POLYMERS, WATER-SOLUBLE

1. Introduction

Water-soluble macromolecules represent a diverse class of polymers ranging from biopolymers that mediate life processes to synthetic polymers of immense commercial utility. In this article water-soluble polymers have been grouped into the categories biopolymers, nonionic, ionic, and associative, based on key structural features. Recently developed controlled polymerization techniques imparting important technological features to water-soluble polymers are also discussed.

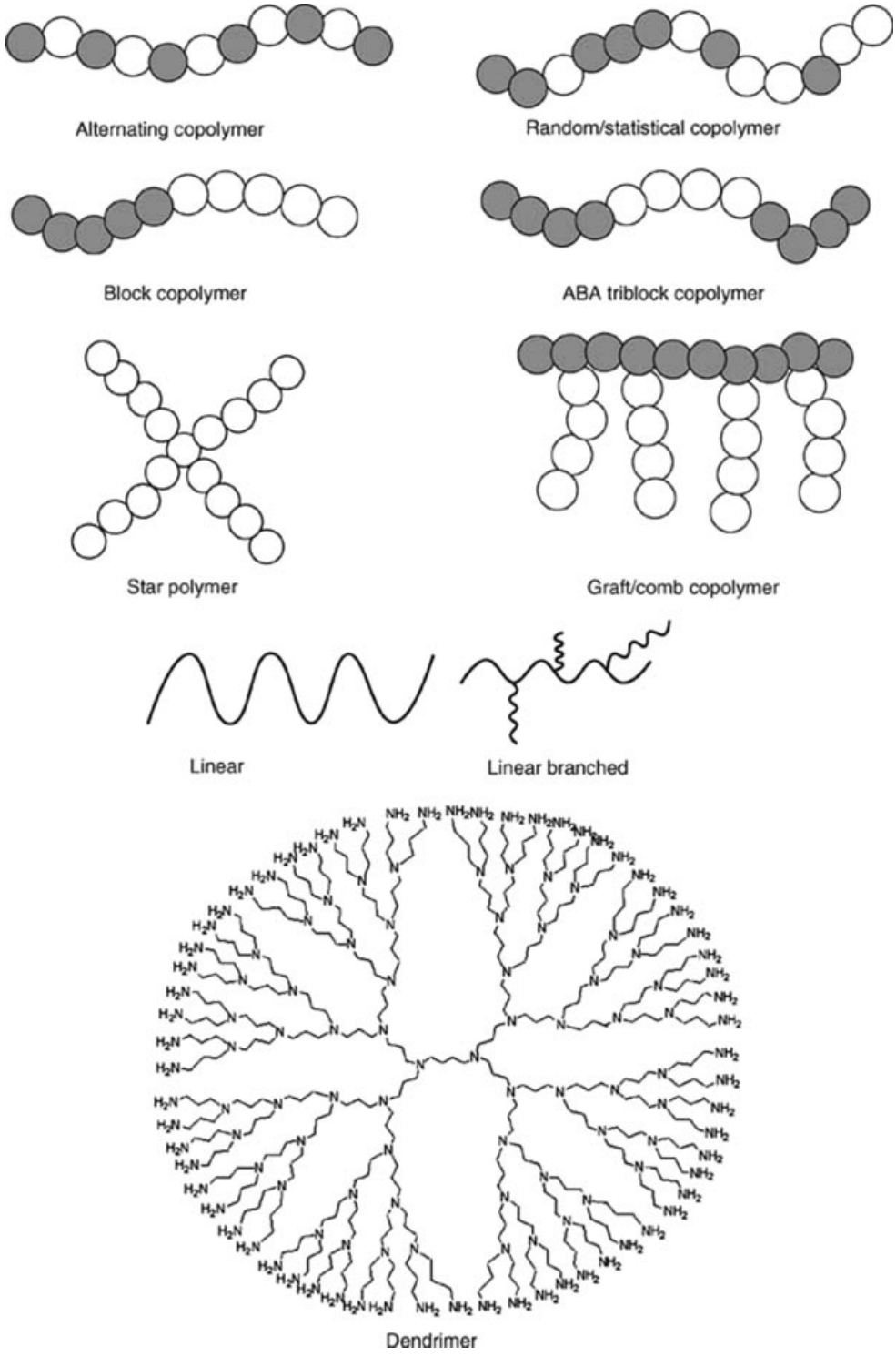


Fig. 1. Structural representation of polymer architectures (1).

2. General Considerations

2.1. Structure. Solution properties and ultimate performance of water-soluble polymers are determined by specific structural characteristics of the hydrated polymer chain. Primary structure depends directly on the nature of the repeating units (bond lengths, valence bond angles) effective compositions, and locations along the backbone. The polymer structure may derive from a single monomer [ie, poly(ethylene oxide) or polyacrylamide] or from multiple monomers. These units may be placed to yield random, alternating, block, graft, or more intricate architectures such as stars or dendrimers (Fig. 1). Biopolymers such as proteins and polynucleotides have multiple repeating units specifically ordered by template polymerization.

Secondary structure in water-soluble polymers is related to configuration, conformation, and intramolecular effects such as hydrogen bonding and ionic interactions. Tertiary structure involves intermolecular and water-polymer interactions; quaternary structure requires multiple chain aggregation or complexation.

A large number of functional groups (Fig. 2) can impart water solubility in copolymers. The degree of solubility is dependent on the number, position, and frequency of these moieties. Hydration relies on interaction at polar (ionic and hydrogen bonding) sites.

2.2. Hydrodynamic Volume. Polymers are often described in terms of hydrodynamic volume (HDV) or that volume occupied by the solvated chain. HDV and molecular shape, determined from light scattering measurements, may be used along with chemical microstructure to predict rheological behavior.

Theoretical attempts to relate dimensions of polymers to chemical structure were pioneered by Flory (2). Statistical macromolecular size in solution can be modeled from first principles by considering the number and length of bonds along with valence bond angles and conformational restrictions. Excluded volume, segmental interactions, specific intramolecular interactions, and chain solvation contribute to dimensions.

Ionic interactions (repulsive or attractive) can also dramatically affect HDV. For charged polymers, ionic effects often dominate behavior, especially in aqueous solutions. Theoretical treatments for predicting polyelectrolyte

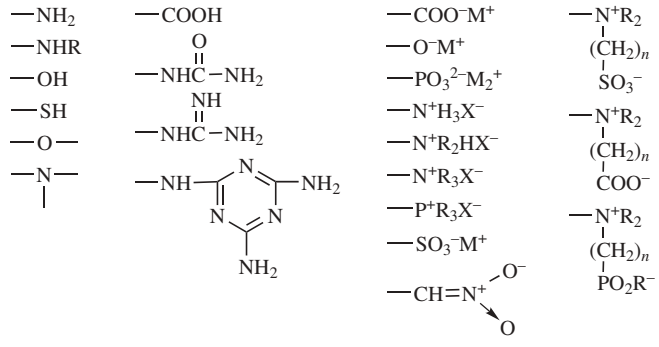


Fig. 2. Examples of functional groups imparting water solubility.

dimensions and phase behavior are discussed by Barrat and Joanny (3); scaling theory for charged polymers is reviewed by Dobrynin, Colby, and Rubinstein (4).

A number of synthetic strategies may be employed to increase macromolecular coil size (HDV) for water-soluble polymers. Monomers with water-soluble moieties may be polymerized to high molecular weight. Effective bond lengths along the backbone may be increased by introducing chain stiffening-elements. These include covalent rings (polysaccharides), charge–charge repulsions (polyelectrolytes), and helical segments (nucleic acids and proteins). The shape of the solvated coil is determined by placement of charged groups, hydrophobic moieties, hydrogen bonds, chiral centers, or restrictive rings along the molecular backbone. The native shapes of globular proteins, for example, are a result of water-induced organization of strategically placed hydrophilic and hydrophobic moieties.

Polymers dissolved in water can have structures (Fig. 3) ranging from random coils to microheterogeneous polymeric vesicles. Solution behaviors of the

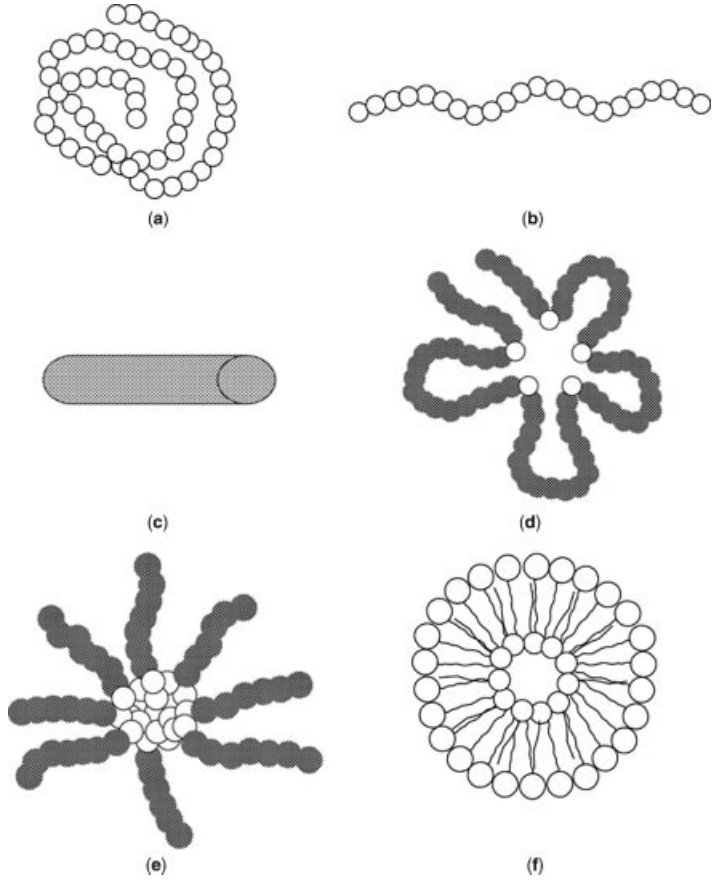


Fig. 3. Structural dependence of molecular shapes of copolymers in aqueous media. (**a**) Hydrated random coil; (**b**) hydrated extended coil; (**c**) rod-like polymer; (**d**) unimeric micelle; (**e**) multimeric micelle; (**f**) vesicle.

various types are quite diverse. Water-soluble random and extended coil polymers are often used for rheology control in various applications. Extended rods in aqueous solution may exhibit lyotropic liquid crystalline behavior. Amphiphilic molecules such as hypercoils, polymeric micelles, and vesicles are used in formulation, drug delivery, and phase-transfer catalysis.

2.3. Role of Water in Solvation/Phase Behavior. Water plays an extremely important role in determining the properties and ultimate utility of polymers in solution. Solvation of polymer chains may involve simple interaction of ionic, polar, or hydrogen-bonded hydrophilic segments of linear chains with water (Figs. 3**a** and 3**b**) or more complex solvation of amphiphilic structures (Figs. 3**d**, 3**e**, and 3**f**). For amphiphilic polymers, water structure around the hydrophobic portion of the chain is thought to be more ordered than in the bulk whereas hydrophilic portions disorder water structure. Amphiphilic macromolecules, including stimuli-responsive copolymers, have been studied in great detail and are the subject of several books and reviews (5–7). Although the precise nature of water structuring is the subject of continuing debate and extensive research, polymer solubility and phase behavior is rationalized in terms of entropy- or enthalpy-dominated events.

Some polymers such as poly(acrylic acid) or polyacrylamide precipitate from aqueous solutions when cooled (normal solubility behavior) whereas others such as poly(ethylene oxide), poly(propylene oxide), or poly(methacrylic acid) phase separate when heated (inverse solubility behavior). Solution turbidimetry is often used to obtain plots of phase-separation temperatures termed *cloud point* vs concentration for fixed solvent conditions. Changes in ionic strength, molecular weight, and addition of co-solvents or structure breakers affect the shapes of phase behavior curves. The important conclusion of such studies is that the total free energy of the polymer and water must be considered to predict phase behavior. The structure and dynamics of water surrounding polynucleotides, proteins, polysaccharides, and lipids are also major determinants of biological activity (8–10).

2.4. Viscosity and Rheology. Viscosity yields important information as to the disposition of the polymer chains in solution and is routinely used to evaluate polymers for particular applications. Dilute solution measurements can yield intrinsic viscosity $[\eta]$, which is a direct indication of the hydrodynamic volume of an isolated polymer chain. This fundamental parameter is related to molecular weight M through the Mark–Houwink–Sakurada (MHS) relationship (eq. 1):

$$[\eta] = KM^a \tag{1}$$

The parameters K and a are characteristics of a polymer chain under specific conditions of solvency and temperature. Values of a can be related to chain extension in dilute solution.

Flexible polyelectrolytes generally are more extended than nonionic polymers owing to charge–charge repulsions along the chain, particularly at low ionic strength. Estimates of $[\eta]$ under such conditions are made by the Fuoss (11) relationship (eq. 2) rather than the traditional Huggins relationship (eq. 3). η_{sp} is the specific viscosity, c is polymer concentration, B and k are characteristic

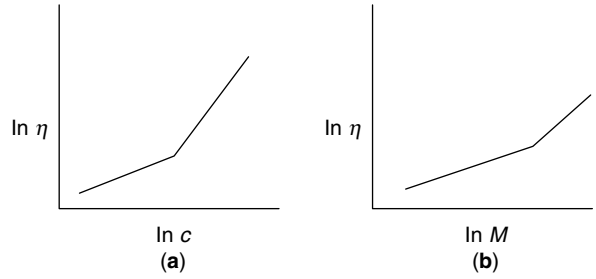


Fig. 4. Relationship between apparent viscosity and (**a**) concentration at constant molecular weight; (**b**) molecular weight at constant concentration.

constants. Alternatively, small-molecule electrolytes may be added in sufficient quantity to suppress the charge–charge interactions and equation 3 may then be used.

$$\frac{\eta_{sp}}{c} = [\eta]/(1 + B\sqrt{c}) \tag{2}$$

$$\frac{\eta_{sp}}{c} = [\eta] + kc \tag{3}$$

The MHS relationship (eq. 1) is often used in conjunction with experimentally determined values of molecular weight and intrinsic viscosity to determine chain stiffness indicated by values of a. Values can range from 0.5 for random coils in theta conditions to nearly 2.0 for extended rods.

In semidilute and concentrated solutions, polymer molecules are no longer isolated from one another. Chain–chain interactions at and above a critical concentration c^*, often termed the *overlap concentration*, lead to increased values of apparent viscosity η. Apparent viscosity can be related to concentration and molecular weight by equation 4, in which b and d are scaling constants.

$$\eta \propto c^b M^d \tag{4}$$

Usually plots of ln η vs ln c at constant molecular weight (Fig. 4**a**) or ln η vs ln M at constant concentration (Fig. 4b) are used to measure entanglement onset. Measurements are made at constant shear rate, temperature, and solvent conditions.

Rheological characteristics of aqueous solutions are dictated by molecular structure, solvation, and by inter- and intrachain associations. In many cases, segmental interactions must be accounted for in more rigorous terms than simple statistical encounters. Enthalpic interactions or entropically driven hydrophobic associations must be considered.

Rheological behavior is dependent on polymer type and can be clearly illustrated, providing appropriate interactive parameters of polymer concentration, ionic strength, pH, shear rate or shear stress, temperature, and time are taken into account. Representative plots are shown in Figure 5 for major behavioral patterns. Figure 5**a** illustrates the shear thickening (dilatant), Newtonian, and

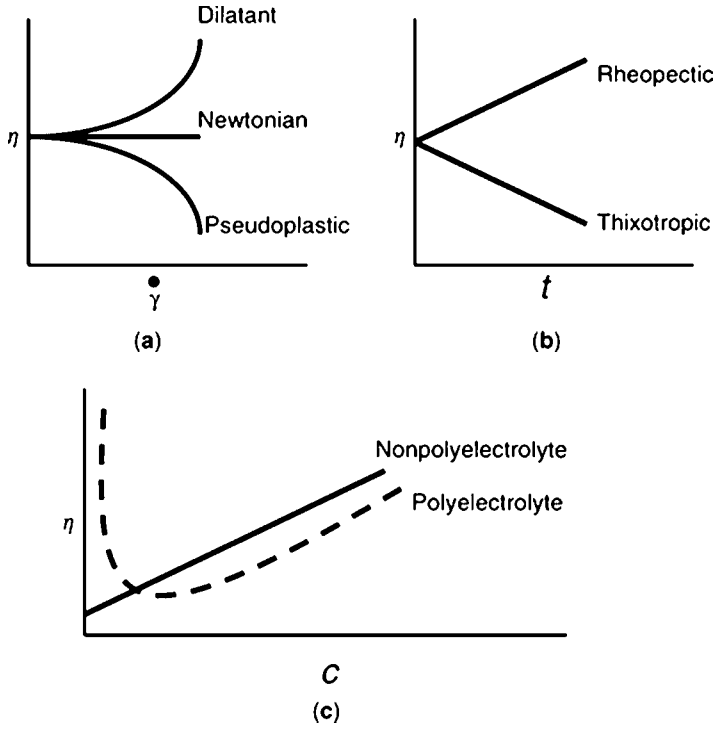


Fig. 5. Rheological characteristics of water-soluble polymers. All variables other than those on the axes are held constant. (**a**) Viscosity vs shear rate; (**b**) viscosity vs time; (**c**) viscosity vs concentrations below c^*.

shear thinning (pseudoplastic) behavior. Figure 5**b** represents time dependence on viscosity for rheopetic and thixotropic polymers. Figure 5**c** illustrates the viscosity-concentration dependence in water for a polyelectrolyte and nonionic polymer in dilute solution.

2.5. Synthetic Methods. Water-soluble copolymers are prepared by step-growth or chain-growth mechanisms. Linear or branched systems may be formed from single monomers or from multiple monomers. Distribution of monomers, along the backbone or side chain, can be controlled in a number of ways. In nearly all cases, sequence selection is obtained by carefully controlling monomer reactivity, concentration, addition order, and reaction conditions. Most chain-growth, water-soluble polymers are prepared by classical free radical polymerization techniques.

Step-growth condensation reactions may be carried out in organic solvents, interfacially, in bulk, microheterogeneously, or on a solid support. Active esters are often employed in solution methods at relatively low temperatures to yield water-soluble polyesters or polyamides. Synthetic polypeptides, polynucleotides, and polysaccharides are commonly made by sequential addition of protected monomer units onto polymer supports.

Major commercial synthetic water-soluble polymers are made by chain-growth polymerization of functionalized alkenes, carbonyl monomers, or strained ring compounds, as illustrated in Figure 6. These may be initiated utilizing free

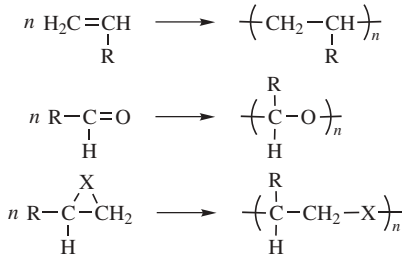


Fig. 6. Synthetic pathways to common water-soluble chain growth polymers.

radical, cationic, anionic or coordinated cationic initiators, depending on monomer structure. Of particular *commercial* interest are syntheses of water-soluble polymers in solutions, dispersions, suspensions, or emulsions. In cases where hydrophobic monomers are to be incorporated with hydrophilic species, microemulsions, or micellar polymerization methodologies are required.

During the last 10–20 years significant advances have occurred in polymer synthesis. Noteworthy is the development of less demanding living polymerization techniques, such as group transfer polymerization (GTP) (12,13) and oxyanionic polymerization (14,15). Most recently, rapid technological advances have been made in the so-called controlled/living free radical polymerizations (CLRP), such as stable free radical polymerization (SFRP) (16,17), atom transfer radical polymerization (ATRP) (18–23), reversible addition-fragmentation chain transfer (RAFT) polymerization (24–27), and tellerium-mediated radical polymerization (TERP) (28–31). Additionally, catalytic chain transfer polymerization (CCTP) (32,33) and living ring-opening metathesis polymerization (LROMP) (34–37) have also been developed. All of these techniques, to some greater or lesser degree, have been employed for the synthesis of novel water-soluble (co)polymers (Fig. 7) with much of the research having been conducted in academic research laboratories (see ANIONIC POLYMERIZATION; LIVING RADICAL POLYMERIZATION).

