Chemical Crystallography and Structural Chemistry

VO 270063-1

Lecture № 1 — 2nd March 2023

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Contents

1 Administrativa

Contact Details

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- personal homepage: `https://homepage.univie.ac.at/tim.gruene`

Course Details

- Place: Seminarraum 3
- Time: 90 minutes lecture Thursdays, 10:15am – 11:45am
- every third lecture will be an exercise in groups

Course Details

2rd	March	Lecture № 1	9th	March	Lecture № 2
16th	March	Lecture № 3	23th	March	Exercise № 1
30st	March	Lecture № 4	20th	April	Lecture № 5
27th	April	Exercise № 2	4th	May	Lecture № 6
11th	May	Exercise № 3	25th	May	Lecture № 7
1st	June	**no lecture**	15th	June	Lecture № 8
22nd	June	Exercise № 4	29th	June	Lecture № 9

- You are welcome to interrupt at any time and ask questions or comment
- Lecture notes will be made available online
- `https://homepage.univie.ac.at/tim.gruene/teaching/chemcryst`

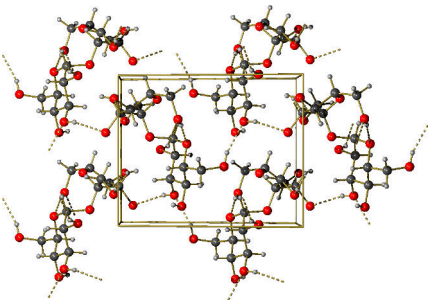
Examination

There will be an **oral** exam with individual appointments.

Course Objective

Chemical Crystallography

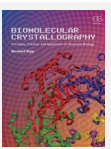
Understanding the value of a chemical structure in chemical research



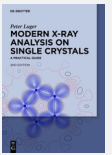
Crystal structure of sucrose, with hydrogen bonds

- what do we learn from a crystal structure?
- what are the **limits** of crystallography
- how can we judge the quality of a crystal structure — are the conclusions justified?

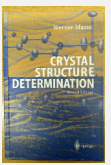
2 Resources: Literature for Crystallography



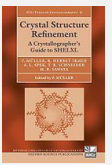
Rupp [1]



Luger [2]

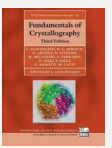


Massa [3]



Muller et al. [4]

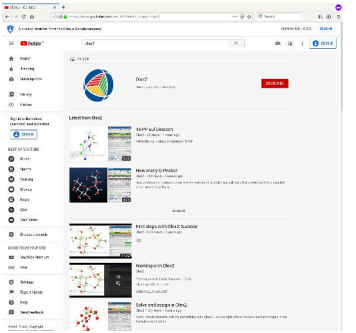
various [5]



Giacovazzo [6]

Online Resources

http://shelx.uni-goettingen.de



Olex2 *etc* on youtube

Journals for Chemical Crystallography

- Acta Crystallographica A–F `journals.iucr.org`: International Union of Crystallography
- Zeitschrift für Kristallographie, `https://www.degruyter.com/journal/key/ZKRI/html`
- Angewandte Chemie Int. Ed. `http://www.angewandte.org`, GDCh
- JACS, Journal of the American Chemical Society `https://pubs.acs.org/journal/jacsat`

and most other journals for chemistry

Crystallographic databases

Most journals require the deposition of structural data structures at publicly available data bases. Crystallography has long been a pioneering discipline of open access data.

Cambridge Structural Database

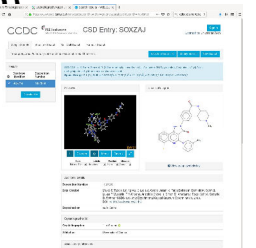
Crystallography Open Database

Inorganic Crystal Structure Database

Protein Data Bank

CRYSTMET ®

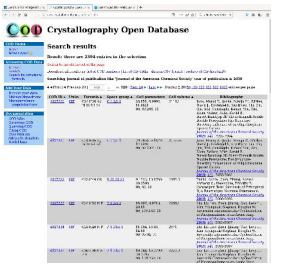
Cambridge Structural Database (CSD)



- `http://www.ccdc.cam.ac.uk`
- founded 1965
- Single crystal and powder diffraction
- organic and metal-organic compounds
- $> 1,000,000$ entries, $\approx 50,000$/year
- X-ray, neutron, and electron diffraction
- "The world repository of small molecule crystal structures"

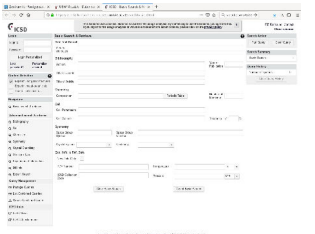
Crystallography Open Database (COD)

- `http://www.crystallography.net`
- Local version available free of charge
- Can be browsed (by journal, by year,...)
- Organic and inorganic structures (minerals)
- "Open-access collection of crystal structures of organic, inorganic, metal-organics compounds and minerals, excluding biopolymers."
- All data from IUCr journals, and from American Mineralogist CSD
- $> 450,000$ entries, $\approx 50,000$/year



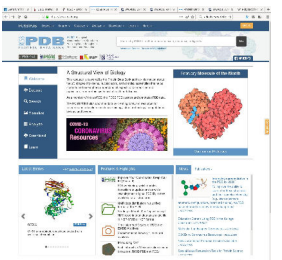
Inorganic Crystal Structure Database (ICSD)

