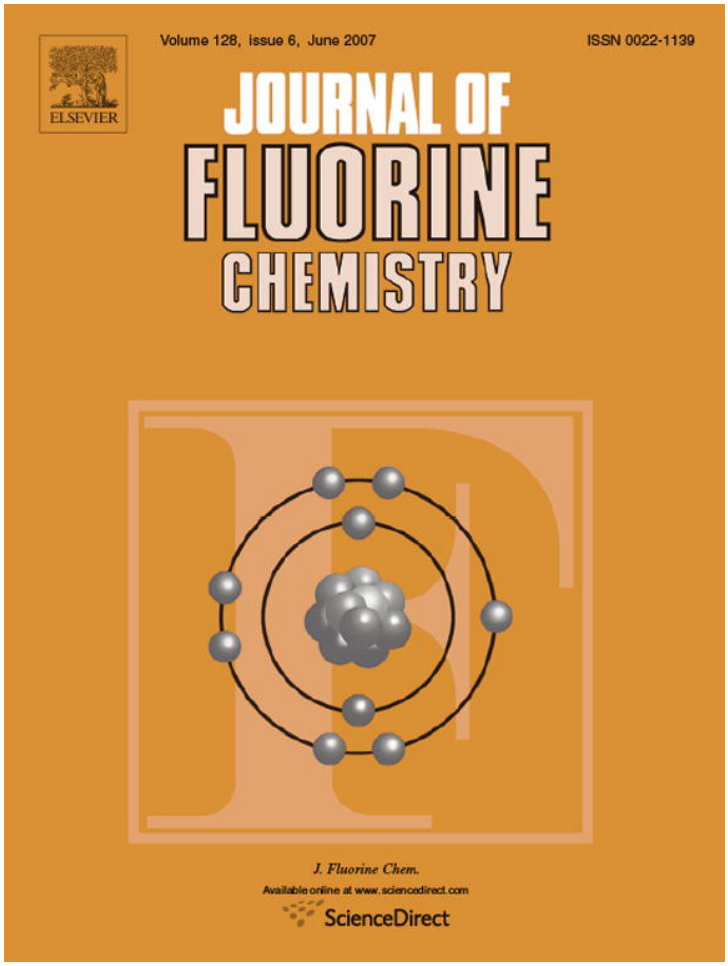

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Journal of Fluorine Chemistry 128 (2007) 595–607
JOURNAL OF FLUORINE CHEMISTRY
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Synthesis and structure of environmentally relevant perfluorinated sulfonamides

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Received 15 December 2006; received in revised form 25 January 2007; accepted 29 January 2007
Available online 6 February 2007

Abstract

Alkylated perfluorooctanesulfonamides are compounds of environmental concern. To make these compounds available for environmental and toxicological studies, a series of *N*-alkylated perfluorooctanesulfonamides and structurally related compounds were synthesized by reaction of the corresponding perfluoroalkanesulfonyl fluoride with a suitable primary or secondary amine. Perfluoroalkanesulfonamidoethanols were obtained from the *N*-alkyl perfluoroalkanesulfonamides either by direct alkylation with bromoethanol or alkylation with acetic acid 2-bromo-ethyl ester followed by hydrolysis of the acetate. *N*-Alkyl perfluorooctanesulfonamidoacetates were synthesized in an analogous way by alkylation of *N*-alkyl perfluoroalkanesulfonamides with a bromo acetic acid ester, followed by basic ester hydrolysis. Alternatively, *N*-alkyl perfluoroalkanesulfonamides can be alkylated with an appropriate alcohol using the Mitsunobu reaction. Perfluorooctanesulfonamide was synthesized from the perfluorooctanesulfonyl fluoride via the azide by reduction with Zn/HCl. All perfluorooctanesulfonamides contained linear as well as branched C_8F_{17} isomers, typically in a 10:1 to 30:1 ratio. The crystal structures of *N*-ethyl and *N*,*N*-diethyl perfluorooctanesulfonamide show that the S–N bond has considerable double bond character. This double bond character results in a significant rotational barrier around the S–N bond ($\Delta G^{\neq}$ = 62–71 kJ mol^{-1}) and a preferred solid state and solution conformation in which the *N*-alkyl groups are oriented opposite to the perfluorooctyl group to minimize steric crowding around the S–N bond.

Keywords: Environmental contaminants; Perfluorooctanesulfonamides; Perfluorobutanesulfonamides; Alkylation; Mitsunobu reaction; X-ray structure

1. Introduction

Perfluorooctanesulfonamides, such as *N*-alkyl perfluorooctanesulfonamidoethanols, *N*-alkyl perfluorooctanesulfonamides and perfluorooctanesulfonamide, have been used for over 40 years in a range of applications including pesticides, surfactants, surface treatments for clothes and home furnishings, paper protection and other miscellaneous applications [1,2]. This group of compounds is ideally suited for these purposes because of unique properties such as excellent spreading characteristics, high surface activity and water and oil repellency. These properties are the result of the high electronegativity of fluorine, its large van der Waals radius compared to hydrogen, and the strong fluorine–carbon bond. Both the strength of the fluorine–carbon bond and the ''shielding'' effect of several fluorine atoms also result in the stability of perfluoroalkyl chains towards chemical, thermal and biological degradation. Medium-to-long chain perfluorinated surfactants, including perfluorooctanesulfonamides are, therefore, highly persistent in the environment and have been detected worldwide in a large range of environmental matrices and in humans, thus raising human health concerns [2].

Unfortunately, perfluorooctanesulfonamides are not readily available from commercial sources, which limits the ability to study the environmental impact and toxicity of these compounds and creates a need for straightforward and well-documented approaches for their synthesis. Perfluorooctanesulfonamides have been synthesized industrially from perfluorooctanesulfonyl

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doi:10.1016/j.jfluchem.2007.01.013

fluoride by reaction with a suitable primary or secondary amine and further modification of the amide, e.g. by alkylation with chloroethanol. Laboratory syntheses of several perfluorooctanesulfonamides, for example, perfluorooctanesulfonamidoethanol [3,4] and *N*-ethyl perfluorooctanesulfonamide [5], have employed the same synthetic approach; however, a comprehensive description of the synthesis and characterization of these compounds for environmental and toxicological studies has not been reported. We herein report the synthesis and characterization of several environmentally relevant alkylated perfluorooctanesulfonamides from commercially available perfluorooctanesulfonyl fluoride for use in such studies. In addition, we synthesized several analogous perfluorobutanesulfonamides because perfluorobutanesulfonate based materials are emerging as a replacement for perfluorooctanesulfonate based materials [6] and as model compounds for the study of their atmospheric chemistry [7].

2. Results and discussion

2.1. Synthesis of N-alkyl and N,N-dialkyl perfluoroalkanesulfonamides from perfluoroalkanesulfonyl fluorides

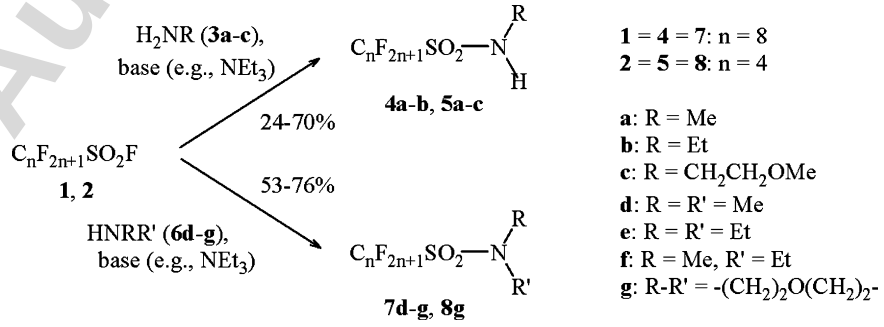
Monoalkylated perfluorooctanesulfonamides are typically synthesized by reaction of perfluorooctanesulfonyl fluoride (**1**) with an excess of the respective amine, e.g. **3a–c**, in diethyl ether or dioxane (for a review see [2]). This reaction initially forms a complex ammonium salt with a proposed formula of $C_8F_{17}SO_2NR^-{\cdot}NRH_3^+{\cdot}NRH_3F$. The desired alkylated perfluorooctanesulfonamide **5a–c** is subsequently isolated after thermal decomposition of this complex salt [8–11] or by treatment of the reaction mixture with hydrochloric or sulfuric acid [11–13]. Following these previous reports, we initially investigated the reaction of perfluorooctanesulfonyl fluoride (**1**) by using an excess of the respective alkyl amine, e.g. methyl- (**3a**) or ethylamine (**3b**), as a base (Scheme 1). Subsequent experiments studied the use of an external base such as triethylamine or pyridine. These efforts and our attempts to further optimize the reaction conditions are summarized in Table 1.

Initial experiments employed the two gaseous amines **3a** and **3b** both as reactants and as base at ambient temperature, both with (Method A) and without solvent (Method C). Although apparently higher yields were obtained under the solvent free conditions of Method C (Entries 1 and 2), the products contained significant amounts of impurities (i.e., showed several peaks in the gas chromatogram) and were slightly colored even after Kugelrohr distillation and/or recrystallization. Therefore, we abandoned this approach and focused on reaction conditions employing a solvent such as diethyl ether. Reaction of perfluorooctanesulfonyl fluoride with **3a** and **3b** at ambient temperature yielded 43% of the desired sulfonamide (Entries 3 and 8). To facilitate the decomposition of the thermally unstable complex ammonium salt we also heated the reaction mixture under reflux after addition of the amine **3b** (Entry 9) [9]. In the case of ethylamine (**3b**) this additional heating step appears to give a slightly higher yield and, therefore, was used in most subsequent reactions.

