chapter 7

specialty Chemicals and Food Additives

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Specialty Chemicals and Food Additives

Introduction

In the production of specialty chemicals, defined in this report as chemicals whose price exceeds $1/lb (50¢kg) in cost, there are many potential applications of biotechnology. * The nearest term applications are in the production of specialty chemicals that are already produced by processes using micro~organisms, e.g., amino acids and enzymes. Enzymes are the direct products of genes, so their production is particularly accessible with new genetic technologies.

A number of specialty chemicals are chemically synthesized. Some, including some vitamins, are synthesized chemically from petrochemicals. Others, including fatty acids and steroids, are synthesized chemically from naturally occurring compounds. Current chemical synthesis production processes often require large energy inputs, have complicated synthesis steps, and yield many byproducts. Potentially, some of the steps in current chemical synthesis processes could be replaced by biological steps catalyzed by enzymes. Enzymes that perform some of the necessary conversions in a very specific manner and with small energy inputs are already known. If appropriate microbial enzymes (or higher organism enzymes) were identified and characterized, the appropriate genetic information could be cloned and expressed fairly rapidly in well-studied micro-organisms to produce or modify compounds such as vitamins, lipids, steroids, and aromatic chemicals. Alternatively, a chemical synthesis production process might be replaced entirely by a biological process if a microorganism were identified that performed the synthesis. Both individual enzymes and biosynthetic pathways consisting of several enzymes can be manipulated genetically to increase production.

Finally, it should be noted that there are some specialty chemicals synthesized in nature, such as complex polysaccharides, for which chemical synthesis is not feasible. Improving the syntheses of these specialty chemicals in controlled microbial processes is beginning to be investigated.

This chapter discusses the applications of biotechnology to the production of specialty chemicals. It also discusses applications to the production of animal feed and human food additives, because many of the genetic techniques applicable to the production of specialty chemicals also apply to the production of such additives. Since the main difference between specialty chemicals and food additives is in the Food and Drug Administration's (FDA's) regulatory approval process for food and food additives, food additives are discussed here as a subset of specialty chemicals.**

The several kinds of products that could be produced using biotechnology, which are discussed in this chapter, are only representative of the large range of products that could be synthesized using biotechnology. The specialty chemicals and food additives market is extremely broad, and many other applications of biotechnology to the production of such products may be evident in the future.

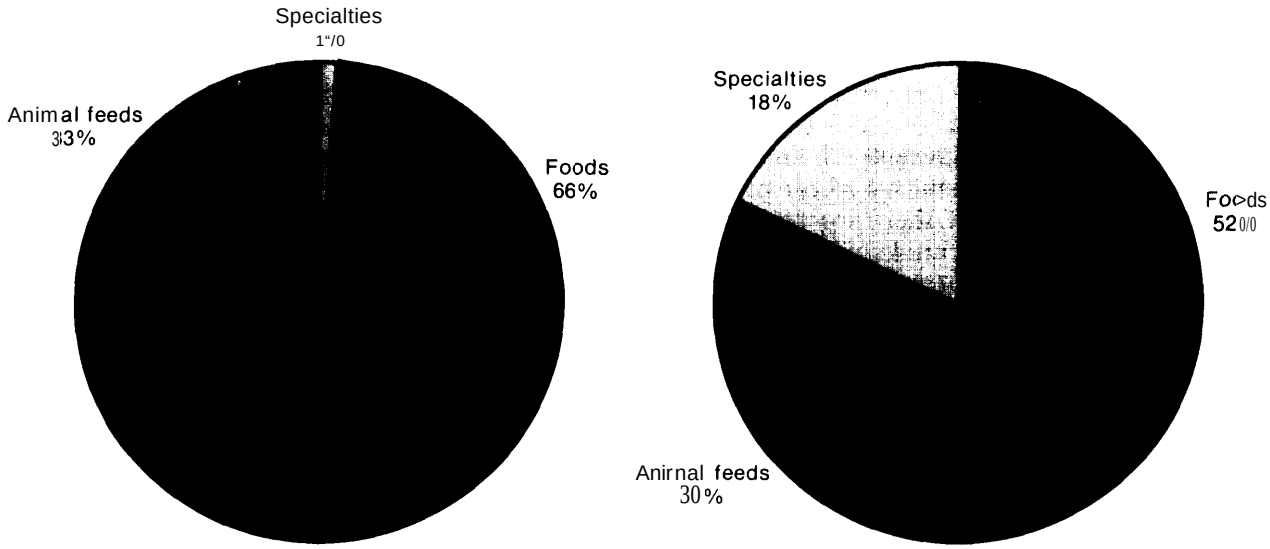
● 'III{' application *of* biotechnology to the production of commodity chemicals, defined in this report as chemicals that sell for less than $1 per pound, is discussed in *Chapter 9: Commodity Chemicals and Energy Production*

.● F-I)A's regulatory approval processes are discussed in *Chapter 15: Health, Safety, and Environmental* **Regulation,**

Amino acids

In 1982, the worldwide sales volume of amino acids was 455,000 metric tons (tonnes) valued at $1.15 billion (see fig. 17), and an annual growth rate of 7 to 10 percent is expected during the remainder of this decade. The world markets for amino acids are currently dominated by Japanese

Figure 17.—Uses of Amino Acids



SOURCE: Office of Technology Assessment, adapted from P. L. Layman, "Capacity Jumps for Amino Acids, " Chem. & Eng. News, Jan 3, 1983

producers, the largest of which is Ajinomoto. Amino acid production in the United States, however, is beginning to expand. W. R. Grace is planning to use a new plant in Maryland to produce pharmaceutical-grade amino acids, and two Japanese producers, Ajinomoto and Kyowa Hakko, are opening plants in the United States (47).

Amino acids have traditionally been used as animal feed and human food additives, and their use as animal feed additives may increase as other proteinaceous feedstuffs become more expensive. Recently, there has been increased use of pharmaceutical-grade amino acids for enteral and intravenous feeding solutions. Important constituents of these feeding solutions are the essential amino acids, those that the human body cannot make. Leading U.S. manufacturers of such solutions are Abbott Labs, Baxter Travenol, and American Hospital Supply (30). As shown in figure 17, the specialty market accounts for only 1 percent of world volume of amino acid production, but amounts to 18 percent of the sales value. The production of pharmaceutical-grade amino acids using biotechnology is receiving attention from both U.S. and Japanese companies (28,47).

Glutamic acid

The largest world market for an amino acid is the market for glutamic acid; the sodium salt of glutamic acid, monosodium glutamate (MSG), is used as a food additive. On the order of 300,000 tonnes of glutamic acid are produced annually worldwide (23,25). Approximately 30,000 tonnes are used in the United States, and about one-half of U.S. needs are met through imports at a price of about $2/kg (10).

MSG is produced by an efficient bioprocess using a strain of *Corynebacterjum.* This strain was first isolated, on the basis of the microorganism's ability to synthesize and excrete glutamic acid, by the Japanese in the late 1950's. Reports through the Japanese patent literature indicate that Ajinomoto, the world's leading MSG manufacturer, is applying recombinant DNA (rDNA) techniques to ***Corynebacterium*** strains in an effort to improve glutamic acid production. *

*Strains of *Corynebacterium* are used extensively in Japan for synthesis of several amino acids, but the Japanese bioprocess industry did not do basic research with these bacteria until recently. However, patents and reports in the literature indicate that Japanese amino acid producing firms have begun application of rDNA tech-

Methionine

Another large market for amino acids is in animal feeds (47). Typical corn/soybean animal feeds have low concentrations of the amino acids methionine and lysine, so their nutritive value in animal diets is Iimited. Methionine and Iysine (see below), therefore, are widely used as animal feed additives. Two companies in the United States, Monsanto and the U.S. affiliate of the West German firm Degussa, produce feed-grade methionine using a chemical process (9). Because this process is quite inexpensive, it is not likely that competitive biological routes to methionine production will be developed in the near future.

