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Review

Nucleic Acid Based Fluorinated Derivatives: New Tools for Biomedical Applications

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Abstract: Nucleic acid-based fluorinated derivatives, e.g., nucleosides or oligonucleotides connected to highly fluorinated chains or labeled with one or more fluorine atoms, have been investigated recently due to their high potential for biomedical applications. This review deals with recent works on nucleoside and oligonucleotide fluorocarbon amphiphiles as well as with properties and applications of fluorine-labeled oligonucleotide analogues.

Keywords: fluorocarbon; amphiphile; lipids; nucleoside; oligonucleotides

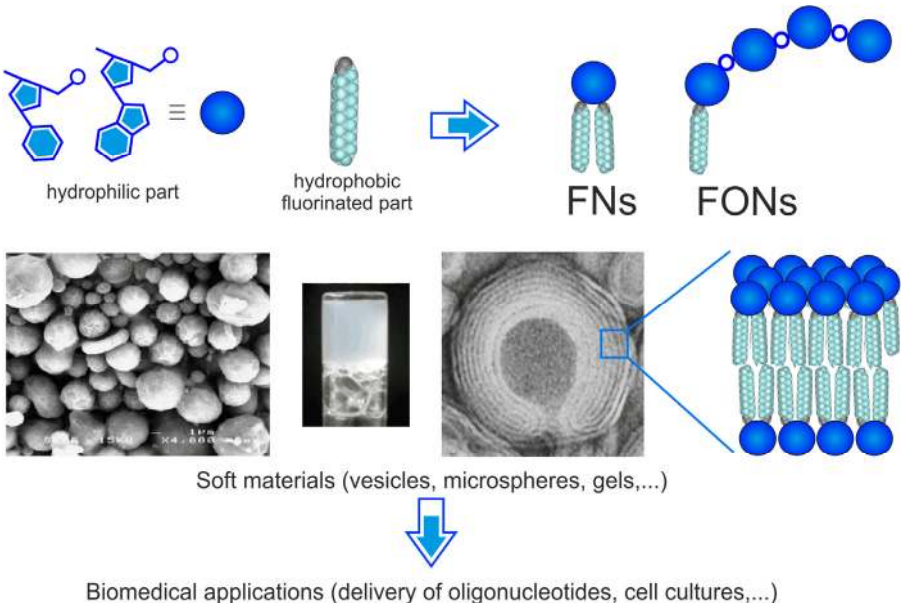
1. Introduction

The nucleic acid architectures stabilized by base-pairing and aryl π–π stacking interactions provides to scientists one of the most sophisticated supramolecular models. Since the determination of the structure of double-stranded DNA (dsDNA) by Watson, Crick, Wilkins and Franklin [1–3], artificial bio-inspired molecules featuring nucleic acid units have become a very powerful strategy to construct supramolecular systems [4–6]. Of particular interest is the design of hybrid amphiphilic nucleolipids featuring a bi-functionality based on the combination of nucleic acids and lipids [7–15]. Interestingly, different bottom-up approaches involving nucleolipids have been used for the construction of nanostructures for different applications, including materials [16–18] and biomedical devices [19–21]. In parallel to nucleolipid derivatives, the combination of nucleobase units with fluorocarbon

hydrophobic and lipophobic moieties to create novel materials, for diagnostics or in medical applications, is still in its infancy. It has been extensively reported that highly fluorinated derivatives possess unique properties, including chemical and biological inertness, strong hydro- and lipophobia. Interestingly, fluorocarbon colloids used for biomedical applications feature high gas solubility, low lipid and water solubility, and outstanding surface characteristics [22].

Hence, material and biomedical sciences could take advantage of the new properties coming from the combination of nucleic acids and fluorocarbon synthetic units for new applications. The availability of chemically modified nucleotides and fluorocarbon synthons and/or reagents, means that Nucleic Acids Fluorocarbon Amphiphiles (NAFAs) could be used in numerous fields of research including engineering, biology and medicine (Figure 1). Recently, the use of nucleoside-based fluorocarbon derivatives has been mainly motivated by three fundamental objectives: (i) construct novel supramolecular materials and/or devices; (ii) develop new drug delivery systems; and (iii) find new therapeutic molecules.

