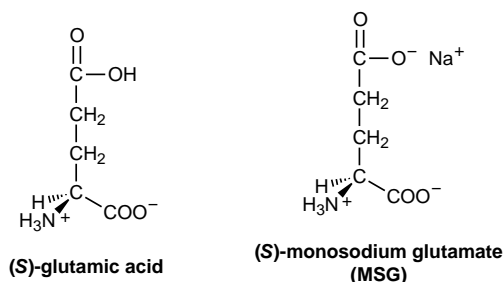


The Monosodium Glutamate Story: The Commercial Production of MSG and Other Amino Acids

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Monosodium glutamate (MSG), first isolated as glutamic acid in 1866, has since become both the basis of a trillion-dollar worldwide industry and a presence in the diet of a majority of the inhabitants of the world.



In this article I present some parts of the “story” of MSG that might be of most interest to chemists, chemistry teachers, and their students.

History

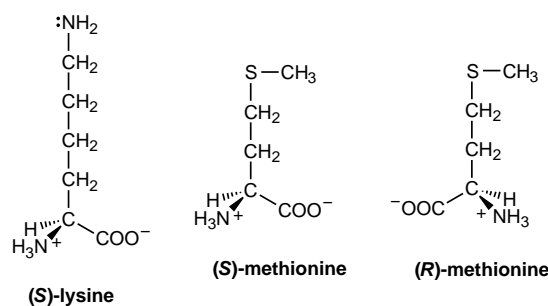
Glutamic acid was first isolated as a pure substance in 1866 by the German chemist Ritthausen through the acidic hydrolysis of gliadin, a component of wheat gluten. It was not until 1908, however, that the Japanese chemist Kikunae Ikeda found that glutamic acid was responsible for the flavor-enhancing properties of the kelp-like seaweed, “konbu”, or *Laminaria Japonica*, that had been used for many centuries in Japan in the preparation of soup stocks. By extracting 40 kilograms of the seaweed with hot water, Ikeda obtained 30 grams of (*S*)-glutamic acid, which he then identified as the taste-enhancing component of konbu. Ikeda immediately patented a process for isolating monosodium glutamate from wheat flour, and in 1909 the first monosodium glutamate was produced commercially under the trade name Ajinomoto (*Aji no moto*; “at the origin of flavor”).

Glutamic acid has now been isolated from innumerable vegetable sources, of which the most practically useful have included wheat gluten, soybean meal, casein, and the residue from the Steffen process for the production of beet sugar, the so-called “Steffen waste”. The preparation of (*S*)-glutamic acid from wheat gluten is described in *Organic Syntheses, Collective Volume 1 (1)*.

Since 1908 the sodium salt of glutamic acid, or MSG, has come into use around the world as an additive, or seasoning, to enhance the flavor of foods. MSG is usually used in combination with salt, and, in general, a suitable quantity of MSG is 10–20% of the quantity of salt to be added. The connection between MSG and taste is described in more detail below.

Commercial Production of Amino Acids

(*S*)-Glutamic acid, relative to other pure amino acids, is produced in the largest quantities around the world. Its two closest competitors are (*S*)-lysine, and (*R,S*)-methionine, as indicated in Table 1.



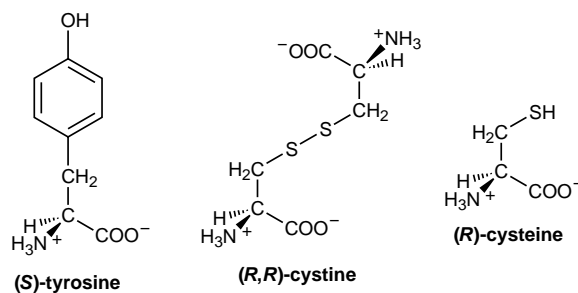
Almost all of the (*S*)-glutamic acid is used as an additive in the human diet, while the (*S*)-lysine and (*R,S*)-methionine are used almost entirely in the supplementation of animal feeds. The various uses of pure amino acids are described in later sections.

Methods of Commercial Production of Amino Acids

There are four general ways to obtain amino acids for commercial use: extraction from natural sources, chemical synthesis, fermentation, and enzymatic catalysis.

Extraction from Natural Sources

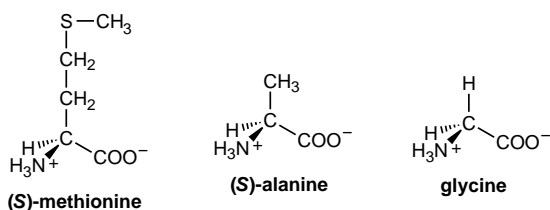
In extraction from natural sources the standard procedure is hydrolysis with aqueous acid, followed by capture of the amino acids by passage of the hydrolysate over a strongly acidic ion exchange resin. After the resin is washed with water, elution with aqueous ammonia frees the amino acids, which are collected in fractions. Extraction is the most economical process for the production of both (*S*)-tyrosine and (*R,R*)-cystine. Reduction of (*R,R*)-cystine gives (*R*)-cysteine.



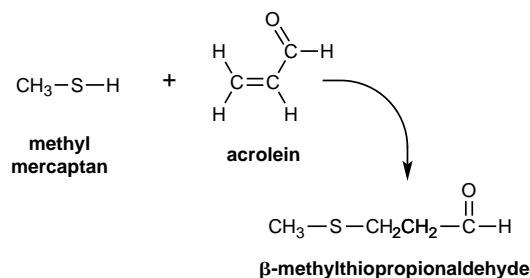
Chemical Synthesis

The advantage of a chemical synthesis is that it can be carried out on a very large scale, and often in a continuous way. The great disadvantage, however, is that it typically gives a racemic mixture of the enantiomeric forms of the amino acid. Thus the product of a chemical synthesis must be resolved into the *R* and *S* forms, followed by recovery and recycling via racemization of the undesired enantiomer.

