Biocatalysis and Biomimetics

In Biocatalysis and Biomimetics; Burrington, J., et al.;
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Biocatalysis and Biomimetics

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Preface

BIOCATALYSIS AND BIOMIMETICS presents a cross section of recent advances in catalytic science and biotechnology. The chapters that follow will serve to illustrate how many of the key challenges in biotechnology can only be addressed by bringing together traditionally "separate" disciplines within chemistry and biology.

A subtitle for this volume might read, "A View of Biotechnology Through the Eyes of a Catalysis Scientist". As such it is not intended as an all-encompassing view of chemical opportunities for biotechnology, nor will it cover the recombinant-DNA or monoclonal antibody methods normally associated with modern biotechnology. Many such reviews are already available. Rather, it is meant to focus on emerging enabling technologies at the interfaces of catalysis and biology that will provide new opportunities for the chemicals industries. Key aspects to be presented within this major theme of catalysis and biotechnology are biomimetics and hybrid catalysts, biocatalytic applications of computers and expert systems, enzyme solid-state structure and immobilization, enzyme structure–activity relationships, and the use of enzymes under novel conditions.

The editors have been fortunate to have assembled contributions from world-class authorities in this field. We sincerely thank all who participated to make this not only a successful symposium, but an important contribution to the literature as well. We also thank the Biotechnology Secretariat for coordination of the symposium cluster on Biocatalysis and Biomimetics and the sponsoring Divisions of Petroleum Chemistry, Inc., and of Industrial and Engineering Chemistry, Inc. We greatly appreciate the contributions from E. I. du Pont de Nemours and Company, Monsanto Company, Eastman Kodak Company and B.P. America. The gracious support and understanding of our wives, Cindy Burrington and Molly Clark, and that of our families is most warmly acknowledged.

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Introduction

Biotechnology: Chemistry Is at the Heart of It

by Mary L. Good

Biotechnology is the study and application of genetic engineering techniques to improve the value of such things as crops, livestock, and pharmaceuticals. It is the adaptation of living systems to produce higher value-added products and processes. Planned are applications in medicine and agriculture that were considered impossible only 15 years ago. They include:

1. genetically altered bacteria for producing medicinals
2. alfalfa engineered to produce valuable proteins
3. livestock as factories for a human blood-clotting protein
4. cleanup of industrial wastes by bacteria
5. bacteria engineered as diagnostic tools

Chemistry is at the core of this fantastic new science of biotechnology. Jacqueline K. Barton of Columbia University has said, "You may notice that neither the words 'chemical' nor 'molecular' is incorporated into 'biotechnology', but the heart of what I think is exciting about this area is indeed chemical." Biotechnology depends on our ability to manipulate chemical structure in biological systems on the molecular level. We are learning how the structures of large biological molecules determine their functions. By altering chemical structure, we are learning how to design molecular properties with increasing precision and predictability.

We have also begun to understand that how well we manipulate these chemical structures may ultimately determine our nation's status in the global economy.

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Several pharmaceutical and diagnostic products produced using recombinant DNA techniques are already on the market and more are on the way. It has been estimated that by the year 2000, the biotechnology market could reach $100 billion. The predictions are that high value-added specialty products are likely to appear first, followed by production of chemicals and feedstocks, and later, biomass conversion.

The U.S. chemical industry has been quick to recognize the potential of this new technology and invest in it. Howard E. Simmons of DuPont tells us that his company spends one-third of its billion-dollar research budget for biotechnology-related research. In the company's Central Research & Development Department, for instance, half of the scientists working on biotechnology programs are chemists. Dow, Monsanto, American Cyanamid, and Eastman Kodak are a few of the other companies following suit.

The U.S. lead in most areas of biotechnology research has been challenged by West Germany, Great Britain, Switzerland, Sweden, and France, but most aggressively by Japan. In the United States, although large companies are forming or acquiring their own biotechnology divisions, the biotechnology development effort is led by small start-up firms that derive early technology from government-sponsored research at the universities. In Japan, large firms such as brewing companies with extensive bioprocess experience lead in biotechnology R&D. Their time scale for strategic planning is 10–15 years, a long-term view compared with the usual 3–5-year planning period in the United States. The National Science Foundation has concluded that the quality of biotechnology research performed in Japan matches that done in the West.

