Green Chemistry

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Journal:	*Green Chemistry*
Manuscript ID	GC-CRV-02-2021-000638.R1
Article Type:	Critical Review
Date Submitted by the Author:	29-Mar-2021
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A Critical Review on the Progress and Challenges to a More Sustainable, Cost Competitive Synthesis of Adipic Acid

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Abstract

Adipic acid is a key organic diacid intermediate used in nylon manufacturing. It is primarily produced by an industrial process that can form nitrous oxide as a byproduct. Nitrous oxide has a 300-fold higher global warming potential than carbon dioxide, and an estimated 10% of its annual global emissions are a result of adipic acid production. These concerns have led to significant efforts for the development of nitrous oxide mitigation technologies as well as more environmentally friendly routes for adipic acid production. New processes include both advanced chemical and biotechnological routes. In this review, we discuss key recent developments in mitigation as well as new technologies. We also provide a critical look at the potential of new technologies to compete with the incumbent process and highlight key remaining technical challenges to the development of greener (environmentally sustainable) and cost competitive (commercially sustainable) processes for adipic acid manufacture.

Key Words: Adipic acid, nylon, sustainability, green chemistry and biosynthesis

Introduction

Adipic acid (ADP), a six carbon diacid, is primarily used in the production of nylon 6,6 (about 75%), it also serves as a starting material for polyurethanes and plasticizers that can be used to make polyvinyl chloride, the world's third-most widely produced synthetic plastic polymer. (1) The annual global production of ADP exceeds 3 million tonnes, growing at a rate of 3-5% annually, with a 10 year average price of $1.60 +/- 0.26/kg.(1–3) The global market for ADP is expected to exceed $8 billion USD by 2025. (2,3) However, historically a major concern of ADP manufacturing is its negative environmental impact. In 2016, U.S. petrochemical production released 37.3 million metric tonnes (MMT) of CO_2 equivalents (CO_2, CH_4 and NO_2). (4–6) The production of adipic acid alone, due to release of nitrous oxide (NOx), was responsible for nearly 20% of these emissions.(4,6) In addition, the ADP manufacturing chain has been responsible for other environmentally hazardous wastes. (4–6) Benzene, the primary feedstock for ADP, is a non-renewable petroleum based feedstock as well a volatile carcinogen.(7,8)

Given the growing demand for ADP and the desire to reduce its negative environmental impact, significant effort has been recruited for the development of a more sustainable process. (9) Work with petroleum-based feedstocks has focused on NOx mitigation strategies and alternative routes to ADP that do not produce NOx. Additionally, both the chemical and biological conversion of renewable feedstocks (such as glucose, glycerol or lignocellulosic sugars) have been extensively evaluated. Unfortunately, to date, current alternative routes to ADP are not competitive with the traditional chemistry.(10) Previous extensive reviews have been dedicated to new catalytic processes, [13] or biotechnology based approaches to manufacture ADP, [1, 10] (for more detailed summaries of technical approaches, we would point the reader to these reviews). Additionally, recent technoeconomic analyses have reported the potential of newer greener processes to reach competitive selling prices.(11,12) A key gap in the current literature in this space is direct critical

comparison of the commercial potential of these new potential processes with each other as well as the incumbent and newer petrochemical alternatives. This review is focused on providing an overview and comparison of new competing routes to ADP from a technoeconomic review. Specifically, we discuss key performance metrics and constraints that any new process must overcome to compete with the incumbent technology, as well fundamental challenges for various routes, as well as more global challenges to biobased ADP that are independent of conversion technology.

Current manufacturing processes

In order to evaluate the potential of new technologies, we first must discuss the incumbent process. ADP is primarily manufactured *via* the Nitric Oxidation (NO) process; a two-step oxidation of cyclohexanone and cyclohexanol mixture (KA) catalyzed by nitric acid. (1,13,14), (15,16) This reaction was developed in the late 1930's and is illustrated in Figure 1b. ADP is typically produced in a one pot reaction starting with benzene as the initial feedstock.(3,17,18) After reduction of benzene to cyclohexane, at high temperature and pressure, cobalt aerobically oxidizes this intermediate to form KA oil. (17,19) KA oil oxidizes more readily than cyclohexane, thus, limited oxidation is necessary to prevent undesired byproducts.(20,21) This results in the need to recycle 90% of unreacted cyclohexane, as illustrated in Figure 1c. Finally, KA oil is oxidized with excess HNO_3 to produce ADP with a conversion yield of ~95%.(3)

Several additional chemical routes have also been described for the manufacture of ADP (Fig. 1), but the initial cyclohexane-based oxidation route accounts for ~93% of the global ADP production (Fig. 1h), with cyclohexane being primarily produced as ADP's precursor. (3) A variant

of the NO process, namely the two-step hydration/oxidation of cyclohexene *via* cyclohexanol is a second process currently used for ADP production (Fig. 1a). (21,22) The major downside of this route, like the NO process, remains the requirement for nitric acid for the final oxidation of cyclohexanol to ADP, and the subsequent generation of NOx.

The major drawback of the final step is the stoichiometric generation of the byproduct nitrous oxide (NOx).(19) NOx is well known for its negative environmental impacts: ozone layer damage, acid rain causation, and a 300-fold higher global warming potential than carbon dioxide CO_2.(23) It is estimated that a complete replacement of the NO process could reduce 7.9 million tonnes of CO_2 equivalents per year. (24) The average personal vehicle is estimated to emit ~ 5.23 metric tonnes of CO_2 annually; the equivalent to taking 1.5 million cars off of the road.(25) Significant effort has been made to recycle and/or thermally decompose NO_2 into N_2 and O_2. Currently, the NOx emissions are abated or recycled using different technologies such as catalytic destruction, thermal decomposition, and as well as using NO_2 for nitric acid production, which can achieve recycling levels of ~ 90%. Current abatement technologies can achieve as high as a 99% reduction in NOx emissions. (3,26–28) However, these steps necessitate *in situ* downstream treatments and, thus, require additional capital expenditures. Despite a large reduction of NOx emissions thanks to newer abatement technologies, there are still a large number of ADP plants worldwide without these recycling processes in place due to differing governmental policies.(3) Additionally, the NO process has been described as one of the least efficient amongst major industrial petrochemical processes currently in use.(3,19) Given the continuously growing global demands for ADP, the development of routes to ADP that eliminate all NOx emissions have remained desirable.

Developing process technologies to compete with the NO process is not a small feat. As mentioned above, benzene is effectively the feedstock for ADP, and at maximal theoretical yields 1 mole of ADP can be produced from 1 mole of benzene, resulting in a yield of 1.87 g ADP/ g benzene (with incorporation of oxygen enabling yields greater than 1g/g). The ten year historical pricing for benzene is estimated at ($1.02/kg +/-0.2/kg). (29,30) Thus translates to >$0.55/kg for the cost of feedstock alone in the production of ADP using this traditional route. We estimate at current overall conversion yields of >90% and with benzene feedstock costs accounting for 70-80% of the cost of production, that operating costs for ADP production via the NO process range from $0.72-$0.87/kg, when produced in fully depreciated assets (Supplemental Table S1). (31,32) The NO process is expected to remain the major route for ADP manufacturing as long as benzene prices are low, unless greener cost competitive technologies can be developed and scaled. (33)

Greener petrochemical routes

The fact that adipic acid, one of the most important platform industrial chemicals, is still being manufactured with an unsustainable, inefficient multistep process involving an aggressive oxidant (HNO_3) and generating large amounts of nitrous oxide gas, have raised many concerns. (3) Despite the development of NOx abatement technologies, the use of NOx free routes to ADP has garnered significant effort. Not only would it greatly alleviate the burden of controlling greenhouse gas emissions, but it also could have the potential to reduce the capital cost investments associated with the installation of abatement systems *in situ*. To address this, various petrochemical feedstocks, and oxidants have been evaluated in the development of new or improved NOx free and more sustainable chemical routes to ADP. (3,13,14,34,35) These routes are discussed below.

Alternative oxidants: H_2O_2 and O_2

Replacing HNO_3 with hydrogen peroxide (H_2O_2) or molecular oxygen (O_2) has been a key strategy to enable a NOx free process. (3,19,36,37) H_2O_2 has a high molecular oxygen (47%) content, high reactivity (enabling the activation of C-H bonds), and produces benign by-products. Over the last two decades, many studies have successfully reported a high yield ADP process from a one step oxidation of cyclohexene (Fig. 1f) with H_2O_2 and a homogenous peroxy tungstate catalyst in acidic conditions (3,36,38–41) It has also been demonstrated at an industrial scale (four 5000 L continuous batch reactors) reaching 99% purity levels. (42)

Studies have also demonstrated a high conversion process of cyclohexanone (92.3%) in water using iron incorporated hexagonal mesoporous silicates and oxidant H_2O_2. ADP selectivity was shown to be 29.4% though additional byproducts, including succinic and glutaric acid, were produced as well. (43)

Unfortunately, life cycle analyses of early processes using H_2O_2 raised concerns over a greater potential for negative environmental impacts than the traditional NO process.(44) Despite H_2O_2 being considered a "green" oxidant, its industrial production *via* the Anthraquinone process is both energy-intensive and polluting. (39,45)

Furthermore, its use, handling and storage present challenges due to its high reactivity as well as its spontaneous dismutation into H_2O and O_2. One of the major drawbacks in using H_2O_2 is the constant competition between its unwanted decomposition and the formation of ADP; further posing a challenge of designing a catalyst favoring H_2O_2 activation, rather than decomposition.

