CHAPTER 1

A REVIEW ON THE APPLICATION OF FUNCTIONALIZED POLYMERS IN ORGANIC SYNTHESIS

INTRODUCTION

Discovery and applications of new reagents has been one of the most fascinating aspects of synthetic organic chemistry. The study of reactive polymers is an area which until recently had been largely neglected. 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. Applications have been found in organic chemistry, inorganic chemistry, biochemistry and biology. It has been found that insoluble polymers can be used for a wide variety of purposes to solve specific synthetic problems in organic chemistry.[1-4]

Organic chemists tended to concentrate on studies of relatively small, well defined molecules or on studies of natural polymers and syhthetic reactive polymers were hardly studied. Polymer chemists, on the other hand, tended to study the preparation and physical properties of polymers and this of course led to the growth of the plastic industry. Insoluble polymers have been employed as stoichiometric reagents, as catalysts, as protecting groups, as substrate carriers, in analytical chemistry, in ion-exchange, in the detection of reaction intermediate, in chromatography, in biologically and pharmacologically active systems, in the immobilization of enzymes and cells, in the application of dyes and colorants and in the field of agricultural chemicals. Ion exchange resins had previously been widely examined as acid and base catalysts[5] though no technological application appears to have developed at that time. Polymeric reagents suitable for non-sequential single-step reactions have been utilised by several research groups. The discovery of polymers as organic molecules and their use in organic synthesis was made by Merrifield in 1963.[6]

SYNTHESIS OF FUNCTIONALIZED POLYMERS

In organic chemistry, hydrocarbons are considered parent compounds, while other organic compounds are considered derivatives. This anology can be extended to organic polymers as well, where polymeric hydrocarbons can be considered parent polymers from which other functionalized polymers are derived.

There are two possible methods of preparing a functionalized polymer. The first method involves starting with a property functionalized monomer and then polymerzing it. The chief advantage of this method is that the resulting polymer is truly homogenous, and the degree of functionalization in such polymers is also fixed and high. Monomer instability and incompatible polymerization conditions tend to limit preparations by this route to relatively simple polymers. The second, and more frequently used method involves first forming a polymeric carrier and subsequently introducing functional groups into the preformed polymer structure. The degree of functionalization is easily controlled in this case, but the distribution of the groups on the polymer matrix may not be uniform.

Structure and Properties of Functionalized Polymers

A functionalized polymers are synthetic macromolecules. Functionalized polymeric supports must possess a structure which permits adequate diffusion of reagents into the reactive sites, a phenomenon which depends on the extent of swelling or solvation, the effective pore size and pore volume and the chemical and mechanical stability of the resins under conditions of a perticular chemical reaction or reaction sequence. These in turn depend on the degree of cross-linking of the resin and the conditions employed during preparation of the resin. Three main types of resins[7] can be identified; (a) microporous or gel-type resins, (b) macroporous resins and (c) macroreticular resins.

Microporous species are prepared from a vinyl monomer and a difunctional vinyl monomer in the absence of any additional solvating media. In the dry state they are microporous, with polymer chains being separated by typical solid state intermolecular distances. On contact with good solvent a soft gel net work is formed with the generation of considerable porosity depending on the degree of cross-linking. Where the latter is $\leq$ 1%, swollen resins generally have low mechanical stability and readily fragment even under carefully handling. In contrast, commercially available microporous resins with $>$ 8% cross-linking are mechanically very stable, but unfortunately give rise to acute diffusional limitations resulting in slow and incomplete reactions. In practice resins of $\sim$ 2% cross-link ratio provide a satisfactory compromise generally allowing adequate preparation by most reagents and yet retaining sufficient mechanical stability to provide ease of handling. Copolymer beads made by suspension polymerization of 98% styrene and 2% divinyl benzene isomers have found very wide application as a result of these factors.

Macroporous resins are prepared with the inclusion of an inert solvent. Where the solvent solvates both monomer and polymer a fully expanded network is formed with a considerable degree of porosity.[8] Removal of solvent causes a reversible collapse of the matrix and in the dry state such materials are similar to microporous resins. In order to achieve mechanical stability in the solvent swollen state it is usual to employ larger quantities of difunctional comonomer in the preparation upto ∽ 20%. Materials of this type are not readily available from commercial sources.

Where the solvent employed during polymerization is good solvent for the monomers but a precipitant for the polymer, the term macroreticular is generally employed to describe the product.[9] The latter is highly porous rigid material which retains its overall shape and volume when the participant is removed. Again it is normal to use a larger quantity of difunctional comonomer, and in the case of some chromatographic applications styrene resins with > 50% divinyl benzene content are employed.[10] This enables such products to be subjected to high pressures, ∽ 1000 psi, in high performance liquid chromatography conditions. The structure of these resins is quite different from the previous two. They have a large and permanent pore volume and reaction sites may be regarded as being located on a permanent interior surface of the resin. Such materials are available from a number of commercial sources. Macroporous species have also been prepared in the presence of large inert molecules which subsequently can be washed away to create permanent voids.[11]

ADVANTAGES AND DISADVANTAGES IN USING FUNCTIONALIZED POLYMERS

(I) Advantages

(1) One of the main advantages of synthesis on insoluble polymer supports was exploited in polypeptide synthesis,[6] namely, that the normal procedures of organic chemistry, especially solvent extraction and separatory flask manipulations, are omitted, which permits the possibility of synthetic chemistry automated. The solid-phase synthetic method also allows excess of reagent and substrate 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. 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. A polymer anhydride[12] acts differently from its solution analogue and the Dieckmann condensation proceeds more selectively on the polymer carrier.[13]

(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.[14]

(5) The use of insoluble functionalized polymers as an alternative means of carrying out reactions under conditions simulating 'high dilution' is an important advantage. The synthesis of cyclic peptides[15] and the Dieckmann condensation[13] 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 stimulating 'high dilution' conditions (advantage 5). This concept was advantageously used in the monocyclation[16] and monoalkylation[17,18] of esters, in the blocking of one functional group of symmetrical bifunctional compounds,[19-21] and in the preparation of an active monomeric species of reduced titanocene.[22]

(7) The stimulation of 'hyperenteropic' conditions by the use of insoluble functionalized polymers was used to advantage in the condensation of an enolizable with non-enolizable ester, both attached to the same polymer.[23]

(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[24] 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.[25,26]

(II) Disadvantages and Discussion

One of the major limitations of the solid-phase synthesis of polypeptides results from the necessity that reaction should proceed to 100% completion.[26] 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 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,[21,27-31] degradation of the polymer has also been noted.[20,32] More stable non-degradable polymers will 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[21] 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 polymers 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,[33] 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.[16,23] Careful selection of a polymer with a suitable loading capacity should allow this problem to be easily controlled.