A major drawback of using excess **3a** or **3b** as a base is the formation of a white precipitate which made it difficult to monitor the addition of the gaseous amines **3a** and **3b** and to workup these reactions. Therefore, we investigated the use of an external base, for example, triethylamine or pyridine, which improved the yield by 13–16%, reduced the reaction time and gave overall more reproducible yields (Entries 6, 12 and 13). Both pyridine and triethylamine gave similar yields. Although the reaction conditions were identical for the synthesis of **4a** and **4b**, the yield of *N*-methyl perfluorooctanesulfonamide **4a** was always lower compared to its ethyl analog **4b**. This difference in yield is probably due to difficulties in handling the low boiling methylamine (Entry 4).

We also studied the influence of selected solvents (i.e., ether, dioxane and dichloromethane) on the yield of the reaction (Entries 5, 10 and 11). Pyridine, which has been used previously as solvent for the synthesis of perfluorooctane-1-sulfonic acid (2,2-dimethoxy-ethyl)-amide from perfluorooctanesulfonyl fluoride **1** [3], was not investigated because it is typically difficult to remove residual pyridine traces. We found that the solvent had little-to-no effect on the overall yield. However, dichloromethane as a solvent resulted in a significantly colored reaction mixture and is, therefore, a less suitable solvent for this type of reaction (Entry 10). This is surprising because reactions of shorter chain perfluoroalkylsulfonyl fluorides and chlorides with alkyl amines can be performed using a broad range of solvents (e.g., dichloromethane) and reaction conditions [2].

To facilitate the conversion of the complex ammonium salt to the desired perfluorooctanesulfonamide, we investigated different aqueous workup conditions such as acidic and basic



Scheme 1. Synthesis of mono- and dialkylated perfluorooctanesulfonamides.

Table 1
Synthesis of mono- and dialkylated perfluorooctanesulfonamides from perfluorooctanesulfonyl fluoride

Entry	Amine	Base	Solvent	Reaction conditions	Method	Percentage linear:isopropyl branched isomer[a]	Yield (%)
1	**3a**	**3a**	None	AT	C	n.d.	70[b,c]
2	**3b**	**3b**	None	AT	C	n.d.	70[b,c]
3	**3a**	**3a**	Ether	AT	A	98:2	43
4	**3a**	**3a**	Ether	Reflux	A	98:2	24–28[d]
5	**3a**	NEt_3	DCM	Reflux	A	92:8	46[e]
6	**3a**	NEt_3	Ether	Reflux	B	92:8	46
7	**3a**	NEt_3	Ether	Reflux	B	98:2	43[f]
8	**3b**	**3b**	Ether	AT	A	96:4	43
9	**3b**	**3b**	Ether	Reflux	B	98:2	48–50
10	**3b**	NEt_3	DCM	AT	B	95:5	57
11	**3b**	NEt_3	Ether	AT	B	97:3	46[g]
12	**3b**	NEt_3	Ether	Reflux[h]	B	96:4	42–58
13	**3b**	Pyridine	Ether	AT	A	98:2	51[i]
14	**3b**	NEt_3	Dioxane	Reflux[g]	B	99:1	56[f]
15	**6d**	NEt_3	Ether	Reflux	E	99:1	55
16	**6e**	NEt_3	None	Reflux	E	94:6	69[b,c]
17	**6f**	NEt_3	Ether	Reflux	B	94:6	53
18	**6g**	**6g**	Ether	Reflux	D	95:5	76

[a] The percentage of the linear and isopropyl branched isomer was determined based on the integral of the respective CF_3 signals.
[b] Slightly yellow, waxy solid with several peaks in the gas chromatogram.
[c] Recrystallized from reagent alcohol/dichloromethane.
[d] The low yield is probably due to the ten times smaller scale of these reaction compared to most reactions reported in this table.
[e] Worked-up with diluted hydrochloric acid to remove traces of pyridine.
[f] Non-aqueous work-up was adopted.
[g] Reaction mixture was hydrolyzed with saturated $NaHCO_3$ solution.
[h] 20 h of reaction time.
[i] Dark brown crude product.
AT = ambient temperature.
DCM = dichloromethane.n.d. = not determined.

aqueous workup (Entries 5 and 11, respectively). Overall, no improvement in the yield of the reaction was observed suggesting that the complex ammonium salt readily decomposes under the reaction conditions employed. In subsequent experiments we avoided an aqueous workup altogether and directly purified the product by column chromatography as outlined in Method B (Entries 7 and 11). The reaction conditions of Method B, with slight modifications (i.e., acetonitrile as solvent), were also employed to synthesize the corresponding perfluorobutane-1-sulfonamides **5a** and **5b** from perfluorobutanesulfonyl fluoride **2** in good yields.

The dialkyl perfluoroalkanesulfonamides **7d–g** and **8g**, compounds of interest as analytical standards, were prepared from fluoride **1** or **2** and the respective dialkyl amines **6d–g** using the same strategies employed for the monoalkyl derivatives **4a** and **4b** (Methods D and E, Entries 15–18). The best results with regard to purity were obtained using an excess of the amine as a base (Method D, entries 15 and 17).

2.2. Isomer composition of perfluorooctanesulfonyl amides

Commercially available perfluorooctanesulfonyl fluoride **1** is manufactured by electrochemical fluorination, a process that results in a significant number of organic and inorganic byproducts. Only approximately 70% of perfluorooctanesulfonyl fluoride **1** are the desired linear isomer [2]. Significant amounts of various branched C_8F_{17} isomers with the general structure $C_8F_{17}SO_2F$ are also present. These include $(F_3C)_2CF(CF_2)_5SO_2F$ (isopropyl), $F_3C(CF_2)_xCF(CF_3)(CF_2)_{5-x}SO_2F$ (internally branched) and $(F_3C)_3C(CF_2)_4SO_2F$ (*t*-butyl). We investigated recrystallization and column chromatography techniques to purify the crude product and, if possible, to remove branched impurities. Among these two purification methods, only column chromatography on silica gel was able to remove a significant percentage of the branched perfluorooctanesulfonamides and other fluorinated impurities. Initial fractions were eluted with ethyl acetate–hexane as eluent and, based on ^1H and ^{19}F NMR spectroscopy, contained a mixture of branched impurities (major), some linear isomer (minor) and other, uncharacterized impurities. The straight chain isomer and some branched impurities were eluted by further increasing the polarity of the mobile phase (up to 7% of ethyl acetate). In these later fractions, the ratios of linear to branched perfluorooctanesulfonamide were determined using ^{19}F NMR spectroscopy. The ratios of linear to isopropyl perfluorooctanesulfonamide $(F_3C)_2CF(CF_2)_5SO_2NRR'$ typically ranged from 10:1 to 30:1 in all perfluorooctanesulfonamides synthesized (e.g., Table 1). All samples also contained small quantities of the *t*-butyl and other branched perfluorooctanesulfonamides. Recrystallization did not remove all branched impurities, but worked well to remove the dark brown color from the crude product.

The perfluorobutanesulfonyl fluoride **2** used in this study was most likely synthesized by electrochemical fluorination of the corresponding butanesulfonyl fluoride [2]. In contrast to

its long chain homologue **1**, the ^{19}F NMR spectrum of perfluorobutanesulfonyl fluoride **2** showed only the four signals of the perfluorobutyl chain. No impurities could be detected in the ^{19}F NMR spectrum even with neat **2**. The high purity of fluoride **2** is not unexpected because the electrochemical fluorination of shorter-chain alkanesulfonyl chlorides and fluorides is known to give the respective fluorides in good purities and excellent yields [1]. As a result, the perfluorobutanesulfonamides **5a–c** derived from fluoride **2** are also free of branched impurities.

2.3. Synthesis of N,N-dialkyl perfluoroalkanesulfonyl amides

N-methyl-*N*-(2-hydroxyethyl)-perfluorooctane-1-sulfonamide **9a** and *N*-ethyl-*N*-(2-hydroxyethyl)-perfluorooctane-1-sulfonamide **9b** were important industrial products and are known environmental contaminants [2]. Both amides have been industrially synthesized by alkylation of the respective amides, for example, **4a** or **4b**, with chloroethanol [14], oxirane [15] or 1,3-dioxolan-2-one (ethylene carbonate) [4]. Following these earlier (patent) reports we initially investigated the synthesis of perfluorooctanesulfonamide **7f** by alkylation of *N*-methyl perfluorooctanesulfonamide **4a** with iodoethane. The desired perfluorooctanesulfonamide **7f** was obtained in 78% yield when sodium methoxide was employed as a base [16], but the reaction was more straightforward and the yields significantly improved when potassium carbonate was used as a base.

We subsequently investigated the alkylation of the *N*-alkyl perfluorooctanesulfonyl amides **4a** and **4b** with bromoethanol using potassium carbonate as base and catalytic amount of sodium iodide in acetone (Scheme 2). Initial experiments gave low yields of the desired sulfonamides **9a** and **9b** due to impurities present in commercially available bromoethanol; however, good yields ranging from 62 to 99% were obtained by alkylation of **4a** and **4b** with freshly distilled bromoethanol. In a second approach (Scheme 2), the *N*-alkyl amide **4a** or **4b** was alkylated with 2-bromoethyl acetate in the presence of the potassium carbonate base and catalytic amount of sodium iodide. The acetates **10a** or **10b** were deacetylated with aqueous potassium hydroxide to yield the desired sulfonamides **9a** and **9b** in 65% and 93% yield, respectively. Because of the overall lower yields, this approach is less suitable for the synthesis of the dialkylated sulfonamides.

