RESEARCH

Chemical and biochemical catalysis to make swellable polymers

The enzyme reaction creates the specificity for these sugar-containing polymers while the chemical catalyst accelerates the process.

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People have always harnessed diverse biological macromolecules to make materials for everyday use, ranging from simple wood products to clothing (cotton and silk) to foods and beverages. Although biological macromolecules are structurally diverse, they are highly specialized with unique functions required for biological efficacy. They are also biodegradable and biocompatible. These characteristics are important in new materials where the desired properties are a result of specific chirality (for optically active supports in chromatography and catalysis), regularity (for nonlinear optical properties), or biodegradability/biocompatibility. As a result, polymer chemists are beginning to investigate synthetic techniques that can mimic nature's ability to create these properties.

In general, the monomers that make up biological macromolecules are structurally and chemically complex. Nowhere is this more evident than in the polysaccharides. These polymers consist of chiral sugar units linked by glycosidic bonds formed only by sugar hydroxyl groups. Nature incorporates substantial stereo- and regioselectivity into the biosynthesis of these macromolecules. Natural polysaccharides have a wide range of physical and chemical properties. These polymers range from cellulose, an abundant polysaccharide that is water-insoluble and crystalline, to hyaluronic acid, a far less abundant material that is highly hydrophilic and water-soluble or water swellable. In this article, we focus on those compounds with hydrophilic properties.

Hyaluronic acid is a charged, linear polysaccharide with viscoelastic properties. It is a highly hydrated polymer that is a component of cartilage, imparting the important mechanical properties required for cushioning bones. It is biocompatible and has many medical applications (*1–4*). Although hyaluronic acid has a wide range of desirable properties, large-scale, nonmedical commercial use is unlikely because it is prohibitively expensive. Thus, there is a strong incentive to develop materials that have hydrophilicity and biocompatibility similar to hyaluronic acid, yet cost less.

The diversity and selectivity of enzymes makes biopolymer synthesis possible. Harnessing the synthetic capabilities of enzymes is now feasible. We have been studying the use of enzymes to synthesize hydrophilic materials based on sugars. Many of the current generation of hydrophilic polymers are prepared by chemical techniques, such as polyvinyl alcohol, polyacrylates, and so on. Nature, however, has not evolved efficient mechanisms to degrade these synthetic materials. Moreover, achieving selectivity using traditional chemical methods to synthesize macromolecules is difficult and tedious. Polymers prepared enzymatically—either acting alone or in combination with chemical reactions—can have selective properties that result in unique materials and applications. These materials are inherently enzymatically degradable and thus biodegradable.

Linear polymers from sugars

Linear polyesters are typically formed by the polycondensation of equimolar amounts of a diol and a diacid (or diester). Acid- or base-catalyzed polyester synthesis is fast and efficient, albeit with little selectivity (*5, 6*). Highly selective polycondensation has been performed using enzymes operating in organic solvents. A nonaqueous reaction medium enables hydrolytic enzymes such as lipases and proteases to catalyze polyester synthesis, often with high degrees of enantioselectivity (*7, 8*). In water,

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these enzymes efficiently catalyze the hydrolysis of ester bonds. Optically active polymers with molecular weights >8000 have been constructed using this approach (*8*). The use of enzymes to prepare optically active polymers from racemic monomers has great potential in the preparation of polymeric reagents for chiral synthesis, adsorbents for chiral separations, and liquid crystals (*9*). An enzymatic route to polymer synthesis is clearly capable of imparting high stereoselectivity. Regioselectivity is also an important part of enzymatic catalysis.

We have focused on the incorporation of sugars into polyesters (*10, 11*). The challenge is twofold. First, a sugar must function as a diol even though more than two chemically reactive hydroxyls are present. Second, an enzyme must be identified that can use sugars as acyl acceptors in nonaqueous media. For example, sucrose contains eight hydroxyl groups, all with reactivity toward chemical acylation. Nonenzymatic linear polycondensation using synthetic catalysts would require blocking six groups, followed by polymerization and deblocking. Such a task is tedious and results in a mixture of isomers and, presumably, a highly irregular polymer structure. Our approach to polymer synthesis was to identify an enzyme that recognized sucrose only at two positions and used it as if it were a diol in polycondensation with diacid derivatives. Following a screen of more than 60 commercially available lipases and proteases, we identified an enzyme (Proleather from Amano, a *Bacillus* protease) that was capable of polymerizing sucrose with adipic acid derivatives in anhydrous pyridine. This solvent was ideal for polyester synthesis—sucrose is highly soluble in it.

