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Review

Synthesis of environmentally relevant fluorinated surfactants—a review

Hans-Joachim Lehmler *

Department of Occupational and Environmental Health, College of Public Health, University of Iowa, 100 Oakdale Campus #124 IREH, Iowa City, IA 52242-5000, USA

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Abstract

In the past years there has been a growing interest in fluorinated persistent organic pollutants such as perfluorooctanesulfonic acid, perfluorooctanesulfonamides, perfluorinated carboxylic acids and fluorotelomer alcohols. Although these compounds have probably been present in the environment for many decades, we are only now beginning to realize that these environmental contaminants may have serious environmental and health effects. This article gives a state-of-the-art review of synthetic approaches that have been employed for the synthesis of these environmentally relevant fluorinated compounds. Perfluorooctanesulfonic acid derivatives, in particular, pose a problem because only a few perfluorooctanesulfonic acid derivatives are available from commercial sources—a fact that limits the ability of researchers worldwide to further study these compounds. Because of the limited literature available, this article also describes synthetic approaches for shorter chain homologues or perfluoroether analogues that can potentially be applied for the synthesis of perfluorooctanesulfonic acid derivatives. The preparation of typical starting materials for the synthesis of perfluorooctanesulfonic acid derivatives such as the perfluoroalkanesulfonyl fluorides and chlorides will be discussed. Subsequently, their conversion into relevant perfluoroalkane sulfonate salts (R_FSO_3M), sulfonamides ($R_FSO_2NH_2$), *N*-alkyl sulfonamides (R_FSO_2NHR, R = alkyl), *N*,*N*-dialkyl sulfonamides ($R_FSO_2NR_2$, R = alkyl), sulfonamidoethanol ($R_FSO_2NRCH_2CH_2OH$, R = –H, $–CH_3$ or $–C_2H_5$) and sulfonamidoacetates ($R_FSO_2NRCH_2CO_2H$, R = –H, $–CH_3$ or $–C_2H_5$) will be described. Many perfluorinated carboxylic acids and fluorotelomer alcohols are available from commercial sources. The review of the synthesis of these two classes of fluorinated compounds includes a review of their industrial synthesis and the synthesis of relevant degradation products.

Keywords: Perfluorinated compounds; Perfluorooctanesulfonate; Perfluorooctanoate; Fluorotelomer alcohols; Properties; Synthesis

Contents

* Tel.: +1 319 335 4414; fax: +1 319 335 4290.
E-mail address: hans-joachim-lehmler@uiowa.edu

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1. Introduction

Fluorinated materials and surfactants have unique properties that make them highly suitable for many industrial processes and consumer applications (Kissa, 2001). Their chemical structures are as diverse as their applications. Several fluorinated surfactants have been detected in the environment and are of great environmental concern because of their persistence, their potential to bioaccumulate, and the possibility of biomagnification. Current concern focuses on perfluoroalkanesulfonic acid derivatives, perfluorinated carboxylic acids and fluorotelomer alcohols; however, other types of fluorinated compounds may enter the environment as well and pose a currently unrecognized environmental problem. This review gives a short introduction for each class of compounds followed by an overview of the laboratory synthesis of these compounds for analytical, environmental and toxicological studies. One major aim of this review is to provide a state-of-the-art review of the synthesis of perfluoroalkanesulfonic acids, *N*-alkylated perfluoroalkanesulfonamides, perfluorinated carboxylic acids and fluorotelomer alcohols. Because of the limited literature available, this article includes synthetic approaches that can potentially be applied for the synthesis of these fluorinated compounds.

Most environmentally relevant perfluorinated carboxylic acids and fluorotelomer alcohols are available from commercial sources in high purity. Thus, for these two classes of fluorinated surfactants, there is only a need to synthesize selected (bio-)degradation products or isotopically labeled compounds; however, there are

no commercial sources for large quantities of most perfluoroalkanesulfonic acid derivatives, especially perfluorooctanesulfonamides. It is, therefore, not surprising that most of the published environmental and toxicological studies with perfluoroalkanesulfonic acid derivatives, especially perfluorooctanesulfonic acid, rely on industrial sources to provide test compounds or analytical standards. This limits the ability of researchers worldwide to independently study these compounds. It is therefore necessary to develop methodologies to prepare perfluoroalkanesulfonic acid derivatives of analytical or environmental interest in the laboratory; however, there is a lack of detailed procedures for the synthesis of these compounds in the peer-reviewed literature. Another important aspect frequently overlooked in the synthetic literature is the fact that perfluoroalkanesulfonyl fluorides, the starting material for the synthesis of most perfluoroalkanesulfonic acid derivatives, are highly impure materials. This makes it challenging to obtain products free of linear or branched homologues or products reflecting the composition of the industrial product.

1.1. Occurrence and toxicity of perfluorooctanesulfonic acid salts (PFOS) and related compounds

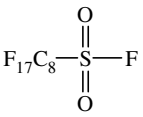
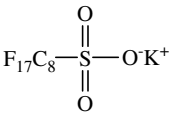
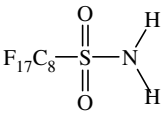
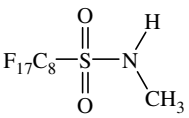
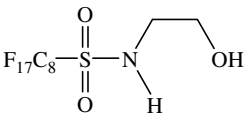
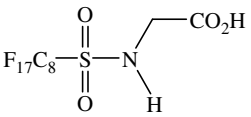
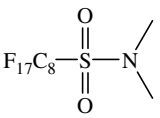
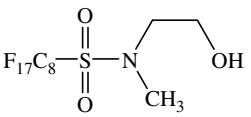
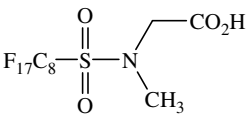
PFOS, its short-chain homologues and related sulfonamides are a class of environmentally persistent chemicals with a wide range of industrial applications such as fire fighting foams, pesticides, and consumer applications including surface coatings for carpets, furniture and paper products (Kissa, 2001; Mabury et al., 2002). PFOS and its derivatives, such as *N*-methyl and *N*-ethyl perfluorooctanesulfonamidoethanol, have been in commercial use for approximately 50 years. Because of some of the concerns discussed below, the primary manufacturer—the 3M Corporation—ceased production of perfluorooctanesulfonyl fluoride in the year 2000 (Renner, 2001). All industrial PFOS derivatives are prepared from this fluoride, which, in turn, is obtained by electrochemical fluorination of octanesulfonyl fluoride (Kissa, 2001). Base-catalyzed hydrolysis of the perfluorooctanesulfonyl fluoride resulted in perfluorooctanesulfonic acid or the respective salts. Sulfonamide derivatives were also obtained from the fluoride. The chemical structures and names of relevant PFOS derivatives are shown in Table 1.

PFOS has been detected in surface water (Hansen et al., 2002; Moody et al., 2003; Boulanger et al., 2004) and wildlife (Giesy and Kannan, 2001; Kannan et al., 2001a,b; Kannan et al., 2002c,d; Martin et al., 2004) at numerous locations in North America ranging from the Gulf of Mexico to the Arctic. It has also been detected in vacuum cleaner dust (Moriwaki et al., 2003), tap water, surface water, and groundwater (Saito et al., 2003; Harada et al., 2003; Taniyasu et al., 2003; Jin et al., 2004; So et al., 2004) and wildlife (Kannan et al., 2002a; Taniyasu et al., 2003) from East Asia (i.e. Japan). There are also reports of PFOS in industrial effluents in Austria (Hohenblum et al., 2003), in fish and wildlife in Europe, the Baltic Sea, the North Sea and the Mediterranean Sea (Kannan et al., 2002b; Hoff et al., 2003; Van de Vijver et al., 2003a,b; Hoff et al., 2004; Van de Vijver et al., 2004), and in wildlife in the Pacific Ocean (Giesy and Kannan, 2001; Kannan et al., 2001a). Only a few investigations have analyzed for the presence of related sulfonamides in environmental samples. Perfluorooctane sulfonamide has been found in wildlife worldwide (Kannan et al., 2002a,b,d) and volatile perfluorooctane sulfonamides have been detected in air samples from Canada (Martin et al., 2002).

Laboratory investigations of the effect of PFOS on aquatic microcosms show toxicity at high PFOS concentrations, but no effect was observed at environmentally relevant concentrations (Sanderson et al., 2002; Boudreau et al., 2003a,b; Sanderson et al., 2004). The mammalian toxicity of PFOS, typically in the form of the potassium salt, and a related compound, *N*-ethyl perfluorooctanesulfonamidoethanol, has been studied in several toxicity studies. For a comprehensive summary of toxicity studies of PFOS see the Draft Report from the Organization for Economic Co-operation and Development, 2002. Nonselective toxicity has been observed in rats, rabbits, rhesus and cynomolgus monkeys. PFOS and *N*-ethyl perfluorooctanesulfonamidoethanol are also known peroxisome proliferators in rodents (Sohlenius et al., 1993; Berthiaume and Wallace, 2002); however, no hepatocellular peroxisomal or cellular proliferation was observed during sub-chronic dietary exposure over an extended period of time, i.e. 4 and 14 weeks (Seacat et al., 2003). PFOS also inhibits gap junctional intercellular communication (Hu et al., 2002), induces carboxylesterases in rat liver (Hosokawa and Satoh, 1993; Derbel et al., 1996), activates both mouse and human peroxisome proliferator-activated receptor α (PPARα) (Shipley et al., 2004), and affects the neuroendocrine system in vivo (Austin et al., 2003). In particular, developmental toxicity has been a major focus of recent research (York et al., 2000; Case et al., 2001; Lau et al., 2001; Grasty et al., 2003; Lau et al., 2003; Thibodeaux et al., 2003; Lau et al., 2004). A major concern in this regard is the compromised postnatal survival of neonate rodents as a result of *in utero* exposure to PFOS.

Limited investigations have been done regarding the mechanisms of the toxicity of PFOS and its amide derivatives. PFOS binds to serum proteins such as albumin and can replace a variety of steroid hormones from specific binding proteins in the serum of birds and fish (Jones et al., 2003). Available human data suggest that PFOS can also bind to human serum proteins. PFOS, *N*-ethyl perfluorooctanesulfonamide and *N*-ethyl perfluorooctanesulfonamidoethanol bind to rat liver fatty

Table 1
Comparison of the IUPAC names and typical names used in the literature

Chemical structure	IUPAC name	Typical literature name (abbreviation)
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonyl fluoride	Perfluorooctanesulfonyl fluoride
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonic acid potassium salt	Potassium perfluorooctanesulfonate (PFOS)
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonamide	Perfluorooctanesulfonamide (FOSA)
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-*N*-methyloctane-1-sulfonamide	*N*-methyl perfluorooctane sulfonamide (*N*-MeFOSA)
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-*N*-(2-hydroxyethyl)octane-1-sulfonamide	Perfluorooctanesulfonamidoethanol (FOSE)
	*N*-[(heptadecafluorooctyl)sulfonyl]glycine	Perfluorooctanesulfonamidoacetate (FOSAA)
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-*N*,*N*-dimethyloctane-1-sulfonamide	*N*,*N*-dimethyl perfluorooctanesulfonamide *N*,*N*-diMeFOSA
	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-*N*-(2-hydroxyethyl)-*N*-methyloctanesulfonamide	*N*-methyl perfluorooctanesulfonamidoethanol (*N*-MeFOSE)
	*N*-[(heptadecafluorooctyl)sulfonyl]-*N*-methylglycine	*N*-methyl perfluorooctanesulfonamidoacetate (*N*-EtFOSAA)

acid-binding protein (L-FABP), thus replacing endogenous ligands from L-FABP (Luebker et al., 2002). This may, in part, explain the toxicity observed in rodents. PFOS and perfluorooctanesulfonamide activate PPARα which results in the activation of a unique set of downstream target genes and may explain some of the biological effects of these compounds in mice and humans (Shipley et al., 2004). Finally, there is evidence that PFOS and its derivatives cause mitochondrial dysfunction by altering the fluidity of the mitochondrial membrane (Starkov and Wallace, 2002; Hu et al., 2003). This observation is surprising because fluorinated surfactants are, in general, thought to be immiscible with hydrocarbon surfactants such as the phospholipid components of a biological membrane (Mukerjee and Yang, 1976). Recent investigations from this laboratory, however, demonstrate that (partially) fluorinated carboxylic acids and alcohols are partly miscible with phospholipids

(Lehmler et al., 2000; Arora et al., 2003; Lehmler and Bummer, 2004), probably due to hydrogen bonding between the carboxylic acid headgroup and the headgroup of the phospholipid.

Data on human exposure to PFOS and its sulfonamide derivatives is currently limited. Occupational exposure assessments of 3M perfluorooctanesulfonyl fluoride manufacturing sites in Antwerp, Belgium; and Decatur, Alabama determined mean serum levels ranging from 0.94 to 2.19 parts per million (Olsen et al., 1999; Olsen et al., 2003a,d). Concentrations of the corresponding sulfonamides were significantly lower (Olsen et al., 2003d). Several biological parameters consistent with the known toxicological effects of PFOS were assessed during these exposure studies, but no substantial changes correlating with PFOS concentration were observed. A recent study investigating the mortality of employees of a perfluorooctanesulfonyl fluoride manufacturing site revealed an increased number of deaths from bladder cancer in workers employed in high exposure jobs (Alexander et al., 2003). Serum concentrations of PFOS and, in several cases, selected sulfonamides have also been studied in blood samples from all over the world (Olsen et al., 2003b,d, 2004; Taniyasu et al., 2003; Harada et al., 2004; Inoue et al., 2004; Kannan et al., 2004; Kubwabo et al., 2004; Kuklenyik et al., 2004). These studies indicate that non-occupationally exposed populations have measurable serum concentrations of PFOS and related sulfonamides. The concentrations of the sulfonamides are an order of magnitude lower compared to concentrations of PFOS (Olsen et al., 2003b). Another study compared PFOS concentrations in the liver and serum of a limited number of donors ($n = 23$). The mean liver-to-serum ratio was approximately 1.3–1 (Olsen et al., 2003c), which is comparable to a toxicological study in cynomolgus monkeys (Seacat et al., 2002).

The source of PFOS in biota and in human serum is currently unknown. PFOS, e.g. the potassium salt, is poorly water soluble (the free acid is readily soluble in water) and sparingly volatile and should, therefore, not be distributed widely in the environment. However, it appears that particle-bound PFOS may be an important source for PFOS in the environment (Sasaki et al., 2003). Furthermore, more volatile precursors such as *N*-methyl perfluorooctanesulfonamidoethanol and *N*-ethyl perfluorooctane-sulfonamidoethanol may also contribute to the widespread distribution of PFOS (Martin et al., 2002). Human exposure may also be the result of exposure via inhalation to indoor air (Shoeib et al., 2004) or house dust (Moriwaki et al., 2003) containing PFOS precursors. Other routes of exposure, such as the diet or drinking water, are probably important as well, but have not been reported in the literature thus far. It is thought that PFOS precursors, e.g. its sulfonamides, ultimately degrade to PFOS under either environmental and/or biological conditions. This theory is supported by the reported biotransformation pathway of *N*-ethyl perfluorooctanesulfonamidoethanol in rats and humans (Xu et al., 2004). This recent study demonstrated the dealkylation of *N*-alkyl perfluorooctanesulfonamides with perfluorooctanesulfonamide as the ultimate dealkylated product. The perfluorooctanesulfonamide is further hydrolyzed by an unknown mechanism to PFOS. In addition, the pesticide *N*-ethyl perfluorooctanesulfonamide is converted into PFOS by Rainbow Trout (*Onchorhynchus mykiss*) liver microsomes (Tomy et al., 2004). It is also well established that *N*-ethyl perfluorooctanesulfonamide is readily metabolized to perfluorooctanesulfonamide in rats (Manning et al., 1991; Grossman et al., 1992).

1.2. Occurrence and toxicity of perfluorooctanoic acid (PFOA) and related perfluorinated carboxylic acids (PFCAs)

PFOA, sometimes referred to as C8, and homologous perfluorinated carboxylic acids (PFCAs) are a class of persistent environmental chemicals that are structurally related to PFOS. The ammonium salt of PFOA is an essential aid in the manufacturing of fluoropolymers, such as polytetrafluoroethylene (PTFE) and polyvinylidine fluoride, where it is used as an emulsifier for the emulsion polymerization of fluoropolymers. The emulsion polymerization process utilizes the generally high surface activity of fluorinated surfactants relative to hydrocarbon surfactants to reduce the total amount of surfactant used in the manufacturing process. The fluoropolymers produced using PFOA and related compounds typically do not contain PFOA. PFOA and its homologues are also used in breathable, waterproof fabrics, biomaterials, insulators for electric wires, planar etching of fused silica, foam fire extinguishers, floating agents and other applications (Kissa, 2001). The chemical structure of PFOA is shown in Fig. 1.

