

The C–H...O and other weak hydrogen bonds

From crystal engineering to virtual screening

Gautam R. Desiraju
School of Chemistry
University of Hyderabad
Hyderabad 500 046

The All-Chemist



G. R. Desiraju, *Nature*, 408, 407, 2000 (Millenium Essay)

Hydrogen bond, X–H...A

Pauling definition (1939)

Under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms instead of only one, so that it may be considered to be acting as a bond between them.

Hydrogen bond, X–H...A

Pimentel–McClellan definition (1960)

A hydrogen bond is said to exist when (1) there is evidence of a bond, and (2) there is evidence that this bond specifically involves a hydrogen atom already bonded to another atom

Non-conventional hydrogen bonds 1937-1982

1937. Glasstone. Acetone–chloroform complex

1939. Pauling definition of hydrogen bond

1962. Sutor. C–H...O hydrogen bonds in purines

1967. Oki. Spectroscopy of O–H... π interactions

1968. Donohue's criticism of C–H...O hydrogen bond

1976. Leiserowitz review on carboxylic acids

1982. Taylor–Kennard paper

Hydrogen bond

Any cohesive interaction $X-H\cdots A$ where H carries a positive and A a negative (partial or full) charge and the charge on X is more negative than on H

(Steiner–Saenger definition)

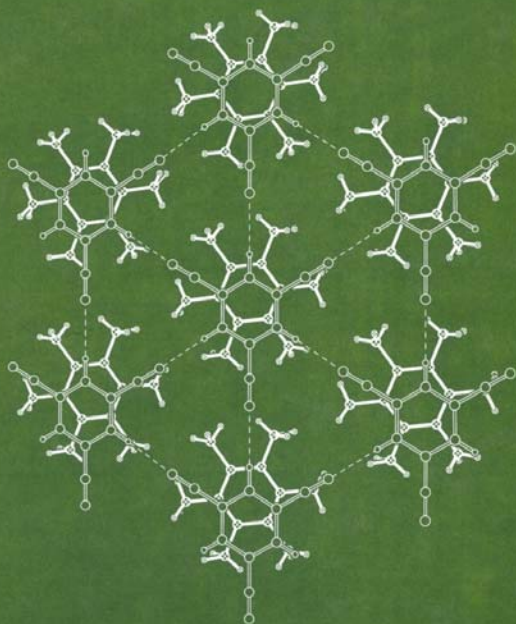


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The Weak Hydrogen Bond

In Structural Chemistry and Biology

Gautam R. Desiraju
and Thomas Steiner



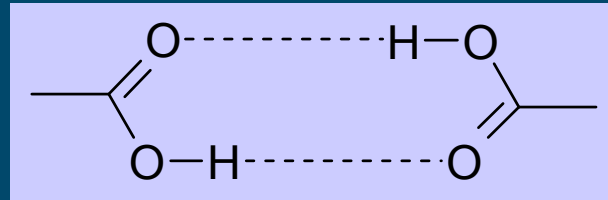
INTERNATIONAL UNION OF CRYSTALLOGRAPHY
OXFORD SCIENCE PUBLICATIONS



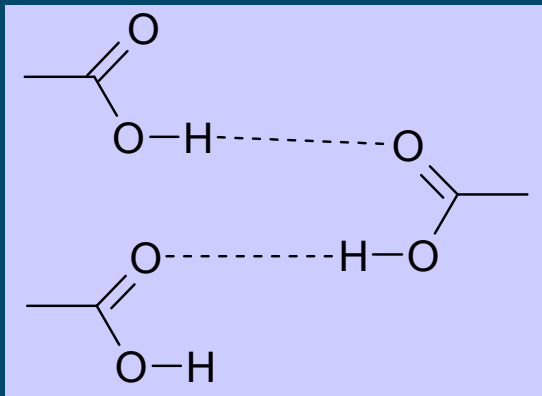
The weak hydrogen bond is an interaction $X-H\cdots A$ wherein a hydrogen atom forms a bond between two structural moieties X and A , of which one or even both are of moderate to low electronegativity (1999) (Desiraju–Steiner definition)

Crystal engineering

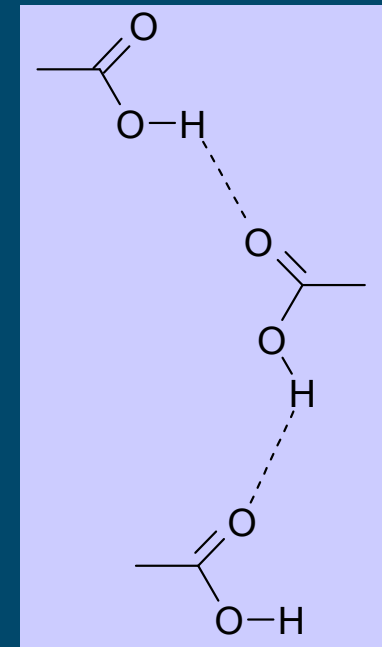
What do carboxylic acids do in the solid state?



