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The PFAS Problem in the Context of Organofluorine Chemistry Research and Teaching

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Abstract: Teaching the rich and unique chemistry of poly- and perfluorinated organic compounds should go hand-in-hand with the awareness of their future impact on environment and health.

Keywords: C–F-bond activation · Organofluorine chemistry · Persistent pollutants · PFAS · Selective fluorination

"*They are actually thinking about shrink-wrapping the skis*." This was the ironical title of an article that appeared in the newspaper *Tages-Anzeiger*, reporting on the disqualification of a Norwegian athlete from one of the first races in the 2023-24 season because the content of 'fluorine' found in the skiwax of her skis was too high.[1] Shrink-wrapping the skis after preparation for the race was thought of as a measure against possible sabotage. Now what does 'fluorine' mean in this context and what is the problem? 'Fluorine' stands here for per- and polyfluoroalkyl substances, PFAS,[2] some of which were, and still partly are, contained in waxes used by skiers and snowboarders, such as *e.g.* perfluorododecanoic acid, PFDoA, and perfluorooctanoic acid, PFOA (Fig. 1).[3] The use of such substances is now prohibited in international skiing competitions because of their possible adverse effects on the environment.[4] A more recent article in the same newspaper (as well as in others) reported finding PFAS in meat produced in the region between St. Gallen and Bodensee.[1b] Such articles are just examples of how the daily press, in recent years, has taken up issues related to PFAS, thereby contributing to the public awarness about the corresponding general environmental and health risks.[5] I consider it therefore appropriate to convey a commensurate type of informed awarness in the context of teaching, in particular when discussing the fascinating chemistry of fluorine, even in introductory courses.

PFAS constitute a very broad class of compounds counting several thousand individual derivatives, some of which have been known for many decades. In a recent overview, Glüge and collaborators have classified *ca.* 1400 PFAS according to *ca.* 200 specific use categories.[6] Thus, PFAS constitute or are contained in breathable membranes, lubricants, emulsifiers, flame retardants, and even food packaging, just to randomly name a few examples of their highly disparate uses. They account for a large part of industrial organofluorine chemistry with an estimated worldwide yearly production of *ca.* 1 million tons.[7a] On one hand they display a series of advantageous and quite unique physicochemical properties, such as *e.g.* pronounced hydrophobicity and oleophobicity and high stability over a wide temperature range, making them very well suited or even ideal for certain specific applications. On the other hand, the very thermodynamic stability, not only due to the very strong C–F bond, along with their very low reactivity, which includes a virtually inexistent biodegradability, make them 'forever chemicals'.[7b] This means that they are persistent chemicals accumulating in the environment, be it waters, soil, air, or organisms, ultimately leading to possible adverse health effects in humans. Thus, this is the quintessence of the problem!

Data collected at various sites worldwide for two of the most widely used, though no longer produced PFAS, PFOA and PFOS (perfluorooctane sulfonic acid, Fig. 1) show that they occur in surface water, groundwater, river water and drinking water in concentrations in the range from below 1 ng/L up to 1000 ng/L, or in certain cases even higher.[7c] Consequently, there is an expanding body of literature concerned with detecting and measuring the content of further PFAS in various systems.[8] The somewhat superficial yet worrisome impression that PFAS can be found essentially everywhere is not too far from being correct.

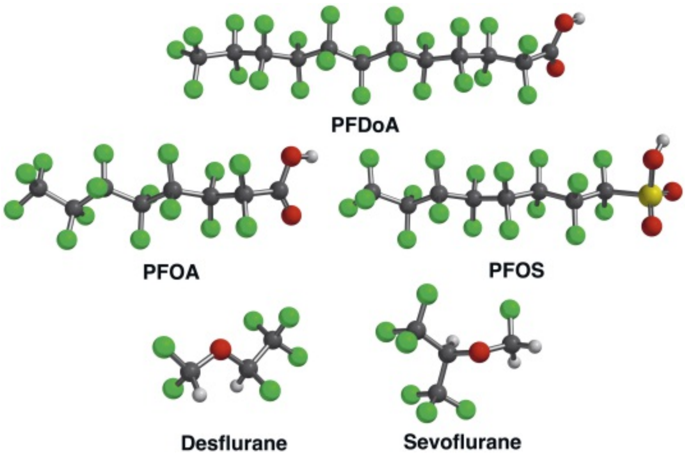

Fig. 1. Molecular structures of selected per- and polyfluoroalkyl derivatives used commercially (calculated by DFT, ωB97X-D, 6-31G*, Spartan'24, Wavefunction, Inc.).

