Chemical Crystallography and Structural Chemistry

(VO 270287)

Lecture 10

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Previous Lecture

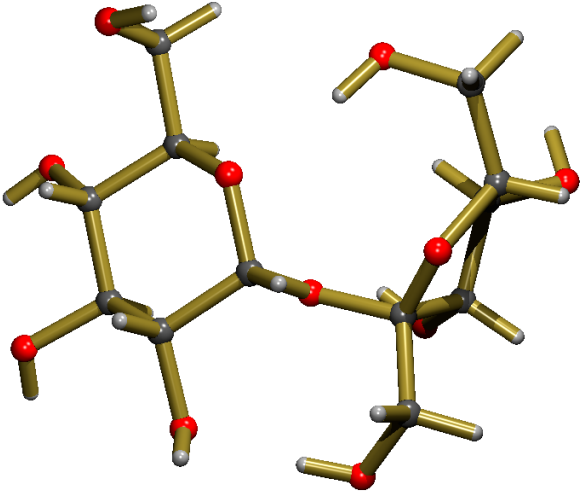
1. Twinning
2. types of twinning
3. how to deal with twinning
4. warning signs of twinning

Today's Lecture

1. Absolute structure / Chirality
   - anomalous signal: breakdown of Friedel's law
   - Flack-Parameter, Parsons' Q-value
   - heavy atom method
2. Charge density refinement
   - limits of the independent atom model
   - multipole expansion
   - chemical features of electron density

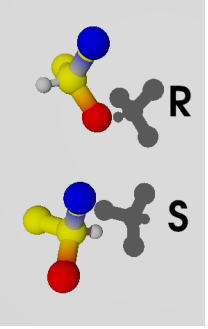
Absolute structure / chirality

Sucrose



Sucrose, CSD Code MELKIA, DOI 10.1021/acs.cgd.7b01526

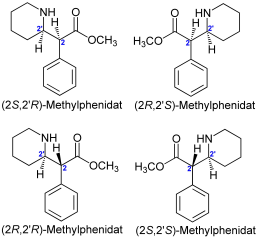
Cahn-Ingold-Prelog *R*/*S*-System



- Heavy atoms arranged around chiral centre with lightest one pointing towards viewer
- Three atoms arranged heavy to light anti-clockwise: *R*
- Three atoms arranged heavy to light clock-wise: *S*

Symptoms of chirality

- chiral compounds are optically active: turn the plane of plane-polarised light
- Usually only one stereoisomer pharmaceutically active. Others add to side effects. (*cf.* E. J. Ariëns:*Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology*, European Journal of Clinical Pharmacology, **26** (1984), pp. 663–668).



Technical blindness to chirality

- Most technologies are "blind" to chirality
- All angles and all bond-distances are identical between enantiomers
- Some methods determine chirality, but not structure (polarised light)
- Only (X-ray) crystallography can determine absolute structure

Friedel's Law

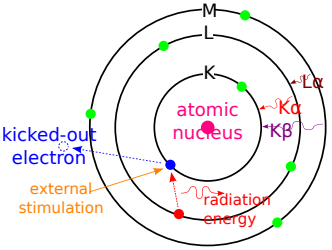
Calculation of the structure factor from atom coordinates (*c.f.* lecture No. 6):

$$F(hkl) = \sum_{\text{in u.c.}}^{\text{atoms } j} f_j(\theta) e^{-8\pi^2 U_j(\theta,\lambda)} e^{2\pi i(hx_j + ky_j + lz_j)} \tag{1}$$

This results in Friedel's law, $I(hkl) = I(\bar{h}\bar{k}\bar{l})$: The diffraction pattern is centrosymmetric, and therefore, the diffraction pattern is blind to chirality.

We have to look more closely!

