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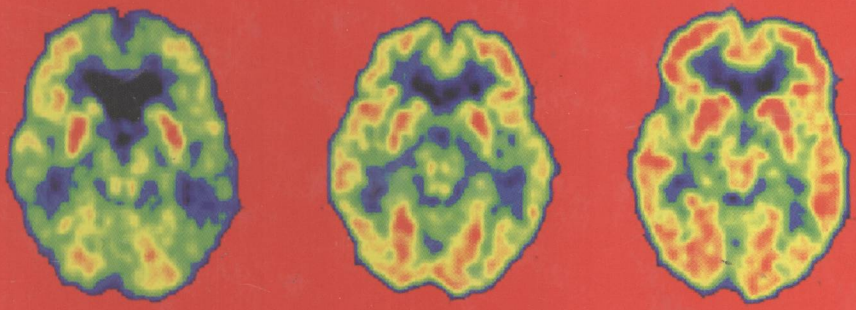
Fluorine and Health



Molecular Imaging, Biomedical Materials and Pharmaceuticals

EDITED BY
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Fluorine and Health

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Front cover illustrations:

-[^{18}F]FDG PET scans depicting glucose metabolism in a monozygotic twin pair and in a control subject. Note the clear reduction in [^{18}F]FDG uptake especially in temporo-parietal areas in the co-twin having Alzheimer disease (left) and similar, but less pronounced, reduction in same brain areas in the cognitively healthy co-twin (middle), as compared to the uptake in a control subject (right) [*Image by courtesy of K. Någren and J.O. Rinne, Turku, PET Centre, Finland and cf. chapter 2 in this book*].

-X-ray derived structure of the fluorinase showing the full structure as a hexamer (dimer of trimers) [*cf. chapter 18 by Hai Deng, D. O'Hagan et al. in this book*].

Contributors

Preface

Recently it was stated that fluorine chemistry is experiencing a renaissance due to the multifaceted reactivity of fluorinating reagents and the outstanding, and sometimes unexpected, properties of compounds containing fluorine. The benefits of these compounds for our society are evident in many fields. Particularly the last two decades have witnessed a spectacular growth of interest in selectively fluorinated molecular compounds. Both low molecular weight molecules and polymers, as well as highly sophisticated materials, are crucial in manifold aspects of medicinal monitoring and health care. This book is designed to acknowledge the extraordinary impact of fluorinated compounds to the general topic of *Fluorine and Health*. The involved subjects are organized in three thematic parts devoted to *Molecular Imaging*, *Biomedical Materials*, and *Pharmaceuticals*.

The first chapters are focused on the key position in biochemical and medicinal analytics of both partially fluorinated low molecular weight compounds labeled with natural ^{19}F-isotope for Magnetic Resonance Imaging (MRI) and tracer molecules labeled with radioactive [^{18}F]-isotope for Positron Emission Tomography (PET). The selective synthesis of molecules exhibiting specific properties or physiological effect constitutes the backbone of every medicinal application of fluorinated compounds. Consequently, the methodology for introducing fluorine itself or fluorinated groups into organic skeletons is largely developed in most chapters. Sensitive PET for high resolution molecular *in vivo* imaging requires the preparation of positron-emitting radiotracers. For this purpose, [^{18}F]-labeled probes are becoming increasingly prerequisite molecules, due to their adequate physical, physiological, and nuclear characteristics, particularly the relatively long half-life of the [^{18}F]-isotope of $\sim$110 min as compared to other light positron-emitting isotopes such as [^{11}C] (20 min), [^{13}N] (10 min), or [^{15}O] (2 min). Thus, the development of selective and fast synthetic methods for fluoroorganic compounds is an important issue.

The PET technique is particularly useful for *in vivo* imaging in oncology, neurology and in cardiology. PET and PET/CT (computed tomography) using [^{18}F]-labeled compounds such as 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) are becoming essential as *in vivo* imaging methods in oncological diagnostics, tumor prognosis and therapy monitoring. Moreover, innovative and more specific new [^{18}F]-tracers for molecular imaging of tumor biology are highlighted in the

framework of their clinical value. Brain imaging using PET is one of the important new tools in monitoring of different neuronal diseases such as Alzheimer's disease, the devastating brain disorder of elderly humans. A number of recently developed [^{18}F]-radiopharmaceuticals have a unique potential for the study of several brain systems of clinical importance. Moreover, the molecular imaging of cardiovascular diseases with [^{18}F]-PET is of great clinical interest, offering the opportunity to investigate noninvasively the cardiovascular physiology and pathophysiology *in vivo* and to contribute to the diagnosis and treatment of diseases having the highest mortality in the industrialized countries. Similarly, the ^{19}F nucleus provides a powerful tool for spectroscopic studies and particularly for MRI, due to its high NMR sensitivity and the fact that there is essentially no background signal in the body. Furthermore, fluorine NMR allows multiple compounds to be examined simultaneously because of the very large chemical shift range of about 300 ppm.

The manifold facets of fluorinated biomaterials are illustrated by examples ranging from inorganic ceramics to perfluorinated organic molecules. Fluorine is an essential trace element in bone mineral, dentine and tooth enamel and is considered as one of the most efficient elements for the prophylaxis and treatment of dental caries. Fluoride-based treatments have been shown indeed to ensure populations developing and maintaining sound dental health. In particular, fluoride ion has an effect on the demineralization/remineralization equilibrium that exists at the tooth surface, shifting it back in favor of remineralization. Fluoride-containing bioactive glasses and ceramics have been found to have an important role in bone repairing materials. Resin-modified glass-ionomers and compomers are dental restoratives which allow fluoride releasing, thus bringing a greater availability and efficiency of the element. Highly diluted fluoridation of drinking water, fluoridated table salt, dentifrices, topical gels, varnishes and mouth-rinses are other types of possible ways to improve dental health, provided small amounts of fluoride are administered.