Insoluble polymer imparts a certain 'steric hindrance' to reaction which varies with the substrate and reactions attempted. The Dieckmann condensation[13] gave reduced yields of products as the substrates became more bulky and the yields of m-formyl compounds were consistently lower than those of related p-formyl compounds.[21]

Polymer Supported Reagents

A polymer supported reagent is a reactive organic group bound to a macromolecular support and used in stoichiometric quantities to achieve the chemical modification of an added substrate (reaction 1)

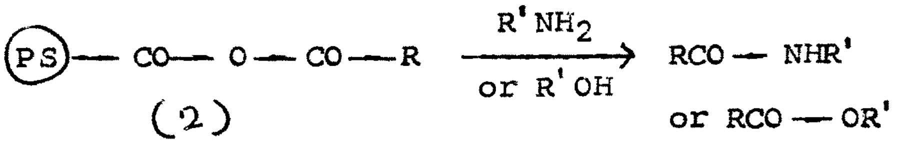
$$\textcircled{P}\!-x \;+\; \text{substrate} \;\longrightarrow\; \underset{\text{polymeric byproduct}}{\textcircled{P}\!-y} \;+\; \text{product} \qquad ..(1)$$

Such groups may be attached to polymeric carriers by physical adsorption or by chemical bonding. Physically adsorbed species are generally unsatisfactory since in use the components tend to dissociate, and they are therefore unsuitable for column or cyclical application.

Although many useful procedures for oxidation processes have been reported, the main disadvantage of these is the relative difficulty in the preparation of the reagents and in the working-up of the reaction mixture. Polymeric redox systems were one of the earliest examples of polymer supported reagents and alleviate these difficulties. The most important classes of polymeric redox systems are the hydroquinone-quinone, thiol-disulphide, pyridine-dihydropyridine, polymer-supported dyes and polymer-supported metal complex systems.[34,35]

Aliphatic peroxy acids explode very readily on impact, and analogous polymer-supported reagents based on polyacrylic acids behave similarly.[27,36,37] Aromatic peroxy acids in contrast are more stable, and the polymer supported analogues of these have proved very useful indeed.[38-40] Cromic acid is a powerful oxidising agent and a supported analogue has been used for the oxidation of alcohols to carbonyl compounds in high yields.[41,42] Insoluble polymeric organotin dihydride[43] was prepared and used as a selective reducing agent for carbonyl compounds and alkyl halides. This polymer-supported reagent combines the advantages of both the monomeric dihydride reagent, i.e. its high reactivity, and the monohydride reagent, i.e. its high stability.

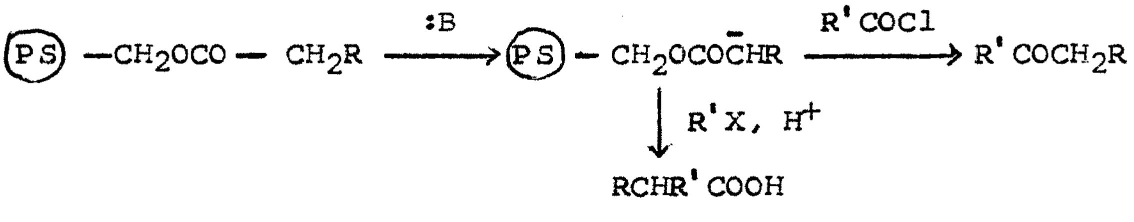
Several functional polymers have been reported in the literature for use in the acylation and alkylation of different substrates. For example, the insoluble polymer containing the anhydride functional group(2) was used for the conversion of an amine or alcohol to amide or ester.[12,44] (Reaction 2)



$$\text{(PS)}-CO-O-CO-R \xrightarrow[\text{or } R'OH]{R'NH_2} RCO-NHR' \text{ or } RCO-OR'$$

..(2)

The insolubility of a resin-bound reagent in all common solvents can have the effect of isolating the reactive groups on the polymer from each other. Patchornik and his co-workers[17,45] have used this property in the crossed alkylation of ester derivatives. The reactive carbanion derivative of a bound ester is first generated and self-condensation with unreacted ester inhibited by the rigid matrix. The production of these stable monoanions then allows reaction with acyl or alkyl halides to give selectively monoacylated or monoalkylated products(reaction 3).



$$\begin{tikzcd} \text{(PS)}-CH_2OCO-CH_2R \arrow[r, ":B"] & \text{(PS)}-CH_2OCO\bar{C}HR \arrow[r, "R'COCl"] \arrow[d, "{R'X,\ H^+}"] & R'COCH_2R \\ & RCHR'COOH & \end{tikzcd}$$

..(3)

Alkylation of carboxylic acids with N-alkyl-N-arytrizene groups supported on polymeric material has been reported.[46](1.1)

Anion exchange resins have been used in nucleophilic substitution reactions. Gordon[47] prepared benzylcyanide by the reaction of benzyl bromide with an anion exchange resin, IRA-400 (cyanide form). When sodium or potassium cyanide is used as the source of nucleophile ($\bar{C}N$), the reaction product had to be isolated from the inorganic material. With resin bound nucleophiles, on the other hand, the reaction was carried out on a column. The product was eluted out while the byproducts remained in the column (1.2).

