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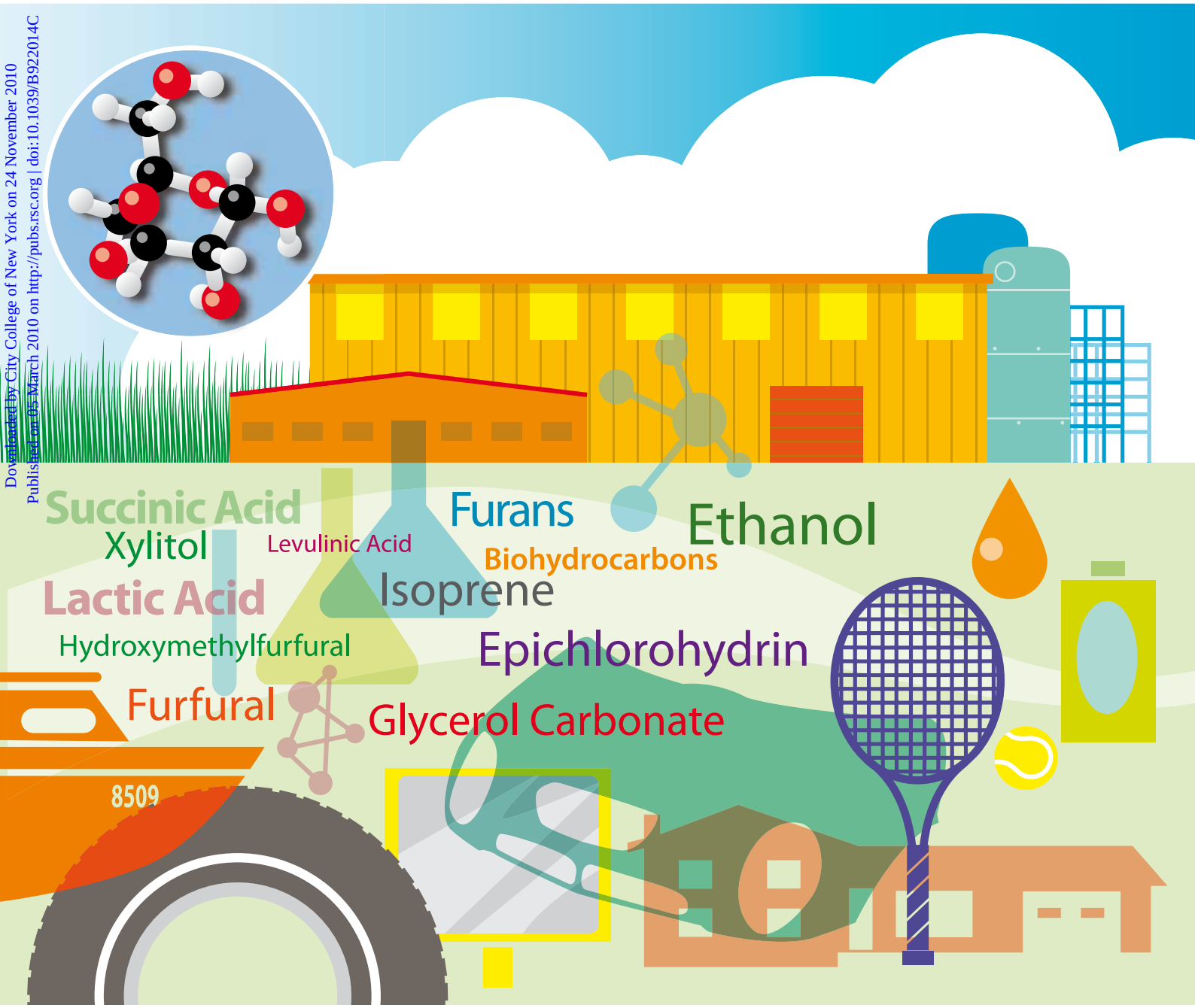

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Technology development for the production of biobased products from biorefinery carbohydrates—the US Department of Energy's "Top 10" revisited

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A biorefinery that supplements its manufacture of low value biofuels with high value biobased chemicals can enable efforts to reduce nonrenewable fuel consumption while simultaneously providing the necessary financial incentive to stimulate expansion of the biorefining industry. However, the choice of appropriate products for addition to the biorefinery's portfolio is challenged by a lack of broad-based conversion technology coupled with a plethora of potential targets. In 2004, the US Department of Energy (DOE) addressed these challenges by describing a selection process for chemical products that combined identification of a small group of compounds derived from biorefinery carbohydrates with the research and technology needs required for their production. The intent of the report was to catalyze research efforts to synthesize multiple members of this group, or, ideally, structures not yet on the list. In the six years since DOE's original report, considerable progress has been made in the use of carbohydrates as starting materials for chemical production. This review presents an updated evaluation of potential target structures using similar selection methodology, and an overview of the technology developments that led to the inclusion of a given compound. The list provides a dynamic guide to technology development that could realize commercial success through the proper integration of biofuels with biobased products.

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Biobased products are the foundation of successful biorefinery development

Biorefinery development has two strategic goals: the displacement of imported petroleum in favor of renewable domestic raw materials (an *energy* goal) and the establishment of a robust biobased industry (an *economic* goal). The energy goal is addressed by the current effort on ethanol, biodiesel and advanced biofuel production (butanol, algal biodiesel, *etc.*) to displace a portion of the huge amount of transportation gasoline (~142×10^9 gallons) and diesel (~60×10^9 gallons) used annually in the US.[1] But despite its high volume, fuel is a low value product. As a result, the return on investment in biofuel-only operations presents a significant barrier to realizing the biorefinery's economic goal. For example, algal oil holds great promise as a source of biodiesel, but remains a long term opportunity as developers try to identify additional revenue streams to cover the high cost of growing and processing algal biomass for oil recovery.[2] Examination of the best means for leveraging existing and advanced fuel processes is needed to assure profitable biorefinery operation. Industrial adoption of renewable carbon requires a financial incentive to justify the use of unfamiliar building blocks, the development of processes to convert these building blocks to final products, and the capital investment necessary to take the technology to commercial scale.

High value, lower volume biobased chemicals provide this incentive. Even though chemical production accounts for only 7–8% of oil imports in the US,[3–5] analyses reveal that a

biorefinery integrating biofuels and chemicals offers a much higher return on investment and meets its energy and economic goals simultaneously.[6,7] Such projections have prompted efforts to add coproducts into existing biorefinery models, such as corn wet and dry mills or pulp and paper operations, as a means to enhance revenue or repurpose existing underutilized infrastructure.[8] However, incorporating chemical products into the biorefinery's portfolio faces two primary challenges:

(1) Biobased chemical production is challenged by a lack of conversion technology. Conversion of renewable carbon to chemicals is the least developed and most complicated of all biorefinery operations, especially when compared to conversion processes available for nonrenewable hydrocarbons.[9] Promising hypothetical scenarios integrating fuels and chemicals do not require that the necessary conversion technology exists.

(2) Biobased chemical production is challenged by an overabundance of targets. Integrated biorefinery development is still in its infancy, and as such has yet to identify a core group of primary chemicals and secondary intermediates analogous to those used by the petrochemical industry. The range of potential targets includes structures already made by the chemical industry (and thus demonstrated as commercial products) as well as new structures formed from biorefinery building blocks. Rational selection processes for sorting these opportunities and portfolios would be a valuable tool.

Addressing these challenges presents an interesting problem for the integrated biorefinery. As the biorefining industry has expanded over the last ten years, its focus has been almost exclusively on single product operations making fermentation ethanol or biodiesel. Since the molecular structure of the desired output is known, engineering process analysis is ideally suited for determining price targets and identifying technologies that offer the best prospects for research investment.[10] But when applied to multi-product chemical scenarios, these analysis techniques are less useful because of fundamental differences between fuel and chemical research (Fig. 1).

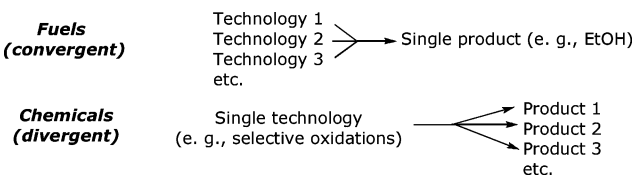

Fig. 1 Research approaches for biobased fuels and chemicals.

Research in fuels tends to investigate a wide number of different technologies to produce a single or very small number of pre-identified outputs, *i.e.*, biofuels research is *convergent*. If a technology for a fuel process does not meet predetermined cost targets, it is discarded in favor of more economical processes. For biofuels, focus on *product identification* leads the choice of technology.

If chemicals are included as part of the biorefinery's portfolio, the number of possible outputs soars. The experience of the chemical industry shows that this complexity is best handled by using broad-based technologies (selective reductions and oxidations, bond making/breaking processes, catalysis, *etc.*) to produce multiple outputs, *i.e.*, chemical production is *divergent*. Process analysis becomes complicated, as each target has its own set of process costs, depending on the market and application. If a technology does not meet the price targets of one product, it need not be discarded, since it may be applicable to a material with a different projected cost structure. For chemical production, focus on the *choice of technology* leads product identification.