Another field of application of fluorinated biomaterials is connected to lesions or evolving disease pathology of blood vessels. In particular, arteries may become unable to insure an adequate transport of the blood to organs and tissues. Polytetrafluoroethylene (PTFE) and expanded e-PTFE are the preferred materials for vascular prostheses. The interactions of blood cells and blood plasma macromolecules with both natural and artificial vessel walls are discussed in terms of the mechanical properties of the vascular conduit, the morphology, and the physical and chemical characteristics of the blood contacting surface.

Conversely, the role of perfluorocarbons for oxygen transport and *in vivo* delivery is investigated. In addition to possible use as temporary blood substitute, these fluorocarbon molecules can be applied as respiratory gas carriers, for instance as lung surfactant replacement compositions for neonates and possibly for the treatment of acute respiratory distress syndrome for adults. Another

important issue concerns the applications of highly fluorinated liquids in ophthalmology. Retinal detachment, a disease that can result in blindness, is treated by performing in retinal scar around the tear and maintaining the retina in contact. For this purpose, dense fluorinated liquids are used in pure form or as mixtures with silicone oils. The state of the art of the application of these highly fluorinated liquids in ophthalmology and their biocompatibility and toxicity is discussed. Prospects concerning future applications of these molecules are also considered. Finally, the various origins of human exposure to fluoride species are detailed, together with invaluable recommendations for adequate intake of fluoride, methods for assessing exposure, and discussion of the benefits and drawbacks (fluorosis) of fluoride intake. These investigations should bring a better understanding of the effect of fluoride species on living organisms.

The main focus of the third part is the synthesis of medicinally relevant fluorinated molecules and their interaction with native proteins. New molecules fluorinated in strategic position are crucial for the development of pharmaceuticals with desired action and optimal pharmacological profile. Among the hundreds of marketed active drug components, there are more than 150 fluorinated compounds. It starts by illustrating how the presence of fluorine atoms modifies the properties of a bioactive compound at various biochemical steps, and possibly facilitates its emergence as a pharmaceutical agent. Recent advances in the development of fluorinated analogues of natural products led to new pharmaceuticals such as fluorinated nucleosides, alkaloids, macrolides, steroids, and amino acids.

More specifically, it is detailed how fluorine substitution of specific positions in prostaglandins and thromboxanes, locally produces hormones with a broad variety of biological functions, affecting not only the molecular conformation but also the drug–receptor complex through a contribution of fluorine to the nature and strength of the interaction. Amine oxidases have critically important functions in organisms for efficient deactivation of very potent biogenic amines and hence come into the focus for therapeutic intervention. These points include the development of selective inhibitors, tools for studies of reaction mechanisms, radiotracers for PET imaging, and of medicinal agents. Synthesis and biochemical evaluation of two types of medicinally relevant enzymes, the flavin-dependent monoamine oxidases (MAO) A and B, and the copper-containing amine oxidases (CAO) are highlighted.

The potential utility of peptides as therapeutics with clinical applications is limited by its metabolic instability or poor transmembrane mobility. Consequently, the preparation of metabolically stable peptide analogs that can either mimic or block the function of natural peptides or enzymes is an important area of medicinal chemistry research. Synthesis of fluoroolefin amide isosteres, its incorporation in peptidomimetics, and the influence of that isosteric substitution on the inhibition of several enzymes such as peptidyl prolyl isomerases, dipeptidyl peptidase IV, and thermolysin is described. Moreover, protein folding and activity

depend on a multitude of molecular interactions. Nevertheless, even interactions of single fluorinated amino acids can highly affect polypeptide folding. Though, the metabolic and structural stability of peptides and proteins containing fluorine substitutes have been studied extensively recently, the *de novo* design of relevant target molecules requires a detailed knowledge of molecular interactions introduced by the fluorine atom. Systematic investigation of different fluorinated amino acids incorporated in a model peptide system based on the α-helical coiled coil motive within a hydrophobic and hydrophilic protein environment led to new insights of protein structure.

Finally, recent developments on research into the first C–F bond forming enzyme are summarized. The fluorinase enzyme isolated from *Streptomyces cattleya* catalyzes the formation of 5′-fluoro-5′-deoxyadenosine from *S*-adenosyl-L-methionine and fluoride. The substrate specificity and subsequent transformation of the fluorinated nucleoside to fluoroacetic acid and to fluoro threonine are discussed.

While conceiving the present book, we had outstanding support by a number of colleagues. We would like to express our deep gratitude to the Associate Advisors: B. Ameduri, P. Atkins, J. Knowles, T. Nakajima, M. Pontié, R. Syvret, S. Tavener, and J. Winfield for their encouraging advice and very helpful suggestions. In particular, we are deeply indebted to all the authors who compiled a truly excellent collection of important current facts connected to *Fluorine and Health*. We believe that the particular chapters constituting this book highlight the outstanding role of fluorine in different areas of medicinal monitoring and health care.

Alain Tressaud and Günter Haufe
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CONTENTS

SECTION 1

Molecular Imaging

CHAPTER 1

Fluorine-18 Chemistry for Molecular Imaging with Positron Emission Tomography

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