Benzyl ethers were similarly prepared by the reaction of benzyl bromide, with resin-bound phenoxide as the nucleophile[47] (1.3).

Arylsulfonyl fluorides[48] were prepared by the reaction of the fluoride form of a resin with arylsulfonyl chlorides.

Cainelli and Manescalchi have shown that reaction of carboxylic acids with the hydroxide form of a macroreticular resin (1.4) gives polymer-supported carboxylates which can be alkylated by treatment with alkyl halides in hexane or ether.[49] Table 1 summarizes some of the results. It can be seen that the primary halides react satisfactory at room temperature, that the secondary halides react satisfactorily at 50°C, but that tertiary halides hardly reacted at all.

Gelbard and Colonna studied the o-alkylation of polymer-supported aryloxides with alkyl halides and with alkyl mesylates.[50] The pattern of reactivity suggests that these reactions proceed by the usual SN^2 mechanism and in agreement with this it was found that S-2-octyl mesylate gave R-2-phenoxyoctane.

Table 1. Alkylation of Polymer-supported Carboxylates to give Esters

Acid reacted with resin	Alkyl halide	Reaction conditions			Yield (percent)
		Solvent	Temperature (°C)	Time (h)	
Benzoic	CH_3I	Hexane	r.t.	2	90
	CH_3OTs	Hexane	r.t.	17	91
	i-PrBr	Hexane	50	13	60
	t-BuBr	Hexane	50	5	Trace
Dodecanoic	CH_3I	Hexane	r.t.	4	93
	i-PrBr	Hexane	50	6	52
	t-BuBr	Hexane	r.t.	200	Trace
Cinnamic	CH_3I	Hexane	r.t.	21	97
	i-PrBr	Hexane	50	14	59
Cyclohexane-carboxylic	CH_3I	Hexane	r.t.	16	76
	i-PrBr	Hexane	50	14	28

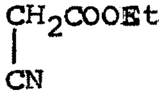
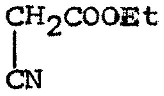
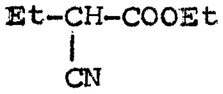
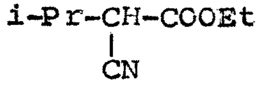
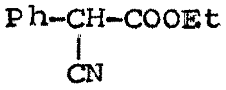
Shimo and Wakamatsu investigated the alkylation of diethyl malonate, ethyl cyanoacetate, cyanoacetamide and various substituted cyanoacetamides using the hydroxide form of resin(1.4) to generate the corresponding carbanion in situ and ethanol or aqueous ethanol as the reaction solvent.[51] A selection of their results is summarized in Table 2. It was shown that the polymer-supported carbanion from cyanoacetamide could be isolated in the dry state.

More recently Gelbard and Colonna have investigated the methylation of β-diketones (1.5) and (1.6) and ketoester (1.7).[50] The polymer-supported carbanions from each of these compounds were prepared in a separate step by treating the hydroxide form of resin (1.4) with the β-dicarbonyl compounds in aqueous alcohol. The supported carbanion was then treated with methyl iodide in hexane, tolune or ethanol. As in similar experiments carried out using phase-transfer catalysis[52] or dipolar solvents,[53] the reaction show a high preference for C-alkylation.

Reactions Using Polymer-supported Substrates

The best known reactions of this type are those employed in the solid phase synthesis of polypeptides,[54] oligosaccharides[55] and oligonucleotides.[56] These reactions can be regarded as examples of the use of polymer-supported protecting groups, and illustrates well the merits of such protecting groups, i.e. easy isolation of polymer-supported products, possible use of excess reagent to obtain high yields of polymer-supported products, automation of reaction procedures etc. Chart 2 shows some polymer supported protecting groups which have been utilised

Table 2. Alkylation of Diethyl Malonate, Ethyl Cyanoacetate and various Substituted Cyanoacetamides

Substrate	Alkylating agent	Reaction solvent	Yield (percent)		
			Monoalkylated	Dialkylated	Starting material
$H_2C(COOEt)_2$	Ethyl iodide	Ethanol	72	-	7
	Allyl bromide	Ethanol	61	12	14
 $\underset{\substack{\vert\\ CN}}{CH_2}COOEt$	Ethyl iodide	Ethanol	51	19	12
	Allyl bromide	Ethanol	31	29	23
 $\underset{\substack{\vert\\ CN}}{CH_2}COOEt$	n-Butyl iodide	Aqueous ethanol	20	-	-
 $Et\text{-}\underset{\substack{\vert\\ CN}}{CH}\text{-}COOEt$	Allyl bromide	Aqueous ethanol	82	-	-
 $i\text{-}Pr\text{-}\underset{\substack{\vert\\ CN}}{CH}\text{-}COOEt$	Ethyl iodide	Aqueous ethanol	48	-	-
 $Ph\text{-}\underset{\substack{\vert\\ CN}}{CH}\text{-}COOEt$	Allyl bromide	Aqueous ethanol	65	-	-

in the solid phase synthesis of natural polymers and which are suitable for the protection of acids, alcohols and amines. Two examples of their use in other areas will be considered.

The first illustrates the use of a polymer-supported protecting group to assist in the isolation of a product formed in only trace amounts.[14] Thus, the acid (1.8) was attached to chloromethyl resin (2.10) and in the presence of the product 1,10-decanediol was reacted with trityl chloride.

At the time it reacted a very small amount of decane derivatives was threaded through the macrocycle and so become trapped on the resin. Other products were washed away and the tritylation reaction repeated 70 times to accumulate a workable amount of threaded macrocycle. The resin was then washed thoroughly and the 'hooplane' (1.9) released from the resin and purified.

