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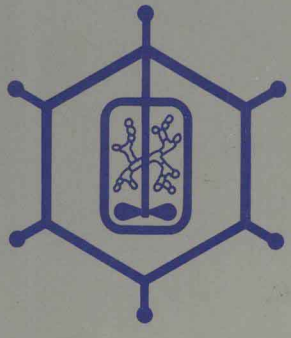
BIOCATALYSTS IN ORGANIC SYNTHESES



EDITED BY

J. TRAMPER
H.C. VAN DER PLAS
P. LINKO

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BIOCATALYSTS IN ORGANIC SYNTHESES

PROCEEDINGS OF AN INTERNATIONAL SYMPOSIUM ORGANIZED UNDER AUSPICES OF THE WORKING PARTY ON IMMOBILIZED BIOCATALYSTS OF THE EUROPEAN FEDERATION OF BIOTECHNOLOGY

Noordwijkerhout, The Netherlands, 14–17 April 1985

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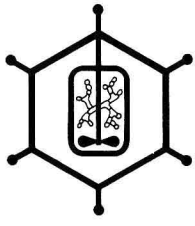

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FOREWORD

The idea for the symposium "Biocatalysts in Organic Syntheses" originated within the Working Party on Applied Biocatalysis (formerly on "Immobilized Biocatalysts") of the "European Federation of Biotechnology" as the outcome of a suggestion made by Dr. Jan Konecny. The Working Party felt unanimously that the existing gap between organic chemists and biotechnologists needs to be bridged in order to realize the full potential of biocatalysts in organic syntheses, and that efforts in this direction would be an appropriate challenge to this group of experts.

It was then thought that by organizing an international symposium to discuss the areas where organic chemistry and biotechnology overlap, would bring the experts of both disciplines together to identify common targets of general industrial interest. On the basis of the discussions held within the Working Party, and of an inquiry addressed to a selected group of industrial companies in Europe and elsewhere, the organizing committee decided on the following scientific programme of five sessions:

I Enzymes as catalysts: potential and limitations.
II Central problems and trends in organic syntheses.
III What can biotechnology do for the chemical industry/research?
IV Broadening the scope of applications of biocatalysts.
V Specific/future applications.

All sessions were based on invited one hour lectures with ample time provided for discussions. The speakers were asked to give a general overview of their specific area of expertise, together with selected, more-detailed examples and future prospects.

This book contains most of the papers presented at the symposium. In the editors' view, the following conclusions could be drawn:

- The introduction of a biocatalytic step in a synthetic route is usually only feasible if the total number of steps in the integral process can be substantially reduced.
- The screening of microorganisms is still the best way to obtain the most promising strain/enzyme for a specific task.
- It is generally difficult for a biocatalytic process to compete with an established chemical process involving depreciated and optimized equipment and established know-how.

- In order to realize the full potential of the application of biocatalysts in organic syntheses, the exploitation of one of their most salient features, regio- and stereo-specificity, is essential.
- Racemic mixtures should preferentially be resolved at an early stage of the integral process, either by classical chemical means or enzymatically.
- The integration both of chemical and biotechnological steps in a synthetic process can often be of great advantage.
- The immobilization of the biocatalyst involved may make a more efficient use of the biocatalyst possible.
- Biocatalysis can often be successfully carried out in a carefully selected organic solvent system, thus significantly broadening the scope of biocatalytic applications.
- Target products should be carefully chosen by learning from the failures and successes of the past.
- Although the potential of biotechnology in organic syntheses is promising, one should not expect many revolutionary applications in the near future as a result of modern protein engineering and (semi)synthetic enzymes.

The Working Party, the Organizing Committee, and a number of invited guests evaluated the outcome of the symposium immediately after its closing, and reached the following conclusions:

- The goals set for the symposium were realized. The great interest for the symposium was indicated by the fact that a large number of applications had to be turned down owing to overbooking. A total of 225 participants attended the symposium, with about one-half of them organic chemists and one-half biotechnologists, showing both the interest of the biotechnologist to apply enzymic methods in organic reactions and of the organic chemist to look for enzymes as tools in organic methodology. It should also be mentioned that an exceptionally large proportion of the participants represented industry.
- The penetration of biocatalysis in organic syntheses will be slow but definite.

