

Editorial

Special Feature *Organo-Fluorine Chemical Science*

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1. Inventing the Fluorine Future

Fluorine is the 13th most abundant element and, with other fluorine containing functional groups, is a most effective element in biological substances, pharmaceuticals, agrochemicals, liquid crystals, dyes, polymers and a wide range of consumer products. This reflects its resistance to metabolic change due to the strength of the C-F bond providing biological stability and the application of its nonstick-interfacial physical characteristics. Its introduction often remains a synthetic challenge. The widespread use of organofluorines has increased the demand for the development of practical and simple reagents and experimental strategies for the incorporation of fluorine into all types of molecular structures and this was the reasoning behind this special feature on *Organo-Fluorine Chemical Science*.

The contributed articles belong to two broad groups: (i) preparation of fluorine materials, polymers; (ii) the synthesis/applications of organo-fluorine molecules.

2. Fluorine-Fatness—Due to Lack of Fitness

Theoretical [1] and experimental observations to explain the molecular origins of fluorocarbon hydrophobicity suggest that the hydrophobicity of a fluorocarbon, whether the interaction with water is as solute or as surface, is due to its “fatness”. In solution, the extra work of cavity formation to accommodate a fluorocarbon, compared to a hydrocarbon, is not offset by enhanced energetic interactions with water. The enhanced hydrophobicity of fluorinated surfaces arises because fluorocarbons pack less densely on surfaces leading to poorer van der Waals interactions with water. The interaction of water with a hydrophobic solute/surface is primarily a function of van der Waals interactions and is substantially independent of electrostatic interactions. This independence is primarily due to the strong tendency of water at room temperature to maintain its hydrogen bonding network structure at an interface lacking hydrophilic sites.

3. Fluorine Materials and Polymers

For over a decade, a major synthetic target in fluorine material science has been the preparation of hydrophobic and superhydrophobic surfaces that are suitable for non-stick self-cleaning and anticorrosion applications. There is great interest in developing practical methods to generate such surfaces.

Jean-Denis Brassard and coworkers [2] in their paper on *Fluorine Based Superhydrophobic Coatings*, synthesized monodisperse silica nanoparticles of ~120 nm diameter via the Stöber process that were further functionalized using fluoroalkylsilane (FAS-17) molecules to incorporate the fluorinated groups with the silica nanoparticles in an ethanolic solution. The synthesized fluorinated silica nanoparticles were spin coated on flat aluminum alloy, silicon and glass substrates. The water contact angles and surface roughness increased with the number of spin-coated thin films layers. The critical size of ~119 nm rendered the aluminum surface superhydrophobic with three layers of coating using as-prepared nanoparticles suspended solution. On the other hand seven layers are required for a 50 vol.% diluted solution to achieve superhydrophobicity. In both the cases, water contact angles were more than 150°, and contact angle hysteresis was less than 2°. The authors considered that their coatings possessed self-cleaning properties. When applied on other substrates, like silicon or glass, superhydrophobicity is obtained by tuning the number of layers of deposition.