- `https://icsd.fiz-karlsruhe.de/`
- inorganic and intermetallic structures
- only licensed access
- $> 215,000$ entries



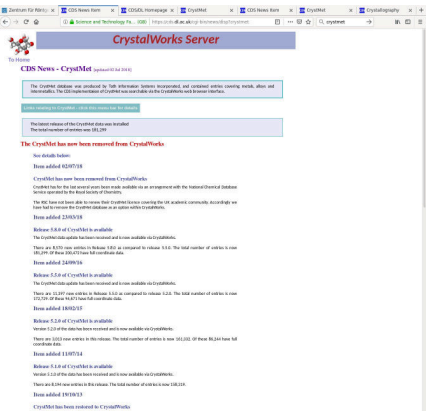
Protein Data Bank (PDB)

- `https://www.pdb.org`
- Search from
  - `www.rcsb.org`
  - `https://www.ebi.ac.uk/pdbe`
  - `https://pdbj.org` (Japanese)
- polypeptides (proteins) and polysaccharides (nucleic acids)
- Crystal structures, NMR structures, EM structures
- Since 2007: data **must** be submitted along with coordinates
- $> 185,000$ structures



CrystMET

- `https://cds.dl.ac.uk/cds/datasets/crys/mdf/llmdf.html`
- Crystal structure data for metals and alloys
- licensed access only



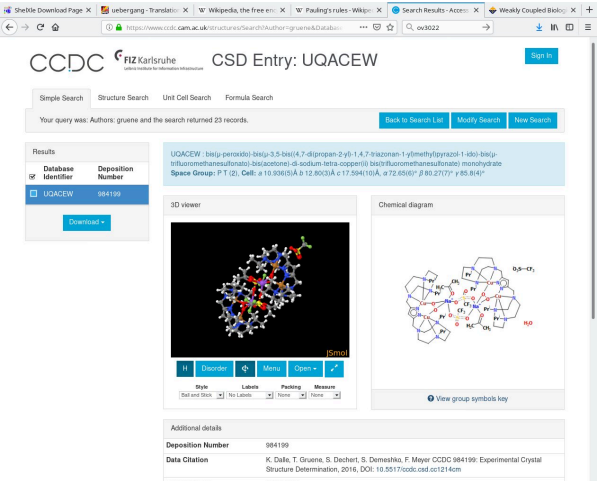
3 Structure, Data, Data Formats, and Visualisation Software

Structural Data: the CIF-file

- Main file format for published structures
- available from CSD, COD, ICSD, journal web-sites, etc
- pure text file
- Can and should contain both structure information (coordinates) and experimental data (hkl-file)

Example: CSD entry UQACEW, CIF-file: 984199.cif

Dalle et al. [7]

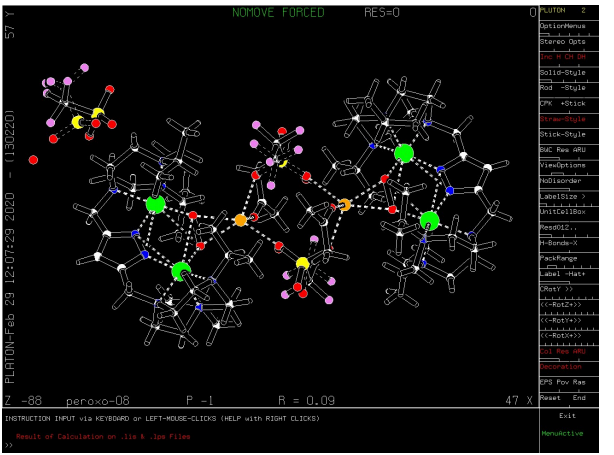


Structural Data: the RES-file

- RES/INS text file: chemical structure in computer language
- developed by George Sheldrick (SHELX programs), late 1960s
- still the most sophisticated format for chemical compounds
- "work" format: refinement and model building

Platon: Validation, format conversion

http://www.cryst.chem.uu.nl/spek/platon

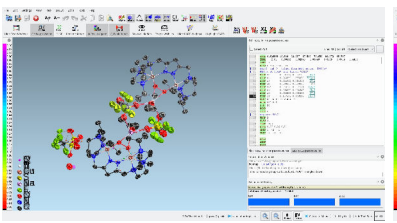


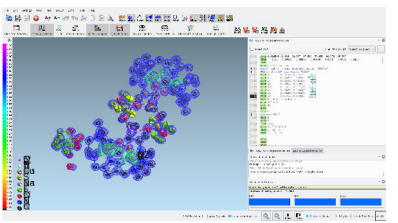
→ 984199_sx.ins and 984199_sx.hkl

ShelXle: Visualisation and Modelling

https://www.shelxle.org/shelx

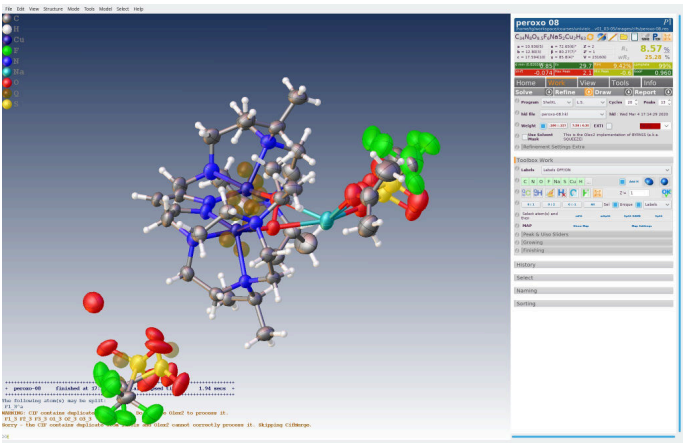
```
#> shredcif 984199.cif
peroxo-08.res extracted, checksum O.K.
peroxo-08.hkl extracted, checksum O.K.
```





