8. Organic Synthesis

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8.1 Definition:

The area of chemistry known as "organic synthesis" focuses on creating organic compounds through chemical reactions from simpler entities or molecules. It entails planning and carrying out the processes necessary to produce particular organic molecules, frequently with the intention of generating compounds with desired characteristics or functions. The molecule to be synthesized in organic synthesis is called the target compound. The target compound is usually derived from a 'scaffold', known as the starting material.

8.2 Introduction:

In the field of chemistry and associated sciences, organic synthesis remains the driving force behind several scientific advancements. Research on organic synthesis has also shown a strong tendency toward focusing on new materials, product specialization, and ways to improve humankind's quality of life. The discipline of organic chemistry's synthesis is based on the creation of organic compounds using carefully thought-out procedures. The field of organic synthesis and its relationships with other scientific fields continue to have a profound impact on human life and well-being. Through smart experimentation, foundational knowledge from the previous two centuries of post-alchemy chemical study has continued to solidify and evolve into the 21st century. Investment in particular fields has led to advances in synthetic chemistry's precision and efficiency, which have improved molecular complexity, increased synthetic yield, and added value to other fields.

History: The 19th century saw the invention of organic synthesis. Wohler's 1828 urea synthesis was the first conscious organic synthesis of a natural substance. This is significant because it represents the first instance of organic synthesis and the conversion of an inorganic substance (ammonium cyanate, or NH4CNO) into an organic substance.

The second significant accomplishment in the history of organic synthesis was the synthesis of acetic acid by Kolbe in 1845 using elemental carbon. It's noteworthy historically that Kolbe used the term "synthesis" to refer to the process of putting together a chemical molecule from other chemicals in his article from 1845.

Perhaps, after urea, the most spectacular total organic synthesis of the 19th century was that of (+)-glucose by E. Fischer. This total synthesis is remarkable not only for the complexity of the target, which included, for the first time, stereochemical elements, but also for the considerable stereochemical control that accompanied it. The organic synthesis of alizarin (1869) by Graebe and Liebermann and indigo dye (1878) by Baeyer are legendary achievements in the field. By the end of the 1800s, glucose, with its oxygen-containing monocyclic structure (pyranose) and five stereogenic centres (four programmable), was the most advanced target molecule available. E. Fischer followed J.H. van't Hoff as the second recipient of the Chemistry Nobel Prize in 1902 (1901).

Timeline of Organic Synthesis in 19th Century:

- **1828** → Wohler synthesized urea from ammonium cyanate.
- **1833** → Thomas Graham produced crystalloids and colloids and also introduced chemists to existence of polybasic acids.
- **1833** → Henri Braconnot nitrates starch, making crude nitrocellulose.
- **1838** → Theophile Pelouze nitrates paper, making crude nitrocellulose.
- **1845** → Christian Friedrich Schonbein used cotton’s apron of his wife on spilt mixture of nitric acid and sulphuric acid. The moping cloth when dried over stove, went poof! And was gone. He discovered synthesis of nitrocellulose from cotton.
- **1846** → Ascania Sobrero discovered nitroglycerin, a shattering explosive.
- **1851** → Hoffmann elimination was published, a method to eliminate nitrogen from alkyl chain.
- **1856** → William Henry Perkin synthesized the very first synthetic dye [8]. He, in outrageous manner, treated aniline with potassium dichromate and was about to discard the resulting mess as just another failure when his eye caught a purplish glint in the material. He added alcohol, which dissolved something out of the mess and turned a beautiful purple. It was termed as ‘Aniline Purple’, which is chemically knows as *Mauveine*.
- **1863** → J. Wilbrand synthesized Trinitrotoluene (TNT) which was originally used as a yellow dye but its destructive power was well-recognized in 1902.
- **1865** → Kekule realized the structure of benzene.
- **1866** → Alfred Nobel invents dynamite using nitroglycerin and kieselguhr**.**
- **1867** → Baeyer synthesized indigo, a synthetic dye.
- **1868** → Baeyer’s student, Karl Graebe synthesized alizarin, an important natural dye.
- **1869** → First synthetic plastic ‘Celluloid’ was formed by John Wesley Hyatt.
- **1875** → Alfred Nobel invents blasting gel by mixing nitrocellulose in nitroglycerin.
- **1890** → E.Fischer synthesized (+)-Glucose.
- **1891** → Bernhad Tollens invents Pentaerythritol tetranitrate (PETN).
- **1899** → Henning synthesized cyclotrimethylenetrinitramine (Cyclonite or RDX)