When it comes to volatile PFAS, hence compounds degrading only very slowly in the atmosphere, there is the very interesting example of highly fluorinated inhalation anesthetics, still commonly used during surgery.[9] Two of them, desflurane and sevoflurane, are shown in Fig. 1. They can all be detected in the air at different locations worldwide, including at the High Altitude Research Station at Jungfraujoch (3570 m asl).[10] Their very low concentrations in the air up there of just up to 0.3 ppt (10^{-12}, measurement of 2014) and obviously their very low toxicity should not divert the attention from the fact that they are very potent greenhouse gases.

According to the restrictive PFAS definition given by the OECD,[2b] any organic molecule containing at least one difluoromethylene or trifluoromethyl group is a PFAS. Thus, this concerns a correspondingly large number of small-molecule drugs or crop protection agents being already on the market or under development.[11] The small fluorinated entities contained in such molecules are often essential molecular features in tuning and optimizing their properties as biologically active compounds. Therefore, fluorination is thought of in these cases as an exclusively beneficial aspect. However, do we know the fate in the environment of a trifluoromethyl group attached to another carbon atom, originally contained in *e.g.* a herbicide? No, we don't![12] A plausible ultimate scenario is the formation of TFA (CF_3COOH), another persistent pollutant.[13] Though the absolute quantities of these industrial compounds are relatively small and only a fraction of those of more common PFAS (the order of magnitude for the production of herbicides is somewhere between 10^3 and 10^4 tons/year and for drugs much lower), we should be concerned by the potential long-term problem of PFAS release and persistency deriving also from such products.

There are increasing activities in various countries concerning the removal and degradation of PFAS. 'Getting PFAS out of drinking water' in order to meet tolerated concentrations in the low ng/L limit as dictated by the Environmental Protection Agency (EPA) and is particular significant in the U.S.[14] Several technologies are currently being considered and implemented, regenerable ion-exchange resins, membrane filtration, and foam fractionation being the most important ones. Such technologies, however, solve only part of the problem, as PFAS removed from water still need to be destroyed. Given their high thermodynamic stability and very low reactivity, innovative drastic methods must be used. Technologies such as the hydrothermal alkaline treatment or supercritical water oxidation, originally developed for the destruction of chemical weapons, are also suited for the disposal of PFAS. More traditional electrochemical oxidation is obviously also applicable, and a new methodology based on a plasma vortex is promising.[15]

PFOA and PFOS – the two 'bad guys' among PFAS – have also been found in *e.g.* human blood and breast milk in concentrations in the ng/L range, which is considered to be very low.[7c] Experiments with animals (mice, fish and amphibians) have been carried out in order to assess the toxicity of PFAS. In zebra-fish, for example, it was found that gene expression, growth and behaviour were affected by the exposure to controlled quantities of both chemicals, whereas in mice pancreatic toxicity and altered gene expression were observed. Studies with human cell lines have pointed out *e.g.* immunotoxicity,[7c] which can imply cancerogenicity. According to a very recent publication[16] there is "sufficient evidence" that kidney cancer, decreased immune response, decreased birthweight and increased serum cholesterol levels can be linked to PFAS exposures. The same paper also discusses progresses in policy and regulations. While there are regulatory differences between countries, it seems that a short-term total ban is not realistic and that the distinction between essential and non-essential use is very important. PFAS in ski-wax (see above) is clearly non-essential, while a trifluoromethyl group in a new drug for the successful treatment of a certain disease should be declared as essential. It is clear that we are facing a unique global environmental and health problem that will require well pondered global solutions.

