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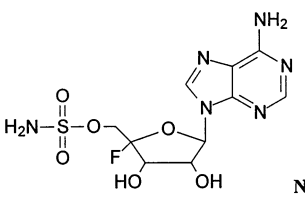
CARBOHYDRATE RESEARCH

Foreword

Fluorine, the 13th element in the ranking of frequency of all the elements, is very rare to find in the organically bound state in nature. It has been identified in only a relatively small number of tropical and subtropical plants and, amongst microorganisms, in two actinomycetes [1]. Just one fluorine-containing carbohydrate derivative has been isolated from an organism — the 4′-fluoro-5′-*O*-sulfamoyladenoside, nucleocidin [1].



Nucleocidin

Nevertheless, the interest in fluorinated analogues of natural substances is increasing continuously, since fluorine, strategically positioned in target molecules, may greatly modify the chemical properties, biological activity and selectivity of those molecules. There are two basic strategies to synthesise organofluorine compounds, the direct introduction of fluorine atoms by fluorinating reagents in a late synthetic step and the use of fluorine-containing 'building blocks'. Both strategies play an important role in the topics presented in this special issue.

Some general remarks on fluorine: the high ionisation potential of fluorine and its relatively low polarizability imply very weak intermolecular interactions, low surface energies, and low refractive indexes for perfluorocarbons. The characteristic substituent effect of fluorine atoms on molecular properties can be attributed to the unique combination of its extreme high electronegativity and moderately small size, its three tightly bound, nonbonding electron pairs, and the excellent match between its 2s or 2p orbitals with the corresponding orbitals of carbon [2,3]. Bondi's [4] accepted values of 1.47 and 1.52 Å for the van der Waals radii of F and O, respectively, indicate that F and O, not H, are very nearly isosteric. It actually has been correctly recognised for some time now that F and OH are 'chemical isosteres' [2]. Nevertheless, the van der Waals radii of F and H (1.20 Å) are similar enough to deceive enzymes when F is introduced for H in a biologically active substance.

Advances in organofluorine chemistry over the past three decades have made the 'unusual' behaviour of fluorinated compounds much more understandable and predictable. Misleading generalisations like 'fluorination increases lipophilicity' and myths about fluorine steric effects must be dispelled. Lipophilicity is an important consideration in the design of biologically active compounds since it often controls absorption, transport, or receptor binding. It is commonly held that fluorination increases lipophilicity, but this is true only for aromatic fluorination and fluorination adjacent to most atoms or groups with π electrons. Monofluorination and trifluoromethylation of saturated aliphatic groups normally decrease lipophilicity [2]. The acidities of acids, alcohols, and amides are always increased by introduction of fluorine, and the effects can be impressive [2] (see also [5]). For example, $(CF_3)_3COH$ is over 10^{13} times more acidic than *t*-BuOH; CF_3SO_2– is one of the most electron-withdrawing groups known [6].

Individual fluorine atoms, difluoromethyl or trifluoromethyl groups may be suitable sensors in studies of transport, metabolism and

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enzymology of fluorinated sugars, e.g., in ^{19}F in vivo NMR spectroscopy. Perfluoroalkyl chains may likewise be useful tools in modified natural products. The marked effects of such chains on the surface activity of carbohydrate-based amphiphiles indicate interesting possibilities of application. Fluorinated chains strongly increase the ability of amphiphiles to form ordered membranes (supramolecular structures). Fluorocarbon chains are more hydrophobic and stiffer than hydrocarbon chains. Because of a large energy difference between the gauche and trans conformations, they prefer the trans form, have less conformational freedom and have an essential helical conformation [7–11]. Fluorophilic-hydrophilic surfactants can be used as emulsifiers for artificial oxygen carriers, drug delivery systems or contrast agents based on fluorocarbons [12,13]. Finally, it is noteworthy that even the lipophobic effects of highly fluorinated carbons may be utilised in catalytic reactions [14].