Anomalous (X-ray) dispersion



EDX-scheme.svg, commons.wikimedia.org

- Incident X-rays can kick out an inner-shell electron
- higher-shell electrons fill the hole
- they emit characteristic radiation
- This is called "anomalous dispersion" in crystallography

Crystallographic description

Anomalous dispersion can be described with a modified atomic scattering factor:

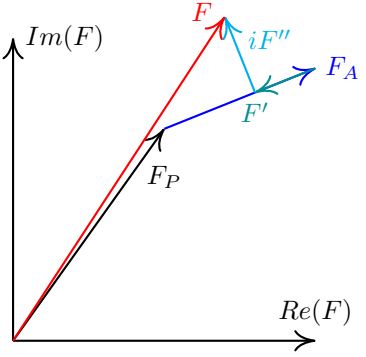
$$f(\lambda, \theta) = f_0(\theta) + f'(\lambda) + if''(\lambda)$$

- $f_0(\lambda)$ "normal" form factor, resolution dependent *cf.* Lecture No. 5
- $f'(\theta)$ absorptive component; wavelength dependent
- $if''(\theta)$ imaginary component, *i.e.* phase shift; wavelength dependent

Anomalous scattering

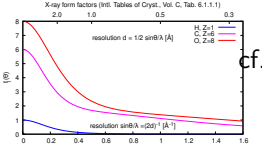
The scattering factor of all atoms, $F(hkl)$, consists of non-anomalous contributions and anomalous contributions:

$$
\begin{aligned}
F(hkl) &= \underbrace{\sum_{\text{atoms } \nu}^{\text{normal}} f_\nu e^{2\pi i \mathbf{hr}_\mu}}_{F_P} \\
&+ \underbrace{\sum f_X e^{2\pi i \mathbf{hr}_X}}_{F_A} \\
&+ \underbrace{\sum f'_X e^{2\pi i \mathbf{hr}_X}}_{F'} \\
&+ \underbrace{i \sum f''_X e^{2\pi i \mathbf{hr}_X}}_{iF''}
\end{aligned}
$$

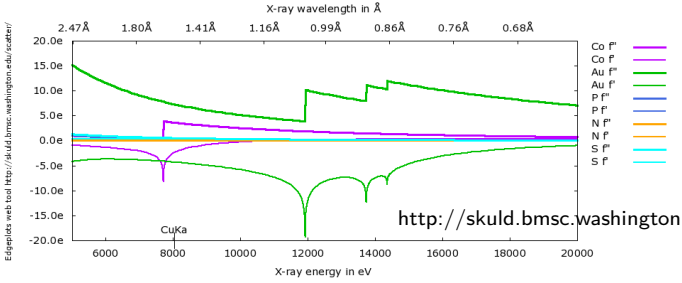


NB: f' usually negative, pointing backwards

Form factor components $f_0(\theta) + f'(\lambda) + if''(\lambda)$



cf. Lecture No. 5



$f'' > 0e$

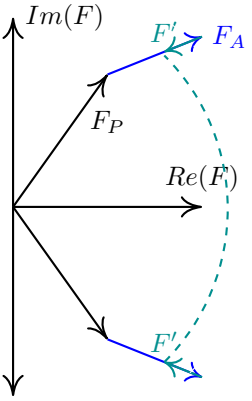
$f' < 0e$

http://skuld.bmsc.washington.edu/scatter/

iF'' breaks Friedel's law

Compare $F(hkl)$ and $F(\bar{h}\bar{k}\bar{l})$:

$$F(\bar{h}\bar{k}\bar{l}) = \underbrace{\sum_{\text{atoms } \nu}^{\text{normal}} f_\nu e^{-2\pi i \mathbf{hr}_\mu}}_{F_P} + \underbrace{\sum f_X e^{-2\pi i \mathbf{hr}_X}}_{F_A} + \underbrace{\sum f'_X e^{-2\pi i \mathbf{hr}_X}}_{F'} + \underbrace{i \sum f''_X e^{-2\pi i \mathbf{hr}_X}}_{iF''}$$

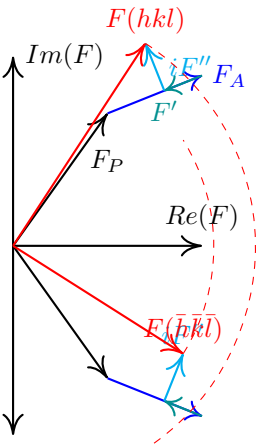


without iF': Friedel's law holds

iF'' breaks Friedel's law

Compare $F(hkl)$ and $F(\bar{h}\bar{k}\bar{l})$:

