Review Article

Itaconic Acid: A Promising and Sustainable Platform Chemical?

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Abstract
Due to the increasing demand and focus for sustainable chemicals and fuels that are independent from fossil resources, itaconic acid gained interest and recognized for market position as a potential bio-based platform chemical. Itaconic acid can be produced via a chemical pathway or a biotechnological pathway, the more effective production way is the latter one, which is currently conducted in industrial scale production. In order to replace fossil-based chemicals, the efficiency of the current production that is mainly operated by using *Aspergillus terreus* has to be improved to achieve the economically feasible process. The recent progress in understanding the biosynthesis pathway, finding new raw materials and microbes as well as applying a more effective downstream process, facilitated the optimization of existing processes and resulted in reduction of production cost. However, there is still need for further optimization to achieve higher final concentrations and to use a broader range of low cost sustainable raw materials. Nowadays, the largest industrial producers of itaconic acid are located in China and the USA. If the production costs can be reduced and the downstream value chain for itaconic acid can be expanded, the market could be grow in the future.

Keywords: Itaconic acid, Biorefinery, Manufacturing, Platform chemicals

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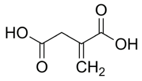
1 Introduction

Today's demand for raw materials in the chemical industry is still 92% covered by fossil resources including oil, natural gas and coal. In view of the scarcity of fossil resources in the coming decades, it is necessary to look for alternative sources of raw materials. On the one hand, these should be as regenerative as possible in terms of sustainable development and, on the other hand, should be able to ensure satisfactory substitution of products previously obtained on a petrochemical basis.

An interesting compound in this context is itaconic acid, also known as methylidenesuccinic acid. Itaconic acid, as shown in Table 1, is a monounsaturated dicarboxylic acid, offering interesting opportunities for the chemical and pharmaceutical industries. It is suitable for a variety of applications due to its special properties. Due to its low productivity, lack of process stability and costly processing, itaconic acid has a high price and is only used in limited quantities for product specialties so far. The price of itaconic acid ranges between 1.5–2.0 USD/kg and the annual world production of itaconic acid exceeded 80,000 t [1]. Itaconic acid is a crystalline, white colored, monounsaturated organic diacid with the formula $C_5H_6O_4$. Some other important chemical properties of itaconic acid are listed in Table 1. Itaconic acid has a molecular weight of 130.1 g/mol and a solubility in water at 20°C of 83.1 g/mol. The boiling and the melting points are at 268°C and 167°C, respectively.

Table 1: Selected properties of itaconic acid

Property	Value
Chemical formula	$C_5H_6O_4$
Chemical structure	
Appearance	White & crystalline
pK_a values	3.84 & 5.55
Molecular weight	130.1 g/mol
Solubility in H_2O at 20°C	83.1 g/L
Boiling point	268°C
Melting point	168°C

Itaconic acid has a methylene group in addition to its two carboxyl groups. This two carboxyl groups are the reasons for the two pK_a values of 3.84 and 5.55, respectively. When, the pH value in an aqueous solution is lower than pH 2.0, the non-dissociated acid occurs mainly. Whereas, at pH values higher than pH 7.0, the dissociated itaconate form is more presented in the solution. For pH values between pH 2.0 and pH 7.0 there will be a solution containing various dissociated forms of the itaconic acid [2].

The variety of available functional groups allows for a variety of reactions and make itaconic acid to be an effective intermediate in the preparation of wide ranges of complex organic compounds or polymers [3]. These includes e.g. complexation with metal ions, esterification with alcohols, preparation of anhydrides and polymerization by addition and condensation [2]. The solubility in solution of itaconic acid depends strongly on the temperature, therefore the concentration and crystallization processes in downstream production are controlled by adjustment of reactor temperatures [1].

2 Choices of Itaconic Production

Currently, itaconic acid can be produced by using either chemical or biological methods. Via chemical method, itaconic acid was identified and characterized in 1837 as a thermolysis product of citric acid. Since then, many chemical synthesis pathways of itaconic acid production have been proposed. Although the thermolysis of citric acid to generate itaconic acid is possible, however, the raw material of this reaction is citric acid, which mainly produced by fermentation of *Aspergillus niger*, and it makes this process relying on the biological method at the end. Furthermore, the product selectivity of the chemical synthesis is relatively low. Thus, only 35 mol % of itaconic acid could be converted from citric acid. Another 41 mol % of substrates could be transformed to mesaconic and citraconic acid and 12 mol % to acetone and acetic acid [4]. Nowadays, nearly all companies are producing itaconic acid by using *Aspergillus terreus* via fermentation making the production becomes a conventional process. In addition to the above mentioned points, the a slim price difference in current market between citric acid and itaconic acid decreases the interest to produce itaconic via chemical process in the economic aspect [5].