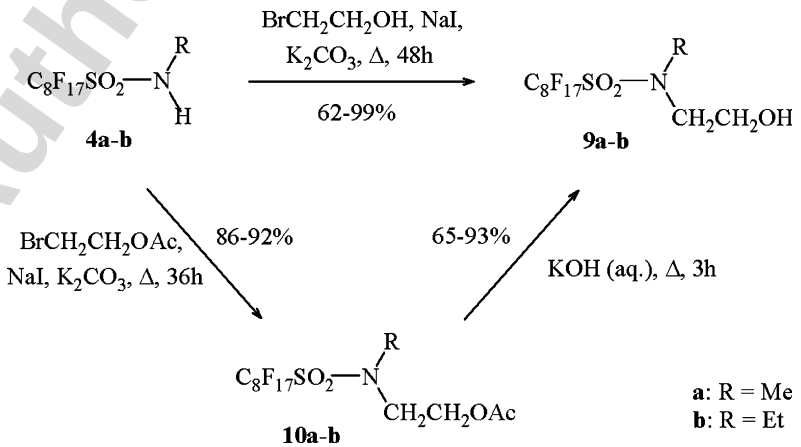
We also employed a similar alkylation reaction for the synthesis of *N*-ethyl perfluorooctanesulfonamideacetate **12**. As shown in Scheme 3, alkylation of an *N*-ethyl perfluorooctanesulfonamide with a bromoacetic acid methyl ester yields the desired ester **11** in good yields. We initially investigated the base catalyzed hydrolysis (2–10% aqueous as well as ethanolic KOH solutions) of ester **11** to obtain the desired acid. These severe reaction conditions gave a complex mixture of uncharacterized decomposition products. However, controlled basic hydrolysis [17] yielded the desired acid **12** in moderate yield and acceptable purity.

2.4. Synthesis of N,N-dialkyl perfluoroalkanesulfonamides using the Mitsunobu reaction

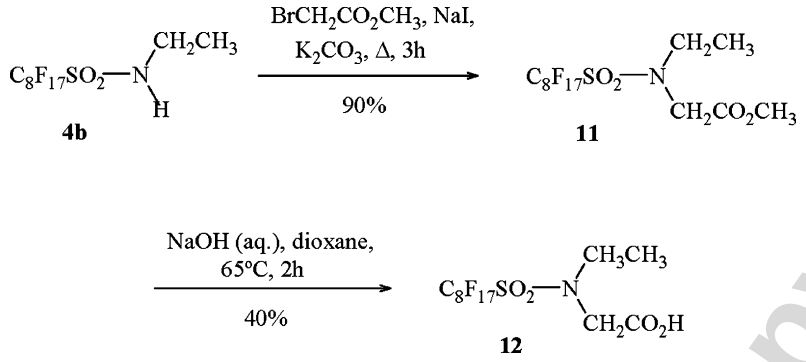
The Mitsunobu reaction has been successfully employed for the *N*-alkylation of derivatives of triflamide ($CF_3SO_2NH_2$) with various alcohols [18–20]. We investigated this approach as an alternative route to *N,N*-dialkyl perfluorooctanesulfonamides. As shown in Scheme 4, the Mitsunobu reaction of **4b** with methyl glycolate gave ester **11** in good yield. The Mitsunobu reaction of **4b** with ethylene glycol did not yield the desired product **9b**; however, the Mitsunobu reaction of **4b** with TBDMS (*t*-butyldmethylsilyl) protected ethylene glycol **13** gave the desired product **14** in 98% yield. Hydrolysis of **14** using hydrochloric acid at 25 °C yielded **9b** in 96% yield. Overall, the Mitsunobu reaction gives the target molecules in good to excellent yields, and thus, is an alternative approach for the alkylation of perfluoroalkanesulfonamides.

2.5. Synthesis of perfluorooctanesulfonamide 17 from perfluoroalkanesulfonyl fluoride

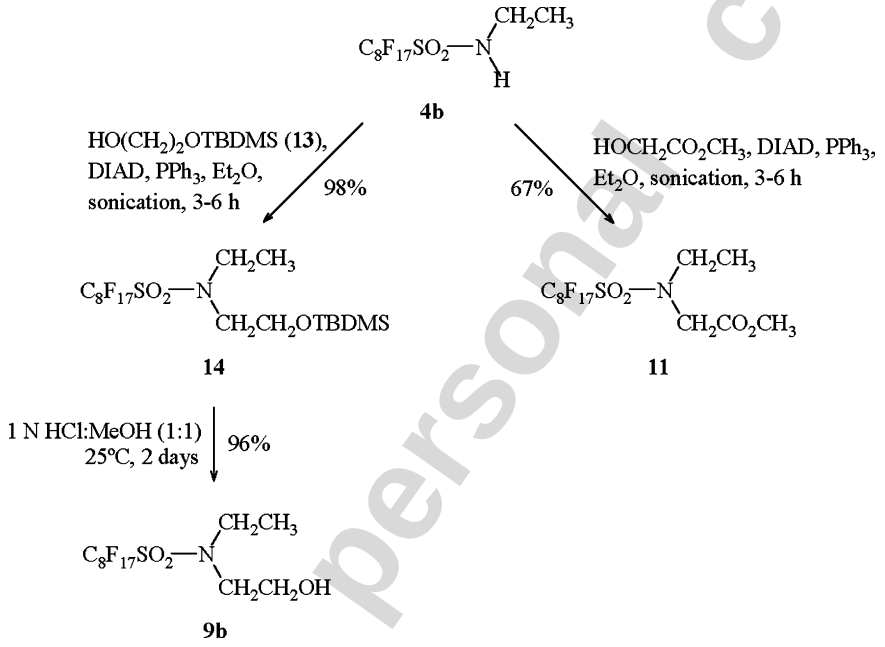
Perfluorooctanesulfonamide **17** can be prepared by reaction of ammonia with perfluorooctanesulfonyl fluoride **1** [8–11]. We explored a different approach that avoids the use of ammonia and, as shown in Scheme 5, prepared the amide **17** in a two-step synthesis via the azide. In the first step, perfluorooctanesulfonyl



Scheme 2. Synthesis of mono- or *N*-alkylated perfluorooctanesulfonamidoethanol **9a** and **9b**.



Scheme 3. Synthesis of 2-(*N*-ethyl perflurooctanesulfonamido)acetic acid **12**.

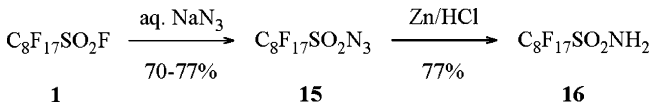


Scheme 4. Synthesis of *N*,*N*-dialkylated perfluorooctanesulfonamides **11** and **14** from *N*-alkylated perfluorooctanesulfonamides using the Mitsunobu reaction.

fluoride was reacted with an aqueous solution of sodium azide at room temperature to yield the perfluorooctanesulfonyl azide **15**. This azide **15** was subsequently converted into the perfluorooctanesulfonamide **16** by treatment with zinc and aqueous hydrochloric acid [21].

2.6. Structure of N-alkyl and N,N-dialkyl perfluoroalkanesulfonyl amides

To fully understand the biological effects of perfluorooctanesulfonamides it is important to know their three-dimensional structures. Although (partially) fluorinated compounds are often very difficult to crystallize [22], typically forming exceedingly thin, poorly stacked platelets, we were able to determine the crystal structure of *N*-ethyl-perfluorooctane-1-sulfonamide (**4b**), *N*,*N*-diethyl-perfluorooctane-1-sulfonamide (**7e**) and 2-(*N*-ethyl-perfluorooctanesulfonamido) acetic acid (**12**).



Scheme 5. Synthesis of perfluorooctanesulfonamide **16**.

The crystal structure of **4b** is shown in Fig. 1. Crystals of amide **4b** are triclinic (space group $P\bar{1}$) with $a = 6.3411(1)$, $b = 9.5670(3)$, $c = 28.2303(9)$ Å, and $\alpha = 88.579(2)^\circ$, $\beta = 85.758(2)^\circ$, $\gamma = 87.348(2)^\circ$. The asymmetric unit contains two independent molecules that are rotational isomers and are enantiomeric to each other (Fig. 1). The crystal structure of **7e** is shown in Fig. 2. Amide **7e** is monoclinic (space group $P2_1/c$) with $a = 7.3103(7)$, $b = 6.4514(6)$, $c = 39.904(4)$ Å, and $\alpha = 90^\circ$, $\beta = 95.089(5)^\circ$, $\gamma = 90^\circ$. An interesting feature of this crystal structure is that the perfluorooctyl chains of the disorder components are enantiomeric—they spiral around both ways, thus resulting in a disordered crystal. This is not surprising because perfluoroalkane chains typically adopt a helical conformation resulting from the larger van der Waals radius of fluorine relative to hydrogen (see Fig. 2B) [23]. The crystal structure of **12** is shown in Fig. 3. Amide **12** is also monoclinic (space group *Pc*; an alternative model in *P2/c* was less satisfactory) with $a = 33.150(3)$, $b = 5.8124(7)$,

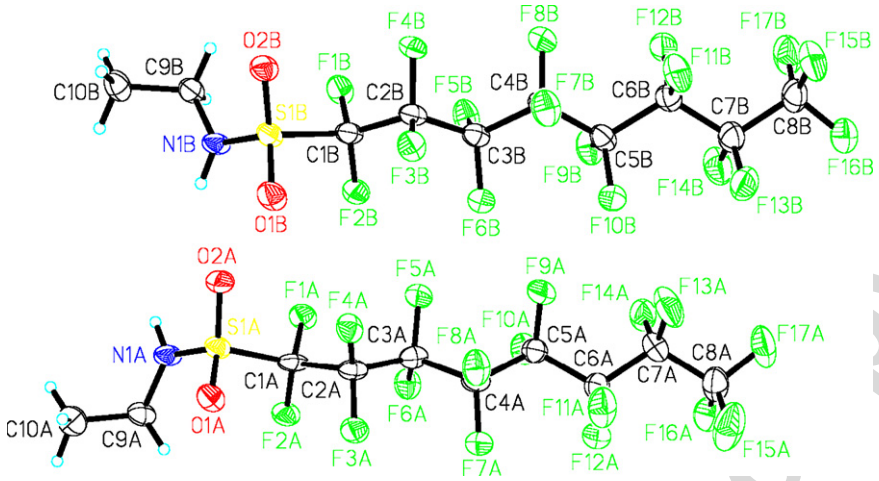


Fig. 1. Structure of *N*-ethyl-perfluorooctane-1-sulfonamide (**4b**). Displacement ellipsoids are drawn at the 50% probability level.