Whereas each of these techniques has its merits, many have severe limitations either with respect to monomer choice or reaction conditions. The most versatile of the above techniques are arguably the CLRP techniques and have received the greatest attention, to date, with respect to the preparation of novel water-soluble (co)polymers (38,39). These techniques generally exhibit the versatility associated with conventional free radical polymerizations but simultaneously bear many of the characteristics associated with living polymerizations. They are highly tolerant of functional substituents with virtually all vinylic monomers being polymerized by one, or more, of the techniques; additionally, polymerization may be conducted under a wide range of conditions (bulk, solution, dispersion, emulsion etc). Also, molecular weights can be tuned via the monomer/initiator ratio; (co)polymers with narrow molecular weight distributions are typically produced and materials with complex architectures, such as blocks or stars, can be obtained (40,41). With specific reference to the preparation of water-soluble polymers, ATRP and RAFT have been the most widely

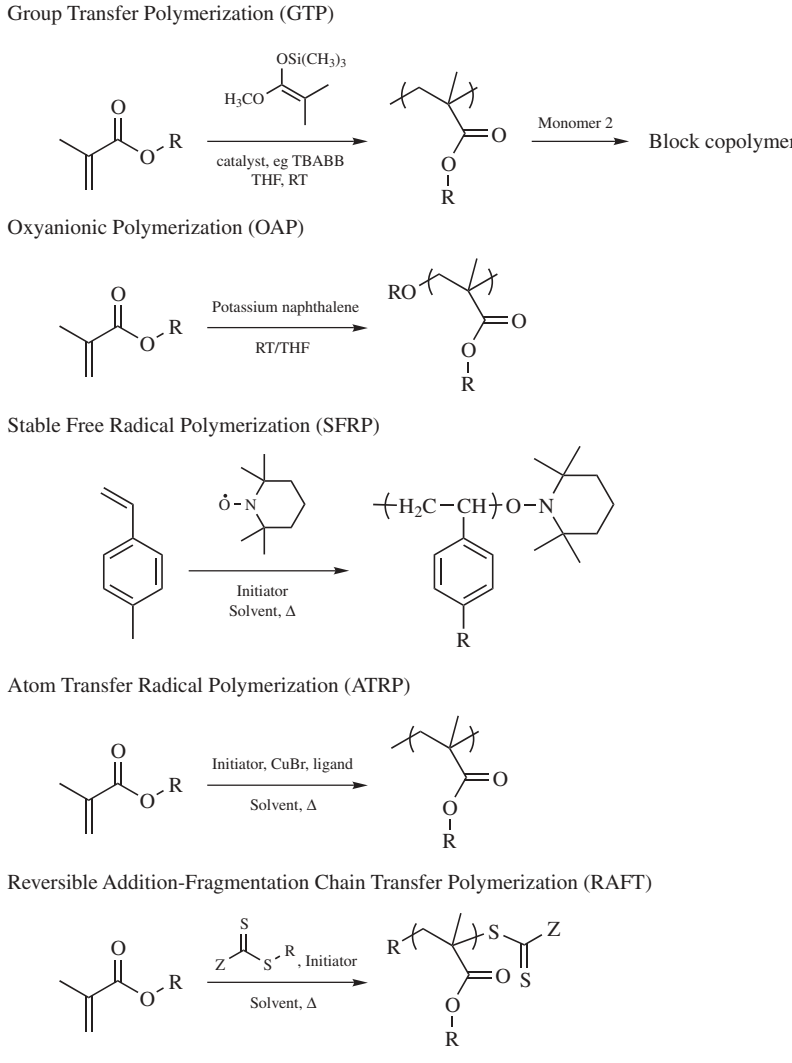
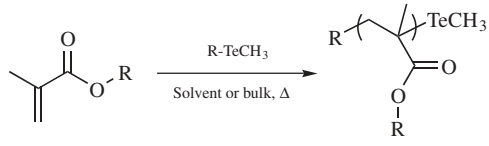


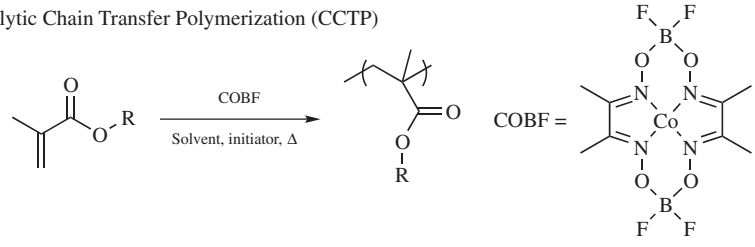
Fig. 7. Controlled or controlled/living polymerization techniques potentially applicable to synthesis of water-soluble or amphiphilic copolymers.

examined, with RAFT being the most versatile, at least with respect to monomer choice. For example, certain species such charged (meth)acrylamido monomers can, at present, *only* be polymerized in a controlled fashion by RAFT (42–45). Key to control in RAFT polymerizations is an appropriate thiocarbonylthio compound, called a chain transfer agent (CTA). While many have proven to be effective, such as the dithioesters, trithiocarbonates, xanthates, and dithiocarbamates (38,46,47), to conduct the polymerizations directly in water requires the use of a suitable water-soluble CTA. Of those reported to date, 4-cyanopentanoic acid dithiobenzoate (CTP) has proven to be the most generally effective (46–48), with others such as2-(1-carboxy-1-methylethylsulfanylthiocarbonylsulfanyl)-2-methylpropionic acid

Tellerium-Mediated Polymerization (TERP)



Catalytic Chain Transfer Polymerization (CCTP)



Living Ring-Opening Metathesis Polymerization (LROMP)

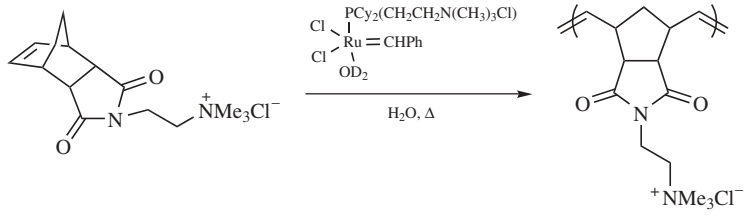
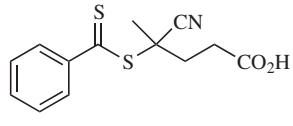
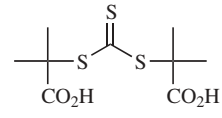


Fig. 7. (*Continued*).

(CTSP) also proving particularly effective for acrylamido and methacrylamido monomers (49,50).



4-Cyanopentanoic acid dithiobenzoate



2-(1-Carboxy-1-methyl-ethylsulfanylthiocarbonylsulfanyl)-2-methyl propionic acid

3. Naturally Occurring Polymers

A large number of water-soluble polymers are derived from biological sources. Termed *biopolymers*, this class includes polynucleotides, polypeptides, and polysaccharides. Because these polymers perform special biological functions, they have specific microstructures and are often perfectly monodisperse. In the following section the general structural features of major biopolymer types will be reviewed as related to water solubility.

3.1. Polynucleotides. *Structure.* Nucleic acids (Fig. 8) are biopolymers that carry genetic information involved in the processes of replication and

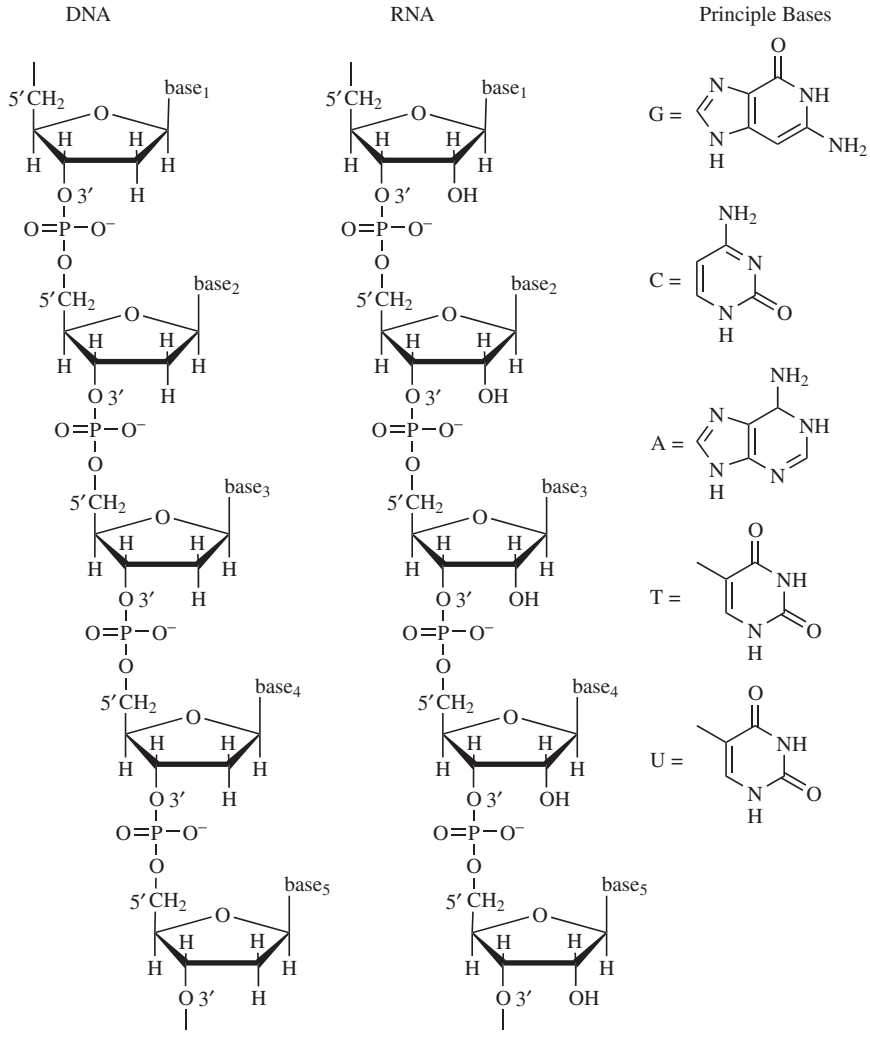


Fig. 8. Structural representations of DNA and RNA; principal bases present in nucleic acid. U,T, and C are the pyrimidines; A and G are the purines.

protein synthesis. The primary structural units of the nucleic acids, the mononucleotides, are composed of a 5-carbon cyclic sugar with a phosphate ester at the C-5 carbon. A heterocyclic amine base (purine or pyrimidine) is attached at C-1. RNA and DNA are terpolymers with sugar phosphate backbones (3′ and 5′ position) and pendent bases on the 1′ position. Deoxyribonucleic acids (DNAs) contain the deoxyribose sugar (no hydroxyl group at the 2′ position on the sugar ring). The usual bases substituted at the 1′ position are adenine (A), guanine (G), thymine (T), and cytosine (C). Ribonucleic acids contain a ribose sugar and the principal bases A, G, C, and uracil (U).

Studies of the structure of DNA by a large number of investigators led to the proposal by Watson and Crick (51) of the classic DNA double helix.

Fig. 9. DNA double-stranded helix (54).

Major contributions as to base content and of X-ray structure were made by the groups of Chargaff (52) and Wilkins and co-workers (53). This proposal not only allowed explanation of DNA stability but also provided a framework for postulation of template polymerization during the replication and transcription processes.

The template synthetic process allows organization of the DNA helix into an assembly having two antiparallel strands of DNA (Fig. 9). The pendent bases on the strands are paired in such a manner that A is always paired with T and G with C. The strong hydrogen bonding of the complimentary pairs in hydrophobic regions orients the hydrophilic-charged phosphate groups outwardly. One negative charge per phosphate unit gives the DNA polyanionic character. The balance of hydrophilic and hydrophobic forces and the presence of divalent ions such as Mg^{2+} are also responsible for chain stability under physiological conditions. Three conformational variations of the double helix have been confirmed by X-ray diffraction—the A, B, and Z forms. Conformational variation, location of certain base-paired sequences, and specific modification (methylation for example) can lead to supercoiling, branching, and direct binding to other polynucleotides or to specific proteins. Such structural organization has major implications in gene regulation (transcription, silencing, etc).

The molecular weights of DNA, depending on the source, can be extremely large. For example, the recently sequenced human genome has been reported to have over 27,000 genes and 3 billion base pairs (55). By contrast, a simple bacterium such as *Escherichia coli* has 5 million (54) chromosomal base pairs. In

addition, the latter contains cyclic DNA, called plasmids, which contain from 1000 to 10,000 base pairs. Recombinant DNA technology is routinely utilized to insert synthetic genes or genes from other species into such plasmids. The resultant recombinant DNA segments then serve as templates for synthesis of specific proteins with pharmacological, agricultural, or materials applications.

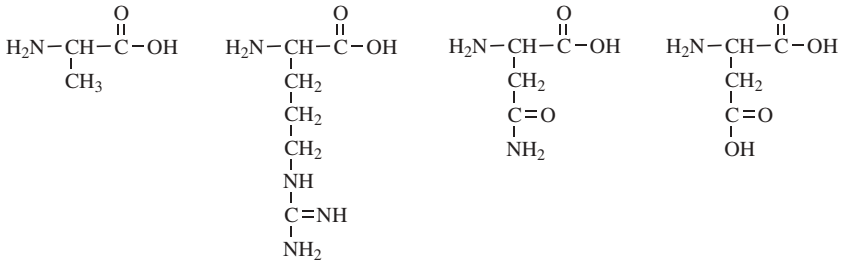
Ribonucleic acids are synthesized from the DNA template through transcription. The mononucleotides contain ribose. Unlike DNAs, RNAs are single stranded, although twisting may occur in a complementary fashion matching base pairs. RNAs are much lower in molecular weight than DNAs. The three major types—messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA)—are involved in a multistep process of protein synthesis (56,57).

Beyond their well-established roles in protein synthesis, RNAs termed *ribozymes* have been shown to catalyze a number of biochemical reactions. Significantly, short hairpin sequences of RNA can hybridize with DNA to suppress (silence) gene expression (58). Alternatively, some of these short RNA sequences bind in a complementary fashion to mRNA resulting in destruction of the latter and preventing protein translation from that gene segment (58).

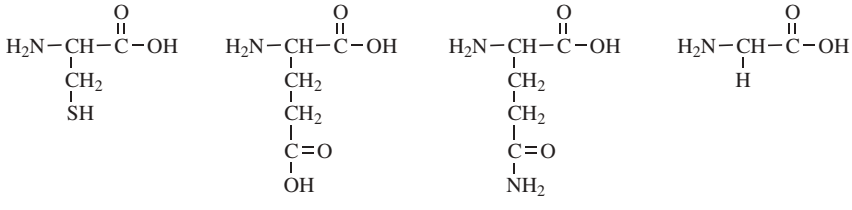
Synthesis. Recently, nucleic acids have been synthesized from mononucleotides, some with altered or substituted bases. Synthetic methods, along with nucleic acid sequencing methods, have allowed rapid advancement in identifying gene sequences responsible for specific protein synthesis. Kornberg and co-workers first prepared synthetic DNAs polymerized from mononucleotides using isolated enzymes, DNA polymerases (59). Likewise, RNA polymerases have been found for synthesis of oligomeric RNAs (60). DNA also can be made from RNA using reverse transcriptase enzymes. The resulting complementary DNA can be greatly amplified using the polymerase chain reaction process (PCR) (61). These are readily characterized and in many instances introduced into plasmids or other vectors for recombinant protein synthesis. Automated synthesis of single-stranded polynucleotides can be accomplished utilizing sequential protection/deprotection chemistry (62). Although entirely synthetic methods are quite slow compared to biosynthesis, designed oligonucleotides for targeting or diagnostic purposes (including micro arrays with variable sequences for rapid screening) can be readily produced. Post-reaction chemistry including ligation and PCR can then be utilized to produce significant quantities of desired oligonucleotides.

3.2. Polypeptides and Proteins. Most polypeptides and proteins are water-soluble or water-swellable. Enzymes are proteins that catalyze all chemical reactions of biological origin. Enzyme functions include oxygen transport, muscle movement, nerve response, nutrient digestion and storage, hormonal regulation, gene expression, and protein synthesis (63).

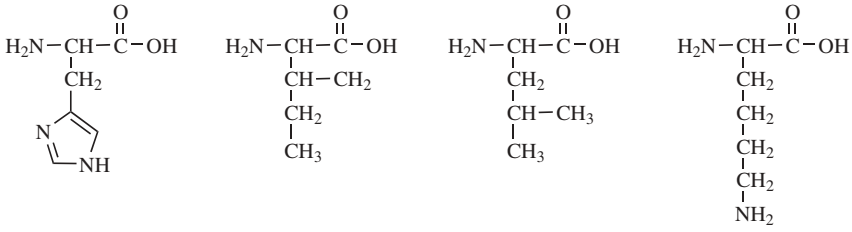
Structure. Despite the large number of functions, all proteins are similar with repeating structures along the backbone chosen from 20 amino acid monomers (Fig. 10). These polymers, the structures of which are assembled from a template coded by mRNA, are monodisperse. Each protein has a unique sequence and molecular weight. The 20 amino acids, capable of appearing in various microstructural combinations, sequence lengths, and total molecular lengths, allow assembly of a nearly unlimited number of distinct proteins with specific physical properties and behavioral characteristics.



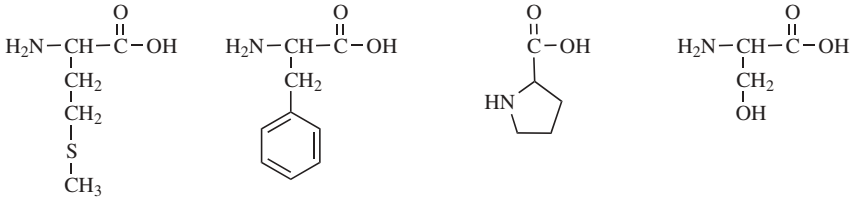
Alanine (Ala) Arginine (Arg) Asparagine (Asn) Aspartic acid (Asp)



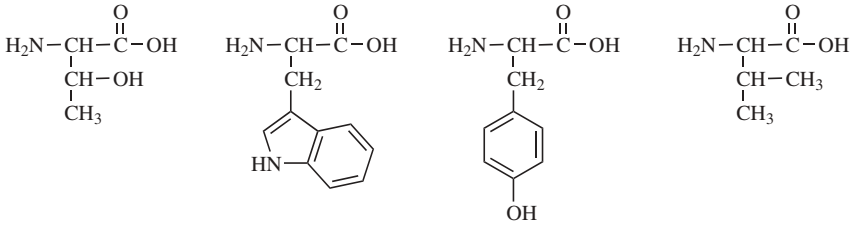
Cysteine (Cys) Glutamic acid (Glu) Glutamine (Gln) Glycine (Gly)



Histidine (His) Isoleucine (Ile) Leucine (Leu) Lysine (Lys)



Methionine (Met) Phenylalanine (Phe) Proline (Pro) Serine (Set)



Threonine (Thr) Tryptophan (Trp) Tyrosine (Tyr) Valine (Val)

Fig. 10. Chemical structures of the 20 amino acids.

Primary structure (covalent bond lengths and bond angles) is determined by the microstructure of the amino acid repeating units along the chain. Numerous procedures, including sequential degradation, gel electrophoresis, dye binding, and immunoassays, have been used to determine sequences (63).

Secondary structure of proteins is determined by configuration and conformation along the backbone of the polymer. The resistance to bond rotation of the C–N bond of the peptide unit, the configuration about the chiral carbon, and conformational restrictions to rotation by short-range charge–charge interactions or intramolecular hydrogen bonding play major roles in secondary structure.

The three-dimensional structure, or tertiary structure, depends strongly on primary and secondary structure with the added elements of long-range intramolecular hydrogen bonding, polar and ionic effects, and chain solvation. An example of the three-dimensional structure of myoglobin is shown in Figure 11. The compact structure illustrates the hydrophobic interior, helical features from intramolecular hydrogen bonding and the L-amino acids, and polar external groups for hydration (see PROTEIN FOLDING).

Many proteins exist in subunits of a composite structure. The organization of these subunits is termed the *quaternary structure* and is particularly important in enzyme-mediated reactions. The tertiary and quaternary structure of native protein in water can be disrupted by addition of electrolytes, alkali solutions, urea, or detergents, and by increasing temperature. The properties change markedly; eg, enzyme activity is often lost. In most cases this denaturation is not reversible. The solubilities of proteins vary considerably based on composition and conditions of ionic strength, pH, and concentration. Those with the highest density of polar groups or electrolyte character are most soluble. Therefore, solubility in water is lowest at the isoelectric point and increases with increasing

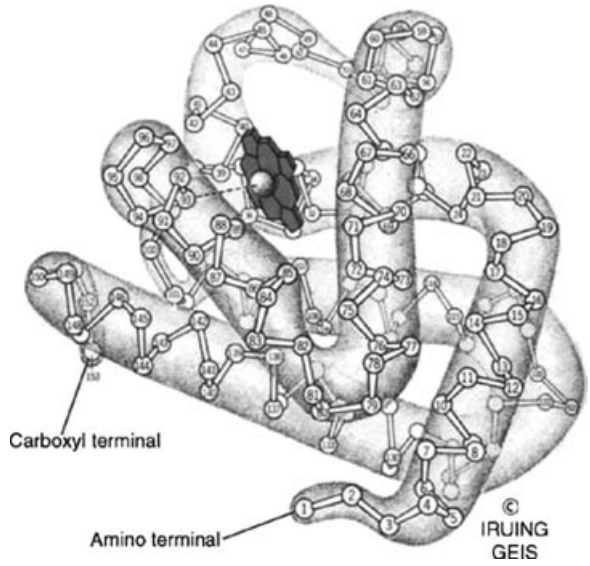


Fig. 11. Tertiary structure of myoglobin (64).

basicity or acidity. A review of enzyme activity as related to protein structure is given by Fersht (65).

