Review Article

APPLICATION OF BIOCATALYST IN CHEMICAL ENGINEERING

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ABSTRACT

The general features of biocatalyst that led to their widespread use in chemical engineering industry are highlighted as well as the details of their impact on selected processes. Biocatalyst offer the basis of many of these technological solutions provided efficient and balanced co operations between industry and academia are further developed.

Introduction to Biocatalysis

Over the last 20 years, many reservations with respect to biocatalysis have been voiced, contending that: (i) enzymes only feature limited substrate specificity; (ii) there is only limited availability of enzymes; (iii) only a limited number of enzymes exist; (iv) protein catalyst stability is limited; (v) enzyme reactions are saddled with limited space–time yield; and (vi) enzymes require complicated co substrates such as cofactors[1] Biocatalysis is one of the main pillars of applied biotechnology, defined by the European Federation of Biotechnology as the "integration of natural sciences and engineering sciences in order to achieve the application of organisms, cells, parts thereof and molecular analogs for products and services", and according to EuropaBio, 2003, "White Biotechnology is the application of Nature's toolset to industrial production". Both definitions have in common that biotechnology, and thus biocatalysis, are looked at as interdisciplinary sciences [2] .

Biocatalysis: Past, Present

1. Past of biocatalysis

One of the oldest examples for the application of biocatalysis at an industrial scale is the production of acetic acid from ethanol (known since 1815) with an immobilized Acetobacter strain. It is remarkable that nearly 200 years ago a process was established using an immobilised biocatalyst (here attached to beech wood shavings). Another important biotransformation established more
than 70 years ago is the production of vitamin C (sorbitesorbose oxidation)[3] .

2. The Present State of Biocatalysis

Biocatalysis has a large impact in the chemical world. The enzyme market alone is a $1 billion global business. Traditionally, microbial and enzymatic processing has been used to convert biologically-derived (or renewable) feedstocks. However, they are increasingly being used with materials derived from fossil fuels. Uses are as divergent as chiral enzymatic transformations within an organic synthesis for a drug or for microbial desulfurization of diesel fuels.

Since pharmaceutical manufacturers are among the major customers of fine chemical manufacturers, the synthetic organic chemical industry will be impacted and transformed by the revolution in biocatalysts. Examples include production of precursors for Glaxo Wellcome's HIV drug, Ziagen, and DSM's Fine Chemicals production, including intermediates for aspartame, amoxicillin, and a variety of classical pharmaceuticals, e.g., diltiazem and captopril, formed by the revolution in biocatalysts. Examples include production of precursors for Glaxo Wellcome's HIV drug, Ziagen, and DSM's Fine Chemicals production, including intermediates for aspartame, amoxicillin, and a variety of classical pharmaceuticals, e.g., diltiazem and captopril. Many other examples of enzymatic routes to chemicals are listed in Table (1). The application or use noted in the table demonstrates the wide use of biocatalysts. One also needs to note the modest use of biocatalysts within certain industrial sectors such as commodity or intermediate chemicals production. In addition, the use, and potential use, of biocatalysts, whole cells, and phytochemicals have caused the appearance of a whole set of new companies dealing with biotransformation. Many, many companies are based on the paradigm of a nursery of small research-based start-up companies feeding into larger established firms [4].

Biocatalysis Cycle

Biocatalytic processes differ from conventional chemical processes, owing mainly to enzyme kinetics, protein stability under technical conditions and catalyst features that derive from their role in the cell's physiology, such as growth, induction of enzyme activity or the use of metabolic pathways for multistep reactions. In the laboratory, new biocatalytic reactions often originate with new enzyme activities. For applications, a more rational approach is needed. The starting point will usually be a product, which can perhaps be produced by one of several possible biocatalytic reactions that convert suitable substrates to the desired product. Fig (2) illustrates the development of such biocatalytic processes. One or more biocatalysts must be identified or develop, a process must be set up, and the resulting bioconversion will ultimately have to be economically feasible. The development of such a process requires the input of many different specialists. Limiting aspects of biocatalytic process

are improved in an iterative manner, gradually leading to an efficient industrial process. In setting priorities for improvements at each process step, a detailed understanding of the costs and improvement potential of each of the partial steps in a process is vital.