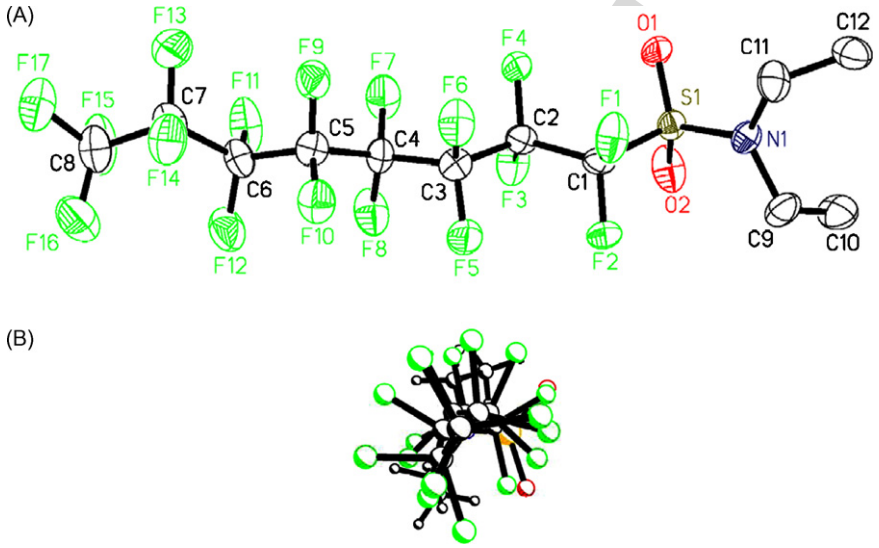


Fig. 2. View of *N*,*N*-diethyl-perfluorooctane-1-sulfonamide (**7e**). (A) Structure of **7e** showing the atom-labelling scheme. (B) View of **7e** along the carbon backbone to illustrate the helical conformation of the perfluorooctyl chain of the major component in the crystal. Displacement ellipsoids are drawn at the 50% probability level.

$c = 10.0365(15)$ Å, and $\alpha = 90°$, $\beta = 91.220(6)°$, $\gamma = 90°$. Since crystallographic study of compounds containing perfluorinated chains is generally very difficult owing to poor quality crystals, the quality of resulting structures is often somewhat lower than for typical small-molecule structure determinations (vide infra). Although this is particularly true of amide **12**, it is nevertheless possible to extract chemically meaningful results from the structure models.

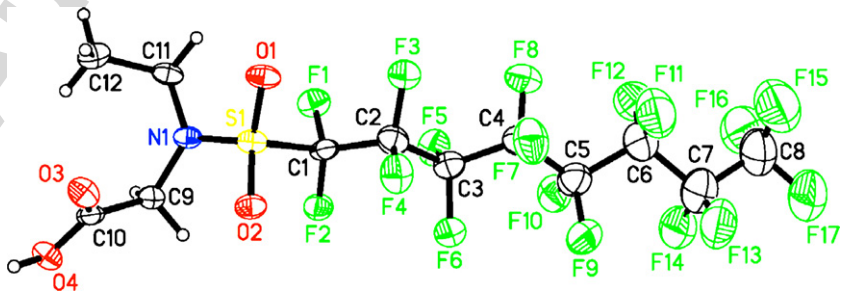


Fig. 3. View of 2-(*N*-ethyl-perfluorooctanesulfonamido) acetic acid (**12**) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

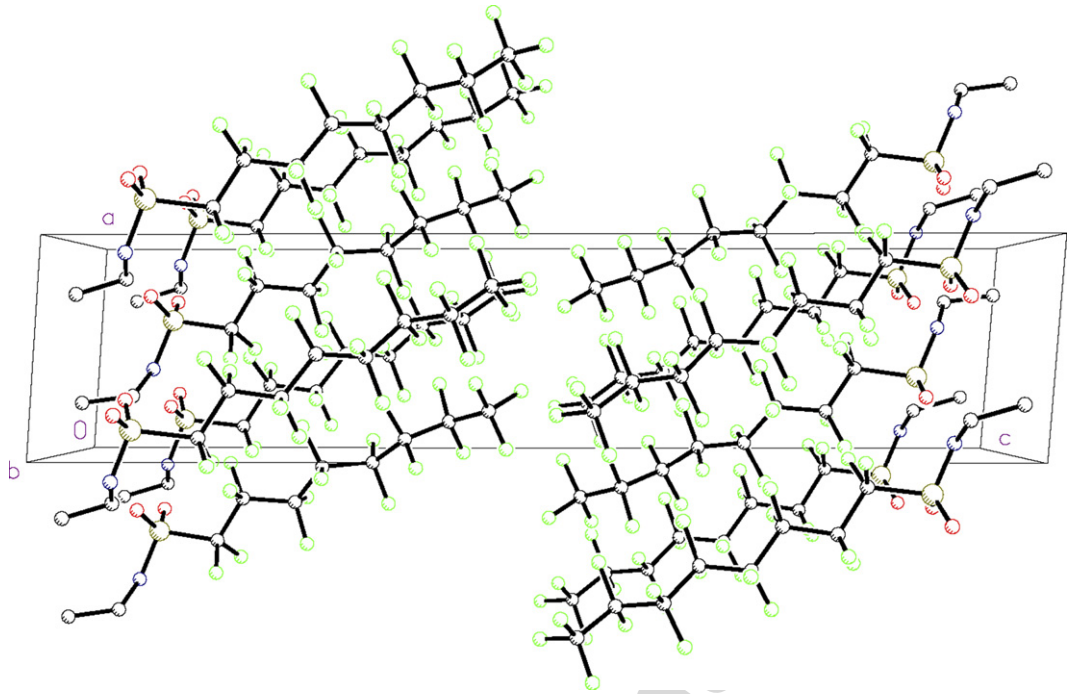


Fig. 4. Packing diagram of *N*-ethyl-perfluorooctane-1-sulfonamide (**4b**), viewed down the *b* axis, illustrating the bilayers of **4b** oriented parallel to the *a*–*b* plane. H atoms have been omitted for clarity.

As illustrated in Figs. 4–6, the packing diagrams of all three crystal structures show segregation of the electronically different parts of the perfluorooctanesulfonamide molecules to form bilayers with a perfluoroalkyl core which are separated by the sulfonamide groups. Specifically, both **4b** and **7e** form bilayers parallel to the *a*–*b* plane (Figs. 4 and 5), whereas, **12** forms bilayers parallel to the *b*–*c* plane (Fig. 6). The respective perfluorooctanesulfonamides molecules are tilted within the bilayer by approximately 60° (**4b**), 35° (**7e**) and 80° (**12**), respectively. The formation of bilayers by all three perfluorooctanesulfonamides is not a surprising observation because A···B interactions (e.g., interactions between different parts of a molecule) are usually less favorable than the mean of A···A and B···B interactions (i.e., interactions between similar parts of a molecule) [22]. This is particularly true for the hydrophobic and lipophobic perfluoroalkyl chains and, in the

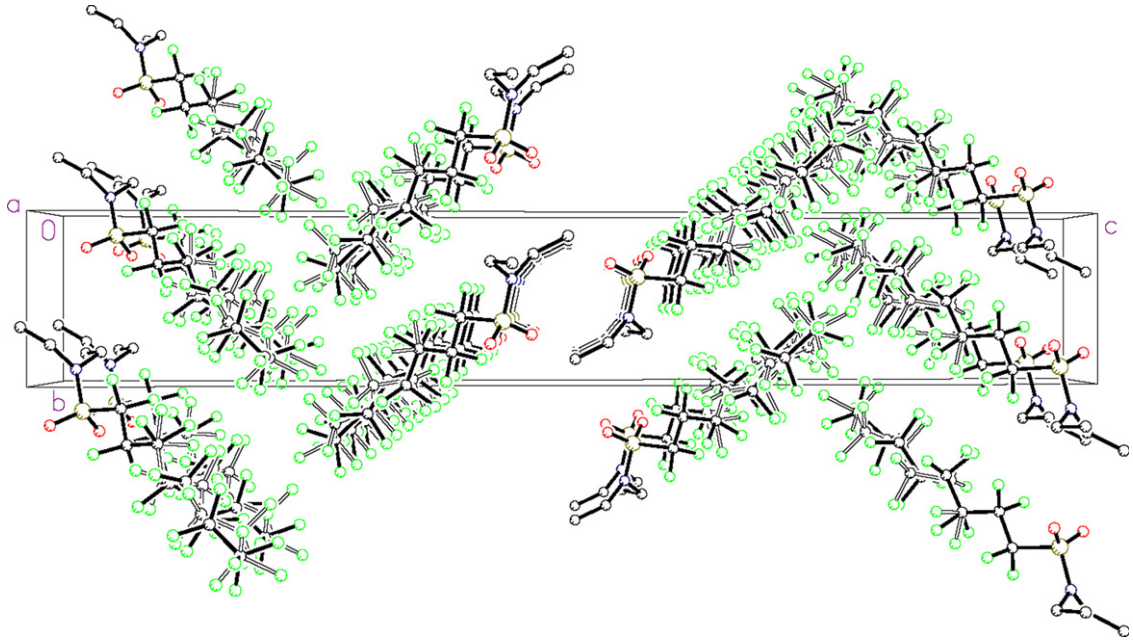


Fig. 5. Packing diagram of *N*,*N*-diethyl-perfluorooctane-1-sulfonamide (**7e**), viewed down the *b* axis, illustrating the bilayers of **7e** oriented paralel to the *a*–*b* plane. H atoms have been omitted for clarity.