Kinoshita [6] described the first biotechnological production of itaconic acid with *Aspergillus itaconicus*. Another fungi, *Aspergillus terreus* achieved a greater final itaconic acid concentration [7]. In 1945, Charles

Pfizer registered the first patent for an industrial scale production of itaconic acid and established the first production plant in the USA 10 years later. Due to constrains in different economical points, for examples labor costs and logistics, nowadays the main factories were mainly located in the Asian region [1]. The production process of itaconic acid by using *Aspergillus terreus* was continuously optimized to be a well established process that the chemical process can no longer compete anymore with the biochemical process [3].

At the beginning phase of development, it was hypothesized that a phosphate limitation was necessary for an overproduction of itaconic acid [5]. Meanwhile, this proposed mechanism has been refuted, even though the metabolism has not been finally well explained yet [8]. Nevertheless, the biosynthesis of itaconic acid, including involved enzymes, has been well researched these days. In microbial biosynthesis pathway of itaconic acid, various types of sugars, for examples glucose, xylose and arabinose could be utilized as carbon source substrates. Those sugars are converted to pyruvate via glycolysis and pentose phosphate pathway as shown in the model of *Aspergillus terreus* [9]. Following this, the pyruvate is transported from the cytosol to the mitochondria, where it is catalyzed to citrate and cis-aconitate via the Kreb's cycle. The formed cis-aconitate is translocated back to the cytosol via the mitochondrial tricarboxylate transporter and converted to itaconate by the cis-aconitate decarboxylase [10]. Overall, out of 1 mol monomer sugar as a substrate, 1 mol of itaconic acid with a maximum theoretical yield of 72% can be produced [9].

The production of itaconic acid in an industrial scale is commonly conducted with *Aspergillus terreus*, a filamentous fungus. This microbe shows relatively high product yields as well as high final concentrations of itaconic acid in the fermentation broth under optimal conditions [11]. Kuenz *et al*. [12] has shown that the formation of itaconic acid in *Aspergillus terreus* has a high dependence on different factors such as oxygen supply, phosphate concentration, pH value, power input and the presence of metal ions. That means, if these factors are not well controlled during the fermentation process, the product formation proceeds under limitation. A common solution regarding the limited oxygen supply is the use of a Stirred Tank Reactor (STR). However, the STR has serious shortcomings. First of all, it is expensive in terms of constructions and operation. Furthermore, since filamentous microorganisms like *Aspergillus terreus* are sensitive to shearing stress, the use of a STR is highly disadvantageous. A promising alternative is an Air-Lift-Reactor (ALR). This reactor does need less energy compared to a STR and does not require mechanical agitation, which leads to high production rate at low power inputs.

To overcome the other limitations, another fungus, *Ustilago maydis*, has been investigated as an alternative itaconic producer. *Ustilago maydis* does not achieve the same production efficiency in the itaconic acid production like *Aspergillus terreus*, however its unicellular and non-filamentous appearance provides advantages for fermentation processes in large scale. An important property of *Ustilago maydis* is its higher tolerance regarding medium impurities, therefore cheap complex raw material could be used [13]. However, more and more cheaper feedstocks, such as agro-wastes, are used to reduce the production cost. This even more highlights the importance of using *Ustilago maydis*. Overall, both in economic and ecological terms, a successful process depends, among other things, strongly on the applied microorganisms that are used. However, further process analysis are required for improve of the effectiveness in industrial scale production.

The raw material selection is a crucial part of the entire production process of itaconic acid. The raw material, also called as feedstock or substrate, has to be of low cost, available throughout the year, and replaceable for example starch, molasses or lignocellulosic substrates [14]. It is also critical that the substrate selection should be well matched to the selected microorganism, since not every microorganism can metabolize and produce the targeted product. Due to a high yield of itaconic acid that can achieved, monosaccharides and disaccharides were used as main feedstocks of the itaconic acid production. In fact, the costs of these carbon sources contribute significantly to the whole production costs (e.g. glucose ranges from 0.35–0.60 USD/kg) [15]. The demand for more economical substrates, such as molasses, starch, wood hydrolysates or corn syrup are increasing [5]. To this extent, other polymeric carbon sources such as sago, sorghum, sweet potato, wheat, potato and cassava were tested. Unfortunately, all of them have the big disadvantage that they are functional sources of human food and animal feed. This fact can lead to ethical conflicts to the world hungers [15].