A study commissioned by the U.S. Department of Commerce predicts that Japan will offer the United States stiff competition in biosensors for the medical market. According to the study, Japan already is competitive in cell culture technology; is now fourth in the world and gaining in protein engineering; and is scaling up its lagging effort in recombinant DNA technology.

What is the role of the American Chemical Society? We have the capabilities and resources, and in terms of our charter an *obligation*, to make a positive contribution toward solving our nation's economic problems and to lead the chemical profession into new areas. Biotechnology will be one of the significant areas for the employment of chemists in the future and will greatly affect our standard of living. The establishment of this Biotechnology Secretariat, which presented its first technical program two years ago, is one proof of ACS' commitment. We have also:

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1. presented a Select Conference on Advances in Biotechnology and Materials Science to many of those who make and interpret national science policy.

2. considered launching a new journal in biotechnology.

3. developed *CA Selects* in several areas of biotechnology.

4. considered a definition for a new certified B.S. degree with an emphasis on biochemistry.

These initiatives, because they have broken new ground, presented a challenge to the Society, one that we have met. Quite frankly, a driving force for change has been the recognition that many trained as chemists are already working in biotechnology fields. As a result, new program initiatives in biotechnology will go through more easily. All we have to do is dream them up.

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Chapter 1

Biocatalysis and Biomimetics

New Options for Chemistry

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As a dominant technology in the chemicals industries, catalysis provides an important long-term commercial target for biotechnology. While enzymes represent the most efficient catalytic systems known, their impact on the chemicals industry relative to traditional catalysts is still small. Developments at the interface of biology and chemistry will be key to overcoming the major barriers to broad industrial application of enzyme catalysis.

The Impact of Catalysis

The overwhelmingly dominant technology in chemicals-related industries is catalysis. Commercial catalytic processes account for over half of all fuels production and for 60% of the 135 MM metric tons of organic chemicals produced annually in the U.S. In fact 20% of the nation's GNP can be attributed to catalytic processes (1). Thus, from a technical standpoint, advances in the chemicals industry are strongly linked to advances in catalysis.

A key property of catalytic processes is selectivity. Catalysis has revolutionized process chemistry by replacement of wasteful, unselective (i.e. multiple-product-forming) reactions with efficient, selective (i.e. one-product-dominating) ones. For example, selective catalytic methanol carbonylation (practiced by BP, BASF Monsanto, Eastman) has to a large extent substituted unselective non-catalytic n-butane oxidation (Celanese, and Union Carbide processes).

Control of reactivity by catalysis provides the capability to shift to lower cost feedstocks. In the twentieth century, advances in catalysis have allowed the substitution of acetylene with olefins and subsequently with synthesis gas as primary feedstocks. For example, production of acrylic acid, traditionally produced by the Reppe process from acetylene and CO, has now been replaced by catalytic oxidation of propylene. The emergence of paraffins, the hydrocarbon feedstock of the future, will depend on development of catalysts for selective alkane C-H activation (2).

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Catalysis has also had a major impact on the functional and specialty chemicals businesses, providing lower cost routes and higher performance materials than would have otherwise been possible. Major examples are from polymer syntheses including Ziegler-Natta, anionic, cationic polymerization processes, for formation of polyolefins, ABS resins, polyesters and other synthetic materials. Future materials areas include high temperature composites, electronic materials and conducting organics.

The role of catalysis in the petroleum industry has been equally revolutionary. Metal-supported systems (e.g. of Topsoe and Shell) for catalytic reforming, hydrodesulfurization and hydrodenitrification, alkylation catalysts and shape selective systems (e.g. zeolites and pillared clays) for catalytic cracking (FCC) and production of gasoline from methanol (Mobil MTG) all represent significant technical and commercial achievements.

Thus, the impact of new technologies on the chemicals industries can be assessed to a large extent by its impact on the commercial practice of catalysis.

Nature's Catalysts

At the molecular level, nature's catalysts, the enzymes (isolated or as microbial systems) provide tremendous rate increases over the corresponding uncatalyzed reactions and virtually quantitative selectivity. The capability to both improve selectivity to a single product and utilize alternate feedstocks is well documented (3-4).

