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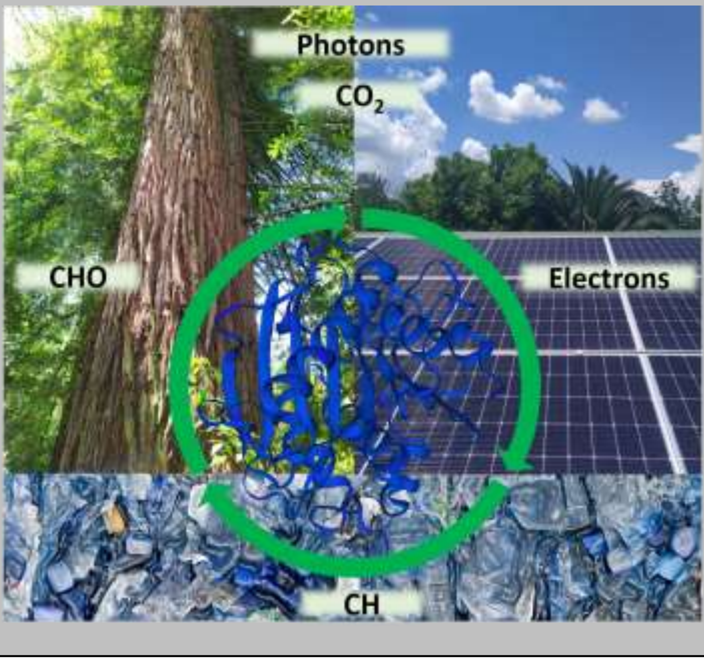
REVIEW

Green Chemistry, Biocatalysis and the Chemical Industry of the Future

Roger A. Sheldon*[a,b] and Dean Brady*[a]

Dedication



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Keywords: Decarbonization, Defossilization, Waste valorization, Circular economy, Biocatalysis.

Abstract: In the movement to decarbonize our economy and move away from fossil fuels we will need to harness the waste products of our activities, such as waste lignocellulose, methane and carbon dioxide. Our wastes need to be integrated into a circular economy where used products are recycled into a manufacturing carbon cycle. Key to this will be the recycling of plastics at the resin and monomer levels. Biotechnology is well suited to a future chemical industry that must adapt to widely distributed and diverse biological chemical feedstocks. Our increasing mastery of biotechnology is allowing us to develop enzymes and organisms that can synthesize a widening selection of desirable bulk chemicals, including plastics, at commercially viable productivities. Integration of bioreactors with electrochemical systems will permit new production opportunities with enhanced productivities and the advantage of using a low-carbon electricity from renewable and sustainable sources.

1. Introduction: The Transition to a Sustainable Economy

1.1. The Big Picture

The daunting global environmental problems - global warming, degradation of the natural habitat and its biodiversity - that we face can be summed up in one word: WASTE. This comprises waste in the atmosphere, that is greenhouse gas (GHG) emissions (mainly CO_2 but also methane, etc.) that are the root cause of climate change (global warming) and waste materials (e.g. plastics) that are polluting our natural habitat with disastrous consequences for flora and fauna.

The problem of waste has to be solved in the economy and (chemical) industry of the future by:

(i) recycling materials (e.g. plastics) in a circular bio-based economy and,
(ii) valorization of unavoidable (e.g. end-of-life) waste back to raw materials.

This involves not only the conversion of CO_2 to feedstocks or materials but also the valorization of other organic waste streams such as the lignocellulosic waste in agricultural and forestry residues, marine waste and food chain supply waste (FCSW).[1] Consequently, Industrialized societies are currently on the cusp of a global energy transition towards a sustainable economy based on sustainable energy and renewable resources in a circular bio-based economy. This will necessitate a decarbonization of the energy sector and a defossilization of the chemicals sector as depicted in Fig. 1.

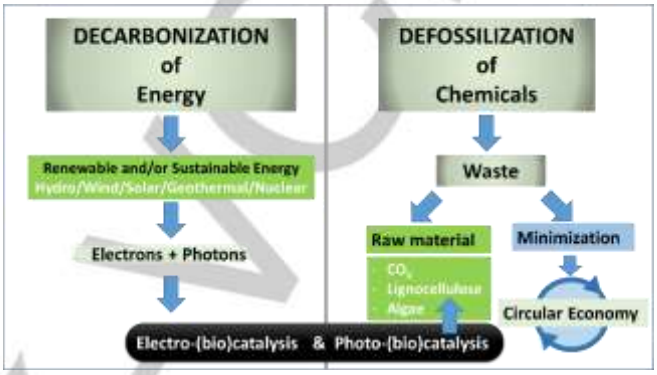

Figure 1. Decarbonization of energy and defossilization of chemicals

1.2 The decarbonisation of the energy sector

The industrial revolution, starting in the mid-18th century, was driven by the unbridled consumption of fossil resources, in particular the combustion of coal to drive the steam engine. It served humanity well for more than two centuries, enabling the growth of the global population to unimaginable proportions based on ever-increasing agricultural and industrial productivities. However, it is abundantly clear that this use of finite fossil resources is not sustainable, even in the relatively short term. Moreover, it has serious environmental consequences, such as anthropogenic climate change and the loss of biodiversity, while extraction of remaining fossil resources will become increasingly difficult and costly. The inevitable conclusion is that the global dependence on fossil fuels will have to be systematically reduced over the coming decades with the goal of completing this transition before the end of the century.

It is unlikely that renewable forms of energy - hydroelectric, wind, solar, geothermal – alone will be able to generate the huge and increasing amounts of energy needed to drive industrial economies.[2] Sustainable nuclear energy will be an important part of the energy mix that supersedes the burning of fossil fuels in highly industrialized countries such as the USA, China and the states of the EU. This will consist of fission of uranium in fast breeder reactors (FBRs) in the short to medium term and molten salt thorium reactors (MSTRs) in the longer term. For more details see the reviews of Brook *et al.*[3] and Pevec *et al.*[4] This will provide surplus, off-peak electricity which can fuel a Power-to-X industry in which liquid fuels and chemicals are produced by electrolytic processes in e-(bio)refineries.[5] This could involve, for example, production of hydrogen by electrolysis of water. This green hydrogen can be used as a transportation fuel, in heating applications or in the production of chemicals. Alternatively, electrolysis of a mixture of water and carbon dioxide can be used to produce a mixture of CO and H_2 (syn gas); the latter can be converted to hydrocarbons using the well-known Fischer-Tropsch process or to oxygenates by chemo-catalytic processes or fermentation.[6]

Yet another alternative is to utilize autotrophic microorganisms[7,8] or artificial autotrophs[9] for biological conversion of CO_2 and solar energy to chemicals in third generation (3G) autotrophic biorefineries.[10] In the chemical industry of the future waste will be treated as a resource in the drive towards a circular economy.

1.3. The role of biocatalysis

In this review we will be concerned with the role that biocatalysis can and will play in this transition of chemical manufacture to a carbon neutral bio-based economy based on the use of renewable sources of organic or inorganic carbon. Biocatalytic processes are green and sustainable:[11]

- Enzymes are derived from inexpensive, renewable resources with stable availability and costs in contrast with the fluctuating prices and availability of scarce precious metal catalysts.
- Enzymes are biodegradable, essentially non-toxic and non-hazardous
- Biocatalytic processes are generally conducted under mild conditions, in water at pressures and temperatures close to ambient. This enables relatively simple coupling biocatalytic steps in cost-effective, environmentally attractive cascade processes.[12]
- Biocatalytic processes generally avoid the need for functional group activation, protection and deprotection steps, thus affording step economic processes,[13] that generate less waste and are more cost-effective and sustainable than conventional processes.
- Enzymes usually exhibit superb chemo-, regio- and stereo-selectivities.

The burgeoning success of biocatalysis in the industrial production of chemicals over the last 2-3 decades was made possible by spectacular advances in molecular biology. Enzyme discovery traditionally involved the collection of field samples for preparation of microbial cultures in the laboratory. This was seriously hampered by the fact that 99% of microorganisms are ‘unculturable’ The development of bioinformatics in combination with Next Generation Sequencing (NGS) technologies[14] dramatically changed this situation by enabling bioprospecting for new enzymes encoded in the genes available in samples collected in the environment. In short, the number of available enzymes dramatically increased.

In parallel, totally new activities were evolved[15] and spectacular improvements in the essential attributes of both new and existing enzymes, namely, activity, stability, and selectivity, were enabled by advances in directed evolution that permits optimization through structural permutations.[16] In industrial processes enzymes need to function with substrates that are often structurally very different to their natural counterparts[17] and at substrate and product concentrations far exceeding those usually experienced in Nature. The classical approach for process optimization is to modify the process to fit the commercially available biocatalyst and end up with a nightmare process. In contrast, it is now possible, with the help of directed evolution, to modify the biocatalyst to fit the ideal process, with regard to parameters such as substrate and product concentration, catalyst and volumetric productivities (Space Time Yields), reaction time, yield and selectivity.[18] Performance metrics necessary for sustainable catalysis in the manufacture of commodity chemicals and biofuels were recently reviewed by Lange.[19]

A serious shortcoming of enzymes is, however, their water solubility, which means that they cannot easily be recovered and recycled. Hence, enzymes are generally used on a throw away basis, which is difficult to reconcile with a circular economy. This liability can, however, be addressed by developing effective methods for enzyme immobilization, on solid supports or retained by membranes in membrane bioreactors, to enable multiple recycling for a cost-effective, environmentally sound process.[20]

In addition to the above developments another important development that stimulates the application of biocatalysis in chemicals manufacture is the emergence of the bio-based circular economy in which chemicals are manufactured from renewable biomass. This generally involves the conversion of carbohydrate substrates in aqueous media, i.e. ideal conditions for biocatalysis.