An example of a chemical synthesis is provided by the preparation of (*R,S*)-methionine. Since both the *R* and *S* isomers of methionine can be metabolized by poultry and swine, resolution is not necessary and, in contrast to most other amino acids, chemical synthesis is predominant for the industrial production of methionine, as well as for racemic alanine and glycine.



The first step of the chemical synthesis of methionine is the conjugate addition of methyl mercaptan to acrolein to give β -methylthiopropionaldehyde.



The addition of methyl mercaptan to acrolein takes place by a nucleophilic mechanism. Attack of the conjugate base of methyl mercaptan ($pK_a = 10.7$) gives a resonance-stabilized anion, which then accepts a proton on carbon to give the addition product, β -methylthiopropionaldehyde.

Table 1. Production and Selected Properties of Amino Acids

Amino Acid	Coded ^a	Essential ^b	Extraction ^c	Chemical Synthesis ^d	Fermentation ^e	Enzyme Catalysis ^f	Production ^g
(S)-Alanine	Y	—	—	—	—	Y	0.15
(R,S)-Alanine	N	—	—	Y	—	—	1.5
(S)-Arginine	Y	Y/N	Y	—	Y	—	0.7
(S)-Aspartic acid	Y	—	—	—	—	Y	2
(S)-Asparagine	Y	—	Y	—	—	—	0.03
(R)-Cysteine	Y	C	Y	—	—	Y	0.3
Cystine	N	—	Y	—	—	Y	—
Glycine	Y	—	—	Y	—	—	3.5
(S)-Glutamic acid	Y	—	—	—	Y	—	80
(S)-Glutamine	Y	—	—	—	Y	—	0.85
(S)-Histidine	Y	Y/N	—	—	Y	—	0.25
(S)-Isoleucine	Y	Y	—	—	Y	—	0.2
(S)-Leucine	Y	Y	Y	—	Y	—	0.2
(S)-Lysine	Y	Y	—	—	Y	—	30
(S)-Methionine	Y	Y	—	—	—	Y	0.15
(R,S)-Methionine	N	—	—	Y	—	—	30
(S)-Phenylalanine	Y	Y	—	Y	Y	Y	1.5
(S)-Proline	Y	—	—	—	Y	—	0.15
(S)-Serine	Y	—	—	—	Y	Y	0.6
(S)-Threonine	Y	Y	—	Y	Y	—	0.2
(S)-Tryptophane	Y	Y	—	Y	Y	Y	0.25
(S)-Tyrosine	Y	C	Y	—	Y	—	0.6
(S)-Valine	Y	Y	—	Y	Y	—	0.2

^aCoded for the genetic code? Y = yes, N = no.

^bEssential for the human diet? Y = yes, Y/N = humans can synthesize some, but not enough during times of stress or rapid growth, C = essential for children.

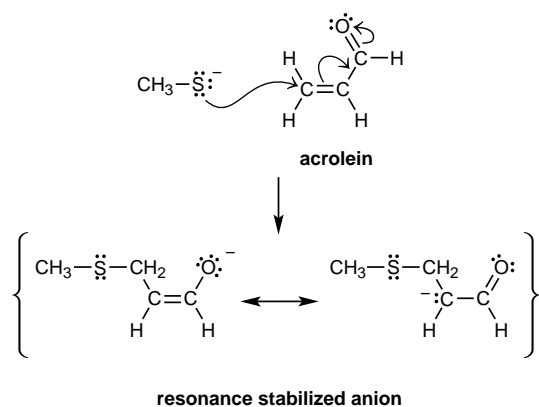
^cSignificant production by extraction from natural sources? Y = yes.

^dSignificant production by chemical synthesis? Y = yes.

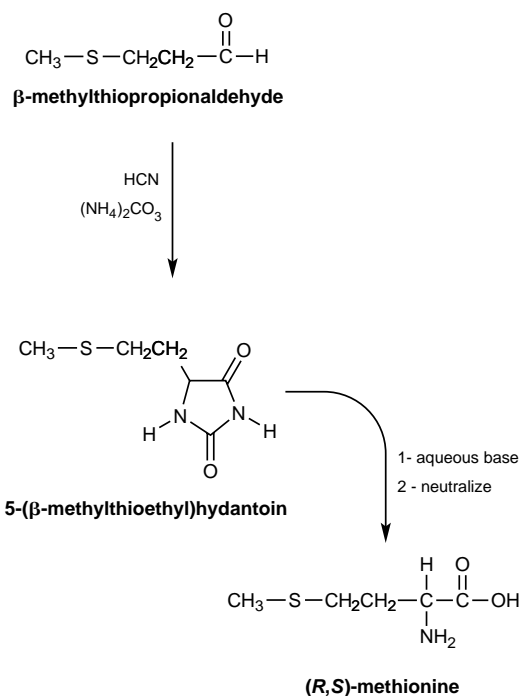
^eSignificant production by fermentation? Y = yes.

^fSignificant production by enzymatic catalysis? Y = yes.

^gEstimated production in Japan in 1987; kilotons per year (kiloton = 10^9 grams). Production methods and quantities from Vol. 2, p 255, ref 2.



β -Methylthiopropionaldehyde is then converted to methionine by the Bucherer method, a modification of the Strecker method in which ammonium carbonate takes the place of ammonia.