Lysine

The production of the amino acid lysine is dominated by three Japanese producers, Ajinomoto, Kyowa Hakko, and Toray Industries (1 1), which together account for 90 percent of the world market. Manufacturers' prices are variable, generally in the range of $3 to $4/kg for feed-grade lysine (43). The United States imports all its Iysine (67) and in 1981 imported approximately 11,000 tonnes (68). A plant for lysine production is being built in Cape Girardeau, MO., by the Japanese manufacturer Kyowa Hakko, and it is projected that the plant initial production of lysine will be 7,500 tonnes per year (40).

Most lysine is produced in a bioprocess using mutant strains of *Cory/nebacterjum.* A substantial increase in lysine production and a corresponding decrease in cost can be expected to result from applying rDNA techniques to these bacteria (30). In production processes, ***Corynebacterium*** mutants already yield large amounts of Iysine from a crude carbon source such as molasses (45). Amplification of Iysine biosynthetic enzymes in these bacteria through gene cloning should result in an increased synthesis rate and amount.

Tryptophan

The amino acid tryptophan is the second limiting essential amino acid in corn and the third limiting essential amino acid in combination feeds for swine and poultry (58). Although tryptophan would seem to be a prime candidate for the animal feed supplement business, marketing analyses have shown that the cost of tryptophan would have to be reduced to the $10/kg range (i.e., about three times the cost of lysine) in order to interest feed formulators in its use [47). The current cost of tryptophan, $95/kg, makes its addition to animal feeds out of the question at this time.

The development of efficient bioprocesses for tryptophan production using either modified ***Corynebacterium*** or enterobacteria (intestinal bacteria) such as *Escherichia coli* could potentially lower tryptophan costs. The current level of understanding of the *E. coli* aromatic amino acid pathway and sophisticated rDNA techniques that are available should facilitate strain construction in the enterobacteria. As for constructing a tryptophan-producing ***Corynebacterium,*** basic understanding of the synthetic pathway and development of a vector system remain to be achieved. Manipulating any micro-organism to produce tryptophan efficiently may be difficult, however, because the synthesis of tryptophan requires a greater expenditure of energy than does that of any other amino acid (l). The yield of tryptophan from a given carbon source, therefore, will be lower than the yield for other amino acids. The yield of product from glucose is an important factor in determining production cost in a bioprocess. Information concerning production cost improvements made by the Japanese companies now manufacturing tryptophan is not available.

Progress has been made in developing a two-step enzymatic process for tryptophan production (32). This approach requires three substrates: glycine, formaldehyde, and indole. The high levels of the two enzymes required for this process are obtained by cloning and amplifying each of the genes for these enzymes. This process has not yet been commercialized, but is being investigated by the new biotechnology firm (NBF)* Genex (US.). Commercialization requires that the three substrates be priced low enough to meet the target price for tryptophan. Another enzymatic process for the production of tryptophan has been devel-

niques to *Corynebacterium*. Genex and W. R. Grace also have research programs to develop genetic techniques for these bacteria (30).

● NBFs, as defined in ***Chapter 4: Firms Commercializing Biotechnology,*** are firms that have been started up specifically to capitalize on new biotechnology.

oped by Mitsui Toatsu Chemicals. Commercial production of tryptophan by this Japanese firm was due to begin in January 1983 (7,12).

The relative costs of corn and soybean meal influence the use of these products as animal feed additives. As the price of soybean meal, the main source of protein, and thus amino acids, in poultry and swine feeds rises relative to feed-corn prices, as is expected during the 1980's, there will be a tendency to use less soybean meal in animal diets if less expensive feedstuffs are available. A reduction in lysine production cost and a substantial reduction in tryptophan cost could result in increased incorporation of these amino acids in animal diets as a substitute for proteinaceous soybean meal.

Aspartic acid

Innovative processes for amino acid production that involve immobilization of whole cells or enzymes for bioconversion of precursors to amino acids are being developed (30). In the case of aspartic acid, a constituent of the sugar substitute aspartame, an immobilized process has reduced the costs of production. An early process for aspartic acid production involved the enzyme aspartase in a one-step batch reaction. The life of the catalyst in this process was, at most, a few days. When the enzyme aspartase was immobilized and a continuous-flow process was developed, a 40-percent saving in aspartic acid production cost was realized (14). The life of enzymes in immobilized systems can be increased many fold, up to several months. Cost savings are due to reductions in the amount of catalyst required, in the size of equipment used, and in the labor needed to operate the system.

Phenylalanine

The demand for the amino acids aspartic acid and phenylalanine as components of the sugar substitute aspartame has spurred process development. Aspartic acid is already available at an attractive price, and the research described below will make reasonably priced phenylalanine available soon (30). Phenylalanine, like tryptophan, requires large amounts of energy for the microbial cell to make. However, it should be possible to genetically manipulate enterobacteria or ***Corynebacterium*** strains to overproduce phenylalanine, thereby making the process economic.

A group of Australian scientists at the University of New South Wales, Kensington, is constructing E. ***coli*** mutants to overproduce phenylalanine in either a batch or continuous-flow bioprocess (15). No report of the commercialization of their process has been made, Amino acid producers in Japan (Ajinomoto and Kyowa Hakko) may also be applying rDNA techniques to improve phenylalanine production by their ***Corynebacterium*** strains in order to reduce phenylalanine costs.

A single-step enzymatic process to produce phenylalanine for use in aspartame is being developed in the United States by Genex and in Japan by Tanabe Seiyaku (31,73). In this process, yeast cells that contain the enzyme phenylalanine ammonia lyase (PAL) are utilized, Under the appropriate conditions, PAL will catalyze the formation of phenylalanine from cinnamic acid and ammonia. The economics of the PAL process are very sensitive to the cost of the major raw material, cinnamic acid, which is currently rather expensive. Recovery of phenylalanine from the PAL process, however, will be much more straightforward than recovery from the complex broth that results from a batch bioprocess. High recovery yields in the PAL process may offset the disadvantage of a more expensive raw material.

Enzymes

Enzymes are proteins whose function in living systems is to catalyze the making and breaking of chemical bonds. They have been used commercially since the 1890's, when fungal cell extracts were first added to brewing vats to facilitate the breakdown of starch into sugar. The size of the

world industrial enzyme market for 1981 was estimated to be 65,000 tonnes at a value of $400 million. A growth rate resulting in 75,000 tonnes valued at $600 million has been predicted for the end of 1985. Fewer than 20 enzymes comprise the large majority of this market. Economic sources of enzymes include a limited number of plants and animals and a few species of microorganisms (33).

The enzyme industry is dominated by two European companies, Novo Industri (Denmark) and Gist-Brocades NV (Netherlands), which together have about 65 percent of the current world market (25), other companies marketing or planning to market large volume enzymes include CPC International (US.), ADM (a division of Clinton, U.S.), Miles (U.S.), Pfizer (U.S.), Dawi Kasi (Japan), Alko (Finland), Finnish Sugar (Finland), and Rohm (a division of Henkel, F, R.G.).

