Biological Applications of Organofluorine Compounds

Anna Allen
MacMillan Group Meeting
November 5, 2009
Outline

Introduction to organofluorine chemistry and the C-F bond

Biological applications of organofluorine chemistry

- Metabolic stability
- Physicochemical changes
- Conformational changes
- Orthogonal reactivity
- Isosteres and notable discoveries

Lead references:

C–F bond fundamentals:

Biological applications:
Organofluorine Compounds

Only about 30 naturally occurring organofluorine compounds are known

- 13 biogenically produced, 8 of which are fatty acid derivatives
- one enzyme discovered (fluorinase) to catalyze C–F bond formation

Despite lack of organofluorines in nature

- 30% of agrochemicals contain C–F bonds
- 10% of pharmaceuticals contain C–F bonds

Why do we incorporate C–F bonds?

Why are Organofluorine Compounds Important?

“Substitution of a C-H bond with a C-F bond can significantly change the properties of arenes; for example, fluorine substitution can increase the metabolic stability of pharmaceuticals.”


“How does the C–F bond accomplish this?

“Thus the trifluoromethyl unit is often present in synthetic drugs and agrochemicals, leading to altered physical and physiological behavior of these materials with respect to uptake, mode of action, and metabolism.”

Properties of the C-F Bond

Organofluorine properties governed by fluorine’s electronegativity and size

- electronegativity, $\chi = 4.0$
- Van der Waals radii 1.47 Å
  (hydrogen 1.20 Å, oxygen 1.57 Å)

- Highly polarized bond
- Strongest single bond to carbon, 105 kcal/mol
  - Significant electrostatic attraction adds to strength
- Very low polarizability
- Tightly held lone pairs on fluorine

Hydrogen Bonding and the C–F Bond

“only the most electronegative atoms should form hydrogen bonds, and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms... It is found empirically that fluorine forms very strong hydrogen bonds, oxygen weaker ones, and nitrogen still weaker ones.”


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Hydrogen Bonding and the C–F Bond

Hydrogen Fluoride

\[ [\text{F} \cdots \text{H} \cdots \text{F}] \]

\[ \sim 40 \text{ kcal/mol} \]

Organofluorine

\[ \text{C–F} \cdots \text{H–X} \]

\[ \sim 1.5 \text{ – 2.4 kcal/mol} \]

Hydrogen Bonding and the C–F Bond

“only the most electronegative atoms should form hydrogen bonds, and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms... It is found empirically that fluorine forms very strong hydrogen bonds, oxygen weaker ones, and nitrogen still weaker ones.”
- Linus Pauling, *The Nature of the Chemical Bond, 2nd Ed., 1939*

![Hydrogen Fluoride](image1)

\[
\text{Hydrogen Fluoride} \quad \text{[F\cdots H\cdots F]} \quad \sim 40 \text{ kcal/mol}
\]

![Organofluorine](image2)

\[
\text{Organofluorine} \quad \text{C–F\cdots H–X} \quad \sim 1.5 – 2.4 \text{ kcal/mol}
\]

“It is interesting that in general fluorine atoms attached to carbon do not have significant power to act as proton acceptors in the formation of hydrogen bonds in the way that would be anticipated from the large difference in electronegativity of fluorine and carbon.”

Hydrogen Bonding and the C–F Bond

Organofluorine Hydrogen Bonds:

C(sp$^3$)–F $\sim$ 2.38 kcal/mol
C(sp$^2$)–F $\sim$ 1.48 kcal/mol

Shortest C–F•••H–X: 2.0 – 2.2 Å
Typical C–F•••H–X: 2.5 – 3.0 Å
(van der Waals distance: 2.65 Å)

Search of 146 272 entries in CSDS:
- 548 compounds with 1163 C–F bonds
- 166 contacts shorter than 2.35 Å
- 40 C–F•••H–O/N contacts
- 1 contact less than 2.0 Å

Organofluorine Hydrogen Bonds:

- high electronegativity
- low polarizability
- low lying 2p electrons

Organofluorines only make weak “hydrogen bonding” interactions

Weak interactions often attributed to exclusively electrostatic attractions

Organofluorine compounds have many biological applications:

- Enhance one or more properties of a target molecule
- As an investigative tool for biological mechanisms
- $^{18}$F-Labeled radiopharmaceuticals/PET imaging
- Perfluorinated liquids in medicine
- Anesthetics
**Increased Metabolic Stability of Organofluorine**

**Problem:** In mammals, lipophilic compounds have a tendency to be oxidized by liver enzymes, particularly Cytochrome P450

**Solution:** Several possible strategies available

- Make the compound more polar
  - Lower bioavailability
- Block the metabolically labile sites
Increased Metabolic Stability of Organofluorine

Lead compound for a cholesterol-absorption inhibitor: SCH 48461

Primary metabolic pathways:
- dealkylation of anisyl groups
- \textit{para} hydroxylation of phenyl
- benzylic oxidation

 Increased Metabolic Stability of Organofluorine

Productive metabolism incorporated and non-productive blocked

Why does incorporation of a fluorine block metabolically labile sites?

Increased Metabolic Stability of Organofluorine

Productive metabolism incorporated and non-productive blocked

- Fluorine inductively deactivates the phenyl groups towards oxidation

What about C–F bond strength?

**Increased Metabolic Stability of Organofluorine**

Productive metabolism incorporated and non-productive blocked

- Fluorine inductively deactivates the phenyl groups towards oxidation

**What about C–F bond strength?**

- Increased stability not due to greater strength of the C–F bond

- Biological oxidations do not involve isolated homolysis of C–H or C–F bond
  - strengths not directly related to oxidation rates

Increased Metabolic Stability of Organofluorine

Bond energies and heats of formation are more relevant

<table>
<thead>
<tr>
<th>Bond</th>
<th>Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–O</td>
<td>111</td>
</tr>
<tr>
<td>C–O</td>
<td>85.5</td>
</tr>
<tr>
<td>F–O</td>
<td>44.0</td>
</tr>
</tbody>
</table>

The formation of F–O bonds unfavourable when compared to C–O and H-O so “attack” at fluorine is generally avoided.

Increased Metabolic Stability of Organofluorine

Inductive effects of fluorine can provide protection as far as β hydrogens

\[
\begin{align*}
\text{Me-} & \text{Me} \quad \xrightarrow{\text{Cl}_2} \quad \text{Me-} & \text{Me} \\
1 & : 4
\end{align*}
\]

\[
\begin{align*}
\text{F}_3\text{C-} & \text{Me} \quad \xrightarrow{\text{Cl}_2} \quad \text{F}_3\text{C-} & \text{Me} & \text{F}_3\text{C-} & \text{Me} \\
5 & : 4 & 1
\end{align*}
\]

Increased Metabolic Stability of Organofluorine

Incorporating fluorine to reduce rate of aryl oxidation is the most common pharmaceutical application.

GW420867X
reverse transcriptase inhibitor

In a few cases, introduction of a fluorine substituent fails to block oxidation.

Increased Metabolic Stability of Organofluorine

Incorporating fluorine to reduce rate of aryl oxidation is the most common pharmaceutical application.

GW420867X reverse transcriptase inhibitor

In a few cases, introduction of a fluorine substituent fails to block oxidation.

NIH shift is observed mostly in \( p \)-fluoroaniline or anilide structures.

Increased Metabolic Stability of Organofluorine

Incorporating fluorine to reduce rate of aryl oxidation is the most common pharmaceutical application.

Increased Metabolic Stability of Organofluorine

**Problem:** In mammals, lipophilic compounds have a tendency to be oxidized by liver enzymes, particularly *Cytochrome P450*.

**Solution:** Several possible strategies available

- Make the compound more polar
  - Lower bioavailability
- Block the metabolically labile sites
- Deactivate metabolically labile sites without blocking
Increased Metabolic Stability of Organofluorine

Hydrolytic stability can also be enhanced by fluorination

prostacyclin (PGI₂)
vasodilator
inhibitor of platelet aggregation

\[ T_{1/2} = 10 \text{ min} \]
\[ \text{pH} = 7.4 \]

6-oxo-PGF₁α
inactive metabolite

Increased Metabolic Stability of Organofluorine

Hydrolytic stability can also be enhanced by fluorination

prostacyclin (PGI₂)
vasodilator
inhibitor of platelet aggregation

T₁/₂ = 10 min
pH = 7.4

Rate of hydrolysis dramatically decreased through induction.

