Structure Determination from X-Ray Powder Diffraction

By Chua Yong Shen
Aim of this presentation

• Highlight the importance of XRD powder techniques for structure determination compound with no single crystal.
X-ray powder diffraction

- a non-destructive technique widely used for the characterization of crystalline materials
- has been traditionally used for phase identification, quantitative analysis and the determination of structure imperfections.
- Some solid can be prepared only as micro crystalline powders or, the structure of some materials which are in the form of hydrocarbons and resins cannot be determined using single crystal diffraction techniques.
• In such cases, the structure of the material can be determined by using powder diffraction data.

• Powder diffractometry projects 3D lattice into a 1D lattice.

• We can determine the orientation, unit cell dimensions, stress/strain, crystal structure, etc from the information obtained in the powder diffraction pattern.
The steps in structure determination process

- Unit cell determination
- Decomposition of powder pattern into integrated intensities
- Assignment of space group from systematic absences
- Forming an approximate solution using Direct or Traditional techniques
- Refinement of the structure, typically by the Rietveld method.
Major drawback of powder diffraction data

• Determination of structure is much more difficult than from single crystal data:
  – Collapse of the 3D crystallographic information into a 1D powder diffraction pattern (create problems in unit cell determination).
X-ray interact with the atoms in crystal structure

Deviation of $2\theta$ results in constructive and destructive interferences
Bragg’s law

Consider a crystal lattice whose interplanar spacing is d. Also the incident radiation strikes the planes (hkl) at an angle $\theta$ as shown.

$$n\lambda = 2d \sin \theta$$

From the equation, we can see that $\sin \theta$ is a measure of $1/d$. We can choose the incident angle by rotating the crystal relative to the beam and the wavelength is fixed. Thus we obtain the interplanar spacing d.

The intensity of the reflected beam is proportional to the product of the intensity of the incident beam and the concentration of electron in the reflecting plane. Thus if we know the unit cell dimensions and the atomic number of each of the atoms, we can calculate the concentration of the electrons and hence the intensity of the reflected beam.
when we want to find the crystal structure of a compound, we need to consider the reverse situation. If we know the size of the unit cell and intensities of the reflections, we can calculate the position of atoms and also the relative number of electron per atom.

It is obvious that all the compounds with different formulae or unit cells have different collections of d-spacings and different intensities of reflections. The observed patterns of spacings can intensities can thus be used to identify an unknown compound in a specific crystalline phase.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Information obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak positions (2θ values)</td>
<td>Unit cell dimensions and symmetry</td>
</tr>
<tr>
<td>Non-indexable lines</td>
<td>Presence of a crystalline impurity</td>
</tr>
<tr>
<td>Width of peaks</td>
<td>Particle Size/ Strain</td>
</tr>
<tr>
<td>Peak intensities</td>
<td>Cell contents and thermal vibrations</td>
</tr>
<tr>
<td>Peak shapes (other than widths)</td>
<td>Stacking faults, Layer defects</td>
</tr>
</tbody>
</table>
Structure determination of powder diffraction patterns

- Crystal structures, which cannot be determined by single crystal approaches because of inappropriate size and quality, can be easily determined using powder diffraction method.

- A structure determination technique can be divided into three stages:
  1. Unit cell determination
  2. Structure Solution
  3. Structure Refinement
1. Unit cell determination

- The size and shape of the unit cell is determined from the positions of the lines, which can also be called ‘indexing’ the pattern.
- In this stage, peak positions are extracted and then trial unit cells are assessed in order to determine the correct lattice parameters.
- With high-resolution data, indexing is rather straightforward. However, with poorer data, particularly when the sample contains more than one crystalline phase, indexing can become a serious bottleneck.
1. Unit cell determination (cont.)

Problems with indexing

• Multiple phases
• Peak overlap
• Low diffraction intensity from light elements
• Preferred orientation
• Peak broadening (instrument, crystallite size, micro-strain, extended defect)
2. Structure solution

- In structure solution an initial approximate structure is obtained from experimental data without having any prior knowledge of the arrangement of the atoms and molecules. This is very important phase in the determination of structure.

