Weak (or non-conventional) hydrogen bonds

1937. Glasstone. Cl₃C–H…O=CMe₂ complex
1939. Pauling definition
1967. Oki and Iwamura. O–H…π interactions (JACS)
1968. Donohue criticism of Sutor
1976. Leiserowitz review on carboxylic acids (Acta Cryst)
1982. Taylor–Kennard paper (JACS)
Weak hydrogen bonds

Bibliography


The weak hydrogen bond is an interaction X–H···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)
6.1. Weak Hydrogen bonds: C-H····O

![Graph showing strong and weak hydrogen bonds, X-H····O.](image)

An important difference in X····O distance (D) Å.
Weak Hydrogen bonds: C-H····O

\[ \text{Cl}_{3-n}R_nC-H\cdots O \]

Weak Hydrogen bonds: C-H····O

Angles, X–H...O
Weak Hydrogen bonds: C-H···X (X halogen)

Electronegativity and Hardness
Fluorine

C─H···F─C

Weak donor
Very weak acceptor

C─H···F─C Interactions in Fluorobenzenes


C─H···F Interactions in the Crystal Structures of Some Fluorobenzenes

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Weak Hydrogen bonds: C-H····X (X halogen)

C–H····F–C Hydrogen Bonds

All C, H, F compounds

Fluorobenzenes
Crystal Engineering

Supramolecular Synthones

Crystal Engineering

Some examples

Etter’s Packing motifs: bonds maximized

Hydrogen bonds are the strongest, thus they are maximized in packing. This gives rise to specific arrangements of the molecules, that can be called packing motifs (also called patterns).
Etter’s patterns grammar

Patterns can be used to describe crystal packing and differentiate polymorphic forms.
Crystal Engineering

Homomeric (self-complementary) hydrogen-bonding synthon

\[ R_2^2 \ (8) \]

Heteromeric (complementary) hydrogen-bonding synthon

\[ G_d \ a \ (n) \]

Graph set:

G = S (self) (intramolecular bonds); C (infinite chains); R (intermolecular rings);
D (discrete) (non-cyclic dimers and other finite structures)
n = number of atoms in a ring or the repeat unit in a chain
d = number of donors
a = number of acceptors
Crystal Engineering

Example

from octahedral metal complexes
catemeric hydrogen bond

3D considering the HB 
(NH⋅⋅⋅O) between the layers 
(coordinated water and amide)

\[ \text{[Ni(isonicotinamide)}_4\text{(H}_2\text{O)}_2\text{][ClO}_4\text{]}_2 \]

Intermolecular Interactions and Polymorphism
Definition Of Polymorphs

• Polymorphs are different crystalline forms of the same pure substance in which molecules have different arrangements and/or different molecular conformation.

• Polymorphic solids have different unit cells.

• Display different properties such as unit packing, thermodynamic, spectroscopic, and mechanical properties.
Intermolecular Interactions and Polymorphism

Polymorphs are unexpected

Polymorphs seems to be more common for compounds with:
- Low solubility in water
- Organic salts
- Formation of hydrates – for large molecules
- Organic solvates – neutral compounds with larger molecular weights
Intermolecular Interactions and Polymorphism

Solid state properties:

- Mechanical
- Superficial
- Spectroscopic
- Thermodynamic
- Kinetic
- Reactivity and/or Stability
Intermolecular Interactions and Polymorphism

Pharmaceutical and biopharmaceutical properties:

- Density
- Melting point
- Higroscopicity
- Electrical and optical properties
- Physical and chemical stability (Reactivity)
- Dissolution velocity
- Apparent Solubility

Drug product stability, dissolution and bioavailability
Quality, safety and efficacy of drug product
Intermolecular Interactions and Polymorphism

Ritonavir: AIDS drug

Ritonavir exhibits conformational polymorphism

Fig. 1. Photomicrographs for ritonavir polymorphs: (A) Form I, (B) Form II.
### Intermolecular Interactions and Polymorphism