Polymer supported trityl chloride (3.11), prepared from 2 percent cross-linked polystyrene,was separately treated with butane-1,4-diol, heptane-1,7-diol and decane-1,10-diol in pyridine. After unattached diol ahad been washed away, the free hydroxyl groups were acylated. The products were then cleaved from the resin. The yields of diol monoacetates were 50-60 percent. In such case 30-50 percent of the diol was recovered, indicating that both the hydroxyl functions of these molecules had reacted with the resin. In this perticular case, using the resin facilitated isolation of diol monoacetate but did not give significantly different proportions of monoprotected and

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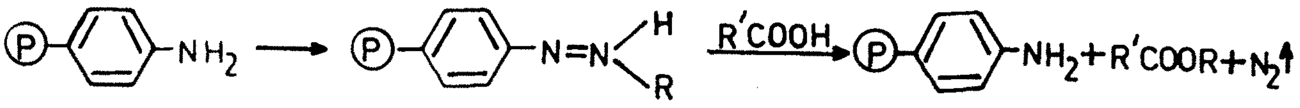

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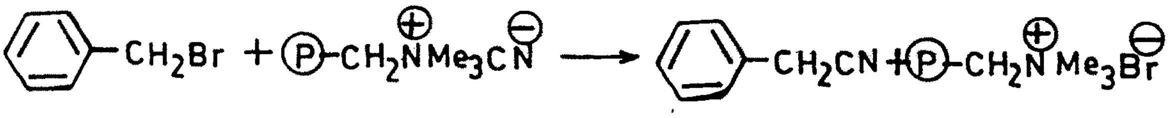

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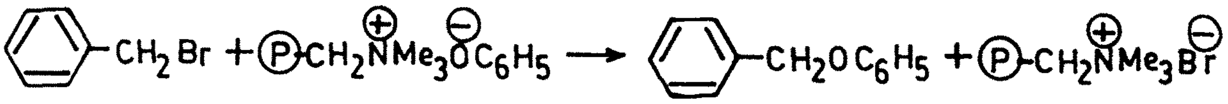

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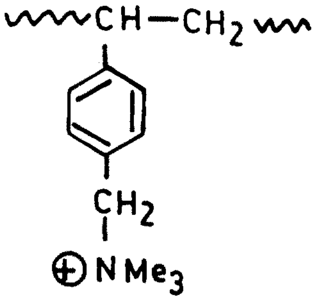

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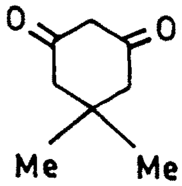

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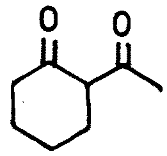

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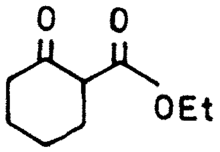

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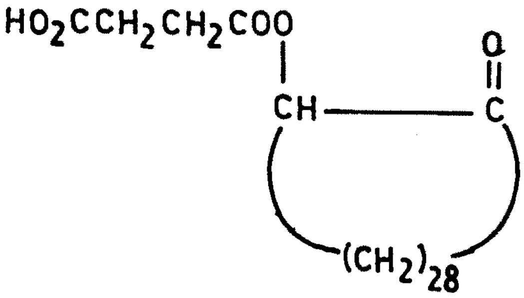

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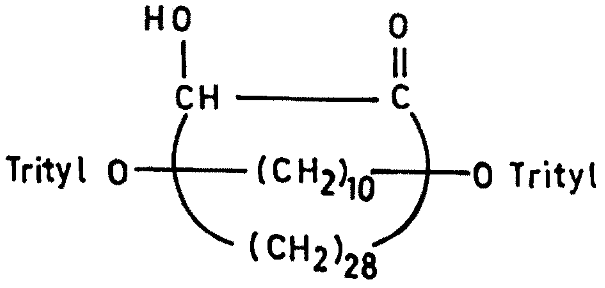

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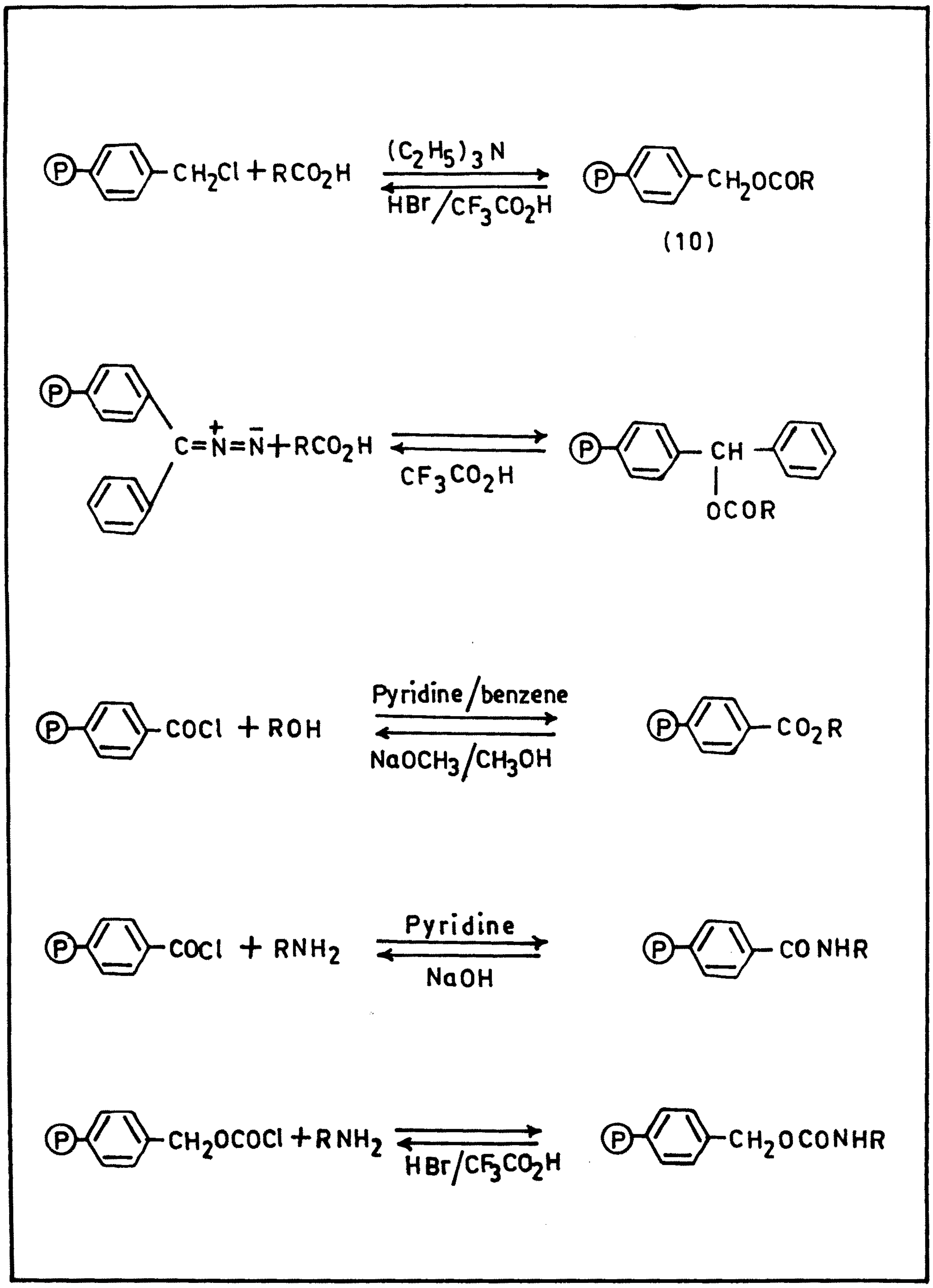