Figure 1. Nucleic Acids Fluorocarbon Amphiphiles (NAFAs), including Fluorocarbon Nucleoside and OligoNucleotide amphiphiles (FNs and FONs, respectively): building blocks for soft materials and biomedical applications.



This short, non-exhaustive review intends to illustrate the role that highly fluorinated amphiphiles may play in chemistry, biology and material science. It consists primarily of an account of the authors' own efforts and experience in the field, hence will be limited to some specific aspects of this chemistry. It also intends to outline the potential applications of fluorinated nucleolipids, ranging from chemistry to biomedical research.

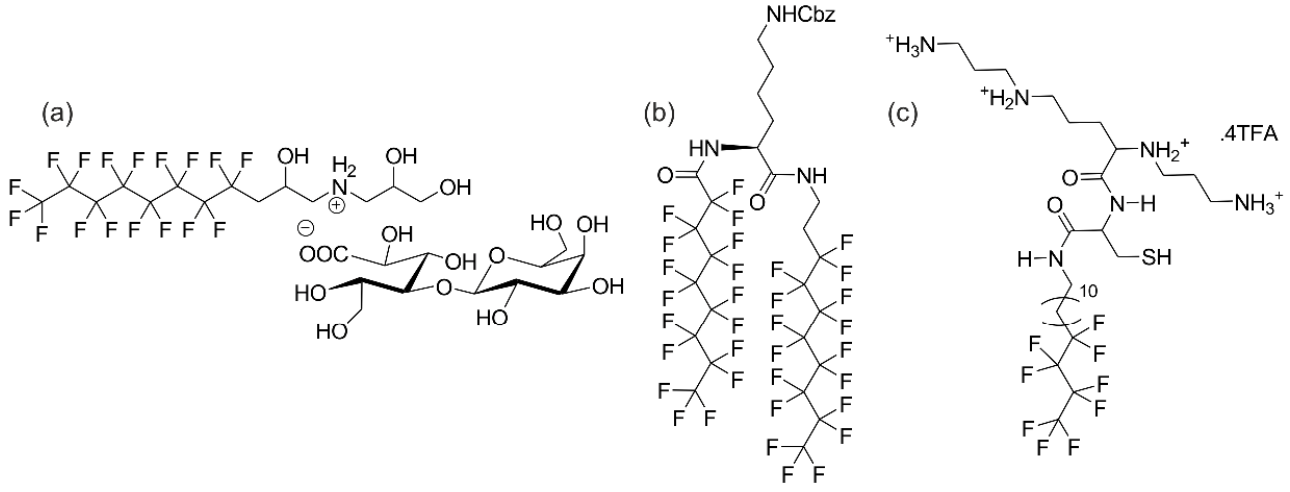
First, we will focus on the recent progress achieved in the fields of fluorocarbon and nucleoside amphiphiles. This first section includes hybrid molecules bearing both a nucleic acid and fluorocarbon chains: namely the Fluorocarbon Nucleoside amphiphiles (FNs). Second, we will present several Fluorocarbon OligoNucleotide amphiphiles (FONs) and fluorinated oligonucleotide analogues.