Timeline of Organic Synthesis in 20th Century

- **1906** → Mikhail Tsvet discovers chromatography.
- **1907** → Emil Fischer artificially synthesized peptide amino acid chains.
- **1908** → Sulfanilamide, a synthetic sulfonamide with antibacterial properties, was synthesized by Paul Gelmo [10].
- **1909** → Baekeland synthesized a copolymer using phenol and formaldehyde, termed as *Bakelite* later.
- **1909** → *Arsphenamine, a synthetic compound* was used by Paul Ehrlich in treating syphilis.
- **1920** → Tsvett technique was reintroduced by Richard Kuhn.
- **1924** → George Eastman synthesized cellulose acetate.
- **1925** → Robert Robinson discovered the structure of morphine, an alkaloid.
- **1928** → Alexander Fleming accidentally discovered penicillin.
- **1930** → Paul Karrer worked out the structure of the carotenoids, an important class of plant pigments.
- **1932** → Gerhard Domagk discovered the antibacterial properties of sulfanilamide. Charles Goodyear synthesized neoprene, a synthetic rubber, now called as elastomers.
- **1933** → Tadeus Reichstein artificially synthesized vitamin C; the first vitamin synthesis.
- **1937** → Dorothy Crowfoot Hodgkin discovered the 3D structure of cholesterol.
- **1940-1950** → Alexander Robertus Todd synthesized nucleotides, the building block of nucleic acids. Acher John Porter Martin and Richard Laurence Millington Synge developed new type of chromatography called paper chromatography. Frederick Sanger tackled Insulin by breaking it down and separating through paper chromatography. William von Eggers Doering synthesized quinine in 1944. Penicillin was prepared on industrial scale in 1945. Robert Robinson discovered the structure of *strychnine*.
- **1950-1960** → Woodward synthesized cholesterol and cortisone in 1951, reserpine in 1956 and chlorophyll in 1960. Vincent du Vigneaud synthesized oxytocin in 1954. Semi-synthetic penicillins were synthesized in 1958. Myoglobin structure was determined in 1960 by using x-ray diffraction technique.
- **1962** → Woodward synthesized a complex compound related to achromycin, a well-known antibiotic.
- **1972** → Albert Eschenmoser and Robert Woodward synthesized Vitamin B_{12}.

8.3 Techniques of Organic Synthesis:

8.3.1 The Reaction:

Three operations usually accompany the carrying out of a reaction on a synthetic scale: stirring, addition of a reagent, and temperature control.

A. Stirring: Reactions involving heterogeneous or viscous mixtures usually need effective stirring of the reaction mixture. Furthermore, in order to avoid high local concentrations or uneven heating or cooling, stirring may be required while adding a reagent to the reaction vessel. The most practical way of stirring is definitely magnetic stirring, which involves a motor-driven magnet and a Teflon or Pyrex-coated stirring bar. This allows for total sealing of the reaction vessel. Only very viscous reaction mixes or those containing significant amounts of solid are suitable candidates for its application. A glass rod is connected by a short piece of rubber tubing to the drive shaft of an electric motor in situations when mechanical stirring is necessary. The rod ends in a Teflon, Pyrex, or wire stirring paddle after entering the reaction vessel through a rubber gasket. A variable transformer can be used to control speed.

B. Addition of reagent: A straightforward dropping funnel supported, if required, by a drying tube can typically be used to add liquids or solutions to the reaction vessel. A pressure-equalizing falling funnel is needed for reactions conducted in an inert atmosphere, vacuum, or pressure. In either scenario, caution is required because a single stopcock setting will cause the addition rate to decrease as the liquid head drops.

C. Temperature control: Using a reflux condenser and a solvent with an appropriate boiling point is the most common way to regulate reaction temperature. A steam bath, hot plate, or heating mantle can be used for heating in these conditions. If it is not convenient to use a refluxing solvent, external temperature control may be required. It is convenient to use a water bath heated by an electric hot plate or burner for reactions that are conducted below 100°. If preferred, magnetic stirring can be done through the water bath when using hot plate-magnetic stirring machines in conjunction with a glass or stainless-steel water bath. Using an oil or wax bath in conjunction with the hot plate will result in higher temperatures.