PFOA has been detected together with PFOS, which is typically the major perfluorinated contaminant, and other perfluorinated surfactants in many environmental samples ranging from surface waters to marine mammals (Kannan et al., 2002a,b,d; Hansen et al., 2002; Martin et al., 2004; So et al., 2004; Van de Vijver

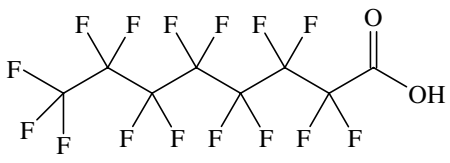


Fig. 1. Structure of perfluorooctanoic acid.

et al., 2004) indicating a global contamination with these chemicals. Interestingly, PFOA is not the only perfluoroalkanoic acid found in environmental samples. A series of PFCAs ranging in chain length from 9 to 15 carbon atoms has been detected in several species collected at various locations in the circumpolar region (Martin et al., 2004) and in harbour porpoises (Phocoena phocoena) from Northern Europe (Van de Vijver et al., 2004). It is not surprising that only perfluorinated acids with a longer carbon chain are found in marine animals because their bioaccumulation has been shown to increase with the chain length of the acid (Martin et al., 2003a,b). For example, perfluorinated acids with a perfluoroalkyl chain length of $\leqslant$6–7 carbons could not be detected on rainbow trout after exposure in a flow-through system and probably have a small or insignificant bioconcentration factor (Martin et al., 2003a). Perfluorononanoic acid (PFNA), and not PFOS, was the major pollutant detected in mink (Martin et al., 2004) suggesting that PFCAs are important environmental contaminants and should be taken into consideration in future risk assessments. It is also interesting to note that the odd numbered, and not the even numbered PFCAs, were the predominant pollutants.

PFOA has been detected in serum of workers at plants that produce or use perfluorinated compounds (Olsen et al., 2000; Sottani and Minoia, 2002; Olsen et al., 2003a,d) as well as in the general population (Olsen et al., 2003b,c, 2004; Harada et al., 2004; Kubwabo et al., 2004). These limited investigations suggest that the levels of PFOA in the general population are much lower than in the workers, and that PFOA levels are typically closely related to PFOS levels. Several occupational biomonitoring studies have been performed by the 3M Corporation at its plants in Cottage Grove, MN; Decatur, AL; and Antwerp, Belgium between 1993 and 2000. These studies found mean serum levels ranging from 0.84 to 6.8 parts per million, with workers from the plant in Antwerp having the lowest PFOS levels (1995: 1.13 ppm; 2000: 0.84 ppm). Workers from the plant at Cottage Grove, MN, had the highest reported PFOA levels with mean serum levels ranging from 5.0 (1993) to 6.8 (1995) parts per million. Several clinical parameters were measured as part of these biomonitoring studies and some correlation with levels of perfluorinated compounds was observed (review by Kudo and Kawashima, 2003). In summary, a significant positive correlation between PFOA and cholesterol, PFOA and triglycerides, as well as PFOA and triiodothyronine was observed. A significant negative correlation between PFOA and HDL as well as PFOA and cholecystokinin-33 was also noted. No correlation was observed for PFOA levels and eleven reproductive hormones in men (Olsen et al., 1998; Kudo and Kawashima, 2003). A retrospective mortality study was performed on 3537 employees of the 3M ammonium perfluorooctanoate manufacturing site in Cottage Grove, MN. The results of this mortality study indicate an increased prostate cancer risk that is significantly associated with the length of employment, i.e. of exposure to PFOA. Overall, these studies are very limited and further long-term monitoring is warranted.

Various aspects of the PFOA toxicity, especially aspects relating to its peroxisome proliferating activity, have been investigated (reviewed by Kudo and Kawashima, 2003) and typically no remarkable toxicity was observed in various animal studies. However, similar to PFOS, the developmental toxicity is currently a major human health concern (reviewed by Lau et al., 2004). In contrast to PFOS, the toxicokinetics of PFOA in laboratory animals and humans has been investigated in some detail. PFOA is readily absorbed following oral and inhalation exposure. High levels of PFOA are found in the liver and plasma, where it binds to proteins such as serum albumin, while levels in adipose tissue are low due to its lipophobic character. PFOA is excreted in both urine and feces. The mean human half-life, determined in a limited study of workers ($n = 9$) exposed to PFOA, is 4.37 years. The biological half-life differs significantly between species and sexes. The differences between sexes are mainly due to differences in the renal clearance and may possibly involve an organic anion transporter.

The source of PFOA and related PFCAs in biota and in humans is currently unknown. PFCAs are man-made compounds and do not occur in nature. Local contamination can arise at manufacturing sites from the use of PFCAs in the production or processing of fluoropolymers, and from the use of PFCA-containing fire extinguishing media. PFOA is also formed in trace amounts during the manufacturing of some telomere-based products, a potential source of PFOA that warrants further investigation; however such local sources cannot explain the global distribution of PFCAs. All PFCAs are strong acids and are expected to be present in the environment in their anionic state and, thus, a non-volatile form. The global distribution of PFCAs is, therefore, not the result of their volatilization and transport to remote regions as is the case with other semi-volatile environmental contaminants, such as polychlorinated biphenyls (PCBs). It has been suggested that, similar to PFOS, the global distribution of PFOA can be explained by the transport and environmental degradation of a neutral, volatile, atmospheric precursor such as fluorotelomer alcohols (Dinglasan et al., 2004; Ellis et al., 2004). Perfluorocarbon chemicals such as PFOS derivatives, PFCAs and fluorocarbon telomers typically have an even number of fluorinated carbon atoms (Kissa, 2001). The presence of odd-numbered PFCAs in environmental samples is, therefore, another puzzling observation (Martin et al., 2004; Van de Vijver et al., 2004) that can be explained be the atmospheric degradation of volatile precursors

such as fluorotelomer alcohols (please see Section 1.3 below). In summary, many questions remain unanswered regarding the origin of PFCAs found in environmental and human samples.

1.3. Environmental relevance of fluorotelomer alcohols (FTOHs)

A variety of fluorotelomers, including FTOHs, are used in a wide range of commercial products (Kissa, 2001). In some applications, such as fire fighting foams, as well as soil, stain, and grease-resistant coatings on carpets, textiles, paper, and leather, the FTOHs are directly released into the environment. The structure of typical FTOHs is $F(CF_2CF_2)_nCH_2CH_2OH$, with n ranging from 2 to 5. Due to the manufacturing process, the fluorocarbon chains tend to be even numbered. In contrast to contaminants such as PFOS and PFOA, FTOHs such as 1H,1H,2H,2H-perfluorodecanol (or 3,3,4,4,5,5,6,6,7,7,8,8,8,9,9,10,10,10-heptadecafluoro-1-decanol, see Fig. 2) have received little attention until recently and minimal literature about their environmental occurrence or toxicity is currently available.

FTOHs are volatile compounds and have been found in the atmosphere with concentrations of up to 135 pg m^{-3} (Martin et al., 2002; Stock et al., 2004). Their estimated half-life in the atmosphere is 20 days which is sufficient to allow for a widespread distribution in the environment (Ellis et al., 2003). Recent investigations show that FTOHs can be degraded in the atmosphere to PFCAs (Ellis et al., 2004), which may explain the occurrence of even- and odd-numbered long-chain PFCAs in animals from the Arctic and Northern Europe (Martin et al., 2004; Van de Vijver et al., 2004). The aerobic biodegradation of 1H,1H,2H, 2H-perfluorodecanol using a mixed microbial system also results in the formation of PFOA (Dinglasan et al., 2004). As shown in Fig. 2, the proposed microbial metabolism pathway of 1H,1H,2H,2H-perfluorodecanol occurs via the aldehyde to the carboxylic acid. This major metabolite is converted via a β-oxidation mechanism to PFOA. Similar to the microbial system, 1H,1H,2H,2H-perfluorodecanol is metabolized in adult male rats to PFOA (Hagen et al., 1981). The observation that inorganic fluoride was detected in plasma as well as urine supports the hypothesis that 1H,1H,2H,2H-perfluorodecanol is metabolized to PFOA by defluorination of the CF_2 group adjacent to the β-CH_2 group.

It is not surprising that the origin of FTOHs in the atmosphere is currently unknown. As discussed above, during some applications FTOHs may be released directly into the environment. Residual amounts of unbound FTOHs from fluoropolymers or biotic and/or non-biotic degradation of FTOH-based products are other likely sources of FTOHs in the atmosphere. In summary, it is currently unclear if FTOHs are, indeed, compounds of environmental concern and/or are major sources of other fluorinated compounds of environmental concern.

1.4. The nomenclature of fluorinated surfactants

Several aspects regarding the terminology and nomenclature should be taken into consideration when dealing with fluorinated surfactants. It is important to realize that fluorinated surfactants can be divided into perfluorinated and partially fluorinated surfactants (Kissa, 2001). The entire hydrophobic tail is fluorinated in a perfluorinated surfactant, whereas the fluorinated tail of a partially fluorinated surfactant still contains some hydrogen atoms (typically methylene groups near the headgroup). Thus, perfluoroalkanesulfonic acid and perfluoroalkanoic acids are truly perfluorinated surfactants. Fluorotelomer derived surfactants such as FTOHs, however, contain several methylene groups as shown in Figs. 2 and 3 and, therefore, are partially fluorinated surfactants. This distinction is important because, as discussed in Section 1.3, methylene groups in the tail can be subject to degradation processes in the environment. In contrast, the tail of a perfluorinated surfactant is stable to degradation and only its headgoup can be degraded as discussed in Section 1.1.

Table 1 shows the IUPAC names of representative examples for the different types of environmentally relevant PFOS derivatives. The IUPAC names are long and impractical to use. Most authors in the field have, therefore, adopted a simplified nomenclature and extensively use abbreviations for these compounds. The most commonly used nomenclature is given in Table 1 for comparison with the IUPAC names. Typically PFOS derivatives are divided into perfluorooctanesulfonamides (FOSAs), perfluorooctanesulfonamidoethanol (FOSEs), and perfluorooctanesulfonamidoacetate (FOSAAs). Short chain homologues of PFOS are named in an analogous manner. In addition, this simplified nomenclature uses the following shortcuts.

(1) The IUPAC name of a fluorinated chain typically includes the position and number of fluorine atoms. For example, the position and number of the fluorine substituents of a $-(CF_2)_7CF_3$ chain is referred to as "1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro" or, depending on the compound, as "heptadecafluoro". To simplify the nomenclature of fluorinated compounds, highly fluorinated alkyl chains are frequently referred to as "perfluoro" chain, e.g. "perfluorooctyl" or "perfluorooctane". Another system for the nomenclature of highly fluorinated compounds uses the symbol "F" to convey the perfluorinated character of a molecule (Young, 1974). In this review the term "perfluoro" will be used to refer to a perfluorinated alkyl chain because this nomenclature is apparently more frequently used in the literature. In the reaction schemes a small

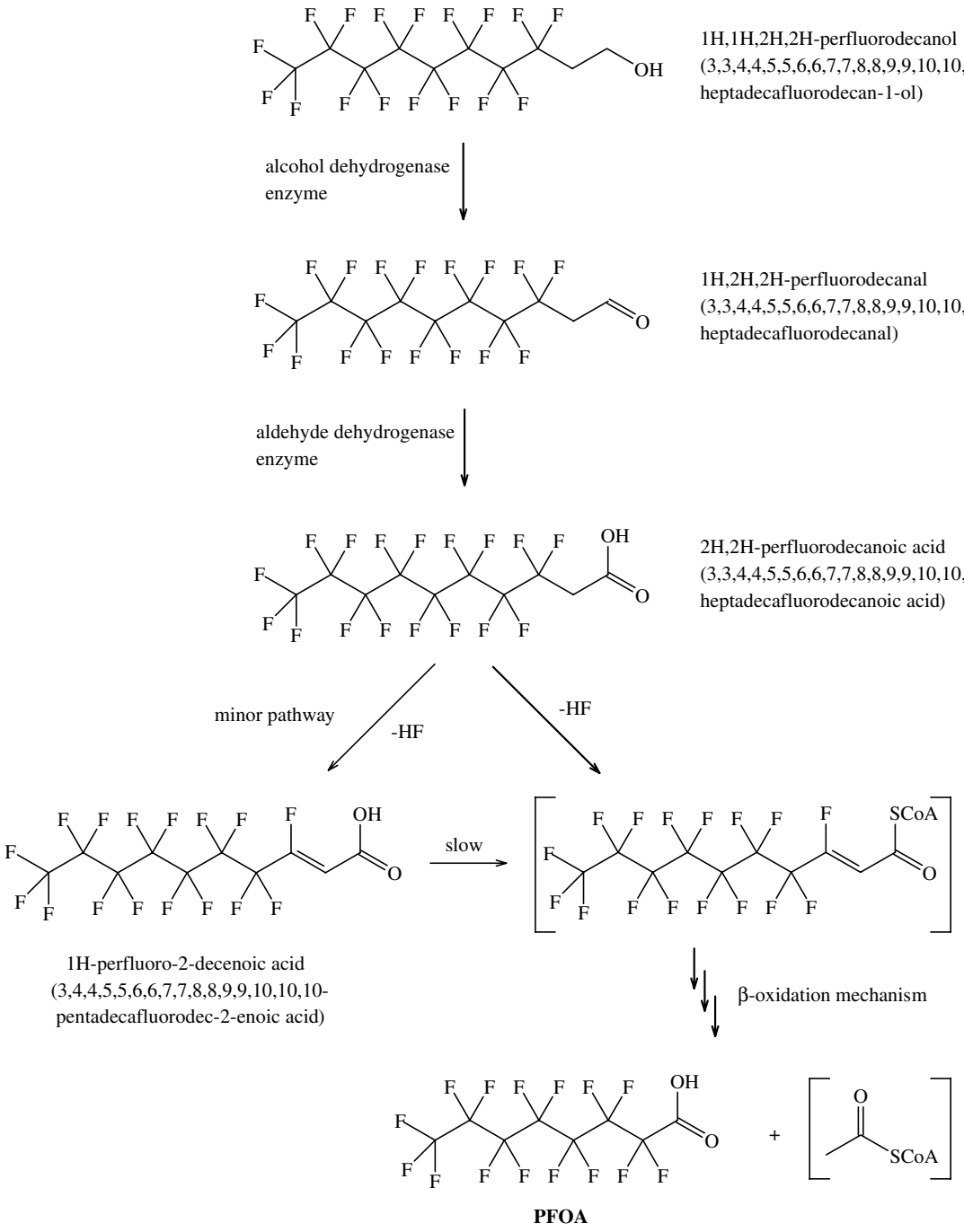


Fig. 2. Proposed aerobic microbial degradation of 1H,1H,2H,2H-perfluorodecanol using a mixed microbial system. Structures in brackets indicate putative intermediates. The names in parentheses are the IUPAC names. Adopted from (Dinglasan et al., 2004).

subscript F will be used in conjunction with the conventional symbol R to represent such a perfluorinated alkyl chain (R_F).

(2) With highly fluorinated compounds it is frequently easier to indicate the position and location of hydrogen atoms in the alkyl chain by providing their position followed by "H". For example 1H,1H,2H,2H-perfluorooctyl iodide has the molecular formula $F(CF_2CF_2)_3CH_2CH_2I$. The IUPAC name of this iodide is 8-iodo-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorodecane.

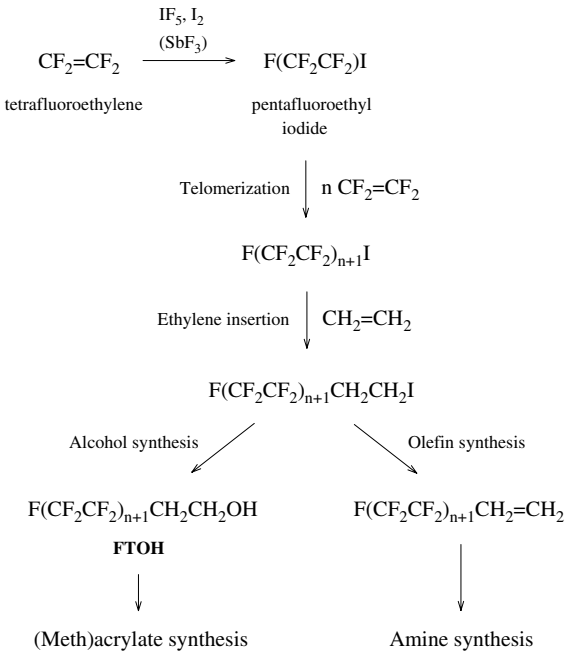


Fig. 3. Industrial synthesis of fluorotelomer alcohols and related compounds using the telomerization of tetrafluoroethylene with perfluoroethyl iodide.