Feedstock costs, low yields and challenges in stream recycling, (44) have to date, resulted in limited large scale development of any H_2O_2 based process. (3,46)

Pure O_2 and air have also been investigated and widely reported as potential oxidants, due to their availability and cost. One air based route involves a 2-step oxidation, where cyclohexane is first oxidized (~8-10%) to cyclohexanol/cyclohexanone (Fig. 1g).(3) The unreacted cyclohexane is then recycled, while the cyclohexanol/cyclohexanone mixture undergoes a second oxidation step with a metal-catalyst, in an acetic acid solvent producing ADP. Yields of ADP through this route have reached 50-70%.(3),[47,48] This process, which has been commercialized, produces significantly higher levels of the byproducts succinic and glucaric acid (Fig 1c.) with reductions in the quality of the final ADP, (14) preventing its use in nylon production. The synthesis of nylon-66 requires high purity ADP (99.8%), (49) and any trace amounts of impurities such as carboxylic acids or metals can act as chain terminators in the polymerization process, and therefore need to be removed.(3) As a result, an issue with several air/O_2 based processes as initially developed is the requirement for acetic acid as a solvent. Acetic acid, a corrosive monoacid that can contaminate ADP product streams if not completely removed, requires additional recovery and recycling, which increases costs. Other variations of this 2-step air oxidation have been investigated mostly by exploring other heterogenous or homogenous metallic catalyst combinations such as Co(III)/Co(II), Mn(III)/Mn(II), V(V), Cu(II) or $Mn(OAc)_2$/$Co(OAc)_2$. (50) However, the development of an all air/O_2-based process leading to polymer grade ADP, has been delayed by the lack of an adequate catalyst enabling conversion yields and product quality competitive with the NO process. Currently, the NO process with NOx mitigation is preferred to using other oxidants.

Alternative feedstocks

In parallel with the exploration of alternative oxidants, alternative carbon feed stocks have also been studied. The investigation of various feedstocks including cyclohexene, phenol, butadiene or adiponitrile have been reported, (3,14,19) most of which are also produced from benzene, leading to a silmar cost structure. Phenol was seen as an interesting alternative feedstock (Fig. 1d), notably due to its very high conversion rate to cyclohexanol (99%) favoring ADP formation with limited amount of side product generation. (14) However, its higher selling price compared to benzene has favored the 2-steps oxidation of cyclohexane, consequently removing it from the list of cost competitive options.(3,14) Additionally, phenol based processes still generate NOx.

Butadiene (1,3-butadiene) has gained interest as a viable alternative feedstock for ADP production. Butadiene is converted to ADP *via* a 2 step homogenous carbonylation (Fig. 1e) first described in the 1970's, with significant recent advancements. (51–54) This route requiring methanol and carbon monoxide shows relatively high conversion yields of 72% and produces dimethyl-adipate which is then converted to adipic acid.(52,55) This route also produces no NOx. Butadiene is an attractive feedstock.(56) Converting butadiene ($0.79/kg) and syngas (CO, ~$0.10/g) to ADP would have estimated costs for feedstocks of only $0.34/kg of ADP at 100% conversion yields. Current estimated yields of only 65-70% would lead to estimated operating costs in the range of ~$0.60-0.74/kg of ADP, again assuming feedstock costs are from 70-80% of the total operating costs for a mature petrochemical process. (31,32) (Supplemental Table S1) This cost structure makes the route through butadiene competitive with the NO process as described above, but not significantly cost advantaged at current yields. Additionally, these estimations do not account for costs that may occur due to the purification and reprocessing of the methanol/water

mixture formed from the conversion of dimethyl-adipate to ADP. To date the market volatility of butadiene pricing (57,58) has impeded the adoption of this technology, but as the technology matures (with catalyst optimization and improved yields) this process may well displace future NO investments.

Biotechnological Routes

In 2012, the International Energy Agency designated ADP as a prime candidate for the development of biobased routes.(24) The theoretical yield of ADP from glucose is 0.923 moles/mole or 0.748 g/g. With glucose at a current estimated price of $0.18/pound this translates to a feedstock cost of $0.531/kg of adipic acid (albeit at 100% conversion yield) which is competitive with the NO Process. Glucose reaching $0.15/pound translates to a feedstock cost of $0.441/kg of adipic acid which would be 20% lower compared to the NO process and competitive with the butadiene based process at current yields (~70%). The relatively high yield of ADP from sugars, enabling cost structures in line with petrochemical processes, makes ADP a good candidate for bioproduction. Several routes to ADP through both direct biosynthesis or direct chemical conversion as well as biosynthesis followed by traditional catalysis will be discussed. It is worth noting that there are fundamental differences in the operating cost structures of chemical and biotechnological processes. While at maturity, feedstock costs may account for up to 80% of operating cost for direct chemical conversions, non feedstock costs are larger in fermentation based processes, accounting for 40-60% of overall operating costs. (10,31,32)

Direct biological bioproduction of ADP

ADP occurs in nature as a metabolic intermediate in the *n*-alkylcyclohexane degradation pathways of several bacteria including *Pseudomonas, Acinetobacter* and *Nocardia*. (59–61) However, the initial heterologous expression of these pathways in *E. coli* resulted in only trace production levels, much too low for industrial production. (62) As a consequence, numerous additional biotechnological routes to ADP have been investigated. These routes either directly produce ADP from various carbon sources or produce ADP *via* the biosynthesis of a precursor subsequently converted to ADP through traditional chemical catalysis. (13,17,59,63,64)

Reverse adipate pathway

The reverse adipate pathway (Fig. 2a) enables ADP production from central metabolites with theoretical conversion yield as high as 0.92 mole of ADP per mole of glucose under aerobic conditions. (1) This pathway, which produces ADP from the metabolites acetyl-CoA and succinyl-CoA, has been previously described in *Thermobifida fusca* (63) and a few other alkane-degrading microbes such as *Rhodococcus sp*., *Acinetobacter sp*., or *Arthrobacter sp.*. (3,17) The pathway is initiated by the conversion of acetyl-CoA and succinyl-CoA into 3-oxoadipyl-CoA, followed by the reduction to 3-hydroxyadipyl-CoA, dehydration to 5-carboxy-2-pentenoyl-CoA, reduction to adipoyl-CoA, and ADP release *via* hydrolysis or transfer of the CoA ester. The final reduction is carried out *via* a 5-carboxy-2-pentenoyl-CoA reductase (62), which has been shown as a major limiting step of the pathway. Enzymes from various sources (*R. eutropha, C. acetobutylicum, A. baylyi, T. gammatolerans*) have been evaluated to construct an improved version of this pathway in *E. coli. (65)* Using this pathway a final titer of 2.23g/L was obtained from glucose when using

an engineered version of *T. fusca.(63)* Recently, Zhao and coworkers (2018) reconstructed the 5-enzymatic steps of the reverse adipate pathway from *T. fusca* in *E. coli*, consisting of the following enzymes: Tfu_0875 (β-ketothiolase), Tfu_2399 (3-hydroxyacyl-CoA dehydrogenase), Tfu_0067 (3-hydroxyadipyl-CoA dehydrogenase), Tfu_1647 (5-carboxy-2-pentenoyl-CoA reductase) and Tfu_2576-7 (adipyl-CoA synthetase).(66) They reported a final titer of 68g/L of ADP from glycerol over a 88h of fed-batch fermentation (with 0.81g/L.h^{-1} productivity and 0.378g/g yield, and 72.7% of theoretical yield).