Olex2: Refinement, Visualisation and Modelling

https://www.olexsys.org/



4 Crystals and Crystal Growth

Crystal Types

- Crystal = Solid state compound with regular composition
- interactions responsible for crystallisation
  1. ionic bond
  2. metallic bond
  3. covalent bond
  4. van-der-Waals interaction
- often not a clear cut between these types
- crystallography can characterise bond types

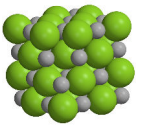
Ionic Crystals

- Composed of anions (negative charge) and cations (positive charge)
- Geometry according to Pauling's rules [8]

Simple example: $NaCl$:

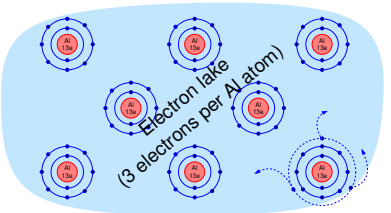
- cubic lattice
- energy difference $Na + Cl \rightarrow Na^+ + Cl^-$: $-6.4eV$

Chrome alum,
i.e. Chromium(III) potassium sulfate
$KCr(SO_4)_2$



cubic lattice of $NaCl$

Metallic Crystals



various forms of iron [9]

Valence electrons dissociate from individual atoms and form an **electron lake** (conduction band)

→ electrical conductivity

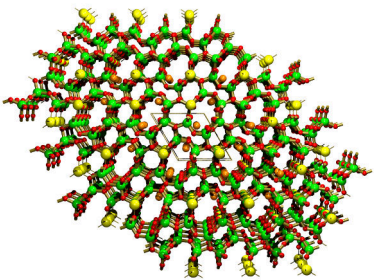
→ thermal conductivity (copper)

→ shiny surface

→ plasticity

Covalent bond

- Two atoms share an electron to reach noble gas configuration.
- Examples: zeolites, MOFs, diamond, quartz
- $\Rightarrow$ high stability
- The entire crystal is a single molecule

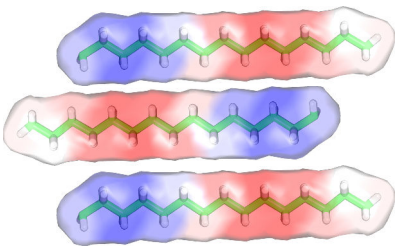


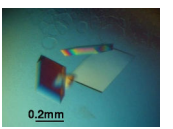
Feldspar Albite $NaAlSi_3O_8$ [10]

Albite crystals [11]

van-der-Waals interaction

- typical for organic and macromolecular compounds
- stochastic charge distribution (dipole moments) causes mutual attraction between molecules
- weak ("soft") interaction





protein crystals in mother liquor

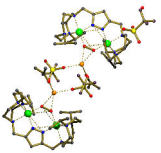
Crystals in Crystallography

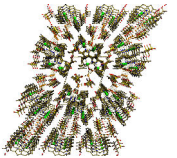
Definition *International Union of Crystallography*:

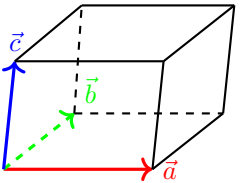
> "A material is a crystal if it has essentially a sharp diffraction pattern."

Crystal in the context of this lecture:
A crystal is composed of a chemical compounds that repeats periodically in all three directions.

Crystals in Crystallography





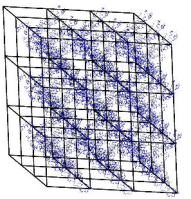


- The periodicity results in the diffraction pattern of the crystal
- The periodicity acts like a signal amplifier
- The smallest unit of the periodicity is an inclined box. It is called the **unit cell of the crystal**.

Crystal Growth

Crystals are

1. solid state materials
2. highly ordered, *i.e.* their entropy is very low compared to amorphous material



Especially for large molecules: weak interaction, *i.e.* low energy gain through crystallisation ⇒ Crystal growth can be difficult

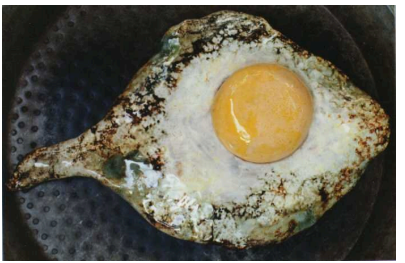
Crystal Growth

Organic compounds: Precipitation from solution
Some means for precipitation (*cf.* LeChatelier's principle)

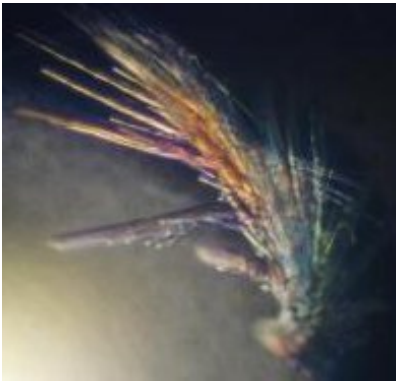
- Changes in temperature or pressure
  - sugar: better soluble in warm water
- precipitant
  - sugar: ethanol
  - high salt concentrations