The α,ω -dialkoxyfluoropolyethers (DA-FPEs) prepared and characterized by Menghua Wu and coworkers [3] in their contribution: *An Environmentally Friendly Class of Fluoropolyether: α,ω -Dialkoxyfluoropolyethers* have been developed as a new class of environmentally friendly hydrofluoroethers (HFEs) with multiple uses; suitable as solvents, long-term refrigerants, cleaning fluids, and heat transfer fluids. Synthetic methodologies for DA-FPEs described here consist of radical-initiated oxypolymerization of olefin, peroxy-elimination reaction in peroxidic perfluoropolyethers (PFPE) and further chemical modification of α,ω -diacylfluoride PFPE. Physical properties of selected α,ω -dimethoxyfluoropolyethers have been evaluated and compared with analogous hydrofluoropolyethers having -OCF₂H as end-groups. The rationalization of the physical properties of these hybrid polymers is quite challenging. The highest boiling points are those of DM-FPEs, the intermediates are HFEs and the lowest ones are PFPEs. The above-mentioned result reflects the typical low intermolecular interactions of perfluorinated compounds. Partially fluorinated ethers, such as HFEs and DM-FPEs (α,ω -dimethoxyfluoropolyethers), display higher boiling temperatures and this is indicative of greater intermolecular polar interactions. Comparison of three similar fluoromethylethers, CF₃OCF₃ (b.p. 214 K; $\mu = 0.49$ D), CF₂HOCF₃ (b.p. 238 K, $\mu = 1.18$ D) and CH₃OCF₃ (b.p. 250 K, $\mu = 2.56$ D) when contrasted to dimethyl ether, CH₃OCH₃ (b.p. 249K, $\mu = 1.30$ D) the dipole moments really tell the story of the degree of polar interactions due to the presence of fluorine atoms. Interestingly, it is known that the presence of oxygen in PFPE impacts on chain flexibility but not on molecular polarity when compared with perfluoroalkyl analogues. Therefore, the glass transition temperature was found to decrease as the oxygen to carbon ratio was increased, maintaining a low cohesive energy density comparable with that of perfluoroalkanes. The progressive substitution of fluorine atoms with hydrogen in the methoxy end caps was found to lead to a stronger dipole and, consequently, to an increase of the boiling point. The boiling point differences between PFPEs and HFEs and between PFPEs and DM-FPEs are not constant but decrease continuously with

the chain length. Since the attractive forces are due to polar terminal groups, their relative intensity decreases as N increases and, as a result, the boiling points of HFES, DM-FPEs and PFPE tend to an asymptote at higher N values. Atmospheric implications and global warming potentials of selected dialkoxyfluoropolyethers were also considered.

Srinivas Hanumansetty and coworkers [4] describe in their article: *Stain Resistance of Cotton Fabrics before and after Finishing with Admicellar Polymerization* that admicellar polymerization permitted the formation of durable finishes that exhibited high performance in stain resistance and stain repellency. The mild method of fabric modification by admicellar polymerization is its greatest advantage. However innovative protocols to implement admicellar polymerization are needed for its application on a commercial scale.

Takashi Okazoe and collaborators [5] in their contribution: *Application of Liquid-Phase Direct Fluorination: Novel Synthetic Methods for a Polyfluorinated Coating Material and a Monomer of a Perfluorinated Polymer Electrolyte Membrane* showcase the utilization of their PERFECT chemical fluorine synthesis procedure for the preparation of novel multifunctional polyfluorinated anti-staining material. Perfluorination with fluorine gas is hazardous, is it possible to engineer the PERFECT process into a flow system to make it greener chemistry?

In the manuscript: *Overview of the Development of the Fluoropolymer Industry*, Hongxiang Teng [6] presents his views on the subject that fluoropolymers are important specialty polymers for their high performance properties and also for the combination of these properties as described in the review. The introduction attributes the reasons to the chemistry of fluorine and replacement of typically all hydrogens by fluorine in these polymers. The author continues to relate properties to structure (the larger size of fluorine relative to hydrogen) and chemistry of fluorine (such as the strong bonds to carbon). These aspects of the chemistry of fluoropolymers create a unique range of “on cursory inspection” unrelated properties. Preparation of FEP (copolymer of fluorinated ethylene and propylene), is said to contain 5% hexafluoropropylene. However the critical aspect of the chemistry of this copolymerization is the reactivity ratios of the two monomers. A difficulty in preparing many of the tetrafluoroethylene copolymers is widely separated reactivity ratios, or in the case of ECTFE (copolymer of ethylene and CTFE), the cross-reaction rates must be large to form an alternating copolymer. The included tables are useful and provide an effective summary to position individual discussions. This review provides a brief summary of fluoropolymers in order of development or manufacturing time. The fluoropolymers provide an example of how the high performance PTFE has been modified using polymer chemistry to decrease absolute properties and increase diversity of properties by substitution of fluorines or copolymerization.