A recent techno-economic analysis comparing the cost-effectiveness of different renewable direct and indirect routes to ADP highlighted that the major costs of the reverse adipate route include feedstock supply (~38%) and separation costs (~40%).(10) The energy associated with the recovery and isolation of ADP from the diacid salt, and the recycling of the ammonia to the fermentation accounts for the majority of the separation expenditures. Thus, further optimization of the separation/recycling processes are key elements in improving the cost-effectiveness for commercial application of this route. (67)

Biosynthetic oxidative routes to ADP

Another approach to the biosynthesis of ADP involves the combination of *β*-oxidation and/or reverse *β*-oxidation with ω-oxidation as illustrated in Fig. 2b-d. *β* - and ω-oxidation are both pathways involved in the degradation of fatty acids *via* the oxidation of either the *β* (2nd carbon after the carboxylic acid) or the ω-carbon (the most distant carbon from the carboxylic group of FA), respectively. (68) When sugars are used as feedstocks, acetyl-CoA can be used to generate longer chain acyl-CoAs, which can be then be oxidized (by either *β* - and/or ω-oxidation)

to yield adipic acid. When fatty acids are used as feedstocks they may first be subjected to ω-oxidation, yielding dicarboxylic acid before undergoing *β*-oxidation and shortened to adipic acid. The order of *β*-, reverse *β*- and ω-oxidation does not matter. (1) By combining these pathways, ADP can be produced from a wide variety of renewable substrates including glycerol (C3 compound), glucose (C6 compound) (69) and fatty acids from vegetable oils (C12 to C20 mixture).(1,13,70) Combining *β* reverse, *β* and ω-oxidation led to titers of 170 mg/L of ADP in *E. coli* with glycerol as sole carbon source. (69) Significantly higher production levels were obtained from yeasts, such as an engineered *Candida tropicalis* reported to produce final titers of ~ 50g/L (with a 0.38g/L.h^{-1} rate) with coconut oil as a carbon source. (9,71) A key to the success with *Candida tropicalis,* was the design of the specificity of the strain to convert a mixture of fatty acids of various chain-lengths to adipic acid by the disruption of enzymes involved in the degradation of C6 acyl-chains. (71),(72) These deletions led to degradation of fatty acids to adipic acid only, which was not further degraded. This process was successfully scaled to 300L (73,74) but further development has stalled. (75) While using glycerol, vegetable oil or fatty acid waste streams have a perceived economic advantage, unfortunately, they do not enable routes to ADP which would be advantaged based on feedstock costs alone. ADP can be produced from glycerol at a yield of 1 mole ADP per 2 moles of glycerol or 0.79g/g. Glycerol has an estimated price of $0.6/kg, (76) resulting in a best case feedstock cost of $0.75/kg of ADP which is not competitive with other routes discussed above. While crude glycerol, a waste stream from the biodiesel industry may be available at lower costs, concerns over purity and the availability of volumes needed for a commercial scale ADP process make this route less attractive. Cost for vegetable oils, soapstocks, and fatty acid distillate waste streams are in the range of ~$0.4-0.7/kg. (77,78) However assuming the average chain length of these lipids to be 16 carbons, with only 1 mole of ADP produced from

a mole of fatty acid, this is equivalent to a yield of only ~ 0.56g ADP / g oil, which translates to a feedstock cost for ADP of $0.7-$1.25/kg, which is not competitive with the NO process or other routes discussed above. As in the case of glycerol, while specific waste streams may be a lower cost, the volumes may not be compatible with that needed for ADP production.

Several other routes enabling the biosynthesis of ADP have been investigated, such as the 2-oxopimelic acid pathway (with a reported titer of 0.3g/L),(1,79,80) and a polyketide synthase based pathway producing ADP from succinyl-CoA and malonyl-CoA intermediates (~0.3mg/L of titer reported from *in vitro* adipic acid production). (1) Even the conversion of lysine into ADP has also been suggested but not demonstrated. (1,64)

Indirect synthesis of adipic acid

Direct routes to ADP have been complemented by the study of several indirect routes, wherein a chemical intermediate is produced *via* fermentation or chemical conversion of a renewable feedstock and then converted with additional chemistry to ADP. The main intermediates studied to date are glucaric acid, succinic acid and *cis,cis* muconic acid (Figure 3, 4, and 5). (1,13,17,59,70) All three of these acids are naturally occurring. (17,81–83) Succinic acid is a well known fermentation product,(84–89) D-glucaric acid has been reported as an end product of the D-glucuronic acid pathway in *E. coli, (17,81)* and muconic acid is an intermediate of the shikimate pathway.(90,91) Additionally, these three acids, which are discussed below, also have potential as industrially interesting chemical platforms beyond intermediates to ADP. (92,93)

Glucaric acid

Glucaric acid is a building block for several polymers and has potential biomedical uses. (81,93,94) Its potential as an intermediate to ADP was described in 2009. (81) Though glucaric acid is a natural metabolite, native pathways from *D*-galactose or *D*-glucose to glucaric acid, contain more than 10 different steps, leading to the engineering of shorter and more efficient biosynthetic routes. (81,95) A 3-step biosynthetic pathway converting glucose to glucaric acid was constructed (Fig.3), involving the combination of three heterologous enzymes: *myo*-inositol-1-phosphate synthase (Ino1), *myo*-inositol oxygenase (MIOX) and uronate dehydrogenase (Udh). (95,96) Using this pathway, Moon and coworkers reported a final titer of 1.13g/L of glucaric acid from glucose (rate of 0.016g/L.h^{-1}, yield of 0.13 mol/mol) using *E. coli* as a host. (81) In this study, the MIOX enzyme was shown as a major bottleneck (17,81) and several strategies taken to further optimize this step, (95,97),(96),(98),(95,97) have led to titers ranging from 1.7g/L to 2.5g/L from glucose and up to 10.8g/L when *myo*-inositol was used as a feedstock. Difficulties in optimizing the glucaric acid titers in *E. coli* were attributed to pH-mediated toxicity of the acid (pKa =2.99). Toxicity of glucaric acid was reported in *E. coli* at concentrations as low as 5g/L depending on pH, while *Saccharomyces cerevisiae* has shown higher tolerance to organic acids under acidic conditions. (96,99) In the light of this, Chen et *al.* engineered *S. cerevisiae* to express a stable MIOX enzyme (gene: *miox4* from *A. thaliana)*, resulting in final titers of glucaric acid of only 6g/L after 200 hours of production. *(98)* Despite these results, titers and rates remain well below those needed for commercial deployment.

Work by Kang and co-workers demonstrated glucaric production in the eukaryotic microbe *Pichia pastoris* with co-expression of MIOX and Udh. As MIOX was also determined to be the rate limiting step in the biosynthetic pathway, they demonstrated use of a fusion expression

strategy with Udh for the enhancement of MIOX specific activity and glucaric acid synthesis. The engineered strain demonstrated higher glucaric acid production with titers up to 6.61 g/L after 80 hours. Though myo-inositol co-feeding, along with glucose, was necessary for optimal production.

In addition to the biological production of glucaric acid, a chemo-catalytic route to ADP through glucaric acid from glucose has been developed. (59) In this process, which has been successfully piloted, sugars are converted to ADP *via* glutaric acid in a 2-step oxidation-hydrodeoxygenation reaction with a final conversion yield of 58%. (34,59,100,101) The efficiency of the glucose oxidation is pH-dependent, resulting in requirements for large amounts of base. While this route shows good overall conversion yield, the combined cost of base with the required separation are challenges to commercial deployment. Improvements are required in the robustness of the catalysts and long-term stability (102,103) as well as in purification of the ADP from glucaric acid. As mentioned above, acid contaminants reduce the quality of ADP. Similar processes converting glucose derived furan-dicarboxylic acid to ADP have also been reported. (103)

Succinic acid

Succinic acid (SA) has been of interest due to its wide application as a precursor of numerous industrial compounds used in the food, pharmaceutical, agricultural and chemical industries, with 1,4-butanediol (1,4-BDO) as one of its derivatives. (86) To date, succinic acid is primarily manufactured *via* an energy intensive catalytic hydrogenation of maleic acid or maleic anhydride. (85) The US Department of Energy has reported SA as a candidate for bioprocesses

development. (24,104) Subsequently, several bio-based routes to SA have been developed and initially commercialized.(84,105,106),[107],[108] Additionally, there has been recent progress in the use of more diverse renewable feedstocks as a carbon source for the production of succinic acid, including carob pods, (109) sweet potato waste, (110) and xylose.(111)

ADP can be produced from succinic acid *via* 1,4-BDO. The conversion of SA to 1,4-BDO is well known with a Pd-Re/TiO_2 catalyst while under 69 barr H_2 at 200°C. (112) Subsequently, 1,4-BDO can be converted to ADP, as illustrated in Figure 4. (113) The catalytic carboxylation of 1,4-BDO has been carried out using a $Rh(PPh)_3COCl$ catalyst to relatively high yields (> 74%) while at 175°C under 48 bar CO .(34) This approach has been initially scaled to a pilot plant. (59) (34) [114] Unfortunately, to date, none of the SA-based routes to ADP have been commercialized. The chemical transformation of succinate to ADP are energy intensive processes that can require additional complex industrial equipment, thus contributing additional expenditures for the final ADP costs. It should also be noted that biotechnological processes enabling the direct production of 1,4-BDO from sugars have been developed, which could also potentially be used for ADP manufacture.(115)

cis, cis -Muconic acid

Muconic acid is an intermediate of the shikimate (amino-aromatic biosynthesis), as well as the β-keto-adipate pathways in several microbes including *K. pneumoniae*, *P. putida* and various *Sphingobacterium sp.*. (1,90,91) Muconic acid can be chemically converted into adipic acid *via* hydrogenation using various catalysts including platinum on activated carbon. (18,49) Conversion yields as high as 97% have been reported. Alternatively, muconic acid can be isomerized to *cis,*

trans or *trans, trans* muconic acid which are potential intermediates in the production of ε-caprolactam, terephthalic acid or trimellitic acid. (1,13,49,59,92,116)