Protein Synthesis. Protein biosynthesis is complex, involving more than 300 macromolecules (63). Five stages can be identified involving (*1*) activation of amino acid monomers and transfer to ribosomes, (*2*) initiation of polymerization, (*3*) propagation, (*4*) termination and release, and (*5*) folding and processing. Ordering of the monomers is dictated by operation of the triplet code in which a sequence of three consecutive nucleotide units on mRNA positions a specific amino acid for polymerization.

Synthetic polypeptides can be made by sequential addition of protected amino acids onto a solid support. This procedure, pioneered by Merrifield (66, 67) has been used to prepare hundreds of peptides of varying sizes and functions. A review of the technique and recent modifications are found in Reference 68.

The study of genes responsible for identifiable biological products and processes (genomics) (69) and the more ambitious study of translated proteins, their isoforms, modifications and interactions (proteomics) (70) has advanced at an incredibly fast pace during the last five years. In a very short time a number of genes have been targeted for recombinant expression in a variety of hosts to produce a wide range of new drugs and to develop new diagnostic markers.

Commercial Use. In addition to the rapid growth of genetically engineered enzymes and hormones for medical and agricultural applications, other water-soluble proteins are isolated from biological sources in a more traditional manner for commercial application. Enzymes are used as detergent additives, for hydrolyzing polysaccharides and proteins, to isomerize various glucose and sucrose precursors, for wine and beer making, for leather tanning, and for mineral recovery. Support-bound enzymes are becoming commercially significant for large-scale substrate conversion.

4. Polysaccharides

Water-soluble polysaccharides are a diverse class of biological macromolecules with a wide range of structural and behavioral characteristics. More than 100 sugars and sugar derivatives comprise the monomers available for polysaccharide synthesis (63). Covalent linkages between repeating units may occur at different ring positions; linear and branched structures with single or multiple monomers may be formed (see POLYSACCHARIDES).

Industrial polysaccharides have traditionally been extracted from renewable resources in the plant and animal kingdom. Examples include starch and gums from plant seeds, pectin from fruits, and algin and carrageenan from algae. Recently, microbial sources have produced commercially useful polysaccharides such as dextran, curdlan, pullulan, xanthan, and pharmacologically active oligosaccharides.

Polysaccharides are cyclolinear or branched polymers formed by enzyme-directed step-growth condensation reactions of various activated sugar molecules (71). Some common monomer units are shown in Figure 12; other units include glycerol and other polyhydroxyalcohols, phosphate, sulfate, malonate, and pyruvate.

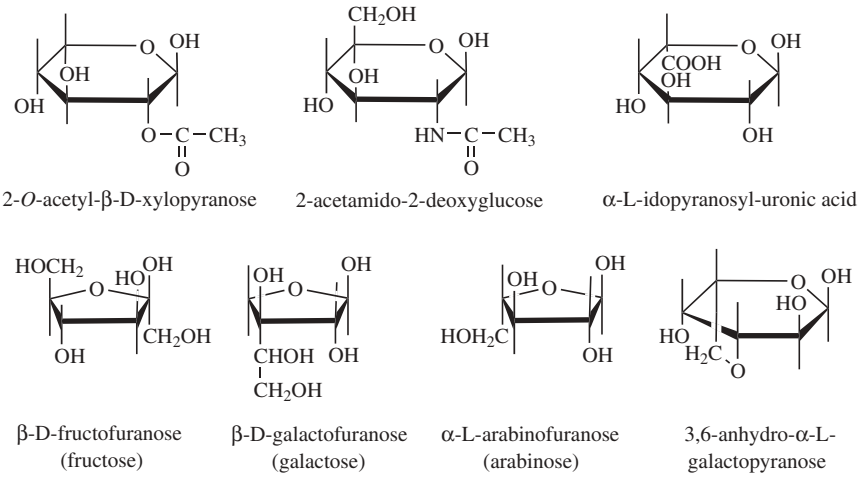


Fig. 12. Common structural units in naturally occurring polysaccharides (71).

Aqueous solution properties, including solubility, phase behavior, and viscosity, are highly dependent on the macroscopic nature (linear, branched) of the chain as well as the chemical microstructure (polar characteristics, sequencing) of the repeating units. As with proteins, the presence of acidic or basic functionality causes pH, electrolyte, and temperature-dependent behavior. Degrees of polymerization may vary from 30 to 1×10^5. Of primary importance in the solution behavior of water-soluble polysaccharides are the configurations of asymmetric carbon atoms in the cyclic monomers and the ring conformations of the resulting covalent backbone units.

Dimerization of glycopyranose (Fig. 13) by condensation of the hydroxyl group at C-1 on one ring with C-4 on the other can lead to two isomers, depending on whether the reaction is equatorial–equatorial or axial-equatorial. The former linkage is designated β, the latter, α. Polymers formed by successive α-1 →4 linkages, eg, amylose, have markedly different properties than polymers formed by successive β-1→4 linkages, eg, cellulose.

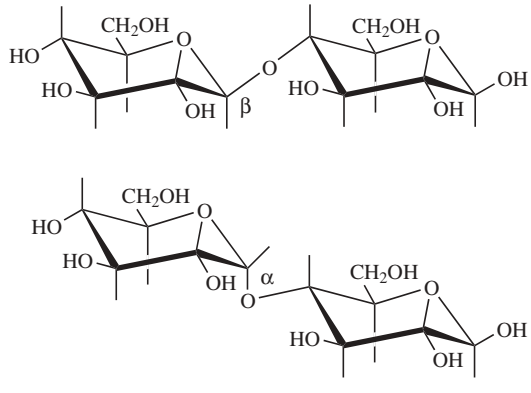


Fig. 13. Dimerization of glucopyranose units to yield α and β structures.

Polysaccharides based on glucopyranose occur with backbones through carbons 1→2, 1→3, 1→4, and 1→6. The less-ordered structures are more water-soluble in general, with the α-1→3 and the β-1→6 forms exhibiting highest aqueous solubility; β structures often form strong inter- or intramolecular hydrogen bonds, making solubilization difficult.

Branched structures, especially for α linked polysaccharides, enhance solubility. Heterogeneity in types of repeating units, backbone linkages, and polar or charged functionality also imparts greater solubility. Excellent reviews of the effects of the structural conformation of monosaccharides are found in References 71 and 72.

Water-soluble polysaccharides can be classified according to structure and commercial applications. Classes include storage polysaccharides, pectins, plant gums, seed and bark mucilage, algal polysaccharides, bacterial and fungal polysaccharides, mucopolysaccharides, and synthetically modified polysaccharides. For more detailed descriptions see References 72–75.

4.1. Storage Polysaccharides. *Starch and Starch Derivatives.* Amylose and amlyopectin are the major components of starch granules found in food reserves of all green plants. Commercial starch is obtained from sources such as corn, sorghum, rice, wheat, and potatoes. The compositions of the amylose and amylopectin vary with source.

Amylose is the linear polysaccharide of α-1→4-D-glucopyranose having a molecular weight of $1.6 \times 10^5 - 2.6 \times 10^6$. Amylose is not water-soluble in an unmodified state but can be dispersed in water. In the solid state it is reported to exist as a left-hand six-fold helix; in solution it behaves like an extended helix (74). Shearing and heating of starch cause hydration and swelling termed *germination*. Gradually the amylose in this dispersion precipitates through association in a process called *retrogradation*.

Amylopectin (Fig. 14), the water-soluble portion of starch, is an α-1→4-D-linked glucopyranose with α-1→6-D-branches. Amylopectin is polydisperse with a molecular weight of $5 \times 10^7 - 4 \times 10^8$.

A number of starch derivatives (73, 74) have been prepared in order to control solubility, viscosity, and phase behavior over a temperature range or under

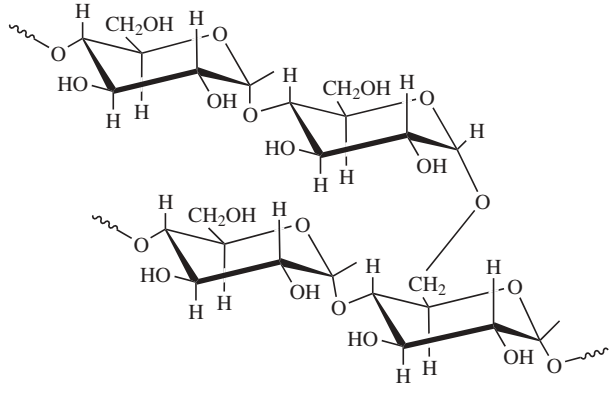


Fig. 14. Structure of amylopectin (73).

conditions of shear and added electrolytes. Major modifications include lowering molecular weight enzymatically or chemically, oxidation, forming derivatives, and cross-linking. Derivatives include starch esters, phosphates, sulfates, and ethers. Cationic, anionic, and amphoteric starches have been prepared as well as starch–graft copolymers, some with super absorbent properties.

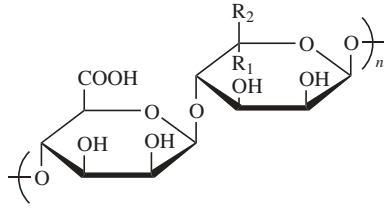
Starch and starch derivatives have a number of applications in the food industry as viscosifiers, gelatinizers, fillers, and paste formers; in the textile and paper industries for coatings, sizing agents, rheology modifiers, and pigment binders; and in the medical area as surgical powders, absorbents, adhesives, and in pharmaceuticals.

Glycogen. Glycogen is the storage polysaccharide in animals and is found in highest concentration in the liver and muscle tissues. The backbone of glycogen is α-1→4-D-linked glucopyranose units with large numbers of α-1→6-D-branch points.

Glucans. Algae form two types of storage polysaccharides. Starch type algal polysaccharides are α-D-glucans similar to those found in land plants, except they contain a small number of α-1→3-D-linkages and are of lower molecular weight (76). Laminaran is the main carbohydrate food reserve of several green seaweeds and is a β-1→3-D-linked D-glucan with β-1→6-D-branches. Other sources include fungi, yeast, flagellates, and diatoms.

Laminaran has two forms distinguished by solubility in cold water. Differences are related to the degree of 1→6 branching. Both are soluble in hot water and have molecular weights from 3500 to 5300. Laminaran has been used for surgical dusting powder and has been reported to have antitumor activity.

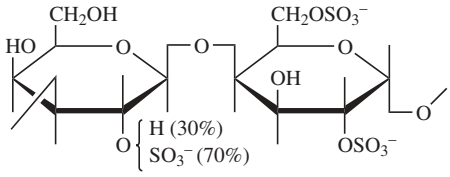
4.2. Algal Polysaccharide. *Alginic Acid*. Alginic acid represents the generic group of polymers (74) composed of D-mannuronic acid and L-guluronic acid extracted from brown algae (77). Alginic acid is not soluble in pure water, but easily dissolves in aqueous solutions of alkali metal hydroxides or carbonates. The structure (77) of alginic acid shown below is complicated with three types of segments: poly(β-1→4-D-mannuronic acid); poly(α-1→4-L-gluronic acid); and those in alternating patterns. The ionic forms of algins are polyelectrolytes with extended structures. The precise properties are determined by the structural disposition of these segments. Alginates are used as thickeners and stabilizers in the food industry, in pharmaceutical, cosmetic, and coating formulations, and as flocculants.



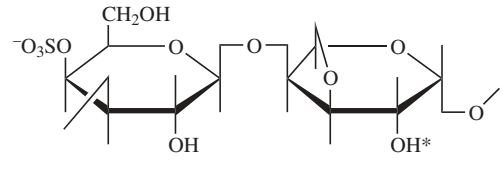
β-D-Mannuronic acid

Sulfated Derivatives. Sulfated algal polysaccharides (78) are a class of heteropolymers with alternating α-1→3-D- and β-1→3-D- (carrageenan and furcellaran) or alternating α-1→3-L- and β-1→3-D- galactans (agar). Conformational differences have been shown between the nongelling λ carregeenan and

gel-forming κ and ι forms (71). OSO_3^- replaces OH^+ in the κ form (72). Molecular weights range from 1×10^5 to 1×10^6.



lambda (λ) carrageenan



kappa (κ) carrageenan

Carrageenan has diverse industrial applications including use in toothpaste, ice cream, chocolate milk, jellies, puddings, pet foods, pharmaceutical and industrial suspensions, antiulcer treatments, shampoos, creams, lotions, and oil/water and water/oil emulsions. Carrageenan reacts with denatured proteins and has been shown to exhibit properties similar to those of the animal mucopolysaccharides, such as anticoagulant activity and induction of growth of new connective tissue.

4.3. Pectins. Pectins (pectic and pectinic acids or their derivatives) are gel-forming water-soluble polysaccharides found in the primary cell walls and intercellular layers in land plants. They are found in abundance in apples, sugar beets, and the rinds of citrus fruits. Pectic acids are poly(α-D-galactopyranoslyuronic acids) with varying degrees of neutralization. Pectinic acids are also galactouronglycans but with significant quantities of methyl ester groups. Pectins are soluble in water and exhibit pseudoplastic behavior. When heated at appropriate pH, in the presence of divalent electrolytes and sugars, they form spreadable gels (74). For this reason pectins are used for making jams and jellies.

4.4. Plant Gums. Plant gums or exudate gums are formed spontaneously at sites of injury to the plant. The exudate is a viscous fluid consisting of complex, highly branched polysaccharides with residues of hexuronic acid and two or more neutral sugars. Many plant gums are used commercially as thickening agents or emulsion stabilizers. Commercially important are karaya gum, gum tragacanth, gum Arabic, and gum ghatti (76).

4.5. Seed Mucilages. Guaran is a purified polysaccharide from the guar plant seed. It is a linear chain of β-1→4-linked D-mannopyranosyl units onto which is linked an α-1→6-D-galactopyranosyl unit (Fig. 15). Molecular weights are estimated to be 2.2×10^5 (79). Guaran forms high viscosity, pseudoplastic solutions at low concentrations, is nonionic, and is little affected by electrolyte addition or pH changes. Guar easily forms gels with transition metal elements or borate ions and is therefore useful in drilling, cementing, and fracturing in oil-filed applications. It has also been used as a thickener and stabilizer in the manufacture of ice cream, cheese, pet foods, and deodorant gels.

4.6. Extracellular Polysaccharides. One of the most important extracellular bacterial polysaccharides is dextran. Dextrans are high molecular weight α-1→6-D-glucopyranose polymers with varying proportions of α-1→4 and α-1→3 branch linkages. Dextran is produced from sucrose by a number of bacteria from the family *Lactobacillaceae*. Dextran has a variety of commercial applications, including use as a plasma substitute, an anticoagulant, or in studies of cells, viruses, and proteins. Fractionated commercial dextrans are used as standards in

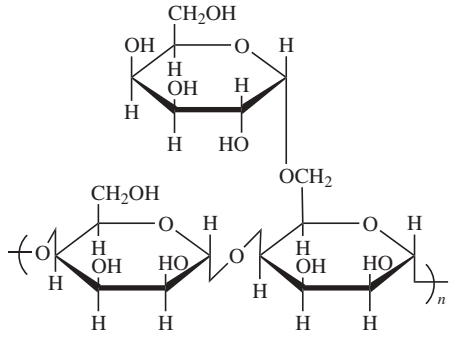


Fig. 15. Structure of guaran.

various studies of the properties of water-soluble polymers. Dextran–graft copolymers have utility in viscosifications, superabsorbancy, and oil-field applications (80).

4.7. Bacterial and Fungal Polysaccharides. Microbes generate a large number of polysaccharides, many of which are not produced by the higher plants or animals. A large number of microbial polysaccharides are used in the food, cosmetic, and pharmaceutical industries. Particular polysaccharides, when isolated from the dried bacteria, have been shown to induce an immune response and generate antibodies in organisms exposed to them. Several of these capsular polysaccharides have been used to develop vaccines for various bacterial infections such as meningitis and typhoid fever (81).

Xanthan (qv) is an extracellular bacterial polysaccharide produced by *Xanthomonas campestris*. Xanthan is a branched polysaccharide with β-1→4-D-glucopyranose units along the backbone. On every other unit the oxygen at C-3 is substituted with a trisaccharide unit. Approximately half the β-D mannose units have a pyruvic acid group linked as an acetal derivative. Molecular weight has been estimated to be 2×10^6.

The solutions are viscous as low polymer concentrations, pseudoplastics, and insensitive to salt, temperature, and pH over a wide range. Much controversy remains as to changes in the tertiary structure with changing solution conditions. Single, double, and even triple helical structures have been proposed as well as quaternary structures from side-by-side double helix dimers (72,75,82).

Other water-soluble microbial polysaccharides include the anionic polysaccharides gellan from *Pseudomonas elodea* and bacterial alginate from *Pseudomonas aeruginosa*, and the neutral polysaccharides scleroglucan, curdlan, and pullulan (72,75,76,83).

Scleroglucan and schizophyllan (Fig. 16) are examples of fungal polysaccharides (72,75,81,84). Their structures are identical except for the distribution of side chains along the polymer backbone. Both are rod-like macromolecules forming triple helices in aqueous solutions. They are used industrially as viscosifiers and in polymer flooding for enhanced oil recovery. They have also been shown to exhibit specific biological activity against cancers and infections.

4.8. Mucopolysaccharides of Higher Animals. Mucopolysaccharides of higher animals are generally found in the connective tissues. They form highly viscous aqueous solutions that gel readily. These polysaccharides consist of amino sugars (D-glucuronic acid or L-iduronic acid) and may have *N*-acetyl, *O*-sulfate, or

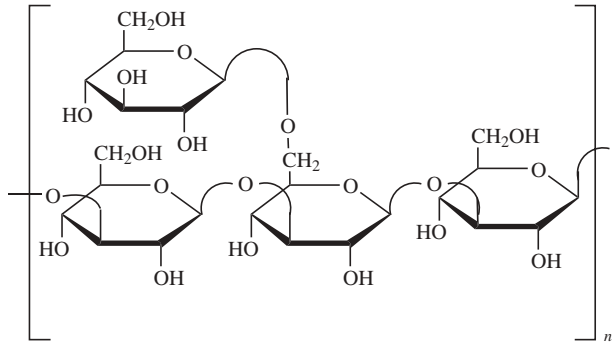
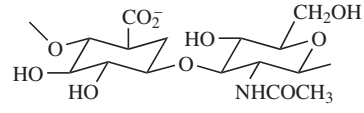


Fig. 16. Structures of scleroglucan and schizophyllan (75).

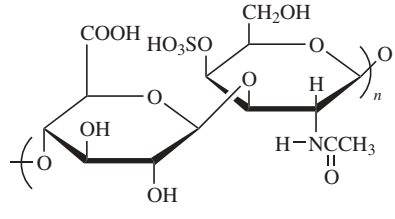
N-sulfate groups. Their functions include induction of calcification; control of metabolites, ions, and water; and healing of wounds. Several of these polymers are under study for medical, cosmetic, and personal care applications.

Hyaluronic acid is a regularly alternating copolymer of D-glucuronic acid and 2-acetamido-2-deoxy-D-glucose (77). It is found in most connective tissues, especially in umbilical cord, vitreous tissue, joint fluid, and skin. It is synthesized by fibroblasts in the mesenchymal tissue and also by bacteria. Hyaluronic acid binds a large amount of water in the interstitial spaces and is thought to be involved with the control of permeability and thus resistance of the tissues to infection. Hyaluronic acid is involved in the wound-healing process and is produced in large amounts at the site of the wound in the days following the injury. Hyaluronic acid also serves as a lubricant in the joints. Commercially, hyaluronic acid has application in postoperative healing in eye surgery.



Hyaluronic acid

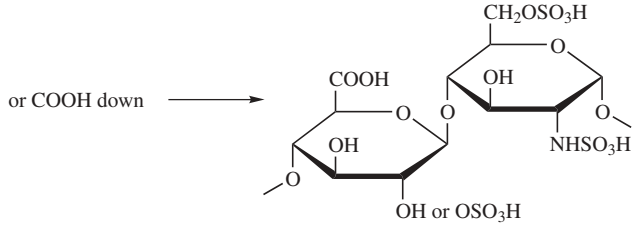
Chondroitin and chondroitin sulfates are found in cartilage, skin, cornea, sclera, and bone. They show high viscosity and water retention and play a role in the connective tissue similar to that of hyaluronic acid. Sulfate groups contribute additional ion-binding capacity. In dermatan sulfate the −COOH group extends axially from the bottom face (77).



