

Connections

Building on:

- Carbonyl chemistry [ch12](#) & [ch14](#)
- Substitution reactions [ch17](#)
- Radical reactions [ch39](#)
- Protecting groups and synthesis [ch24–ch25](#)
- The aldol reaction [ch27](#)
- Making double bonds [ch31](#)
- Cycloadditions [ch35](#)
- Heterocycles [ch43–ch44](#)
- Organometallics [ch48](#)
- The chemistry of life [ch49](#)
- Natural products [ch51](#)

Arriving at:

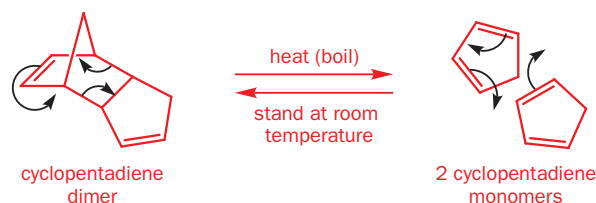
- Some molecules react together to form oligomers
- Some molecules spontaneously polymerize
- Polyamides, polyesters, and polycarbonates are formed by substitution reactions at carbonyl groups
- Polyurethane foams are formed by nucleophilic attack on isocyanates
- Epoxy adhesives work by polymerization via substitution reactions at saturated carbon
- The most important polymers are derived from alkene monomers
- Alkenes can be polymerized by radical, cationic, anionic, or organometallic methods
- Cross-linking or co-polymerization changes the physical properties of polymers
- Reactions on polymers are involved in paint drying, rubber strengthening, and the chemical synthesis of peptides

Most of the things you can see about you at this moment are made of organic polymers. Skin, clothes, paper, hair, wood, plastic, and paint are among them. Teeth, muscle, glue, cling film, starch, crab shells, and marmalade are all polymer-based too. In this chapter we will explore the world of polymers. We will ask questions like these:

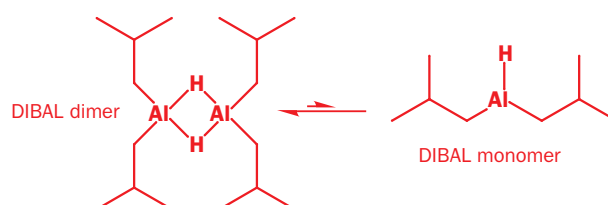
- What makes a molecule prefer to react with others of its kind to form a polymer?
- What mechanisms are available for polymerization reactions?
- How can polymerization reactions be controlled?
- How are the properties of polymers related to their molecular structure?

Monomers, dimers, and oligomers

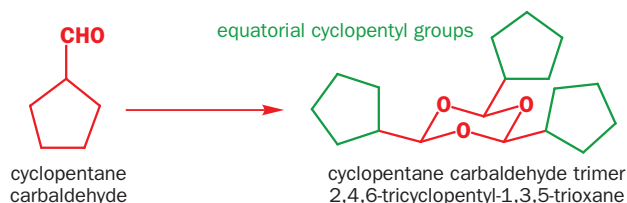
Cyclopentadiene featured in Chapter 35 as an important diene in the Diels–Alder reaction. If you try to buy ‘cyclopentadiene’ you will find that the catalogues list only ‘dicyclopentadiene’ or ‘cyclopentadiene dimer’. The dimerization of cyclopentadiene is reversible: the monomer dimerizes by a Diels–Alder reaction at room temperature to give the dimer and the reaction is reversed on heating. So the dimer is a good source of the monomer.



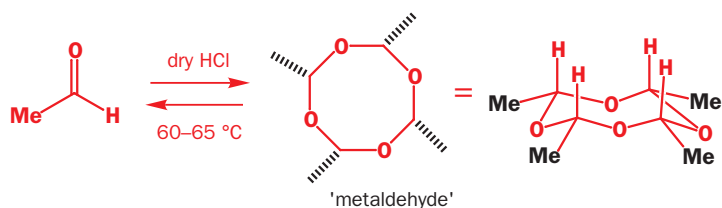
Other familiar cases of stable dimers are neutral boron and aluminium hydrides. DIBAL, for example, exists as two molecules linked by Al–H–Al bonds in a four-membered ring. Again, the dimer is a practical source of monomer for chemical reactions.



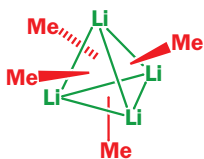
Simple aldehydes easily form trimers. When cyclopentanecarbaldehyde is prepared, it is a colourless liquid. On standing, particularly with traces of acid, it forms the crystalline trimer. The trimer is a stable six-membered heterocycle with all substituents equatorial



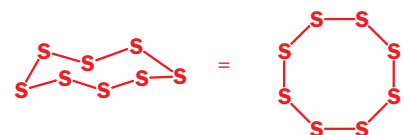
Acetaldehyde (ethanal) forms a liquid trimer called 'paraldehyde', which reverts to the monomer on distillation with catalytic acid. More interesting is 'metaldehyde', the common slug poison, which is an all-*cis* tetramer (2,4,6,8-tetramethyl-1,3,5,7-tetroxocane) formed from acetaldehyde with dry HCl at below 0°C. Metaldehyde is a white crystalline solid that has all the methyl groups pseudoequatorial, and it reverts to acetaldehyde on heating.



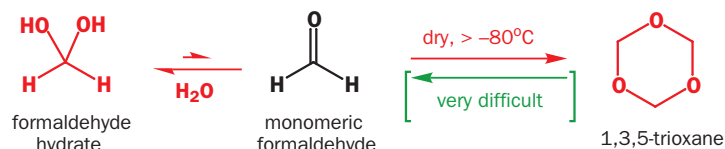
Another tetramer is methyl lithium. MeLi is a very reactive compound in the monomeric state, and it crystallizes as a tetramer: a tetrahedron of lithium atoms with a methyl group 'plugged in' to the centre of each face.



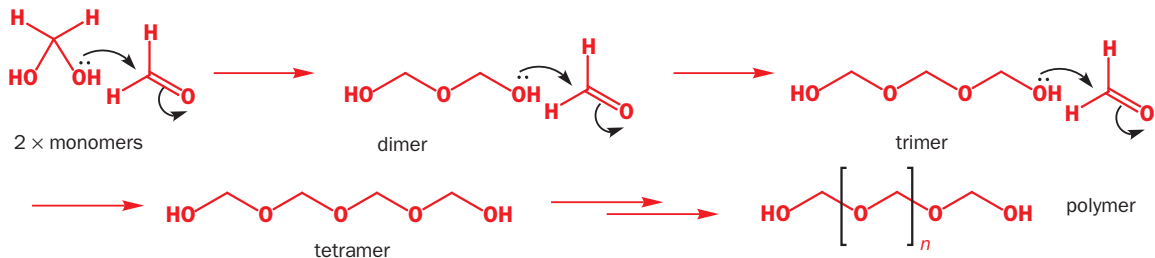
Whereas oxygen gas consists of diatomic molecules O₂, crystalline sulfur is S₈, a cyclic octomer. Such multiples are usually called **oligomers** (*oligo* = a few). The monomer in this case would be the sulfur atom. The shape of the S₈ ring is very similar to that of the eight-membered ring of metaldehyde.



If you buy formaldehyde (methanal), which is in fact a gas, b.p. -19°C, you have four choices. You can buy a 37% aqueous solution 'formalin' which is mostly hydrate in equilibrium with a small amount of formaldehyde, or the crystalline trimer (1,3,5-trioxane), or a white solid called (misleadingly) 'paraformaldehyde', or another white solid called polyoxymethylene.

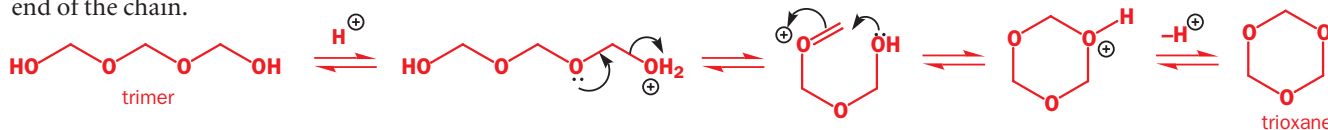


Trioxane is not a good source of formaldehyde as it is very stable but the two other solids are good sources. Both paraformaldehyde and, more obviously, polyoxymethylene are **polymers**. Each molecule of either polymer consists of a large number of formaldehyde molecules reacted together.



Paraformaldehyde is made by evaporation of aqueous formaldehyde to dryness and is a water-soluble polymer. Polyoxymethylene is made by heating formaldehyde with catalytic sulfuric acid and is *not* soluble in water. They are both linear polymers of formaldehyde, so how can they be so different? The answer is in the polymer chain length—the *n* in the diagram. Paraformaldehyde is water-soluble because it has short chain lengths, about *n* = 8 on average, and so it has many hydrophilic OH groups. Polyoxymethylene has much longer chain lengths, *n* > 100 on average, and so has very few OH groups per monomer of formaldehyde.

Trioxane is formed when the trimer cyclizes instead of continuing to polymerize. All the oligomers and polymers of formaldehyde have this potential as there is a hemiacetal group at each end of the chain.



● Summary of what we know so far

Not much, you might think. Actually we have mentioned some important things about polymerization, which we will discuss further in the pages that follow.

- Polymerization tends to occur at low temperature
- Depolymerization tends to occur at high temperature
- Polymerization competes with cyclic oligomer formation
- Different polymers of the same monomer can have different chain lengths
- The chain length varies about a mean value in a given polymer
- The properties of polymers depend on chain length (among other things!)

Check back over these last few pages to make sure you see which pieces of evidence establish each of these points.

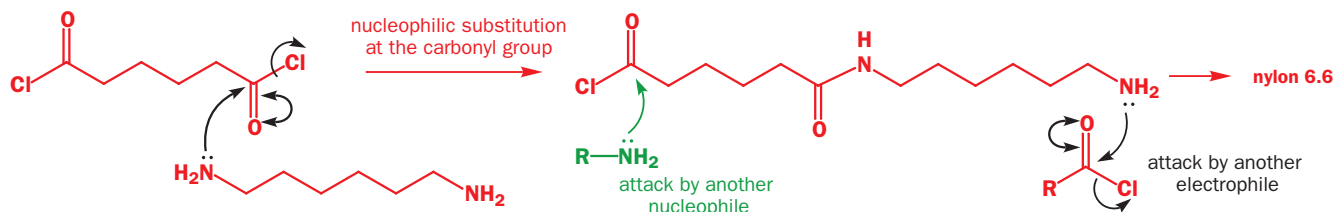
There is no exact limit to the terms oligomer and polymer. You have just seen us refer to paraformaldehyde—on average an octamer—as a polymer. The terms monomer, dimer, trimer, tetramer, etc. do have exact meanings. Oligomer usually means > 3 and < 25 but different authors will use the term in different ways.

Polymerization by carbonyl substitution reactions

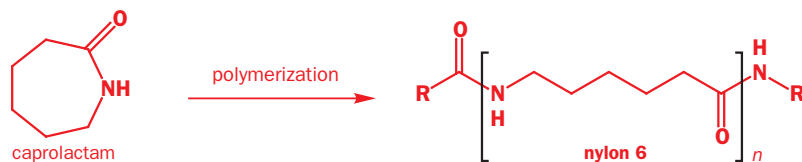
In general, carbonyl compounds do not polymerize by themselves. It is only the exceptional reactivity of formaldehyde as an electrophile that allows repeated nucleophilic addition of hemiacetal intermediates. A more common way to polymerize carbonyl compounds is to use two different functional groups that react together by carbonyl substitution to form a stable functional group such as an amide or an ester. Nylon is just such a polymer.

Polyamides

You may have carried out the nylon rope trick in a practical class. The diacid chloride of adipic acid is dissolved in a layer of a heavy organic solvent such as CCl_4 and a layer of aqueous hexane-1,6-diamine is carefully placed on top. With a pair of tweezers you can pick up the film of polymer that forms at the interface and draw it out to form a fibre. The reaction is a simple amide formation.

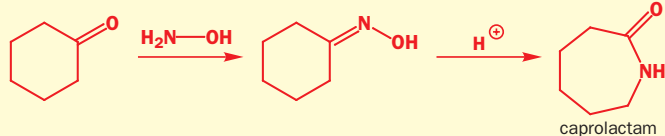


After the first amide is formed, one end of the new molecule is nucleophilic and the other electrophilic so that it can grow at both ends. The polymer is made up of alternating $-\text{NH}(\text{CH}_2)_6\text{NH}-$ and $-(\text{CH}_2)_4\text{CO}-$ units, each having six carbon atoms, and is called 'nylon 6.6'. Another and much simpler way to make nylon is to polymerize caprolactam. This monomer is a cyclic amide and the polymer does not have alternating units—instead, each unit is the same.

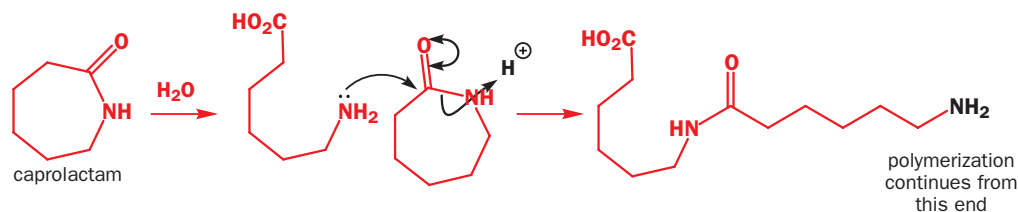


Caprolactam

Caprolactam can be made by the Beckmann rearrangement of the oxime of cyclohexanone. (Check that you can draw the mechanisms, of both these reactions and look at Chapters 14 and 37 if you find you can't.) Cyclohexanone used to be made by the oxidation of cyclohexane with molecular oxygen until the explosion at Flixborough in Lincolnshire on 1 June 1974 that killed 28 people. Now cyclohexanone is made from phenol.



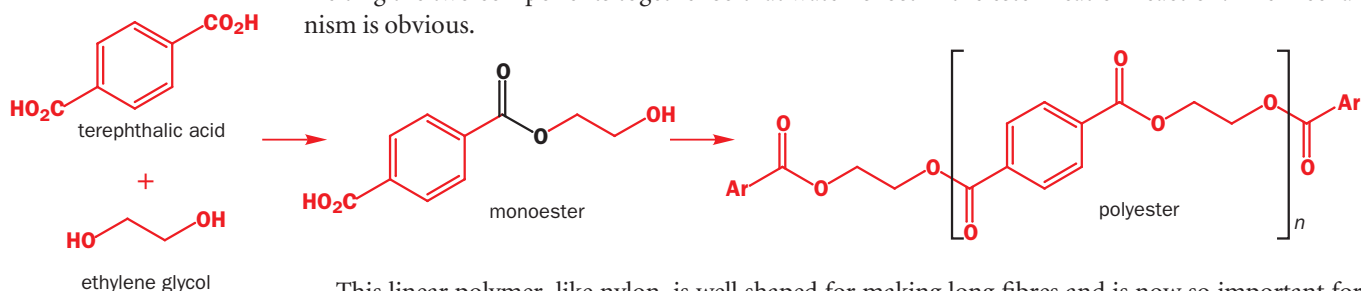
So how is this polymerization initiated? A small amount of water is added to hydrolyse some of the caprolactam to 6-aminohexanoic acid. The amino group can then attack another molecule of caprolactam and so on. The amount of water added influences the average chain length of the polymer.



These synthetic polyamides are made up of the same repeating unit but will inevitably have a range of molecular weights as the polymer length will vary. This is a different story from that of the natural polyamides—peptides and proteins—that you met in Chapter 49. Those polymers were made of twenty or so different monomers (the amino acids) combined in a precise order with a precise stereochemistry and all molecules of the same protein have the same length. Nonetheless, some of their uses are almost identical: both nylon and wool are polyamides, for example.

Polyesters

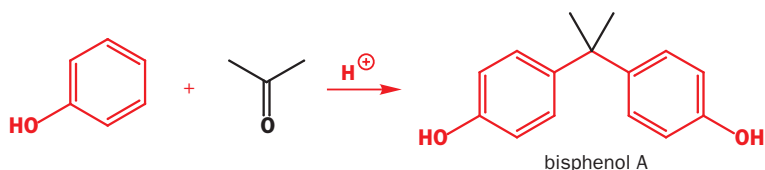
Much the same act can be carried out with dicarboxylic acids and diols. The most famous example is the polymer of ethylene glycol (ethane-1,2-diol) and terephthalic acid, which can be made simply by melting the two components together so that water is lost in the esterification reaction. The mechanism is obvious.