2. Power to chemicals

2.1 The impact of decarbonization of energy on chemicals production

The goal of the states of the European Union is to decarbonize the energy sector over the next three decades. The important question is not if this is possible but how will it be achieved? The possibility of continuing with fossil resources is not an option. The primary source of energy will be green electricity generated by a mix of hydroelectric, wind, solar, renewable biomass and flexible nuclear technologies.[21,22]

Characteristic features of electricity, in contrast with those of fossil resources, are that it is generated within the confines of a power transmission grid and it has to be used immediately following its generation. Obviously it is not really compatible with the intermittency of demand for electricity. The most reliable solution to creating flexibility is chemical energy storage, i.e. storage and transport of excess renewable energy as molecules rather than electrons.[10, 23] This could be, for example, as hydrogen produced by electrolysis of water and subsequently to e.g. methanol, or “green oil”. Thus, a circular carbon economy could be, for example, based on the coupling of methanol combustion and CO_2 hydrogenation with hydrogen generation by water electrolysis.

2.2 Electricity to chemicals: Electrobiocatalysis in e-biorefineries

Renewable Power-to-X technologies (P2X) represent a platform for flexible utilization of excess green electricity to convert simple inorganic molecules - H_2O, CO_2, O_2 and N_2 – into H_2, syn gas (CO/H_2), H_2O_2, NH_3, methanol[24], or even methane and liquid hydrocarbon fuels such as jet fuel, and a plethora of downstream organic molecules in e-refineries.[25,26] This would also enable the integration of renewable power into other energy consuming sectors, such as transportation, in addition to chemicals manufacture. In this way, decarbonization of electricity generation contributes to reducing the carbon footprint of various industries.

One way forward with P2X is to exploit the synergy of microbial and electrochemical conversions in electro-biorefineries.[27] First generation (1G) biorefineries were based on energy-rich crops, e.g. bioethanol from sugar cane. However, the use of food crops is unsustainable and attention turned to non-edible feedstocks, such as waste lignocellulose (2G) and algal polysaccharides (3G) or organic waste streams in general.[28] There are other major differences with traditional refineries, e.g. biobased feedstocks usually have a substantial water content and its removal would involve high energy costs. Hence, aqueous process liquids will be the order of the day in e-biorefineries. Furthermore, bio-based feedstocks contain a variety of functional groups, in contrast to fossil feedstocks which consist simply of hydrocarbons.

2.2.1 Microbial electrochemical technology (MET)

Microbial electrochemical technology (MET) employs electro-active microorganisms to catalyze bioelectrochemical processes for valorization of carbon compounds. This is sub-divided into microbial electrosynthesis (MES) [29] and electrofermentation. The former is defined as the reduction of carbon dioxide to multicarbon compounds with electrons donated from an electrode. It is a potentially green and sustainable method to convert a mixture of CO_2 and H_2O to liquid biofuels and commodity chemicals that are currently produced from fossil resources in petrochemical refineries.[30] This is achieved by coupling green electricity generation to the carbon and energy metabolism of electroactive acetogenic and methanogenic microorganisms that mediate the reduction of CO_2 to, for example, acetic acid, ethanol, formate, methanol and methane.

MES mimics photosynthesis by utilizing green electricity for anodic generation of electrons and protons from water. The electrons and protons are transferred, via an external electrical circuit and proton exchange membrane (PEM), respectively, to the cathode, where they enable microorganisms, so-called electroautotrophs, to conduct the reduction of CO_2, derived from ambient air or industrial flue gases to valuable chemicals (see Fig. 2).

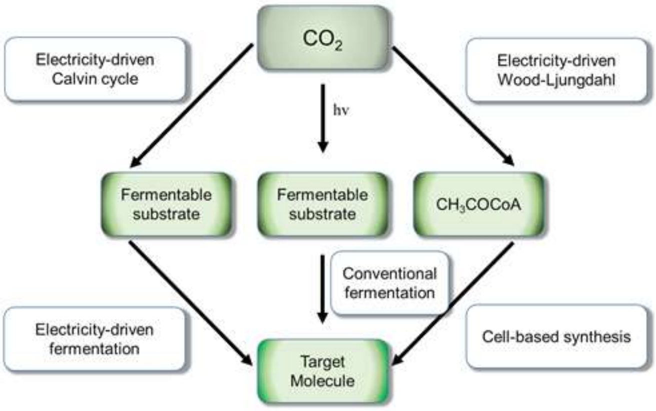

Figure 2. MET for valorization of CO_2.

Electron transfer can proceed (i) indirectly via H_2 generated at the cathode, (ii) via natural or synthetic redox mediators, such as quinones, or (iii) via extracellular electron uptake from the cathode to the microbial electron system in, for example, the phototrophic bacterium, *Rhodopseudomonas palustris*.[31] Microbial CO_2 fixation pathways in autotrophic microorganisms include the reductive pentose phosphate cycle, reductive tricarboxylic acid (TCA) cycle and the reductive acetylCoA pathway, also known as the Wood-Ljungdahl pathway.[32] Some microorganisms can utilize electrons directly from solid electron donors such as electrodes or from H_2 as a form of electron carrier during carbon fixation.[33]

A variety of chemicals have been produced from CO_2 by MES, including acetic acid, ethanol and glycerol, but to date only the production of bio-based acetic acid using acetogenic bacteria has been commercialized.[22,34] The initial products of CO_2 reduction can be further converted to downstream products by conventional fermentation or electrofermentation (EF) as shown in Fig.2). In EF the anode accepts electrons during fermentation (anodic EF) and electron transfer occurs between fermentative bacteria and heterotrophic electroactive bacteria.

In cathodic EF the cathode supplies electrons to bacteria to enable reduction of organic molecules and electron transfer is similar to that in MES (see Fig. 3) [35] It is instructive to compare EF to conventional fermentation. For example, production of butanol by fermentation of glucose requires 3 kg of glucose per kg of butanol whereas production by EF in an e-biorefinery requires only renewable electricity and CO_2.[36]

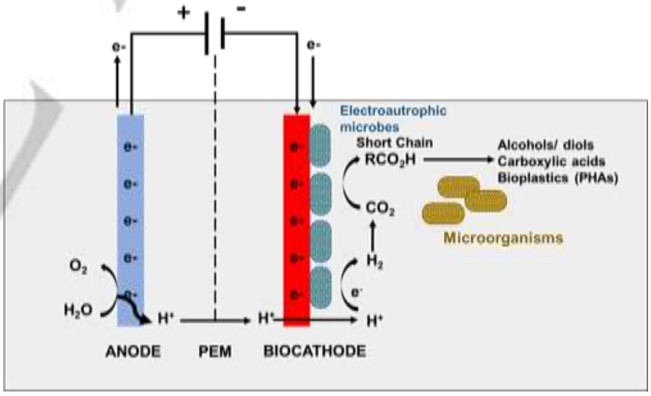

Figure 3. Production of chemicals by electrofermentation.

An interesting variation on this theme, particularly in the context of a circular bio-economy, is the direct production of bio-based polymers such as polyester plastics from CO_2 in an e-biorefinery. Polyhydroxyalkanoates (PHAs) are sustainable, biodegradable plastics that are accumulated in certain microorganisms as a source of energy and carbon.[37] They have similar physical properties to polyethylene (PE) and are, therefore, possible alternatives for PE in single use packaging applications. In MES systems CO_2 can be reduced to short chain fatty acids, such as acetic and butyric acids, which are further converted by PHA accumulating microorganisms (Fig. 3).

A potentially attractive alternative to conversion of CO_2 to platform chemicals using MET is to convert the CO_2 to syn gas (CO/H_2) by electrolytic reduction followed by Fischer-Tropsch chemocatalytic conversion to hydrocarbons or fermentation.[6]

Yet another, perhaps less glamorous, alternative is to combine a classical fermentation process with a separate electrochemical oxidation or reduction of the fermentation product. Electroorganic chemistry is currently experiencing veritable renaissance[38] and examples of using electroly reductions have been described e.g. in the electrochemic reduction of cis, cis-muconic acid to adipic acid.[39] Similarly, t combination of fermentative production of medium chain leng carboxylic acids with electrochemical Kolbe decarboxylati affords drop-in fuel additives.[40] The analogous phot decarboxylation of such fatty acids is discussed in Section 3.

Similarly, Turner combined Tempo-catalyz electrochemical oxidation of alcohols with enzymatic reducti amination of the resulting ketones to afford a mild a environmentally attractive route to chiral amines from alcoh (see Fig. 4) in an aqueous medium.[41]

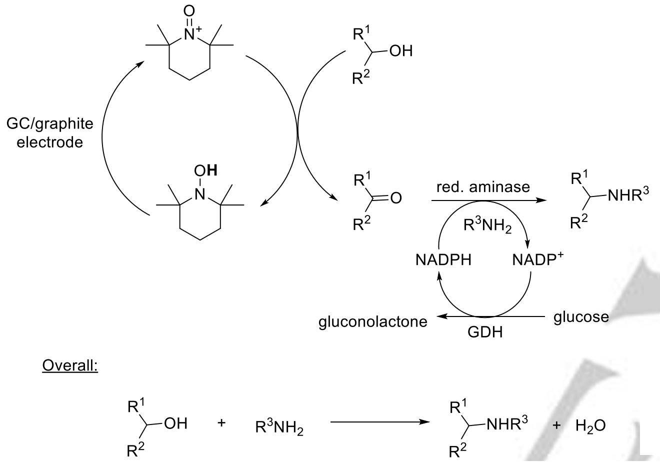

Figure 4. Electrobiocatalytic conversion of alcohols to amines

2.2.2 The scope of electrobiocatalysis

Electrobiocatalysis can involve either an electroactive microbial cell, as in the preceding examples, or an oxidoreductase. Electricity driven reactions with oxidoreductases, as isolated enzymes, involve the electrochemical regeneration of redox cofactors such as NAD/NADH as an alternative to conventional co-factor regeneration systems involving a second enzyme and a co-substrate, e.g. glucose/glucose dehydrogenase (GDH). Advances in metabolic and protein engineering can be mobilized to optimize such systems.

