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SYNTHON IS A STRUCTURAL UNIT WITHIN A MOLECULE THAT CAN BE FORMED AND/OR ASSEMBLED BY KNOWN SYNTHETIC OPERATIONS

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ABSTRACT: *Retrosynthetic analysis is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures without assumptions regarding starting materials. Each precursor material is examined using the same method. This procedure is repeated until simple or commercially available structures are reached. E.J. Corey formalized this concept in his book* ***The Logic of Chemical Synthesis****. The power of retrosynthetic analysis becomes evident in the design of a synthesis. The goal of retrosynthetic analysis is structural simplification. Often, a synthesis will have more than one possible synthetic route. Retrosynthesis is well suited for discovering different synthetic routes and comparing them in a logical and straightforward fashion. A database may be consulted at each stage of the analysis, to determine whether a component already exists in the literature. In that case, no further exploration of that compound would be required. Synthon approach is followed by the following terminologies: Disconnection (A retrosynthetic step involving the breaking of a bond to form two (or more) synthons), Retron (A minimal molecular substructure that enables certain transformations), Retrosynthetic tree (A directed acyclic graph of several (or all) possible retrosyntheses of a single target), Synthon (An idealized molecular fragment), Target (The desired final compound), Transform (The reverse of a synthetic reaction; the formation of starting materials from a single product).*

KEYWORDS: Carbocation, Carbanion, Electrophile, Nucleophile, Disconnection, Synthon, Synthetic Equivalent, Target Molecule, Functional group inter–conversion, Functional Group addition, Functional Group Removal, Connective transform, Ring transform, Rearrangement transform.

INTRODUCTION: In retrosynthetic analysis, a synthon is a destructural unit within a molecule which is related to a possible synthetic operation. The term was coined in 1967 by E. J. Corey. He noted in 1988 that the word synthon has now come to be used to mean synthetic building block rather than retrosynthetic fragmentation structures.[1-5] Elias James "E.J." Corey (born July 12, 1928) is an American organic chemist. In 1990, he won the Nobel Prize in Chemistry for his development of the theory and methodology of organic synthesis, specifically retrosynthetic analysis. Regarded by many as one of the greatest living chemists, he has developed numerous synthetic reagents, methodologies and total syntheses and has advanced the science of organic synthesis considerably.

Nobel Laureate Elias James Corey: The inventor of synthon approach

In planning the synthesis of phenylacetic acid, two synthons are identified: a nucleophilic "COOH−" group, and an electrophilic $PhCH_2^+$ group. Of course, both synthons do not exist per se; synthetic equivalents corresponding to the synthons are reacted to produce the desired reactant. In this case, the cyanide anion is the synthetic equivalent for the COOH− synthon, while benzyl bromide is the synthetic equivalent for the benzyl synthon.

The synthesis of phenylacetic acid determined by retrosynthetic analysis is thus:

$PhCH_2Br + NaCN \rightarrow PhCH_2CN + NaBr$; $PhCH_2CN + 2H_2O \rightarrow PhCH_2COOH + NH_3$

Types of synthons: 1. C_2 synthons: acetylene, acetaldehyde (C_2 for two carbon atoms) 2. $-C_2H_4OH$ synthon: ethylene oxide (for two carbon atoms having total C_2H_4 bondage) 3. Carbocation synthons: alkyl halides (C^+ as carbocation or electrophile) 4. Carbanion synthons: Grignard reagents [CH_3MgX: CH_3^- & MgX^+], organolithiums [CH_3Li: CH_3^- Li^+], substituted acetylides [H–C≡C–Ag: H–C≡C$^-$ & Ag^+] (C^- as carbanion or nucleophile).

Synthon term was coined by Corey and was suggested to designate structural units within a molecule which are related to possible synthetic operations. Now a day's scientists are finding new ways to synthesize complex organic molecules and most of them are of medicinal value. Among all of these methods "synthon approach" or "retrosynthetic approach' is the more systematic approach which depends on the perception of the structural features in the reaction products and the manipulation of structures in the reverse synthetic sense. In this method the structure of the molecule to be synthesized (called as target molecule) is taken into consideration. This is then disconnected into simple and then simpler molecules called as precursors. This process is called as analysis which produces simple starting materials and shows different pathways. Once disconnection is over, the desired molecule is synthesized by the most suitable way taking easily available cheap starting materials.[6-10]

In analyzing a target structure the synthetic chemist first tries to recognize structural fragments that correspond to known synthons.