- There are two techniques for structure solution:
  a) Traditional approach
  b) Direct space approach
2. Structure solution (cont.)

a) Traditional approach:
- The intensities are taken from the powder pattern and they are used in the calculation that is used for single crystal diffraction data. But this may not be a reliable approach as there are many overlapping peaks and hence the intensities values obtained are not exact.
- This problem can be overcome by using improved techniques for extracting intensities or new strategies in which the pattern is obtained without extracting intensities.
2. Structure solution (cont.)

• This comparison is done using an appropriate R-factor. Most of the direct space approaches use the weighted R-factor which is $R_{wp}$.

$$R_{wp} = 100 \times \frac{\sum W_i(y_i(obs) - y_i(calc))^2}{W_i(y_i(obs))^2}$$

• Here $y_i(obs)$ is the intensity of the $i$-th data point in the experiment powder pattern. $y_i(calc)$ is the intensity of the $i$-th data point in the calculated powder diffraction profile. $W_i$ is the weighting factor for the $i$-th data point. $R_{wp}$ thus considers the intensities point by point instead of the integrated intensities. This reduces the peak overlap and uses the powder diffraction data as measured.
2. Structure solution (cont.)

b) Direct space approach

i) Monte Carlo Method
ii) Simulated Annealing
iii) Genetic Algorithm

Step 1: Generate trial structures
Step 2: Random displacement on trial structure
Step 3: Calculate powder diffraction pattern/Intensities/structure factors
Step 4: Compare with experimental data
Step 5: Accept or reject on basis of a criterion function
Step 6: Use as new trial structures as input
3. Structure Refinement

- Structure refinement is a method to get the exact structure from the data obtained in the earlier structure solution.
- If the structure solution is a good approximation to the original structure, a good quality structure may be obtained by Structure Refinement.
- Structure refinement is generally carried out by the Rietveld method.
X-ray powder diagram (Lab data) → Indexing if possible → Unit cell, possible space groups → Molecular geometry and other available information → Crystal structure calculation (Energy minimization) → Possible crystal structures → Calculation of X-ray powder diagrams → Comparison of calculated and experimental powder diagrams → Calculated crystal structure (close to experimental structure) → Synchrotron data, if available → Rietveld refinement → Crystal structure
Brief Talk On The Nobel Prize in Chemistry 2010

XU Wei-Liang, 27th Nov, 2010
Three scientists shared this year’s Nobel Prize in Chemistry for developing techniques in coupling reactions catalyzed by \( \text{Pd}(0) \).

Richard Heck: University of Delaware, Heck reaction, 1968
Ei-ichi Negishi: Purdue University, Negishi coupling, 1976
Akira Suzuki; Hokkaido University, Suzuki reaction, 1979
Heck reaction:

\[ R-X + R'\text{-}\text{alkene} \xrightarrow{\text{Pd}^0, \text{base}} R\text{-}\text{alkenyl} \]

\( X=\text{I, Br, OTf, etc} \)

Negishi Coupling:

\[ R-X + R'-\text{Zn-X'} \xrightarrow{\text{ML}_n} R-R' \]

\( X, X'=\text{Cl, Br, I, OTf} \)
\( M=\text{Ni, Pd} \)

Suzuki Reaction:

\[ R_1-\text{BY}_2 + R_2-X \xrightarrow{\text{Pd catalyst, Base}} R_1-R_2 \]

\( Y=\text{OH, O-R} \)
Suzuki Reaction:

\[
\text{r-Bu} = \text{B} = \text{O} + \text{Br} = \text{C} \xrightarrow{\text{benzene/NaOEt}} 80 \degree \text{C, 4 h}} \quad 98\% \\
\text{n-Bu} = \text{C} = \text{H}
\]


Mechanism:

Analysis of Elementary Steps in the Reaction Mechanism

Oxidative Addition

\[
\text{Br-} \xrightarrow{\text{Pd}^0\text{Ln}} \text{Br-Pd-L} \xrightarrow{\text{isomerization}} \text{Br-Pd}^\text{II}-\text{Br}
\]

- Relative reactivity of leaving groups: \( I^- > OTf^- > Br^- > Cl^- \).
- Oxidative addition is known to proceed with retention of stereochemistry with vinyl halides and with inversion with allylic and benzylic halides.


