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A Study on Polymeric Reagent Uses in Organic Synthesis

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Abstract – The key benefits of the use of polymeric carriers in organic synthesis are solubilization, immobilization and the development of unique microenvironmental and steric results. Recent development has been explored in the usage of polymer reagents in organic synthesis.

For high-efficiency acylation (e.g. peptide synthesis), for halogenation, for oxidation and reduction in the Wittig reaction, condensation and other reactions, polymeric transfer agents were used. This method typically requires an abundance of polymeric reagent such that a sufficient product yield is reached in solution. Side compounds stay stuck to the polymer in several of these reactions, enabling chemical purification.

In his peptide synthesis, Merrifield originated organic synthesis of polymer carriers. The 'hoop lane' synthesis, selective mono reactions of bifunctional compounds, and oligosaccharide synthesis are recent examples of synthesis using the same method. An abundance of soluble reagent is typically used in this reaction form.

Reactive agents in polymer transporters is used in cycling reactions, ester enolate reactions, mixed ester condensations, coordinated unsaturated catalyst preparations, and enzyme subunit isolation. The effectiveness of these reactions depends on the chain length and concentration of the molecules connected and polymer interconnection, reaction temperature and time.

Key Words: - Polymeric Reagent, Organic Synthesis, Synthetic Polymers

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INTRODUCTION

Synthetic polymers have long been used for technical applications nearly exclusively. Unlike the chemistry of their preparation, the chemical processes of polymers had not been researched until the 1950s. But a modern approach to polymers has steadily evolved in recent decades. Polymers are used as carriers for comparatively low molecular weight reagents in this strategy. The so-called 'polymer reagents' are then processed in a suitable solvent with a soluble reagent. The reaction product is collected in solution or stays bound to the solvent, depending on the specific situation. In the following scenario, the substance is independently authorized. The goal of these reactions is therefore to modify compounds which react with the polymer rather than the polymer itself. This then represents a different idea from both the biological chemist or biochemist, on the one hand, and the polymer chemist, on the other.

The polymer functions as an enzyme carrier or as a nonbiological catalyst. Through eliminating the polymer catalyst, reactions using certain catalysts may be terminated at any desired time. In the first polymeric reagents in biochemistry and organic synthesis respectively, polymer-attached enzymes and ion exchange resins were used.

Table 1. Types of chemical uses of polymeric reagents*

1. Ⓟ—A + substrate → Ⓟ—A + product	polymers as catalyst carriers (enzymes and non-biological catalysts)
2. Ⓟ—A + B + C + D → Ⓟ—A~B + C + D; Ⓟ—A + B	separations by specific binding to polymers (affinity chromatography, metal ion separation)
3. Ⓟ—A + B → Ⓟ + A–B	polymeric transfer agents
4. Ⓟ—A + B → Ⓟ—A–B →C Ⓟ—A – B – C → → Ⓟ + A–B–C	Merrifield-type and other organic syntheses
5. Ⓟ—A →B Ⓟ + A′; Ⓟ—A′	Intramolecular and other 'matrix isolation' reactions on polymeric carriers
Ⓟ = Insoluble polymer	

* Only main reaction types are presented. In the following review some reactions will be described which do not exactly fit any one of these types.

In form 2 a compound B is isolated by the reversible, precise attachment to a polymer-attached reagent A from a complex mixture. The compound B is obtained strictly after isolation of the formed complex from the mixture by extracting

it from the polymer. This scheme is a popular method of extracting biological compounds by affinity chromatography and metal ions by polymer-assembled unique ligands.

In type 3 the polymer serves as a reagent that moves a chemical group to (or from) a soluble reagent. Redox polymers, namely the movement of reagents by electron, were the first polymers of this kind. This technique typically utilizes excess polymer to guarantee the completeness of the reaction.

Sequence 4 is the now established synthesis of the Merrifield form. In the step-by - step construction of molecules made up of recurring, related parts, such as polypeptides, polynucleotides or polysaccharides, the polymer serves as carrier here. Usually excess soluble reagent is used. After the synthesis is complete, the substance is isolated from the polymer. A similar scheme may reflect a variety of other organic syntheses.

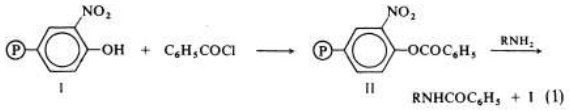
In type5, a rigid polymer allows to regulate intramolecular reactions (e.g. cyclisation's) of polymer molecules, A, by avoiding intermolecular reactions. The substance A 'is obtained directly or after a different cleavage stage in solution. This method is a general way to distinguish reactive organisms from each other.