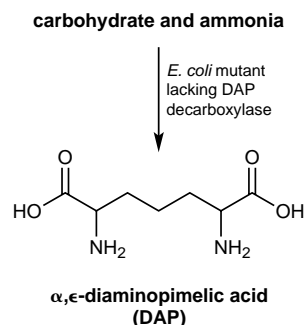


Fermentation Methods

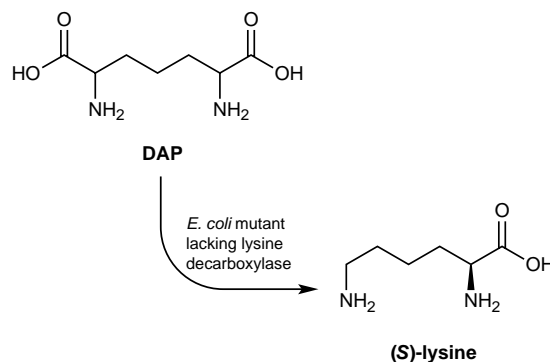
Although it is possible to prepare any natural amino acid by fermentation, a microbiological process, the special mutants that allow production to be done on a large scale have been developed only for the preparation of (*S*)-lysine and (*S*)-glutamic acid. The carbon sources for these syntheses are typically cane or beet molasses, raw sugar, or a starch hydrolysate. Ammonia is the source of nitrogen, and oxygen is provided by passing compressed air into the fermenting mixture.

An early fermentation process for the production of lysine made use of a pair of *E. coli* mutants. Normal *E. coli* can synthesize its own lysine from carbohydrates and ammonia, but the first mutant lacked the α,ϵ -diaminopimelic de-

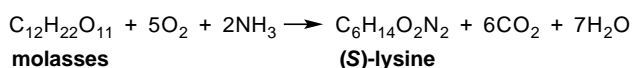
carboxylase that normally converts α,ϵ -diaminopimelic acid (DAP) to lysine.



After the concentration of DAP had reached a maximum in the presence of the first mutant, the first mutant was removed and another *E. coli* strain was added. This second mutant produced DAP decarboxylase, but lacked lysine decarboxylase, thus allowing lysine to accumulate.



A second method for the production of lysine is a single-stage fermentation process, now generally used for the microbial synthesis of lysine. This process makes use of a mutant of *Corynebacterium glutamicum* in which feedback mechanisms of product inhibition are overcome. Molasses is the most common carbon source, and this contains sufficient biotin to provide the more than 30 $\mu\text{g/L}$ needed to suppress the excretion of glutamic acid. The final concentration of lysine is nearly 60 g/L, and the fermentation cycle takes between 48 and 72 hours. The balanced equation is:



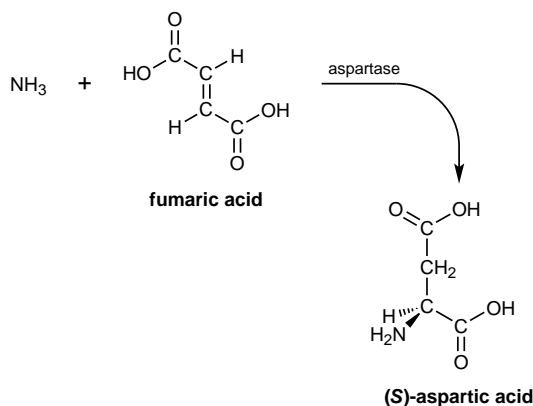
The yield of lysine from carbohydrate, according to the stoichiometry, is nearly 40%.

Enzymatic Synthesis of Amino Acids

In the fourth method for synthesis of amino acids, the enzymatic procedures, pure enzymes are used, rather than the enzyme systems of living microorganisms, as in the fermentation methods.

At one time, for example, (*S*)-aspartic acid was produced mainly by the enantioselective, enzyme-catalyzed, addition of ammonia to fumaric acid, a substance that could be sup-

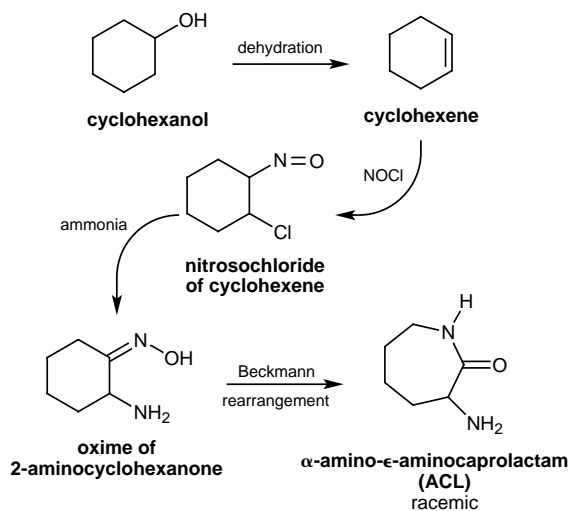
plied in large quantities and at low cost.



Since only the naturally occurring isomer of aspartic acid was formed, resolution was not necessary. This method has since been supplanted by a continuous microbiological process in which the reacting solution passes over a fixed bed of an immobilized microorganism.

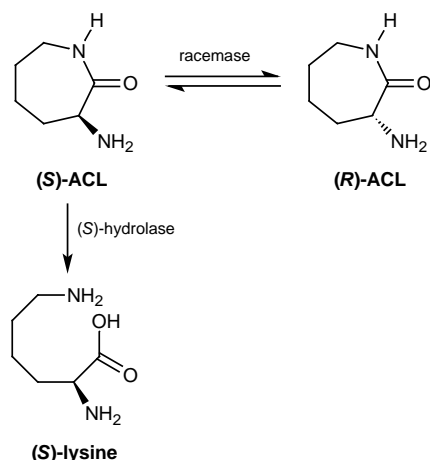
A Chemical and Enzymatic Synthesis of (*S*)-Lysine

Before moving on to consideration of the various methods for the industrial preparation of glutamic acid and monosodium glutamate, we will consider a synthesis of (*S*)-lysine that combines both chemical and enzymatic processes. In this synthesis α -amino- ϵ -aminocaprolactam (ACL) is prepared from cyclohexanol via cyclohexene, nitrosochloride of cyclohexene, and the oxime of 2-aminocyclohexanone, which then undergoes Beckmann rearrangement to ACL.