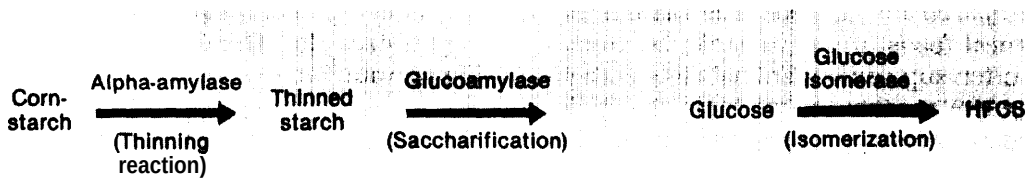
The leading enzymes on the world market in terms of volume are the proteases, amylases, and glucose isomerase (25). Alkaline protease is added to detergents as a cleaning aid and is widely used in Western Europe. Trypsin, another type of protease, is important in the leather industry. Two amylases, alpha-amylase and glucoamylase, and glucose isomerase are corn-processing enzymes. The reactions catalyzed by these three enzymes represent the three steps by which starch is converted into high-fructose corn syrup (see fig. 18). Fructose is sweeter than glucose and can be used in place of table sugar (sucrose) in preparation of candy, bread, carbonated beverages, and in canning. Historically, the United States imported sugar, but with the commercial development of an economic process for converting glucose to fructose in the late 1960's, corn sweeteners have decreased the amount of sugar imported. About $1.3 billion in U.S. payments for sugar imports was saved in 1980 because of the domestic use of corn sweeteners (17).

The process for converting glucose to fructose is catalyzed by the enzyme glucose isomerase. Initially, the conversion was done using a batch reaction; in 1972, however, a continuous system using immobilized glucose isomerase was initiated (36). The immobilized glucose isomerase process represents the largest immobilized enzyme process used in production in the world. A large processing plant can convert 2 million pounds of corn starch into high-fructose corn syrup per day (19).

Because of expanded sales in, for example, the detergent and high-fructose corn syrup markets, demand for enzymes will increase. The application of rDNA techniques to microbial enzyme production is expected to facilitate the expansion of the enzyme industry (25). Additionally, enzymatic activities of higher organisms could be cloned into micro-organisms, also expanding the enzyme industry, The fact that enzymes are direct gene products makes them good candidates for improved production through rDNA technology. For example, a 500-fold increase in the yield of a Iigase, used for connecting DNA strands in rDNA research, was obtained by cloning the gene for that enzyme on an E. coli plasmid vector (25). Several research enzymes now on the market are produced by microorganisms modified using rDNA techniques, Some are restriction endonu - cleases used for cutting DNA, and others are DNA-modifying enzymes. Companies that market these enzymes include Bethesda Research Laboratories (U.S.), New England Biolabs (U.S.), P-L Biochemical (U.S.), and Boehringer Mannheim (F. R. G.) (30).

Recombinant DNA technology could potentially be used to increase glucose isomerase produc -

Figure 18.—Conversion of Starch Into High Fructose Corn Syrup (HFCS)



SOURCE Off Ice of Technology Assessment

tion in microaganisms and to improve the enzyme's properties. An improved glucose isomerase would have the following properties:

- a lower pi-l optimum to decrease the browning reaction caused by the alkaline pH now required;
- thermostability so that the reaction temperature can be raised, thus pushing the equilibrium of isomerization to a higher percentage fructose; and
- improved reaction rates to decrease production time.

Improvements in glucose isomerase will first come from the cloning of its gene into vectors and micro-organisms that have been developed for high production. It is also possible that screening a broad range of micro-organisms will yield enzymes with some improved properties. Finally, it will be possible in the future to identify the regions of the enzyme that are responsible for its various properties, such as pH optimum, and to direct changes in the gene structure to modify these properties.

Rennet is an enzyme that is essential to the cheese industry because of its milk+ lotting properties. The world market for rennet from various sources is valued at approximately $64 million, over half of which is the more valuable calf rennet (25). The increasing scarcity of calf rennet has made this enzyme a very attractive candidate for gene cloning and subsequent production in a microbial bioprocess. The first announcement of the cloning of the rennet gene came from a Japanese scientist (53). Since then, it also has been cloned by four NBFs: the U.S. firms Genex, Collaborative Research (29), and Genencor (56), and the British firm Celltech (24,35). The first marketing of calf rennet produced by genetically manipulated bacteria is likely to occur in 1984 (30).

Enzymes, such as urokinase and streptokinase, are being used increasingly for treatment of human disorders. Their use and importance are discussed in ***Chapter 5: Pharmaceuticals.*** Many other enzymes are used for research and medical purposes in small quantities. Because rDNA technology potentially allows the construction of enzymes with improved stability and faster reaction rates, the use of enzymes industrially and medically could increase dramatically.

Vitamins

In 1981, the U.S. Department of Commerce reported that sales of vitamins for human use amounted to $1.1 billion (69). This market is expected to grow substantially over the next decade because of the current trend toward a more health- and nutrition-conscious population. A smaller but significant sector of the human vitamin market is for food processing and fortification.

Another important use of vitamins is in commercially prepared animal feeds. The vitamin content of natural feedstuffs is variable, so animal producers often supplement animal diets with vitamins. The U.S. market for vitamins as supplements in commercially prepared animal feed is large but is expected to increase an average of only 2.5 percent annually over the next decade ***(26)*** because of a decrease in the consumption of animal products.

Vitamins are either synthesized chemically or isolated from natural sources, and to date, biotechnology has had essentially no impact on vitamin production. Nevertheless, some opportunities do exist for reducing vitamin production costs using biotechnology. First, the cost of existing bioprocesses for vitamin production, such as that for vitamin B12, might be reduced by using a genetically manipulated microa-ganism that synthesizes the vitamin in larger amounts at a higher rate. Second, some steps in a chemical synthesis might be replaced by biological steps, or the chemical synthesis might be replaced entirely by identifying microorganisms able to synthesize particular vitamins. Once such microbes have

been identified, vitamin synthesis can be enhanced by various biochemical, traditional genetic, and rDNA techniques. Finally, a micro-organism might be identified that produces a vitamin precursor. Such a micro-organism might then be genetically modified so that it would produce the vitamin itself by introducing a gene (or genes) that specifies an enzyme that would convert the precursor to the vitamin.

There are technical problems that introduce risks to research programs for new process developments for vitamins. one major problem is the dearth of information concerning vitamin biosynthetic pathways, especially in micro-organisms. Another problem is that any new biotechnology-based process will have to be very efficient to compete with the established chemical production methods.

Since vitamins are naturally occurring substances, they all have the potential for biotechnological production. The discussion below concentrates on vitamins B2, B12, C, and E to illustrate the range of biosynthetic pathways and potential problems for industrial production.

Vitamin B2

Riboflavin (vitamin B2) is known to be synthesized in small quantities by micro-organisms, but is manufactured primarily by chemical synthesis. The synthesis of riboflavin by the bacterium ***Bacillus subtilis*** has been studied extensively by a group of Soviet scientists (13), and strains of B. ***subtilis*** that overproduce and excrete riboflavin have been isolated (22). Because B. ***subtilis*** has been the subject of extensive studies by U.S. and European scientists, techniques such as DNA transformation, protoplasm fusion, and gene cloning have been developed for this bacterium (21). The availability of such techniques should facilitate the construction of a strain of B. ***subtilis*** for the production of riboflavin.