(3) All environmentally relevant fluorinated surfactants have a single hydrophobic chain and a headgroup, e.g. –OH, $–SO_3^-$, SO_2NRR' and COO^-, in position 1 of the alkyl chain. The position of the headgroup is therefore normally omitted in the name of the respective surfactant.

This simplified terminology for fluorinated compounds will be used in this review for ease of reading. For a more detailed overview of the nomenclature of highly fluorinated compounds please see Banks (1970).

2. Properties of fluorinated surfactants

Fluorinated compounds have unique properties which make them highly suitable for the large number of technical and consumer applications discussed in Section 1 (Kissa, 2001). These properties—such as high surface activity, solubility behavior, density and weak intermolecular interactions—not only are responsible for their industrial usefulness and the behavior of these compounds in the environment or a biological system, but also should be taken into consideration during their synthesis in the laboratory. This section is intended to give the reader some insights into the problems typically encountered during the synthesis of perfluorinated surface active materials.

Fluorinated surfactants are highly surface active compared to their hydrocarbon analogs (Kissa, 2001). As with the synthesis of surface active materials in general, an aqueous workup of reaction mixtures is often not advised. For example, several perfluorooctyl sulfonamide derivatives apparently form microemulsions with solvents such as *n*-hexane and chloroform, thus making it difficult if not impossible to recover the surfactant. Also, the evaporation of some solvents under reduced pressure can result in excessive foaming, thus making it difficult to remove the solvent with typical laboratory procedures (i.e., using a rotary evaporator).

Fluorinated materials as well as fluorinated surfactants are, in general, hydrophobic and lipophobic at the same time (Patrick, 1971; Mukerjee and Yang, 1976). For example, most fluorinated solvents are immiscible with water and hydrocarbon solvents, thus resulting in a system with three separate phases. Typically the fluorocarbon phase will be the lower phase because of the high density of fluorocarbon materials. This phase behavior has been extensively used in "fluorous synthesis" to separate a fluorinated catalyst or product from the reaction mixture (Endres and Maas, 2000; Curran, 2003). Similarly, PFOS forms a third phase with octanol and water. Thus, it is impossible to determine the octanol-water partition coefficient of PFOS. From a synthesis point of view, the solubility of perfluorinated compounds is different from typical hydrocarbon compounds and difficult to predict. From our experience two solvents, methanol and/or acetone, are typically good solvents for perfluorinated compounds such as PFOS; however, this statement represents the author's own laboratory experience and should not be generalized.

Also, the van der Waals interactions of perfluoroalkyl groups are weak, although the melting points of fluorocarbon materials, in general, are higher compared to the hydrocarbon analogs. The weak van der Waals interactions can impact the handling of fluorinated compounds in two ways. First, fluorinated compounds, especially ones with a perfluorocarbon tail, are often difficult to crystallize (Lehmler et al., 2004). Second, fluorinated compounds can be very volatile and should not be stored under vacuum for an extended period of time.

3. Synthesis of PFOS and its amides

3.1. Preparation of PFOS precursors

3.1.1. Synthesis of perfluoroalkanesulfonyl fluorides by electrochemical fluorination

Perfluorooctanesulfonyl fluoride is the precursor for most, if not all, industrial perfluorooctanesulfonyl derivatives (Kissa, 2001). Its structure is shown in Table 1. The fluoride, which is available from commercial sources, is therefore a logical starting material for the

laboratory scale synthesis of any PFOS derivative. The fluoride and its homologues (e.g., perfluorohexane- and perfluorobutanesulfonyl fluoride) are typically manufactured by the Simons Electrochemical Fluorination or ECF. During this process, the corresponding hydrocarbon compound, typically the fluoride, is fluorinated in anhydrous HF following the general formula (Burdon et al., 1957; Gramstad and Haszeldine, 1957b; Niederpruem et al., 1973; Hollitzer and Sartori, 1987; Ignat'ev et al., 1999):

$$C_nH_{2n+1}SO_2F + (2n+1)F^- \xrightarrow{HF} C_nF_{2n+1}SO_2F + (2n+1)H^+(4n+2)e^-$$

Short-chain sulfonyl fluorides can be obtained in excellent yields; however, the yield of this fluorination decreases steadily with increasing chain-length (87% for perfluoromethane-, 79% for perfluoroethane-, 25% for perfluorooctane-, and 12% for perfluorodecanesulfonyl fluoride). Electrochemical fluorination can also be used to synthesize perfluoro-α,ω-alkanedisulfonic acid derivatives (Herkelmann and Sartori, 1989; Jüschke et al., 1997).

The electrochemical fluorination of octanesulfonyl chloride results in a number of breakdown products such as short-chain perfluoroalkanesulfonyl fluorides containing 1–7 carbon atoms, perfluorooctane and other short-chain perfluoroalkanes, SO_2F_2, SF_6, PFCAs containing 1–7 carbon atoms, as well as longer chain products (Gramstad and Haszeldine, 1957b). Typically these byproducts (for example perfluorooctane—which is a major product of the reaction) are formed by cleavage of the carbon–sulfur bond and then by cleavage of carbon–carbon bonds; however, the cleavage of the carbon–sulfur bond is not required for the breakdown of the carbon chain. The formation of PFCAs suggests the electrochemical oxidation of the perfluorocarbon chain to perfluoroalkanoic acid fluorides, which are subsequently hydrolyzed by moist air after removal from the electrolysis cell (Gramstad and Haszeldine, 1957b). As a result of the side reactions, commercially available perfluoroalkanesulfonyl fluorides such as perfluorooctanesulfonyl fluoride are complex mixtures containing only ~70% of the *n*-perfluorooctanesulfonyl compound. Consequently, all products obtained from this fluoride are also complex mixtures (see Table 2).

Compared to alkanesulfonyl fluorides and chlorides, alkanesulfonic acids are the least suitable starting materials for electrochemical fluorination. The yields of perfluoroalkanesulfonic acids obtained from the free acids are much lower compared to the alkanesulfonyl fluorides and chlorides (Gramstad and Haszeldine, 1957a,b). Another major disadvantage of this approach is the formation of water which may form explosive oxygen difluoride.

Table 2
Impurities in a commercial sample of potassium perfluorooctanesulfonate or FC-95 (Seacat et al., 2003)

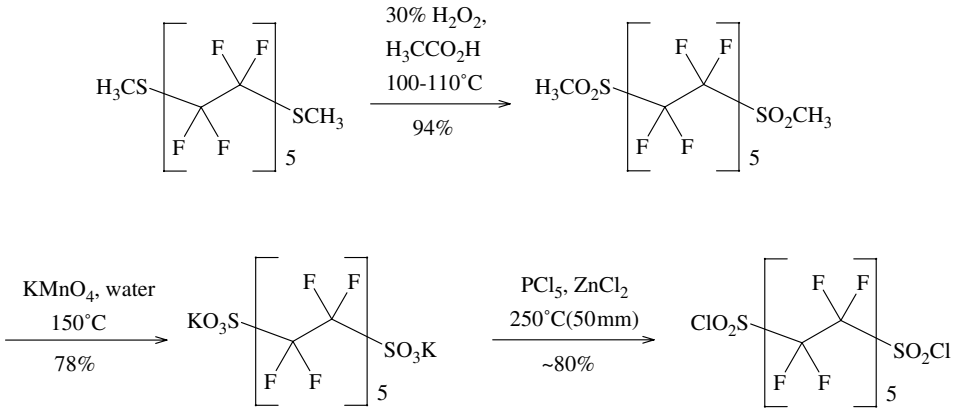
Identified impurity	Content in sample [%]
Lesser homologs (C2–C7, predominantly C6)	9.38
Metals (calcium, magnesium, sodium, nickel, iron)	1.45
Inorganic fluoride	0.59
Perfluorinated S(VI) containing compounds	0.68
Perfluorinated acids (C2, C4, C5 and C8)	0.73
Hydrocarbon sulfonate salts	0.15
Terminal cyclopentyl perfluorooctane sulfonate	0.11

The yield of the electrochemical fluorination can reportedly be improved by the addition of butadiene sulfones (Niederpruem et al., 1973). This additive is highly soluble in anhydrous HF and increases the conductivity of the electrolyte solution. Butadiene sulfone itself is fluorinated to perfluorobutanesulfonyl fluoride and, therefore, needs to be added continuously to the reaction. The use of this additive increases the yield of perfluorooctanesulfonyl fluoride by approximately 70% (Niederpruem et al., 1973). It may act by trapping radicals formed at the anode, but the mechanism by which it increases the yield of the electrochemical fluorination of long-chain sulfonic acid derivatives is still unknown.

Electrochemical fluorination of alkanesulfonamides also results in the corresponding perfluoroalkanesulfonyl fluorides (Satori and Jünger, 1996). The S–N bond undergoes quantitative fission resulting in the formation of the corresponding alkanesulfonyl fluorides which are subsequently perfluorinated. As with using the sulfonyl fluorides as starting materials, the yield of this fluorination reaction decreases with increasing chain length of the sulfonamide. Yields range from 96% for perfluoromethane sulfonamide to 40% for perfluoropropane sulfonamide.

3.1.2. Synthesis of perfluoroalkanesulfonyl chlorides

Perfluoromethanesulfonyl chloride is a common starting material for many organic reactions (Hendrickson et al., 1977). Its higher homologues, in addition to perfluotoalkanesulfonyl fluorides, are good starting materials for the synthesis of a broad variety of PFOS derivatives. Unfortunately, the long-chain (i.e. with more than 1 carbon atom) chlorides are not available from commercial sources. They can be prepared from the corresponding acid by chlorination with PCl_5 (Coffman et al., 1949; Krespan, 1979; Kamigata et al., 1984; Conte et al., 1991); however, the yield of this reaction can range from low to good (Krespan, 1979; Conte et al., 1991). $SOCl_2$ (Conte et al., 1991), $POCl_3$ (Conte et al., 1991) as well as a number of Lewis acids (Behr and Cheburkov, 2001) generally give low yields of the desired sulfonyl chloride. Instead, $SOCl_2$ can be used



Scheme 1. Synthesis of dipotassium perfluoroalkane-disulfonic acids from the corresponding dimethylthioperfluoroalkane.

to convert the hydrates of perfluoroalkanesulfonic acids into the anhydrous acid as described for 1,1,2,2-tetrafluoroethanesulfonic acid monohydrate (Coffman et al., 1949). Metal (e.g. potassium) perfluoroalkanesulfonates can be directly converted into the corresponding sulfonyl chloride using $PCl_5 \cdot 2ZnCl_2$ in an excess of $ZnCl_2$ (van Dyke Tiers, 1963; Ward, 1965; Hendrickson et al., 1977). This reaction proceeds in yields from 54–94%, and only small amounts of the perfluoroalkanesulfonic anhydride are formed. An example for the application of this chlorination reaction is shown in Scheme 1.

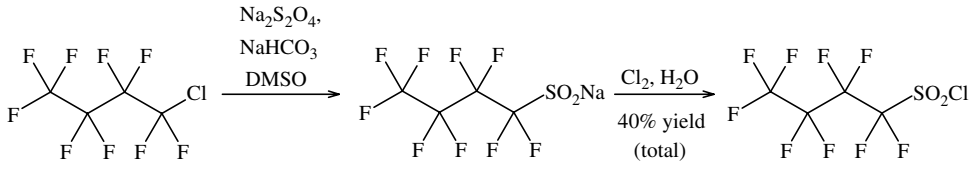
Another route to perfluoroalkanesulfonyl chlorides uses the corresponding sulfinyl derivatives as starting materials, which can be readily obtained by the reaction of perfluoroalkyl iodide (Qui and Burton, 1993), bromide (Tordeux et al., 1989) or chloride (Long and Chen, 1999) with sodium dithionite in the presence of sodium bicarbonate. Depending on the starting material, different reaction conditions and solvent systems such as acetonitrile–water (Qui and Burton, 1993), DMF-water (Tordeux et al., 1989) or DMSO (Long and Chen, 1999) have been employed for this reaction. Sodium dithionite can be replaced by hydroxymethanesulfinates such as Rongalite (sodium salt) or Decrolin (zinc salt) (Tordeux et al., 1989).

The sulfonyl chloride is prepared by passing chlorine gas through an aqueous solution of the sodium sulfinates or the corresponding acids (Harzdorf et al., 1973; Tordeux et al., 1989; Qui and Burton, 1993; Long and Chen, 1999). For example, *n*-perfluorobutanesulfonyl chloride can be synthesized from *n*-perfluorobutyl chloride in a total yield of 40% as shown in Scheme 2 (Long and Chen, 1999). Higher yields (95%) of perfluorobutanesulfonyl chloride apparently can be obtained by chlorination of the sulfinic acid itself (Harzdorf et al., 1973); however, the differences in the yields may also be due to differences in the reaction conditions. This approach is of particular interest for the synthesis of pure *n*-perfluoroalkyl sulfonyl derivatives for analytical and toxicological studies.

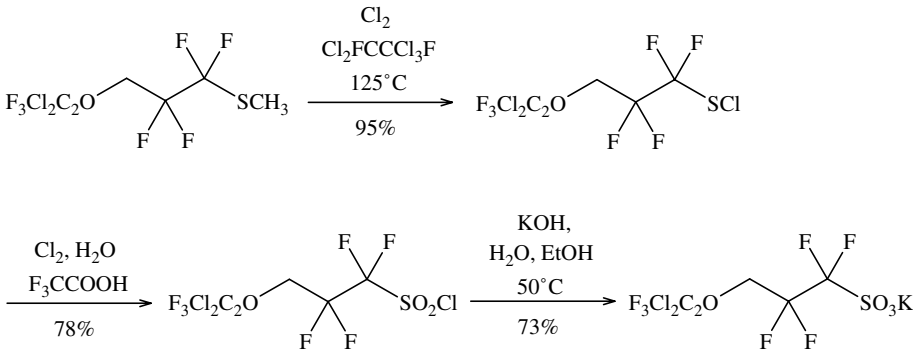
A third approach employs methyl- and benzylthioperfluoroalkanes which can be converted directly to the sulfinyl chlorides by reaction with chlorine at elevated temperatures (Nguyen and Wakselman, 1991; Feiring et al., 1999). The sulfinyl chlorides are subsequently converted into the sulfonyl chloride by treatment with chlorine in perfluoroacetic acid and water (Nguyen and Wakselman, 1991; Feiring et al., 1999) or with aqueous sodium hypochlorite (Feiring et al., 1999). An example of such a reaction sequence is shown in Scheme 3.

3.1.3. Synthesis of perfluoroalkanesulfonyl fluorides using metal fluorides

Perfluoroalkanesulfonyl chlorides are good starting materials for the synthesis of the respective fluorides. CsF (Radchenko et al., 1978) and, more commonly, KF (Benefice-Malouet et al., 1986; Qui and Burton, 1993) have been employed for this conversion. In a similar reaction, NaF has been used to convert the perfluoroalkanesulfonic



Scheme 2. Synthesis of perfluorobutanesulfonyl chloride from perfluorobutyl chloride by chlorination of the intermediate sulfinic acid.



Scheme 3. Conversion of methylthioperfluoroalkanes into the sulfonyl chloride via the sulfinyl chloride.

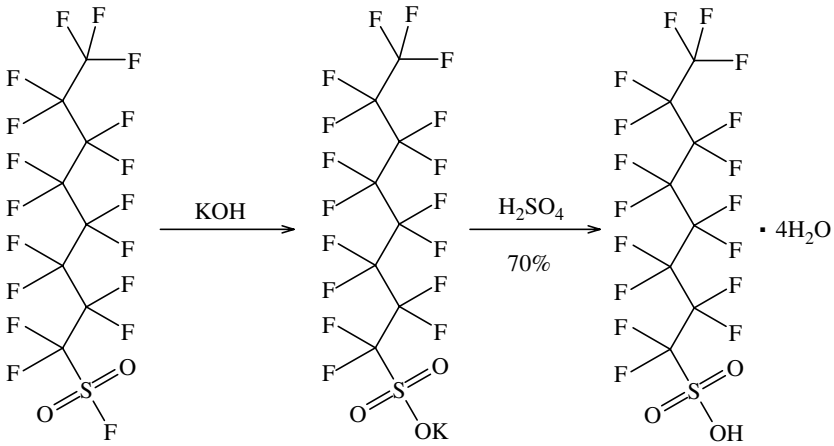
acid anhydride to the corresponding fluoride (van Dyke Tiers, 1963). The conversion of perfluoroalkanesulfonyl chlorides to fluorides is important because perfluoroalkanesulfonamides are normally obtained from the corresponding fluoride (see Section 3.3) and not from the chloride. However, homogenous perfluoroalkanesulfonyl chlorides can be more readily obtained by the dithionite route which avoids the electrochemical fluorination step. Thus, the conversion of the chloride to the fluoride may be a key step in any synthesis of pure, i.e. single chain, perfluoroalkyl sulfonamides.