A broad range of oxidoreductases – both metalloenzymes and non-metalloenzymes – have been studied.[42] Common motifs of the former include heme and non-heme Fe, Cu, Mo and W. Examples of non-metalloenzymes include FMN of FAD and PQQ-dependent enzymes. Both oxygen and hydrogen peroxide have been used as the terminal oxidant. Enzymatic oxidations with hydrogen peroxide, catalyzed by peroxidases have the limitation that the enzymes are unstable towards oxidation by the hydrogen peroxide. An advantage of *in situ* electrolytic generation is that the concentration of hydrogen peroxide can be maintained at a low level. A pertinent example is the enzyme, chloroperoxidase (CPO) from *Caldariomyces fumago,* which catalyzes a variety of oxidations including enantioselective olefin epoxidation and sulfoxidations.[43] Inactivation of the CPO was reduced, but not fully prevented, by combining CPO catalyzed sulfoxidation with electrolytic *in situ* hydrogen peroxide generation.[44]

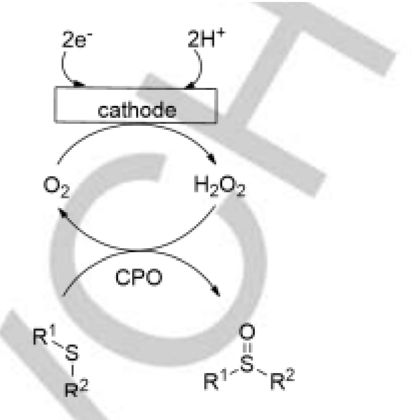

Figure 5. Electrobiocatalytic enantioselective sulfoxidation

In the 'electrochemical leaf' concept[45] a minimum of two enzymes operating in a cascade are entrapped in a nanoporous metal oxide, e.g. indium-tin oxide, electrode. One of these enzymes is ferredoxin-$NADP^+$ reductase (FNR), a small photosynthetic flavoenzyme that is ubiquitous *in vivo* where it channels electrons into biosynthesis.[46] The second enzyme is one of the hundreds of NADP(H)-dependent dehydrogenases.

This concept has the potential to be used to drive a multitude of reactions, including multi-enzyme cascade processes.[47,48] It was exploited, for example, in the one-pot, two electrode deracemization of chiral secondary alcohols (see Fig. 6).[49]

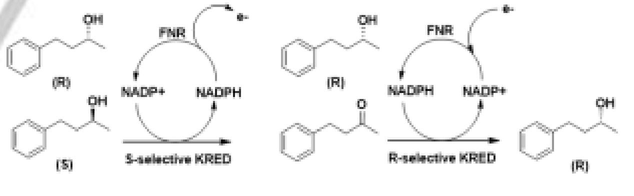

Figure.6 Electrobiocatalytic sec-alcohol deracemization

Looking into the future, one could envisage combining nitrogenase-catalyzed electrobiocatalytic nitrogen fixation with a hydrogenase for the industrial production of ammonia.[50] Taking this idea a step further leads to the production of (chiral) amines from N_2.[51]

It is clear that great strides forward are being made on the road to a future chemical industry based on the production of an array of commodity chemicals from green electricity, CO_2 and H_2O in e-biorefineries. However, several technological challenges still need to be addressed in order to meet this lofty goal.[32, 52]

These include:

- (bio)reactor design for scale-up,[5,53,54,55,56]
- metabolic engineering for optimization of pathways.
- optimization of downstream processing, e.g. using electrodialysis and electrobiocatalytic flow reactors[57]
- maximization of production rate for base chemicals and

broadening the scope to higher value chemicals and materials.

2.3 Light to chemicals: Photobiocatalysis

Solar energy can be converted to electricity, using solar panels, and the electricity used to, for example, convert CO_2 to chemicals. Alternatively, solar energy can be used directly to produce chemicals. Indeed, in parallel with the ascent of electrocatalysis the use of photocatalysis in organic synthesis has made enormous strides in the last decade.[58,59,60,61,62] It is perhaps not surprising, therefore, that the advantages of photocatalysis are being combined with those of biocatalysis, to exploit the power of photobiocatalysis which forms the subject of two excellent reviews.[63,64] Examples of photobiocatalysis in organic synthes are conveniently divided into three main categories:

2.3.1 Combining photochemocatalysis and biocatalytic conversions

The use of photochemistry to provide redox equivalents for a diverse group of reactions involving oxidoreductases (see Fig. 7) currently accounts for the lion's share of light-driven biocataly transformations.

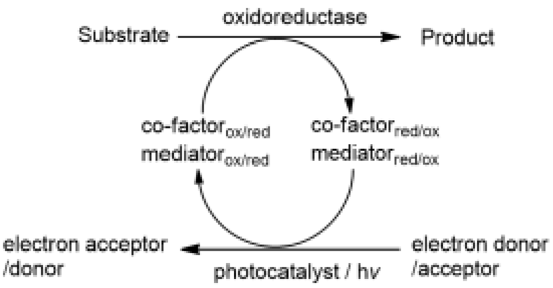

Figure 7. Photocatalytic generation of redox equivalents

These reactions involve coupling a photosensitizer with sacrificial electron donor, e.g. EDTA, triethanolamine, ascorb acid or even water, to (re)generate a reduced cofactor, e. NAD(P)H or $FMNH_2$, or oxidant (H_2O_2). Transfer of an electron a hydrogen atom from the electron donor to the light-excited sta of the photosensitizer is immediately followed by direct electr or hydride transfer, or indirectly via a mediator, to the oxidiz cofactor. This obviates the need for cofactor regeneration throu addition of a second substrate and/or enzyme. A wide range photosensitizers, including metal nanoparticles, organic dyes and semiconductors such as TiO_2, ZnS, and, more recently, graphene oxide[51] have been used for NAD(P)H generation coupled wi for example, formate dehydrogenase (FDH) catalyzed reduction of CO_2.The various possibilities for activating oxidoreductases by direct or indirect transfer of photo-induced electrons was recently reviewed by Park and coworkers.[65]

Fig.

Most cases involve a flavin as the cofactor, in conjunction with, for example, EDTA as sacrificial hydride donor.[66] However, the use of such sacrificial organic donors leads to the formation of unwanted waste and is not really green or sustainable. This can be avoided by coupling photo-induced water oxidation to flavin-based cofactor regeneration. A striking example of this approach is provided by the ene-reductase (ERED) catalyzed reduction of enones with $FMNH_2$ generation mediated by Au-TiO_2 or V-TiO_2 as photocatalysts and water as the ultimate hydride donor (Fig. 8).[67]

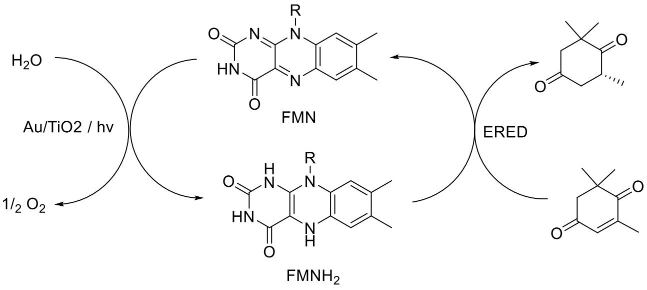

Figure 8. ERED catalyzed reduction with photocatalytic cofactor regeneration

Photochemocatalysis and biocatalysis have also been integrated in various photobiocatalytic cascade processes.[68,69]

2.3.2 Combining photobiocatalysis and biocatalytic conversions.

Photoautotrophic organisms, such as plants (eukaryotes) algae (eukaryotes) and cyanobacteria (prokaryotes), have developed intricate biological machinery to perform so-called oxygenic photosynthesis in which sunlight provides the energy to reduce CO_2 to a variety of carbon compounds, including glucose, with electrons being supplied by water as the electron donor, resulting in the co-production of dioxygen. It can be used for light-driven regeneration of cofactors such as NAD(P)H and $FMNH_2$ (Fig. 9).

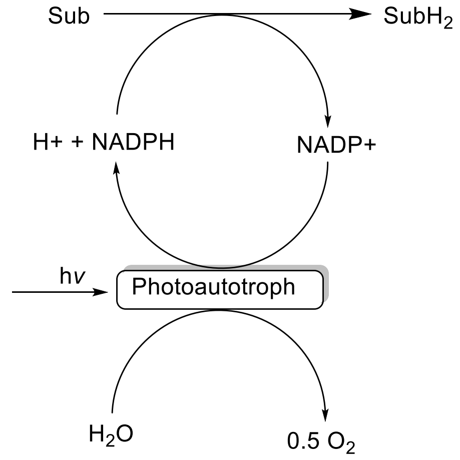

Figure 9. Coupling of NAD(P)H-dependent biotransformations with photoautotrophic organisms

In particular, the ability of cyanobacteria to use light as an energy source and CO_2 as a source of carbon has recently attracted much attention as a potential gateway to sustainable production of commodity chemicals.[70,71] Cyanobacteria are the only prokaryotes able to perform oxygenic photosynthesis. They were the primordial pioneers in CO_2 fixation and still account for ca. 20% of global recycling of CO_2.[72]

Whole-cell biocatalytic processes in industry are largely based on the use of heterotrophic bacteria to produce a variety of chemicals by fermentation of sugars, mostly glucose, as the carbon source (see section 3). Cyanobacteria, thanks to their photoautotrophic metabolism, require only sunlight, water, and minimal nutrients to enable the direct conversion of atmospheric CO_2 to a plethora of platform chemicals and biofuels.[73,74] Moreover, by combining the capacity of cyanobacteria for oxygenic CO_2 fixation with metabolic pathway engineering and synthetic biology, sequestered carbon can be redirected into new biochemical pathways that enable the synthesis of a variety of commodity chemicals from CO_2, water and visible light.[75,76,77,78,79] Several proof-of-concept studies, ranging from fine to bulk chemicals, have demonstrated their potential[76] and some reactions, e.g. ethanol production, have been scaled up to pilot plant level.[80]

