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### ARTICLE

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# Phase-out-compliant fluorosurfactants: Unique methimazolium derivatives including room temperature ionic liquids

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Expedient alkylations of 1-methyl-3H-imidazole-2-thione, a pharmaceutical active ingredient available in bulk quantities, provide high yield access to numerous protonated, or quaternized imidazoliums with chemospecific attachment of the fluoroponytail at the 2-mercapto functionality. The deprotonated primary target products represent valuable nitrogen heterocyclic bases, capable of further substitution, and salt or complex formation. Specific physicochemical characteristics that are relevant for phase and surface responsive behavior, e.g. critical micelle concentration, oleophobicity, depression of the aqueous surface tension, foam formation, emulsification of microgranular PTFE, are investigated for selected representatives and compared to the properties of common fluorosurfactants and ionic liquids. Remarkably, it is found that halogen bonding between iodide counterions of respective polyfluoroalkylmethimazolium systems and 1-iodoperfluoroalkanes, serving as the  $\sigma$ -hole partner of the halides, greatly affect the solubility profile of the resulting molecular adducts. Single-crystal X-ray structure determinations are carried out across the new fluorous substance classes. Strikingly, the helical arrangement of fluorine atoms along the chains typically encountered in polyfluorinated compounds is not found as the prevailing conformation. Rather, they are outnumbered by structural motifs exhibiting the rare zig-zag (linear alkane-like) chain conformation. Key derivatives are also subjected to preliminary ecotoxicological testing.

### Introduction

Polyfluorinated compounds (PFCs) are anthropogenic substances with a set of unique physical and chemical properties imparted by the fluorinated domain of the molecule. Beginning with the discovery of PTFE in the late 1930s, a rapid development of various PFCs combined with a growing understanding of their properties has unlocked numerous application areas.<sup>1</sup> In particular their water and oil repellency, thermal stability, low human immune response, oxygen affinity,<sup>2, 3</sup> and surfactant properties qualify PFCs for a broad portfolio of industrial and consumer-use products.<sup>4</sup> Meanwhile,

a plethora of poly- and perfluorinated compounds with and without various functional groups is available. For instance, unfunctionalized polymeric PFCs can be used as coating materials to render metals resistant towards chemical impact. Combining a poly- or perfluorinated alkyl chain with a polar functional group (e.g. perfluoroalkyl acids) allows for the impregnation of paper and textiles. The omniphobic tails are pointing away from the treated surface, creating a water and oil repelling layer which is desired for paper-based packaging material, and outdoor and technical clothing. These amphiphilic structures can also be utilized as surfactants and dispersants used as leveling agents for paints, lubricants, mist suppression, and, depending on the presence of co-solvent and salts, antifoaming agents, as well as foaming agents.<sup>5</sup> The latter have gained importance for firefighting. In particular, aqueous filmforming foams (AFFFs) are the most effective agents currently available to fight flammable liquid fires at airports or in military, industrial, and municipal settings.<sup>6</sup> PFCs are also found in a broad range of medical applications. Organofluorocarbon derivatives are used as artificial blood substitutes,7,8 anesthetics, ocular tamponades, and sexual doping agents.<sup>9</sup> PFCs are produced worldwide in large quantities and it became difficult to gauge global trends reliably.

There is, however, a flip-side to this. Starting in the late 1960s, continuous research on the toxicity of PFCs has raised considerable concerns on their ubiquitous use.<sup>10</sup> Long-chain PFCs bioaccumulate in humans and animals as they move along the food chain. By the early 2000s, it became apparent that



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### ARTICLE

almost all human blood samples collected worldwide contained measureable quantities of many PFCs at the ng/ml level.<sup>1, 11, 12</sup> Contamination with organofluorocarbon substances is not confined to certain distinct areas but has also entered remote regions through "global distillation", a phenomenon which describes the emission of organic pollutants in temperate regions and their transport to polar regions where they bioaccumulate in the environment (see section *Ecotoxicological considerations*).

These environmental and toxicological issues have stimulated intense research for replacement substances. Among others, it has also put a spotlight on fluorinated ionic liquids (FILs). FILs are ionic liquids (ILs) of which either the anion or cation or both contain a fluorinated moiety. FILs with a fluorous domain in the anion are predominant due to their easier synthetic accessibility via simple anion metathesis. Common anions are hexafluorophosphate, tetrafluoroborate, trifluoromethanesulfonate (triflate),

bis(trifluoromethanesulfonyl)amide (triflimide), and perfluoroalkylsulfonates.<sup>13</sup> Furthermore, a large number of organic cations with one or several perfluoroalkyl substituents have been introduced. Typical quaternized cations comprise imidazolium,<sup>14-16</sup> oxazolidinium,<sup>17</sup> morpholinium,<sup>17</sup> triazolium,<sup>18, 19</sup> pyridinium,<sup>20</sup> pyrrolidinium,<sup>21</sup> ammonium,<sup>22, 23</sup> and phosphonium<sup>24, 25</sup> structures. A comprehensive review on the properties and applications of reported FILs was given recently by Pereiro *et al.*<sup>26</sup>

Indisputably, FIL-related fluorosurfactants will hardly meet the whole set of unparalleled properties offered by classical PFCs, but nevertheless they bear considerable potential for certain applications. In this article we describe selected representatives of this new series of cationic fluorosurfactants with respect to their unique features relevant for the many facets of fluorous materials science. One key problem associated with FILs and related substances is their high cost due to limited syntheses yields. In particular, the abovementioned fluorous cations suffer from very low quaternization yield.27 This is a considerable problem as the fluorosubstituents are typically rather expensive and a high yield conversion is required to render FILs commercially feasible. We have bypassed this problem by using methimazole (1-methyl-3H-imidazole-2thione) as the basis for the fluorous cation, since it is exceptionally susceptible to high-yield alkylations. As an active pharmaceutical ingredient, namely an antithyroid agent used for the treatment of hyperthyroidism associated with Grave's disease, or preparing the overactive thyroid gland for surgery, it is also readily available.<sup>28, 29</sup> Mercaptoimidazole-based ILs and related salts with one or two perfluoroalkyl-ethyl residues allow for a more cost-competitive access to novel fluorosurfactants with high structural variability. To the best of our knowledge, polyfluoroalkyl derivatized methimazoles have not been reported by other groups.