Dimer



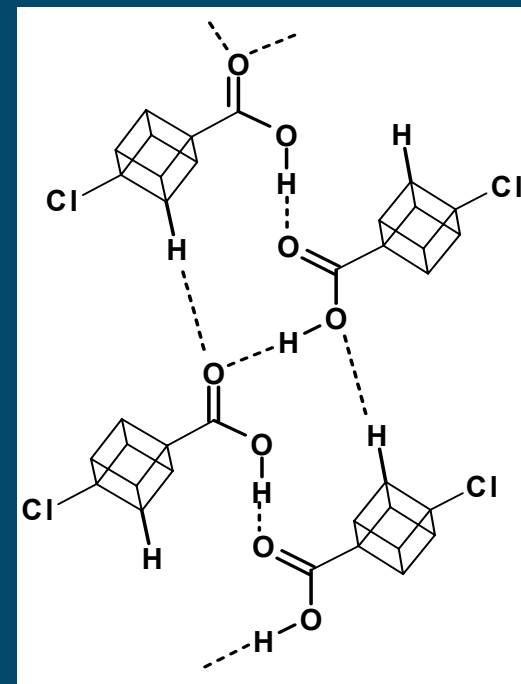
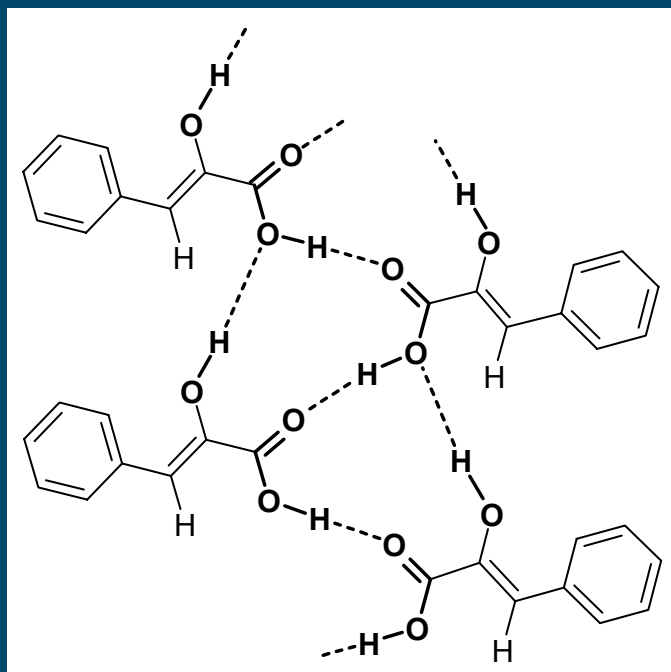
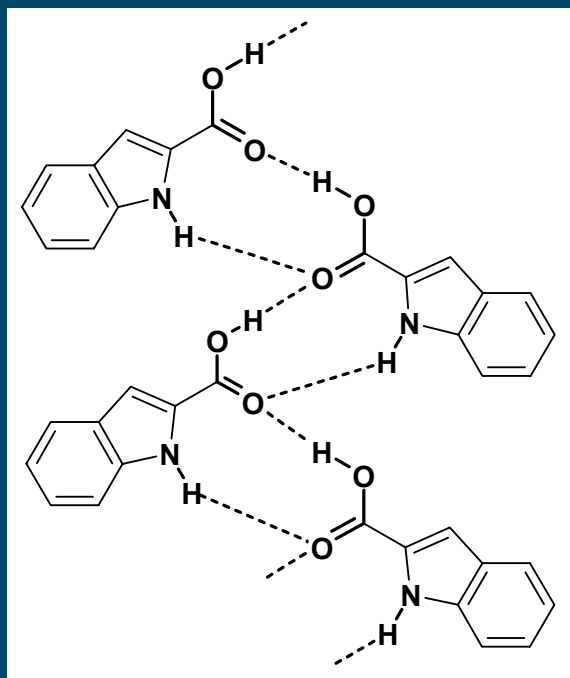
syn-Catemer