Engineered shikimate biosynthetic pathways leading to muconic acid production have been developed (Fig. 5) and tested in different host strains, with *E.coli* showing the best production to date (when compared to *S, cerevisiae* or *P. putida)*. (1,17,117,118) In *E. coli*, there is tight control of the shikimate pathway *via* the feedback inhibition of DAHP synthase (a key pathway enzyme encoded by isozymes *aroF*, *aroG*, and *aroH*). Aromatic amino acids (tyrosine, tryptophan and phenylalanine) inhibit DAHP synthase. To bypass this natural regulation, Niu et al. (2002) constructed an *E. coli* strain with a feedback resistant shikimate pathway resulting in a final titer of 36.8 g/L of muconic acid after a 48h fed-batch fermentation (22% overall yield, mol/mol from glucose). (18) Further optimizations performed on both the same strain and the fermentation process resulted in what is so far the highest final titer reported or muconic acid of 59.2g/L (30% yield, mol/mol) from glucose. (92,119) Only recently has an enzyme capable of converting muconic acid to adipic acid been described. A bacterial enoate reductase capable of reducing muconic to adipic acid paves the way to a complete conversion of renewable feedstocks to adipic acid *via* muconic acid. (120,121)

Additional work on biosynthesis in *E. coli* has been done by Yan and co workers using glucose and glycerol feedstocks.(122) The authors extended the native shikimate pathway to produce salicylic acid, which was followed by conversion to muconic acid by introducing a salicylate 1-monoxygenase (SMO) and catechol 1,2-dioxygenase (CDO). Through modular optimization, the muconic acid titer was improved 275 fold compared resulting in 1.45 g/ L after 48 hours. However, managing the cellular toxicity of SA remains a challenge that may limit muconic production.

In *Pseudomonas putida*, Beckham and coworkers achieved high atom efficiency in the production of muconic acid from lignin-derived aromatic compounds through aromatic catabolic pathways.(123) Coupling strain engineering and bioprocess development, bottlenecks such as intermediate accumulation, precursor transport limitations, and product toxicity were discovered, resulting in muconic acid titers of 50g/L titers (.49g/L*hr). Despite these exciting results, enhanced tolerance of *P. putida* to higher MA is still needed.

From a processing review, producing muconic acid in a low-pH tolerant organism such as *S. cerevisiae* is of interest. Curran et al. demonstrated first heterologous production of muconic acid in the host by introducing a three step synthetic pathway composed of dehydroshikimate dehydratase, protocatechuic acid decarboxylase, and catechol 1,2-dioxygenase.(118) They obtained yields up to 141 mg/ liter by flux increasing strain modifications such as: knockout of aro3 to overexpress feedback resistant mutant aro4, zwf1 deletion, rewiring pentose phosphate pathway to avoid the oxidative shunt, and overexpression of tkl1. However, given the lack of eukaryotic enzymes, PCA was shown to be a hurdle as it was determined to be the bottleneck of the pathway.

Muconic acid can also be obtained via chemical conversion from lignin-derived catechol. Recently, Bruijnincx and coworkers designed a biomimetic synthetic non-heme iron (iii) complex catalyst that is generated *in situ* for the intradiol cleavage of catechol. (124) They demonstrated the use of benign oxidants and low process loadings (0.1 mol%) for activity. However, unfavorable enthalpic binding of oxygen to the active catalyst (23.8 kJ mol^{-1}) plays a limiting factor for the observed reaction rate, needing a temperature of 80 C for a TOF of 120/hr. An alternative sustainable design that was developed by Darcel and coworkers.(125) Using a simple inorganic

iron salt catalyst, they demonstrated high yields (up to 84%) using H_2O_2 as the terminal oxidant. However, the development of an efficient and cost-effective lignin valorization process remains a hurdle.

Furthermore, one of the most important catalytic reactions in large scale petrochemical processes is the hydrogenation of C-C bonds.(126) Unfortunately, these processes use precious, costly metals (such as Pt, Pd and Rh), metal catalysts (such as Ni and Fe), external H_2, and can require high temperature and pressures.(127,128) Despite significant progress, metal catalyst free hydrogenation is still a challenging research area. It could be more beneficial to focus efforts on the conversion of unsaturated precursors via a biocatalytic approach (such as via enoate reductase or 5-carboxy-2-pentenoyl-CoA reductase as previously discussed) or developing green methodological alternatives (such as electrocatalytic hydrogenation with hydrogen generated *in situ(129)* and earth abundant catalysts(130)) for ADP production.

In the case of these indirect routes to ADP (through succinic, *cis, cis*-muconic or glucaric acid) estimated production costs are all in large part driven by feedstock costs. Production through succinic acid is interesting, in that yields of 1.7 moles of succinic acid can be produced from 1 mole of glucose. We estimate that under the best conditions this process can lead to best case operating costs of $0.92-$1.86/kg of ADP. Again, these estimates assume $0.18/lb glucose, and in the case of a fermentation based process, feedstocks to account for 40-60% of the overall operating costs as outlined in Supplemental Table S1.(31,32) The route to ADP through *cis, cis*-muconic acid from glucose goes through a 7 carbon intermediate and can at best yield 0.86 moles of ADP from 1 mole of sugar, but while the subsequent chemical conversion is similar to the succinic acid process in that it requires hydrogen, it requires half of the amount, and it also differs from the succinic acid process in that it does not require CO. As a result, best case estimates for operating

costs for the *cis, cis*-muconic acid route from glucose approach $0.79/kg, with current converison yields as low at 30% leading to estimates of up to $3.77/kg. Lignin and its derivative offer another potential feedstock for *cis, cis*-muconic acid, and although best case technoeconomic models have been published, these assume a low end cost for this feedstock.(12) Lignin, depending on assumptions and purity has been estimated in the best case to have a $0.04/kg cost, to costing upwards of $0.50/kg ($500/ton) for purified streams. (12,131) This is further complicated by the fact that lower cost, unpurified input streams will likely require increased downstream purification costs as discussed below. In the event that lignin feedstock prices as low as $0.04/kg can be realized at scale, the route to ADP through *cis, cis*-muconic acid has potential as an attractive alterantive to the incumbent process with operating costs estimated between $0.15/kg and $0.28/kg. Of course this is a best case scenario, and likely some level of lignin purification or upgrading will be needed if only to provide a consistent input to a large scale process from an agricultural feedstock. Lastly, routes to ADP through glucaric acid (either biotechnological or chemical) have a maximal conversion yield of 1 mole of ADP from 1 mole of glucose, additionally requiring hydrogen as a reductant (Supplemental Table S1). These conversion yields lead to best case operating cost estimates of $0.88/kg ADP for the chemical routes through glucaric acid and $0.97/kg in the case of the biotechnological routes. This difference is again due to the difference in cost structure of these types of processes as described above. Current best case conversion yields demonstrated using these two routes would be estimated to lead to operating cost estimates of $1.65/kg ADP, for the chemical route, and over $13.00/kg ADP for the biotechnological route.