Modification of Physicochemical Properties

Most oral drugs are absorbed and distributed through passive transport must be able to pass through the cell membrane.

Lipophilicity must be tuned to enter the lipid core but not become trapped.

![Diagram of a cell membrane with labels for hydrophilic and hydrophobic regions.](image)
Modification of Physicochemical Properties

Most oral drugs are absorbed and distributed through passive transport must be able to pass through the cell membrane.

Lipophilicity must be tuned to enter the lipid core but not become trapped.

Fluorination can be used to modify lipophilicity
Modification of Physicochemical Properties

“Fluorination always increases lipophilicity”
Modification of Physicochemical Properties

"Fluorination usually increases lipophilicity"

common fluorination misconception

Modification of Physicochemical Properties

“Fluorination usually increases lipophilicity”

common fluorination misconception

General Rules:

- Aromatic fluorination increases lipophilicity

- Monofluorination and trifluoromethylation of saturated alkyl groups decreases lipophilicity

- Per/polyfluorination increases lipophilicity

- Fluorination adjacent to a basic functional group increases lipophilicity

reduce polarizability

Modification of Physicochemical Properties

Fluorination adjacent to a basic functional group increases lipophilicity induction from nearby fluorine decreases the pKa

\[ \begin{align*}
\text{H}_2\text{N} & \text{CH}_3 & \text{H}_2\text{N} & \text{CH}_2\text{F} & \text{H}_2\text{N} & \text{CHF}_2 & \text{H}_2\text{N} & \text{CF}_3 \\
10.7 & 8.97 & 7.52 & 5.7
\end{align*} \]

Modification of Physicochemical Properties

Fluorination adjacent to a basic functional group increases lipophilicity. Induction from nearby fluorine decreases the pKa.

<table>
<thead>
<tr>
<th></th>
<th>H₂N-CH₃</th>
<th>H₂N-CH₂F</th>
<th>H₂N-CHF₂</th>
<th>H₂N-CF₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>10.7</td>
<td>8.97</td>
<td>7.52</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Decreasing pKa can increase bioavailability but decrease receptor binding.

R₁ = R₂ = H  pKa = 9.7
Poor bioavailability, excellent binding

R₁ = F, R₂ = H  pKa = 8.7
Good bioavailability, good binding

R₁ = R₂ = F  pKa = 6.7
Excellent bioavailability, poor binding

5HT₁D agonists for migraine relief

Modification of Physicochemical Properties

Altering the pKa can also increase drug activity: increase concentrations of the active form

mifentidine
histamine H2 receptor antagonist

What is the active form?

Modification of Physicochemical Properties

Altering the pKa can also increase drug activity: increase concentrations of the active form

mifentidine histamine H2 receptor antagonist

What is the active form?

Effects on Molecular Conformation

The large dipole of the C–F bond and the size of the fluorine atom play a significant role in the conformational behaviour of organofluorine compounds.

single atom substitution usually imparts little steric demand

multi-atom substitution can have more drastic steric consequences

conformational changes can be subtle and sometimes difficult to predict

Effects on Molecular Conformation

Most common fluorine modification: Substituting C–H for C–F

Despite size difference, only small steric and geometric perturbations

Effects on Molecular Conformation

Most common fluorine modification: Substituting C–H for C–F

Substituting CH$_2$ with CF$_2$

Despite size difference, only small steric and geometric perturbations

Effects on Molecular Conformation

Most common fluorine modification: Substituting C–H for C–F

Despite size difference, only small steric and geometric perturbations

Substituting CH₂ with CF₂

unstable monolayer

stable monolayer in water

stable monolayer in water

conformational flexibility

**Effects on Molecular Conformation**

**Distortion Increases:** methoxybenzene and trifluoromethoxybenzene do not adopt similar ground state conformations

Effects on Molecular Conformation

Distortion Increases: methoxybenzene and trifluoromethoxybenzene do not adopt similar ground state conformations

CH$_3$ and CF$_3$ not simple isosteres!
CF$_3$ closer in size to iPr

Effects on Molecular Conformation

Effect of conformation on cholesteryl ester transfer protein inhibitors.