syn,anti-Catemer

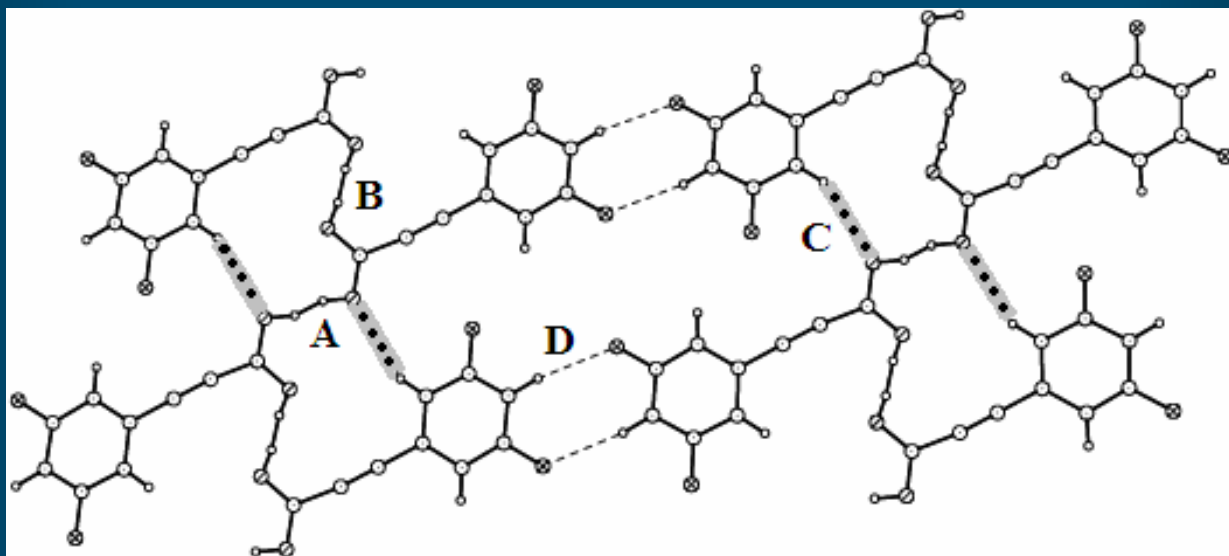
Supportive interactions

Interaction homology



G. R. Desiraju, Chem. Comm., 1995, 2005

syn-anti Catemer in 3,5-Difluorophenylpropionic Acid



Supportive C–H...O and C–H...F bonds

D. Das and G. R. Desiraju, Chem. Asian J., 1, 231-244, 2006

C–H···N Hydrogen Bonds

Linear Motifs and Structural Insulation



Dulmage and Lipscomb, *Acta Cryst.*, 4, 330, 1951

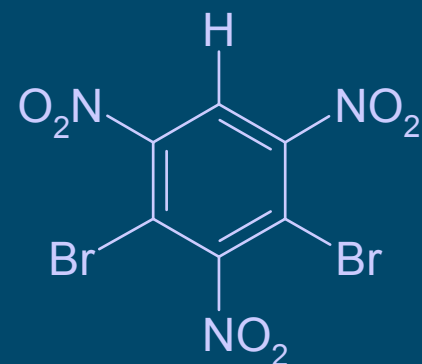
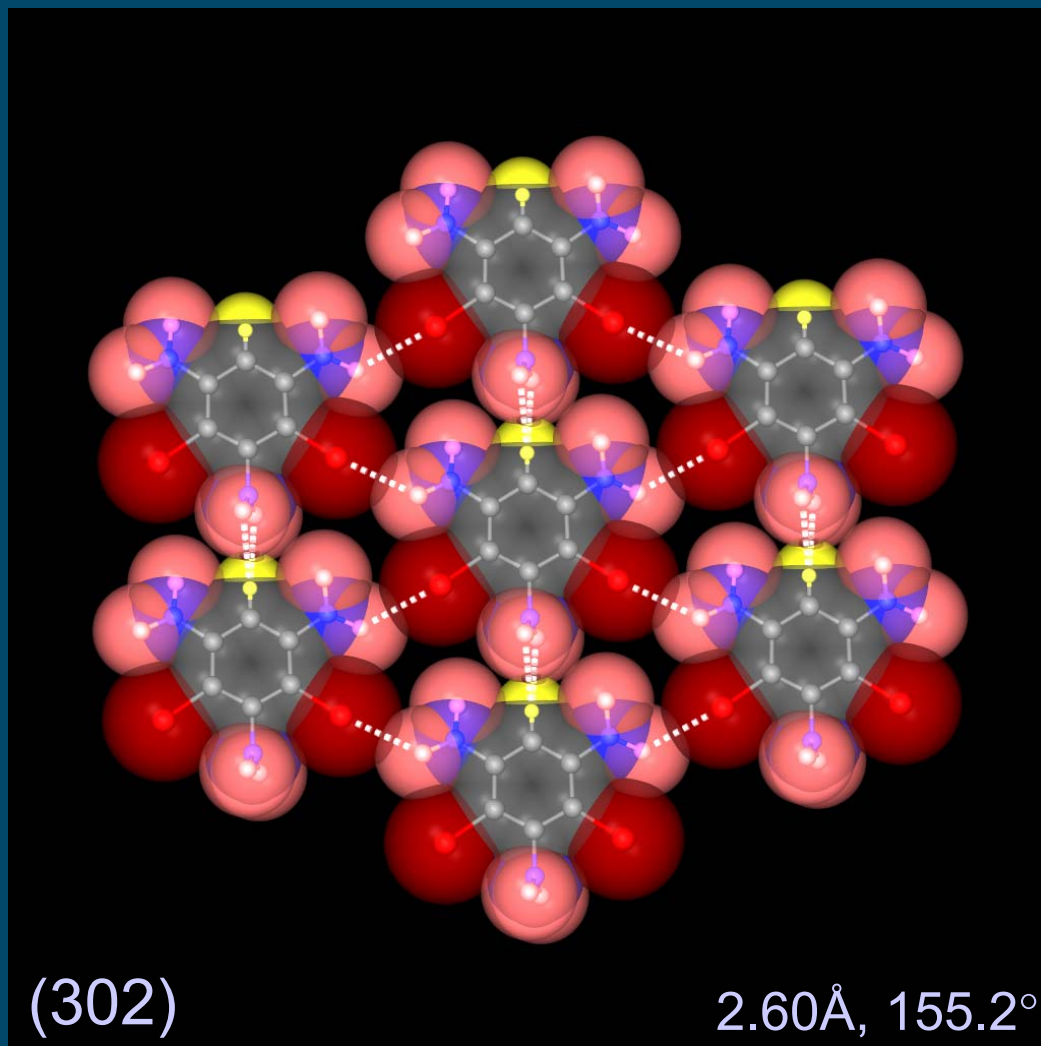