(P)-C6H4-CH2Cl + RCO2H
(C2H5)3N
HBr/CF3CO2H
(P)-C6H4-CH2OCOR
(10)
C=N+=N− + RCO2H
CF3CO2H
CH
OCOR
COCl + ROH
Pyridine/benzene
NaOCH3/CH3OH
CO2R
COCl + RNH2
Pyridine
NaOH
CONHR
CH2OCOCl + RNH2
HBr/CF3CO2H
CH2OCONHR

di-protected diol than might have been obtained using classical procedures.

More successful results were, however, obtained using the polymer-supported trityl chloride (3.12), also prepared from 2 percent cross-linked polystyrene. This resin is more rigid than (3.11) and the results are good.

Polymer Supported Catalysts

Catalytic species can be bound to polymeric carriers without losing their basic catalytic activity. Immobilization of a variety of conventional chemical catalysts on polymeric supports has received wide application during recent years. Ion-exchangers, esterolytic catalysts, phase-transfer catalysts, and photosensitizers have all been prepared. A common advantage in using a polymer-supported catalyst is found in the ease of separation at any stage of the reaction, thus offering the possibility of arresting further progress of the reaction. Besides, an immobilized catalyst is sometimes more stable to atmospheric conditions, has greater bench stability and does not cause undesirable side reactions as is the case with homogeneous catalysts. In industrial applications, they provide for the adoption of continuous flow processes in place of batch operations and, in many cases, the catalyst can be reused many times, thus lowering the cost of operation.

Ion-exchangers were probably the first polymer-supported catalysts to be used in organic synthetic reactions as substitutes for low molecular-weight and water-soluble acid base catalysts. The use of resin acids or resin bases as catalysts for certain reactions is so well-established that many of them were being used in industry while other polymer-supported catalysts were still in the process of development. As an example, isopropyl alcohol can be manufactured by direct hydration of propene using sulfonate resin[57] as catalyst.

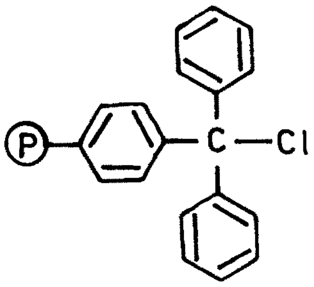
Among a number of metal chlorides used in organic synthesis, anhydrous aluminium chloride is undoubtedly one of the most effective Lewis acid catalysts. During the chloromethylation of polystyrene, using aluminium chloride as catalyst, it was observed that all aluminium chloride could not be removed, even after repeated washing. This was attributed to the formation of a tightly bound polystyrene-aluminium chloride complex. Complex formation was demonstrated by the increase in colour (yellow) intensity of the polymer, and by the development of a new characteristic i.r. band at 1650 cm^{-1}. This complex could act as a mild Lewis acid catalyst for certain organic preparations.

The cracking and isomerization of alkenes is catalyzed by Lewis acids. With normal Lewis acids such reactions take place at temperatures and pressures much higher than ambient. Recently, it has been reported that certain "super acids", a combination of Lewis and proton acids, can catalyze such reactions under milder conditions. A "super acid polymer catalyst" was obtained by binding aluminium chloride to sulfonated, macroporous Co(polystyrene-DVB).[59,60] The catalyst was active in bringing about cracking and isomerization of n-hexane at 357°C at atmospheric pressure.