This linear polymer, like nylon, is well shaped for making long fibres and is now so important for making clothes that it is usually just called 'polyester' rather than by the older names such as 'Terylene'.

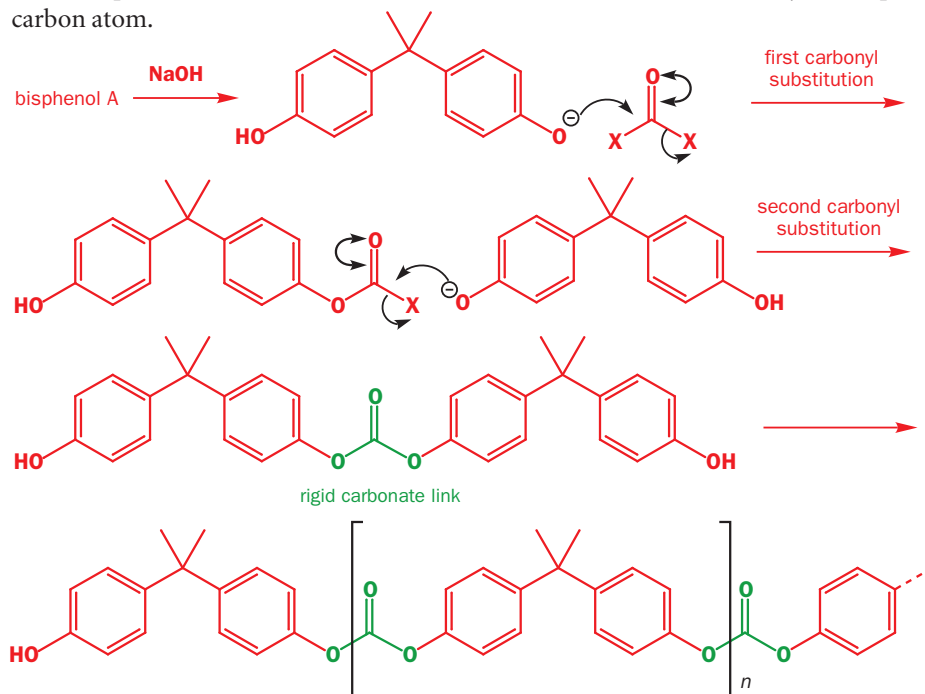
Polycarbonates

These too are made by carbonyl substitution reactions, but this time the nucleophile is aromatic and the electrophile is an aliphatic derivative of carbonic acid such as phosgene (COCl_2) or a carbonate diester $[\text{CO}(\text{OR})_2]$. The aromatic nucleophile is a diphenol but the two OH groups are on separate rings joined together by an electrophilic aromatic substitution. This compound is called bisphenol A and has many other applications.



Make sure that you can draw the mechanism for this reaction—two electrophilic aromatic substitutions are involved (Chapter 22). If you need a hint, look at the synthesis of Bakelite on the next page.

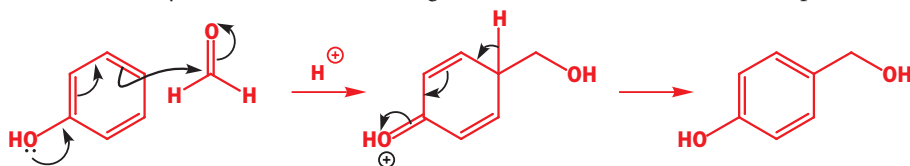
The diphenol reacts with the carbonic acid derivative, which is doubly electrophilic at the same carbon atom.



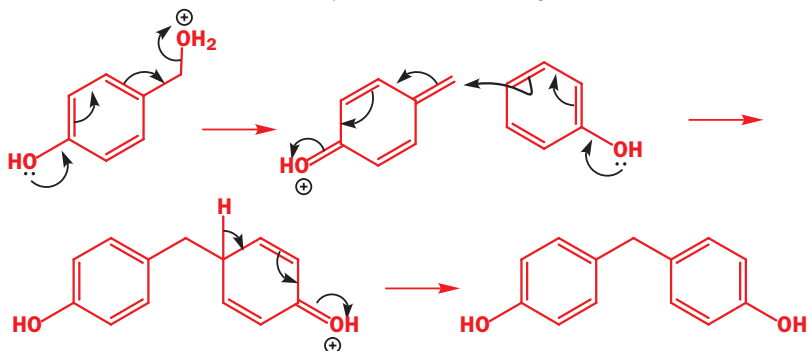
After two carbonyl substitutions the rigid carbonate ester group is formed. This polymer is neither as flexible nor as linear as the previous examples. The carbonate portion is conjugated to the benzene rings and held rigidly in the conformation shown by the anomeric effect (Chapter 42). The only flexibility is where the CMe_2 group links the two benzene rings. This is a polymer that combines transparency, lightness, and strength with just enough flexibility not to be brittle. Your safety glasses are probably made of polycarbonate.

Polymerization by electrophilic aromatic substitution

The first synthetic polymers to be of any use were the 'phenol formaldehyde resins' of which the most famous, Bakelite, was discovered by Bäckeland at the turn of the century. He combined phenol and formaldehyde in acid solution and got a reaction that starts like the bisphenol A synthesis.

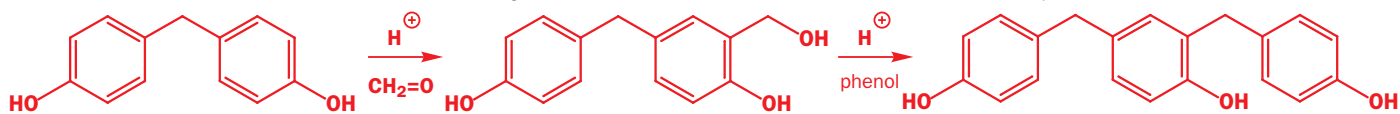


A second acid-catalysed electrophilic aromatic substitution now occurs to link a second phenol to the first. The rather stable benzylic cation makes a good intermediate.

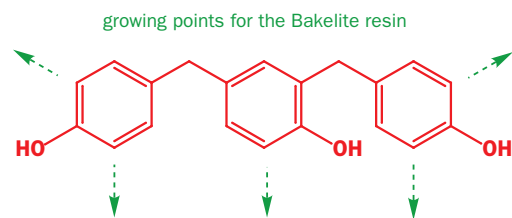


■ If you tried a moment ago, as we suggested, to write the mechanism for the formation of bisphenol A, this is what you should have done (but with acetone, of course, instead of formaldehyde).

Formaldehyde is reactive enough to continue and put another substituent ortho to the OH group in one of the rings. The mechanisms are the same as those we have just written.



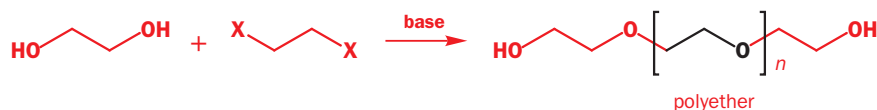
The carbon chains are *meta* related on the central ring so for the first time we have a **branched polymer**. Complexity can rapidly increase as more phenols linked through more formaldehydes can be joined on to this core structure at several points. Each benzene ring could, in theory, form three new C–C bonds.



These polymers have the useful property of being **thermosetting**—they are made from liquid mixtures that polymerize on heating to form a solid polymer, and can therefore be moulded easily.

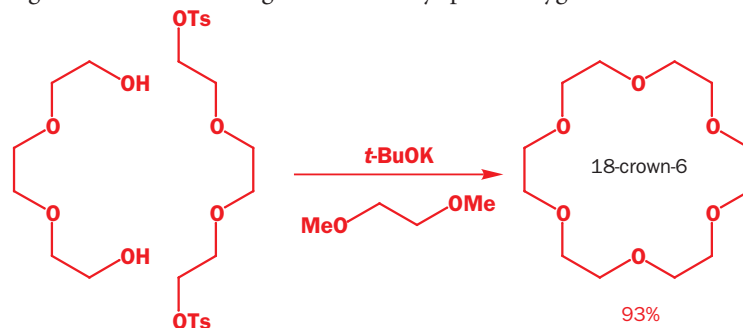
Polymerization by the S_N2 reaction

In principle, co-polymerization of a 1,2-diol and a 1,2-dihalide might lead to a polyether.

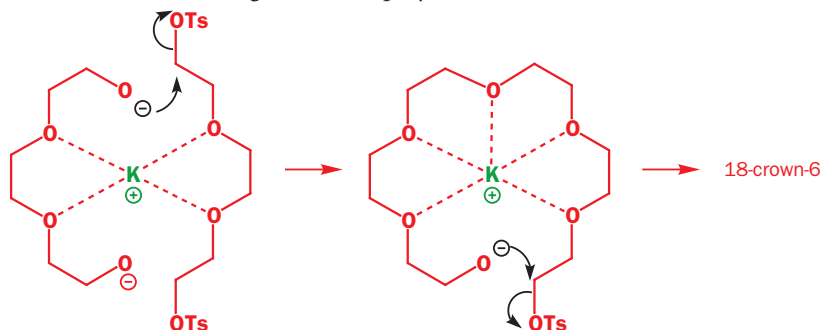


This route is not used because of the large amounts of base needed. One molecule of base is consumed for each new C–O bond made, and these reactions terminate quickly before long chains are made. It is more useful for making the cyclic oligomers called ‘crown ethers’. 18-Crown-6 has an eighteen-membered ring with six evenly spaced oxygen atoms.

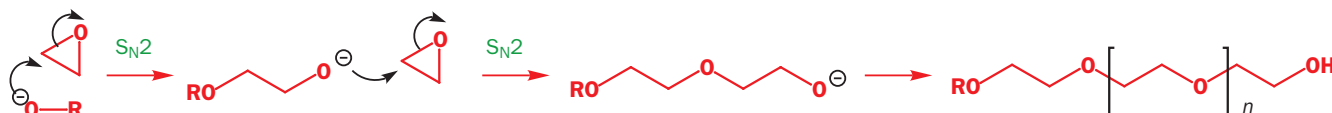
■ We mentioned the inventor of crown ethers, Charles Pedersen, on p. 974.



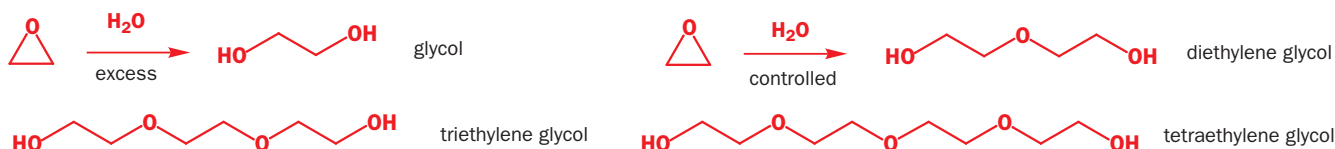
These crown ethers have cavities ideal for complex formation with metal ions. This one, 18-crown-6, is the right size for potassium ions, and a solution of KMnO₄ and 18-crown-6 in benzene, so-called ‘purple benzene’, is a useful oxidizing agent. The high-yielding oligomerization is a template reaction with a potassium ion holding the two reagents together. If a base such as Bu₄N⁺OH[−] (which cannot form complexes) is used with the same reagents, linear polymers result.



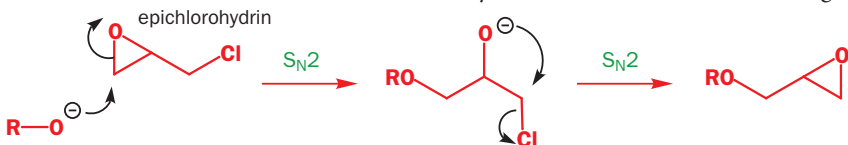
A more practical way to make linear polyethers is by polymerization of epoxides. Each time an epoxide is opened by a nucleophile, it releases a nucleophilic oxyanion that can attack another epoxide, and so on. The whole process can be initiated by just a catalytic amount of a nucleophile such as an alkoxide or an amine.



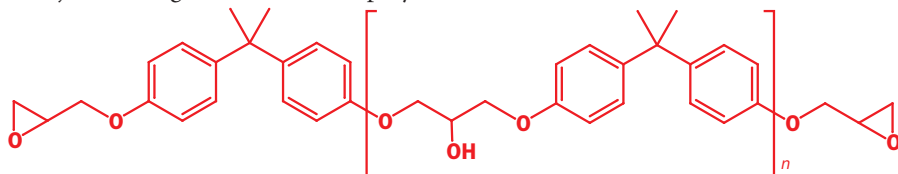
This reaction cannot be controlled—once it is initiated, it runs to completion. Treatment of ethylene oxide with controlled amounts of water does lead to the important coolant ethylene glycol (excess water) and the oligomers di-, tri-, and tetraethylene glycol. These are important solvents for polar compounds. Triethylene glycol is also the starting material for the synthesis of 18-crown-6 above.



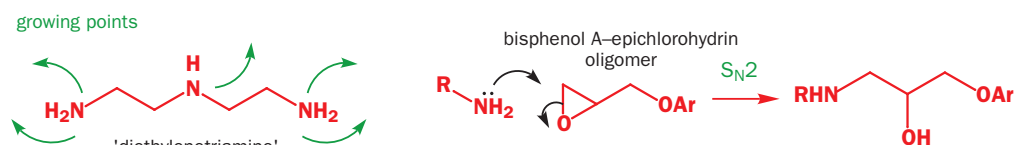
A subtle method of controlling the reaction so that it can be made to run at will is to use bisphenol A as the diol and epichlorohydrin as the epoxide. Epichlorohydrin reacts with nucleophiles at the epoxide end, but the released alkoxide ion immediately closes down at the other end to give a new epoxide.



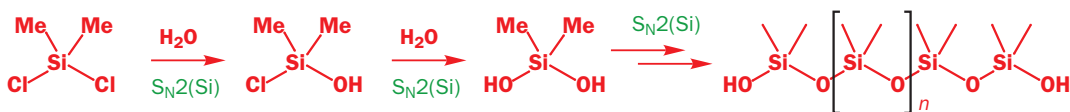
With bisphenol A in alkaline solution, this reaction happens twice and a bis adduct is formed. Further reaction with more bisphenol A creates oligomers with about 8–10 bisphenol A molecules and an epoxide at each end. This is a reasonably stable neutral compound with two terminal epoxides, just waiting for initiation for polymerization to start.



In the CIBA–Geigy glue Araldite, strong enough to glue aeroplane wings on to the fuselage, a solution of this oligomer is mixed with a solution of a polyfunctional amine such as diethylenetriamine. Since each NH₂ group can react twice and the NH group once with epoxides, the final polymer has a densely cross-linked structure and is very strong. The reaction is again a simple S_N2 process.



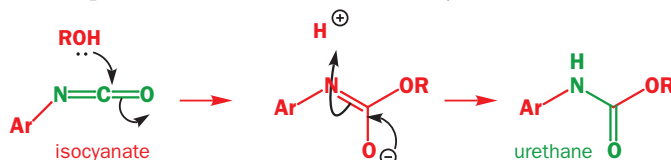
A totally different kind of polymer is a poly-silylether. Dimethylsilyl dichloride polymerizes easily on treatment with hydroxide. Silicon is more susceptible to the S_N2 reaction than is carbon and long chains grow quickly.



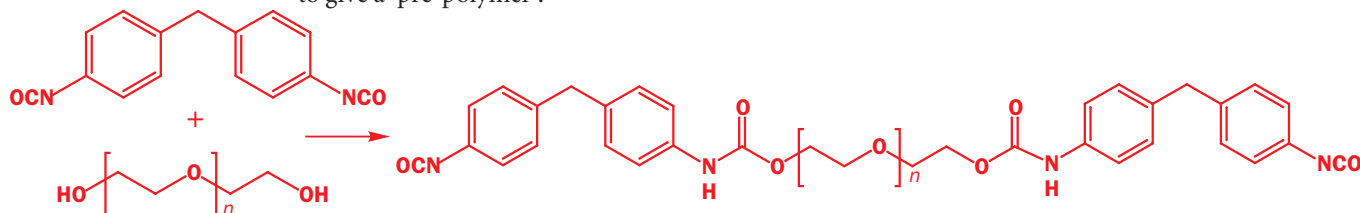
This linear poly(dimethylsiloxane) is an oil and is used in the lab in oil baths as it is more stable and less smelly than conventional paraffin baths at high temperatures.

