

One hundred years of methionine

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It is 58 years since Gabriel Garcia Marquez wrote his unbelievably tedious and dreary novel *100 years of solitude*. The title, by far the most memorable writing in the entire book, is however worth stealing to commemorate the Japanese biochemist Satoru Otake*, who isolated methionine in 1925 [1]. At first I had the idea of repeating his experiment, until reading his protocol, which calls for "about 20 tons" of yeast to yield about 0.6 grammes of product. Possibly there was a mistake in the units, but even buying 20 kilos of dried yeast is far beyond the budget I had in mind. The paper is silent on the procurement of this material, but possibly very good friends with a brewery might have been helpful. The idea of emailing a supplier, or ordering reagents via the internet, was still some way in the future, but this did not deter Otake, who also expended a considerable volume of mercury salts to separate the new amino acid from leucine. Which brings me to the naming of amino acids, a minor but unremarked scandal in the annals of modern science.

If you have managed to extract and purify a previously unknown compound from asparagus, it is perhaps understandable to call it asparagine. Especially if the year is 1806 and you are French, and enjoying a minor respite in the wars with England. There is however little excuse for the names of leucine (white) or arginine (silver), which are as relevant to thousands of inorganic minerals as they are to the substance in question. Cysteine was discovered (as cystine) in a kidney stone by Wollaston, the English chemist who made a fortune from purifying platinum and palladium, among numerous other achievements. It is named after the urinary bladder, or cyst. Names are important. Of course we can call leucine 2-amino-4-methyl-pentanoic acid, but this is obviously 2-long-4-everyday-use, especially if we are referring to an amino acid incorporated into a polymer. Methionine was discovered after almost all the other common proteinogenic amino acids. Threonine came last, in 1935, and was named after the sugar threose, which also has two chiral centres, despite the fact isoleucine does too. Most of the amino acids were discovered in the 19th century. Cheese (or protein derived from milk, known as casein) was a popular place to look, and tyrosine is named after it. Lysine is named for the process (of lysis) rather than the source material. Neumeister [2] suggested the name tryptophan in 1890 to refer to the (then undefined) component of proteins responsible for producing a strongly coloured product in the presence of glyoxylic acid or other reagents. The name derives from Greek, *to be broken*, and (loosely) *to bring to light*. In 1901, the amino acid tryptophan was isolated in Cambridge by breaking down casein, with trypsin in this case [3]. The original British spelling was tryptophane. It has been suggested the "ophane" part was just made up, so possibly we are fortunate that proline did not become prophane, but this *imino* acid was discovered by artificial synthesis rather than isolation from a natural material, and named after pyrrolidine, the parent cyclic secondary amine. Alanine is the only other amino acid to be discovered by synthesis, and named under the mistaken impression it was an aldehyde.

So by 1925 the basic chemistry of proteins was fairly well understood, and the hunt was largely over for the amino acid residues found in proteins. Methionine had been found a few years earlier in hydrolytic products of casein by J. Howard Mueller at Columbia University in New York, but at first he gave an incorrect formula for it [4]. Otake, working with others in Japan, had already isolated what we now call S-adenosyl methionine [5], but was still intrigued by sulfur-bearing compounds in yeast, and having isolated the new amino acid he produced the correct formula. Mueller is

hardly to be criticised for his mistaken formula, given the difficulties of analysis at the time. We tend to forget that most of the chemical elements were discovered using equipment of astonishing simplicity, and chemical analysis relied on extraordinary precision and tenacity. Mueller had, in any case, produced the correct formula first, in a subsequent paper of 1923 [6].

Mueller's initial approach had been to use charcoal to remove from a meat broth some substances that greatly assisted bacterial growth, with the aim of discovering the identity of these essential substances by adding them back. Bacterial growth was assessed by eye, comparing the turbidity of the solution to seven standard tubes containing insoluble barium salts suspended in water. Mueller soon found that commercial hydrolysates of casein were more convenient for isolating amino acids than preparing his own, but many difficulties remained. By 1922 he had realised that his earlier preparation of the new sulfur-bearing amino acid contained co-purified phenylalanine, and the contaminant had thrown out the calculation of the molecular formula. He determined the correct formula to be $C_5H_{11}SNO_2$. During a stay at Gowland-Hopkins's laboratory in Cambridge in the summer of that year, it was suggested to him that his new amino acid might be ethyl cysteine, an isomer of the true structure [6]. Mueller knew in 1923 however that this compound had been prepared decades earlier, and its properties did not match his new amino acid, which was stable to boiling in alkali. His paper [6] ends with the words "The structure has not yet been determined."