Metals, alloys, and salts are often crystallised from melt. See e.g. Leibniz-Institut für Kristallzüchtung, `https://www.ikz-berlin.de`

Preliminaries for structure determination



need for crystals(instead of amorphous precipitation)

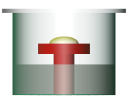


need for single crystals

Examples for Crystallisation

1. Dissolve in Tetrahydrofuran (THF) in glass vial
2. Cover with parafilm: slow evaporation of THF
3. Store at $-80°C$

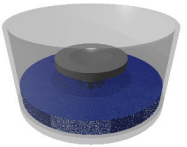
1. Dissolve in organic solvent (EtOH, Isopropanol, ...)
2. Store sealed on water reservoir
3. Uptake of water (vapour) reduces solubility of compound



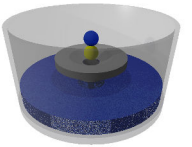
Twinned structures (cf. end of term) can often be improved with elevated temperature during crystal growth (30-40°C).

(see *e.g.* W. Massa, *Crystal Structure Determination*, Ch. 7)

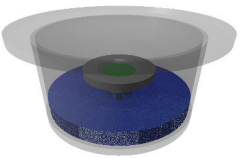
Crystallisation with vapour diffusion



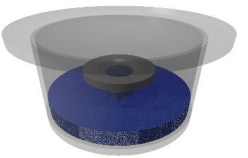
Well with mother liquor (ML) with precipitant



Mix ML with compound solution (V_{drop}=1 µl+1 µl)



Seal well (V_{drop}=2 µl)



After equilibration: V_{drop}=1 µl

Crystallisation with vapour diffusion

1. Compound dissolved in 100 % isopropanol, concentration c
2. Mother liquor: 90 % isopropanol, 10 % water

Setup procedure

	Volume	H_2O	i-PrOH	conc^n	soluble?
before	1 µl	0 %	100 %	c	yes
mixing	2 µl	5 %	95 %	$c/2$	yes
equilibration	1 µl	10 %	90 %	c	no

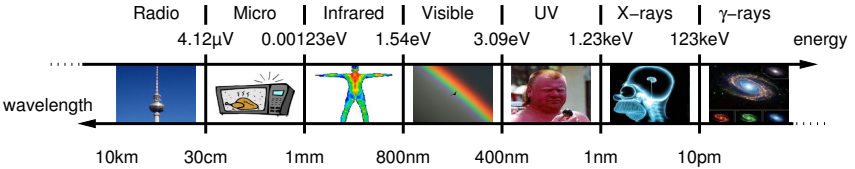
Remarks

- composition of mother liquor fine tunes end state
- insoluble compound precipitates
- slow diffusion enhances crystallization

5 X-rays and Diffraction

X-rays as electromagnetic radiation

X-rays are one type electromagnetic radiation — like visible light, UV-radiation, or radio waves



- Energy E and wavelength λ are equivalent ($E = h\frac{c}{\lambda} = 12.4keV\text{Å}/\lambda$):
- Long wavelength $\lambda \leftrightarrow$ low energy E.
- Short wavelength $\lambda \leftrightarrow$ high Energie E.

X-rays as electromagnetic radiation

- Typical wavelength range for structure determination: 0.5-2 Å (24.8 - 6.2 keV).
- Inhouse X-ray instruments:

  CuK_α: 1.54 Å $\leftrightarrow$ 8.0 keV
  MoK_α: 0.71 Å $\leftrightarrow$ 17.3 keV
  AgK_α: 0.56 Å $\leftrightarrow$ 22.1 keV
  WK_α: 0.21 Å $\leftrightarrow$ 59.3 keV (medical applications)

- 1 Å $= 10^{-10}$ m $= 100$ pm

Generation of X-rays

1. **X-ray fluorescence** (mainly laboratory sources) electron beam at specific energy hits metal surface (Cu or Mo). This creates
   a) Bremsstrahlung (background)
   b) X-ray fluorescence

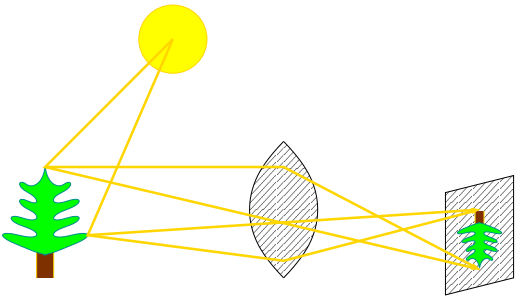
   Examples: rotating anode, liquid jet anode
2. **Synchrotron radiation** Acceleration of electron bunches in a magnetic field

Why X-rays?