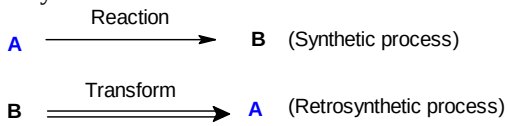


Figure-1: Structural fragments.

The retrosynthetic process through which the organic chemist establishes a synthetic plan of an organic compound, implies the disconnection of some bonds as the result of applying a transform to a given retron, to give synthons, after being conveniently elaborated, constitute the intermediate precursors for the synthesis of the target molecule.

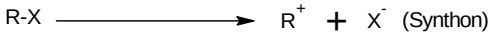


Figure-2: Synthon production by Retrosynthesis.

For E.g,
$-C_2H_5^-$ is ethyl donor (nucleophile or carbanion) synthon from reagent C_2H_5Li & $-C_2H_5^+$ is ethyl acceptor (electrophile or carbocation) synthon from reagent C_2H_5Li.
E.g 2: The electrophile in the below reaction is the carbonyl group of acetone (disconnection a) or propanone (disconnection b) and the nucleophile an organometallic reagent such as ethyl magnesium bromide (disconnection a) or methyl lithium (disconnection b). The carbanion is defined ***synthon*** whereas the organometallic reagent from which it is generated is defined ***synthetic equivalent.***[11-15]

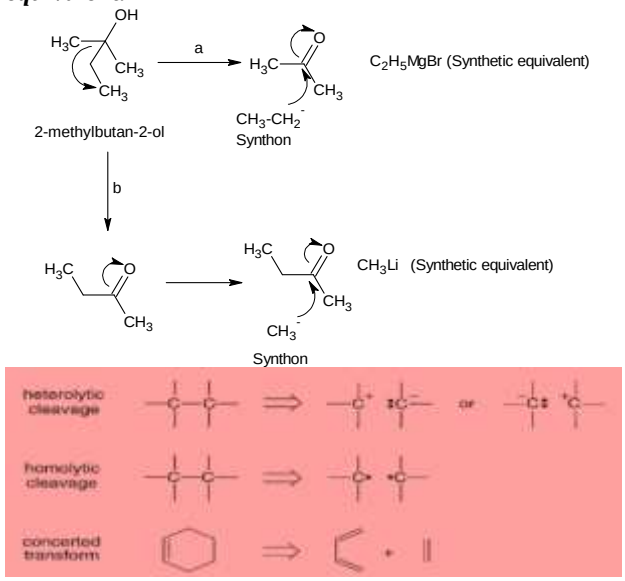


Figure-3: Connection & Disconnection.

In recognition of the importance of equivalency, a special term "synthon" was coined by Corey. This term was suggested to designate "structural units within a molecule which are related to possible synthetic operations". Now a days the organic chemists all over the world are busy on synthesis of complex organic molecules. Different types of reaction pathways have been taken for these syntheses. Even computers are also helping hands in synthetic work. In a chemical synthesis suitable reactants are chosen which undergo transformation into product molecules under specific reaction condition, i.e. Reactants [Reaction/Pathway] Product. To get a desired product easily by using less economy is important. Most of the organic complex molecules possess medicinal value. So, at present worldwide competition is going on among the chemists to find out the most viable way using easily available cheap starting materials for the synthesis of various drugs. At present, drug–designing prefers to the easy and economic process so that better result could be drawn by applying this synthon approach. In this thesis some drugs have been synthesized by applying Retrosynthetic or Antithetic approach.
Analysis: Target molecule => Offspring => Offspring Reagent
Synthesis: Offspring –» Reagent Interim Product –» Target Molecule

The synthon approach as a pragmatic tool in synthetic process: In analyzing a target structure the contemporary synthetic chemist first tries to recognize structural fragments that correspond to known synthons. Therefore, from the very beginning, retrosynthetic

analysis can be directed at the most promising and economical pathways of structure assemblage; with due elimination of low probability variants. This type of synthetic planning is often referred to as synthon approach. Frequently a retrosynthetic disconnection of a structure leads to two fragments that are recognized as a well known synthon with its corresponding set of reagents, while other looks like a bizarre species with no obvious equivalent reagents. In such cases it makes sense to analyze carefully the latter fragment with the hope of identifying a real synthetic equivalent.

