The Use of Insoluble Polymer Supports in Organic Chemical Synthesis

By C. C. Leznoff
DEPARTMENT OF CHEMISTRY, YORK UNIVERSITY,
DOWNSVIEW, ONTARIO, CANADA

1 Introduction

Insoluble polymer supports have been widely used as 'handles' to facilitate the synthesis of polypeptides,[1-3] polynucleotides,[4-6] and even polysaccharides.[7,8] The scope of the insoluble polymer support method of preparing peptides and even proteins was demonstrated in the synthesis of Ribonuclease A in an automated synthetic procedure.[9] The use of polymer supports in repetitive 'sequential-type' organic synthesis of polypeptides, essentially based on the joining of a few simple monomer units, has been adequately discussed elsewhere[10,11] and an excellent critical evaluation of this method as applied to polypeptide synthesis has been reported.[12]

It is only very recently that insoluble polymers have been used in general organic synthesis unrelated to repetitive 'sequential-type' syntheses of polypeptides, polynucleotides, and polysaccharides. It has now been found that insoluble polymers can be used for a wide variety of purposes to solve specific synthetic problems. In this review, the uses of insoluble polymers in solving some of these difficult synthetic problems are outlined and the advantages and disadvantages of organic synthesis on insoluble polymer supports compared with classical synthesis are described.

2 Polymeric Reagents

In many synthetic organic chemical procedures, a chemical reagent is used, which after reaction gives a by-product. This by-product can sometimes be difficult to separate from the desired product of the reaction. If the chemical

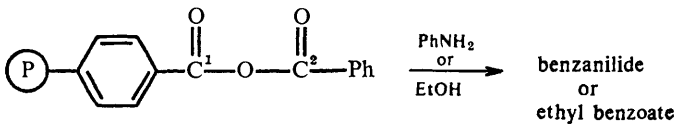
[1] R. B. Merrifield, *J. Amer. Chem. Soc.*, 1963, **85**, 2149.
[2] R. B. Merrifield, *Science*, 1965, **150**, 178.
[3] D. Yamashiro and C. H. Li, *J. Amer. Chem. Soc.*, 1973, **95**, 1310.
[4] R. L. Letsinger and V. Mahadevan, *J. Amer. Chem. Soc.*, 1966, **88**, 5319.
[5] F. Cramer and H. Koster, *Angew. Chem. Internat. Edn.*, 1968, **7**, 473.
[6] H. Koster, *Tetrahedron Letters*, 1972, 1527.
[7] J. M. Frechet and C. Schuerch, *J. Amer. Chem. Soc.*, 1971, **93**, 492.
[8] R. D. Guthrie, A. D. Jenkins, and J. Stehlicek, *J. Chem. Soc.* (*C*), 1971, 2690.
[9] B. Gutte and R. B. Merrifield, *J. Amer. Chem. Soc.*, 1969, **91**, 501.
[10] J. M. Stewart and J. D. Young, 'Solid Phase Peptide Synthesis,' W. H. Freeman, San Francisco, 1969.
[11] G. R. Marshall and R. B. Merrifield, in 'Biochemical Aspects of Reactions on Solid Supports,' Academic Press, New York, 1971.
[12] E. Wunsch, *Angew. Chem. Internat. Edn.*, 1971, **10**, 786.

reagent can be covalently linked to an insoluble polymer carrier and successfully used in organic synthesis, then the by-product of the reagent, after reaction, will remain attached to the insoluble polymer and can be separated from the desired product of reaction by simple filtration. This concept forms the basis for the recent syntheses of a number of polymeric reagents, described below according to their function.

A. Peracid Reagents.—One of the earliest reports on the use of insoluble polymers in organic synthesis involved the formation of an insoluble peracid reagent for use in epoxidation of olefins.[13] A cross-linked poly(methacrylic acid) was treated with a sulphonic acid and H_2O_2 to give a polymer containing *ca.* 0.005 ml of peracid/g of polymer. This insoluble peracid, on reaction with olefins, gave epoxides in high yield. The polymer could be re-used until all the peracid groups had reacted and could then be reconverted into the peracid form as before. The advantage of using this insoluble peracid reagent lies in the fact that the epoxide product can be obtained by simple evaporation of the solvent, the acid by-product remaining attached to the polymer.

B. Acetylating and Similar Reagents.—By use of a co-polymer of styrene, divinylbenzene, and benzoyl-isomaleimide, an insoluble polymer was formed, which on reaction with acid and acetic anhydride gave a polymer containing succinyl acetate groups.[14] This polymer, on reaction with cyclohexylamine, gave *N*-acetylcyclohexylamine in quantitative yield by simple filtration.

Letsinger's 'popcorn' polymer,[15] prepared from styrene, *p*-vinylbenzoic acid, and divinylbenzene, has been used for preparing insoluble anhydrides.[16] The insoluble acid polymer was converted into the acid chloride and treated with benzoic acid to give an insoluble polymer containing benzoic anhydride functional groups. This polymer, on reaction with aniline or ethanol, gives benzanilide or ethyl benzoate in high yield as shown in Scheme 1. For the products to have been obtained in high yield nucleophilic attack must have occurred exclusively



(1)

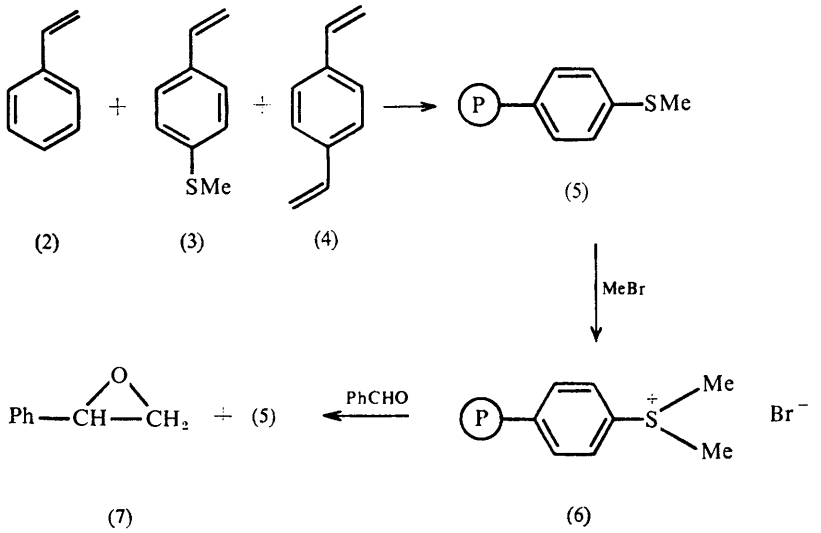
Scheme 1

[13] T. Takagi, *J. Polymer Sci., Part B, Polymer Letters*, 1967, **5**, 1031.
[14] Y. Yanagisawa, M. Akiyama, and M. Okawara, *J. Polymer Sci., Part A-1, Polymer Chem.*, 1969, **7**, 1905.
[15] R. L. Letsinger, M. J. Kornet, V. Mahadevan, and D. M. Jerina, *J. Amer. Chem. Soc.*, 1964, **86**, 5163.
[16] M. B. Shambhu and G. A. Digenis, *Tetrahedron Letters*, 1973, 1627.

at C-2. The authors suggest that steric hindrance at C-1 may be a cause of this unusual effect. This procedure may simplify the formation of some sensitive esters or amides, but to be effective the polymeric reagent should be used in large excess to ensure complete reaction of starting materials. If the polymer, containing anhydride functional groups, can be repeatedly regenerated after use, this procedure may be of some practical use.