### **Experimental**

### Materials and Methods.

Methimazole ( $\geq$ 98%) was purchased from Alfa Aesar and used as received. All other chemicals were purchased from Sigma-Aldrich.

#### Synthesis procedures.

Detailed synthesis procedures, melting points of solid substances, and analytical results are described in the Supporting Information.

2-(1H,1H,2H,2H-perfluorooctylthio) 1-methylimidazolium iodide **IIa3** 

100.0 g (0.876 mol) of 1-methyl-1,3-dihydro-2H-imidazole-2thione (methimazole) and 500.0 g (1.05 mol) of 1H,1H,2H,2Hperfluorooctyl iodide were dissolved in 500 ml of ethanol under gentle heating. Following complete dissolution, the reaction mixture was refluxed for 36 h; after cooling, the solution was concentrated to about half of its initial volume. To this warm saturated solution, 700 ml of diethyl ether were added quickly under stirring, which caused the product to precipitate. The resulting mixture was shaken for several minutes, after which the product was filtered off and washed with another 700 ml of diethyl ether. Finally, the obtained white, waxy product was dried in high vacuum overnight to afford 500.0 g (0.850 mol, 97% of theoretical yield) of II-a3. II-a3 turns yellow after some time, which is most likely due to heightened oxygen affinity of the perfluoroalkyl groups, which in turn leads to faster oxidation of the iodide ion to e.g. triiodide. Single crystals of II-a3 were obtained by slow evaporation of a solution of II-a3 in dichloromethane. IR (ATR, neat): v = 3084, 2946, 2832, 1574, 1484, 1441, 1363, 1316, 1295, 1212, 1182, 1139, 1093, 1074, 1030, 959, 912, 773, 722, 706, 687, 633, 567, 529, 410 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,  $\delta$ ): 10.81 (1H, s(br), note: the position of this signal seems to be strongly dependent on solute concentration), 7.50 (1H, d), 7.44 (1H, d), 3.91 (3H, s), 3.76 (2H, t), 2.61 (2H, tt) ppm.<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>,  $\delta$  ): 140.65 (s), 124.58 (s), 121.72 (s), 124-100 (6C, m), 36.21 (s), 31.39 (t), 27.88 (t) ppm; mp: 125 °C.

### Methods.

NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer. IR spectra were obtained with a Bruker ALPHA-P FT spectrometer in ATR mode. High resolution mass spectra were measured with a Finnigan MAT 95 mass spectrometer. DSC and TGA were recorded with Perkin-Elmer DSC 7 and TGA 7 instruments at a heating rate of 10 °C min<sup>-1</sup> under nitrogen. Crystallographic data for the structure determinations of II-a1, II-a3, II-b3, II-k2, V-a3 and IX are listed in Table S1 and geometric parameters for hydrogen bonds in the ESI, Table S3. Ellipsoid plots of the molecular structures are shown in Figs. S2 - S5, S7, and S8 (Electronic Supporting Information). Intensity data were recorded, using MoK radiation ( $\lambda = 0.71073$  Å), on an Oxford Diffraction Gemini-R Ultra diffractometer ( $\omega$  scans; II-a1, II-a3, II-k2) or a Nonius KappaCCD diffractometer ( $\phi$  and  $\omega$  scans; IIb3, V-a3, IX). The structures were solved by direct methods and refined by full-matrix least-squares techniques.<sup>30, 31</sup> The

positions of non-hydrogen atoms were located in difference maps and their displacement parameters were refined anisotropically. The fluoroalkyl chains of the cation and  $C_8F_{17}I$ moieties of II-k2 were refined using a two-component disorder model (see Fig. S6 of the Supporting Information) with occupancy ratios of 55:45 and 60:40, respectively, and 448 restraints were applied on C–C, C–F, F…F and C…C distances, and on thermal parameters. The fluoroalkyl chain of IX was refined by applying a two-component disorder model (see Fig. S9 of the Supporting Information) with a 1:1 occupancy, and 1139 restraints were applied on C–C, C–F, F…F and C…F and C…C distances, and on thermal parameters.

The surface tension of aqueous solutions of selected soluble fluorosurfactants was recorded using the drop shape analysis instrument Kruess DSA25E, equipped with illumination, a height-adjustable desk, video camera and Advance 1.4.2 software (Kruess, D-Hamburg, Germany). Using the pendant drop technique at ambient conditions (24-25°C, 20 RH%), the surface tension of all aqueous solutions was measured in series of 10 drops each. The drop was suspended from a needle (outside diameter: 1.83 mm) and the drop volume is increased by a dosimeter. A recommended B-value (0.4 to 0.6), computed constantly by the software, allows for a proper adjustment of the drop volume.

#### Ecotoxicological measurements.

Cell viability assay with IPC-81 cells. Briefly, promyelocytic rat cells from the IPC-81 cell line were incubated with the test substances for 48 h. Subsequently, cells were incubated for 4 h in 96-well plates with 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H-tetrazolium monosodium salt (WST-1) reagent. Each plate contained blanks (no cells) and controls (no toxicant). The cell viability assays with IPC-81 were generally carried out for a 1:1 dilution series. Each dose response curve was recorded for 9 parallel dilution series on three different 96well plates. Two independent experiments with different stock solutions of each compound were performed. Positive controls with Carbendazim were checked in regular intervals. A detailed description of the test procedure is described by Ranke et al.<sup>32</sup> Acute immobilization assay with Daphnia magna. The 48 h acute immobilization test with the crustacean Daphnia magna was assessed using the commercially available Daphtoxkit F (MicroBioTest Incorporation, Gent, Belgium) in accordance with the ISO standard (ISO 6341). The tests with neonates less than 24 h old, obtained by the hatching of ephippia, were performed at 20 °C in the dark. 5 pre-fed animals were incubated with the test substances in 10 mL of mineral medium (67.75 mg L<sup>-1</sup> NaHCO<sub>3</sub>, 284 mg L<sup>-1</sup> CaCl<sub>2</sub> \*2H<sub>2</sub>O, 123.25 mg L<sup>-1</sup> MgSO<sub>4</sub> \*7H<sub>2</sub>O, 5.75 mg L<sup>-1</sup> KCl). The number of immobilized or dead organisms was checked after 24 and 48 h. The relative toxicity of the samples was expressed as a percentage of the unaffected organisms compared to the controls. All the substances were tested in three independent experiments.