Types of synthons: Antithetical disconnections are thought to divide the target molecule at C – C bond into a negative carbanion and positive carbocations made as units in synthesis are called donor synthons (d) and acceptor synthons (a). They are derived from reagents with functional groups. For example: $–C_2H_5$ is the ethyl donor synthon from reagent C_2H_5Li. $–C_2H_5$ in the ethyl acceptor synthon from reagent C_2H_5I. Synthons are numbered according to the relative positions of a functional group (FG) and the reaction carbon atoms.[16-20]

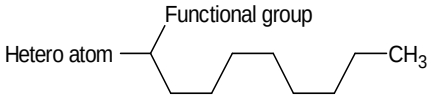
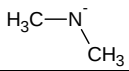
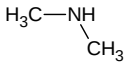
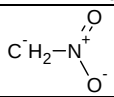
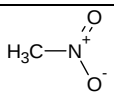
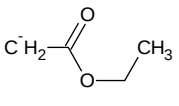
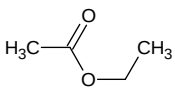
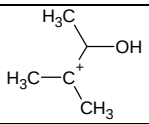
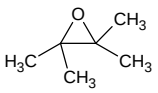
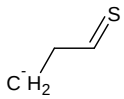
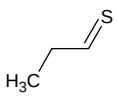
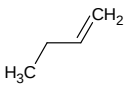
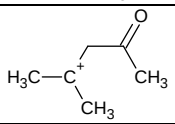
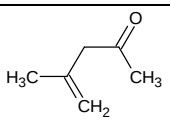
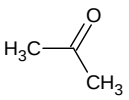


Figure-4: Antithetical disconnections.

If the electronegative heteroatom of the functional group forms covalent bonds with acceptor synthons, we call it a d° synthons. If the carbon –1 of the functional group is itself reacting that one has a d^1 and a^1 synthon. If the $–C_2$ atom to the functional group is the reactive one, we have d^2 or a^2 synthon. If the carbon atom (C_3) is the reactive one we call it d^3 or a^3 synthon. Alkyl synthons without functional groups are called alkylating synthon.

Table-1: Synthon types and reagents.

Synthon type	Example	Reagent	Functional group	Synthon type	Example	Reagent	Functional group
d^0			-NH-	a^0	$P^+(CH_3)$	CH_3-P-Cl	$-P(CH_3)_2$
d^1			$-NO_2$	a^1	$R-CO^+$	R-CO-X	-CO-X
d^2			$-COOC_2H_5$	a^2			
d^3				a^3			
Alkylide	CH_3^-	$LiCH_3$	–	Alkyl a	CH_3^+	$H_3C—X$	–

Retrosynthetic process: If there is any "golden rule" for success in planning a synthesis of a more or less complex organic compound it is to work the problem backward i.e. the chemistry must follow the reverse path that in practice will be followed in the laboratory. For, this, the target molecule is submitted to some type of "disconnection" or "mental degradation" which gives structural subunits named synthons, which are then disconnected again and the process repeated until different sequences of intermediate precursors, that go from the target down to possible target materials are generated. In the contrast to the synthetic process in the laboratory, Corey refers to this process as a retrosynthetic process and represent it by a double arrow, introducing also the terms transform and retron, as opposed to reaction and synthon.[21-25]

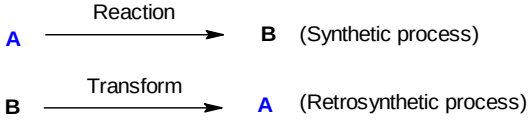


Figure-5: Synthesis & Retrosynthesis process.

Hence retrosynthetic process is termed as "a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simpler structure along a pathway which ultimately leads to simple or commercially available starting material for a chemical synthesis". According to the formalization of E.J. Corey, the retrosynthetic process through which the organic chemist establishes a synthetic plan of an organic compound, implies the disconnection of some bonds as the result of applying a transform to a given retron, to give synthons, after being conveniently elaborated, constitute the intermediate precursors for the synthesis of the target molecule.

