MALONIC ACID: A BIOADVANTAGED CHEMICAL

Dr. Jeffrey Dietrich, Lygos CTO

LYGOS' FIRST PRODUCT: MALONIC ACID

Malonic acid is a C3-dicarboxylic acid currently used as an intermediate in the synthesis of numerous flavors/fragrances and pharmaceuticals. While capable of being used in a wider variety of applications, demand has been held back by malonic acid's high cost and environmentally hazardous production process. At Lygos we are developing a microbial process to produce malonic acid. We outline here why we find malonic acid to be an ideal chemical to produce biologically from both economic and technical perspectives.

LOWER SUGAR COSTS

The petrochemical industry is based on raw material inputs (*e.g.*, methane, C2-C4 linear hydrocabrons, naptha, *etc.*) comprised near exclusively by hydrogen and carbon. In contrast, industrial biotechnology processes generally use sugar as the raw material; here, over half the mass is comprised by oxygen. To produce a fuel from sugar most of this oxygen must be stripped from the molecule, equating to a less efficient (lower yielding) process. In contrast, organic acids are oxygen rich and can be produced at a high yield from sugar. For example, the theoretical yield of three fuel molecules – biodiesel, butanol, and ethanol – ranges from 35-51% w/w from sugar; in contrast, the theoretical yield of three organic acids – lactic acid, citric acid, and malonic acid – ranges from 100-113% w/w. Lygos' first product, malonic acid, can be produced at a yield greater than 100% because CO_2 is sequestered during production of the product.

SHUTDOWN ECONOMICS

Not only is biology well suited for producing organic acids, these molecules are also expensive to produce petrochemically. Incorporation of oxygen into petrochemical raw materials comes at a monetary, and often environmental cost. For example, maleic anhydride, an intermediate material used for production of 1,4-butanediol (1,4-BDO) among other things, is produced from n-butane or benzene and currently sells for around $1.75/kg. In turn, this sets the price floor for derivative chemicals and explains, in part, the number of industrial biotech companies producing 1,4-BDO.

In the case of malonate, one of the starting raw materials is the chlorinated compound monochloroacetic acid. This chemical trades for near $1/kg, or roughly the same price as a fuel molecule. By combining a high-yielding microbial process and economies of scale, we can achieve shutdown economics using a microbial process.

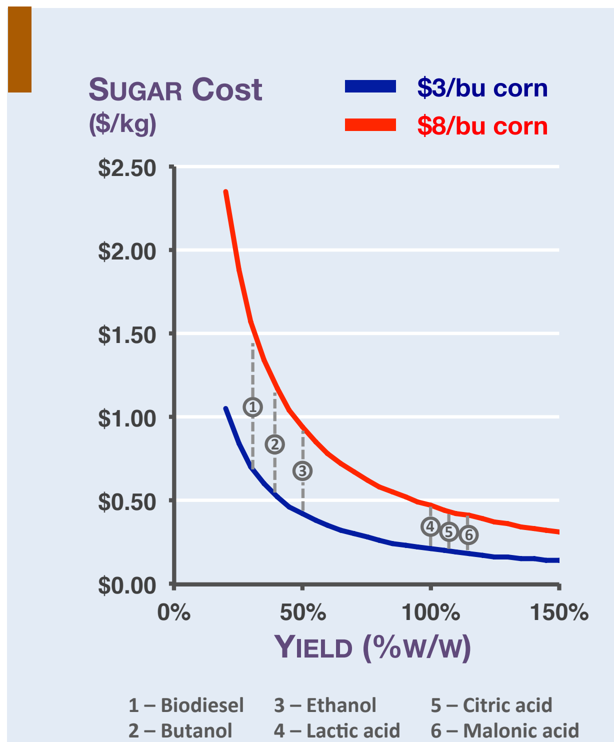
LOW PH FERMENTATIONS

Not surprisingly, producing an organic acid increases the acidity of the fermentation medium. Most microbes have low tolerance for acids and grow poorly at low pH. This feature brings distinct benefits when producing chemicals at industrial scales as it provides a route to mitigate the risk of microbial contamination. The challenge is that the microbe we are using to produce the organic acid must be able to grow at low pH. The most commonly used microbes in industry and academia, *E. coli* and *S. cerevisiae* (brewer's yeast), grow at neutral pH and are not well suited for producing these products.

At Lygos, we exclusively develop acid-tolerant yeast and fungi. We have developed a suite of molecular biology tools and protocols necessary to engineer these microbes, providing us with a competitive advantage as we optimize our microbes for improved performance.

BIOADVANTAGED CHEMICALS

In short, bioadvantaged chemicals are those where the petroleum industry cannot compete with biology, where biological production offers a strong economic or technical advantage over a petrochemical process. Malonic acid is just one example of a bioadvantaged chemical, and at Lygos we are working on developing a suite of these products.



The raw material cost to produce a kilogram of various products. Each chemical can be produced at a maximum theoretical yield from sugar (x-axis). More sugar is required to produce a kilogram of a low-yield product (*e.g.*, biofuels) relative to a high-yield product (*e.g.*, organic acids). This characteristic also makes higher yielding products less sensitive to increases in raw material prices.