamide or nylon. Very often these are acid-catalysed processes, although the condensations of acid chlorides or isocyanates with amines or alcohols proceed without the aid of a catalyst (Scheme 1). The mechanism of each reaction step is usually the same as in simple monomeric systems and chain propagation can occur at both ends of the growing macromolecule. Considerable care is required in preparing the pure monomeric components since high molecular weight products can be achieved only by taking reactions to high conversions. Also molecular weights can be very conveniently controlled by the use of small quantities of monofunctional additives.

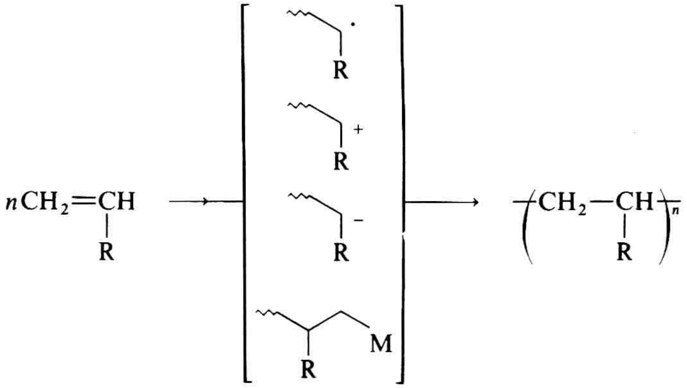

HO2C(CH2)4CO2H + H2N(CH2)6NH2
H+ −H2O
CO(CH2)4CONH(CH2)6NH n
a polyamide (Nylon-6,6)
HO2C— —CO2H + HOCH2CH2OH
H+ −H2O
CO CO2CH2CH2O n
a polyester
[poly(ethyleneterephthalate)]
HOR1OH + OCNR2NCO
a polyurethane
OR1OCONHR2NHCO n
H2NR1NH2 + OCNR2NCO
NHR1NHCONHR2NHCO n
a polyurea

Scheme 1

Addition polymerization takes place, in contrast, by a single chain reaction propagated by a reactive intermediate:

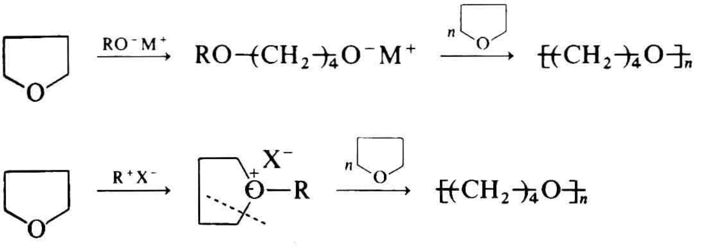


Vinyl monomers can be polymerized to high molecular weight polymer using free radical, anionic, cationic, or Ziegler–Natta type catalysts.[7] With each type of initiator the polymerization mechanism involves propagation, transfer, and termination processes:



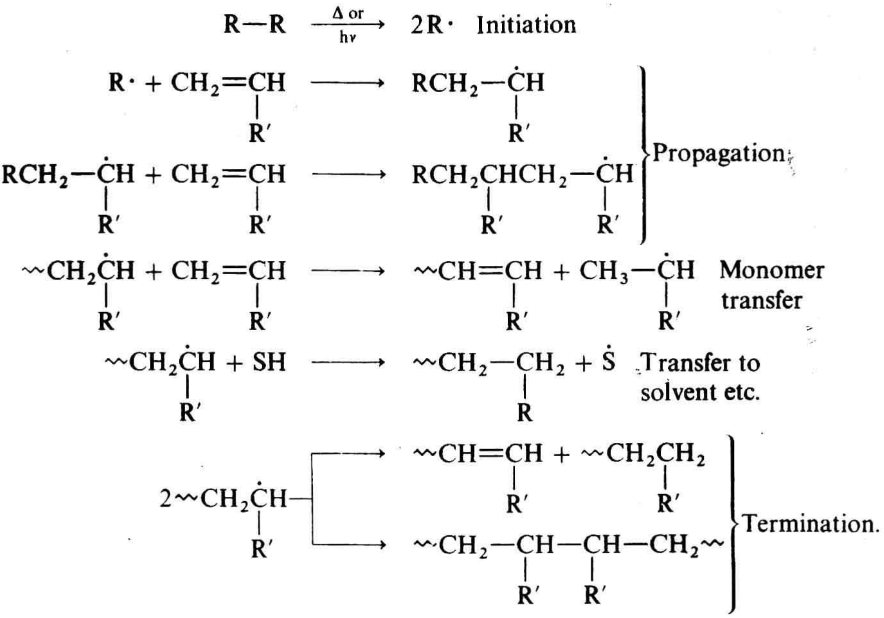
(M = transition metal ion)