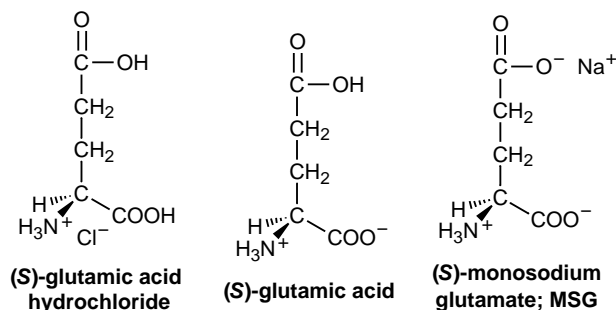
The racemic ACL is then hydrolyzed in the presence of immobilized (*S*)-ACL-hydrolase to give (*S*)-lysine and unreacted (*R*)- α -amino- ϵ -aminocaprolactam. A racemase that interconverts (*R*)- and (*S*)-ACL is present in an immobilized form as well. Thus as (*S*)-ACL is hydrolyzed to (*S*)-lysine, (*R*)-ACL is racemized to replace (*S*)-ACL until finally all of the racemic ACL has been converted to (*S*)-lysine. In this way, 100 g/L racemic ACL can be converted in 25 hours to

(*S*)-lysine in a yield of 100%. The method can be represented in this way:



Glutamic Acid and Monosodium Glutamate

All methods for the industrial production of (*S*)-monosodium glutamate first produce either (*S*)-glutamic acid hydrochloride or (*S*)-glutamic acid.



The crude, crystalline glutamic acid is first suspended in water and then dissolved, neutralized and converted to the monosodium salt by the addition of sodium hydroxide. The solution is decolorized using activated carbon, if necessary, and concentrated under vacuum at 60 °C before cooling for crystallization. The crystals are isolated by centrifugation and then dried.

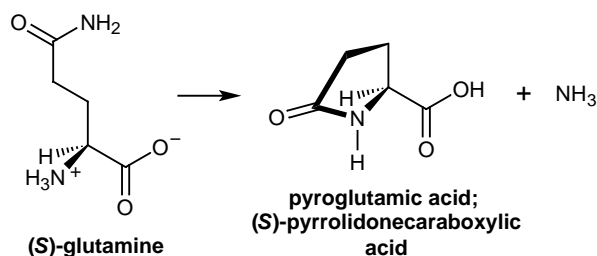
Isolation of Glutamic Acid from Protein Hydrolysates

From 1909, when the production of glutamic acid was first undertaken, until 1965, when fermentation methods became more important, the isolation of glutamic acid from protein hydrolysates was predominant. The main raw material was wheat gluten, which contained up to 25% glutamic acid by weight. The gluten was subjected to hydrolysis by aqueous HCl, the hydrolysate was then concentrated under reduced pressure, further acidified by the addition of concentrated HCl, and finally cooled to crystallize (*S*)-glutamic acid hydrochloride, which was very much less soluble in concentrated HCl than the hydrochlorides of any of the other amino acids.

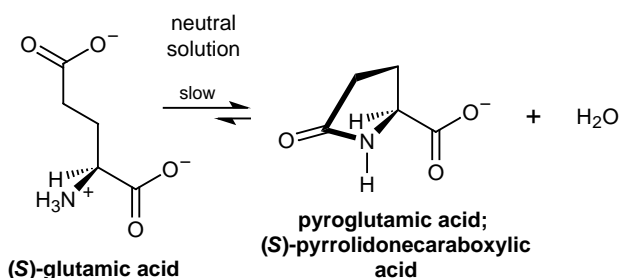
The hydrochloride was collected by filtration, dissolved in warm water, and filtered to remove insoluble humic materials formed by the reactions of amino acids with carbohydrates. The acidic filtrate was then adjusted by addition of sodium hydroxide or ammonia to a pH of 3.2, the isoelectric pH of glutamic acid, and the pH at which glutamic acid has its lowest solubility, 0.864 g/100 mL of water at 25 °C. The crude (*S*)-glutamic acid that crystallizes was then converted to (*S*)-monosodium glutamate as previously described.

Glutamic Acid from Steffen Waste

There was a time, more or less between the two World Wars, when in this country and in some parts of Europe glutamic acid was recovered from the waste that remained from the Steffen process for isolation of sugar from sugar beets, the "Steffen waste", and from "vinasse", the material remaining from the distillation of ethanol produced by the fermentation of beet molasses. Glutamic acid occurs in beets primarily as glutamine, which cyclizes to pyroglutamic acid, or pyrrolidonecarboxylic acid, during the processing of the beets.



In neutral solution, the equilibrium between glutamic acid and pyroglutamic acid favors the cyclic form, as indicated here and in Figure 1.



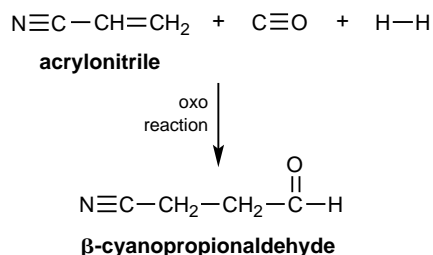
In neutral solution the equilibration between the cyclic and open form is slow, and the closed form is favored. In contrast, the hydrolytic equilibration between forms is rapid in strongly acidic and strongly basic solutions, and the open forms are favored.