C. Allylic Bromination.—Co-polymerization of maleimide and divinylbenzene, followed by addition of bromine, gave an insoluble polymer containing the *N*-bromosuccinimide moiety.[17,18] Unfortunately, reactions of polymeric bound NBS (PNBS) gave mixtures of polybrominated products. For example, PNBS on reaction with ethylbenzene gave 40% α-bromoethylbenzene and 31% α,β-dibromoethylbenzene. These PNBS polymers did not give high yields of allylic bromides when compared with the classical use of NBS, and the advantage of being able to filter off the succinimide bound to the polymer is offset by the low yields and multiple products of the reaction.

D. Ylide Reagents.—A dimethylsulphonium methylide attached to an insoluble polymer[19] has been used in the synthesis of styrene oxide, as shown in Scheme 2. This early example of an insoluble ylide reagent may be very useful in that the insoluble reagent, obtained after reaction, is re-generable for repeated reactions.

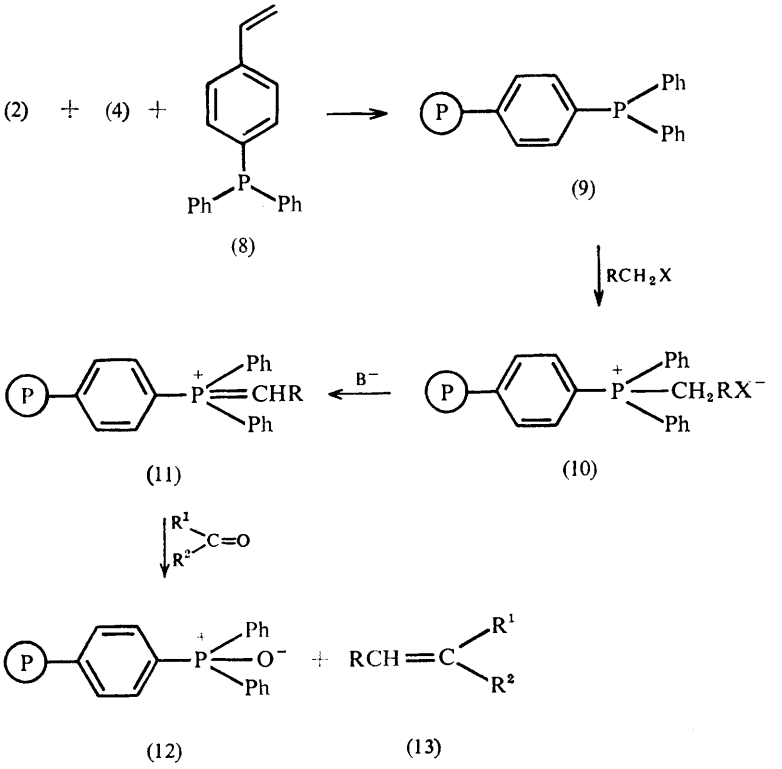


Scheme 2

[17] Y. Yanagisawa, M. Akiyama, and M. Okawara, *Kogyo Kagaku Zasshi*, 1969, **72**, 1399.
[18] C. Yaroslavsky, A. Patchornik, and E. Katchalski, *Tetrahedron Letters*, 1970, 3629.
[19] S. Tanimoto, J. Horikawa, and R. Oda, *Kogyo Kagaku Zasshi*, 1967, **70**, 1269.

One advantage in using the insoluble ylide in this case may be the use of a non-odourous polymeric reagent as compared with the handling of a noxious, volatile sulphide in the classical synthesis.

It is well known that, in the Wittig reaction, one complication that sometimes arises is the difficulty of separation of the Wittig product from the usual by-product, triphenylphosphine oxide. By attaching the Wittig reagent to an insoluble polymer, the triphenylphosphine oxide remains attached to the polymer after reaction and is simply filtered from the desired product. Polymer-bound Wittig reagents can be readily synthesized[20,21] by the co-polymerization of (2), (4), and *p*-styryldiphenylphosphine (8), as shown in Scheme 3. Wittig reagents similar to (11) were also prepared (i) by the reaction of sodium diphenylphosphine with the bromination product of a co-polymer of (2) and (4)[22,23] and (ii) by the reaction of chlorodiphenylphosphine on the reaction product of Bu^nLi with a copolymer of (2), (4), and *p*-bromostyrene.[21] The yields of olefins obtained in

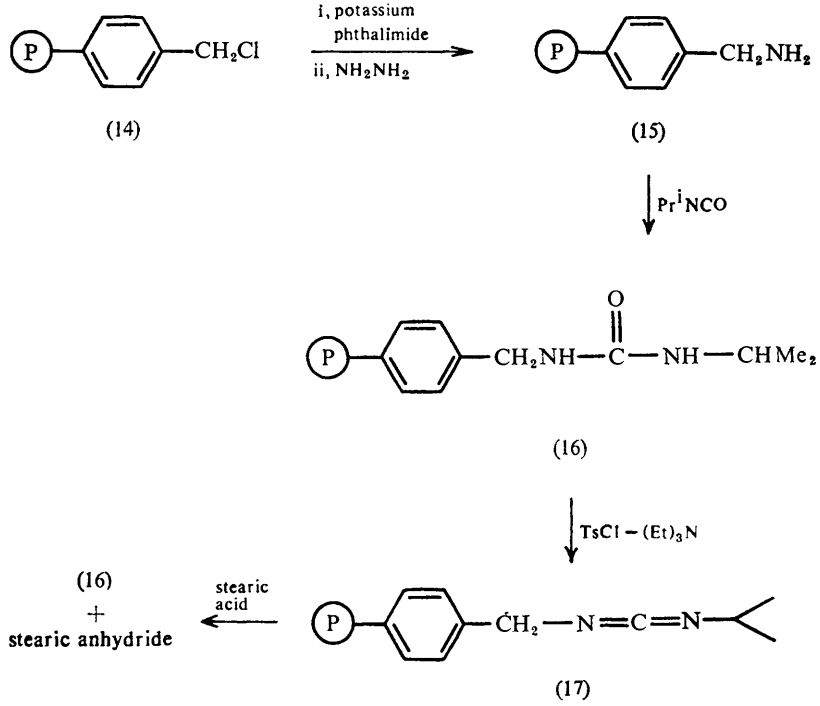


Scheme 3

[20] F. Camps, J. Castells, M. J. Ferrando, and J. Font, *Tetrahedron Letters*, 1971, 1713.
[21] S. V. McKinley and J. W. Rakshys, jun., *J.C.S. Chem. Comm.*, 1972, 134.
[22] W. Heitz and R. Michels, *Angew. Chem. Internat. Edn.*, 1972, **11**, 298.
[23] W. Heitz and R. Michels, *Annalen*, 1973, 227.

these reactions were similar to those of classical reactions, and recently the polymer-bound triphenylphosphine oxide (12) was reported to be readily converted into (9) and hence (11) for subsequent use in Wittig reactions.[23]

E. Condensation Reagents.—Carbodi-imides are used as condensing agents in the synthesis of peptides and nucleotides, and some insoluble polymer-bound carbodi-imide derivatives have been prepared for use in peptide synthesis.[24] Weinshenker and Chen[25,26] synthesized insoluble polymer-bound carbodi-imides for other purposes as outlined in Scheme 4. Polymer-bound (17) was used in the synthesis of anhydrides.[25] Simple filtration and evaporation of the solvent yielded the anhydride and provides a simple procedure for isolation of anhydrides from the reaction mixture. The use of polymer (17)[26] in the Moffatt oxidation[27] of alcohols gave good yields of aldehydes with the advantage that the by-product urea remains attached to the polymer and is removed by simple filtration. Polymer (16) recovered after reaction was reported to be readily converted back into (17) but suffered some loss of activity owing to the formation of *N*-acylureas.