**Instrumental analysis.** To determine the differences between the nominal and real concentrations of test compounds, a VWR

Hitachi HPLC-UV system (containing the L-2130 HTA-pump, L-2130 degasser, L-2200 autosampler, L-2300 column oven, L-2450 diode array-detector and the EZChrom Elite software, VWR, Darmstadt, Germany) was used. Separation was achieved with a RP18 phase (Multospher100, RP18-5 $\mu$  125x4, CS-Chromatographie Service GmbH, Langerwehe, Germany) and a flow rate of 1 mL min <sup>-1</sup>. For III-a3, the mobile phase consisted of 70 % acetonitrile and 30 % 20 mM ammonium acetate + 0.1 % formic acid (pH 3.8) and for IX, the percentage was adjusted to 40:60. A detection wavelength of 220 nm and an injection volume of 50 $\mu$ L were used for the quantification. The calibration curve was obtained by injecting six concentrations of test compound in the range of 1-12.5 mg L<sup>-1</sup> into the corresponding mobile phase.

### **Results and discussion**

### Synthetic approach.

Poly- and perfluorinated precursor chemicals required to introduce a fluorous domain into the cationic moiety are still expensive commodities. Targeting FILs for large-scale applications, it is thus imperative to maximize the conversion yield regarding the fluorous compound. Nucleophilic substitution via the Menshutkin reaction is one of the most common synthesis routes to quaternize amine and imine structures and yield bulky organic cations. However, perfluorinated alkyl halides suffer from a substantially decreased  $S_N2$  reactivity due to the pronounced electronwithdrawing effect of the fluorine atoms. The strongly deactivating effect of the fluoro substituents is also prevailing when they are bonded in alpha position to the leaving group, e.g. in 1H,1H,-perfluoroalkyl iodide.14, 21 Only if the halide is separated by one additional methylene group (e.g. 1H,1H,2H,2H,-perfluoroalkyl iodide), is the reactivity of the leaving group increased sufficiently to permit a  $S_N2$  reaction. However, 1H,1H,2H,2H-perfluoroalkyl halides are prone to elimination reactions. In the attempt to quaternize amine and imine structures, their basicity promotes the E2 side reaction, which results in the respective non-reactive 1H,1H,2H,2H,perfluoroalk-1-ene.<sup>33, 34</sup> Consequently, the yield of the quaternized target structure is reduced and expensive fluoroprecursor lost.

In regard to ionic liquid synthesis, methimazole attracted interest due to its structural analogy to the archetypal 1methylimidazole. Fortunately, and in contrast to imidazolium systems, the respective mercaptans are not prone to carbene formation at the C2 position. Methimazole shows two tautomeric forms: 2-thiol and 2-thione.<sup>35</sup> Thus, methimazole has two nucleophilic sites that can potentially be alkylated to yield either the respective 2-alkylisothiuronium form or the Nalkylated (quaternized) 1-methyl-2-mercapto imidazolium. MacFarlane and coworkers have shown that upon alkylation with alkyl halides methimazole reacts via S-alkylation of the thione tautomer.36-39 The respective 2alkylmercaptoimidazolium halides,



## ARTICLE

Table 1 Chemical structures of methimazole-based cations and neutral compounds.



2-ethylthiolonium iodide and 2-butylthiolonium chloride, both showed melting points below 100 °C and could be turned into room temperature ILs upon anion metathesis to form the corresponding triflimide,<sup>36, 40</sup> triflate,<sup>36</sup> dibutyl phosphate,<sup>41</sup> or hexafluorophosphate.<sup>41</sup> Alternatively, Rogers and coworkers have capitalized on the tendency of 1,3-dialkylimidazolium cations to form carbenes by reacting them with sulfur at the C2 position to yield neutral 2-thioimidazole derivatives<sup>42</sup> which were further alkylated to form cyclic thiouronium ILs by the group of Wasserscheid.<sup>43</sup>

Following the MacFarlane route, we used methimazole as starting material, capitalizing on the noticeably reduced basicity of its thione form which favors the  $S_N2$  reaction over the undesired E2 when derivatized with perfluoroalkyl ethyl iodide. Three commercially available substrates of different fluorinated chain length (- $C_2F_5$ , - $C_6F_{13}$ , - $C_8F_{17}$ ) were used as alkylating agents, resulting in the respective 2-(1H,1H,2H,2H-perfluoroalkylthio)-1-methylimidazolium iodide (I-III-a3, Table 1) with good yields. Interestingly, the yield increased with the length of the fluorinated residue. Amongst those three

perfluoroalkyl ethyl iodides, 1H,1H,2H,2H-perfluorooctyl iodide is currently the cheapest commodity chemical available in bulk quantities. Therefore, subsequent anion metathesis to introduce a fluorous counterion was performed using II-a3. The various anions are summarized in **Table 2**. The iodides (I-III-a3) were also converted into the respective neutral species (**dep-I**-III) through deprotonation with bicarbonate. The neutral compound offered the possibility to introduce further anions via stoichiometric addition of the respective acids. Moreover, these affordable fluorous amine bases represent promising reagents and starting materials in their own right since they offer manifold further chemical opportunities, for example as metal-complexing agents (e.g. **dep-II-**Ti. **Table 1**).