The efficient photosynthesis machinery, high growth rate and quantum efficiency of cyanobacteria, compared with land plants, and the fact that they don't require arable land, makes them attractive targets for the industrial production of chemicals. Nonetheless, there are still many technical challenges to be overcome. Redesign and scale-up of the bioreactors is probably the biggest challenge. Other technical obstacles to be overcome are the difficult cultivation techniques and slow growth rates compared to the highly engineered bacteria currently used as production hosts for commodity chemicals and biofuels. Interestingly, the bio-based plastics, polyhydroxyalkanoates PHAs) can be produced directly from CO_2 using cyanobacteria but better productivities were observed using a hybrid mixotrophic system comprising an autotrophic cyanobacterium and a heterotrophic bacterium working synergistically.[81]

Cyanobacteria can also be used for the production of higher added value chemicals, e.g. pharmaceutical intermediates. For example, the light-driven enantioselective reduction of aryl methyl ketones catalyzed by whole cells of a wild-type cyanobacterium, *Synechococcus elongatus* PCC 7942, was already described by Nakamura and co-workers[82,83] in 2000. Yields of up to 90% and ee's of >99% were observed (see Fig. 10). Space time yields and product concentrations (50 mg/L) were low and would need to be increased by 2-3 orders of magnitude to be industrially viable. On the other hand, biocatalyst substrate ratios were considerably lower than with, for example, Baker's yeast.

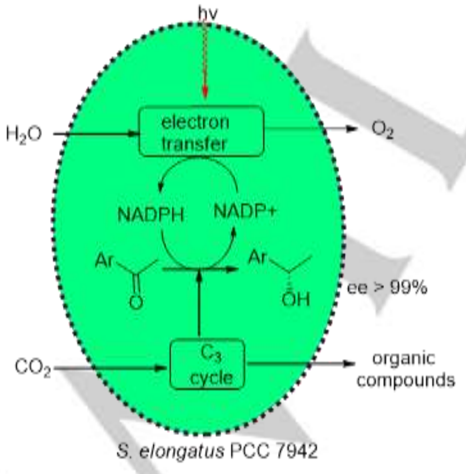

Figure 10. Cyanobacterium catalyzed enantioselective reducti of ketones

Artificial photosynthesis in recombinant heterotrophic bacteria

Heterotrophs such as *S. cerevisiae* and *E. coli,* have been optimized as hosts and production chassis for a broad range of commodity chemicals. Hence, one way forward in optimizing the performance of autotrophs such as cyanobacteria is to harness the power of synthetic biology to enable the creation of autotrophic CO_2 fixation pathways in heterotrophs such as *S. cerevisiae* and *E. coli*.[9] *S. cerevisiae* has the advantage of higher tolerance for toxic substrates such as formate as well as more endogenous carbon anabolic enzymes.

2.3.3. Photoenzymes: natural light-driven enzymes

Photoenzymes require a continual source of light to catalyze a reaction. This diverse group of enzymes catalyzes a variety of light-driven reactions involving different mechanisms. It probably contains much unexplored potential for applications in industrial organic synthesis.

Probably the most well-known photoenzymes are those belonging to the photosystem that enables photosynthesis in plants. Two lesser known groups of light-driven proteins are the photolyases which are responsible for repair of DNA damage caused by UV irradiation in many organisms and the enzymes which play a key role in chlorophyll synthesis.

Recently, it was shown that the microalga, *Chlorella variabilis* NC64A produces an enzyme, fatty acid photodecarboxylase (CvFAP), which catalyzes the visible light-driven decarboxylation of a broad range of fatty acids to straight-chain alkanes and alkenes,[84] in near quantitative yields and very promising turnover numbers.[85] Decarboxylation is initiated by electron transfer from the fatty acid to a photo-excited flavin adenine dinucleotide (FAD) in a quantum yield of >80%. This is coupled to hydride transfer from a cysteine residue in the active site of FAP enzymes.[86]

However, photochemical processes in general suffer from productivities that are orders of magnitude too low for industrial viability owing to a reactor design based on external illumination with poor light penetration in suspensions of photocatalyst. This serious shortcoming was overcome by employing a new reactor concept of internal illumination using small (1 cm diameter) wirelessly powered light emitters (WLEs). [87] Indeed, the rates of light-induced, FAP-catalyzed decarboxylation of fatty acids were dramatically increased using WLEs as a source of intensified internal illumination.[88]

The enzyme is also referred to as a microalgal alkane synthase and is of interest for the conversion of fatty acids derived from triglycerides to a mixture of straight chain hydrocarbons which depending on their chain lengths, constitute potential sources of next generation biofuels, including biodiesel in two steps from waste triglycerides (Fig. 11).[89]

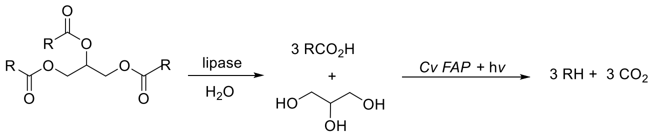

Figure. 11. Conversion of triglycerides to biodiesel range hydrocarbons

Similarly, bio-LPG can be produced by decarboxylation of short-chain carboxylic acids[90,91] and even jet fuel range alkanes as an alternative process to catalytic hydrodeoxygenation.[92]

FAP-catalyzed decarboxylations have also been incorporated as steps in the synthesis of chiral secondary alcohols from renewable unsaturated fatty acids.

3. Biomass to Chemicals

Looking toward a largely decarbonized energy future where cheap electricity is generated by renewables and nuclear energy, the chemical industry will undergo a considerable transformation in which the flow of carbon is integrated in a circular economy (Fig. 12). It is also widely accepted that renewable biomass will become the main source of carbon, and fortunately the abundance of renewable biomass greatly exceeds the mass of feedstock required for chemicals production by orders of magnitude. An estimated 181.5 billion tonnes of lignocellulose are produced annually, of which 7 billion tonnes are produced from dedicated agricultural, grass and forest land, providing 4.6 billion tonnes from agricultural residues.[93] This completely overshadows the production of a mere 400 million t/a of organic chemicals in petrochemical refineries. The conversion of this biomass into chemicals[94] can be through multiple technologies[95]

Advances in biotechnology in combination with pervasive cheap electricity will provide new opportunities, while decentralized renewable electricity sources will facilitate biorefinery production facilities in agricultural areas, where biorefinery location and scale are dictated by biomass location and density (typically a 50 km harvest radius).

3.1 The transition: petrochemical refineries to biorefineries.

The feedstocks of petrochemical refineries are crude oil and natural gas (methane). These are converted via distillation and cracking processes to the six hydrocarbon building blocks - ethylene, propylene, butadiene, benzene, toluene and xylenes (BTX) - that form the basis of the petrochemical industry. The seventh basic chemical, methanol, is produced by steam reforming of the methane in natural gas. It is worth noting, however, that the manufacture of these chemicals represents less than 10% of a barrel of crude oil. The other 90% is accounted for by the most important products of an oil refinery: liquid fuels. The three olefins are produced by steam cracking of various hydrocarbon fractions. The three aromatic hydrocarbons (BTX) are by-products of olefin production by cracking of the naphtha fraction. Ethylene is by far the most important base chemical with an annual production of ca. 200 million tonnes and roughly a third to a half of that is converted to polyethylene. Other commodity chemicals, largely oxygenates, derived from lower olefins and BTX, are mainly produced by gas phase aerobic oxidations. Products derived from ethylene include ethylene oligomers for detergents, ethylene oxide, vinyl acetate (for PVC) and ethanol. However, only about 7% of the global production of industrial ethanol is from ethylene. The other 93% (ca. 90 million t/a in 2018)[96] is produced by fermentation.

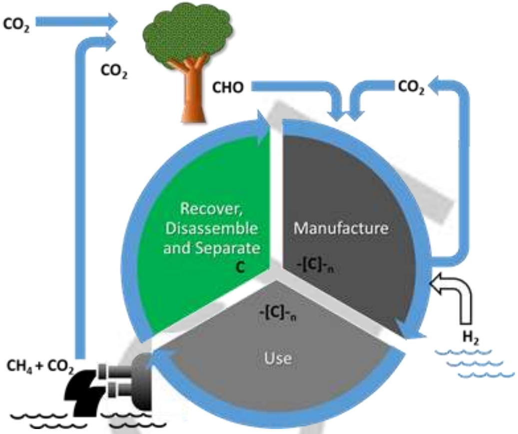

Figure 12. Carbon flow in a circular economy

The currently ongoing transition to carbon neutral production of liquid biofuels and commodity chemicals from renewable biomass is responsible for the recent emergence of biorefineries. The feedstocks of traditional biorefineries are polysaccharides and their carbohydrate building blocks and triglycerides. Currently they are based on 1st generation (1G) biomass, such as corn or wheat starch and sugar cane or beet However, this is not perceived as sustainable in the long term owing to direct or indirect competition with food production. In the long term 2G biorefineries will be based largely on unavoidable waste lignocellulosic biomass from agricultural and forestry residues or food supply chain waste or end-of-life plastic waste. On the other hand, currently 97% of bioethanol is produced from 1G and only 3% from 2G feedstock.[96] 3G aquatic biomass from macroalgae, microalgae, and cyanobacteria is also being considered as a feedstock. However, 3G biomass is composed of a variety of polysaccharides which includes, in addition to starch and cellulose, polysaccharides not present in 1G and 2G biomass that generally lack lignin and hemicellulose.