Polymerization by nucleophilic attack on isocyanates

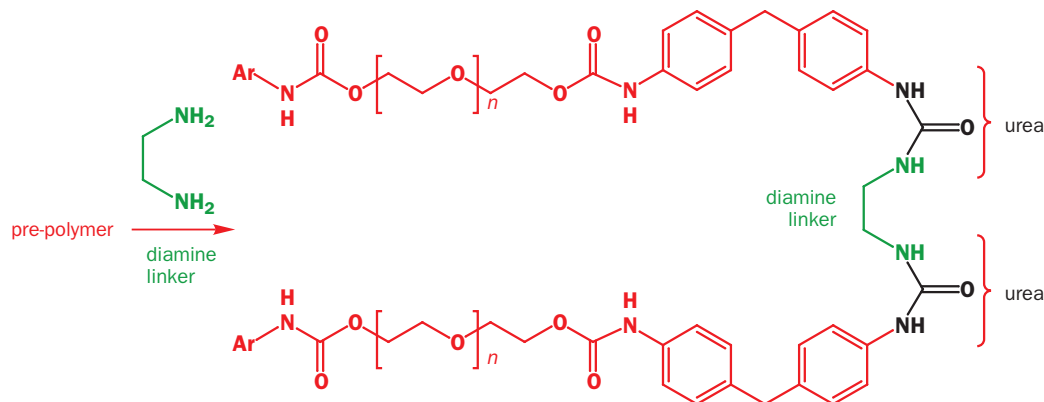
Isocyanates react with alcohol nucleophiles to give **urethanes**—hybrids between carbonates and ureas—half-esters and half-amides of carbonic acid. Nucleophilic attack occurs at the very reactive linear (sp) carbon in the centre of the isocyanate.



To make a polymer it is necessary to react aryl diisocyanates with diols. Some important polymers of the type, called **elastanes**, are made by using long-chain aliphatic diols from partly polymerized epoxides, rather like those discussed in the last section, and reacting them with diaryl diisocyanates to give a 'pre-polymer'.



The next stage is to initiate an exothermic linking of the residual terminal isocyanates with simple diamines. The reaction is again nucleophilic attack on the isocyanate, but the new functional group is now a urea rather than a urethane. Showing just one end of the growing polymer:



These polymers have short rigid portions (the aromatic rings and the ureas) joined by short flexible 'hinges' (the diamine linker and the CH₂ group between the aromatic ring) and long very flexible portions (the polyether) whose length can be adjusted. The polymer is easily stretched and regains its shape on relaxation—it is an **elastomer**.

Why should it matter that the second polymerization is exothermic? If the diamine linker is added as a solution in a volatile hydrocarbon such as heptane, the heat of the polymerization causes the heptane to boil and the polymer becomes a foam. What is more, the length of the polyether chain determines what kind of foam results. Shorter (~500 -OCH₂CH₂O- units) chains give rigid foams but longer chains (>1000 -OCH₂CH₂O- units) give soft foams. This is only a bare outline of one of the many skills polymer chemists now have in the design of materials. The results are all around us.

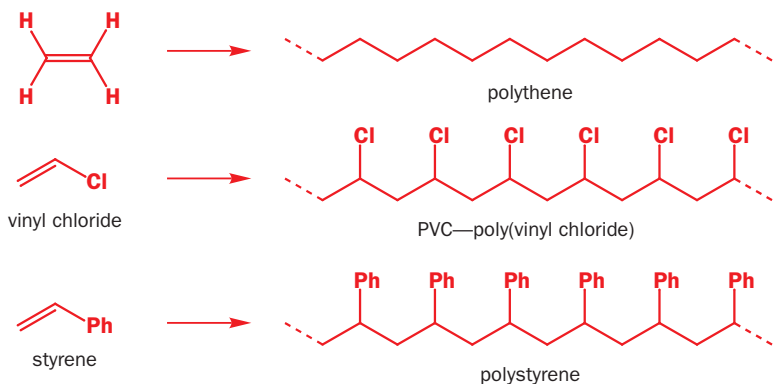
So far we have discussed polymerization that has been essentially of one kind—bifunctional molecules have combined in normal ionic reactions familiar from the rest of organic chemistry where a nucleophilic functional group attacks an electrophilic functional group. The new bonds have generally been C–O or C–N. We need now to look at the polymerization of alkenes. In these reactions, C–C bonds will be formed and many of the reactions may be new to you.

Polymerization of alkenes

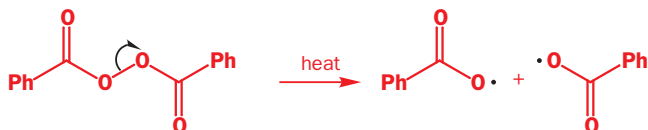
Formaldehyde polymerizes because the two resulting C–O σ bonds are very slightly more stable than its C=O π bond, but the balance is quite fine. Alkenes are different: two C–C σ bonds are always considerably more stable than an alkene, so thermodynamics is very much on the side of alkene polymerization. However, there is a kinetic problem. Formaldehyde polymerizes without our intervention, but alkenes do not. We will discuss four quite distinct mechanisms by which alkene polymerization can be initiated—two ionic, one organometallic, and one radical.

Radical polymerization of alkenes: the most important polymerization of all

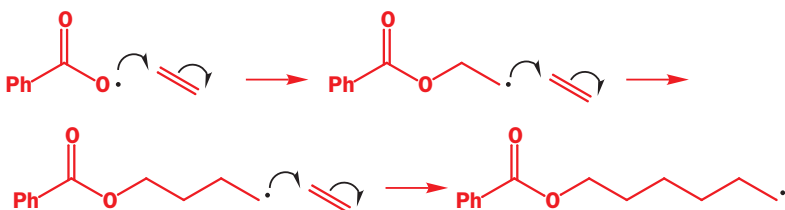
We will start with the radical mechanism simply because it is the most important. A bigger tonnage of polymers is made by this method than by any other, including the three most familiar ones—polythene (polyethylene), PVC (poly(vinyl chloride)), and polystyrene.



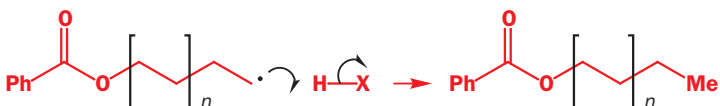
Polythene is difficult to make and was discovered only when chemists at ICI were attempting to react ethylene with other compounds under high pressure. Even with the correct reagents, radical initiators like AIBN or peroxides (Chapter 39), high pressures and temperatures are still needed. At 75 °C and 1700 atmospheres pressure ethylene polymerization, initiated by dibenzoyl peroxide, is a radical chain reaction. The peroxide is first cleaved homolytically to give two benzoate radicals.



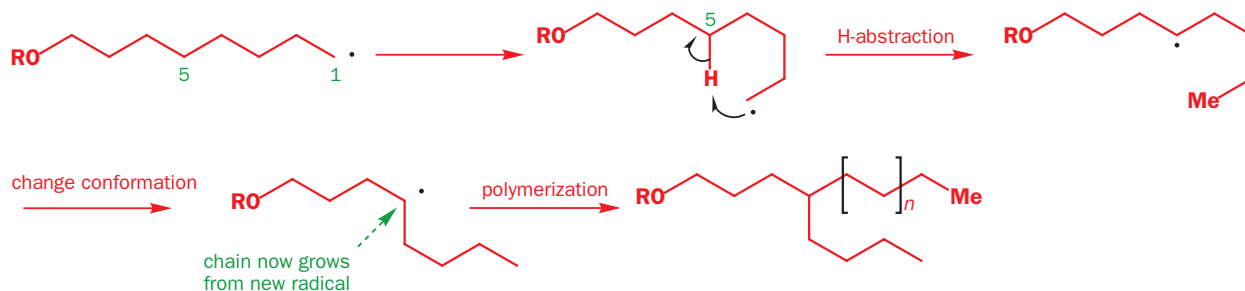
These oxyradicals add to the alkene to give an unstable primary carbon radical that adds to another molecule of alkene, and so on.



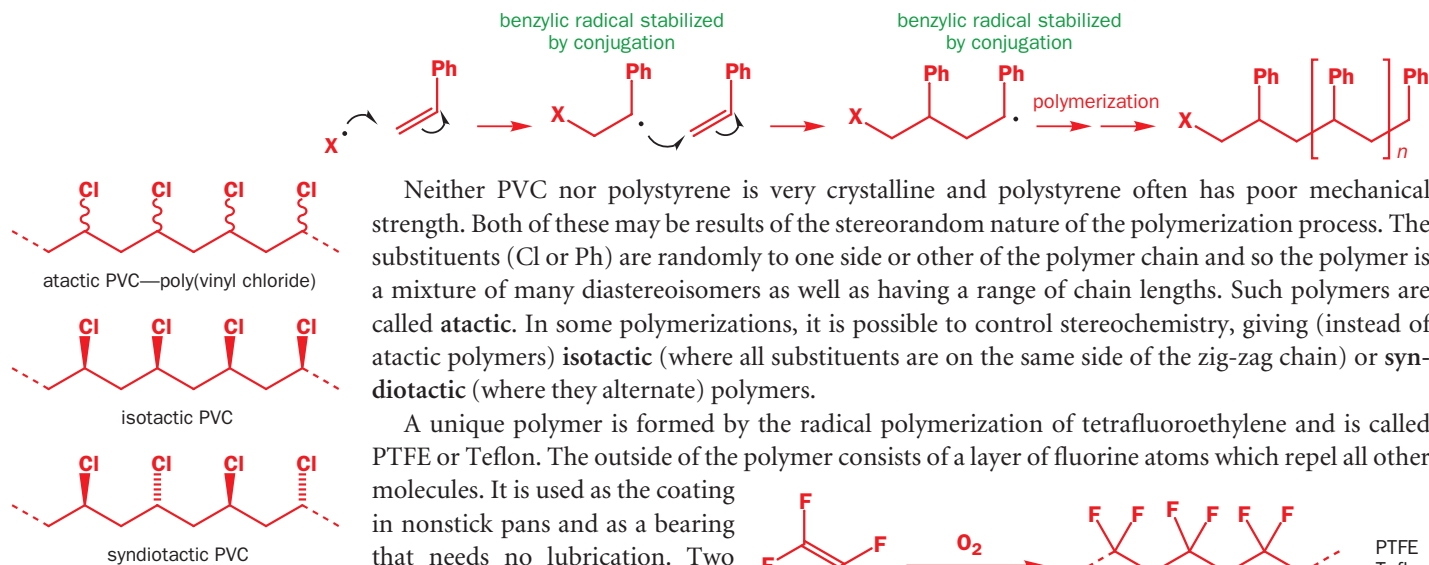
Eventually, the chain is terminated by combination with another radical (unlikely) or by hydrogen abstraction from another polymer molecule. This approach to polythene synthesis, using ethylene liquefied by pressure and small amounts (<0.005% by weight) of peroxide, produces relatively low molecular weight polymer as a white solid.



Radical polymerization can lead to branched polymers by intramolecular hydrogen atom transfer, a process sometimes called **backbiting**. Removal of H through a six-membered transition state moves the growing radical atom five atoms back down the chain, and leads to butyl side-chains. A more stable secondary radical is produced and chain growth then occurs from that point.

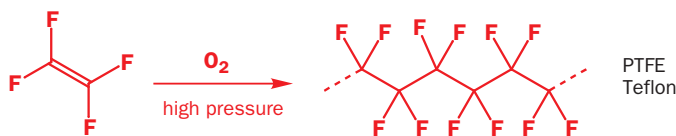


Radical polymerization of vinyl chloride and styrene is much easier than that of ethylene because the intermediate radicals are more stable. You saw in Chapter 39 that any substituent stabilizes a radical, but Cl and Ph are particularly good because of conjugation of the unpaired electron with a lone pair on chlorine or the π bonds in the benzene ring.



Neither PVC nor polystyrene is very crystalline and polystyrene often has poor mechanical strength. Both of these may be results of the stereorandom nature of the polymerization process. The substituents (Cl or Ph) are randomly to one side or other of the polymer chain and so the polymer is a mixture of many diastereoisomers as well as having a range of chain lengths. Such polymers are called **atactic**. In some polymerizations, it is possible to control stereochemistry, giving (instead of atactic polymers) **isotactic** (where all substituents are on the same side of the zig-zag chain) or **syndiotactic** (where they alternate) polymers.

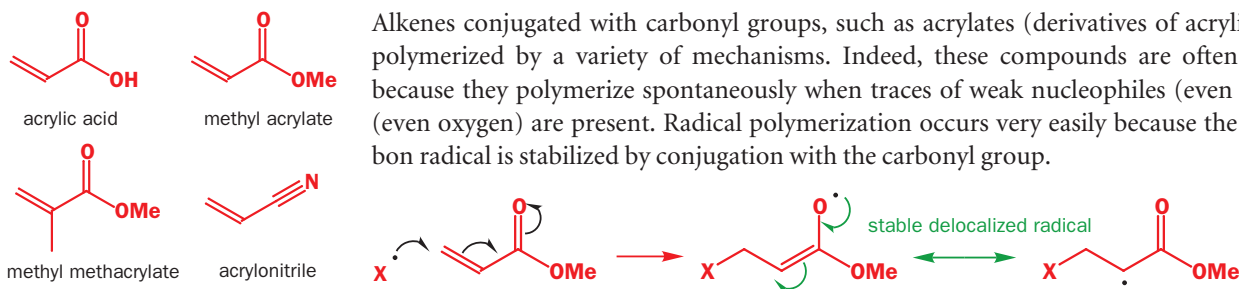
A unique polymer is formed by the radical polymerization of tetrafluoroethylene and is called PTFE or Teflon. The outside of the polymer consists of a layer of fluorine atoms which repel all other molecules. It is used as the coating in nonstick pans and as a bearing that needs no lubrication. Two pieces of Teflon slide across one another almost without friction.



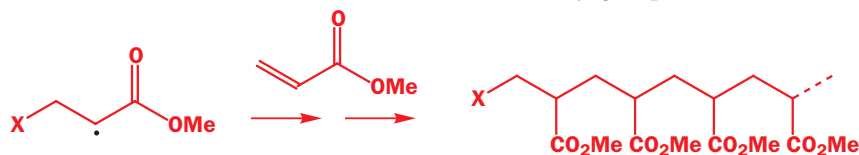
Something else is special about this polymerization—it is done in solution. Normally, no solvent is used because it would be difficult to separate from the polymer product. However, PTFE interacts with no other molecules. It precipitates from all known solvents and can be isolated easily by filtration.

Acrylics—easily made polymers of acrylate esters

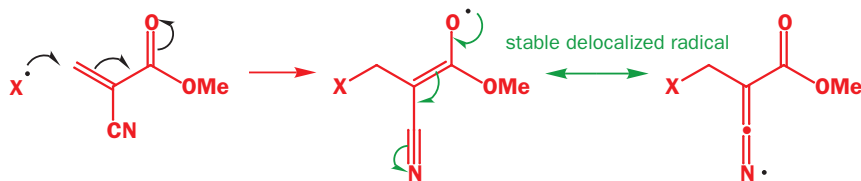
Alkenes conjugated with carbonyl groups, such as acrylates (derivatives of acrylic acid), are easily polymerized by a variety of mechanisms. Indeed, these compounds are often difficult to store because they polymerize spontaneously when traces of weak nucleophiles (even water) or radicals (even oxygen) are present. Radical polymerization occurs very easily because the intermediate carbon radical is stabilized by conjugation with the carbonyl group.



Polymerization follows the mechanism that we have seen several times already, and each radical has the same additional stabilization from the carbonyl group.



With two stabilizing groups on the carbon radical, polymerization becomes even easier. A famous example is ‘SuperGlue’, which is methyl 2-cyanoacrylate. The monomer in the tube polymerizes on to any surface (wood, metal, plastic, fingers, eyelids, lips, ...) catalysed by traces of moisture or air, and the bonds, once formed, are very difficult to break. The intermediate radical in this polymerization is stabilized by both CN and CO₂Me groups.



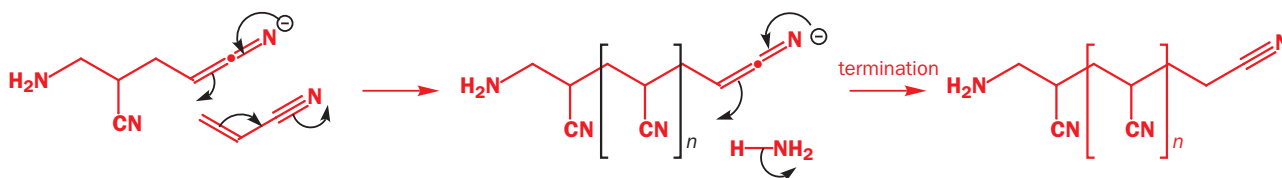
Though there are many other polymers made by radical pathways, we need now to look at the two main ionic routes—*anionic* and *cationic* polymerization.