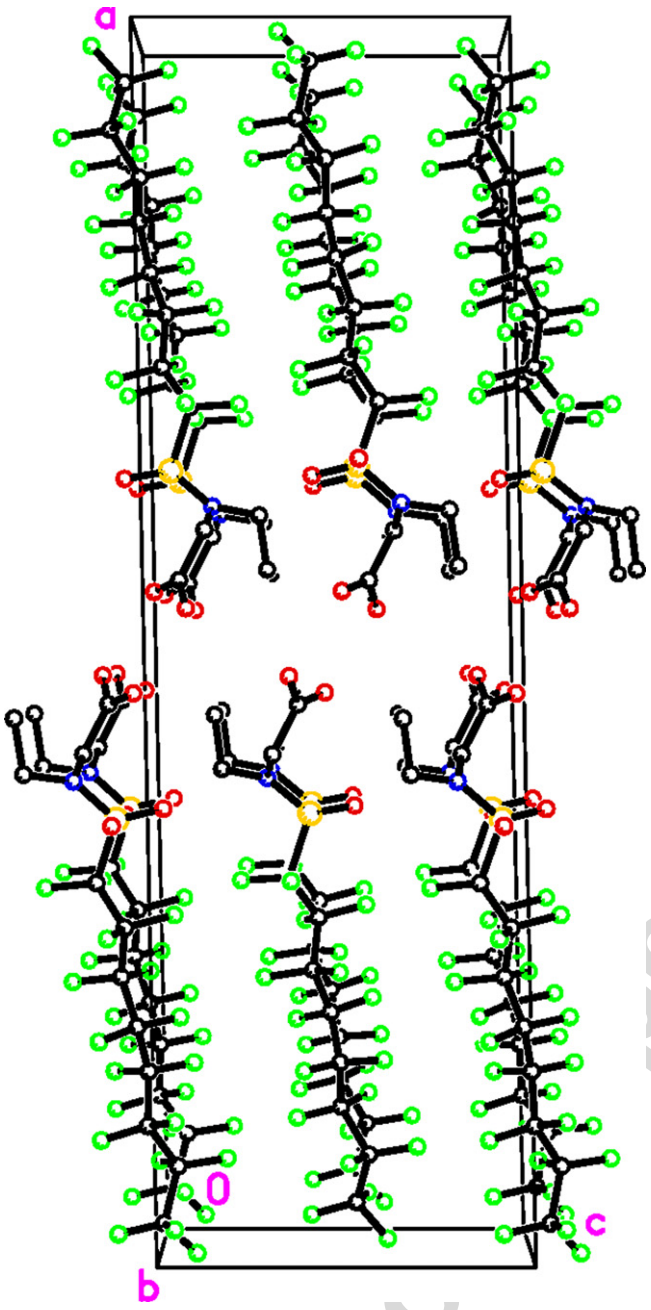


Fig. 6. Packing diagram of 2-(*N*-ethyl-perfluorooctanesulfonamido) acetic acid (**12**), viewed down the *b* axis, illustrating the bilayers of **12** oriented paralel to the *b*–*c* plane. H atoms have been omitted for clarity.

case of **12**, the –COOH groups which from dimers linked by hydrogen bonds in the crystal structures.

The crystal structures of **4b**, **7e** and **12** have several structural similarities that are the result of both steric and electronic effects. The $–CH_2N(R)–S(=O)_2–CF_2–$ (R=H or CH_2) fragment in all three structures adopts a staggered conformation with a trigonal planar nitrogen atom. The ethyl groups in both structures are on the site opposite to the perfluorooctyl group to minimize steric crowding around the S–N bond. A similar conformation has been reported for *N*,*N*-dibenzyl-perfluorobutane-1-sulfonamide in both the solid state and in solution [16]. The S–N bonds of **4b** (1.574(5) and 1.576(5) Å), **7e** (1.581(5) Å) and **12** (1.590(9) Å) are short due to hyperconjugation with the perfluorooctyl chain [16]. For comparison, the unweighted sample mean for $C–SO_2–N(H)C$ and $C–SO_2–N(C)C$ bonds is 1.633 ± 0.019 and 1.642 ± 0.024, respectively [24]. The short S–N bond length suggests an appreciable double-bond character, and thus a hindered rotation around the S–N bond.

Table 2
Geminal-coupling-constant values, coalescence temperature, chemical shift difference at the coalescence temperature $\Delta\nu$ and barriers of rotation about the S–N bond $\Delta G^{\neq}$ for several sulfonamides in d_6-acetone

Sulfonamide	Geminal coupling constant[a] (Hz)	Coalescence temperature (K)	$\Delta\nu$ (Hz)	Free energy of activation $\Delta G^{\neq}$ (kJ mol^{-1})
7e	14.4	309	36	64
7f	14.3	312	99	62
9a[b]	n.d.	319	129	63
9b[b]	14.6	315	52	64
10a[b,c]	15.1[b]	319	136	63
	12.1[c]	307	104	63
10b[b]	15.5	307	47	63
12	n.d.	312	3	71

n.d. = not determined.
[a] Determined at temperatures below 273 K, i.e. well below the coalescence temperatures of the respective sulfonamide.
[b] $–NCH_2CH_2OR$.
[c] $–NCH_2CH_2OR$.

We used ^{1}H NMR spectroscopy to further investigate the hindered rotation around the S–N bond of all dialkylated perfluorooctanesulfonamides. At ambient temperature several of the $–N–CH_2–$ systems show magnetically nonequivalent protons and at temperatures below 0 °C typical geminal coupling constant of approximately 14.3–18.5 Hz were observed (Table 2). The free energy of activation $\Delta G^{\neq}$ for several $–N–CH_2–$ systems was estimated using variable temperature NMR spectroscopy to be approximately 62–71 kJ mol^{-1} [16,25]. These values are in good agreement with literature values [16].

3. Conclusions

In summary, the synthesis and characterization of several environmentally relevant perfluorooctanesulfonamides and related perfluorobutanesulfonamides from fluoride **1** or **2** is described. These sulfonamides are needed for environmental and toxicological studies but are also useful as analytical standards. The purification of the perfluorooctanesulfonamides represented a challenge because of the impurities present in commercial perfluorooctanesulfonyl fluoride (**1**). Although fluorinated impurities can largely be removed by column chromatography, some branched C_8F_{17} isomers are still present in the final product. The ratio of these branched isomers to the linear sulfonamides can be easily determined using ^{19}F NMR spectroscopy.

4. Experimental

4.1. General experimental procedures

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance-300 spectrometer. All NMR chemical shifts (δ) are reported in parts per million (ppm) and were determined relative to TMS for ^{1}H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. Signals of the linear perfluoroalkyl chains were assigned and labeled as described previously [26]. A GC 6890 series (Agilent Technologies, Palo Alto, CA, USA) gas chromatograph equipped with a J&W Scientific HP-1 capillary column (Agilent Technologies, Wilmington, USA) and a flame ionization detector was used to monitor the reactions and to determine the purity of all compounds. The following program was employed: initial temperature: 50 °C, initial time: 1 min, rate: 10 °C/min, final temperature: 250 °C, final time: 2 min. Combustion analyses were obtained from Atlantic Microlab Inc. (Norcross, GA, USA).

Volatile amides without acidic protons were analyzed in the University of Iowa High Resolution Mass Spectrometry Facility using a ThermoFinnigan Voyager GC–MS system (ThermoFinnigan, San Jose, CA, USA) equipped with a ZB-1 column (Phenomenex, Torrance, CA, USA). Additional structural confirmation for amide with acidic protons was provided by LC/MS/MS. In short, solutions of the purified derivatives were dissolved in methanol at a concentration of 5 μg/mL and subsequently infused into a Micromass Quattro LC/MS/MS system equipped with an electrospray (ESI) interface and operated in the negative ion monitoring mode. Confirmation was obtained by observation of the corresponding deprotonated molecular ions ($[M–H]^-$) coupled with MS/MS product ion scans of the deprotonated molecular ions showing unique and predictable fragmentation of the precursor ions. The observed fragmentation patterns of several perfluorooctanesulfonamides were consistent with spectra obtained from samples that had been provided by the 3M Company [27,28].