- Oxidative addition initially gives a cis complex that rapidly isomerizes to its trans isomer.

Transmetallation

- Organoboron compounds are highly covalent in character, and do not undergo transmetallation readily in the absence of base.

- The role of the base during transmetalation is unresolved. Boron "ate" complexes, formed via quaternization of the boron with a negatively charged base, are frequently invoked.

Reductive Elimination

- Isomerization to the cis complex is required before reductive elimination can occur.
- Relative rates of reductive elimination from palladium(II) complexes:
  
  aryl–aryl > alkyl–aryl > n-propyl–n-propyl > ethyl–ethyl > methyl–methyl

<table>
<thead>
<tr>
<th>Conditions</th>
<th>R−BY₂ + X−R'</th>
<th>R−R'</th>
<th>P(Ph₃)₄</th>
<th>benzene, 80 °C</th>
<th>base</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Bu−O−B(Ph)−Br</td>
<td>NaOEt</td>
<td>2</td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph−Br</td>
<td>NaOEt</td>
<td>2</td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br−CH₂−CH₂−Br</td>
<td>NaOEt</td>
<td>2</td>
<td>81&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I−Ph</td>
<td>NaOEt</td>
<td>2</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br−Ph</td>
<td>NaOEt</td>
<td>2</td>
<td>98&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl−Ph</td>
<td>NaOEt</td>
<td>2</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>H₂CO−Br−Ph</td>
<td>NaOEt</td>
<td>4</td>
<td>93&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I−Ph</td>
<td>2M NaOH</td>
<td>6</td>
<td>62&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Br−Ph</td>
<td>2M Na₂CO₃</td>
<td>6</td>
<td>88&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Cl−Ph</td>
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<td>6</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Br−CH₂−CH₂−Br</td>
<td>2M NaOH</td>
<td>2</td>
<td>87&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>n-Bu−O−B(Ph)−Br</td>
<td>2M NaOH</td>
<td>2</td>
<td>99&lt;sup&gt;d&lt;/sup&gt;</td>
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</tbody>
</table>

- The conditions shown above are the original conditions developed for the cross coupling by Suzuki and Miyaura.
- The reaction is stereo- and regiospecific, providing a convenient method for the synthesis of conjugated alkadienes, arylated alkenes, and biaryls.
- Note that under the conditions shown above, aryl chlorides are not acceptable substrates for the reaction, likely due to their reluctance to participate in oxidative addition.

Experimental procedure for Suzuki reaction

1. Charge your reaction flask with your aryl bromide and your aryl boronate, then add your solvent (THF, dioxane, DMF and toluene are often used) and degas the reaction mixture either by freeze-pump-thaw cycling or simply by bubbling with an inert gas such as nitrogen or argon for 30 minutes.

2. Now add your palladium catalyst (Pd(PPh3)4 and PdCl2(PPh3)2 are often used) and then a degassed aqueous solution of your base (K3PO4, Na2CO3, K2CO3, Et4NOH are often used). Keep the reaction mixture under an inert atmosphere such as nitrogen or argon.

3. Your Suzuki reaction is now ready to take off. All you need to do is to heat it up to gentle reflux with good stirring to make sure that the biphasic reaction mixture is properly mixed. Your reaction will typically be completed after refluxing over night.