Numerous transition metal complexes have been described in recent years, which are useful catalysts for hydrogenation, isomerisation, hydroformylation, etc. Many of these catalysts have now been attached to resins.[61] This has the advantage that the valuable catalyst is easily removed from the reaction mixture and is available for re-use. One of the earliest of these polymer-supported catalysts to be described was the polymer-supported analogue of the hydrogenation catalyst K_2PdCl_4. This was prepared by treating the hydroxide form of an anion exchange resin with this salt.[62] Most of the monomeric catalysts contain triphenyl-phosphine ligands and polymer-supported analogues of these catalysts have generally been prepared by replacing one or more of these ligands with phosphine residue of resin (3.13). For example, when a suspension of the resin in tolune was stirred with $(Ph_3P)_3RhCl$, the polymer-supported hydrogenation catalyst (3.14) was obtained. Reaction of the resin with $(Ph_3P)_2Ni(CO)_2$ and with $(Ph_3P)_3RhH(CO)$ similarly gave the cyclo-digermerisation catalyst (3.15) and hydroformylation catalyst (3.17) respectively. In the hydroformylation of pent-1-ene, catalyst (3.16) produced a substantially higher ratio of hexan-1-al to 2-formylpentane than the corresponding homogeneous catalyst, especially when the resin had a high phosphine content and the ratio of phosphine to Rhodium was high. The reasons for this are not clear. Often the polymer-supported catalysts are somewhat less active than their soluble counterparts, probably because the substrates need to diffuse into the resins. The diffusion problem can be avoided by using a linear polymer[63] though the catalyst is not as easily recovered or by attaching the catalyst only to the surface of a resin or other suitable material,[64] though the catalyst will probably have a lower activity per unit weight. Polymer-supported catalysts are not always less active, however, the catalyst obtained by treating the polymer-supported titanocene derivative (3.17) with n-butyl lithium is ca 70 times more active as a hydrogenation catalyst than the non supported analogue probably because the active groups are well spaced on a 20 percent cross-linked resin, and dimerisation leading to inactive products occurs less readily than in solution. Another example is the polymer-supported catalyst(3.18). This has been used to catalyse the hydrogenation of cyclo-octa-1,4-diene to cyclo-octene and cyclo-octane. The activity of the catalyst increases as the ratio of phosphine to Iridium decreases, and if the ratio is less than 5:1 the catalyst is substantially more active (ca×100) than the corresponding homogeneous catalyst. It is suggested that the greater activity arises because the restricted mobility of the polymer-supported phosphine ligands makes them less efficient than monomeric phosphine at intercepting the reactive co-ordinatively unsaturated Iridium intermediates.

The use of phase-transfer catalysts bound to polymeric supports has been reported. The catalytic functional groups anchored to the polymer were (i) quaternary ammonium salts (4.19 a,b,c), (ii) phosphonium salts (4.19 d), (iii) crown ethers (4.19 e) and cryptands (4.19 f). Chloromethylated, 2-4%

CHART-3



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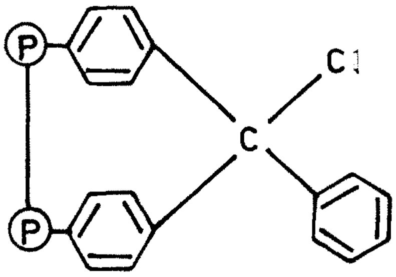

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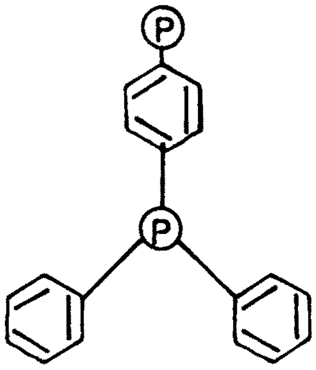
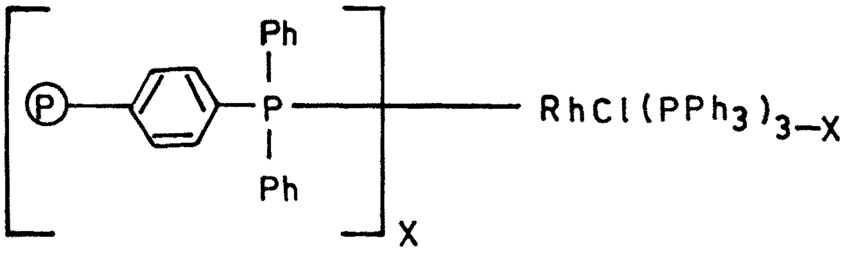


(13)

Polymer–supported catalysts ——



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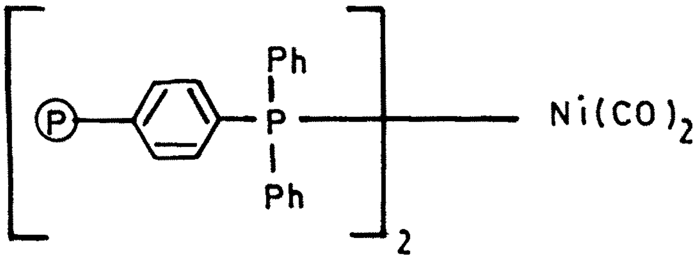

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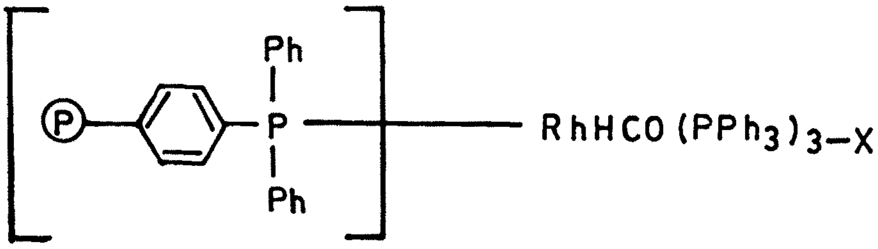

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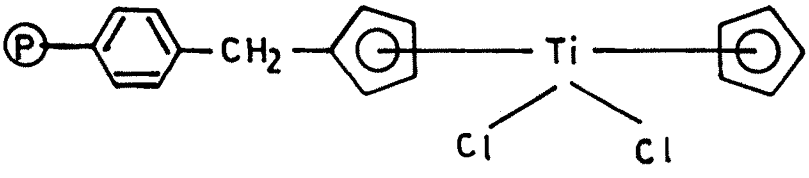