The paper on *Nanoimprint Resist Material Containing Ultraviolet Reactive Fluorine Surfactant for Defect Reduction in Lithographic Fabrication* by Satoshi Takei and Atsushi Sekiguchi [7] describe their development and optimization of using 4.5 wt% of the fluorine surfactant 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,1-heptadecafluoro-2-hydroxyundecyl acrylate as a template release component in their formulation of nanoimprint resist materials. The fluorine surfactant effectively contributed to providing a clean separation technology for mass-production using UV curing nanoimprint lithography.

The focus of Yen-Ting Chen and coworkers [8] in *Optimization of Fluorine Plasma Treatment for Interface Improvement on $HfO_2/In_{0.53}Ga_{0.47}As$ MOSFETs* was to optimize the effects of CF_4/O_2

plasma power wattage and treatment time on $\text{HfO}_2/\text{In}_{0.53}\text{Ga}_{0.47}\text{As}$ gate stack. This resulted in significant improvement of the effective channel mobility (μ_{eff}), transconductance (G_m), drive current (I_d), and sub-threshold swing (SS). With F incorporation, they have successfully developed excellent interface quality of HfO_2 directly on $\text{In}_{0.53}\text{Ga}_{0.47}\text{As}$ without using interface passivation layer. Fluorinated samples exhibit low interface trap density (D_{it}) of $4.9 \times 10^{11} \text{ cm}^{-2} \text{ eV}^{-1}$, which is the lowest value compared to prior reported $\text{HfO}_2/\text{In}_{0.53}\text{Ga}_{0.47}\text{As}$ gate stacks. Incidentally, Hou and coworkers [9] have reported a simple technique to synthesize highly crystalline InGaAs NWs by a novel two-step chemical vapor deposition (CVD) method with a high growth yield. The NWs exhibit impressive electrical performance with a $I_{\text{ON}}/I_{\text{OFF}}$ ratio of $\sim 10^5$ and field-effect mobility of $\sim 2,700 \text{ cm}^2/(\text{V}\cdot\text{s})$ when configured in the back-gate NW field-effect transistors (FETs).

Yosuke Mizuno and Kentaro Nakamura [10] in their article *Enhancement of Brillouin Scattering Signal in Perfluorinated Graded-Index Polymer Optical Fibers* studied two methods to enhance the Brillouin Stokes signal in perfluorinated graded-index polymer optical fibers [PFGI-POFs]. The backscattered Brillouin light spectrum properties of [PFGI-POFs] with 62.5- μm core diameter were investigated. The Stokes power was extremely high compared to that of a PFGI-POF with 120- μm core, and the Brillouin threshold power for 5-m PFGI-POF was estimated to be 53.3 W. It was also shown that employing a PFGI-POF longer than ~ 50 m is not an effective way to enhance the Stokes signal. In addition, it was theoretically found that it is difficult to reduce the Brillouin threshold power of PFGI-POFs at 1.55- μm wavelength below that of long silica single-mode fibers even if their core diameter is sufficiently decreased to satisfy the single-mode condition. Finally, the Brillouin linewidth narrowing effect was confirmed. The authors conclude that these results will be a good guideline for developing practical Brillouin systems using PFGI-POFs, as well as for designing new PFGI-POF structures for Brillouin applications in future.

As urea and amide derivatives are ideal functional groups for the design of low molecular weight gelators, attributed to their rigidity, strength and ability to form highly directional hydrogen bonds, Anilkumar Raghavanpillai and Vincent Franco [11] in their article *Self-Assembled Fluorinated Organogelators for Surface Modification* prepared some novel alkyl- and perfluoroalkyl-containing urea and amides from amino acid derivatives and investigated their utilization as low molecular weight organogelators. Most of these compounds showed excellent gelation behavior in organic solvents at low concentrations. A few organogelators selected from the initial screening were used for surface modification of fibrous substrates to create hydrophobic and oleophobic composites. The hydrophobic and oleophobic behaviors of these composites were ascribed to a combination of increased surface roughness and the alkyl/fluorinated functionalities present in the gelator backbone. In general the urea-amide derivatives were better gelators than the corresponding bis- or tris-amide derivatives. Analogous urea-ester derivatives failed to gel in any organic solvents, indicating a combination of urea and amide functionalities, or multiple amide groups, are desirable to induce gelation. The nonwoven surfaces impregnated with perfluoroalkyl-containing organogelators showed excellent oleophobic behavior. Superior hydrophobic and oleophobic behavior exhibited by these composites were attributed to a combination of micro-structured surface morphology created by the xerogel and the presence of fluorocarbon/hydrocarbon functionalities in the gelator backbone.

