Connecting the Dots: Unraveling the Disconnection Approach in Organic Synthesis

Subject: Organic Synthesis
Subject Code: MDSE(C)-404C
(M.Sc. Chemistry IVth Sem)

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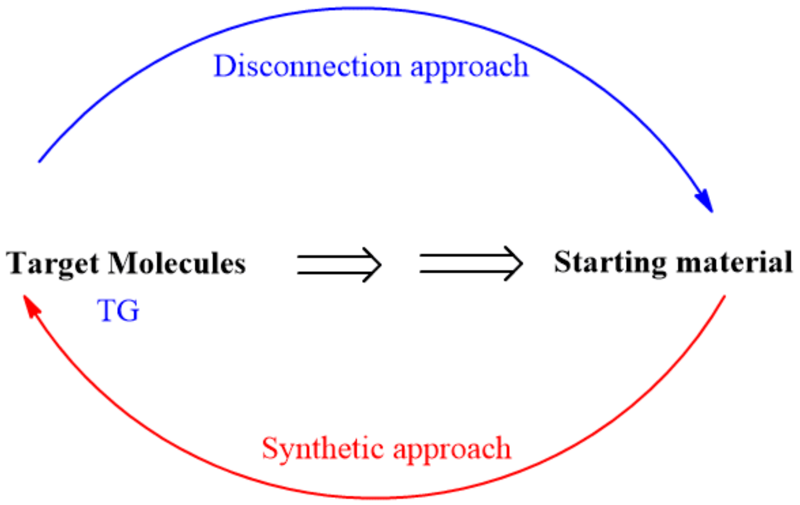
DISCONNECTION APPROACH OR RETROSYNTHETIC ANAYSIS

- Retrosynthesis is a technique used in organic chemistry to plan the synthesis of complex molecules by breaking them down into simpler precursor structures.
- The process involves working backward from the target molecule (the molecule you want to synthesize) to simpler, more readily available starting materials.
- The goal is to identify a sequence of chemical reactions that can be used to build the target molecule.
- In retrosynthesis, chemists analyze the structure of the target compound and then reverse-engineer it, considering possible reactions, functional group transformations, and known synthetic pathways. By doing this, they can design a step-by-step strategy for the synthesis of the molecule.



DISCONNECTION APPROACH / RETROSYNTHETIC ANALYSIS

Retrosynthetic analysis involves working **backwards** from the target molecule to identify simpler precursors. This **creative** process encourages chemists to think outside the box, leading to novel **synthesis** pathways and innovative solutions.

The **disconnection approach** emerged in the late 20th century, pioneered by chemists like **E.J. Corey**. This innovative strategy transformed the landscape of organic chemistry, enabling the **synthesis** of complex molecules through systematic breakdown and analysis.

The disconnection approach plays a pivotal role in **drug design**. By breaking down complex drug molecules, chemists can identify simpler, more effective compounds, thus accelerating the development of new **therapeutics** and improving patient outcomes.

Many **natural products** have been synthesized using the disconnection approach. By analyzing their structures, chemists can devise synthetic routes that mimic nature's complexity while allowing for **modifications** to enhance efficacy.

A double line arrow ($\Rightarrow$) is called a retrosynthetic arrow and is commonly used to indicate a reaction written backward ; the actual reaction is in reverse.