There are two ways to depolymerize and (partially) deoxygenate lignocellulose: thermochemical and hydrolytic. One involves either pyrolysis (to yield a mixture of pyrolysis oil and charcoal), or gasification to afford syn gas (a mixture of carbon monoxide and hydrogen - analogous to syn gas from coal gasification).[97] The syn gas can be subsequently converted to liquid fuels and platform chemicals using the Fischer-Tropsch process (which has been operating in South Africa since 1955). Alternatively, it can be transformed to biofuels and platform chemicals using fermentation.[98,99]

3.2 Commodity chemicals by fermentation

Ethanol fermentation from carbohydrates is one of humanity's earliest chemical technologies, and ongoing development of yeast cultures and fermentation technologies now enables ethanol concentrations of up to 15% by volume.[100] The bioethanol can be dehydrated over an aluminum oxide catalyst to afford ethylene for a cost-price that is comparable to that from an oil refinery,[101] but with greatly reduced CO_2 emissions (20-30% of CO_2 emissions of ethylene production from crude oil). The production of other lower alcohols, e.g. 1-butanol and isobutanol is imminent. [102, 103]

Irrespective of the exact nature of the building blocks, the scenarios for conversion to commodity chemicals involve a switch from hydrocarbons to carbohydrates (plus fatty acids and glycerol) as the base chemicals. This represents a veritable renaissance in carbohydrate chemistry.[104] Many commodity chemicals are so-called oxygenates that are currently produced in petrochemical refineries by catalytic aerobic oxidation or hydration of olefins or aromatics. In contrast, they can be produced from monosacharides, such as glucose, directly by fermentation or by catalytic oxidation or reduction. The reactions are performed in water and are safer than aerobic oxidations of hydrocarbons. They are also more redox efficient routes than via initial conversion to hydrocarbons. This includes diols such as 1,3-propane diol (PDO) and 1,4-butane diol (1.4-BDO) [104] and a variety of mono- and di-carboxylic acids, e.g. (acetic, citric, lactic, maleic, fumaric, itaconic, and succinic acids and natural amino acids such as glutamic acid, lysine, threonine and methionine,[105] Each of these products can be isolated and act as the starting chemical feedstocks for further chemo- or biocatalytic transformations. Sequential fermentations, rather than integration of all pathways into a single organism, may be more practical is some cases.[106]

The majority of high-volume, commodity chemicals are industrial monomers - olefins, diols, dicarboxylic acids, diamines, hydroxy acids, amino acids - used in the production of polyolefins, polyesters and polyamides. The latter two are interesting targets for biocatalytic production of both the raw materials and the final polymers (see Section 4).

Advances in metabolic engineering have enabled improved yields of fermentation products by systematically diverting the flow of metabolites, disarming feedback regulation, and rebalancing redox potential through adjusting the level of enzyme expression in metabolic pathways.[107, 108] For example, the commercial production of 1,3-PDO, used for carpet fiber polytrimethylene terephthalate production, in a recombinant *E. coli* involved numerous genetic modifications to improve yields.[109] Fermentations are now also being applied to the production of non-natural compounds, such as the commercial production of the plastic monomer 1,4-BDO, which was achieved through insertion of an entirely new five step metabolic pathway into *E. coli* [110, 111] This process is economically superior to the petrochemical route, which involves gas-phase oxidation of butane, and clearly demonstrated what fermentation technology for bulk chemicals can achieve.

Biological catalysts are also compatible with electrochemical systems[112] as they function both under mild conditions and in aqueous environments, as demonstrated by the electrosynthesis of acetate by a mixed microbial community.[113] Weusthuis and co-workers point out that anaerobic fermentations typically have higher productivities than aerobic fermentations (oxygen is poor soluble and promotes oxidation to CO_2). Hence, they suggested that anaerobic processes be integrated into electrobiochemical systems to balance redox potentials when using anaerobic fermentations for chemical production.[114] Electrochemical systems can also be applied in fermentations elsewhere, such as the continuous removal of carboxylic acids using membrane electrolysis cell, permitting simultaneous pH control.[115] Electocatalysis *in situ* is also possible - electrocatalytic hydrogenation of muconic acid directly in the fermentation broth, eliminating the preceding separation step prior to the chemical hydrogenation.[116] The resultant 3-hexenedioicacid was obtained in 94% yield and used in the synthesis of bio-based unsaturated nylon-6,6 (see also section 2). Fermentations generally run at mild reaction temperatures and close to ambient pressures. Hence, fermenters are generally cheap reactors to construct, which offsets the lower reactor productivity compared to many chemical processes.[18] The lower CAPEX costs also allows for operation at smaller scale, which may be the future of chemical production as a consequence of the distributed nature of biomass sources.

Whole cell Biocatalysis

Intensification of processes reduces the process costs by decreasing recovery costs from dilute solutions. To achieve this the enzyme catalyst needs to be more volumetrically active and more stable at high reactant concentrations and elevated temperatures. Retention of enzymes in the cell is advantageous for production of bulk chemicals with low profit margins per mass as it avoids the cost of extracting, purifying and immobilizing enzymes. Hence whole cell biocatalysis involves cellular systems, often with simplified metabolism and over-expression of key enzymes that provide many of the benefits of cell free biocatalysis but at a cost closer to that of microbial fermentation.[117] Whole cell Biocatalysis will be particularly useful in value addition to primary fermentation products or specific components available from biomass.[118]

Although individual reactions with higher productivities can often be achieved with metal catalyzed reactions, biological multi-step catalysis offers fewer unit operations and hence offers overall process benefits when deriving products from biological feedstocks. Biological catalysts are also self-propagating and highly selective, thereby overcoming toxicity problems experienced with metal catalysts.

Cell free Biocatalysis

Further reaction intensification is possible through cell-free biocatalysis systems. Although cascades of individual commercial enzymes can be combined for the production of high value products, it is likely that cell-free lysates of engineered microbes would be cheaper.[119] This approach does come with its own challenges, such as the requirement for a separation system for regeneration of enzyme cofactors (Fig. 13), but it has the potential to greatly increase yields and process intensity. An example of the promise of this approach was the 20,000 L demonstration of the production of vitamin B8 (myo-inositol) from starch.[120] The researchers simplified the process by creating a 5 step enzymatic pathway and expressing genes for the enzymes from thermophiles in a mesophilic host. The contaminating cellular enzymes were deactivated simply by lysing the cells and heating to eliminate the mesophile host enzymes. This permitted a 98.9% yield at 95 g/L myo-inositol product at 70°C. New research is speeding up the development of these techniques.[121]

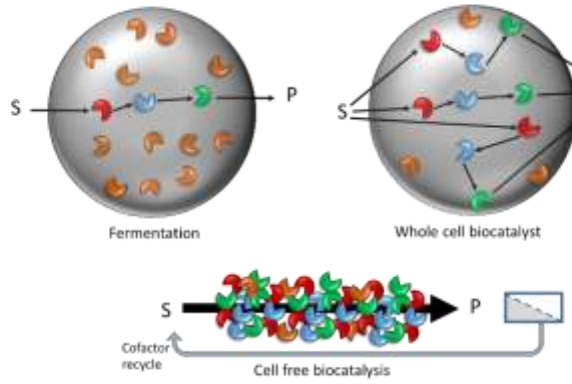

Figure13. Comparison of biocatalytic systems with increasing process intensity converting substrate (S) into product (P).

3.3 Plants to chemicals

Assuming a future where crude oil is no longer the chemical feedstock, other sources of carbon are required. This carbon has traditionally been extracted from plants. Sucrose or glucose (the latter from starch hydrolysates), and occasionally glycerol [122] have been the carbon sources in commercial fermentations. However, the demand for starch recently increased dramatically when it was diverted to bioethanol fuel production, causing a spike in food prices and demonstrating a need for alternative and more abundant carbon sources that will not compete with food in a world with an increasing population. This has led to the development of technologies for hydrolysis of non-food biomass, including quickly growing inedible plants and diverse agricultural waste streams. Lignocellulosic biomass waste includes corn stover, wood mill, pulp and paper waste, sugar cane bagasse, wheat straw, rice straw, sorghum bran[123], brewers spent grain, spoilt produce and fruit processing waste in more than sufficient amounts to replace fossil fuels.[124] Once hydrolyzed the biomass releases sugars for fermentation, as well as fatty acids, amino acids and aromatics. However, compared to starch and sucrose fermentation, lignocellulose presents some additional technical challenges. Lignocellulose is a complex polymer with a wide variety of chemical bonds, and requires both physical and chemical pre-treatments[125,126] to open up the fiber, as well as multi-enzyme cocktails to cope with the many chemical bonds. Subsequently the fermenting organism must be able to metabolize various hexose and pentose sugars. To alleviate this problem attempts are being made to use cell free enzyme cascades using enzymes that are sufficiently promiscuous to convert a range of pentoses. The simultaneous conversion of both D-xylose and L-arabinose via an achiral intermediate, α-ketoglutarate semialdehyde, yielded 1,4-BDO using a modified oxidative Weimberg pathway.[127]

In spite of technical constraints it appears that lignocellulose based bioethanol in second generation biorefineries is achieving cost parity with the 1G starch and sucrose based processes.

An alternative to agricultural wastes are fast growing plants that can be grown specifically as feedstock on marginal land. Switchgrass[128] is the usual example, but bamboo and non-food varieties of common crops such as sorghum and pearl millet are also under consideration.[129] These plants can be selected and genetically modified to facilitate processing and enhance yields.

For some time researchers have also tried to exploit eukaryotic microalgae, which are fast growing, more efficient than terrestrial plants in photosynthesis, and do not require agricultural land.[130] However, algal polysaccharides and their constituent monosaccharides differ somewhat from those in lignocelluose and hence require unique pre-treatment, hydrolytic enzymes and fermentative organisms.[131] In addition, to reach optimal growth rates and avoid microbial contamination and seasonal productivity loss, expensive enclosed photobioreactors with high operating costs are required for cultivation.[132,133,134,135] Blue-green algae (cyanobacteria) such as *Spirulina sp.* are photosynthetic prokaryotes[136] that accumulate large amounts of glycogen, which fortunately can be hydrolyzed to glucose analogous to starch hydrolysis. One useful characteristic is that microalgae are able to simultaneously clean-up wastewaters and produce products such as bioplastics from the available carbon.[137] Coupling biorefinery wastewaters to microbial electrolysis cells can provide synergies by improving H_2 production by the cells while simultaneously decreasing the COD of the wastewater.[138] The hydrogen can be used in subsequent reduction reactions, both chemical and biological.

