Hexafluoroisopropanol as a highly versatile solvent

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Part 1

Physical and chemical properties of HFIP

- Physical properties
- Enhanced acidity
- Reduced nucleophilicity
- Hydrogen-bond donating ability
- Redox stability
- Cation stabilization
Physical and chemical properties of HFIP

**Physical properties**

HFIP does not absorb UV light, is thermally stable and is miscible with both water and most common polar organic solvents. The low boiling point (bp = 59 °C; for comparison, the bp of iPrOH is 82.2 °C).

**Enhanced acidity**

HFIP in aqueous solution ($pK_a = 9.3$) compared with iPrOH ($pK_a = 17.1$)

**Reduced nucleophilicity**

\[
H_3C–OTs + NuH \rightarrow H_3C–Nu
\]

\[
N_{OTs}(HFIP) = -4.23 \quad \text{log} k = s_N (E + N)
\]

Physical and chemical properties of HFIP

**Hydrogen-bond donating ability**

THF: $\text{bp} = 66^\circ \text{C}$

**Redox stability**


Physical and chemical properties of HFIP

*Cation stabilization* \( \varepsilon = 15.7 \)

\[
\text{HFIP} \quad k \text{ (s}^{-1}) = 2.2 \times 10^4 \\
\text{HFIP–H}_2\text{O} \quad k \text{ (M}^{-1} \text{ s}^{-1}) = 9.5 \times 10^4 \\
\text{HFIP–MeOH} \quad k \text{ (M}^{-1} \text{ s}^{-1}) = 1.8 \times 10^6 \\
\text{HFIP–Br}^- \quad k \text{ (M}^{-1} \text{ s}^{-1}) = 1.5 \times 10^{10}
\]

HFIP–H\(_2\)O (98:2) \( k \text{ (s}^{-1}) = 2.0 \times 10^4 \\
HFIP–H_2O (95:5) \quad k \text{ (s}^{-1}) = 1.7 \times 10^5 \\
HFIP–H_2O (90:10) \quad k \text{ (s}^{-1}) = 1.0 \times 10^6 \\
HFIP–H_2O (70:30) \quad k \text{ (s}^{-1}) = 7.5 \times 10^6

HFIP in organic chemistry

- Activation of hydrogen peroxide
- Activation of organic functionalities
- Activation of hypervalent iodine reagents
- Metal-free C–H activation
Activation of hydrogen peroxide

**a**

 activation of a cyclic ketone with hydrogen peroxide in the presence of a Brønsted acid catalyst in HFIP at 55 °C.

**b**

 activation of an olefin with hydrogen peroxide in HFIP at 60 °C.

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Activation of organic functionalities

Carbonyl or acetal activation

Schmidt reaction

\[
\begin{array}{c}
\text{TiCl}_4 \text{ or AcCl (cat.)} \\
\text{HFIP, 25 °C}
\end{array}
\]

Friedel–Crafts acylation

\[
\begin{array}{c}
\text{HFIP} \\
\text{RT}
\end{array}
\]

Hosomi–Sakurai reaction

\[
\begin{array}{c}
\text{HFIP–CH}_2\text{Cl}_2 (4:1), \text{RT}
\end{array}
\]

Activation of organic functionalities

Imine

Plausible mechanisms for the formation of β-amino ketones in the presence of HFIP

Activation of organic functionalities

Epoxide

Nucleophilic epoxide opening

Concerted addition of arene to the proton activated oxirane

Activation of organic functionalities

**Alcohol**

Nucleophilic substitution

![Reaction scheme](image)

amines, sulfonamides, carbamates; allyl silanes and 1,3-dicarbonyl compounds.

**Halide**

![Reaction scheme](image)

Activation of hypervalent iodine reagents

Hypervalent iodine reagents

C–H / C–H cross-coupling

Metal-free C–H activation

Electrochemical methods

C–H and N–H electrochemical oxidative coupling
C–H and N–H electrochemical oxidative coupling

Organometallic and inorganic chemistry

- Metal-catalysed C–H activation
- Non-classical hydrogen bonding between HFIP and transition metal complexes
Metal-catalysed C–H activation

Non-classical hydrogen bonding between HFIP and transition metal complexes

Formation of a dihydrogen bond between [NbCp2H3] and HFIP

Proton transfer through dihydrogen bonding

Protonation at B–H vs M–H

Part 5

Supramolecular and polymer science

- HFIP in polymerization reactions
- Electrospinning and electrocasting
Supramolecular and polymer science

Molecular tweezers

HFIP in polymerization reactions

Radical polymerization reactions

HFIP in polymerization reactions

Cationic polymerization

\[
\beta\text{-Pinene} \xrightarrow{\text{HFIP}} \text{PBP} \quad \text{Ring-opening cationic polymerization}
\]

Polymerization of pinene

\[
\alpha\text{-Pinene} \xrightarrow{\text{O}_2 \rightarrow ^1\text{O}_2} \text{Pinocarvone} \xrightarrow{\text{Visible light}} \text{PBP} \quad \text{Ring-opening radical polymerization}
\]

HFIP has recently become a very popular solvent or additive with applications across the spectrum of chemistry. It possesses a wide range of interesting and unique properties.

Uncovering the interactions of HFIP with functional groups within organic molecules or with metal complexes may reveal new modes of activation that will lead to new modes of reactivity.
Acknowledgement

- Prof. Huang
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- All members in E201

Thanks for your attention!
Activation of hydrogen peroxide

Postulated mechanism for the rearrangement of 3 to 2

Activation of hypervalent iodine reagents

PhI(OOCOCF₃)₂ (PIFA) (CF₃)₂CHOH

PhI(OOCOCF₃)₂

CT-complex (B)

(π-complex)

Nu⁻

SET: Single Electron Transfer

Nu⁻

cation radical (D)

PhI

Nu=N₃, OAc, etc.

PhNu +

MeO

MeO

MeO

MeO

OMe

Nu

Nu

2-4

R

R

R

R

R

R

R

R
C–H and N–H electrochemical oxidative coupling