2. Fluorocarbon Nucleoside Amphiphiles (FNs)

2.1. Fluorocarbon Amphiphiles

Due to their unique properties, fluorocarbon chains represent a useful building block for the construction of supramolecular systems. Perfluoroalkyl chains have a larger cross section and are more rigid than their hydrogenated counterparts. They are considerably more hydrophobic and are lipophobic as well. As a result, when dispersed in water, fluorinated amphiphiles exhibit an enhanced capacity to self-assemble into highly stable and well-defined assemblies such as films, membranes, micelles, vesicles and other stable supramolecular systems [23,24]. The self-assembling behavior of a variety of synthesized single and double chain neutral, zwitterionicor anionic fluorinated phospholipids [25–28], glycolipid [29,30], glycophospholipids, glycopeptides [31,32] was already explored (Figure 2) [33], to evaluate the impact of the fluorinated chains on the properties of the resulting aggregates. It enhances stability, low permeability to both hydrophilic and lipophilic material and reduces interaction with biological media. These fluorinated amphiphiles possess a considerable potential for the delivery of materials such as drugs, prodrugs, markers, contrast agents and nucleic acids. Recently, new perfluorinated dimerizable polycationic amphiphiles were designed by Vierling *et al*. to evaluate the ability of the monomer to condense DNA and of the dimer to form stable nanoparticles capable of efficient cell transfection [34]. Although formulation of small-sized cationic monomolecular DNA nanoparticles (<40 nm) with the dimerizable perfluorinated succeeded, spermine-based amphiphiles proved to be poor non-specific transfection agents in vitro. Improvements are still in progress [35,36].

Figure 2. Examples of fluorocarbon amphiphiles; (**a**) sugar-based fluorocarbon amphiphile [30]; (**b**) fluorinated amphiphilic building block used for the synthesis of glycopeptide conjugates [32]; and (**c**) perfluorinated dimerizable polycationic amphiphile [34].

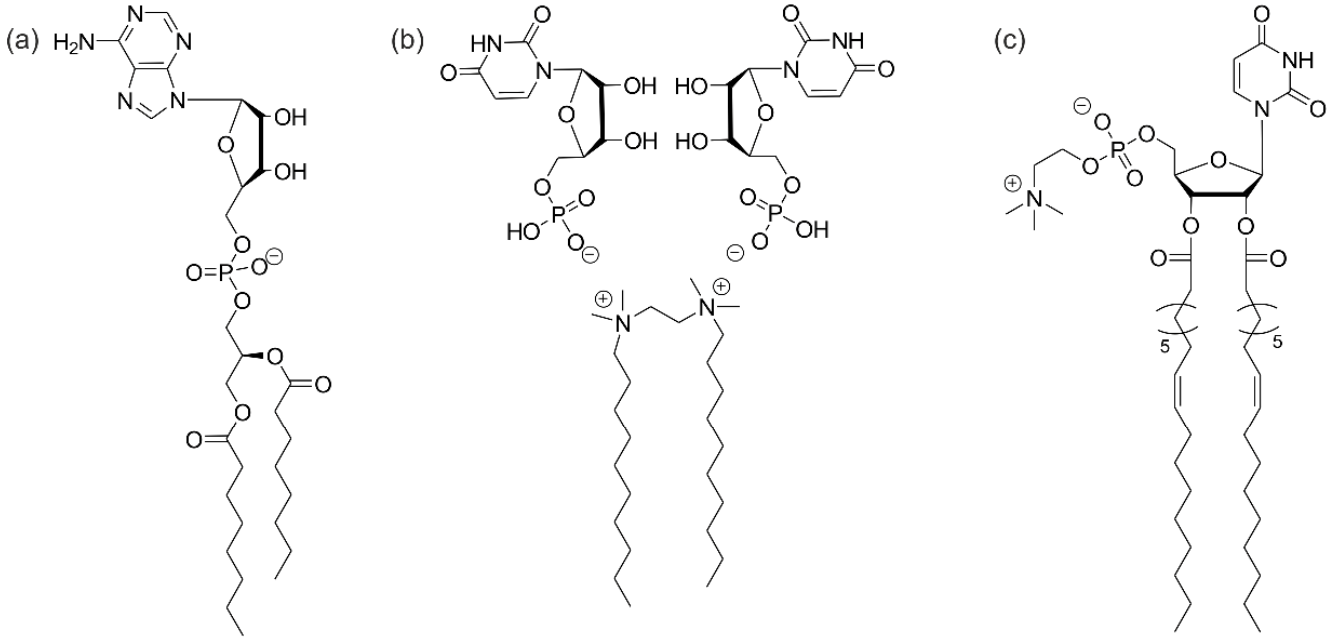


2.2. Nucleoside Amphiphiles

Nucleoside-based lipids commonly named nucleolipids [7] are hybrid molecules composed of a nucleobase, a nucleoside, a nucleotide or an oligonucleotide (either DNA or RNA), and a lipophilic moiety, which might be either simply a single- or double-chained alkyl moiety. Several improved