Atom distances of molecules about 1–2 Å: required resolution d

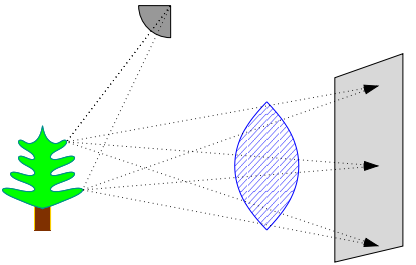
Optical instruments are limited in resolution to $d > \lambda/2$ (later: derivation *via* Bragg's law)

Optics and Imaging (Microscope / Telescope)



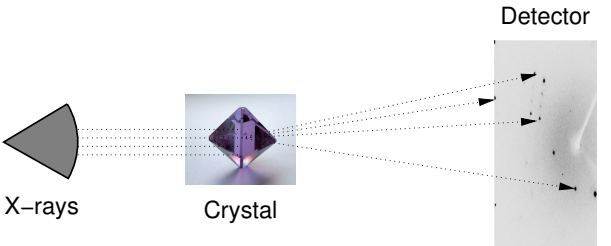
Objects scatter light. In order to see the object, the scattered light must be focused by **at least** one lens

X-ray Scattering



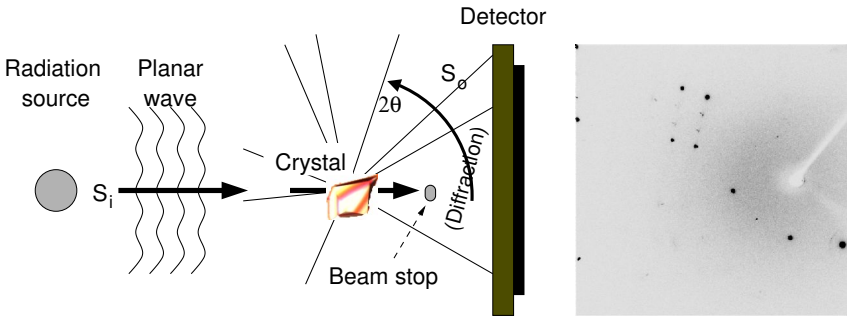
X-ray lenses do not exist: It is not possible to create a direct image of an object with X-rays.

X-ray Scattering by Crystals: Diffraction



The periodicity of the crystal results in a focussing of the scattered X-rays into **discrete spots**. The spots (reflections) can be measured without lenses. The crystal acts like a signal amplifier.

The X-ray Diffraction Experiment

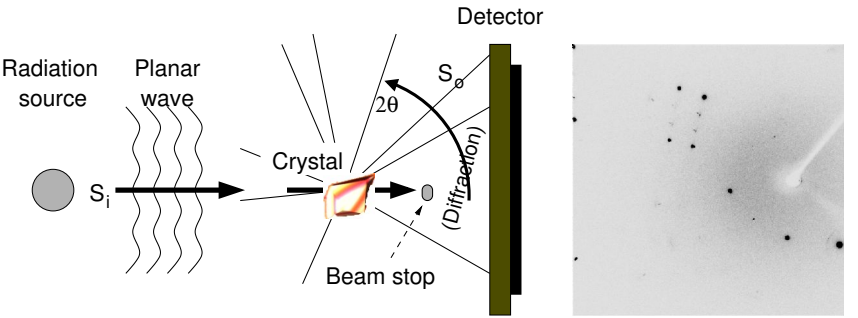


The crystal diffracts X-rays. This creates a **diffraction pattern** recorded by the detector.

The reflection spots are not images of the atoms

Typical laboratory X-ray Diffractometer

Data collection experiment



Reflections are data point. Each one contains different information. In order to collect as many data points as possible:

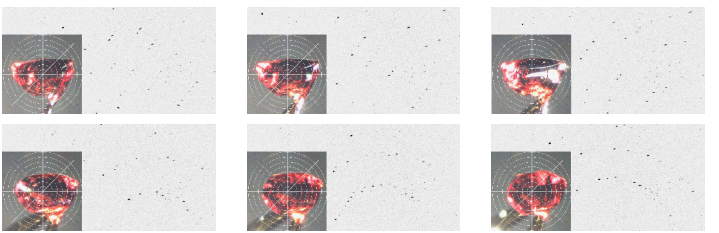
1. Rotation of the crystal (about one of three different axes, called ϕ–, ω–, and χ–circles)).
2. Rotation of the detector around the crystal, called 2θ–circle. This is parallel to the ω–circle).

The Data Set

The reflections can be described as three dimensional **reciprocal lattice**. The two dimensional detector records an intersection of the three dimensional lattice.

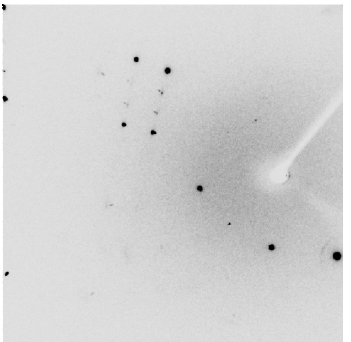
The full experiment results in a **data set**.

One data set consists of several runs (1–20). One run is the rotation of the crystal about a single axis. Per run, 180–2,000 **frames** are recorded. One frame corresponds typically to 0.1° – 0.5° rotation of the crystal.