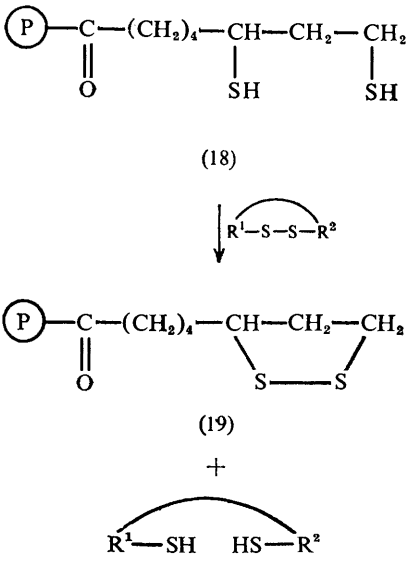


Scheme 4

[24] M. Fridkin, A. Patchornik, and E. Katchalski, in 'Proceedings of the 10th European Symposium on Peptides,' 1969, p. 166.
[25] N. M. Weinshenker and C. M. Chen, *Tetrahedron Letters*, 1972, 3281.
[26] N. M. Weinshenker and C. M. Chen, *Tetrahedron Letters*, 1972, 3285.
[27] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 5661, 5670.

An insoluble polymer incorporating 3,5-diethylphenylsulphonyl chloride groups, for use as a condensing agent in forming internucleotide bonds, has been prepared.[28] Thus, 3,5-diethylstyrene was co-polymerized with (4) and chlorosulphonated to give the desired poly-(3,5-diethylstyrene)-sulphonyl chloride, which was used in oligonucleotide synthesis. The advantage of using this insoluble polymeric reagent instead of soluble tri-isopropylbenzenesulphonyl chloride was due to the fact that no tri-isopropylbenzenesulphonic acid by-product contaminated the resulting nucleotide product. Classically, the by-product also caused emulsion problems eliminated by using the polymeric reagent. No mention was made of regenerating the polymeric reagent after the condensation was completed.

F. Disulphide Reducing Agent.—Very recently Gorecki and Patchornik[29] have synthesized polymers, based on Sephadex, Sepharose, cellulose, and polyacrylamide to which is attached dihydrolipoic acid. The polymeric dithiol reacts with disulphides (including proteins) to give the reduced protein or the thiols as shown schematically in Scheme 5. Polymer (19) can then be reduced for re-use.



Scheme 5

3 Polymeric Catalysts

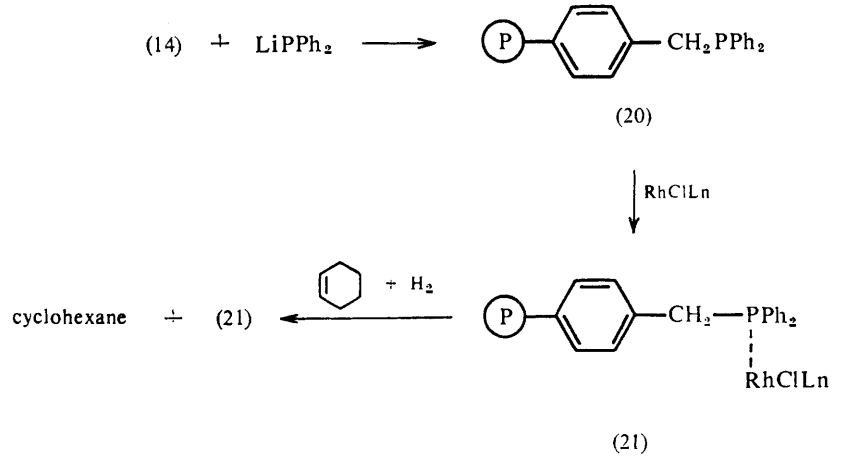
The use of both soluble and insoluble catalysts in chemical reactions is as old as chemistry itself, but recently several groups have attached some 'classical' catalysts to an insoluble organic polymer backbone. The isolation of catalytically

[28] M. Rubinstein and A. Patchornik, *Tetrahedron Letters*, 1972, 2881.
[29] M. Gorecki and A. Patchornik, *Biochim. Biophys. Acta.*, 1973, **303**, 36.

active monomeric species on an insoluble organic polymer backbone sometimes changes the specificity and activity of the catalyst from those observed when the catalyst is used independently of the polymer. Many catalysts on the insoluble matrix also show enhanced stability to hydrolysis and oxidation.

A. Hydrogenation Catalysts.—An ion-exchange resin, Amberlyst A 27 (in the $^-$OH form), reacted with K_2PdCl_4 to give an insoluble resin of low capacity that was capable of reducing cyclohexene, styrene, and nitrobenzene.[30] This polymer-bound catalyst was reported to be more active than a similar 'classical' catalyst. The resin was re-used eight times without serious loss of activity. The ease of recovery of the catalyst and its greater activity constitute advantages of the polymer-supported catalyst.

The attachment of a rhodium hydrogenation catalyst to a cross-linked polystyrene polymer was achieved by several groups[31–33] in a variety of similar ways, one of which[31] is shown in Scheme 6. The rhodium catalyst attached to the



Scheme 6

polymer appeared to be more selective than the normal catalyst; for example, polymer (21) reduced cyclohexene at a rate identical to the non-polymer-supported catalyst but reduced cyclododecene at 1/5 the normal rate and Δ^5-cholestene was reduced only very slowly. Careful selection of the type of polymer catalyst used is brought out by the results of Collman *et al.*,[32] whose polymer-

[30] R. Linarte Lazcanot and J. E. Germain, *Bull. Soc. chim. France*, 1971, 1869.
[31] R. H. Grubbs and L. C. Kroll, *J. Amer. Chem. Soc.*, 1971, **93**, 3062.
[32] J. P. Collman, L. S. Hegedus, M. P. Cooke, J. R. Morton, G. Dolcetti, and D. N. Marquardt, *J. Amer. Chem. Soc.*, 1972, **94**, 1789.
[33] M. Capka, P. Svoboda, M. Cermy, and J. Hetflete, *Tetrahedron Letters*, 1971, 4787.

bound rhodium hydrogenation catalyst exhibited much intermolecular aggregation, causing much reduced activity and thereby diminishing the usefulness of the catalyst. Another group[33] showed that hydrosilation and hydroformylation of olefins could also be achieved using polymer-supported rhodium catalyst.

Grubbs *et al.*[34] have recently prepared a titanocene attached to a 20% cross-linked chloromethylated polystyrene polymer for use as a hydrogenation catalyst. Because of the attachment of the titanocene complex to the insoluble polymer backbone, dimerization of the reduced titanocene complex was avoided. Thus the free titanocene complex was only 0.5 times as active as the polymer-bound catalyst and there is therefore an advantage in using the polymer-supported catalyst.

B. Aluminium Chloride Catalysts.—A cross-linked polymer of (2) and (4) reacted with $AlCl_3$.[35,36] This polymer-bound $AlCl_3$ was stable to the atmosphere and was used in the preparation of di(dicyclopropylmethyl) ether in high yield[35] compared with classical procedures, which gave high molecular weight by-products. Thus the polymer-bound catalyst is easier to handle and gives purer products in chemical reactions.