Downstream Purification

Beyond catalytic bottlenecks, separation and purification are a critical hurdle in the development of biobased ADP and biobased products more broadly. These unit operations have a significant impact on the total production cost and product quality.(10,67,132,133) Thus, to be competitive with current petrochemical routes, a high yield purification resulting in a quality product is essential. (134) Even small amounts of organic acids can reduce the quality of the resulting ADP, even from a petroleum feedstock. As mentioned above, even a currently commercial petrochemical alternative to the NO process has had limited market penetration simply due to impurities which result in ADP that is not suitable for nylon manufacture. The impurity profile of ADP or its precursors derived from bio-based feedstocks is more diverse, and includes sugars amino acids, organic acids and salts, which can affect the production of adipic acid or downstream processing.(135,136) For example, even at the ppm level, amino acids are known catalyst poisons that can enact both reversible and irreversible hydrogenation catalyst deactivation.(137) Current methods for carboxylic acid purification may include many stepwise processes including reactive extraction, precipitation, electrodialysis, and membrane filtration.(134,138)

Many of these approaches have been applied to the purification of ADP or its precursors. Recently, work by Vardon and colleagues utilized mucconic acid's solubility in ethanol to improve the purity of bio-produced cis,cis- mucconic acid (from a purity of 97.71% to 99.8%). (49) Though a significant advance with a large reduction in elemental impurities (Figure 6A), the net recovery was only 81.4% and the presence of elemental N (90 ppm) is still above the requirements for polymer-grade adipic acid (20 ppm). Additionally, Han and co-workers recently demonstrated the improved recovery of glutaric acid from culture broth using extraction.(139) They were able to extract glutaric acid (to a purity of 97.2%) with an overall recovery of 69.7% by using a pH shift

and n-butanol extraction. Additionally, as solvent recovery plays an important factor for these extraction processes, (138) they demonstrated a high n-butanol recovery yield (78.6%). In several cases, reactive extraction has been shown to be applicable for the recovery of several dicarboxylic acids (134) and has been reviewed as a potential competitive alternative to current extraction technologies.(138,140) Gorden and coworkers demonstrated two different methods to extract cis-cis muconic acid from aqueous buffered solution.(141) This was either by a pH shift or a double reactive extraction strategy which uses a water soluble amine to regenerate the acid that was first extracted into an organic phase. Whereas the pH shift approach obtained a 99.08% yield, the double extraction method allowed for a full recovery of the cis-cis muconic acid from the organic phase with select amines. This double extraction method may be advantageous as pH shifting increases salt impurities, and may lead to cis-cis muconic acid salts instead of the acid.(141) Though these results show further development in downstream recovery for dicarboxylic acids, the purification of cis-cis muconic from real worls fermentation broth has yet to be demonstrated.

As typical organic solvents are generally toxic, flammable and volatile, with the potential to cause harmful environmental effects, it is desirable to find new sustainable extraction methods.(142) Toward this aim, the use of less toxic, biodegradable, lower cost extraction solvents, such as with deep eutectic solvents, are being investigated. Deep eutectic solvents (DES) are a mixture of two or more components that liquify upon contact, develop melting point depression, and separate from the remaining solution due to high density differences. The use of DES was initially focused on the extraction of hydrophobic molecules, such as fatty acids and other biomolecules, from aquatic environments.(143) Recently, Riverio and co workers demonstrated the extraction of adipic and succinic acids from aqueous solutions with derivatives of trioctylphosphine oxide (TOPO), a previously reported hydrophobic DES (see Figure 6c).(142)

For adipic acid, the extraction efficiencies with TOPO as well as TOPO-decanoic acid (TOPO-decAc) and TOPO-dodecanoic acid (TOPO-dodecAc) at extraction efficiencies up to 82.32%. The differing results for TOPO, TOPO derivatives, as well as ADP and succinic acids support the idea for creating a "designer DES", which may be beneficial in extracting ADP from unwanted acid impurities, and providing a more sustainable extraction alternative to current solvents. However, important hurdles still need to be addressed including acid regeneration from the DES and solvent recovery for reuse.

Though progress has been made for downstream diacid acid recovery, differing issues such as method selectivity from broth, solvent recycling, and purity all while meeting cost-efficiency goals need to be solved for respective processes. Importantly, the purity demands for polymerization grade ADP are high and no currently reported DSP has met these specifications, particularly with real word material. Thus, the development of a method that can compete with current petrochemical processes is still a critical need.

Future Outlook

To date, despite the numerous advances described above and the desire for NOx free processes and more sustainable feedstocks, no newer cleaner routes to ADP have been successfully commercialized. Several promising approaches towards the NOx free production of adipic acid have been developed relying on either traditional chemistry, biotechnology or the combination of both. The status and challenges associated with each of these routes are compared in Table 1, and Figure 7. Specifically in Figure 7, we compare crude estimates of the potential operating costs for several key potential processes. The most promising routes include: the chemical route from

butadiene, the direct biotechnological route to ADP *via* the reverse adipate pathway, and the chemical oxidation of glucose *via* D-glucaric acid. These routes are all well past proof-of-concept and have the largest potential for near term commercial deployment.

The major challenges shared by one or more new routes to ADP, whether chemical or biotechnological, are primarily around feedstock costs (as well as feedstock purity) and supply and challenges associated with the purification needed to manufacture polymerization grade ADP. To date, butadiene and renewable sugars are both anticipated to be competitive feedstocks for ADP manufacture when compared to benzene, with sugars offering the potential of a petroleum-free pathway. (17) As lower cost routes to the production of sugars from lignocellulosic biomass are developed bioprocesses may be favored. (144,145). With respect to purification, the most advanced chemical and biological approaches all have to deal with contaminating organic acids that need to be completely eliminated from the final product. More crude lignocellulosic feedstocks likely will be accompanied by a more diverse impurity profile and a need for a more intense purification process. A major challenge for these greener routes lies in these additional separation/purification steps needed which can result in lower overall yield and higher process costs. (10,67,132,133) To date, while the yield of many purification approaches has been investigated, a major limitation in many studies is the quantification of acidic contaminants which may impact ADP quality at even low levels. Significant efforts are expected to be needed to reduce the costs of producing highly pure ADP.

It is worth mentioning that competitive operating costs alone likely overestimate (sometimes greatly overestimate) the commercial competitiveness of a given process, and the total return on capital cost investments needs to be considered. (31,32) Many petrochemical plants have reduced capital cost for the same capacity when compared to biobased plants, particularly new to

the world biobased plants. (31,32) This provides an additional competitive barrier to these alternative technologies.

Fortunately, as discussed above, several promising strategies towards the production of greener adipic acid have been developed and some have already been tested at pilot scale. (1,17,59) Lower cost feedstock stream will be critical to the competitive commercial deployment of any of these new technologies. (59)

Acknowledgements

We acknowledge the following support: ONR YIP # N00014-16-1-2558, and DOE EERE grant #EE0007563 and financial support from DMC Biotechnologies, Inc. We would like to thank John Efromson for extracting historical price data from the U.S. International Trade Commission database https://dataweb.usitc.gov/.

Author Contributions

J. Rios, J. Lebeau, T. Yang, S. Li, and M.D. Lynch wrote, revised and edited the manuscript.

Conflicts of Interest

M.D. Lynch has a financial interest in DMC Biotechnologies, Inc and Roke Biotechnologies, LLC.