Anionic polymerization is multiple conjugate addition

We have seen in Chapter 23 how alkenes conjugated with electron-withdrawing groups undergo conjugate addition to give an enolate anion as an intermediate. This enolate anion is itself nucleophilic and could attack another molecule of the conjugate alkene. Acrylonitrile is polymerized in liquid ammonia at low temperature by this method. Small amounts of alkali metal are added to generate NH₂[−], initiating polymerization.

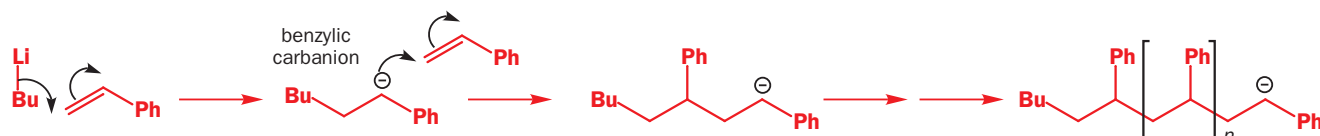


The chain grows by repetition of the last step: each new C–C bond-forming step produces a new anion stabilized by the nitrile group. Termination probably occurs most frequently by proton capture from the solvent. The result is poly(acrylonitrile).

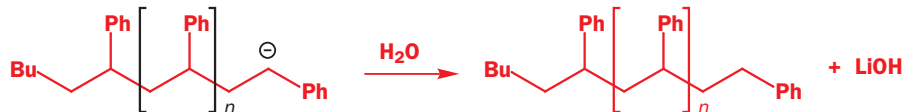


‘Living polymers’ by the anionic polymerization of styrene

Nucleophilic addition to styrene is possible only because the intermediate carbanion is stabilized by conjugation into the benzene ring. It needs a more reactive carbanion than the benzyl anion to initiate the polymerization, and an unstabilized nonconjugated organolithium compound like butyl lithium is the answer.



It is clear enough how the chain is propagated, but how is it terminated? You might expect protonation to bring things to a close, but there cannot be any acid (even a weak one) present—if there were, it would have already been destroyed by the butyl lithium. To terminate the polymerization, a weak acid must be added in a separate step—water will do.



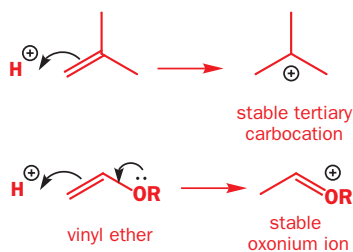
When this polystyrene sample is analysed, it is found to consist of a remarkably narrow range of chain lengths—almost all the chains are the same. Such polymers are known as **monodisperse**. This result must mean that all the BuLi molecules must add immediately to a styrene molecule and that chain growth then occurs at the same rate for each chain until the styrene is used up.

There is a useful expansion of this idea. Under the conditions of the polymerization (before the water is added), these almost identical chain lengths all end with a carbanion. If, instead of adding water, we add another monomer (say, 4-chlorostyrene) it too will add to the end of the chain and polymerize until it is used up, producing new chains again of about the same length. This will be the situation after the second polymerization.



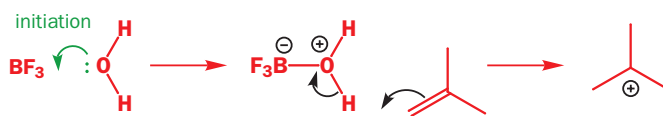
And still the polymer is active towards further polymerization. Indeed, these polymers are called ‘living polymers’ because they can go on growing when a new monomer is added. The final result, after as many monomers have been added as is required and the living polymer has been quenched, is a polymer with blocks of one monomer followed by blocks of another. These polymers are called **block co-polymers** for obvious reasons.

Cationic polymerization requires stabilized carbocations



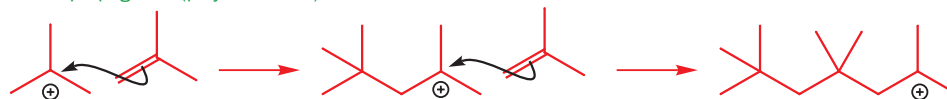
Cationic polymerization is used only for alkenes that can give a tertiary carbocation on protonation or for vinyl ethers that can give an oxonium ion. In other words, the cation intermediate must be quite stable. If it isn't, the chain is terminated too quickly by loss of a proton.

The initiator for isobutene (2-methylpropene) polymerization is usually a Lewis acid with a proton source. We shall illustrate isobutene polymerization with BF_3 as the Lewis acid and water as the proton source.



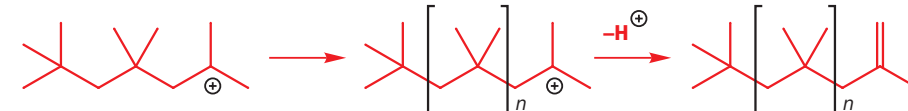
The tertiary carbocation can now act as an electrophile and attack the alkene to form another tertiary carbocation of similar stability and reactivity to the first. So the polymerization continues.

Chain propagation (polymerization)

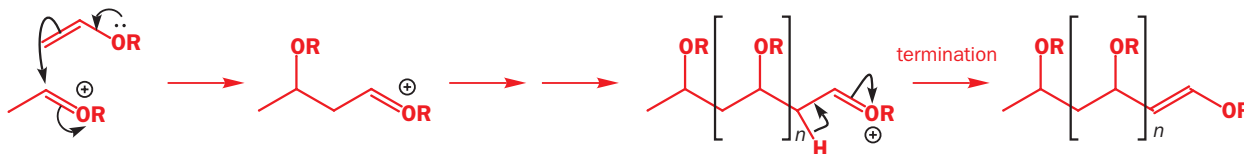


The termination will be the loss of a proton to form an alkene (an E1 reaction). Providing that the tertiary carbocation is reasonably stable, this will be a slower process than chain elongation, especially as there are no good bases around, and long polymer chains may result.

termination



The polymerization of vinyl ethers follows much the same mechanism, using the oxonium ion as an intermediate instead of the tertiary carbocation. Termination might again be by loss of a proton or by picking up a nucleophile at the oxonium ion centre.

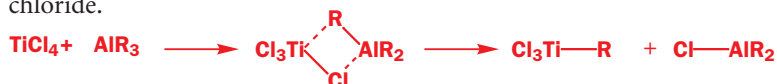


One of the best polymers for building strong rigid heat-resistant objects is polypropylene but this can be made by none of the methods we have examined so far. We need now to look at the polymerization of alkenes in the coordination sphere of a transition metal.

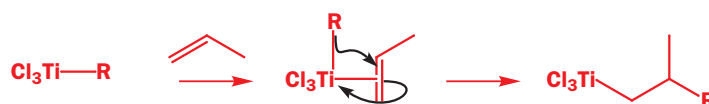
Ziegler–Natta polymerization gives isotactic polypropylene

Propylene can be polymerized by a titanium/aluminium catalyst developed by Ziegler and Natta. The mere fact that polymerization is possible is remarkable, but this polymer also has stereoregularity and can be isotactic. The overall process is shown on the right.

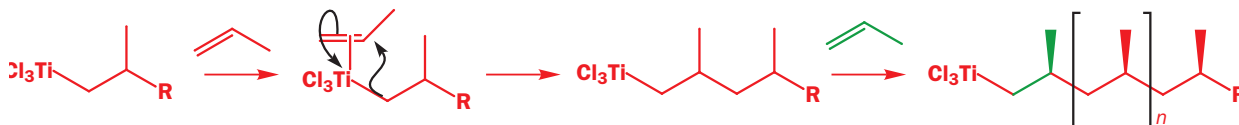
The mixed metal compounds react to form a titanium σ complex that is the true catalyst for the polymerization. An alkyl group is transferred from aluminium to titanium in exchange for a chloride.



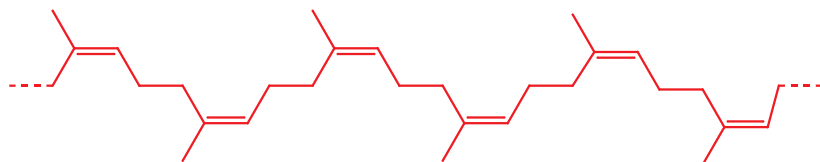
The alkyl–Ti σ complex can form a π complex with the first molecule of propene and then carry out a carbo-titanation of the π bond. This establishes the first C–C bond.



Insertion of the next propene by a repeat of the previous step now starts the polymerization. Each new C–C bond is formed on the coordination sphere of the Ti atom by transformation of a π complex into a σ complex. Repetition of this process leads to polymerization. We have shown the polymer with isotactic stereochemistry, and this control over the stereochemistry reflects the close proximity of the new propene molecule and the growing polymer.



One important elastane polymer that can be made by polymerization in a Ziegler–Natta fashion is rubber. Natural rubber is a polymeric terpene (Chapter 51) made from mevalonic acid and has a branched structure with regular trisubstituted alkenes, which are all in the *Z*-configuration.

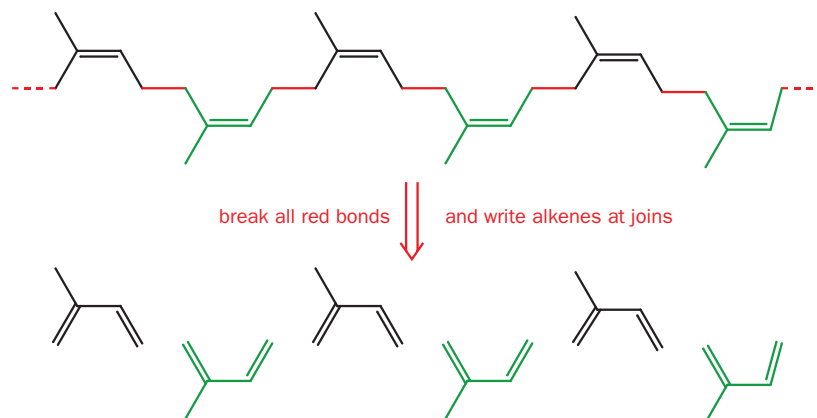


Looked at as a polymer, rubber is made up of C_5 units joined together by C–C bonds. We should naturally expect to make a hydrocarbon polymer from alkenes, so if we separate these C_5 units we find that they are dienes rather than simple alkenes. If you have read Chapter 51, they might be familiar to you as the isoprene units from which terpenes were originally supposed to be made.

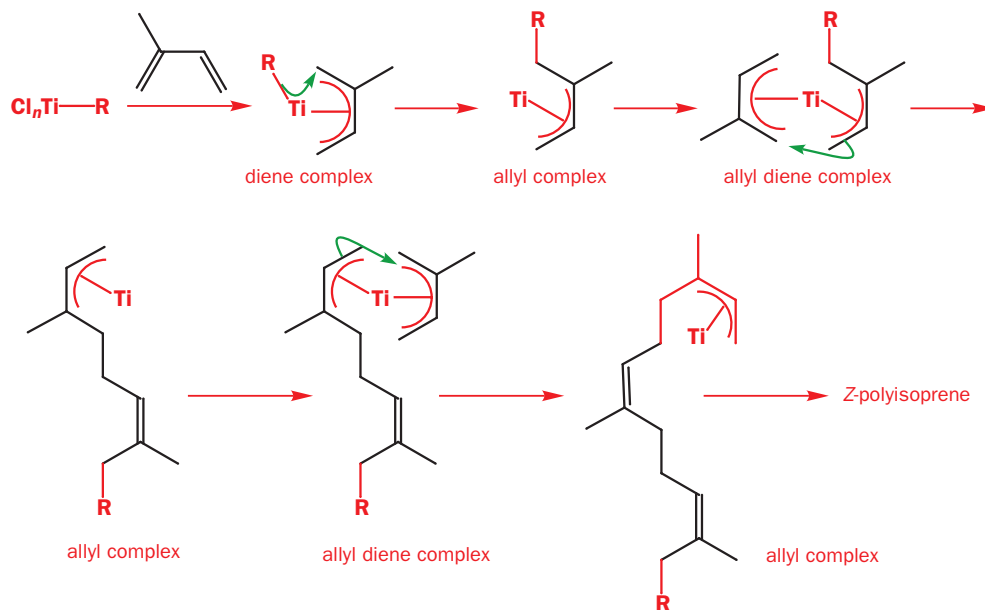
■ The organometallic principles relating to this section can be found in Chapter 48.

► This is a simplification as the catalyst is a solid and the active Ti atom almost certainly Ti(III) rather than Ti(IV) as we have shown here. The third Cl ligand is in fact shared with other Ti atoms in the crystal. Coordination of the active Ti(III) atom must be such that each σ complex is a 16-electron species while the π complexes are 18-electron species.

► In fact, the reaction can lead either to isotactic or syndiotactic polymer depending on the detailed structure of the catalyst.



The all-*cis* structure of natural rubber is vital to its elasticity. The all-*trans* compound is known and it is hard and brittle. Though dienes such as isoprene can easily be polymerized by cationic methods, the resulting ‘rubber’ is not all-*cis* and has poor elasticity and durability. However, polymerization of isoprene in the Ziegler–Natta way gives an all-*cis* (90–95% at least) polyisoprene very similar to natural rubber.



One possible explanation is that each isoprene unit adds to the titanium (and we will drop the pretence at this point that we have any idea which other ligands are on the Ti atom) to form an η^4 diene complex. This must necessarily have the *s-cis* conformation. Addition of R to one end of this complex gives an η^3 allyl complex still maintaining the *cis* configuration. The next diene then adds to form a new η^4 diene complex, couples to the allyl complex, and so on. As the chain grows, each diene is added as an η^4 complex and an all-*cis* polymer results.

Co-polymerization

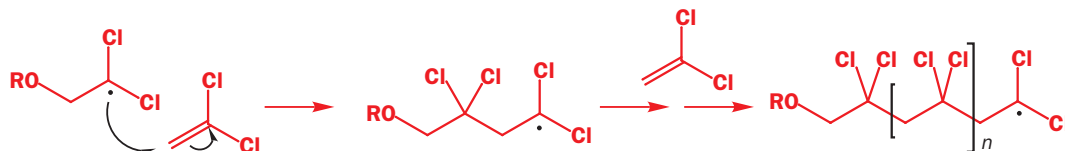
If two or more monomers polymerize to give a single polymer containing different subunits, the product is a **co-polymer** and the process is called **co-polymerization**. Protein synthesis is an example from nature: amino acids are polymerized stepwise to give proteins of precise sequence and precise length. We can do the same thing chemically providing that we do it in a stepwise fashion—we shall discuss this later. In most cases, chemical co-polymerization cannot be precisely ordered, but still gives useful results.

It may have surprised you, when you read the fine print on packaging, that some quite different materials are made out of the same polymer. PVC, for example, is widely used in clothing, ‘vinyl’ floor and seat coverings, pipework, taps, and lab stopcocks. Some of these applications require strength and rigidity; others flexibility. How is this possible with the same polymer? Some variation can be achieved by the addition of **plasticizers**—additives that are blended into the polymer mixture but are not chemically bonded to it. Another approach is to use a co-polymer with a smaller amount of a different (but often similar) monomer built randomly into the growing polymer chain. This is quite different from the alternating co-polymers that we saw under carbonyl substitution polymerization, such as nylon 6.6 or the block co-polymers we met a page or two back.

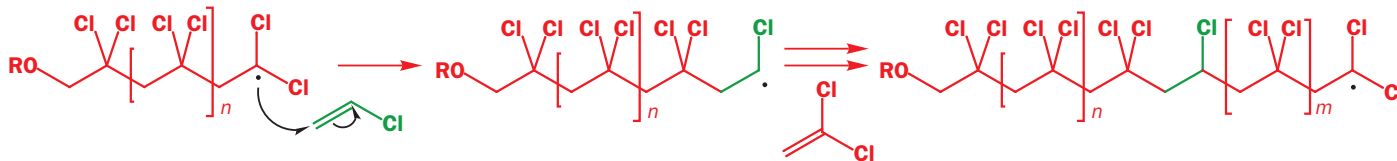
We will choose the example of elastane films for food wrapping—‘ClingFilm’. These can be made from poly(vinylidene dichloride) (this is poly(1,1-dichloroethene)) into which a small amount of vinyl chloride is co-polymerized. The method is radical polymerization and the initiator usually a peroxide in aqueous suspension.



