RECENT ADVANCES IN THE USE OF POLYMERS AS CHEMICAL REAGENTS

A. Patchornik and M. A. Kraus

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Abstract—Some recent developments in the preparation of polymeric reagents and their use in various chemical reactions are described. Improved polymeric acyl transfer reagents were prepared. They possess good mechanical properties and are therefore easy to handle and pure products are obtained by their use. With one of these polymeric reagents pure peptides may be obtained in high yield in reactions lasting only 10–30 min. Polymeric alkylating and condensing agents are described. Specific polymeric chelating agents were obtained by impregnating macroporous polymers by the appropriate chelating compounds. The use of polymers as protecting groups in synthesis is discussed. Recent results on the simultaneous use of two different polymeric reagents for analytical and synthetic purposes are cited.

The use of polymers as chemical reagents has increased greatly in recent years. The main types of polymeric reagents developed have been polymer bound catalysts (biological and non-biological), specific polymeric adsorbents for biologically active compounds and for metal ions, polymeric transfer agents and polymeric carriers for peptide synthesis and other organic syntheses.[1] Polymers have also been used as immobilizing media and as means for separating different active species from each other.[1]

In this article some recent developments in the field of polymeric reagents will be discussed.
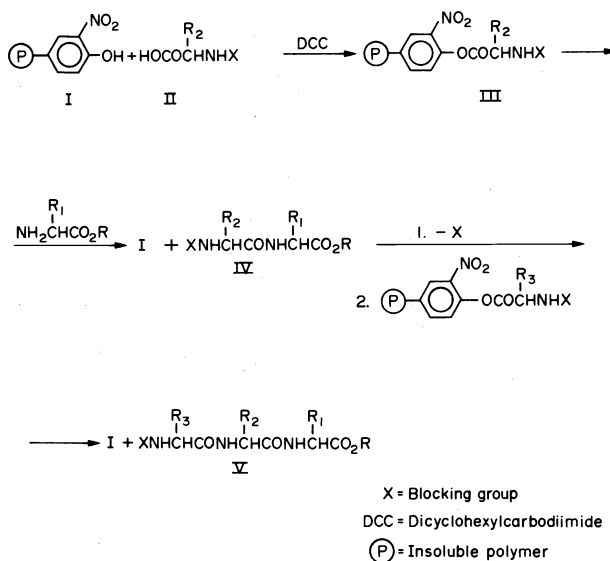
Polymeric acyl transfer agents have been suggested as efficient reagents for peptide synthesis.[2] Their use is outlined in Scheme 1.

Polymeric active esters of N-blocked amino acids (III) are treated with soluble, C-blocked amino-acids or peptides. The product peptide is obtained in solution and may be separated from the reaction mixture by filtering off the polymer. An excess of the insoluble polymeric reagent III may be employed and thus high yields of products IV, V are obtained. The first polymer of type I prepared was cross linked poly(3-nitro-4-hydroxystyrene). Considerable yields of peptides as long
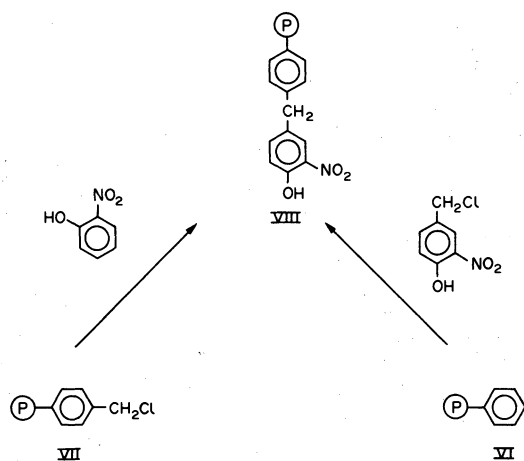
as bradykinin could be obtained by its use.[3] However improved polymeric carriers were sought because of a number of disadvantages inherent to the use of the above polymeric reagents. They are powdery and are thus often difficult to filter and wash; a more convenient physical form such as beads was desirable. Some of these polymeric reagents disintegrate partially, liberating fine particles into solution; a polymer backbone more stable mechanically and chemically was needed. The above polymers are capable of swelling only in a limited number of solvents thus making the accessibility of the reactive sites very solvent dependent. A polymer possessing high accessibility irrespective of solvent or at least in a large number of solvents was sought. Reactions utilizing the above polymers were sometimes much slower than similar reactions with soluble active esters. Polymers of higher reactivity are desirable for faster reactions.