Chondroitin sulfate

Dermatan sulfate (β-heparin) is found in the skin, lungs, tendons, spleen, brain, and heart. Dermatan sulfate exhibits high water retention and acts in a way similar to the chondroitin sulfates. It is also an anticoagulant.

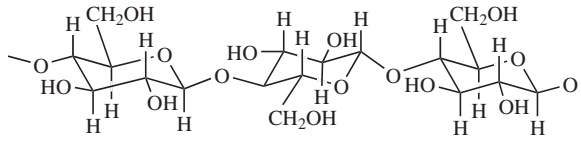
Heparin (85) is found in the heart, liver, lung, spleen, muscle, kidney, and blood. It is synthesized in the mast cells and has a molecular weight of 5000–25,000. Heparin is a mixture of polysaccharide chains of varying lengths and heterogeneity. It consists of 2-acetamido-2-deoxy-α-D-glucopyranosyl, α-D-glucopyranosyluronic acid, and L-iduronic acid residues containing various proportions of *O*-sulfate, *N*-sulfate, and *N*-acetyl groups. It is an anticoagulant and antilipemic agent and is widely used in cardiovascular surgery and therapy.



Heparin

4.9. Synthetically Modified Polysaccharides. Water solubility can be conferred on a number of naturally occurring polysaccharides by synthetic derivations producing charged or polar functionality. Two of nature's most abundant polysaccharides, cellulose and chitin, have been synthetically modified in a multitude of ways to produce polymers with significant commercial utilization (86,87).

Cellulose Derivatives. Cellulose is a β-1→4-D-anhydroglucopyranose copolymer (see below) that serves as the major structural component of plants. When the cellulose molecule is extended, it is a flat ribbon with hydroxyl groups protruding laterally and is capable of forming both intra- and intermolecular hydrogen bonds. This form allows the strong interaction with neighboring chains that makes dissolution difficult. In fact, strongly interactive solvents are necessary for solubilization. Molecular weights range from 5×10^5 to 1.5×10^6, depending on the source. Water-soluble cellulose ethers can be prepared by nucleophilic substitution, ring opening, or Michael addition mechanisms (72).



Cellulose

Carboxymethylcellulose (CMC) is usually prepared by the reaction of cellulose with the sodium salt of chloroacetic acid in aqueous alkaline organic slurries. The extent of substitution on C-2, C-3, and C-6 is related to the degree of disruption of hydrogen bonding, steric factors, and reaction conditions (72,87). The acid

form of CMC is a polyelectrolyte with limited solubility and a pK_a of 4. The monovalent metal or ammonium salts are soluble; divalent cations result in borderline solubility; multivalent cations allow gel formation. Solutions of sodium CMC are pseudoplastic for high viscosity grades with degrees of substitution (DS) of 0.9–1.2. Solutions of less uniformly substituted, high molecular weight CMC with low DS are thixotropic; CMC is stable over the pH range 4–10 (see CELLULOSE ETHERS).

CMC is used in sizing for textile and paper applications and as a thickener, stabilizer, suspending agent, or binder in foods, pharmaceuticals, and cosmetics. CMC is a fluid loss and rheology modifier in drilling muds.

Hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) are prepared by nucleophilic ring opening of ethylene oxide and propylene oxide, respectively, by the hydroxyl anions on the anhydroglucose ring of cellulose. Reactions are conducted commercially in caustic aqueous slurry processes (72). Laboratory methods recently have been reported for preparation of cellulose ethers, esters, and carbamates under homogeneous reaction conditions in organic solvents (88–91). Such solvents may lead to development of new commercial processes for cellulose derivatives with more uniform substitution.

HEC is a nonionic polymer with little surface activity in solution and is compatible with a wide range of surfactants and salts. Solutions are pseudoplastic at higher molecular weights and concentrations. Molecules behave as rigid rods in dilute aqueous solution. Commercial HEC has molar substitution (MS) between 1.8 and 3.5 degree of substitution of 0.8–1.8.

HPC is more hydrophobic than HEC owing to the presence of the methyl group on the side chain. The polymer is soluble in organic solvents but phase separates from water above 45°C. In concentrated solutions, HPC exhibits lyotropic liquid cryalline behavior (61). Commercial HPC has MS values between 3.5 and 4.5 and DS values of 2.2–2.8 (72,87).

HEC is used in coatings, cements, thickeners, pharmaceuticals, oil-well fracturing, cementing, and drilling applications, and in cosmetics, inks, paper finishes, lubricants, gels, and agricultural formulations. HPC is used for warp sizing, flocculations, wetting, thickening, binding, formulation of hair sprays, cosmetics, pharmaceuticals, and personal care items.

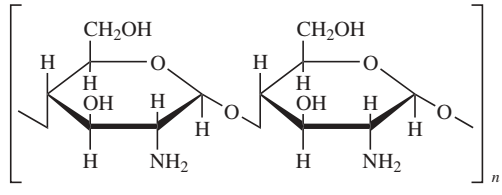
Methylcellulose is prepared commercially by reaction of the respective methyl chloride or dimethyl sulfate with alkali cellulose with organic slurry systems, batch methods, or continuous processes (72,87). The methyl ether derivatives have a DS range from 1.5 to 2.0, the uniformity of which depends on the heterogeneity of the reaction medium and other reaction conditions. Substitution occurs preferentially at the C-6 and C-2 positions. Methylcellulose exhibits both an upper and lower critical solution temperature as signified by gel formation on heating or cooling homogeneous solutions. Uses for methyl cellulose include gelling fluids, viscosifiers, pharmaceutical coatings, and food additives.

Hydroxypropylmethylcellulose (HPMC) is one of the many mixed ethers of cellulose. It is prepared by reactions of alkali cellulose with methyl chloride and propylene oxide in a slurry process. Reaction conditions may be varied to control compositions despite the greater reactivity of methyl chloride. HPMC is an extremely effective viscosifier compared to conventional cellulose ethers. Its

microheterogeneous nature, phase behavior, and interaction with surfactants allow use in food, pharmaceutical, and coatings applications (72,87).

Cellulose sulfates and phosphates are water-soluble derivatives prepared by reactions of alcohol/water/organic diluent mixtures of sulfuric or phosphoric acids. Phosphate derivatives are flame retardant but have not been commercialized (72).

Chitin Derivatives and Chitosan. Chitin (92) is a water-insoluble, high molecular weight polymer of 2-acetamido-2-deoxy-D-glucopyranosyl units linked through β-1→4-D bonds. This most abundant skeletal material of invertebrates is recovered from shrimp, crab, or lobster waste materials. Fungi are also an important commercial source of chitin. Chitin may be converted to chitosan by partial or complete deacetylation. In the protonated form (see below), this cationic polyelectrolyte is water-soluble with a number of potential commercial uses including flocculation, viscosification, wound healing, medical dressing, pharmaceutical formulation, drug delivery, membrane technology, and animal nutrition.

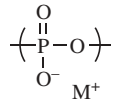


Chitosan

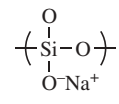
Chitin can be derivatized (92–95) by reaction of the hydroxyl substituents on carbons 3 and 6 of the anhydroglucose ring. *N*-substituted derivatives at C-2 can be obtained from reactions on chitosan or partially deacetylated chitin. Hydroxyethylchitin and other water-soluble derivatives are useful wet-end additives in papermaking and flocculants for anionic waste streams (see CHITIN AND CHITOSAN).

5. Inorganic Water-Soluble Polymers

Poly(metaphosphoric acid) (96,97) is formed by controlled dehydration of NaH_2PO_4. The lower molecular weight sodium hexametaphosphate is available commercially. High molecular weight analogues can be prepared with various cations. The other widely abundant inorganic polymers, poly(silicic acid) and its sodium or potassium salts are highly branched, associated, high viscosity polymers. Aqueous solutions of silicates have been used as raw materials for centuries in window-glass formation and insulating-glass fibers (96).



Poly(phosphoric acid) salt

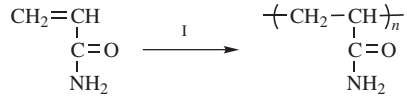


Poly(silicic acid) salt

6. Nonionic Polymers

A number of commercially available and experimental nonionic monomers including those shown in Figure 17 have been utilized to prepare a large number of water-soluble (co)polymers. Water solubility is a result of a high concentration of polar or hydrogen-bonding functional groups on the repeating units. Major commercial polymers are based on acrylic, vinyl, oxide, or imine functionality.

6.1. Polyacrylamide. Acrylamide (AM) monomer is polymerized by free-radical initiators, eg, azo compounds, redox, catalysts, light, and radiation. This monomer is unique among vinyl and acrylic monomers because it can be polymerized to ultrahigh molecular weight (10^6–10^7). This extraordinary feature of acrylamide polymerization is attributed, in part, to the ease of purification of AM monomer and to the unusually high ratio of its propagation to termination rate constants (k_p/k_t). In fact, AM has the highest k_p/k_t of any free radically polymerizable monomer. Polyacrylamide (PAM) can be prepared via solution, inverse emulsion, inverse microemulsion, or precipitation techniques (98–100) (see ACRYLAMIDE POLYMERS).



Low temperature initiation, high monomer concentration, and a small amount of added 2-mercaptobenzimidazole, a radical scavenger, are reported to be the optimal reaction conditions for preparing high molecular weight, soluble polymers. High total solids concentrations usually result in intractably high solution viscosities. Inverse emulsion polymerization offers the opportunity for lowered viscosities without compromising polymer molecular weights (101–103).

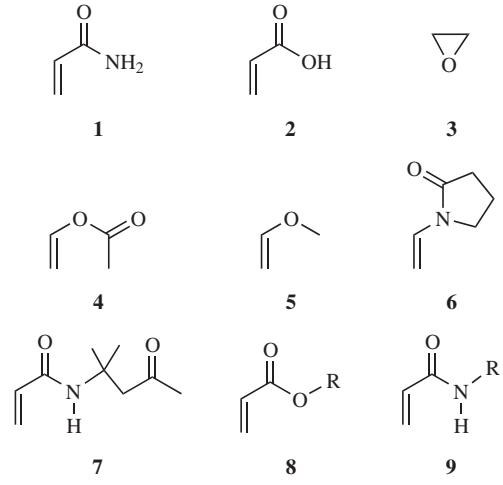


Fig. 17. Examples of uncharged monomers utilized in the synthesis of water-soluble, nonionic copolymers.

Inverse microemulsion polymerization results in rates 10–200 times faster than conventional inverse emulsion systems (104). Precipitation polymerization can also be accomplished using a solvent (eg, *tert*-butyl alcohol) that dissolves the AM monomer but not the PAM (100).

Solution polymers are usually isolated by precipitation or dialysis/freeze drying. However, such solid products are hard to re-dissolve. Recently this problem was overcome by the discovery that water-in-oil (w/o) emulsions of polyacrylamide can be inverted by adding a water-soluble surfactant to produce an oil-in-water (o/w) emulsion. Thus a low HLB surfactant is used for polymerization and a high HLB surfactant is used for phase inversion (103). The resulting polymers re-dissolve easily. Inversion must be complete or polymer (activity) is lost.

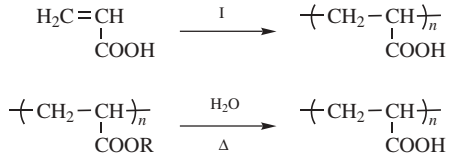
AM is difficult to polymerize by any of the "controlled/living" polymerization techniques. However, McCormick and co-workers have recently made significant progress in this area by reporting the CLRP, via RAFT, of AM in both aqueous and organic media (47,49,50). To achieve "living" conditions, judicious choices must be made with respect to RAFT chain transfer agent (CTA) and polymerization conditions.

PAM has reported T_g values of 165 and 188°C. No matter which value is correct, it is clear that PAM remains glassy to relatively high temperatures. Although PAM is slow to dissolve, it is soluble in water in all proportions. However, PAM solution viscosities show a time dependence, attributed to intramolecular conformational changes (98). Because PAM can be polymerized to very high molecular weight, it is a highly efficient aqueous viscosifier. Solution viscosities of nonionic PAM are insensitive to changes in pH (between 1 and 10). Above pH = 10, it is subject to hydrolysis. Solutions of nonionic polyacrylamide are also tolerant of electrolytes (eg, NaCl). Viscosities increase with increasing molecular weights, according to equation 5.

$$[\eta] = 1.0 \times 10^{-2} M_w^{0.755} \text{ (water, } 25^\circ \text{ C)} \tag{5}$$

Polyacrylamides function as flocculating agents, in rheology control, and as adhesives.

6.2. Poly(acrylic acid). Poly(acrylic acid) (PAA) can be prepared by direct free-radical polymerization of in aqueous solution (6) or by precipitation polymerization in benzene. Alcohols and mercaptans are commonly used chain-transfer agents for regulating polymer molecular weight. Alternatively, PAA can be prepared by hydrolysis of poly(alkyl acrylates) (6).



Both RAFT and NMP controlled/living techniques are suitable for the direct polymerization of acrylic acid. The RAFT polymerization of AA has been reported in DMF (24,105), various alcohols (106,107), water (108), and dioxane (109)

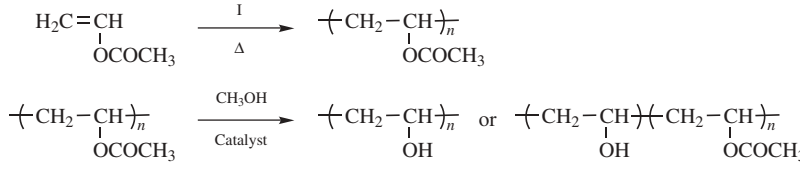
employing a variety of RAFT CTAs including dithioesters, xanthates, dithiocarbamates and trithiocarbonates. AA is also susceptible to controlled polymerization by NMP (110,111).

The T_g of PAA has been variously reported as 75, 106, and 126°C, depending on the mode of measurement. However, the highest value is probably the most accurate. Solid polymers are hard, clear, brittle materials. In aqueous solutions, viscosity increases with increasing molecular weight. PAA undergoes a number of reactions in solution, ie, hydrolysis, esterification, dehydration, and complex formation with polyethers. PAA is an excellent thickener for lattices. PAA has been used in oil recovery, as a dispersant for inorganic pigments, as a flocculant, and as an adhesive.

6.3. Poly(ethylene oxide). Poly(ethylene oxide) (PEO) is prepared by ring-opening polymerization of the ethylene oxide monomer 3 (112,113). Polymers of molecular weight greater than 1×10^5 are prepared by heterogeneous catalysis (eg, alkaline earth carbonates) in low boiling aliphatic hydrocarbons. Few of the details of the commercial manufacture have been made public (see ETHYLENE OXIDE POLYMERS).

PEO is a white free-flowing powder with commercial grades from 100,000 to 5 million molecular weight (114). It has a T_m of about 65°C and a T_g of −45 to −53°C. Above the melting point it can be processed as a thermoplastic, ie molded or extruded. However, owing to its high melt viscosity, incorporation of plasticizer is often desired. PEO resins are completely soluble in water at room temperature, but show a lower critical solution temperature (LCST) near the boiling point of water. The LCST is lowered by the addition of inorganic salts according to the following order: $PO_4^{3-} > SO_4^{2-} > F^- > Cl^- > I^- > K^+ > Na^+ > Li^+$. Aqueous solutions of high molecular weight PEO show high extensional and shear viscosities and pseudoplastic rheology.

6.4. Poly(vinyl alcohol). Poly(vinyl alcohol) (PVA) is manufactured by alcoholysis/hydrolysis of poly(vinyl acetate), which is, in turn, produced by free-radical polymerization of vinyl acetate monomer 4 (114). (see VINYL ALCOHOL POLYMERS).



Polymerization of vinyl acetate monomer can be effected by bulk, solution, or emulsion techniques. The poly(vinyl acetate) formed is then dissolved in solvent (eg, CH_3OH) and alcoholized/hydrolyzed with acidic or basic catalysts. Vinyl acetate can also be polymerized in a controlled fashion via RAFT/MADIX (115). PVA is insoluble in CH_3OH and precipitates. It is isolated by filtration, washing, and drying.

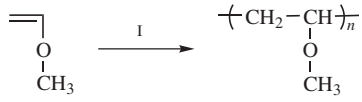
Properties of PVA depend on the degree of alcoholysis/hydrolysis and polymer viscosity/molecular weight. Bulk/film properties (eg, tensile strength, tear resistance, elongation, and flexibility) of PVA increase with increasing extent

of alcoholysis/hydrolysis and with increasing viscosity/molecular weight. The tensile strength is exceptional compared with other water-soluble polymers. Water solubility/sensitivity is at a maximum at 88% alcoholysis/hydrolysis. Beyond that level, polymer–polymer interactions via intramolecular H-bonding become so extreme that solvation of the polymer becomes difficult.

Other noteworthy properties of PVA are its film-forming ability, its barrier, adhesive, and emulsifier properties, and its grease, oil, and solvent resistance. PVA films and coatings do not require a curing cycle because tough films can be formed by evaporation. PVA film also has remarkable gas impermeability, forming barriers to oxygen, nitrogen, carbon dioxide, hydrogen, helium, and hydrogen sulfide. However, PVA does exhibit permeability to ammonia and water vapor. Its adhesive binding strength is attributable, in part, to its film-forming ability and its high strength. PVA has surface activity as an o/w emulsifier and/or protective colloid. Oil and solvent resistance increases with extent of hydrolysis.

Poly(vinyl alcohol) is used alone or combined with extenders, pigments, etc, in the preparation of high wet-strength adhesives for paper. It is an excellent binder for textiles and sizing agent for paper and can be used to emulsify a wide range of materials including vegetable oils, mineral oils, solvents, plastics, waxes, and resins. Its emulsifying, binding, film-forming, and thickening behaviors are useful in cosmetic formulation. PVA films can also be used for making oxygen tents.

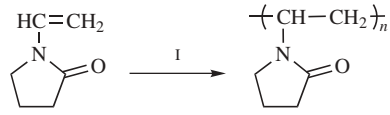
6.5. Poly(methyl vinyl ether). Methyl vinyl ether (MVE) is isomeric with PPO, but is significantly more water-soluble. Indeed, it is the methyl ether derivative of poly(vinyl alcohol). MVE is readily polymerized using carbocationic methods (116–18). This also facilitates the preparation of novel MVE-based block copolymers. Purification of homo polymers and copolymers prepared by the termination of living poly(methyl vinyl ether) (PMVE) with *n*-alcohols involves a combination of solvent removal, dialysis, and freeze drying (118).



MVE can also be polymerized under alternating free radical conditions with, for example, maleic anhydride to yield poly(9-methylvinylether-alt-maleic anhydride).

The T_g of PMVE is −34°C (119) and as such exists in a rubbery state at standard temperatures and pressures. PMVE exhibits broad solubility. Common solvents include benzene, halogenated hydrocarbons, ethanol, *n*-butanol, acetone, ethylacetate, cold water, heptane and cyclohexenes. Common nonsolvents include hexane, ethylene glycol, and dioxyl ether (119). PMVE is readily soluble in water, but like many nonionic water-soluble polymers, PMVE exhibits inverse temperature water-solubility. The cloud point varies over a broad range depending on MW. For example, low molecular weight PMVE with a D_p of 19 is reported to have a cloud point of 18°C while some commercial grades have significantly higher cloud points at ca 35°C (117).

6.6. Poly(*N*-vinylpyrrolidinone). *N*-Vinylpyrrolidinone (NVP) monomer polymerizes under free-radical conditions via bulk, solution, and suspension methods.



Azo initiators are preferred over persulfate initiators because the latter react with the monomer. One of the curious features of this polymerization is that it has a maximum rate of polymerization in the presence of about 1 mol of water (120,121). Presumably, a specific complex forms between the monomer and a water molecule. NVP does not polymerize to particularly high molecular weight, in part because it is difficult to purify the monomer.

The T_g of PNVP is 175°C, but this value is reduced considerably by small amounts of water. Dry-cast films of PNVP are hard and transparent. However, the presence of strong intermolecular dipole–dipole interactions causes it to have a high processing temperature. Consequently, PNVP has never found acceptance for molded parts. PNVP has interesting solution properties. It is readily soluble in water and forms complexes with a wide variety of substances, eg, iodine, polyacids, phenolics. Solutions of PNVP are stable to electrolytes. Solution viscosities increase with increasing polymer molecular weight. PNVP (bulk or solution) is also characterized by high thermal or thermohydrolytic stability and chemical resistance. PNVP is also compatible with a wide range of hydrophilic and hydrophobic resins and modifiers.