Ultimately, a second fluorinated residue was introduced via alkylation of the free nitrogen in **dep-I** and **dep-II**. However, the second alkylation proceeded with lower yields. This can be attributed to the increased basicity of the 2-((perfluoroalkyl-ethyl)-thio)- 1-methylimidazole structure which cannot tautomerize anymore and, thus, promotes the competing E2 reaction.



# ARTICLE

Table 2 Overview of anions; similar anions are grouped indicated by the same minor-case letter.
---

a1	Cl <sup>O</sup>	f1	e₀ ↓	$F_2$	F <sub>2</sub> CCF <sub>3</sub>	j1	SO <sup>O</sup> NH SO <sup>O</sup> SO <sup>O</sup>
a2	B <sup>r⊖</sup>	f2	$\Theta_0 \xrightarrow{O_{F_2}} O_{F_2}$	$F_2 F_2$ C C C C $F_2 F_2$	$F_2$ $F_2$ $F_2$ $F_2$ $F_2$	j2	
a3	IΘ	g1: n=1				j3	о но-Сө
b1	$BF_4^{\Theta}$	g2: n=4		0		k1	Θ <sub>II</sub> (CF <sub>2)5</sub> CF <sub>3</sub>
b2	$PF_6^{\Theta}$	g3: n=6		<sup>⊖</sup> 0 <sup>-</sup> C <sub>n</sub> F <sub>2n+</sub>	1	k2	⊖ <sub>I</sub> (CF <sub>2)7</sub> CF <sub>3</sub>
b3	$[SiF_6]^{2\Theta}$	g4: n=8				I	G = O O O O O O O O O O O O O O O O O O
c1	$NO_3^{\Theta}$	h1	$-SO_3^{\Theta}$	h2	$H_2N$ — $SO_3^{\Theta}$	m	$O_2N$ $V_2$ $NO_2$ $NO_2$
c2	$H_2PO_4^{\Theta}$	h3		°o <sub>3</sub> s		n	
c3	$ClO_4^{\Theta}$	h4		SO <sup>P</sup> SO <sup>P</sup> 3	Ə 3	0	F <sub>3</sub> C CF <sub>3</sub>
d1	[ <sup>Mn</sup> (hfac <sub>)3</sub> ] <sup>⊖</sup>	h5		N <sup>₽</sup> <sub>2</sub> So <sup>Θ</sup> <sub>3</sub>	.රි	р	M <sup>e</sup> OSO <sub>3</sub> <sup>⊝</sup>
d2	[FeCl₄] <sup>⊖</sup>	i1	Ţ		SO <sup>⊕</sup> 3	q	
e1: n=1 e2: n=3 e3: n=7	Θ <sub>0</sub> C <sub>n</sub> F <sub>2n+1</sub>	i2			so <sup>9</sup> 5'		

### ARTICLE

#### Surfactant properties.

Naturally, just as for the majority of hydrocarbon-based surface active agents, fluorosurfactants are also composed of two structural key motifs: the polar hydrophilic head group and, as the highly hydrophobic cooperative counterpart, a fluorous domain. The van der Waals interactions between fluorinated chains are weak, resulting in low cohesive energy of fluorocarbons. Consequently, they offer a host of remarkable features like high gas solubility,7,8 low surface tension, high surface activity in aqueous solutions, and low critical micelle concentration (cmc). As a result, surfactants comprising fluorous tags can even be operative in hydrocarbon solutions<sup>5</sup>. fluorosurfactants are outperforming Generally. their hydrocarbon-tailed analogues,44,45 showing the same trend of decreasing cmc values with growing chain length.<sup>46</sup>

Due to their high water solubility, we selected II-h3, II-j2, V-a1, VI-a1, and IX for surface tension experiments and cmc determinations. Only phase out-compliant PFCs with a fluorous tail length of 6 were measured, along with PFOS as a reference. No auxiliary co-solvents were employed for solubilisation of the fluorous surfactants.

Notably, II-a1 is soluble in water in high concentration (>1000 g/l at 25 °C), but it led to turbidity at room temperature upon dilution (<0.5 wt%). Heating the dispersions does not regain clear solutions, which would correspond to an observable Krafft point. On the other hand, addition of small quantities of acid provided clear solutions again. This phenomenon might thus be attributed to pH dependency, given that the water insoluble neutral imidazole-derivative dep-II is formed. Therefore, a dilution series was prepared in order to confirm this interpretation by pH-measurements. At lower concentrations of II-a1, the resulting pH, which corresponds to a pKa of about 3.5, increased sufficiently to form turbid solutions (a video of this phenomenon including tabulated data are included in the supplementary section). This interpretation is further supported by the fact that only protic members of this series form turbid aqueous solutions upon dilution; for example, 2-(1H,1H,2H,2H-perfluorooctylthio)-1,3-dimethylimidazolium chloride, VI-a1 is lacking this phenomenon.

For the substances II-h3 and II-j2, a very rare phenomenon for ionic fluorosurfactants<sup>5</sup> was observed – the aqueous solutions of these substances showed the formation of a cloud point,<sup>5</sup> meaning that the solutions turn turbid upon heating. At concentrations of 0.25 wt% and 0.5 wt% respectively, the binary phase systems were actually turbid at room temperature. Therefore, the measurements for II-j2 and II-h3 at these concentrations have to be interpreted with caution (a video of this phenomenon is presented in the supporting information).



← II-h3 → 80 →

**Fig. 1** Surface tension of aqueous solutions of selected fluorosurfactants and the reference substance PFOS at different concentration levels.

It should be emphasized that this behavior was only observed for protic imidazolium systems, which underlines the importance of hydrogen bonding and acid-base equilibria for this effect.