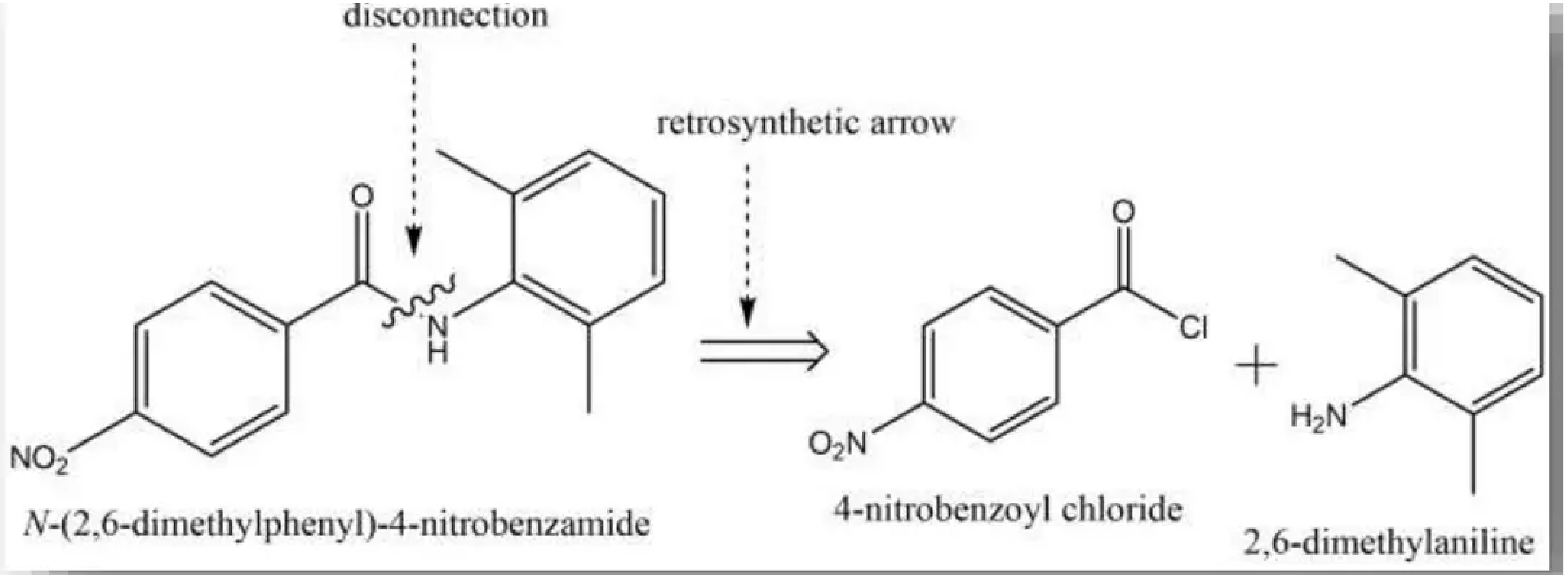
$$X + Y \longrightarrow Z$$

normal synthesis

$$Z \Longrightarrow X + Y$$

retrosynthesis

Disconnections very often take place immediately adjacent to, or very close to functional groups in the target molecule. This is pretty much inevitable, given that functionality almost invariably arises from the forward reaction.



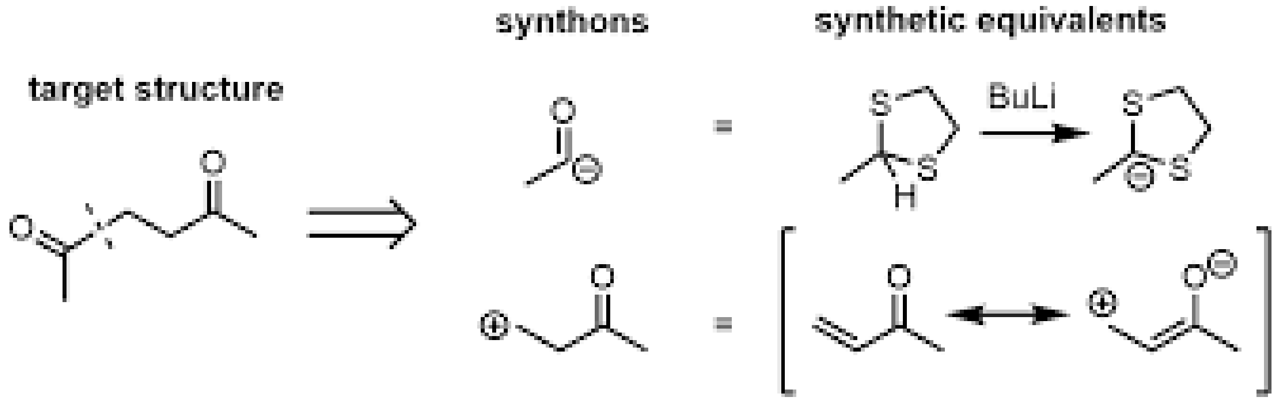
Synthons and Synthetic Equivalents

Synthons are idealised fragments (reagents) usually cations or anions resulting from a disconnection.

Synthons need to be replaced by reagents (synthetic equivalents) in a suggested synthesis.

Synthons are not themselves reagents. They may occasionally be intermediates in the reaction pathway. By disconnecting bonds to synthons rather than to actual reagents (synthetic equivalents) we can indicate the polarity of bond-forming reaction we are going to use without specifying the details of the reagent.

Synthetic equivalents are real chemical compounds (reagent) carrying out the function of a synthon.



Overall important points for choosing a disconnection

- Recognize the functional group in the target molecule.
- For compounds consisting of 2 parts joined by a heteroatom, disconnect next to the heteroatom.
- Disconnection next to aromatic ring should not be a priority.
- Consider alternative disconnections and choose routes that avoid chemo selectivity problems—often this means disconnecting reactive groups first
- Disconnection must correspond to known, reliable reactions.

Retrosynthetic Analysis- STEPS

Step 1. Recognize the functional groups in the target molecule

Step 2. Disconnect by known methods and reliable reactions

Step 3. Repeat 1 and 2 until the readily available starting materials are obtained

Step 4. Design as many alternative retrosynthetic routes as possible

Synthesis- STEPS

Step 1. Write down the synthetic schemes containing the detailed reaction conditions according to the analyses

Step 2. Compare the pros and cons between the syntheses designed; the number of steps, availability of reagents/starting materials, selectivity (chemo-/regio-/stereo-), economy, process, etc