nucleolipids have been reported hereafter (Figure 3) [37–47]. Most nucleolipids have a polar head group at the 5' position and hydrophobic groups at both the 2' and 3' positions, patterned after natural glycerol phospholipids, which are key components of the cellular membrane. Nucleolipids were designed to interact with nucleic acids through hydrogen bonding, π–π stacking, and nucleobase recognition, as well as electrostatic interactions and the hydrophobic effect. Several cationic [12,48–51] and anionic [52,53] nucleolipids were first investigated as potential agents for the delivery of nucleic acids into cells. Indeed their self-assembled structures into lipoplexes mimic cellular membranes and their cationic properties attract both anionic oligonucleotides and negatively charged cellular membranes. New versions comprising neutral, zwitterionic, and anionic nucleolipids are currently evaluated.

Figure 3. Examples of nucleoside amphiphiles; (**a**) diC_8PA [37]; (**b**) a gemini nucleotide [39]; and (**c**) a zwitterionic nucleolipid.



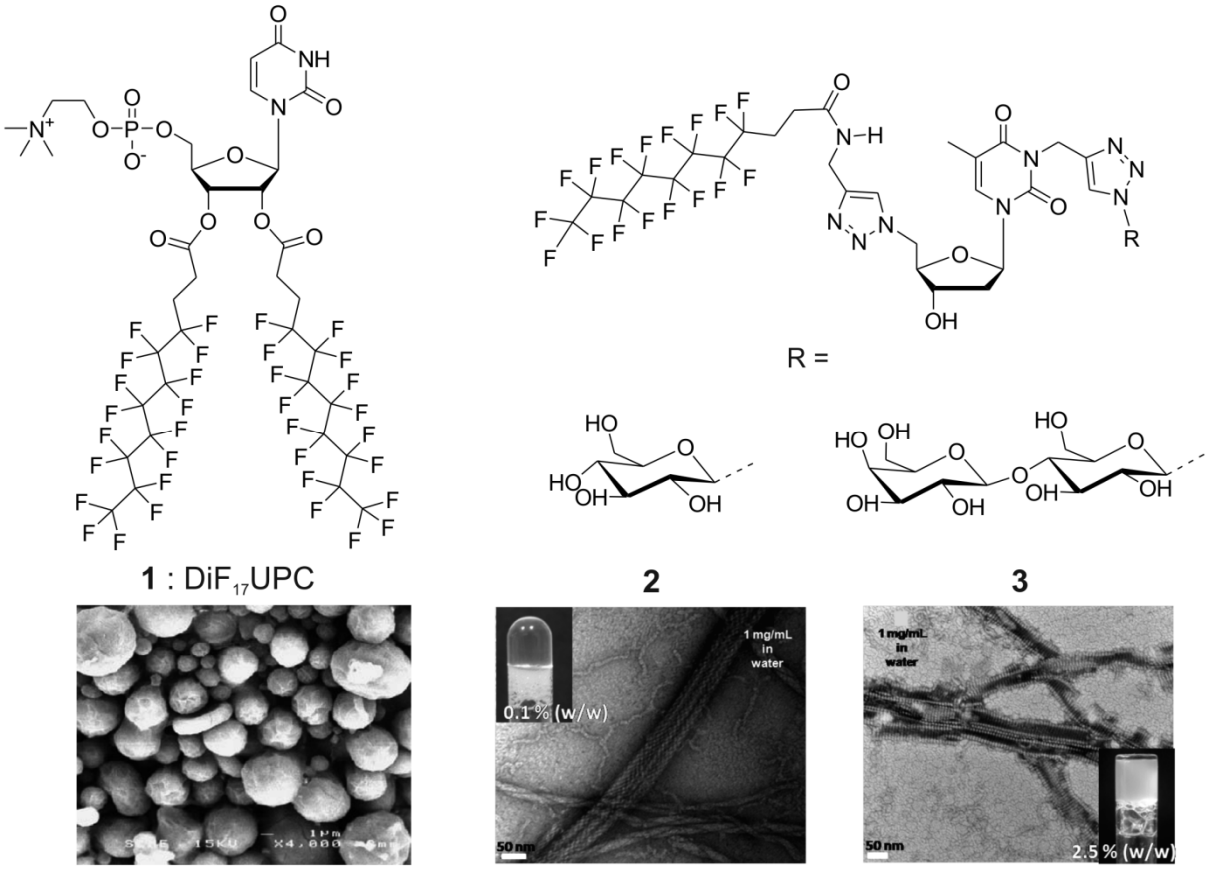
2.3. Hybrid Fluorocarbon Nucleoside Amphiphiles