Nonetheless, target-based approaches using process analysis methodology employed for biofuels persist as a means to winnow a huge number of possible biobased chemical targets to a manageable size.[11–13] Pre-identifying specific molecular structures prior to research is perceived to have several advantages, particularly in an industrial setting. It offers defined opportunities for decision makers when prioritizing limited research funds. It can also reduce risk, as preliminary process engineering estimates and life cycle analyses can address "what if" questions. The approach may also be more adaptable to a manufacturer's existing infrastructure and equipment.

However, the approach that is successful in existing single product biofuel scenarios is poorly suited for multi-product chemical scenarios, particularly when technology is in flux. The sheer number of new and existing structural possibilities suggests that the chances of process analysis correctly identifying a commercial winner are small. The analysis can be limited to structures currently manufactured by the petrochemical industry, but this approach can lead to uneconomical force fits of highly oxidized renewables into processes designed for highly reduced products.[14–16] Finally, structural pre-identification approaches have a short shelf life. Life cycle and process analyses employed at the beginning of a search may become moot as new technology is developed, and approaches once thought to be too expensive are rendered viable.

Accordingly, a number of evaluations have appeared that examine technology needs and opportunities.[17–22] The primary advantage of this approach is the tailoring of broad-based processes to the building blocks available from biorefinery process streams. It identifies those structures most easily obtained from a given conversion process, rather than trying to force a conversion process to fit a pre-identified structure. A technology-based approach also mirrors the experience of the petrochemical industry whose success was the result of research identifying technologies most applicable to the properties of the raw material, and the structures most easily made from these technologies. Distillation of crude oil provided kerosene. Kerosene production drove a study of thermal cracking, steam cracking and catalytic cracking.[23] Cracking technology led to olefins, gasoline and aromatics. In each case, the product slate from the processes changed and expanded. The primary disadvantage of this approach is its high-risk nature and need for longer-term programmatic commitment, making it harder to justify in a commercial environment.

The DOE "Top 10" reports successfully marry technology development needs with product identification

In light of these contrasting approaches to biorefinery development, the challenge for integrating biobased chemicals is finding the appropriate balance between the clear need for fundamental

Table 1 The DOE top chemical opportunities from carbohydrates, 2004

Succinic, fumaric and malic acids
2,5-Furan dicarboxylic acid
3-Hydroxypropionic acid
Aspartic acid
Glucaric acid
Glutamic acid
Itaconic acid
Levulinic acid
3-Hydroxybutyrolactone
Glycerol
Sorbitol
Xylitol/arabinitol

technology while demonstrating that this technology will lead to identifiable marketplace products. In 2004, the US Department of Energy (DOE) released the first of two reports outlining research needs for biobased products. This publication described a group of 15 (despite being colloquially known as the DOE "Top 10" report) target structures that could be produced from biorefinery carbohydrates.[24,25] Its methodology was an effort to provide a rational selection mechanism and a middle ground between a broad technology development approach and a target pre-identification approach. By developing a list of specific structures, the report embraced product identification as a guide for research. The targets reflected a methodology that included factors such as known processes, economics, industrial viability, size of markets, and the ability of a compound to serve as a platform for the production of derivatives. The evaluation led to the identification of the products shown in Table 1.

Nonetheless, the report simultaneously embraced fundamental research needs as a guide for product identification. Table 1 was not a closed list. By using these initial structures as a backdrop, the report was able to identify broad technology needs for the biorefinery. The intent of the report and its methodology was to catalyze identification and development of the technologies necessary for synthesis of multiple members of the list, or, ideally, structures not considered in the report.

Evaluation of recent technology advances provides a revised list of biobased product opportunities from carbohydrates—The "Top 10 + 4"

In the six years since the original DOE report, considerable progress in biobased product development has been made. This review revisits that report and presents an updated group of candidate structures based on advances since 2004. Some of the compounds described in this review are members of DOE's original list, and loosely represent advances made as a result of successful product pre-identification. Several new compounds also appear, and represent advances in technology development.

The need for improved conversion technology remains a challenge for the biorefinery. Thus, the amount of research activity reported in the literature was used as an initial screen to identify high interest compounds or processes. Correspondingly, limited research activity suggested that a given compound should receive lower priority. Several organic acids (fumaric, malic, aspartic, glucaric, glutamic and itaconic) from the 2004 list were in this category. However, research activity alone was not considered sufficient for inclusion on the list. Table 2 shows additional criteria used for prioritizing opportunities from the initial screen. The criteria are similar to those used in the 2004 report, and listed roughly in the order of importance as used in this evaluation, although the relative difference between adjacent criteria is small. Cost evaluations will ultimately be a crucial issue in commercial utility, but in parallel with the original DOE report, were not included in this evaluation. Since the technology base is still developing, cost structures will change as a result of ongoing research activity. Table 3 summarizes the compounds discussed in this review and the criteria employed for their inclusion, plus the broad technology areas represented by each structure.

Table 2 Criteria used in evaluating biobased product opportunities from carbohydrates

1. ***The compound or technology has received significant attention in the literature.*** A high level of reported research identifies both broad technology areas and structures of importance to the biorefinery.
2. ***The compound illustrates a broad technology applicable to multiple products.*** As in the petrochemical industry, the most valuable technologies are those that can be adapted to the production of several different structures.
3. ***The technology provides direct substitutes for existing petrochemicals.*** Products recognized by the chemical industry provide a valuable interface with existing infrastructure and utility.
4. ***The technology is applicable to high volume products.*** Conversion processes leading to high volume functional equivalents or utility within key industrial segments will have particular impact.
5. ***A compound exhibits strong potential as a platform.*** Compounds that serve as starting materials for the production of derivatives offer important flexibility and breadth to the biorefinery.
6. ***Scaleup of the product or a technology to pilot, demo, or full scale is underway.*** The impact of a biobased product and the technology for its production is greatly enhanced upon scaleup.
7. ***The biobased compound is an existing commercial product, prepared at intermediate or commodity levels.*** Research leading to production improvements or new uses for existing biobased chemicals improves their utility.
8. ***The compound may serve as a primary building block of the biorefinery.*** The petrochemical refinery is built on a small number of initial building blocks: olefins, BTX, methane, CO. Those compounds that are able to serve an analogous role in the biorefinery will be of high importance.
9. ***Commercial production of the compound from renewable carbon is well established.*** The potential utility of a given compound is improved if its manufacturing process is already recognized within the industry.

Omission of a specific compound does not mean a target or process is without merit. Rather, the compounds that are included represent those with the best balance between criteria given the current state of technology. The reader must note that categorizations such as those in Table 2, as well as other evaluations of biorefinery technology and opportunities,[26–42] include some subjectivity because the biorefining industry is in a state of rapid change and expansion. Three examples provide some illustration how the criteria of Table 2 were employed. Furandicarboxylic acid (FDCA) retains its place in the revised list. Neither FDCA nor any of its derivatives from the 2004 report were, or have yet become, commercial products. Nonetheless, improvements in the production of FDCA and its derivatives offer the potential of providing biobased replacements for polymers—the largest segment of

Table 3 New top chemical opportunities from biorefinery carbohydrates, criteria for their inclusion and resulting technology needs

Compound	Criteria for inclusion	Illustrative general biorefinery technology needs
Ethanol	1, 2, 3, 4, 5, 6, 7, 8, 9	Selective alcohol dehydrations; improved biochemical production of alcohols from biomass (rate, yield, titer, product, pH, inhibitor tolerance); engineering of optimal fermentation organisms
Furans	*Furfural*: 1, 2, 7, 8, 9	Selective dehydrations of carbohydrates; new catalysts and reaction media for dehydration; reactive separations; selective oxidations of alcohols; improved oxidation and dehydration catalysts; catalytic systems for reactions in aqueous solution
	HMF: 1, 2, 5, 8 *FDCA*: 1, 4, 5	
Glycerol and derivatives	1, 2, 3, 4, 5, 6, 7, 8, 9	Reactions in aqueous solution; selective reductions and oxidations of polyols; improved biological conversions of polyols
Biohydrocarbons	*Isoprene*: 1, 2, 3, 4, 6, 7	Improved biohydrocarbon production; engineering of organisms to convert sugars to hydrocarbons; optimizing rate, yield, titer, product tolerance
	Biohydrocarbons: 1, 2, 6	
Lactic acid	1, 2, 4, 7	Optimization of bioconversion of carbohydrates; bioprocesses with high rate, yield, titer, product, pH and inhibitor tolerance; engineering of organisms to produce single materials
Succinic acid	1, 2, 5, 6	Bioconversion of carbohydrates; optimization of yield, rate, titer, separation; engineering of organisms for optimal production of target
Hydroxypropionic acid/aldehyde	1, 3, 4, 5	Optimization of bioconversion of carbohydrates; bioprocesses with high rate, yield, titer, product and inhibitor tolerance; engineering of organisms to produce single materials; selective dehydrations of alcohols; selective reductions of carbonyl groups, new selective hydrogenation catalysts; chemical processes in aqueous solution
Levulinic acid	1, 2, 3, 5, 6, 8	Selective dehydrations of carbohydrates; improved separations of products; utility of co-product schemes by biorefinery; improved catalysts for selective carbohydrate conversion processes
Sorbitol	1, 2, 3, 4, 5, 6, 7, 8, 9	Selective hydrogenolysis of polyols; new catalysts for reduction of carbohydrate derivatives; selective dehydrations of polyols; comparative assessment of chemical and biochemical conversion technology; selective bond breaking/bond making technology for polyols
Xylitol	1, 2, 5, 8, 9	Selective hydrogenolysis of polyols; new catalysts for reduction of carbohydrate derivatives; selective dehydrations of polyols; comparative assessment of chemical and biochemical conversion technology; selective bond breaking/bond making technology for polyols