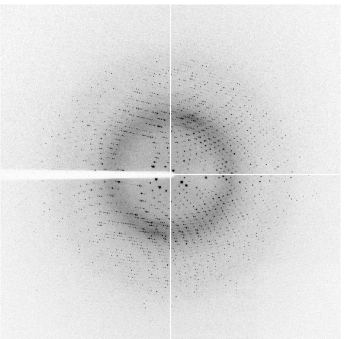
courtesy Olivera Cvetkovic (AK Hultzsch)

Examples of Data Frames



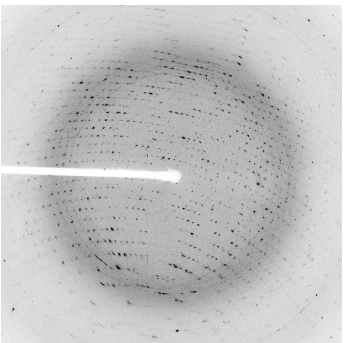
- Small molecule, unit cell dimensions: $a = 10.56$Å, $b = 11.64$Å, $c = 16.14$Å, $\alpha = \beta = \gamma = 90°$
- Small unit cell: $\Rightarrow$ few reflections
- Reflections beyond edge of detector: $\rightarrow 2\theta$ offset of detector necessary
- black reflections = data; grey regions: noise, neglectable

Examples of Data Frames



- Macromolecule. unit cell dimensions: $a = 92.6$Å, $b = 92.6$Å, $c = 128.9$Å, $\alpha = \beta = 90°, \gamma = 120°$
- Many more reflections
- Reflexes form patterns (lunes, "Kugeldreiecke")
- Intensity reduces towards edge of detector

Examples of Data Frames



- Macromolecule. unit cell dimensions: $a = 111.7$Å, $b = 80.5$Å, $c = 70.3$Å, $\alpha = \gamma = 90°, \beta = 94.2°$
- smeared reflexes
- ice rings (formed during measurement, or due to poor shock-freezing conditions)
- Closer look: small spots between "patterns": twinned crystal, not a single crystal.

6 Objectives of a Crystal Structure

Why Crystal Structure Determination?

The Structure provides atom coordinates: arrangement of elements in 3D space

Organic Chemistry:

- Success (or failure) of synthesis
- Determination of absolute structure
- Polymorphism: different crystal packing of the same compound

Inorganic Chemistry:

- Bonding geometry, coordination geometry (of metals ...)
- Polymorphism: different crystal packing of the same compound
- Space group determination: space group symmetry relates to electro-optical properties (thermal expansion, piezo-material, ...)

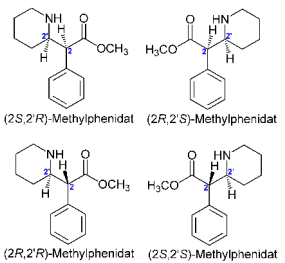
Comparison with other Structural Methods

NMR : chemical environment, sum formula. Not absolute structure

Rotational spectroscopy: (and gas phase electron diffraction): bond distances (**much more precise** than crystal structure)

Crystallography : Virtually no size limit (protein complexes $>$ 1.5 MDa; differentiation of element types

Examples: Absolute structure and degree of purity [12]

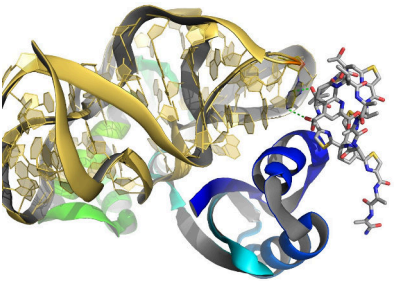


- Methylphenidate (*alias* Ritalin): medication to treat Attention Deficit Hyperactivity Disorder (ADHD).
- Two chiral centres, *four* stereoisomers
- Typical: only one stereoisomer with desired effect.
- Remaining stereoisomers: side effects

`http://de.wikipedia.org/wiki/Methylphenidat`

The crystal structure is the only method to determine the absolute structure and the degree of purity of mixtures.

Structure based Drug Development



The antibiotic *Thiostrepton* together with its target DNA. Dr. K. Pröpper.

Knowledge of structure of ligand and target:

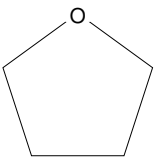
- Improvement of chemical interaction
- Improvement of shape / surface: Functionality and access to cell or nucleus.
- Uptake in body (cf. `http://de.wikipedia.org/wiki/Insulinpräparat`)

7 Crystal Diffraction: Why do crystals produce reflections?

Independent Atom Model (IAM)

Crystal structure determination is based on the **independent atom model** (IAM):

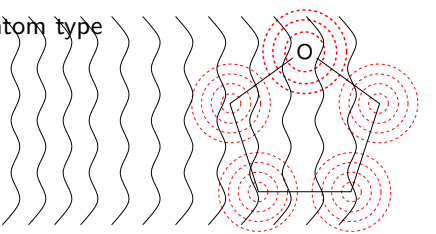
- the molecule consists of spherical atoms



Independent Atom Model (IAM)

Crystal structure determination is based on the **independent atom model** (IAM):

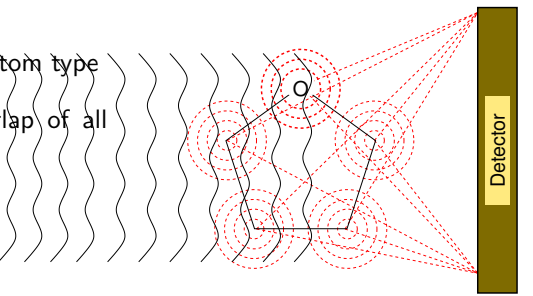
- the molecule consists of spherical atoms
- upon irradiation, each atom re-emits a small spherical wave independently from the others
- the strength depends on the atom type



Independent Atom Model (IAM)

Crystal structure determination is based on the **independent atom model** (IAM):

- the molecule consists of spherical atoms
- upon irradiation, each atom re-emits a small spherical wave independently from the others
- the strength depends on the atom type
- the detector records the overlap of all (tiny) waves

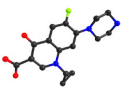


Independent Atom Model (IAM)

- every atom emits a tiny signal
- individual molecules are too weak to detect
- the crystal **amplifies** the signal

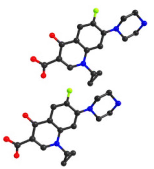
To understand, we introduce the **unit cell** and the **crystal lattice**.