Shallcross and Carpenter, *Acta Cryst.*, 11, 490, 1958



Thaimattam and Desiraju, *New. J. Chem.*, 1307, 1998

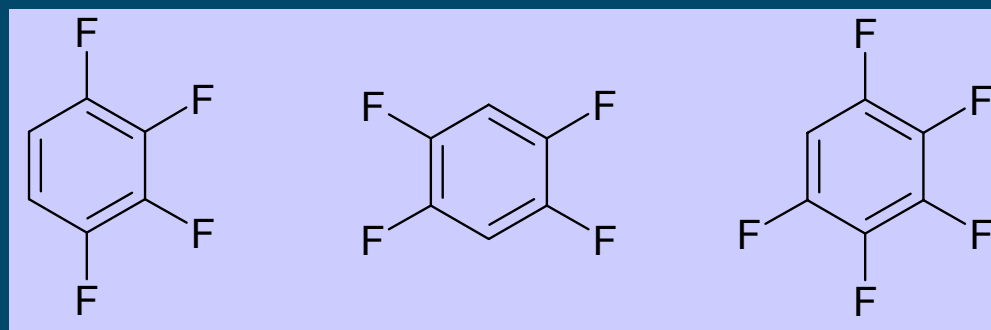
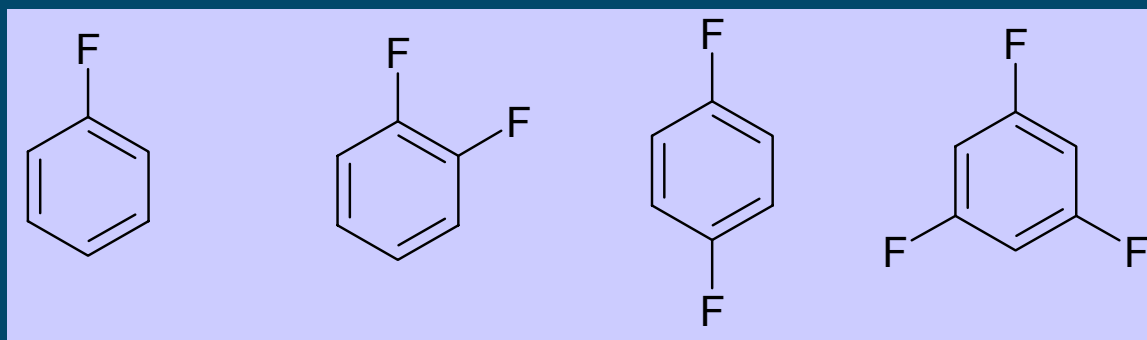
A functional crystal



Space group *C2*

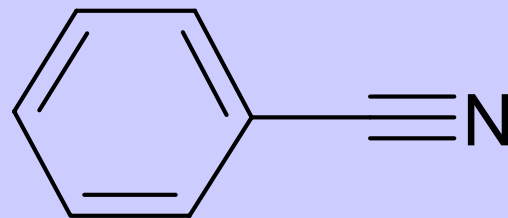
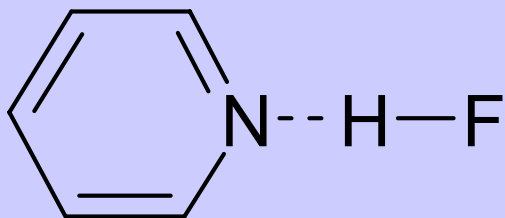
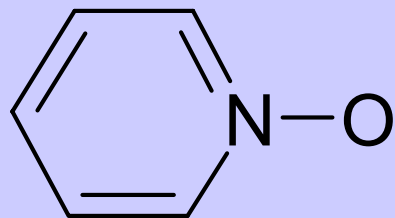
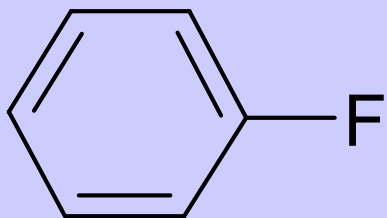
Intense powder SHG
signal at 1.06 μm

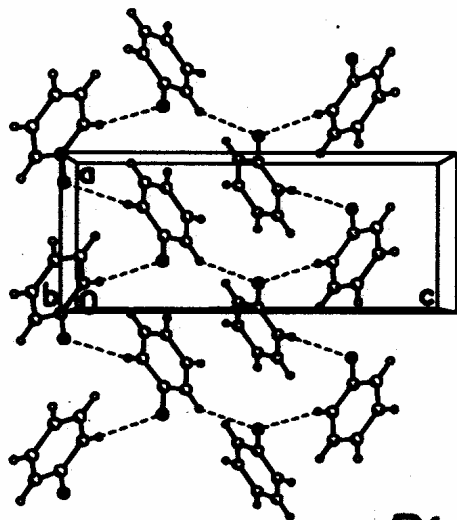
C–H···F–C Interactions in Fluorobenzenes



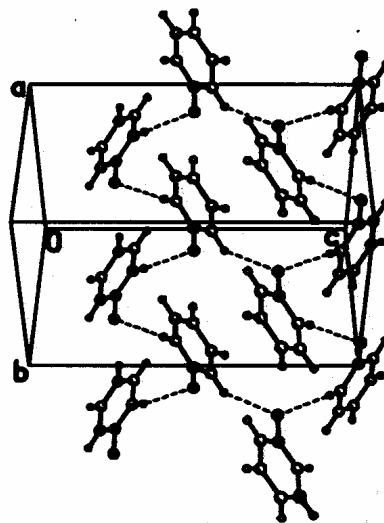
Desiraju, Boese et al, JACS, 120, 8702, 1998