the chemical industry. A combination of this potential with the development of more efficient HMF production and one pot dehydration/oxidation of sugars to FDCA led to its retention. Conversely, glutamic acid was included in 2004 because its status as an existing commercial product suggested high potential as a source of new, albeit speculative, derivatives. Since glutamic acid has remained a terminal product of the chemical industry and research activity in either glutamic acid production or its use as a platform was minimal, other products received higher priority. Similarly, glucaric acid, a renewable building block used in new polyamides,[43,44] was omitted because it failed to pass the first screen. Little new information appeared since the original DOE report, yet its production is currently being investigated at the pilot scale by Rivertop Renewables. The proprietary carbohydrate oxidation technology is reported to be cost effective, environmentally benign and free of the waste products associated with conventional HNO_3 oxidation.[45] A commercial success would return glucaric acid to the list.

The criteria used in this evaluation may be insufficient for others developing their own list. A commercial chemical producer assessing issues such as unique market position, proprietary access to a specialized feedstock, experience in the field, specific IP, or existing infrastructure would probably end up with a much different group of opportunities. However, we believe that the criteria of Table 2 offer a reasonable starting point for identifying promising technologies and products for the biorefinery. A summary of the performance of the final group of compounds against these criteria is provided in Table 4.

Overview of the revised top chemical opportunities from biorefinery carbohydrates

The following sections provide a more detailed overview of the recent technology advances that contributed to identification of the compounds in Table 3 and the ability of these compounds to address the criteria of Table 2.

Ethanol

Biochemical transformation of biomass into fuel is represented almost entirely by fermentation ethanol. Many excellent reviews are available describing processing technology, cost structure, energy balance and research needs.[46–55] Ethanol was specifically omitted from DOE's original list because its expected high production volume categorized it as a so-called supercommodity. Recent technology developments and strategic commercial partnerships have positioned ethanol as a feedstock for chemical production, improving its platform potential. Ethanol and related alcohols (propanol, butanol) are of interest as precursors to the corresponding olefins *via* dehydration, providing a direct interface between the biorefinery and the conversion infrastructure of the petrochemical industry.[56]

Ethanol dehydration was the source of most ethylene in the early part of the 20th century, and can be carried out at extremely high conversion and selectivity in fluidized bed reactors over activated alumina. Vapor phase dehydration of ethanol at 400 °C affords a 99.9% selectivity to ethylene at 99.5% conversion.[57]

Table 4 Ranking of compounds against criteria in Table 2[a]

Compound	1. Extensive recent literature	2. Multiple product applicability	3. Direct substitute	4. High volume product	5. Platform potential	6. Industrial scaleup	7. Existing commercial product	8. Primary building block	9. Commercial biobased product
Ethanol	+++	+++	+++	+++	+++	+++	+++	+++	+++
Furfural	+++	++	+	++	+	+	+++	++	+++
HMF	+++	++	+	+	++	+	+	++	+
FDCA	+++	+	+	+++	++	+	+	+	+
Glycerol/derivatives	+++	+++	+++	+++	+++	+++	+++	+++	+++
Isoprene	+++	++	+++	+++	+	+++	+++	+	+
Biohydrocarbons	+++	++	+++	+	+	+	+	++	+
Lactic acid	+++	+++	+	+++	++	+	++	+	+
Succinic acid	+++	+++	+	+	+++	+++	+	+	+
HPA	+++	+	+++	+++	++	+	+	+	+
Levulinic acid	+++	++	+++	++	+++	+++	+	+++	+
Sorbitol	+++	+++	+++	+++	+++	+++	+++	+++	+++
Xylitol	+++	+++	+	+	+++	+	++	+++	++

[a] +++ = Good performance against criterion; ++ = emerging performance against criterion; + = lower performance against criterion.

However, with the advent of the petrochemical industry and the concomitant availability of cheap oil, production of ethylene from ethanol was discarded in favor of steam cracking processes. More recently, the low cost of sugar cane in Brazil coupled with increasing crude oil prices has spurred renewed interest in ethanol dehydration. Dow,[58] Braskem (Brazil's largest plastics producer)[59] and Solvay[60] have announced separate projects to build ethanol-to-ethylene plants based on sugarcane. Dow and Braskem will ultimately manufacture "green" polyethylene while Solvay will use ethylene to supply its polyvinylchloride capacity. The Braskem (180 000 tonnes per year) and Solvay (55 000 tonnes per year) projects are currently underway, while Dow (estimated polyethylene capacity of 320 000 tonnes per year) recently announced a delay in their construction plans.

Ethanol can also be oxidized to commodity chemicals using nanoscale gold catalysts. Ethanol oxidation over Au/TiO_2 or $Au/MgAl_2O_4$ gives nearly 95% selectivity to acetic acid at >90% conversion.[61] Kinetic isotope experiments and Hammett correlations suggest that the oxidation proceeds by generation of a cationic site at the alcohol, stabilized by the gold.[62] Further, ethanol can be oxidized in high yield over gold nanocatalysts or Mo–V–Nb mixed oxides[63] to give acetic acid and ethyl acetate.[61,64]

Furans

The dehydration of 5- and 6-carbon sugars to give furans is a well-known transformation for the preparation of furfural and hydroxymethylfurfural (HMF). These compounds were omitted from the original DOE list because of a static market for furfural, and the lack of high yield, selective conversion processes for HMF. Technology development has improved the dehydration of sugars to furans, improving their potential as platform chemicals in the biorefinery (Fig. 2).

Furfural. Xylose is the conventional starting material for furfural production. Treatment of xylose in a toluene–water mixture at 160° using modified acidic zirconia catalysts gave a 45% selectivity to furfural at 95% conversion.[65] Titanate and niobate catalysts,[66] silica-supported heteropolyacid catalysts[67] and niobium silicate catalysts have also been investigated.[68] In each case, the selectivity of the dehydration was moderate, consistent with the low yield/selectivity normally observed for the conversion of xylose to furfural. However, dehydration using a micro-mesoporous silica functionalized with sulfonic acid groups gave an 82% selectivity to furfural at 91% conversion.[69]

Hydroxymethylfurfural. C_6 sugars are converted to HMF upon dehydration. HMF is reactive, and can undergo conversion to levulinic and formic acids subsequent to its formation, leading to product mixtures and modest yields. Much higher yields of HMF are realized in ionic liquid media. Dehydration of fructose in methyl imadizolium chloride gives a 92% yield of HMF.[70] A recent report describes the conversion of glucose to HMF in 70% yield using a $CrCl_2$ catalyst in 1-ethyl-3-methylimadazolium chloride. The $CrCl_2$ is thought to promote isomerization of glucose to the furanoid form of fructose, leading to an intermediate more susceptible to dehydration.[71] Separation of the HMF from the ionic liquid is difficult, and in one case, required a continuous extraction of the reaction medium for several hours.[70] An alternative dehydration used choline chloride/citric acid as the ionic liquid medium to give HMF yields of 90% at 80 °C. The process could be carried out in a biphasic ionic liquid/EtOAc system to achieve 70% extraction of HMF in 20 min.[72]

Fructose is commonly employed as a starting material for HMF production. In acetone–water or methanol–water, fructose is converted to HMF at 77 and 78% selectivity and 98 and 99% conversion, respectively. DMSO offers advantages for dehydration of fructose as it eliminates HMF decomposition to levulinic and formic acids. In DMSO solution and in the presence of lanthanide ions, fructose is catalytically dehydrated to HMF in >90% yield. As observed for ionic liquids, the use of DMSO presents difficulty in separating the HMF for further use.[73] To minimize the use of DMSO, fructose was dehydrated in a 70/30 mixture of acetone–DMSO with a strongly acidic ion exchange resin to give nearly 90% yield of HMF after 20 min.[74]

Furanix, a division of the Dutch company Avantium, has developed technology to minimize levulinic and formic acid formation by isolating HMF as the corresponding ether or ester. Dehydration of fructose with ethanol in the presence of a variety