4. Work-up typically consists of an aqueous wash followed by column chromatography and recrystallisation to afford your desired product.
Catalyst

Catalyst and Ligands: The most commonly used system is Pd(PPh$_3$)$_4$, but other palladium sources have been used including Pd$^{II}$ pre-catalysts that are reduced to the active Pd$^0$ in situ:

- Pd$_2$(dba)$_3$ + PPh$_3$
- Pd(OAc)$_2$ + PPh$_3$
- PdCl$_2$(dpff) (for sp3-sp2 couplings-see section on B-alkyl Suzuki reaction)

* "Ligand-free" conditions, using Pd(OAc)$_2$, have also been developed. Side reactions often associated with the use of phosphine ligands (phosphonium salt formation and aryl-aryl exchange between substrate and phosphine) are thus avoided.


* Use of N-heterocyclic carbenes as an alternative to phosphine ligands:

![Chemical structures](image)

- The nucleophilic N-heterocyclic carbene 1 is the active ligand, and is formed in situ from 2.
- The use of ligand 1 allows for utilization of aryl chlorides in the Suzuki reaction (see the section on bulky, electron rich phosphines as ligands for use of aryl chlorides as coupling partners as well).

Bulky, Electron-Rich Phosphines as Ligands for the Suzuki Reaction

![Chemical structures and reactions](image)

<table>
<thead>
<tr>
<th>R</th>
<th>ligand</th>
<th>Pd source</th>
<th>base</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>PPh₃</td>
<td>Pd₂dba₃</td>
<td>Cs₂CO₃</td>
<td>dioxane</td>
<td>80</td>
<td>5</td>
<td>0³</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>Pd₂dba₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>KF</td>
<td>THF</td>
<td>23</td>
<td>6</td>
<td>95²</td>
</tr>
<tr>
<td>CH₃O</td>
<td>Pkt-Bu₃</td>
<td>Pd₂dba₃</td>
<td>Cs₂CO₃</td>
<td>dioxane</td>
<td>80</td>
<td>5</td>
<td>89²</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>KF</td>
<td>THF</td>
<td>45</td>
<td>6</td>
<td>93²</td>
</tr>
<tr>
<td>NH₂</td>
<td>Pkt-Bu₃</td>
<td>Pd₂dba₃</td>
<td>Cs₂CO₃</td>
<td>dioxane</td>
<td>80</td>
<td>5</td>
<td>92²</td>
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<tr>
<td>CH₃</td>
<td>Pkt-Bu₃</td>
<td>Pd₂dba₃</td>
<td>Cs₂CO₃</td>
<td>dioxane</td>
<td>80</td>
<td>5</td>
<td>91²</td>
</tr>
</tbody>
</table>

- Previous to the introduction of the bulky, electron-rich phosphine ligands shown above, most aryl chlorides were not suitable substrates for the Suzuki reaction.
- These ligands are either commercially available (Pkt-Bu₃) or readily synthesized from commercial starting materials (1-4).
- The increased activity of the ligands shown above allows for the Suzuki reaction of aryl bromides at room temperature.

Organoborane: R-BY₂

Organoboranes: A variety of organoboranes may be used to effect the transfer of the organic coupling partner to the reactive palladium center via transmetallation. Choice of the appropriate organoborane will depend upon the compatibility with the coupling partners and availability (see section on synthesis of organoboranes).

Some of the more common organoboranes used in the Suzuki reaction are shown below:

- Use of Aryltrifluoroborates as Organoboranes for the Suzuki Reaction:

  \[
  \begin{align*}
  &\text{Benzylic B(}\text{OR})_2 \quad \text{R-B(}\text{OR})_2 \\
  &\text{Pd(OAc)}_2, \text{K}_2\text{CO}_3 \\
  &\text{CH}_3\text{OH, reflux, 2h, 95%}
  \end{align*}
  \]

  - The aryltrifluoroborates are prepared by treatment of the corresponding arylboronic acid with excess KHF₂.
  - According to the authors, aryltrifluoroborates are more robust, more easily purified, and less prone to protodeboronation compared to aryl boronic acids.
Synthesis of organoboron compounds:

Synthesized by n-butyl lithium and halogen substituted compounds

\[ \text{Synthesis of organoboron compounds:} \]

- \( \text{B(O-i-Pr)}_3 \) (1 equiv)
- \( \text{Et}_2\text{O}, -78 \degree \text{C} \rightarrow 23 \degree \text{C}, 4 \text{ h} \)
- \( \text{HCl/Et}_2\text{O}, 0 \degree \text{C}, 30 \text{ min} \)

84%

Advantages of Suzuki reaction:

1. Mild reaction condition
2. Tolerance of activative functional group
3. Insensitity to moisture
4. Low toxicity

Disadvantages of Suzuki reaction

1. Aryl chlorides are not usually good substrates because they tend to react very slowly.
Negishi Coupling: mechanism
Preparation of Organozinc reagent:

1. Direct reaction of organic halide with zinc or activated zinc.

\[
\text{R-X} \xrightarrow{\text{Zn}} \text{R-ZnX}
\]

2. Transmetallation of the corresponding organolithium or Grignard reagents with a zinc halide.

\[
\begin{align*}
\text{R-Li} & \xrightarrow{\text{ZnX}_2} \text{RZnX+LiX} \\
\text{R-MgX} & \xrightarrow{\text{ZnX}_2} \text{RZnX+MgX}_2
\end{align*}
\]
The **palladium catalyst** (0.01 mmol Pd) is charged into the reaction vessel. **3-iodobenzotrifluoride** (144 mL, 1 mmol) is then introduced, followed by addition of a **THF solution of 4-methylphenylzinc iodide** (0.5 M, 3 mL, 1.5 mmol). The resulting mixture is **stirred at 50 °C for 18 h**, cooled, and then filtered. The resin is washed with THF (2 × 3 mL), the THF filtrates combined and evaporated. The evaporation residue is dissolved in a minimum amount of THF and filtered through a silica gel pad to remove any residual zinc compounds. The pad is rinsed with ether, and the combined ether filtrates evaporated. The crude product thus obtained is purified by **flash chromatography on silica gel** (column size 1.5 × 2.5 cm) using hexane as eluent. The purified product, 4-methyl-3’-trifluoromethylbiphenyl, is isolated as a colorless oil.
Organozinc halides are milder; react directly with the bromides or chlorides; tolerate a variety of sensitive groups such as nitriles, esters, amides, ethers, sulfides, and ketones to give functionalized organozinc reagents.
Examples for Negishi Reaction

Extremely Active Catalyst for the Negishi Cross-Coupling Reaction

The First Negishi Cross-Coupling Reaction of Two Alkyl Centers Utilizing a Pd-N-Heterocyclic Carbene (NHC) Catalyst

Negish Coupling of Secondary Alkylzinc Halides with Aryl Bromides and Chlorides
Heck reaction:

One of the benefits of the Heck Reaction is its outstanding \textit{trans} selectivity.

Two different mechanisms involved:
1. Neutral mechanism when $X$ is a strong sigma donor such as Cl, Br, or I.

2. Cationic mechanism when $X$ is OTf, Oac, or $\text{Ag}^+$, $\text{Ti}^+$, quaternary ammonium, and phosphonium salts are used to help displacement from halides.
neutral mechanism
Cationic mechanism

Scheme 3: Cationic Mechanism
Examples for Heck Reaction


New N-Heterocyclic Carbene Palladium Complex/Ionic Liquid Matrix Immobilized on Silica: Application as Recoverable Catalyst for the Heck Reaction

Pd(quinoline-8-carboxylate)\(_2\) as a Low-Priced, Phosphine-Free Catalyst for Heck and Suzuki Reactions
Disadvantages for Heck reaction:

1. Substrates used in the reaction cannot have beta hydrogens because they will undergo rapid beta hydride elimination to give olefins.

\[ \text{Valid: } \begin{array}{c}
\text{+} \\
\text{Invalid: } \\
\end{array} \]

2. Aryl chlorides are not usually good substrates because they tend to react very slowly.
The end