The synthesis of an improved nitrophenol polymer is described in Scheme 2.

The best synthetic route was found to be the Friedel–Crafts alkylation of polystyrene in bead form by 4-hydroxy-3-nitrobenzyl chloride.[4] The good mechanical properties of the starting polymers (VI, commercial
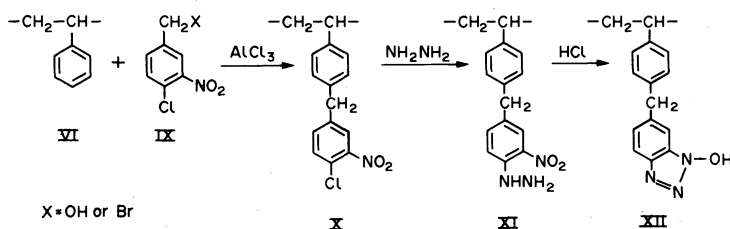
X = Blocking group

DCC = Dicyclohexylcarbodiimide

℗ = Insoluble polymer

Scheme 1.

Scheme 2.

dry. Acylations using these polymeric active esters were indeed found to be very fast and were usually complete within 10–30 min. A comparison of hydroxybenzotriazole polymer(PHBT) with hydroxynitrobenzyl polystyrene (PHNB) in the synthesis of the same peptide—one containing many bulky amino-acids—is given in Scheme 4.

Scheme 4. Comparative preparation of a "problematic" tetrapeptide.

polystyrene-2% divinylbenzene or macroporous polystyrene XE-305, Rohm and Haas) are retained. The polymeric active esters may be used in a large number of solvents. Amino acids may be attached to the polymer at high concentrations and reaction rates are of the same order as those of reactions with similar soluble esters. Usually pure peptides are obtained simply by filtration and evaporation of the solvent. A protected derivative of the luteinizing hormone-releasing hormone (LH-RH) was prepared recently using the improved polymeric nitrophenol active esters in 69% overall yield.[5]
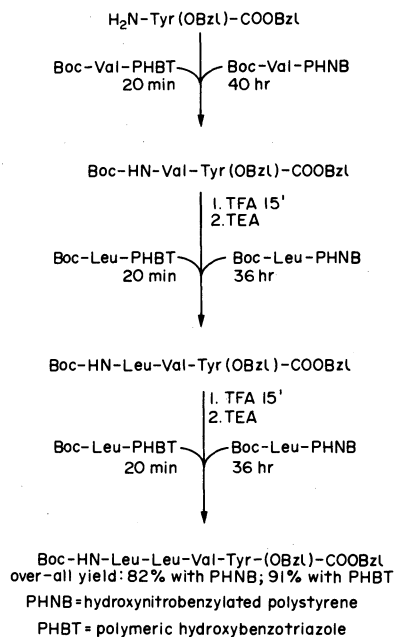
In spite of the clear advantage of the improved polymeric active esters over those used previously, some further improvement was desired. It was observed that peptide coupling rates were markedly reduced when bulky amino acids such as valine or leucine were situated at the amino terminus of the growing peptide chain or were used as the polymer activated carboxylic components. The synthesis of 1-hydroxybenzotriazole-containing polymers was therefore undertaken. (It is well known that hydroxybenzotriazole esters of amino acids are highly active acylating agents.) The synthesis is described in Scheme 3.