Figure 1 depicts the synthesis of poly(sucrose adipate) prepared using this approach. Only the 6 and 1′ positions of sucrose—the primary hydroxyl on the glucose moiety and the internal primary hydroxyl on the fructose moiety—were acylated in the resulting polymer. This ensured that the material was not crosslinked. Water-soluble polymers were prepared that contained up to 100 sucrose units. In addition to sucrose, raffinose, lactose, and fructose have been incorporated into polyester backbones.

A protease was used to prepare this sugar-based polyester. In their native environment in aqueous solutions, proteases catalyze peptide bond (and to some extent ester bond) cleavage in aqueous solutions. They are specific for amide/ester functionalities and use water as a nucleophile to effect hydrolysis. By using an organic solvent to eliminate bulk water, sugar molecules can act as nucleophiles in transesterification reactions. As can be seen in this example, enzymes often catalyze unexpected reactions when taken out of their natural environment.

The sugar-diacid ester linkages are susceptible to enzymatic degradation. In fact, the same enzyme that catalyzes the polymerization of sucrose in anhydrous pyridine degrades the polymer in water. This is a vivid example of the principle of reaction microreversibility. A variety of lipases were also capable of catalyzing the depolymerization of poly(sugar adipate)s in water, nearly completely breaking it down to sucrose and adipic acid.

Adding the power of chemical catalysis

Complete enzymatic synthesis of polyesters is compelling, yet it limits the chemistries available to the synthetic polymer chemist. For example, although hydrolases like Proleather catalyze transesterification reactions in organic media without the need for complex cofactors, complex enzyme pathways are required for carbon–carbon bond formation. As a result, the majority of poly(ethylene/acetylene)-based materials are not easily synthesized using enzyme technology. Moreover, enzyme-catalyzed polymerizations are typically slow; sometimes days are required for preparative-scale reactions to yield high molecular weight products.

Enzymes are less efficient for transacylating larger polymer chains, presumably because of diffusional limitations in reactions between enzymes and unnaturally large substrates. Thus, enzymes may be better suited for selective modification of monomers. This, however, may be all that is necessary to impart the required regio- and stereoselectivity into a polymer.

A combined chemical/enzymatic (or chemoenzymatic)

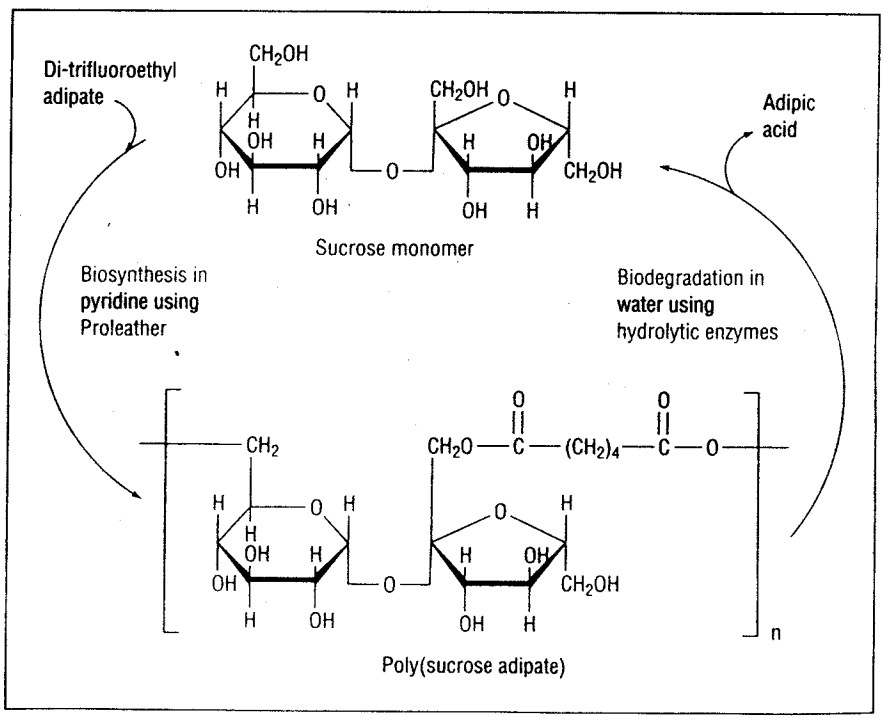

Figure 1. **Biopreparation and biodegradation of poly(sucrose adipate).** Synthesis takes place in anhydrous pyridine catalyzed by Proleather (an alkaline protease from a *Bacillus* species). The number of repeating units is as large as 100.

