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Minireviews

Angewandte
International Edition
Chemie
www.angewandte.org

Interfaces with Fluorinated Amphiphiles: Superstructures and Microfluidics

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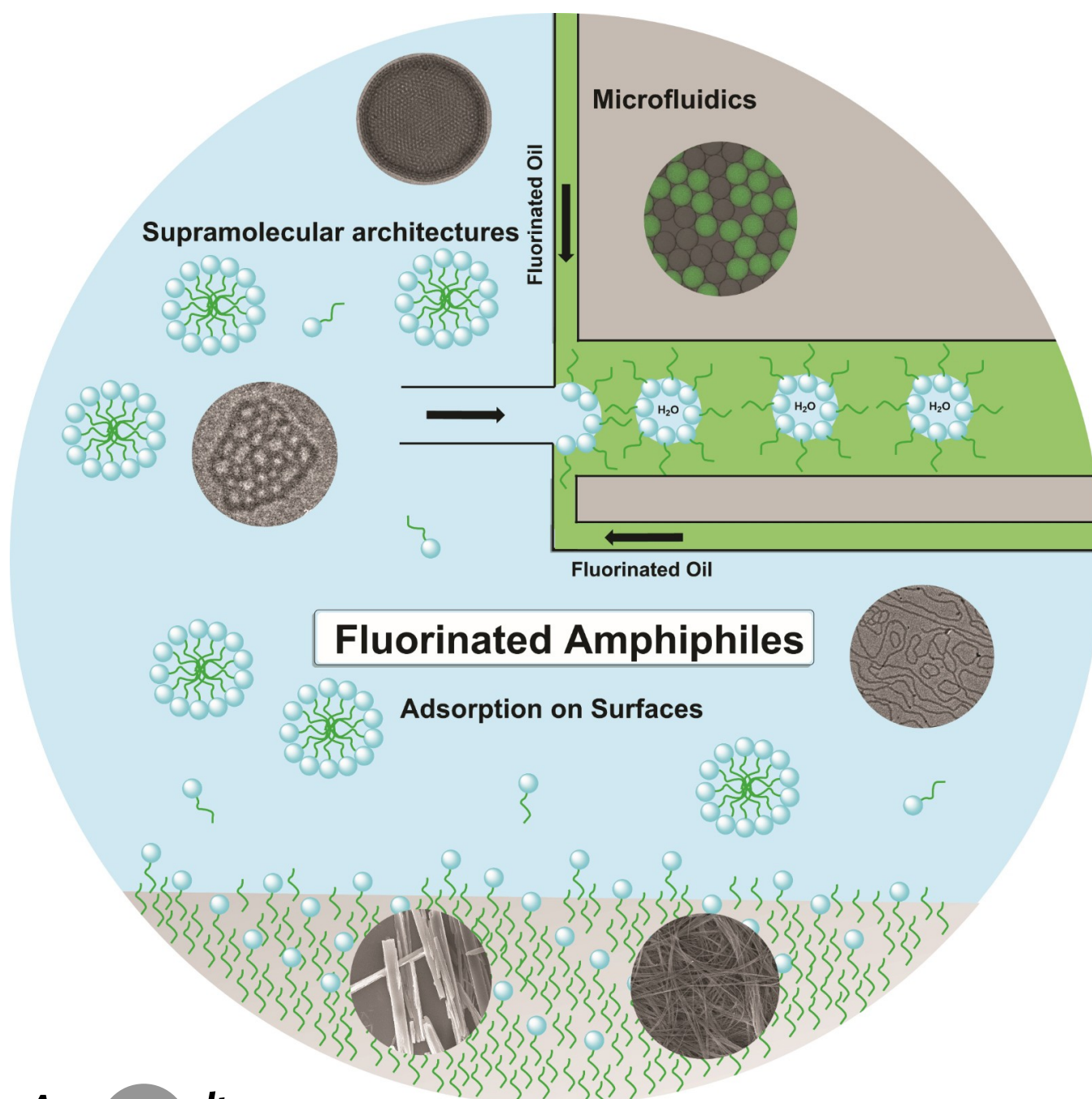
Abstract: This Minireview discusses recent developments in research on the interfacial phenomena of fluorinated amphiphiles, with a focus on applications that exploit the unique and manifold interfacial properties associated with these amphiphiles. Most notably, fluorinated amphiphiles form stable aggregates with often distinctly different morphologies compared to their nonfluorinated counterparts. Consequently, fluorinated surfactants have found wide use in high-performance applications such as microfluidic-assisted screening. Additionally, their fluorine-specific behaviour at solid/liquid interfaces, such as the formation of superhydrophobic coatings after deposition on surfaces, will be discussed. As fluorinated surfactants and perfluorinated materials in general pose potential environmental threats, recent developments in their remediation based on their adsorption onto fluorinated surfaces will be evaluated.

1. Introduction

"The many fluorous pioneers have in fact created an expanded universe, with [···] unusual phenomena and exploitable properties that have no counterparts in old-world chemistry".[1]

This quote from the seminal *Handbook of Fluorous Chemistry* highlights the particular features of fluorous compounds that have made them a unique domain at the border of organic and inorganic chemistry. As the fluorous effect leads to special interfacial phenomena, highly fluorinated compounds have been the focus of research in a broad range of disciplines—ranging all the way from catalysis to materials sciences.[2] The formation of surprisingly stable and structurally interesting superstructures of fluorinated amphiphiles and the ease of preparing superhydrophobic and slippery surfaces by simply coating them with self-assembling fluorinated gelators are only a few highlights of this research.

Perfluoroalkanes (PFAs) have many unique properties:[3] because of the larger fluorine atoms, the average volumes of CF_2 and CF_3 groups are larger than CH_2 and CH_3 groups. PFA chains are thus more rigid, and their cross-sections are larger (ca. 30 Å^2 vs. ca. 20 Å^2). In marked contrast to the alkanes' preferred zigzag conformations, longer PFA chains form 13_6 helices. According to newer computational results, the main reason for this unusual structure is hyperconjugation between the σ_{C-F} and the corresponding antiperiplanar σ^*_{C-C} orbitals,[4] rather than steric repulsion between the fluorine atoms along the chain. The strong C–F bond makes PFAs quite chemically inert. As fluorine is highly electronegative, C–F bonds have significant dipoles (C–H: 0.4 D, C–F: 1.39 D) but low polarizability, leading to low intermolecular attractive London dispersion and, thus, low viscosity,

high compressibility, low surface tension, low heats of vaporization, and low boiling points.

