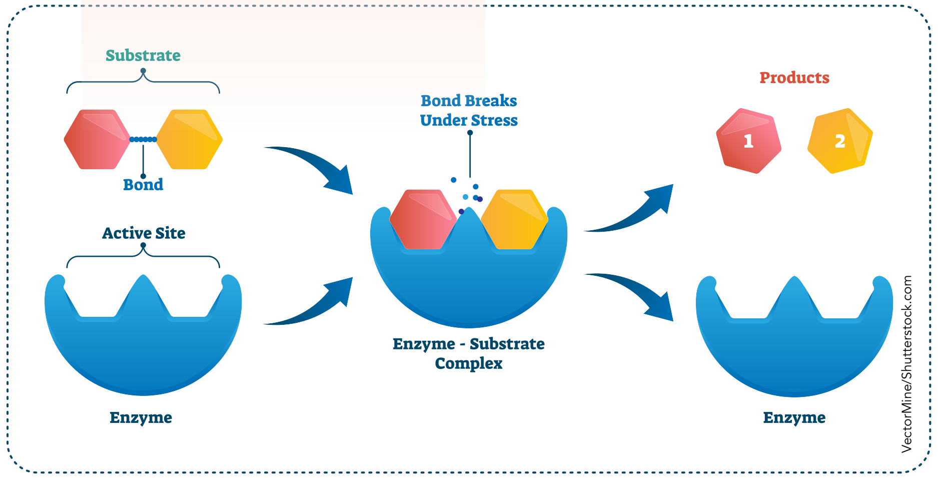
Efficient, low-energy chemical synthesis using enzymes for biocatalysis

Chemical synthesis and manufacture can be an incredibly energy-intensive and polluting industry. This is because many reactions require very high temperatures and/or extreme conditions, along with the use of many toxic reagents for the right chemistry to take place. There is an ever-increasing interest in finding milder reactions and alternative catalysts to produce many of the chemicals we need for pharmaceuticals, healthcare, and other speciality applications. Professor Thomas Moody, Vice President of Technology Development and Commercialisation at Almac Sciences, UK, has been developing new reaction alternatives, including the use of biocatalysts, to achieve highly selective reaction outcomes under more environmentally friendly conditions.

Chemical manufacture and its associated reactions can be highly complex processes. Simply put, chemical manufacture involves the breakage or formation of chemical bonds in a specific order. This designed order of reactions should be performed to produce the desired product with minimal side products, to maximise efficiency and to lower the burden on the purification step(s).

The ideal reaction needs to be cost-effective, robust, selective, and have an excellent product yield. Taking into account other factors, such as the safety risks, availability of raw materials, reactor design and availability, product quality, etc, this can be a challenging balancing act. This is what makes designing new reactions and routes to chemical products so difficult. For the chemical manufacturing industry there is another challenge – scalability. Most industrial-scale synthesis processes (for the pharmaceutical industry, for example) need to be capable of producing tens to hundreds of kilograms of product per day at commercial scale. If a reaction works efficiently on a small scale, that does not necessarily mean the same process can simply be repeated on a larger scale. This is where process chemists come into play, as new route design or engineering is required.



AN ENVIRONMENTAL CHALLENGE

For a reaction to work or to obtain the desired selectivity, chemists often turn to higher or sub-zero temperatures, use very specialised equipment, or use a toxic metal catalyst. However, this has many obvious associated environmental problems. High temperatures or sub-zero cooling require the use of large amounts of energy, and toxic metal catalysts make for highly hazardous waste that needs extensive treatment before it can be disposed of.

Despite the perceived complexity of chemistry in a laboratory environment, nature has fine-tuned its chemical armoury as an expert in crafting highly complex chemical natural products with outstanding selectivity, even at room temperature.

ENZYMES: NATURE'S BIOCATALYSTS

The secret to nature's mastery of chemical reactions are enzymes. Enzymes are nature's 'biocatalysts'; they reduce the energetic barriers for chemical reactions and speed up their rates to form the exact products that are needed. This is possible due to enzymes' excellent selectivity – often down to their own very complex chemical structures – and from the design of their 'active sites'. These are designed only to bind chemical species with specific properties on which they can then perform their chemical magic to make very specific products.

Chemical manufacture can be highly complex and often requires extreme conditions that have associated environmental costs.

Professor Thomas Moody, Vice President of Technology Development and Commercialisation at Almac Sciences, based in Craigavon, UK, has been exploring how biocatalysts can be harnessed to help out with chemical synthesis in the lab for over 20 years. Since joining Almac in 2001, Moody has sought ways to add value to the business through new approaches and solutions. He quickly realised the value of biocatalysis for the company, and began working on developing the necessary technology, bringing together a multi-disciplinary scientific and international team. Moody has published over 100 papers in the area of biocatalysis, from enzyme discovery, enzyme development, chemical and biochemical process development, to enzyme engineering.

Working with enzymes on an industrial scale can be prohibitively expensive.

A recent article published by Moody and his team focused on a particular oxidation reaction to create sulfoxides from sulfides. The paper demonstrated that enzymes can offer a more environmentally friendly synthetic route to these types of transformations. The team also explored how the use of other oxidative and reductive enzymes (tailored with specific reagents and solvents) help reduce waste and eliminate harsh chemical reagents from the synthetic process.