and gives rise in general to macromolecular chains with a range of molecular weights or degrees of polymerization. Specialized techniques employing anionic polymerization are available for producing polymers with a monodispersed molecular weight, i.e. constituent chains all of the same length.[8] As well as vinyl monomers certain cyclic monomers can also undergo addition polymerization, but in these cases the reaction mechanisms are always ionic. An example is the ring opening polymerizations of tetrahydrofuran:



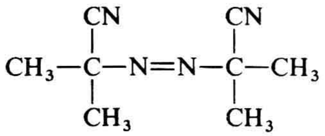
Macromolecules with a significant polydispersity in their molecular weights are usually obtained in these polymerizations.

For those vinyl polymers most widely used as supports, free-radical polymerization is generally employed in their synthesis. The mechanism of free radical polymerization involves a series of elementary reactions (Scheme 2).



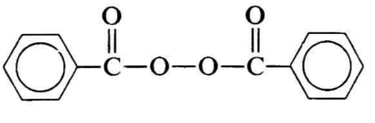
Scheme 2

Typical radical initiators are azobisisobutyronitrile (**1**) and benzoyl peroxide (**2**), both of which cleave readily on heating or irradiation with ultraviolet light, the former being the most commonly employed. Both are readily soluble in a wide range of monomers and organic solvents. For polymerizations carried out in aqueous solutions, water-soluble inorganic persulphates make useful initiators.



$$CH_3-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CN}{|}}{C}}-N=N-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CN}{|}}{C}}-CH_3$$

(1)



(2)

Standard kinetic analysis of the free radical reaction scheme has produced mathematical expressions for both the rate of polymerization and the average degree of polymerization (number of monomer segments) of the polymer formed, in terms of the concentrations of initiator and monomer and the various rate constants for the elementary processes.[9] For all common monomers the latter are now well documented in the literature.[10] Thus for a given set of reaction conditions the rate of polymerization and the molecular weight of the product can be predicted, or alternatively the required conditions calculated in order to produce a given rate and a given molecular weight.

Although from a preparative point of view it is possible to synthesize a polymer simply by adding an appropriate amount of initiator to a known weight of neat liquid monomer (*bulk polymerization*), the process has a number of major disadvantages. Thus vinyl polymerizations are generally highly exothermic (ΔH polymerization is typically ~ -80 J mol^{-1} [10]), hence reactions performed in the bulk can accelerate rapidly and in extreme cases cause rapid and violent volatilization of residual monomer. The most satisfactory way of avoiding these problems is to carry out polymerization either in solution or in suspension. In *solution polymerization* the monomer is simply dissolved in a suitable solvent to act as a diluent and heat transfer agent, and the polymerization is initiated as before. If the solvent chosen is compatible with both the monomer and the polymer, the latter is formed in solution and can be isolated by addition of a non-solvent which causes precipitation. On the other hand, if the reaction solvent is not compatible with the polymer, then the latter precipitates as it forms.