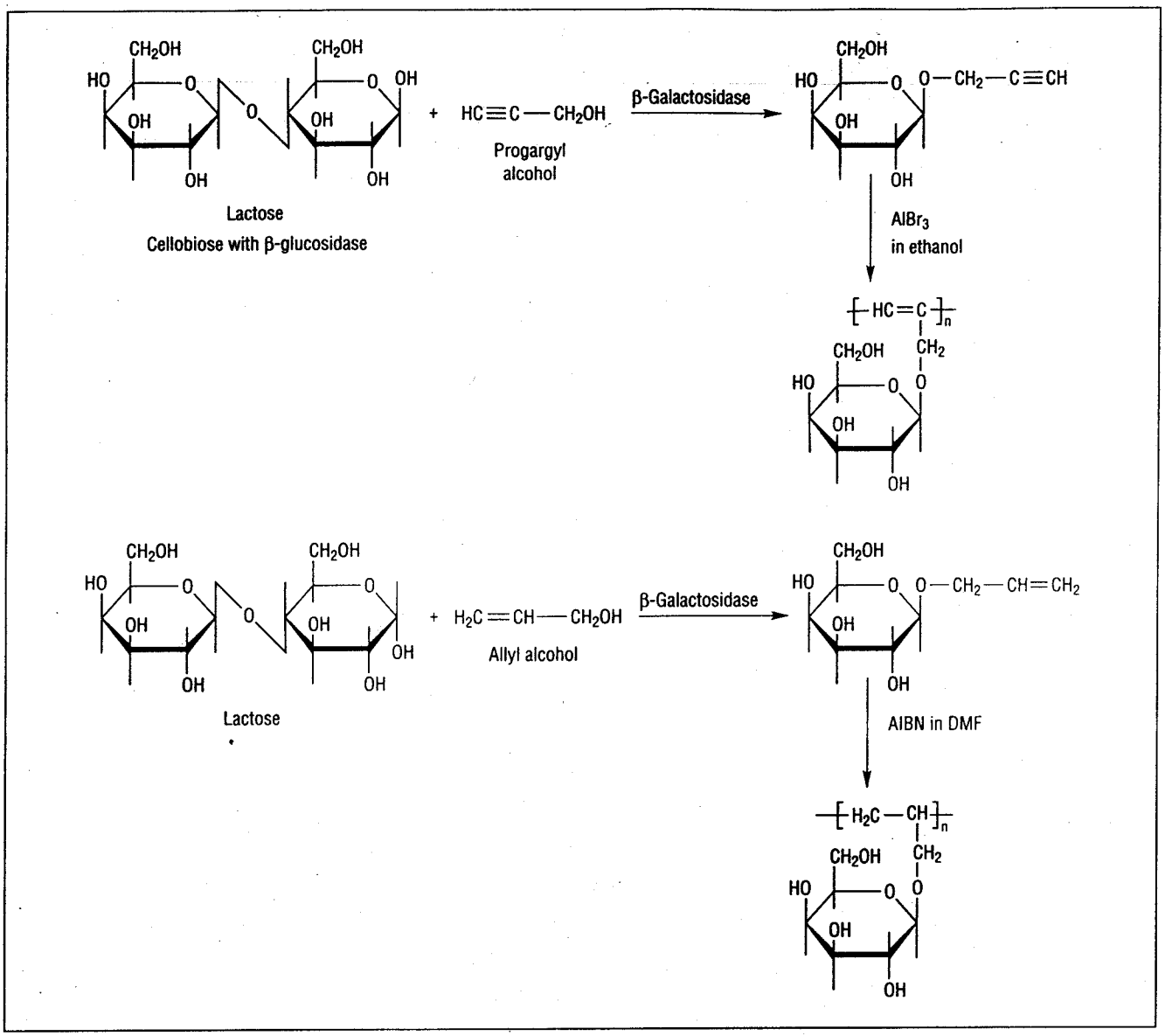

Figure 2. **Chemoenzymatic synthesis of sugar-based poly(acetylene and ethylene)s.** The high selectivity of enzymatic catalysis is evident by the formation of only the absolute anomer of the propargyl glycoside. Polymerization chemically leads to polymers with up to 6 units. Polymerization with $([C_6H_5])_3P)_2Ni(CO)_2$ yields polymers with molecular weights exceeding 37,000.

process has advantages inherent in each type of catalysis—high selectivity due to the biocatalyst and high reactivities (and sometimes novel chemistries) associated with chemical catalysts. A chemoenzymatic approach is ideally suited for the synthesis of sugar-based polymers. The enzyme reaction can be geared toward specifically modifying the properties of the sugar monomer. The resulting monomers can be polymerized using a nonselective chemical catalyst. We have invented a number of linear sugar-containing polymers using chemoenzymatic synthesis including poly(sugar acetylene)s (*12*) and poly(sugar acrylate)s (*13*). In both cases, selective enzymatic modification of a sugar is performed initially, followed by a nonselective chemical polymerization.