C. Photosensitizer Catalysts.—A polymer of (2) and (4) reacted with Rose Bengal to give an insoluble photosensitizer capable of acting as a catalyst in photosensitized oxidations.[37] An enol diether underwent photosensitized oxidation to give a diester. Cyclohexadiene added oxygen in the presence of the polymer and light to give the *endo*-peroxide, and an olefin gave a hydroperoxide in an 'ene' reaction. All these reactions gave products in yields similar to those in reactions using soluble Rose Bengal. In addition, the insoluble polymer can be repeatedly used without deterioration of activity. The advantage in this procedure again lies in the fact that the dye can be separated from the product by simple filtration.

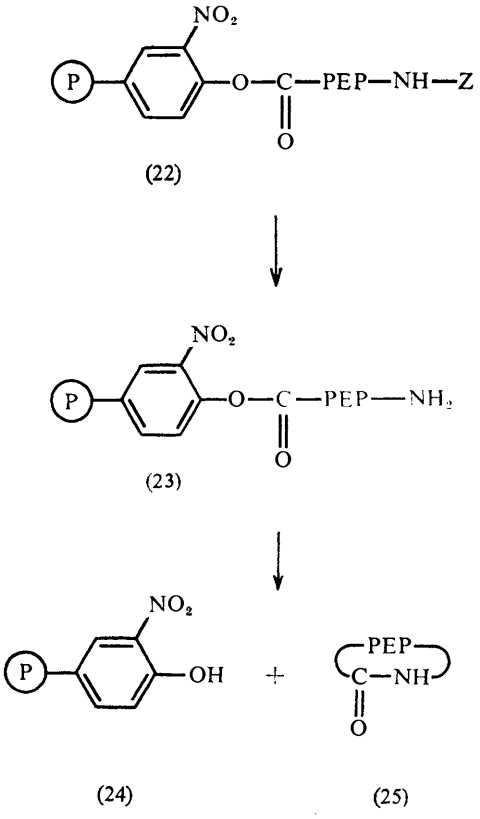
4 Polymers in Synthetic Applications

Very few reports have appeared in the literature in which insoluble organic polymer supports have been used in general organic synthesis, as mentioned in the Introduction. Each report describes the use of insoluble polymers in synthesis in quite unique ways and will be discussed separately below.

A. Synthesis of Cyclic Peptides.—The synthesis of macrocyclic compounds is a synthetic problem that has interested chemists for a long time and although macrocyclic compounds have been synthesized by acyloin condensations, Dieckmann condensations, and acetylene coupling reactions, for example,

[34] R. H. Grubbs, C. Gibbons, L. C. Kroll, W. D. Bonds, jun, and C. H. Brubaker, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2373.
[35] D. C. Neckers, D. A. Kooistra, and G. W. Green, *J. Amer. Chem. Soc.*, 1972, **94**, 9285.
[36] E. C. Blossey, L. M. Turner, and D. C. Neckers, *Tetrahedron Letters*, 1973, 1823.
[37] E. C. Blossey, D. C. Neckers, A. L. Thayer, and A. P. Schaap, *J. Amer. Chem. Soc.*, 1973, **95**, 5820.

yields are often low or unpredictable and often accompanied by linear and other cyclic by-products. The synthesis of macrocyclic peptides falls into this category and is really a problem different from peptide synthesis by the repetitive addition of monomer units. Fridkin *et al.* used an insoluble cross-linked poly-(4-hydroxy-3-nitrostyrene) (22) and treated it with protected peptides to give an insoluble polymer, containing an active ester group at one end of a peptide. Deprotection of the amino end of the peptide and intramolecular cyclization afforded cyclic peptides[38] as shown in Scheme 7. Insoluble polymers containing a limited num-



Scheme 7

ber of functional groups attached to the polymer backbone can be used in such a way as to conduct reactions at 'high dilution'.

The polymer-support method of synthesis of cyclic peptides thus favours

[38] M. Fridkin, A. Patchornik, and E. Katchalski, *J. Amer. Chem. Soc.*, 1965, **87**, 4646.

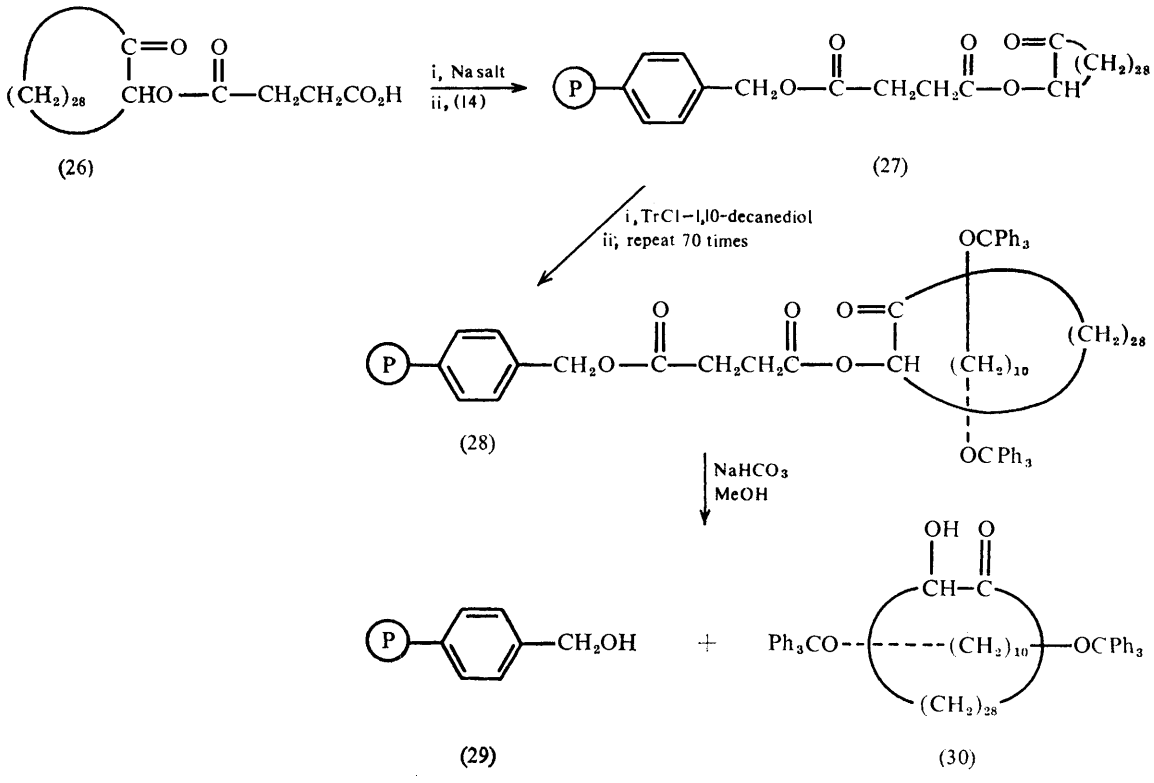
formation of cyclic monomers compared with the linear and cyclic oligomers formed in classical synthesis. No mention was made of using polymer (24) in further reactions. The active esters formed by reaction of (24) and protected amino-acids were subsequently used as polymeric reagents in polypeptide synthesis.[39]

B. Synthesis of a Threaded Macrocycle.—The synthesis of stable topological molecules such as catenanes[40] has been the goal of chemists for some time now, and although Schill[41] has synthesized such compounds, the synthetic routes have been long and arduous. Although Wolovsky[42] may have detected catenanes by a more direct route, the availability of simple catenanes in quantities greater than 1 mg remains a desirable goal.

