doi:10.2533/chimia.2026.417 Chimia 80 (2026) 417–420

Chemical Education

Division of Chemical Education

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Natural, Unnatural Fluorine!

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Abstract: The rich variety of compounds containing the element fluorine, be it natural products, synthetic materials, or even minerals are well-suited for a critical discussion of the opposites 'natural' and 'unnatural'.

Keywords: Elemental fluorine · Fluorine-containing minerals · Natural organofluorine compounds· Organofluorine chemistry

When teaching chemistry at introductory level, be it first-year general chemistry at a university or even more so at high schools, a simpleminded juxtaposition natural/unnatural may be very important to students and needs to be dealt with.[1] Something is natural when it exists in or derives from nature, whereas it is unnatural in case when it does not exist in nature, hence it is artificial (adapted from Oxford dictionary). 'Artificial', *i.e.* 'man-made' can be intended to specifically mean 'synthetic', 'chemical'. People tend to attach to the two adjectives 'natural' or 'unnatural' positive or negative connotations, respectively, in particular when it comes to products of common use. Something natural is almost by definition good, better, whereas its chemical counterpart or alternative is often considered to be less good or plainly bad, no matter how uninformed and superficial this judgement may be. However, chemists may find the distinction to be at times at least ambiguous or not important at all – think of the concept 'total synthesis of natural products', which non-chemists might consider self-contradictory.[2]

If one wants to focus on a single element and its compounds when explaining and discussing issues related to the 'natural/unnatural' dichotomy, I think that fluorine is very well suited. Fluorine – «A small atom with a big ego»[3] – has always been celebrated as a very special and unique element, to which chemists attribute many superlatives,[4] such as *e.g.* highest electronegativity, highest standard reduction potential, strongest single covalent bond to carbon (and other elements), and highest reactivity of all elements. Despite its 'just' monovalent nature, fluorine is able to engage the noble gases Kr and Xe in a rich and unique chemistry[5] and the introduction of fluoro substituents, or highly fluorinated alkyl or aryl groups may significantly modify reactivity and structural properties of organic molecules.[6]

Fluorine is found in nature as fluoride ions in the form of three main minerals: Fluorite (also called fluorspar, CaF_2), cryolite (Na_3AlF_6), and fluoroapatite ($Ca_5(PO_4)_3F$). Such minerals account for an estimated content of *ca.* 600 ppm fluorine in the continental Earth's crust, this being a factor of *ca.* 4 larger than the corresponding value for chlorine. On the other hand, the fluorine content in the oceans is very low and amounts to 1.3 ppm, in strong contrast to chlorine with 19,000 ppm. This means that fluorine in nature is somewhat boringly buried away in the form of essentially insoluble salts. This can possibly be interpreted as a reason why nature has never really 'learned' any organofluorine chemistry, in terms of being able to construct C–F bonds. As we will see below, only very few notable exceptions are known so far.

Elemental fluorine, F_2, has been made for the first time by Henri Moissan on the 26th of June 1886 by electrolysis of a solution of KF in HF in a U-shaped Pt tube, as illustrated in Fig. 1.[7] This was an important milestone in the history of chemistry, recognized by the Nobel Prize in 1906, and still constitutes the basis for the industrial production of fluorine. This was boosted by the Manhattan project[8] that led during World War II to the development of the first nuclear weapons. Fluorine is necessary for the production of UF_6, the volatile uranium compound that allows the enrichment by gas centrifugation of the isotope ^{235}U needed for nuclear fission. It is clear that the underlying fundamental chemistry can by no means be viewed as natural. Correspondingly, because of its high reactivity, fluorine has long been thought to be non-existent in nature. Simplistically speaking, if it somehow formed in nature, it would, as a gas, quickly find something to react with and could not accumulate to any significant extent. This was common knowledge often found in textbooks of inorganic and general chemistry until not so long ago.