For interfacial phenomena, it is most important that their low polarizability makes PFAs lipo- and hydrophobic, as apparent from the separation of three phases from mixtures of water, PFAs, and a suitable organic solvent.[5] The nonmiscibility with water can be understood as a solvophobic effect, which leads to phase separation arising mostly from two factors: the strong hydrogen bonding between the water molecules, and an entropic gain of water molecules in bulk water as compared to the more highly ordered water molecules that surround the PFA chains in a mixed phase. The nonmiscibility of PFAs with lipophilic solvents results from an interplay of several factors. One component is certainly a similar solvophobic effect: the attractive forces in a pure alkane and a pure PFA phase are together stronger than the intermolecular forces between alkanes and PFAs. Although dispersion is the dominant attractive force between alkanes,[6] dipole interactions are more important between PFA molecules. Hasegawa's stratified dipole array (SDA) model[7] assumes that the local C–F dipoles along the PFA chain almost completely cancel each other out, while residual dipoles remain at the two terminal CF_3 groups. The SDA model was developed for aggregates of PFAs and has been tested with monolayers of fluorinated chains at the water/air interface. It not only explains the melting-point jump at the critical chain length of perfluorinated C$_7$ chains, but also rationalizes why C$_7$ chains form tetragonal arrangements, while C$_9$ chains form hexagonal ones—a result of the helical structure and the relative orientations of the two terminal CF_3 dipoles (90° for C$_7$, 120° for C$_9$). Even when one considers the liquid PFA to be much less ordered than such aggregates, the interactions between the residual dipoles at the chain termini will contribute to the interactions between PFA molecules in the liquid. Furthermore, theoretical studies[8] suggest that, to avoid size mismatches, alkanes must form more globular, coiled structures when mixing with PFAs. As a result of all these effects, the phase separation of alkanes from PFAs is typically observed at room temperature. The observation that homogeneous mixed PFA/alkane phases exist above a certain critical temperature supports the idea that enthalpic effects such as those discussed here dominate the phase behaviour at low temperatures, while a favorable mixing entropy overrides these effects at higher temperatures, with $\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} < 0$.

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Angew. Chem. Int. Ed. **2023**, *62*, e202213866 (2 of 11)

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2. Liquid/Liquid Interfaces

### 2.1. Supramolecular Architectures of Fluorinated Amphiphiles

Amphiphiles with fluoroalkyl chains are chemically and thermally robust, possess exceptional bio-inertness, and show hydro- as well as lipophobic effects. Aggregates of fluorinated amphiphiles often form supramolecular struc-tures of low curvature, with very stable and well-defined assemblies, such as membranes, films, vesicles, micelles, and other complex morphologies, such as perforated bilayer vesicles, rings, branched cylinder micelles, and mesh phases.[9, 10]

Fluorinated amphiphiles usually combine hydrophobic per- or polyfluorinated segments and hydrophilic non/ fluorinated segments. In contradiction to their name,

Florian Junge studied chemistry at Freie Universität Berlin and since the beginning of 2021 has been working on his doctoral thesis under the supervision of Rainer Haag as a member of the collaborative research centre "Fluorine specific interactions". His research focuses on the preparation and analysis of fluorinated surface coatings and fluorinated cationic adsorber materials for fluorinated amphiphiles.
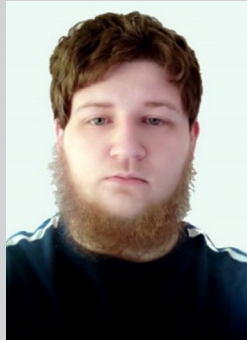
Michał Pachnicz obtained a bachelor degree in chemistry at Freie Universität Berlin in 2022. The focus of his Bachelor thesis was the investigation of the physical and chemical basis of the fluorous effect. Currently he is studying for a master degree in chemistry at Freie Universität Berlin.
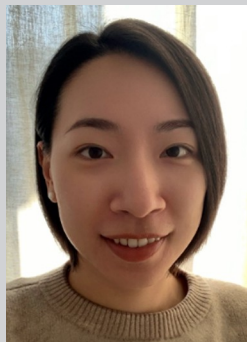
Pin-Wei Lee is currently working on her doctoral thesis at Freie Universität Berlin under the supervision of Christoph Schalley and has been a member of the collaborative research center "Fluorine specific interactions" (SFB 1349) since April 2021. Her research focuses on the fabrication and analysis of drop-cast fluorinated xerogel coatings and the combination of supramolecular materials with polymeric materials.

Rainer Haag is Professor of Organic and Macromolecular Chemistry at Freie Universität Berlin. His research interests include dendritic and linear polyglycerols as multivalent virus inhibitors, macromolecular nanotransporters for DNA and drug delivery as well as fluorous interactions. In 2022, he received an Advanced Grant from the European Research Council. Together with the company Dendropharm, he received the 2016 Berlin-Brandenburg Innovation Award. Since 2019 he has been an elected member of the German Academy of Science and Engineering (acatech).

Janos Wasternack obtained his bachelor degree at Humboldt Universität zu Berlin with a BA thesis on photoswitchable anion sensors in the group of Stefan Hecht, and his master degree at Freie Universität Berlin. For his master thesis in the group of Christoph Schalley, he developed novel fluorous diacetylene gelators as UV-responsive surface coatings. He is currently working on his PhD thesis under the supervision of Prof. Schalley in the fields of fluorous materials as well as photo- and redox-switchable mechanically interlocked species.

Christoph Schalley received his PhD with Helmut Schwarz at Technical University Berlin in 1997 on the gas-phase chemistry of peroxides. This was followed by postdoctoral research on supramolecular encapsulation with Julius Rebek, Jr. at the Scripps Research Institute in La Jolla. His current research interests range from self-assembly and self-sorting through multivalent molecular recognition to soft materials such as supramolecular gels. He was awarded the Mattauch-Herzog Prize from the German Society for Mass Spectrometry in 2006 for his work on the gas-phase chemistry of non-covalent complexes.

Abhishek Kumar Singh received his PhD from the Department of Chemistry, University of Delhi, India, under the supervision of Sunil K. Sharma. His PhD thesis focused on glycerol- and oligoglycerol-based amphiphilic architectures for biomedical applications. He is currently a postdoctoral researcher in Rainer Haag's group, working on the synthesis of various types of surfactants. His research focuses on the synthesis of oligoglycerol-based surfactants for various biological applications.

fluorinated amphiphiles are not synthesized by fluorination of their non-fluorinated derivatives. On the one hand, per- and polyfluorination can rarely be achieved by nucleophilic substitution with fluoride or other organic fluorinating agents. On the other hand, treatment of amphiphiles under harshly fluorinating conditions is hazardous and hardly controllable or selective. To overcome these challenges, either the hydrophilic group is synthesized from a per- or polyfluorinated precursor in a divergent manner, or the hydrophilic group is coupled to the per- or polyfluorinated segment through a click, addition, or substitution reaction in a convergent approach. Thus, the available functional groups for the desired perfluorinated segment dictate the synthesis route. The most abundant functional groups for per- and polyfluorinated precursors include: perfluorinated alkyl iodides (for radical telomerization and addition reactions), polyfluorinated alkyl iodides (for coupling with nucleophiles), alcohols (for coupling with electrophiles)[11] and carboxylic acids (for ester[12]/amide[13–15] coupling). The introduction of propargyl groups or use of fluorinated thiols (accessible from polyfluorinated alkyl iodides)[16] enables the use of Huisgen[12] and thiol-ene click reactions.[17] Polymeric fluorinated amphiphiles can additionally be synthesized by copolymerization of non-fluorinated with fluorinated mono-mers (e.g. polyfluorinated methacrylates).[11]

A positive side effect of fluorine moieties in supramolecular structures is that they can be imaged with good contrast by cryo-transmission electron microscopy (cryo-TEM) because of their high electron density. Von Berlepsch et al.[17] synthesized a series of non-ionic amphiphiles with different dendritic oligoglycerol (G1-G3) head groups and one or two fluorinated alkyl chains connected through spacers of different lengths. These amphiphiles form uniform branched and perforated superstructures. G3 head groups, in combination with the single- and double-chain ponytails and the G2 head group with a single fluorinated chain, form spherical micelles. In marked contrast, the decreased size of the G1 hydrophilic end group results in wormlike assemblies (with C_3 spacers), while perforated bilayer vesicles as well as planar-network-like structures are found with C_6 spacers. Among the most notable structural observations in this study were stomatosomes, namely perforated vesicles, which are observed from the combination of G2 head groups with two fluorinated tails and different length spacers (C_0, C_3, and C_6; Figures 1a,b). These stomatosomes were found to be metastable and to transform into a bicontinuous cubic network with double diamond symmetry.