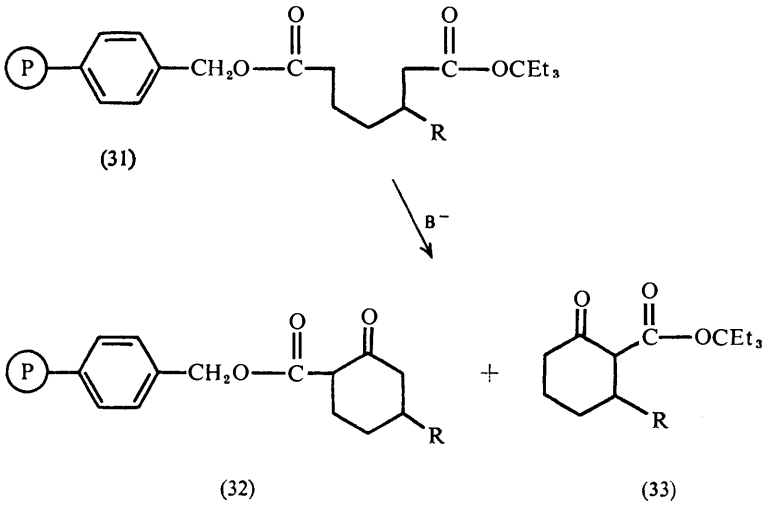
Harrison and Harrison[43] realized the potential of insoluble polymer supports in solving this problem. They reasoned that if a macrocyclic ring could be attached to an insoluble polymer, then a series of reactions could be attempted to thread the macrocycle to give stable topological compounds. Even if only a small percent of macrocyclic rings were threaded, undesirable, non-threaded by-products would simply be washed away from the polymer by filtration. This procedure could be repeated many times and even automated if desired to give a high yield of a threaded macrocyclic compound. Cleavage of the threaded macrocycle from the polymer would yield the desired topological molecule. Their procedure is outlined in Scheme 8. The threaded macrocycle (30) was obtained in 6% yield as an oil. This synthesis demonstrates the potential of using insoluble polymers (i) to 'fish out' a minor component of a complex reaction mixture and (ii) to concentrate that minor component by means of repetition of the critical reaction on a constant substrate.

C. Dieckmann Cyclization Reaction of Mixed Esters.—Although the base-induced cyclization of symmetrical diesters was well known. the Dieckmann cyclization of mixed esters had not been described previous to the report of Crowley and Rapoport.[44] They showed that a normal Dieckmann cyclization of a benzyl triethylmethyl diester yielded a mixture of keto-esters, inseparable by chromatographic methods. The use of polymer supports in the Dieckmann condensation of mixed esters affords two advantages: (i) the cyclization step gives higher yields owing to the 'diluent' effect of the polymer, previously mentioned (p. 73), and (ii) the mixture of keto-esters formed becomes automatically separated as one keto-ester becomes liberated into solution and the other remains attached to the insoluble polymer. Such a scheme is outlined in Scheme 9. Thus cyclization of (31) gave polymer-bound keto-ester (32) and soluble keto-

[39] M. Fridkin, A. Patchornik, and E. Katchalski, *J. Amer. Chem. Soc.*, 1966, **88**, 3164.
[40] E. Wasserman, *Sci. Amer.*, 1962, **207**, No. 11, p. 94.
[41] G. Schill, E. Logemann, and W. Vetter, *Angew. Chem. Internat. Edn.*, 1972, **11**, 1089.
[42] R. Wolovsky, *Chem. Abs.*, 1972, **76**, 3466m.
[43] I. T. Harrison and S. Harrison, *J. Amer. Chem. Soc.*, 1967, **89**, 5723.
[44] J. I. Crowley and H. Rapoport, *J. Amer. Chem. Soc.*, 1970, **92**, 6363.


i, Na salt
ii, (14)
(26)
(27)
i, TrCl–1,10-decanediol
ii, repeat 70 times
(28)
NaHCO3
MeOH
(29)
(30)

Scheme 8



Scheme 9

ester (33). If R is a bulky ethyl group, the cyclization step is retarded and gives the liberated keto-ester in only 15% yield compared with 46% when R is H.

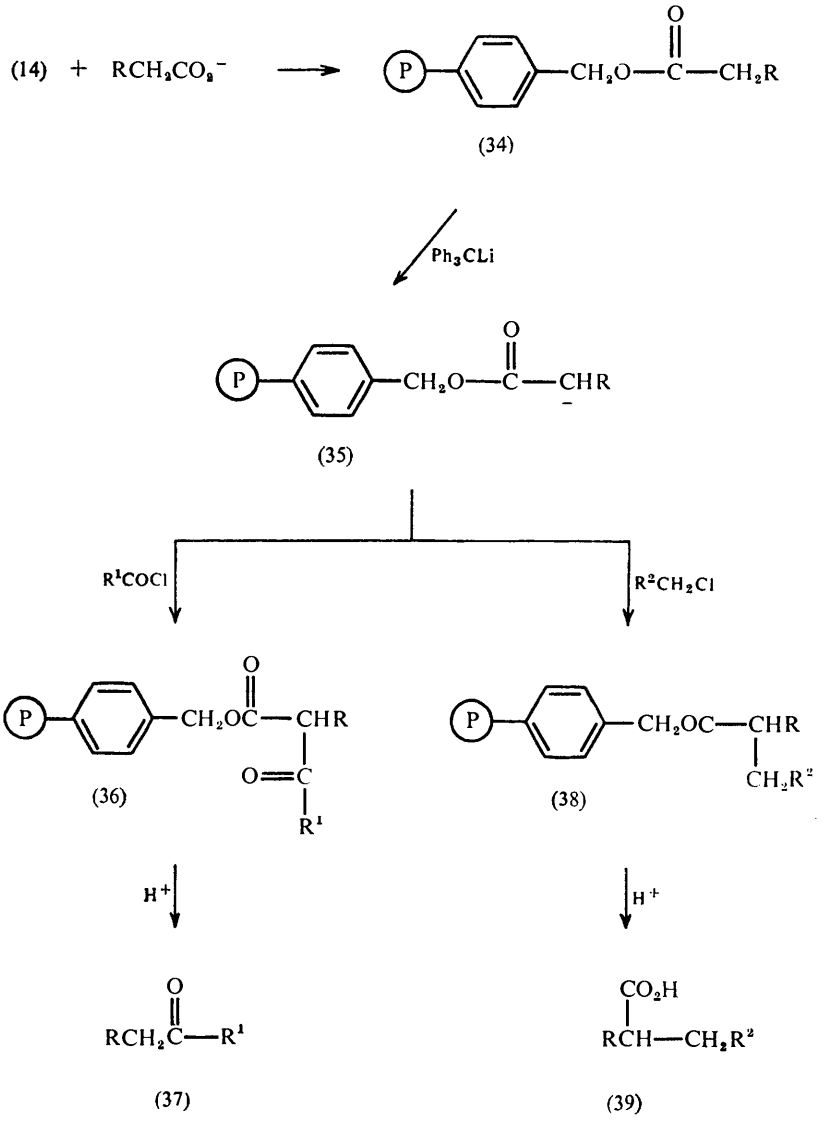
D. Monoacylation and Alkylation of Esters.—When attempting to monoacylate or monoalkylate an ester, common competing reactions which tend to lower yields are self-condensation of the ester and diacylation or dialkylation.