Figures & Captions

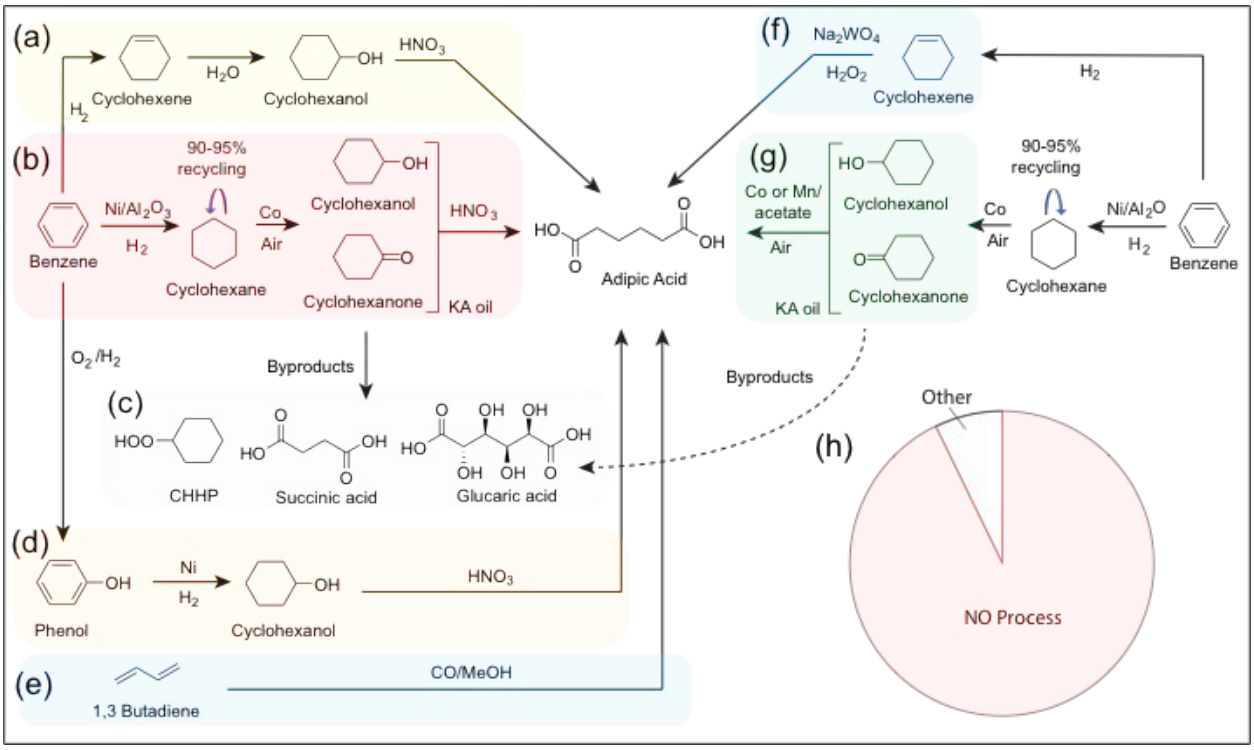

Figure 1: Current and advanced chemical routes for the manufacture of ADP. **(a)** A variant of the NO Process (2-step hydration/oxidation of cyclohexene). Benzene is reduced to cyclohexene and converted to cyclohexanol through hydration. Cyclohexanol will then be oxidized to ADP by excess HNO_3. **(b)** The Nitric Oxidation (NO) Process. Benzene is first reduced to cyclohexane, which is then converted to ketone-alcohol (KA) oil through an oxidation tightly controlled to reduce byproducts. The KA oil will then be oxidized to ADP by excess HNO_3. **(c)** Byproducts produced by non specific oxidation of KA oil include glucaric acid, succinic acid and cyclohexyl hydroxy peroxide (CHHP). **(d)** An alternative route to ADP using phenol as feedstock, which is first reduced to cyclohexanol using a nickel based catalyst **(e)** A route to ADP *via* 1,3-butadiene. 1,3-butadiene reacts with carbon monoxide and methanol and forms ADP. **(f)** An alternative route using H_2O_2 as the oxidant. Cyclohexene, which is generated from benzene, is oxidized to ADP by H_2O_2. **(g)** An example of a 2-step air-based oxidation route of cyclohexane. KA oil is generated from benzene and oxidized to ADP by air in acetic acid with Co or Mn as catalysts. **(h)** Global breakdown of industrial supply of ADP. The NO process accounts for ~93% of the global ADP production, while the combined 2-steps nitrous oxidation of cyclohexene and the carbomethoxylation of butadiene account for the rest.

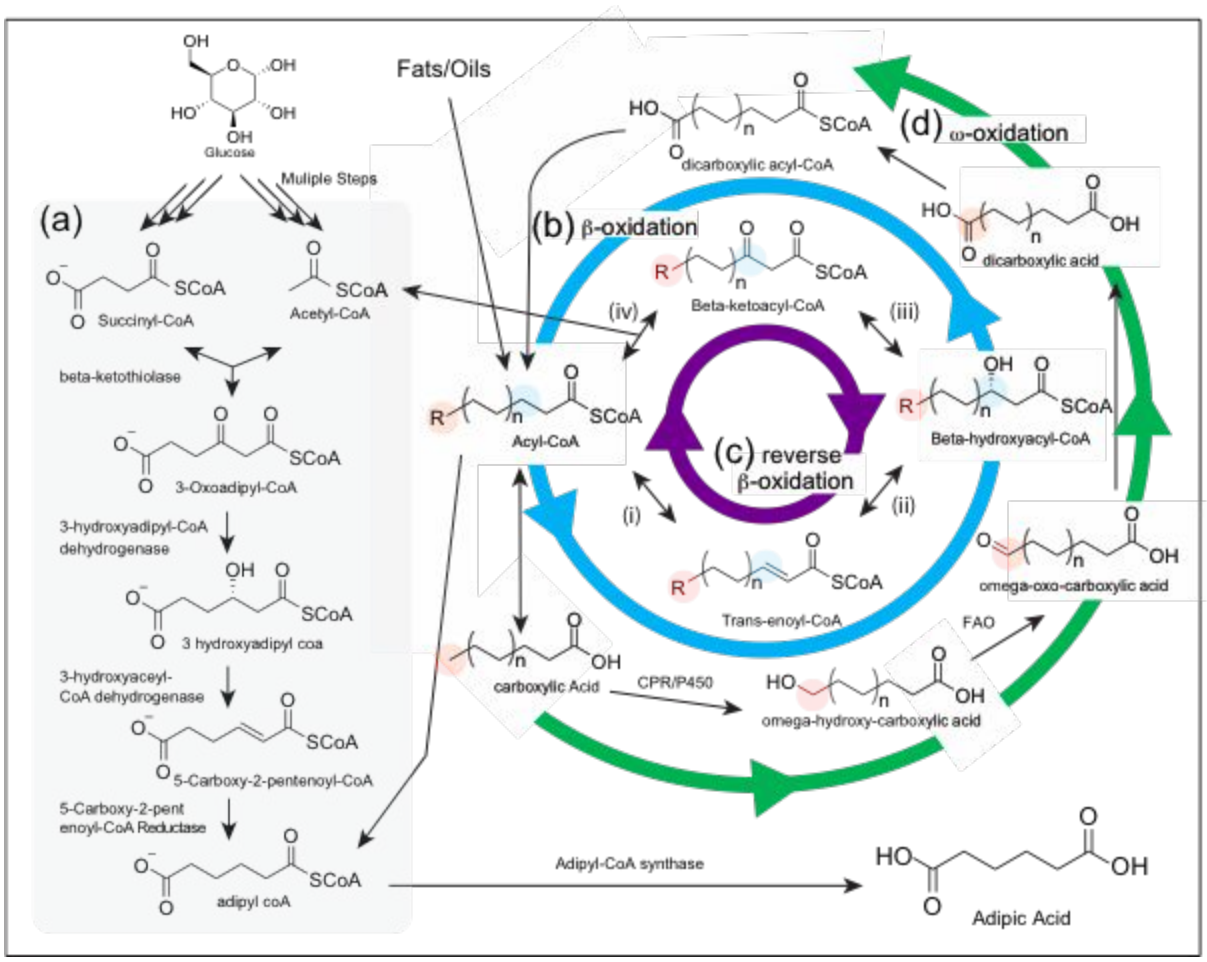

Figure 2: Direct biological conversion of renewable substrates to adipic acid. **(a)** The reverse adipate pathway for ADP biosynthesis. Acetyl-CoA and succinyl-CoA, generated from glucose through central metabolism are condensed into the 3-oxoadipyl-CoA *via* a beta-ketothiolase and then reduced to 3-hydroxyadipyl-CoA by a 3-hydroxyacyl-CoA dehydrogenase. 3-hydroxyadipyl-CoA is then converted to 5-carboxy-2-pentenoyl-CoA by a 3-hydroxyadipyl-CoA dehydrogenase. 5-Carboxy-2-pentenoyl-CoA reductase and adipyl-CoA synthetase catalyse the next 2 steps to adipyl-CoA and then to adipic acid. **(b-d)** Combinations of β-oxidation, reverse β-oxidation and ω-oxidation can lead to the biosynthesis of ADP from diverse feedstocks including sugars as well as fats and oils. **(b)** β-oxidation (blue circle) enables the stepwise shortening of acyl-CoAs at the β carbon (highlighted in blue), leading to a 2 carbon shorter acyl-CoA and acetyl-CoA. Steps include (i) oxidation of an acyl-CoA to a trans-enoyl-CoA, (ii) hydration of the enoyl-CoA to a β-hydroxyacyl-CoA, (iii) oxidation to a β-ketoacyl-CoA and cleavage to a shorter acyl-CoA and acetyl-CoA. **(c)** Reverse β-oxidation (purple circle) as the name implies is the reversal of β-oxidation leading to longer acetyl-CoA produced from a shorter acyl-CoA and acetyl-CoA. β-oxidation and reverse β-oxidation can operate on acyl-CoAs as well as ω-substituted acyl-CoAs as indicated by the red highlighted R-group, including acyl-CoAs with an ω-terminal carboxylic acid. **(d)** the ω-oxidation pathway begins with a cytochrome P450 reductase (CPR/P450) producing an ω-hydroxy fatty acyl chain. The fatty ω-alcohol then undergoes successive rounds of oxidation to produce various length dicarboxylic acids. These dicarboxylic acids can subsequently be shortened via β-oxidation to produce adipic acid. Similarly longer chains acyl-CoAs produced via reverse β-oxidation from acetyl-CoA can undergo ω-oxidation then β-oxidation to produce adipic acid.