Commercial polystyrene-2% divinylbenzene (DVB) or macroporous polystyrene (XE-305) in bead form are treated with 3-nitro-4-chlorobenzyl bromide. The product is treated with hydrazine and cyclization of the substituted hydrazine XI yields the desired polymeric hydroxybenzotriazole.[6] The polymer derived from polystyrene-2% DVB swells well in dimethylformamide, dichloromethane and chloroform. The macroporous polymer, in which accessibility is less solvent dependent, may also be used with water containing organic solvents. Amino acid esters of these polymers were easily obtained and were found to be stable for extended periods when stored

The difference between the two polymers may clearly be seen. While reactions of 36–40 hr are necessary with the PHNB polymers, PHBT polymers were reacted for only 20 min. Moreover, the overall yield with PHBT was higher than with PHNB. PHBT can be used successfully both in micro scale syntheses (10 μmol) and in large scale preparations (10–20 mmol).

Recently polymeric alkyl transfer agents were prepared.[7] The synthesis is described in Scheme 5.

These polymers offer advantages similar to those of other polymeric reagents, namely insolubility and ease of separation of excess reagent. The use of such polymeric reagents is exemplified in Scheme 5 in the alkylation of phenol.

A polymeric sulfonyl chloride was used as a condensing agent in dinucleotide synthesis[8] as described in Scheme 6.

Common difficulties in similar syntheses utilizing soluble sulfonyl chlorides were eliminated by using the polymeric reagents. Thus little sulfonation of R'OH was observed and no difficulty was encountered in removing the sulfonic acid formed in the reaction.

Scheme 3. Preparation of polystyrene-bound 1-hydroxybenzotriazole.
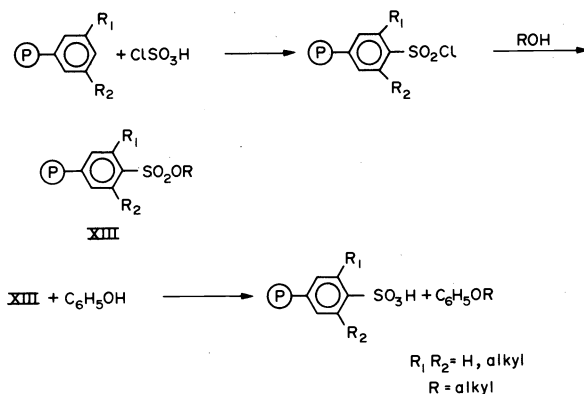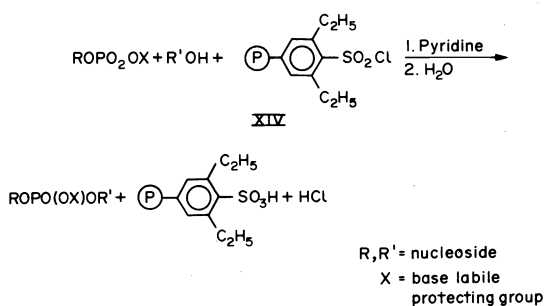
Scheme 5.

Scheme 6.

Metal chelates with polymeric ligands have been known for some time. For example, a polymeric Schiff base was shown to form chelates with zinc, copper, iron, nickel and cobalt ions.[9] Polyvinlyamine yields chelates with copper, nickel, zinc and cobalt.[10] A copper chelate could be obtained from poly(acryloyldiethylamlonate).[11] Poly(4-vinylpyridine)[12] and poly(2-vinylpyridine)[13] form complexes with various transition metal ions. Crown-ether containing polymers are capable of complexing alkali metal ions.[14]