We shall concentrate on certain aspects of the use of polymer reagents in organic synthesis, particularly those we have recently been interested in (Table 1 reaction types 3,4 and 5). Other issues such as immobilized enzymes[1], ion exchange resins as catalysts[2], redox polymers[3], Merrifield synthesis and chromatography[4] have been well reviewed. There have also been several brief articles on the usage of polymer carriers in organic synthesis recently [6, 7].

POLYMERIC TRANSFER AGENTS

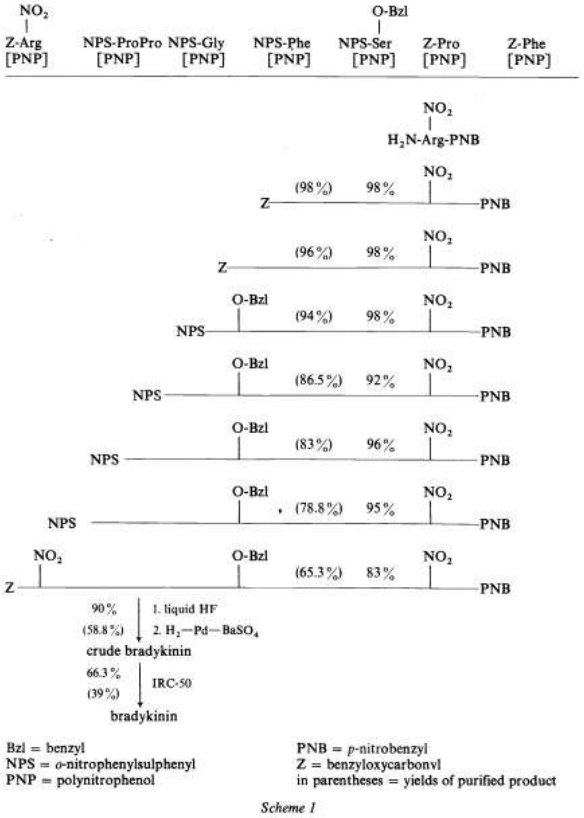
(A) Acylation by polymers

In 1965 it was shown in our laboratory that polymers can be used as acylating agents[8]. By attaching benzoic or acetic acids to poly (4-hydroxy-3-nitropyrene) (I) active polymeric esters (II) were obtained, which could be used in arylations of amines[9] (equation 1)



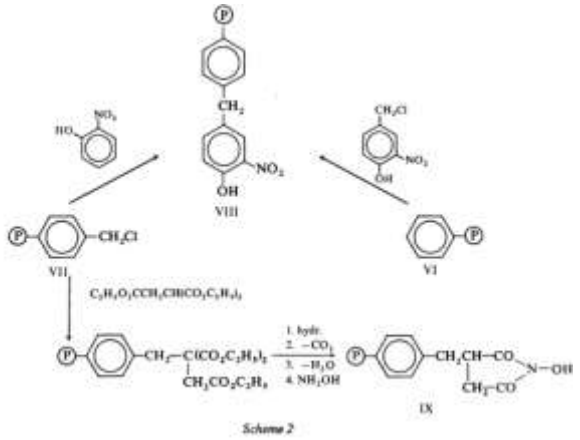
This method contributed to an overall peptide synthesis[9], defined in equation 2.

Nitrophenol polymer-containing amino acids as active esters (III) are handled with a soluble peptide amino acid that has a free amino group. The result of and stage in the synthesis (IV), (V), is generated as solution as compared to the Merrifield synthesis and can be filtered if desired. Excess polymeric reagent achieves large commodity yields. The nonapeptide bradykinin as an illustration of a multistep synthesis with this approach was synthesised in an overall range of 39 percent [10] (scheme 1). The covered peptide displayed total biological activity. Although the above polymeric reagents have achieved tremendous popularity, they experience some drawbacks. Their powdered shape allows filtration and washing complicated and forbids their usage for continuous synthesis on a panel. Other polymer preparations appear to



Scheme 1

Partially disintegrate, dropping tiny particles into solution. Moreover, these polymers only swell in a small number of highly polished solvents, while for flexible peptide synthesis a wider variety of solvents is preferable. In comparison, some reactions using these polymers have been shown to be much slower than analogue solutions. Therefore, new polymers have been pursued which have the chemical reactivity and the desirable physical properties of the above polymers. Via pre-formed bead polymers such polymers could be developed as starting materials, "[11] as defined in Scheme 2.