Four related compounds

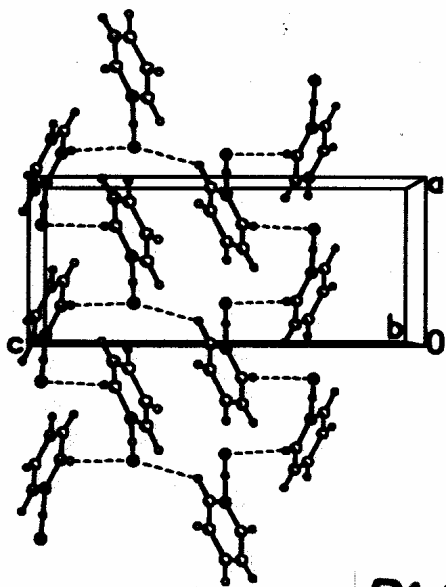




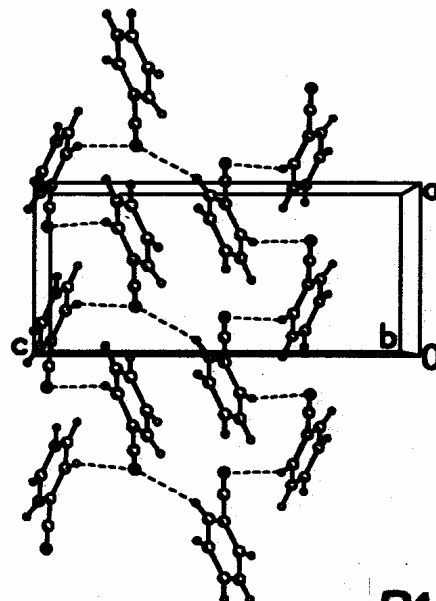
$P4_32_2$



$C222_1$

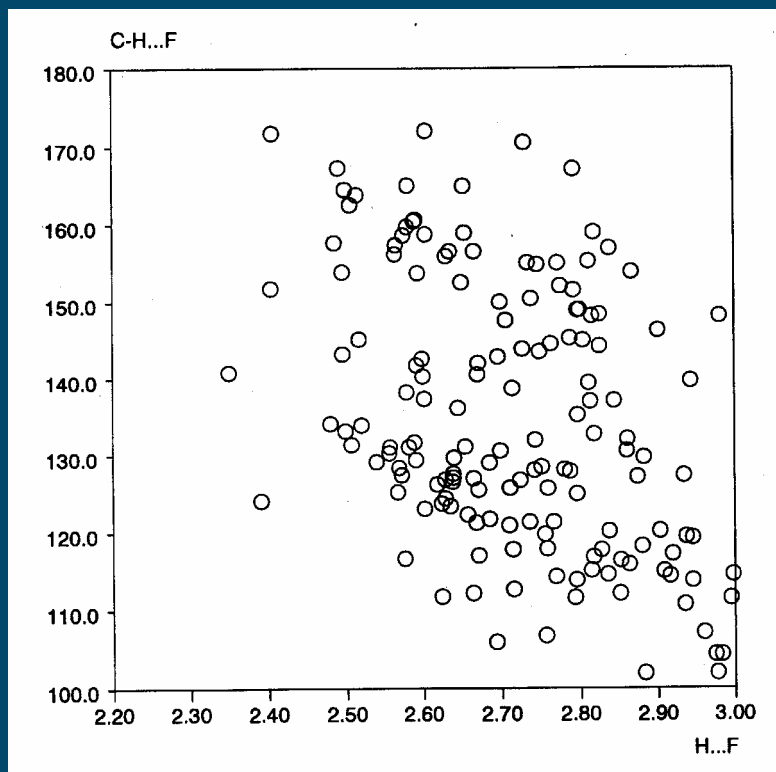


$P4_12_2$

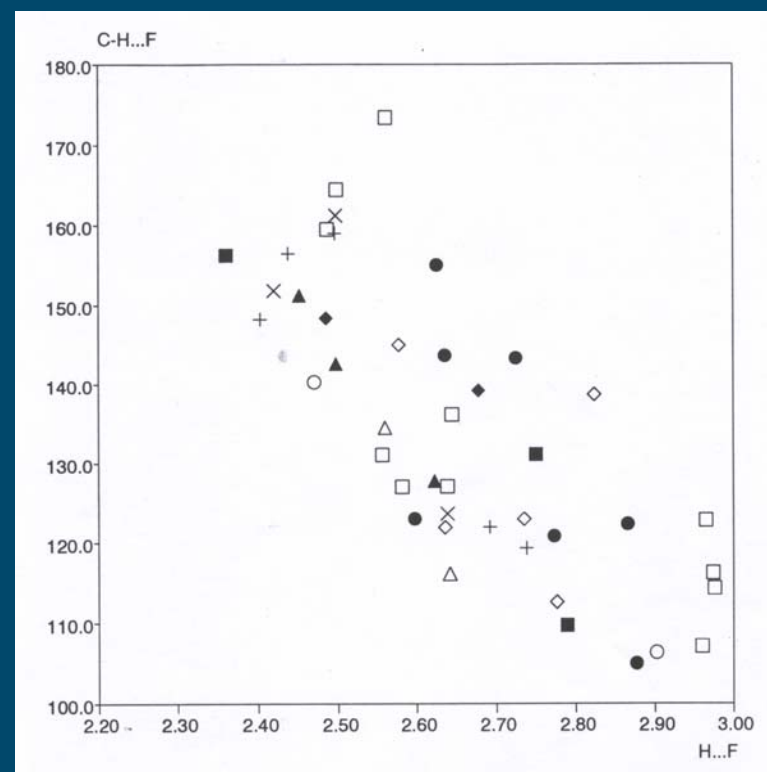


$P4_22_2$

C-H...F-C Hydrogen Bonds

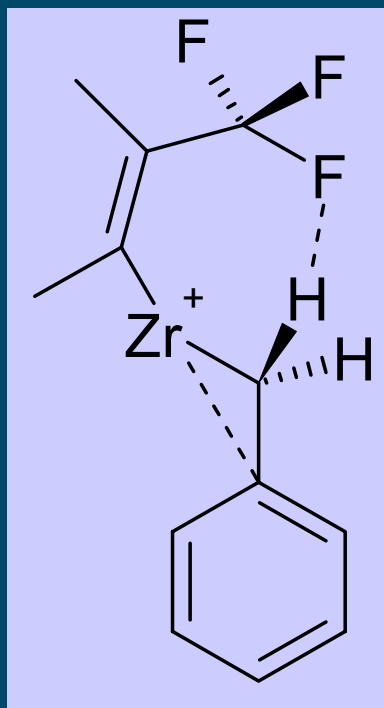


All C, H, F compounds

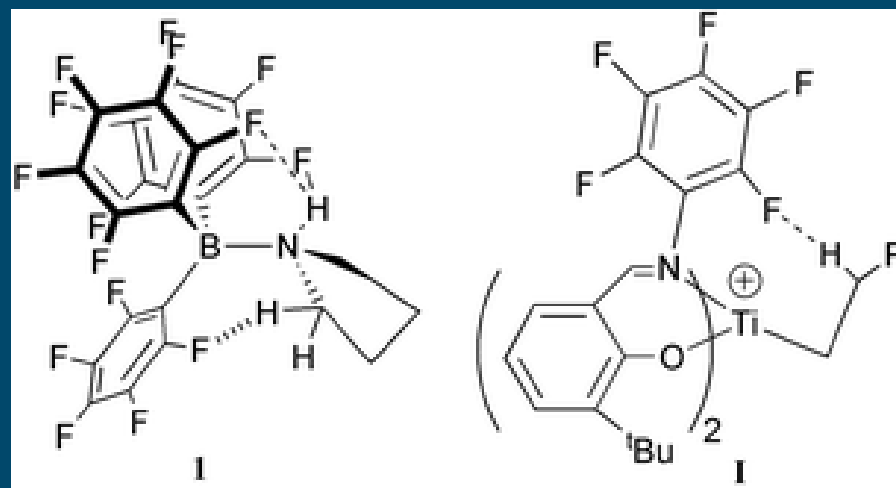


Fluorobenzenes

Weak and reversible C–H...F–C Hydrogen Bonds Applications. Polymerization catalyst.



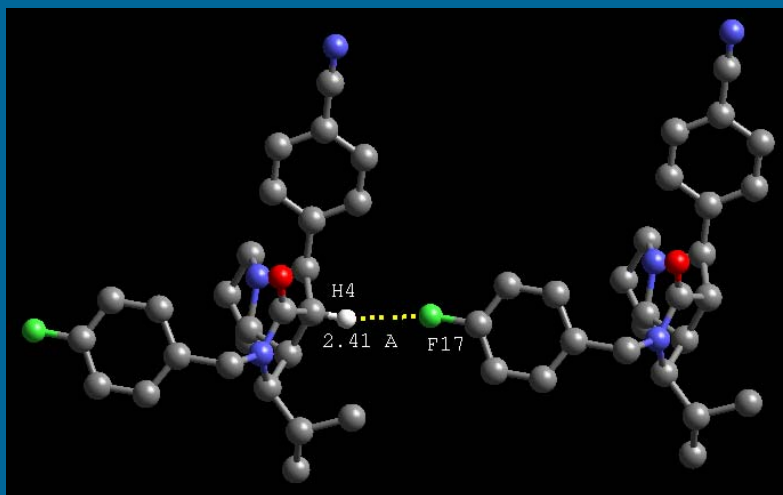
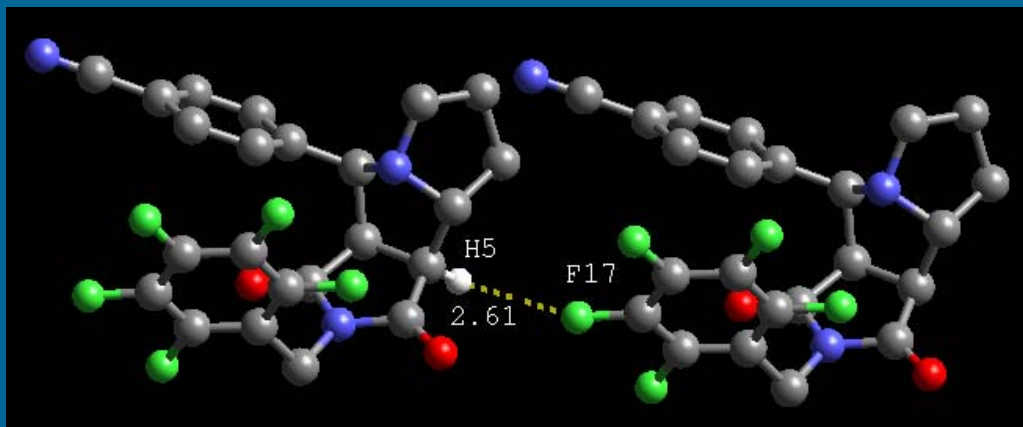
Stereoselective polymerisation
Chan et al,
Angew. Chem. Int. Ed.,
42, 1628, **2003**



Boron adducts
Lancaster et al, Chem. Comm.,
2148, **2003**

Decrease of β -H transfer
Fujita et al,
JACS, 124, 3327, **2002**
JACS, 125, 4293, **2003**

Weak and reversible C–H···F–C hydrogen bond Applications. Drug design



Binding in thrombin
Diederich et al,
Angew. Chem. Int. Ed.,
42, 2507, 2003

Hydrogen bridge (*Wasserstoffbrücke*)



Electrostatics

Charge transfer (covalency)

Dispersion/repulsion (van der Waals)

Polarisation



Hydrogen bridges in crystal engineering. Interactions without borders.
G. R. Desiraju, *Acc. Chem. Res.*, 35, 565-573, 2002