3.2. Perfluorooctanesulfonic acid and its metal salts

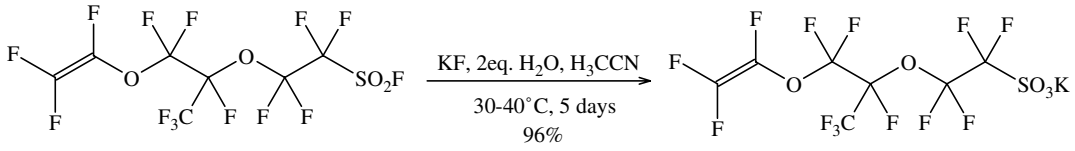
PFOS salts (for example the potassium, lithium or ammonium salts) are useful surfactants and are prepared industrially as well as in the laboratory by hydrolysis of the fluoride. Although the free acid is commercially available as a 40% aqueous solution, the pure acid is not only difficult to obtain but also corrosive. Free perfluorooctanesulfonic acid is, therefore, of little interest as an analytical standard or test compound for toxicological studies. Instead, a metal salt is commonly employed in the laboratory.

Perfluoroalkanesulfonyl fluorides are only slowly hydrolyzed by water. For example, perfluorooctanesulfonyl fluoride is minimally hydrolyzed by water at 180 °C, even after several days (Gramstad and Haszeldine, 1957b). Only partial hydrolysis of difluoromethanesulfonyl fluoride was observed after 4–5 h at 25 °C (Chen and Wu, 1990); whereas complete conversion of the same fluoride was achieved in water at room temperature over several days (Sokol'skii and Knunyants, 1961). The fact that short-chain sulfonyl fluorides are more readily hydrolyzed may be due to their higher solubility in water. In the case of difluoromethanesulfonyl fluoride, the conversion to the acid increased with increasing temperature in acetonitrile–water mixtures and complete conversion could be achieved at 80–100 °C (Chen and Wu, 1990). The presence of salts such as sodium sulfate and sodium chloride had little effect on its hydrolysis.

Because of the slow hydrolysis of the fluorides of long-chain perfluoroalkanesulfonic acids especially, the approach outlined in Scheme 4 is more suitable for the



Scheme 4. Preparation of potassium perfluorooctanesulfonic acid and perfluorooctanesulfonic acid tetrahydrate.



Scheme 5. Hydrolysis of perfluoroalkanesulfonyl fluorides using potassium fluoride in aqueous acetonitrile.

synthesis of free sulfonic acids. Potassium perfluorooctanesulfonate can be synthesized by hydrolysis of the fluoride with aqueous potassium hydroxide (Gramstad and Haszeldine, 1957b; Hebert et al., 2002). The potassium salt is only slightly water soluble (≈2% at 25 °C) and precipitates from the aqueous solution. Other bases, such as sodium hydroxide (Zhang et al., 2002), calcium hydroxide (van Dyke Tiers, 1963) and barium hydroxide (Burdon et al., 1957; Gramstad and Haszeldine, 1957b; Ignat'ev et al., 1999) in water, have also been employed to synthesize salts of perfluoroalkanesulfonic acids. $NaHCO_3$ in water/acetone is not suitable for the hydrolysis of perfluoroalkanesulfonyl fluorides (Shafer et al., 2000). Similarly, sulfonyl chlorides can be hydrolyzed in good yields to the corresponding potassium salt using KOH in ethanol–water at 50 °C (Feiring et al., 1999). In the second step shown in Scheme 4, the free acid (for example perfluorooctanesulfonic acid) can be released from the salt by treatment with concentrated sulfuric acid (Gramstad and Haszeldine, 1957b; Ignat'ev et al., 1999). The free acid can then be separated from the sulfuric acid by careful fractional distillation (Gramstad and Haszeldine, 1957b). This process is also used industrially to synthesize commercial perfluorinated sulfonic acid ionomers such as Nafion® (Shafer et al., 2000). The free acid can also be obtained using hydrochloric acid; however, in this case it is necessary to favor the perfluoroalkanesulfonic acid formation by displacing the equilibrium by NaCl removal from the reaction mixture. This can be achieved by using methanol in which NaCl is insoluble (Conte et al., 1991).

Perfluoroalkanesulfonates can also be synthesized in a KF-assisted hydrolysis reaction in acetonitrile as shown in Scheme 5 (Shafer et al., 2000). Although this reaction is slow and only two equivalents of water are used, the potassium sulfonate can be obtained in an essentially quantitative yield after filtration of unreacted KF and presumed KHF_2. The combination of KF, water and acetonitrile is necessary for the reaction to proceed. The sulfonyl fluoride shows no hydrolysis reaction in wet acetonitrile, water, or KF in dry acetonitrile. The KF is thought to activate the sulfonyl fluoride group to nucleophilic attack while the acetonitrile is necessary to solubilize the fluoride.

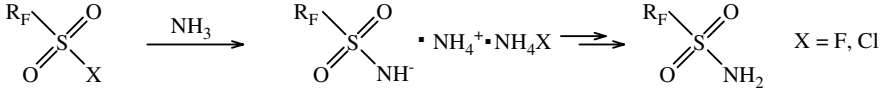
Another interesting route to perfluoroalkane-α,ω-disulfonates uses the corresponding α,ω-bis(methylthio)perfluoroalkanes as starting materials (Ward, 1965). As shown in Scheme 1 for the perfluorodecane derivative, the bismethylthio derivatives can be oxidized in good yields to the corresponding disulfones using 30% hydrogen peroxide in glacial acetic acid (Ward, 1965). The disulfones can also be obtained with chromic acid at 100 °C or by refluxing with fuming (90%) nitric acid. In a more recent publication, the oxidation of methyl- or other alkyl thioperfluoroalkanes with HOF in acetonitrile was reported (Feiring et al., 1999). Subsequent treatment of the disulfones with aqueous potassium permanganate gives the potassium salts of the corresponding perfluoroalkanedisulfonic acid. The salts can be converted into the sulfonyl chlorides by treatment with $PCl_5 \cdot 2ZnCl_2$ as described in Section 3.1.2 (van Dyke Tiers, 1963; Ward, 1965).

3.3. Synthesis of perfluoroalkanesulfonamides

3.3.1. Reaction of perfluoroalkanesulfonyl halides with ammonia

Perfluorooctanesulfonamide (Table 1) has been detected in the environment (Kannan et al., 2002a,b,d) and, most recently, in humans (Olsen et al., 2003b,d, 2004). This compound is a potent uncoupler of oxidative phosphorylation with an IC_{50} of approximately 1 μM (Starkov and Wallace, 2002) and inhibits gap junctional intercellular communication (Hu et al., 2002). Its origin in the environment is currently unknown, but very likely it is a dealkylation product of *N*-alkylated and *N*,*N*-dialkylated perfluoroalkane sulfonamides (Manning et al., 1991; Grossman et al., 1992; Tomy et al., 2004).

Perfluoroalkanesulfonamide is typically synthesized by a reaction of the corresponding perfluoroalkanesulfonyl fluoride or chloride with liquid ammonia. As illustrated in Scheme 6, initially a complex ammonium salt



Scheme 6. Reaction of perfluoroalkane sulfonyl halides with ammonia: Preparation of perfluoroalkane sulfonamides.

is formed (Roesky et al., 1970; Meußdoerffer and Niederprüm, 1972; Bussas and Kresze, 1982; Podol'skii et al., 1990). The desired amide can be isolated by dissolving this salt in dioxane and exchanging $R_FSO_2NH^-$ with Cl^- by passing anhydrous HCl through the solution. Subsequently, ammonium chloride and fluoride are filtered off to give the sulfonamide in >90% yield (Meußdoerffer and Niederprüm, 1972). A more straightforward approach utilizes the fact that the respective fluoride salts are thermally unstable. As a result, the sulfonamides can be extracted with (boiling) diethyl ether (Roesky et al., 1970; Bussas and Kresze, 1982; Podol'skii et al., 1990). When the counter ion X^- is chloride, however, the initially-formed complex salt is thermally stable (Podol'skii et al., 1990) and the isolation of the amide from the chloride salt is not possible. This fact is noteworthy because pure perfluoroalkanesulfonamides, i.e. sulfonamides containing no impurities of lesser homologues, could be synthesized via the sulfinic acid–sulfonyl chloride route outlined in Section 3.1.2. For such a synthesis it might be advantageous to convert the chloride into the fluoride before preparing a sulfonamide derivative (see Section 3.1.3).

3.3.2. Synthesis of perfluoroalkanesulfonamides from the corresponding sulfonyl fluoride via the azide

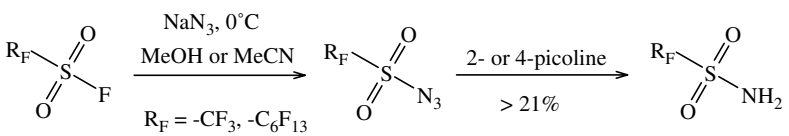
Another synthesis of perfluoroalkanesulfonamides employs the corresponding azides as an intermediate. This approach may be useful for the synthesis of ^{15}N labeled sulfonamides. Perfluoroalkanesulfonyl azide can be conveniently prepared in good yields by the reaction of the corresponding fluoride or chloride with sodium azide in methanol or acetonitrile at 0 °C or ambient temperature (Beyer and Thieme, 1966; Volkov et al., 1979; Kamigata et al., 1985; Zhu, 1992; Xu and Zhu, 1999). The azides are colorless liquids with a characteristic pungent odor (Zhu, 1992). They are stable at room temperature but decompose at 120 °C. A variety of reactions of perfluoroalkanesulfonyl azide, e.g. with pyridine and other unsaturated compounds (Zhu, 1992; Xu and Zhu, 1999, 2001) or during irradiation (Zhu, 1994), sometimes results in the formation of considerable amounts of the respective sulfonamide as a byproduct (Zhu, 1992; Xu and Zhu, 1999, 2001), thus suggesting the use of perfluoroalkanesulfonyl azides as starting materials for sulfonamides. Indeed, in the presence of hydrogen donors such as 2- and 4-picoline, the thermal decomposition of the azide results in the formation of the respective perfluoroalkanesulfonamide in good yield as shown in Scheme 7 (Xu and Zhu, 1999). Alternatively, the azides can be converted into the corresponding perfluoroalkanesulfonamides by reduction with hydrogen sulfide (Volkov et al., 1979) or zinc/ethanol (Zhu et al., 2001).

3.4. Alkylated perfluoroalkanesulfonamides

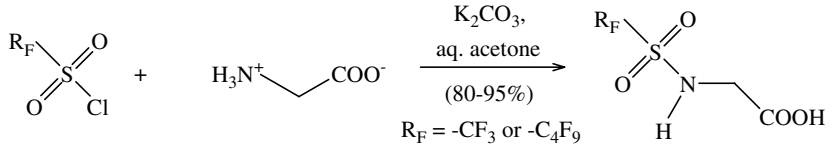
Alkylated perfluoroalkanesulfonamides such as *N*-alkyl perfluorooctanesulfonamide and *N*-alkyl perfluorooctanesulfonamidoethanol are industrial chemicals used as active ingredients in pesticides and for the surface treatment of a variety of consumer products (Table 1). They have been found in air samples in Canada (Martin et al., 2002) and in human serum (Olsen et al., 2003b,d, 2004). This class of compounds is generally considered to be one possible precursor for PFOS in the environment. Synthetic routes to these compounds are, therefore, of considerable interest.

3.4.1. N-substituted perfluoroalkanesulfonamides

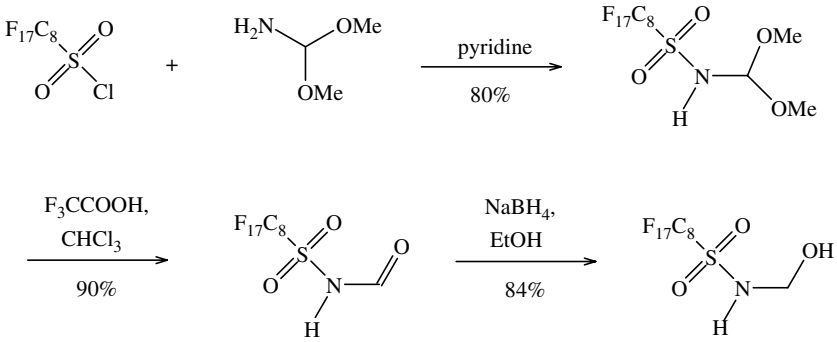
Similar to the sulfonamides, *N*-functionalized perfluoroalkanesulfonamides are typically synthesized by the reaction of the sulfonyl fluoride or chloride with the corresponding primary amine in the presence of a base. This can be accomplished using a broad range of solvents and reaction conditions—for example in water or aqueous DMF in the presence of equimolar amounts of sodium or potassium hydroxide (DeChristopher et al., 1974; Benefice-Malouet et al., 1986), in an organic solvent such as THF (Takeuchi et al., 1997), diethyl ether (Trepka et al., 1974; Kas'yan et al., 1997) or dichloromethane (Cho and Chun, 1999) with an organic base, or by direct reaction of excess amine with the neat sulfonyl fluoride (Roesky et al., 1970; Zhu et al., 1994). Yields are generally good to excellent (70–90%). Similar to the synthesis of sulfonamides (Section 3.3.1), an ammonium salt is formed initially during this reaction. The *N*-alkyl perfluoroalkane sulfonamide can be separated from the salt after acidification with concentrated hydrochloric or sulfuric acid in good yield (DeChristopher et al., 1974; Zhu et al., 1994). This approach has also been employed to synthesize sulfonamidoacetates from the corresponding sulfonyl chloride as shown in Scheme 8 (Supuran and Scozzafava, 2000). Aqueous acetone is used as a solvent while a variety of bases such as $NaHCO_3$, $KHCO_3$, NaOH or Et_3N can be employed



Scheme 7. Preparation of perfluoroalkane sulfonamides via the azide.



Scheme 8. Synthesis of perfluoroalkane sulfonamidoacetates from the corresponding sulfonyl chloride and glycine.



Scheme 9. Synthesis of perfluorooctanesulfonamidoethanol from perfluorooctanesulfonyl fluoride and aminoacetaldehyde dimethylacetal.

as a base. In spite of the fact that this is a heterogeneous reaction, the yields are >80%.

The reaction of perfluorooctanesulfonyl fluoride with a primary amine has been employed in the synthesis of perfluorooctanesulfonamidoethanol as outlined in Scheme 9 (Xu et al., 2004). Reaction of perfluorooctanesulfonyl fluoride with aminoacetaldehyde dimethylacetal in anhydrous pyridine yields the *N*-(2,2-dimethoxyethyl)-perfluorooctanesulfonamide. The dimethylacetal is converted into the respective aldehyde with perfluoroacetic acid in chloroform. Subsequent reduction with sodium borohydride in ethanol yields the desired perfluorooctanesulfonamidoethanol. All three reaction steps yield the desired product in good-to-excellent yields (80–90%). However, each product was purified by column chromatography on silica gel using an ethyl acetate-hexane based mobile phase, which is tedious and time consuming.

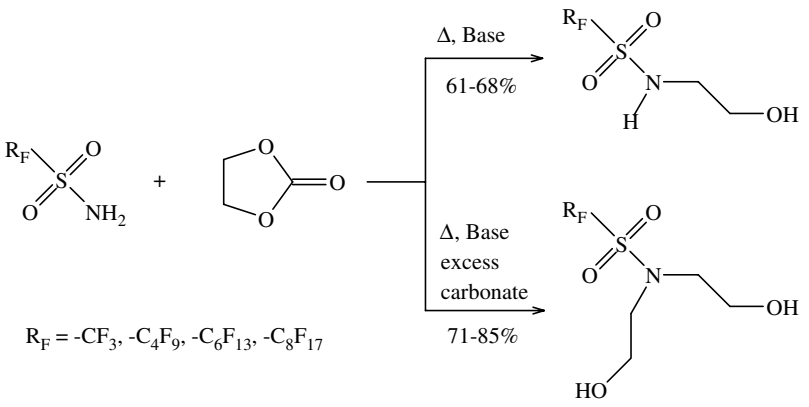
Interestingly, there are discrepancies in the literature with regard to the reaction of ethanol amine and related derivatives with perfluoroalkyl sulfonyl fluorides. This reaction is reported to directly result in the corresponding perfluorooctanesulfonamidoethanol derivatives (Ohtoshi, 1989). However, according to Niederprum and co-workers (Niederpruem et al., 1973), the reaction of ethanol amine with perfluoroalkanesulfonyl fluorides results in the formation of several products that cannot be separated. One possible side reaction is the intermediate formation of sulfonyl esters (Gramstad and Haszeldine, 1957a). This previous report is in agreement with our own futile attempts to synthesize sulfonamidoethanols directly from ethanol amine and perfluorooctanesulfonyl fluoride.