Insoluble polymer carriers can be used to prevent these competing side reactions. By incorporating an ester on an insoluble polymer carrier, the ester becomes immobilized and isolated, thereby existing in an environment of 'high dilution'. The isolation of the esters prevents self-condensation. In addition, the reaction of the polymer-bound ester with one equivalent of base produces stable monoanions that cannot undergo self-condensation and can thus react with acyl or alkyl halides to give monoacyl or alkylated products[45,46] as shown in Scheme 10.

Alkylation of an ester on a cross-linked polystyrene polymer containing β-phenylethanol groups has also been accomplished.[47] Dialkylation of a malonic diester [attached to (14) *via* the salt of the monoester] with α,ω-dibromoalkanes was reported to give good yields of five- and six-membered-ring carbocycles.[45]

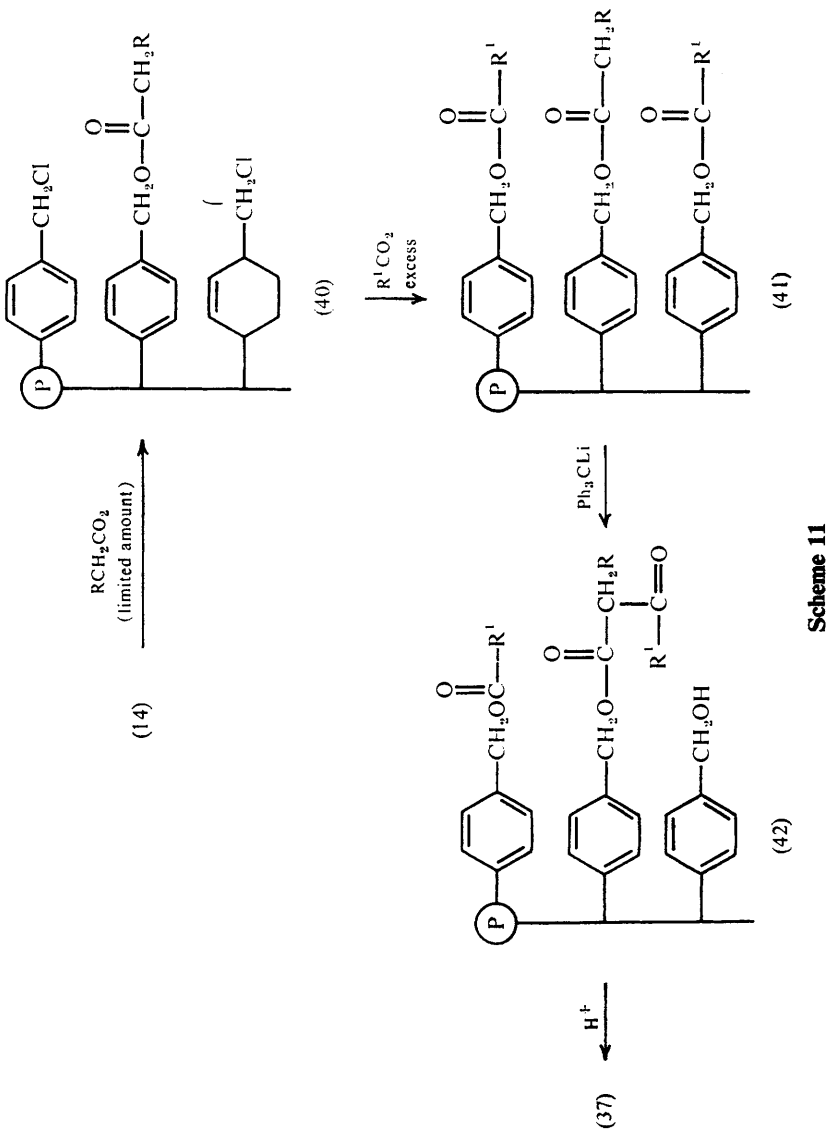
One problem in the use of insoluble polymers in ester condensations was clearly demonstrated by Patchornik and Kraus,[48] who showed that when a polymer was highly loaded (1.5 mmol g^{-1}), the possibility of intramolecular self-

[45] A. Patchornik and M. A. Kraus, *J. Amer. Chem. Soc.*, 1970, **92**, 7587.
[46] M. A. Kraus and A. Patchornik, *Israel J. Chem.*, 1971, **9**, 269.
[47] F. Camps, J. Castells, J. Font, and F. Vela, *Tetrahedron Letters*, 1971, 1715.
[48] M. A. Kraus and A. Patchornik, *J. Amer. Chem. Soc.*, 1971, **93**, 7325.



Scheme 10

condensation became a reality. In an elegant synthesis of a mixed ester condensation of an enolizable and a non-enolizable ester, this problem was used to advantage as shown in Scheme 11. Thus an intrapolymeric reaction was carried out leading



Scheme 11

to high yields of the unsymmetrical ketones (37). The lower the concentration of the enolization ester compared with that of the non-enolizable ester, the higher the yield of ketone. As a suitable loading capacity of the polymer is reported to be only 0.1 mmol g^{-1} for the enolizable ester, then insufficient

capacity diminishes the usefulness of this method. By use of one polymer containing an enolizable ester and another containing a non-enolizable ester, under identical reaction conditions as before, it was clearly demonstrated that intermolecular reactions between two insoluble polymers did not occur. It has always been assumed to be highly unlikely that two insoluble moieties would react and this concept was re-affirmed in this instance.

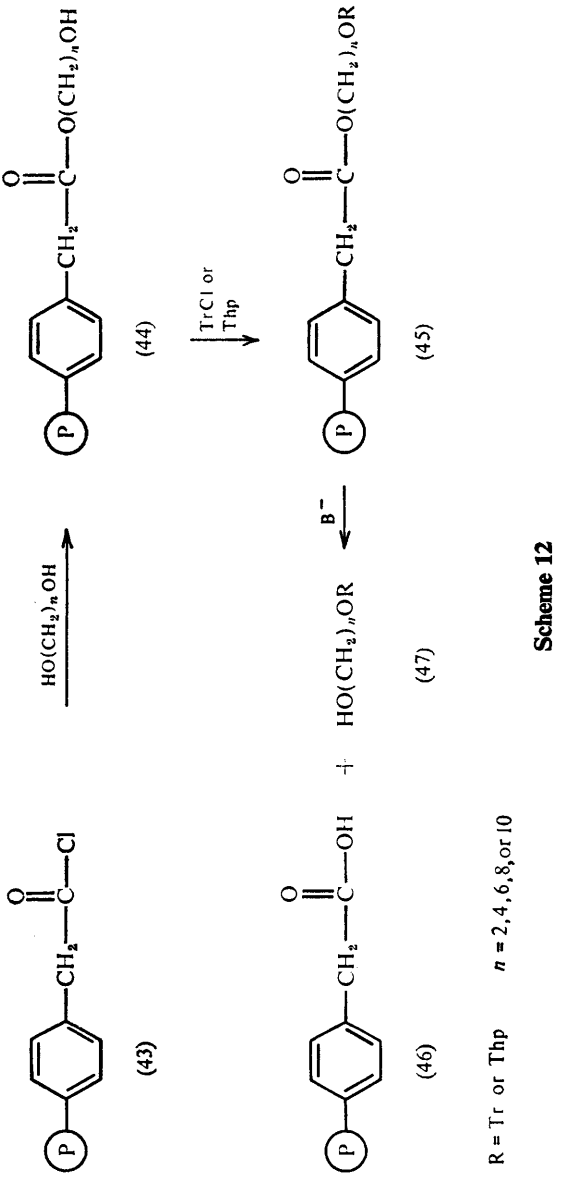
E. Monoreactions on Symmetrical Bifunctional Compounds.—Chemical reactions performed on symmetrical bifunctional compounds are straightforward provided one wishes both functional groups to undergo reaction. If it is desired that only one functional group react in a synthetic scheme, direct reaction of 1 equivalent of bifunctional compound and 1 equivalent of reagent invariably gives a mixture of unreacted starting material, over-reacted product, resulting from reaction at both functional groups, and the desired monoreacted product. For these reasons symmetrical bifunctional compounds are not often used in organic syntheses. Although blocking groups are often used in the course of organic synthesis, no general blocking group capable of reacting with only one functional group of a completely symmetrical bifunctional compound was available. Insoluble polymer supports have now been used as blocking groups for this purpose and facilitate the use of readily available symmetrical bifunctional compounds in organic synthesis.[49–51] As a functionalized insoluble polymer can provide an environment of 'high dilution', reaction of a large excess of a symmetrical bifunctional compound with this polymer ensures that only one of the functional groups reacts with the polymer. In addition, the mono-blocked symmetrical bifunctional compound can be simply filtered from the excess of symmetrical bifunctional compound used.