New fluorinating reagents and methods (for books and reviews see Refs. [15–21]) reported by specialists in fluorine chemistry are sometimes not practicable in carbohydrate chemistry because of selectivity problems. Nevertheless, various fluorinating agents turned out to be suitable in carbohydrate chemistry [22–24].

Various kinds of reviews [22–34] and two special issues [35,36] on '*Fluorosugars*' have already been published in periodicals and monographs. The following presentation of topics focuses on new developments after publication of former reviews [22–33] and on interesting new fields of applications. Thus, the topics '*Glycosyl Fluorides in Enzymatic Reactions*' (**S.J. Williams and S.G. Withers**), '*Fluorinated Cyclitols*' (**D.C. Baker**)[1], '*Liquid Crystals Based on Fluorinated Carbohydrates*' (**R. Miethchen and M. Hein**), and '*Preparation of Fluorine-18 labelled Sugars and Derivatives and Their Application as Tracer for Positron-Emission-Tomography*' (**B. Beuthien-Baumann et al.**) summarise the activities on these research fields for the first time. Although glycosyl fluorides are easily accessible using numerous fluorinating reagents, a stereoselective synthesis requires, besides (thermodynamically or kinetically) controlled conditions, carefully selected reagents. Glycosylations with glycosyl fluorides have become important in the last two decades, i.e., after effective agents were found for the efficient activation of glycosyl fluorides. Updates to these research fields are given by **M. Yokoyama** ('*Methods of Synthesis of Glycosyl Fluorides*') and **K. Toshima** ('*Glycosyl Fluorides in Glycosylations*'). Carbohydrate chemists focus particular attention on sugars fluorinated in non-glycosidic positions, because of the manifold possibilities of their application as moieties in bioactive substances: newest developments in this field are summarised by **K. Dax et al**. ('*Synthesis of Deoxyfluoro Sugars from Carbohydrate Precursors*'). The pharmacologically interesting nucleoside analogous derivatives of such fluorosugars are separately discussed in the topic '*Fluorinated Nucleosides*' (**K.W. Pankiewicz**).

The second strategy of the organofluorine chemistry, the so-called 'building block' method using fluorinated synthons, is likewise indispensable to carbohydrate modifications. The review of **R. Plantier-Royon** and **C. Portella** ('C-*Difluoromethylene-containing*, C-*Trifluoromethyl and* C-*Perfluoroalkyl Carbohydrates. Synthesis by Carbohydrate Transformation or by Building Block Methods*') describes numerous examples. Certainly C-fluorinated reagents are fluorinated synthons in the wider sense, but C-, N-, O-, S-fluoroalkylations or acylations of carbohydrates are not respected as examples of the 'building block' method as a rule. During the past 20 years, much attention has focused on the potential applications of emulsified perfluorochemicals in medicine and biology. In particular such emulsions as '*blood substitutes*', carbohydrate-based amphiphiles containing perfluoroalkyl chains are suitable emulsifiers. The topic '*Carbohydrate- and Related Polyol-derived Fluorosurfactants: An Update*' reported by **J.G. Riess** and **J. Greiner** describes syntheses of amphiphiles with perfluoroalkyl hydrophobes and their manifold properties relevant to application. The liquid-crystalline behaviour of such compounds is

[1] To appear in a forthcoming issue.

reported in the chapter on fluorinated carbohydrate-based mesogens (**R. Miethchen and M. Hein**). In addition to the latter topic, we refer to an update on '*Highly fluorinated thermotropic liquid crystals'* published in the *Journal of Fluorine Chemistry* [37].

An update of the excellent former review of R. Czuk and B. Glaenzer [31] is very useful and essential. **M. Michalik et al.** ('*NMR Spectra of Fluorinated Carbohydrates'*) undertook this area of responsibility. Analysis of the structure, conformation and configuration of sugars can be very expressively supported by evaluation of the corresponding NMR spectra. Fluorine coupling constants and chemical shifts are of greater magnitude than those of proton analogues and ^{19}F NMR spectroscopy may be an effective method for studying the metabolism of fluorinated compounds in biological systems.

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