A major selectivity advantage of biological catalysts over traditional systems includes the ability to form single products (chemical selectivity) as well as single optical isomers (stereoselectivity). Specific examples where biological routes are preferred commercially include fermentative processes for the amino acids monosodium glutamate (MSG), lysine, aspartic acid, citric acid and phenylalanine (5). Many other chemicals have also been produced by fermentative processes (6).

Enzymes also provide a potential means to utilize alternate feedstocks which cannot be selectively activated by conventional catalysts, or to improve selectivity over traditional systems. For example, the hydroxylase enzymes convert paraffins to alcohols with virtually 100% selectivity, a reaction which has no analogue in traditional catalysis (7). The Nitto acrylonitrile to acrylamide process is an example of how biocatalysis can improve selectivity over traditional catalysis (8-10).

Coaxing Nature to Work Harder

The exciting technical opportunities in biocatalysis are tempered by the major barriers to commercialization which still exist. Most notably, these include low stability of an expensive catalyst, and the high separation and capital costs associated with low concentrations of reactants and products.

These significant barriers are largely responsible for the lack of substantial commercial impact of enzyme and microbial catalysts on the chemicals-related industries. High fructose corn syrup and amino acids by fermentation remain the only significant chemicals produced by biotechnology and represent only a tiny fraction of industrial chemicals output.

Prospects

Advances in the life sciences over the past 30 years have produced the new enabling technologies normally associated with modern biotechnology, namely genetic engineering and monoclonal antibody methods. While these will surely be key to many new products, particularly in health care and agricultural markets, these methods alone are not likely to permit a major impact on the chemicals industries.

Along with the development of these enabling biological methods, catalysis and other technologies (such as computer modeling and expert systems), which already have a major influence on the chemicals industries, have also made major technical advances. The integration of biotechnology with these more traditional areas represents a means to capture the technical advances across a number of chemicals-related disciplines.

For example, the importance of the complimentary roles of surface, bulk and interfacial structure in heterogeneous catalysis (11-13), also indicates the need to address these issues in explaining and predicting catalytic behavior of enzyme systems as well.

From this cross-disciplinary approach a number of new enabling technologies are now emerging. The combination of biological and chemical catalysts to produce hybrid catalysis or "biomimetic" systems has shown some promise in capturing the high selectivity of enzymes with the favorable processing characteristics of traditional catalysts (see D. Clark, R. H. Fish, R. DiCosimo contributions, this publication). The growing body of information on structure/function relationships of enzymes is being accelerated by advanced crystallographic methods and the use of computer modeling and expert systems (see G. A. Petsko, G. Klopman, W.A. Goddard contributions, this publication). New methods of enzymology, including novel immobilization and reaction conditions (see T. A. Hatton, N. Herron, R. Sipehia contributions, this publication) have demonstrated the potential to improve catalytic performance.

These advances can collectively be viewed as the growing field of biocatalysis and biomimetics. Along with the biotechnical developments, these provide another option for exploiting the potential of enzyme catalysis in the chemicals industry. The following chapters present representative examples of current advances in this emerging field.

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Chapter 2

Biomedical Science and Technology

The Interdisciplinary Challenge

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Interdisciplinary bridges across chemistry, chemical engineering science and medicine are compelling challenges to progress basic insights and solutions for major problems in the life sciences and technologies. An analysis of the molecular spectrum identifies some trends, basic phenomena and skills involved, and examples of basic focal points for the joining of existing but largely segregated skills.

Interdisciplinary Research - Vogue or Reality?

"Interdisciplinary" is a word used frequently these days. Perhaps some of us think -or even hope- that it is a vogue that will pass. It is a fact, however, that our institutions, communications and activities in the sciences have become increasingly subdivided into "specialties". As researchers, we generally keep drilling deep in our own specialty parcels, with but occasional excursions to adjacent fields. Our institutions (organizational units, departments, course structures, journals, funding organizations, "peer" groups, etc.) are neatly subdivided, categorized, organized. All these factors, by interdependence and mutual perpetuation, mold the character of education, attitudes, professional language, and the opportunities as well as constraints in the choice, type and execution of research, career, the structure of knowledge, etc.

Perhaps the word "interdisciplinary" will go away. But the concept will not, because society needs it. There is a growing awareness that real problems in our society

NOTE: This chapter was presented as the plenary address of the symposium, Impact of Surface and Interfacial Structure on Enzyme Activity.