3.4 Carbon dioxide to chemicals

Human activities yield abundant CO_2. Concrete production, oil refineries, ammonia production, steel plants, Fischer-Tropsch synthesis of alkanes, burning of biomass for electricity co-generation (e.g. Kraft black liquor from the pulp and paper industry), sewage works, municipal waste sites and fermentations are just some sources of anthropogenic CO_2 emissions.[6, 139,140] This is released into the atmosphere and subsequently captured by photosynthesis. In a second generation biorefinery we then harvest the plant, depolymerize it, and then feed it to an organism that converts it to the target chemical. Obviously there is a potential shortcut that can be achieved by growing organisms that directly convert CO_2 to the desired chemical. .[141] This could involve photosynthetic organisms in photo-bioreactors, or simply organisms that directly add CO_2 to a chemical precursor.

The problem with CO_2 as a carbon source is that it is quite dilute in the atmosphere (412.5 ppm or 0.04 percent). However, anthropogenic point sources provide a handy concentrated supply. In the production of chemicals by fermentation carbon dioxide is inevitably a by-product, with the amount of CO_2 produced by fermentations being roughly a kg CO_2 per kg of product. It has been calculated that 19.4 - 25.8 million metric tonnes of CO_2 are generated in the production of 26 billion liters of alcohol by the global beverage industry.[142] In 2017 the 216 biorefineries in the U.S. alone produced 59.4 billion liters of fuel bioethanol[143], with a concomitant emission of 45 Mt CO_2 from the fermentation process.[144] The CO_2 generated by fermentation is highly pure (99%) and concentrated and hence cost estimates for CO_2 capture and compression from fermentation are among the lowest of all CO_2 point sources. This can be fed into subsequent bioreactors as a carbon source (Fig. 14).

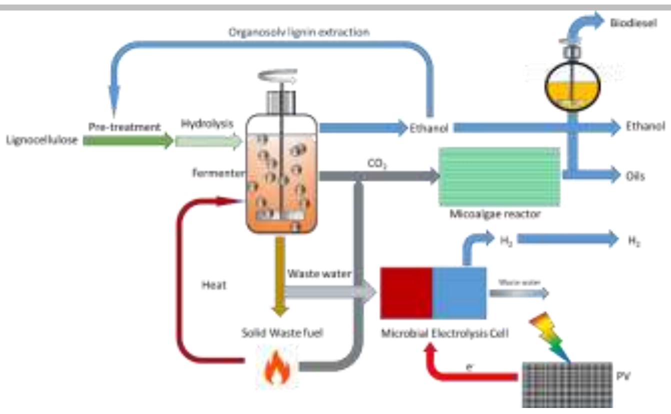

Figure 14. A hypothetical integration of an advanced biorefinery.

Another source of CO_2 is biogas. Kirschke *et al.* have determined that anthropogenic production of methane is 331 Tg yr-1, of which 200 Tg yr-1 (200 million tonnes) is generated by agriculture and waste.[145] The generation of waste food, solid waste from fermenters, human sewerage and manure is inevitably proportional to the human population and hence will become increasingly available up until peak population is reached. Biogas is in itself a source of methane as fuel, although the sources are highly dispersed. After methane (70%) the major component biogas is CO_2 (30%), which has to be separated out to upgrade the biogas to fuel grade biomethane, i.e. up to another nearly 100 Tg yr^{-1} of CO_2 becomes available. Should the biomethane be burnt as fuel there would be the possibility of recovering a portion of the additional 550 Mt CO_2 generated.

Methane itself can be used as a carbon feedsrock, but it is perhaps best suited to heating and cooking using existing natural gas infrastructure.

Feeding CO_2 into photo-bioreactors can provide a wide range of chemicals such as ethanol, oils and carotenoids. The CO_2 fixation by algae needs to be intensified, through genetic engineering and mutation[146] However, photosynthesis need not be involved. Production of ethanol from CO_2 using gas fermenting organisms has been commercialized by Lanzatech;[147] researchers are developing organisms to produce a wide variety of products by this means, some of which have been scaled up to pilot scale.

Succinate is a chemical that can be efficiently produced through fermentation. The major application is in the production of the biodegradable plastic polybutylene succinate through esterification with 1,4-butanediol. *Actinobacillus succinogenes* is a heterotrophic bovine rumen bacterium with exceptional capacity to over-produce succinate.[148] It is not fastidious about its carbon source and can accept both a wide range of carbohydrates and CO_2.[149] Zhang *et al.* demonstrated *A. succinogenes* uptake of a by-product CO_2 stream generated by a *Zymomonas mobilis* ethanol producing fermentation.[150] They found the CO_2 fixation rate by *A. succinogenes* was 188 fold greater than by a culture of the photosynthetic microalga *Chlorella vulgaris*. (Bio)succinic acid would be central to a post-oil world, and an integrated biorefinery that produces multiple polymers can be envisaged (Fig. 15). By selection of the six known CO_2 assimilation pathways (Table 1) it is feasible to engineer metabolic flux towards specific final products.[151] There are even attempts to modify useful heterotrophs into autotrophs by including the genes for these pathways into the genome, creating artificial autotrophic microorganisms.[9]

Table 1: The six known non-photosynthetic CO_2 assimilation pathways

Metabolism	CO_2 assimilation mechanism	Major products
Aerobic	Calvin-Benson-Bassham (CBB cycle)	Lactic acid Polyhydroxybutyrate (PHB)[152]
	3-Hydroxypropionate bi-cycle (3HP bi-cycle)	3-Hydroxypropionate Pyruvate[153]
	3-Hydroxypropionate /4-hydroxybutyrate cycle (3HP/4HB cycle)	3-Hydroxypropionate / 4-hydroxybutyrate Succinate acetyl-CoA[154]
Anaerobic	Reductive citric acid cycle (rTCA),	Citric acid
	Wood-Ljungdahl pathway	Acetate, butyrate, ethanol, formate, methane [147,159]
	Dicarboxylate /4-hydroxybutyrate cycle (DC/4HB cycle)	4-Hydroxybutyrate

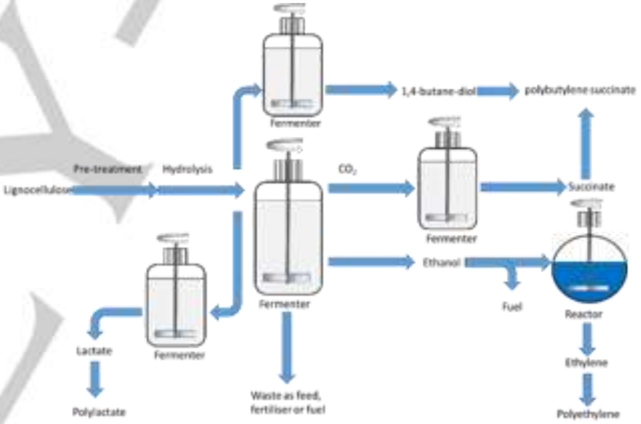

Figure 15. Potential for plastics production in an integrated biorefinery.

The remarkable construction of a non-photosynthetic pathway for the direct synthesis of starch from CO_2.has been recently reported[155] A 13 enzyme artificial starch anabolic pathway was developed[156,157] that starts with a non-enzymatic zinc catalyzed conversion to methanol. This first step was necessary due to the enzyme responsible for the corresponding reaction, formate dehydrogenase, having only very low CO_2 reduction activity, although this can possibly be improved by enzyme engineering.

Another opportunity provided by cheap electrical energy is the capacity to use electrolysis of CO_2 to yield carbon monoxide (CO) in an electrobiocatalytic CO_2 conversion process. When combined with water electrolysis to yield hydrogen (H_2) this allows for highly productive gas fermentation to ethanol. This approach could add value to bioethanol production by increasing ethanol yield by 45%.[158] A practical demonstration of this technology using *Clostridium* fermentation generated butanol and hexanol.[6] The system could conceivably also be used with syngas (CO, H_2) generated from waste plastic. Genetic tools are being applied to further develop the technology of gas phase fermentations to improve yields and diversify product ranges.[159]

In short, our increasing mastery of biology is allowing us to develop organisms with the capacity to generate a widening array of desirable bulk chemicals with commercially viable productivities. In the movement to decarbonize our economy and move away from fossil fuels we will need to harness the waste products of our activities, such as waste lignocellulose, methane and carbon dioxide. Fermentation technology is well suited to a future chemical industry that must adapt to widely distributed and diverse biological chemical feedstocks.

4. The Circular Economy: Waste-free by Design.

4.1. The plastic pollution challenge

The global production of industrial monomers from petrochemical feedstocks represents a considerable percentage of the total chemicals production. In a circular economy these polymers must be recycled, preferably as such or as the original monomers. A particularly poignant example of what happens if this is not done is certainly the global problem of plastic pollution.

