Magic Fluorine Chemistry for Medicinal Chemistry Applications

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Presentation Outline

- Fluorine facts
- History background
- Commercial applications
- Medicinal chemistry
  - Organofluorine Chemistry
  - Fluorous Chemistry
Fluorine Facts

Atomic Number: 9
Relative Atomic Mass: 18.998
Group # VIIA (halogens)
Quantum # I = ½ (\(^1^9\)F NMR, MRI)
\(^1^9\)F Abundance ≈ 100%

<table>
<thead>
<tr>
<th>Element</th>
<th>Van der Waals radii (Å)</th>
<th>Electronegativity (Pauling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>1.47</td>
<td>3.98</td>
</tr>
<tr>
<td>O</td>
<td>1.52</td>
<td>3.44</td>
</tr>
<tr>
<td>N</td>
<td>1.55</td>
<td>3.04</td>
</tr>
<tr>
<td>C</td>
<td>1.70</td>
<td>2.55</td>
</tr>
<tr>
<td>H</td>
<td>1.20</td>
<td>2.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond</th>
<th>Average Bond Strength (KJ/Mol)</th>
<th>Average Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-F</td>
<td>485</td>
<td>1.39</td>
</tr>
<tr>
<td>C-C</td>
<td>356</td>
<td>1.53</td>
</tr>
<tr>
<td>C-O</td>
<td>336</td>
<td>1.43</td>
</tr>
<tr>
<td>C-H</td>
<td>416</td>
<td>1.09</td>
</tr>
</tbody>
</table>
History of Fluorine

- **Hydrogen fluoride** (HF) was first reported by Scheele in 1771.
- In 1836 Dumas and Pelig reported the synthesis of organofluorine compound *fluoromethane*.
- In 1886 Henri Moissan isolated molecular elemental *fluorine gas* ($\text{F}_2$).
- Belgian chemist Swarts’ work between 1890 and 1938 on simple aliphatic fluorocarbons is widely considered as establishing the foundations of *organofluorine chemistry*.
- The chemistry of perfluorinated (fully fluorinated) organic compounds began in 1926 when Lebeau and Damiens synthesized *carbon tetrafluoride* ($\text{CF}_4$).
• In the 1930’s, Midgley and Henne extended Swarts’ exchange reaction methods for chlorofluorocarbon (CFC).

• In WWII, Uranium hexafluoride (UF₆) used in the U-235 enrichment process for making atomic bombs.

• DuPont and GM were the pioneers of the application of CFCs as refrigerants. Later CFC’s found diverse applications as fire extinguishers, blowing/cleaning agents.

• Most recent applications are related to organofluorine products (containing F-C bonds).
Nature Occurring Organofluorine Compounds

• Only 13 known nature organofluorine compounds (2003)

• Most of these are tropical plant metabolites makes the plants acutely toxic (traces of fluoroacetic acid found in the plant, gifblaar (*Dichapetalum cymosum*) in the South African veldt are believed to be responsible for numerous cattle deaths from errant grazing)

• Mother nature (the best chemist) does not seem to specialize in fluorine chemistry

• F is the 13th most abundant element in the earth’s crust (*Fluorspar, CaF₂*)
Why?

Possible reasons:

• Nature needs fluoride ion (F\textsuperscript{-}) to be a nucleophile in aqueous solution. But fluoride ion is generally only available in insoluble mineral forms, and even the soluble ones provide a fluoride ion so well-solvated it is a poor nucleophile, which makes ionic or radical fluorination mechanisms unlikely.