A similar transition of superstructures of fluorinated dendritic Janus-type amphiphiles was observed in a recent study by Rosati et al.[18] The hydrophobic segment used contained a superhydrophobic moiety with a high number of fluorine atoms in a confined space that was synthesized from a perfluoro-*t*-butoxy group (Figure 1a), while the hydrophilic segment was a polyester dendron based on 2,2-bis(hydroxymethyl)propionic acid. Whereas amphiphiles with a 1st or 2nd generation polyester head group formed stable spherical aggregates and micelles, 3rd generation amphiphiles initially formed multilamellar dendrimersomes.
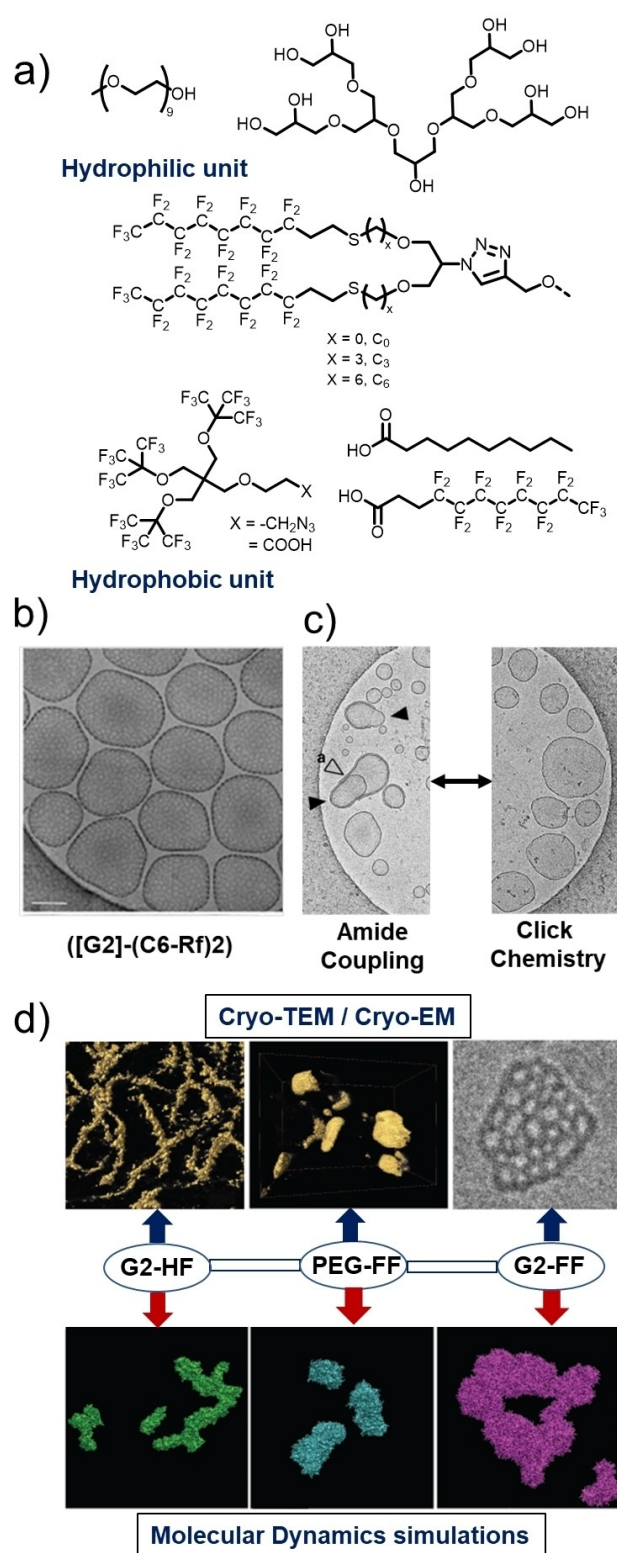
Figure 1. a) Hydrophilic and hydrophobic segments of fluorinated amphiphiles. b) Formation of stomatosomes from ([G2]-(C6-Rf)₂). c) Aggregation behaviour of branched fluorinated amphiphiles synthesized by two different approaches. d) Amphiphiles with different ratios of alkyl and fluoroalkyl chains with two different polar head groups (PEG and oligo-glycerol G2). Figure adapted from Von Berlepsch et al.,[17] Singh et al.,[19] and Rashmi et al.[12] with permission from the Royal Society of Chemistry and the respective authors.

Within 48 h, tubular superstructures were formed through a sheetlike transition state. The intense ^{19}F NMR signal almost vanished during the formation of the tubular structures, indicating stronger interactions and thus stiffer fluorinated moieties than in the spherical dendrimersomes. Notably, no such transition to tubular structures was observed if trifluoroethanol was used as a cosolvent instead of ethanol. Coarse-grained and other simulations indicated that this effect could be attributed to fluorous interactions between the fluorinated dendrons and the cosolvent.

Singh et al.[19] reported two non-ionic branched amphiphiles with two different chemical approaches, namely, using an amide and a triazole, to link the same fluorous dendron to a G2-oligoglycerol dendron. Both compounds showed the formation of well-defined vesicles, while the different linkers supported slightly different aggregation behaviour. The amphiphile with an amide linkage showed the formation of multivesicular (MVVs) and multilamellar (MLVs) vesicles along with the smaller unilamellar vesicles (SUVs), while the amphiphile with triazole moiety only showed the formation of unilamellar vesicles (Figures 1a,c).

Rashmi et al.[12] investigated two series of amphiphiles with either PEG-550 or dendritic G2 oliglycerol head groups and two hydrophobic alkyl chains, two fluorinated ponytails, or a combination of both (Figures 1a,d)—here abbreviated as PEG-HH, PEG-HF, PEG-FF, and G2-HH, G2-HF, and G2-FF). A morphological cryo-TEM and cryo-electron tomography (cryo-ET) study, together with coarse-grain molecular dynamics calculations using the Martini model, shows G2-HH and PEG-HH to form micelles with respective diameters of 7.5 and 6 nm. Replacing one of the alkyl groups with a fluorinated chain led to thread-like micelles (PEG-HF and G2-HF). Furthermore, the amphiphiles with two fluoroalkyl chains (PEG-FF and G2-FF) showed a clear difference in their morphologies: PEG-FF aggregated in sheetlike structures with discoidal patches of various diameters, and G2-FF exhibited wormlike micelles of micrometre lengths incorporated in highly branched networks in which the diameter of all strands was about 7.5 nm. The morphology of these networks resembled the previously obtained "stomatosome" architectures.