Odake's 1925 paper makes clear that his compound is identical to Mueller's, although the optical rotary power is a little different from his quoted value, and also notes that it is not ethyl cysteine. It does not however offer a name for the new material, despite Wikipedia stating so on its English page on methionine. Wikipedia (rightly much discredited for its lack of a balanced epistemological approach in the weighing of claims or evidence) does however provide a few useful links relevant to this history. The Wikipedia Japanese page has none of this historical content, and is perfectly useless for the hunter of such information. In fact the name methionine was not bestowed until 1928, by Barger and Coyne [7]. They determined the compound to be 2-amino-4(methylthio)butanoic acid by first demonstrating the presence of a methylated thiol group, and then complete synthesis from β -methylthiol-propaldehyde. The racemic product was found to be identical with Mueller's acid, except in optical activity. After consultation with Mueller, Barger and Coyne suggested the name methionine as a suitable abbreviation, to reflect the methylthiol group. Subsequent work improved on the chemical synthesis, giving much greater yield.

Synthetic racemic methionine turned out to be very important in Germany in the late 1940s, where the population suffered chronic protein deficiency in the aftermath of the war. The company Degussa AG (now part of Evonik) began production in 1948, and over the next year increased output 100-fold, from 300 kg to 30 tons per month. In the 1950s it was realised that egg-laying performance of hens could be increased with extra methionine in the feed, and a new market was born. Today, animal nutrition is the major use for methionine, which is produced on a scale of well over a million tons per year. The story is not quite over though, as countries have scaled back the use of synthetic DL-methionine, which is banned for organic farming in jurisdictions such as the US. The search is still on for fermentation processes to produce L-methionine in huge quantities at the lowest price. Despite the name, chicken feed is big business - animal feedstuffs are worth over 5000 million pounds a year in the UK market alone. Over the last couple of decades, meat demand has exploded in China, which in 2022 opened a new methionine plant in Nanjing with

a 180,000 ton per year capacity. Evonik expanded US production at the same time, and methionine is as popular as ever.

So hurrah for methionine, even if it's really 103 years old, or only 97. I sometimes ask prospective students, or a class, what their favourite amino acid is. The question is difficult because it has no right answer that they have been drilled with beforehand, but I am happy with any response except alanine (worth a measly 150 million dollars globally in 2022, and not an essential amino acid). Side-chains like tyrosine, asparagine and serine do a lot of the work of antibodies binding to antigens; histidine is crucial to a lot of enzymes and binds haem groups; tryptophan does the colour chemistry and glycine is so often conserved in proteins because it's the only one small enough to fit the fold. Somehow they are all outdone by methionine, the precursor of S-adenosylmethionine (SAM), which provides methyl groups for the synthesis of adrenaline and melatonin, among many other essential compounds. Methionine is even the precursor for cysteine, and must therefore be at least as useful, quite apart from being the first amino acid put into any nascent polypeptide by a ribosome. As a protein crystallographer I learned to love methionine for binding platinum, although others chose to replace it with selenomethionine for phasing their X-ray diffraction data. It really is jolly useful all round, and it has sensible name.

A very comprehensive history of amino acid discovery up to 1931 is given by Vickery and Schmidt [8], and I commend it to the interested reader. (German was still the language of chemistry at the time, and the authors make extensive quotes assuming some measure of fluency.) They give a separate section on each of the 21 amino acids that had at the time been demonstrated to be products of the hydrolysis of proteins, and list all 21 names in a table, chronologically ordered by date of discovery. Cystine comes first, found in 1810 in a kidney stone, as mentioned. Asparagine isn't on the list, or glutamine either. Threonine was still unknown. There are iodogorgoic acid (iodinated tyrosine), thyroxine, oxyproline and oxyglutamic acid instead, and the confusion wasn't cleared up until the 1960s when Nirenberg and others determined the genetic code. Many of the problems stemmed from chemical lability, but methionine, of course, you can boil in alkali and it doesn't care. It really should be everyone's favourite amino acid, and 1925 seems a perfectly good time to celebrate the achievements of John Howard Mueller and Satoru Otake.

*Modern rendering with Roman letters would place a bar over the initial O, or put an *h* after it, to indicate the long vowel. The name Ohdake ("big bamboo") is written 大竹 in Japanese.

Acknowledgement

I am grateful to Tassos Perrakis of NKI, Amsterdam, for commenting on the manuscript. Methionine, he informs me, directly translates from the Greek με-θειον and means *with-sulfur*.

References

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