Poly(sugar acetylene)s. These compounds were prepared by regioselective chemoenzymatic synthesis (*12*). Propargyl alcohol was used as a glycosyl acceptor in the transglycosylation reactions of glycosidases with various disaccharides including lactose, maltose, and cellobiose (Figure 2). For example, reaction of propargyl alcohol with lactose catalyzed by β-galactosidase in aqueous buffer containing 25% (v/v) propargyl alcohol resulted in the stereospecific formation of propargyl-β-D-galactopyranoside in 42% yield. The β-galactosidase reaction is absolutely specific for the formation of β-galactosides. Polymerization of propargyl-β-D-galactopyranoside with $AlBr_3$ in ethanol resulted in the formation of oligomeric poly(acetylenic) species (M_w = 1300). Similar polymers have been prepared from propargyl-β-glucoside and propargyl α-glucoside (from cellobiose and maltose, respectively). These materials are water-soluble and may be useful as electrically conducting hydrophilic films or resins.

In addition to poly(acetylenic) materials, poly(ethylenic) compounds have also been prepared chemoenzymatically (*12*). The reaction of lactose with allyl alcohol yields a galactoside with a double-bond aglycon (Figure 2). (A glycon is the sugar portion of a glycoside molecule; an aglycon is the nonsugar portion.) Polymerization by free radical catalysts results in polymers with molecular weights >30,000.

Poly(sugar acrylate)s. Perhaps the most successful group of polymers prepared by chemoenzymatic means

are poly(acrylate)s that contain pendant functional groups. *Pseudomonas* lipase and subtilisin Carlsberg have been used to stereoselectively acylate racemic alcohols and amines in anhydrous *tert*-butyl ether or 3-methyl-3-pentanol giving optically active (ee >90%) acrylate and methacrylate derivatives (*14*). The monomers were subjected to free radical bulk polymerization using AIBN. Polymers with M_w up to 4×10^6 were prepared. The chirality of the pendant groups was unaffected by the polymerization reaction.

We have used the chemoenzymatic approach to prepare poly(sugar acrylates) (Figure 3). Once again, the large number of reactive hydroxyl groups on sugars presented a challenge for selective acylation. Monoacylation is required to form linear polymers. Diacylated (or higher acylated) acrylate derivatives would undergo unwanted crosslinking. In the presence of vinyl acrylate, a number of bacterial proteases catalyzed the monoacylation of sucrose in the 1′ position using a bacterial subtilisin (an alkaline protease) in pyridine. Yields of sucrose 1′-acrylate in excess of 80% were obtained in 24 h (*15*).

Sucrose 1′-acrylate was polymerized in water, dimethylformamide (DMF), and DMF/H_2O mixtures using several free radical initiators including an azo-type initiator, 2,2′-azobis(2-amidinopropane) hydrochloride, and three redox initiators: $H_2O_2/FeSO_4$ (which generates hydroxyl radicals via classical Fenton's chemistry); ammonium persulfate (AP)/$FeSO_4$; and AP/H_2O_2/$FeSO_4$ (*15*). The highest molecular weight was achieved in water with AP/H_2O_2/$FeSO_4$.

The intrinsic viscosity of the poly(sucrose acrylate) in water was plotted against its molecular weight using the Mark–Houwink relationship, $\eta = K M^a_w = 2.97 \times 10^{-4} M^{0.55}_w$ where η is expressed in dL/g. Mark–Houwink is a relationship between intrinsic viscosity and molecular weight. The *a* value provides an indication of the polymer–solvent interactions and the polymer structure in solution (*16*), typically varying from 0.5 to 1.0, with 0.5 indicating a random coil structure and 1.0 a more rodlike, extended shape. The *a* value of poly(sucrose acrylate) in water is close to 0.5, indicating that the internal polymer interactions are comparable to the polymer–water interactions. This suggests that the high density of sugar hydroxyl moieties may form a compact network of hydrogen bonds within the molecule, not unlike water.

This hydrogen-bonding network may also result in the formation of helical structures. Figure 4 shows a molecular model of the related poly(O-methylglucoside acrylate), prepared by energy minimization of a 40-mer polymer in water. It appears to give a helical network of O-Me glucoside residues (red) surrounding the nonpolar poly(acrylate) backbone (blue). Thus, the hydrophilic sugar groups shield the hydrophobic polyacrylate backbone. Many natural polysaccharides also exist in double or triple-helical form.