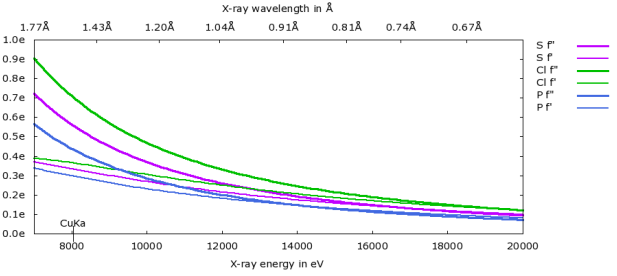
$$F(\bar{h}\bar{k}\bar{l}) = \underbrace{\sum_{\text{atoms } \nu}^{\text{normal}} f_\nu e^{-2\pi i \mathbf{h}\mathbf{r}_\mu}}_{F_P} + \underbrace{\sum f_X e^{-2\pi i \mathbf{h}\mathbf{r}_X}}_{F_A} + \underbrace{\sum f'_X e^{-2\pi i \mathbf{h}\mathbf{r}_X}}_{F'} + \underbrace{i \sum f''_X e^{-2\pi i \mathbf{h}\mathbf{r}_X}}_{iF''}$$



$iF''(hkl)$ breaks the symmetry with $iF''(\bar{h}\bar{k}\bar{l})$

Measuring the anomalous difference

- Anomalous effect can be very small (organic compounds)
- requires very accurate data
- Consider choice of wavelength (near, but above absorption edge)
- In presence of anomalous signal: $F(hkl)$ and $(F\bar{h}\bar{k}\bar{l})$ are called "Bijvoet pair", instead of "Friedel pair"



Chirality from anomalous data

Both model and inverted model are compared with the data

1. Refine structure "model 1"
2. Calculates $|F^1_{\text{calc}}(hkl)|$
3. Invert the structure "model 2" and calculate $|F^2_{\text{calc}}(hkl)|$
4. Calculate $R1$ and $wR2$ *via*

$$|F_{\text{calc}}(hkl)| = (1-k)|F^1_{\text{calc}}(hkl)| + k|F^2_{\text{calc}}(hkl)|$$

Chirality from anomalous data (cont'd)

4. Calculate $R1$ and $wR2$ *via*

$$|F_{\text{calc}}(hkl)| = (1-k)|F^1_{\text{calc}}(hkl)| + k|F^2_{\text{calc}}(hkl)|$$

5. Optimise k by minimising $R1$

$k \approx 0$ correct hand

$k \approx 1$ incorrect hand: invert model

between 0 and 1 mixture of both hands or poor data

k is called the **Flack parameter** (Howard D. Flack, University of Geneva).

Flack parameter & Parsons' coefficient

- Parsons' quotient

$$Q(hkl) = \frac{I(hkl) - I(\bar{h}\bar{k}\bar{l})}{I(hkl) + I(\bar{h}\bar{k}\bar{l})}$$

- same as before: compare calculated with observed data
- Parsons' coefficient more sensitive than "conventional" Flack parameter
- *cf*: S. Parsons, H.D. Flack, T. Wagner, *Acta Crystallogr.* (2013) B69, S. 249–259
- enables absolute structure determination from light-atom only structures

Chirality of light-atom only structures

All atoms exhibit an anomalous signal. For C, H, N, O, it is very weak, requires very good data.
Options in case the anomalous signal is too weak, data too poor:

- soak single heavy (salt): same structure, amplification of anomalous signal
- Co-crystallisation of molecule with known chirality (*cf.* NMR)

→ X-ray data determine chirality relative to the known molecule

→ If know molecule inverted: also invert the model.