Scheme 2

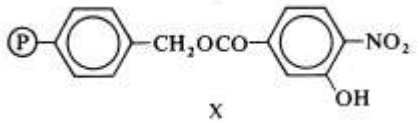
The product (VIII) from Friedel – crafts alkylation of polystyrene in the form of 4-hydroxy-3- nitro benzyl chloride – was the most effective of these polymers. The polymeric reagent preserves the mechanical properties of original polystyrene—2% divinylbenzene. It swells in many solvents such as dimethylformamide, methylene chloride and benzene. It is quick to clean and wash the polymer. The amino acids were normally binded to the polymer (using DCC) in three to five hours. Loading of approximately 1,0—1,5 mmol of amino acid per gramme of polymer with a polymer of approximately 2.0 mmol nitrophenol groups / g was typically achieved. For peptide synthesis, a polymer-attached amino acid (with a double excess) is handled five to twelve hours with a soluble amino acid or peptide ester. Reaction speeds are close to those in solution analogue reactions. They can be improved by heating. In certain instances, organic solvent evaporation, achieved by filtration of the polymer, creates pure crystalline materials. Table 2 summarizes a few cases.

Table 2. Peptide synthesis with 4-hydroxy-3-nitrobenzylated polystyrene

Peptide	Yield, %	No. of coupling steps
Z-Phe-Gly-OBzl	>99	1
Z-Phe-Leu-OMe	>99	1
Boc$_2$-His-Pro-Phe-OBzl(NO$_2$)	96	2
Z$_2$-Lys-Ala-Ala-OBzl(NO$_2$)	99	2
Z-pGlu-His(DNP)-Trp-Ser(OBzl)-Try(OBzl)-Gly-Leu-Arg(NO$_2$)Pro-GlyObzl	63	9

The synthesis of the Z-Asp (OBzl)Cyst(Z)Gly OBzl[12] peptide revealed that this process is used for the preparation of large quantities of the substance. About 20 g of polymeric reagent is used for each of the two coupling phases. The amount sum was 80 — 100 ml. Component yields were essentially quantitative (about log).

Literature[l2]a has also documented another nitrophenol polymer (X) obtained by modification of polystyrene beads. However, it appears that a C-C bond,

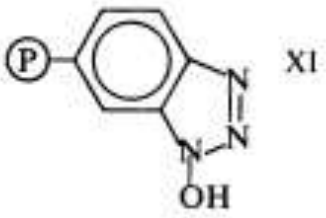


X

It is preferable less susceptible to hydrolysis than an ester bond. The purity and yields of this polymer are therefore smaller than those of polymer VIII.

The reaction of insulin to carbobenzoxy alanyl co-polyethylene N-hydroxy maleimide demonstrated that the peptide synthesis by polymeric active esters would not prevent reactions with broad peptides (due to potential steric effects). Insulin alienation was quantitative[13].

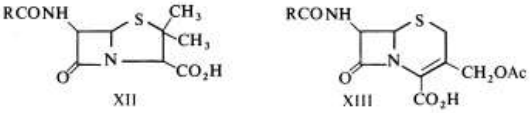
We recently prepared an N-hydroxy benzotriazole moieties (XI)[14] polymer holding.



XI

Amino acid syntheses bound to this polymer are quicker mucous than for other active polymer esters. In five to thirty minutes also reactions with the polymeric variants of voluminous amino acids such as valine, leucine and proline are completed (6—24 hours are possible with other polymers).

We used polymer esters in penicillin (XII) and cephalosporin (XIII) high quality syntheses.



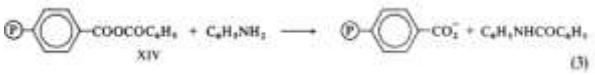
XII XIII

Specific analytical methods for determining polymeric active esters were created, mainly based on non-aquatic titrations.

In our laboratory preliminary work on the automation of peptide synthesis by the active ester process are currently ongoing.

In peptide synthesis, some classes of investigators have used polymeric active esters. Wieland and Bin used ion ally linked p, p'-dihydroxy diphenyl polymers[15] and azophenol groups[16]. N-hydroxy maleimide polymers is used for blood and coworkers[17]. Marshall and Lienor suggested the use of p-hydroxyphenyl siphon polymers[18], along with his party, Okawara and his team documented N-hydroxy succinimide and hydroxamic acid-containing polymers[19]. Guarneri et al.[20] used an insoluble nitroso amino pyrazole insoluble active ester.

A polymeric mixed anhydride (XIV), as defined in equation 3, was recently identified as successful acylating agent [21].