4.2. General procedures for the synthesis of N-alkyl perfluorooctanesulfonamide derivatives

- *Method A*: Perfluorooctanesulfonyl fluoride **1** (5.0 g, 10 mmol) was placed under a nitrogen atmosphere in a three necked round bottom flask containing dry ether (75 mL) and equipped with a reflux condenser. A two-fold excess of the respective alkyl amine **3a** or **3b** (30 mmol) was passed slowly through the reaction mixture at 0–5 °C over a period of 1 h, the reaction mixture was allowed to stir for 24 h at ambient temperature and heated under reflux for 1 h. The reaction mixture was cooled to room temperature and a white precipitate was filtered off. The precipitate was washed with ether (30 mL). The solvent was removed by rotary evaporation under reduced pressure. The crude product was further purified by column chromatography using silica gel (25–40 μm mesh) with hexane and ethyl acetate as eluent (gradient from 100% to approximately 93% hexane).
- *Method B*: Perfluoroalkanesulfonyl fluoride **1** or **2** (25 g, 50 mmol) and triethylamine (10.1 g, 100 mmol) were placed under a nitrogen atmosphere in a three necked round bottom flask containing dry ether or acetonitrile (100 mL) and equipped with a reflux condenser. The respective alkyl amine **3a** or **3b** (60 mmol) was passed slowly through the reaction mixture over a period of 3 h at 0–5 °C, the reaction mixture was allowed to stir for 14 h at ambient temperature and refluxed for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed from the reaction mixture by rotary evaporation under reduced pressure. The resultant crude product was dissolved in acetone (20 mL), absorbed on silica gel (25–40 μm mesh) and purified by column chromatography as described under Method A.
- *Method C*: An excess of the alkyl amine **3a** or **3b** was slowly passed through perfluorooctanesulfonyl fluoride **1** (3.65 g, 7.3 mmol). The mixture was stirred at ambient temperature for 5 h and the resulting dark brown, waxy solid was treated with Zn (2 g) and HCl (5 mL) to decolorize the product. The product was purified by Kugelrohr distillation to yield the product as a slightly brown, waxy solid. Crystals of **4b** suitable for crystal structure analysis were obtained by recrystallization from reagent alcohol/dichloromethane at 4 °C.

4.2.1. N-methyl-perfluorooctane-1-sulfonamide (*4a*)

mp 104 °C (Lit. 101–103 °C [4]); IR (KBr); ν 3335 (–NH–), 1439, 1362, 1241, 1206, 1182, 1152, and 1126 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO): δ 1.9 (3H, s, –CH_3), 8.4 (1H, br s, –*H*N–); ^{13}C NMR (75 MHz, d_6-DMSO): δ 29.0 (–*C*H_3); ^{19}F NMR (288.8 MHz, d_6-DMSO): δ −80.6 (CF_3), −112.1 (α-CF_2), −119.8 (β-CF_2), −121.2 (3 × CF_2), −122.2 (ζ-CF_2), −125.7 (θ–CF_2); MS, *m/z* (rel. int.): 512 $[M - H]^+$ (100%). Anal. Calcd for $C_9H_4F_{17}NO_2S$: C, 21.07; H, 0.79; S, 6.25; N, 2.73. Found: C, 21.23; H, 0.72; S, 6.45; N, 2.97.

4.2.2. N-Ethyl-perfluorooctane-1-sulfonamide (*4b*)

mp 87 °C (Lit. 87–88.5 °C [29] and 120 °C [5]); IR (KBr); ν 3318 (–NH–), 1454, 1363, 1238, 1206, 1152, 1126, and 1072 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO): δ 1.2 (3H, t, J = 7.2 Hz, –CH_3), 3.2 (2H, "q", J = 7.2 Hz, –CH_2–), 9.3 (1H, br s, –*H*N–); ^{13}C NMR (75 MHz, d_6-DMSO): δ 15.1 (–*C*H_3), 38.7 (–*C*H_2–); ^{19}F NMR (288.8 MHz, d_6-DMSO): δ −80.6 (CF_3), −112.1 (α-CF_2), −119.8 (β-CF_2), −121.1 (3 × CF_2), −122.2 (ζ-CF_2), −125.7 (θ–CF_2); MS, *m/z* (rel. int.): 526 $[M - H]^+$ (1 0 0). Anal. Calcd for $C_{10}H_6F_{17}NO_2S$: C, 22.78; H, 1.15; S, 6.08; N, 2.66. Found: C, 23.03; H, 1.28; S, 6.15; N, 2.85.

4.2.3. N-Methyl-perfluorobutane-1-sulfonamide (*5a*)

Eighty percent; mp 36–37 °C; IR (KBr): ν 3338 (–NH–), 1429, 1364, 1235, 1206, 1186, and 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.03 (3H, s, –CH_3), 5.13 (1H, br s, –*H*N–). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.7 (–*C*H_3); ^{19}F NMR (288.8 MHz, $CDCl_3$): δ −81.28 (CF_3), −112.72 (α-CF_2), −121.94 (β-CF_2), −126.51 (γ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 312(100), 219(22), 112(10). Anal. Calcd for $C_5H_4F_9NO_2S$:

C, 19.18; H, 1.29; S, 10.24; N, 4.47. Found: C, 19.11; H, 1.15; S, 10.06; N, 4.38.

4.2.4. N-Ethyl-perfluorobutane-1-sulfonamide (**5b**)

Sixty-one percent; mp 35–36 °C (Lit. 40 °C [9]); IR (KBr): ν 3321 (–NH–), 1437, 1373, 1238, 1206, 1190, and 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, J = 7.2 Hz, –CH_3), 3.41 (2H, q, J = 7.2 Hz, –CH_2–), 5.06 (1H, br s, –H N–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.0 (–CH_3), 40.3 (–CH_2–); ^{19}F NMR (288.8 MHz, $CDCl_3$): δ –81.30 (CF_3), −113.20 (α-CF_2), −121.83 (β-CF_2), −126.53 (γ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 326(100), 219(25), 126(10). Anal. Calcd for $C_6H_6F_9NO_2S$: C, 22.03; H, 1.85; S, 9.80; N, 4.28. Found: C, 22.31; H, 1.89; S, 9.78; N, 4.31.

4.2.5. N-(2-Methoxy-ethyl)-perfluorobutane-1-sulfonamide (**5c**)

Forty-seven percent; Colorless liquid; IR (Neat): ν 3310–3146 (–NH), 1434, 1376, 1237, 1188, 1140, 1082, and 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.40 (3H, s, –OCH_3), 3.48–3.56 (4H, *m*, –NCH_2CH_2O–), 6.11 (1H, br s, –N*H*–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.4 (–NCH_2–), 59.0 (–OCH_3), 71.4 (–CH_2O–); ^{19}F NMR (288.8 MHz, $CDCl_3$): δ –81.29 (CF_3), −113.25 (α-CF_2), −121.80 (β-CF_2), −126.00 (γ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 358 $[M + H]^+$ (1), 326 $[M–OCH_3]^+$ (5), 312 $[M–CH_2OCH_3]^+$ (18), 248(18), 219(30), 131(30), 69(100). Anal. Calcd for $C_7H_8F_9NO_3S$: C, 23.54; H, 2.26; S, 8.98; N, 3.92. Found: C, 23.55; H, 2.26; S, 8.88; N, 3.87.

4.3. General procedures for the synthesis of N,N-dialkyl perfluorooctanesulfonamides (**7d–g** and **8g**)

- *Method D*: Perfluorooctanesulfonyl fluoride **1** (25 g, 50 mmol) was dissolved in anhydrous ether (100 mL) under a nitrogen atmosphere. The dialkyl amine **6d–g** (100 mmol) was added slowly to the reaction mixture over a period of 30 min, allowed to stir for 16 h at room temperature and heated under reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed by rotary evaporation under reduced pressure. The crude product was purified by column chromatography as described above under Method A.
- *Method E*: Perfluorooctanesulfonyl fluoride **1** (3.65 g, 7.3 mmol) and *N*,*N*-diethylamine (3.8 mL, 37 mmol) were stirred at ambient temperature for 4 h. Excess *N*,*N*-diethylamine was removed under reduced pressure and the product was recrystallized at 4 °C from reagent alcohol/dichloromethane to give **7e** as a slightly yellow, waxy solid.

4.3.1. N,N-dimethyl-perfluorooctane-1-sulfonamide (**7d**)

mp 80–81 °C; IR (KBr); ν 2966, 1483, 1369, 1238, 1212, 1149, and 1061 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone): δ 3.2 (6H, s, –CH_3); ^{13}C NMR (75 MHz, d_6-acetone): δ 39.6 (–CH_3); ^{19}F NMR (288.8 MHz, d_6-acetone): δ −81.3 (CF_3), −112.0 (α-CF_2), −121.0 (β-CF_2), 122.1 (3 × CF_2), −123.2 (ζ-CF_2), −125. 6 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 526 $[M - H]^+$ (1), 108(100). Anal. Calcd for $C_{10}H_6F_{17}NO_2S$: C, 22.78; H, 1.15; S, 6.08; N, 2.68. Found: C, 22.82; H, 1.04; S, 6.16; N, 2.68.

4.3.2. N,N-Diethyl-perfluorooctane-1-sulfonamide (**7e**)

mp 48–50 °C; IR (KBr); ν 2992, 1468, 1385, 1244, 1217, 1155, 1055, and 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.3 (6H, t, J = 7.1 Hz, –CH_3), 3.4–3.7 (4H, m, –NCH_2–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (–CH_3), 42.9 (–NCH_2–); ^{19}F NMR (288.8 MHz, $CDCl_3$): δ −81.3 (CF_3), −113.1 (α-CF_2), −120.7 (β-CF_2), −122.2 (3 × CF_2), −123.2 (ζ-CF_2), −126.6 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 540 $[M - CH_3]^+$ (11), 448 $[C_8F_{16}SO]^+$ (8). Anal. Calcd for $C_{12}H_{10}F_{17}NO_2S$: C, 25.96; H, 1.82; S, 5.77; N, 2.52. Found: C, 25.95; H, 1.86; S, 5.76; N, 2.64.