For the production of glutamic acid from pyroglutamic acid, the hydrolysis was carried out at a pH between 10.5 and 11.5 at 85 °C for two hours. These conditions are sufficiently mild that racemization is not a problem, and the solution is basic enough that the major form at equilibrium is the dianion, 4, as indicated in Figure 1. After hydrolysis, the pH of the hydrolysate is adjusted to 3.2, the isoelectric pH, and the (*S*)-glutamic acid is thus precipitated. The remainder of the procedure was as described above. The glutamine content of Steffen waste and of vinasse is about half of the glutamic acid content of wheat gluten, corn gluten, or de-

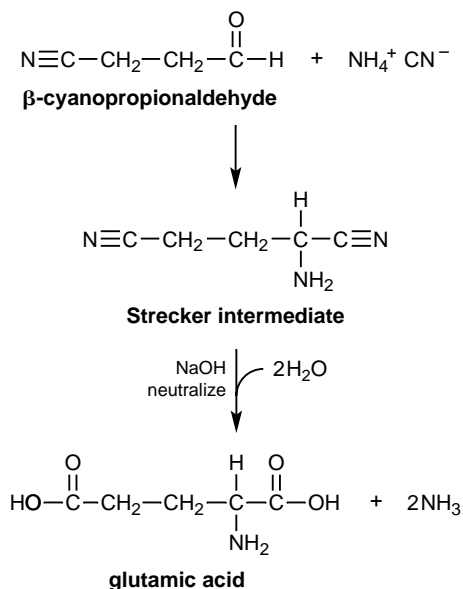
fatted soy beans, and is also quite variable. For these and other reasons, such as the variable quality of the starting materials, the production of MSG from molasses was never easy.

Glutamic Acid by Chemical Synthesis

Before World War II there was no chemical synthesis that could compete with the extraction methods. After the War, the discovery of the oxo reaction, and its application to acrylonitrile, available from either acetylene plus HCN or from propylene by oxidation in the presence of ammonia, made possible the synthesis of β -cyanopropionaldehyde, the key intermediate for the synthesis of glutamic acid.



β -Cyanopropionaldehyde was then converted to glutamic acid by the Strecker process in which the aldehyde is converted to the amino analog of a cyanohydrin, which is then hydrolyzed to glutamic acid.



There is a lot to appreciate in this synthesis, which was continuous in operation, with all materials present in a liquid phase that was contained at high temperature under pressure. It was additive in carbon (there were no carbon-containing byproducts), and the two equivalents of ammonia produced in the hydrolysis were recycled for use in the synthesis of ammonium cyanide. The amino nitrogen of the glutamic acid had its origin in the ammonia of the ammonium cyanide, and the five carbon atoms of the product came from acrylonitrile, carbon monoxide, and methane, the last two substances being relatively inexpensive carbon sources.

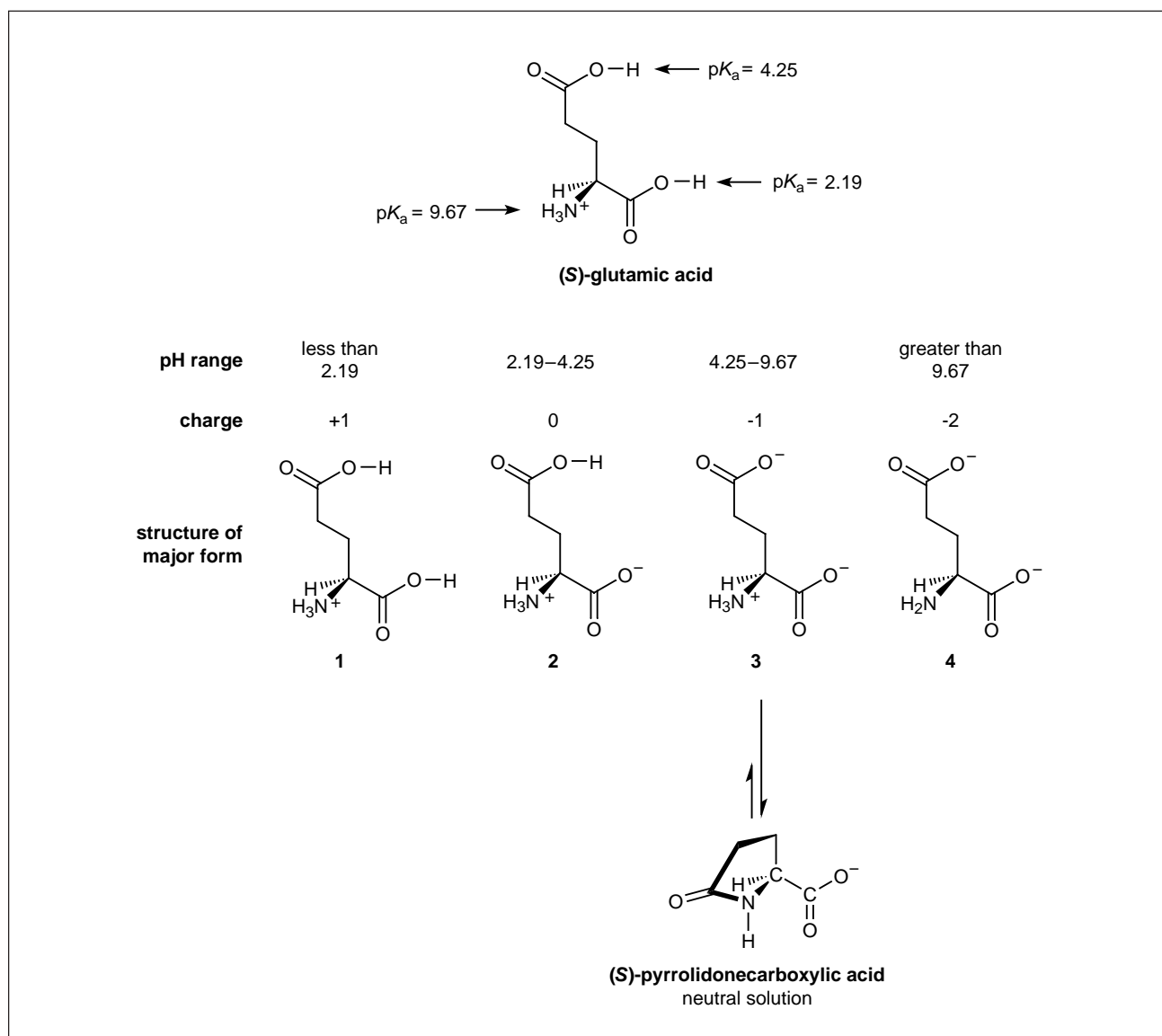


Figure 1. Forms of glutamic acid. Isoelectric pH = 3.22, the pH of minimum solubility where the average charge is 0. The average charge is 0 at this pH because most of the time the glutamic acid molecule is present as **2** (charge = 0), half of the rest of the time as **1** (charge = +1), and half of the rest of the time as **3** (charge = -1). The isoelectric pH of 3.22 is exactly half way between 2.19 and 4.25.