Polymerization continues adding vinyl chloride or vinylidene dichloride more or less at random. At first, several dichloroalkene molecules will add, simply because there are more of them.



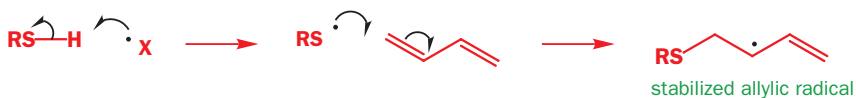
Every now and then a vinyl chloride adds in, followed again by a number of dichloroalkenes to give the co-polymer.



Eventually, polymerization will be terminated by the usual methods and the final co-polymer will have a random mixture of dichloroalkene (mostly) and monochloroalkene, roughly in proportion to their availabilities in the polymerization mixture. The precise properties of the resulting polymer will depend on the ratio of the two monomers.

Synthetic rubbers can be made by co-polymerization of alkenes and dienes

Radical co-polymerization of styrene and butadiene produces a material that is very like natural rubber. The initiator is a one-electron oxidizing agent, and a thiol (RSH) is used to start the polymerization process. The mixture is about 3:1 butadiene:styrene so there are no long runs of one monomer in the product. We will use butadiene as the starter unit.

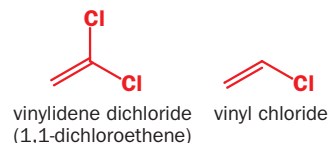


The first radical is an allylic radical, stabilized by conjugation with the remaining alkene in the old butadiene molecule. Addition could now occur to another butadiene or to styrene.



The product is the stabilized benzylic radical with the more stable *trans* double bond. Stabilization of radicals in allylic and benzylic groups is about the same, so the two monomers will react roughly in proportion to their concentration. The final product will be a random co-polymer of about 3:1 buta-

▶ A polymer is a chemical compound while a plastic is a mixture of a polymer and other substances (plasticizers, pigments, fibres, etc.), which allow it to be used in a certain way.

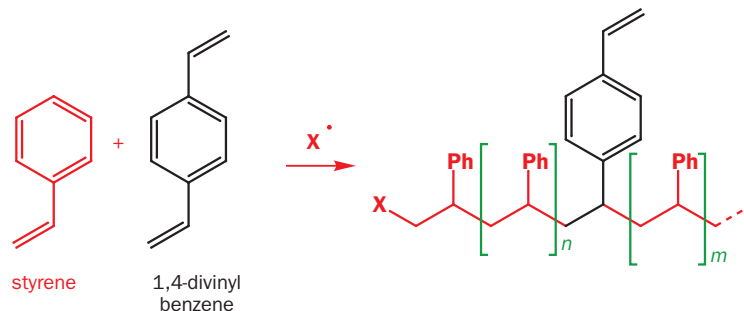


diene to styrene with mostly *E*-alkenes. It is an elastomer used for tyres and other applications where a tough and flexible ‘rubber’ is needed.

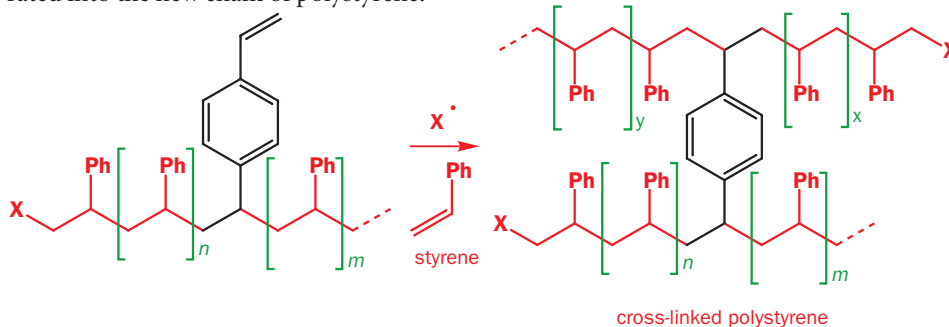
Cross-linked polymers

Many linear polymers are too flexible to be of use in making everyday objects because they lack the strength, the rigidity, or the elasticity for the job. Linear polymers can be stiffened and strengthened by bonds between the chains. This process is known as **cross-linking** and we will look now at some ways in which this can be achieved.

All that is really needed is a co-polymer with a small amount of a compound similar to the main monomer but with at least one more functional group than is strictly necessary to form a linear polymer. For example, a small amount of 1,4-divinylbenzene co-polymerized with styrene leads to a linear polymer in which some of the phenyl rings carry a 4-vinyl group.

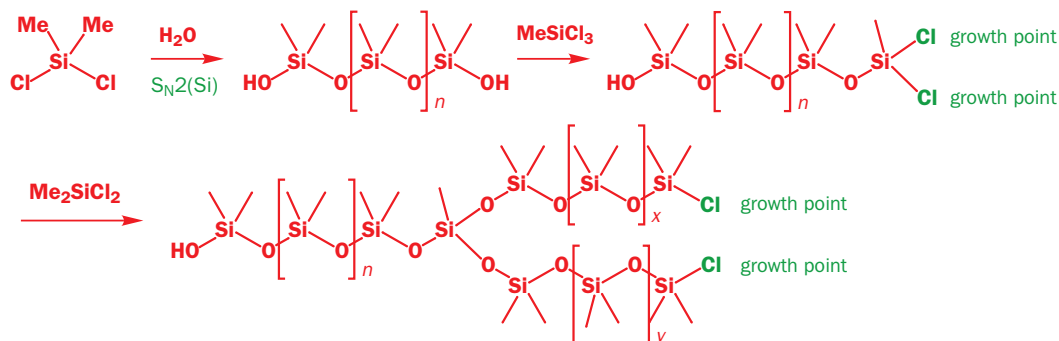


When another chain polymerizes nearby, the spare vinyl group in the first chain may be incorporated into the new chain of polystyrene.



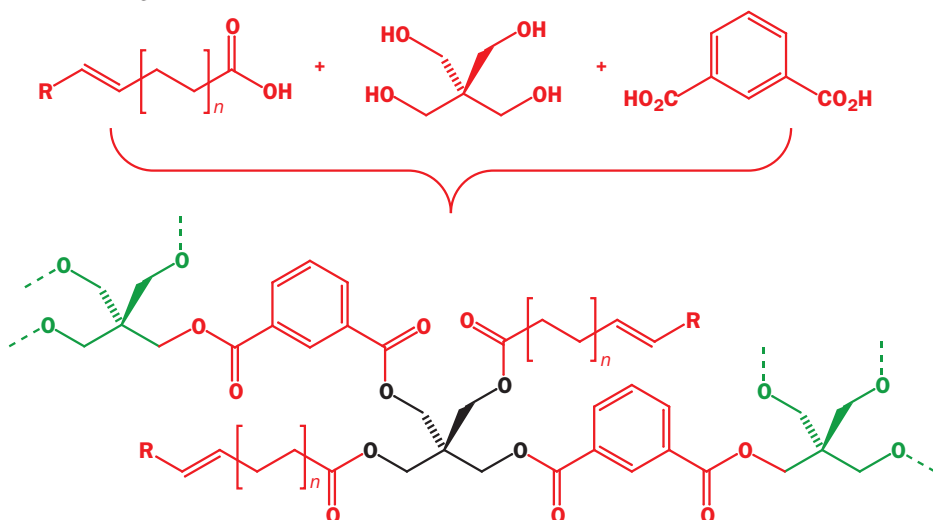
Not all of the spare vinyl groups will be caught up in a new chain of polymerizing styrene, but that need not matter if there are enough of them. It is simply a question of adding enough 1,4-divinylbenzene to get the required degree of cross-linking. These cross-linked styrenes are often made into small beads for polymer-supported reagents, as described below.

Divinyl benzene has two identical ‘arms’, which become growing points in polymerization. In the polymerization of Me_2SiCl_2 we had two growing points (the two chlorine atoms) on each monomer. To get cross-linking we need a third, provided by (a small amount of) MeSiCl_3 .



The four-armed cross-linking agent known as pentaerythritol is made from acetaldehyde and formaldehyde in aqueous base. The four arms are arranged in a tetrahedron around a quaternary carbon atom.

Co-polymerization of pentaerythritol and two other monomers—an unsaturated acid and benzene 1,3-dicarboxylic acid—gives a network of polymer chains branching out from the quaternary carbon atom at the centre of pentaerythritol. The reaction is simply ester formation by a carbonyl substitution reaction at high temperature ($> 200\text{ }^{\circ}\text{C}$). Ester formation between acids and alcohols is an equilibrium reaction but at high temperatures water is lost as steam and the equilibrium is driven over to the right.

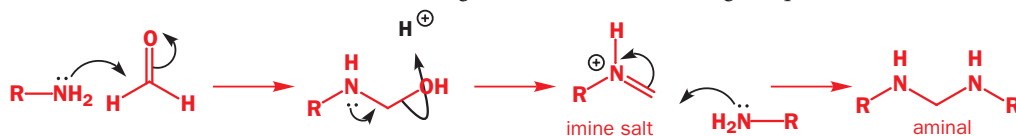


The black pentaerythritol at the centre of the polymer is shown with two each of the ester side chains, though this need not be the case, of course. The green pentaerythritol molecules are the growing points of the network of polymer chains. It is obvious why the benzene dicarboxylic acid is helpful in linking growing points together, but what is the point of the long-chain unsaturated acid? These are naturally occurring acids as described in Chapter 51 and the alkenes are used for further cross-linking under oxidative conditions as described in the next section. Such polymers are called ‘alkyd resins’ and are used in paints. They form emulsions in water (‘emulsion paints’) and the ester groups do not hydrolyse under these conditions as water cannot penetrate the polymer network. As the paint ‘dries’ it is cross-linked by oxygen in the air.

It is not necessary to have quite such a highly branched cross-linking agent to make a network of polymer chains. A triply branched compound is the basis for one of the strongest polymers known—one that we take for granted every time we use the kitchen. It is made by a very simple reaction.

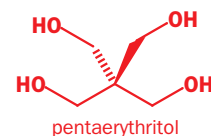
Melamine

You saw a carbonyl addition reaction forming a polymer right at the beginning of the chapter—the polymerization of formaldehyde. If an amine is added to formaldehyde, condensation to form imines and imine salts occurs readily. These intermediates are themselves electrophilic so we have the basis for **ionic polymerization**—electrophilic and nucleophilic molecules present in the same mixture. Reaction with a second molecule of amine gives an **aminal**, the nitrogen equivalent of an acetal.



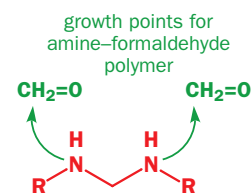
There are now two nucleophilic atoms in the molecule. Each can react with formaldehyde to form more C–N bonds and so on, making two growth points for the polymer.

We do better if we have two or even three nucleophilic amino groups present in the same molecule. With three amino groups we will produce a branching polymer of great strength



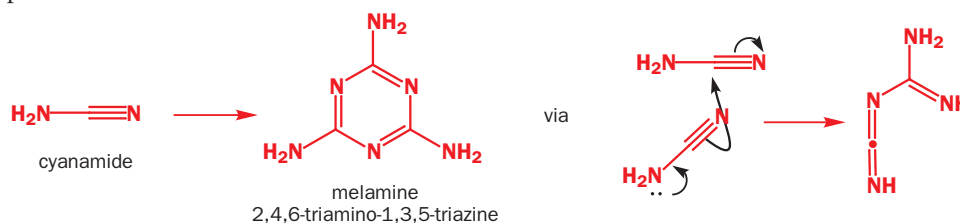
■ Pentaerythritol is made by a Cannizzaro reaction: see Chapter 27, p. 713.

■ This is also the first step of the Mannich reaction: Chapter 27, p. 712.

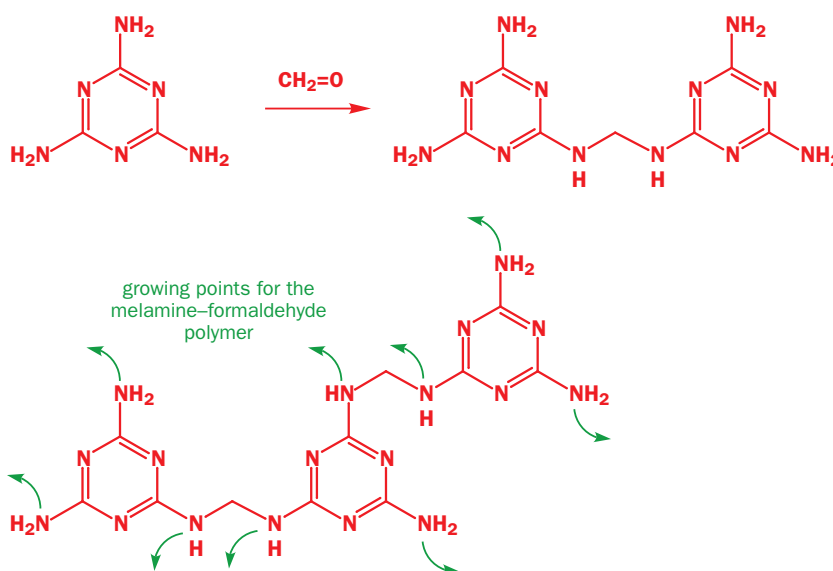


and the most important of the triamines is melamine. This compound is itself produced by the trimerization of a simple compound, cyanamide $\text{H}_2\text{N}-\text{CN}$, and has given its name to a group of plastics.

You should be able to write the full mechanism for the formation of melamine: the first step is given.



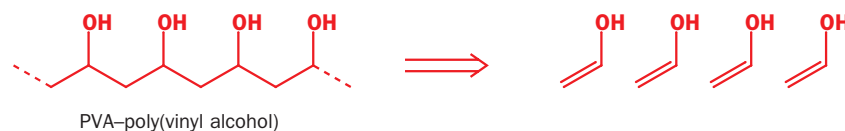
When the triamine reacts with formaldehyde, branched polymerization can occur by the same mechanism as the one we drew above for simple amines. Further condensations with formaldehyde allow amines to be attached in many places, and each new amine itself adds many new growing points. An exceptionally strong polymer results.



These resins are used to make ‘unbreakable’ plastic plates and for the famous kitchen surface ‘Formica’. Partly polymerized melamine–formaldehyde mixtures are layered with other polymers such as cellulose (Chapter 49) and phenol–formaldehyde resins and the polymerization is completed under pressure with heat. The result is the familiar, tough, heat-resistant surface.

Reactions of polymers

We have so far given the impression that all polymers are formed fully armed, as it were, from monomers already having the correct functionality. This is, indeed, often the case because it can be very difficult to persuade polymers to carry out any reactions—reagents cannot penetrate their interiors. Polyester fabrics can be washed without any of the ester linkages being hydrolysed in the washing machine because the water cannot penetrate the fibres. However, some useful reactions, including ester hydrolysis, can be carried out on complete polymers.



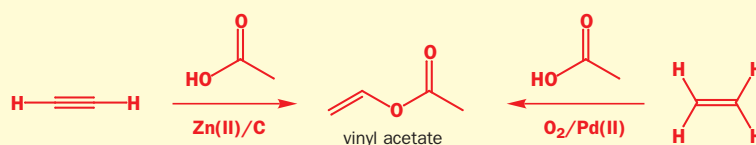
Poly(vinyl alcohol) is an important example. Inspection of the structure reveals that this is a typical alkene polymer but the monomer would have to be vinyl alcohol—the unstable enol of acetaldehyde. The way to make the polymer is to start with something else and only later

convert the polymer product into poly(vinyl alcohol). The most common method of doing this is to use radical polymerization of vinyl acetate, the enol ester of acetaldehyde, and hydrolyse the ester afterwards.

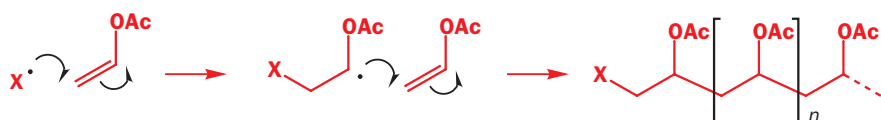
Vinyl acetate

Vinyl acetate is manufactured on a large scale by two routes.