PNVP has found applications in a wide variety of industries, including medicine, pharmaceuticals, cosmetics, textiles, beverages, adhesives, and paper (121,122). For example, PNVP was an early plasma and blood volume extender. It is used extensively in pharmaceutical tablets. Its complex with iodine is a germicide. It is used as a component in cosmetics, hair shampoos, and sprays and is a stabilizing agent for beer. PNVP also exhibits excellent adhesion to glass (see *N*-VINYLAMIDE POLYMERS).

7. Polyelectrolytes

Polyelectrolytes are polymers with charged functional groups attached along the chain. These polymers are usually classified as either polyanions (negative charges) or polycations (positive charges). Associated with the polyions are counterions or gegenions of the opposite charge in sufficient numbers to maintain electroneutrality (123).

Water-soluble polyelectrolytes exhibit a number of common traits with water-soluble nonionics. However, differences arise from the presence of charges on the macromolecular backbone and more mobile counterions electrostatically bound to an extent determined by pK_a, solvent, and local dielectric effects. Generally, phase behavior and enhanced solubility result from increased segmental hydration and increased free energy of mixing.

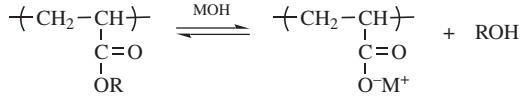
The interactions between fixed charges on the polymer chain in dilute solution normally expand (repulsive) or contract (attractive) coil dimensions. Counterion binding also influences hydrodynamic volume and involves specific ion binding as well as atmospheric ion binding. Theoretical discussions of these effects can be found in References 123 and 124.

Polyelectrolytes with flexible chains and high charge density are more expanded in water than nonionic polymers, especially at low ionic strength. Determination of intrinsic viscosity is difficult in this regime (Fig. 5**c**). Electrostatic repulsions not only cause increases in hydrodynamic volume but also increases in shear sensitivity or non-Newtonian behavior.

The extent of ionization of polybases or polyacids depends on the relative base or acid strength, degree of solvation, and dielectric constant of the solvent. Poly(acrylic acid), for example, ionizes progressively in aqueous basic solution to yield a copolymer with ionized acrylate units and un-ionized acrylic acid units along the backbone; neighboring group hydrogen-bonding effects accelerate initial ionization. Eventually, however, ionization becomes more difficult owing to excessive buildup of charge along the backbone.

Polyelectrolytes have been studied extensively because molecular structures can be tailored to allow large conformational changes with pH, temperature, or added electrolytes. Molecular parameters that influence behavior include number, type, and distribution of charged repeat units on the chain, hydrophobic/hydrophilic balance, distance of charged moiety from the backbone, and counterion type. Solution properties including phase behavior, hydrodynamic volume, and binding can be altered, offering utilization in flocculation, adhesion, stabilization, compatibilization, viscosification, suspension, etc.

7.1. Anionic Polyelectrolytes. Anionic poly(acrylic acid) (PAA) can be synthesized in two ways, ie direct polymerization of 1A (Fig. 18) or via hydrolysis of a suitable precursor polymer (6). In the direct method, salts of acrylic acid are homopolymerized or copolymerized by free-radical initiation in aqueous media. Usually the rate of polymerization of the ionic monomer is lower than the corresponding nonionic monomer, presumably owing to charge repulsion between the growing chain and the incoming ionic monomer. Direct polymerization of acrylic acid salt solutions has some commercial advantages because the nonvolatility of acrylic acid salts allows simultaneous polymerization and spray drying (or drum drying) to produce high molecular weight polymers directly. Hydrolysis (saponification) is the alternative method for producing anionic poly(acrylic acid). Hydrolysis of syndiotactic esters gives syndiotactic salt, and hydrolysis of isotactic esters gives isotactic salts.



The T_g of anionic poly(acrylic acid) [eg poly(sodium acrylate)] is substantially higher (251°C) than that of nonionic poly(acrylic acid) (102°C) because of the strong intermolecular forces due to ionomeric clustering. Physical/mechanical properties (eg, moduli) are also generally higher for salts vs free acids in the bulk phase. Atactic and syndiotactic salts of acrylic acid are water-soluble, but

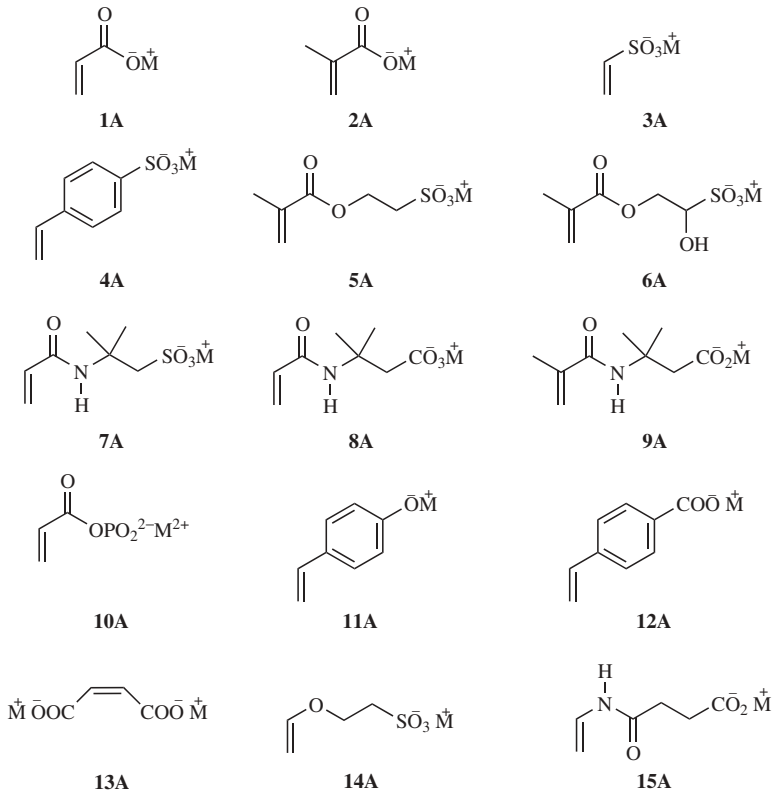
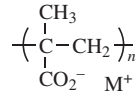


Fig. 18. Examples of monomers utilized in preparing anionic polyelectrolytes.

isotactic forms are not. Salts of poly(acrylic acid) show characteristic polyelectrolyte solution behavior (6).

The applications of anionic poly(acrylic acid) include use as latex thickeners, oil-field chemicals, dispersants, and flocculants. In addition, poly(acrylic acids) containing small amounts of cross-linking agents are water-swellable polymers that have found use as superabsorbents.

Poly(methacrylic acid) and Its Salts. A wide variety of methods have been used to prepare poly(methacrylic acid) (PMAA) (6). Free-radical polymerization by hydrogen peroxide, persulfate, or redox systems in aqueous solution yields atactic polymer with syndiotactic tendency. At higher pH, a higher syndiotactic content is produced. Stereoregularity can be obtained by hydrolysis of appropriate precursor polymers.



Poly(methacrylic acid) salt

Controlled structure PMAA can be prepared by the deprotection of an appropriate precursor polymethacrylate which has itself been polymerized

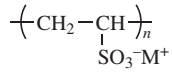
under living conditions. Both anionic polymerization and GTP have been used to prepare PMAA employing a variety of PMAA precursor monomers such as benzyl methacrylate (125), *tert*-butyl methacrylate (126), trimethylsilyl methacrylate (127) and 2-tetrahydropyranyl methacrylate (128,129). Removal of the protecting group yields the desired PMMA.

The sodium salt of methacrylic acid 2A has also been polymerized directly in aqueous media via ATRP employing a PEO macro-initiator (130). Short chain, controlled structure oligomers of PMAA may also be prepared by CCTP (131).

Poly(methacrylic acid) in the nonionized form in solution has a compact conformation and low intrinsic viscosity. Upon ionization to the polyelectrolyte form, chain expansion occurs and viscosity increases. Unlike PAA, PMAA shows inverse solubility-temperature behavior. The presence of chain-stiffening methyl groups and their added hydrophobicity are responsible for the phase and viscosity behavior. Tacticity also plays an important role.

PMAA and its copolymers with acrylamide are used in viscosification and flocculation. Copolymers of MAA and its salts have been used as components of superabsorbents, coatings, adhesives, and in drilling operations.

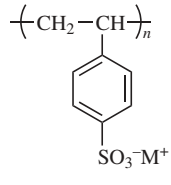
Poly(vinylsulfonic acid) and Its Salts. Poly(vinylsulfonic acid) (PVSA) is prepared by polymerization of ethylenesulfonic acid or its sodium salt 3**A** under free-radical conditions. It is purified precipitating aqueous solutions of the sodium salt form with methanol or dioxane.



Poly(vinylsulfonic acid) salt

The sodium and ammonium salts of PVSA are soluble in water but insoluble in organic solvents (6). The calcium salt is insoluble. Potentiometric titration studies indicate that PVSA is a strong acid that ionizes completely in water. Ion binding selectivity with alkali metals has been observed in viscosity and phase separation studies. Mark–Houwink–Sakurada (MHS) parameters of $K = 2.22$ and $\alpha = 0.65$ have been obtained for sodium PVSA in $0.5\,M$ NaCl at 25°C.

Poly(styrenesulfonic acid) and Its Salts. Poly(styrenesulfonic acid) (PSSA) (6) may be prepared by free-radical polymerization of the monomer in solution using the free acid, sodium, or potassium salt **4A** form.



Poly(styrene sulfonate) salt

PSSA may also be prepared by sulfonation of polystyrene or by hydrolysis of poly(*n*-propyl *p*-vinylbenzenesulfonate). The latter cases allow preparation of tactic structures. Copolymers can also be prepared by free-radical copolymerization

of appropriate monomers or post-reaction. Polymers are purified by precipitation of aqueous solutions with methanol, alkaline methanol, or other alcohols. Controlled structure PSSA homopolymers and block copolymers may also be prepared directly in aqueous media via RAFT using 4-cyanopentanoic acid dithiobenzoate as the CTA and V-501 as the radical source (48). NMP has been successfully employed in the preparation of near-monodisperse PSSA homo/copolymers. For example, PSSA homopolymer can be prepared in an ethylene glycol/water mixture (3:1 vol/vol) using TEMPO and sodium bisulfite/potassium persulfate as the redox initiating pair (132, 133).

Atactic PSSA is soluble in water, methanol, and ethanol but insoluble in hydrocarbons. PSSA salts are insoluble in common organic solvents but soluble in water. Ultraviolet and fluorescence spectrometry measurements can yield information on features including local environment, neighboring groups, and tacticity. MHS values and solution properties are reviewed in Reference 56. Cross-linked PSSA has been used commercially as an ion-exchange resin and in heavy metal binding studies. Fractionated PSSA has been offered as a standard for aqueous gel-permeation chromatography.

Other Sulfonic Acids. Extensive development work has been conducted on acrylic sulfonate-containing monomers. 2-Sulfoethyl methacrylate (SEM) monomer **5A** has proved to be of limited commercial value owing to the hydrolytic instability of the ester linkage. However, recently well-defined homopolymers of 3-sulfopropyl methacrylate (SPMA) were prepared under aqueous RAFT conditions with 4-cyanopentanoic acid dithiobenzoate and V-501 as the CTA/initiator pair at 70°C (39). This same hydrolytic instability has been a serious problem with 3-sulfo-2-hydroxypropyl methacrylate. In contrast, 2-acrylamido-2-methylpropanesulfonic acid (AMPSA) **6A**, prepared by the reactions of SO_3 with isobutylene followed by the Ritter reaction with acrylonitrile (134), is quite hydrolytically stable.

AMPS or 2-acrylamido-2-methyl propanesulfonate **7A** is highly reactive in both homo- and copolymerizations and can be incorporated by homogeneous, solution, or emulsion polymerization techniques. With advances in CLRP, acrylamido monomers such as AMPS (specifically in its Na+ form) are now easily polymerized in a controlled manner, as homopolymers, statistical copolymers, or block copolymers. Indeed PAMPS and its copolymers may be prepared under facile conditions via RAFT, directly in water employing CTP and V-501 as the CTA/initiator pair (42,44,45). Applications include improving emulsion stability (135), flocculation (136), improving dry strength in paper (137), sludge dispersal in boiler-water treatment (138), and silt control in cooling water systems (139). Copolymers of the sodium salt of AMPS with acrylamide copolymers (140–142) and ampholytic terpolymers (143,144) have potential in oil-field applications and in superabsorbency, respectively.

Other Anionic Carboxylate Monomers. The anionic carboxylate monomers **8A** and **9A**, prepared by the Ritter reaction involving acrylonitrile or methacrylonitrile and 3,3-dimethylacrylic acid have been copolymerized in the sodium salt form to yield calcium-tolerant copolymers with utility in enhanced oil recovery (145–148). Monomer **8A**, for example, has been copolymerized with **7A** under RAFT conditions to yield novel stimuli-responsive water-soluble polymers capable of reversible pH-induced micellization (42,44).

Sodium 4-vinylbenzoate **12A** has also been polymerized under both NMP and ATRP conditions (133,149).

Other examples of specialty anionic monomers shown in Figure 18 include salts of vinylphosphonates **10A**, vinylphenolates **11A**, vinyl benzoate **12A**, maleic acid **13A**, 3-vinyloxypropane sulfonates **14A**, and *N*-vinylsuccinimidic acid **15A**.

7.2. Cationic Polyelectrolytes. Cationic polymers are a class of polyelectrolytes that derive their unique properties from the density and distribution of positive charges along a macromolecular backbone as well as molecular weight. Chain conformation and solubility depend on the extent of ionization and interaction with water. Cationic functional groups can strongly interact with suspended, negatively charged particles or oil droplets and are useful for many applications (76,150–153) including waste treatment and paper making. A number of the most common monomers utilized for preparation of cationic polyelectrolytes are shown in Figure 19.

Polymethacrylic Cationics. Poly(2-(dimethylamino)ethyl methacrylate). 2-(Dimethylamino)ethyl methacrylate [DMAEMA, **1C** (Fig. 19)] is readily polymerized under a variety of conditions such as conventional free radical polymerization (154), living free radical polymerization, specifically ATRP and RAFT, anionic polymerization (155), group transfer polymerization (156) and oxyanionic polymerization (157,158). For example, conventional free radically prepared copolymers of **1C** with *N*-vinyl-2-pyrrolidone (159,160), *N*-phenylmaleimide (161), and ethylene (162) have been reported. While **1C** is readily polymerized via both ATRP and RAFT, to date ATRP has received the most attention as a means of preparing controlled-structure homo- and copolymers of **1C** in both aqueous (163) and organic media (164,165) with Cu(I) species as the catalysts employing a variety of different ligands (166–169). It should be noted that under certain conditions **1C** may undergo a transesterification reaction when polymerized via ATRP in MeOH and MeOH/H_2O mixtures (170). It is also possible to directly polymerize quaternized versions of 1C via aqueous or mixed H_2O/MeOH ATRP (171). **1C** has been successfully polymerized via RAFT in EtOAc with CTP and V-501 as the CTA/initiator pair (172), and also under bulk conditions with cumyl dithiobenzoate and AIBN (173).

Synthesis of Other Amine-Containing Polymethacrylates. Figure 19 shows the structures of other amine-containing methacrylic monomers. Like poly(2-dimethylamino)ethyl methacrylate) (PDMAEMA), the homopolymers of these monomers are water-soluble, albeit under somewhat more limiting conditions. The copolymerization of **2C** with methacrylic acid has been reported under conventional free radical conditions in methanol using AIBN as the initiator (174). The controlled polymerization of **2C**, **3C**, **4C**, and **5C** have been reported under GTP conditions (175–179) and oxyanionic conditions (15,180). Homopolymers of **2C** have also been prepared under ATRP conditions (181). Interestingly, **6C** can be polymerized in a controlled fashion by both oxyanionic and classical anionic techniques even though it contains a secondary amine species (180, 182).

Aqueous Solution Characteristics. The behaviors of the polyamine methacrylates in aqueous media are both interesting and varied. The polymer from **1C** is a weak polybase which is soluble over most of the useful pH range. However, in its non ionized form, and like most nonionic water-soluble polymers,

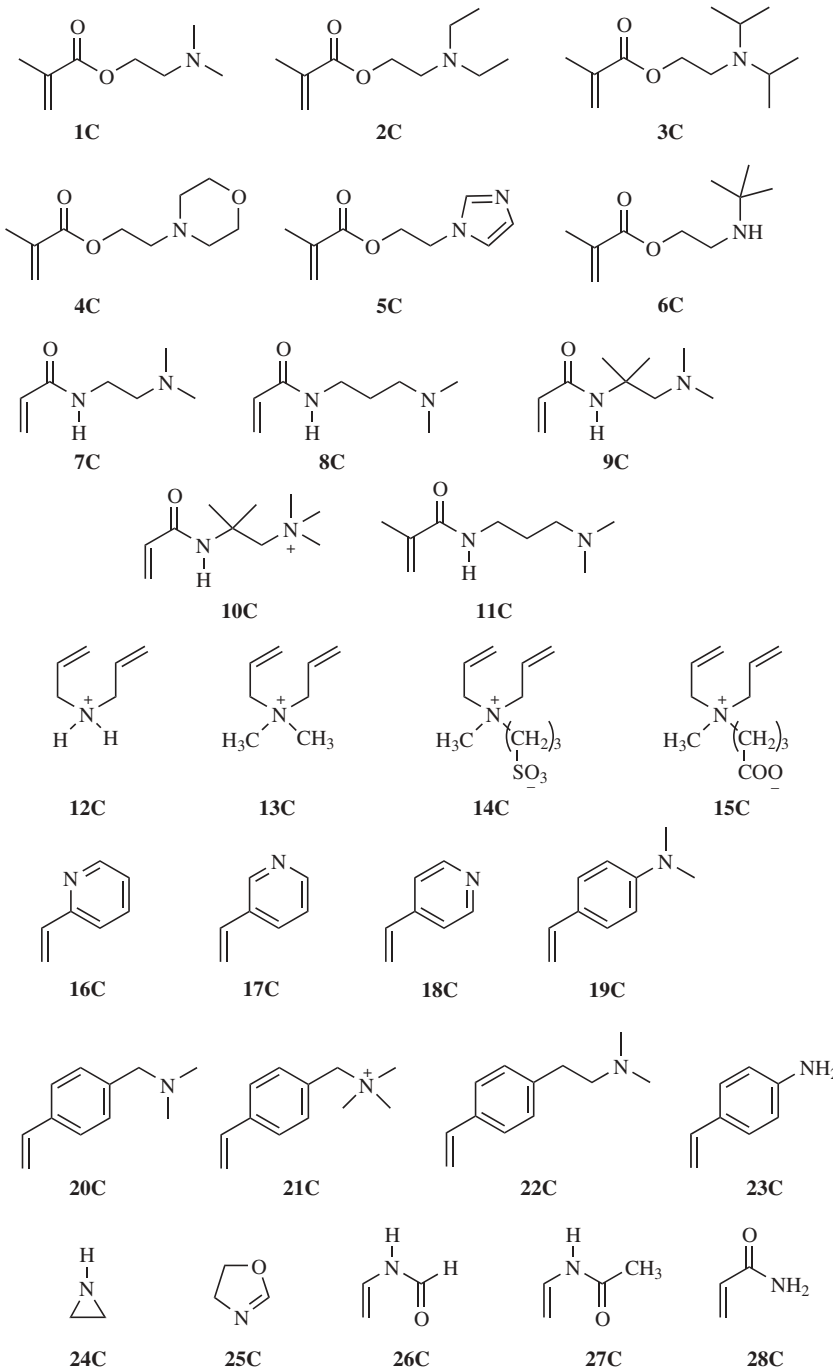


Fig. 19. Chemical structures of common amine-containing monomers (**1C–23C**) and reactive precursors (**24C–28C**) to amine-containing polymers.

it shows inverse-temperature water-solubility. The neutral polymer has a lower critical solution temperature (LCST), or cloud-point (C_p), between ~32 and 47°C depending on its molecular weight. In its protonated form, however, it remains readily soluble up to 100°C.

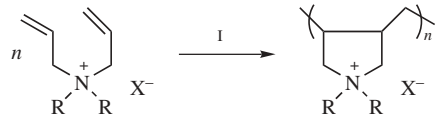
The other "common" tertiary amine polymethacrylates, PDEAEMA, PDiPAEMA, and PMEMA from **2C** and **3C**, are also responsive to applied stimuli in aqueous solution. These are only soluble in aqueous media at low pH, ie under those conditions in which the tertiary amine residues are protonated and thus cationic. Under basic conditions, where the 3° amine groups are neutral both species are hydrophobic and thus phase separate. So, simply adjusting the pH of an aqueous solution for homopolymers derived from **2C** or **3C** results in phase separation. Polymers from **4C** and **1C** are soluble over the entire useful pH range, but do have an LCST in the range 34–54°C, the exact C_p being molecular weight dependent. However, the former is also susceptible to changes in electrolyte concentration. Certain salts such as sodium sulfate readily "salt out" this polymer inducing a phase change (183). These various responses to different applied stimuli have been exploited for the synthesis of novel self-assembled polymeric micelles.