Resolution of Racemic Glutamic Acid

The great disadvantage of chemical synthesis is that the two enantiomeric forms are produced, while the desired material is a pure enantiomer. In the case of glutamic acid, the desired material is the *S* isomer, since the *R* isomer is tasteless. The racemic product must therefore be resolved to isolate the *S* isomer.

One method of resolution, described in a patent issued to the Aginomoto Company (3), required no materials other than racemic glutamic acid and seed crystals of the two enantiomers, and could be run continuously! The resolution took place in a vessel that was divided into two equal compartments by a vertical perforated plate or screen that would allow passage of the supersaturated solution containing the racemic material, but not the seed crystals of the pure enantiomers, which were present separately in the two compartments. The two compartments were stirred, which kept the

seed crystals well suspended in the solution. As the seed crystals grew they tended to migrate to the bottoms of the compartments from whence they were occasionally removed, having increased in mass by a factor of about 6. At the same time that the old crystals were removed, they were replaced by an equivalent number of new seed crystals. During the time that the seed crystals were growing, an equivalent mass of new racemate as a supersaturated solution was added to the top of the vessel, while, to keep the liquid level constant, some of the solution was allowed to overflow through a screen that did not allow the seed crystals to pass. It was this overflow that was heated and used to dissolve the fresh racemate thus providing, after fifteen degrees of cooling, the supersaturated solution that was added at the top of the vessel.

Since the solution of the racemate circulating via the screen throughout the entire vessel was being simultaneously depleted in both enantiomers, spontaneous crystallization of

the “wrong” enantiomer in the “right” compartment was not a problem.

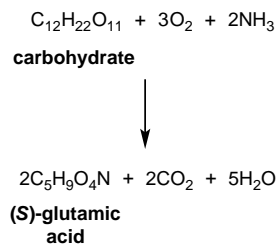
The entire process, developed by the Ajimoto company over ten years of research and two years of pilot plant operation, was put into operation in 1963. Initially, production was 300 tons per month, later increasing to 1000 tons per month. The life of the process, however, was only 10 years, when it was replaced by microbiological fermentation methods.

Racemization of Recovered (*R*)-Glutamic Acid

In this chemical synthesis of (*S*)-glutamic acid via resolution of the racemate, the undesired (*R*)-glutamic acid was racemized by heating in aqueous sulfuric acid, and recycled by using the aqueous acidic solution of the racemized material to neutralize the basic solution of the newly synthesized racemate, and to set the pH of the mixture to 3.2 for crystallization of the racemate.

Glutamic Acid by Microbial Fermentation

In the early 1950s it was discovered that *E. coli* excreted small quantities of amino acids, and that the quantity could be increased by addition of ammonium salts to the culture medium. Soon thereafter bacteria were discovered that could produce large quantities of (*S*)-glutamic acid, and that a particular bacterium, later named *Corynebacterium glutamicum*, could give (*S*)-glutamic acid in a yield of about 30% from carbohydrate according to the stoichiometry of the reaction:



The accumulation of (*S*)-glutamic acid in the culture medium is determined not only by its rate of biosynthesis but also by its escape through the cell membrane. When biotin, a vitamin essential for cell growth is present in sufficient concentration for an optimal rate of proliferation, the cell membrane is impermeable to glutamate, giving an inferior accumulation of glutamate. Since both beet and cane molasses are rich in biotin, these materials could not be used as sources of glucose in microbial fermentations until biotin-inhibiting additives were discovered. The less than optimal rate of proliferation of the bacteria in the biotin-limited fermentation was then partially overcome by the addition of sugar to increase the carbohydrate content of the culture medium. In this way the ultimate concentration of (*S*)-glutamic acid that could be achieved was raised to about 80 g/L. The necessary nitrogen could be supplied by ammonium salts, urea, or, best, by gaseous ammonia, which could not only provide the nitrogen but also maintain the pH of the culture medium between 7 and 8 without diluting the culture medium. Since the fermentation is aerobic, oxygen is supplied by aeration, and the fermenter is stirred. The medium and all materials are sterilized, and all operations and variables, including temperature, pH, and dissolved oxygen concentra-

tion, are automatically controlled during the 35–45 hour time for fermentation. The bacterial culture is grown up in stages from lyophilized seed through reinvigoration in a test tube, shake flask culture, 15 hours in a 10,000 liter seed fermenter, and then the 200,000 liter main fermenter (a volume equal to that of a 19-foot cube).

At the end of the fermentation the fermented broth is sterilized and then centrifuged to remove the microorganisms and any other solids. The clear liquid is then concentrated under reduced pressure, the pH is adjusted to 3.2, the isoelectric point of glutamic acid, and the resulting crystals of (*S*)-glutamic acid are converted to MSG as described previously.

The big advantage of the fermentation method is that it reliably produces only the desired *S* enantiomer of glutamic acid. The disadvantage is that it is fundamentally a batch process. In this well-developed process the accumulation of (*S*)-glutamic acid can be as high as 100 g/L (10 metric tons per 200,000 liter fermenter), and the yield as great as 60%.

