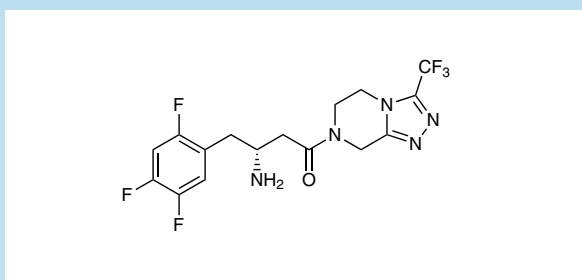


Naturally Occurring Organic Fluorine Compounds

Kentaro Sato

Valuable Fluorinated Compounds

One of the major trends in recent organic reaction development is the introduction of fluorine atom. Because fluorine is the most electronegative element of all elements, the overall property of a given molecule can be changed to great extent by introducing fluorine atom(s). The atomic radius of fluorine is similar to that of hydrogen at the same time, so the size of the molecule is not affected as much. Due to these properties, the number of compounds containing fluorine is increasing in pharmaceutical drugs and organic electronics materials and so is the demand for effective fluorination reactions.



An example of fluorine containing drug, sitagliptin (antidiabetic drug)

Of course, fluorine containing compounds are found in familiar areas outside of chemistry labs. Teflon[®] is not only the essential material for laboratory equipment but is also used as non-stick coatings of kitchenware. Chlorofluorocarbons (CFCs) were once used as refrigerants, but its manufacture has been banned after the destructive reactivity of CFCs against the ozone layer became widely recognized. Today, less harmful alternatives of CFCs (hydrochlorofluorocarbons or HCFCs) are used instead.

Fluorine containing compounds such as these are all very useful, but in nature fluorine occurs in the form of inorganic minerals like fluorite (CaF₂) and cryolite (Na₃AlF₆) and fluorinated organic compounds are extremely rare. C-F bonds have strength and some unique properties, but Mother Nature doesn't seem to have utilized them so much. Still, there have been about 30 natural products discovered that contain C-F bonds. In this article, let us take a glance at these naturally occurring fluorine containing compounds.

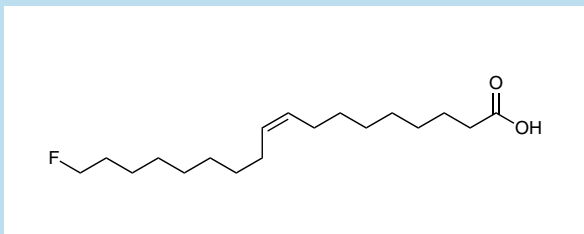
Deadly Poison-Monofluoroacetic Acid

The most famous naturally existing organic fluorine containing compound is probably monofluoroacetic acid (FCH₂CO₂H). This compound is found in a South African plant called "Gifblaar," which is known to be so poisonous that ingesting only a half of its leaf is enough to kill a cow. The compound is regulated as one of the "specified poisonous substances" in Japan and it is illegal to own or give it without permission. Let us be careful not to synthesize it by mistake.

Acetic acid is an important biological substance, so it may sound strange that structurally close monofluoroacetic acid has such high toxicity. But in fact, that resemblance is the very reason why it is so toxic. As mentioned before, fluorine is about as large as hydrogen, therefore monofluoroacetic acid can enter the citric acid cycle by camouflaging acetic acid and inhibits the cycle, inducing the toxicity.

Some other plants belonging to the Dichapetalaceae family that includes Gifblaar synthesize fatty acids with a fluorine atom attached on its end of the alkyl chain. The

examples such as ω -fluorostearic acid and ω -fluorooleic acid are known. These are considered to be biosynthesized when monofluoroacetic acid is taken into the regular fatty acid biosynthetic pathway. These ω -fluoro fatty acids are metabolized in the body to produce monofluoroacetic acid, therefore show strong toxicity too and are the cause of many known cases of animal food poisoning.



ω -Fluorooleic acid

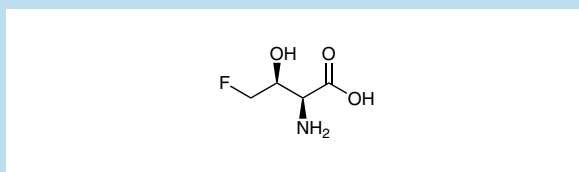
Biosynthesis of Fluorine-Containing Natural Products

Then how is monofluoroacetic acid biosynthesized? One of the strains of actinomycete bacteria produces monofluoroacetic acid and its biosynthetic pathway has been elucidated. In this case, S-adenosylmethionine (SAM) is converted into 5'-fluoro-5'-deoxyadenosine (5'-FDA) by the action of the fluorinase enzyme. 5'-FDA is then thought to decompose to form monofluoroacetaldehyde and get oxidized to monofluoroacetic acid.

The fluorinase is an exceptionally unique enzyme capable of catalyzing the formation of C-F bonds. There is therefore an expectation that it can be developed into a useful tool for synthesizing fluorine containing compounds.

A compound called fluorothreonine is also known, and its biosynthetic origin is again considered to be monofluoroacetaldehyde. More compounds biosynthesized

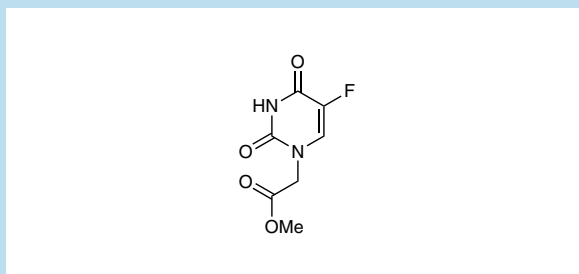
from monofluoroacetaldehyde or monofluoroacetic acid are likely to be discovered in the future.