ORGANIC SYNTHESIS

In a new study published in 2021, the team describes the use of a well-established enzyme known as *Candida antarctica lipase B*, otherwise known as CALB. This enzyme has become the workhorse enzyme for many (hydrolase) reactions in the pharmaceutical industry because it is functionally active and able to catalyse reactions in both water and organic solvent environments. Many enzymes can easily be denatured by changes in the environment, with the result that they can no longer catalyse reactions; for example, the natural biological environment of enzymes is water, so their function can be impaired by many solvents (or organic contaminates). CALB is a very robust catalyst in this respect.

Another challenge in working with enzymes on an industrial scale is they can be difficult to 'extract' and reuse to help lower the cost of production. However, CALB has already been modified and attached to a solid support which can facilitate easy removal and reuse, and has been successful in reactions at production scale. To date, most of the reactions of CALB has been to catalyse hydrolysis of bonds. Moody's work has shown CALB's ability to facilitate and be involved in oxidative reactions.

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By using ethyl acetate as solvent and reactant, the team minimised the number of chemical reagents and eliminated some dangerous chemical waste.

INDUSTRIAL APPLICABILITY

Moody and his team have demonstrated for the first time that CALB can be used to facilitate oxidation of sulfides to form sulfoxides. Sulfoxides are very important compounds found in many pharmaceutical products (eg, Omeprazole – a commonly used antacid).

The research team showcased the synthesis of multiple sulfoxides from a number of different starting materials by adding both the CALB enzyme and a peroxyacid precursor with success.

Moody and his team have another trick for improving the environmental impact of this new synthetic approach: to use ethyl acetate as both a solvent and the peroxyacid precursor simultaneously. Many organic solvents pose significant safety risks and health hazards, and often large quantities are required for reactions, producing a sizeable amount of chemical waste. By using the solvent as a reactant in the synthesis process, the number of chemical reagents can be minimised. Ethyl acetate is also relatively non-toxic, particularly in comparison to many other commonly used solvents. It also has a much lower boiling point which means it can be removed with relative ease.

Moody and his team have been able to show that enzymes can offer a more environmentally friendly synthetic route.

ENVIRONMENTAL AND SOCIETAL BENEFITS

Green chemistry is all about considering the health, environmental, and safety impact of the reagents used, as well as the overall 'atom efficiency' of a process. The atom efficiency is a measure of the mass of the desired compound as a proportion of the total mass of all the products/waste produced. A high atom efficiency equates to fewer unwanted side reactions, and excellent selectivity offered by biocatalysts is a good way of achieving this for chemical reactions.

Finding ways to make dual use of reagents and enzymes will help to continually improve the overall atom efficiency and minimise waste streams for processes. This team's discoveries add to the way we perform chemical reactions.

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Nearly 20 years on, Moody's work has seen biocatalysis evolve from a new, specialised technology to become a mainstream business specialism for Almac. As well as contributing to the company's own success, these developments increase Almac's contribution to wider society too. Chemical synthesis is a hugely important area in our lives as it provides us with many of the molecules we need for medicines, healthcare, and everyday materials. The environmental impact of the sector is significant and finding ways to improve it will have positive consequences for us all.

Behind the Research

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W: www.almacgroup.com/api-chemical-development/biocatalysis-solutions

Research Objectives

Developing new environmentally friendly approaches to traditional toxic and energy-intensive chemical synthesis and manufacture.

Detail

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Bio

Professor Thomas Shaw Moody is Vice President of Technology Development and Commercialisation at Almac Sciences and Arran Chemical company. He is responsible for driving new technology processes from conception to commercial scale-up across multi-disciplinary research applications, including biocatalysis, flow chemistry, radiochemistry, custom synthesis, and commercial manufacture. He has more than 20 years of extensive academic and industrial experience in the field of organic and bioorganic synthesis.

Collaborators

- Silvia Anselmi
- Siyu Liu
- Seong-Heun Kim
- Sarah M Barry
- Daniele Castagnolo

References

Anselmi, S, Liu, S, Kim, S, et al, (2021) A mild and chemoselective CALB biocatalysed synthesis of sulfoxides exploiting the dual role of AcOEt as solvent and reagent, *Organic and Biomolecular Chemistry*, 19, 156–161. doi.org/10.1039/d0ob01966f

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Personal Response

What do you think the next big developments in biocatalysis will be?

" Biocatalysis is now part of many organic synthesis labs. Chemists are using enzymes for many types of reactions because the catalysts are now available. The future will see more and more processes running with enzymes as they are extremely selective. The future will see cascades of enzymes and chemical reactions working in tandem, performing multiple reactions within one pot, resulting in more cost-effective processes that are sustainable. As flow chemistry matures and users want end-to-end solutions for their processes, enzymes will be immobilised and packed in beds so that flow chemistry can perform both chemical and biochemical processes in tandem. We will see cell factories in the future producing complex natural and unnatural products that will be used in new medicines and in new materials. The future will be exciting, and enzymes will be at the heart of the synthesis. It is time to give an enzyme reaction a go… "