Poly(meth)acrylamido Cationics. (Meth)acrylamido species are one of the most important commercial class of water-soluble monomers with wide-ranging applications. Cationic polyacrylamides are most often prepared by the normal free radical polymerization of the amine-containing monomer, and then most often in a copolymerization. For example, the protonated form of 9C and the monomer **10C** are both readily copolymerized with **28C** to yield high molecular weight statistical copolymers in which the molar composition is virtually identical to the feed composition (184,185).

The controlled polymerization of amine-containing (meth)acrylamido monomers has, until recently, remained elusive. None of the classical living techniques can be employed and of the controlled free radical polymerization techniques only RAFT has the versatility required for this particular class of monomer. Even so, there is only one report of the controlled polymerization of an amine-containing monomer, namely *N*-[3-(dimethylamino)propyl] methacrylamide, **11C** (186). 11C is readily homopolymerized in aqueous media (neutral pH) at 70°C using 4-cyanopentanoic acid dithiobenzoate as the RAFT CTA and V-501 as the azo initiator, at an initial molar ratio of 5/1. Under these conditions reasonable control was attained as evidenced by the molecular weight control and resulting polydispersities. Control over the RAFT polymerization of 11C was attained by conducting the polymerizations in a buffered solution (pH = 5.0). Under these conditions possible side reactions such as monomer hydrolysis followed by aminolysis of the CTA is essentially eliminated (such side reactions have been previously shown to be significant in the homopolymerization of **28C**) (47,186).

Amine functionality can also be introduced into acrylamido polymers via post-polymerization modification of polyacrylamide from monomer **28C**. Strategies include the Mannich reaction (introduction of tertiary-amine functionality), Hofmann degradation (yields polyvinylamine residues) and transamidation reactions. The Mannich reaction is reversible; however, subsequent quaternization of the Mannich product prevents the reverse reaction (187).

Polydiallylammonium Cationics. Diallyl ammonium monomers, such as **13C**–**15C** in Figure 19, can be polymerized via so-called cyclopolymerization (188).



DADMAC **13C**, for example, can be readily polymerized under these cyclopolymerization conditions to yield PolyDADMAC in which a structure composed of 5-membered *N*-heterocycles predominates. **13C** will readily polymerize at ~35°C employing ammonium persulfate as the initiator. **13C** is readily copolymerized with other diallyl monomers, with acrylamido monomers such as **28C** or diacetone acrylamide, or quaternized **1C**. Extensive reviews of cyclopolymerization and cyclocopolymerization can be found in Reference 188. Recent examples of cyclocopolymerization with sulfobetaine (**14C**) and carboxybetaine (**15C**) diallyl ammonium monomers are given in References (188–191).

8. Polyvinylpyridines

2-, 3- and 4-vinylpyridines (**16C**, **17C**, and **18C**) are all readily polymerized under normal free radical conditions. Of these species, **18C** has been the most widely studied. An extensively studied derivative of **17C** is 2-methyl-5-vinylpyridine (or 6-methyl-3-vinylpyridine) and its quats (192–195). For example, 1,2-dimethyl-5-vinylpyridinium methyl sulfate is readily polymerized in aqueous solution at room temperature with common free radical initiators such as AIBN or potassium persulfate. In fact it will spontaneously polymerize at concentrations in excess of ~75% (196).

It is also possible to prepare vinylpyridine-based (co)polymers in a controlled fashion with predetermined molecular weights and narrow molecular weight distributions. For example, the controlled polymerization of **16C** and **18C** is possible via anionic polymerization (197–201).

Also, **16C**, **17C**, and **18C** have been polymerized via nitroxide-mediated controlled radical polymerization employing a variety of different nitroxides (202–209). For example, **17C** may be polymerized under bulk or solution conditions (in ethylene glycol) employing 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as the persistent free radical and benzoyl peroxide as the free radical initiator to yield controlled structure homopolymers with narrow molecular weight distributions (210). More recently, the controlled polymerization of **18C** using a β-phosphonylated nitroxide, namely *N-tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) nitroxide, was reported and was shown to be extremely effective for the homopolymerization of **17C** as well as facilitating the synthesis of novel AB diblock copolymers (202).

The controlled polymerizations of **16C** and **18C** have also been reported using RAFT chemistry (211,212). Triblock copolymers of **17C** and styrene were prepared using dibenzyl trithiocarbonate as the RAFT CTA and AIBN as the azo initiator. The RAFT polymerization of **16C** and **18C** has additionally been

achieved using cumyl dithiobenzoate and AIBN as the CTA/initiator pair (212). Homopolymers of **16C** and **18C** were prepared under bulk conditions at 60°C. Excellent control over both the molecular weight and molecular weight distribution was observed with the polydispersity indices for the homopolymers all in the range 1.10–1.25. It was also shown that the corresponding AB diblock copolymers of **16C** with **18C** could be readily prepared using either homopolymer as the macro-CTA for the polymerization of the second block (212).

As well as NMP and RAFT, **16C** and **18C** have been polymerized via ATRP (213–215). For example, **18C** may be polymerized in a controlled fashion using 1-phenylethyl chloride as the initiator and CuCl/5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazamacrocyclotetradecane (Me_6[14]aneN_4) as the catalyst/ligand pair in propanol at 40°C (215).

Polymers from **16C** and **18C**, and presumably **17C**, may be hydrogenated to form the corresponding polyvinylpiperidines (6), or oxidized to the corresponding water-soluble *N*-oxide. The polyvinylpyridines may also be readily derivatized via quaternization with an appropriate alkylating agent, such as methyl iodide. The monomeric quats are readily water-soluble but can be prone to spontaneous polymerization above critical concentrations (216). The nature of the counterion can also affect the propensity of the quaternized monomers to autopolymerize.

8.1. Aqueous Solution Characteristics. The polymer from **16C** becomes water-soluble at a critical degree of ionization (protonation) of ca 30 mol% (217). In comparison, the polymer from **18C** only becomes water-soluble at an apparent degree of ionization of 70 mol%. The polymeric quats behave as strong polyelectrolytes and are readily water-soluble.

9. Amine-Containing Styrenic Monomers

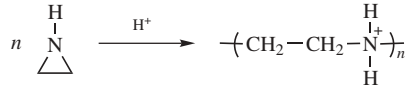
Several amino-styrenic monomers are known; for example see **19C**–**23C** in Figure 19. The simplest of these, the primary amine species 4-vinylaniline (or 4-aminostyrene), **23C**, is susceptible to polymerization under conventional free radical conditions, as are **19C**–**22C**. For example, the UV-induced graft polymerization of **23C** from a Si surface was recently disclosed (218). These monomers tend to polymerize most effectively in aqueous media in their hydrochloride salt form. Given the reactive nature of the amine functionality in **23C** it is also a suitable precursor for the synthesis of novel amide-based styrenics (219). The controlled polymerization of **19C**, **20C**, and **22C**, under classical anionic conditions is also possible (220,221). For example, AB diblock copolymers of **22C** with styrene can be prepared at −78°C, in THF using cumyl potassium as the initiator with **22C** being polymerized first. Near-monodisperse *n*-butyl quats of **19C**, **20C**, and **22C** have also been reported. These were prepared by the post-polymerization modification of polymers from **19C**, **20C**, and **22C** with *n*-butyl bromide (220).

Homo and copolymers comprised of amine-containing styrenic monomers have also been reported by controlled free radical polymerization techniques. Both NMP and RAFT have been employed with varying degrees of success. For example, **20C** was block copolymerized with sodium 4-styrenesulfonate

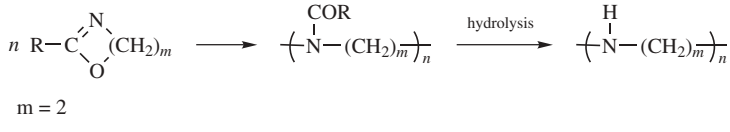
which was employed as a macro-initiator and had been prepared using TEMPO in a 3:1 ethylene glycol water mixture at 120°C with potassium persulfate as the initiator (133). More recently, McCormick and co-workers reported the synthesis of novel diamine AB diblock copolymers comprised of **21C** with the protonated form of **20C** (48). These were prepared directly in aqueous media using CTP as the RAFT CTA and V-501 as the azo initiator. Well defined block copolymers were obtained with excellent control over the molar mass and molar mass distribution. Also, new RAFT-synthesized AB diblock copolymers of *N*,*N*-dimethylacrylamide and **20C** have been reported (222). This work demonstrated the importance of blocking order in RAFT polymerizations when the two comonomers are from different monomer families. While highly efficient blocking was achieved when *N*,*N*-dimethylacrylamide was polymerized first, very poor crossover efficiencies were seen in the case of the styrenic-based macro-CTA.

9.1. Aqueous Solution Characteristics. The amine monomers tend to be water-soluble only in their protonated or quaternized forms. For example, homopolymers from **19C** are water-soluble at pH's below ~5.3; above this value they are hydrophobic and phase separate. This behavior is completely reversible and has been exploited by several researchers for the preparation of reversible pH-induced supramolecular nanoassemblies (48).

9.2. Poly(ethylene imine). Poly(ethylene amine) (PEI) is the simplest polybase. It can be prepared directly via the acid-catalyzed polymerization of ethyleneimine (aziridine, **24C**). **24C** may be prepared via a number of routes with ethanolamine being a convenient precursor (223). The cationic polymerization of **24C** is very rapid due to the release of the ring strain associated with the monomer. However, the synthesis of PEI under these conditions leads to highly branched structures due to chain transfer reactions involving the −NH− species in the polymer backbone. Cyclic products can also be produced under these conditions. Copolymerization with an appropriate comonomer can reduce the degree of chain branching (224).



The polymerization of suitable precursor monomers, with subsequent conversion to PEI, is the only route to truly linear products. The most common precursors studied are the substituted oxazolines, with the 2-substituted-2-oxazolines **25C** being the most thoroughly investigated (225).



9.3. Polyvinylamine. Along with PEI, polyvinylamine (PVAm) prepared from **26C** is the simplest polybase, and is related to PEI in a similar manner to the relationship between PVOH and PEO, ie as constitutional isomers. Also like PVOH, PVAm cannot be prepared by the direct polymerization of the vinyl amine

monomer because it very readily tautomerizes to acetaldehyde imine.

Vinyl amine Acetaldehyde imine (ethylideneamine)

As such, PVAm must be prepared by indirect methods employing protected monomers which, once polymerized, can be converted to PVAm. The most common employed precursors are the *N*-vinylamides (eg **26C** and **27C**) which after polymerization may be converted to PVAm via hydrolysis. For example, suitable precursors include poly(*N*-vinylacetamide) (PNVA) (226) and poly(*N*-vinylformamide) (PNVF) (227). PNVF is more readily hydrolyzed than other *N*-vinylamides. It is also possible to prepare PVAm via the Hofmann degradation of polyacrylamide prepared from **28C** (228). These precursor polymers are typically prepared using normal free radical polymerization chemistries and as such have broad molecular weight distributions. Recent advances in controlled radical polymerization methodologies, and especially the RAFT technology, should facilitate the synthesis of controlled-structure near-monodisperse PVAm. For example, it is now possible to polymerize **28C** in a controlled fashion under RAFT conditions (49,50). There is also at least one report detailing the RAFT polymerization of **26C** (229).

10. Miscellaneous Cationic Monomers

While the most common, amine-based species are not the only type of cationic monomers/polymers. There are several other functional species capable of yielding cationic species, namely the sulfonium (230), phosphonium (231,232), and pyrylium (233) species. Several examples of such species are shown in Figure 20.

For example, the statistical free radical polymerizations of **32C** and **33C** with *N*-isopropyl acrylamide were successfully conducted in DMSO employing AIBN at 50°C (234,235). This yielded readily water-soluble copolymers with a thermosensitive component. Such copolymers are also interesting since they can exhibit antibacterial properties against *Escherichia coli* and *Staphylococcus aureus* (234,236,237). Novel water-soluble sulfonium monomers such as **31C** can be polymerized and used as precursor polymers for the synthesis of light-emitting polymers such as poly(2,5-bis(trimethylsilyl)-1,4-phenylenevinylene (238).

10.1. Polyzwitterions. Amphoteric water-soluble polymers are polymeric systems containing both anionic and cationic charges. Such polyzwitterions may be subdivided into two major families, the *polyampholytes* and the *polybetaines* (239). Each of these groups may be further subdivided into specific types of each (see below). Figure 21 shows a number of monomers which have been used in pairs (cationic with anionic) to form polyampholytes.

Polyampholytes. Polyampholytes are those materials in which the anionic and cationic charges reside on *different* mer units. Due to this, polyampholytes may be either charge balanced or unbalanced depending on the molar ratio of the anionic/cationic monomers. Polyampholytes may also be subdivided into four

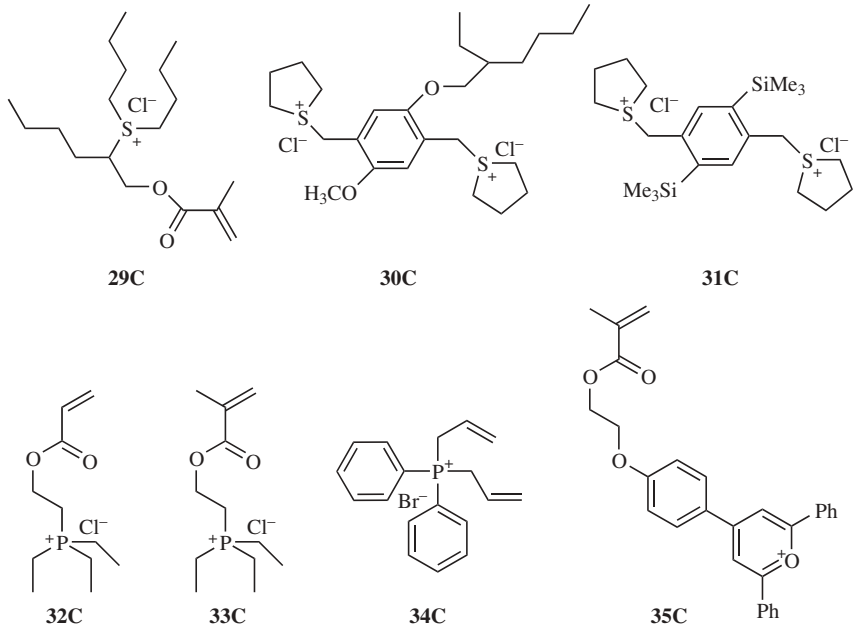


Fig. 20. Specialty cationic monomers.

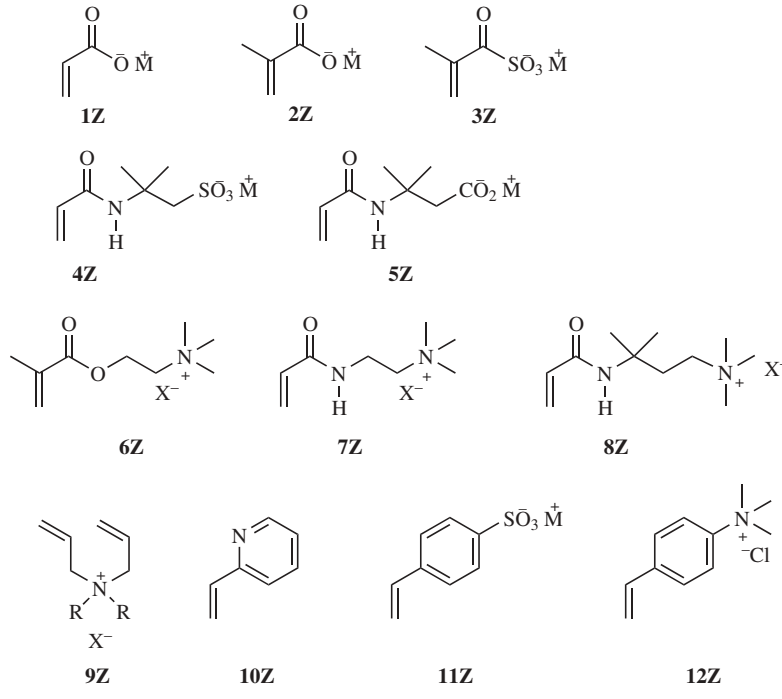


Fig. 21. Monomer pairs utilized in preparing polyzwitterions.

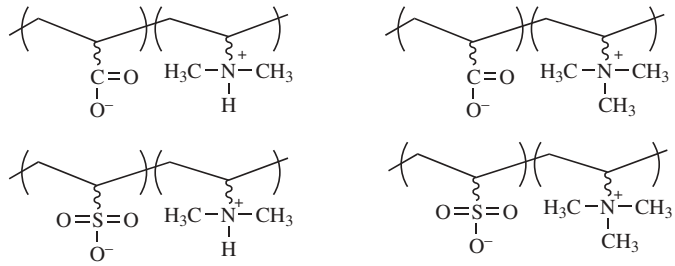


Fig. 22. Polyampholyte structures.

inherently different types. There are those in which the anionic and cationic residues may be neutralized, those where the cationic residue may be neutralized but the anionic residue is insensitive to changes in pH, those in which the anionic charges may be neutralized but the cationic residues are insensitive to pH changes, and finally those in which both the anionic and cationic residues are insensitive to changes in the pH (see Fig. 22).

Synthesis. Polyampholytes are most readily prepared by the direct statistical copolymerization of anionic and cationic monomers typically in aqueous media, via conventional free radical polymerization. Examples of such materials were first reported in the 1950s (240–244). Using this approach a wide range of copolymers and terpolymers, often with a neutral hydrophilic monomer such as acrylamide, have been reported. For example, early reports of statistical polyampholytes include the methacrylic acid-*stat*-2-(dimethylamino)ethyl methacrylate copolymers (245), from **1Z** and **2Z** with **6Z** and the *N*,*N*-diethylallylamine-*stat*-acrylic acid copolymers from **1Z** and **6Z** (246). More recently, synthesis and properties of novel polyampholytic terpolymers have been described (247–250). For example, the aqueous solution properties of novel ampholytic terpolymers of acrylamide, sodium 3-acrylamido-3-methylbutanoate **5Z** and 3-(acrylamidopropyl)trimethylammonium chloride **8Z** have been studied in detail (187).

It was not until the 1970s that the first block polyampholytes were reported (251,252). Anionic polymerization was used to prepare precursor AB diblock copolymers of 2-vinylpyridine **10Z** with trimethylsilyl methacrylate (TMSMA). The TMSMA residues were subsequently hydrolyzed to poly(methacrylic acid) residues to yield the corresponding AB diblock polyampholytes. Anionic polymerization has also been employed to prepare other block polyampholytes (253–258). GTP has also been successfully employed for the preparation of block polyampholytes. As with anionic polymerization, protected acid monomers must be employed since methacrylic acid (MAA) cannot be polymerized directly by this technique. A variety of protected monomers have been reported to be suitable as a means of introducing MAA residues, with 2-tetrahydropyranyl methacrylate being the most effective (Fig. 23).

For example, AB diblock and ABC triblock polyampholytes comprised of basic DMAEMA **6Z** and acidic MAA residues, and hydrophobic methyl methacrylate residues in the case of the triblocks, have been reported (128,259–262).

While these living polymerization techniques do offer the ability to prepare block polyampholytes they are both synthetically demanding and somewhat

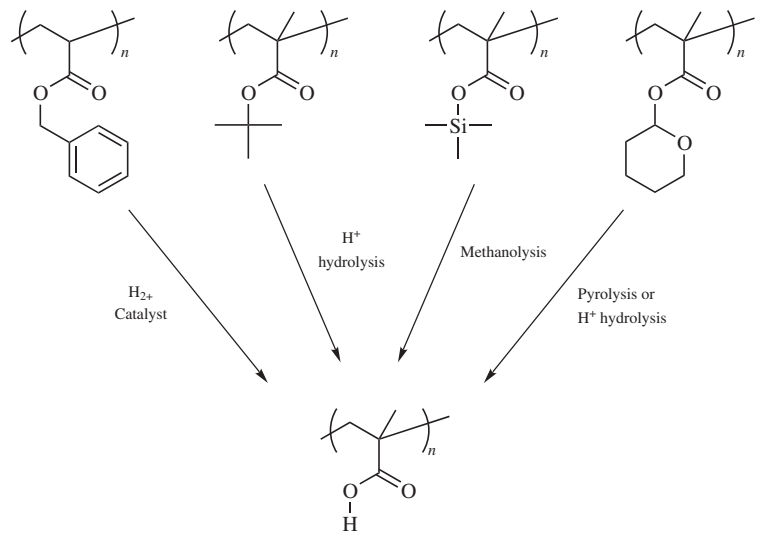


Fig. 23. Deprotection chemistry utilized to produce polymethacrylic acid or its salts.

limiting with respect to monomer choice for example. There are a handful of reports detailing the synthesis of block polyampholytes using controlled/living polymerization techniques discussed earlier (Fig. 24). For example, Gabaston and co-workers have described the TEMPO-mediated SFRP of block copolymers of sodium 4-styrenesulfonate **11Z** with 4-(dimethylamino)methyl styrene **12Z** (133), and several authors have reported the synthesis of block polyampholytes using ATRP although they still employed protecting group chemistry for the methacrylic acid residues (263–265).