Only one monoalkylation of unsubstituted perfluoroalkane sulfonamides has been reported in the literature (Niederpruem et al., 1973). The desired sulfonamidoethanol can be obtained by the reaction of a sulfonamide with one equivalent of ethylene carbonate at elevated temperatures in the presence of a base, e.g. potassium hydroxide, pyridine, triethylamine or potassium carbonate. As shown in Scheme 10, the bisalkylation product is obtained under the same reaction conditions if an excess of ethylene carbonate is employed. The yield of this reaction is generally >60%. This reaction is highly suitable for the synthesis of environmentally relevant sulfonamidoethanols; however, in our laboratory this reaction did not result in the desired products (Nauduri and Lehmler, unpublished results).

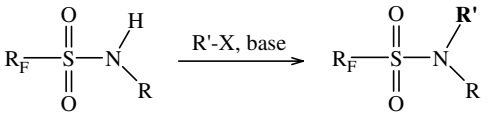
3.4.2. N-Alkylation of N-substituted perfluoroalkanesulfonamides

N-Substituted perfluoroalkanesulfonamides can be further modified by alkylating the N–H group using a variety of reagents as shown in Scheme 11. This methodology has been most frequently employed for the synthesis of perfluoromethanesulfonamides, but can also be adapted for the synthesis of compounds with a longer perfluorinated tail.

The *N*-alkylation of *N*-substituted perfluoroalkanesulfonamide with alkylhalogenides (or benzyl halogenides) can readily be achieved with K_2CO_3 in acetone



Scheme 10. Alkylation of perfluoroalkane sulfonamides with (*i*) one equivalent or (*ii*) excess ethylene carbonate.

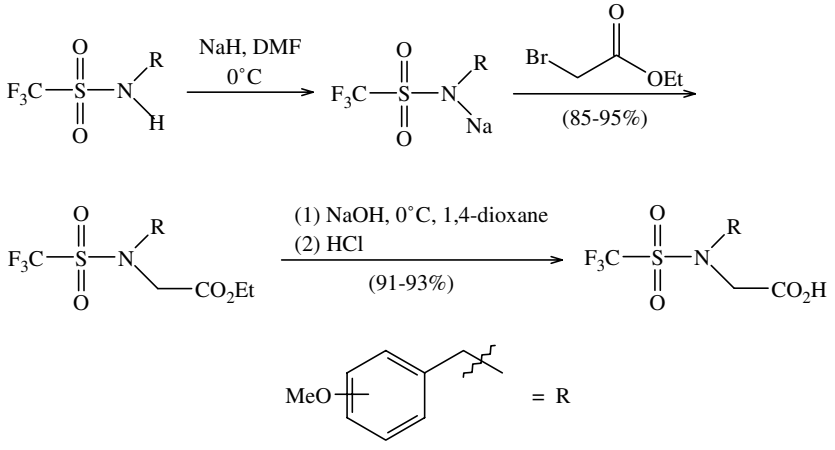


Scheme 11. *N*-alkylation of *N*-substituted perfluoroalkane sulfonamides.

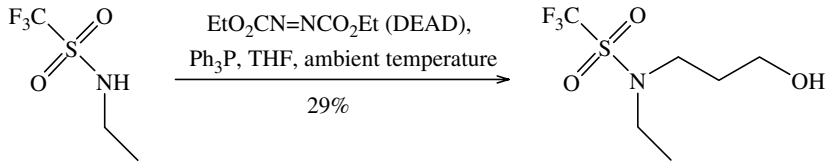
at ambient temperature (Hendrickson et al., 1975; Harris et al., 1993; Ostwald et al., 1994; Dohle et al., 2001). Reported yields are generally >95%. Alternatively, the alkylation reaction can be performed in acetonitrile with triethylamine as a base (Supuran and Scozzafava, 2000). This approach can be adopted for the synthesis of hydroxyalkyl and carboxylic acid derivatives of environmental interest. For example, *N*-benzyl-perfluoromethanesulfonamide can be alkylated by chloroalkanols such as 3-chloropropanol using K_2CO_3 and NaI in DMF (50 °C, 18 h, 71% yield) (Lutz et al., 1998). Alternatively, NaOMe may be useful as a base for this reaction (Lu et al., 1985). This reaction has also been employed by 3M to manufacture sulfonamidoethanols.

Unsymmetrical disubstituted sulfonamides with a carboxylic acid function can also be synthesized by alkylation of *N*-alkyl perfluoroalkanesulfonamides. The *N*-benzyl sulfonamide is converted into the sodium salt with a strong base such as NaH (Kawase et al., 1997) or NaOEt (Lyapkalo et al., 2002), respectively. Alkylation of the sodium salt with ethyl bromoacetate in DMF proceeds rapidly with yields between 85 and 97%. The carboxylic acid is obtained by saponification with NaOH in dioxane (e.g., Scheme 12).

Finally, the Mitsunobu reaction is another approach that has been employed to synthesize unsymmetrical *N*,*N*-dialkylated perfluoroalkanesulfonamides. The Mitsunobu reaction has the advantage that alcohols instead of alkyl halogenides can be used as starting materials. For example methyl- (Edwards et al., 1990) and



Scheme 12. Synthesis of *N*-substituted perfluoroalkane sulfonamideacetates.



Scheme 13. Preparation of *N*-alkyl perfluoroalkane sulfonamidoalkanols using the Mitsunobu reaction.

2-methylpropyl-groups (Bell et al., 1995) have been introduced in good yields using the Mitsunobu reaction. Another example for the potential usefulness of the Mitsunobu reaction is the synthesis of *N*-Ethyl perfluoromethanesulfonamidopropanol outlined in Scheme 13. In this reaction the sulfonamide is obtained in 29% yield by reacting *N*-ethyl-perfluoromethanesulfonamide with a twofold excess of the corresponding diol using DEAD (diethyl azodicarboxylate) and triphenylphosphine in THF (Edwards et al., 1990). The yield of this reaction may be increased by further optimizing the reaction conditions or by using different, more reactive reagents such as *N*,*N*,*N*′,*N*′-tetramethyl azidodicarboxamide (TMAD) and tributylphoshpine (Bell et al., 1995). Until now this reaction has only been employed to synthesize *N*,*N*-dialkylated perfluoromethanesulfonamides, but it can probably be extended to the synthesis of long-chain *N*,*N*-dialkylated sulfonamides and it may be useful for the synthesis of radiolabeled sulfonamidoethanols.

3.4.3. Synthesis of N,N-dialkyl perfluoroalkanesulfonamides

N,*N*-dialkyl perfluoroalkanesulfonamides (Table 1) can also be obtained in a single step by reacting a secondary amine with the respective perfluoroalkanesulfonyl fluoride (Chen and Qiu, 1986; Huang et al., 1987b; Katritzky et al., 1988; Lyapkalo et al., 2002; Roesky et al., 1970). Excess amine usually functions as a base in these reactions; but in some cases, the amine has been converted into the lithium salt by treatment with BuLi before the reaction with the fluoride (Lyapkalo et al., 2002). The yields of these reactions are typically acceptable to excellent.

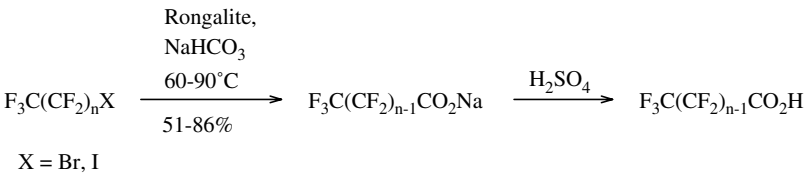
There are only two direct bisalkylations of perfluoroalkanesulfonamides reported in the literature. Perfluoroalkanesulfonamides react with excess ethylene carbonate in the presence of a base to yield the bis(hydroxyethyl)sulfonamides (>61% yield) as shown in Scheme 10 (Niederpruem et al., 1973). The bismethylated sulfonamides were also obtained by alkylation of a sulfonamide with methyl iodide in DMF in the presence of KOH and CS_2 (Li et al., 1994). Instead of the desired carbodithioimidates, the *N*,*N*-dimethylamide was isolated in 76% yield. This is a interesting reaction because of earlier reports that the monoalkylation of perfluoroalkyl sulfonamides does not proceed cleanly (Hendrickson et al., 1975).

3.5. Purification of perfluoroalkanesulfonic acid salts and perfluoroalkanesulfonamides

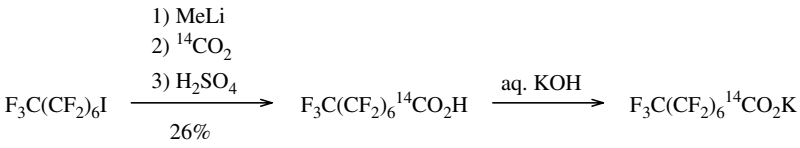
As discussed in Section 3.1.1, technical perfluorooctanesulfonyl fluoride can be considered as a complex mixture of different sulfonyl fluorides. This is the result of its production, the electrochemical fluorination process. Products derived from perfluorooctanesulfonyl fluoride are therefore also complex mixtures as shown in Table 2. This applies to industrial products as well as to compounds synthesized in the laboratory; however, for toxicological and analytical studies, it is important to have access to pure (i.e., free of linear and branched homologues) samples of perfluorooctanesulfonic acid and its derivatives. It is, therefore, surprising that only a few attempts have been made to purify products obtained from technical grade perfluorooctanesulfonyl fluoride.

We have recently synthesized potassium perfluorooctane sulfonate and explored several methods to purify this salt. Column chromatography on silica gel did not improve the purity, whereas, treatment with charcoal or heating under vacuum significantly improved the purity of the product (Nauduri and Lehmler, unpublished results). Alternatively, the potassium salt can be purified by several recrystallizations from hot water (Hebert et al., 2002). This will remove most sulfonic acid salts with a shorter chain length due to their higher water solubility. Overall, recrystallization appears to be a highly suitable and straightforward approach to purify PFOS derivatives.

Another approach has been reported for a piperazine derivative of perfluorooctanesulfonic acid which was purified by chromatography at high loading on basic alumina followed by recrystallization from hexane (Katritzky et al., 1988). Although this clean-up resulted in a material that was homogenous in terms of its physical properties (i.e., melting point and chromatographic behavior), still 10% of branched homologues were present. Column chromatography on silica gel has also been successfully employed to purify perfluorooctanesulfonamidoethanol and its precursors (Xu et al., 2004). Columns of PFOS derivatives can be conveniently monitored either by gas chromatography or thin layer chromatography using chloroplatinic acid as a chromatographic spray reagent (Wong, 1971).



Scheme 14. Synthesis of perfluoroalkanoic acids from perfluoroalkyl iodides using Rongalite-$NaHCO_3$ as an oxidizing agent.



Scheme 15. Synthesis of perfluorooctanoic-1-^{14}C acid from perfluoroheptyl iodide and $^{14}CO_2$.

4. Synthesis of perfluorinated carboxylic acids and their metal salts

4.1. Synthesis of perfluorinated carboxylic acids by electrochemical fluorination

Perfluorooctanoic acid (Fig. 1) and related carboxylic acids can be synthesized by electrochemical fluorination of the corresponding carboxylic acid (Kissa, 2001); however, the yield of this reaction is only 10–20%. Slightly higher yields can be obtained by fluorination of the corresponding anhydrides. For example, acetic acid and acetic acid anhydride form perfluoroacetyl fluoride in a 17% and 32% yield, respectively. One major disadvantage of this approach is the formation of water which may form explosive oxygen difluoride. In addition, the electrochemical fluorination of acids with $\geqslant 6$ carbon atoms results in the formation of cyclic perfluoroethers and other byproducts. This process was, therefore, not useful for the industrial synthesis of PFCAs.

Better yields can be obtained when carboxylic acid chlorides or fluorides are fluorinated instead of the free acid (Kissa, 2001). For example, the fluorination of acetyl fluoride yields 76% of perfluoroacetyl fluoride following the general reaction scheme:

$$C_nH_{2n+1}COF + (2n+1)F^- \xrightarrow{HF} C_nF_{2n+1}COF + (2n+1)H^+ + (4n+2)e^-$$

The yield of the fluorination decreases with increasing chain length of the starting material. The yield is also lower when the readily-available acid chlorides, and not the fluorides, are employed as starting materials. The perfluoroalkanoic acid fluorides are useful starting materials for the synthesis of esters, amides, or other intermediates for surfactants. Hydrolysis of the acid fluorides results in either the free carboxylic acids or the respective metal, e.g. potassium and ammonium, salts. Due to the environmental concerns outlined in Section 1.2 the 3M Corporation discontinued manufacturing of PFOA using electrochemical fluorination between the years of 2000 and 2002.

4.2. Miscellaneous syntheses of perfluorinated carboxylic acids

Several laboratory syntheses of perfluoroalkanoic acids have been reported. These include photooxidation of the corresponding sulfinyl derivatives (Hu et al., 1989) and reaction of perfluoroalkyl iodides with alkynes in the presence of urease or catalase (Kitazume and Ikeya, 1988). Perfluoroalkanoic acids can also be synthesized from perfluoroalkyl iodides using strong oxidizing agents such as chlorosulfonic acid (Hauptschein and Braid, 1961a), fluorosulfonic acid (Hauptschein and Braid, 1961b) or a halogen fluorosulfate (Shack and Christe, 1980). Good-to-excellent yields of perfluoroalkanoic acids with 3–12 carbon atoms can be obtained by the oxidation of primary perfluoroalkyl bromides or iodides with a Rongalite ($HO–CH_2–SO_2Na$)–$NaHCO_3$ reagent in aqueous dipolar aprotic solvents such as DMSO and DMF (Huang et al., 1987a). The general reaction scheme for this synthesis is shown in Scheme 14. Perfluoroalkanoic acids can also be synthesized by extension of perfluoroalkyl iodides by one carbon atom. As shown in Scheme 15, perfluorooctanoic-1-^{14}C acid was synthesized by lithiation of perfluoroheptyl iodide at -100 °C followed by carbonation with $^{14}CO_2$ (Reich et al., 1987). The resulting acid was converted into the corresponding potassium salt by heating under reflux in aqueous KOH.

5. Synthesis of fluorotelomers

5.1. Telomerization of tetrafluoroethylene

Typical precursors of perfluorinated materials can not only be synthesized by electrochemical fluorination

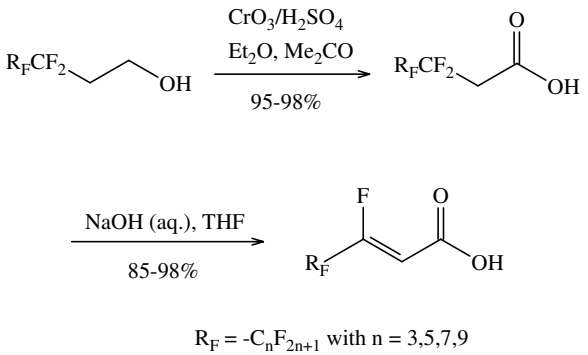
(see Sections 3.1.1 and 4.1), but also by radical telomerization of fluoroalkenes such as vinylidene fluoride, tetrafluoroethylene, chlorotrifluoroethylene, trifluoroethylene and hexafluoropropene (Ameduri and Boutevin, 1997; Kissa, 2001). Telomerization is defined as a radical process by which a telogen such as perfluoroethyl iodide reacts with one or more unsaturated molecules called taxogens, for example tetrafluoroethylene. A simplified commercial telomerization process is outlined in Fig. 3. The first step is the synthesis of the telogen, perfluoroethyl iodide, by reacting tetrafluoroethylene with IF_5 and I_2 (Kissa, 2001). Telomerization of tetrafluoroethylene with perfluoroethyl iodide results in a mixture of even-carbon-numbered telomers of the general structure $F(CF_2CF_2)_{n+1}I$. The chemistry of the resulting perfluoroalkyl iodides is limited and further functionalization to intermediates useful for the synthesis of surfactants (for example alcohols or amines) is not possible. The perfluoroalkyl iodides are, therefore, reacted in a radical coupling with ethylene resulting in 1H,1H,2H,2H-perfluoroalkyl iodides of the general formula $F(CF_2CF_2)_{n+1}CH_2CH_2I$. These iodides are converted into olefins, fluorinated carboxylic acids, fluorotelomer alcohols (FTOHs), and other fluorinated intermediates.