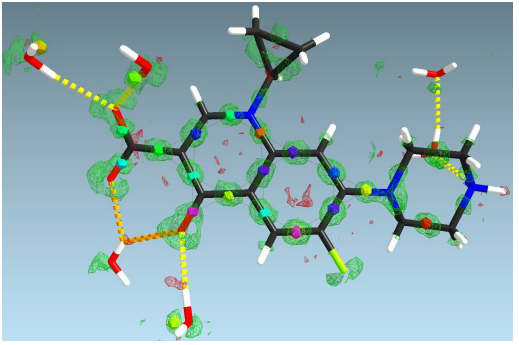
Summary absolute structure

- (physical) origin of anomalous signal
- anomalous signal breaks Friedel's law
- Flack parameter to determine chirality

Ultra-high resolution: limits of the IAM and charge density refinement

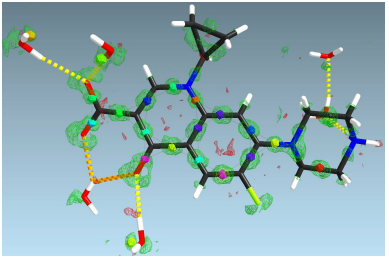
Data better than model

- X-rays interact with electron (cloud)
- Independent atom model (IAM) centres electron cloud about the nucleus
- Particularly strong deviation in hydrogen (single electron)



Unspherical valence electrons

The IAM assumes spherical atoms. Sufficient up to ≈ 0.7 Å resolution.
Provides 3D-structure: atom positions, chirality



Structure of Ciprofloxacin, *J. Holstein et al., Cryst. Eng. Comm. 2012 (14), pp. 2520–2531* (0.43 Å)

Ciprofloxacin at 0.43 Å: data "better" than model:

- IAM: does not model valence electrons
- dipole moments at terminal atoms O, F

X-ray crystallography beyond the IAM

- Ultra-high resolution provides insight into the chemical bond
- Residual density with "Independent Atom Model"
- necessary: different model to describe chemistry
- This will provide more information than "just" the structure

Starting point

The equation

$$F(hkl) = \int \rho(x,y,z) e^{2\pi i(\vec{h}\cdot\vec{x})} d^3x$$
$$= FT(\rho(x,y,z))$$

remains valid — definition of the structure factor

- Context with experiment: $I(hkl) = |F(hkl)|^2$
- So far with IAM: $\rho(x,y,z)$ calculated from form factors $f_i(\theta,\lambda)$ and ADPs U_{ij}.
- Extending the IAM description of $\rho(x,y,z)$ of the unit cell at better precision.

Requirements to the extended model

- Fourier transformation should be computable (fast)
- should make chemical sense
- limited number of parameters

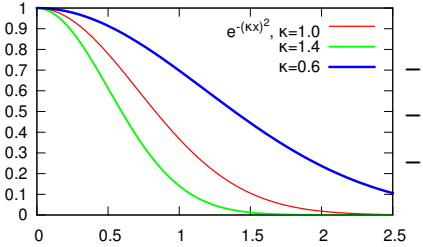
Models for the description of $\rho(x, y, z)$

1. spherical atoms with κ-Formalism (predecessor of the multipole model; Coulson 1961)
2. Hirshfeld-Formalism (1976): $\cos^n$ summation
3. multipole model (MPM) with spherical harmonics (Hansen & Coppens 1978)
4. Invariom model (B. Dittrich *et al.*, 2004)

The κ-Formalism - Coulson 1961

- Idea: exchange of valence electrons
- still spherically symmetric like IAM

$$\rho_{\text{atom}}(r) = \rho_{\text{core}}(r) + P_\nu \kappa^3 \rho_{\text{valence}}(\kappa r)$$



- P_ν population of the valence shell
- $\kappa < 1$ expansion of valence shell
- $\kappa > 1$ contraction of valence shell

- *cf.* Brown & Spackman, "*A Model Study of the κ-Refinement Procedure for Fitting Valence Electron Densities*", Acta Cryst. **A**47 (1991), S. 21–29

Hirshfeld refinement

describes the deformation of electron density for every atom with cosine functions with dependence on bond direction

$$\Delta\rho_i(n,\vec{k}) = \sum_{n,\vec{k}} N_n r_i^n e^{-\alpha_i r_i} \cos^n \theta_{i,\vec{k}}$$

- n: 0,..., 4
- α_i: shape parameter per atom
- N_n: normalisation constant
- $\theta_{i,\vec{k}}$: angle between $\vec{r}_i$ and $\vec{k}$, bond direction
- up to 35 parameters per atom

(Hirshfeld, Hope, "*An X-ray Determination of the Charge Deformation Density of 2-Cyanoguanidine*", Acta Cryst **B**36 (1980), 406–415)