Finally, given my direct experience in fluorine chemistry as a researcher, I wish to add some brief personal considerations. My contributions to synthetic organofluorine chemistry since 2006 have involved, among other aspects, the development of reagents for perfluoroalkylation, mainly trifluoromethylation.

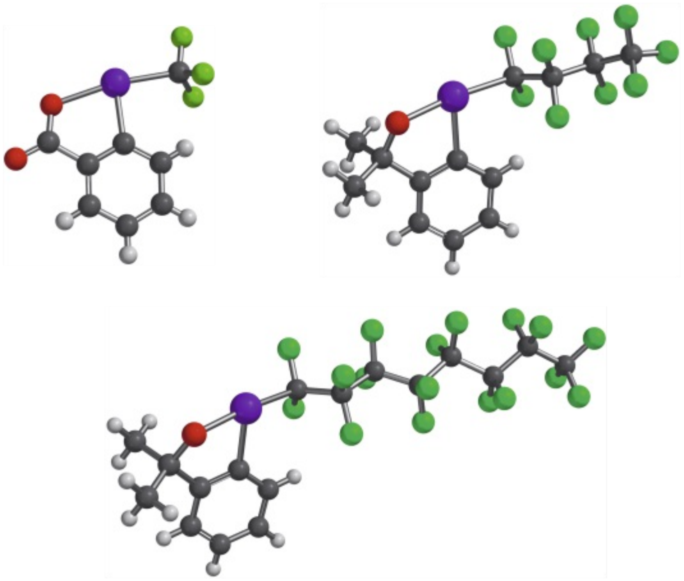

Fig. 2. X-ray crystal structure of three hypervalent iodine reagents for electrophilic trifluoromethylation, perfluorobutylation and perfluorooctylation, respectively (CCDC 239458, 1825243, 1825244).[17]

Fig. 2 shows the structure of three such reagents[17] now known to efficiently enable the transfer of the perfluoroalkyl group to a great variety of substrates. The result is thus the making of new PFAS, though this was not necessarily the primary target of my original research endeavor which has also never been guided by any industrial collaboration. It was rather more directed towards understanding the fundamental aspects of structure and reactivity of such newly designed reagents. Nevertheless, my interest and work in this area of chemistry has taught me the following: As synthetic chemists we have learned how to efficiently put fluorine into organic molecules, but we do not quite know yet how to take it out again! This may sound somewhat simplistic. In fact, however, the body of literature concerned with the activation of the C–F bond, *i.e.* its cleavage, is indeed way smaller than that related to fluorination, *i.e.* the formation of new C–F bonds. Hence, I am convinced that increased research efforts in the area of C–F-bond activation[18] have not only the potential to be very rewarding from a scientific point of view, but are actually necessary as one possible way to counteract the PFAS problem by expanding our knowledge on how to selectively degrade these compounds. Correspondingly, this would be my choice of a new research avenue, had I to take one, however, not as a matter of jumping onto an alarmistic bandwagon, but as a more general matter of taking responsible action as a scientist.

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[1] a) *Tages-Anzeiger*, 4 November **2023**: https://www.tagesanzeiger.ch/angst-im-ski-weltcup-nach-disqualifikation-jetzt-wollen-sie-die-ski-einschweissen-363490145178. b) *Tages-Anzeiger*, 28 August **2024**: https://www.tagesanzeiger.ch/pfas-st-gallen-verhaengt-verkaufsverbot-fuer-fleisch-734538835793.

[2] For a brief introduction, see *e.g.*: a) US Environmental Protection Agency, https://www.epa.gov/pfas/pfas-explained and documents linked therein. For a general terminology and current definition of PFAS, see b) OECD. "Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance. Series on Risk Management" No. 61.; **2021**, https://one.oecd.org/document/ENV/CBC/MONO(2021)25/en/pdf. Accordingly, PFAS are defined as fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it). For further details, the reader is encouraged to consult the quoted literature, both in form of recent original and review articles.