While solution polymerization is convenient in the laboratory it tends to be unnecessarily expensive on a large scale and in this case *suspension polymerization* is usually employed. In this technique[11–13] the liquid monomer (or comonomer mixture) is suspended in an excess of an immiscible solvent which acts as an efficient heat transfer agent. Hydrophobic monomers such as styrene are suspended in water, whereas a reverse suspension system is utilized for hydrophilic species, such as acrylamide, aqueous solutions of which are dispersed in hydrocarbon or chlorocarbon solvents. In principle the factors influencing the two types of suspension reaction are the same, though more information is available on oil-in-water systems, which are more commonly encountered. Usually suspension is maintained by continuous stirring of the reaction mixture and also by the use of various suspension stabilizers such as polyvinylalcohol and calcium phosphate. The free radical initiator employed is one which dissolves in the monomer phase, and polymerization is again achieved by a thermal fragmentation of the catalyst. During polymerization spherical liquid monomer droplets are converted into spherical solid polymer particles, often referred to as 'beads' or 'pearls'. Kinetically the system behaves simply as a bulk polymerization, with the gross volume broken down into tiny fragments. The bead product is readily collected by conventional filtration and washed free of stabilizer and other contaminants. After drying it is a free-flowing material and is conveniently handled on a large scale. Though the technique of

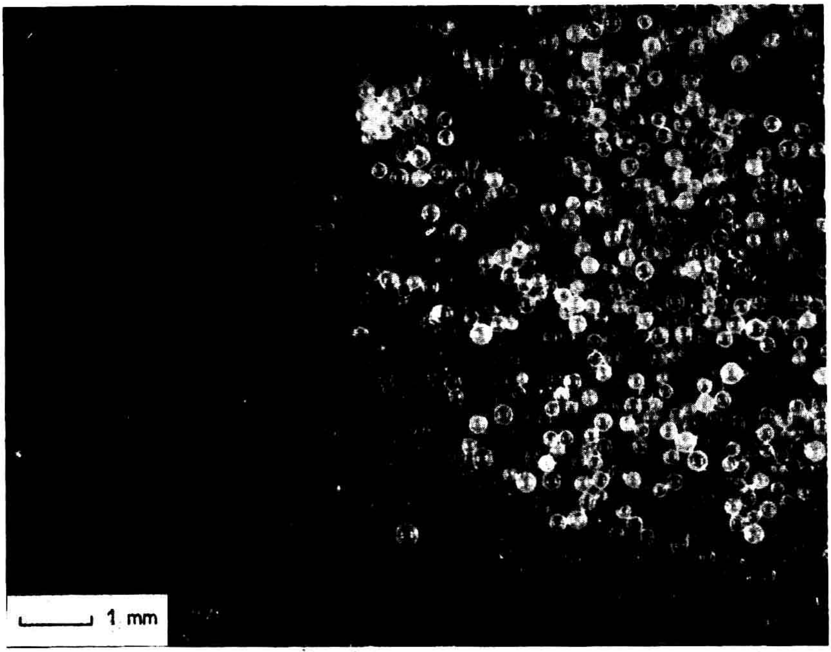


Figure 1 Styrene/divinylbenzene copolymer beads prepared by suspension copolymerization.

suspension polymerization tends to be somewhat of an art rather than a science, a number of fundamental principles have been developed and more detailed information is available in the Appendix.

1.2.2 Conformation of Linear Polymers in Solution

An organic macromolecule is generally a linear, long-chain species consisting of many monomeric units linked together. In an appropriate solvent such molecules can dissolve to form a true molecular solution. In this state the polymer chain generally exists as a random coil, which, depending on the thermodynamics of polymer/solvent interactions, may be highly expanded or tightly contracted.[14] A few macromolecules can exist in solution with more precise geometries, e.g. as a 'rigid rod'. Generally a highly compatible or good solvent will give rise to an expanded coil conformation, and as the solvating medium is made progressively worse the coil contracts and eventually precipitation takes place. In dilute solutions (approximately <2 per cent by weight) polymer coils are effectively separated; however, if the concentration is increased interchain