Vitamin B12

Vitamin B12 is currently produced by a microbial bioprocess (27). The U.S. market for vitamin B12 is supplied both by U.S. and European firms. One U.S. company (Merck) supplies the major part of the feed-grade vitamin B 12 market, while imports from Europe account for the major portion of the pharmaceutical grade (30). The current manufacturers' price for vitamin B 12 is approximately $8,000/kg for pure material (9). *

Reducing the cost of vitamin B12 production will require genetic modifications of bacterial strains so that the micro-organisms synthesize vitamin B 12 more efficiently. Vitamin B 12 is one of the most complex molecules of living systems, however, and its biosynthetic pathway has not been definitively characterized.

Vitamin C

The U.S. market for vitamin C is very large, 17,500 tonnes in 1982 (30). Approximately two-thirds of this volume is supplied by U.S. producers, while the remaining third is imported. The current price of vitamin C is approximately $12/kg (9).

Although some of the synthesis of vitamin C is done microbially, efforts to replace other steps with bioconversions have not been successful (18). The synthesis of vitamin C has been reported in a few micro-organisms (50). The first step in developing a vitamin C bioprocess, therefore, will be screening for a potential production organism. Analysis of the biosynthetic pathway must be done, because little is known about microbial pathways for vitamin C synthesis. Once the rate-limiting steps of the pathway have been identified, rDNA techniques could possibly be used to increase production. A complicating factor in a vitamin C bioprocess is the fact that this vitamin, in solution, is readily oxidized when exposed to air. Controlling dissolved oxygen and completing vitamin C with other compounds are two potential techniques for controlling the rate of vitamin breakdown during production. The wealth of unknowns makes it impossible at this time to predict a time frame for developing an improved vitamin C production process.

● The prices in this reference are for small volumes. "l'he purchase of large quantities of these chemicals can result in a substantial price reduction,

Vitamin E

If an approach to natural vitamin E production using biotechnology could be developed, its impact would be quite significant. In 1979, approximately 3,200 tonnes of vitamin E were used in the United States (39). Of this amount, 700 tonnes were the natural form of vitamin E. The remaining 2,500 tonnes were synthetic forms. Synthetic vitamin E is a mixture of closely related compounds that vary in biological activity, whereas the natural vitamin preparation consists of only the most active compound. Demand for vitamin E as an antioxidant could increase the market for this vitamin by as much as 1,500 tonnes per year, depending on FDA's decisions concerning continued use of chemical antioxidants. The U.S. demand for natural vitamin E is met by two U.S. manufacturers, Eastman Chemicals and Henkel, and 95 percent of synthetic vitamin E is produced in the United States (30). The May 1983 price of the synthetic vitamin mixture was $27/kg (9). The price of the natural vitamin was several times that amount, depending on the activity of the preparation.

Natural vitamin E is now purified from vegetable oil by a process that involves several steps. If a one-step fermentation process could be developed based on a high-producing microbial strain, the manufacturing cost of natural vitamin E might be lowered substantially.

Blue-green algae are the only well-characterized micro-organisms that are known to produce vitamin E (20,55). It might be possible to increase vitamin E synthesis by altering the biosynthetic pathway in blue-green algae, but the biochemistry and physiology of this pathway is poorly understood, and gene cloning in these microorganisms is at a rudimentary stage of development.

The discovery in bacteria, such as E. coli B. ***subtilis,*** and ***Pseudomonas,*** of a compound that is potentially a vitamin E precursor suggests another route for vitamin E production (37). These bacteria are well-characterized species for which genetic transfer techniques are developed. Construction of a vitamin E-producing strain first would involve isolating mutants that overproduce the precursor, Then the genes for the enzyme that catalyzes the conversion of the precursor to vitamin E could be isolated from blue-green algae and introduced into the potential production strain. Although the savings in production cost of vitamin E could be great, this project involves a substantial amount of risk related to the lack of information concerning the biosynthesis of this vitamin. For example, it is not known if only one enzyme is needed for the conversion of precursor to vitamin, how complex such an enzyme is, how many genes encode it, and what cofactor requirements it might have.

Summary

Biotechnological techniques for improving the efficiency of vitamin production are similar to those being used in amino acid process development. The research and development (R&D) effort for vitamins will be more extensive than that for the amino acids, because vitamin biosynthetic pathways are more complex and less understood. In some instances, screening programs to identify micro-organisms with potential for producing a particular vitamin may be required. Furthermore, for some micro-organisms that have good potential for vitamin production, it will be necessary to develop techniques of genetic manipulation. In summary, the impact of biotechnology on vitamin production will be more long range than its impact on the production of either amino acids or enzymes.

Single-cell protein

The term "single-cell protein" (SCP) refers to cells, or protein extracts, of micro-organisms grown in large quantities for use as human or animal protein supplements. Although SCP has a high protein content, it also contains fats, carbohydrates, nucleic acids, vitamins, and minerals. Interest in SCP production is not new, as evidenced by the fact that Dutch, German, and Brit-

ish patents for SCP production were issued as early as 1920 (51). Interest in SCP has waxed and waned throughout the ensuing years, but SCP production has never achieved great significance, mostly because of economic considerations (49,64). With the advent of new biotechnology and the threat of potential world food shortages, interest in SCP may once again return (49).

SCP can be used as a protein supplement for both humans and animals. In animal feed, it is a replacement for more traditional supplements, such as soybean meal and fishmeal. For humans, S(;P is used either as a protein supplement or as a food additive to improve product functionality, for example, flavor, whipping action, or fat binding (49). The use of SCP in human food presents a problem: humans have a limited capacity to degrade nucleic acids. Therefore, additional processing is necessary before SCP can be used in human food. The animal feed market is more attractive for SCP, not only because there is less processing of the product, but also because the regulatory approval process is less stringent.

Relative protein content of the various commercial sources of concentrated protein is shown in table 38. Nutritionally, the amino acid composition of SCP resembles meat, fish, and shrimp meal rather than vegetable protein. It has been shown through extensive testing both in the United States and abroad to be a suitable substitute for at least part of the former high-cost protein sources. The high protein content, good storage properties in dry form, texture, and bland odor and taste of SCP suggest real potential in feed and food markets. In prepared aquiculture feeds where, for juvenile animals, protein content up to 50 percent and above is required, SCP appears to be an attractive product. Another application is as a calf, lamb, or kid starter, thus leaving more milk for human consumption.

Table 38.—Typical 1982 Selling Prices of Selected Microbial, Plant, and Animal Protein Products

Product	Protein content (%)	1982 selling price ($/kg)
Food-grade products:		
Candida uti/is (tortula yeast)	50 to 55	$1.87 to $2.24
K/uyveromyces *ffagi/is*	*45* to *50*	*2.09* to **2,29**
Soy protein concentrate	72	0.88 to 1.03
Soy protein isolate	92	2.59 to 2.68
Dried skim milk	37	1.16 to 1.21
Feed-grade products:		
Saccharomyces cerevisiae	*45* to 50	$0.48 to $0.66
Soybean meal	***44***	0.19 to 0.20
Meat and bonemeal	50	0.19 to 0.21
Fishmeal	65	0.23 to 0.40

SOURCE J H Litchfield, "Single.Cell Proteins, " Science 219'740-746, 1963.

Incentives for production of SCP are fourfold. First, some parts of the world, for example, the high rainfall, tropical areas, have agricultural feed and food products high in carbohydrates; in such places, there is a chronic shortage of protein, which results in deteriorated physical and mental health. SCP would raise the protein content of food. Second, the land in other regions, including the Middle East and Africa south of the Sahara, cannot produce sufficient food of any type to prevent hunger. Here also an SCP supplement would be an asset. Third, there is demand worldwide for very high protein ingredients for feeds in the aquiculture industry, i.e., in the production of shrimp, prawns, trout, salmon, and other finfish and shellfish. Finally, SCP does not rely on temperature, rainfall, or sun for survival. At least one of the variety of feedstocks is usually available in almost any country or region of the world. The security of having such an internal source of protein is attractive to many countries.