However, in 2012 Kraus and coworkers have unequivocally shown by solid-state ^{19}F NMR spectroscopy that the mineral antozonite (Fig. 2), a variety of fluorite, indeed contains elemental fluorine as inclusions in non-negligible amounts (*ca.* 0.5 mg F_2 per g in the analysed samples, meaning that 1 out of *ca.* 1000 fluoride ions of the original CaF_2 has been oxidized).[9] How has F_2 been formed in these samples? Evidently by radioactivity, since antozonite is found at many locations worldwide where uranium

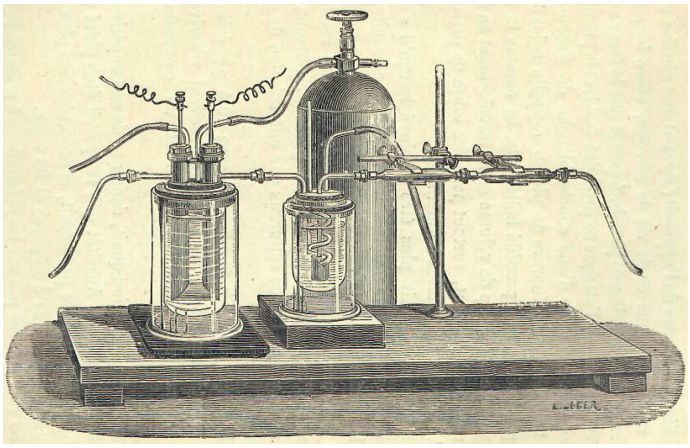


Fig. 1. Advanced apparatus for the production of F_2 as developed by Henri Moissan. Note that the Pt U-shaped tube (left) is kept cold in a bath of evaporating CH_3Cl, by which temperatures as low as -50°C can be reached.[7]

(and partly thorium) minerals also occur and indeed contains trace amounts of uranium. However, it is not the α-radiation deriving from this element causing the formation of F_2, but the β-radiation originating from corresponding daughter nuclides such as ^{234}Th, ^{234m}Pa, ^{214}Pb, ^{214}Bi, ^{210}Pb, and ^{210}Bi. Experiments carried out with synthetic CaF_2 confirm that irradiation with low-energy electrons is able to generate elemental fluorine.[10] Note that the dark colour of antozonite (CaF_2 is otherwise colourless) is due to the presence of clusters of Ca atoms, concomitantly forming with fluorine. Thus, the peculiar quintessence of the story is that natural radioactivity is responsible for the formation of elemental fluorine in nature, under very special circumstances. This fluorine remains trapped in cavities of crystalline CaF_2 virtually forever.

Fig. 2. A sample of the mineral antozonite containing elemental fluorine as microscopic inclusions. The edge of the largest visible cube is *ca.* 5 mm (photo by the author; I received this sample as a Christmas present in December 2022 from a group of first-semester ETH students fascinated by fluorine chemistry).

Let us turn our attention to organofluorine compounds. If I tell a young student that fluoroacetic acid (FCH_2COOH) formally derives from the replacement of a single hydrogen atom in the methyl group of acetic acid by a fluorine atom and that it is very toxic, she will most likely think that I am talking about a synthetic material, as opposed to the natural product acetic acid, as a common ingredient in a salad dressing. While it is clear that FCH_2COOH can indeed be made synthetically, *e.g.* from sodium chloroacetate and KF by a Halex-type reaction, I am actually referring to fluoroacetic acid as a natural product, *i.e.* a product made by living organisms, thereby surprising the student! It is obvious that synthetic and natural fluoroacetic acid are molecularly identical and that a distinction between the two concerning chemical properties at large is actually nonsense. The important question here is how and maybe why nature makes this compound. However, before discussing the rare naturally occurring organofluorine compounds, it is important to note that more than 8000 halogen-containing natural products are known to date.[11] The main sources are marine organisms, such as algae and sponges, but also plants and bacteria. These compounds cover a stupefying variety of structures and degrees of halogenation and Fig. 3 shows four examples.

