Supramolecular Synthesis on the Diffractometer: 
*in situ* Co-crystallization

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Supramolecular Synthesis on the Diffractometer

**synthesis in organic chemistry applies covalent bonds**

- Linkage by covalent bonds between same molecules corresponds to polymerization
- Linkage by covalent bonds between unlike molecules corresponds to organic synthesis

**supramolecular synthesis applies non-covalent bonds**

- Linkage by non-covalent bonds between same molecules corresponds to crystallization
- Linkage by non-covalent bonds between unlike molecules corresponds to co-crystallization

**What synthesis is in organic chemistry**

**Is co-crystallization in supramolecular chemistry**
What is a co-crystal?

**multicomponent crystals**

- salts, solvates (hydrates), clathrates, intercalates, mixed crystals, solid solutions, domain crystals, inclusion compounds, host-guest compounds, racemates(?), etc.

**stoichiometric**
- no salt!
- no solvent

**non-stoichiometric**
Can two solvents make a co-crystal or is it a super-solvate?

R. Boese, unpublished
Supramolecular Synthesis on the Diffractometer

Co-crystallization with small molecules deserves special considerations & techniques

• Selection of partners

Acetylene (mp -84 °C) is a very small and versatile molecule with proton donor (pKs = 25) and \( \pi \)-acceptor abilities.

Acetylene is the second smallest organic molecule!
- and the smallest to make co-crystals.

Acetylene is polymorphic.
Supramolecular Synthesis on the Diffractometer

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Cmca,
V = 209.1
Supramolecular Synthesis on the Diffractometer

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Pa3, V=227.54
Supramolecular Synthesis on the Diffractometer

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\[ \text{Diagram showing molecular interaction} \]
Supramolecular Synthesis on the Diffractometer

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![Supramolecular Structure](image)
Supramolecular Synthesis on the Diffractometer

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Supramolecular Synthesis on the Diffractometer

Co-crystallization with small molecules deserves special considerations & techniques

• Selection of partners, quadropolar interactions

\[ \delta\text{O} \quad \delta\text{O} \quad \delta\text{O} \]
\[ \text{O} \quad = \quad \text{C} \quad = \quad \text{O} \]

\[ \delta\text{H} \quad \delta\text{H} \quad \delta\text{H} \]
\[ \text{H} \quad -\quad -\quad \text{H} \]
Supramolecular Synthesis on the Diffractometer

Co-crystallization with small molecules deserves special considerations & techniques

• Selection of partners

\[ \text{O} \equiv \text{C} \equiv \text{O} \]

\[ \text{H} \equiv \text{H} \]

\[ \text{O} \equiv \text{C} \equiv \text{O} \]
Supramolecular Synthesis on the Diffractometer

Co-crystallization with small molecules deserves special considerations & techniques

- Selection of partners
Supramolecular Synthesis on the Diffractometer

A thermodynamic picture from the viewpoint of a crystallographer

Lattice energy

acetylene

C₂H₂ · CO₂

CO₂
A thermodynamic picture from the viewpoint of a crystallographer

Supramolecular Synthesis on the Diffractometer

Lattice energy

acetylene

\[ \text{C}_2\text{H}_2 \cdot \text{CO}_2 \]

\[ \frac{1}{2} \]

\[ \frac{1}{2} \]
M.T. Kirchner, D. Bläser, R. Boese
Acetylene – Benzene (1:1)

R. Boese, T. Clark, A. Gavezzotti
Acetylene – Benzene (1:1)

Titan – one of Saturn’s moons
taken from Cassini spacecraft (started 1997, arrived 2004)
Acetylene – Benzene (1:1)

Comparison of size – Earth – Titan - Moon
Acetylene – Benzene (1:1)

*Huygens shuttle (2005)* – atmosphere of Titan
Acetylene – Benzene (1:1)

‘lake‘ Ontariolacus (mare), the shores – and dunes, Probably consisting of co-crystals with acetylene

Temperature ca. 100 K

Dunes up to 300 m high and several hundred km long

Resembling the situation on Earth ca. 5 billion years ago
Acetylene – Benzene (1:1)

’lake‘ Ontariolacus (mare), the shores – and dunes,
Probably consiting of cocrystals with acetylene

Temperature
c.a. 100 K

Mountains
existing of
methan
hydrates

We were not able so far to cocrystallize
hydrogen cyanide and acetylene:

HCN and HCCH
Acetylene – Benzene (1:1)

Acetylene – Perfluorobenzene (1:2)

R. Boese, T. Clark, A. Gavezzotti

unpublished
Both co-crystals can be considered as sections from the acetylene orthorhombic lattice, starting with chains (left) or clusters of three molecules (right).
The archetype of organic co-crystals or supramolecular synthesis!

Acetylene – Ammonia (1:1)

The ammonia hydrogen atoms are disordered, so that an alternating coordination is realized as shown in the drawing.