[3] For analyses of ski wax products, measurements of PFAS contents in snow, and PFAS exposures related to waxing activities of skiers and snowboarders, see for example: a) S. Fang, M.M. Plassmann, I.T. Cousins, *Environ. Sci.: Processes Impacts* **2020**, *22*, 2142, https://doi.org/10.1039/D0EM00357C. b) G. L. Carlson, S. Tupper, *Chemosphere* **2020**, *261*, 128078,

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https://doi.org/10.1016/j.chemosphere.2020.128078. c) K.A. Crawford. B.T. Doherty, D. Gilbert-Diamond, M.E. Romano, B. Claus Henn, *Environ. Res*. **2022**, *215*, 114335, https://doi.org/10.1016/j.envres.2022.114335.

[4] Following the ban of fluorinated ski waxes by the International Ski Federation (FIS), the U.S. Environmental Protection Agency (EPA) has released an enforcement alert, https://www.epa.gov/system/files/documents/2022-01/pfasskiwax.pdf.

[5] For recent surveys of the public opinion and perception about the uses of PFAS, see *e.g.*: a) J.A. Kemper, E. Sharp, S. Yi, E.M. Leitao, L.P. Padhye, M. Kah, J, L.-Y. Chen, K. Gobindlal, *J. Cleaner Prod*. **2024**, *442*, 140866, https://doi.org/10.1016/j.jclepro.2024.140866. b) A.K. Karinen, H. Tobi, J. Devilee, A.T. de Blaeij, S. Gabbert, *Environ. Sci. Policy* **2024**, *153*, 103666, https://doi.org/10.1016/j.envsci.2023.103666. See also: c) E. Suffill, M.P. White, S. Hale, S. Pahl, *Environ. Sci. Europe* **2024**, *36*, 111, https://doi.org/10.1186/s12302-024-00930-9.

[6] J. Glüge, M. Scheringer, I.T. Cousins, J.C. DeWitt, G. Goldenman, D. Herzke, R. Lohmann, C.A. Ng, X. Trier, Z. Wang, *Environ. Sci.: Processes Impacts* **2020**, *22*, 2345, https://doi.org/10.1039/d0em00291g.

[7] For selected recent reviews focussing on the environmental problem deriving from PFAS, see: a) M.G. Evich, M.J.B. Davis, J.P. McCord, B. Acrey, J.A. Awkerman, D.R.U. Knappe, A.B. Lindstrom, T.F. Speth, C. Tebes-Stevens, M.J. Strynar, Z. Wang, E.J. Weber, W.M. Henderson, J.W. Washington, *Science* **2022**, *375*, 512, https://doi.org/10.1126/science.abg9065. b) J. Fang, S. Li, R. Qiu, W.-x. Zhang, *Front. Environ. Sci. Eng*. **2024**, *18*, 131, https://doi.org/10.1007/s11783-024-1891-5. c) M. Antonopoulou, A. Spyrou, A. Tzamaria, I. Efthimiou, V. Triantafyllidis, *Sci. Tot. Environ*. **2024**, *913*, 169332, https://doi.org/10.1016/j.scitotenv.2023.169332 and literature cited therein.