Recently a potentially simpler and more versatile method of obtaining chelating polymers was suggested. In this method the chelating group is neither incorporated into the polymer backbone nor chemically attached to it, but is impregnated on the surface of the polymer (usually of the macroporous type). Thus for example a polymeric reagent highly selective for gold (in the presence of platinum group metals) could be obtained by impregnating a macroporous polymer with diethyleneglycol dibutyl ether.[15a]
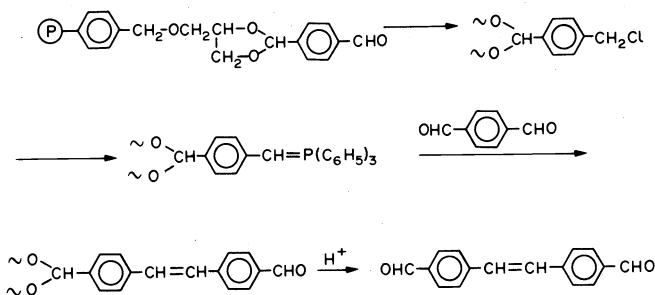
Similarly a selective chelating agent for palladium was obtained by impregnating macroporous polystyrene with β-diphenylglyoxime.[15b]

It should be noted that physical adsorption is an attractive alternative to covalent binding of reactive moieties to a polymeric backbone in the preparation of polymeric reagents. Also other modes of binding such as that present in graphite inclusion compounds have been used recently.[16]
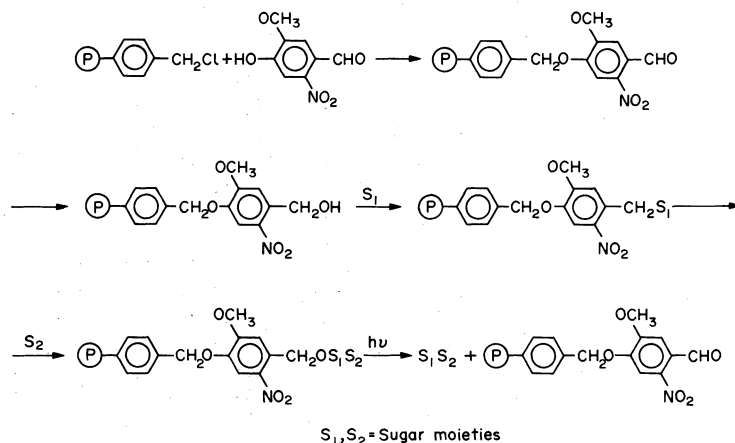
Polymers have been used recently as protecting groups in synthetic chemistry. In one approach one functional group of a symmetrical bifunctional molecule is protected by the polymer while the other group which remains free is elaborated chemically. The originally protected group is then reexposed by detaching the product from the polymer.[17] An example of such a sequence[18] is given in Scheme 7.

In another approach the polymer acts as a photosensitive protecting group. An ortho nitrobenzyloxy group may be photooxidized to the corresponding nitroso aldehyde. The synthesis of a polymeric nitrobenzyl alcohol is described in Scheme 8. This polymer was used in the sequential synthesis of a disaccharide as described in the Scheme. The product was cleaved from the polymer by irradiation.[19]

Another novel approach to polymeric reagents utilizes the fact that two compounds, which usually react with each other, are made mutually inert by attachment to two batches of insoluble polymer respectively.[20] Use was recently made of two polymeric reagents in an elegant method to demonstrate the existence of reactive intermediates in reactions.[21] This is shown in Scheme 9. The cyclobutadiene precursor polymer (XV) was treated with Ce^{4+} in the presence of the trapping polymer (XVI). The formation of polymer (XVII) constitutes a proof that free cyclobutadiene is formed in this reaction.
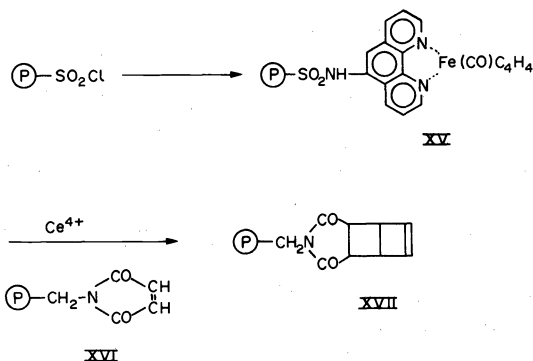

Scheme 7.