Economically feasible SCP production is dependent on the efficient use of an inexpensive feedstock by a microorganism. A large variety of feedstocks have been used for SCP production over the years, including carbon dioxide, methane, methanol, ethanol, sugars, petroleum hydrocarbons, and industrial and agricultural wastes. These feedstocks have been used industrially with different micro-organisms, including algae, actinomycetes, bacteria, yeasts, molds, and higher fungi. The choice of a feedstock includes such considerations as cost, availability, efficient growth of the microorganism, and requirements for pretreatment (49).

SCP has yet to become an important source of protein, mainly because of high production costs. Some Scp-production processes that were economical at one time have not remained so because of changes in prices of competitive sources of protein such as soybean meal or fishmeal. In comparison to SCP, these protein sources are quite

inexpensive (see table 38), In fact, the price of most SCP processes would have to be decreased one-half to one-fifth for SCP to be competitive with soybean meal and fishmeal.

Through the years, the high cost of SCP relative to that of these other sources of concentrated protein has prevented extensive utilization of SCP, primarily in animal feeds. In the case of SCP produced from methanol, for example, the methanol represents approximately 50 percent of the cost of the product. In the United States, the cost of SCP made from methanol exceeds the average cost of fishmeal by a factor of 2 to 5. A plant in the United Kingdom (ICI) is operating at a loss because of such a situation (49,52). In some parts of the world, such as the Middle East, low-cost methanol and high shipping costs for fishmeal and other natural protein sources make the cost differential considerably less. In countries without methanol, biomass presents an option as a cheap feedstock source. However, this market has not been developed yet.

It is possible that the application of biotechnology will help to reduce the cost of production of SCP. Strains of micro-organisms could be improved using rDNA techniques. Improvements could include increasing the production of proteins with a better amino acid balance* or improving the ability of the microorganism to utilize the feedstock efficiently. Technological improvements in the process and recovery steps would also be important. The use of automated, continuous processes could improve the efficiency of production. Recovery steps could be aided by using micro-organisms that have been genetically manipulated to excrete protein. Additionally, it is possible that an enzyme that degrades cell walls could be cloned and produced in large amounts. Its use would help in the production of a protein concentrate from cells. New technologies will probably improve the production of SCP, but widespread introduction of SCP will be governed by economic and regulatory factors.

Several companies in Western and Eastern Europe, the United States, and Japan have built SCP production plants in the last 15 years (3,5,64). Many of these are no longer operating because of high production costs and regulatory approval problems. Nevertheless, there are several companies operating plants, including Shell Chemicals (Netherlands), British Petroleum (U.K.), ICI (U.K.), Rank Hovis McDougall (U.K.), Sosa Texaco (Mexico), Finnish pulp and Paper Institute (Finland), Amoco (U.S.), Phillips Petroleum (U.S.), Pure Culture Products (U.S.), Rhinelander Paper Corp. (US.), and Amber Laboratories (U.S.). In addition, there is one plant in the German Democratic Republic, and there are several in the U.S.S.R.

The center of SCP technology is in England, especially at ICI (71). The ICI process uses aerobic bacteria with methanol and ammonia as feedstocks. The bacteria are grown in the world's largest continuous bioprocess system with computerized control and monitoring of performance. The product, Pruteen®, contains 80 percent crude protein as well as a high content of essential micronutrients, especially B group vitamins. Pruteen® is used in animal feed diets (poultry, swine, fish) and as a milk replacer (calves). In 1981, ICI had scaled up its process to produce 3,000 tons of SCP per month. It is beginning research using rDNA technology to facilitate protein harvesting (49). So far, however, the production of Pruteen" has not been economic even though it is twice as nutritious as soybean meal (52).

Two of the SCP plants in the United States (Amber and Rhinelander) use wastes produced in other parts of their plants for feedstocks, assuring a constant and inexpensive source of raw materials for SCP production (49). This type of small-scale operation using internally generated wastes as feedstocks may be the most appropriate use of SCP technology in the United States and other countries where animal- and plant-derived protein sources are abundant.

The U.S.S.R. is actively pursuing the production of SCP. The Soviets consider the construction of plants to produce SCP a high priority in order to decrease their dependency on foreign sources of protein for animal feed (5). The U.S.S.R. produces about 1 million tons of SCP per year, but production has not increased since 1976 (62). About half of the Soviets' SCP feedstock is cellulose, and the balance is petroleum. The current Five-Year Plan

*As do proteins from plants, proteins from micro-organisms often lack one or more essential amino acids. Most commercial SCP products are low in methionine (51).

calls for doubling SCP production by 1985 to 2 million tons per year, but the Soviets will have to produce a total of 3 million tons per year in order to be able to stop importing soybeans for use as a protein source.

Low-cost or waste biomass feedstocks have been cited as one means to product cost reduction. Inedible biomass can serve as an indirect feedstock for SCP processes by high-temperature conversion to synthesis gas and then to methanol (2).

Engineering improvements expected include bioreactor designs for continuous operation and high cell density. High cell densities decrease cost, because at high cell densities, the cell suspension leaving the fermenter can be dried without pre - concentration of the cells by centrifugation, and because extracellular nutrients are recovered in the product.

Conventional genetic and rDNA methods for SCP production are currently being directed toward the following goals: 1) broadening the range of utilizable feedstocks; 2) increasing the optimum bioprocessing temperature and achieving a concomitant decrease in cooling requirements; 3) increasing the efficiency of utilization of the feedstock with the associated benefit of decreased generation of heat; 4) optimizing the balance of the essential amino acids in the product; and 5) producing of high-value products in conjunction with the SCP (e.g., growth stimulators) which may be either left in the SCP product or isolated from the broth.

The future of SCP depends largely on reduction in cost and improvement in quality. Means to meet these requirements involve lower cost feedstocks, improved engineering of the conversion and recovery processes, and upgrading the yield and quality of the product through conventional genetic and rDNA methods. The renewed interest in all of biotechnology, in part due to rDNA technology, is leading to increased effort in developing economically competitive SCP with improved qualities.

Complex lipids

Lipids are water-insoluble compounds found in cells whose many functions include serving as the structural components of membranes and storing of metabolic fuel. The term lipid designates a general class of compounds that includes the complex lipids (saponifiable lipids) which contain fatty acid components and simple lipids (nonsaponifiable lipids) which have no fatty acid component. The simple lipids include some vitamins, steroid hormones, and other highly specialized fat-soluble biomolecules.

Complex lipids are readily available and are extracted from natural sources. Some lipids such as sophorolipids have commercial uses. By far the most valuable attributes of lipids, however, are the products that can be derived from them, including fatty acids and fatty alcohols and the potential of lipids to replace petroleum feedstocks (48). Biotechnology could be used to develop new methods for economical production of lipid-derived products.

Fatty acids

Fatty acids are important industrial chemicals used in cosmetics, plastics, lubricating greases, rubber compounding, polymer emulsifiers, specialty household cleaners, foods, paints, varnishes, and flotation reagents (46). In the United States alone, the present consumption of fatty acids is about 1.65 billion pounds annually (46). The major sources of fatty acids are the naturally occurring fats and oils of plants and animals. The major plant sources of fatty acids in the United States are tall oils and coconut oil, and the major animal source is tallow (46). Synthesizing fatty acids from petroleum feedstocks is possible, but the process requires complex reactions and is more expensive than obtaining the acids from natural sources.