It is important to note that industrial telomerization typically results in intermediates with an even number of carbon atoms. For example, odd-numbered perfluoroalkyl iodides are not readily available from commercial sources. It is possible to prepare odd-numbered perfluoroalkyl iodides using the photochemical reaction of perfluoromethyl iodide with tetrafluoroethylene (Haszeldine, 1953). Overall, these telomerization reactions cannot easily be performed in the laboratory because of the volatility of the starting materials/products and because the resulting mixture of perfluoroalkyl iodides is difficult to separate.

5.2. Laboratory synthesis of environmentally relevant FTOHs and related compounds

As summarized in Fig. 2, fluorotelomer alcohols such as 1H,1H,2H,2H-perfluorodecanol are biodegraded via a 1H,2H,2H-perfluoroalkanal to the corresponding 2H,2H-perfluoroalkanoic acid. Another metabolite is a α,β-unsaturated carboxylic acid of the general structure $R_FCF{=}CHCOOH$. This section gives a short overview of the laboratory synthesis of these metabolites and their homologues.

All FOTHs are available in good purity from commercial sources and only a few synthetic routes to these alcohols have been reported in the literature. Typically an intermediate of the production scheme shown in Fig. 3 is used as starting material for the laboratory synthesis of FTOHs. For example, 1H,1H,2H,2H-perfluoroalkyl iodides can be converted into the alcohols



$R_F = -C_nF_{2n+1}$ with n = 3,5,7,9

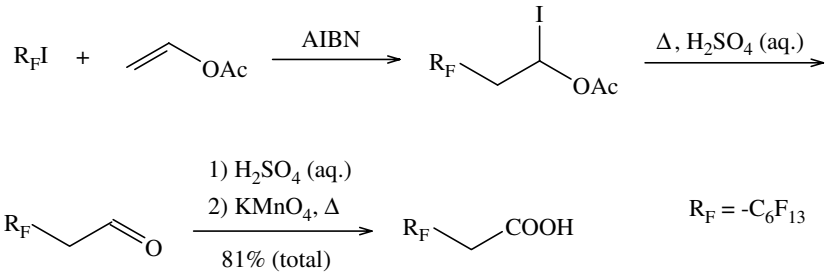
Scheme 16. Synthesis of 2H,2H-perfluoroalkyl carboxylic acids via oxidation of a FTOH using Jones' reagent.

using metallic zinc–copper couple in butyl phosphate followed by oxidation of the resulting organo-zinc compound (Blancou et al., 1983). Other approaches utilize the hydroboration of 1H,1H,2H-perfluoro-1-alkenes (Brown et al., 1999; Ramachandran et al., 1999; Ramachandran and Jennings, 2002).

1H,2H,2H-Perfluoroalkanals, initially formed during the biodegradation of FTOHs, can be synthesized by oxidation of commercially available alcohols using the Dess-Martin periodinane (Leveque et al., 1998; Rocaboy et al., 2000). Oxidation of fluorinated alcohols using pyridinium chlorochromate and $DMSO/(COCl)_2$ is less straightforward because of the formation of an α,β-unsaturated aldehyde as a byproduct (Leveque et al., 1998). The corresponding 2H,2H-perfluoroalkyl carboxylic acids can be synthesized from the corresponding alcohols using Jones' reagent as shown in Scheme 16 (Achilefu et al., 1995). The acid can be readily converted into the α,β-unsaturated acid, e.g. 2H-perfluoro-2-decenoic acid (see Fig. 2 for the structure), with aqueous NaOH in THF (Dinglasan et al., 2004).

1H,2H,2H-perfluoroalkanals and 2H,2H-perfluoroalkanoic acids can be synthesized using perfluoroalkyl iodides as starting materials (Huang et al., 1990; Laurent et al., 1992; Napoli et al., 1994). This approach employs the well-established radical addition of the perfluoroalkyl iodides to an appropriately functionalized vinyl compound (Brace, 1962, 1972, 1982). In the example shown in Scheme 17 perfluorohexyl iodide is added to vinyl acetate. The resulting adduct is hydrolyzed to the aldehyde and oxidized with $KMnO_4$ to the desired acid.

Depending on the reaction conditions, 2H,2H-perfluoroalkyl carboxylic acids and their α,β-unsaturated analogues can be synthesized from perfluoroalkylated β-bromoacetates (Jedidi Yaich et al., 2002). Conversion of the respective β-bromoacetates into the bromozinc derivatives followed by hydrolysis yields 2H,2H-perfluoroalkanoic acids in 68–78%. The α,β-unsaturated acids are obtained in a 68–72% yield by the heating of the bromozinc derivatives at 110 °C.



Scheme 17. Synthesis of 2H,2H-perfluoroalkyl carboxylic acids from perfluoroalkyl iodides.

6. Conclusions

The chemistry of industrial-grade PFOS derivatives, PFCAs and FTOHs can be considered to be well developed. This may seem to be a surprising statement but it applies only to the manufacturing of these compounds on an industrial scale. As a result of their industrial importance, their synthesis is proprietary information and has never been published. The literature describing their synthesis on a laboratory scale, however, is very limited, and in some cases, the synthetic procedures reported in the literature appear to be conflicting. The synthesis of PFOS derivatives, in particular, is a challenge for the synthetic chemist. Since they are highly impure materials of industrial origin, perfluoroalkanesulfonyl fluorides are only of limited usefulness as starting materials for the PFOS derivatives needed as test compounds and analytical standards. One possible approach outlined in Section 3.1.2 is the synthesis of perfluoroalkanesulfonyl fluorides from the corresponding perfluoroalkyl iodides via the sulfinic acids and the chloride. Although this approach has not been employed for the synthesis of PFOS and its derivatives, it has been utilized for the synthesis of related compounds. In addition, the starting materials are highly pure (i.e. do not contain (branched) impurities). The synthesis of short chain analogs (i.e., perfluoromethane) of perfluoroalkanesulfonamides is well established in the literature and could be utilized to synthesize a variety of sulfonamides of interest such as radiolabeled compounds for metabolism and other studies (Sections 3.3 and 3.5); however, the properties of perfluorinated compounds change drastically with increasing length of the perfluoroalkyl chain and generalizations of the synthetic approaches outlined in this article should be avoided.

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References

Achilefu, S., Mansuy, L., Selve, C., Thiebaut, S., 1995. Synthesis of 2H,2H-perfluoroalkyl and 2H-perfluoroalkenyl carboxylic acids and amides. J. Fluorine Chem. 70, 19–26.

Alexander, B.H., Olsen, G.W., Burris, J.M., Mandel, J.H., Mandel, J.S., 2003. Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. Occup. Environ. Med. 60, 722–729.

Ameduri, B., Boutevin, B., 1997. Telomerization reactions of fluorinated alkenes. Top. Curr. Chem. 192, 165–233.

Arora, M., Bummer, P.M., Lehmler, H.-J., 2003. Interaction of a partially fluorinated heptadecanoic acid with diacyl phosphatidylcholines of varying chain length. Langmuir 19, 8843–8851.

Austin, M.E., Kasturi, B.S., Barber, M., Kannan, K., MohanKumar, P.S., MohanKumar, S.M., 2003. Neuroendocrine effects of perfluorooctane sulfonate in rats. Environ. Health Perspect. 111, 1485–1489.

Banks, R.E., 1970. Fluorocarbons and their Derivatives. MacDonald, London.

Behr, F.E., Cheburkov, Y., 2001. A Lewis acid catalytic process for preparing fluorocarboxylic acid halides. J. Fluorine Chem. 112, 369–372.

Bell, K.E., Knight, D.W., Gravestock, M.B., 1995. *N*-benzyltriflamide: a generally useful Mitsunobu reagent for the amine synthesis. Tetrahed. Lett. 36, 8681–8684.

Benefice-Malouet, S., Blancou, H., Teissedre, R., Commeyras, A., 1986. Mise au point d'un procede de preparation catalytique de perfluoroalkyl sulfonamide par addition d'ethylamine a un chlorure d'acide perfluoroalcane sulfonique. J. Fluorine Chem. 31, 319–332.

Berthiaume, J., Wallace, K.B., 2002. Perfluorooctanoate, perflourooctanesulfonate, and *N*-ethyl perfluorooctanesulfonamido ethanol; peroxisome proliferation and mitochondrial biogenesis. Toxicol. Lett. 129, 23–32.

Beyer, H., Thieme, E., 1966. 1,3-Dipolar addition to pyridinium and isoquinolinium betaines. J. Prakt. Chem. 31, 293–303.

Blancou, H., Benefice, S., Commeyras, A., 1983. Methode quantitative pour la preparation de perfluoroalcoyl-ethanol $R_FCH_2CH_2OH$ a partir de perfluoroalcoyl-2 iodo-1 ethane $R_FCH_2CH_2I$ ($R_F = C_nF_{2n+1}$, *n* pair). J. Fluorine Chem. 23, 57–65.

Boudreau, T.M., Sibley, P.K., Mabury, S.A., Muir, D.G., Solomon, K.R., 2003a. Laboratory evaluation of the toxicity of perfluorooctane sulfonate (PFOS) on *Selenastrum capricornutum*, *Chlorella vulgaris*, *Lemna gibba*, *Daphnia magna*, and *Daphnia pulicaria*. Arch. Environ. Contam. Toxicol. 44, 307–313.

Boudreau, T.M., Wilson, C.J., Cheong, W.J., Sibley, P.K., Mabury, S.A., Muir, D.C., Solomon, K.R., 2003b. Response of the zooplankton community and environmental fate of perfluorooctane sulfonic acid in aquatic microcosms. Environ. Toxicol. Chem. 22, 2739–2745.

Boulanger, B., Vargo, J., Schnoor, J.L., Hornbuckle, K.C., 2004. Detection of perfluorooctane surfactants in Great Lakes Water. Environ. Sci. Technol. 38, 4064–4070.

Brace, N.O., 1962. Long chain alkanoic and alkenoic acids with perfluoroalkyl terminal segments. J. Chem. Soc., 4491–4498.

Brace, N.O., 1972. Relative reactivities and stereochemistry of addition of iodoperfluoroalkanes to cyclic olefins. J. Org. Chem. 37, 2429–2433.

Brace, N.O., 1982. Some approaches to the synthesis of fluorinated alcohols and esters. II. Use of F-alkyl iodides for the synthesis of F-alkyl alkanols. J. Fluorine Chem. 20, 313–327.

Brown, H.C., Chen, G.-M., Jennings, M.P., Ramachandran, P.V., 1999. Markovnikov hydroboration of perfluoroalkylethylenes. Angew. Chemie Int. Ed. 38, 2052–2054.

Burdon, J., Farazmand, I., Stacey, M., Tatlow, J.C., 1957. Fluorinated sulphonic acids. Part I. Perfluoro-methane-, -octane-, and -decane-sulphonic acids and their simple derivatives. J. Chem. Soc., 2574–2578.

Bussas, R., Kresze, G., 1982. Synthese von 2-Alkensulfinamiden—Struktur–Reaktivitäts–Beziehungen für *N*-Sulfinylverbindungen als Enophile. Liebigs Ann. Chem., 545–563.

Case, M.T., York, R.G., Christian, M.S., 2001. Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. Int. J. Toxicol. 20, 101–109.

Chen, Q.-Y., Wu, S.-W., 1990. An improved method for synthesizing difluoromethanesulfonic acid. J. Fluorine Chem. 47, 509–514.

Chen, Q.-Y., Qiu, Z.-M., 1986. Studies on fluoroalkylation and fluoroalkoxylation. Part 10. Electron-transfer-induced reactions of perfluoroalkyl iodides and the dialkyl malonate anion and β-fragmentation of the halotetrafluoroethyl radical. J. Fluorine Chem. 31, 301–317.

Cho, B.T., Chun, Y.S., 1999. Catalytic enantioselective reactions. Part 12. Enantioselective addition of diethylzinc to aldehydes catalyzed by zinc complexes modified with chiral β-sulfonamido alcohols. Synth. Commun. 29, 521–531.

Coffman, D.D., Raasch, M.S., Rigby, G.W., Barrick, P.L., Hanford, W.E., 1949. Addition reactions of tetrafluoroethylene. J. Org. Chem. 14, 747–753.

Conte, L., Napoli, M., Scipioni, A., Guerrato, A., 1991. A new method for recovering waste alkaline perfluoro-*n*-butanesulfonate. J. Fluorine Chem. 53, 277–283.

Curran, D.P., 2003. A bird's eye view of fluorous reaction and separation techniques. Actual. Chim., 67–71.

DeChristopher, P.J., Adamek, J.P., Lyon, G.D., Klein, S.A., Baumgarten, R.J., 1974. Simple deaminations. V. Preparation and some properties of *N*-alkyl-*N*,*N*-disulfonimides. J. Org. Chem. 39, 3525–3532.

Derbel, M., Hosokawa, M., Satoh, T., 1996. Differences in the induction of carboxylesterase RL4 in rat liver microsomes by various perfluorinated fatty acids, metabolically inert derivatives of fatty acids. Biol. Pharm. Bull. 19, 765–767.

Dinglasan, M.J.A., Ye, Y., Edwards, E.A., Mabury, S.A., 2004. Fluorotelomer alcohol biodegradation yields poly- and perfluorinated acids. Environ. Sci. Technol. 38, 2857–2864.

Dohle, W., Kopp, F., Cahiez, G., Knochel, P., 2001. Fe(III)-catalyzed cross-coupling between functionalized arylmagnesium compounds and alkenyl halides. Synlett, 1901–1904.

Edwards, M.L., Stemerick, D.M., McCarthy, J.R., 1990. Stereospecific synthesis of secondary amines by the Mitsunobu reaction. Tetrahed. Lett. 31, 3417–3420.

Ellis, D.A., Martin, J.W., De Silva, A.O., Mabury, S.A., Hurley, M.D., Sulbaek, A.M.P., Wallington, T.J., 2004. Degradation of fluorotelomer alcohols: a likely atmospheric source of perfluorinated carboxylic acids. Environ. Sci. Technol. 38, 3316–3321.

Ellis, D.A., Martin, J.W., Mabury, S.A., Hurley, M.D., Andersen, M.P.S., Wallington, T.J., 2003. Atmospheric lifetime of fluorotelomer alcohols. Environ. Sci. Technol. 37, 3816–3820.

Endres, A., Maas, G., 2000. The fluorous phase: organic chemistry with highly fluorinated reagents and solvents. Chem. Unserer Zeit 34, 382–393.

Feiring, A.E., Wonchoba, E.R., Rozen, S., 1999. Synthesis of partially fluorinated monomers and polymers for ion-exchange resins. J. Fluorine Chem. 93, 93–101.

Giesy, J.P., Kannan, K., 2001. Global distribution of perfluorooctane sulfonate in wildlife. Environ. Sci. Technol. 35, 1339–1342.

Gramstad, T., Haszeldine, R.N., 1957a. Perfluoroalkyl derivatives of sulfur. VII. Alkyl trifluoromethanesulfonates as alkylating agents, trifluoromethanesulfonic anhydride as a promoter for esterification, and some reactions of trifluoromethanesulfonic acid. J. Chem. Soc., 4069–4079.

Gramstad, T., Haszeldine, R.N., 1957b. Perfluoroalkyl derivatives of sulphur. Part VI. Perfluoroalkanesulphonic acids $CF_3(CF_2)_nSO_3H$ ($n = 1$–7). Dalton Trans., 2640–2645.

Grasty, R.C., Grey, B.E., Lau, C.S., Rogers, J.M., 2003. Prenatal window of susceptibility to perfluorooctane sulfonate-induced neonatal mortality in the Sprague–Dawley rat. Birth Defects Res. Part B Dev. Reprod. Toxicol. 68, 465–471.

Grossman, M.R., Mispagel, M.E., Bowen, J.M., 1992. Distribution and tissue elimination in rats during and after prolonged dietary exposure to a highly fluorinated sulfonamide pesticide. J. Agric. Food Chem. 40, 2505–2509.

Hagen, D.F., Belisle, J., Johnson, J.D., Venkateswarlu, P., 1981. Characterization of fluorinated metabolites by a gas chromatographic-helium microwave plasma detector—the biotransformation of 1H,1H,2H,2H-perfluorodecanol to perfluorooctanoate. Anal. Biochem. 118, 336–343.