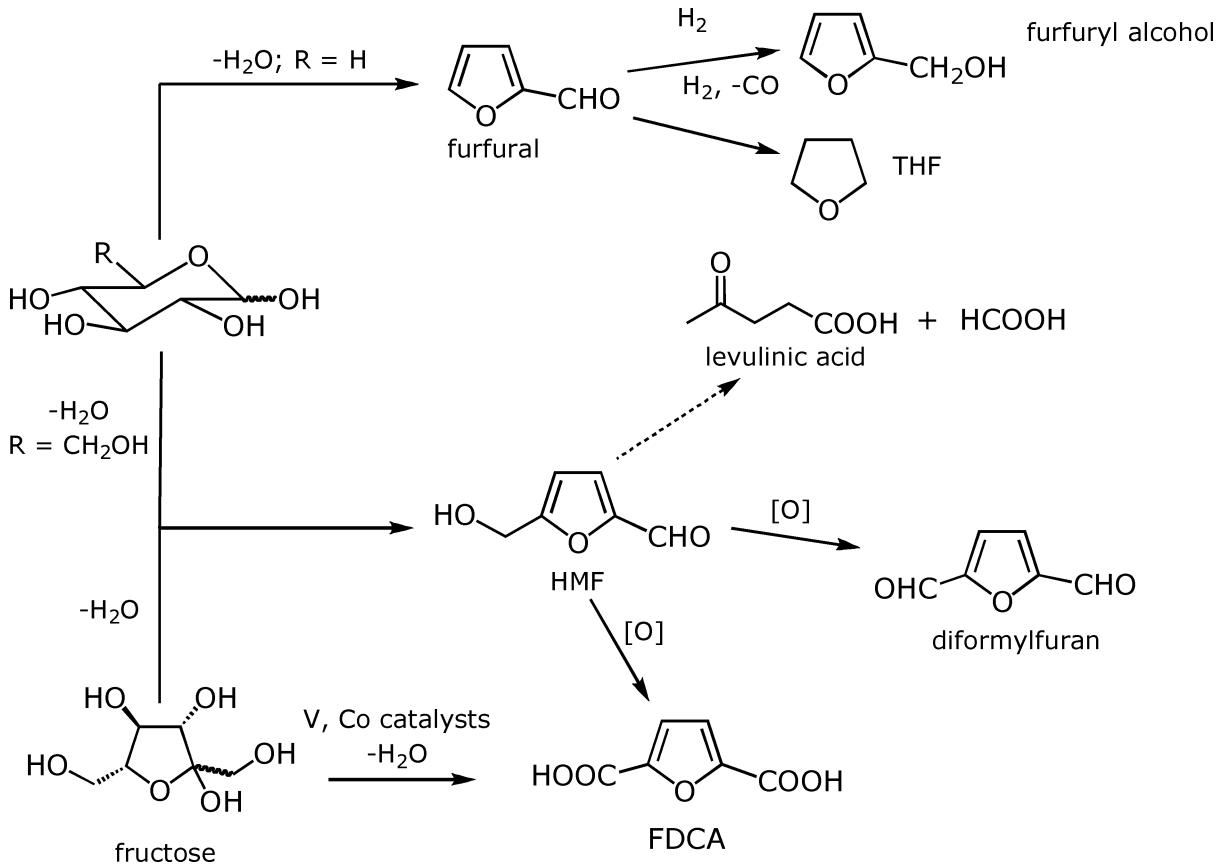

Fig. 2 Synthesis and transformation of furans.

of solid acid catalysts at 175–225 °C gave ethoxymethylfurfural in 38% selectivity at 98% conversion.[75] Similar reaction with acetic acid gave acetoxymethylfurfural in 20% selectivity at 98% conversion.[76] Execution of the same reaction in ionic liquids resulted in a marked improvement. Dehydration of fructose in a mixture of 1-ethyl-3-methylimadazolium chloride and 3-methylimadazolium bis(trifluoromethanesulfonyl) imide gave 75% yield of acetoxymethylfurfural and a 20% yield of HMF.[77]

Furan-2,5-dicarboxylic acid and diformylfuran. Furan-2,5-dicarboxylic acid (FDCA) has been suggested as an important renewable building block because it can substitute for terephthalic acid in the production of polyesters.[78] Several routes to FDCA have been reported, but all proceed *via* oxidation of HMF with air over different catalysts. Thus, improvements in HMF synthesis benefit production of FDCA. Oxidation of HMF under strongly alkaline conditions over a Pt/Pb catalyst gives quantitative formation of FDCA with 99% selectivity in two hours.[79] HMF oxidation was also studied with a series of conventional metal bromide catalysts (Co, Mn, Zr) used for the oxidation of *para*-xylene to terephthalic acid.[80] Depending on the oxidation conditions, either 2,5-diformylfuran or FDCA was isolated in 57% and 60% yield respectively.

One pot dehydration and oxidation of fructose to FDCA *via* intermediate HMF has been investigated. Vanadyl phosphate catalysts in DMSO converted fructose to FDCA in 97% selectivity at 84% conversion. When the solvent was changed to DMF, 93% selectivity at 56% conversion was observed. An attempt to carry out the reaction in water gave only minimal conversion to FDCA.[81] Alternatively, $Co(acac)_3$ in a silica sol–gel system gave 99% selectivity to FDCA from fructose at 72% conversion.[82] Very recently, formation of the dibutyl ester of FDCA in yields of 50–60% by the reaction of galataric acid and butanol in the presence of sulfuric acid has been reported.[83]

Glycerol and derivatives

Glycerol is not a carbohydrate, but structurally it can be considered as a "mini-sugar", in that transformations appropriate to glycerol may be applied to carbohydrates. Moreover, glycerol is a particularly important material because of its ready availability and strong potential to become a primary building block for the biorefinery. Technology for its manufacture is established, and processes for its conversion into higher value materials has received significant recent research attention. An expanding biodiesel market and the demand for green biofuels suggests that large amounts of inexpensive glycerol will be available. Indeed, higher value products from glycerol could provide an important revenue stream and reduction of dependence on subsidies for an industry that faces overcapacity issues on the fuel side.[84] Biodiesel-derived glycerol could be burned for process fuel value if the market becomes saturated, but higher value uses allow expanded production of biobased chemicals from an inexpensive feedstock. Some projections indicate costs as low as $0.11 per kg for crude glycerine solutions. Several technologies have emerged as candidates for conversion of glycerol into

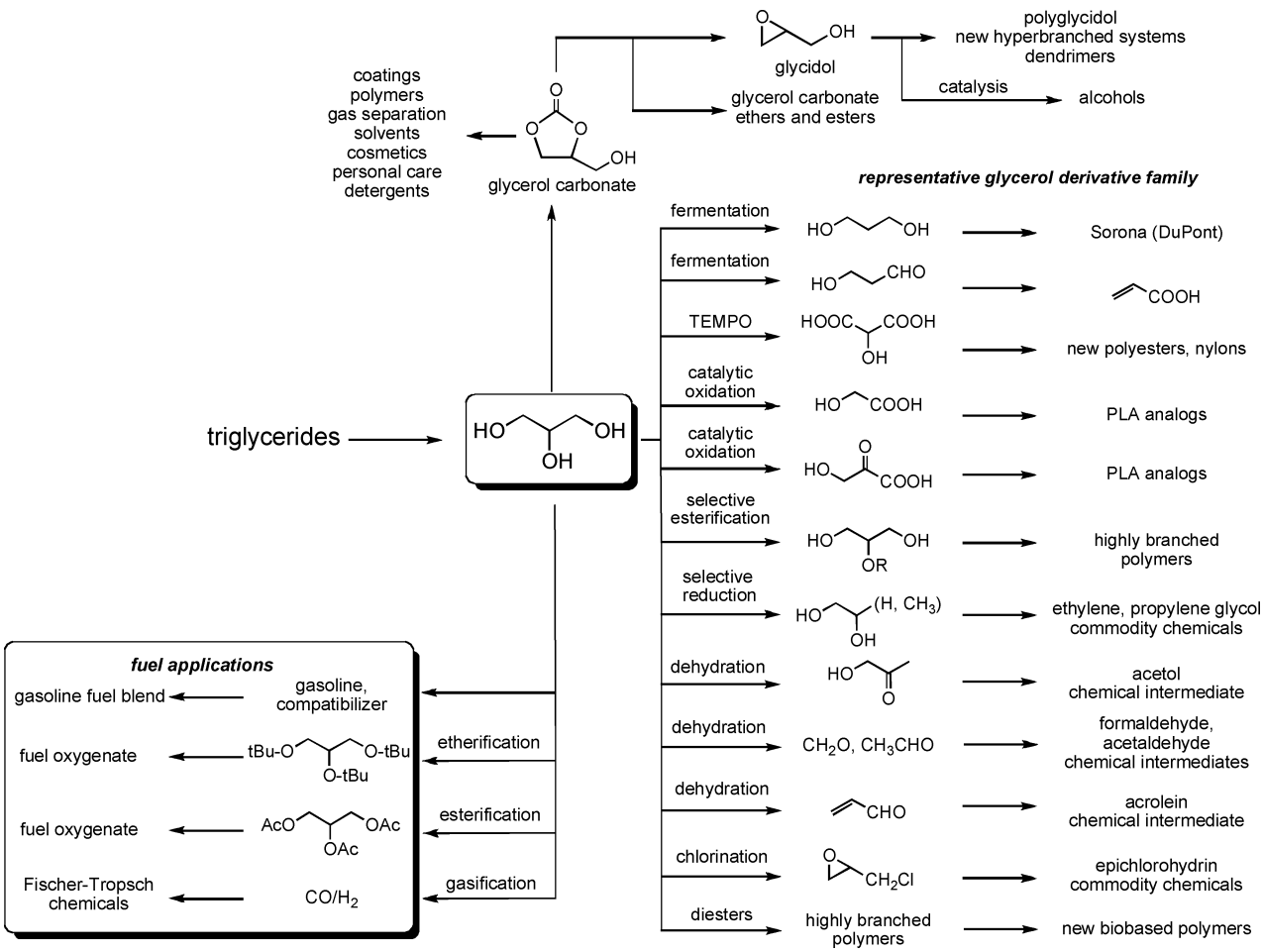

Fig. 3 Glycerol as a primary biorefinery building block.