[8] For examples of reports on assessing PFAS contents in various environmental contexts, including rain water, soil, drinking water, cosmetics, etc., see *e.g.*: a) I.T. Cousins, J.H. Johansson, M.E. Salter, B. Sha, M. Scheringer, *Environ. Sci. Technol*. **2022**, *56*, 11172, https://doi.org/10.1021/acs.est.2c02765. b) I. Kourtchev, B.G. Sebben, S. Brill, Cybelli, G.G. Barbosa, B. Weber, R.R. Ferreira, F.A. Farias D'Oliveira, C.Q. Dias-Junior, O.A.M. Popoola, J. Williams, C. Pöhlker, R.H.M. Godoi, *Sci. Tot. Environ*. **2024**, *944*, 173918, https://doi.org/10.1016/j.scitotenv.2024.173918. c) M. Säve-Söderbergh, I. Gyllenhammar, T. Schillemans, E. Lindfeldt, C. Vogs, C. Donat-Vargas, E. Halldin Ankarberg, A. Glynn, L. Ahrens, E. Helte, A. Åkesson*, Environ. Internat*. **2024**, *187*, 108727, https://doi.org/10.1016/j.envint.2024.108727. d) P.J. Brahana, R. Patel, B. Bharti, *ACS Environmental Au* **2024**, *4*, 173, https://doi.org/10.1021/acsenvironau.3c00079. e) C. Couteau, C. Brunet, R. Clarke, L. Coiffard, *Food Chem. Toxicol*. **2024**, *187*, 114625, https://doi.org/10.1016/j.fct.2024.114625. f) X. Hong, L. Tao, L. Guo, L. Luo, J. Lv, R. Li, J. Hu, C. Gao, H. Wang, D.-X. Xu, Z.-Z. Cheng, B.-X. Mai, Q. Tang, Y. Huang, *Environ. Sci. Technol*. **2024**, *58*, 5129, https://doi.org/10.1021/acs.est.3c10511. g) T. Wanzek, E. Hawley, J. Merrill, R. Deeb, D. Sedlak, J. Field, C. Higgins, *Groundwater Monitor. Remed*. **2024**, *44*, 30, https://doi.org/10.1111/gwmr.12657. h) D. Dias, J. Bons, A. Kumar, M.H. Kabir, H. Liang, *Lubricants* **2024**, *12*, 114, https://doi.org/10.3390/lubricants12040114. i) E. Vujic, S.S. Ferguson, K.L.R. Brouwer, *Toxicol. Sci*. **2024**, *200*, 213, https://doi.org/10.1093/toxsci/kfae061.

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[11] The question whether trifluoromethyl derivatives are to be considered PFAS has been discussed very recently. See: B. Barbu, *Chemical & Engineering News* **2024**, *102*, Issue 26, 26 August 2024, p. 16: https://pubs.acs.org/doi/pdf/10.1021/cen-10226-feature1.

[12] As an example, the sulfonylurea herbicide Prosulfuron (Syngenta) contains a unique 3,3,3-trifluoropropyl substituent attached to a benzenesulfonyl moiety. It is known that the main product deriving from hydrolytic degradation of Prosulfuron in the soil is 2-(3,3,3-trifluoropropyl) benzenesulfonamide and bacterial oxidation leads to hydroxylation of the corresponding benzylic position. The known road of the CF_3 group ends here. See: a) European Food Safety Authority, M. Anastassiadou, M. Arena, D. Auteri, A. Brancato, L. Bura, L Carrasco Cabrera, E. Chaideftou, A. Chiusolo, F. Crivellente, C. De Lentdecker, M. Egsmose, G. Fait, L. Greco, A. Ippolito, F. Istace, S. Jarrah, D. Kardassi, R. Leuschner, A. Lostia, C. Lythgo, O. Magrans, I. Mangas, I. Miron, T. Molnar, L. Padovani, J. M. P. Morte, R. Pedersen, H. Reich, M. Santos, R. Sharp, A. Stanek, J. Sturma, C. Szentes, A. Terron, M. Tiramani, B. Vagenende, L. Villamar-Bouza, *ESFA Journal* **2020**, *18*, 6181, https://doi.org/10.2903/j.efsa.2020.6181. b) R.P. Hultgren, R.J.M. Hudson, G.K. Sims, *J. Agric. Food Chem.* **2002**, *50*, 3236, https://pubs.acs.org/doi/pdf/10.1021/jf011477c. c) C. Menniti, J.-P. Cambon, J. Bastide, *J. Agric. Food Chem.* **2003**, *51*, 3525, https://pubs.acs.org/doi/pdf/10.1021/jf0340815. d) K. Kulowski, E.L. Zirbes, B.M. Thede, J.P.N. Rosazza, *J. Agric. Food Chem*. **1997**, *45*, 1479, https://pubs.acs.org/doi/pdf/10.1021/jf9604495.

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[14] For a report on current efforts concerned with the removal of PFAS from drinking water, see: B.E. Erickson, *Chemical & Engineering News* **2024**, *102*, Issue 20, 1 July 2024, p. 26: https://pubs.acs.org/doi/pdf/10.1021/cen-10220-cover.

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[18] For a recent short review about progresses in the area of C–F-bond activation, see: R. Doi, S. Ogoshi, *Eur. J. Org. Chem*. **2024**, *27*, e202301229, https://doi.org/10.1002/ejoc.202301229.