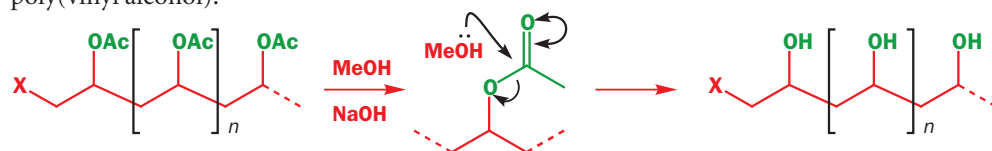
Satisfy yourself that you can at least see what is happening here—if you are stuck on the Pd(II)-catalysed reaction, refer to Chapter 48 and look at oxypalladation and the Wacker reaction for clues.



The polymerization of the enol acetate goes in the usual way.



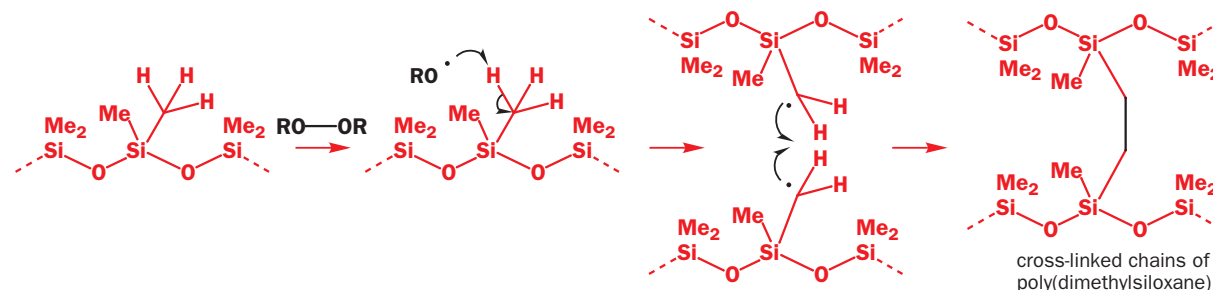
The complete polymer may now be attacked by reagents that cleave the ester groups. Water is a possibility, but methanol penetrates the polymer better and ester exchange in alkaline solution gives poly(vinyl alcohol).



Poly(vinyl alcohol) is soluble in water, unlike almost all other polymers, and that gives it many uses in glues and even as a solubilizing agent in chemical reactions to make other polymers. Poly(vinyl acetate) is used in paints.

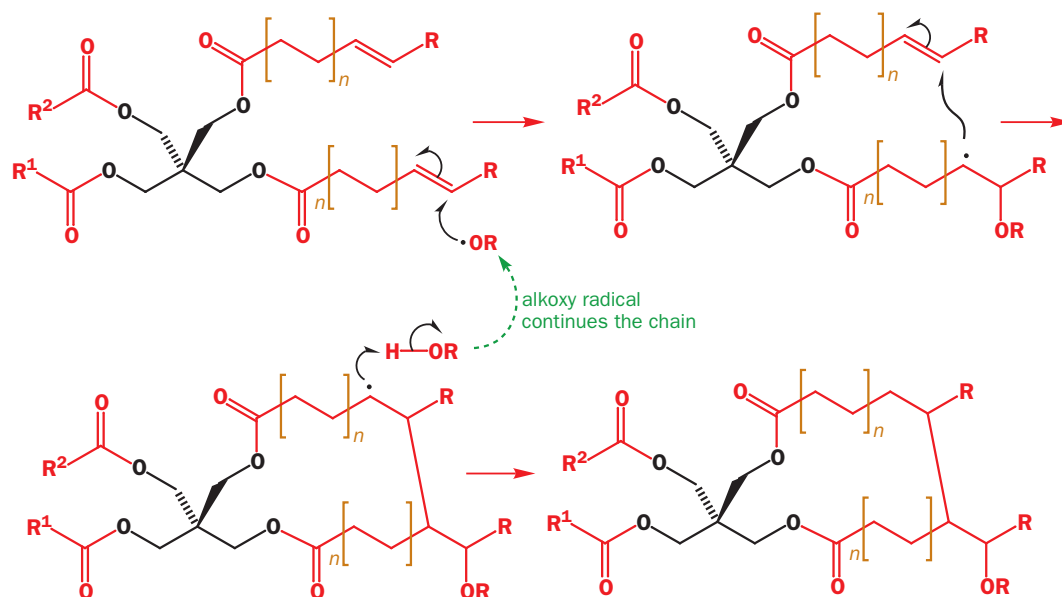
Cross-linking of pre-formed polymers

We have already discussed cross-linking during polymerization but cross-linking is often carried out after the initial polymer is made. You saw earlier how poly(dimethylsiloxane) can be cross-linked by co-polymerization with MeSiCl_3 . An alternative way of cross-linking the linear polymer uses radical reactions to convert silicone oil into silicone putty. Peroxides are used in this process.



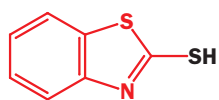
A similar sort of reaction occurs during the cross-linking of alkyd resins for paint manufacture. You may recall that the alkenes are incorporated in these resins for a reason not yet made clear. Now these alkene units come into their own. Oxygen is the reagent and it works by radical dimerization of the chains (see overleaf).

The most important of all of these types of reactions is the vulcanization of rubber. Originally, the raw rubber was just heated with sulfur (S_8) and cross-linking of the polyisoprene chains with short chains of sulfur atoms gave it extra strength without destroying the elasticity. Nowadays, a vulcanizing initiator, usually a thiol or a simple disulfide, is added as well. Some examples are

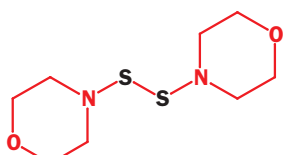


cross-linked alkyd resin

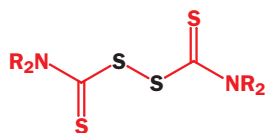
vulcanization initiators



benzothiazole-2-thiol



dithio-bis-morpholine

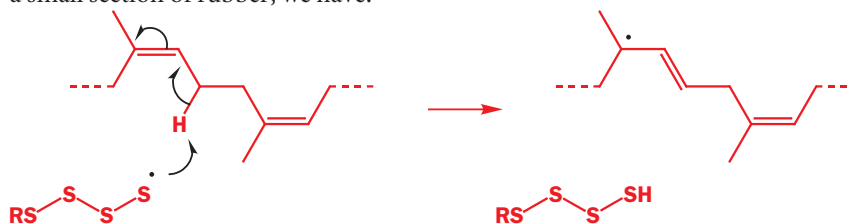


tetraalkyl thiuram disulfide

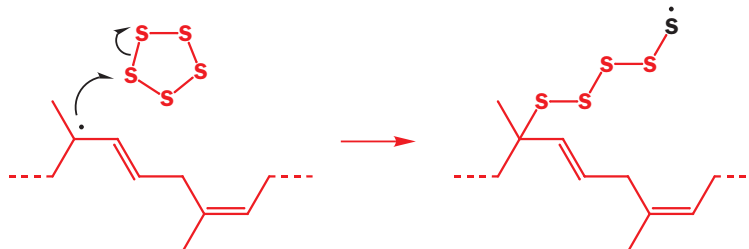
shown in the margin. The thiols give sulfur radicals with oxygen and the disulfides cleave easily as the S-S bond is weak (about 140 kJ mol^{-1} in S_8). We will write all these as RS^\cdot . The initiators either attack the rubber directly or attack sulfur to open the S_8 ring.

The newly released sulfur radical can bite back on to the sulfur chain and close a ring of 5–7 sulfur atoms, releasing a short chain of sulfur atoms attached to the initiator and terminating in a sulfur radical.

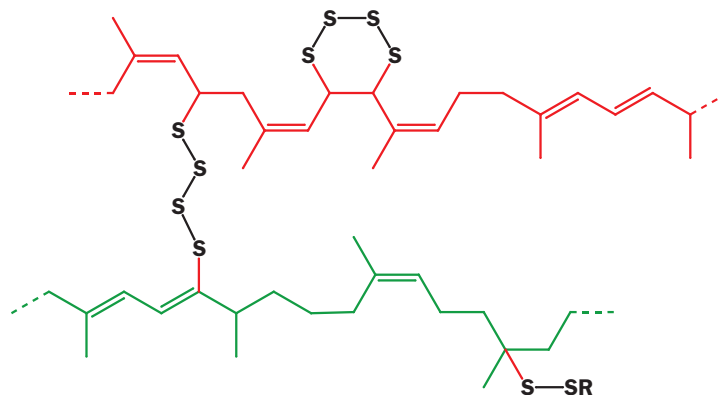
Now the attack on rubber can start. We know that vulcanized rubber has many *E*-alkenes, whereas unvulcanized rubber is all *Z*-alkenes. This suggests that the sulfur radicals do not add to the alkenes but rather abstract allylic hydrogen atoms. Writing only a small section of rubber, we have:



The new allylic radical can do many things, but it might, for example, capture one of the sulfur rings present (S_5 to S_8). We will use the S_5 ring we have just made.



This sulfur radical can attack another chain to give a cross-link or bite back to give a link within the same chain. Many different sulfur links are formed and the next diagram summarizes a part of the vulcanized rubber structure. There is some license here: in reality the links would not be as dense as this, and more than two chains would be involved. Notice the two chains joined by one cross-link, the internal cross-link in the black chain, the attachment of the initiator (RS) to the green chain, and the (*E,E*)-dienes in both chains.



We have not given compositions of complete plastics in general, but you might like to know the typical composition of a motor tyre. Notice that the ratio of sulfur to rubber is about 1:40—that gives an idea of how many cross-links there are. Notice also that the rubber contains a great deal of carbon to improve the wear of the rubber. The roles of the other materials are explained in the table.

Typical composition of rubber motor tyre

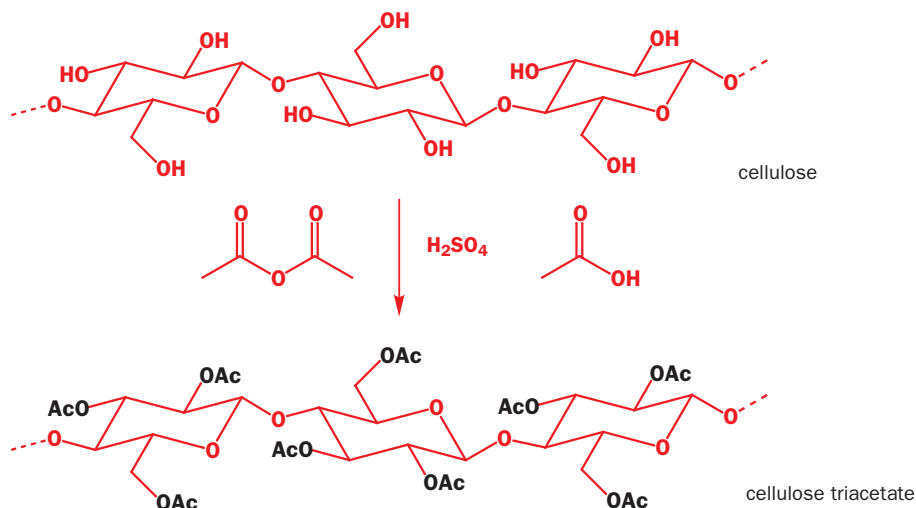
Component	Parts by weight, %	Function
rubber	61	basic structure
carbon black	27	reinforcement
oils and waxes	4.9	processing aid
sulfur	1.5	vulcanizing agent
organic disulfide	0.4	accelerates vulcanization
zinc oxide (ZnO)	3	activates vulcanization
stearic acid	0.6	activates vulcanization

This makes only 98.4% in total and there are small amounts of other materials such as antioxidants to prolong the life of the rubber.

Though synthetic diene polymers have now replaced natural rubber in many applications, they too need to be cross-linked by vulcanization using essentially the same reactions, though the details vary from product to product and from company to company.

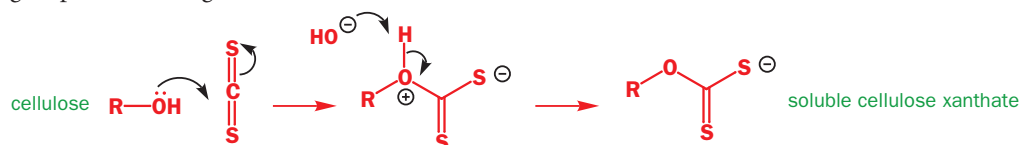
Chemical reactions of cellulose

We met cellulose, the bulk polysaccharide of woody plants, in Chapter 49. It is a strong and flexible polymer but no use for making fabrics or films as it cannot be processed. One solution to this problem is to carry out chemical reactions that transform its properties. Acid-catalysed acetylation with acetic anhydride gives a triacetate with most of the free OH groups converted into esters.



The starting material for this process is wood pulp, cloth, or paper waste and the acetic acid is added first to 'swell' the material and allow it to take up the reagents better. Organic solvents often do this to polymers. The anhydride now carries out the acid-catalysed acetylation and the cellulose triacetate, unlike the cellulose, dissolves in the reaction mixture. The new polymer is often known simply as 'acetate'.

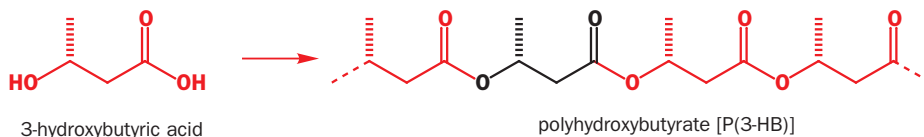
Another cellulose product is rayon. This is really cellulose itself, temporarily modified so that it can be dissolved and processed to give films or fibres. The starting material (from wood, cloth, or paper) is impregnated with concentrated NaOH solution. Addition of CS₂ allows some of the OH groups to react to give a 'xanthate' salt that is soluble in water.



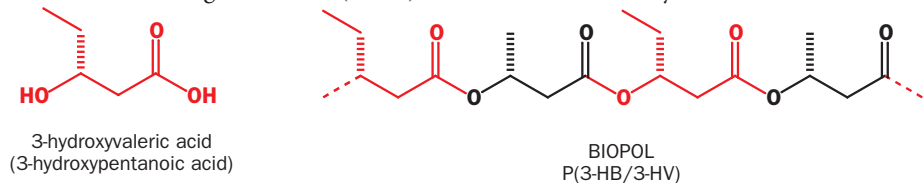
Injection of the viscous solution of cellulose xanthate into an acidic (H₂SO₄) bath regenerates the cellulose by the reverse of this reaction, as a film or a fibre depending on the process. The result is known as 'cellophane' if it is a film or 'viscose rayon' if it is a fibre.

Biodegradable polymers and plastics

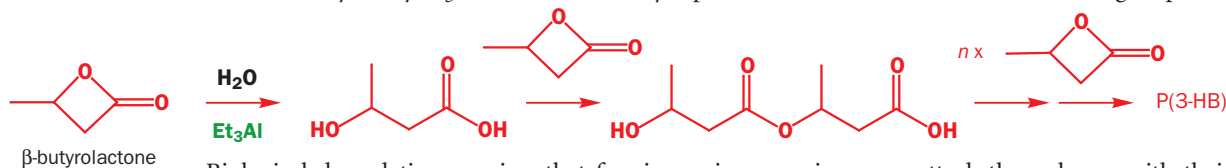
It is necessary to take only a short walk in most cities to see that plastics are not very easily degraded biologically, and it is becoming more important to design plastics, for packaging at least, that have built-in susceptibility to bacteria or fungi. Natural polymers based on proteins and polysaccharides do have that advantage, and one approach is to use a near-natural polymer, poly(hydroxybutyrate) or P(3-HB). This compound is found in some microorganisms as massive (by microorganism standards!) whitish granules occupying substantial parts of the cell—up to 80% of its dry weight of the cell. It seems that it is used as a storage compound (like starch or fat in our case) for excess carbohydrates in the diet.



A co-polymer of P(3-HB) and poly(hydroxyvalerate) P(3-HV) is also found in microorganisms and performs the same function. This polyester forms the basis for a good strong but flexible plastic for containers such as toiletries, and is produced by ICI under the name 'BIOPOL'. Microorganisms must be able to degrade both P(3-HB) and BIOPOL since they themselves use them to store energy.



BIOPOL and the two simple polymers P(3-HB) and P(3-HV) are manufactured by fermentation. They can also be produced chemically by the polymerization of a four-membered lactone (β -butyrolactone). The polymerization is initiated by a water molecule that opens the first lactone ring. The reaction is catalysed by Et₃Al and continues by repeated esterification of the released OH group.