2.2. Stabilization of Microdroplets

Microfluidics has gained a significant foothold in bioanalytics, where millions of picolitre- and nanolitre-sized droplets are produced, monitored, and sorted at kHz rates. These devices could revolutionize high-throughput screening because they can operate at such small volumes. This feature has spurred exciting research and product development in chemistry and biology, including small-scale organic synthesis, single-cell barcoding, single-cell ChIP-seq, combinational drug screening, therapeutic antibody discovery, directed enzymatic evolution, and digital ELISA.[13,20] Often, these droplets are metastable and exhibit premature coalescence, which can be avoided with fluorosurfactants that enhance their stability. A biologically inert fluorinated oil is generally used to dissolve these fluorosurfactants; such an oil is immiscible with aqueous and organic solutions, thus making it an ideal platform for trapping biomolecules in droplets.[13,20]

In addition, surfactants must ensure that biomolecules do not adsorb at the interface. Several surfactants with fluorotelomer tails have been used (mainly C_6 to C_{10}), but they do not provide long-term emulsion stability. It was found that oligomeric perfluoropolyethers (PFPEs), when used as the main component of the hydrophobic part of copolymers, have very good solubility in fluorocarbon oil and can provide effective steric stabilization by forming a dense layer on the outer droplet surface. However, PFPE-based surfactants are commercially available only with ionic head groups, such as poly(perfluoropropylene glycol) carboxylate ("Krytox"). As a consequence of the charged carboxylate group in Krytox, oppositely charged biomolecules interact, lose their activity, and agglomerate at the droplet interface.[14]

Therefore, fluorosurfactants with non-ionic headgroups are required for biological assays. A series of non-ionic triblock copolymer surfactants combining polyethylene glycol with perfluoropolyethers (PEG-PFPE2) were reported by Holtze et al.[21] Surfactants with 600 g mol^{-1} PEG and 6000 g mol^{-1} PFPE performed best in droplet formation and stabilization. However, the polydispersity of PEG and PFPE often results in polymer mixtures, causing the final products to vary from batch to batch. In addition, during thermal cycling in, for example, a polymerase chain reaction, a considerable number of droplets fuse. Finally, PEG molecules are somewhat hydrophobic and thermoresponsive, which can affect biological assays.[15] Fluorosurfactants with linear and dendritic oligoglycerols have offered dramatic improvements of data quality in droplet-based high-throughput drug screening assays and microdroplet PCR as compared to commercially available PEG-based surfactants (Figure 2a). A systematic study of dendronized fluorosurfactants with glycerol and dendritic triglycerol polar head groups and fluorous PFPE chains of three different lengths as non-polar tails revealed that a combination of dendritic triglycerol with one of the two longer PFPE chains of 2 and 4 kDa was the best choice for microdroplet PCR and small-molecule droplet retention (Figure 2b). Chowdhury et al. also reported[13] four surfactants with linear as well as dendritic structures with three and four hydroxy groups and a common PFPE chain of a lower 2 kDa molecular weight (Figure 2a). Compared to dendritic triglycerol, diglycerol, and tris, the polar head group with a linear triglycerol chain appears to be most effective for minimal leakage of the water-soluble fluorescein dye from the droplets (Figure 2c). Furthermore, a multi-step post-modification of the hydroxy groups of the linear triglycerol surfactants changes its chemical functionality by introducing a small active functional group. This post-functionalized surfactant still effectively stabilizes the droplets and creates a reactive droplet interface, thus enabling the possibility of "droplet fishing" and demonstrating another advantage of linear surfactants: allowing chemical modification of the droplet interface without affecting the droplets' stability and monodispersity. In addition, fluorosurfactants with oxidisable thioether head
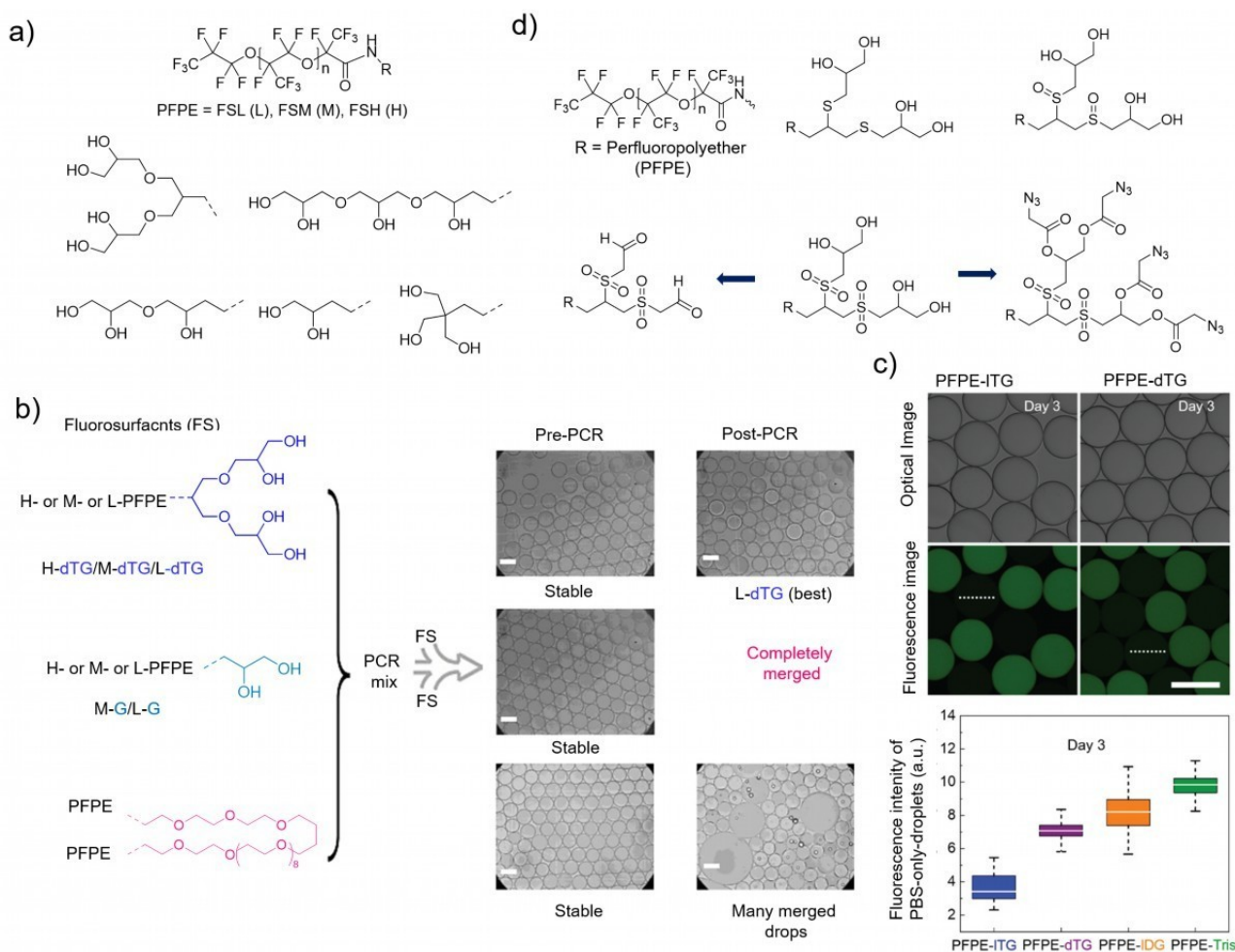
Figure 2. a) Types of fluorosurfactant with different head groups. b) PCR stability of dendritic triglycerol with a low molecular weight (L-dTG), glycerol, and PEG-PFPE2. c) Micrograph showing the inter-droplet diffusion of a fluorescence dye sodium fluorescein salt after 72 h. d) Functional surfactants containing redox-responsive headgroups, e.g. multiple thioethers, sulfoxides, and sulfones. Figure adapted from Chowdhury et al.[13, 15] with permission from the Royal Society of Chemistry and the respective authors.

groups have been introduced.[22] These surfactants exquisitely use various oxidation states of the thioether, multivalence, tenability of the OH groups, and oxidisable 1,2-diols available in the polar head group. Oxidation of the thioether to sulfoxides and sulfones helps increase the polarity of the surfactant head group. Moreover, surfactants with OH groups and a thioether, sulfone, or sulfoxide showed excellent compatibility with single cells and drug-inducible gene expression in the droplet, thus demonstrating the advantages of a higher degree of oxidation that can be used to manipulate the robustness of the microdroplets. (Figure 2d).