Moreover, such unusual solubility characteristics might indicate liquid crystal phase formation as already described for related systems.<sup>47-49</sup>

The effect of the substances discussed herein on the surface tension of aqueous solutions is depicted in Figure 1 (values are given in the ESI, Table S6). Solutions of VI-a1 show very high surface tension and cmc values at the measured concentrations in contrast to the other substances. This might be attributed to the less pronounced hydrogen bonding between the surfactant and water. IX exhibits a very high drop of the surface tension at the cmc. The substances II-h3 and II-j2 do not show a clear cmc value at the measured concentrations. However, the surface tension values of the respective aqueous solutions lie in the range of commercial surfactants.<sup>50</sup> As expected, the lowest cmc and surface tension values are observed for solutions of the doubly fluoroponytailed salt V-a1. Despite the monovalent cation, the values of V-a1 are very close to those of doubly charged, doubly C6 fluoroalkylated gemini fluorosurfactants.<sup>51</sup> In conclusion, highly fluorous methimazolium derivatives can reach performance levels that surpass most of the hitherto reported surfactants.<sup>34, 52</sup> In particular, the cmc of complex fluorosurfactants stemming from topical design can reach values even lower by an order of magnitude.53, 54 By further alteration of the methimazole CH3- group with synergistic moieties, for instance polyethylene glycol, propane sulfonate, or an omniphobizing third fluorinated group, the cmc and / or the surface tensions of aqueous solutions of imidazolium-based surfactants are also very likely to compete in the record setting pace.



### ARTICLE



**Fig. 2** a) Definition of eight torsion angles which characterize the conformation of the 1-methyl-2-((perfluorohexylethyl)thio)imidazole fragment of **II** (gray = C, lightblue = H, blue = N, green = F, yellow = S) and corresponding fragments of **V** and **IX**. b) Overlay of the four experimental conformations of cation **II** and matching fragments in **V**-a3 and **IX** (H atoms and minor disorder components omitted for clarity), obtained from a series of least-squares fits of their 1-methyl-2-thioimidazole fragments (drawn in ball-and-stick style). Klyne-Prelog notation<sup>55</sup> for the torsion angles  $t_{A_Y}$ ,  $t_B$ ,  $t_C$  and  $t_D$  describing the geometry of the chain fragment attached to the imidazole ring (ap = antiperiplanar, ac = anticlinal, sc = synclinal). N–H···X<sup>-</sup> and I···I<sup>-</sup> interactions (black and blue dashed lines, respectively) in the crystal structures of c) **II**-a1 (X = Cl<sup>-</sup>), e) **II**-b3 (X = F) and f) **II**-k2 (X =  $\Gamma$ ) (gray = C, light blue = H, blue = N, light green = F, yellow = S, green = Cl, magenta = I, light yellow = Si). Symmetry transformations: (i) x+1, y, z; (iii) x-1, y, z; (iii) x, y+1, z.

#### Structural analyses.

Crystallographic data for the structure determinations are listed in the ESI, Table S3 and thermal ellipsoid plots are shown in the Supporting Information (Section 2. Crystal structures). The 1methyl-2-((perfluorohexylethyl)thio)imidazole fragment is a common structural unit of the cations II and V and the zwitter ion IX. It displays a flexible conformation that can be characterized in terms of eight torsion angles (Figure 2a). An overlay of the corresponding six experimental conformations illustrates its high adaptability to different crystal packing situations (Figure 2b). Closer analysis reveals, however, that all fundamental geometrical differences originate from the five torsion angles  $t_A-t_E$  which characterize the SC<sub>2</sub>H<sub>4</sub> unit and its orientation relative to the imidazole ring. The C<sub>6</sub>F<sub>13</sub> fluoroalkyl tail adopts the expected all-*trans* conformation in all investigated crystals (torsions  $t_1-t_3$ ). Due to the size of the fluorine atom, a fluoroalkyl chain (C<sub>n</sub>F<sub>2n+1</sub>) generally exhibits greater stiffness than a corresponding alkyl chain, resulting in a loss of *gauche/trans* freedom.<sup>56</sup> In II-b3, the fluoroalkyl tail exhibits a twist angle (average deviation of  $t_1$ ,  $t_2$ , and  $t_3$  from 180°) of 14°. This is the typical geometry found in perfluorohexane<sup>57</sup> and other C<sub>n</sub>F<sub>2n+1</sub> chains which adopt a helical rather than a planar zig-zag conformation.<sup>56</sup> The Cambridge Structural Database<sup>58</sup> (CSD, version 5.37) contains 47 CH<sub>2</sub>C<sub>6</sub>F<sub>13</sub> chain fragments belonging to 35 unique crystal structures (*R*1 > 0.075, "no errors"), of which 43 possess an all-*trans* geometry with an average twist angle of 11° (ESI Figure S1a).

### ARTICLE

Only four of these chains exhibit an almost planar structure with a twist angle of less than 4°. By contrast, an almost planar  $C_6F_{13}$  chain is found in all but one (II-b3) crystal structures investigated by us, namely in II-a1 (twist angle 2°), II-a3 (3°), II-k2 (2° and 4° for two disorder components) and in V-a3 (two chains with 1° and 2° in the cation). The  $C_6F_{13}$  chain of the zwitter ion of IX exists in two disordered conformations whose twist angles are 0° and 8°, while the  $C_8F_{17}$  fragment of the 1-iodoperfluorooctane molecule of II-k2 has a twist of 10°.

This predominance of nearly planar fluoroalkyl chain fragments in the investigated set appears to contradict the established view that, owing to the size of the fluorine atom,  $C_n F_{2n+1}$  chains adopt a twist conformation in order to minimize steric repulsion between fluorine substituents which are bound to carbon atoms in the relative 1,3-positions.4, 59 However, a few structures containing untwisted experimental crystal fluoroalkyl chains are known60-62 and have been discussed previously as enabling a higher number of intermolecular C-F···F-C contacts<sup>60</sup> or as being "probably the result of thermal disorder involving partial unwinding of the chains".<sup>59</sup> We do not find sufficient evidence in the crystal data of II-a1, II-a3, II-k2, and V-a3 to support the latter interpretation, while planar and helical fluoroalkyl chain fragments are disordered in the crystal structure IX. Comprehensive geometry optimization calculations are available in the ESI.