The economic feasibility of a biocatalytic process depends on several factors Fig (2) depending on the type of biocatalyst to be used, specific reactor and hardware configurations are needed . In addition, biocatalytic processes are typically highly heterogeneous. In theory, this would necessitate specific designs of the catalyst – hardware interface. But in practice, a limited number of hardware designs is found today in large industrial processes, allowing the application of biocatalysts based on only a few concepts[5].

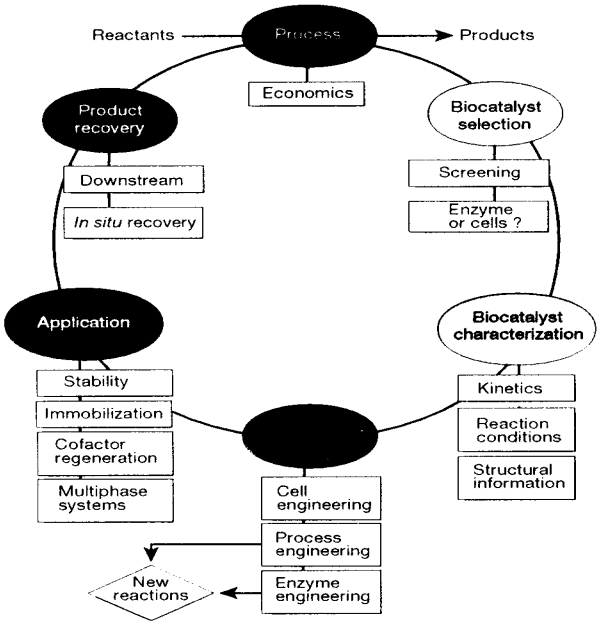

Fig 2 Biocatalyst cycle

WHY BIOCATALYSTS NEED TO BE ENGINEERED

Three of the six examples in Table (2) involve unnatural substrates. The ability of the enzymes to accept these synthetic intermediates is due to good luck, not evolutionary pressure in nature. One reason to engineer enzymes is to better accommodate unnatural substrates. Enzymes involved in the uptake of nutrients (lipases, proteases) often have broad substrate specificity because they must act on a broad range of possible food sources. The broad substrate range of many enzymes is critical to their usefulness because it allows chemists to use enzymes to catalyze reactions on their synthetic intermediates, and not just on biochemical intermediates. Another common reason to engineer enzymes is to increase their stability under the reaction conditions. Reaction conditions can differ dramatically from those present in a cell. Reaction conditions may involve high temperatures, extremes of pH, high substrate and product concentrations, oxidants, and organic cosolvents. Sometimes an enzyme must tolerate these conditions for only a few minutes or hours, but in a continuous manufacturing process, an enzyme may need to tolerate them for months. A third reason to engineer enzymes and metabolic pathways is to create new reactions or new biochemical pathways. For example, Ran and Frost expanded the substrate range of an aldolase and thus created a new metabolic pathway to make shikimic acid for an influenza drug synthesis[6] .

Comparison of Biocatalysis with other Kinds of Catalysis

Many chemical reactions can occur spontaneously; others require to be catalyzed to proceed at a significant rate. Catalysts are molecules that reduce the magnitude of the energy barrier required to be overcame for a substance to be converted chemically into another[4]. Thermodynamically, the magnitude of this energy barrier can be conveniently expressed in terms of the free-energy change. As depicted in Fig. (3), catalysts reduce the magnitude of this barrier by virtue of its interaction with the substrate to form an activated transition complex that delivers the product and frees the catalyst. The catalyst is not consumed or altered during the reaction so, in principle, it can be used indefinitely to convert the substrate into product; in practice, and however, this is limited by the stability of the catalyst, that is, its capacity to retain its active structure through time at the conditions of reaction.