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are not optimally served by the convenience (and comforts) of orderly compartmentation. We recall (1) a 1979 meeting in Princeton, attended by leading scientists from diverse fields, including Nobel Laureates, in which the keynote speaker, Ashly Montagu, observed that

"The present degree of specialization has resulted in a condition of intellectual isolationism. This manifests itself in .... inability to see ... relevance of content, methods and models of other ... disciplines, existence of an inbred ... philosophy ... largely irrelevant to ... problems of modern life."

Ten years before that, an observation, outspoken but humorously true, was that of E. Haskell (2) (Connecticut Review, p. 84, April, 1969):

"The multiversity has now become the modern tower of Babel, each of whose departmental languages grows ever less understandable to members of all other departments."

The evolving field of biomedical science and technology appears to be one that recognizes from the outset that it must deal with "real" and "relevant" problems of health, life, and, literally, with survival; that there is little time or value to engage in moral debate over what is "pure", basic, or applied research. Louis Pasteur, whom we could well call the father of biomedical science and technology, stated nearly a century ago "There is only one science: A basic science and its application."

As we address biomedical problems, as Pasteur did, we surely deal with "real" problems, "relevant" to society, and we are forced thereby to look to the skills of all the disciplines. It is significant that many of these most important pieces of knowledge to be embraced and used exist already at a quite basic level of the sciences, not buried in great depths of specialized sophistication.

In that spirit, let us examine some very basic science concerning the nature and behavior of the molecules that are the actors in all of life. From whatever we touch to the mechanisms of life itself, we deal with molecules and molecular processes. Figure 1 displays molecules, molecular complexes, and molecular systems of our world, in the order of their molecular weights (M.W.). From left to right we have molecular entities of ever increasing sizes and complexities.

Molecular Entities, Phenomena, Skills

Moving from simple gases, through inorganic and organic compounds, somewhere we get to peptides, oligomers and to polymers, macromolecules like proteins or polysaccharides; we move on to complexes or interacting systems of molecules, like neurons or cell organelles; to systems of systems, like cells, organisms, organs, people, and societies, each an associative, dynamic molecular system of ever increasing order. Mathematically and actually,

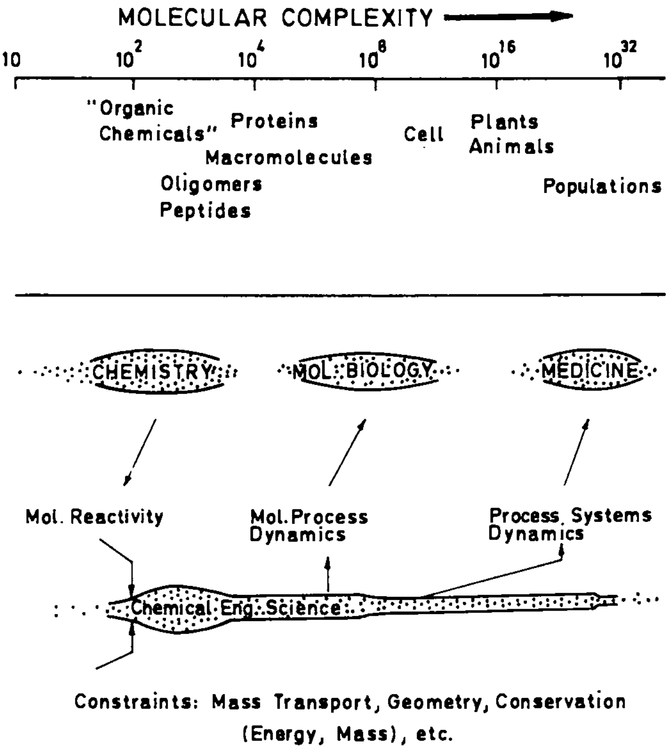

Figure 1. Molecules and Molecular Systems. Their size (molecular weights); increasing complexity; the relevant, major 'location' of activity of traditional disciplines.

diversity increases even more rapidly than molecular weight. One of us, as a molecular system, would correspond to a M.W. of about 10^{28}, and obviously, no two of us will have the same "molecular weight". Of course, we have yet ignored the immense diversity of possible variants in chemical composition and (e,g, isomeric) structure, within any given molecular weight.