In the crystal structures of II-a1 (X = Cl), II-a3 (X = I), and II-b3 (X = I), cation and anion moieties are linked by  $N{-}H{\cdots}X^{-}$  bonds (Figure 2c, d, f; Table S3 of the Supporting Information). The crystal structure of II-k2 contains additionally an iodo C–I···I<sup>-</sup>  $\sigma$ hole-type halogen bond<sup>49</sup> [ $d_{11\cdots 12}$  = 3.5736 (6) Å,  $\angle$  (C13–I1…I2) = 171.37(16)°] between the 1-iodoperfluorooctane molecules and the anion (Figure 2f). In the case of II-b3, each hexafluorosilicate ion serves as a bridge, via N-H…F bonds, between two cations (Figure 2e). In addition to these interactions, the molecular packing in all investigated crystal structures are dominated by C-F…F-C contacts (see Table S4). These are formed primarily within molecular stacks and specifically between molecules whose fluoroalkyl residues are oriented either in opposite directions (II-a3) or in the same direction (II-a1, II-b3, II-k2, V-a3, X) (ESI, Figure S10). The crystal structures of the latter group contain centrosymmetric units with two neighboring stacks of fluoroalkyl chains at the center. In II-k2, V-a3, and X, C-F…F-C interactions between neighboring stacks occur almost exclusively between terminal  $\mathsf{CF}_3$  groups while larger sections of the  $\mathsf{C}_6\mathsf{H}_{13}$  chains are additionally involved in the case of II-a1 and II-b3. An individual short C-F…F-C contact affects the lattice energy only very slightly, but the combined effect from multiple weak interactions of this kind (see Table S4) should be significant. In two-dimensional stacks, planar fluoroalkyl chains should facilitate a higher number of short intermolecular C-F…F-C contacts than their helical counterparts. Deviations from the ideal helical geometry in solid-state structures appear to be the result of a fine balance between molecular structure and crystal packing, as the energy difference between twisted and planar fluoroalkyl chains (see above) may be compensated by the

presence of slightly more C–F…F–C contacts or by other weak interactions.

#### Ecotoxicological considerations.

General aspects of biosafety and environmental benignity of ionic fluorosurfactants. As mentioned introductorily, some of the long-chain PFASs, specifically perfluoroalkyl acids (PFAAs) and related substances, have been classified as SVHCs (Substance of Very High Concern), as well as vPvB (very persistent and very bioaccumulative) chemicals. However, a detailed toxicological assessment of specific PFCs remains difficult as the toxicokinetic peculiarities of these xenobiotics differ considerably between animal species and even between different genders of the same species.<sup>1, 63, 64</sup> However, the tendency of bioaccumulation seems to be associated with the perfluoroalkyl chain length, with chains  $\geq 8$  being more bioaccumulative than those with  $\leq 7$ . In 2009, perfluorooctane sulfonate (PFOS) and related compounds were added to the Annex B of the Stockholm Convention of Persistent Organic Pollutants (POPs),<sup>65</sup> leading to the discontinuation of the large-scale production of PFOS and to a phaseout of many other related compounds.<sup>1, 66</sup> Shortly after, perfluorooctanoic acid (PFOA) faced the same fate when ECHA released Annex 15 of its restriction proposal in 2014 demanding the stop of the manufacture, use, and market placement of PFOA.67

Due to the technical indispensability of fluorosurfactants and, in view of their undesired impacts on humans and the environment, global producers have stepped up research and development efforts to replace poly- and perfluoroalkyl substances (PFASs) as well as their potential precursors with homologues or other types of (non)fluorinated chemicals.68 Major concerns regarding the production and release into the environment of an ever increasing number of PFASs have been raised recently in the Madrid Statement on PFASs.<sup>69</sup> While many fluorinated alternatives are being marketed, little information is publicly available on their chemical structures, properties, uses, and toxicological profiles.<sup>69</sup> The most common replacements can be categorized into two groups. The first group comprises shorter-chain homologues of long-chain PFAAs and their precursors, even though lower fluorinated simple analogues may display insufficient surface-tension lowering properties in aqueous systems. The second group consists of functionalized perfluoropolyethers (PFPEs), especially perfluoroethers of carboxylic and sulfonic acids (PFECAs and PFESAs). Both these types of substitutes are structurally similar to their archetypical carboxylic and sulfonic acids (PFCAs and PFSAs), with fluorinated chain segments joined together by ether linkages.<sup>70</sup> However, recent experience with the substitution of other chemicals has revealed a "lock-in" problem. This means that a compound is replaced on the market by another member from the same family of chemicals which is technically and economically feasible, but the alternative may be prone to the same safety hazards as a result of its similar physicochemical properties.68 Therefore, the replacement of a toxic constituent

by a structural analogue does not necessarily result in a safer product. Such a switch which does not resolve the original problem has been termed a "regrettable substitution".<sup>71</sup> If the superior surfactancy of fluorous detergents has to be kept uncompromised, then any substitution by PFAS-based alternatives is likely to be a "regrettable" one.