Biological degradation requires that fungi or microorganisms can attack the polymer with their enzymes. This happens efficiently with very few polymers (because these enzymes do not exist) and is, of course, the reason that they are used: people tolerate ugly plastic window frames because they don't rot.

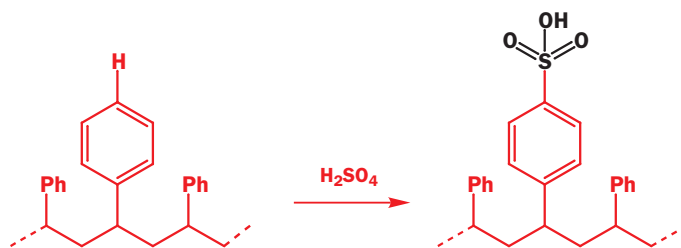
One way in which most polymers do decay is by the action of oxygen in the air and of light. You will be familiar with the way that some polymers go yellow after a time and some become brittle. Coloured plastics, in particular, absorb light and oxygen-induced radical reactions follow. The polymer becomes too cross-linked and loses flexibility. One ingenious application of this natural process helps to degrade the polythene rings that hold cans of beer in packs. These are often discarded and decay quite quickly because some carbon monoxide has been incorporated into the polyethylene to make it more sensitive to photolysis.

Chemical reagents can be bonded to polymers

We have left this subject to the end of the chapter because it uses all of the principles we have established earlier on. It requires an understanding of radical polymerization, co-polymerization, cross-linking, functionalization of polymers after they have been made, and so on. This is a rapidly growing subject and we can only outline the basics.

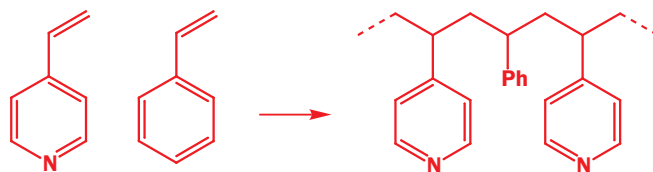
If you are already wondering why anyone would bother to attach reagents to polymers, just think of the problems you have had in the lab in separating the product you want from the other products of the reaction, often the spent reagent and inorganic by-products. If the reagent is attached to a polymer, the work-up becomes easier as the spent reagent will still be attached and can just be filtered off. Polymer-supported reagents can often be reused and their reactions can even be automated.

You may already be familiar with ion-exchange resins and we will start with them. They are commonly based on the co-polymer of styrene and 1,4-divinyl benzene we discussed earlier. The polymerization is carried out in an emulsion in water so that the organic molecules are in tiny droplets. The resulting polymer forms as more or less spherical beads of less than a millimetre in diameter. They can be put through a series of sieves to ensure even sizes if required. The surface of each bead is coated with benzene rings (attached to the polymer backbone) that can be sulfonated in the *para* position just like toluene.

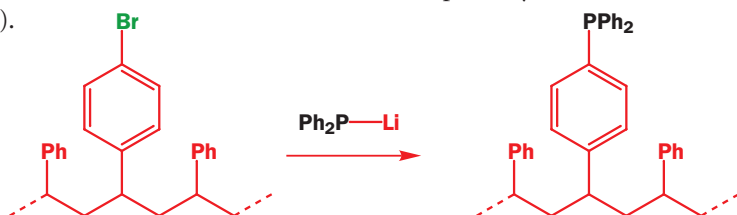


A good proportion of the rings become sulfonated, and the outside of each bead is now coated with strongly acidic sulfonic acid groups. The polymer is an acidic reagent that is not soluble in any normal solvent. It can be packed into a column or simply used as a heterogeneous reagent. In any case, whatever reaction we are doing, there is no difficulty in separating the organic product from the acid.

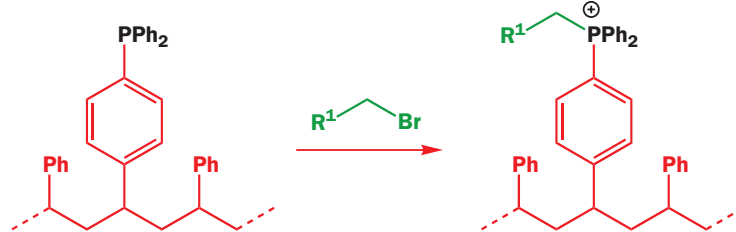
A useful *basic* polymer is made by co-polymerization of 4-vinyl pyridine and styrene.



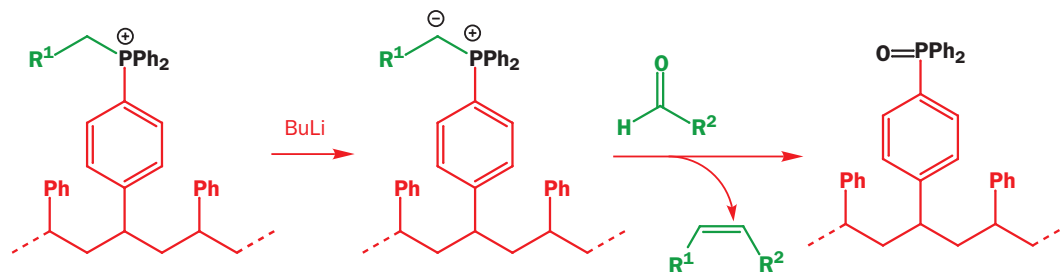
These polymers are reagents in themselves, but a new style of chemistry is being developed around the idea of attaching reagents to the polymer. Poly 4-bromostyrene (or a co-polymer with styrene itself) allows a number of different groups to be attached in the place of the bromine atom. One example is a polymer-bound Wittig reagent. The phosphine can be introduced by nucleophilic displacement with $\text{Ph}_2\text{P-Li}$, an excellent nucleophile, by the addition-elimination mechanism (Chapter 23).



Though we have shown only one bromine atom and hence only one Ph_2P group on the polymer, almost all of the benzene rings in polystyrene can be functionalized if the bromopolymer is made by bromination of polystyrene in the presence of a Lewis acid. Now the phosphine can be alkylated with an alkyl halide of your choice to form a phosphonium salt, still on the polymer.

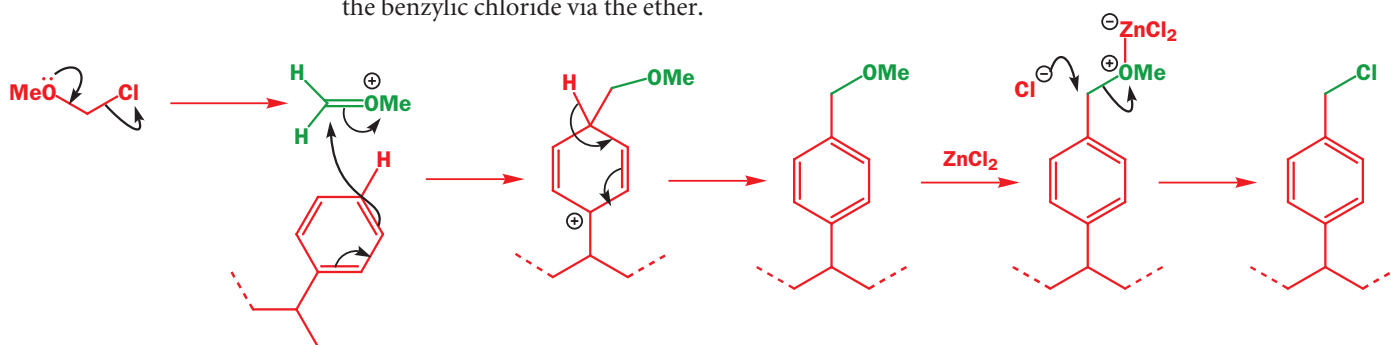


Treatment of the polymer with BuLi and then the aldehyde gives a Wittig reaction (Chapter 31) that releases the alkene product but leaves the phosphine oxide bound to the polymer.

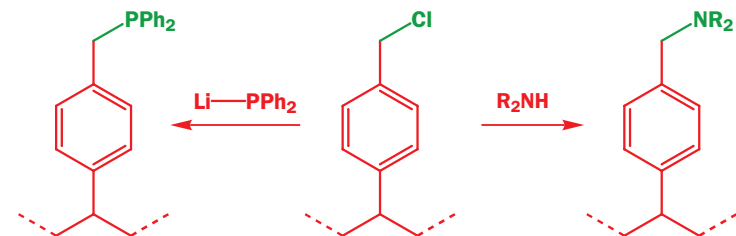


The phosphine oxide can be reduced back to the phosphine (for example, with Cl_3SiH) while still bound to the polymer and the polymer-bound reagent can be used again. Separation of $\text{Ph}_3\text{P}=\text{O}$ from alkene products after a Wittig reaction can be quite a nuisance so the ease of work-up alone makes this an attractive procedure.

It is not necessary to attach the functional group directly to the benzene ring. There are some advantages in separating the reaction from the polymer by a 'spacer', normally a chain of aliphatic carbon atoms. It may allow reagents to approach more easily and it may allow a higher 'loading' of functional groups per bead. Even a spacer of one CH_2 group makes $\text{S}_{\text{N}}2$ reactions not only possible but favourable at the benzylic position and the most important of these spacers is introduced by chloromethylation. Reaction of the cross-linked polystyrene with MeOCH_2Cl and a Lewis acid gives the benzylic chloride via the ether.



The chloromethylated resin can now be combined with many different nucleophiles. Amines give basic ion-exchange resins while $\text{Ph}_2\text{P-Li}$ gives a phosphine suitable for complexation to transition metals.



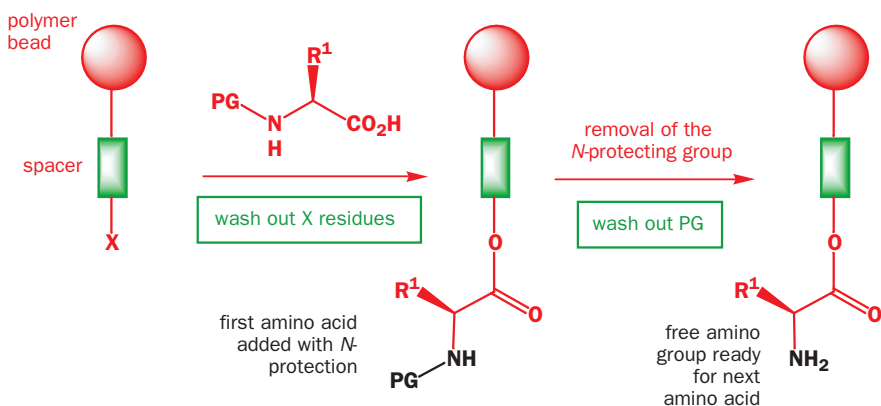
Automated peptide synthesis uses polymer-bound reagents

Automated polymer-based synthesis comes into its own when a stepwise polymerization is required with precise control over the addition of particular monomers in a specific sequence. This is almost a definition of peptide synthesis. Nature attaches each amino acid to a different ‘polymer’ (transfer RNA) and uses a ‘computer program’ (the genetic code) to assemble the polymers in the right order so that the amino acids can be joined together while bound to another polymer (a ribosome). No protection of any functional groups is necessary in this process.

Chemical synthesis of peptides uses a similar approach but our more primitive chemistry has not yet escaped from the need for full protection of all functional groups not involved in the coupling step. The idea is that the first amino acid is attached to a polymer bead through its carboxyl group (and a spacer) and then each *N*-protected amino acid is added in turn. After each addition, the *N*-protection must be removed before the next amino acid is added. The growing peptide chain is attached to the polymer so that all waste products, removed protecting groups, excess reagents, and inorganic rubbish can be washed out after each operation.

■ This subject was introduced in Chapter 25 and we will not repeat here all the details of how protecting groups are added and removed. Please refer to that chapter if you need more explanations of the reactions. We will concentrate here on the role of the polymer.

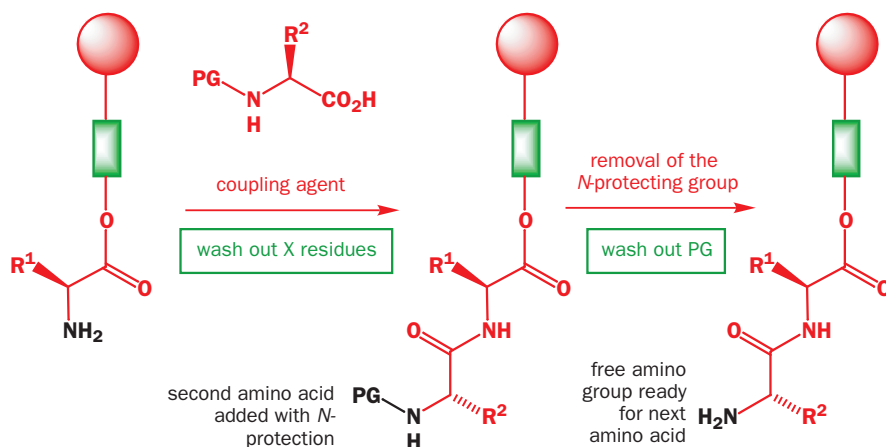
stage 1: attachment of the first (C-terminal) amino acid



Stage 1 involves two chemical reactions—linking the first amino acid to the polymer and removing the *N*-protecting group—and two washing operations. These four steps would take time if everything were in solution but, with the compounds attached to polystyrene beads, they can be carried out simply by packing the beads into a column chromatography-style and passing reagents and solvents through.

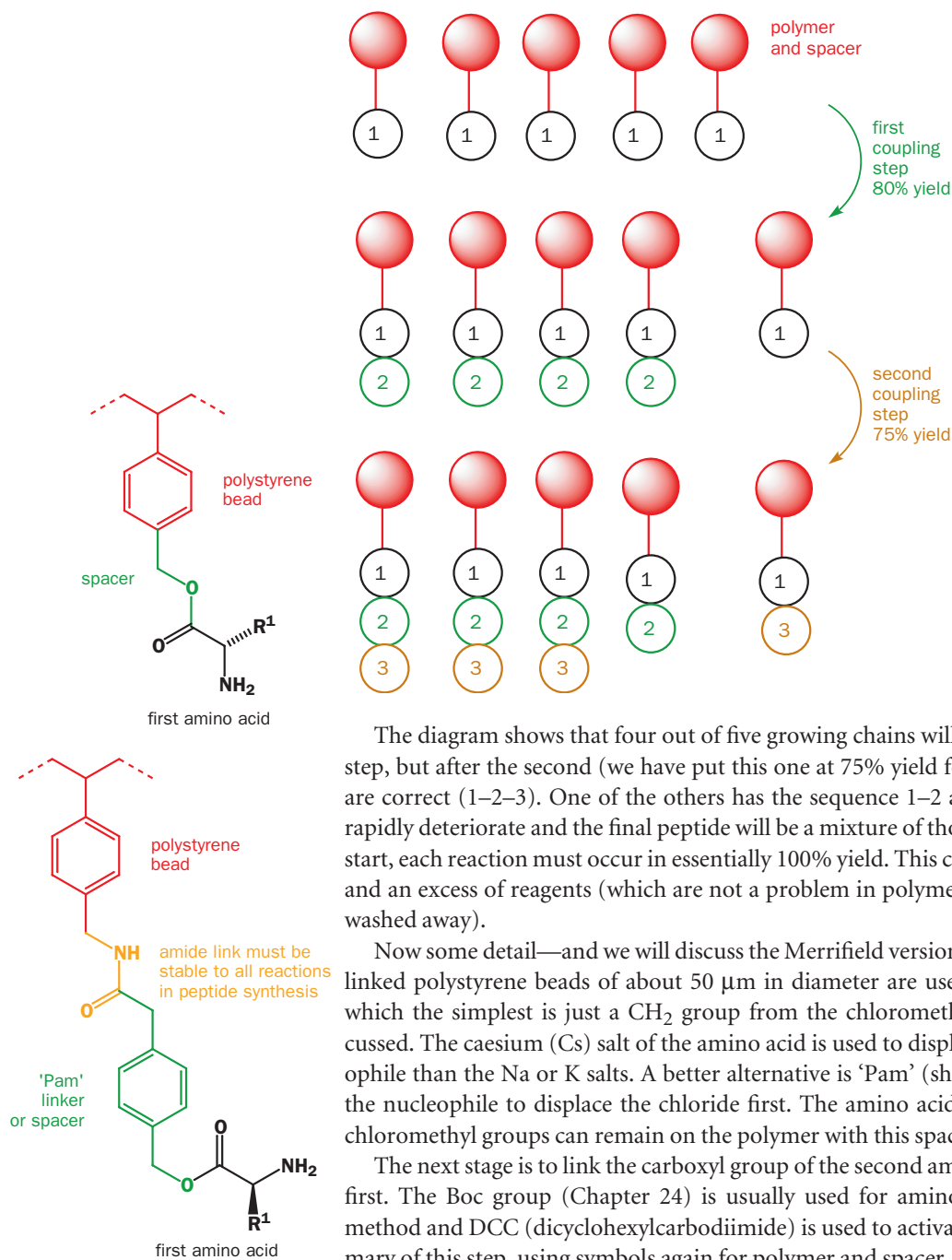
Stage 2 involves the addition of the second *N*-protected amino acid with a reagent to couple it to the free amino group of the amino acid already in place. Removal of the protecting group from the new amino acid is needed, followed by washes, as in stage 1.

stage 2: formation of the first peptide bond



This process must now be repeated until all of the amino acids have been added. Finally, all the side-chain protecting groups must be removed and the bond joining the peptide chain to the polymer must be broken to give the free peptide. That is the process in outline, but we need now to look at some of the chemistry involved.