On the other hand, the electric heating equipment can be the most practical high temperature heater. Finally, they are made of nonferrous materials and may be used with magnetic stirring. Heating mantle temperatures can be very precisely adjusted with the use of a variable transformer, and their interior temperature can be easily checked with the help of the built-in thermocouple. The reaction mixture is cooled through the utilization of a suitable cooling bath, the composition of which is contingent upon the intended reaction temperature.

8.3.2 Adsorption of Impurities:

A. Decolorization: Activated charcoal is used to remove small amounts of colored impurities from the organic material solution. Charcoal (1–2% of the weight of the organic solute) is added when the solution reaches a boiling point. Gravity forces the heated mixture through a filter into a receptacle with a tiny amount of the solvent that is maintained boiling.

Premature crystallization is prevented and the filter cone is heated by the boiling solvent. Following the completion of filtration, extra solvent is removed by distillation, and crystallization is encouraged. When using charcoal for decolorization, water and the majority of organic solvents work well as media.

B. Drying agents: It is usually preferable to remove any remaining water from organic liquids or solutions before distillation or crystallization. Care must be taken while choosing the drying agent to minimize product loss due to reaction or complexing, while still enabling sufficient drying for the intended use.

C. Removal of solvent: It is frequently essential to remove a significant amount of solvent before distillation or crystallization. Careful fractional distillation of the whole solution is necessary if the solvent and result have comparable boiling points (within 75°). In other situations, the solvent can be eliminated via rotational evaporation, fast distillation at atmospheric pressure, or boiling in a steam bath. When used in conjunction with a heated water bath and aspirator pressure, the rotary evaporator can quickly remove most solvents that boil at temperatures as high as 120°/1 atm.

8.3.3 Purification of Product:

A. Crystallization and Recrystallization:

Recrystallization is a solvent-based process for purifying impure compounds; it is also referred to as fractional crystallization. The idea behind the purification process is that most substances become more soluble at higher temperatures. This indicates that the amount of solute that may dissolve in a solvent increase with temperature. An impure chemical is dissolved at a high temperature to create a highly concentrated solution (the impurities must also be soluble in the solvent). Cooling is applied to the solution. The solubility of the substance being cleansed and the contaminants in the solution both decrease as the temperature drops. If there was more impure material than impurities, the impure substance would then crystallize before the impurities. Since the impurities won't crystallize quite yet, they will remain in the solution and the impure substance will crystallize in a purer form. At this stage, a filtration procedure is required to isolate the purer crystals. One can forecast the result of a recrystallization process using solubility curves.

B. Drying of Solids:

Spreading a solid that is air-insensitive over a sizable sheet of filter paper and letting the solvent or moisture evaporate will quickly dry the material. But a lot of organic solids need to be dried under low pressure in a vacuum desiccator or vacuum oven because they are air or moisture-sensitive. Furthermore, vacuum drying is required for a sample to be completely dried before it can be examined using combustion analysis.

8.4 Applications:

Organic synthesis is an important field with a wide range of applications:

- **Pharmaceuticals:** It is essential to the discovery and development of new drugs that treat diseases and improve human health.
- **Agrochemicals:** It is used to create pesticides, herbicides, and fungicides for agricultural applications that increase crop yields and shield plants from pests and diseases.
- **Materials Science:** It helps create polymers, plastics, and other materials used in industries ranging from electronics to construction.
- **Fine Chemicals:** It is used in the synthesis of fragrances, flavors, dyes, and pigments for use in cosmetics, food, textiles, and other consumer goods.
- **Biotechnology:** Organic synthesis is utilized to create molecules for use in biotechnology, such as enzymes, nucleic acids, and other biomolecules for research, diagnostics, and therapeutic applications.
- **Energy:** The development of materials for energy conversion, harvesting, and storage, such as fuel cells, batteries, and organic solar cells, depends in part on organic synthesis.
- **Environmental Remediation:** It is the process of creating substances for cleaning up the environment, like catalysts and adsorbents to take out contaminants from the soil, water, and air.
- **Medicinal Chemistry:** The creation of new medications and treatments is aided by the use of organic synthesis in the design and synthesis of compounds with particular biological activity.
- **Natural Product Synthesis:** Through organic synthesis, natural products can be produced for biological activity studies or to be developed into agrochemicals or medications.
- **Peptide and Protein Synthesis:** Research, diagnostics, and therapeutic applications including peptide-based medications and biologics all need the production of peptides and proteins, which are produced using organic synthesis techniques

8.5 Future Prospectives:

Three emerging growing disciplines in organic synthesis include: enzyme catalysis, photocatalysis, and green chemistry.