This reaction demonstrated an interesting selectivity for assault on carbonyl further from the polymer. As a clarification, steric impediments to the method of the polymer backbone were mentioned. Polymeric sulphonic mixed — acetyl ant anhydrides have recently been mentioned as acetylating agents. However, alcohol reaction was slower than ethanol[22].

(B) Halogenations by polymers

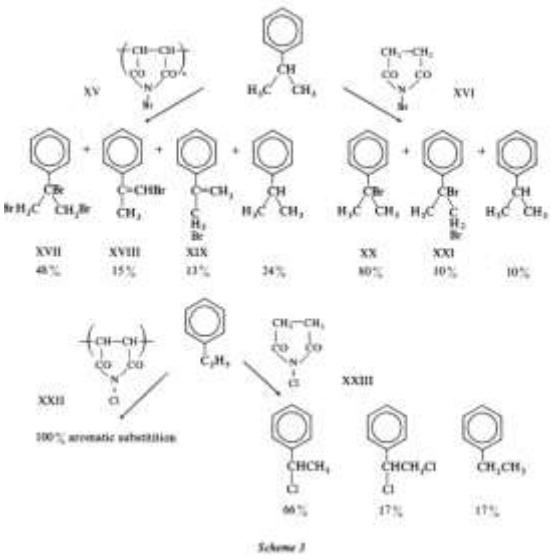
Polymeric halogenating agents provide benefits for care, elimination of excess reagents and separation of goods. The mixed polyvinyl pyridine bromine complex proved to be a moderate and useful bromine donor (e.g. in addition to double bonds). Poly (p-styrene iodide-chloride) (recovered by chlorine treatment with poly-p-iodothyrine) have been successfully used for cyclohexene-transdichlorocyclöhexane chlorination.

The chemistry has remained significantly unchanged compared with the analogue low-molecular weight reagent in reactions of the polymeric reagents mentioned so far. However, poly-N-bromo- and-N-chloromaleimide, as shown in Scheme 3, showed unique reaction paths, different to those of their corresponding monomers.

These distinctions are clarified by the polar existence of the polymeric base, which creates a special microenvironment, independent of the solvent used, while halogenated. This induces the dehydrobromination in x-methyl styrene of the postulated main reaction product (XX). Then, the formation of products can be easily explained by consecutive bromination and dehydrobromination steps (XVII), (XVIII) and (XIX). Indeed, when the solvent was modified from CC14 to CH3CN in reactions with monomeric N-Bromo succinimide (XVI), the product distribution was identical to the polymer. In addition, aromatic substitution by monomeric N-chlorosuccinimide (XXIII) to the reaction mix of toluene chlorination has improved from 16 to 95 percent.

Both soluble and cross-related polyps (p-vinyl benzoyl chloride) have recently been prepared and used in carboxylic acid transformations into their chlorides (50-90 percent yield).

There may be a very peculiar polymer reagent in which the reactive groups are not bound with clear covalent connexons. Recently, compounds for graphite insertion have been shown to be polymeric reagents. The compound derived from the graphite process was then used for 1,1'-binaphthyl and 7-keto methyl cholate bromination.

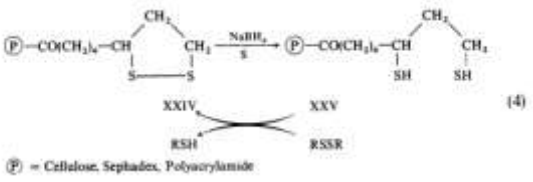


(C) New oxidizing and reducing polymers

Redox polymers (normally variants of quinone) were among the first synthesized polymeric reagents. Just a few recent additions to polymers with peracid groups are identified. The polymer, consisting of cation exchange resin comprising carboxylic and sulphonic acid groups, transforms the carboxylic acids into diols by treating with hydro-Geno-peroxide. A polymer that transformed olefins into epoxides using a resin that only includes carboxy groups as its starting content.

In aniline oxidation azobenzene[24] the usage of poly(p-iodosodiacetate) as a polymer reagent was seen. Polymers containing isoalloxazine is prepared and used for the oxidation of methyl almond.

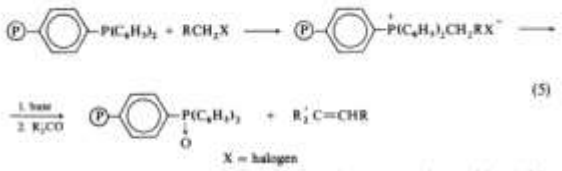
Recently, as seen in equation 4, we have developed a polymer useful for quantitative reduction of disulfide bonds in peptides and proteins.