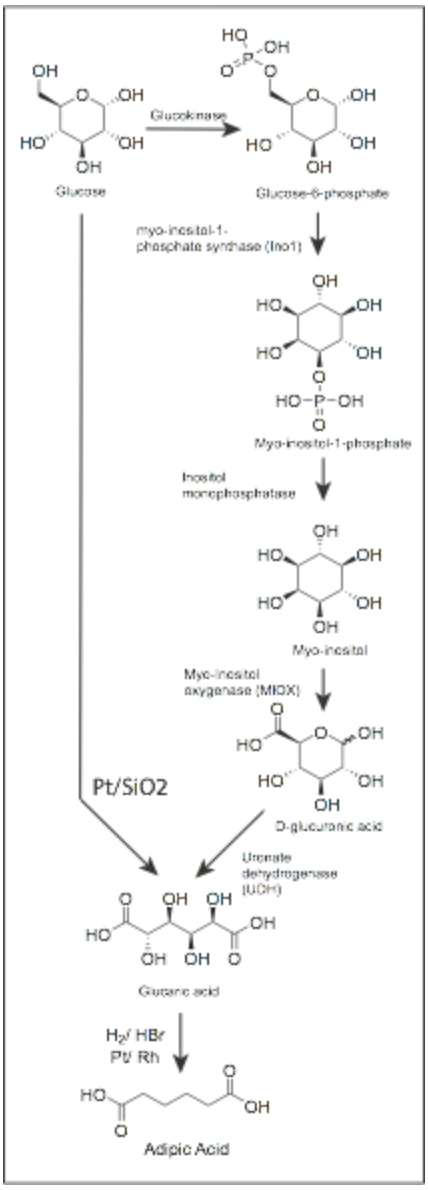

Figure 3: Production of adipic acid *via D*-glucaric acid**. (Left)** The 2-step oxidation of glucose to *D*-glucaric acid, using a Pt/SiO_2 catalyst under 5 bar O_2 at 90 °C. **(Right)** A metabolic pathway for biosynthesis of glucaric acid from glucose. Glucose is first phosphorylated to *D*-Glucose-6-phosphate (G6P) by glucokinase. G6P is isomerized to myo-inositol-1-phosphate by a myo-inositol-1-phosphate synthase. Inositol monophosphate produces myoinositol, which undergoes oxidation catalyzed by a *myo*-inositol oxygenase (MIOX) to yield *D*-glucuronic acid. *D*-glucuronic acid then undergoes a second oxidation (catalyzed by a uronate dehydrogenase (Udh)) and ring opening to yield *D*-glucaric acid. Glucaric acid produced from both routes undergoes hydrodeoxygenation with HBR and Pd–Rh/ Davisil 635 catalyst under 49 bar H_2 at 140°C to give adipic acid.

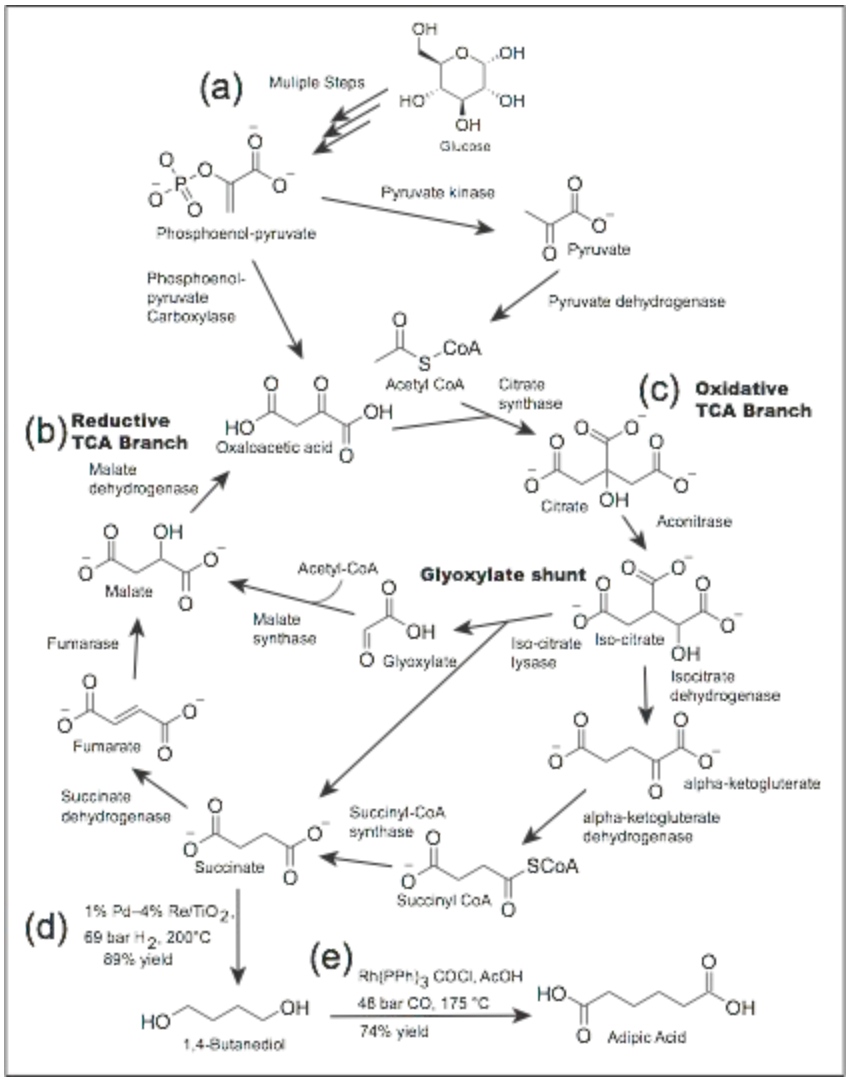

Figure 4: Production of adipic acid *via* succinic acid (SA). SA is produced from glucose *via* microbial fermentation. **(a)** Glucose is first converted to the 4-carbon and 2-carbon central metabolites oxaloacetate and acetyl-CoA. These metabolites are then converted to SA product either via the **(b)** reductive or **(c)** oxidative routes through the tricarboxylic acid cycle. SA can then undergo a 2-step process to give adipic acid *via* 1,4-butanediol (1,4-BDO). **(d)** SA is first hydrogenated to 1,4-BDO, which then **(e)**. undergoes catalytic carboxylation by a $Rh(PPh)_3COCl$ catalyst to yield adipic acid.

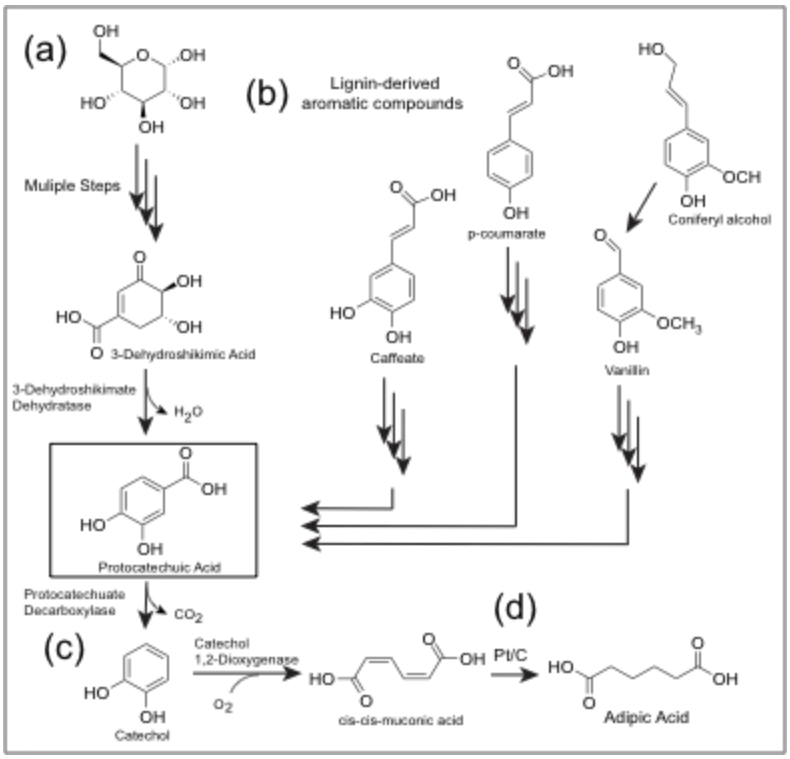

Figure 5: Production adipic acid *via* muconic acid. **(a)** Biosynthesis of *cis, cis*-mucinic acid from glucose. 3-Dehydroshikimate is produced from glucose through the metabolic steps in aromatic amino acid synthesis 3-dehydroshikimate dehydratase then converts 3-dehydroshikimate to protocatechuic acid (PA). **(b)** PA is also the product of degradation pathways for various lignin derived aromatic compounds such as caffeate, *p*-coumarate, vanillin, coniferyl alcohol. **(c)** PA then undergoes decarboxylation by protocatechuate decarboxylase to give catechol. Catechol is further oxidized by catechol-1,2-dioxygenase to give *cis*-*cis* mucconic acid. **(d)** Mucconic acid is chemically reduced to adipic acid using a Pt/C catalyst and H_2.