Because of the hydrophilicity of the sugar groups, the poly(sugar acrylate)s are highly water-soluble and many applications for these linear polymers are possible. For example, we are preparing densified samples by casting these poly(sugar acrylate)s. If the correct properties are achieved, these water-soluble polymers could be used as a packaging material. Because of the multiple hydroxyls remaining on the sugar groups these materials can be customized, and other applications are possible. For example, attachment of ionic groups to free hydroxyl moieties on the polymer will result in mutual repulsion causing increased spreading of the polymer chains in an aqueous solution. These ionic polymers may be used as viscosity-enhancing agents and as flocculants in the purification of municipal water supplies (*17*).

Today's hydrogels

Hydrogels are lightly crosslinked polymeric materials that absorb large amounts of water and other polar sol-

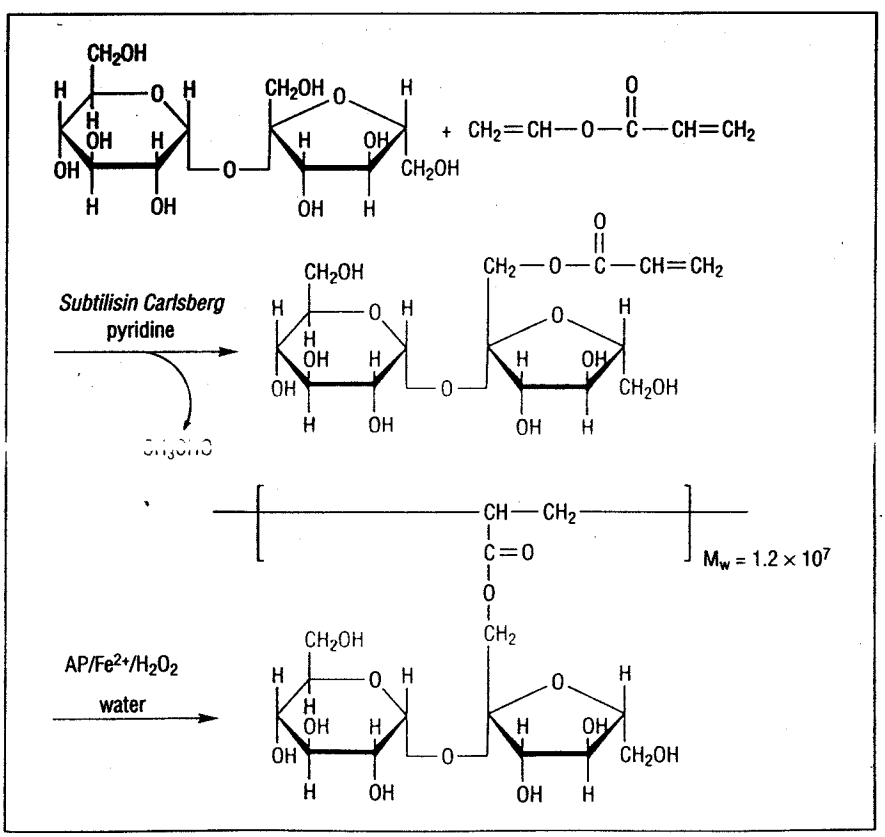

***Figure 3.* Chemoenzymatic synthesis of poly(sucrose acrylate).** The exquisite regioselectivity of subtilisin Carlsberg in anhydrous pyridine results in acylation only at the 1′ position. The monoacrylate is now primed for chemical polymerization in water. Polymers with molecular weights exceeding 10 million have been prepared.

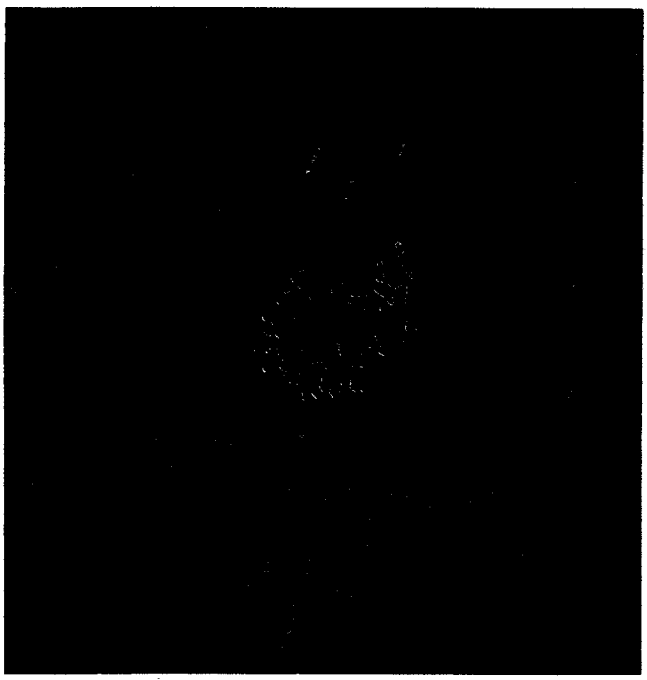

Figure 4. **Computer-generated molecular model of poly(oMe-galactoside 6-acrylate).** The poly(acrylate) backbone is shown in yellow and the sugar pendants are shown in gray.