$S_1, S_2 = $ Sugar moieties

Scheme 8.

Scheme 9.

In similar manner the transient existence of acyl imidazole in imidazole-catalysed reactions of active esters was proven.[22]

The formation of isocyanates from carbamates and of ketenes from active β-ketoesters by elimination was also demonstrated by this method.

The striking effect of two highly reactive compounds rendered mutually inert by attachment to two polymers was demonstrated in an experiment in which polymeric trityllithium was mixed with a polymeric active ester. The two reagents are infinitely stable in the presence of each other. However, upon addition of an enolizable ketone reaction occurs immediately. The ketone is first enolized by the polymeric base; it is then acylated by the second polymeric reagent and the α-acylated ketone is obtained.[23]

REFERENCES

[1]A. Patchornik and M. A. Kraus, First Int. Conf. on Org. Synthesis, Louvain, August 1974. *Pure & Appl. Chem.* **43**(3/4) (1975).

[2]M. Fridkin, A. Patchornik and E. Katchalski, *J. Amer. Chem. Soc.* **88**, 3164 (1966).

[3]M. Fridkin, A. Patchornik and E. Katchalski, *J. Amer. Chem. Soc.* **90**, 2953 (1968).

[4]R. Kalir, M. Fridkin and A. Patchornik, *Europ. J. Biochem.* **42**, 151 (1974).

[5]M. Fridkin, *Proceedings, 4th American Peptides Symposium*, New York (1975).

[6]R. Kalir, A. Warshawsky, M. Fridkin and A. Patchornik, *Europ. J. Biochem.* **59**, 55 (1975).

[7]B. Cohen, M. A. Kraus and A. Patchornik, unpublished results.

[8]M. Rubinstein and A. Patchornik, *Tet. Letters*, 2881 (1972).

[9]C. S. Marvel and N. Tarkoy, *J. Amer. Chem. Soc.* **79**, 6000 (1957).

[10]Ph. Teyssie, C. Decoene and M. T. Teyssie, *Makromol. Chem.* **84**, 51 (1965).

[11]G. Egle, *Makromol. Chem.* **86**, 181 (1965).

[12]Y. Kurimura, E. Tsuchida and M. Kaneko, *J. Pol. Sci. A*-1, **9**, 3511 (1971).

[13]H. G. Biederman, E. Griessl and K. Wichmann, *Makromol. Chem.* **172**, 49 (1973).

[14]S. Kopolow, T. E. Hogen and I. Smid, *Macromol.* **4**, 359 (1971).

[15a]A. Warshawsky, *Talanta*, **21**, 962 (1974).

[15b]A. Warshawsky, *Talanta*, **21**, 624 (1974).

[16]A. P. Lecuyer, J. L. Luche, H. B. Kagan, G. Colin and C. Mazieres, *Bull. Chim. Soc., France*, 1960 (1973).

[17]C. C. Leznoff and J. Y. Wong, *Can. J. Chem.* **51**, 3756 (1973).

[18]J. Y. Wong, C. Manning and C. C. Leznoff, *Angew. Chem. (Int.)* **13**, 666 (1974).

[19]U. Zehavi and A. Patchornik, *J. Amer. Chem. Soc.* **95**, 5673 (1973).

[20]M. A. Kraus and A. Patchornik, *J. Amer. Chem. Soc.* **93**, 7325 (1971).

[21]J. Rebek and F. Gavina, *J. Amer. Chem. Soc.* **96**, 7112 (1974).

[22]J. Rebek, D. Brown and S. Zimmerman, *J. Amer. Chem. Soc.* **97**, 454 (1975).

[23]M. A. Kraus, B. Cohen and A. Patchornik, unpublished results.