**Ritonavir:** AIDS drug

**Solubility**

<table>
<thead>
<tr>
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<th>Ethanol/water</th>
<th>Form I</th>
<th>Form II</th>
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<tr>
<td><strong>Ethanol/water</strong></td>
<td>99/1</td>
<td>90/10</td>
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<tr>
<td><strong>Form I</strong></td>
<td>90mg/mL</td>
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<tr>
<td><strong>Form II</strong></td>
<td>19mg/mL</td>
<td>60</td>
<td>30</td>
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</table>
Intermolecular Interactions and solid forms

API (active pharmaceutical ingredient)
Intermolecular Interactions and solid forms

Definition of SALTS:
- Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal;
- An ionic or electrovalent crystalline solid.

Fluoxetine HCl, the active ingredient of Prozac
Co-crystals

**CO-CRYSTALS** (Multicomponent crystals):
“A cocrystal is a crystalline entity in which more than one molecular substance is incorporated into the unit cell.” Zaworotko, M. J. (2006) J. Pharm. Sci. 95(3), 499 – 516.

Pharmaceutical co-crystals

I component: API (active pharmaceutical ingredient)

II component: pharmacologically allowed
Pharmaceutical co-crystals

Co-crystals

Complementary hydrogen-bond functionalities

I component: API

II component: co-former

Acid Dimer

Amide Dimer

Acid pyridine heterosynthron

Acid amide heterosynthron

Crystal Growth & Design, 2009, 9, 1106
CO-CRYSTALS (Multicomponent crystals) new definition:
Co-crystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio.

Should it be deemed appropriate to keep solvates and hydrates separately classified from co-crystals?

Co-crystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.
Supercritical fluid (SCF) is a very good solvent; diffuse through solids like a gas and dissolve materials like a liquid: CO$_2$ is the most frequently used supercritical fluid for cocrystallization as solvent, as anti-solvent.

Extrusion is the process of converting an unprocessed material or mixture of materials that have been ground to a product of uniform shape and density by pressing them through a die under controlled conditions.
Intermolecular Interactions and solid forms

Cocrystals
(anhydrous/nonsolvated)
A:B
A = solid
B = solid

Hydrates/Solvates
A:B
A = solid
B = liquid

Salts
(anhydrous/nonsolvated)
A^+B^-
A = solid
B = generally solid or liquid
Co-crysals....Hydrates or Salts...an example

An interesting example is aminophylline, which is a compound composed of 2 mol of theophylline and 1 mol of ethylenediamine.
Co-crystals....Hydrates or Salts...an example

Co-crystals and salts in the scientific community are sometimes ambiguous

Depakote, Depakine

The crystal structure of escitalopram oxalate reveals the presence of
i) protonated escitalopram cations that hydrogen bond to
ii) oxalate dianions,
iii) water molecules, and
iv) oxalic acid

All molecules in the same crystal.
Co-crystals examples

API: Carbamazepina (CBZ)
Co-crystals..examples

I component: API (CBZ)  II component

-No hydrates
-Better bioavailability
Organic-Inorganic Ionic Co-crystals

Ionic co-crystals: neutral molecule and a salt

Organic-Inorganic ionic co-crystals: neutral molecule and inorganic salts (e.g. alkali and alkaline earth halides, sulfates, phosphates etc.)

co-crystal formed by benzoic acid and sodium benzoate

CrystEngComm, 2018, 20, 2212
Organic-Inorganic Ionic Co-crystals

Pharmaceutical applications

Improve lithium therapeutics of lithium salicylate and nicotinate by forming co-crystals with the amino acid L-proline
Mechanochemical treatment of urea with Mg$^{2+}$ and Ca$^{2+}$ salts results in the facile synthesis of ionic co-crystals as fertilizer materials, able to enhance nitrogen cycle sustainability by decreasing NH$_3$ emissions.