The editors,
June 1985

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SESSION I

ENZYMES AS CATALYSTS: POTENTIAL AND LIMITATIONS

Chairman: U. von Stockar

Co-chairman: E. J. Vandamme

J. Tramper, H.C. van der Plas and P. Linko (Eds.), *Biocatalysts in Organic Syntheses.*
Proceedings of an International Symposium held at Noordwijkerhout,
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THE SCOPE OF BIOCATALYSTS IN ORGANIC CHEMICAL PROCESSING

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Novo Industri A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark

The diversity and complexity of organic molecules in nature is a remarkable reflection of the power of enzymes as catalysts for organic chemical reactions. Almost any conceivable structural type of organic compounds has been constructed in nature thanks to the enzymes; yet these often highly intricate and complex structures have been generated under the mildest conditions of temperature and pH. Even the careful regulation of complex biosynthetic networks in living matter rely, to a large extent, on inherent control mechanisms of the enzymes which, clearly, are the most powerful and efficient catalysts known, besides being most subtle and delicate (7).

TABLE 1
Advantages of enzymes as catalysts in organic chemical processing.

- **Enzymes catalyze a wide variety of organic reactions**
- **Enzymes are very efficient catalysts**
- **Enzymes are enantioselective**
- **Enzymes are regioselective**
- **Enzymes are chirale catalysts**
- **Enzymes are effective under mild conditions**
- **Enzymes are selective in regard to their substrates**
- **Enzymes can be prepared by fermentation**

In view of the lavish use of the enzymes made by nature for synthesis of organic compounds and the extraordinary efficiency of these catalysts it would seem obvious to make use of these catalysts also in preparative organic chemistry. In fact, the properties of the enzymes would, indeed, fulfil many requirements of the preparative organic chemist, cf. Table 1. Most important, the regio- and enantioselectivity of the enzymes, besides their substrate specificity, can be invaluable to the organic chemist like the ability of the enzymes to function under the mildest conditions compatible with even the most fragile organic molecules. Moreover, one would expect the price of these extraordinary catalysts to be rather modest due to the possibility of preparing the enzymes by microbial fermentation.

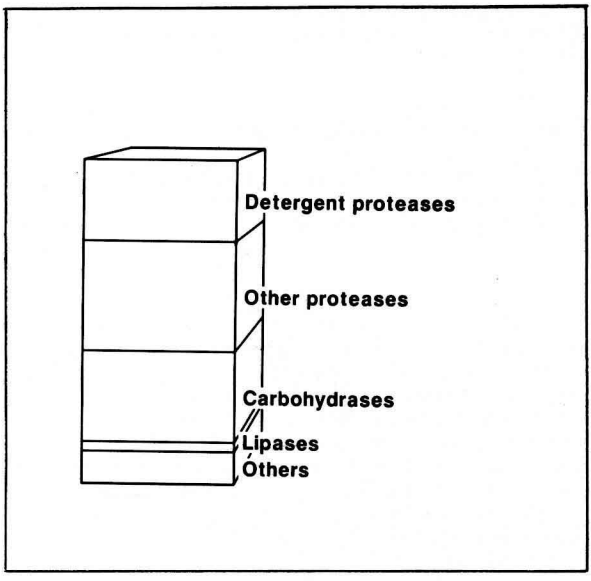
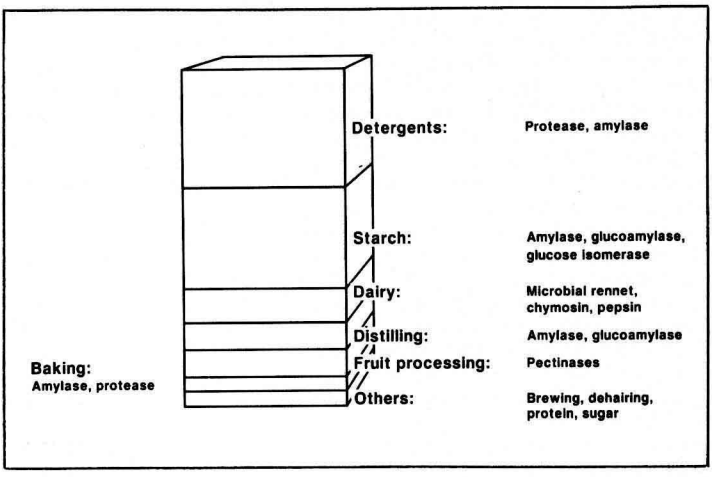


Fig. 1.
Distribution of industrial enzymes by volume.

The, potentially, exceedingly wide scope of the enzymes in preparative organic chemistry thus easily envisioned is in striking contrast to the present situation concerning the use actually made of the enzymes in industrial chemical processing. From Figures 1 and 2, which summarize the distribution of the current enzyme production on enzyme types and application areas, it is thus apparent that the proteases, carbohydrases and lipases account for more than 95% of the total production of technical enzymes which still find essentially all their applications within the traditional areas listed in Figure 2 (2). It is noteworthy that only about a dozen of the several thousand enzymes known is actually produced in sizeable quantities and that the production of enzymes for the organic chemical industry is still too small to be visible in the overall picture.