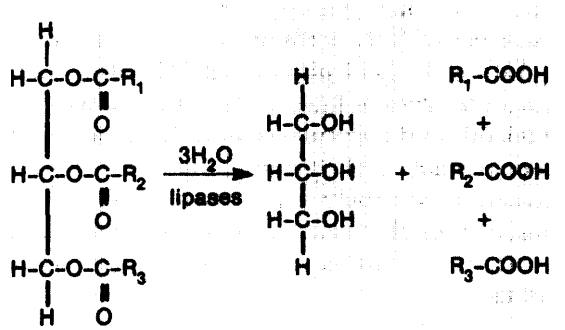
Fats and oils are composed of triglycerides, which can be broken down to free fatty acids and glycerol, a valuable coproduct. The usual decom -

position method is a chemical process whereby the triglycerides are continuously hydrolyzed (16). This chemical process is efficient; 99 percent of the available triglycerides are hydrolyzed to free fatty acids and glycerol. Because the process requires both high temperatures and high pressure, however, it is also energy-intensive.

An attractive alternative to chemical hydrolysis of triglycerides is an enzymatic process that uses lipases to split the triglycerides into free fatty acids and glycerol (see fig. 19). Such a process does not require severe reaction conditions and is therefore more energy-efficient. Two Japanese companies have begun to commercialize the production of fatty acids from natural oils and fats using lipases. Miyoshi Oil and Fat Co. has reportedly constructed two plants for the lipase-catalyzed production of fatty acids. Its initial plant reportedly is producing 300 tons of fatty acids annually. Similarity, the Nippon Oil and Fat Co. has begun trial operation of a pilot plant at its Amagaski facility, It plans to produce initially about 1,000 tons of fatty acids per month. These Japanese companies report that the lipase-based production of fatty acids is both energy- and labor-efficient (38,39).

Because of their stability and lack of cofactor requirements, lipases are good candidates for use in an immobilized enzyme process. At the present time, however, the apparent requirement of lipases for an emulsified substrate represents a barrier to an immobilized enzyme process. Research on both process design and the identification of lipases that are more amenable to immobilization should result in the development of an immobilized enzyme process for the production of fatty acids. Such process development might take several years.

Figure 19.—Hydrolysis of Triglycerides



SOURCE Off Ice of Technology Assessment

The cost of obtaining sufficient quantities of lipase will have a major impact on the economic viability of such processes. The application of biotechnology to develop or improve techniques for the recovery and reuse of lipases would be desirable. Supplies of specific lipases could be increased through gene cloning and amplification.

Fatty alcohols

Fatty alcohols are important industrial chemicals. The plasticizer ester industry uses large quantities of shorter chain (6 to 10 carbons) alcohols, while alcohols of longer length (11 to 18 carbons) are used to make detergents. Fatty alcohols can be synthesized chemically from ethylene, which is derived from petroleum feedstocks. Alternatively, some Japanese companies use a chemical process to convert fatty acids obtained from coconut oil into fatty alcohols (30). Although the Japanese chemical process does not rely on nonrenewable petroleum feedstocks, it does require extreme reaction conditions and therefore high energy consumption. A number of microaganisms are capable of converting fatty acids to fatty alcohols, but these biological conversions are also energy consumptive. Furthermore, both the substrate and product are toxic to micro-organisms. Hence, the development of a biological process would require, at best, a number of years of R&D effort.

Microbial oils

Although naturally occurring fats and oils can currently be obtained cheaply from plants and animals, there is a resurgence of interest in exploiting microorganisms for the production of oil. Israel, for example, is actively pursuing the development of a microbial source for oil (57) to reduce its dependence on imports. A number of eukaryotic oil-producing micro-organisms have already been identified, and preliminary research in developing micro-organisms as a source of oil is underway. It is impossible to predict when such

processes will be commercial. The United States has sufficient plant and animal sources for fats and oils, but the supply is affected by climate. European countries, unless they develop a microbial source, will have to rely on imported materials to satisfy demands for vegetable oils and fats (57).

Sophorolipids

There is increasing interest in identifying and exploiting microbial biosurfactants (biologically derived emulsifying agents). one group of glycolipids, the sophorolipids, shows considerable promise for use as biosurfactants. Sophorolipids can be produced from vegetable oils by the yeast ***Torulopsis.*** These sophorolipids are comparable in activity to other surfactants, but are produced by the yeast in much higher yield and are easily separated from reaction broths, thus minimizing costs. Further characterization of the sophoro - lipids and their potential markets is required before applications of biotechnology to their production are likely to be considered.

Steroids

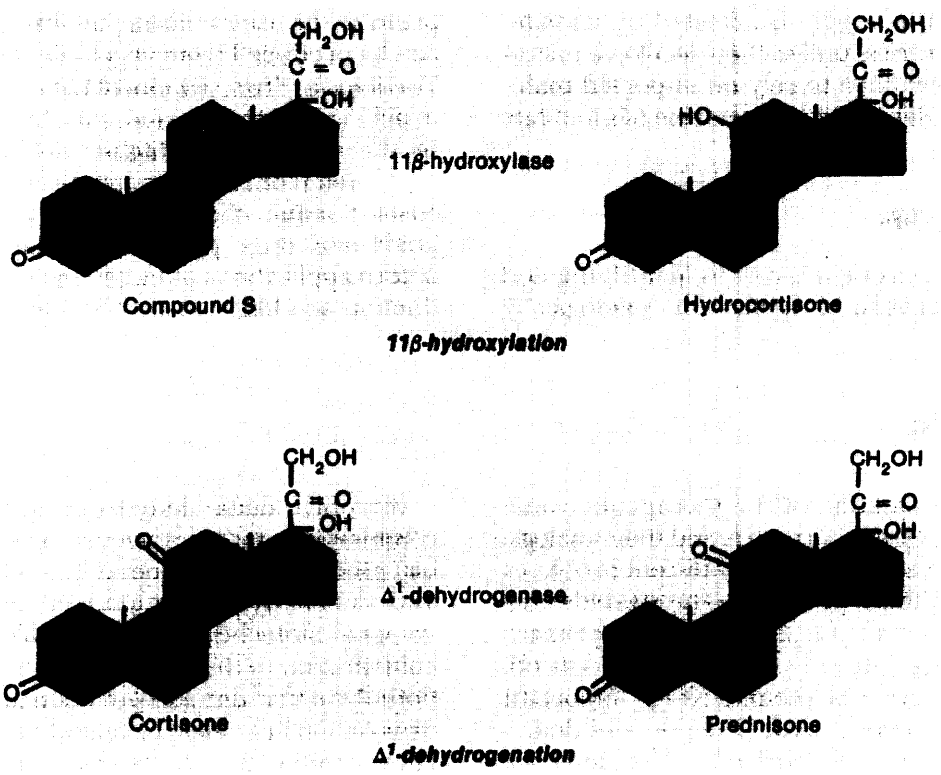
With the recognition of the therapeutic value of the natural steroid hormones and their analogs, it became necessary to develop efficient processes for producing these products. The steroids currently in therapeutic use are synthesized primarily by modifying naturally occurring steroids obtained from plants. Two commercially important modifications, 11-beta -hydroxylation and delta l-dehydrogenation, are difficult to achieve via chemical routes, but micro-organisms have been reported to perform both reactions. Examples of a microbial 11-beta -hydroxylation and a delta 1 dehydrogenation are shown in figure 20.