The monoterpene halomon (**1**) has been studied as an anticancer agent,[12] compound **2** is a perbrominated 2,2'-bipyrrole derivative (75.7 wt-% bromine),[13] indole **3** is a rare compound containing three different halogens,[14] and the chlorosulfolipid **4** is responsible for seafood poisonings. Additionally, it is very

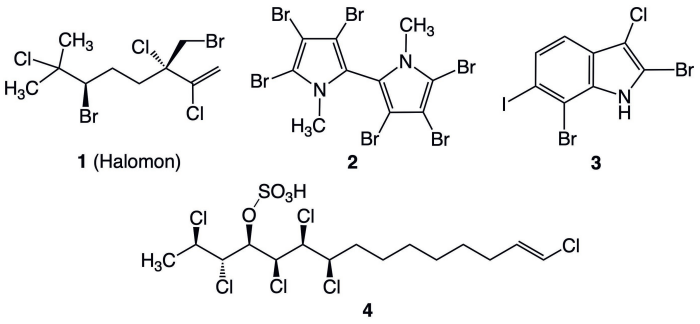


Fig. 3. Examples of highly halogenated (Cl, Br, I, but no F) natural products.

interesting from a total synthesis point of view because of the contiguous chloro-substituted stereogenic centres.[15]

In strong contrast to the large number of natural products containing chlorine and/or bromine and/or iodine, there is only a handful of structurally different organofluorine compounds made in nature by organisms (see Fig. 4).[16] These compounds are exclusively monofluoro derivatives of mostly carboxylic acids, the simplest of which is fluoroacetic acid (**5**). Besides ω-fluorooleic acid (**9**), about ten further ω-fluoro fatty acids are additionally known. It appears that the biosynthesis of such compounds, including 4-fluorothreonine (**6**) and fluoropentanoic acid **7** depends on a single fluorination pathway branching out at later stages. Nucleocitin (**8**), an antibiotic made by *Streptomyces calvus*, is the notable exception (selective fluorination at position 4 of a ribose would be difficult, but very interesting also from a purely synthetic point of view).[17]

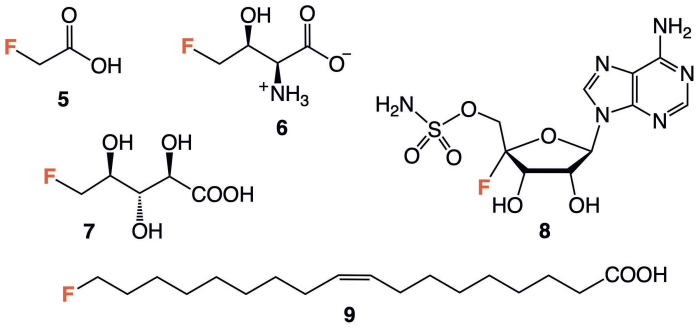


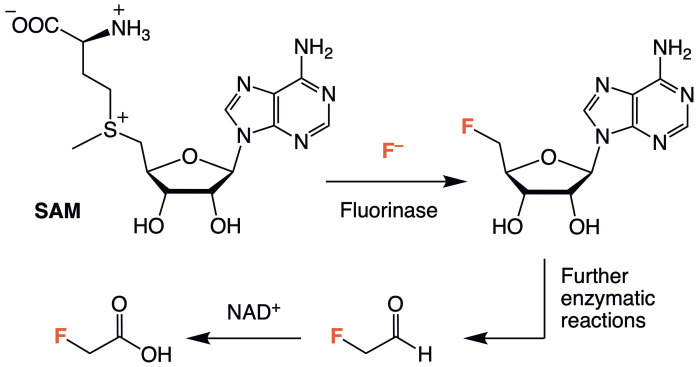
Fig. 4. The known, main naturally occurring organofluorine compounds.

Fluoroacetate occurs in several poisonous plants growing in various regions worldwide. One of these is the prostrate shrub *Gifblaar* (Fig. 5), which constitutes a serious problem for cattle in South Africa due to the high toxicity of such a simple compound as fluoroacetate. Fluoroacetate is metabolized to fluorocitrate, which leads to a blockage of the tricarboxylic acid cycle (TCA, or Krebs cycle), a fundamental biochemical pathway in mammalian and many other organisms. Synthetic sodium fluoroacetate (so-called compound 1080) has thus been widely utilized in many countries as a rodent poison,[18] though its use is now restricted.