One may well wonder whether this deep discrepancy between promise and practice is a reflection of some kind of inherent disadvantage of the enzymes in regard to organic chemical processing or whether other circumstances have limited their use within this area, so far. Some possible disadvantages of the enzymes as organic catalysts may, in fact, readily be mentioned, cf. Table 2. Many enzymes are thus readily inactivated under extreme conditions as, for example, at high temperatures or under strong acidic or basic conditions. Likewise, many enzymes are readily inactivated by exposure to reactive organic compounds of well-established use in preparative organic chemistry, and they are usually thought to function optimally in aqueous solutions only, rather than in organic solvents often needed to solubilize the majority of organic chemicals of interest. Moreover, enzymes are often inhibited by their substrates and their products at concentrations far below those usually considered necessary for an economical process.

Fig. 2.
Distribution of enzyme sales on industries.



Although clearly valid for the large majority of known enzymes these possible disadvantages of the enzymes can by no means be considered as owing to some inevitable, inherent property of the enzymes. Rather, experience shows that enzymes active under the most unusual conditions may in fact be found, if desired. As a respond to a requirement of the starch industry enzyme producers have, for example, provided vast quantities of carbohydrases

TABLE 2
Disadvantages of enzymes as catalysts in organic chemical processing.

- **Enzymes are inactivated by many organic reagents, under strong acidic or basic conditions, and at high temperatures**
- **Enzymes exhibit a limited activity in most organic solvents**
- **Enzymes are subject to product- and substrate inhibition**
- **Enzymes may provoke allergic reactions**

active in water at temperatures close to 100 °C. Likewise, as a respond to a requirement of the detergent industry the enzyme producers have furnished proteases active in water at temperatures as high as 90 °C under strongly alkaline conditions never before thought to be compatible with enzyme activity. Work on lipases, which catalyze hydrolytic cleavage of triglycerides and transacylations as visualized in Figure 3, has, similarly, revealed that these remarkable enzymes function under highly unusual conditions, for example as suspensions in their pure substrates or even in organic solvents like hexane at temperatures as high as 100 °C (9). Since, in addition, dramatic improvements of the stability and reactivity of enzymes can often be achieved by chemical modification, immobilization, and other techniques, and since, for example, the potentials of enzyme engineering and the occurrence of microbial life under the most extreme conditions hold great promise in regard to the development of highly resistant enzymes, there is clearly little justification for the view that enzymes are fragile catalysts with properties which will necessarily seriously limit their use in preparative organic chemistry. Rather, it is quite likely that, given sufficient efforts, enzymes can, in most instances, be found and made to function in a satisfactory manner in accordance with the imagination of even the most daring organic chemist.

However attractive and versatile the enzymes are as organic catalysts it should, of course, not be forgotten that, for many years, synthetic organic chemistry has undergone an intense development. For decades, new synthetic methods, reagents and catalysts have been developed at an amazing rate. The very limited use made of enzymes in organic chemical processing may, therefore, be a mere reflection of the existence of suitable, classical chemical approaches or other techniques for preparation of organic chemicals of industrial interest.

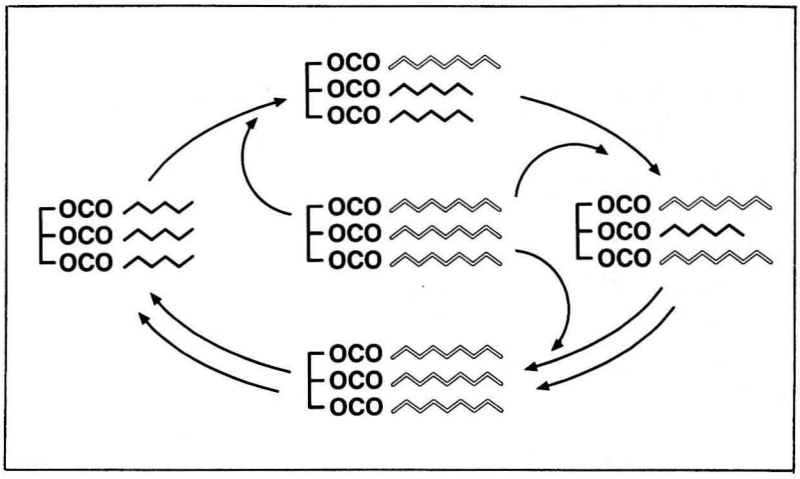


Fig. 3. Lipase catalyzed transacylation of triglycerides.

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