The global production of plastics in 2018 was 390 million tonnes (174 million tonnes of packaging and 216 million tonnes non-packaging). Of this total 92% (360 million tonnes) consisted of virgin plastics and only 8% (30 million tonnes) of recycled plastics. Around 385 million tonnes of plastics products were consumed and 250 million tonnes of post-consumer plastic waste were generated. 75 million tonnes were landfilled, 50 million tonnes burned for energy recovery, 75 million tonnes were improperly disposed in the environment, and 50 million tonnes recycled (Fig. 16).[160,161] Plastics for packaging applications consist primarily of polyolefins – polyethylene (PE), polypropylene (PP) and polystyrene (PS) - and polyethylene terephthalate (PET) and the required monomers account for ca. 4% of the global production of petrochemicals.[162]

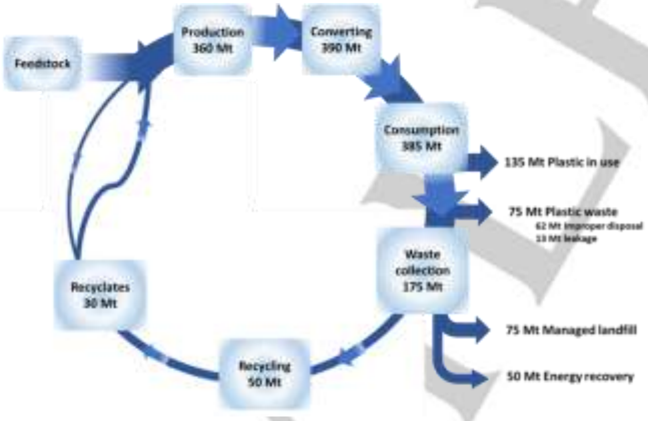

Figure 16. The plastic cycle: the current fate of plastics.

Only 9% of all the plastics ever produced have been recycled and plastic detritus is ubiquitous in the environment where it generally doesn't degrade as such but fragments slowly into microplastics and nanoplastics. The detrimental consequences of plastic pollution for the environment, economy and society are profound. It is worth noting, for example, that failure to recycle plastics represents a cost of Euro 105 billion for the EU alone.[163]

In 2020 Weston and co-workers[164] reported a new species of the *Eurythenes* amphipod that was discovered at a depth of 6900 meters in the Mariana Trench of the North-West Pacific Ocean. It had microplastic fibers, with 84% similarity to PET, in its gut. Before we even knew this species we had already contaminated it with plastic. To complete the irony the new species was given the name, *Eurythenes plasticus*,

It is crystal clear that a linear take-make-use-dispose economy, that favors production of virgin plastic over plastic recycling, is not conducive to the ultimate goal of zero waste chemicals manufacturing. In the new industrial élan of the post-transition era a resource efficient and environmentally benign circular economy will take front seat. It will be based on the principles of designing out waste and pollution, keeping products and materials in the loop, and regenerating natural systems.[165,166] Polymers such as single use plastics, will be produced from renewable carbon and designed to enable efficient recycling.[167]

4.2. Design for recycling

A primary goal of the circular economy is optimization of resource efficiency and minimization of waste generation by multiple rounds of recycling. The recycling, disposal and redesign of plastics has recently been reviewed by Lange.[168] The descending order of priority for recycling of plastics is:

1. Closed-loop recycling to the original plastic, e.g. PET bottles to PET bottles via recovery of PET monomers.
2. Open-loop recycling to other products, often of lower value.
3. Conversion to basic petrochemicals, e.g. by pyrolysis.
4. Energy recovery through incineration.

A fundamental barrier to plastics recycling is the difficulty of competing with the price of virgin raw materials which ignores external social and environmental costs. The answer is evident: application of the principle of extended producer responsibility (EPR) by introducing a plastics tax, thereby internalizing the costs of waste management, or by demanding a minimum content of recycled plastic.

With polyolefins, for example, the preferred option would be to depolymerize to the olefin monomers which is technically feasible with PS[169] but not with PE and PP. An attractive alternative is, therefore, pyrolysis to a naphtha-like mixture of hydrocarbons which could be converted to a mixture of olefin monomers in a steam cracker, for example. The various possibilities for catalytic, chemical recycling of polyolefin plastic waste have been recently reviewed by Weckhuysen and co-workers.[170] Alternatively, we could avoid the problem by substituting polyolefin plastics with more readily recycled plastics.

4.3 Biocatalytic recycling of plastics

Polymers containing hydrolyzable bonds, e.g. polyesters and polyamides, such as PET and Nylon, can be converted to the original monomers by acid- or base-catalyzed or enzyme-catalyzed hydrolysis. The possibilities and limitations of biotechnological recycling of plastics were recently reviewed by Blank and Bornscheuer and co-workers. [171] One approach to solving the problem of environmental pollution with PE and PP is to substitute polyolefin packaging materials with, preferably bio-based, polyesters such as polybutylene succinate (PBS) and polyhydroxy alkanoates (PHAs) which can be converted to their monomeric constituents by enzymatic hydrolysis. Research in this area was stimulated by the discovery, by Oda, Miyamoto and co-workers in 2016,[172,173] of a bacterium, *Ideonella sakaiensis*, in soil from an industrial waste PET-recycling facility, which catalyzed the hydrolysis of PET. The bacterium secreted two different hydrolases: the so-called PETase that catalyzes the hydrolysis of PET to mono-2-hydroxyethyl terephthalic acid (MHET) and a second enzyme that catalyzes the hydrolysis of MHET (Fig. 17).

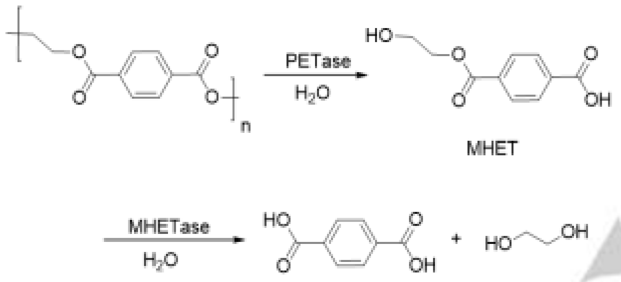

Figure 17. Enzymatic hydrolysis of PET to terephthalic acid and ethylene glycol.

This landmark publication stimulated a profusion of activity on so-called PETase[174,175,176] which was shown to contain structural features common to both lipases and cutinases.[177] The latter catalyzed PET depolymerization via hydrolysis[178,179] or glycolysis with ethylene glycol.[180] A cutinase also catalyzed the hydrolysis of PET in polymer blends with PE or polyamide.[181]

Kanaya and co-workers[182] identified a cutinase, from leaf-branch compost (LC-cutinase) in a Japanese public park, which catalyzed the hydrolysis of PET at 70°C, which is close to the glass transition temperature of PET of around 75°C. This enzyme was already at least 33 times more active than other cutinases but Marty and co-workers at the French biotech company Carbios, and the University of Toulouse, used computer-aided protein engineering to produce a variant which catalyzed the hydrolysis of PET in 90% conversion in less than 10 h at 72°C. The enzyme loading of 3 wt%, a PET concentration of 20% and a volumetric yield of 16.7 $g.l^{-1}h^{-1}$ [183] have industrial viability at a cost of ca. 4% of that of the virgin polymer.[184]

Similarly, a genetically engineered anaerobic thermophilic bacterium, *Clostridium thermocellum*, achieved high-level secretory expression of LC-cutinase.[185] In addition to catalyzing the depolymerization of PET at 60°C the microbial cells catalyzed the efficient hydrolysis of cellulose which suggests that they could be used to recycle textile waste containing both polymers.

Based on the above developments we can conclude that depolymerization of polyesters to the corresponding monomers will be an industrially viable proposition in the near future, especially if costs of virgin *versus* recycled plastic are compared on a level playing field. Alternatively, the crude hydrolysate, containing terephthalic acid and ethylene glycol, from the depolymerization step could be used as a feedstock for the microbial production of other commodity chemicals in so-called open-loop recycling. For example, an engineered *Pseudomonas putida* was able to synthesize PHAs or a building block for bio-based polyurethanes.[186]

4.4 Biodegradability of plastics

What is often considered to be an important property of plastics is their biodegradability. However, there are various technical and socio-economic arguments that are not in favor of biodegradable plastics.[15] For example, even plastics that readily degrade in a marine environment are still an environmental hazard for several months. Moreover, the label biodegradable can be interpreted as meaning that littering is not a problem.

Nonetheless, plastics that are biodegradable-on-demand at their end-of-life (EoL), after multiple recycling, command special attention. A striking example is provided by the self-degrading poly-lactate (PLA) developed by Carbios.[187] An extremely thermostable esterase that could withstand the extrusion temperature of 170°C was embedded in PLA during manufacture to enable its biodegradation at its EoL.

4.5. Bio-based plastics for sustainability

The way forward is the utilization of polymers derived from renewable raw materials, to enable carbon neutral production of plastics with reduced environmental footprints, i.e. the sustainable macromolecular materials of the 21st century.[188,189] Utilization of renewable biomass is a *sine qua non* for lower GHG emissions. PLA production from corn-starch affords a 27% reduction in GHG emissions, for example, compared with PE from fossil resources[190] and bio-based PET is responsible for 25% less GHG emissions than PET from fossil resources.[191,192] The trends and challenges in the production of plastics from renewable feedstocks have been highlighted in an excellent review by Hatti-Kaul and co-workers.[193] Indeed, the recent publication of several reviews on this subject attests to its current importance.[194,195,196,197,198]

Bio-based plastics can be drop-in products, e.g. PE produced from ethylene derived from bioethanol. Alternatively, they can be totally new polymers e.g. PHAs (see later). An important advantage of drop-in products is that they are already established in the market. Moreover, there is no need to change production equipment and processes. In contrast, if the bio-based resin is different, e.g. PLA to replace PET, different additives and processing technology may be required and the product will have different mechanical properties and barriers to diffusion of e.g. water and oxygen. Such problems can possibly be resolved by employing polymer blends.[199]

The primary motive for switching to bio-based plastics is climate change mitigation through reductions in CO_2 emissions but the accompanying facile recyclability and biodegradability are delightful bonuses. Furthermore, employing renewable feedstocks should not be in competion with food production or be responsible for deforestation /or loss of biodiversity. This is achieved by valorizing waste streams as the feedstock, e.g. lignocellulosic waste from agricultural and forestry residues[94,200] and food supply chain waste[201] in 2nd generation (2G) biorefineries.