• First fluorinase enzyme was only found until 2002 (Nature, 416, 279).

\[ \text{S-Adenosylmethionine} \quad \text{F}^- \quad \text{Fluorinase} \quad \text{5'-Fluoro-5'-deoxyadenosine} \]
Material Chemistry - Fluoropolymers

- Dupont
- 3M
- Gore
- Gore-Tex

Teflon
Polytetrafluoroethylene (PTFE)

Non-stick cookware

Waterproof breathable fabrics

Stainmaster carpet

Biocompatible materials for implants and cosmetic surgeries
Fluoromaterials and Solvents

Surfactant

Liquid crystals

Ionic liquids

Fluorinated solvents

Organic layer

Aqueous layer

Fluorous layer $\text{C}_6\text{F}_{14}$
Medical Application - $^{19}$F MRI

Nuclear Magnetic Resonance Imaging
Bio Application - Artificial Blood

Perfluorodecaline

good $O_2$ and $CO_2$
dissolving power, nontoxic
and highly stable

Scuba Mouse
Top 200 Pharmaceutical Products by Worldwide Sales in 2009

Compiled and Produced by the Njardarson Group (Cornell University): Daniel J. Mack, Matthew Brachacek, Alexandra Plichta, Jon T. Njardarson
Medical Application - Drugs

~1/5 Drugs on the market containing fluorine
Figure 1.3  Examples of fluorine-containing drugs and drug candidates.
Features of Organfluorine Molecules

Chemically:
- small size
- lipophilic
- high electronegativity
- low reactivity

Biologically:
- electronegativity effect of neighbouring functionalities
- strength C-F bonds resistant to metabolic processes
- increases lipid solubility (bioavailability)
- synthesis of isosteric analogues of drugs
- useful for studying biochemical processes
Fluorine Chemistry

Publisher: Elsevier
Editor: W. Dolbier
IF (2010): 1.719

ACS Division of Fluorine Chemistry

To Annette and Alexander:
“The fury of the chemical world is the element fluorine. It exists peacefully in the company with calcium in fluorspar and also in a few other compounds; but when isolated, as it recently has been, it is a rabid gas that nothing can resist.”

Scientific American, April 1888

“Fluorine leaves nobody indifferent; it inflames emotions be that affections or aversions. As a substituent, it is rarely boring, always good for a surprise, but often completely unpredictable.”

Fluorous Chemistry
A New Field of Fluorine Chemistry
Started from 1994

Perfluorinated (fluorous) molecules are lipophobic and hydrophobic

**Triphasic Cocktail** - Organic/aqueous/fluorous

**Biphasic System** - Temperature-dependent miscibility
Fluorous Biphasic Catalysis

Two phases

One phase

Two phases

"Heavy fluorous" - high fluorine content (60%)
• Use phase tagging technique for easy separation

• Render molecules to fluorous by attaching to fluorocarbon tag

• Fluorous molecules separated from non-fluorous molecules base on fluorophilicity

• Fluorous tag are highly selective for separation, but low reactive
Fluorous Chemistry - Challenges

1) Persistent nature of perfluorinated compounds
2) Potential toxicities of some perfluorinated compounds
3) Cost of F-solvents for BP reaction & LL extraction
4) High fluorine content only good for catalysis

“Light Fluorous Synthesis” - A Possible Solution

1) Haircut of heavy fluorous ponytails (lower the cost)
2) Fluorous solid-phase extraction (F-SPE) for seperation
3) No F-solvents for reactions and separations
4) Better solubility/reactivity in common organic solvents

Heavy and Light Fluorous PMB Linkers

102 fluorines for F-LLE
17 fluorines for F-SPE
Fluorous Separation Techniques

“Heavy fluorous”
Need fluorous solvent

F-LLE

“Light fluorous”
Don’t need fluorous solvent

F-SPE

Fluorous Silica Gel

F-SPE silica gel (~100 mm)
Selective retention of light fluorous molecules

Fluorous SPE (F-SPE)

Fluorophobic Solvent (MeOH-H$_2$O)
Fluorophilic Solvent (MeOH)

- Use MeOH-H$_2$O as elution solvent
- Cartridge can be reused after wash with acetone or THF

Left tube: beginning of fluorophobic wash (80:20 MeOH:H₂O);
Center tube: end of fluorophobic wash;
Right tube: end of fluorophilic wash (100% MeOH)
Light Fluorous Compounds