Yoshihiro Tsujimoto, Kazunari Yamaura and Eiji Takayama-Muromachi [12] in their paper *Oxyfluoride Chemistry of Layered Perovskite Compounds* review recent progress and new challenges

in the area of oxyfluoride perovskite, especially layered systems including Ruddlesden-Popper (RP), Dion-Jacobson (DJ) and Aurivillius (AV) type perovskite families. Each of the fluorinating agents that have been reported so far, including F_2 gas, NH_4F , XeF_2 , CuF_2 and PVDF and PTFE, exhibits a distinct fluorinating power and reaction pathway. Examples are given illustrating that the fluorine contents in the resultant material depend on the choice, not only of the fluorinating agent, but also the anion lattice of the precursors. Synthetic strategies are proposed to further extend RP type perovskite compounds, with particular reference to newly synthesized oxyfluorides, Sr_2CoO_3F and $Sr_3Fe_2O_{5+x}F_{2-x}$ ($x \sim 0.44$). In future it will be interesting to explore the applications of these extended fluorinated oxyfluoride Perovskite compounds.

4. Synthesis/Applications of Organo-Fluorine Molecules

Organofluorine compounds possess desirable physical properties that are utilized widely in pharmaceuticals, agrochemicals, polymers and as biomaterials. In the case of medicinal chemistry, fluorine functionalities including $-R_F$, $-F$, $-CF_3$, $-OCF_3$ impart valuable *drug like* physiological properties on molecules that improve receptor binding selectivity, increase lipophilicity and metabolic stability. The practical synthesis of organofluorine compounds is an important scientific endeavor.

Christel Dolain and coworkers contribution [13]: *Nucleic Acid Based Fluorinated Derivatives: New Tools for Biomedical Applications*, reviews recent developments in the preparation of nucleic acid-based fluorinated derivatives, e.g., nucleosides or oligonucleotides connected to fabricated by coupling highly fluorinated chains or labeled with either a nucleoside or an oligonucleotides-modified with one or more fluorine atoms, have been investigated recently due to their high potential for biomedical applications. The application of nucleoside-based fluorocarbon derivatives is focused on three broad objectives: (i) construction of novel supramolecular materials and/or devices; (ii) development of new drug delivery systems; and (iii) discovery of new therapeutic molecules. The authors' review recent research on highly fluorinated nucleic acids derivatives, in particular nucleoside and oligonucleotide fluorocarbon amphiphiles as well as those with properties and applications of fluorine-labeled fluorinated oligonucleotide analogues. The review succeeds in showcasing the future potential role that highly fluorinated amphiphiles could play in chemistry, biology and material science.

Synthesis of Some New Fluorinated Hexahydroquinoline and Acridinedione Derivatives in Trifluoroethanol is the article contribution by Cosmas Okoro, Mumiye Ogunwale and Tasneem Siddiquee [14] in which they describe a facile one-pot synthesis of new fluorinated hexahydroquinoline derivatives via an unsymmetric Hantzsch reaction utilizing 5-trifluoromethyl-1,3-cyclohexanedione, aldehydes, acetoacetate ester, and ammonium acetate in trifluoroethanol. The reaction is simple and rapid with high yield. The reaction was extended to the synthesis of hexahydroacridinedione under similar conditions. The biological activities of the products will be investigated.