Fluorosurfactants, in contrast to the much more watercompatible aliphatic fluorine-free counterparts, show unique modes of phase interaction.<sup>72</sup> This behavior is predominantly driven by their inherent tendency to form aggregated fluorous domains which leads to significant differences between static and dynamic wetting. Therefore, physicochemical research on novel fluorosurfactant structures offers innovative potential in materials science.73 It is important that such investigations are complemented by the appropriate eco-toxicological studies. In general, less toxic short-chain fragments do not permit as strong omniphobicity and surface tension lowering activity in polar solvents. Fortunately, these technical limitations can be overcome by manifold assemblies of the fluorous pigtails in the form of cooperatively arrayed, branched systems, whose performance is similar to that of the archetypes.<sup>74, 75</sup> This unconventional concept was pioneered based on a platform of oligomeric (fluorooxetane) fluorosurfactants.<sup>76, 77</sup> Indeed, some of the newly developed, fluoro-pigtail surfactants possess not only the demanded surface enrichment and wetting dynamics, but exhibit less negative environmental impacts and tunable biological properties.<sup>78</sup> Most notably, they are eliminated rapidly from living systems.<sup>79</sup> These alternatives have already been approved by regulators for manufacture, sale and use.<sup>80</sup> As briefly stated above, the second approach to realize environmentally more acceptable anionic fluorosurfactants relies on intersections of fluoroalkylene fragments by ether linkages. Among these ethereal fluororganics, the fluoropolymer processing aids ADONA (ammonium 4,8-dioxa-<sup>82</sup> and 3H-perfluorononanoate)<sup>81,</sup> GenX (ammonium perfluoro(2-methyl-3-oxahexanoate))<sup>83, 84</sup> have already been introduced as replacements of the SVHCs perfluorooctanoic acid and perfluorooctanesulfonic acid, respectively.<sup>80</sup> A range of structural motifs have emerged from replacement programs of PFASs, but it has been difficult to find substitutes that meet demanding functional and performance requirements.85 Despite fundamental structural differences, the physicochemical profiles of the novel fluorinated alternatives do not deviate significantly from those of their predecessors. Most of the alternatives are suspected to be as persistent and pollutive in the environment as the long-chain PFASs,86 and theoretical models predict that the fluorinated alternatives will be globally distributed in the environment in similar ways to their predecessors. To date, information on such replacements, including their chemical identity, has not been published or made easily accessible to the public.<sup>68</sup> It is highly desirable and long overdue that all producers promptly disclose the structures of their recent and future developments in advance of their commercialization.87-89 In conclusion, it should be emphasized that the scarcity of experimental data still prevents meaningful hazard and risk assessments for most of the aforementioned substances. In particular, ion pairs composed of a fluorinated

cation and a fluorous anion are almost unexplored and hold much promise for unique phase affinity profiles and anti-fouling effects.

Ecotoxicological considerations regarding Methimazole derivatives. In this study, III-a3 and IX have been selected for preliminary (eco)toxicological testing. The cytotoxicity assay with leukemia rat cell line IPC-81 was used to measure general cell viability and to screen for effects on basic cell functions and structures of cells. This test has been proven useful to determine acute toxicological effects of various classes of chemicals.90-92 Moreover, the immobilization test with the water flea Daphnia magna was conducted. The crustacean plays a very important ecological role in freshwater habitats, because it serves as a major food source for a whole range of aquatic vertebrates and invertebrates. It is a sensitive test organism routinely used for assessing the hazards posed by toxicants.

Two standard ionic liquids, 1-butyl-3-methylimidazolium chloride ([C<sub>4</sub>MIM]Cl, [79917-90-1]) and 1-methyl-3-octylimidazolium chloride ([C<sub>8</sub>MIM]Cl, [64697-40-1]) have been selected for comparison.

#### Nominal vs. actual concentrations:

The deviations between the nominal and actual concentrations of the test compounds in biological media have been determined for selected samples using the HPLC-UV technique. All prepared solutions appeared fully dissolved in Daphnia and cell media however, the recovery rates differ largely for the investigated compounds III-a3 and IX (data not shown). For IIIa3 only 10 to 30 % from the nominal concentration (in the range of 5 to 105 mg L-1, measured from two independent experiments) could be verified in both test media at the beginning of the test. The deviation was larger the lower the nominal concentration was set. On the other hand, the zwitterionic compound IX could be recovered in the range of 90 to 110 % of the nominal concentration. Such deviations of less than 20 % from nominal concentrations are considered to be still in the normal range according to the OECD guideline 221<sup>93</sup> and can be considered as the fully bioavailable fraction within the toxicity tests. For III-a3 this fraction is strongly influenced by e.g. limited media solubility and/or adsorption on the surfaces of test vessels.

### (Eco)Toxicity:

The half-maximum-effect concentrations (EC<sub>50</sub>) and confidence intervals are presented in Table 3. No EC<sub>50</sub> value could be determined in acute *in vitro* cell tests with isolated rat cells (IPC-81) for any of the investigated ILs. **IX** showed no effects up to the highest tested concentrations of 500 mg L<sup>-1</sup> indicating a low influence on the basal function of the used cells. Due to low solubility of **III-a3**, only low concentrations of maximal 30 mg L<sup>-1</sup> could be tested and no adverse effects on cell viability at such concentrations were observed. With regards to the acute toxicity towards *Daphnia magna*, **III-a3** shows an EC<sub>50</sub> value of at least two orders of magnitude lower (higher toxicity) than **IX**.

### ARTICLE

Substance	EC₅₀ value in µM (confidence interval)				
	Cell toxicity	Daphnia magna			
$ \begin{array}{c} N \\                                   $	> 30	< 0.5			
$ \begin{array}{c} \stackrel{N}{\underset{N}{\overset{\otimes}{\underset{N}{\overset{\otimes}{\overset{\otimes}{\overset{\otimes}{\overset{\otimes}{\overset{\otimes}{\overset{\otimes}{\overset{\otimes}{\overset$	> 500	47.9 (40.7 – 55.0)			
(CAS: 79917-90-1]	626 <sup>32</sup> (530 – 751)	14.8 <sup>94</sup> (12.8 – 17)			
(CAS: 64697-40-1]	23.6 <sup>32</sup> (21 – 26.6)	0.013 <sup>95</sup> (0.006–0.023; tested as Br⁻)			

 Table 3 Toxicological comparison of fluorous methimazolium vs. alkyl-quaternized imidazolium salts.