4.3.3. N-Ethyl-N-methyl-perfluorooctane-1-sulfonamide (**7f**)

mp 44–46 °C; IR (KBr); ν 1375, 1240, and 1150 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone): δ 1.3 (3H, t, J = 7.2 Hz, –CH_3), 3.2 (3H, s, –NCH_3), 3.3–3.8 (2H, m, –NCH_2–); ^{13}C NMR (300 MHz, d_6-acetone): δ 13.9 (–CH_3), 35.4 (–NCH_3), 47.2 (–NCH_2–); ^{19}F NMR (288.8 MHz, d_6-acetone): δ −80.5 (CF_3), −112.1 (α-CF_2), −119.9 (β-CF_2), −121.2 (3 × CF_2), −122.1 (ζ-CF_2), −125.6 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 526 $[M - CH_3]^+$ (2), 462 $[C_8F_{16}SON]^+$ (4). Anal. Calcd for $C_{11}H_8F_{17}NO_2S$: C, 24.41; H, 1.49; S, 5.92; N, 2.59. Found: C, 24.68; H, 1.41; S, 5.98; N, 2.49.

4.3.4. 4-(Heptadecafluorooctane-1-sulfonyl)-morpholine (**7g**)

mp 118 °C (Lit. 127–129 °C [30]); IR (KBr): ν 1390, 1268, 1184, 1148, 1134, 1113, 1080, and 969 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone): δ 3.4–4.1 (8H, m); ^{13}C NMR (75 MHz, d_6-acetone): δ 48.0 (–NCH_2–), 67.2 (–CH_2O–); ^{19}F NMR (288.8 MHz, d_6-acetone): δ −80.51 (CF_3), −112.03 (α-CF_2), −119.83 (β-CF_2), −121.15 (3 × –CF_2–), −122.11 (ζ-CF_2), −125.63 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 569 $[M]^+$ (23), 526(14), 486(4), 442(5), 150(100), 134(34), 56(82); Anal. Calcd for $C_{12}H_8F_{17}NO_3S$: C, 25.32; H, 1.42; S, 5.63; N, 2.46. Found: C, 25.45; H, 1.56; S, 5.56; N, 2.65.

4.3.5. 4-(Nonafluorobutane-1-sulfonyl)-morpholine (**8g**)

Sixty-one percent; mp 81 °C; IR (KBr): ν 1390, 1265, 1236, 1187, and 1138 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone): δ 3.3–4.1 (8H, m); ^{13}C NMR (75 MHz, d_6-acetone): δ 48.0 (–N–CH_2–), 67.2 (–CH_2–O–); ^{19}F NMR (288.8 MHz, d_6-acetone): δ −80.62 (CF_3), −112.28 (α-CF_2), 120.92 (β-CF_2), −125.62 (γ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 369 $[M]^+$ (7), 326(6), 242(7), 150(98), 134(24), 86(100). Anal. Calcd for $C_8H_8F_9NO_3S$: C, 26.03; H, 2.18; S, 8.68; N, 3.79. Found: C, 26.23; H, 2.22; S, 3.75; N, 8.67.

4.4. General procedure for the N-alkylation of N-alkyl perfluoroalkanesulfonamide derivatives **4** and **5**

The respective *N*-alkyl perfluorooctanesulfonamide **4** or **5** (5.0 mmol), dry potassium carbonate (1.4 g, 10 mmol) and

corresponding bromo- or iodo-alkyl derivative (5.5 mmol) were dissolved in acetone (25 mL) and the resultant mixture was heated under reflux until complete conversion. The reaction mixture was allowed to cool to room temperature and filtered. The precipitate was washed with acetone (2 × 10 mL) and the solvent was removed by rotary evaporation under reduced pressure. The crude product was purified by column chromatography using silica gel with hexane and ethyl acetate (96:4) as eluent.

4.4.1. N-(2-Hydroxyethyl)-N-methyl-perfluorooctane-1-sulfonamide (**9a**)

Ninety-six percent; mp 83 °C; IR (KBr); ν 3420 (–OH), 1384, 1219, and 1151 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone): δ 3.2 (3H, s, –CH_3), 3.4 (1H, m, –NCH_2–), 3.7 (3H, m, –CH_2CH_2OH), 4.1 (1H, t, J = 5.5 Hz, –CH_2OH); ^{13}C NMR (75 MHz, CD_3OD): δ 37.2 (–CH$_3$), 54.3 (–NCH_2–), 60.6 (–CH$_2$OH); ^{19}F NMR (288.8 MHz, CD_3OD): δ –80.5 (CF_3), −112.6 (α-CF_2), −119.8 (β-CF_2), −121.2 (3 × CF_2), −122.1 (ζ-CF_2), −125.6 (θ-CF_2); MS, *m/z* (rel. int.): 616(50), 141(100), 119(55), 223(15). Anal. Calcd for $C_{11}H_8F_{17}NO_3S$: C, 23.71; H, 1.45; S, 5.75; N, 2.51. Found: C, 23.82; H, 1.33; S, 5.82; N, 2.53.

4.4.2. N-Ethyl-N-(2-hydroxyethyl)-perfluorooctane-1-sulfonamide (**9b**)

Ninety-nine percent; mp 70 °C (Lit. 65–71 °C [4]); IR (KBr); ν 3412 (–OH), 1384, 1212, and 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.3 (3H, t, J = 7.1 Hz, –CH_2CH_3), 2.2 (1H, br s, –CH_2OH), 3.3–3.8 (4H, m, –CH_2–), 3.8 (2H, "t", J = 5.3 Hz, –CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (–CH_2CH_3), 45.0 (–NCH_2CH$_3$), 49.9 (–NCH_2CH$_2$OH), 60.8 (–CH$_2$OH); ^{19}F NMR (288.8 MHz, $CDCl_3$): δ −81.3 (CF_3), −112.6 (α-CF_2), −120.7 (β-CF_2), −122.2 (3 × –CF_2–), −123.2 (ζ-CF_2), −126.6 (θ-CF_2); MS, *m/z* (rel. int.): 630(60), 141(100), 119(75), 223(15). Anal. Calcd for $C_{12}H_{10}F_{17}NO_3S$: C, 25.23; H, 1.76; S, 5.61; N, 2.45. Found: C, 25.27; H, 1.83; S, 5.71; N, 2.59.

4.4.3. 2-(N-Methyl-perfluorooctylsulfonamido) ethyl acetate (**10a**)

Eighty-six percent; mp 82–83 °C; IR (KBr); ν 1732 (–C=O), 1380, 1373, 1236, 1204, and 1151 cm^{-1}; ^1H NMR (300 MHz, d_6-acetone): δ 2.9 (3H, s, –OCOCH_3), 3.2 (3H, s, –NCH_3), 3.5–4.1 (2H, m, (–NCH_2–), 4.2–4.5 (2H, br m, –CH_2OCOCH$_3$); ^{13}C NMR (75 MHz, d_6-acetone): δ 21.7 (–OCOCH$_3$), 37.6 (–CH$_3$), 51.8 (–NCH_2–), 62.2 (–CH_2OCOCH$_3$), 171.9 (–OCOCH$_3$); ^{19}F NMR (288.8 MHz, d_6-acetone): δ −80.5 (CF_3), −111.7 (α-CF_2), −119.9 (β-CF_2), −121.2 (3 × –CF_2–), −122.2 (ζ-CF_2), −125.6 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 539 [M − CH_3COOH]$^+$ (12), 526 [M − $C_3H_6O_2$]$^+$ (28), 462 [$C_8F_{16}SON$]$^+$ (40). Anal. Calcd for $C_{13}H_{10}F_{17}NO_4S$: C, 26.06; H, 1.68; S, 5.35; N, 2.34. Found: C, 26.11; H, 1.59; S, 5.57; N, 2.46.

4.4.4. 2-(N-Ethyl-perfluorooctylsulfonamido) ethyl acetate (**10b**)

Ninety-two percent; mp 104 °C; IR (KBr); ν 2966, 2934, 1732 (C=O), 1379, 1240, 1214, and 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.3 (3H, t, J = 7.1 Hz, –CH_3), 2.1 (3H, s, –OCOCH_3), 3.4–3.9 (4H, m, –NCH_2–), 4.3 (2H, t, J = 5.6 Hz, –CH_2OCOCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (–CH$_3$), 20.6 (–OCOCH$_3$), 44.4 (–CH$_2$CH$_3$), 46.4 (–NCH_2–), 61.2 (–CH$_2$OCOCH$_3$), 170.6 (–OCOCH$_3$); ^{19}F NMR (288.8 MHz, d_6-acetone): δ −80.5 (CF_3), −112.0 (α-CF_2), −119.8 (β-CF_2), −121.1 (3 × –CF_2–), −122.1 (ζ-CF_2), −125.6 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 553 [M − CH_3COOH]$^+$ (5), 540 [M − $C_3H_5O_2$]$^+$ (42), 448 [$C_8F_{16}SO$]$^+$ (27). Anal. Calcd for $C_{14}H_{12}F_{17}NO_4S$: C, 27.42; H, 1.97; S, 5.23; N, 2.28. Found: C, 27.37; H, 1.79; S, 5.26; N, 2.35.

4.4.5. Methyl 2-(N-ethyl-perfluorooctanesulfonamido) acetate (**11**)

Ninety percent; mp 55–56 °C; IR (KBr); ν 1756, 1379, 1202, 1180, 1167, and 1124 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 1.24 (3H, t, J = 7.1 Hz, –CH_3), 3.5–3.7 (2H, m, –CH_2CH$_3$), 3.78 (2H, s, –CH_2CO$_2$–), 4.27 (2H, s, –CO$_2$CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 13.9 (–CH$_3$), 46.9 (–CH$_2$CH$_3$), 49.2 (–CH$_2$CO$_2$–), 53.1 (–CO$_2$CH_3), 170.1 (–CO$_2$CH$_3$); ^{19}F NMR (288.8 MHz, CD_3OD): δ −80.48 (CF_3), −112.41 (α-CF_2), −119.69 (β-CF_2), −121.15 (3 × CF_2), −122.13 (ζ-CF_2), −125.59 (θ-CF_2); GC–MS 40 eV, *m/z* (rel. int.): 600 [M + H] (68), 540(50), 448(40), 56(100); Anal. Calcd for $C_{13}H_{10}F_{17}NO_4S$: C, 26.06; H, 1.68; S, 5.35; N, 2.34. Found: C, 26.22; H, 1.73; S, 5.32; N, 2.41.