Understanding/predicting chemical reactions relies on the ability to calculate (simply) the energy and thermodynamics involved in the transformations. Jon Baker and Max Muir's contributed paper [15]: *Further Successes of the Meisenheimer Model* illustrate that this concept is true. Their model involves calculating the energy of all possible Meisenheimer complexes at a standard level of *ab initio* theory using the fluoride ion as a "typical" nucleophile, the preferred site for nucleophilic

substitution then corresponds to the most stable (lowest energy) complex. This simple approach that predicted the principal site for 15 nucleophilic substitutions in aromatic perfluorocarbons has been extended and reliably tested by comparison to the series of recently published NH_2 amination reactions of perfluoro-arenes in liquid ammonia by Malykhin and coworkers. The model accurately predicted the experimental results for all of the $\text{S}_{\text{N}}\text{Ar}$ reactions therefore confirming the model's general utility. The authors conclude with the prediction that their model predicts that mono-amination of 1-trifluoromethyl-2-amino 3,5,6-trifluorobenzene in liquid ammonia should produce almost exclusively 1-trifluoromethyl-2,6-diamino-3,5-difluorobenzene.

Joseph Sloop [16] and coworkers present interesting organofluorine synthesis in their paper: *Novel Fluorinated Indanone, Tetralone and Naphthone Derivatives: Synthesis and Unique Structural Features*. They analyzed the uncommon product outcomes from the Claisen condensation coupled with the fluorinating reagent Selectfluor® with the above ketones.

The article entitled: *Computational Study on the Acid Catalyzed Reactions of Fluorine-Containing 2,4-Dialkoxy-3,4-dihydro-2H-pyrans with Aromatic Compounds* by Norio Ota [17] and coworkers illustrated that the predicted product outcomes from DFT calculations were consistent with the experimental data and mechanistic pathways to products when fluorinated dihydropyrans were reacted with aromatics.

Fluorine-18, widely used in clinical positron emission tomography (PET) imaging in biomedical science because its optimal physical decay properties ($t_{1/2} = 110$ min, $E_{\beta^+, \text{max}} = 0.6$ MeV) facilitates multistep syntheses and PET images of high quality. Wängler and coworkers [18] in their review *Silicon-[^{18}F] Fluorine Radiochemistry: Basics, Applications and Challenges* describe the radiochemical science surrounding $\text{Si}-^{18}\text{F}$ bond synthesis, the application of $\text{Si}-^{18}\text{F}$ tracers for PET imaging and some of the remaining challenges regarding the optimization/balance of the *in vivo* physic-chemical properties of these radiochemicals in relation to their stability and biodistribution. The increased application of ^{18}F Fluoro-click-bioconjugation to the variety of bio-scaffolds employed, promises to be an effective strategy able to counter balance the high lipophilicity-hydrophilicity nature of the radiochemical carriers, thereby enhancing target visualization via PET with only minute retention of radioactivity in other tissues and organs.

One of the most significant classes of synthetic antibacterials are fluoro-quinolone antibiotics. The article: *A Study of Fluorinated β -Nitrostyrenes as Antimicrobial Agents* by King Lo *et al.* [19] examined the effect of the presence of fluorine functionalities in β -methyl- β -nitrostyrenes on their antimicrobial activity. The MIC values confirmed that fluorinated β -methyl- β -nitrostyrenes had the highest antimicrobial activity against Gram negative, Gram positive bacteria and the fungus *C. albicans*. However the correlations between MIC and K_{D} [$\log\text{P}$] values were not straightforward. Similarly it was also difficult to correlate the position of fluorine substitution on the benzene ring or the effect of multiple fluorine substituents with antibacterial activity and $\log\text{P}$ values. Can aromatic ring fluorine/hydrogen exchange influence membrane permeability? Generally, aromatic F/H substitution tends to increase compound lipophilicity, in direct contrast to what was observed. Alternatively, the reason for the effectiveness of fluorine substitution on the aromatic ring may be connected with the high electronegativity of fluorine, although size factors could also be important. Perhaps the electronegativity of fluorine could affect binding affinity to the binding site of the bacteria, thus causing inhibition of the enzyme. Further investigations with other fluorine-substituted

compounds to determine the structural features required for the optimal anti-bacterial activity of β -methyl- β -nitrostyrene compounds, and where the activity occurs, are currently being carried out.

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