The bioavailable fraction in the test was below the limits of quantification (0.5 mg L<sup>-1</sup>) however, at such small concentrations, III-a3 caused strong effects on Daphnids. With  $EC_{50}$  values of < 0.5 mg L^-1 for III-a3 and 48 mg L^-1 for IX the compounds would be classified as "very toxic to aquatic life"  $(EC_{50} \le 1 \text{ mg L}^{-1})$  or "harmful to aquatic life"  $(EC_{50} > 10 \text{ mg L}^{-1})$  but <100 mg L<sup>-1</sup>), respectively, according to GHS (Globally Harmonized System of Classification and Labeling of Chemicals). In comparison to standard ILs, the effect of IX is lower than observed for [C<sub>4</sub>MIM]Cl and [C<sub>8</sub>MIM]Cl (in case of Daphnia two to three orders of magnitude). For III-a3 such comparison is difficult since no defined effect concentration could be determined. However, the strikingly increased toxicity of 8:2 fluorotelomer salt III-a3 (in comparison to 6:2 fluorotelomer system IX) can be explained by its higher hydrophobicity in archetypical accordance to its elongated perfluoroalkyl residue, as well as the less hydrophilic iodide counterion. The interdependence of toxicity and hydrophobicity of IL cations (the so-called "sidechain effect") has been widely reported for

several different biological tests.<sup>96-98</sup> This has led to the rule of thumb that the greater the hydrophobicity of a cation, the greater the observed acute toxic effect.

On the other hand, sole structural characteristics with key influence on the surfactancy of detergents and tensides<sup>99</sup> cannot be correlated conclusively to their general toxicological profiles<sup>100, 101</sup> since, especially for segmented fluorosurfactants, the specific modes of bio-physico-chemical action are complex and mostly lacking detailed overall insight.<sup>102</sup> Predictions on the toxicity of organic fluorine compounds based on chemical structural elements can be rather unreliable. As a matter of fact, closely related substances may possess vastly different toxic properties.

To date, no biotic degradation studies have been performed. Admittedly, even if the head group of the cation is vulnerable towards degradation, such processes would result likewise in the release of precariously persistent and environmentally hazardous C<sub>6</sub> or C<sub>8</sub> –perfluoroalkylated pollutants. However, it has to be emphasized in this context that the most likely ultimate degradation product of C6-fluorotelomer thiol chemistry,<sup>102</sup> namely 6:2-fluorotelomer sulfonic acid<sup>103</sup> (6:2-FTS), is assessed to be much safer<sup>80</sup> than its infamous predecessors, particularly the "classical Teflon toxins" PFOA and PFOS.

Preliminary ecotoxicological results indicated that 6:2 FTS is not bioaccumulative according to published regulatory criteria.<sup>80</sup> The potassium salt of 6:2 FTS ( $C_6F_{13}CH_2CH_2SO_3^-K^+$ , CAS# 59587-38-1) had an oral LD50= 2,000 mg/kg (rat), and was not irritating to skin (rabbit). It was not mutagenic in the bacterial reverse mutation test with *Salmonella typhimurium* and it was negative in the Unscheduled DNA Synthesis (UDS) test in mammalian cells and negative for clastogenicity in micronucleus and chromosome aberration assays.<sup>80</sup>

For all fluorous methimazolium salts examined so far, chemical degradation readily takes place via hydrolysis at elevated pH (excess of caustic soda), leading to intermediate 1H,1H,2H,2Hperfluoro-1-octanethiol, [34451-26-8]. Only scarce toxicological data are available for this compound.<sup>104</sup> Notably, in our hands, it is readily oxidized by ambient air in aqueous solution, leading primarily to the corresponding disulfide [42977-22-0],<sup>105</sup> which is prone to further oxidation.<sup>106</sup> In conclusion, such non-volatile fluorous ILs and related salts can combine a highly desired couple of toxicological features: They are suitable for use as constituents of antiseptic aqueous formulations, or as coatings with antifouling action, but, on demand, are intentionally degradable by design.<sup>107</sup> Open issues remain, though, as the cleaved fluorotelomer would require appropriate recycling, but neutral fluorous degradation products are separable from aqueous phases with minimal efforts.<sup>108-110</sup> Further details of oxidative conversion pathways will be reported in a forthcoming communication.

### Conclusions

The performance attributes of fluorinated surfactants are unique and cannot be achieved with any other types of surfactants.<sup>111</sup> Despite justified environmental and health

concerns, there remains a need for fluorinated surfactants in many industries. Most of the indispensability arguments are profound and refute prevailing innuendos and the myth of their complete replaceability.<sup>112-114</sup> Even rather new fields of application are conceivable. For example, omniphobic ionic liquids, that are non-wetting for semipolar substrates such as zeolithes or metal-organic frameworks, should in principle be suited as substitutes of mercury metal in Hg-porosimetry, although their general physical behavior in terms of gas solubility may require delicate methodical and instrumental adjustments.<sup>115</sup> All the more, statutory phaseout regulations, succinctly termed "the Shrinking Case for Fluorochemicals", 113 as well as public alertness should stimulate and promote further dedicated exploration of preferably short chain<sup>116</sup> fluoro surfactant constituents. And indeed, in this green context, pushed by the goals of utmost harm reduction, topical research is just about to gain momentum, and again starts to unravel new stunning interrelations of their toxicological,117 as well as physicochemical property profiles,<sup>118</sup> especially details of micelle formation<sup>119</sup> and lyotropic behavior.<sup>47, 120</sup>

Unfortunately, the adequate coverage of all relevant multidisciplinary aspects, including comprehensive ecotoxicological research,<sup>121</sup> represents a burden, as it is almost impossible to predict the toxicity of organic fluorine compounds on the basis of chemical structure related elements. As a matter of fact, closely related substances may possess strikingly different toxic<sup>104</sup> as well as physical properties. For example, the extremely varying solubility in water for the series of II-a1, II-a2, and II-a3 consisting of identical cations, depends strongly on the choice of halide counterion (see experimental section).

Under above inducements, optimized procedures for product work-up and anion metathesis have been elaborated as a basis for the easy synthetic access of a plethora of members of a new modular fluorosurfactant construction kit, relying on costefficient thione-thioether chemistry. The resulting derivatives are environmentally more acceptable than the first generation of processing aids in the manufacture of fluoropolymers. In continuation of the undertakings presented in this preliminary work, we will disclose related research dealing with the synthesis and characterization of polymerizable cationic fluorosurfactants in due course.

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ARTICLE

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