4.5. Synthesis of 2-(N-ethyl-perfluorooctanesulfonamido)acetic acid **12**

Methyl 2-(*N*-ethyl-perfluorooctanesulfonamido) acetate **11** was dissolved in 1N NaOH (1.5 equiv., 1.4 mL) and 1,4-dioxane (3 mL), stirred for 2 h at 65 °C, diluted with water (20 mL) and filtered. The filtrate was acidified with 1N HCl (10 mL) and extracted with ethyl acetate (∼20 mL). The organic layer was washed with water (2 × 20 mL) and dried over sodium sulfate. The solution was treated with charcoal, filtered and concentrated under reduced pressure to give **12** as a white solid in 40% yield.

mp 156–157 °C (Lit. 162 °C [31]); IR (KBr); ν 1728, 1379, 1201, 1168, 1149, and 1124 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.25 (3H, t, J = 7.1 Hz, –CH_3), 3.63 (2H, q, J = 7.1 Hz, –CH_2CH$_3$), 4.24–4.56 (2H, m, –CH_2CO$_2$–); ^{13}C NMR (75 MHz, CD_3OD): δ 13.9 (–CH$_3$), 46.8 (–CH$_2$CH$_3$), 49.1 (–CH$_2$CO$_2$–), 170.1 (–CO$_2$H); ^{19}F NMR (288.8 MHz, CD_3OD): δ −80.64 (CF_3), −112.38 (α-CF_2), −119.0 (β-CF_2), −121.13 (3 × CF_2), −122.04 (ζ-CF_2), −125.59 (θ-CF_2); MS, *m/z* (rel. int.): 584(95), 141(35), 369(20), 499(20), 223(10), 217(10). Anal. Calcd for $C_{12}H_8F_{17}NO_4S$: C, 24.63; H, 1.38; S, 5.48; N, 2.39. Found: C, 24.37; H, 1.59; S, 5.71; N, 2.29.

4.6. Synthesis of N,N-dialkyl perfluorooctanesulfonamides using the Mitsunobu reaction

4.6.1. General procedure for the Mitsunobu reaction [18]

A solution of DIAD (diisopropyl azodicarboxylate, 0.3 g, 15 mmol) in ether (2 mL) was added slowly to a sonicated

mixture of alcohol **13** [32] or methyl glycolate (10 mmol), *N*-ethyl-perfluorooctanesulfonamide **4b** (10 mmol) and triphenylphosphine (0.4 g, 15 mmol) in anhydrous ether (3 mL) at 0 °C. After completion of the addition, the reaction mixture was sonicated at 25 °C until the starting material had disappeared. The solvent was removed under reduced pressure and the product was purified by column chromatography using silica gel using ethyl acetate (0–5%) and hexane (100–98%) as eluent.

4.6.2. 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-octane-1-sulfonic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-ethyl-amide (**14**)

Ninety-eight percent; mp 29 °C; IR (KBr); ν 2932, 1391, 1243, 1215, and 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (6H, s, 2 × –SiCH_3), 0.90 (9H, s, –C(CH_3)$_3$), 1.28 (3H, t, J = 7.2 Hz, –CH_2CH_3), 3.35–3.75 (4H, m, –N(CH_2CH_3)CH_2 CH_2–), 3.81 (2H, t, J = 5.5 Hz, –CH_2O–); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.6 (2 × –SiCH_3), 13.9, 18.1, 25.7 (–C(CH_3)$_3$), 45.1, 49.7, 62.2; ^{19}F NMR (288.8 MHz, $CDCl_3$): δ −81.26 (CF_3), −112.95 (α-CF_2), −120.78 (β-CF_2), −122.18, −122.22 (3 × CF_2), 123.20 (ζ-CF_2), −126.63 (θ-CF_2); Anal. Calcd for $C_{18}H_{24}F_{17}NO_3SSi$: C, 31.54; H, 3.53; S, 4.68; N, 2.04. Found: C, 31.64; H, 3.48; S, 4.57; N, 2.07.

4.7. Procedure for the hydrolysis of TBDMS protected ether **14**

The TBDMS protected ether **14** (0.15 mmol) was dissolved in 1N HCl and methanol (5 mL, 1:1, v/v) and stirred for 2 days at ambient temperature. The solvent was removed under reduced pressure. The product was extracted with ethyl acetate (5 mL), the combined organic extracts were washed with water (2 × 5 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give **9b** in 96% yield.

4.8. Synthesis of perfluorooctane-1-sulfonamide (**16**)

Perfluorooctanesulfonyl fluoride **1** (2.0 g, 3.9 mmol) was dissolved in ether (5 mL) and an aqueous solution of sodium azide (1.2 g, 19 mmol, in 1 mL of water) was added. The reaction mixture was allowed to stir at room temperature for 12 h. Extraction with ether (15 mL) and evaporation of the solvent gave crude perfluorooctane-1-sulfonyl azide **15** as a colorless liquid. The crude azide **15** was directly converted into the amide **16** without further purification. The azide **16** was added to a suspension of Zn dust (1.3 g, 20 mmol) in ether (5 mL). Hydrochloric acid solution (5N, 3 mL) was added slowly to this suspension until the Zn dust was completely dissolved. The mixture was stirred for 24 h at room temperature and extracted with ether (3 × 10 mL). Evaporation of the solvent under reduced pressure gave a waxy, brown solid. This solid was dissolved in reagent alcohol and the sulfonamide **16** was precipitated as a white waxy solid with dichloromethane.

IR (KBr); ν 3344, 3176, 3058, 1378, 1229, 1203, and 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.2 (2H, br s, NH_2); ^{19}F NMR (288.8 MHz, $CDCl_3$): δ −80.7 (CF_3), −112.8 (α-CF_2), −119.8 (β-CF_2), −121.1 ζ-CF_2), −122.2 (3 × –CF_2–), −125.7 (θ-CF_2); GC–MS *m/z*, (rel. int.): 499.9 $[M]^+$ (30). Anal. Calcd for $C_8H_2F_{17}NO_2S$: C, 19.25; H, 0.40; S, 6.42; N, 2.81. Found: C, 19.49; H, 0.41; S, 6.35; N, 2.90.

4.9. X-ray crystallography [33]

Flaky platelet crystals of **4b** (synthesized using Method C), **7e** (synthesized using Method E) and **12** were obtained by recrystallization from reagent alcohol/dichloromethane at 4 °C. These crystals proved far too small for analysis on conventional small-molecule diffraction equipment but gave recordable, albeit weak, diffraction using Cu Kα X-rays on a specially configured hybrid small/macromolecule diffraction system based on the Bruker-Nonius X8 Proteum (Nonius FR-591 rotating anode X-ray generator, Bruker Helios graded multilayer optics, Nonius Kappa goniometer, Bruker SMART 6000 CCD detector, CryoCool LN2 low temperature device from CryoIndustries of America).

For each crystal, initial unit cell parameters were obtained using APEX2 software [34] from ω-scans at six different ϕ and χ angles. Final cell parameters were obtained (program SaintPlus in APEX2 [34]) using spot positions from all data collection frames. Crystal decay (negligible) was checked in each case by re-measurement of a portion of the first data collection scan. A total of 17,923, 19,116 and 3455 reflections were collected for **4b**, **7e** and **12**, respectively. Merging of symmetry equivalents resulted in 6071 (4288 with $I > 2\sigma(I)$), 3491 (2988 with $I > 2\sigma(I)$) and 1951 (1594 with $I > 2\sigma(I)$) reflections for **4b**, **7e** and **12**, respectively. Correction of Lorentz and polarization effects, data reduction, merging and an empirical absorption correction for each dataset were performed within the APEX2 package (programs SaintPlus and Sadabs [34]). The structures were solved by direct methods using SHELXS97 [35] and refined by full-matrix least-squares against F^2 using SHELXL97 [35]. All non-hydrogen atoms in both structures were refined with anisotropic displacement parameters (ADPs).

The structure of **7e** was extensively disordered and refinement required strong restraints. Similar bond lengths and angles within and between each disordered pair (major:minor component ratio 62:38) were restrained to similar values (commands 'SADI' and 'SAME' in SHELXL) and anisotopic displacement parameters (ADPs) were subject to rigid-body ('DELU' in SHELXL97) and approximate isotropic ('ISOR' in SHELXL97) restraints. Further, the ADPs of disordered pairs of atoms in close proximity (C3, C3′; C6, C6′; C8, C8′) were constrained to be the same.

All hydrogens atoms in both **4b**, **7e** and **12** were found in difference Fourier maps and were subsequently placed at calculated positions using appropriate riding models with distances of 0.98 Å (C–H_3), 0.99 Å (C–H_2) and 0.88 Å (N–H in **4b**). Isotropic displacement parameters were fixed at either 1.2 times (C–H2, N-H), or 1.5 times (C–H3) the U_{eq} of the carrier atom.

Acknowledgment

The authors would like to thank Air Products and Chemicals Inc. (Allentown, PA, USA) for a donation of free lecture bottles

of methyl and ethyl amine. This work was supported by grants from the National Institute of Environmental Health Sciences (ES12475 (HJL)) and the National Science Foundation (NIRT 0210517 (HJL) and NSF MRI grant #0319176 (SP)). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the funding agencies.

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