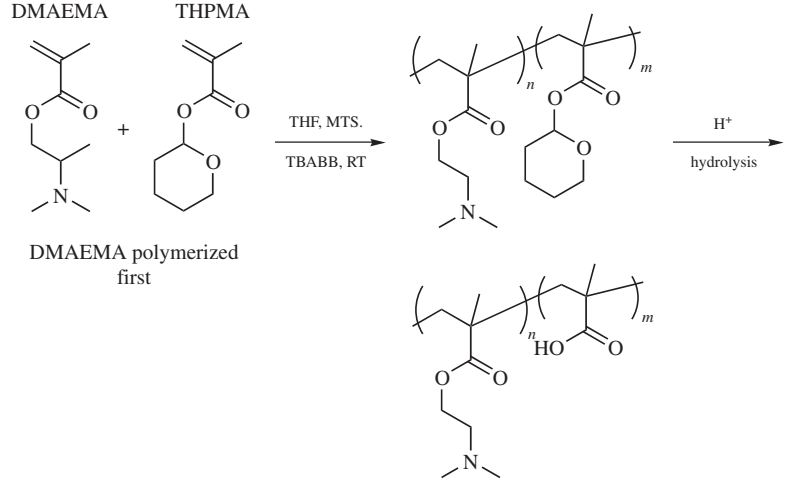


Fig. 24. GTP synthesis of AB diblock polyampholytes.

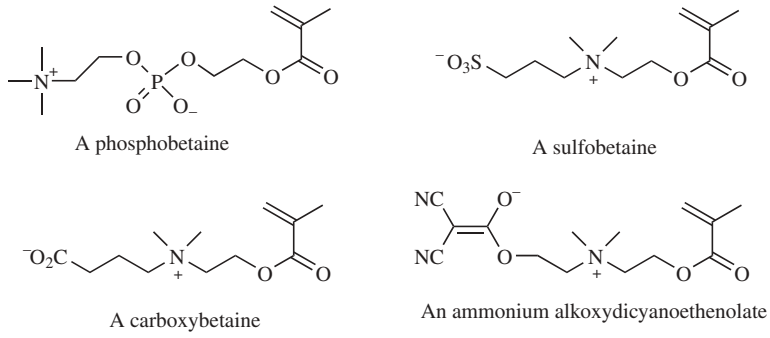


Fig. 25. General structures of selected methacrylic-based betaines.

Solution Properties. The aqueous solution behavior of polyampholytes is dictated by coulombic interactions between the basic and acidic residues. Polyampholytes have the ability to exhibit both polyelectrolyte and antipolylelectrolyte behavior in aqueous media. Which type of behavior is exhibited depends on factors such as solution pH, copolymer composition, the relative strengths of the acidic and basic residues, and the presence/absence of low molecular weight electrolyte (239). A feature of polyampholytes—in particular those comprised of weak acidic and basic residues—is the so-called *isoelectric point*, or IEP. This is simply defined as the solution pH at which the polyampholyte is electrically neutral. Statistical polyampholytes often remain soluble at and around the IEP whereas block polyampholytes tend to be soluble above and below but insoluble at this critical pH. The IEP may be determined either by titration or by measuring the reduced viscosity as a function of pH—the IEP also represents the point at which the polyampholyte chain is in its most compact conformation and thus corresponds to the minimum in reduced viscosity (239,266). With a knowledge of the respective pK_a's and copolymer composition it is also possible to predict the IEP (267).

Polybetaines. *Polybetaines* are materials in which the anionic and cationic functional species are part of the *same* mer unit (Fig. 25). Because of this the number of anionic, or potentially anionic, residues is always exactly equal to the number of cationic residues. The cationic residue in polymeric betaines is typically a quaternary ammonium species. The anionic functionality can vary and leads to the classification of polymeric betaines as sulfobetaines (sulfonate functional group), carbo or carboxybetaines (carboxylate functional groups), phosphobetaines (phosphate functional group), and etheneolatebetaines (dicyanoetheneolate functional group) (239).

Synthesis. Betaine monomers may be prepared in a number of different ways. For sulfobetaines, the most common, and easiest, method is to react a monomer containing a tertiary amine residue with either 1,3-propanesultone or 1,4-butanesultone (268). This is an extremely facile reaction and proceeds readily at RT in common solvents such as THF or CH_3CN to yield the corresponding sulfobetaine monomer. Alternatively, the tertiary amine functionality may be reacted with a haloalkylsulfonate species (269). Carboxybetaine monomers may be prepared via a number of different routes (Fig. 26). They may be obtained from the reaction of a suitable lactone (270) with a tertiary amine species, although this is somewhat limited to highly strained lactones to avoid competing

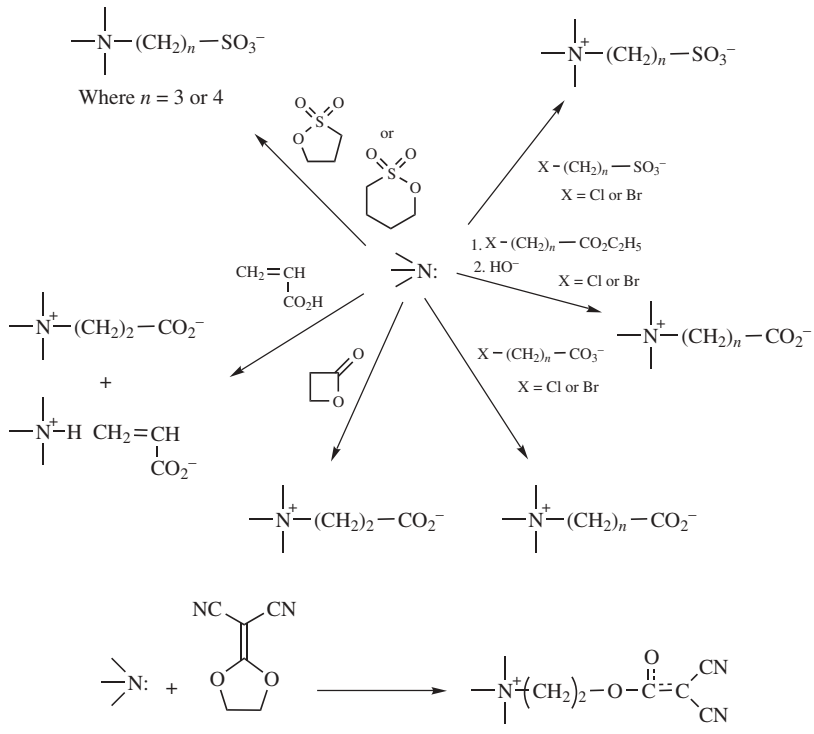


Fig. 26. General synthetic routes for sulfo/carboxybetaines.

nucleophilic attack at the carbonyl group. Alternatively they can be obtained from the Michael addition of a tertiary amine to acrylic acid (271), although again this route is prone to side reactions and simple salt formation. Perhaps the most versatile route for the preparation of carboxybetaines involves the reaction of a tertiary amine with a haloalkylcarboxylate to yield the carboxy betaine directly, or by reaction with the corresponding haloalkylester to yield the quaternized species followed by ester hydrolysis to yield the carboxybetaine (272,273).

Phosphobetaine monomers may also be prepared via a number of routes (239,274). Probably the most common phosphobetaine monomer is 2-(methacryloyloxy)ethyl phosphorylcholine (MPC), although other derivatives are also known (275–278). MPC is prepared from the reaction of 2-hydroxyethyl methacrylate with 2-chloro-2-oxo-1,3,2-dioxaphospholane, followed by ring opening of the intermediate phospholane with trimethylamine (Fig. 27). This is a general synthetic procedure which can be applied to any alcohol functional monomer. There are very few examples of the dicyanoetheneolate betaines. These particular species are prepared from the reaction of a tertiary amine monomer with 2,2-dicyanoketene-1,2-ethylene acetal (279–281).

Polymeric betaines are most readily prepared by the direct polymerization of the betaine monomers, typically in aqueous salt solution. Since their initial report in 1957, by Ladenheim and Morawetz (282), there have been a large number of polymeric betaines reported based on many different families of monomers (239). Polymeric betaines may also be prepared under condensation

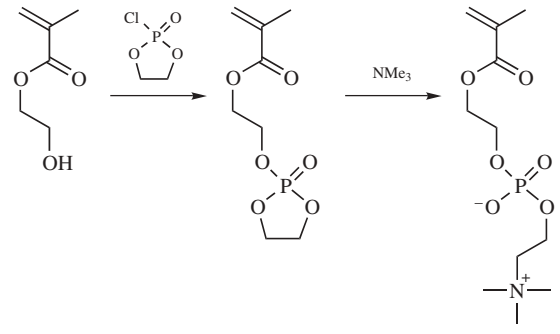


Fig. 27. Synthesis of MPC.

polymerization conditions thus yielding polymers in which the betaine functionality is attached directly to the (co)polymer backbone (283–285).

Controlled structure polymeric betaines were reported for the first time only recently (286). The first examples were those prepared from the post-polymerization modification of poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), and its block copolymers, which had been prepared under GTP conditions (286,287). Initial reports detailed the modification of hydrophilic-hydrophobic block copolymers, but this was subsequently extended to the selective modification of diamino hydrophilic-hydrophilic block copolymers (276).

The *direct* polymerization of betaine monomers in a controlled fashion has been reported by ATRP (288–291), and, most recently, via RAFT (38,43,292,293). Methacrylic derivatives of carboxy-, sulfo-, and phosphobetaines have been prepared via ATRP, while RAFT is more versatile with respect to monomer choice, and examples of styrenic, methacrylic and acrylamido sulfobetaines have been disclosed.

Solution Properties. Zwitterionic polymers show interesting aqueous solution behavior. As a general rule, they are *insoluble* in pure water due to the formation on intra- and interchain ion contacts resulting in an ionically cross-linked network-type structure. Polyampholytes and polybetaines which are not soluble become soluble upon the addition of low molecular weight electrolytes, such as NaCl (Fig. 28). This dissolution process can best be understood in terms of the low molecular weight electrolyte penetrating the ionically cross-linked network whereupon the ions screen the net attractive interactions between the

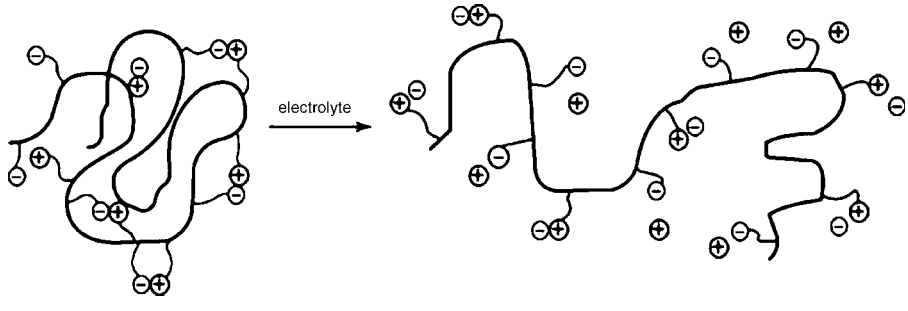


Fig. 28. Schematic illustration of polyampholyte response to added electrolyte.

polymer chains and hence promote solubility. The addition of the salt also results in antipolylelectrolyte behavior, ie chain expansion upon the addition of the salt.

10.2. Applications of Polyzwitterions. Polyzwitterions have wide-ranging applications. For example, statistical polyampholytes comprised of 2-vinylpyridine **10Z** and acrylic acid **1Z** have been evaluated as desalination membranes, while others have been used in sewage treatment, flocculation, coagulation, drilling fluids, enhanced oil recovery, and drag reduction.

Polymeric betaines have applications in areas similar to those of the polyampholytes described above. Additionally, phosphobetaines in particular have found application in the biomedical field. (Co)polymers comprised of MPC and various alkyl methacrylates (294,295) for example have been shown to exhibit both good bio and hemocompatability and have found application as coatings for medical devices such as catheters or arterial stents as well as materials for contact lens application. The success of MPC-based materials, and other phosphobetaines, is attributed to their biomimetic characteristics, ie their structural and chemical similarity to naturally occurring phospholipids. Recently, sulfobetaine-based materials were also shown to exhibit similar properties indicating that these bio/hemocompatability characteristics may not be unique to polymer phosphobetaines but perhaps to polybetaines in general (296).

11. Stimuli-Responsive Amphiphilic Polymers

Amphiphilic copolymers with appropriate balance of hydrophilic and hydrophobic sequences along or pendent to the micromolecular backbone can self-organize in water (297). In principle, intramolecular (closed) or intermolecular (open) associations can result. Intramolecular self assembly can, for example, lead to unimeric or multimeric micelles (Fig. 29**a**, **b**) with solution behavior resembling that of small molecule surfactants above their critical micelle concentration. Intermolecular assembly (Fig. 29**c**) often results in network or associative thickening behavior. Judicious choice of polymerization methods and conditions, monomer selection, post reactions, etc allows molecular construction of a wide variety of systems capable of self-assembly. Strategic placement of functional groups along the macromolecular backbone can also lead to reversible association in response to external stimuli including pH (298,299), ionic strength (300), light (301–303), temperature (304), and shear stress (297,305).

The earliest synthetic polymeric micelles, often referred to as *polysoaps*, were prepared as biological protein mimics (306–308). Copolymers synthesized by partial *n*-dodecylation of poly(2-vinyl pyridine) or by hydrolysis of poly(maleic anhydride-*alt*-alkylvinyl ethers) possessed surfactant-like properties in water (309–312). The initial associative thickeners, on the other hand, were prepared by (*1*) substitution of water-soluble cellulose derivatives with long chain alkyl groups (153, 313–317) (*2*) partial esterification of poly(styrene-*alt*-maleic anhydride) with nonionic surfactants (318–321), (*3*) step growth polymerization of hydrophobically modified diisocyanates with poly(oxyethylene glycols) (322), or (*4*) by statistical chain growth free radical polymerization of a variety of hydrophobic and hydrophilic monomers under heterogeneous reaction conditions including emulsion polymerization (323, 324) and micellar polymerization (325–330).

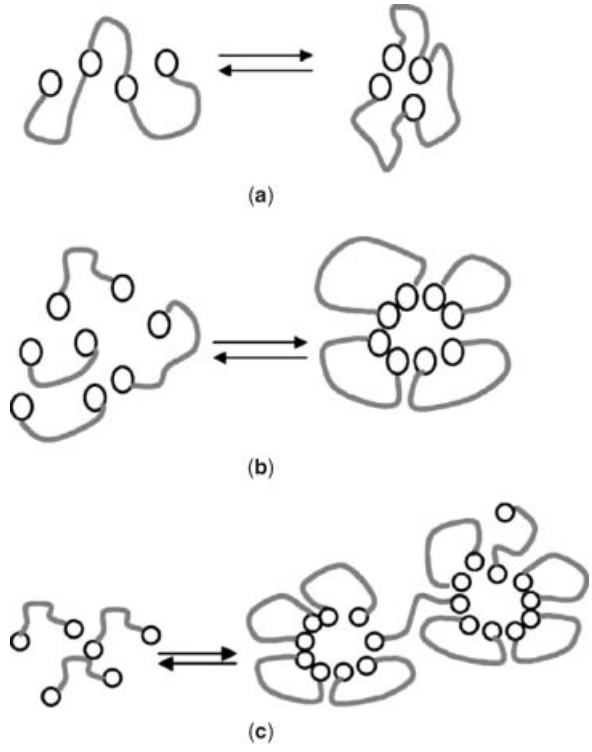


Fig. 29. Behavior of amphiphilic copolymers in response to stimuli.

Despite a number of successes in preparing polymers with aqueous solution behavior depicted in Figs. 21**a** and 21**c**, little understanding of the nature of associative polymer domains existed prior to 1990. As well, studies of block copolymer associations had been limited to phase behavior in selective organic solvents. Since then, rapid developments in characterization of reversible microdomains via static and dynamic fluorescence spectroscopy (331–351), NMR spectroscopy (345,352–359) light scattering (171,175,360–364), and rheological techniques (365–370) have led to a better understanding of the structural parameters governing assembly/disassembly in water. Likewise, the development of facile controlled/living free radical polymerization techniques for preparing block copolymers with well-defined structures has led to better models for study.

It can be established that the extent of closed or open associations depends on the architectures of the macromolecular chains. Molecular parameters affecting such associative behavior include hydrophilic and hydrophobic block lengths, placement and molecular weight of the segments, polymer concentration, flexibility and spacer lengths side-chain functionality. Responsiveness to pH, electrolyte, and to temperature changes depends markedly on the nature of the functional groups (cations, anions, zwitterions), their proximity to hydrophilic or hydrophobic units, and the ionic strength of the surrounding aqueous media. Some theoretical models have been put forth that describe unimolecular micelle formation progressing to bridged micelles and eventually networks (371–373).

12. Statistical Amphiphilic Polymers

Statistical amphiphilic polymers with ionic charges along the macromolecular backbone represent most of the stimuli-responsive systems reported in the literature. In principle, hydrophilic monomers from Figures 17–20 or 21 can be copolymerized with hydrophobic comonomers or macromonomers under conditions allowing sufficient incorporation of the latter. The most successful methods have been "micellar" polymerization (324,325,347,348) in which high concentrations of surfactants are added to solubilize the hydrophobic monomer in the aqueous phase or emulsion polymerization utilizing macromonomers having amphiphilic character (323,324). Table 1 gives examples of associative polymers and the type of responsiveness reported in the literature. A comprehensive review (305) presents

Table 1. **Copolymer Compositions[a] Responsiveness, and References for Stimuli-Responsive Polyelectrolytes**

Polymer Composition	Response	Ref.
K-S	pH, salt	(312, 374–380)
K-T	pH, salt, shear	(374, 336, 381–383)
E-H-Fl	pH, salt, shear	(374, 384)
I-P	salt, shear	(374, 385–388)
G-B-R	salt, shear	(374, 389, 390)
E-Q-B	pH, salt, shear	(374, 391, 392)
E-B-Fl	pH, salt, shear	(374, 393)
B-R-D	pH, salt, shear	(374, 365, 366)
E-Q	shear	(374, 394, 395, 396–404)
E-R	shear	(374, 394, 395, 396–404)
E-S	shear	(374, 394, 395, 396–404)
E-U	shear	(374, 405, 406)
E-B-U	pH, salt, shear	(374)
B-Q	pH, salt, shear	(305, 407)
B-Fl	pH	(305, 408, 410)
A-S	pH, salt, shear	(305, 411)
B-Fl	pH, salt, shear	(305, 412)
B-Q	pH, salt, shear	(305, 345, 413)
A-R	pH, salt, shear	(305, 363, 364)
B-E-Q	pH, salt, shear	(305, 404, 414, 415)
B-Fl	pH, salt, shear	(305, 349, 409)
C-F-Q	pH, salt, shear	(305, 416)
Y	pH, salt, shear	(305, 417)
Z	pH, salt, shear	(305, 418)
Z-T	pH, salt, shear	(305, 382)
Z-T-Fl	pH, salt, shear	(305, 336, 381)
I-P-Fl	pH, salt, shear	(305, 385, 419–422)
I-R	pH, salt, shear	(305, 423–426)
I-R-P	pH, salt, shear	(305, 427)
E-A-R	pH, salt, shear	(305, 428)
E-I-R	pH, salt, shear	(305, 429, 430)
O-V	pH, salt, shear	(305, 431–436)
U-M	pH, salt, shear	(305, 276)
U-N	pH, salt, shear	(305, 437)

[a]Letters refer to repeating units in Figure 30.

details of the synthetic routes to and behavioral characteristics of associative polyelectrolytes as determined by a wide variety of analytical techniques.

12.1. Well-Defined Amphiphilic Copolymers. Well-defined, controlled structure amphiphilic copolymers may be prepared using a range of polymerization techniques that includes anionic, cationic, and controlled free radical approaches. The materials may be "simple" AB diblock copolymers or more structurally complex species such as ABA or ABC triblock copolymers for example.