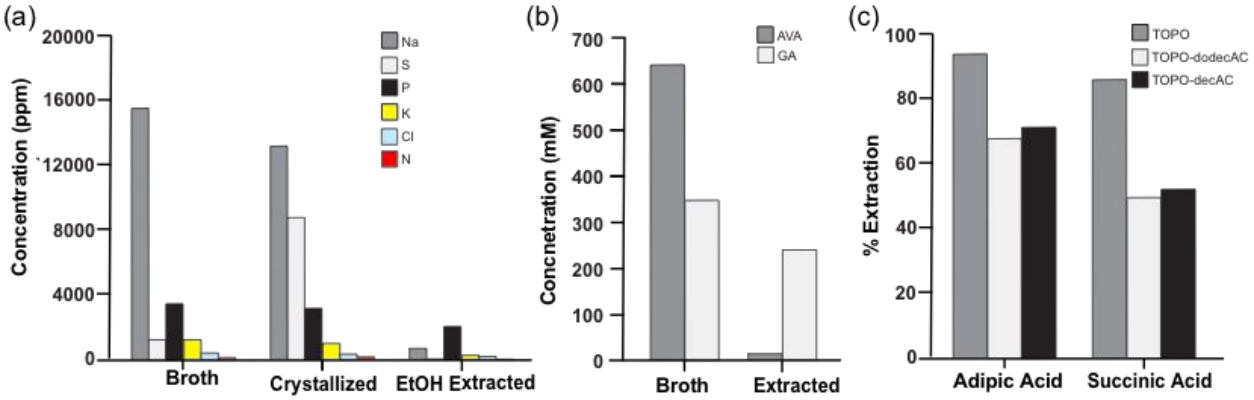

Figure. 6 (a) Elemental impurities that need to be separated from biosynthesized muconic acid , in the culture broth, after crystallization, and after ethanol extraction. Despite decrease of impurities of using ethanol as an extraction method, the N concentration (90 ppm) is still above the limit of 20 ppm max. Data extracted from (49) **(b)** n-Butanol led to a selective extraction of glutaric acid (GA) from culture broth despite containing 5-aminovaleric acid (AVA). Data extracted from (139) **(c)** Comparison of the extraction efficiency of DES TOPO and its derivatives, TOPO-dodecAC and TOPO-decAc, in the purification of adipic acid and succinic acid from aqueous fermentation broth. Data extracted from (142)

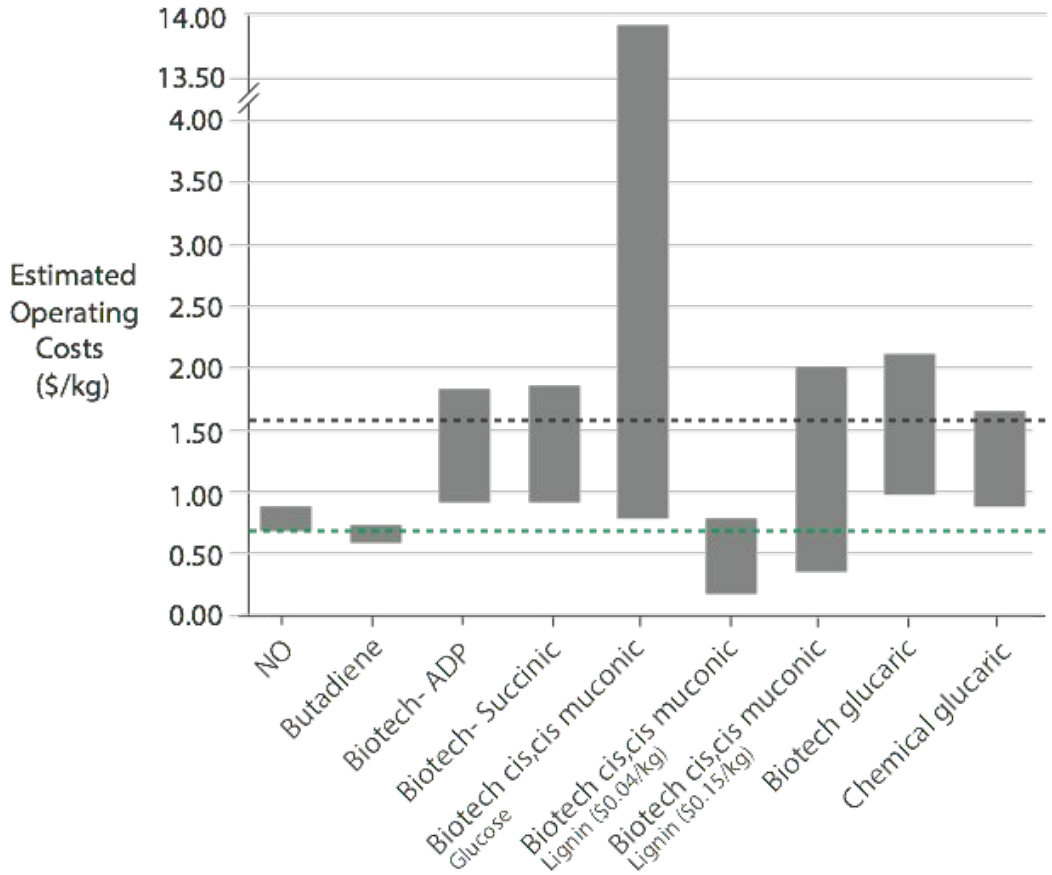

Figure 7. Comparison of estimated operating cost ranges for alternative processes synthesizing adipic acid. The ten year average ADP selling price (1.60/kg) is given as the black dashed line, and the best case operating costs of the NO process marked by the green dashed line. The gray bars indicate the estimated operating costs, with the low end achieved near maximal conversion yields and the high end supported by current performance.

Table 1: Comparison of maturity and challenges for Chemical and Biotechnological Routes to ADP

Maturity	Route(s)	Feedstock(s)	Best demonstrated performances	Challenges
1	Carbomethoxylation (Petrochemical route)	Butadiene	Adipic acid (*In vitro*) Cat:Co salt, MeOH/CO 72% conversion yield	- Catalyst optimization - Recycling
2	Reverse adipate (Bio-route)	Glucose/ Glycerol	Adipic acid (*E. coli*) 68g/L & 0.81g/L-h^{-1} 72.7% bioprocess yield	- Strain & Pathway Optimization - ADP Purification
3	2-step glucose oxidation (Chemo-catalysis)	Glucose (a)	D-glucaric acid (*In vitro*) Cat.1**:** 4%Pt/SiO_2, 5 bar H_2, 90°C, 8h 66% conversion yield	- Separation/purification - Catalyst optimization
		D-glucaric acid (b)	Adipic acid (*In vitro*) Cat.2: Pd–Rh/Davisil635, HBr, 49 bar, 140°C, 3h 89% conversion yield	
		Glucose→Adipic acid	Overall yield (a+b): 58%	
4	β- and/or reverse β-oxidation/ω-oxidation (Bio-route)	Fatty acids mixture (coconut oil)	Adipic acid (*C. tropicalis*) 50g/L & 0.38g/L-h^{-1} >80% bioprocess yield	- Feedstock Costs - Fermentation titers & rate - ADP Purification
5	Shikimate pathway (Bio-chemocatalytic route)	Glucose (a)	*cis,cis*-muconic acid (*E. coli*) 59.2g/L & 0.67g/L-h^{-1} 30% bioprocess yield	- Strain & Pathway Optimization - ADP Purification
		cis,cis-muconic acid (b)	Adipic acid (*In vitro*) Cat.: 10%Pt/C, 34 bar H--$_2$; RT, 2.5h	- Catalyst optimization - ADP Purification

			97% conversion yield	
		Glucose → Adipic acid	Overall yield (a+b): 29%	
6	Succinate route (Bio-chemocatalytic route)	Glucose (a)	Succinate (*Candida krusei*) Prod: 30ktpa 35% overall yield	- ADP Purification - Catalyst optimization
		Succinate (b)	1,4-BDO (*In vitro*) Cat: 1%Pd-4%Re/TiO_2, 69 bar H2, 200 °C 89% conversion yield	
		1,4-BDO (c)	Adipic acid (*In vitro*) Cat: Rh(PPh)3COCl, 48 bar CO, 175 °C 74% conversion yield	
		Glucose → Adipic acid	Overall yield (a+b+c): 23%	
7	Myo-inositol pathway (Bio-chemocatalytic route)	Myo-inositol	D-glucaric acid (*S. cerevisiae*) 6g/L & 0.03g/L-h^{-1} Yield not reported	- Fermentation rate & yield - Enzymes expression & activities - Feedstock Costs - ADP Purification
8		Myo-inositol	D-glucaric acid (*E. coli*) 4.85g/L & 0.07g/L-h^{-1} Yield not reported	- Fermentation rate & yield - Enzymes expression & activities - Toxicity tolerance - ADP Purification
9		Glucose	D-glucaric acid (*E. coli*) 2.5g/L & 0.05g/L-h^{-1} Yield not reported	- Fermentation rate & yield - Enzymes activities - ADP Purification
		D-glucaric acid	Adipic acid (*In vitro*) 89% conversion yield	- ADP Purification - Catalyst optimization

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