The first fluorinase enzyme from the bacterium *Streptomyces cattleya* has been reported by O'Hagan and coworkers in 2002.[19] As shown in Scheme 1, *S*-adenosyl methionine (SAM), usually involved in biochemical methyl-transfer processes, is the substrate undergoing this unique nucleophilic substitution by fluoride, leading to the formation of a C–F bond. The amino acid methionine serves here as a leaving group (this would not be a chemist's first choice for a simple S_N2 reaction!).[20] Subsequent enzymatic processes first afford fluoroacetaldehyde and eventu-

Fig. 5. *Gifblaar*, *Dichapetalum cymosum* (source: Prof. Christo Botha, Univ. of Pretoria, https://commons.wikimedia.org/w/index.php?curid=15565006).

ally fluoroacetic acid. Note that natural halogenations involving all other halogens are commonly catalysed by haloperoxidase enzymes, thereby exploiting electrophilic or radical mechanisms. These are clearly inaccessible for fluorine in an aqueous medium such as a living cell is.



Scheme 1. The biosynthesis of fluoroacetic acid in the bacterium *Streptomyces cattleya*.

Given the very small number of fluorine-containing natural products, it can be safely claimed that virtually all of organofluorine chemistry is synthetic and thousands of fluorinated compounds have been and continue to be made. The greatest share of derivatives with low fluorination degrees are mainly used as APIs (active pharmaceutical ingredients)[21] or agrochemicals, mainly as crop-protecting agents[22] (see Fig. 6). Roughly 20% of newly approved small-molecule drugs contain at least one or up to a few F atoms (usually less than 10). The corresponding portion for agrochemicals is about twice as high. Thus, the beneficial effect of single fluorine atoms or small fluorinated groups in biologically active compounds is that they contribute to the fine-tuning of essential properties, such as *e.g.* lipophilicity, metabolic resistance, and pharmacokinetics, just to name three.

The most unnatural class of fluorinated compounds is without any doubts that of so-called PFAS (poly- or perfluorinated alkyl substances). I have written a column in this journal before on this topic as related to teaching[23] and I shall not go into any detail here. However, given the significance of the environmental problem caused by PFAS, it is important to mention, or at least

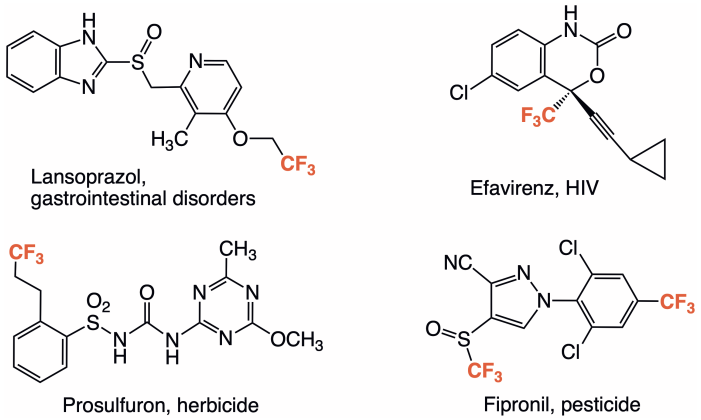


Fig. 6. Examples of synthetic biologically active compounds containing CF_3 groups (commercial name and area of application are indicated).

to imagine a possible new loop back to the natural world, so to speak. Indeed, current research efforts aim at finding microorganisms able to decompose PFAS,[24] or even conceivably to 'teach' micro-organisms by genetic engineering how to efficiently cleave the C–F bond. We will see!

In conclusion, it should have become clear that my stance on the black-and-white categories 'natural/unnatural' is that they cannot be the only and best advisor when judging all sorts of products we may get exposed to on a daily basis. Both natural and unnatural products may be beneficial or hazardous,[25] it very much depends not on whether but on how we use them. Responsible chemistry, when appreciated as such, should contribute to relativize the widespread believe that 'natural' is always better.

Received: April 25, 2026

[1] This column is inspired by a presentation I gave several times at high schools and by parts of a course I used to teach for ongoing chemistry teachers.

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