3. Solid/Liquid Interfaces

3.1. Fluorous Adsorption of Fluorinated Amphiphiles at Surfaces

Interfaces between liquids and fluorous solids can be used to adsorb fluorous or fluorine-tagged molecules from solution by fluorine-specific interactions, which is especially common in fluorous catalysis. Fluorous tags that are used in catalysis or synthetic chemistry usually contain at least six consecutive difluoromethylene groups to obtain sufficient fluorophilicity for adsorption onto fluorous surfaces.[23–26]

The concept of fluorine-specific adsorption of fluorous molecules from a liquid phase onto a solid fluorous column and filter materials was more recently tested for the removal of fluorinated amphiphiles and other emerging perfluoroalkylated environmental pollutants (PFAs) from contaminated water.[27–29] PFAs, especially the fluorous surfactants perfluorooctyl sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were found to induce adverse health effects, such as cancer or liver toxicity.[27] Consequently, advisory levels for PFAs as low as $70 \, ng \, L^{-1}$ (sum of PFOS and PFOA concentration) in municipal water were defined by legislative authorities.[28] Industrially applied PFA-adsorbing materials are either granular or powdered activated carbon (PAC), which adsorb PFAs like most hydrophobic materials, or polymeric anion-exchange resins with cationic amine or

ammonium groups for the electrostatic binding of negatively charged PFAs along with other environmentally occurring anions.[29]

As adsorber materials for fluorous amphiphilic substances need to be produced on a ton scale to purify whole contaminated water streams, Du and co-workers[29] chose vermiculite, a cheap silicate, as the basis for their fluoroalkylated PFAS adsorber system. A cationic surfactant, 3-(((perfluorooctyl)sulfonyl)amino)-*N,N,N*-trimethylpropanammonium iodide (PFQA) was intercalated into the vermiculite layers. Magnetite nanoparticles were incorporated into the adsorber material by a ball milling procedure. The magnetite nanoparticles assembled at the surface of the vermiculite (Figure 3a) and increased its dispersibility in water along with the possibility for a magnetic removal of the adsorber after the treatment procedure. The removal efficiency of PFOS by this fluorous vermiculite was unaffected by the presence of octanesulfonate, the non-fluorinated analogue of PFOS. This clearly detectable selectivity of the fluorous vermiculite for the PFOS can be attributed to fluorous interactions between the PFOS and the intercalated PFQA. Furthermore, the PFOS adsorption performance of the fluorous vermiculite was tested with a real wastewater sample containing multiple PFAs, but most notably $22.5 \, \text{mg L}^{-1}$ PFOS. Whereas the fluorous vermiculite showed almost quantitative removal of PFOS at a dose of 150 mg vermiculite per litre of wastewater, a commercially available, non-fluorinated anion-exchange resin and powdered activated carbon removed only 30 to 35 % PFOS at the same dose of the respective adsorber material. In contrast, lower doses of the commercially available non-fluorinated anion-exchange resin were required for PFOS adsorption from artificial PFOS solutions. This experiment showed that PFOS adsorption onto the fluorous vermiculite was less affected by impurities in the wastewater sample than the adsorption of PFOS onto non-fluorous adsorbers, a result that further suggested a fluorine-specific adsorption process onto the fluorous vermiculite surface.

A similar approach of combining fluorous groups with positive charges for the adsorption of negative PFAs was applied by Kumarasamy et al.[28] A perfluoropolyether chain of a commercially available cross-linking agent was used as the fluorous domain. Cationic charges were introduced by methylation of the tertiary amine copolymer. In a direct comparison of the fluorous hydrogel to industrially applied non-fluorous PAC and ion-exchange resins, consistently higher PFA removal efficiencies were detected. Interestingly, derivatives of the hydrogel that consisted solely of fluorous groups or cationic amine groups did not show a consistent PFA adsorption, revealing the importance of the interplay of fluorous and electrostatic interactions for effective PFA adsorption under the applied experimental conditions.

Another study reported an uncharged hydrogel that was cross-linked with fluorous poly(methacrylamide) particles (Figure 3b).[27] As a consequence of its electroneutrality, its removal efficiency of cationic, neutral, and zwitterionic PFAs was comparable to the removal efficiency of the most
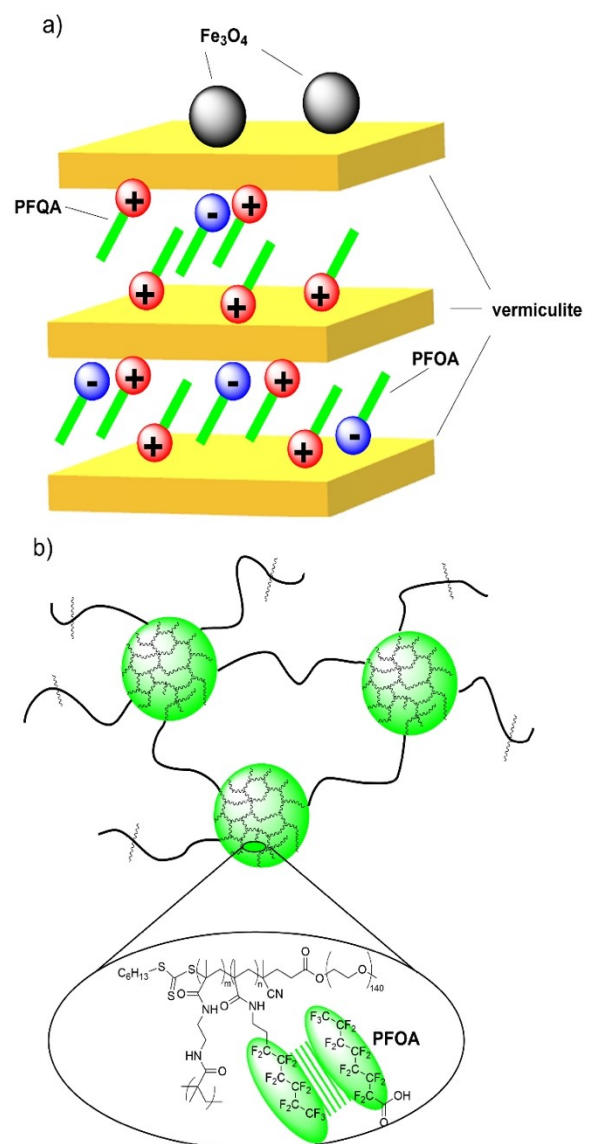
Figure 3. a) Ball-milled vermiculite can be loaded with magnetite nanoparticles for dispersibility in water and magnetic removal. When the cationic fluorous surfactant PFQA is intercalated into the structure of the vermiculite, anionic fluorous surfactants such as PFOA can be adsorbed on to the vermiculite by fluorous interactions.[29] b) Adsorption of PFOA through fluorous interactions onto cross-linked fluorous polyacrylamide particles that are embedded in a polyacrylamide hydrogel.[27]

commonly addressed negatively charged PFOS. Broadening and a slight shift of the ^{19}F NMR signal from the CF_3 group of the studied PFAs was only observed in the presence of fluorous poly(methacrylamide) particles. No changes in the ^{19}F NMR spectra of the PFAs were observed when the PFAs were mixed with the corresponding non-fluorous poly(methacrylamide) particles, a result that instead indicates there is a fluorous interaction in the adsorption process of PFAs onto the fluorous particles of the hydrogel. Recycling of the hydrogel was possible by washing with a mixture of organic solvents.