Reagents

C₆F₁₃(CH₂)ₙ

F-Tag

C₈F₁₇(CH₂)ₙ

Linkers

Catalysts

Scavengers
Fluorous Synthesis

I. Fluorous Molecules
   - Catalysts
   - Reagents
     - Scavengers
     - Linkers (Tags)

II. Fluorous Separation Tools
   - Liquid-liquid extraction
     - Solid-phase extraction
     - Chromatography

Fluorous Techniques for Medicchem Applications

1) Solution-phase reaction kinetics
2) Easy adaptation of literature procedures
3) Monitoring reactions by TLC, HPLC, LC-MS, or NMR
4) Chromatography-free separations (F-SPE)
5) Integrating with microwave, MCR, DOS, SPS…
6) Recovery of fluorous materials
Medichem program requires large numbers of compounds (libraries) for screening

- Compound purification is the bottle-neck in library synthesis
- Combinatorial Chemistry and high-throughput synthesis
Integrated Fluorous Technology for parallel and HTP Synthesis

Fast reaction  Quick analysis  Easy separation

MW Reactor + LC-MS + F-SPE

Fluorous Tagging Strategies

- Tagging reagents/catalysts/scavengers

![Chemical reaction diagram]

- Tagging reactants for parallel and mixture syntheses

![Chemical reaction diagram]

Synthesis of Sclerotigenin Analogs

Microwave-Assisted Fluorous Multicomponent Reactions

excess non-fluorous components

F-intermediate fished out by F-SPE

F-SPE

clean product

Atom economy, fast reaction, simple separation

Synthesis of Benzodiazepinediones

Diversity Oriented Synthesis (DOS)

Benzodiazepine-Fused System

[3+2] product

Hydantoin-fused Hexahydrochromeno[4,3-\textit{b}]pyrroles

One-pot synthesis
Single fluororous linker
8 Diastereomers

target molecule

active to Alzheimer disease
tricyclic thrombin inhibitor
Fluorous Diastereomeric Mixture Synthesis (FDMS)

6 Diastereomers Isolated from a Mixture of 8

- **1a** (cis-anti-trans)
- **1b** (trans-anti-cis)
- **1c** (cis-anti-cis)
- **1d** (trans-anti-trans)
- **1a'** (cis-syn-cis) (not isolated)
- **1b'** (trans-syn-trans) (not isolated)
- **1c'** (cis-syn-trans) (not isolated)
- **1d'** (trans-syn-cis)
TLC of fluorous and non-fluorous mixtures

**Fluorous TLC**
- Sample A: Contains 1 and 3
- Sample B: Contains 2 and 3

**Non-fluorous TLC**
- 4 diastereomers

**Normal TLC**
- 2:1 hex-EtOAc
- 4:1 MeOH-H₂O
**Organocatalysis**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Metal free &amp; environmental friendly</td>
<td>- Low efficiency &amp; high catalyst loading (5-30%)</td>
</tr>
<tr>
<td>- Novel catalysis mechanism</td>
<td>- Recycling is necessary</td>
</tr>
<tr>
<td>- Mimic natural chemo- and biocatalysis</td>
<td>- Good structure amendablility</td>
</tr>
<tr>
<td>- Good structure amendablility</td>
<td></td>
</tr>
</tbody>
</table>

PS-organocatalysts are recyclable, but may have low activity because of the heterogeneous natural F-organocatalysis is homogeneous and recyclable

F-Imidazolidinone (MacMillan) Catalyst

\[
\begin{align*}
\text{organic catalyst} & \quad \text{fluorous catalyst} \\
\end{align*}
\]

**Diels-Alder Reaction**

\[
\text{Cyclopentadiene} + \text{Maleic Anhydride} \xrightarrow{\text{cat. (10 mol %)}} \text{endo (major) product} + \text{exo product}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield</th>
<th>Endo:Exo</th>
<th>ee% (Endo)</th>
<th>Cat Recovery</th>
<th>Purity of Recovered Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic</td>
<td>82%</td>
<td>90.3 : 9.7</td>
<td>88.4</td>
<td>65%\textsuperscript{a}</td>
<td>74%</td>
</tr>
<tr>
<td>Fluorous</td>
<td>86%</td>
<td>93.4 : 6.6</td>
<td>93.4</td>
<td>84%\textsuperscript{b}</td>
<td>99%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} by acid-base extraction. \textsuperscript{b} by F-SPE

Comparison of Organic and Fluorous catalysts analyzed by chiral GC.