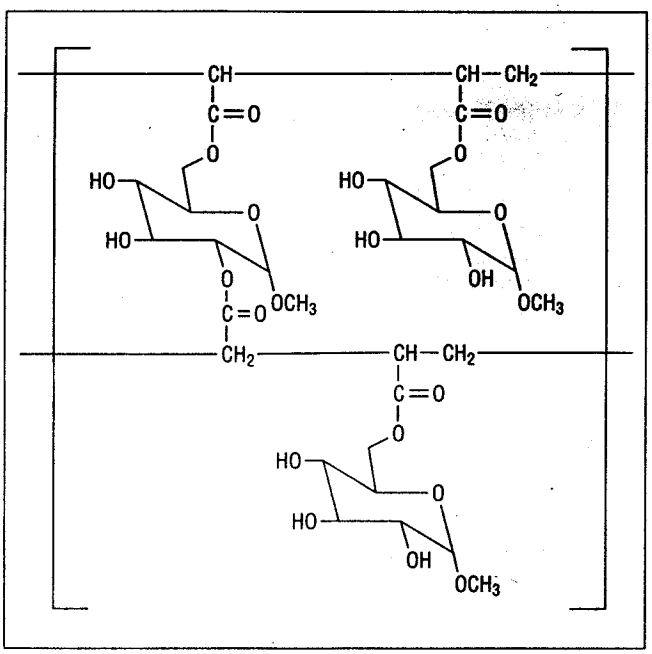

Figure 5. **Network structure of a sugar-based hydrogel.** A variety of sugars have been used in poly(acrylate) synthesis, including methyl glycosides of glucose, galactose, and mannose; phenyl glycosides of glucose and galactose; and *ortho*-nitrophenyl glucoside.

vents. In a sense, the monomer reacts to form a single polymer molecule with nearly infinite molecular weight. Although the linear form of a hydrophilic polymer is often highly water-soluble, the crosslinked hydrogel cannot dissolve because of its size. Instead, the molecule absorbs the water and swells. These materials generally absorb at least 10 times their own weight in water and are routinely used as lightweight water absorbents. They have been investigated as drug delivery matrices, bioimplantables, contact lens materials, and functional components of permselective membranes (*18–20*). Increasing the density of crosslinks usually leads to increased strength, but decreased swelling, of the gels.

Many common hydrogels are produced by polymerizing a water-soluble (meth)acrylic acid-containing monomer in the presence of a small amount—typically <5% (w/w)—of crosslinking agent. Typical examples are poly(hydroxyethylmethacrylate) PHEMA and poly(hydroxyethylacrylate) PHEA, which swell to 2–4 times their weight in water.

For applications where water absorbency is important, but the weight and volume of the dry material must be minimized for ease of transportation, even greater water absorbency is desired. This has led to the development of the so-called superabsorbent polymers. Hydrogels based on poly(acrylonitrile) and poly(acrylamide) have been reported to absorb as much as 300 times their weight in water (*21*). However, poly(acrylonitrile) and poly(acrylamide) are prepared from monomers that are potential neurotoxins. Therefore, they are not generally useful as water absorbents that must come into contact with humans. In addition, these superabsorbent materials release absorbed water too readily when deformed (squeezed). Hydrogels based on starch copolymerized with polyacrylonitrile have also been developed (*22*). However, the biocompatibility of these materials is limited. Thus, there is a need for a nontoxic, biocompatible material that can absorb and tightly hold large amounts of water. The water absorbency of these materials is enhanced by the hydrophilic groups, such as the nitrile or amide groups on the acrylate. It seems logical, therefore, to expect that attaching a sugar group to a (meth)acrylate would further increase the hydrophilicity of the gels and perhaps increase the water-absorbent capabilities of these materials.

Our hydrogels

We extended our methodology of preparing sugar-containing polymers to the synthesis of hydrogels from sugar-based starting materials (*23*). The initial step is the enzyme-catalyzed acylation of sugars in pyridine with vinyl acrylate to the corresponding monoacrylate derivatives. Sucrose and a number of monosaccharide derivatives were used. The monosaccharides are particularly appealing because sugars with different glycons and aglycons can be used to impart different properties to the resulting hydrogel matrix. The sugar acrylate monomers were polymerized in water with 0.1% (w/w) sodium persulfate and 1% (w/w) β-methylglucoside 2,6-diacrylate as a crosslinker to produce hydrogels that absorb upwards of 300 times their weight in water. Figure 5 depicts a representative structure of a glucose-based hydrogel. This absorbance is remarkable given the lack of any charged (ionic) groups in the hydrogel material; the level of water absorbency is comparable to gels made from poly(acrylonitrile) and poly(acrylamide) derivatives.