Hydrogen bond

The master-key of molecular recognition

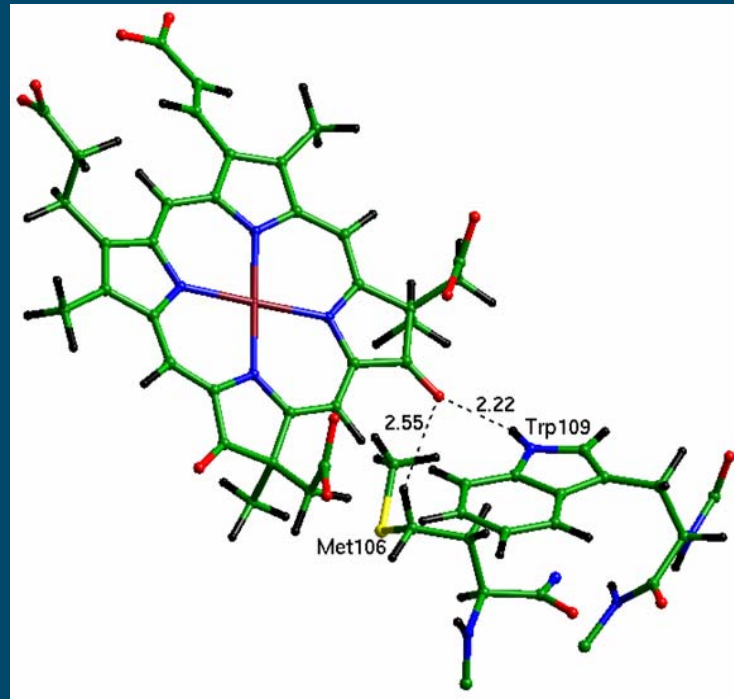
Strength	<i>Affinity</i>
Directionality	<i>Specificity</i>
Weakness	<i>Hydrophobicity</i>
Flexibility	<i>Reversibility</i>

Strong or weak?

Anti-cooperative synthon in
Cytochrome Cd1 nitrite reductase / Heme D/ Heme C

C–H...O (2.55 Å)

N–H...O (2.22 Å)

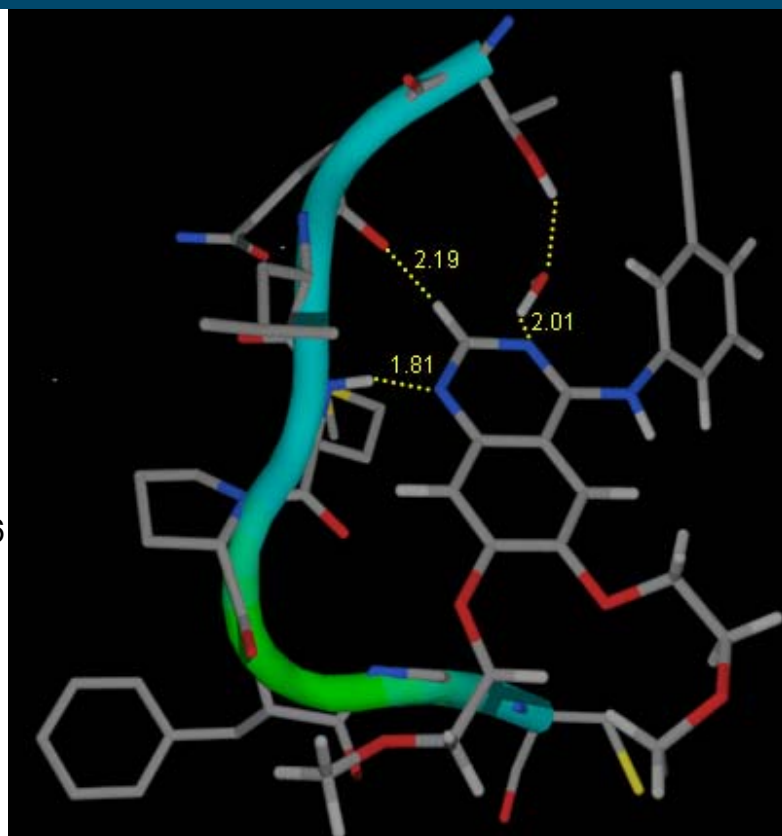
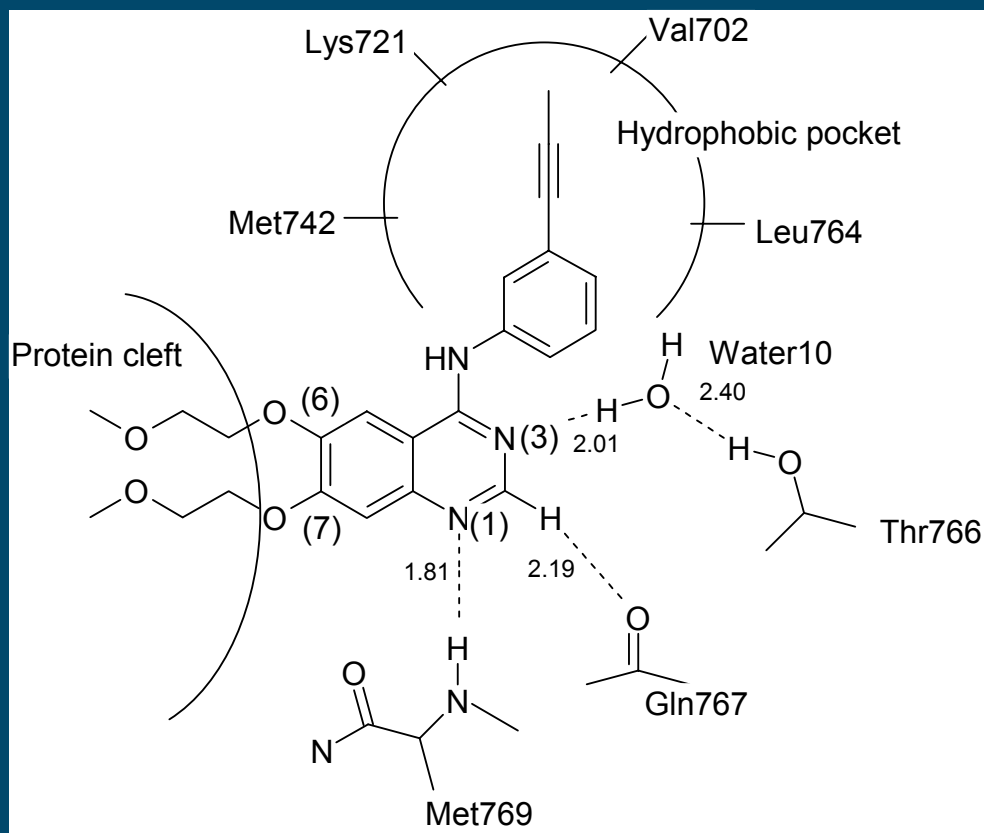