The decoration of surfaces of adsorbers with fluoroalkyl groups has been shown to improve the selective removal of amphiphilic fluorous pollutants from contaminated water on a laboratory scale. The PFA removal efficiency of all the fluorous PFA adsorbers presented herein was hardly affected by the presence of other organic substances or changes in the pH value, in contrast to typical observations of traditional non-fluorous PFA adsorbers such as PAC or ion-exchange resins.[27–29]

Despite these initial reports, a detailed understanding of the interplay between fluorous and electrostatic interactions as well as the critical parameters that affect the adsorption of fluorous amphiphiles still needs to be developed. The effect of the type of fluoroalkyl group used for surface functionalization of the PFA adsorber on the fluorous interaction with PFAs has not been addressed yet, but might be key to increasing the currently challenging selective adsorption of short-chain PFAs such as perfluorobutyric acid (PFBA).[28,29] Owing to the high price of fluoroalkylating agents, the production costs of fluorous adsorber materials are significantly higher than their non-fluorous counterparts. However, if the superior selectivity of fluorous adsorbers towards PFAS, and thus higher expected water volumes until breakthrough occurs in comparison to classical non-fluorinated adsorber materials, can be maintained on an industrial-scale filtration setups, fluorous adsorber materials might also become an economical viable solution for water purification.

3.2. Superhydrophobic and Slippery Surfaces Based on the Deposition of Fluorinated Amphiphiles

Superhydrophobic surfaces can be achieved through self-assembly of fluoroalkyl chain-containing amphiphiles. Krafft prepared various partial fluorinated amphiphilic building blocks that will self-assemble into different two- or three-dimensional nanostructures that can further be deposited on solid surfaces.[30] For example, micelles formed with fluoroalkyl-alkyl diblock amphiphiles were found to self-stack into a layer at the surface that could be used for surface patterning. Superhydrophobic surface coatings can also very easily be made by the deposition of side-chain-fluorinated low molecular weight gelators (LMWGs). The small and easy-to-synthesize fluorous gelators self-assemble into a supramolecular gel with micrometre roughness, while the omniphobic fluorinated side chains impart water and hydrocarbon repellence. Wei et al. demonstrated the use of such LMWGs based on cyclohexyl diamide to fabricate superhydrophobic coatings by this method (Figure 4).[29] The molecular design of the gelator contains a bis-amide core and two perfluorinated alkyl chains attached to the amide groups. The bis-amide system is widely adopted in the field of low molecular weight gelators because of its well-known tendency towards hydrogen-bond formation. The coating is obtained by deposition of a sol of the LMWG onto glass cover slips whereupon gelation and subsequent drying of the gel leaves a layer of superhydrophobic xerogel on the surface.[31]

To obtain mechanically stable and highly omniphobic coatings, several criteria must be met by the system of gelator, solvent, as well as casting and drying conditions: Formation of a uniform coating requires screening of suitable solvents as well as concentration and "amount per surface area" of the gelator. Very high contact angles are mainly obtained from hierarchical surface structuring, namely, a microstructure with a superimposed nanostructure. The hierarchical protrusions on the surface lead to low surface energies because the contact area of the liquid and solid phases is minimised by trapped air within the solid phase (Cassie–Baxter wetting model). To obtain this degree of structuring and, therefore, high omniphobicity, careful screening of the gelator parameters, for example, chain length of the fluorous ponytails, is also necessary, as the packing behaviour of derivatives with different chain lengths varies dramatically.[32]

The hierarchical structuring is closely linked to the assembly processes during gelation: The two amide groups of the LMWGs enable strong intermolecular hydrogen bonds between the adjacent molecules, which lead to the formation of thin nanofibres, which bundle up into fibrils and eventually get entangled to form a three-dimensional network. The latter is preserved during drying, whereby the xerogel coating is formed and providing the roughness required for strong omniphobicity. The resemblance of the two-tier roughness of the hierarchical structure is confirmed by scanning electron microscopy, where the larger bundles were observed to be formed from thinner fibers. The fluorinated chains were also essential for the resulting assembled structure. If the C_7F_{15} chains (water contact angle (WCA) $\cong$ 158°) were replaced by C_7H_{15} chains, the aggregates lost the defined two-tier hierarchical structure, and the formed coating was only slightly hydrophobic (WCA $\cong$ 95°).[31]

The length of the fluorinated chains significantly affects the xerogel properties. Upon substituting the C_7F_{15} chains by C_3F_7 chains, the structure of the self-assembled aggregates was found not to be fibrous. Even though the superhydrophobicity was preserved (WCA $\cong$ 155°), the resulting coatings were less stable. This discovery led to further investigation of the effect of the side-chain lengths on the formed coating.[32] The results show that the length of the fluorinated side chains on the bis-amide-based gelator has a dramatic effect on several aspects of the formed coatings: with the length of the side chains ranging from three to ten carbon atoms, the compounds formed structures ranging from fibrous to crystalline. There was a distinct drop in surface energies above a side-chain length of C_7F_{15}; however, this decrease was not consistently proportional. Nevertheless, all the aggregate arrangements observed on the samples were hierarchically structured, as revealed by scanning electron microscopy, and were thus adequate to give high water contact angles. The morphologies of the coatings were more homogeneous with less-crystalline compounds. The coating stabilities were also very diverse, as seen in the effect of a merely one CF_2 group difference between C_6F_{13} and C_7F_{15}. The coating made from the former (C_6F_{13}) deteriorated rapidly upon flushing with water, while the
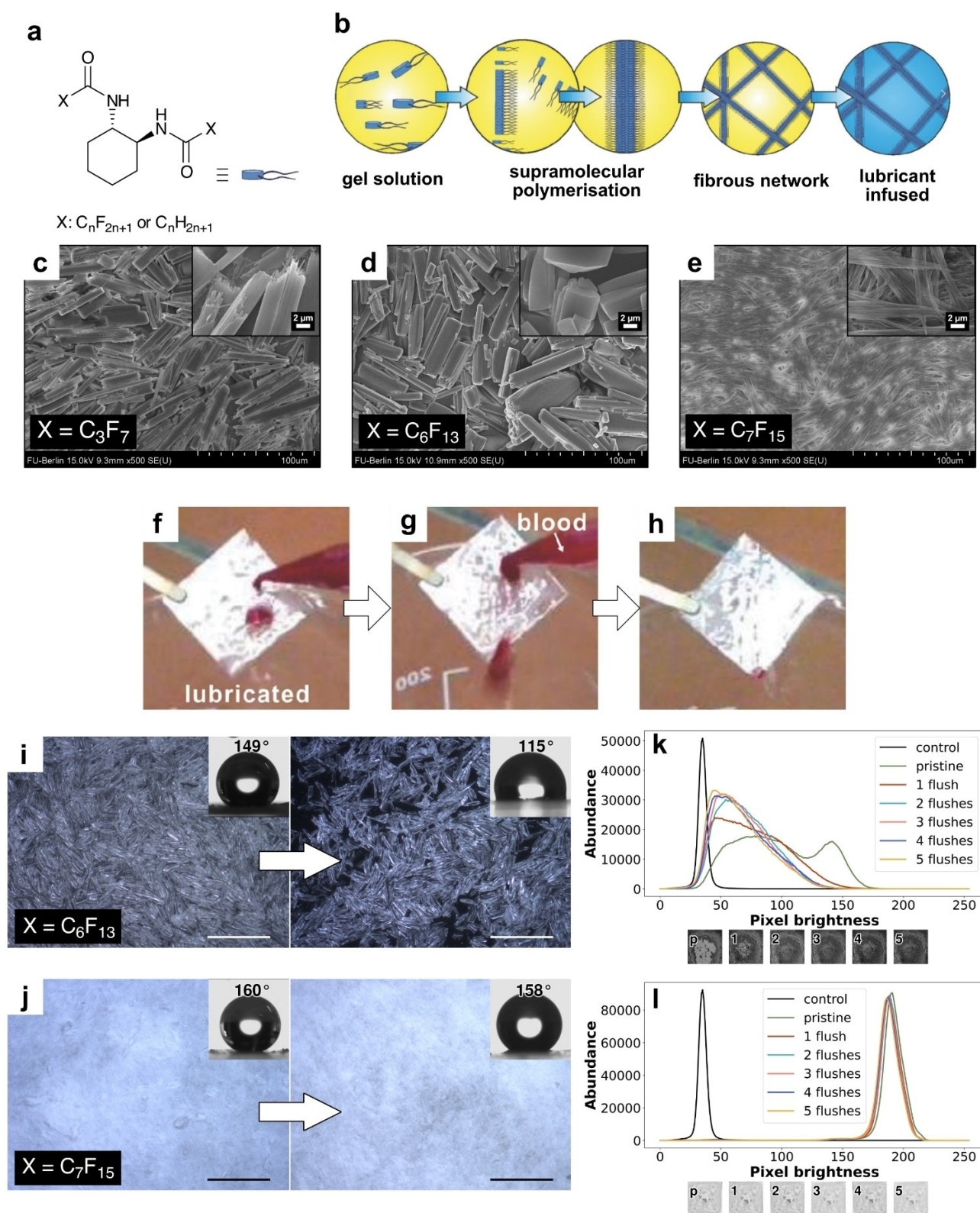
Figure 4. a) General chemical structure of the gelators based on the cyclohexyl diamide core. b) Proposed assembly mechanism for the C_7F_{15}-substituted gelator.[31] c)–e) Two-tier hierarchical structure of the self-assembled structures of gelators with different side chains.[31,32] f)–h) Self-cleaning towards blood observed on lubricated slippery surface.[31] i) and j) Optical micrographs showing the varying extent of impairment during water-flow stability tests of the coatings made from gelators with different side chains.[32] k) and l) Change in the macroscopic appearances of the coatings in (i) and (j), respectively, analysed by pixel brightness.[32] Figure adapted with permission from Wei et al.[31] and Lee et al.[32] Copyright 2014 Wiley-VCH & 2021 American Chemical Society.