Microbial reactions have been identified for the hydroxylation of virtually every position of the steroid nucleus. Because whole-cell bioconversions for introducing the 1 l-beta-hydroxyl group occur at low levels and are plagued by the formation of byproducts, they have not been developed for commercial use. Further study of the enzymatic process should establish whether the byproducts are the result of many steroid-metabolizing enzymes or a lack of specificity of the 1 l-beta-hydroxylating enzyme. If the enzyme is specific, it may be possible to obtain the desired conversion levels by cloning and expressing at high levels the genes that encode the 11-beta-hydroxylase.

Microbial delta I-dehydrogenations are used commercially today. However, an efficient microbial process that combines delta-dehydrogenation and 11-beta-hydroxylation has not vet been developed. Biotechnology could make a significant contribution to the steroid industry by achieving both the delta l-dehydrogenation and 11-beta-hydroxylation in a single biological process step. The latter reaction is catalyzed by a complex enzyme, so it is unlikely that an immobilized enzyme system could be developed for it. Therefore, the most efficient process would be to have the two reactions carried out by one cell.

The steroid market is readily accessible to bio - technology. Microbial processes are used routinely in the manufacture of steroid products. Furthermore, bioconversions with potential value to the steroid industry have been identified, and rDNA technology could be used to construct a microorganism that more efficiently converts the steroid substrate to the desired product. The primary barriers to further biotechnological applications in the manufacture of steroids are the lack of rDNA host/vector systems for some of the micro-organisms involved and a lack of understanding of the specific enzymatic processes of steroid synthesis.

Figure 20.— Microbial Modifications of Steroid Molecules



SOURCE: Genex Corp., "Impact of Biotechnology on the Specialty Chemicals Industry," contract paper prepared for the Office of Technology Assessment, U.S. Congress, April 1983

Aromatic specialty chemicals

Aromatic compounds occur in many household products, medicines, agricultural products, pesticides, paints, cosmetics, and dyes, and their synthesis is a major component of the specialty chemical industry (6). Aromatic compounds that contain a hydroxyl group on the aromatic ring are an important group of specialty chemicals. Examples are the parabens and their esters, which are used as preservatives; 2,4-dichlorophenoxy - acetic acid (2,4-D), which is the most extensively used herbicide; and N-acetylated para-aminophenol, an aspirin substitute. The synthesis of each of these compounds requires the specific hydrox - ylation of the aromatic ring.

The chemical hydroxylation of the aromatic ring is generally an inherently expensive step in the synthesis of an aromatic specialty chemical. This expense often results from the nonspecificity of the hydroxylation reaction, which forms unwanted byproducts and is therefore an inefficient use of the starting material. Additional processing may be required in order to remove the byproducts and to dispose of them properly. Chemical hydroxylations also require severe reaction conditions and therefore consume a large amount of energy. In addition, chemical reactions can result in the formation of undesirable contaminants. One highly publicized case is the dioxin

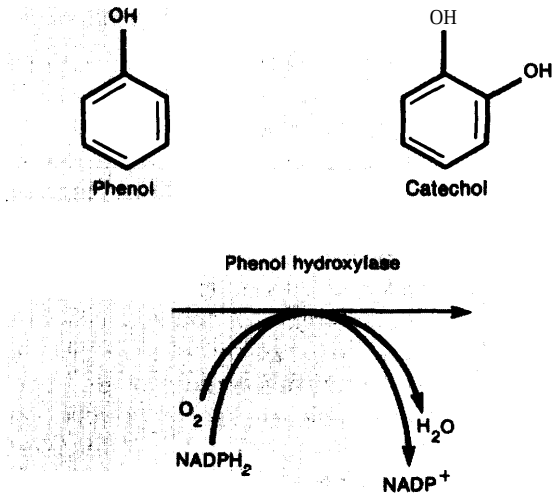
contamination that occurs during the chemical synthesis of 2)4,5 -trichlorophenoxy acetic acid (2,4,5-T), an herbicide and a component of the now banned Agent Orange.

By replacing a chemical reaction with a biological process, biotechnology has the potential to decrease the manufacturing cost of aromatic specialty chemicals, especially in processes that involve aromatic hvdroxylations. Many microarganisms are able to grow on aromatic compounds, and aromatic hydroxylations are key reactions in these growth pathways. These enzymatic reactions occur under mild conditions and result in specific hydroxylations of the aromatic ring. Furthermore, using enzymatic reactions, hydroxyla - tions can be obtained at positions not readily hydroxylated by chemical reactions. The development of bioprocesses for aromatic hydroxylation reactions represents a valuable biotechnological opportunity for the specialty chemical industry.

Microbial aromatic hydroxylations are mediated principally by oxygenates that catalyze the direct incorporation of molecular oxygen into the aromatic ring (6,54,65)66). An example of an aromatic hydroxylation mediated by a microbial oxygenase is shown in figure 21. Many oxygenates have been studied in detail; while differences do exist among the various types of oxygenates, oxygenates generally are complex enzyme systems that require cofactors for activity.

As found in nature, the conversion efficiencies of most aromatic hydroxylations are generally too low to be commercially viable (30). However, the conversion efficiency could be improved by cloning the gene(s) encoding the oxygenase and expressing the cloned gene at high levels in an appropriate production strain. Once the oxygenase gene(s) have been cloned and expressed in an appropriate production strain, more research time and effort will be required for process development. One major consideration is how to minimize the toxic effects of the aromatic compounds on microorganisms. One solution would be to develop an immobilized enzyme process; however, because of the complexity of the hydroxylation reaction it may not be possible to apply this technology. Toxic effects in bioprocesses have been minimized by innovative process design, and it is anticipated that there will continue to be significant advances in this area of research. Another consideration in developing an effective process is that the substrates and products are not soluble in water. Again, innovative process design could minimize this problem.

Figure 21.—An Example of a Microbial Aromatic Hydroxylation



SOURCE Office of Technology Assessment

Polysaccharide biopolymers

Biopolymers are naturally occurring macromolecules that include proteins, nucleic acids, and polysaccharides. The discussion here will emphasize the polysaccharide biopolymers and the opportunities for the application of biotechnology to their synthesis,

The major commercially available water-soluble biopolymers are ***used as viscosifiers (thickening*** agents), flocculating agents (aggregating agents), and lubricants. Currently, there is a trend toward increased use of synthetic polymers as flocculating agents in place of natural products (70). This

trend, however, is sensitive to the availability and cost of the petroleum feedstocks required for manufacturing synthetic polymers, and biopoly - mers will be important if the price of oil rises.

The market for viscosifiers is several times larger than that for flocculants. The currently used viscosifiers, unlike flocculants, are biopoly - mers obtained from plants, especially seaweed. Although these sources are not dependent on petroleum feedstocks, the use of plants as biopoly - mer sources has several disadvantages, including labor costs associated with extraction and purification, limited availability of the sources, and a supply that can be affected by adverse climatic conditions. Microorganisms could provide a constant and reliable supply of these products (72). Microbial biopolymers produced in controlled processes would not suffer from the problems associated with climate, disease, and other factors that normally affect plant products. Furthermore, microbial biopolymers have relatively uniform chemical and physical properties.

These attributes have led to increasing interest in the production of biopolymers that could be used in novel applications as well as in place of commercial biopolymers that are not now microbially produced. For example, alginate is a commercially important gum obtained from kelp. The markets for alginates demand different specific characteristics such as solution viscosities and gelling qualities. The alginates obtained from kelp can vary in composition, so they must be separated, evaluated, and categorized for the different markets. Alginate is also synthesized by ***Azotobacter vinelandii*** **(41).** Because the composition of the microbial alginate can be closely controlled by bio - processing conditions, separate microbial bioprocesses could be developed to produce specific alginates with uniform chemical and physical properties. Another microbial biopolymer that has been developed by the Kelco Co. and has recently become commercially available is gellan. Gellan is a ***Pseudomonas*** polysaccharide that can be used as a solidifying agent for laboratory media or food products (44).