chemicals (Fig. 3) particularly in glycerol reduction, dehydration and fermentation.[85–87]

Glycerol reduction processes. Catalytic hydrogenolysis converts glycerol into a family of derivatives, including ethylene glycol, propylene glycol, acetol and lactic acid. Suppes has reported a selective hydrogenolysis of glycerol to propylene glycol, a commercial material with an annual production of over 450 million kg.[88] Reduction of glycerol at 200 psi H_2 and 200 °C over a copper chromite catalyst gives propylene glycol selectivities of nearly 90% at 65% conversion. The mechanism of the reaction is suggested to be an initial dehydration of glycerol to acetol, followed by selective reduction of the carbonyl group. Suppes' route also offers product control. By altering the process conditions, acetol can be made as the primary product in greater than 90% selectivity by eliminating the hydrogen and using reactive distillation to convert glycerol to acetol.[89] Industrial interest in biobased propylene glycol has been significant. Senergy has licensed Suppes' technology and is reportedly piloting the process. Archer Daniels Midland (ADM) announced that a new propylene glycol plant will be starting in 2010. The plant will have a capacity of 100 000 tonnes per year and is closely linked to ADM's existing biodiesel production. Glycerol from biodiesel will be purified and converted to propylene glycol *via* catalytic hydrogenolysis. Additional industrial projects have been announced by Cargill, Virent and Dow.[90]

Alternative reductions of glycerol give different product profiles. Treatment of glycerol with hydrogen in the presence of Ru/C or Pt/C leads to mixtures of ethylene and propylene glycol. Carrying out the reduction in the presence of hydroxide bases induces formation of lactic acid as the major product.[91] In contrast, propylene glycol is formed in greater than 80% selectivity at 80% conversion using Ru/TiO_2 and Li_2CO_3 as the base.[92] A number of papers describe related catalytic hydrogenolysis of glycerol to propylene glycol, including processes using Ru/C and an Amberlyst resin,[93–95] and Cu/ZnO catalysts.[96] Treatment of neat glycerol with hydrogen and RANEY® Ni at 190° yields propylene glycol in 71% selectivity at 97% conversion.[97]

Glycerol dehydration processes. Catalytic and thermal dehydration of glycerol provides several derivatives. Depending on the conditions employed, dehydration occurs *via* loss of a primary hydroxyl group, leading to hydroxypropionaldehyde and acrolein, or at the secondary hydroxyl group, leading to hydroxyacetone. Acrolein has received recent attention as a precursor to acrylic acid, a high volume chemical with an annual production of 1.2×10^9 kg. Acrolein is produced in 86% selectivity at 70% conversion by treating glycerol in hot compressed water for 8 s under supercritical conditions

in the presence of H_2SO_4 or $Zn(SO_4)_2$ promoters.[98] Glycerol dehydration has also been carried out in the gas phase over supported acid catalysts. Acrolein was formed in 65% selectivity at 100% conversion over 15 wt% WO_3/ZrO_2.[99] A related catalyst, mesoporous silicotungstic acid, gave 85% selectivity to acrolein at nearly 100% conversion at 275 °C.[100]

Glycerol as a biochemical feedstock. Glycerol is a feedstock in biochemical transformations, with the majority of current research focused on its conversion to 1,3-propanediol (1,3-PDO). 1,3-PDO is one of the components of DuPont's Sorona (1,3-PDO and terephthalic acid), a polymer used in textiles and carpeting. Glucose is the current feedstock for 1,3-PDO using a transgenic *Escherichia coli* developed by Genencor and DuPont.[101] This organism is the basis of a recently opened commercial production facility in Loudon, TN.

Glycerol can also be biochemically converted to 1,3-PDO.[102] Inexpensive glycerol offers an alternative to glucose fermentation, and the advantage of a higher yield of 1,3-PDO. Glucose-based processes give high 1,3-PDO concentrations (>125 g L^{-1}), but their yield (g 1,3-PDO per g glucose) is only 30–40%. In contrast, the theoretical yield from glycerol is 67%. Fermentation of glycerol approaches the theoretical limit with genetically modified *Clostridium acetobutylicum*,[103] achieving concentrations of over 84 g L^{-1} in fed-batch cultures at a rate of 1.7 g L^{-1} h^{-1}. A drawback to production of 1,3-PDO from glycerol has been a need to use purified glycerol sources for most organisms. Various research groups are addressing this limitation with new fermentative organisms.[104,105] Fermentation of unpurified glycerine with engineered *C. acetobutylicum* gave no loss in productivity.[106] 1,3-PDO is also formed at a concentration of 53 g L^{-1} and a productivity of 1.7 g L^{-1} h^{-1} by treatment of crude or purified glycerol with *Klebsiella pneumoniae* in fed batch processes,[107] and from crude glycerol by *Clostridium butyricum* transgenics. The latter fermentation has been projected as an economical source of 1,3-PDO if the glycerol cost is $0.31 per kg.[108]

Cameron and coworkers have reported that minimizing the amount of methyl glyoxal and glycerol-3-phosphate produced during fermentation using engineered *E. coli* improves the conversion of glycerol to PDO by removing these two enzyme inhibitors.[109] Cameron *et al.* have also described engineering *E. coli* for a biochemical production of 1,2-propanediol.[110] This process proceeds through dihydroxyacetone as a metabolic intermediate, implying that proper choice of organism could lead to either 1,2- or 1,3-PDO from glycerol, since one of the first intermediates in 1,3-PDO production is also dihydroxyacetone.[102]

Glycerol carbonate. Glycerol carbonate offers interesting opportunities to the chemical industry, as it can be prepared directly and in high yield from glycerol. Glycerol carbonate has been investigated as a component in gas separation membranes, polyurethane foams[111] and surfactants,[112] as a nonvolatile reactive solvent, as a component in coatings, and as a source of new hyperbranched polymers.[113] At low glycerol costs, glycerol carbonate could replace dimethyl carbonate in the production of green polycarbonates and polyurethanes. Glycerol carbonate is prepared by the reaction of glycerol with urea at 120° in diethylene glycol for 24 h (58% yield)[114] or the treatment of glycerol with ethylene or propylene carbonate.[115] Direct production of glycerol carbonate from glycerol and carbon dioxide under supercritical conditions or in the presence of tin or cerium catalysts has also been reported.[116,117] Recently, glycerol carbonate has been synthesized biochemically in high yield by the reaction of glycerol and dimethyl carbonate in the presence of an immobilized lipase from *Candida antarctica*.[118]

Epichlorohydrin. Recent work has examined the use of glycerol as a starting material for the production of epichlorohydrin. Traditional routes to epichlorohydrin hydroxychlorinate propylene, and proceed through 1,3-dichloro-2-propanol as an intermediate, which is treated with base to form epichlorohydrin.[9] This process also forms the 1,2-dichloro isomer, which is much less reactive. In contrast, glycerol forms the 1,3-isomer with high selectivity, making it a viable starting material for epichlorohydrin. The kinetics and mechanism of this reaction have been examined.[119] A new Dow process exploits this selectivity, providing an interface between biobased building blocks and high volume industrial products (Fig. 4).[120]

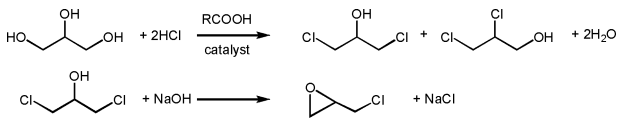

Fig. 4 Conversion of glycerol to epichlorohydrin.

Reaction of glycerol with 2 equivalents of HCl in the presence of a carboxylic acid catalyst (generally HOAc) forms 1,3-dichloro-2-propanol and very small amounts of the 1,2-isomer. Further treatment with base induces ring closure and elimination of a single equivalent of NaCl. The reaction sequence offers several advantages over the commercially practiced route *via* propylene hydrochlorination, including improved regioselectivity of the chlorination step, reduction of byproduct formation, and a decrease in chlorinated waste from 2 equivalents to one. Under optimum conditions, glycerol is chlorinated to the 1,3-isomer in 93% yield. A similar process with a proprietary catalyst has been patented by Solvay and is under commercial development. By using glycerol as the starting material, the Solvay process reduces chlorinated residues eightfold and water use by 90% over conventional epichlorhydrin processes. The company is planning to build a 100 000 tonne per year facility in Thailand to be operational by the end of 2009.[121]

Biohydrocarbons

Considerable work has appeared describing new processes for the biochemical production of hydrocarbons from biorefinery sugars. Such processes will be important for expansion of the biorefinery, as they provide a direct drop-in interface between the biorefining industry and the existing petrochemical industry.