R. Boese, D. Bläser, and G. Jansen

*J. Am. Chem. Soc.*, 2009, 131 (6), 2104-2106
The archetype of organic co-crystals or supramolecular synthesis!

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R. Boese, D. Bläser, and G. Jansen
The archetype of organic co-crystals or supramolecular synthesis!

Acetylene – Ammonia (1:1)

R. Boese, D. Bläser, and G. Jansen
Acetylene - Acetonitrile (2:1)

Acetylene is one-fold coordinated, nitrogen is four-fold coordinated

unpublished
acetylene + 2,5-dimethylpyrazine

M.T. Kirchner, R. Boese, A. Gehrke, and D. Bläser

acetylene - formaldehyde

acetylene - acetone

unpublished

acetylene - DMSO

acetylene - DMSO

acetylene - dioxane

Oxygen is almost trigonal surrounded

unpublished
Acetylene is one-fold coordinated, the methanol molecules resemble the Form II lattice, with acetylene squeezed into the original lattice.

M.T. Kirchner, D. Das, and R. Boese
Acetylene - Phenol

Acetylene molecules disordered

unpublished
Acetylene + Water

Gashydrates

• Methane + Water
• Temperature: below 8 °C
• pressure above 20 bar

M.T. Kirchner, R. Boese, W.E. Billups, and L.R. Norman
Gashydrates

‘burning ice’
Another example

Formic acid - Formamide

Most common hetero-synthon for co-crystals of APIs
Another example
formic acid - formamide

Two complexes with each two independent molecules

Common synthon for amides

Uncommon acid-amide synthon

unpublished
Co-crystals

take-home message
Co-crystals of small molecules

- secondary contacts often dominate the packing
- C-H⋯π is very flexible
- two- or three-fold coordinated nitrogen can easily accept three or more hydrogen atoms
- the lone pair electron density of nitrogen is rather diffuse
- the lone pairs at the carbonyl group do not direct hydrogen atoms; more than two hydrogen bridges are possible

Co-crystals of small molecules are difficult to predict!
in situ Co-crystallization

Co-crystallization (supramolecular synthesis) can be performed by various means:

- Co-crystallization from solution
- Co-grinding
- Solvent drop co-grinding
- Co-sublimation
- Co-melting
Co-crystallization

Short version:

- Fill capillary
- Mount it
- Switch on LT-device
- Grow crystal
- Check crystal quality
- Collect data
- Solve structure
Co-crystallization

with small molecules deserves special considerations & techniques

- Selection of partners (1)
- Mixing of liquids in appropriate ratios (2)
- Mixing of gases by co-condensation (3)
- Transfer of capillaries to the diffractometer (4)
- Cooling and finding appropriate crystallization conditions (5)
- Growing crystals preferably by IR-laser (OHCD) (6)
- Checking crystal quality by X-ray scanning (7)
- Selection of reflections belonging to the same reciprocal lattice (8)
- Determination of lattice constants (9)
- If attributed to that of the neat starting components, overcoming frustration (10)
- Start again with one of point 1-9
- As an alternative install a Raman Spectrometer
Co-crystallization

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**in situ** Crystallization Techniques:

What is it?

What is it for?

What did we do with it?

Crystallization on the diffractometer in capillaries (at low temperatures)

Why is simple cooling less successful for growth of single crystals?
"in situ" Crystallization Techniques:

we need to heat!

T

T_melt

critical size

metastable region

critical size

time

V_{crystal growth}

V_{nucleation}
**in situ** Crystallization Techniques:

we need to heat!

- Distortion of cooling process
- Controlled up and down with cooling device
  - Lipscomb, 1965
- Wire loop heater
  - Struchkov, 1977
- Heated plate
  - Simon, 1976
- Heating with IR light from a halogen lamp
  - Mootz & Boese, 1985
- Heating with IR light from a CO₂-laser
  - Boese, 1992
Optical Heating and Crystallization Device

LT-device

CO₂-laser

laser diode

ZnSe-lens

rotating mirror

mirror

O.H.C.D.
in situ  Crystallization Techniques:

Why with IR-laser?

Advantages:
- growing from bottom to top
- optical observation
- no mechanical stress for capillary
- control on heat
- control on position
- high temperature gradient

Boese, 1992
undistorted crystallization zone
undistorted crystallization zone
in situ Crystallization Techniques:

What is it?

What is it for?

What did we do with it?

- low melting compounds
- compounds with low phase transitions
- compounds which decompose without solvent
- crystallization under increased pressure (gases)
- cocrystallization under increased pressure
- gas clathrates
sample preparation
sample preparation
sample preparation
Diffractometer
Diffractometer with Raman spectrometer

- Cooling
- Capillary
- Detector
- X-ray beam
- TV camera
- Observation microscope
- CO₂-laser
Diffractometer with Raman spectrometer
the end