Out of plane orientation of phenyl substituent results in more efficient binding to target protein.

Effects on Molecular Conformation

Effect of conformation on cholesteryl ester transfer protein inhibitors.

Fluorinated ethers possible isosteres for metabolically unstable 2-furyl compounds

Effects on Molecular Conformation

1,2-Fluorine bond attraction: the *gauche* effect

![Diagrams showing 1,2-fluorine bond attraction](image)

0.0 kcal/mol 0.7 kcal/mol

Effects on Molecular Conformation

1,2-Fluorine bond attraction: the *gauche* effect

\[
\begin{array}{cc}
\text{H} & \text{F} \\
\text{H} & \text{F} \\
\text{H} & \text{F} \\
\text{H} & \text{H}
\end{array}
\quad
\begin{array}{cc}
\text{H} & \text{F} \\
\text{H} & \text{F} \\
\text{F} & \text{H} \\
\text{F} & \text{H}
\end{array}
\]

0.0 kcal/mol \quad 0.7 kcal/mol

*Gauche* effect present in other heteroatom systems

- stabilization even greater for *N*-\(\beta\)-fluoroethylamides

Effects on Molecular Conformation

Fluorine vicinal to oxygen influences conformation in Indinavir analogs.

Syn fluorohydrin analogs maintain the required fully extended chain.

Effects on Molecular Conformation

Fluorine interacts with formal charges to induce conformational preferences

Charge-Dipole Interactions

Large axial or gauche preference when a formal charge is present

Much larger energetic preference than gauche effect alone

Effects on Molecular Conformation

Charged-dipole interactions can probe protein-ligand interactions.

\[
\begin{align*}
\text{GABA} & \quad \text{(S)-3F-GABA} & \quad \text{(R)-3F-GABA} \\
\text{H}_3\text{N}^+ & \quad \text{H}_3\text{N}^+ & \quad \text{H}_3\text{N}^+ \\
\text{C} & \quad \text{F} & \quad \text{F} \\
\text{O}_2^- & \quad \text{O}_2^- & \quad \text{O}_2^- \\
\end{align*}
\]

How does the neurotransmitter \(\gamma\)-aminobutyric acid (GABA) bind to proteins?

- In GABA\(_A\) receptors (ligand-gated ion channels) (S)- and (R)-3F-GABA interacted similarly.
- In GABA transaminase (metabolizing enzyme) (S)-3F-GABA has a much higher affinity.

**Effects on Molecular Conformation**

Charged-dipole interactions can probe protein-ligand interactions.

Zwitterionic GABA has a protonated amine - charge-dipole interactions

How does the neurotransmitter \(\gamma\)-aminobutyric acid (GABA) bind to proteins?

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Effects on Molecular Conformation

Charged-dipole interactions can probe protein-ligand interactions.

Possible conformations of 3F-GABA

Effects on Molecular Conformation

Charged-dipole interactions can probe protein-ligand interactions.

Possible conformations of 3F-GABA

Disfavoured

**Effects on Molecular Conformation**

Charged-dipole interactions can probe protein-ligand interactions.

GABA<sub>A</sub> receptors bind (R)- and (S)-3F-GABA equally.

Effects on Molecular Conformation

Charged-dipole interactions can probe protein-ligand interactions.

GABA transaminase has higher affinity for (S)-3F-GABA

Exploitation of Orthogonal Reactivity

Hydrogen and fluorine have minor steric differences but show orthogonal reactivity.

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Hydrogen and fluorine have minor steric differences but show orthogonal reactivity

\[ \text{Me}_2\text{C} \text{H} \xrightarrow{- \text{H}^+} \text{Me}_2\text{C} = \text{Me} \]
\[ \text{Me}_2\text{C} \text{F} \xrightarrow{- \text{F}^+} \text{Me}_2\text{C} = \text{Me} \]
\[ \text{Me}_2\text{C} \text{H} \xrightarrow{- \text{F}^-} \text{Me}_2\text{C} = \text{Me} \]
\[ \text{Me}_2\text{C} \text{F} \xrightarrow{- \text{H}^-} \text{Me}_2\text{C} = \text{Me} \]