Multipole model — Hansen & Coppens, 1978

$$\rho_{\text{atom}}(x,y,z) = p_c\rho_{\text{core}}(r) + p_\nu\kappa^3\rho_{\text{valence}}(\kappa r) + \sum_{l=0}^{l_{\text{max}}} \kappa'^3 R_l(\kappa' r) \sum_{m=-l}^{l} p_{lm} d_{lm}(\theta,\phi)$$

$$d_{lm} = \begin{cases} N'_{lm} P_l^m(\cos\theta)\cos(m\phi) & m \geq 0 \\ N'_{lm} P_l^m(\cos\theta)\sin(m\phi) & m < 0 \end{cases}$$

$$P_l^m(x) = \left(\sqrt{1-x^2}\right)^m \left(\frac{d}{dx}\right)^{l+m} \frac{1}{2^l l!}(x^2-1)^l$$

- p_c, p_ν, p_{lm}: populations
- $R_l(\kappa' r)$ description of s-shell electron in transition metals.
- $P_l^m(x)$: "*associated Legendre polynomials*"
- closely related to spherical harmonics

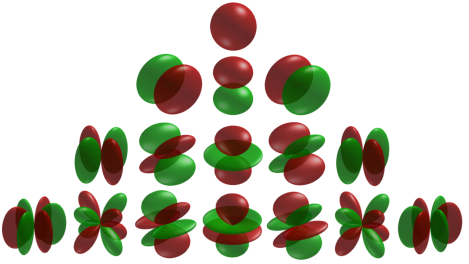
$$Y_{lm}(\theta,\phi) = \sqrt{\frac{2l+1}{4\pi}\frac{(l-m)!}{(l+m)!}} P_l^m(\cos\theta) e^{im\phi}$$

Visualisation of spherical harmonics

- electrostatic potential of 2^l point charges with total charge = 0e.
- arbitrarily complex charge distribution

→ deformation of ρ_{atom}

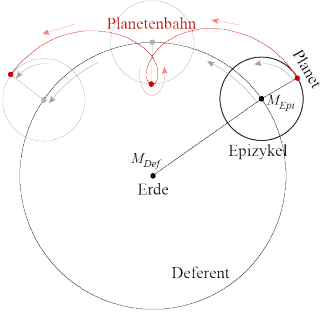
- favourable properties for certain differential equations like Maxwell equations, Schroedinger equation



http://en.wikipedia.org/wiki/Spherical_harmonics

Number of parameters in MPM

- parameter = number to match model with data
- chemical interpretation depends on refined parameter values
- too many parameters: overfitting, uncertainty of correctness of the model



http://de.wikipedia.org/wiki/Geozentrisches_Weltbild, according to Ptolemy

Number of parameters in MPM

$$\rho_{\text{atom}}(x,y,z) = p_c\rho_{\text{core}}(r) + p_\nu\kappa^3\rho_{\text{valence}}(\kappa r) + \sum_{l=0}^{l_{\text{max}}} \kappa'^3 R_l(\kappa' r) \sum_{m=-l}^{l} p_{lm} d_{lm}(\theta,\phi)$$

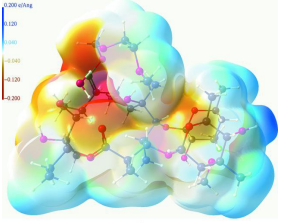
1. ρ_{core}: x, y, z, U_{ij}, p_c: ≥ 10 parameters
2. ρ_{valence}: κ, p_ν
3. MPM parameters increase quickly with l_{max}: $(l_{\text{max}}+1)\times\kappa' + \sum_{l=1}^{l_{\text{max}}} 2(l+1) \times N'_{lm}$, p_{lm}

multipole model in crystallography usually uses $l_{\text{max}} = 3$ or $l_{\text{max}} = 4$

up to 35 parameters per atom, compared with 9 for the IAM
ultra-high resolution required

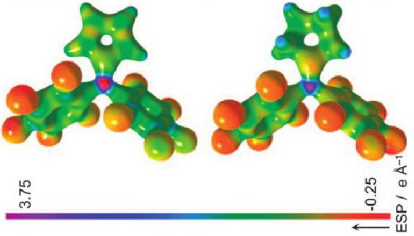
MPM: electrostatic potential of molecules