latter (C_7F_{15}) gave rise to one of the most stable coatings in the tested range.

Linking the stability of the coatings to their surface energy, the crystallinity, and the aggregate morphology is subject to current investigation by the Schalley group. Counterintuitively, these correlations do not linearly follow the chain length of the ponytails.[32]

The system so far mimics the properties of lotus plants, but another interesting concept can be derived from the *Nepenthes* pitcher plant: This carnivorous plant catches small insects, which fall into its pitcher and cannot escape the steep walls because of the trap interior's slippery lining, which comprises a hierarchical structure infused with a lubricant. This principle was adopted to enhance the slipperiness of omniphobic coatings. Wong et al. have demonstrated the use of fluorous lubricant (e.g. Fluorinert FC-70) to create extra slippery surfaces on pre-structured, low-surface-energy materials, such as porous teflon membranes and polyfluoroalkylsilane-functionalized textured epoxy.[33] The lubricant was simply deposited onto the structured substrate to form the lubricating film. Here, the complete wetting and adhesion of the lubricant on the substrate are assured by the large surface area of the substrate and its affinity for the fluorous lubricant. The nanostructure of the substrate plays a critical role: not only taking in, but more importantly, immobilizing the infused lubricating film. Compared to non-lubricant-infused superhydrophobic surfaces, the lubricant-infused surfaces show extreme liquid repellency as well as enhanced optical transparency. Wei et al. likewise demonstrated the addition of fluorous lubricant to a textured xerogel coating to facilitate slipperiness of conventional superhydrophobic surfaces. The fibrous network of the xerogel works as the trap to secure the lubricating fluid so that it is not washed away easily. The slippery surface shows self-cleaning towards not only water, but also more complex liquids such as blood and human serum.[31] This confirms the liquid repellency to be independent of the texture morphology, assuming that the lubricant layer has adequate thickness and coverage.

Such omniphobic surface coatings have great medical potential as demonstrated by Leslie et al.[34] In this study, the lubricant was coated through the silanization of samples with a covalently binding monolayer of fluorocarbons. The fluorocarbon monolayer retains the lubricant as a mobile layer, and the surface shows extreme repellency towards human blood, only if both the monolayer and lubricant components are present. This approach is easily applicable to any surface with various geometries and shows great potential for medical applications.

4. Summary and Outlook

The low polarizability of perfluoroalkyl groups caused by the compensation of most dipoles in the fluorous chains translates into generally weak intermolecular forces and pronounced hydro- as well as lipophobicity. Thus, the introduction of perfluoroalkyl groups into amphiphiles dramatically influences their interfacial behaviour. The examples highlighted here include the formation of unique aggregate morphologies, the remarkable stabilization of microdroplets in emulsions of water and perfluorinated oils, and superhydrophobic surface coatings based on amphiphilic fluorous gelators. Despite the considerable potential of fluorous molecules for these applications, their use is currently limited to laboratory-scale applications—mostly because of their difficult preparation, environmental persistency, and the lack of detailed knowledge on the fluorous effect.

Most fluorous interface phenomena have been studied in systems that contained perfluorohexyl chains or even longer perfluoroalkyl groups. Despite the generally strong fluorous effects of these rather large perfluoroalkyl groups, the translation of fluorous phenomena to less fluorinated systems with lower environmental persistency seems to be important for broader applicability.

Some of the applications presented herein already use some fluorous groups that are believed to be less toxic and less bio-accumulative as an alternative to conventional long linear perfluoroalkyl groups. Examples include the branched system from Rosati et al.[18] where the three perfluoro-*t*-butyl groups were separated by ether bonds for biodegradability or the PFPE-containing amphiphiles used for microfluidics.[13–15] Besides heteroatom-containing or short and branched fluorous groups,[35] another type of more sustainable fluorous moiety consists of polyfluorinated groups with hydrogen atoms within the fluorinated chain.[36] Despite promising surface properties comparable to traditional fluorinated amphiphiles, sustainable fluorous moieties are more difficult to synthesize.[11,37] A key research area of fluoroorganic chemists, which is essential for replacing the traditional persistent fluorinated amphiphiles, is to understand in more detail the fluorous properties of the many new sustainable fluorinated structures and to develop scalable synthetic procedures.

If achieved, this more-detailed understanding of fluorous interactions could ultimately be aimed at the development of models for more accurate computation of fluorous properties. Among the many interesting examples would certainly be a model for predicting aggregate morphology based on the molecular structure of a fluorous amphiphile, similar to the packing parameter of non-fluorous amphiphiles.

Further progress in the still rather unexplored field of fluorous chemistry may prove rewarding because of the unique and outstanding properties of fluorous amphiphiles. In particular, their generally high biocompatibility, aggregate versatility, and chemical stability can certainly significantly contribute to the development of high-performance materials.