The Unit Cell



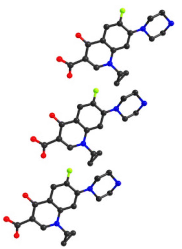
"Periodicity of the unit cell"?

The Unit Cell



"Periodicity of the unit cell"?

The Unit Cell



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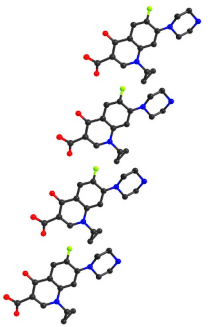

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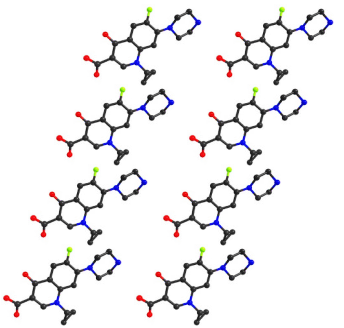
The Unit Cell



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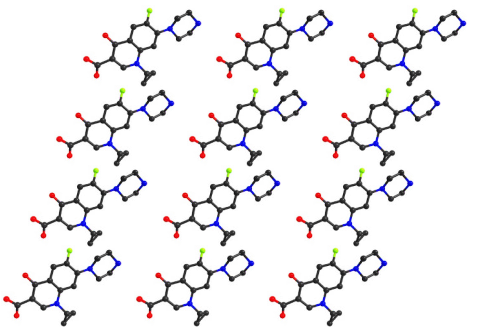
The Unit Cell



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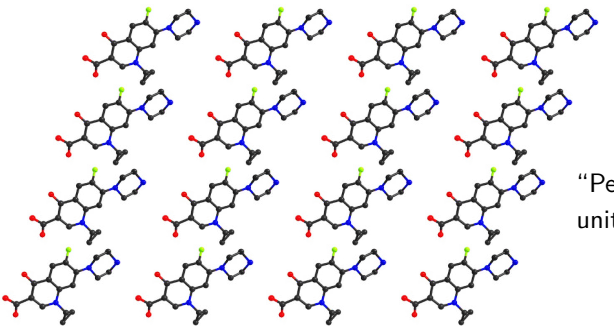
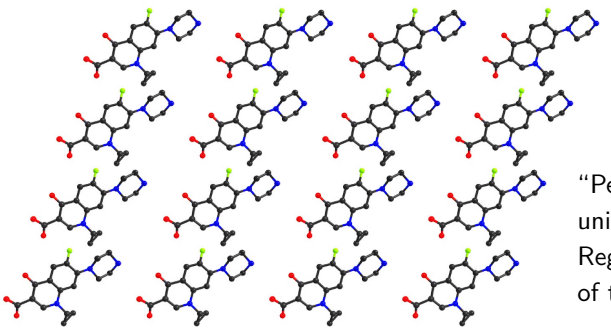
The Unit Cell



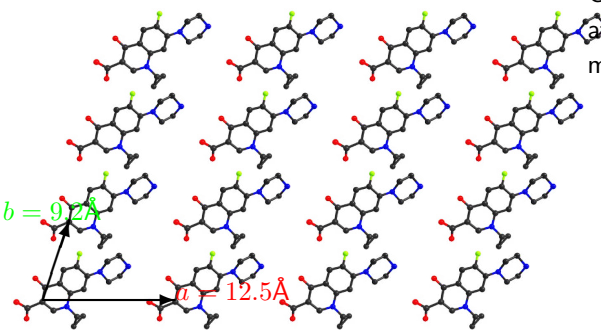
"Periodicity of the unit cell"?

The Unit Cell



"Periodicity of the unit cell":
Regular repetition of the molecule

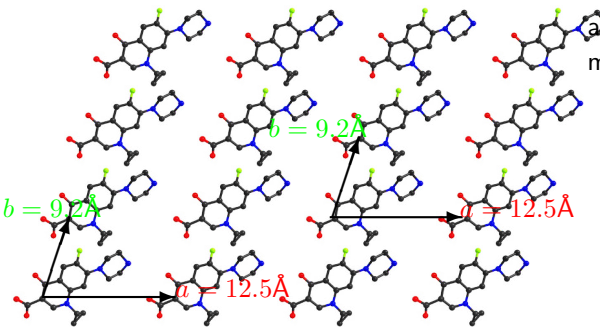
The Unit Cell



Periodicity of the unit cell:

Connect two equivalent atoms in two equivalent molecules

The Unit Cell

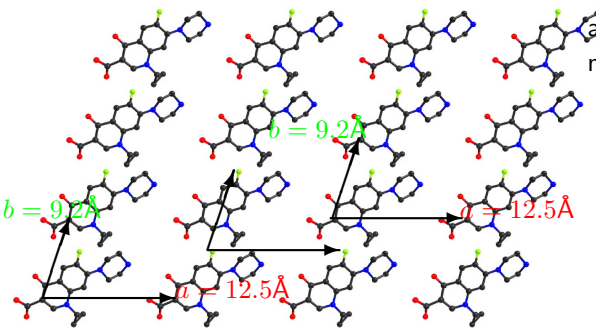


Periodicity of the unit cell:

Connect two equivalent atoms in two equivalent molecules

- connection can be shifted throughout the crystal

The Unit Cell

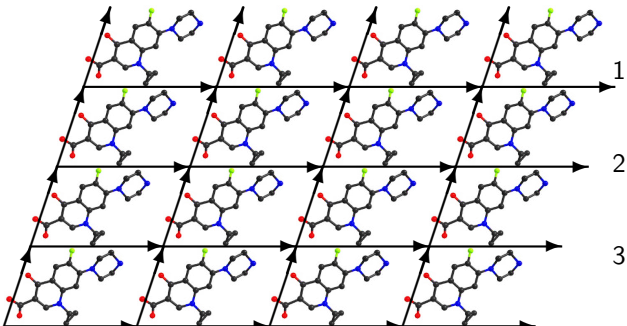


Periodicity of the unit cell:

Connect two equivalent atoms in two equivalent molecules

- connection can be shifted throughout the crystal
- can be any atom

The Unit Cell



1. select arbitrary reference point
2. connect to next equivalent point
3. in all three directions

This results in the **crystal lattice**. The smallest parallelepiped (smallest box) forms the **unit cell** of the crystal.

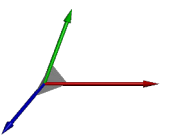
The Unit Cell

A three-dimensional box requires six parameters:

- unit cell constants a, b, c (edge lengths)
- angles between the edges

$$\alpha = \angle(b, c) \qquad \beta = \angle(c, a) \qquad \gamma = \angle(a, b)$$

- constants and angles are independent from the orientation of the crystal
- when written as vectors $\vec{a}$, $\vec{b}$, $\vec{c}$, they also describe the orientation of the crystal with respect to the instrument.



The convention a: red, b: green, c: blue comes from computer graphics, where colours are described as *rgb*.

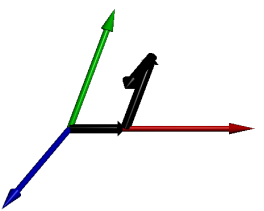
Fractional Coordinates

Atom coordinates are often described with *fractional coordinates*.
Every position in the crystal has unique coordinates (x, y, z)

$$x * \vec{a} + y * \vec{b} + z * \vec{c}$$

(x, y, z) are called the **fractional coordinates** of this position.
For any position *inside* the unit cell:

$$0 \leq x, y, z \leq 1.$$



The position (0.3, 0.6, 0.5).

Fractional Coordinates

Atom coordinates are often described with *fractional coordinates*.
Every position in the crystal has unique coordinates (x, y, z)

$$x * \vec{a} + y * \vec{b} + z * \vec{c}$$

(x, y, z) are called the **fractional coordinates** of this position.
For any position *inside* the unit cell:

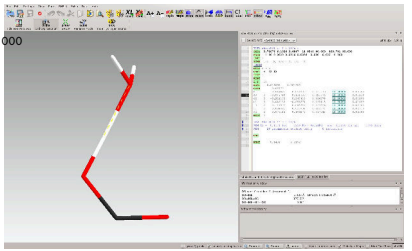
$$0 \leq x, y, z \leq 1.$$

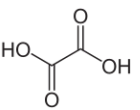
Fraction coordinates facilitate the use of symmetry operators. They are normally used in crystallographic computing.

- SHELXL ins-files always use fractional coordinates.
- Macromolecular PDB-files use orthogonal coordinates.

Example: ins-file for Oxalic Acid

```
TITL Oxalic Acid in P 1 21/n 1
CELL   0.71073 6.1026 3.4867  11.9540 90.000  105.791 90.000
ZERR    4.00 0.0020 0.0016 0.0036  0.000  0.027  0.000
LATT 1
SYMM  1/2 - X, 1/2 + Y, 1/2 - Z
SFAC C H O
UNIT  4  12 12
LIST 6
RIGU
L.S.  10
WGHT  0.0180  1.3244
FVAR   0.09892
C1  1 -0.045033  0.058931  0.051985  11.00000  0.00919
O3  3 -0.048452  0.131974  0.321439  11.00000  0.01180
O2  3 -0.221285  0.243842  0.036277  11.00000  0.01151
O1  3  0.085162 -0.055871  0.150165  11.00000  0.01216
H3  2 -0.142238 -0.045413  0.350385  11.00000  0.02677
H1  2  0.023619  0.022591  0.223012  11.00000  0.02363
H2  2  0.079486  0.197530  0.387391  11.00000  0.02464
HKLF  4
END
```



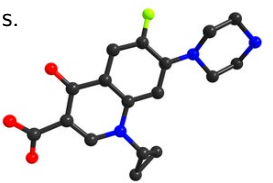


Summary: The Unit Cell

The crystal structure is described by

1. the unit cell parameters $a, b, c, \alpha, \beta, \gamma$
2. positions and element types of the atoms inside the unit cell

The whole crystal is the result of integer translations (= shifts without gaps or overlaps) of the unit cell in all three directions.



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