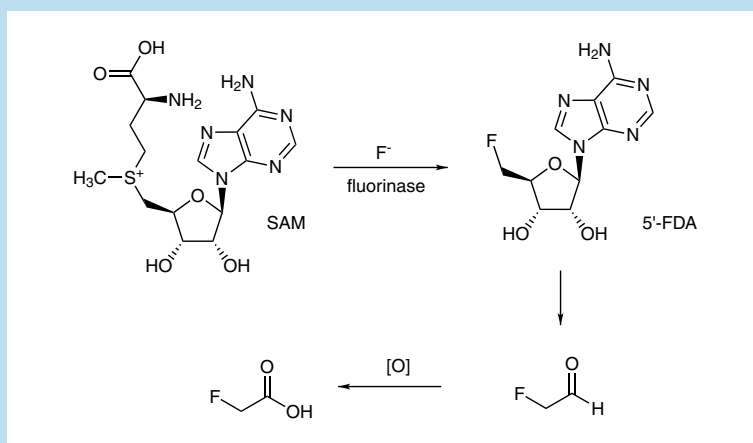
Fluorothreonine

More Examples of Fluorine-Containing Natural Products

Many marine natural products containing bromines or chlorines are known, but those containing C-F bonds are much rarer. The rarity is considered likely due to the low concentration of fluorine in sea water and the fact that fluorine doesn't participate in biosynthesis as cationic species unlike bromine. However, in 2003 a Chinese research group discovered fluorine-containing compounds from the extract of a marine sponge called *Phakellia fusca*. The news drew attentions especially because the compounds turned out to be structural analogues of 5-fluorouracil, which is a famous anti-cancer drug. These compounds are again considered to be biosynthesized from monofluoroacetaldehyde.

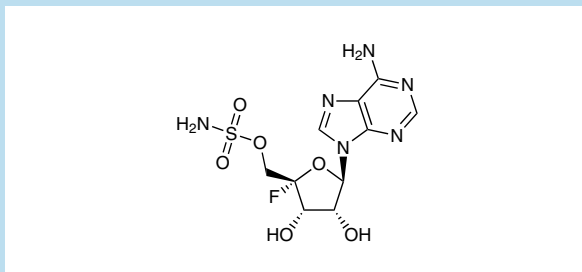


5-FU derivative from marine sponge



Biosynthetic pathway of monofluoroacetic acid

As another example, a natural fluorine-containing compound called nucleocidin is known. This compound has antimicrobial property through the inhibition of protein synthesis. Its structure is unique in that the 4-position of the ribose unit is fluorinated, which makes you wonder about its biosynthetic pathway.



Nucleocidin

Natural or Unnatural?

In addition to these, some unexpected compounds have been found in nature. Carbon tetrafluoride, tetrafluoroethylene (the raw material of Teflon®), and trichlorotrifluoroethane (F₂CIC-CFCl₂ or Freon 113), all of which you would never expect to exist naturally, are among the examples. These compounds are not spillovers from artificial source, but they are actually thought to exist naturally. However, they are not biosynthesized by living organisms but are believed to be formed from the reactions between fluorine-containing volcanic gases and organic compounds under high temperature conditions. There are quite a few instances in which compounds that were previously thought of as purely manmade turns out to also exist in nature, and this one makes a perfect example.

Also worth mentioning is that trifluoroacetic acid is sometimes detected in rainwater at certain concentrations. The concentrations are suggested to be too high to be explained as being originated from artificial sources. The question of where it came from is yet to be answered.

Natural Elemental Fluorine

In 2012, the amazing discovery of elemental fluorine gas (F₂) in nature was reported. Fluorine gas is known to be extremely reactive and reacts with even noble metals like platinum and noble gases like xenon. The news that it can exist in nature was therefore completely unexpected.

The elemental fluorine was discovered from mineral rocks called antozonite. The rock is a type of fluorite (CaF₂) that contains radioactive uranium and it had been well-known that it releases a pungent smell when you crush the rock. It was named antozonite because the origin of the smell was initially believed to be “anti-ozone,” which meant the cation of oxygen speculated to exist in the rocks.

The research group of the Technical University of Munich analyzed antozonite using ¹⁹F-NMR and was able to prove the existence of molecular fluorine embedded within the rocks. Because antozonite is mainly made of calcium fluoride as mentioned earlier, the rocks can contain the fluorine gas within itself without reacting with it.

But where did the fluorine gas come from in the first place? According to the German group, the key to answering the question is apparently in the radioactive uranium contained in antozonite. The nuclear decay of uranium gives off daughter nuclides and some of them emit beta and gamma rays. Therefore, the group is proposing that the slow nuclear irradiation of calcium fluoride over the period of millions of years caused the formation of elemental fluorine inside the rocks.

The existence of elemental fluorine in nature seemed farfetched at first, but it is much more plausible now thanks to this research. This story is a great reminder to us about the remarkable depth of the natural world, and it also tells us about the importance of believing in your research and departing from conventional wisdom.

Introduction of the author :

Kentaro Sato

[Brief career history] He was born in Ibaraki, Japan, in 1970. 1995 M. Sc. Graduate School of Science and Engineering, Tokyo Institute of Technology. 1995-2007 Researcher in a pharmaceutical company. 2007-Present Freelance science writer. 2009-2012 Project assistant professor of the graduate school of Science, the University of Tokyo.

[Specialty] Organic chemistry

[Website] The Museum of Organic Chemistry <<http://www.org-chem.org/yuuki/MOC.html>>