Isoprene. Isoprene is a high value hydrocarbon with a world market of $1–2 billion. The immediate precursor to isoprene and naturally occurring polyisoprenoids is isopentenyl diphosphate (IPP). Two biosynthetic routes to IPP have been described.[122,123] In eukaryotes and archaea, IPP is formed by *via* mevalonate. In certain bacteria, an alternate path is followed that proceeds through methylerythritol phosphate.

In late 2008, Genencor and Goodyear announced a joint program to commercialize the manufacture of isoprene from bacterial sources by 2012 as a domestic approach to rubber production. Although Genencor has not revealed the exact process under development, they have licensed patented technology from the University of Colorado.[124] This patent describes the use of several *Bacillus* species (*B. subtilis* and *B. amyloliquefaciens*) as high yield producers of isoprene.[125] In March 2009, Genencor announced delivery of the first shipments of bioisoprene to Goodyear.[126]

Other hydrocarbons. Production of long chain hydrocarbons from *Botryococcus braunii*, a green microalga, has been suggested as a biological source of hydrocarbons and ether lipids. Depending on the race of *B. braunii*, hydrocarbons, ether lipids, epoxides, triacylglcerols or sterols have been identified. The biosynthesis of botryococcene hydrocarbons has been examined, and is suggested to proceed through a nonmevalonate formation of isoprenoid building blocks.[127] Currently, large-scale cultivation of these species has not proven economically viable, but advances in genetic engineering of these materials as a potential solution to the limiting factors has been reviewed.[128]

Bioproduction of long chain hydrocarbons was reported using a bacterium isolated from sewage disposal sludge and identified as *Vibrio furnissii*. Using short chain fatty acids as the feedstock, extracellular production of hydrocarbons ranging from C_{15} to C_{24} in yields as high as 120% of cell dry weight was observed.[129] Further examination showed that *V. furnissii* M1 could produce a variety of hydrocarbons using either volatile organic acids or sugars commonly found in organic waste sources.[130] The mechanism of formation was suggested to be a stepwise reduction of the starting organic acid group to the aldehyde, alcohol, and finally, alkane.[131] More recently, attempts to reproduce this work have failed to produce alkanes using *V. furnissii*.[132] Further work is necessary to confirm whether the original observations are accurate. Several *Arthrobacter* species were reported to synthesize long chain C_{29} alkenes.[133]

Organic acids

Organic acids constitute a significant fraction of those compounds available in a minimum number of steps from biorefinery carbohydrate streams, and as such have received much attention as platform chemicals.[134] The following section presents additional details on recent advances in the utility of selected organic acids.

Lactic acid. Lactic acid is a well-recognized biobased chemical, commercially produced by glucose fermentation using organisms such as *Lactobacillus delbrueckii*,[135] as well as other organisms and biomass sources.[136] Current commercial fermentation gives about a 90% yield of calcium lactate based on glucose fed, which is neutralized to give pure lactic acid. The neutralization produces approximately 1 ton of $CaSO_4$ for every ton of lactic acid, presenting a waste disposal problem in commercial operation. Alternative separation and purification technologies based on desalting and water splitting electrodialysis have been examined to eliminate the neutralization step.[135] More recently, engineered yeast species, such as *Pichia stipitis* have been reported to ferment xylose to lactate.[137] The process offers the possibility of converting all lignocellulosic sugars to a high value chemical, and performing the fermentation at lower pH, perhaps eliminating the need for subsequent neutralization.

The primary use for lactic acid is the production of polylactic acid (PLA, Fig. 5). Although lactic acid can undergo direct polymerization, the process is more effective if lactic acid is first converted to a low molecular weight pre-polymer (MW ~ 5000) and then depolymerized to the lactide. A wide range of catalysts is known to promote the lactide polymerization.[138,139] The resulting polymer exhibits performance properties similar to or exceeding polystyrene, a storage resistance to fatty foods and dairy products equivalent to polyethylenterephthalate, excellent

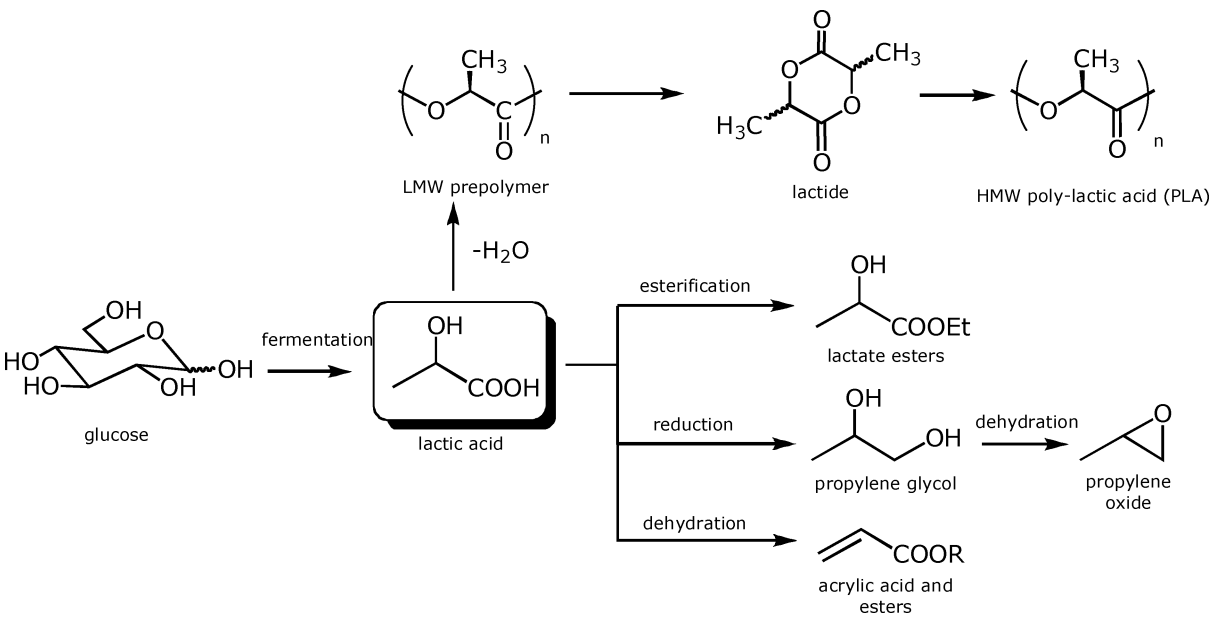

Fig. 5 Overview of lactic acid conversions.

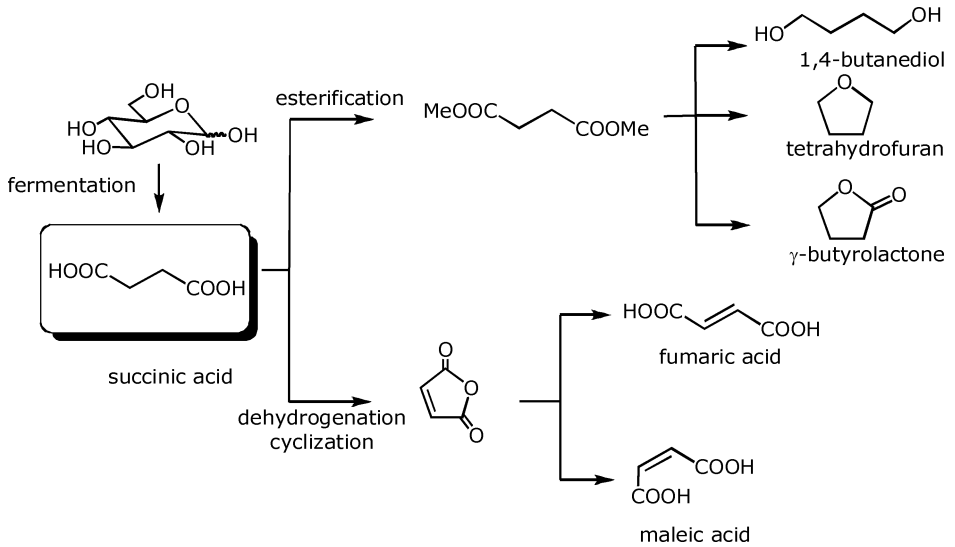

Fig. 6 Succinic acid as a platform chemical.

barrier properties for flavors and aromas, and good heat sealability.[140] Cargill-Dow has published an extensive life cycle analysis of the polymer.[141]