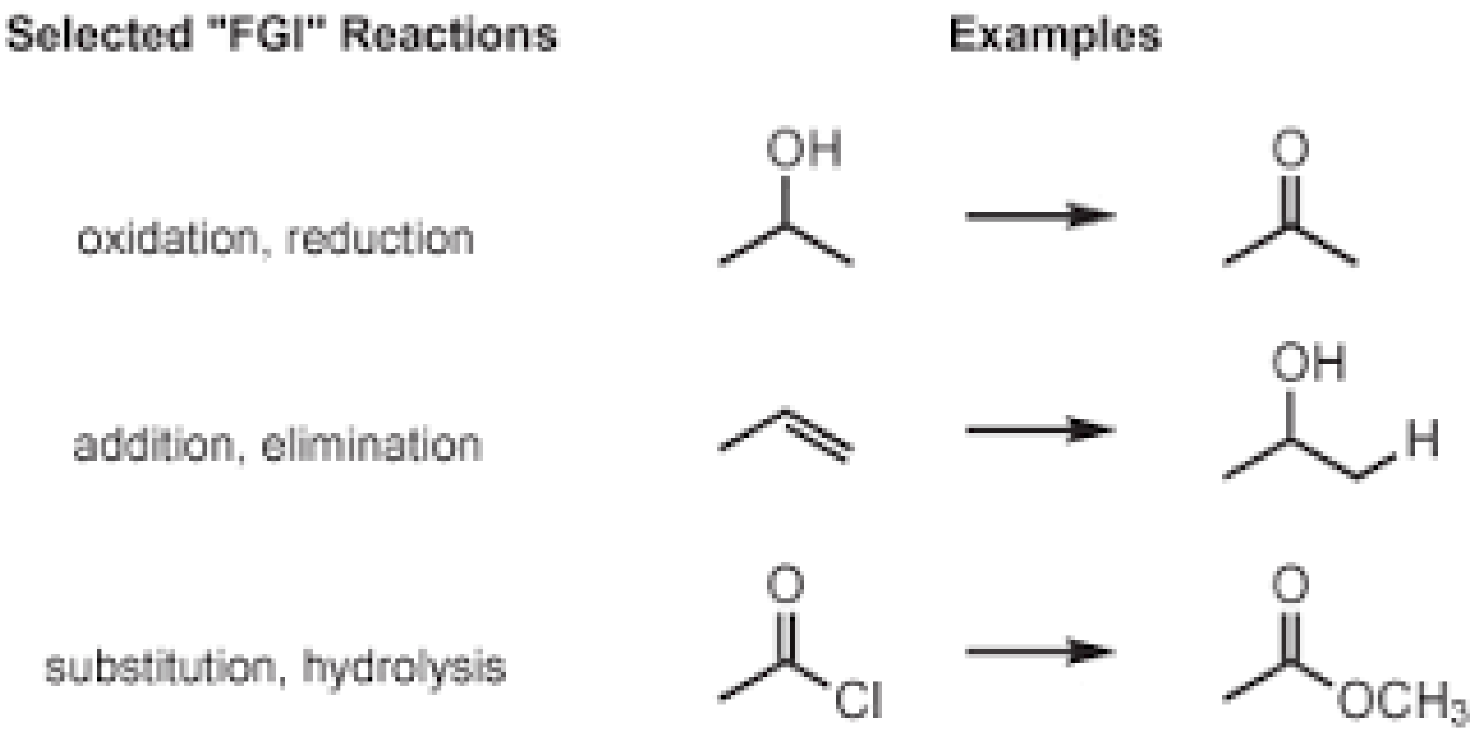
Step 3. Modify the selected synthetic plan whenever unexpected problems are encountered

Functional Group Interconversion (FGI)

Functional group interconversion is the process of converting one functional group into another during retrosynthetic analysis. FGI mostly involve oxidation, reduction, and substitution.

It is applicable where we do not have real and workable reaction reverse to a disconnection.

Functional group interconversion (FGI) is essential in the disconnection approach. By strategically transforming **functional groups**, chemists can manipulate molecular structures, enhancing the **synthesis** process and expanding the toolkit available for organic synthesis.



Conclusions

At the heart of the disconnection approach are **key principles**: retrosynthetic analysis and functional group interconversion. These concepts allow chemists to envision possible synthetic routes by **disconnecting** bonds and identifying **building blocks**.

Creativity is key in the disconnection approach. Chemists often employ **out-of-the-box** thinking to devise unconventional pathways, leading to the discovery of new reactions and **synthetic methodologies** that challenge traditional norms.

The disconnection approach in organic synthesis is more than just a method; it is a **philosophy** that encourages creativity and innovation. By connecting the dots between simple and complex structures, we can unlock new possibilities in **synthesis**.

Conclusions

The disconnection approach connects various fields, including **materials science**, **biochemistry**, and **medicinal chemistry**. This interdisciplinary collaboration fosters innovation and pushes the boundaries of what is possible in organic synthesis.

The future of the disconnection approach is bright, with advancements in **computational chemistry** and **machine learning**. These technologies will enhance our ability to predict synthetic routes, making organic synthesis more efficient and **sustainable**.

Despite its advantages, the disconnection approach presents challenges such as **selectivity** and **yield** issues. Overcoming these hurdles requires innovative thinking and a deep understanding of **reaction mechanisms** to achieve optimal results.