The combination of the self-assembly potential of nucleoside amphiphiles with the hydrophobic character of highly fluorinated chains is of high relevance to prepare new self-assembled structures with tunable physico-chemical properties and functions. To assess whether fluorinated chains can enhance the scope of supramolecular assemblies formed by hybrid fluorocarbon nucleoside amphiphiles, different molecules were synthesized (Figure 4).

The fluorocarbon amphiphile **1** is based on a uridine backbone modified by a phosphocholine moiety at the 5' position, and two *2H*,*2H*,*3H*,*3H*-perfluoroundecanoyl side chains at the 2' and 3' positions. One of the goals of the study was to characterize the properties of such new compounds and to compare those results with that observed for the analogous hydrocarbon nucleoamphiphiles. In aqueous solution, fluorocarbon nucleoamphiphiles were surprisingly able to form large vesicular assemblies and unexpected lamellar phases below their T_m, contrary to hydrocarbon analogs that self-assemble into helical structures below their T_m and bilayers above it [54]. These highly hydrophobic fluorocarbon amphiphiles exhibited interesting hybrid microspherical supramolecular

assemblies in the presence of thorium that were characterized by Scanning Electron Microscopy (SEM) [55].

Figure 4. Chemical structures of compounds **1-3**, and corresponding electronic microscopy images of $DiF_{17}UPC/Th^{4+}$ microspheres (SEM image from [55]), and supramolecular assemblies formed by GNFs **2** and **3** in water (TEM images from [58]).



Recently, two glycosyl-nucleoside fluorinated amphiphiles (GNFs) were designed to construct new supramolecular hydrogels. Molecules **2** and **3** feature both sugar moieties attached to a thymidine base and a *2H*,*2H*,*3H*,*3H*-perfluoroundecanoyl side chain at the 5' position, linked via triazole bridges resulting from "click" chemistry. The self-assembly and gelation properties of such molecules were investigated. Similarly to their hydrocarbon analogs [56,57] GNFs stabilize hydrogels at low concentrations (0.1% w/w for compound **2**). GNFs gelators displayed supramolecular networks of varying morphologies, such as nanofibers and helical springs, which are correlated to the presence of fluorocarbon chains. Moreover, fluorocarbon amphiphile GNF **2** proved to be not toxic for human cells (Huh7) whereas hydrocarbon analogue becomes toxic above 100 μM, demonstrating the greater potential of such fluorocarbon nucleoside amphiphiles for biomedical applications [58].