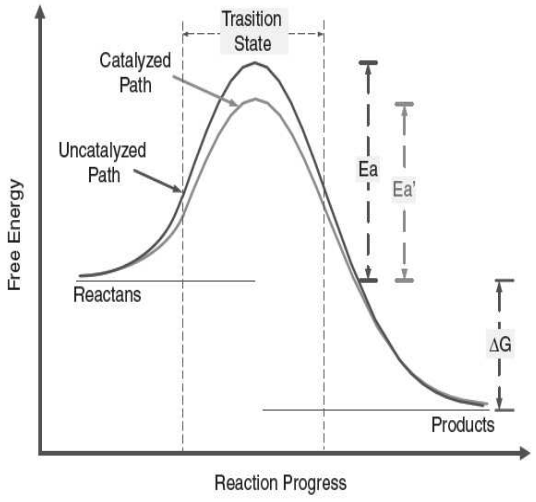

Fig. 3 Mechanism of catalysis. Ea and Ea_ are the energies of activation of the uncatalyzed and catalyzed reaction. ΔG is the free energy change of the reaction.

Enzymes have been naturally tailored to perform under physiological conditions. However, biocatalysis refers to the use of enzymes as process catalysts under artificial conditions (in vitro), so that a major challenge in biocatalysis is to transform these physiological catalysts into process catalysts able to perform under the usually tough reaction conditions of an industrial process. Enzyme catalysts

(biocatalysts), as any catalyst, act by reducing the energy barrier of the biochemical reactions, without being altered as a consequence of the reaction they promote [7].

Advantages and Disadvantages of Biocatalysts

Advantages of Biocatalysts[1,4]

- Enzymes are very efficient catalysts.
- Enzymes are environmentally acceptable.
- Enzymes act under mild conditions.
- Enzymes are compatible with each other.
- Enzymes are not restricted to their natural role.
- Enzymes can catalyze a broad spectrum of reactions.

Disadvantages of Biocatalysts [1,4]

- Enzymes are provided by nature in only one enantiomeric form.
- Enzymes require narrow operation parameters.
- Enzymes display their highest catalytic activity in water.
- Enzymes are bound to their natural cofactors.
- Enzymes are prone to inhibition phenomena.

Industrial Example of Biocatalysis

1. High-Fructose Corn Syrup: 11 Million Tons per Year

The isomerization of glucose to fructose, catalyzed by the enzyme xylose isomerase, is by far the largest-scale biocatalytic process. Already known for several decades, this process was scaled up when fructose demand soared in the 1970s. The reason was a combined increase in sugar prices and a customer preference shift to low-calorie foods (fructose is three times as sweet as sucrose, giving consumers more sweetness for fewer calories). The process uses a 95% glucose syrup feed, which is highly viscous and requires relatively high temperatures (55–65 ºC). The isomerization equilibrium gives roughly a 50:50 glucose/fructose ratio. To maximize the space-time yield, the actual product ratio produced is typically 58:42. The product is then concentrated to a 55:45 glucose/fructose ratio, which has the same sweetness weight equivalent (dextrose equivalent, or DE) as sucrose. This is the so-called high-fructose corn syrup (HFCS), which is ubiquitous in to days processed foods. The key to the successful scale-up was the immobilization of the enzyme, which increased stability and reduced the enzyme costs to an acceptable level. The isomerization step is typically carried out in a parallel series of packed-bed reactors, where the enzyme is immobilized on silica or inert cellulose carriers Figure(4). A ton of immobilized xylose isomerase can catalyze the production of 5000 tons of HFCS. Current research is concentrating on developing a more thermostable enzyme variant which would reach the 55:45 ratio directly in the reactor column[8].

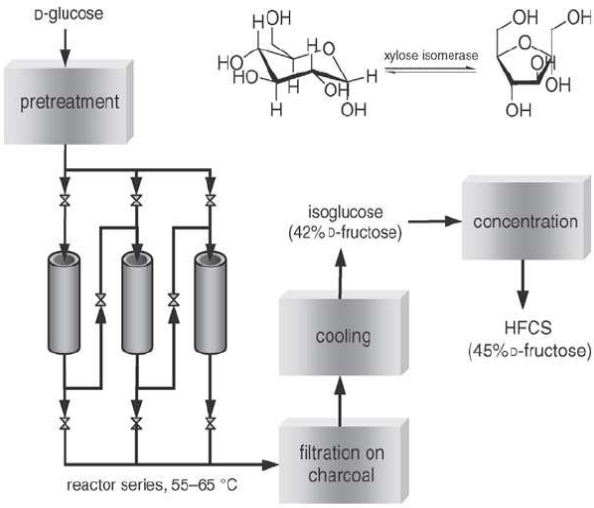

Figure 4 Simplified block diagram of the HFCS process.

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