Hansen, K.J., Johnson, H.O., Eldridge, J.S., Butenhoff, J.L., Dick, L.A., 2002. Quantitative characterization of trace levels of PFOS and PFOA in the Tennessee River. Environ. Sci. Technol. 36, 1681–1685.

Harada, K., Saito, N., Inoue, K., Yoshinaga, T., Watanabe, T., Sasaki, S., Kamiyama, S., Koizumi, A., 2004. The influence of time, sex and geographic factors on levels of perfluorooctane sulfonate and perfluorooctanoate in human serum over the last 25 years. J. Occup. Health 46, 141–147.

Harada, K., Saito, N., Sasaki, K., Inoue, K., Koizumi, A., 2003. Perfluorooctane sulfonate contamination of drinking water in the Tama River, Japan: Estimated effects in resident serum levels. Bull. Environ. Contam. Toxicol. 71, 31–36.

Harris, J.M., Walton, J.C., Maillard, B., Grelier, S., Picard, J.P., 1993. Hydrogen abstraction from silylamines; an investigation of the 1,2-migration of the trimethylsilyl group in aminyl radicals. J. Chem. Soc. Perkin Trans. 2, 2119–2123.

Harzdorf, C., Meußdoerffer, J.N., Niederprüm, H., Wechsberg, M., 1973. Über Perfluoralkansulfinsäuren. Liebigs Ann. Chem., 33–39.

Haszeldine, R.N., 1953. Reactions of fluorocarbon radicals. XII. The synthesis of fluorocarbons and of fully fluorinated iodo-, bromo-, and chloroalkanes. J. Chem. Soc., 3761–3768.

Hauptschein, M., Braid, M., 1961a. Fluorocarbon halosulfates and a new route to fluorocarbon acids and derivatives. I. Polyfluoroalkyl chlorosulfates. J. Am. Chem. Soc. 83, 2500–2505.

Hauptschein, M., Braid, M., 1961b. Fluorocarbon halosulfates and a new route to fluorocarbon acids and derivatives. II. Polyfluoroalkyl fluorosulfates. J. Am. Chem. Soc. 83, 2505–2507.

Hebert, G.N., Odom, M.A., Craig, P.S., Dick, D.L., Strauss, S.H., 2002. Method for the determination of sub-ppm concentrations of perfluoroalkylsulfonate anions in water. J. Environ. Monit. 4, 90–95.

Hendrickson, J.B., Bair, K.W., Bergeron, R., Giga, A., Skipper, P.L., Sternbach, D.D., Wareing, J.A., 1977. Uses of the triflyl [trifluoromethanesulfonyl] group in organic synthesis. A review. Org. Prep. Proced. Int. 9, 173–207.

Hendrickson, J.B., Bergeron, R., Sternbach, D.D., 1975. New Gabriel synthesis of amines. Tetrahedron 31, 2517–2521.

Herkelmann, R., Sartori, P., 1989. Synthesis of perfluoropropane-1,3-disulfonic acid and perfluoro-1,4-disulfonic acid. J. Fluorine Chem. 44, 299–307.

Hoff, P.T., Scheirs, J., van de Vijver, K., van Dongen, W., Esmans, E.L., Blust, R., de Coen, W., 2004. Biochemical effect evaluation of perfluorooctane sulfonic acid-contaminated wood mice (*Apodemus sylvaticus*). Environ. Health Perspect. 112, 681–686.

Hoff, P.T., Van de Vijver, K., Van Dongen, W., Blust, R., De Coen, W., 2003. Perfluorooctane sulfonic acid in bib (*Trisopterus luscus*) and plaice (*Pleuronectes platessa*) from the Western Scheldt and the Belgian North Sea: distribution and biochemical effects. Environ. Toxicol. Chem. 22, 608–614.

Hohenblum, P., Scharf, S., Sitka, A., 2003. Perfluorinated anionic surfactants in Austrian industrial effluents. Vom Wasser 101, 155–164.

Hollitzer, E., Sartori, P., 1987. The electrochemical perfluorination (ECPF) of propanesulfonyl fluorides. Part I. Preparation and ECPF of 1-propanesulfonyl fluoride and 1,3-propanedisulfonyl difluoride. J. Fluorine Chem. 35, 329–341.

Hosokawa, M., Satoh, T., 1993. Differences in the induction of carboxylesterase isozymes in rat liver microsomes by perfluorinated fatty acids. Xenobiotica 23, 1125–1133.

Hu, C.-M., Xu, Z.-Q., Huang, W.-Y., 1989. Photooxidation of perhalofluorosulfinates. A simple and effective method for the synthesis of perhalofluorocarboxylic acids and their esters from the corresponding sulfonyl fluorides. J. Fluorine Chem. 42, 145–148.

Hu, W., Jones, P.D., Upham, B.L., Trosko, J.E., Lau, C., Giesy, J.P., 2002. Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines in vitro and Sprague–Dawley rats in vivo. Toxicol. Sci. 68, 429–436.

Hu, W.y., Jones, P.D., DeCoen, W., King, L., Fraker, P., Newsted, J., Giesy, J.P., 2003. Alterations in cell membrane properties caused by perfluorinated compounds. Comp. Biochem. Physiol., Part C: Toxicol. Pharmacol. 135C, 77–88.

Huang, B.-N., Haas, A., Lieb, M., 1987a. A new method for the preparation of perfluorocarboxylic acids. J. Fluorine Chem. 36, 49–62.

Huang, T.-J., Dong, Z.-X., Shreeve, J.M., 1987b. 1,1,2,2-tetrafluoro-2-(polyfluoroalkoxy)ethanesulfonyl fluorides. Inorg. Chem. 26, 2604–2606.

Huang, W., Lu, L., Zhang, Y.-h., 1990. Studies on sulfinatodehalogenation. XV. Sodium dithionite-initiated addition of per- and polyfluoroalkyl halides to ethyl vinyl ether and chemical conversions of products. Chin. J. Chem. 23, 281–288.

Ignat'ev, N., Kucherina, A., Sartori, P., 1999. Comparative electrochemical fluorination of ethanesulfonyl chloride and fluoride. Acta Chem. Scand. 53, 1110–1116.

Inoue, K., Okada, F., Ito, R., Kato, S., Sasaki, S., Nakajima, S., Uno, A., Saijo, Y., Sata, F., Yoshimura, Y., Kishi, R., Nakazawa, H., 2004. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. Environ. Health Perspect. 112, 1204–1207.

Jedidi Yaich, B., Ould Amanatouallah, A., Chaabouni, M.M., Baklouti, A., 2002. Reactivite D' α-bromoacides et esters *F*-alkyles: synthese de *F*-alkyl acides ethanoiques et *F*-alkyl acides 3-fluoroprop-2-enoiques. J. Fluorine Chem. 114, 47–50.

Jin, Y.-b., Liu, X., Qin, H.-m., Ma, Y.-x., Fan, Y.-o., Zhang, Y.-h., Saitou, N., Sasaki, K., Koizumi, A., 2004. Status quo of perfluorooctane sulfonate (PFOS) pollution in tap water and different waters in partial areas of China. Zhongguo Huanjing Kexue 24, 166–169.

Jones, P.D., Hu, W., De Coen, W., Newsted, J.L., Giesy, J.P., 2003. Binding of perfluorinated fatty acids to serum proteins. Environ. Toxicol. Chem. 22, 2639–2649.

Jüschke, R., Velayutham, D., Sartori, P., 1997. A comparative study of the electrochemical fluorination (ECF) of 1,*n*-alkanebis(sulfonylfluorides) ($n = 1$–3). J. Fluorine Chem. 83, 145–149.

Kamigata, N., Kawakita, O., Izuoka, A., Kobayashi, M., 1985. 1,3-Dipole cycloaddition of azides with nitroso compounds: ESR studies. J. Org. Chem. 50, 398–400.

Kamigata, N., Yamamoto, K., Kawakita, O., Hikita, K., Matsuyama, H., Yoshida, M., Kobayashi, M., 1984. Reactions of trifluoromethanesulfonyl azide with aromatic compounds. Bull. Chem. Soc. Jpn. 57, 3601–3602.

Kannan, K., Franson, J.C., Bowerman, W.W., Hansen, K.J., Jones, P.D., Giesy, J.P., 2001a. Perfluorooctane sulfonate in fish-eating water birds including bald eagles and albatrosses. Environ. Sci. Technol. 35, 3065–3070.

Kannan, K., Koistinen, J., Beckmen, K., Evans, T., Gorzelany, J.F., Hansen, K.J., Jones, P.D., Helle, E., Nyman, M., Giesy, J.P., 2001b. Accumulation of perfluorooctane sulfonate in marine mammals. Environ. Sci. Technol. 35, 1593–1598.

Kannan, K., Choi, J.W., Iseki, N., Senthilkumar, K., Kim, D.H., Giesy, J.P., 2002a. Concentrations of perfluorinated acids in livers of birds from Japan and Korea. Chemosphere 49, 225–231.

Kannan, K., Corsolini, S., Falandysz, J., Oehme, G., Focardi, S., Giesy, J.P., 2002b. Perfluorooctanesulfonate and related fluorinated hydrocarbons in marine mammals, fishes, and birds from coasts of the Baltic and the Mediterranean Seas. Environ. Sci. Technol. 36, 3210–3216.

Kannan, K., Hansen, K.J., Wade, T.L., Giesy, J.P., 2002c. Perfluorooctane sulfonate in oysters, Crassostrea virginica, from the Gulf of Mexico and the Chesapeake Bay, USA. Arch. Environ. Contam. Toxicol. 42, 313–318.

Kannan, K., Newsted, J., Halbrook, R.S., Giesy, J.P., 2002d. Perfluorooctanesulfonate and related fluorinated hydrocarbons in mink and river otters from the United States. Environ. Sci. Technol. 36, 2566–2571.

Kannan, K.C.S., Falandysz, J., Fillmann, G., Kumar, K.S., Loganathan, B.G., Mohd, M.A., Olivero, J., Van Wouwe, N., Yang, J.H., Aldous, K.M., 2004. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. Environ. Sci. Technol. 38, 4489–4495.

Kas'yan, A.O., Okovityi, S.I., Krasnovskaya, O.Y., Kas'yan, L.I., 1997. Amines and sulfonamides containing an adamantane fragment. Theoretical and experimental study. Russ. J. Org. Chem. 33, 985–990.

Katritzky, A.R., Davis, T.L., Rewcastle, G.W., Rubel, G.O., Pike, M.T., 1988. Design and synthesis of novel fluorinated surfactants for hydrocarbon subphases. Langmuir 4, 732–735.

Kawase, M., Motohashi, N., Niwa, M., Nozaki, M., 1997. Use of the triflamide group for Friedel-Crafts acylation of *N*-(β-phenethyl)amino acids to 3-benzazepine derivatives. Heterocycles 45, 1121–1129.

Kissa, E., 2001. Fluorinated surfactants and repellents. Surfactant Science Series 97. Marcel Dekker, New York.

Kitazume, T., Ikeya, T., 1988. A remarkably simple route to perfluoroalkylated olefins and perfluoroalkanoic acids. J. Org. Chem. 53, 2350–2352.

Krespan, C.G., 1979. Some new reactions of perfluorinated sulfonic acids. J. Org. Chem. 44, 4924–4929.

Kubwabo, C., Vais, N., Benoit, F.M., 2004. A pilot study on the determination of perfluorooctanesulfonate and other perfluorinated compounds in blood of Canadians. J. Environ. Monit. 6, 540–545.

Kudo, N., Kawashima, Y., 2003. Toxicity and toxicokinetics of perfluorooctanoic acid in humans and animals. J. Toxicol. Sci. 28, 49–57.

Kuklenyik, Z., Reich, J.A., Tully, J.S., Needham, L.L., Calafat, A.M., 2004. Automated solid-phase extraction and measurement of perfluorinated organic acids and amides in human serum and milk. Environ. Sci. Technol. 38, 3698–3704.

Lau, C., Butenhoff, J.L., Rogers, J.M., 2004. The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicol. Appl. Pharmacol. 198, 231–241.

Lau, C., Rogers, J.M., Hanson, R.G., Barbee, B.D., Narotsky, M.G., Schmid, J.E., Richards, J.H., 2001. Developmental toxicity of perfluorooctane sulfonate (PFOS) in the rat and mouse. Teratology 63, 290.

Lau, C., Thibodeaux, J.R., Hanson, R.G., Rogers, J.M., Grey, B.E., Stanton, M.E., Butenhoff, J.L., Stevenson, L.A., 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: Postnatal evaluation. Toxicol. Sci. 74, 382–392.

Laurent, P., Blancou, H., Commeyras, A., 1992. Synthesis of fluoroalkylethanals: R_FCH_2CHO. Tetrahed. Lett. 33, 2489–2492.

Lehmler, H.-J., Bummer, P.M., 2004. Mixing of perfluorinated carboxylic acids with dipalmitoylphosphatidylcholine. Biochim. Biophys. Acta 1664, 141–149.

Lehmler, H.-J., Jay, M., Bummer, P.M., 2000. Mixing of partially fluorinated carboxylic acids and their hydrocarbon analogs with diplamitoylphosphatidylcholine at the air–water interface. Langmuir 16, 10161–10166.

Lehmler, H.-J., Parkin, S., Brock, C.P., 2004. Packing conflicts in the $Z' = 5$ structure of $CF_3(CF_2)_3(CH_2)_{10}COOH$. Acta Cryst. B 60, 325–332.

Leveque, L., Le Blanc, M., Pastor, R., 1998. Synthesis of per(poly)fluoroalkyl aldehydes $R_F(CH_2)_nCHO$. Tetrahed. Lett. 39, 8857–8860.

Li, A., Bin, X., Zhu, S.-z., 1994. A one-pot synthesis of (*S*,*S*)-dialkyl-*N*-perfluoroalkylsulfonyl)carbodithioimidates. J. Fluorine Chem. 69, 257–259.

Long, Z.-Y., Chen, Q.-Y., 1999. The activation of carbon-chlorine bonds in per- and polyfluoroalkyl chlorides: DMSO-induced hydroperfluoroalkylation of alkenes and alkynes with sodium dithionite. J. Org. Chem. 64, 4775–4782.

Lu, H., Guo, C., Wang, S., Chen, Q., 1985. Synthesis of acrylates of fluorinated alcohols. Huaxue Xuebao 43, 970–975.

Luebker, D.J., Hansen, K.J., Bass, N.M., Butenhoff, J.L., Seacat, A.M., 2002. Interactions of fluorochemicals with rat liver fatty acid-binding protein. Toxicology 176, 175–185.

Lutz, C., Lutz, V., Knochel, P., 1998. Enantioselective synthesis of 1,2-, 1,3- and 1,4-aminoalcohols by the addition of dialkylzincs to 1,2-, 1,3- and 1,4-aminoaldehydes. Tetrahedron 54, 6385–6402.

Lyapkalo, I.M., Reissig, H.-U., Schäfer, A., Wagner, A., 2002. Study of unusually high rotational barriers about S–N bonds in nonafluorobutane-1-sulfonamides: The electronic nature of the torsional effect. Helv. Chim. Acta 85, 4206–4215.

Mabury, S.A., Martin, J., Moody, C., Ellis, D., Muir, D., 2002. Fluorinated surfactants—environmental and analytical chemistry. Organohalogen Compd. 59, 276–278.

Manning, R.O., Bruckner, J.V., Mispagel, M.E., Bowen, J.M., 1991. Metabolism and disposition of sulfluramid, a unique

polyfluorinated insecticide, in the rat. Drug Metab. Dispos. 19, 205–211.

Martin, J.W., Mabury, S.A., Solomon, K.R., Muir, D.C.G., 2003a. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (*Oncorhynchus mykiss*). Environ. Toxicol. Chem. 22, 196–204.

Martin, J.W., Mabury, S.A., Solomon, K.R., Muir, D.C.G., 2003b. Dietary accumulation of perfluorinated acids in juvenile rainbow trout (*Oncorhynchus mykiss*). Environ. Toxicol. Chem. 22, 189–195.

Martin, J.W., Muir, D.C., Moody, C.A., Ellis, D.A., Kwan, W.C., Solomon, K.R., Mabury, S.A., 2002. Collection of airborne fluorinated organics and analysis by gas chromatography/chemical ionization mass spectrometry. Anal. Chem. 74, 584–590.

Martin, J.W., Smithwick, M.M., Braune, B.M., Hoekstra, P.F., Muir, D.C., Mabury, S.A., 2004. Identification of long-chain perfluorinated acids in biota from the Canadian Arctic. Environ. Sci. Technol. 38, 373–380.