Figure 6 depicts a hydrogel prepared from β-methylglucoside 6-acrylate, both in its dried and swollen state. Note that the gel swells significantly when immersed in water. The diacrylate crosslinker employed in our studies is tailored to function for our sugar-based materials. It has several important attributes. First, it is a hydrophilic material, so when it is used as a crosslinker, it will not dramatically diminish the hydrophilicity of the sugar monomers. Second, the crosslinker is a sugar-based acrylate and is expected to polymerize at nearly the same rate as the sugar acrylate monomers. This should guarantee uniform crosslinking throughout the hydrogel matrix and block

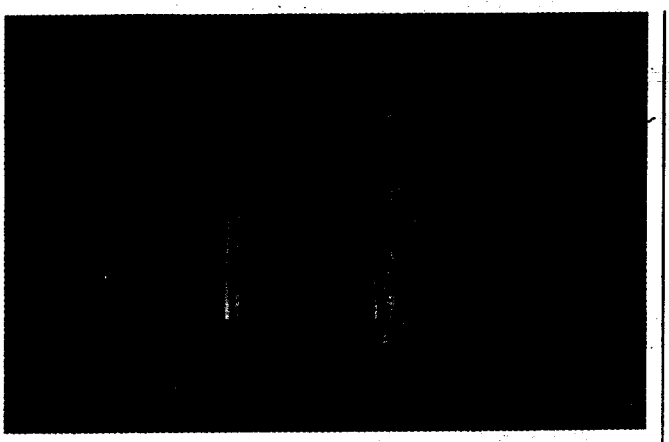

***Figure 6.* Swollen and dried sugar-based hydrogel.** The dried gel (based on methyl glucoside) swells to more than 300 times its weight in deionized water in <3 h. The gel swells to >100 times its weight even in the presence of 1 M NaCl.

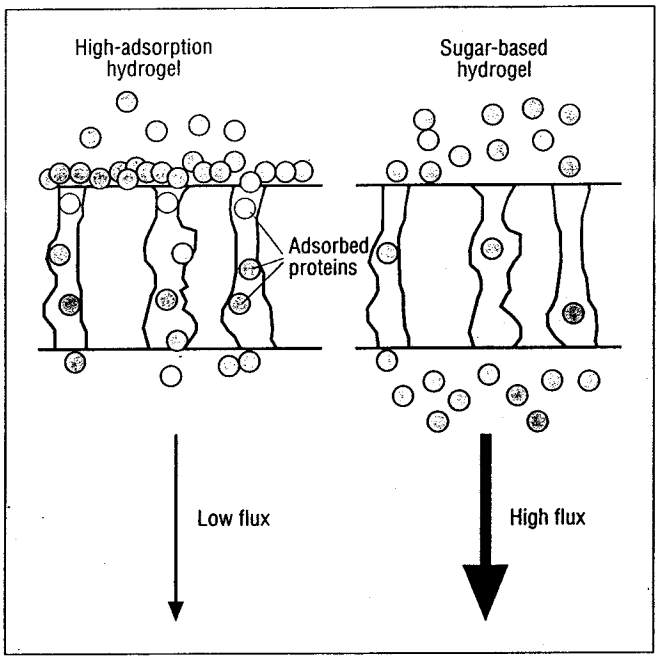

***Figure 7.* Schematic of pore blockage through protein adsorption.** Sugar-based gels are expected to reduce protein adsorption, a common failure of membrane separations.

copolymer formation is avoided. As expected, increasing the crosslinker content lowers water absorbencies; however, even at 20% (w/w) diacrylate crosslinker, the hydrogel still swells to 72 times its weight in water. Thus, the sugar-based crosslinker does not dramatically affect the hydrating capacity of the hydrogels.

Another feature of these hydrogels is their independence of swelling with extremes of pH (ranging from 4 to 9), and their ability to absorb more than 100 times their weight in water even at high ionic strength (up to 1 M NaCl). This is important as many hydrogel uses involve contact with bodily fluids which have a reasonable ionic strength (0.15 M, pH 7.2), as well as industrial applications involving a wide range of pH values. The swelling of conventional hydrogels, particularly charged materials such as poly(acrylic acid), is a strong function of pH and ionic strength. Materials that absorb 300 times their weight of pure water may only absorb less than 10 times their weight if the ionic strength is increased to 0.15 M. The lack of a pH effect also suggests that the poly(sugar acrylate)s are essentially uncharged, and no free acrylic acid moieties are formed (via hydrolytic cleavage of the sugar pendant groups) during gel preparation and usage.