Under this spectrum, I have indicated where the center of gravity, or focus of interest has been of a few of our named disciplines.

Starting on the left (Figure 1), chemistry has first dealt with the realm of chemical (atomic) composition and structure of molecules, and focused on reactivity of molecules (or its parts), progressing from simple toward more complex structures. At the other end of the spectrum, medicine has always dealt with the vast biological complexity of people.

Early in this century, a few chemical and medical scholars of a few universities in Austria-Hungary and southern Germany crossed the constraints of disciplinary boundaries. It led to the beginnings of biochemistry (3), to at least four Nobel Prizes (4), and to vitamins. It was a decisive step toward bridging the vacuum between the right and the left of our spectrum, by applying the chemical skills of composition and structure to various biological entities of relatively small to fair molecular complexity, with a growing and, finally, a major emphasis on the complexity of proteins.

Molecular biology is certainly a prominent outgrowth of that trend and discipline, with it's center of gravity heavily in the realm of structural detail of proteins, and the significance and relationship of that sophistication to informational phenomena (recognition, immune response, replication, genetics, etc).

We face the challenge of increasingly bridging the large remaining gaps. We might say that we know many pieces, but we know too little of how they effect the whole. What are some of the phenomena that are fundamental to a successful march across this bridge?

As we progress from left to right, we move from problems of composition, structure and reactivity of *compounds* to those of the dynamics of interacting *processes* and *process systems ;* generally we move from individual entities to systems, and these become directed to very specific *missions* to be achieved, with mandatory *efficiency*, and within the constraints of many physical and chemical parameters acting upon the process system as a whole.

During the last few decades, the study of processing systems, their constraints, behavior and performance for specific missions has centered largely in the compartments of chemical engineering science. It is important to discard any image of 100 foot towers that may arise at the word "engineering". Fortunately, the fundamentals of chemical engineering science are equally applicable to chemical process systems of any dimension.

Chemical Engineering and Bio-Medicine

For example, chemical engineering science has evolved much basic knowledge, qualitative and quantitative guidelines for the understanding and design of porous, heterogeneous catalysts for chemical processes. They deal with criteria that define how large the catalytic materials or regions may be to support a desired conversion rate; how that relationship depends on the concentration of the molecules undergoing conversion; how the size and geometry of catalytic regions can effectively accomplish a sequence of reactions, inhibit it, or side-track it (5,6).

All these considerations are basic and equally applicable to the broad variety of biochemical reaction systems. We can use them to determine the optimal size of catalyst particles in a giant petroleum cracking process; but they have interdisciplinary, i.e. universal applicability to any molecular process systems (7) including the biochemical transformation processes at the dimensions of organs, cells, organelles, and smaller molecular units.

By way of an example illustrated in Figure 2, "chemical engineering" criteria can provide relationships between the maximum allowable dimensions of the intracellular enzymatic reaction systems, or the minimum concentrations of metabolic intermediates they are to process, required to achieve certain desired magnitudes of turnover numbers (6b). At the time of this publication, applying chemical engineering science useful in the chemical process industry to cellular processes was an excursion with a very small audience, in spite of the universal applicability of its criteria. Only occasionally, the biochemist has applied the concepts, often after independent efforts; for example, Nevo and Rikmenspoel showed that such an "engineering" criterion links the optimal (and actual) physical length of the tail of spermatozoa firmly to the concentration of the ATP generated at its base (6c).

Today, chemical engineering science is logically able to apply its skills to phenomena of the molecular processing *systems* characteristic of bio-medicine and to their "modelling" to develop rigorous and quantitative foundations. The basic need for the bridges in our spectrum of knowledge (Figure 1) to span the territory of chemical systems, promises fruitful results from an increasing partnership between the sciences of medicine, chemical engineering and chemistry.

Quite in line with the above quoted comment by Haskell, such partnership will mainly require courage, effort and patience to overcome a divisive language barrier. It is, I believe, the only barrier that stands in the way to a meeting of minds, and to an explosive acceleration towards major insights and revelations.

The detailed interaction and dynamics of several molecular entities and parameters in an entire process *system*., is of crucial importance throughout biology and medicine. It is well illustrated by the battle of an army of macrophage, seeking, meeting and annihilating invading pathogens. A recent study of my chemical engineering and medical colleagues (8) is another example of the