3. Fluorocarbon OligoNucleotide Amphiphiles (FONs) and Fluorinated Oligonucleotide Analogues

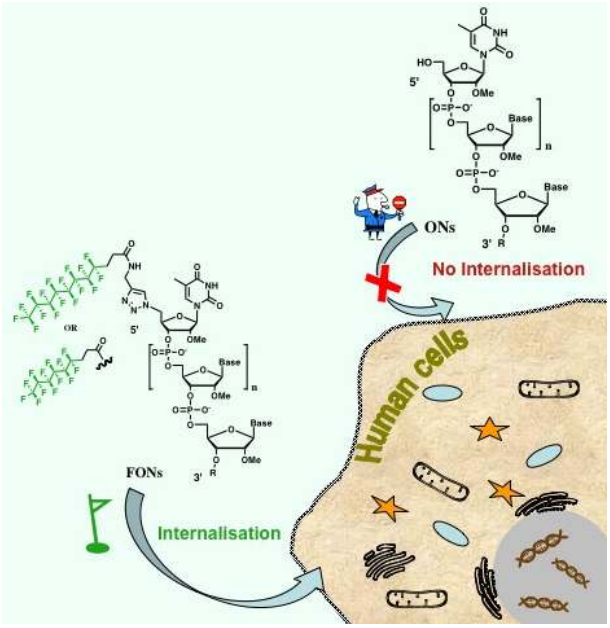
In the previous section, several examples of nucleoside-based fluorinated amphiphiles have been discussed for gel stabilization. In this section we will discuss on Fluorocarbon OligoNucleotide amphiphiles (FONs). The fluorine atom is likely a mimic of either a hydroxyl group (in terms of

electronegativity) [59–62] or a hydrogen atom (in terms of steric factor). In this context, we will also provide an overview on properties and applications of oligonucleotides carrying fluorine modifications at different positions.

3.1. Fluorocarbon OligoNucleotide Amphiphiles (FONs)

Recently our group has reported on the synthesis and biological properties of FONs [63]. In previous studies, our group already reported on the synthesis and cellular uptake studies of lipid-oligonucleotide conjugates (LONs) [64,65]. The main purpose of attaching a fluorocarbon chain to a polyanionic oligonucleotide (ONs) was to study how cellular uptake or internalization of ONs are influenced by the nature of the hydrophobic moieties. To address this issue, Godeau *et al.* have synthesized two FONs featuring C_8F_{17} and C_6F_{13} chains using 1,3-dipolar Huisgen's reaction [66] via a "*post synthetic*" modification approach. Three different human cell lines were incubated with either FONs or LONs or unconjugated ONs for comparative study of cellular internalization (Figure 5). Moreover, internalization kinetics of FONs, LONs and unconjugated ONs with Huh7 cells were also evaluated. Keeping in mind the hydrophobic and lipophobic properties of fluorocarbon chains, it can be hypothesized that FONs self-assemble outside the cell to form nano aggregates. It is likely that these nanoobjects would be uptaken by the cell via an endocytosis pathway. It is worth mentioning here that to the best of our knowledge, there is no earlier report on oligonucleotide amphiphiles featuring perfluorinated chains.

Figure 5. Conjugation of fluorocarbon chain to the oligonucleotide (FONs) allows the delivery of highly polyanionic oligonucleotides into human cells.