While a number of microbial biopolymers are being developed for commercial applications as gums, plastics, and other products, only xanthan gum, dextran, polytran, and gellan are currently being produced commercially (44,72). In terms of production volume, xanthan gum is the major microbial polysaccharide. At present, over 20,000 tons of xanthan gum are manufactured in the United States annually (30). Xanthan gum's primary use is as a food additive for stabilizing liquid suspensions and for gelling soft foods, such as ice creams and cheese spreads. More recently, it has been used in the new clear-gel toothpastes. The use of xanthan gum in enhanced oil recovery is still experimental, but this appears to be the largest potential market for this product. * Xanthan gum is commercially produced in an aerobic batch bioprocess using the bacterium ***Xanthomonas campestris (30),***

The importance of polysaccharide biopolymers is likely to grow. For example, the microbial poly - saccharide pullulan is synthesized by ***Aureobasidium pullulans*** from a number of substrates (42). Pulhdan has potential applications in the cosmetic industry, in diet foods, and, more importantly, as a biodegradable plastic to be used in place of wraps and plastic containers. Plastic wraps and containers are now made from petroleum-based plastics which are not biodegradable and are dependent on nonrenewable feedstocks. The Japanese are already at the pilot plant stage for the microbial production of pullulan, and pullulan has the potential to develop into a significant market.

Another microbial biopolymer that is expected to be available commercially in 1983 is emulsan. A potent hydrocarbon emulsifier, emulsan is expected to gain widespread use in cleaning oil-contaminated vessels, oil spill management, and enhanced oil recovery (4). * * Like many biologically produced polymers, emulsan exhibits a specificity that generally is not observed in chemically synthesized materials; the emulsifying activity of emulsan is substrate-specific, acting only on hydrocarbons that have both aliphatic and cyclic components. Emulsan was originally discovered by researchers in Israel (34,59,60,61,75).

● Enhanced oil recovery is discussed in ***Chapter*** 8: *Environmental* ***Applications.***

*** ● *See*** discussion in ***Chapter 8****: Environmental Applications*

Emulsan was awarded patents in the United States in 1982, and Petrofirm, USA, a subsidiary of Petroleum Fermentations, N. V,, headquartered in Netherlands Antilles, is developing emulsan as a commercial product (4). To date, the development has been confined to strain improvement through mutation and selection techniques. Because of the complexity surrounding the microbial biopolymer, the feasibility of applying rDNA technology for strain improvement is uncertain.

IJseful microbial biopolymers can extend beyond the polysaccharides. For example, polyhy - droxybutyrate (PHB), a metabolic product of the bacterium Alcaligenes eutrophus, has potential commercial applications as a biodegradable thermoplastic that could be used as a surgical material. The unique electrical properties of PHB are also useful in other specialty markets (8). ICI (U. K.) soon will market a PHB product known as Biopol®, made with a bioprocess using glucose as a feedstock. ICI does not know yet what Biopol ” first markets will be. PHB has-properties similar to polypropylene but costs substantially more. Its edge is its biodegradability, and ICI believes that its customers will pay the higher price for this quality (63).

There are several inherent problems in using bacteria to produce polysaccharides (30). There are probably at least 100 enzymatic steps important in the production of these biopolymers, very few if any of urhich have been identified. Therefore, it is much more likely that classical genetic selection techniques will be more useful than rDNA techniques initially for improving the characteristics of the compounds. Before it is possible to predict the role that rDNA technology will play in microbial biopolymer production, the producing micro-organism will have to be characterized genetically and physiologically. It will also be important to have an understanding of the complex biochemical pathways for the production of the biopolymer and its regulation. Most biotechnology advances will only appear several years into the future, if at all.

More immediate improvements in the production of microbial biopolymers might be realized by the development of novel bioreactor designs. The polysaccharides have very large molecular weights and are viscous, two characteristics that preclude the use of most standard bioreactors. One way to generate a large quantity of polysac - charides is to maintain live cells in an immobilized cell bioreactor. The cells cannot be microencapsulated, because the product is too large to be washed away. Therefore, they need to be attached to a solid surface by a procedure that does not damage the cells. Another critical research area is improved product recovery from the broth. Current methods for the recovery of xan - than gum, for example, often result in preparations that contain water-insoluble solids such as nonviable cells and residual medium constituents, For xanthan gums to be used in enhanced oil recovery, it is important to have a product free of cells and other fine particulate because the fluid must be able to flow through porous rocks.

Another area of research is the identification of thermophilic polysaccharide producers. Devel - opment of a thermophilic micro-organism could result in substantial gains in productivity and lower process costs due to energy conservation. Screening thermophiles for polysaccharide production is an active area of research (74). To date, no thermophilic xanthan gum producers have been identified. Thermophilic ***Bacillus*** and ***Clos - tridium*** bacteria are being screened for the production of polymers that would be useful as bio - surfactants (74).

Commercial aspects of biotechnology in specialty chemicals

Some specialty chemicals are currently made using bioprocesses, most notably amino acids and enzymes. The amino acid markets are dominated by Japanese companies, especially Ajinomoto and Kyowa Hakko, whereas the enzyme markets are dominated by two European firms, Notro and Gist-

Brocades. Japan also leads the world in the biotechnological production of fatty acids, a relatively new process.

Most of the opportunities for the use of biotechnology in the production of specialty chemicals are still in planning or early development stages. Many potential bioprocesses would replace chemical processes, necessitating a large investment in new plants. Thus, the potential of a process using biotechnology must justify this investment. On the other hand, enzymes that could withstand high temperatures and pressures could be used to replace existing chemical steps without having to change the basic chemical process. Enzymes with these characteristics are beginning to be studied.

U.S. companies are beginning to enter some specialty chemical markets with biotechnology products. Corn sweetener companies are planning to market enzymes that they have produced for in-house use for some time. Other established firms, such as W. R. Grace, are entering markets with biotechnologically derived specialty chemicals. Several U.S. NBFs, such as Genex, Genentech, Chiron, Amgen, Ingene, Enzo, and Industrial Genetics, have stated interests in specialty chemical markets. Although 20 percent of U.S. companies using biotechnology say they are working in the specialty chemicals field, their interests are not well known and most of their research is highly proprietary.

Priorities for future research

The most glaring lack of knowledge for the successful application of biotechnology to the production of specialty chemicals is in the identification and characterization of microaganisms that perform particular chemical conversions. often when industrially useful reactions in microorganisms have been identified, the micro-organism is so poorly understood that the application of new biotechnology is not possible. There are many opportunities for the specialty chemical industry to expand and improve its production capabilities using biotechnology, but before it can take advantage of these opportunities, useful micro-organisms, especially those that function at high temperature and pressure, will have to be screened and identified.

For the specialty chemical industry to take full advantage of biotechnology, sharing of information between industrial chemists and biologists is needed. The sharing of information has to proceed beyond identification of specific steps in a chemical synthesis that are inherently expensive to discussion of the total process for the manufacture of a specialty chemical. Broad discussion could suggest a bioconversion that uses a less expensive starting material and that would replace several steps of the chemical process. Processes for the manufacture of many specialty chemicals could ultimately combine chemical and biological steps, thereby resulting in more economic and energy-efficient manufacturing.

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