Prevent \textit{in vivo} racemization

(S)-thalidomide teratogenic effects

\[
\begin{align*}
\text{\text{N}} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{N}
\end{align*}
\]

\textit{in vivo}

(R)-thalidomide sedative effects

\[
\begin{align*}
\text{\text{N}} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{N}
\end{align*}
\]

Exploitation of Orthogonal Reactivity

Hydrogen and fluorine have minor steric differences but show orthogonal reactivity

Prevent *in vivo* racemization

Exploitation of Orthogonal Reactivity

Hydrogen and fluorine have minor steric differences but show orthogonal reactivity

Exploit this inherent orthogonal reactivity to design enzyme inhibitors

Thymidylate synthase (TS):
- converts dUMP to dTMP

dTMP required for DNA biosynthesis
Inhibition of TS causes apoptosis

Thymidylate synthase suicide inhibitors:

5-Fluorouracil
treatment of various cancers

Trifluridine
herpes antiviral drug

Exploitation of Orthogonal Reactivity

Thymidylate synthase mechanism:

Exploitation of Orthogonal Reactivity

Thymidylate synthase inhibition using 5-Fluorouracil:

FdUMP

activated
tetrahydrofolate

no elimination can occur
enzyme now inactive

**Exploitation of Orthogonal Reactivity**

Thymidylate synthase inhibition using Trifluridine:

\[
R = \text{OPO}^{+}\text{OH}
\]

![Thymidylate synthase inhibition diagram](image)

**Chem. Soc. Rev. 2008, 37, 320.**
Fluorinated Isosteres

Substituting C–OH with C–F

Sterically/electronically neutral change
- both electronegative atoms
- similar size match

Other considerations:
- loss of acidic hydrogen
- loss of hydrogen bond donor ability
- limited (or no) hydrogen bond acceptor ability

Use to explore roles of C–OH hydrogen bonding versus C–O bond polarity

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

Collagen:
- Most abundant protein in animals
- Tight triple helix in connective tissue
- High tensile strength and thermal stability

What structural aspect of collagen causes its stability?

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

amino acid sequence
Xaa-Yaa-Gly

Xaa and Yaa usually proline or (4R)-hydroxyproline

(4R)-hydroxyproline
(Hyp)

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

Are the bridging water molecules the source of the stability?

High entropic cost of immobilizing >500 water molecules per helix

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

(4R)-fluoroproline (Flp)

Synthesize (ProFlpGly)$_{10}$:

- weaken (or remove) hydrogen bonds
- retain polarity of the C–X bond

CD spectra of (ProYaaGly)$_{10}$

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

Stability of collagen relies on the polarized C–X bond and not water bridges.

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

Collagen’s triple helix requires \textit{trans} peptide bonds favoured by Hyp and Flp

- Where does this preference come from?

\[ X_3 + \text{cis} \xrightarrow[]{} K_{\text{trans/cis}} X_3 + \text{trans} \]

<table>
<thead>
<tr>
<th>X</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>4.6</td>
</tr>
<tr>
<td>OH</td>
<td>6.1</td>
</tr>
<tr>
<td>F</td>
<td>6.7</td>
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Fluorinated Isosteres

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**Fluorinated Isosteres**

**Code for Collagen’s Stability Deciphered - Using Fluorine**

Collagen’s triple helix requires *trans* peptide bonds favoured by Hyp and Flp

- Where does this preference come from?

\[ \text{cis} \xleftrightarrow{K_{\text{trans/cis}}} \text{trans} \]

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</table>

* cis/trans ratio from conformation

\[ \text{cis} \xleftrightarrow{K_{\text{trans/cis}}} \text{trans} \]

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<td>F</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Fluorinated Isosteres

Code for Collagen’s Stability Deciphered - Using Fluorine

The *gauche* effect present between fluorine and nitrogen.

Favourable $O_0\cdots C_1$ interaction stabilizes *trans* peptide bond.

Collagen stability stems from shape preference not hydrogen bonded water network

Fluorinated Isosteres

Vinylfluorides are steric and polar hydrophobic mimetics of amide bonds.

Polar hydrophobicity:

Maintaining the electrostatic charge distribution while decreasing overall polarizability.