Symmetrical diols have been shown to react exclusively at one alcohol function with a cross-linked polystyrene polymer containing acid chloride functional groups,[52] to give an insoluble mono-blocked diol capable of further reaction at the free alcohol end. Reaction of this polymer with trityl chloride[49] or tetrahydropyran (Thp)[50] gave the appropriate ethers as shown in Scheme 12. Liberation of the ethers from the polymer by treatment with base gave mono ethers from symmetrical diols plus a polymer containing carboxylic acid groups (46).

The polymer (43) was regenerated from (46) by treatment with thionyl chloride, but the regenerated (43) had only one-half the capacity of first-prepared (43). Thus a polymer-support method was shown to be useful (i) as a blocking agent for symmetrical diols, and (ii) as a means of organic synthesis of monoethers from symmetrical diols, although the yields of the reaction were only adequate and the polymer was not suitable for re-use.

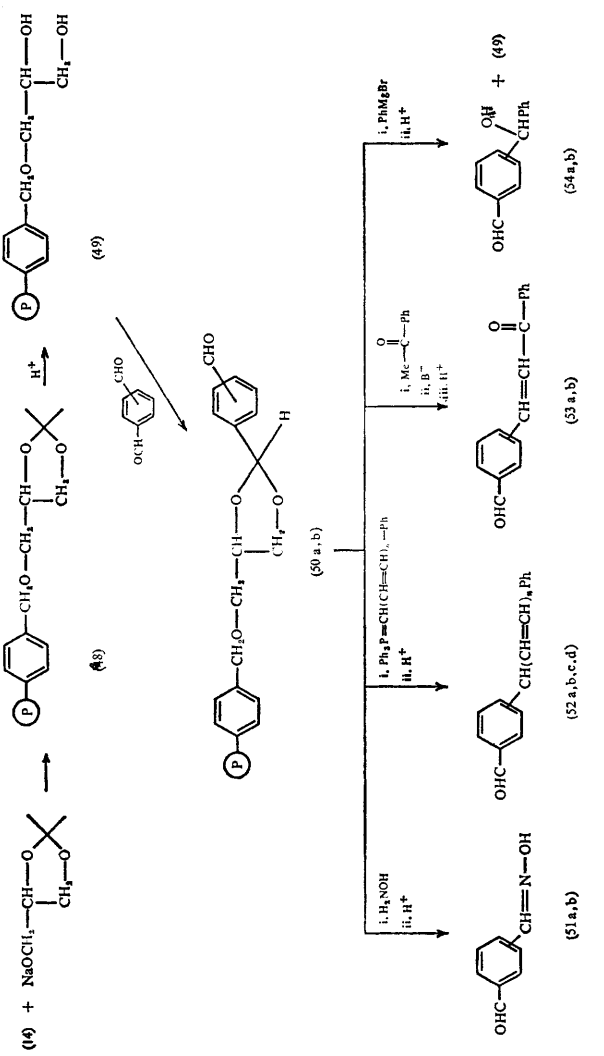
Leznoff and Wong[51] have recently prepared an insoluble polymer containing

[49] C. C. Leznoff and J. Y. Wong, *Canad. J. Chem.*, 1972, **50**, 2892.
[50] J. Y. Wong and C. C. Leznoff, *Canad. J. Chem.*, 1973, **51**, 2452.
[51] C. C. Leznoff and J. Y. Wong, *Canad. J. Chem.*, 1973, **51**, 3756.
[52] T Kusama and H. Hayatsu, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 319.



Scheme 12

a diol functional group for use as a mono-blocking agent of symmetrical dialdehydes. The free aldehyde group was then used in a variety of reactions to prepare largely unknown formyl-substituted compounds as outlined in Scheme 13.



Scheme 13

Thus reaction of polymers (50a) and (50b) with hydroxylamine followed by acid cleavage from the polymer gave the rarely known mono-oxide of terephthalaldehyde (51a) and the unknown mono-oxime of isophthalaldehyde (51b). Similarly, the Wittig reactions of (50a) and (50b) with benzylphosphonium reagents gave, after acid hydrolysis, *p*- and *m*-formylstilbenes (52a) and (52b) respectively, and with cinnamylphosphonium reagents 1-*p*- and 1-*m*-formylphenyl-4-phenylbuta-1,3-dienes (52c) and 52d) in high yields respectively. Some

of these products were previously unknown despite much research on the photocyclization reactions of substituted stilbenes[53] and substituted 1,4-diphenylbuta-1,3-dienes.[54] Similarly, the Grignard reaction of phenylmagnesium bromide on (50a) and (50b) gave, respectively, after acid hydrolysis from the polymer, *p*- and *m*-formylbenzhydrols (54a) and (54b), unknown compounds in quantitative yield. The crossed aldol condensation of (50a) and (50b) with acetophenone similarly gave *p*- and *m*-formylchalcones, (53a) and (53b) in quantitative yield, despite the fact that ethanol, a 'poor' solvent for swelling the polymer, was used as solvent for the reaction. The syntheses of the mono-oximes, the formyl stilbenes and butadienes, the formylbenzhydrols, and the formylchalcones by the solid-phase method demonstrate that insoluble polymers can be used (i) as a practical recommended procedure for the synthesis of formyl substituted compounds, and (ii) as a means of blocking one group of symmetrical bifunctional compounds. In addition, polymer (49) was liberated after reaction and used repetitively without serious deterioration.

5 Advantages and Problems of Insoluble Polymer Support Methods in Organic Synthesis

A. Advantages.—(1) One of the main advantages of synthesis on insoluble polymer supports was exploited in polypeptide synthesis,[1] namely, that the normal procedures of organic chemistry, especially solvent extraction and separatory flask manipulations, are omitted, which permits the possibility of synthetic chemistry being automated. The solid-phase synthetic method also allows excesses of reagents and substrates to be separated from the reaction product by simple filtration, thus avoiding complex chromatographic procedures.

(2) The automatic removal of a by-product of a chemical reagent by virtue of the reagent's attachment (and hence also the by-product) to an insoluble polymer has been exploited (see Section 2). This by-product could often be reconverted into the original valuable reagent.