Promising alternative substrates that are cheap as well as not in conflict with food and feed applications, are agro-wastes. Examples of such agriculture residues are jatropha seed cake or molasses. For the most agro-wasted substrates, an appropriated pretreatment is necessarily, because they contain non-digestible carbohydrates like cellulose and hemicellulose [14]. Additionally, agro-waste substrates have characters that needed to be overcome, for example, inconsistency of composition of feedstocks, low conversion rate of product, presence of inhibitors, impurities of by-products [15]. An overview of achieved yields of itaconic acid from different raw materials and types of microorganisms is given in Table 2. Furthermore, pretreatments need to be improved to increase the released ratios of free sugars from lignocellulosic biomass and to reduce undesired by-products and inhibitos, such as furfural and hemifurfural.

Table 2: Itaconic acid yields ($g_{itaconic\ acid}/g_{substrate}$) obtained from using different types of substrates and microorganisms

Substrate	Microorganisms	Yield	Reference
Beech wood hydrolysate	*A. terreus* NRRL 1960	0.30	[16]
Corn stover hydrolysate	*A. terreus* Mutant AT-9	0.36	[17]
Banana waste extract	*A. terreus* Mutant bN 45	0.35	[18]
Wheat bran hydrolysate	*A. terreus* CICC40205	0.41	[19]
Wheat chaff hydrolysate	*A. terreus* DSM 23081	0.41	[2]
Glucose	*A. terreus* DSM 23081	0.62	[12]
Sago starch	*A. terreus* SKR10	0.34	[20]
Corn starch	*A. terreus* TN-484	0.50	[21]
Corn starch	*A. terreus* NRRL1960	0.34	[22]
Cassava flour	*A. terreus* NRRL1960	0.19	[23]
Glycerol	*U. vetiveriae* TZ1	0.18	[24]
Citrate	*E. coli* BL21(DE3)	0.64	[25]
Glucose	*Ustilago maydis* MB215	0.24	[26]

3 Downstream Processing

Despite the raw materials costs are the biggest part to determine the final product costs of organic acids, the downstream processes including recovery and purification, are responsible for up to 30 to 40% of the final product costs [26]. Itaconic acid production also has this process pattern. Even though the biotechnological production of itaconic acid is already industrially established, the demand for improvements in fermentation and recovery steps is still high [28]. The recovery and purification process of itaconic acid, as an organic acid, could be conducted with various techniques and frequently with a series of different separation techniques, for examples crystallization, extraction, electrodialysis, precipitation and adsorption, to obtain the target specifications of products to meet with the market demand.

Via fermentation, itaconic acid can be easily recovered by evaporation or cooling in an acidic environment, which make itaconic acid became insoluble and precipitate. However, undesired co-produced by-products such as succinic acid, malic acid and α-ketoglutaric acid are also co-separated with itaconic acid, which decrease the quality of the end product [1]. After evaporation, the filtrate is concentrated to crude precipitates. The resuspended precipitates could be further upgraded by cooling crystallization. The colored crude crystals are subsequently de-colored by filtering with activated carbon to remove colored contaminants from fermentation broth. Then, the recrystallization process is conducted to obtain the pure crystal with high quality for market demand.

In addition to the conventional separation process, the improvement of downstream process of itaconic acid production has been continuously demonstrated. One of the example is the application of liquid-liquid extraction. Based on the different solubilities of any substances in two immiscible solvents, the itaconic acid is solubilized in different degree in different types of solvents. Long-chain alcohols, esters and alkanes are often used as solvents. However, itaconic acid has a higher solubility in aqueous environments than in organic environments, conventional liquid-liquid extraction cannot be applied effectively [27]. Therefore, reactive liquid-liquid extraction is applied by using organophosphorus compounds or tertiary or quaternary amines to increase itaconic acid solubility in another extraction agent.

Organophosphates and aliphatic amines have good thermal stability, which easily recovered and recycled by distillation [5]. Tri-n-octylamine (TOA), a long-chain aliphatic amine, was used as the extractants, while 1-octanol was used as a diluent in a system of reactive liquid-liquid extraction. The recovery of itaconic acid is improved to be readily for scale-up of industrial production.

4 Current Market Situation

The demand for environmentally friendly and sustainable products and processes is growing worldwide. The growth for bio-based products is additionally encouraged by governmental policies. Due to increasing regulations, many companies get additional incentive, e.g. tax exemption, to look for alternative and renewable products and processes, respectively. However, the green and renewable biochemical products has a main challenge to compete with the position of conventional products in terms of quantity and quality.

As a bio-based chemical, itaconic acid has a high potential in the chemical market with a broad range of applications. According to Transparency Market Research (2015), itaconic acid is still considered as a niche product, although it currently has broad range of applications, mainly to substitute the use of plastic monomers [28]. The use of itaconic acid has several advantages over conventional fossil-derived chemicals in terms of sustainability. Thus, itaconic acid as a monomer of polymer synthesis is biodegradable. It is non-toxic and has a large variations of polymeric derivatives by combining with other monomers to form heteropolymers.