A. Enzyme catalysis: In the future, enzyme catalysis in organic synthesis is expected to develop and have a major impact. The following are some important viewpoints:

- **Green Chemistry:** Enzymes provide more sustainable and ecologically favorable synthesis methods by serving as environmentally friendly substitutes for conventional chemical catalysts. It is expected that future research will concentrate on creating enzymatic procedures that use less energy and produce less waste.

- **Chemoenzymatic Synthesis:** Complex compounds can be synthesized with excellent efficiency and selectivity when chemical and enzymatic catalysis are combined. Subsequent investigations are anticipated to examine novel approaches for merging enzymatic and chemical transformations to optimize synthesis pathways and gain access to a wide range of chemical spaces.
- **Cascade reactions:** Enzymes have the ability to catalyze a series of successive reactions in one pot, a process known as a "cascade reaction." This allows for the efficient synthesis of complex compounds from basic starting components. Subsequent research endeavors are anticipated to center around broadening the range of cascade reactions and refining enzyme cascades for industrial use.
- **Non-Natural Substrates:** Enzymes can be made more useful in organic synthesis by modifying them to accept non-natural substrates. In order to increase the range of substrates that enzymes can bind to and facilitate the synthesis of new chemical entities, future efforts are probably going to require more directed evolution and protein engineering.
- **Bioproduction of medications:** Regio and stereo-selectivity, gentle reaction conditions, and decreased environmental effect are some of the benefits of using enzymatic synthesis in the bioproduction of medications. Future perspectives include the development of enzymatic processes for the production of complex drug molecules and the integration of enzymatic synthesis into pharmaceutical manufacturing pipelines.

B. Photocatalysis:

Photocatalysis in organic synthesis holds immense promise for the future. Some key perspectives include:

- **C-H Functionalization:** It provides chances for direct C-H functionalization, opening up more cost-effective and efficient synthesis pathways that can expedite the synthesis of intricate organic compounds.
- **Late-Stage Functionalization:** Photocatalysis can help complicated compounds get functionalized at a later stage, which allows for very selective and precise modification of materials, natural products, and pharmaceuticals.
- **Flow Chemistry:** Combining photocatalysis and flow chemistry can improve automation and scalability, allowing for more effective and controlled continuous manufacturing operations.
- **Sustainable Manufacturing:** Photocatalytic technologies can help develop sustainable manufacturing techniques by utilizing renewable energy sources like sunshine and lowering dependency on fossil fuels and energy-intensive procedures.

- **New Reaction Discovery:** Research on photocatalysis is still being conducted, and this work is revealing new pathways and transformations that lead to new chemicals that can be synthesized.
- **Biocatalysis Synergy:** Combining photocatalysis with biocatalysis can have synergistic effects that can overcome the limitations of individual catalytic systems and enable new reaction cascades.
- **Applications of Materials Science:** Beyond organic synthesis, photocatalysis has applications in materials science, including solar energy conversion, pollutant degradation, and photocatalytic water splitting, all of which aid in the creation of sustainable technology.

8.6 Conclusion:

Hence ever since organic synthesis was first introduced in 1828, and since then, it has progressed to unprecedented heights in terms of molecular diversity and complexity. Its impact on science and society is growing as a result of its equally amazing applications that keep branching out into new areas. Organic synthesis laid the groundwork for an entirely new wave of scientific pursuits and enterprises, ranging from colors and pharmaceuticals to polymers and plastics. Efforts in total synthesis produced a large number of rather complicated physiologically active compounds (natural or synthesized) for use in pharmaceutical and biological research. Biomolecules like proteins, polysaccharides, nucleic acids, and their smaller cousins, oligonucleotides, peptides, and carbohydrates, were made possible by additional synthetic efforts. Organic synthesis also produces fine chemicals for use as fuels, herbicides and pesticides, vitamins, diagnostic and medical equipment, perfumes, cosmetics, fabrics, and a variety of high-tech materials for use in computers, televisions, and other information technologies, as well as space and transportation vehicles. Only the developments in the realm of organic synthesis made these applications conceivable. Therefore, it is crucial to keep developing this discipline for its own sake and to always think of new applications for it.