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Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

[1] J. A. Gladysz, D. P. Curran, I. T. Horváth in *Handbook of fluorous chemistry* (Eds.: D. P. Curran, I. T. Horváth, J. A. Gladysz), Wiley-VCH, Weinheim, **2004**, p. XXI–XXII.

[2] R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496.

[3] "Fluorous Chemistry": J. A. Gladysz, M. Jurisch in *Topics in Current Chemistry Vol. 308* (Ed.: I. Horváth), Springer, Berlin, **2011**, pp. 1–23.

[4] R. A. Cormanich, D. O'Hagan, M. B. Bühl, *Angew. Chem. Int. Ed.* **2017**, *56*, 7867; *Angew. Chem.* **2017**, *129*, 7975.

[5] For an excellent tutorial review on the fluorous effect, see: M. Cametti, B. Crouse, P. Metrangolo, R. Milani, G. Resnati, *Chem. Soc. Rev.* **2012**, *41*, 31.

[6] Special dispersive interactions with fluorous chains have been highlighted in a recent analyses of the crystal packing of perfluorocarbon/aromatic co-crystals, see M. Saccone, A. Pace, I. Pibri, G. Cavallo, P. Metrangolo, T. Pilati, G. Resnati, G. Terraneo, *CrystEngComm* **2021**, *23*, 7324.

[7] T. Hasegawa, T. Shimoaka, N. Shioya, K. Morita, M. Sonoyama, T. Takagi, T. Kanamori, *ChemPlusChem* **2014**, *79*, 1421.

[8] P. Morgado, A. R. Garcia, L. F. G. Martins, L. M. Ilharco, E. J. M. Filipe, *Langmuir* **2017**, *33*, 11429.

[9] M. P. Krafft, J. G. Riess, *Chem. Rev.* **2009**, *109*, 1714.

[10] M. P. Krafft, *Adv. Drug Delivery Rev.* **2001**, *47*, 209.

[11] S. M. S. Hussain, A. A. Adewunmi, A. Mahboob, M. Murtaza, X. Zhou, M. S. Kamal, *Adv. Colloid Interface Sci.* **2022**, *303*, 102634.

[12] R. Rashmi, H. Hasheminejad, S. Herziger, A. Mirzaalipour, A. K. Singh, R. R. Netz, C. Böttcher, H. Makki, S. K. Sharma, R. Haag, *Macromol. Rapid Commun.* **2022**, *43*, 2100914.

[13] M. S. Chowdhury, W. Zheng, A. K. Singh, I. L. Hao Ong, Y. Hou, J. A. Heyman, A. Faghani, E. Amstad, D. A. Weitz, R. Haag, *Soft Matter* **2021**, *17*, 7260.

[14] O. Wagner, J. Thiele, M. Weinhart, L. Mazutis, D. A. Weitz, W. T. S. Huck, R. Haag, *Lab Chip* **2016**, *16*, 65.

[15] M. S. Chowdhury, W. Zheng, S. Kumari, J. Heyman, X. Zhang, P. Dey, D. Weitz, R. Haag, *Nat. Commun.* **2019**, *10*, 4546.

[16] S. Y. Dieng, B. Bertaïna, A. Cambon, *J. Fluorine Chem.* **1985**, *28*, 341.

[17] H. von Berlepsch, B. N. S. Thota, M. Wyszogrodzka, S. de Carlo, R. Haag, C. Böttcher, *Soft Matter* **2018**, *14*, 5256.

[18] M. Rosati, A. Acocella, A. Pizzi, G. Turtù, G. Neri, N. Demitri, Nonappa, G. Raffaini, B. Donnio, F. Zerbetto, F. B. Bombelli, G. Cavallo, P. Metrangolo, *Macromolecules* **2022**, *55*, 2486.

[19] A. K. Singh, B. Schade, M. Rosati, R. Rashmi, V. Dichiarante, G. Cavallo, P. Metrangolo, R. Haag, *Macromol. Biosci.* **2022**, *22*, 2200108.

[20] T. S. Kaminski, P. Garstecki, *Chem. Soc. Rev.* **2017**, *46*, 6210.

[21] C. Holtze, A. C. Rowat, J. J. Agresti, J. B. Hutchison, F. E. Angl, C. H. J. Schmitz, S. Köster, H. Duan, K. J. Humphry, R. A. Scanga, J. S. Johnson, D. Pisignano, D. A. Weitz, *Lab Chip* **2008**, *8*, 1632.

[22] M. S. Chowdhury, X. Zhang, L. Amini, P. Dey, A. K. Singh, A. Faghani, M. S. Henneress, R. Haag, *Nano-Micro Lett.* **2021**, *13*, 147.

[23] F. Begum, M. Ikram, B. Twamley, R. J. Baker, *RSC Adv.* **2019**, *9*, 28936.

[24] G. Guday, P. Nickl, M. Adeli, R. Haag, *ACS Appl. Nano Mater.* **2020**, *3*, 1139.

[25] Y. Kobayashi, S. Inukai, N. Kondo, T. Watanabe, Y. Sugiyama, H. Hamamoto, T. Shioiri, M. Matsugi, *Tetrahedron Lett.* **2015**, *56*, 1363.

[26] N. Audic, P. W. Dyer, E. G. Hope, A. M. Stuart, S. Suhard, *Adv. Synth. Catal.* **2010**, *352*, 2241.

[27] Q. Quan, H. Wen, S. Han, Z. Wang, Z. Shao, M. Chen, *ACS Appl. Mater. Interfaces* **2020**, *12*, 24319.

[28] E. Kumarasamy, I. M. Manning, L. B. Collins, O. Coronell, F. A. Leibfarth, *ACS Cent. Sci.* **2020**, *6*, 487.

[29] Z. Du, S. Deng, S. Zhang, W. Wang, B. Wang, J. Huang, Y. Wang, G. Yu, B. Xing, *Environ. Sci. Technol.* **2017**, *51*, 8027.

[30] M. P. Krafft, *J. Fluorine Chem.* **2012**, *134*, 90.

[31] Q. Wei, C. Schlaich, S. Prévost, A. Schulz, C. Böttcher, M. Gradzielski, Z. Qi, R. Haag, C. A. Schalley, *Adv. Mater.* **2014**, *26*, 7358.

[32] P.-W. Lee, T. Kaynak, D. Al-Sabbagh, F. Emmerling, C. A. Schalley, *Langmuir* **2021**, *37*, 14390.

[33] T.-S. Wong, S. H. Kang, S. K. Y. Tang, E. J. Smythe, B. D. Hatton, A. Grinthal, J. Aizenberg, *Nature* **2011**, *477*, 443.

[34] D. C. Leslie, A. Waterhouse, J. B. Berthet, T. M. Valentin, A. L. Watters, A. Jain, P. Kim, B. D. Hatton, A. Nedder, K. Donovan, E. H. Super, C. Howell, C. P. Johnson, T. L. Vu, D. E. Bolgen, S. Rifai, A. R. Hansen, M. Aizenberg, M. Super, J. Aizenberg, D. E. Ingber, *Nat. Biotechnol.* **2014**, *32*, 1134.

[35] M. A. Miller, E. M. Sletten, *Org. Lett.* **2018**, *20*, 6850.

[36] G. Kostov, F. Boschet, B. Ameduri, *J. Fluorine Chem.* **2009**, *130*, 1192.

[37] R. Zhou, Y. Jin, Y. Shen, P. Zhao, Y. Zhou, *J. Leather Sci. Eng.* **2021**, *3*, 6.