Optical Purity of (*S*)-Monosodium Glutamate

No matter what the method of manufacture, there is always the possibility of racemization or incomplete resolution, which would contaminate the desired pure *S* isomer with the unwanted *R* isomer. The specifications for purity include allowable quantities of water and salt, total nitrogen, as well as a minimum degree of optical activity, approximately 99.5% of that of “pure” MSG (0.5% racemate; 0.25% *R* isomer). Much smaller quantities of any contaminating *R* isomer can be detected by a more sensitive enzymatic assay.

If the product is contaminated with an unacceptable quantity of the *R* isomer, this contaminant can be removed completely by taking advantage of the fact that the racemate is “absolutely insoluble” in saturated aqueous solutions of (*S*)-monosodium glutamate at any temperature.

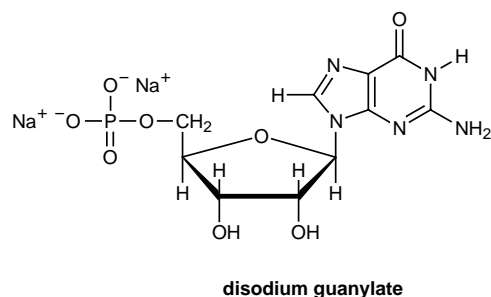
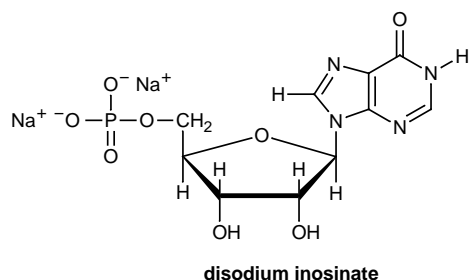
The Flavor Properties of Monosodium Glutamate

The taste threshold for monosodium glutamate is about 0.3 grams in a liter of water, considerably lower than the taste thresholds for salt (2 g/L) or sugar (sucrose; 5 g/L). The optimum salt concentration for soup is about 10 g/L; less than 8 g/L tasting “flat” and more than 12 g/L being “too salty”. The minimum useful concentration of MSG is 1 g/L (about 1/10 that of salt); the usual range of concentration is from 2 to 3 g/L, and MSG is not too concentrated at 5 g/L. This wide range of useful concentrations is unusual for a seasoning.

The flavor sensation of MSG is unlike that of any of the other four or five basic flavor sensations of sweet (sucrose), sour (lemon juice), salt (sodium chloride), bitter (quinine), or pungent (mustard or chili peppers). The flavor sensation of MSG is often described as “meaty” and has been given the name “*umami*” (deliciousness). Cohnheim (4) stated that “*die Glutaminsäure schmeckt nicht süß, sondern fade und nur schwach sauer*,” which can be translated to “Glutamic acid does not taste sweet, but insipid and only weakly sour.”

In addition, MSG has the ability to enhance natural taste. At a concentration of about 0.2 g/L it gives an effective improvement in the quality of sake, the traditional Japanese rice wine.

MSG also has a strong synergistic effect with disodium inosinate and disodium guanylate, which are found in meat, fish, vegetables, and mushrooms. These substances are almost tasteless in the absence of MSG, but addition of even a small quantity of MSG to food that contains these nucleotides produces an *umami* that is as much as six or eight fold greater than that to be expected from the quantity of MSG added. Not surprisingly, small quantities of the nucleotides have been added to MSG to create an enhanced source of *umami*.



This synergistic effect with MSG seems to be unique to these two nucleotides.

Uses of Amino Acids

All of the 20 natural amino acids are commercially available and have their uses in flavoring, dietary supplementation, infusion solutions, and “elemental diets”.

Flavorings

Almost all *S* amino acids have a taste, though the minimum concentration that can be tasted is fairly high, the molar concentration being about twice that needed for sucrose. Glycine, (*S*)-alanine, (*S*)-serine, and (*S*)-threonine taste sweet, but the *S* isomers of most of the other amino acids (excepting, of course, (*S*)-glutamic acid) taste bitter. In contrast, the *R* isomers of almost all the amino acids taste sweet (ref 2, p 558). Most dipeptides have a bitter taste, the famous exception being the methyl ester of (*S*)-aspartyl-(*S*)-phenylalanine (Aspartame), which is 150–200 times sweeter than sucrose. After (*S*)-glutamic acid, (*R,S*)-methionine, and *S*-lysine; glycine, which is added to saccharine to hide its bitter aftertaste, *S*-aspartic acid, and *S*-phenylalanine, the components of Aspartame, rank fourth, fifth, and sixth, respectively, in annual world production (Table 1).

Amino acids are added to many foods and condiments as the hydrolysate of vegetable proteins such as soy or wheat

protein. Soy sauce is essentially hydrolyzed soy or wheat protein, and “hydrolyzed vegetable protein” is widely used as a flavor component of many snack foods. Lay’s Memphis Barbecue Flavored Potato Chips contain, among other ingredients, salt, MSG, hydrolyzed corn, soy, or wheat protein, disodium inosinate, and disodium guanylate. These same ingredients are present in Kikkoman Sweet and Sour Sauce.