Lactic acid has been suggested as a platform chemical for the production of several downstream chemicals. Lactic acid undergoes ready esterification to give lactate esters, of interest as new "green" solvents.[142] Catalytic reduction of lactic acid leads to propylene glycol, which can be further dehydrated to give propylene oxide. Alternatively, lactic acid can be dehydrated to give acrylic acid and esters, but in practice this conversion proceeds in low yield.[143] Lactic acid can be spun using wet, dry, and electrospinning techniques to give biodegradable fibers for apparel, furniture, and biomedical materials, such as dissolving sutures.[144] New nanostructural materials prepared from lactic acid using electrospinning have found use in neural tissue engineering.[145]

Succinic acid. Succinic acid is a widely investigated chemical building block available from biochemical transformation of biorefinery sugars.[146] Using *Anaerobiospirillum succiniciproducens* as the fermentative organism and a three stage continuous cell recycle bioreactor, optimized processes producing 10.4 g L^{-1} h^{-1} and a final concentration of 83 g L^{-1}, equivalent to 1.35 mol succinic acid per mol sugar have been reported.[147] Recent investigations using engineered *Mannheimia succiniciproducens* have commercial potential, as high yields of succinic acid are observed with little or no formation of acetic, formic or lactic acid byproducts.[148] Recombinant *E. coli* also gives effective production of succinate from glucose (1.3 moles succinate per mol glucose).[149] The process has been licensed by Roquette, and is part of a Roquette/DSM joint venture to commercialize succinic acid by the end of 2009.[150] An alternative *E. coli* strain originally developed by the US Department of Energy[151] has been licensed by Bioamber, which recently commissioned a 2000 tonne per year production facility.[152]

Succinic acid offers strong potential as a platform chemical. Succinate esters are precursors for known petrochemical products such as 1,4-butanediol, tetrahydrofuran, γ-butyrolactone or various pyrrolidinone derivatives. As with lactic acid, succinic acid is isolated initially as a salt. Electrodialysis has been examined as a means to convert the salt to the corresponding acid while minimizing waste. Direct hydrogenation of the aqueous fermentation broth has also been studied.[153] Succinic acid is a component of biobased polymers, such as nylons or polyesters.[154,155] A recent publication describes the conversion of succinic acid into a new polyester for coating applications upon polymerization with isosorbide, a renewable building block also available in high yield from glucose.[156] The market potential for succinic acid and its immediate derivatives has been projected to be as much as 245×10^3 tonnes per year, with an estimated market size for succinic acid-derived polymers being as high as 25×10^6 tonnes per year. The use of succinic acid as a platform chemical is summarized in Fig. 6.

3-Hydroxypropanoic acid and 3-hydroxypropionaldehyde. Glycerol is converted to 3-hydroxypropionaldehyde (3-HPA) *via* fermentation.[157] Although research on 3-HPA is still exploratory, it is of interest as the central component in a network of several high volume biorefinery products. Bioproduction of HPA suffers from product inhibition because of its toxicity.[158] New processes mediate its toxic effects, including product removal during fermentation,[159] conversion of 3-HPA into its semicarbazide derivative *in situ* after fermentation with *Klebsellia pneumonia*,[160] or fermentation using *Lactobacillus reuteri*. In aqueous solution, *L. reuteri* exhibits significantly higher tolerance toward 3-HPA than other organisms and converts glycerol to reuterin, a natural antimicrobial that is an equilibrium mixture of 3-HPA, 3-HPA hydrate, and the 3-HPA dimer. The antimicrobial properties of reuterin have been used in the food industry to inhibit growth of *Listeria* or *E. coli* in meat and dairy products.

Fig. 7 summarizes several possible derivatives of 3-HPA. Large scale use of 3-HPA would result from combining the high yield of 3-HPA from *L. reuteri* or other processes with conventional catalytic hydrogenation to give 1,3-propanediol.[161–163] A one-pot approach is possible, as 3-HPA hydrogenations in

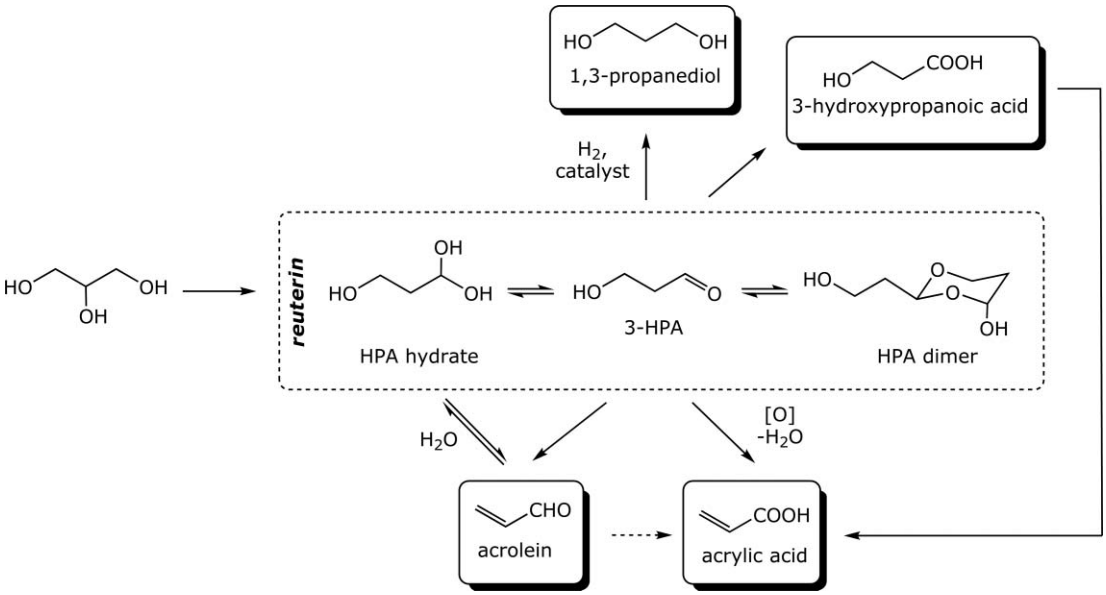

Fig. 7 Production of 3-HPA and related derivatives.

aqueous solution have been reported.[164] Alternatively, 3-HPA is a precursor to acrolein and acrylic acid. Heating of aqueous 3-HPA solutions gives acrolein, the current industrial precursor to acrylic acid. However, no commercial process based on this technology has been developed.[165]

3-HPA is also a precursor to 3-hydroxypropanoic acid, which has been observed in low concentrations from a number of biosynthetic conversions of glycerol.[166] Catalytic dehydration of 3-hydroxypropionic acid forms acrylic acid and acrylate esters.[167] A recent study has described potential routes and an economic evaluation for the direct biochemical production of acrylate based on the observation of the acrylate coenzyme A ester as a common intermediate in several metabolic pathways.[168] Research has been carried out to engineer appropriate metabolic pathways to favor acrylate production, but yields remain low.[169,170]

Levulinic acid. Levulinic acid is of interest as a primary biorefinery building block and platform chemical because of its simple and relatively high yield production from acid treatment of C_6 sugars. However, its isolation and purification can be complicated by the presence of intractable materials. Accordingly, the complex mechanism behind its formation continues to be investigated (Fig. 8). Heeres and coworkers have reported a series of kinetic investigations on the formation of levulinic acid and its intermediates from both monomeric sugars and cellulose. Formation of levulinic acid proceeds by initial loss of water to form HMF as an intermediate. Readdition of water to HMF induces ring cleavage to form levulinic acid and an equivalent of formic acid. Kinetically accessible reactions also drive formation of intractable humins from the starting sugar or intermediate HMF.[171–173] The results of the mechanistic study suggest that ideal conditions for levulinic acid formation from glucose may be obtained with dilute sugar solutions and high acid concentrations.

High yield industrial production of levulinic acid from C_6 polysaccharides has been achieved by Biofine Renewables using a proprietary two reactor system to minimize conditions suitable for side product formation.[174] Reactive extraction of levulinic acid from aqueous media with a family of different solvents containing Amberlite LA-2 has been investigated as a means to improve isolation and purification.[175] Recently, production of levulinic acid from lignocellulosic feedstocks such as wheat straw and water hyacinth has been reported.[176,177] The latter work showed good agreement between experimentally observed rates and the kinetic models established in earlier studies, to give a 53% molar yield of levulinic acid.