(3) Another property of insoluble functionalized polymers that has been used to advantage is the fact that the insoluble polymer has a different steric and polar environment from solution analogues. This property has been especially exploited in using polymer supports as hydrogenation and Lewis acid catalysts (see Section 3). A polymer anhydride[16] acts differently from its solution analogue and the Dieckmann condensation proceeds more selectively on the polymer carrier.[44]

(4) The advantage of using a functionalized insoluble polymer to 'fish out' a desired minor component from the bulk of a reaction product was demonstrated in the synthesis of a threaded macrocycle.[43]

(5) The use of insoluble functionalized polymers as an alternative means of carrying out reactions under conditions simulating 'high dilution' is an important

[53] E. V. Blackburn and C. J. Timmons, *Quart. Rev.*, 1969, **23**, 482.
[54] C. C. Leznoff and R. J. Hayward, *Canad. J. Chem.*, 1970, **58**, 1842.

advantage. The synthesis of cyclic peptides[37] and the Dieckmann condensation[44] are examples of the utilization of this advantage.

(6) Insoluble functionalized polymers can be used to serve the concurrent functions of 'immobilization' of the substrate to the polymer (advantage 1) and that of simulating 'high dilution' conditions (advantage 5). This concept was advantageously used in the monoacylation[45] and monoalkylation[46,47] of esters, in the blocking of one functional group of symmetrical bifunctional compounds,[49–51] and in the preparation of an active monomeric species of reduced titanocene.[34]

(7) The simulation of 'hyperenteropic' conditions by the use of insoluble functionalized polymers was used to advantage in the condensation of an enolizable with a non-enolizable ester, both attached to the same polymer.[48]

(8) The flexibility of attaching and interconverting a wide variety of functional groups on a preformed insoluble polymer has been used to advantage for attaching many different types of substrates to the polymer. This flexibility was utilized recently in (*a*) attaching a sugar moiety to an insoluble polymer and performing an asymmetric synthesis of atrolactic acid with regeneration of the polymer[55] and (*b*) in preparing an insoluble polystyrene polymer, containing an optically active amino-acid copper complex for use in the preparative chromatographic separation of DL-amino-acids.[56,57]

B. Problems and Discussion.—One of the major limitations of solid-phase syntheses of polypeptides results from the necessity that reactions should proceed to 100% completion.[12] The number of synthetic steps in a typical synthesis of a polypeptide is very high and this requirement for quantitative reactions may not be as necessary for other synthetic uses of functionalized insoluble polymers. Thus final cleavage of the polypeptide from the polymer can give a series of closely related peptides, inseparable by chromatography. In other synthetic schemes, final cleavage should give compounds having a wide variety of molecular weights and properties and easily separable by chromatography.

In the final step of any synthesis on insoluble polymers, it is necessary to cleave the synthesized product from the polymer. This cleavage step sometimes causes difficulties in that incomplete cleavage (perhaps resulting from steric hindrance of the polymer) occurs or that too vigorous conditions for cleavage are used resulting in some decomposition of the product. The cleavage step remains a difficult problem and should be carefully examined before embarking on any synthetic scheme.

The stability of the polymers used in synthetic schemes and as polymeric reagents is an important problem. Ideally, the polymers should be recovered after use and simply regenerated in a usable form many times over. Although this capability has been achieved in some cases,[13,19,23,29,30,51] degeneration of the polymer has also been noted.[26,50] More stable, non-degradable polymers will

[55] M. Kawama and S. Emoto, *Tetrahedron Letters*, 1972, 4855.
[56] S. V. Rogozhin and V. A. Davankov, *Chem. Comm.*, 1971, 490.
[57] R. V. Snyder, R. J. Angelici, and R. B. Meck, *J. Amer. Chem. Soc.*, 1972, **94**, 2660.

have to be found before some of these polymer-support methods find wider general use. There is no doubt that special problems require special polymers and a polymer suitable for polypeptide synthesis will not be suitable for polynucleotide synthesis (which may require a more polar polymer) or macrocyclic condensations (which may require a more rigid polymer).

The role of the solvent plays an important part in chemical reactions on insoluble polymer supports and it is generally thought that reactions should be done in 'good' solvents like dimethylformamide, pyridine, and benzene, which swell the polymer, and avoided in 'poor' solvents like ethanol, methanol, and dioxan–alcohol. This generally accepted limitation should be carefully examined for each attempted reaction as a recent report[51] has demonstrated the synthesis of formylchalcones on an insoluble polymer in ethanol in almost quantitative yield.

The capacity of the polymer for an organic substrate may not be an important limitation in polypeptide synthesis on insoluble polymer supports, but a polymer capable of a certain minimum loading is essential when generally applied to preparative organic chemistry. For example, silica gel was successfully used as an inorganic insoluble polymer support for peptide synthesis,[58] but its very low capacity makes its use in other applications unlikely.

Another problem that arises in the use of polymer supports in peptide and organic synthesis involves the possibility of intrapolymeric attack of one moiety attached to one part of the polymer on another moiety on an adjacent or remote part of the polymer.[45,48] Careful selection of a polymer with a suitable loading capacity should allow this problem to be easily controlled.

It was previously mentioned that the steric effect of the polymer backbone can be used to advantage for some synthetic purposes. More often the insoluble polymer imparts a certain 'steric hindrance' to reaction which varies with the substrate and reactions attempted. The Dieckmann condensation[44] gave reduced yields of products as the substrates became more bulky and the yields of *m*-formyl compounds were consistently lower (although still good) than those of related *p*-formyl compounds.[51] It is likely that steric hindrance due to the bulky polymer backbone resulted in lower yields in these reactions and this problem may be a difficult one to overcome in some synthetic schemes.

The difficulty of determining exactly the course and extent of a chemical reaction on insoluble polymer supports has long been a problem in solid-phase peptide synthesis.[59–62] I.r. spectroscopy of KBr pellets of the insoluble polymer and cleavage of the substrate from the insoluble polymer after every reaction represent two methods of following chemical reactions on insoluble supports. The former method is not universally applicable, because only transformations which involve change of functional groups and which have intense i.r. absorption

[58] E. Bayer, G. Jung, I. Halasz, and I. Sebastian, *Tetrahedron Letters*, 1970, 4503.
[59] J. Garden, jun. and A. M. Tometsko, *Analyt. Biochem.*, 1972, **46**, 216.
[60] A. M. Felik and M. H. Jimenez, *Analyt. Biochem.*, 1973, **52**, 377.
[61] W. S. Hancock, D. J. Prescott, P. R. Vagelos, and G. R. Marshall, *J. Org. Chem.*, 1973, **38**, 774.
[62] A. M. Tometsko, *Biochem. Biophys. Res. Comm.*, 1973, **50**, 886.

can be readily followed. This method also is not quantitative. The latter method presents a clearer idea of the quantitative yields of every reaction, but it is time-consuming and sometimes unreliable if the cleavage step itself is not quantitative. Other methods of following the course of peptide synthesis on insoluble supports have also been reported.[63,64]

6 Conclusion

The use of functionalized insoluble polymers in general organic synthesis will undoubtedly greatly increase owing to the many advantages that this procedure affords. The selection and synthesis of new, more suitable, polymers and their applications in synthetic schemes will provide the basis for much research in the years to come.

The author is grateful to the Weizmann Institute of Science for providing facilities helpful in the preparation of this review.

[63] B. F. Gisin, *Analyt. Chim. Acta*, 1972, **58**, 248.
[64] H. B. Stegmann, H. Breuminger, and K. Scheffler, *Tetrahedron Letters*, 1972, 3793.