Dietary Supplementation

As indicated in Table 1, (*S*)-glutamic acid ranks number one in industrial production, and (*S*)-lysine and (*R,S*)-methionine follow in second and third place. While (*S*)-glutamic acid is used almost exclusively as an additive in the human diet, (*S*)-lysine and (*R,S*)-methionine are used almost entirely as supplements in the feeding of domestic animals. The requirements for amino acids in the diets of animals are almost exactly the same as those of the human, which are indicated in Table 1. While the protein components of animal feed, typically a mixture of grain and fish proteins, supply all of the essential amino acids, these protein sources do not provide the essential amino acids in the same relative quantities needed to synthesize the various proteins of the animal that consumes them. The concept here is the same as that of the limiting reagent, in the sense that the animal will run out of one essential amino acid first. Thus methionine is called the “first limiting amino acid” in soy protein and in fish protein, with (*S*)-lysine being second limiting, while in wheat, rice, and maize proteins, (*S*)-lysine is first limiting. As an example of supplementation with methionine, a “pig fattening feed” is composed of barley, wheat, or corn (35%), soybean meal (19%), tapioca meal (20%), corn gluten feed (15%), meat and bone meal (3%), beet molasses (2%), mineral premix (2.43%), vitamin-trace element premix (0.50%), and (*R,S*)-methionine (0.07%); all percent by weight (Vol. A2, p 82, of ref 5).

Although there is much evidence in support of the benefits of protein supplementation in human diets, the practice is almost entirely limited to infant formulas. A can of “Soy Formula” contains, in addition to water (87%), corn syrup solids (7%), vegetable oil (3%), and soy protein isolate (2%), 15 vitamins, 12 minerals, and a little *S*-methionine.

Infusion Solutions

Intravenous nutrition with the eight essential amino acids (Table 1) is well established. A standard infusion solution also contains the semi-essential amino acids *S*-arginine and (*S*)-histidine, and often glycine, (*S*)-alanine, (*S*)-proline, (*S*)-serine, and (*S*)-glutamic acid. For optimal use of the amino acids, there must be a separate but simultaneous infusion of glucose.

Elemental Diets

An elemental diet is a diet made up of pure chemical substances that include the amino acids, carbohydrates, fats (C_8 and C_{10} triglycerides), vitamins, minerals, and compounds of the trace elements. They supply all the nutritional needs, are completely absorbed, and have no residue. They were developed originally for astronauts¹ but are now used for management of impaired gastrointestinal function or inflammatory bowel disease.

Health and Safety

Monosodium glutamate, which is present as glutamic acid in the acidic environment of the stomach, is metabolized in the same way that the glutamic acid from the proteins of a normal diet is metabolized. Since the 80 grams of protein in the normal diet contain about 15 grams of glutamic acid, one would not expect an additional fraction of a gram of MSG consumed as a flavor enhancer to cause a health problem. Reference 2, Vol. 2, p 577 and ref 5, Vol. A16, p 715, contain more information and further references concerning the health and safety aspects of MSG, including discussions of the “Chinese-Restaurant Syndrome”.²

Summary

There are a great many interesting and imaginative applications of organic chemistry to be found in the industrial world. Examples presented in this article include the enantiospecific enzymatic synthesis of (*S*)-alanine, the enantiospecific syntheses of (*S*)-lysine and (*S*)-glutamic acid by microbial fermentation, and the chemical synthesis of racemic glutamic acid from acrylonitrile, carbon monoxide, methane, and ammonia.

Sometimes a racemate must be resolved, and I have described two very clever methods that have been used in the commercial synthesis of amino acids: the continuous resolution of racemic lysine by immobilized microorganisms that, together, selectively produce the desired enantiomer and racemize the precursor so as to give a 100% yield of the desired stereoisomer (an example of “dynamic kinetic resolution”), and the continuous resolution of racemic glutamic acid using no external agents other than seed crystals of the two enantiomers! Finally, application of the concept of the limiting reagent to the supplementation of the diet of domestic animals leads, in the case when all components are equally limiting, to minimization of the quantity of both feed required and waste produced.

Sources

Most of the information in this paper was obtained from the *Kirk-Othmer Encyclopedia of Chemical Technology*, 2nd, 3rd, and 4th editions (2), *Ullman's Encyclopedia of Chemical Technology*, 5th edition (5), and *Riegel's Handbook of Industrial Chemistry*, 9th edition (6). The article by A. Maureen Rouhi presents some of our understanding of the mechanism of the perception of taste (7).

Notes

1. The Ajinomoto Company Web site states: “Originally, these preparations had been developed for astronauts in the U.S. Elemental diets are practically totally absorbed in the body, with almost

no unused portion. This was seen as a great advantage in the narrowness of the spaceship. Later, progress in the design of spacecraft made their center aisle much more spacious and the elemental diets were shunned. For, although they present no problem in nutritional terms they tend to be less tasty than an ordinary meal.”

2. The first publication concerning what is now called the “Chinese-Restaurant Syndrome” makes interesting reading (8). The publication is actually a letter to the editor, not a research article, and the phrase “Chinese-Restaurant Syndrome” does not appear in the letter but is the heading above the letter. The author is Robert Ho Man Kwok, M.D. The first sentence of his letter is “For several years since I have been in the country, I have experienced a strange syndrome whenever I have eaten out in a Chinese restaurant, especially one that served Northern Chinese food.” He then describes the symptoms, and mentions that they simulate but are milder than those of his hypersensitivity to acetylsalicylic acid. The first sentence of the second paragraph is “The cause is obscure.” He then goes on to consider several possible causes. Perhaps an ingredient in the soy sauce; however, the same type of sauce used in his home cooking does not result in the symptoms. “Some have suggested” cooking wine, which is used generously in most Chinese restaurants. The paragraph concludes with the sentence “Others have suggested that it may be caused by the monosodium glutamate seasoning used to a great extent for seasoning in Chinese restaurants”. The third paragraph is: “Another alternative is that the high sodium content of the Chinese food may produce temporary hypernatremia [high sodium], which may consequently cause intracellular hypokalemia [low potassium] resulting in numbness of the muscles, generalized weakness, and palpitation. The Chinese food causes thirst, which would also be due to the high sodium content. The syndrome may therefore be due merely to the large quantity of salt in the food, and the high dissociation constant of the organic salt, monosodium glutamate, may make the symptoms more acute”. He then solicits more information about “this rather peculiar syndrome”.

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