Organic catalyst: 88.4% ee

Fluorous catalyst: 93.4% ee
"Organofluorine" & "Fluorous" Chemistries

Organofluorine Chemistry
- Reaction-oriented chemistry
  (fluoropolymers and fluorinated drugs)
- Associate with transformation of C-F bonds
- Fluorine atom(s) in the product

Fluorous Chemistry
- Purification/labeling-based chemistry
- Use highly fluorinated group to tag substrates
- No C-F bond formation is necessary
- Products do not need to have fluorine

Broad Applications

- Microwave Reaction
  - 1997
- Triphasic Reaction
  - 2001
- Mixture Synthesis
  - 2001
- Biomolecule Purification
  - 2001
- Microreactor
  - 2003
- Microarray
  - 2006
- Diversity-Oriented Synthesis
  - 2004
- Nanotechnology
  - 2006
- Biphasic Catalysis
  - 1994
- Parallel Synthesis
  - 1997

Solution-Phase Reaction
Fluorous Chemistry
Fluorous Separation

Over 2000 Publications

SciFinder search on “Fluorous”

Key Contributors
- Dennis P. Curran (246)
- John A. Gladysz (152)
- Wei Zhang (118)
- Istvan T. Horvath (83)
Two Special Issues in 2002 & 2006

Tetrahedron Symposium-In-Print “Fluorous Chemistry”

Guest Editors: J. A. Gladysz and D. P. Curran
Tetrahedron 2002, 58, 3823-4131

“Fluorous Synthesis”

Guest Editor: W. Zhang
QSAR Comb. Science 2006, 25 (8-9), 679-768
Fluorous Conferences

1st Int. Symp. on Fluorous Technologies
Bordeaux, France, July 3-6 2005
Co-Chairmen: J.-M. Vincent and R. H. Fish

2nd Int. Symp. on Fluorous Technologies
Yokohama, Japan, July 29-August 1, 2007
Chairman: Junzo Otera

3rd Int. Symp. on Fluorous Technologies
Jackson Hole, USA, Aug. 23-28, 2009
Chairman: D. P. Curran

ACS Symp. “Recent Advances in Fluorous Chemistry”
ACS National Meeting, Washington D.C
August 27-31, 2005
Chairman: D. P. Curran
Green chemistry aspects of fluorous techniques—opportunities and challenges for small-scale organic synthesis

Wei Zhang*

Fluorous chemistry has a potential to become a combinatorial green chemistry technology. This critical review discusses its applications for small-scale organic synthesis in the discovery, medicinal chemistry, and academic labs.
UMB Alumni in Green Chemistry

Dr. Paul Anastas
BS: 1984 UMB, Ph.D: 1988 Brandies
Yale University, EPA Assistant Administrator

Dr. John C. Warner
BS:1984 UMB, Ph.D: 1988 Princeton
Warner Babcock Institute of Green Chemistry Institute
President and Chief Technology Officer

Dr. Berkeley W. Cue
BS:1969 UMB, Ph.D: 1973 Univ. Alabama
VP Pfizer Global R&D (retired)
BWC Pharma Consulting, LLC
Chairman, ACS Green Chemistry Institute Governing Board
Welcome to green chemistry at UMASS Boston!

The Center for Green Chemistry at UMass Boston is housed in the Science Building on the Harbor Campus. We are affiliated with the Chemistry Department in the College of Science and Mathematics.

We are proud to be the first program in the country to offer a Ph.D. in Chemistry with a track in Green Chemistry.

Our faculty is committed to research designed to benefit society.

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3rd Int. Symp. of Green Chemistry at UMB
Sept. 30 to Oct. 1, 2010
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