Combination of the electron distribution with positively charged nuclei directly results in the Coulomb potential of the unit cell



ESP of Roxithromycin

J. Holstein *et al.*, Acta Cryst. **B**66 (2010) 568ff



ESP of $(C_6F_5)_2BNC_4H_4$ and $(C_6F_5)_2BNC_4H_8$

U. Flierler *et al.*, Chem. – Eur. J. (2009), Vol. 15, 4595–4601

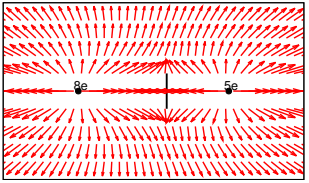
Chemical interpretation: QTAIM

http://commons.wikimedia.org/wiki/File:Fuscherkarkopf-_Sinwelleck.JPG

QTAIM – "Quantum Theory of Atoms in Molecules"

- Richard Bader (≈ 1960)
- Definition of **atom** and **bond** in solid state materials
- Atom: peak of electron density
- Bond: connecting line (vertex)

bond critical points — *bcp*



field lines between two charges

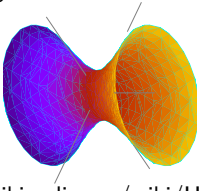
- electron cloud = negative charge
- attracted by nuclei
- between two atoms: cancellation

bond critical points — *bcp*

According to "quantum theory of atoms in molecules" (QTAIM): two atoms are chemically bound if there is a (3,-1)-critical point ("bind critical point") on their common (charge) surface

bond critical point position (x_c, y_c, z_c):

1. $\nabla\rho(x_c, y_c, z_c) = 0$ — cancellation of field lines
2. Hesse matrix $H(\rho(x_c, y_c, z_c)) = \left(\frac{\partial^2\rho(x_c,y_c,z_c)}{\partial x_i \partial x_j}\right)$ with
   - two negative eigenvalues: decreasing ρ perpendicular to bond
   - one positive eigenvalue: increasing ρ along bond



http://en.wikipedia.org/wiki/Hyperboloid

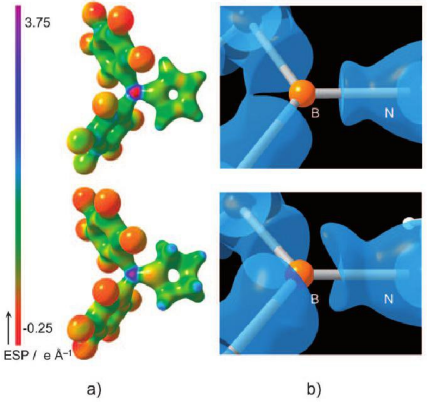
The Laplace surface

- Surface presentation of

$$\nabla^2\rho(x,y,z) = \frac{\partial^2\rho}{\partial x^2} + \frac{\partial^2\rho}{\partial y^2} + \frac{\partial^2\rho}{\partial z^2}$$
$$= \text{trace}(H(\rho(x,y,z)))$$

- $\nabla^2\rho(x,y,z) < 0e\text{Å}^{-5}$ electron concentration, characteristic for **covalent bond**
- $\nabla^2\rho(x,y,z) > 0e\text{Å}^{-5}$ electron sink, indicates an **ionic bond**

The Laplace surface



U. Flierler *et al.*, Chem.–Eur. J. (2009), Vol. 15, 4595–4601

- $\nabla^2\rho(x,y,z)$ for
  - $(C_6F_5)_2BNC_4H_4$ and
  - $(C_6F_5)_2BNC_4H_8$
- Plotting of

$$\nabla^2\rho(x,y,z) = 0e\text{Å}^{-5}$$

- reactive surface (of the Boron): Location of change of sign of the "Laplacian"

Summary

- IAM needs only few parameters, with spherical atoms

$\Rightarrow$ no information about electron distribution

- Multipol model: more detailed description. More parameters require ultra high resolution data

$\Rightarrow$ Properties derived from the detailed electron density

  - electrostatic potential
  - bond critical points bcp's as eigenvalues of the Hesse matrix of $\rho(x_c, y_c, z_c)$

End of lecture