Hydrophilic-Hydrophobic Block Copolymers. These materials represent the "simplest" type of amphiphilic block copolymer. Materials are comprised of one block which is inherently hydrophobic, such as polystyrene or poly(methyl methacrylate), and a second block which is hydrophilic such as poly(methacrylic acid). For example, anionic polymerization may be employed for the synthesis of AB diblock copolymers comprised of styrene with 2- (438) or 4-vinylyridine (439). In the case of the styrene-2-vinylpyridine copolymers, self-assembly, under appropriate aqueous conditions, leads to the formation of block copolymer micelles with styrene forming the hydrophobic core and the 2-vinylpyridine forming the stabilizing corona. These block copolymer micelles are highly stable in 0.1 *M* HCl. Similarly, styrene–acrylic acid block copolymers may likewise be prepared via anionic polymerization using *tert*-butyl acrylate as a protected precursor for the acrylic acid residues. Such block copolymers exhibit similar self-assembly behavior in aqueous media (440,441). Other examples of such hydrophilic-hydrophobic block copolymers capable of supramolecular self-assembly include the poly(2-(dimethylamino)ethyl methacrylate-*block*-methyl methacrylate) (442) and the poly(3-(*N*-2-methacroyloyethyl)-*N*,*N*-dimethylammonio)propanesulfonate-*block*-methyl methacrylate) copolymers (287,443). In both instances the block copolymers were prepared via group transfer polymerization. Cationic polymerization also offers a route to amphiphilic vinyl ether-based AB diblock copolymers. For example, the synthesis and micellization properties of isobutyl vinyl ether-*block*-methyl tri(ethyleneglycol) vinyl ether copolymers have been reported (444). Also the self-association of AB diblocks comprised of methyl tri(ethyleneglycol) vinyl ether (hydrophilic block) and benzyl vinyl ether (hydrophobic block) have been investigated (445). In water, micelles with hydrodynamic diameters in the range 10–26 nm were observed depending on the molar composition of the block copolymer.

Hydrophilic/Tunably Hydrophilic/Hydrophobic Block Copolymers. The next level of complexity for amphiphilic block copolymers are those comprised of one block which is permanently hydrophilic with the second block being tunably hydrophilic/hydrophobic, ie under a set of conditions A, the second block is readily water soluble and thus the block copolymer exists as unimers, but upon the application of a certain stimulus (change in pH or temperature for example) to condition B the second block becomes hydrophobic. Provided appropriate block copolymer compositions are employed this will lead to self-assembly. Additionally, such behavior is typically completely reversible. While there are now numerous examples of such "smart" self-assembly these types of systems have not been as thoroughly investigated as the inherently hydrophilic/hydrophobic species, with perhaps one notable exception being the PEO/PPO and PEO/PPO/PEO, PPO/PEO/PPO block copolymers.

Group transfer polymerization has proven to be an extremely useful technique for the synthesis of such AB diblock copolymers. For example, the synthesis

of AB diblock copolymers in which the A block was 2-(dimethylamino)ethyl methacrylate (**1C** in Fig. 19) and the B block was either **2C** or **3C** in Figure 18 have been reported. **1C** is temperature responsive whereas **2C** and **3C** are both pH responsive. At low pH when both the tertiary amine blocks (**1C**+**2C** or **1C**+**3C**) are protonated the block copolymers are molecularly dissolved. Raising the solution pH above the p*K*a of tertiary amine residues for **2C** and **3C** renders these blocks hydrophobic and as such the block copolymers self-assemble to form micelles with the hydrophobic **2C** (or **3C**) residues in the core, stabilized by coronal chains of 1. Supramolecular self-assembly is completely reversible—lowering of the pH back below the respective p*K*a's results in molecular redissolution (183).

More recently controlled free radical polymerization methodologies have been employed for the preparation of novel "smart" AB diblock copolymers. Nitroxide-mediated polymerization was utilized for the synthesis of sodium

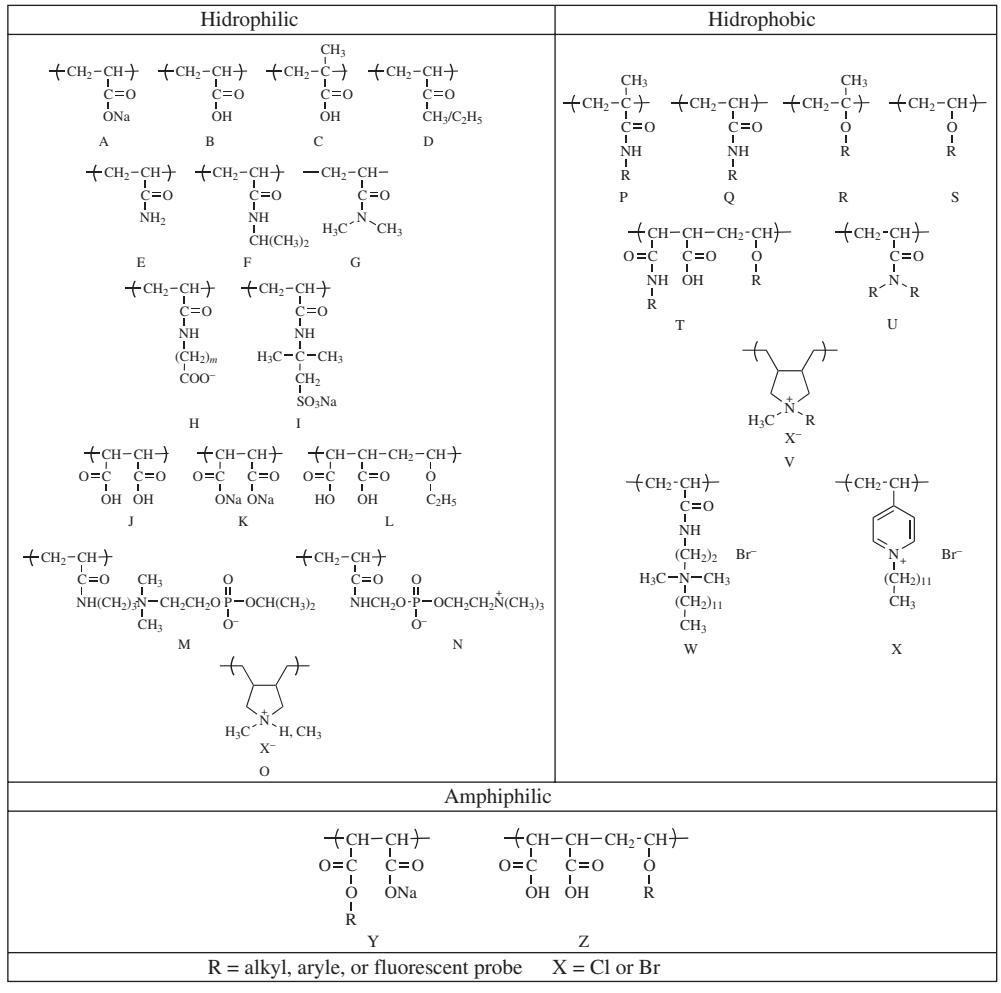
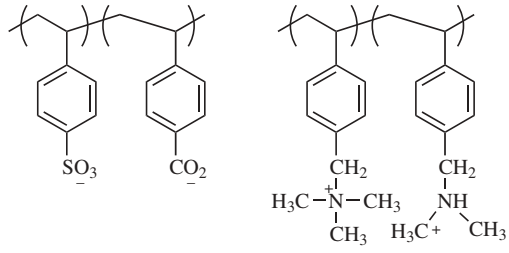


Fig. 30. Polymer segments utilized in statistical polymers with stimuli-responsive associative behavior in water. For polymers incorporating a fluorescent probe the letters Fl are used in Table 1.

4-styrenesulfonate-block-sodium 4-vinylbenzoate block copolymer (133). These strong acid/weak acid species exhibit reversible pH-induced self-assembly, with the sodium 4-styrenesulfonate residues remaining ionized and thus permanently hydrophilic over the useful pH range whereas the sodium 4-vinylbenzoate block can be reversible protonated (the carboxylate residue has a pK_a ~4.0). The same block polymers can also be prepared via RAFT, albeit with somewhat more control. Other workers reported the preparation of such AB diblock copolymers as well as some analogous amine-based styrenic diblock copolymers, (48) shown below.



Similarly, such AB diblocks may be prepared based on the acrylamido family of monomers. For example, the synthesis of novel AB diblock copolymers comprised of the two anionic monomers sodium 2-acrylamido-2-methylpropanesulfonate (AMPS) and sodium 3-acrylamido-3-methylbutanoate (AMBA) have been reported (42,44). By analogy with the styrenic block copolymers, these AMPS-AMBA species also exhibit reversible pH-induced self-assembly by virtue of the fact that the AMBA residues may be reversible protonated, switching the residues from a hydrophilic (high pH) to a hydrophobic (low pH) state. Similar AB diblocks of AMPS with sodium 6-acrylamidohexanoate which also exhibit pH-induced micellization have been reported by Yusa and co-workers (45). RAFT has additionally proven very useful for the preparation of AB diblock copolymers comprised of blocks from different monomer families. For example, AB diblocks of *N*,*N*-dimethylacrylamide (DMA) with *N*,*N*-dimethylbenzyl vinyl amine (DMBVA) were recently disclosed. These particular blocks are also capable of undergoing reversible pH-induced micellization (222). The DMA residues are nonionic, permanently hydrophilic whereas the styrenic-based DMBVA block is water soluble in its protonated form, but hydrophobic in its nonionized state. As such, simply raising the pH of an acidic solution of the block copolymer results in self-assembly and the formation of aggregates with the hydrophobic DMBVA blocks residing in the core which is stabilized by the DMA block. RAFT has also been utilized for the preparation of AB diblocks in which one of the blocks is a salt-responsive specie (293). For example, AB diblocks of *N*,*N*-dimethylacrylamide with 3-[2-(*N*-methylacrylamido)-ethyldimethylammonio]propanesulfonate (MAEDAPS).

Doubly "Smart" Block Copolymers. Doubly "smart" or responsive copolymers are those in which *both* the blocks of the copolymer are tunably hydrophilic/hydrophobic. As such this potentially facilitates the preparation of both normal and inverse micelles in the *same* solvent (NB: normal and inverse micelles are well known but switching between the two often requires a change of solvent). Some

authors have termed such materials *"schizophrenic" block copolymers*. At present these represent the least studied of the amphiphilic block copolymers. Examples of such materials include the poly(2-(*N*-morpholino)ethyl methacrylate-*block*-2-(diethylamino)ethyl methacrylate) (177,446) and the poly(propylene oxide-*block*-2-(diethylamino)ethyl methacrylate) copolymers (447). A number of these types of block copolymers have been studied (263,264,448,449). As a representative example, a precursor poly(2-(dimethylamino)ethyl methacrylate-*block*-2-(*N*-morpholino)ethyl methacrylate) (DMAEMA-MEMA) copolymer was reacted with 1,3-propanesultone to yield the corresponding sulfopropylbetaine-MEMA block copolymer (Fig. 31) (448). At temperatures between 30 and 40°C a block copolymer comprised of an equimolar ratio of the two comonomers exists as molecularly dissolved unimeric chains. Upon raising the temperature above the cloud point of the MEMA block, the copolymer self-assembles forming polymeric micelles with the now-hydrophobic MEMA residues residing in the core with the sulfobetaine blocks in the corona.

Sulfobetaine-core micelles were obtained by lowering the solution temperature below 20°C at which point increased attractive electrostatic interactions result in phase separation of the sulfobetaine block and thus micelle formation.

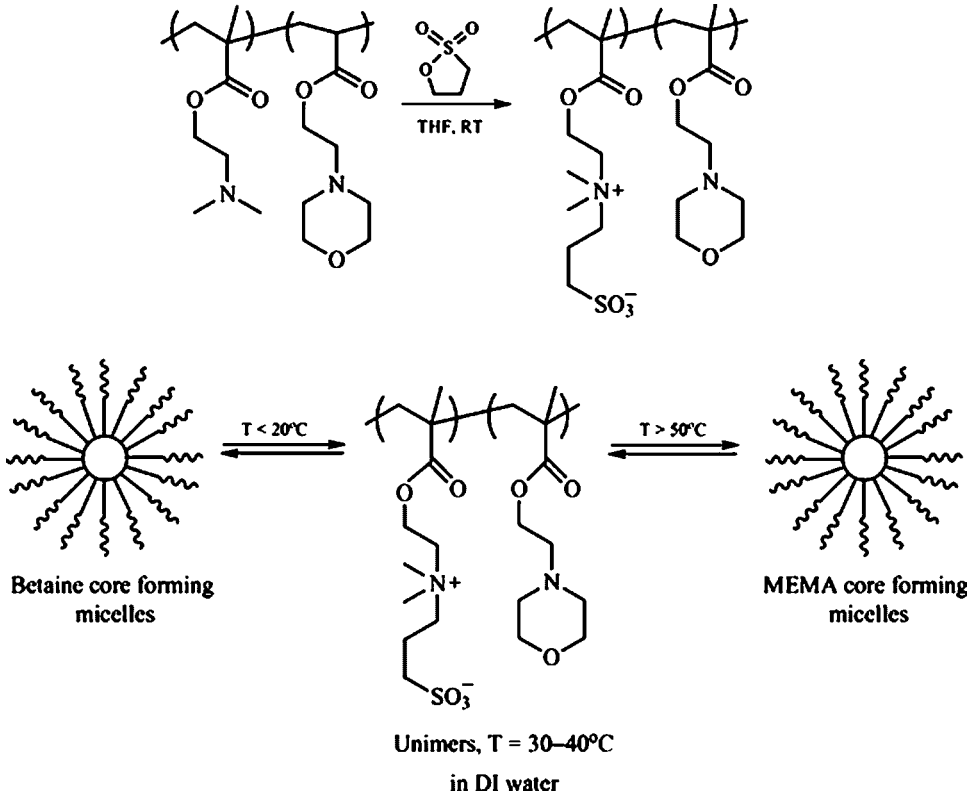


Fig. 31. An example of a "schizophrenic," methacrylic-based AB diblock copolymer and conditions leading to self-assembly.

A similar doubly temperature responsive block copolymer, prepared via RAFT, was reported which was based on acrylamido monomers (292).

Shell and Core Cross-Linked Nanoassemblies. Shell or core cross-linked nanoassemblies represent a group of materials which can, in principle, be derived from any of the amphiphilic species described in the earlier sections. Clearly the self-assembled structures described above are dynamic species. However, one can envisage the need for "locked" structures for certain applications. One method to achieve this is via cross-linking of either the coronal or core chains. To facilitate either approach there must be a suitable reactive species in the core or corona susceptible to chemical modification after self-assembly.

Shell cross-linked micelles, also referred to as *knedel* or *SCK micelles*, were first reported in 1997 (450,451). For example, an amphiphilic AB diblock copolymer comprised of hydrophobic polystyrene with hydrophilic partially quaternized poly(4-vinylpridine) was prepared by the sequential living anionic polymerization of styrene and 4-vinyl pyridine followed by quaternization of some of the 4-vinylpyridine residues with 4-vinylbenzyl chloride. Micelles are prepared by dissolving the quaternized block copolymer in a mixture of water and THF. Finally, shell cross-linking is accomplished by polymerizing the styrenic residues in the shell (present as a result of the quaternization reaction) in the presence of a free radical initiator (452). Examples in which the micelle coronal shell consists of hydrophilic acrylic acid residues, with a variety of hydrophobic cores, may be conveniently shell cross-linked using 2,2′-(ethylenedioxy)bis(ethylamine). Thus, cross-linking is achieved via an amidation reaction using a bifunctional primary amine (453–457). Other examples of these novel nanomaterials include those with polysilane cores and partially cross-linked poly(methacrylic acid) coronas (458,459), and micelles in which the reactive, cross-linkable functionality is either methacrylic acid or DMAEMA residues, with the actual cross-linking being achieved with bis-(2-iodoethoxy)ethane (460–462). The effectiveness of bis-(2-iodoethoxy)ethane as a cross-linking agent is illustrated in Figure 32.

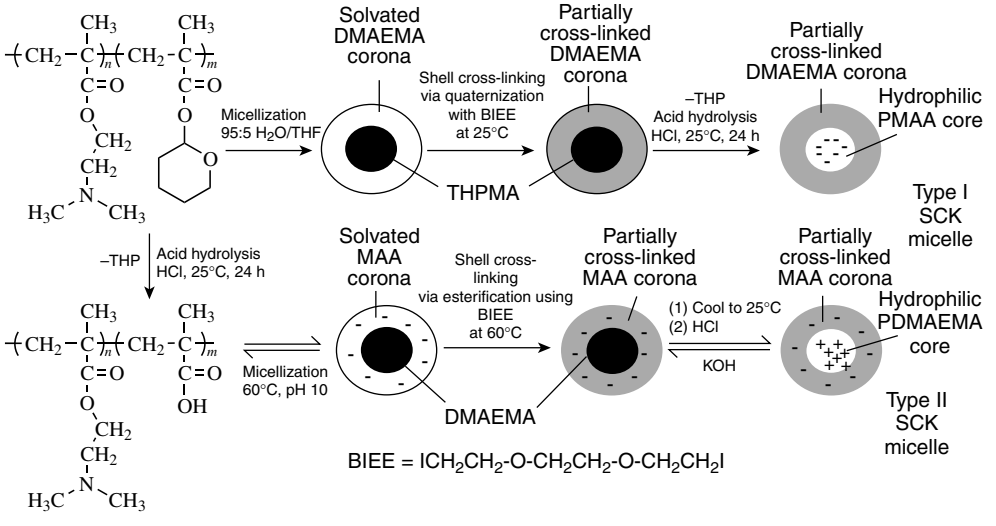


Fig. 32. An example of bis-(2-iodoethoxy)ethane as a cross-linking agent.

Here so-called Type I and Type II zwitterionic SCK micelles can be prepared from the hydrophilic-hydrophobic precursors poly(2-(dimethylamino)ethyl methacrylate-*block*-2-tetrahydropyranyl methacrylate) (DMAEMA-THPMA) copolymers prepared via group transfer polymerization (128,129,461). Micellization of the DMAEMA-THPMA block copolymers in a water/THF mixture (95:5) results in the formation of core-shell structures in which the hydrophobic THPMA species forms the core and the hydrophilic DMAEMA species the corona. The reactive tertiary amine residues in the coronal may be cross-linked using bis-(2-iodoethoxy)ethane in a *quaternization* reaction (Menshutkin Reaction). Subsequent hydrolysis of the micelles cores leads to the formation of the Type I SCK species. Alternatively, the DMAEMA-THPMA precursor block copolymers may be initially deprotected to form the block polyampholytes. Heating an aqueous solution of this block polyampholyte above the cloud point of the DMAEMA residues results in the formation of inverse micelles in which the now-hydrophobic DMAEMA residues form the micelle core and ionized poly(methacrylic acid) chains form the corona. These carboxylate coronal chains may also be cross-linked using bis-(2-iodoethoxy)ethane, in this instance via an esterification reaction.

A potential drawback of shell cross-linking is the need to perform such chemistries under relatively dilute conditions to avoid the occurrence of inter-particle cross-linking. However it was recently demonstrated that SCK micelles could be successfully prepared at high solids with ABC triblock copolymers in which the *C block* forms the *micelle core*, the *A block the outer coronal chains* and the *cross-linkable B block the inner coronal chains*. Here, the outer A block is effectively acting as a steric barrier to inter-particle cross-linking (463,464).

Most recently the core cross-linking approach was adopted for the preparation of novel nanoassemblies derived from pH-responsive AB diblock copolymers prepared via RAFT (222). Here the A block was the permanently hydrophilic DMA species with the tunably hydrophilic/hydrophobic DMBVA forming the B block. In aqueous media, at high pH, these block copolymers form core-shell structures with the DMA residues forming the corona and the DMVBA chains in the core. Addition of a hydrophobic, difunctional, alkyl halide namely 1,4-bis-bromomethylbenzene results in this species being sequestered into the hydrophobic core of the micelles where it reactions with the tertiary amine residues via the Menshutkin reaction to yield the core-cross-linked species. Successful core cross-linking was verified via NMR spectroscopy, dynamic light scattering and transmission electron microscopy.

13. Concluding Remarks

Water-soluble polymers are an extremely important class of materials that permeate every facet of our lives. This class of materials encompasses a wide range of interesting species ranging from naturally occurring proteins, peptides, RNA, DNA, and sugars (carbohydrates) to complex synthetic nanoassemblies such as the well-defined core-cross-linked AB diblock polymeric micelles.

Clearly there have been significant advances in the field of water-soluble polymers since the previous edition of this encyclopedia. Arguably the most important development in recent years has been the discovery and application

of more facile controlled/living polymerization techniques for the synthesis of highly functional, well-defined, model, materials. Of these, the controlled/living free radical polymerization techniques, and especially reversible addition–fragmentation chain transfer (RAFT) are proving to be especially versatile.

It is likely that such developments will continue to revolutionize water-soluble polymer synthesis in the years to come with chemists taking up the challenge to prepare ever more complex structures capable of supramolecular self-assembly for a wide variety of specialized applications.

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