One of the most promising applications of itaconic acid are synthesized latex, methyl methacrylate, unsaturated polyester resins and superabsorbent polymers. The synthesized latex accounts for more than 50% of the global market share of itaconic acid [29]. It is mainly used in the form of styrene butadiene rubber as a polymer stabilizator. However, the latex market is already well covered today and there is no big growth potential expected [30]. Although, great potential is predicted for itaconic acid as a industrial feedstock for methyl methacrylate. This ester is still mainly produced from acetone cyanohydrin, but could be increasingly synthesized with itaconic acid in the future. A typical application of methyl methacrylate is acrylic glass for LCD screens or other video equipment. Furthermore, it is also used for the production of two-component adhesives. In the construction industry, unsaturated polyester resins are still mainly produced by maleic anhydrides. However, the synthesis with itaconic acid is a promising alternative, due to their similar structure.

Resins derived from itaconic acid are consequently synthesized to polyesters, plastics and artificial glass, replacing plastics and rubbers made from petroleum. As already mentioned, acrylic and methacrylic acid can be obtained which also accounts for the largest part of itaconic acid processing and is mainly used for the production of polymers. For plastics and coatings itaconic acid provides especially favorable characteristics as light color, ease of painting, separation and antiseptic properties. Major area of this first type of application is the building industry with its strong demand for sealing materials, adhesives and elastic fillers.

A smaller fraction of itaconic acid derivatives is used as detergents, additives and biologically active compounds for agricultural and pharmaceutical use. The reaction of itaconic acid with amines creates N-substituted pyrrolidones, which are applied in many detergents, shampoos, pharmaceuticals and herbicides. The medical and pharmaceutical industry uses itaconic acid for example as a hardening agent for contact lenses, in binders for diapers and feminine napkins and for biocompatible cement (glass ionomer cement), used in dentistry. Other, more special applications are for example emulsion paints, where itaconic acid helps to improve the adhesion of the paint or water treatment technologies.

In 1945, Pfizer was the first company that produces itaconic acid in an industrial scale. Since then, other companies such as Iwata Chemical from Japan, Rhodia from France or Cargill from the United States appeared at the itaconic acid market as well [1]. Due to the production stop of Rhodia, Pfizer and Cargill, the Chinese have become the largest producer of itaconic acid. Enormous investments on the part of the Chinese government in the biotechnology sector have consolidated its position. According to Huang *et al.* [30], Qingdao Kehai Biochemistry Company with a production volume of 10,000 tons per year has about 50% of the total capacity of the itaconic acid production of the Chinese and 18% of the worldwide market. This company exports pure itaconic acid to Europe as well as to North and South America [29].

Aside from China, just India and the USA are notable itaconic acid producer on the global market at the moment [31]. Hereby, the itaconic acid market in Asian area can be seen as a model for the establishment of further production location in other countries. New technologies and other itaconic acid applications could serve as a catalyst. In addition, the above mentioned pressure on companies by governmental constraints could further accelerate the upswing of the itaconic acid market. An example of this constraints is the ban of using detergents that contain sodium (poly-) phosphate in the European Union. Sodium (poly-) phosphate could be replaced by itaconic acid derivatives and therefore, a new and large market would emerge. Lastly, other world areas such as South Africa, Saudi Arabia and the United Arab Emirates may also be targets for itaconic acid market due to their increasing preferences for bio-based products [31].

5 Conclusions

Itaconic acid is a promising bio-based chemical with vast applications in chemical industries. It can be mainly used as a substitute for acrylic and methacrylic acid and further for detergents, cleaners and bioactive compounds. The increasing demand of bio-based products is a gateway for the development of itaconic acid derivatives for new applications in the fields of pharmacy, chemistry or agriculture. However, the production capacity of itaconic acid currently exceeds the demand by far and itaconic acid occupies only a niche market. The high production cost of itaconic acid results in a relatively high product price and this excludes the application of itaconic acid for many processes. Its use is limited due to low volume markets and a further replacement of petroleum-based chemicals is only expected when the price of itaconic acid falls below 1.5 USD/kg. To achieve this aim, further studies on reducing the production cost and on increasing the overall process productivity are required. Many technical innovations discussed in this review need to be further promoted as itaconic acid has potential to replace a large amount of petroleum-derived chemicals. To compete with them, the currently slow rate of development of viable end use applications must be anticipated as petroleum-based products are still a cheap option due to relatively stable petroleum prices.

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