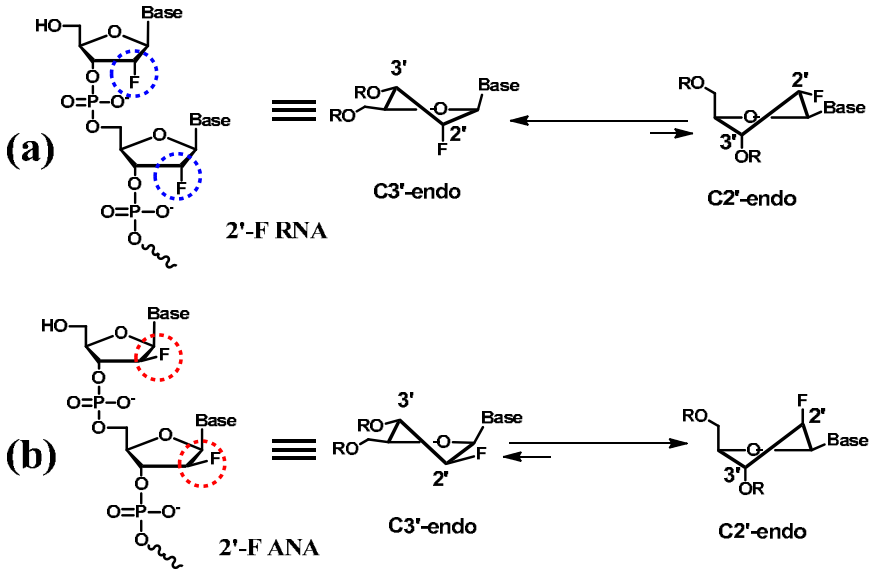


3.2. Application of Fluorinated Oligonucleotide Analogues

Various groups have been interested in the synthesis and application of fluorinated oligonucleotide analogues. There are different possible sites for the modification of an oligonucleotide with one or more fluorine atoms for various biological and therapeutical applications. Fluorine atoms have a strong

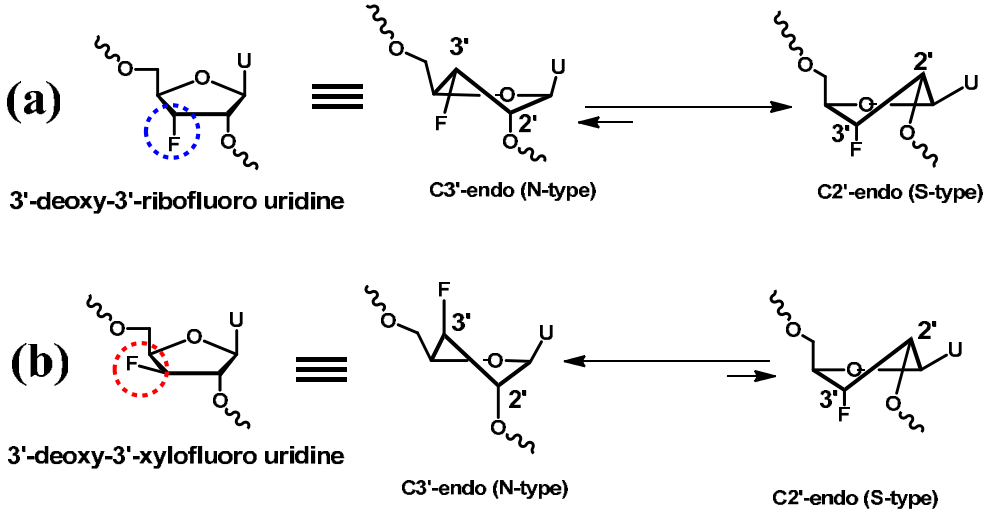
influence on both the electronic and the conformational properties of the nucleic acids' furanose ring. The 2'-position in the ribose moiety of RNA is prime target for chemical modifications. Extensive research work is going on towards the study of structural properties, biological applications and delivery strategies of oligonucleotides-incorporated with 2'-deoxy-2'fluoronucleotide in combination with other structural modifications [67–84]. Oligonucleotides containing 2'-deoxy-2'fluoronucleosides have been synthesized for regiospecific cleavage of RNA by RNase H [67]. Incorporation of 2'-deoxy-2'-fluoronucleotide into oligonucleotides induces substantial enhancement in their binding affinities to RNA targets [68]. Damha *et al.* have shown that fluorine-induced sugar pucker in 2'-deoxy-2'fluoro-β-D-ribonucleicacid (2'-F RNA; C3'-*endo*) and 2'-deoxy-2'fluoro-β-D-arabinonucleicacid (2'-F ANA; C2'/O4'-*endo*) can improve the activity of siRNA (Figure 6) and enhance its serum stability. They have also provided the evidences for an important role of a pseudohydrogen bond between the $F^{2'}$ and H^{8} of the nucleobase for 2'-F ANA:RNA duplex stability [72–84].

Figure 6. Structure and sugar puckering equilibrium for (**a**) 2'-deoxy-2'-fluororibonucleic acid (2'-F RNA); C3'-endo is the most stable conformation for 2'-F RNA. (**b**) 2'-deoxy-2'-fluoroarabonucleic acid (2'-F ANA); C2'-endo is the most stable conformation for 2'-F ANA.