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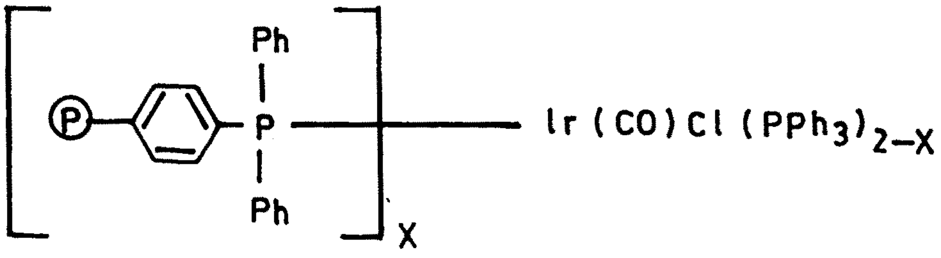

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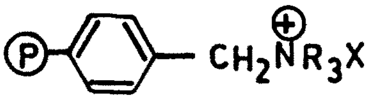
CHART-4



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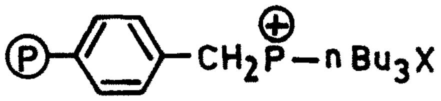
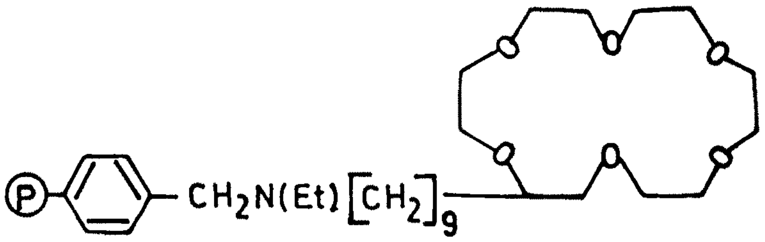
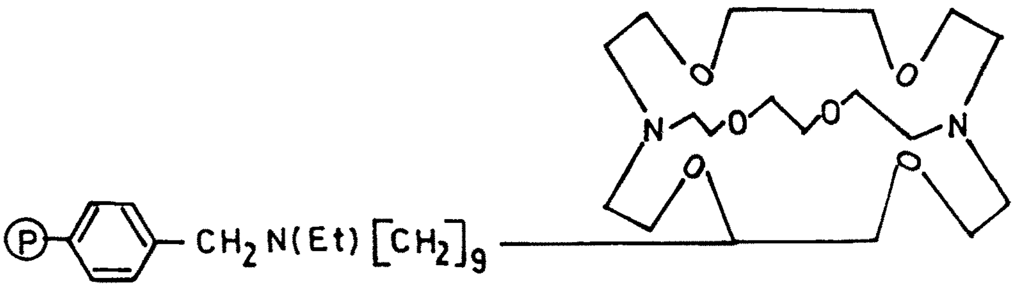


(19) d

a, R = Me
b, R = n-Bu
c, R = n-Oct
X = Halogen



(19) e



(19) f

cross-linked polystyrene and silica gel were used as the support polymers, and the catalyst groups were anchored either by the reaction with the corresponding amine or phosphine cryptand.[64-67]

Organic Synthesis on Polymeric Carriers

There are a number of areas where polymer molecules have been employed as a convenient support upon which to carry out a synthesis. Completion of the latter is followed by cleavage of the product from the support. In principle, the synthesis can be a very complex one involving many steps, and quite clearly a resin support offers a convenient method of isolating and purifying the product at all stages of the synthesis. The same carrier principle has also been used in a asymmetric synthesis.

For the synthesis of an optically active organic compound from an achiral substrate, derivatization with a chiral reagent is necessary. This derivatization must also be reversible so that after the derived substrate has been transformed into the optically active product, the reaction can be reversed to recover the asymmetric product. An alternative approach involves reacting an achiral substrate with a chiral reagent or catalyst. Both the approaches have been used for asymmetric synthesis [i.e. polymer supports used for reversible derivation (binding) of the substrate and chiral polymer supports used to bind an otherwise homogeneous catalyst .] The reduction of an α-keto acid, after derivatization to an ester with an optically active alcohol (L-menthol), is a well-known example of asymmetric synthesis.

In conventional cyclization reactions a high dilution technique is used in order to promote intramolecular reaction. When a rigid polymer support is used, the concentration of molecule to be cyclized on the polymer can be made higher than normally used in solution. This has reduced the synthetic problems encountered in the preparation of macrocyclic compounds such as cyclic peptides,[68-70] and threaded macrocydes.[14] Dieckmann[13] and other cyclization[71,72] have also been improved by this approach.

Among the various advantages associated with functionalized insoluble polymers, the possibility of maintaining mutual separation of reactive functional groups bound to the same polymer support is perticularly attractive, and exploitation of this has been described earlier. This technique involves the generation of reaction intermediate from an insoluble polymeric precursor and its trapping by a second solid-phase reagent. The isolation and detection of an adduct provide positive evidence for the liberated free reactive intermediate.[73,16]

Polymer-bound Formulations[74]

Polymer-bioactive formulations have become increasingly used especially in areas outside pharmacology. The principle of controlled release from these formulations is that a bond to the polymer undergoes fission to release the agent at a designed rate. Polymers that have been used include synthetic and naturally occuring preparations as indicated in Chart 5(a). There are two approaches : the first includes polymerisation of a monomer containing covalently linked agent, it can also involve copolymerisation with any inert comonomer, the second to an existing polymer.

The ready availability of waste cellulosic type material such as bark, saw-dust or kraft-lignin has led to investigation of their potential use as a matrix for herbicides used extensively in agriculture and forestry. These materials have the advantage of not only being biodegradable but also contributing to the humus content of the soil. The herbicide 2,4-D (5.20) is water soluble at neutral and higher pHs so it can readily leach out of the soil. By attaching the herbicide to lignin or to a cellulose byproduct, an ester is produced that slowly releases the herbicide on hydrosis, Chart 5(b). This type of controlled release system has also been employed with other matrices such as synthetic polymers.