Meußdoerffer, J.N., Niederprüm, H., 1972. Bis-perfluoralkansulfonylimide $(R_FSO_2)_2NH$. Chemiker-Zeitung 96, 582–583.

Moody, C.A., Hebert, G.N., Strauss, S.H., Field, J.A., 2003. Occurrence and persistence of perfluorooctanesulfonate and other perfluorinated surfactants in groundwater at a fire-training area at Wurtsmith Air Force Base, Michigan, USA. J. Environ. Monit. 5, 341–345.

Moriwaki, H., Takatah, Y., Arakawa, R., 2003. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes. J. Environ. Monit. 23, 753–757.

Mukerjee, P., Yang, A.Y.S., 1976. Nonideality of mixing of micelles of fluorocarbon and hydrocarbon surfactants and evidence of partial miscibility from differential conductance data. J. Phys. Chem. 80, 1388–1390.

Napoli, M., Scipioni, A., Conte, L., Legnaro, E., Krotz, L.N., 1994. A modified procedure for preparing perfluoroalkyl acetic acids from perfluoroalkyl iodides. J. Fluorine Chem. 66, 249–252.

Nguyen, T., Wakselman, C., 1991. A new route to perfluorinated sulfonic acid resin intermediates. Eur. Polym. J. 27, 435–438.

Niederpruem, H., Voss, P., Wechsberg, M., 1973. Hydroxyalkylierung von Perfluoroalkansulfonamiden. Liebigs Ann. Chem. 23, 11–19.

Ohtoshi, S., 1989. Synthesis and specific properties of fluorosurfactants. Sekiyu Gakkaishi 32, 277–285.

Olsen, G.W., Gilliland, F.D., Burlew, M.M., Burris, J.M., Mandel, J.S., Mandel, J.H., 1998. An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. J. Occup. Environ. Med. 40, 614–622.

Olsen, G.W., Burris, J.M., Mandel, J.H., Zobel, L.R., 1999. Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. J. Occup. Environ. Med. 41, 799–806.

Olsen, G.W., Burris, J.M., Burlew, M.M., Mandel, J.H., 2000. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem. Toxicol. 23, 603–620.

Olsen, G.W., Burris, J.M., Burlew, M.M., Mandel, J.H., 2003a. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. J. Occup. Environ. Med. 45, 260–270.

Olsen, G.W., Church, T.R., Miller, J.P., Burris, J.M., Hansen, K.J., Lundberg, J.K., Armitage, J.B., Herron, R.M., Medhdizadehkashi, Z., Nobiletti, J.B., O'Neill, E.M., Mandel, J.H., Zobel, L.R., 2003b. Perfluorooctanesulfonate and other fluorochemicals in the serum of American Red Cross adult blood donors. Environ. Health Perspect. 111, 1892–1901.

Olsen, G.W., Hansen, K.J., Stevenson, L.A., Burris, J.M., Mandel, J.H., 2003c. Human donor liver and serum concentrations of perfluorooctanesulfonate and other perfluorochemicals. Environ. Sci. Technol. 37, 888–891.

Olsen, G.W., Logan, P.W., Hansen, K.J., Simpson, C.A., Burris, J.M., Burlew, M.M., Vorarath, P.P., Venkateswarlu, P., Schumpert, J.C., Mandel, J.H., 2003d. An occupational exposure assessment of a perfluorooctanesulfonyl fluoride production site: biomonitoring. AIHA J. 64, 651–659.

Olsen, G.W., Church, T.R., Larson, E.B., van Belle, G., Lundberg, J.K., Hansen, K.J., Burris, J.M., Mandel, J.H., Zobel, L.R., 2004. Serum concentrations of perfluorooctanesulfonate and other fluorochemicals in an elderly population from Seattle, Washington. Chemosphere 54, 1599–1611.

Ostwald, R., Chavant, P.-Y., Stadtmüller, H., Knochel, P., 1994. Catalytic asymmetric addition of polyfunctional dialkylzincs to β-stannylated and β-silylated unsaturated aldehydes. J. Org. Chem. 59, 4143–4153.

Patrick, C.R., 1971. Physicochemical properties of highly fluorinated organic compounds. Chem. Brit. 7, 154–156.

Podol'skii, A.V., Kachalkova, M.I., Ilatovskii, R.E., Kodess, M.I., Kolenko, I.P., 1990. Preparation of perfluoroalkanesulfonamide ammonium salts. Russ. J. Org. Chem., 1242–1244.

Qui, W., Burton, D.J., 1993. A useful synthesis of ω-iodoperfluoroalkanesulfonyl fluorides and perfluoroalkane-α,ω-bis-sulfonyl fluorides. J. Fluorine Chem. 60, 93–100.

Radchenko, O.A., Il'chenko, A.Y., Markovskii, L.N., Yagupol'skii, L.M., 1978. Isoperfluoroalkanesulfinic and -sulfonic acids. I. Heptafluoropropane-2-sulfinic and -sulfonic acids. Russ. J. Org. Chem. 14, 251–254.

Ramachandran, P.V., Jennings, M.P., 2002. Investigation of the factors controlling the regioselectivity of the hydroboration of fluoroolefins. Chem. Commun., 386–387.

Ramachandran, P.V., Jennings, M.P., Brown, H.C., 1999. Critical role of catalysts and boranes for controlling the regioselectivity in the rhodium-catalyzed hydroboration of fluoroolefins. Org. Lett. 1, 1399–1402.

Reich, I.L., Reich, H.J., Menahan, L.A., Peterson, R.E., 1987. Synthesis of carbon-14-labeled perfluoroctanoic and perfluorodecanoic acids; purification of perfluorodecanoic acid. J. Label. Compd. Radiopharm. 24, 1235–1244.

Renner, R., 2001. Growing concern over perfluorinated chemicals. Environ. Sci. Technol. 35, 155A–160A.

Rocaboy, C., Bauer, W., Gladysz, J.A., 2000. Convenient syntheses of a family of easily recoverable fluorous primary, secondary, and tertiary aliphatic amines $NH_{3-x}[(CH_2)_m(CF_2)_7CF_3]_x$ ($m = 3$–5; $x = 1$–3)-fine tuning of basicities

and fluorous phase affinities. Eur. J. Org. Chem. 23, 2621–2628.

Roesky, H.W., Holtschneider, G., Giere, H.H., 1970. Trifluoromethylsulfonylstickstoff-Verbindungen. Z. Naturforsch. 25b, 252–254.

Saito, N., Sasaki, K., Nakatome, K., Harada, K., Yoshinaga, T., Koizumi, A., 2003. Perfluorooctane sulfonate concentrations in surface water in Japan. Arch. Environ. Contam. Toxicol. 45, 149–158.

Sanderson, H., Boudreau, T.M., Mabury, S.A., Cheong, W.J., Solomon, K.R., 2002. Ecological impact and environmental fate of perfluorooctane sulfonate on the zooplankton community in indoor microcosms. Environ. Toxicol. Chem. 21, 1490–1496.

Sanderson, H., Boudreau, T.M., Mabury, S.A., Solomon, K.R., 2004. Effects of perfluorooctane sulfonate and perfluorooctanoic acid on the zooplanktonic community. Ecotoxicol. Environ. Saf. 58, 68–76.

Sasaki, K., Harada, K., Saito, N., Tsutsui, T., Nakanishi, S., Tsuzuki, H., Koizumi, A., 2003. Impact of airborne perfluorooctane sulfonate on the human body burden and the ecological system. Bull. Environ. Contam. Toxicol. 71, 408–413.

Satori, P., Jünger, C., 1996. Die elektrochemische Fluorierung von Alkansulfonamiden und Alkandisulfonamiden. J. Fluorine Chem. 79, 71–75.

Seacat, A.M., Thomford, P.J., Hansen, K.J., Clemen, L.A., Eldridge, S.R., Elcombe, C.R., Butenhoff, J.L., 2003. Subchronic dietary toxicity of potassium perfluorooctanesulfonate in rats. Toxicology 183, 117–131.

Seacat, A.M., Thomford, P.J., Hansen, K.J., Olsen, G.W., Case, M.T., Butenhoff, J.L., 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. Toxicol. Sci. 68, 249–264.

Shack, C.J., Christe, K.O., 1980. Halogen fluorosulfate reactions with fluorocarbons. J. Fluorine Chem. 16, 63–73.

Shafer, G.J., Forohar, F., DesMarteau, D.D., 2000. Synthesis of potassium 3,6-dioxa-Δ^7-4-trifluoromethyl perfluorooctyl sulfonate from hydrolysis of 3,6-dioxa-Δ^7-4-trifluoromethyl perfluorooctyl sulfonyl fluoride. A simple high yield conversion catalyzed by KF. J. Fluorine Chem. 101, 27–29.

Shipley, J.M., Hurst, C.H., Tanaka, S.S., DeRoos, F.L., Butenhoff, J.L., Seacat, A.M., Waxman, D.J., 2004. Trans-activation of PPARα and induction of PPARα target genes by perfluorooctane-based chemicals. Toxicol. Sci. 80, 151–160.

Shoeib, M., Harner, T., Ikonomou, M., Kannan, K., 2004. Indoor and outdoor air concentrations and phase partitioning of perfluoroalkyl sulfonamides and polybrominated diphenyl ethers. Environ. Sci. Technol. 38, 1313–1320.

So, M.K., Taniyasu, S., Yamashita, N., Giesy, J.P., Zheng, J., Fang, Z., Im, S.H., Lam, P.K.S., 2004. Perfluorinated compounds in Coastal Waters of Hong Kong, South China, and Korea. Environ. Sci. Technol. 38, 4056–4063.

Sohlenius, A.K., Eriksson, A.M., Hogstrom, C., Kimland, M., DePierre, J.W., 1993. Perfluorooctane sulfonic acid is a potent inducer of peroxisomal fatty acid beta-oxidation and other activities known to be affected by peroxisome proliferators in mouse liver. Pharmacol. Toxicol. 72, 90–93.

Sokol'skii, G.A., Knunyants, I.L., 1961. Fluorine-containing β-sultones. XI. Preparation of fluoromethane- and difluoromethanesulfonyl fluorides. Russ. Chem. Bull., 1606–1610.

Sottani, C., Minoia, C., 2002. Quantitative determination of perfluorooctanoic acid ammonium salt in human serum by high-performance liquid chromatography with atmospheric pressure chemical ionization tandem mass spectrometry. Rapid Commun. Mass Spectrom. 16, 650–654.

Starkov, A.A., Wallace, K.B., 2002. Structural determinants of fluorochemical-induced mitochondrial dysfunction. Toxicol. Sci. 66, 244–252.

Stock, N.L., Lau, F.K., Ellis, D.A., Martin, J.W., Muir, D.C.G., Mabury, S.A., 2004. Polyfluorinated telomer alcohols and sulfonamides in the North American Troposphere. Environ. Sci. Technol. 38, 991–996.

Supuran, C.T., Scozzafava, A., 2000. Protease inhibitors. Part 7: Inhibition of clostridium histolyticum collagenase with sulfonylated derivatives of L-valine hydroxamate. Eur. J. Pharm. Sci. 10, 67–76.

Takeuchi, Y., Satoh, A., Suzuki, T., Kameda, A., Dohrin, M., Satoh, T., Koizumi, T., Kirk, K.L., 1997. Enantioselective fluorination of organic molecules. I. Synthetic studies of the agents for electrophilic, enantioselective fluorination of carbanions. Chem. Pharm. Bull. 45, 1085–1088.

Taniyasu, S., Kannan, K., Horii, Y., Hanari, N., Yamashita, N., 2003. A survey of perfluorooctane sulfonate and related perfluorinated organic compounds in water, fish, birds, and humans from Japan. Environ. Sci. Technol. 37, 2634–2639.

Thibodeaux, J.R., Hanson, R.G., Rogers, J.M., Grey, B.E., Barbee, B.D., Richards, J.H., Butenhoff, J.L., Stevenson, L.A., Lau, C., 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: Maternal and prenatal evaluations. Toxicol. Sci. 74, 369–381.

Tomy, G.T., Tittlemier, S.A., Palace, V.P., Budakowski, W.R., Braekevelt, E., Brinkworth, L., Friesen, K., 2004. Biotransformation of *N*-ethyl perfluorooctanesulfonamide by Rainbow Trout (*Onchorhynchus mykiss*) liver microsomes. Environ. Sci. Technol. 38, 758–762.

Tordeux, M., Langlois, B., Wakselman, C., 1989. Reactions of bromotrifluoromethane and related halides. 8. Condensations with dithionite and hydroxymethanesulfinate salts. J. Org. Chem. 54, 2452–2453.

Trepka, R.D., Harrington, J.K., Belisle, J.W., 1974. Acidities and partition coefficients of fluoromethanesulfonamides. J. Org. Chem. 39, 1094–1098.

Van de Vijver, K.I., Hoff, P.T., Das, K., Van Dongen, W., Esmans, E.L., Jauniaux, T., Bouquegneau, J.M., Blust, R., de Coen, W., 2003a. Perfluorinated chemicals infiltrate ocean waters: link between exposure levels and stable isotope ratios in marine mammals. Environ. Sci. Technol. 37, 5545–5550.

Van de Vijver, K.I., Hoff, P.T., Van Dongen, W., Blust, R., De Coen, W.M., 2003b. Exposure patterns of perfluorooctane sulfonate in aquatic invertebrates from the Western Scheldt estuary and the southern North Sea. Environ. Toxicol. Chem. 22, 2037–2041.

Van de Vijver, K.I., Hoff, P.T., Das, K., Van Dongen, W., Esmans, E.L., Siebert, U., Bouquegneau, J.M., Blust, R., De Coen, W.M., 2004. Baseline study of perfluorochemicals in harbour porpoises (*Phocoena phocoena*) from Northern Europe. Mar. Pollut. Bull. 48, 992–997.

van Dyke Tiers, G., 1963. The chemistry of fluorocarbon sulfonic acids. I. Preparation of anhydrides and sulfonyl halides. J. Org. Chem. 28, 1244–1246.

Volkov, N.D., Nazaretyan, V.P., Yagupol'skii, L.M., 1979. Preparation of halodifluoromethanesulfonic acid derivatives. Synthesis, 972–975.

Ward, R.B., 1965. The hydrolysis and oxidation of α,ω-bis(methylthio)polyfluoroalkanes. J. Org. Chem., 3009–3011.

Wong, F.F., 1971. Use of chloroplatinic acid as a chromatographic spray for sulfur compounds. J. Chromatogr. 59, 448–451.

Xu, L., Krenitsky, D.M., Seacat, A.M., Butenhoff, J.L., Anders, M.W., 2004. Biotransformation of *N*-ethyl-*N*-(2-hydroxyethyl)perfluorooctanesulfonamide by rat liver microsomes, cytosol, and slices and by expressed rat and human cytochromes P450. Chem. Res. Toxicol. 17, 767–775.

Xu, Y., Zhu, S., 1999. Study on the reactions of fluoroalkanesulfonyl azides with pyridine and its derivatives. Tetrahedron 55, 13725–13734.

Xu, Y., Zhu, S., 2001. A new route to fluorine-containing aziridines and α-amino esters. Tetrahedron 57, 669–674.

York, R.G., Case, M.T., Christian, M.S., 2000. Rat and rabbit developmental toxicology studies with two perfluorinated compounds administered orally. Int. J. Toxicol. 19, 35.

Young, J.A., 1974. Revised nomenclature for highly fluorinated organic compounds. J. Chem. Document. 14, 98–100.

Zhang, L., Dolbier, W.R., Sheeller, B., Ingold, K.U., 2002. Absolute rate constants of alkene addition reactions of a fluorinated radical in water. J. Am. Chem. Soc. 124, 6362–6366.

Zhu, S.-z., 1992. Synthesis of fluoroalkanesulfonyl azides and their reaction as fluoroalkanesulfonyl nitrene precursors. Tetrahed. Lett. 33, 6503–6504.

Zhu, S.-Z., 1994. Synthesis and reactions of fluoroalkanesulfonyl azides and *N*,*N*-dichlorofluoroalkanesulfonamides. J. Chem. Soc. Perkin Trans. 1, 2077–2081.

Zhu, S.-Z., Xu, Y., Wang, Y.-L., Peng, W.-M., 2001. Reactions of fluoroalkanesulfonyl azides with diethyl phosphite, a new method for the synthesis of *N*-fluoroalkanesulfonylphosphoramidates. Chin. J. Chem. 19, 1259–1262.

Zhu, S.-Z., Zhang, J., Xu, B., Li, A., 1994. Synthesis of dialkyl *N*-alkyl-*N*-perfluoroalkanesulfonyl phosphoramidates. Phosphorus, Sulfur Silicon Relat. Elem. 89, 77–82.