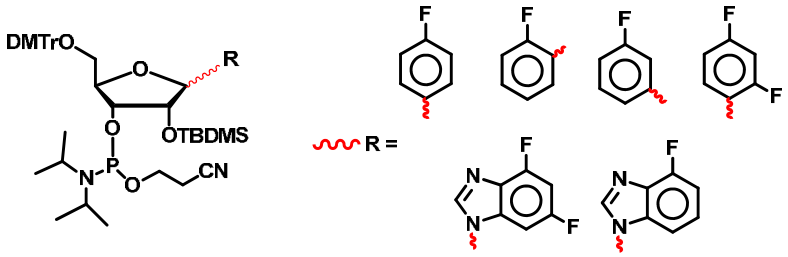
On the other side, very interesting and novel studies have been carried out by Erande *et al.* using 3'-deoxy-3'ribofluoro/xylofluoro uridine incorporated oligonucleotides (2'-5'-strand) [85]. They have shown the effect of incorporation of one or more unit of 3'-deoxy-3'-fluoronucleosides (having either locked or frozen S-type/Ntype sugar conformations) on the stability of *iso*DNA:RNA duplexes. For the first time, evidences were given that the DNA strand prefers S-type geometry in stable *iso*DNA:RNA duplexes (Figure 7) [85].

Figure 7. Structure and sugar puckering equilibrium for (**a**) 3'-deoxy-3'-ribofluorouridine. (**b**) 3'-deoxy-3'-xylofluorouridine.S-type (C2'-endo) conformation (preferred by 3'-deoxy-3'-ribofluorouridine) stabilized *iso*DNA:RNA duplexed while N-type (C3'-endo) conformation (preferred by 3'-deoxy-3'-xylofluorouridine) destabilized *iso*DNA:RNA duplexes.



To investigate the forces (hydrogen bonding, base stacking and solvation) which are responsible for stability of the secondary structure of nucleic acids, Engels *et al.* have synthesized novel nucleic acid analogues in which nucleobases are replaced by their steric mimics, containing one or more fluorine atom. They have utilized fluorobenzene and fluorobenzimidazole derivatives (Figure 8) [86,87]. They have discussed how C–F···H–C hydrogen bonds affect the stability of the secondary structure of nucleic acids in details.

Figure 8. Monomer building blocks for the incorporation of fluorine derivative into RNA oligonucleotides by solid-phase synthesis.



Owing to the favorable NMR properties of fluorine atom (^{19}F), fluorinated oligonucleotide derivatives provide a sensitive probe for structural study of nucleic acids in the solution state and their interactions with other biological moieties [71,88–95]. Barhate et *al.* have synthesized nucleosides with perfluorinated *tert*-butyl group and successfully incorporated it into the oligonucleotide at different positions and demonstrated as a sensitive ^{19}F NMR probe of nucleic acid conformation [95]. Oligonucleotides, labeled with radioactive isotopes, are new imaging tools to study gene expression at the nucleic acid and protein levels. Due to its positron-emission properties, fluorine-18 (radioactive isotope of fluorine) is widely used for oligonucleotide labeling for *in vivo* PET (Positron Emission Tomography) imaging. Dollé *et al.* [96–100]. have developed an original method for labeling

oligonucleotides with ^{18}F in different positions. Several other research groups have also synthesized ^{18}F labeled oligonucleotide analogues for imaging studies with PET [101–103].

4. Conclusions

The nucleic acids fluorocarbon amphiphiles belong to a new class of hybrid bioinspired molecules, which is clearly connected to soft materials, nanosciences and biomedical technology. It is a promising and exciting time for NAFAs and the emerging devices developed so far clearly open up interesting routes for the design and development of nanodevices, therapeutic strategies and biotechnological tools.The potential innovations using these fluorocarbon molecules are numerous in terms of chemical architectures, physicochemical and biological properties. This short survey highlights the interest to combine nucleic acids with fluorocarbons for developing soft and complex matters. The history of this field is still at the beginning and we can imagine that remarkable achievements will be realized in the future.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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