The mechanical properties of sugar-based hydrogels are strongly influenced by the crosslink content. Below 10% (w/w) diacrylate crosslinker, the gels are easily deformed (with elastic moduli of 0.02–0.04 MPa), though they return to their original conformation when the stress is released. The gels become substantially stronger at 20% (w/w) diacrylate crosslinker and have mechanical strength similar to more conventional hydrogels such as PHEMA and poly(acrylamide) (*24*). Thus, this material appears to have the unique attributes of high mechanical strength along with high water absorbency.

The chirality of the sugar-based gels can be altered by changing the position of the acrylic acid ester linkage on the sugar or changing the nature of the sugar monomer—for example, by changing the glycon or aglycon functionalities of the monomer. Proteins or cells are capable of chiral recognition. By altering the chirality of a sugar-based hydrogel, it may be possible to alter the hydrogel's ability to interact with its biological environment. This may have particular relevance in clinical applications of these materials.

Based on the results of the linear polymers, the hydrogels are also expected to be biodegradable. Thus only about 16% (w/w, in the case of monosaccharide poly[acrylate]s) of the non-swelled polymer (the acrylate backbone) represents an environmentally stable residue. Sugar-based hydrogels provide an attractive commercial alternative as water-absorbent materials.

In summary, the chemoenzymatic synthesis of sugar-based hydrogels offers a unique approach to developing nontoxic, highly water-absorbent materials for applications such as general water absorbents, water-treatment additives, and eventually biomedical devices. The high specificity of enzymes coupled with the efficiency of chemical polymerization provides an economical approach to hydrogel synthesis as well as the preparation of a biodegradable matrix. These materials may have significant commercial potential as replacements for existing water absorbents.

Membrane applications

We are currently examining the use of poly(sugar acrylate) hydrogels as membranes for separating biological materials such as proteins. Current hydrogel membranes have distinct limitations because of membrane fouling caused by sorption of the protein (with subsequent denaturing) on the membrane itself. Initial indications suggest that incorporating the sugar side chains in these materials significantly enhances the biocompatibility of the resulting membranes. This leads to reduced sorption of proteins by the membrane and better separations with longer membrane life. Figure 7 shows a schematic of this process.

Biotechnology applications

Sugar-based hydrogels have many potential uses in biotechnology. In affinity chromatography, hydrogels offer a high concentration of sugar ligands for specific binding of plant and animal lectins and might lead to improved routes to their purification.

Chiral sugar-based hydrogels might provide for unique matrices for gel electrophoresis. Preliminary studies in our

laboratories demonstrate that poly(O-methylglucoside 6-acrylate) was useful as a substitute for poly(acrylamide) in the gel electrophoresis-based separation of charged sugars. Both protein and cells can be entrapped in hydrogels, stabilizing them and altering their biological activity. Sugar-based hydrogels offer an unusual water environment that may have a profound influence on the stability, activity, and specificity of these immobilized biocatalysts.

Sugar-based polymers and hydrogels might also represent a new substrate for cell growth. Replacing agar, normally used in culture plates, with polymers and hydrogels containing specific sugars may improve the adhesion or growth characteristics of microbial and mammalian cells.

Clinical applications

A number of clinical applications for currently available hydrogels may be amenable to new sugar-based hydrogels. Clinical analyses relying on permselective hydrogels for electrochemical or optical biosensors offer an opportunity to exploit sugar-based hydrogels. Hydrogels are currently being studied as drug carriers for the transdermal sustained release of a variety of drugs as well as the rectal delivery of narcotics and tranquilizers.

Bioprosthesis applications include the use of hydrogels in contact lenses, wound dressings and bandages, cerebral spinal fluid shunts with reduced bacterial adhesion, hemosorbents for hemoperfusion applications, and antithrombotic coatings for use in extracorporeal devices. Hydrogel bioimplants have been studied as pericardial (fluid around the heart) substitutes, synthetic joint cartilage (hyaluronic acid substitute), intracorneal implants (permalens) for treating myopia, matrix in bone surgery, and use in the reconstruction of organs by permitting appropriate cellular organization into tissues (*25–27*). In all these applications, a chiral, sugar-based hydrogel capable of specific interactions with proteins and cells, and with a high degree of biodegradability and biocompatibility, would be extremely useful.

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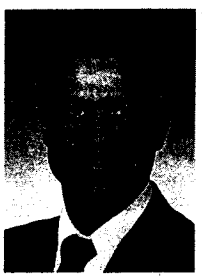

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