Fluorinated Isosteres

Vinylfluorides are steric and polar hydrophobic mimetics of amide bonds.

- Dipole orientation similar but weaker
- Limits (or removes) hydrogen bonding capacity
- Increases lipophilicity and possibly membrane penetration

**Fluorinated Isosteres**

thymine (T)  

difluorotoluene (F)

difluorotoluene is a nearly perfect isostere for thymine

dipole ~4.19 D  
dipole ~1.84 D

Fluorinated Isosteres

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dipole ~1.84 D

**Fluorinated Isosteres**

![Chemical structures of thymine (T) and difluorotoluene (F) with corresponding text explaining their similarity as isosteres.]

- **thymine (T)**
- **difluorotoluene (F)**

Difluorotoluene is a nearly perfect isostere for thymine.

**Probe function of Watson-Crick hydrogen bonds in DNA structure and replication.**

Fluorinated Isosteres

Factors may stabilize DNA structure:
- Watson-Crick hydrogen bonds
- Base stacking interactions
- Steric “fit” of base pairs
- Solvation of external backbone
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- Watson-Crick hydrogen bonds
- Base stacking interactions
- Steric “fit” of base pairs
- Solvation of external backbone
Fluorinated Isosteres

Substitution of difluorotoluene for thymine does not disrupt DNA structure

Fluorinated Isosteres

Substitution of difluorotoluene for thymine does not disrupt DNA structure

- Results in destabilized duplex (~3-4 kcal/mol)
- No selectivity for a natural base

<table>
<thead>
<tr>
<th></th>
<th>$T_m$(°C)</th>
<th>$\Delta G$(kcal)</th>
<th></th>
<th>$T_m$(°C)</th>
<th>$\Delta G$(kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.A</td>
<td>42.5</td>
<td>-9.7</td>
<td>F.A</td>
<td>26.2</td>
<td>-6.2</td>
</tr>
<tr>
<td>T.G</td>
<td>33.3</td>
<td>-7.5</td>
<td>F.G</td>
<td>23.6</td>
<td>-6.0</td>
</tr>
<tr>
<td>T.C</td>
<td>29.5</td>
<td>-6.6</td>
<td>F.C</td>
<td>23.7</td>
<td>-5.8</td>
</tr>
<tr>
<td>T.T</td>
<td>29.1</td>
<td>-6.8</td>
<td>F.T</td>
<td>24.0</td>
<td>-5.9</td>
</tr>
</tbody>
</table>

Watson-Crick hydrogen bonds contribute significantly to stabilization of DNA helix

Fluorinated Isosteres

Are Watson-Crick hydrogen bonds required in DNA polymerase enzymes?

Fluorinated Isosteres

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Difluorotoluene shows thymine-like polymerase activity

- similar efficiency of thymine
- similar selectivity for adenine

Fluorinated Isosteres

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- similar selectivity for adenine

Could this be the A-Rule?

Fluorinated Isosteres

Are Watson-Crick hydrogen bonds required in DNA polymerase enzymes?

Fluorinated Isosteres

Are Watson-Crick hydrogen bonds required in DNA polymerase enzymes?

- dFTP successfully incorporated into the elongating primer
- F–A base pair synthesized with high efficiency and specificity

Fluorinated Isosteres

Conclusions:
- Replication of DNA base pairs can occur without Watson-Crick hydrogen bonds
- Steric effects are the main arbiters of DNA replication fidelity

Unanswered Question: Is this general over all classes of polymerases?

**Fluorinated Isosteres**

Conclusions:
- Replication of DNA base pairs can occur without Watson-Crick hydrogen bonds
- Steric effects are the main arbiters of DNA replication fidelity

The steric effect is being accepted as a key factor in replication fidelity.

*L. Stryer, Biochemistry*

4th Ed (1995): “The likelihood of binding and making a phosphodiester bond is very low unless the incoming nucleotide forms a Watson-Crick base pair with the opposing nucleotide on the template.”

5th Ed (2001): “The specificity of replication is dictated by hydrogen bonding and the complementarity of shape between bases.”


“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.”

- Manfred Schlosser

“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.”
- Manfred Schlosser


“Small atom with a big ego.”