Bio-based plastics are produced (i) directly from bio-based monomers, e.g. PLA from lactic acid derived from fermentation, (ii) directly by fermentation, or (iii) from natural polymers such as starch, cellulose and chitin.[202] Examples of bio-based monomers, produced by fermentation or chemocatalytic conversion of glucose, are depicted in Figure 18. In the chemical industry of the future they will be produced in 2G biorefineries from waste lignocellulose and 3rd generation (3G) polysaccharides from algae and photosynthetic bacteria, to take advantage of the fact that arable land and fresh water are not necessary for their cultivation. For example, alginate and carrageenan from macroalgae (seaweed), can function as feedstocks for bio-based plastics.[203]

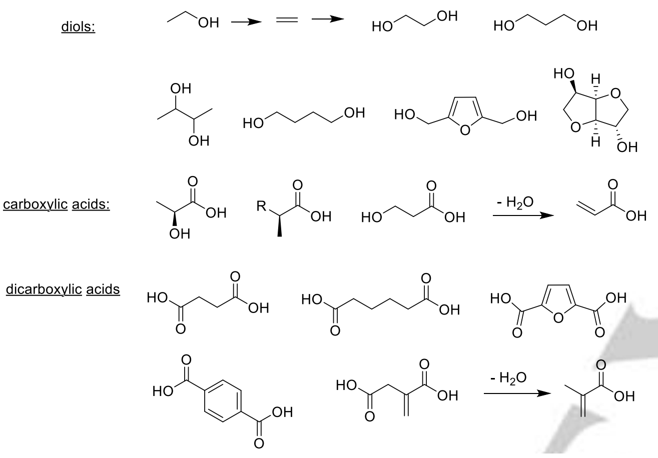

Figure 18. Bio-based monomers for thermoplastics.

Drop-in bio-based PET, containing 2 carbons derived from bioethanol and 8 carbons from fossil-based *p*-xylene is currently the market leader[204] and is 20% biobased (Fig. 19). Considerable research effort is currently being devoted to the synthesis of bio-based terephthalic acid to enable an industrially viable production of 100% bio-based PET.[205,206]

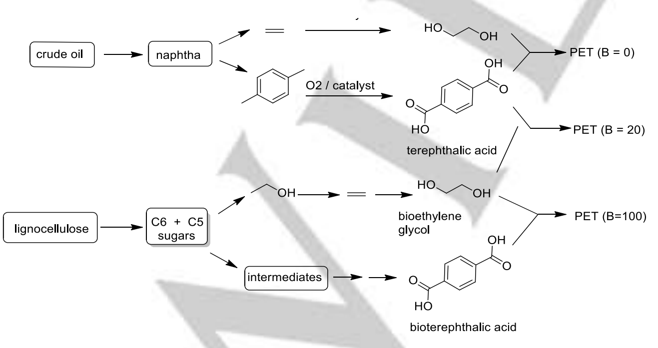

Figure 19. Production of fossil vs biobased PET

Polyethylene furan 2,5-dicarboxylate (PEF), developed by Avantium,[207] is a 100% bio-based alternative to PET. It is produced from ethylene glycol and furan-2,5-dicarboxylic acid (FDCA). The latter is produced by chemo-[208] or biocatalytic oxidation[209] of 5-hydroxymethylfurfural (HMF) that is in turn derived from acid catalyzed dehydration of glucose (Fig. 20). In addition to being bio-based with a reduction in GHG emissions of up to 55%, PEF has superior thermal, mechanical, and gas barrier properties compared to fossil-derived PET.[210,211] Similarly, a 100% bio-based equivalent of polytrimethylene terephthalate (PTT) can be produced from FDCA and bio-based 1,3-propane diol.[212]

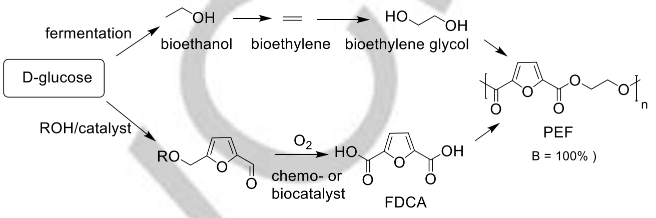

Figure 20. Production of PEF.

PHAs are particularly exciting because they are produced by direct fermentation of low-cost waste streams, e.g. municipal[213,214] and paper mill[215] waste water, even waste polystyrene,[216] and they are biodegradable. They function as a carbon and energy source for acetogenic bacteria, reaching up to 90% of the dry weight of the bacterium. Depending on their exact structure, physical properties are comparable with those of PE and PP, making them suitable for, *inter alia*, applications in single-use plastic packaging. However, their high production costs and lower mechanical stability make widespread commercialization a challenge.

Newlight Technologies produced a PHA by aerobic fermentation of methane or biogas from landfills and converted it to a thermoplastic, so-called 'AirCarbon'. The latter was licensed to IKEA for use in home furnishing products.[217] Composites of PHAs with inexpensive natural fibers with superior physico-mechanical properties have also been described.[218]

According to a recent review of bio-based plastics in food packaging[219] the total production of bio-based plastics has reached 7.5 million tonnes per annum, including bio-based polyurethanes, which is 2% of fossil-based plastics. However, the gap is rapidly narrowing. Replacing conventional packaging plastics with bio-based alternatives has become a priority of the food packaging industry[220] and will become the centerpiece of the bioplastics market.[221] Next generation industrial biotechnology is coming to the rescue. Fast-growing, thermophilic *Halomonas spp*, designed and constructed using synthetic biology, is providing a basis for commercially viable production of PHAs with improved properties.[222]

Considering that the manufacturing processes of fossil-based plastics have been optimized over a period of more than half a century, it is not surprising that their bio-based cousins with their relatively short development times, are more expensive. This difference is decreasing and the number of applications increasing, albeit too slowly to seriously impact the problem of plastic pollution. This situation would change overnight if EPR were to be implemented in the pricing of polyolefins, analogous to the case of lead-free gasoline in the 1970s.

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According to a recent review of the environmental impact of bio-based plastics,[223] substituting two thirds of the global plastics demand with bio-based alternatives would enable an annual reduction of 241-316 million tonnes of CO_2 equivalents. The authors also noted that vulnerable stakeholders should be supported and protected by governments and NGOs

Bio-based plastics are also produced directly from natural biopolymers, such as polysaccharides, e.g. starch-based plastics and cellulose acetate fibers. Less explored polysaccharides such as chitin,[224] the second most abundant natural polymer after cellulose, are potential sources of packaging plastics. Chitin nanofibers were processed into useful packaging materials which combined excellent gas barrier properties with flexibility and optical transparency.[225]

Similarly, polyamide and polyurethane plastics were produced from long-chain fatty acids derived from plant oils (e.g. castor oil, sunflower oil).[226] Waste proteins, e.g. the huge amounts of waste keratin from wool, hair and chicken feathers[227] represent another commercially interesting source of novel materials.

On the other hand, looking further into the future, why not cut out the middleman (plants) and produce plastics directly from carbon dioxide in e-biorefineries? This will be enabled by future availability of sustainable (green) electricity from the decarbonized energy sector and the coupled economically and environmentally attractive source of green hydrogen from water electrolysis.[228] As discussed earlier, carbon dioxide can be converted to syn gas as a source of monomers for plastics produced by existing petrochemical technologies or by fermentation.[229] Alternatively, PHAs can be produced directly from light, CO_2 and water.[75] The earlier mentioned Air Carbon technology can convert carbon dioxide to polyurethanes and thermoplastics.[230]

5. Conclusions and Prospects

Mounting concern regarding global issues such as climate change, environmental pollution and the loss of biodiversity have focused public attention on how dependent we are on chemistry. The solution to these global problems is not less chemistry but more, better chemistry. It has become evident that we need to shift from a fossil resource-based economy to a sustainable circular economy based on renewable or sustainable energy and carbon-neutral chemicals manufacture from renewable biomass. In this new global scenario waste will be seen as, on the one hand, something to be avoided by redesigning processes for zero waste generation and products for circularity. On the other hand, unavoidable waste, such as lignocellulosic waste from agricultural and forestry residues, and food supply chain waste, will be seen as a resource to be valorized. Actually, this is not an entirely new scenario. In 1848, two centuries ago, the iconic German chemist, A. W. von Hofmann, observed:

“In an ideal chemical factory there is, strictly speaking, no waste but only pro-ducts. The better a real factory makes use of its waste, the closer it gets to its ideal, the bigger is the profit.”

Thanks to the phenomenal developments in biotechnology over the last two decades, biocatalysis is ideally positioned to play a key role in these developments. Thanks to ground-breaking developments in synthetic biology and metabolic engineering of microbial pathways, fermentation of renewable feedstocks is the method of choice for the manufacture of a steadily increasing number of commodity chemicals. And thanks to the availability of green electricity and solar energy in a decarbonized energy sector the scene will be set for a sustainable chemical industry of the future in which CO_2 and organic waste streams are processed in e-biorefineries.

“The time has come, the walrus said”. Lewis Carroll.

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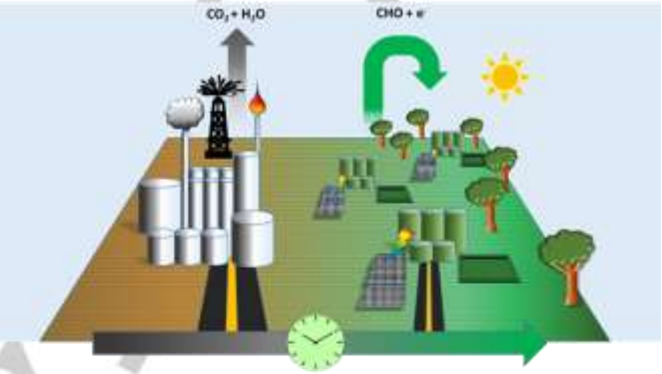

The chemical industry is transitioning to a biorefinery network using biocatalysis, autotrophic and heterotrophic fermentation, electrobiocatalysis and photobiocatalysis to retain carbon in a circular economy.

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Figure captions

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