Lipoyl residues are attached to polymers chosen so as to swell in aqueous solutions. The oxidized polymer (XXIV) may be easily and quantitatively regenerated by reaction with sodium borohydride. The polymer could be used for the quantitative reductions of glutathione and oxytocin and the activation of papain.

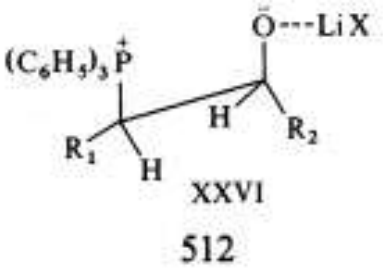
(D) Polymeric Wittig reagents

Three different groups reported on the preparation of alkylidene transferring polymers and their use in the Wittig reaction (equation 5).



(5)

Olefin yields are usually similar to reactions of soluble phosphonium reagents. One drawback of the polymeric reagents is that triphenylphosphine oxide is bound to the polymer, and is often difficult to extract. Another benefit involves steric regulation of the reaction. The inclusion of lithium salts in the Wittig reaction, due to favored complexation of threolay betaine form (XXVI), is considered to contribute to the formation of trans olefines.



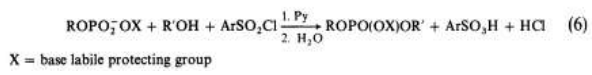
XXVI

512

In the absence of lithium ions, cis olefins are formed. Lithium bases are however also used to manufacture ylid. The use of polymeric phosphonium reagents allowed full removal of lithium ions possible (by filtration of the polymer and washing) before adding to the carbonyl compound. In reality, high yield cis olefins were obtained.

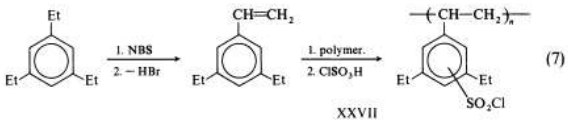
(E) Polymeric condensing agents

Barred chlorides of aryl sulphonyl are used in ohgonucleotide synthesis as condensing agents, as defined in Equation 6.



(6)

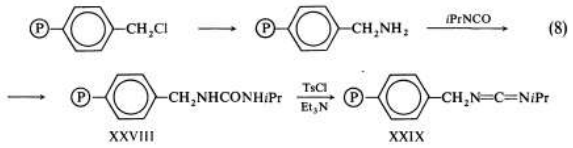
Any R'OH sulphonating and difficulties for full removal of sulphonic acid produced are typical complications of these reactions. No such problems were found with the usage of polymeric sulfonyl chloride (XXVII) as seen in equation 7.



XXVII

(7)

The reaction rates and outputs of the reactions with soluble reagents were similar; nevertheless, the product purity was much higher. A polymer carbodiimide has recently been prepared according to equation 8



XXVIII XXIX

(8)

This reaction can be effectively used in the Moffat oxidation in transforming acids to anhydrides and alcohols to aldehydes. The developed urea derivatives (XXVIII) stay bound to the polymer and are quickly removed from the reaction mix. This removes a significant challenge in the usage of carbodiimides. The urea derivative may also be transformed to the diamide (XXIX). However, the regenerated reagent is less successful than the initial since some diamide groups are blocked due to development of N-acyl urea.

Other polymeric diamides were used as condensing agents for the preparation of N-ethoxycarbonyl-2,2-dihydro-quinoline (EEDQ) for the same reason of peptide synthesis.

Other polymeric reagents mentioned in recent literature and not addressed here include a sulphonium ylide polymer (aldehyde converted to epoxide's); metallurgical polymers [poly-p-lithium styrene and poly-p-(4- lithiobutyl) styrene]; polymeric Edman reagent used in gradual peptide degradation; and polymer-containing Girard polymers; and pharmacologically active polymeric reagent Polymeric reagent Edman

CONCLUSION

Polymer-aided solution-phase synthesis is also commonly used in science and industry. In recent years, it has become a popular method for the rapid generation and purification of chemical libraries of solution process in the pharmaceutical and agrochemical industries. Polymeric reagents are able to minimize or even eradicate chromatographic processes of oxidation, as they are easily separated by filtration from the reaction mixtures. However, more industrial implementations rely heavily on designing new high-load, recyclable and cheap supports in the future. In this sense, the biodegradability and non-toxicity of natural polymers, including chitin, chitosan, cellulose, carrageen etc., may be of primary importance. The promise of these exciting materials should also be extensively studied.

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