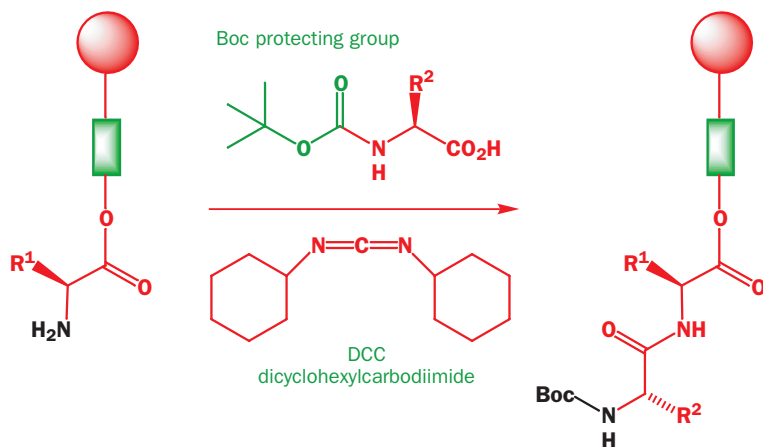
It is obviously important that all reactions are very efficient. Suppose that the coupling step joining the second amino acid on to the first goes in 80% yield. This may not seem bad for a chemical reaction, but it would mean that 20% of the chains consisted of only the first amino acid while 80% contained correctly both first and second. Now what happens when the third amino acid is added?



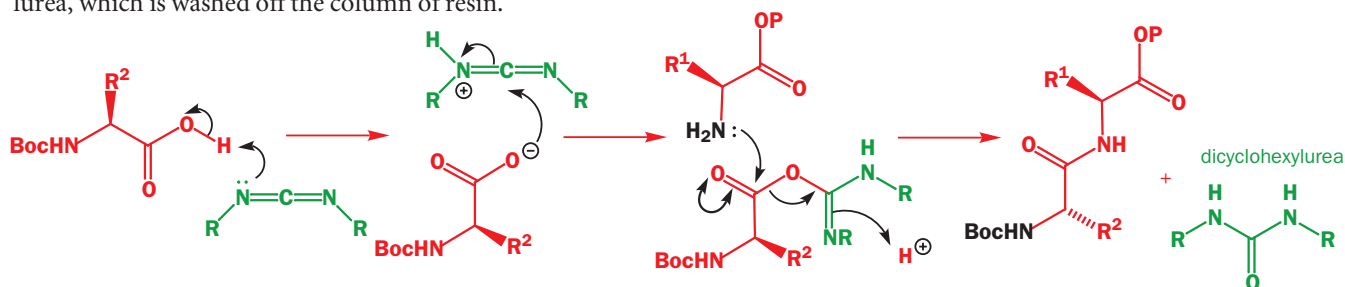
The diagram shows that four out of five growing chains will be right (1-2) after the first coupling step, but after the second (we have put this one at 75% yield for convenience) only three of the five are correct (1-2-3). One of the others has the sequence 1-2 and the other 1-3. This situation will rapidly deteriorate and the final peptide will be a mixture of thousands of different peptides. So, for a start, each reaction must occur in essentially 100% yield. This can be achieved with efficient reactions and an excess of reagents (which are not a problem in polymer-supported reactions as the excess is washed away).

Now some detail—and we will discuss the Merrifield version of peptide synthesis. Spherical cross-linked polystyrene beads of about 50 μm in diameter are used and attached to various spacers of which the simplest is just a CH_2 group from the chloromethylated polystyrene we have just discussed. The caesium (Cs) salt of the amino acid is used to displace the chloride as it is a better nucleophile than the Na or K salts. A better alternative is 'Pam' (shown in the margin). It can be used as the nucleophile to displace the chloride first. The amino acid is then added after purification. No chloromethyl groups can remain on the polymer with this spacer.

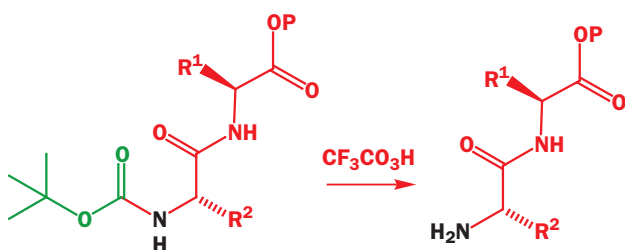
The next stage is to link the carboxyl group of the second amino acid on to the amino group of the first. The Boc group (Chapter 24) is usually used for amino group protection in the Merrifield method and DCC (dicyclohexylcarbodiimide) is used to activate the new amino acid. Here is a summary of this step, using symbols again for polymer and spacer.



The details of the reaction mechanism with DCC were given in Chapter 43, p. 1172, and can be shown more easily if we mark the polymer and spacer as 'P' and the cyclohexyl groups as 'R'. The DCC is protonated by the free carboxylic acid and is then attacked by the carboxylate anion. The intermediate is rather like an anhydride with a C=NR group replacing one of the carbonyl groups. It is attacked by the amino group of the polymer-bound amino acid. The by-product is dicyclohexylurea, which is washed off the column of resin.



Now the Boc group must be removed with acid (such as $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2) and washed off the column leaving the free NH_2 group of amino acid number two ready for the next step.



The synthesis continues with repetition of these two steps until the peptide chain is complete. The peptide is cleaved from the resin, usually with HF in pyridine or $\text{CF}_3\text{SO}_2\text{OH}$ in $\text{CF}_3\text{CO}_2\text{H}$ and given a final purification from small amounts of peptides of the wrong sequence by chromatography, usually HPLC.

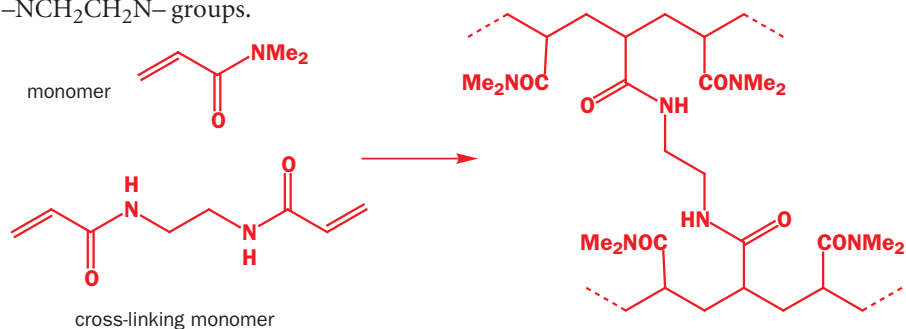
This process is routinely automated in commercially available machines. Solutions of all of the protected amino acids required are stored in separate containers and a programmed sequence of coupling and deprotection leads rapidly to the complete peptide in days rather than the years needed for solution chemistry. The most dramatic illustration of this came with the publication of a heroic traditional synthesis of bovine pancreatic ribonuclease A (an enzyme with 124 amino acids) by Hirschmann, side-by-side with one by Merrifield using functionalized polystyrene as we have described. The traditional method required 22 co-workers, while the Merrifield method needed only one.

Peptide synthesis on polyacrylamide gel

Another method of polymer-supported peptide synthesis has been developed by Sheppard. Most things are different in this approach, which is better adapted for polar solvents and automated

The mechanism of this reaction is discussed in Chapter 25.

operation. The polymer is a polyacrylamide cross-linked with bis-acrylamides joined by $-\text{NCH}_2\text{CH}_2\text{N}-$ groups.

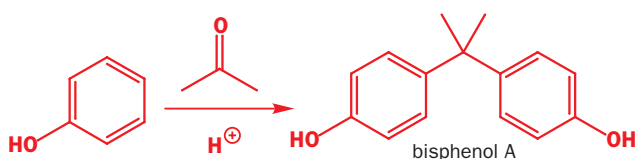


Polar solvents such as water or DMF penetrate the beads, making them swell much more than do the polystyrene resins. This exposes more reactive groups and increases the loading of peptide chains on each bead. The first amino acid is attached through its carboxyl group to an amino group on the polymer, added during or after polymerization by incorporating more 1,2-diaminoethane. The favoured amino protecting group is now Fmoc (see Chapter 24), which has the advantage that it can be removed under basic conditions (piperidine) which do not affect acid-labile side-chain protecting groups.

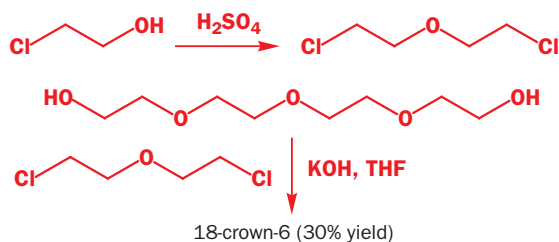
Methods like these have made polymer-supported synthesis so valuable a method that it is now being developed for many reactions old and new. A recent (1999) issue of the journal *Perkin Transactions 1* reported two syntheses of natural products in which every step was carried out using a polymer-supported reagent. Polymers are vital to us in everyday life in a multitude of ways and new polymers are being invented all the time. We have done no more than scratch the surface of this subject and you should turn to more specialized books if you want to go further.

Problems

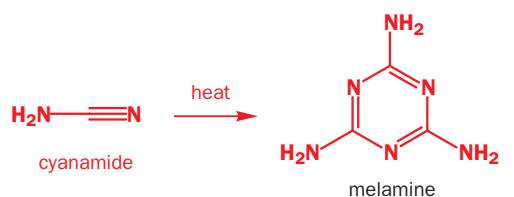
1. The monomer bisphenol A is made by the following reaction. Suggest a detailed mechanism.



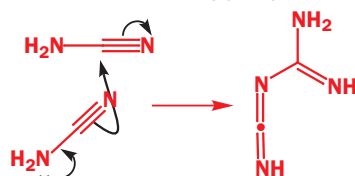
2. An alternative synthesis of 18-crown-6 to the one given in the chapter is outlined below. How would you describe the product in polymer terms? What is the monomer? How would you make 15-crown-5?



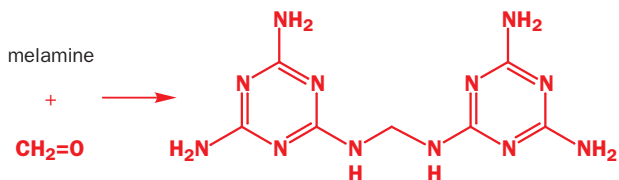
3. Melamine is formed by the trimerization of cyanamide and a hint was given in the chapter as to the mechanism of this process. Expand that hint into a full mechanism.



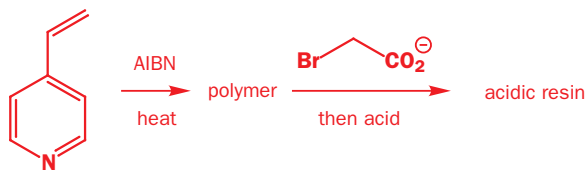
hint about the first step:



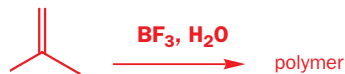
Melamine is polymerized with formaldehyde to make formica. Draw a mechanism for the first step in this process.



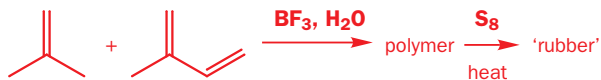
4. An acidic resin can be made by the polymerization of 4-vinylpyridine initiated by AIBN and heat followed by treatment of the polymer with bromoacetate. Explain what is happening and give a representative part structure of the acidic resin.



5. An artificial rubber may be made by cationic polymerization of isobutene using acid initiation with BF_3 and water. What is the mechanism of the polymerization, and what is the structure of the polymer?



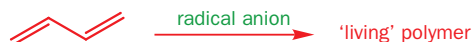
This rubber is too weak to be used commercially and 5–10% isoprene is incorporated into the polymerizing mixture to give a different polymer that can be cross-linked by heating with sulfur (or other radical generators). Draw representative structures for sections of the new polymer and show how it can be cross-linked with sulfur.



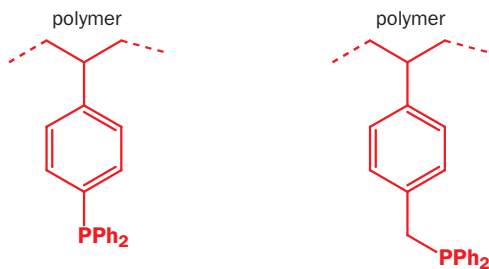
6. When sodium metal is dissolved in a solution of naphthalene in THF, a green solution of a radical anion is produced. What is its structure?



This green solution initiates the polymerization of butadiene to give a 'living polymer'. What is the structure of this polymer and why is it called 'living'?



7. We introduced the idea of a spacer between a benzene ring (in a polystyrene resin) and a functional group in the chapter. If a polymer is being designed to do Wittig reactions, why would it be better to have a Ph_2P group joined directly to the benzene ring than to have a CH_2 spacer between them?



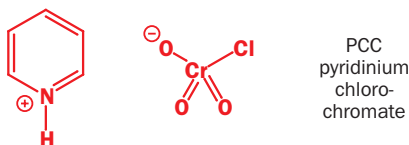
useful for Wittig reactions

useless for Wittig reactions

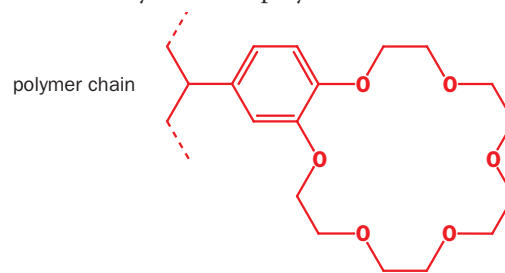
If you need a hint, draw out the reagents that you would add to the polymer to do a Wittig reaction and work out what you would get in each case.

8. A useful reagent for the oxidation of alcohols is 'PCC' (pyridinium chlorochromate). Design a polymeric (or at least polymer-bound) reagent that should show similar reactivity.

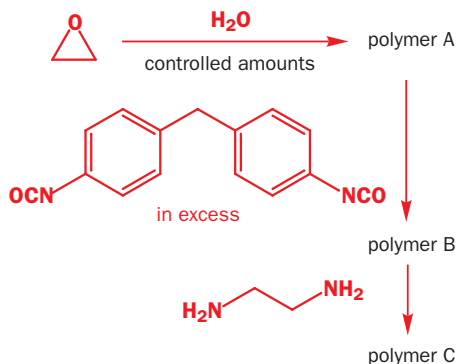
What would be the advantage of the polymer-bound reagent over normal PCC?



9. A polymer that might bind specifically to metal ions and be able to extract them from solution would be based on a crown ether. How would you make a polymer such as this?



10. What is a 'block co-polymer'? What polymer would be produced by this sequence of reactions? What special physical properties would it have?



11. Why does polymerization occur only at relatively low temperatures often below 200°C ? What occurs at higher temperatures? Formaldehyde polymerizes only below about 100°C but ethylene still polymerizes up to about 500°C . Why the difference?

12. Poly(vinyl chloride) (PVC) is used for rigid structures like window frames and gutters with only small amounts of additives such as pigments. If PVC is used for flexible things like plastic bags, about 20–30% of dialkyl phthalates such as the compound below are incorporated during polymerization. Why is this?