The use of levulinic acid as a platform chemical continues to be studied.[178] Manzer has reported elegant, high yield catalytic transformations of levulinic acid into substituted pyrrolidones, lactones and levulinate esters.[179] Supported heteropoly acids (HPAs) have been investigated as catalysts for the conversion of levulinic acid into diphenolic acid, a potential green replacement for bisphenol A in the production of polycarbonates.[180] With Cs substituted HPAs, diphenolic acid selectivities of greater than 80% for the *para*, *para* isomer at 30–40% conversion have been reported.[181] Ketals of levulinic acid are being investigated commercially by Segetis as a source of new biobased monomers and polymers for applications as solvents, polyurethanes and thermoplastics.[182] Acid-catalyzed reaction of levulinic acid with glycerol affords good yields of a polymeric material that is cleaved by subsequent treatment with NaOMe in MeOH.[183]

Sugar alcohols

Xylitol. Xylitol is prepared commercially by catalytic hydrogenation of xylose but several biochemical reductions have also been investigated. Although biochemical reduction cannot yet compete with chemical reduction economically,[184] an important advantage would be the ability to use crude biomass hemicellulose hydrolysate (the primary source of xylose) as a starting material, rather than isolated and purified xylose. Engineered *Saccaromyces cerevisiae* and various *Candida* yeasts have been examined, with *Candida* having the advantage of being natural

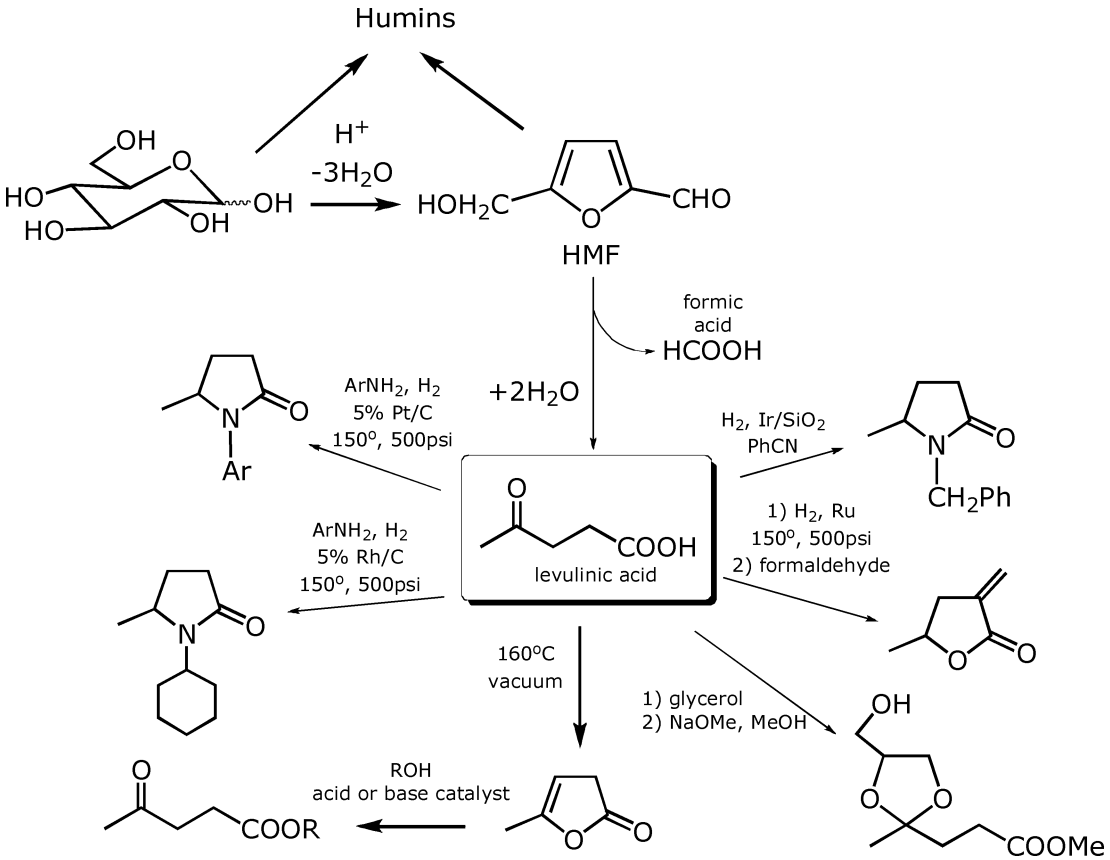

Fig. 8 Formation and transformations of levulinic acid.

xylose consumers, and being better able to maintain the redox balance necessary for high yield xylitol production.[185,186] Xylose concentrations of up to 38 g L^{-1} were observed in batch systems using engineered *E. coli* expressing xylose reductase from *C. boidinii*.[187] An issue in biochemical and chemical production of xylitol is the parallel reduction of arabinose frequently present in hemicellulose solutions used as starting material. The formation of arabinitol as a side product complicates product isolation. Using directed evolution of fungal sources of xylose reductase, a mutant was identified that exhibited a 16.5-fold preference for xylose over arabinose. When expressed in *E. coli*, highly selective production of xylitol from a mixed solution of xylose and arabinose was observed.[188]

Sorbitol. Biochemical production of sorbitol has also been investigated, although chemical reduction of glucose is well established and produces over 500 000 tons of sorbitol per year. A number of high yielding biochemical routes to sorbitol have been reported, focusing primarily on *Zymomonas mobilis* as the fermenting organism. Starting from sucrose or mixtures of fructose and glucose, production of sorbitol and gluconic acid as co-products in nearly quantitative yield has been observed.[189] More recently, efficient conversion of glucose to sorbitol in 97% of the theoretical yield using resting cells of an engineered *Lactobacillus plantarum* has been reported.[190]

Sugar alcohols are promising intermediates for the production of hydrocarbons as drop-in products for the petrochemical refinery. Huber and Dumesic have reported the chemical conversion of sorbitol to light alkanes *via* aqueous phase reforming.[191] Pt/Al_2O_3 is the preferred catalyst for the transformation, and promotes conversion of sorbitol into hexane at 50% selectivity. The remainder of the sugar is converted to lighter materials (Fig. 9). The bifunctional catalyst induces several reactions. Sorbitol is dehydrated on the catalyst's acidic sites, and the resulting intermediates are hydrogenated on the metal sites. Through several dehydration and reduction cycles, sorbitol is converted to hexane. Reforming of the sorbitol on metal sites leads to the formation of CO_2 and H_2, which is converted to methane. Light hydrocarbons result from hydrogenolysis of the sorbitol.

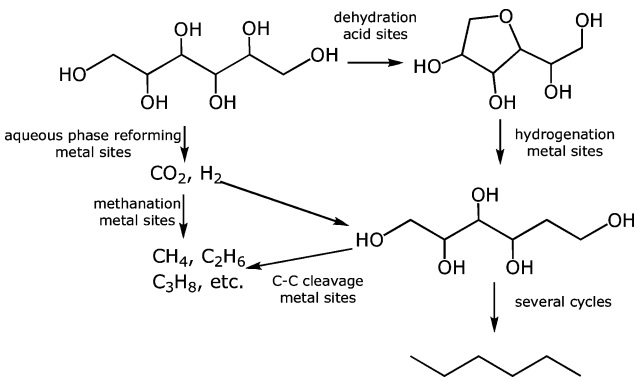

Fig. 9 Proposed intermediates in the aqueous phase reforming of carbohydrates to light alkanes.

Concluding comments

Integrating biobased products into the biorefinery faces a tension between "what structures result easily from a given technology?" (*i.e.*, a lack of conversion processes) and "what product should we make?" (*i.e.*, an overabundance of targets). Answers to these questions will result from fundamental research in biomass transformation evolving into the best commercial opportunities. The methodology presented in DOE's 2004 report and updated in this review attempts to provide a framework for using specific chemical structures to select broader biomass conversion technologies and research opportunities.

We note that advanced biofuels will play an important role in near-term biorefinery development and will supplement first generation ethanol and biodiesel.[192,193] Space limitations prevented a discussion of new opportunities in biofuels (such as biobutanol), but as the number of fuel candidates increases, methodology and selection criteria similar to those used for bioproducts should also be applicable to the identification and prioritization of advanced biofuels. Regardless of whether chemicals or fuels are evaluated, it is important to reiterate a theme of the original report. The list of compounds highlighted in this review should not be interpreted as an attempt to "pick winners". Rather, the list is a dynamic guide to technology development, which, if successful, may lead to commercial opportunities using the structures in Table 3 or families of new products not currently on the list. The "Top 10" of 2015 will be different from that of 2009.

Unfortunately, projections are relatively easy—implementation will be an entirely different issue that is outside of the scope of this review. Success depends on finding the right mix of ongoing efforts in biofuels with opportunistic, patient integration of biobased products as conversion technology develops and expands. Biobased products will be crucial in realizing the biorefinery's strategic energy and economic goals, but diversifying the portfolio beyond biofuels to incorporate products will include assessment of:

- The fit of a product within the business plans of the biorefinery owners and operators;
- Final product cost and purity and utility as either a platform or terminal output;
- The value proposition of incorporating new technology into an integrated operation;
- Whether the cost of integration and capital investment for products is justified, *i.e.*, whether in the short term the greatest benefit would be realized simply by an increase in fuel production;
- How integrated biorefineries and standalone bioproduct facilities compare, and whether process economics can withstand the costs of infrastructure development in the absence of biofuels;
- Market needs that could serve as drivers for inclusion of biobased products, such as avoidance of undesirable chemical reagents or product diversification needs.

None of these concerns will be unique to biorefinery development. The status of today's petrochemical industry is the result of successfully addressing these issues. Proper combinations of a product and technology selection process with reasonable business development plans offer the prospect for a similar outcome within a mature biorefining industry.

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