Compounding formulations are those in which an agent is used with a 'filler' that is usually a polymer. Release of the agent from the compound material is by three main processes; (i) diffusion-dissolution where the agent, which is soluble and then escapes; (ii) when the agent is insoluble in the elastomer and is held mechanically, water may diffuse into the filler matrix and leach out the agent, (iii) the agent is released following slow dissolution of the matrix in the solvent, usually water.

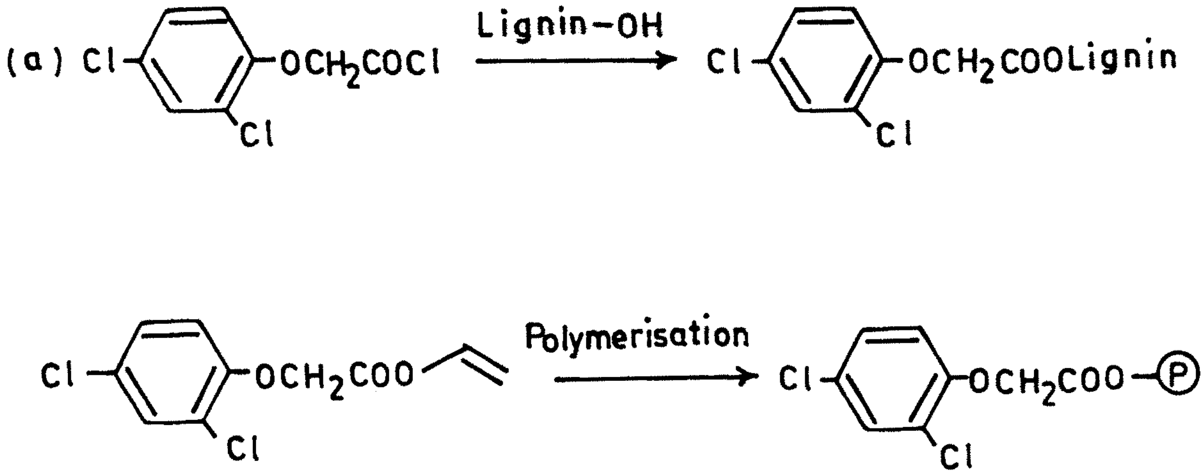
Probably the best known examples of controlled release technology are in marine antifouling. Classical antifouling paint coatings contain a mixture of resin and cuprous oxide among other ingradients. The rosin slowly dissolves by virtue of its acidic group and releases the copper salts by an exfoliation process. Some of the copper oxide forms a slime of basic copper carbonate that adheres strongly to the ship's hull from which the biologically effective cupric ion is slowly released.

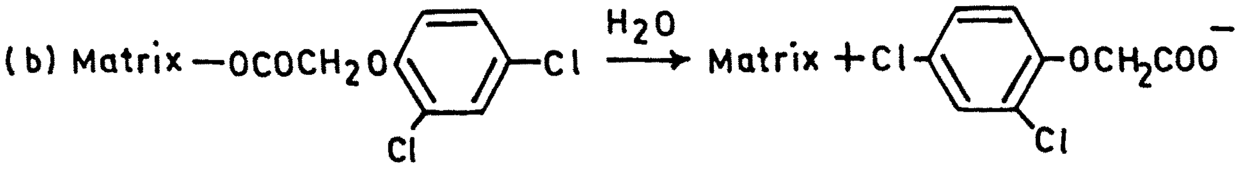
Expoliation is also the main release mechanism that operates with the modern trialkyltin-antifouling agents where rosin or synthetic acid resin is the compounding agent. Exfoliation is the basis of the new 'self polishing' antifouling paint systems where a tin acrylate ion groups thus revealed(5.21) increase in number eventually resulting in the surface film of polymer chain being dissolved and washed away by the water flow. A new surface is thereby revealed and any rough patches are levelled out at the surface which is being continually renewed.

Diffusion dissolution is utilised in contact insecticide traps the insecticide e.g. pyrethroid is placed in a reservoir together with an insect attractant such as vanillin. The reservior is placed between two plastic barriers and attached to a backing strip. The attractant and pesticide diffuse through the strip of plastic and the insect, attracted to the strip, is killed on contact with the pesticide. This method is clearly superior to the insecticide spray if the attractant is selective and only small amounts of agent are needed.

Water-born pests require special treatment because of the diluting effect of the medium. Compounding of Bayluscide (5.20) in a neoprene support gives protection as a molluscicide against Schistomiasis, the major snail-borne parasitic disease carried by water snails. An alternative method is to use drip feed into irrigation or drainage ditches. Aquitic weeds are also killed by compounding certain herbicides, surface weeds such as water hyacinth and duckweed, for example, are effectively controlled with butoxyethyl 2,4-D-(5.22), incorporated into rubber and used with a flotation attachment. Bottom growing plants such as alligator weeds are attacked by similar preparations except that the formulation has a sinker to keep the herbicide release at the bottom.

CHART–5





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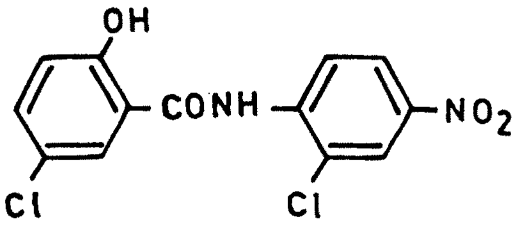

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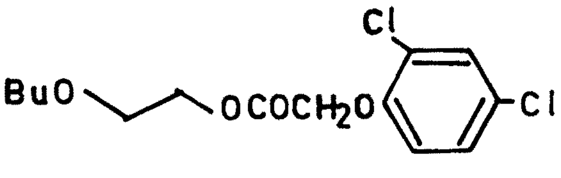

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