(PDB ID: 1QKS)

S. Sarkhel and G. R. Desiraju, *Proteins*, 54, 247, **2004**
S. K. Panigrahi and G. R. Desiraju, *Proteins*, 56, 000, **2006**

EGFR Kinase Inhibitor

Virtual screening of erlotinib analogs



Bonds and bridges

Pauling's definition

Under certain conditions an atom of hydrogen is attracted **by rather strong forces** to two atoms instead of only one, so that it may be considered to be acting as a **bond** between them.

Modern definition

Under certain conditions an atom of hydrogen is attracted to two atoms instead of only one, so that it may be considered to be acting as a bridge between them.

Conclusions

The C–H...O and other 'weak' hydrogen bonds/bridges are specific interactions with distinct structural consequences

Many C–H...O bonds may be considered to be structure determining

Presence or absence of a single weak interaction may result in a cascade of changes

Different weak interactions may be of varying importance in determining crystal packing

A Palette of Hydrogen Bonds



Steiner



Nangia



Nangia

Boese



Howard

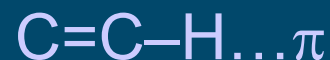


Howard



Viswamitra

Howard



Braga

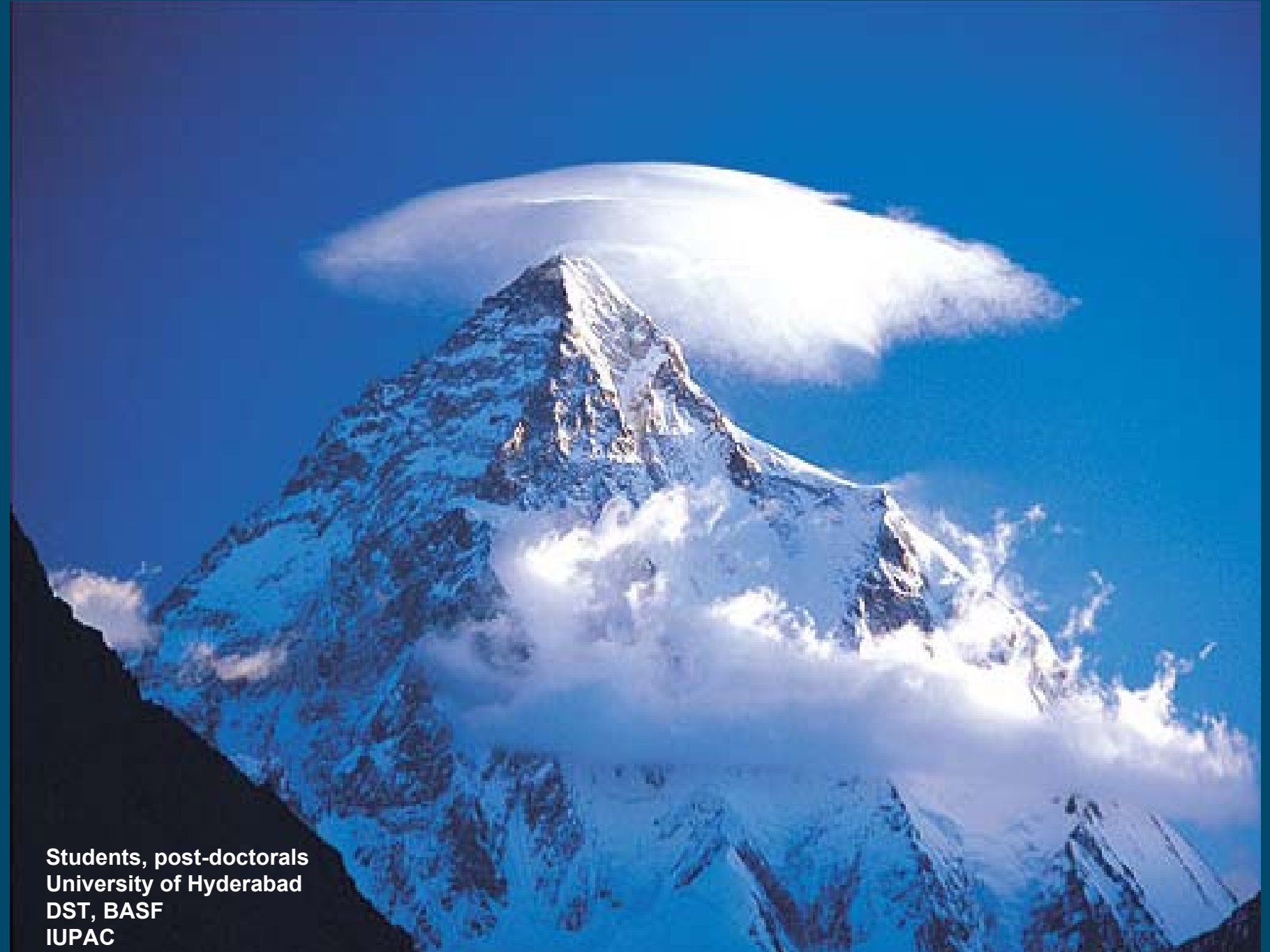
Agostic

Braga



Boese

Guru Row



Students, post-doctorals
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