Terminology used in synthon approach: The following terms are used during the retrosynthetic operation: (a) Disconnection (b) Synthon (c) Synthetic Equivalent (SE) (d) Target Molecule (TM) (e) Functional group inter–conversion (FGI) (f) Functional Group addition (FGA) (g) Functional Group Removal (FGR) (h) Connective transform (i) Ring transform (j) Rearrangement transform

The above terminologies used in synthon approach are discussed in brief as follows:

(a) Disconnection: It is an imaginary process in which the bonds are broken to get simple possible starting materials. This is also called as "transform". A curred line (R〰〰R) is used at the point of disconnection of bond and a double line arrow (⟹) is used for representing disconnection.

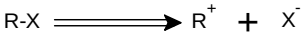


Figure-6: Disconnection.

(b) Synthon: It is an idealized fragment obtained by disconnection and may or may not be involved in the reaction but helps to work out reagents to be used.

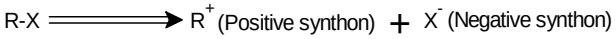


Figure-7: Positive Synthon & Negative Synthon.

(c) Synthetic equivalents (SE): It is the compound/reagent which generates the synthon. For example: CH_3I is the synthetic equivalent of the synthon CH_3^+ as the synthon CH_3^+ can be obtained from CH_3I. Similarly CH_3Li is the synthetic equivalent of CH_3^- synthon.

(d) Target molecule (TM): The molecule whose synthesis is to be planned by retrosynthetic approach is the target molecule.

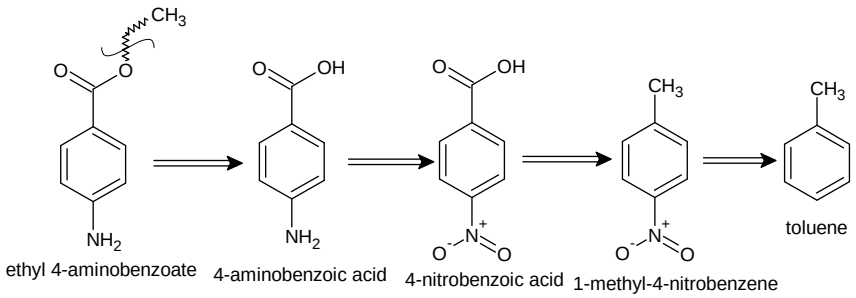


Figure-8: Target Molecule.

(e) Functional group interconversion (FGI): It is the operation of changing one functional group to another either by interconversion, substitution, elimination, oxidation or reduction, so that the disconnection becomes easier. It is denoted by the symbol.

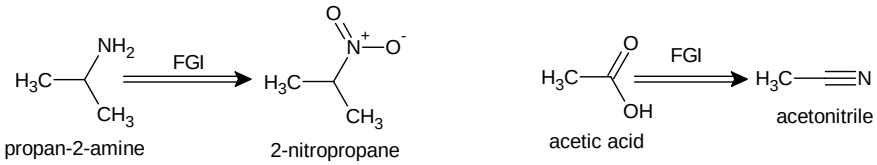


Figure-9: Functional group interconversion.

(f) Functional group addition (FGA): Sometimes it becomes necessary to add a functional group during analysis so as to make the disconnection easier. The same functional group is then removed during synthesis.

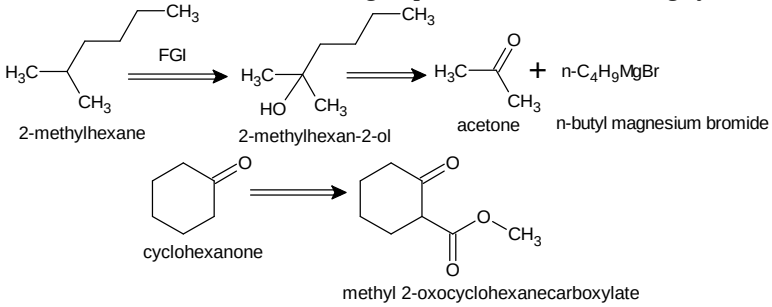


Figure-10: Functional group addition.

(g) Connective transform: The transform which connects the path between two functional groups.

Figure-11: Connective transform.

Example: Cleavage of an α, β –epoxy atoms & Hydrolysis of a lactone.

(h) Ring transform: The transform which forms or modifies some particular type of ring.

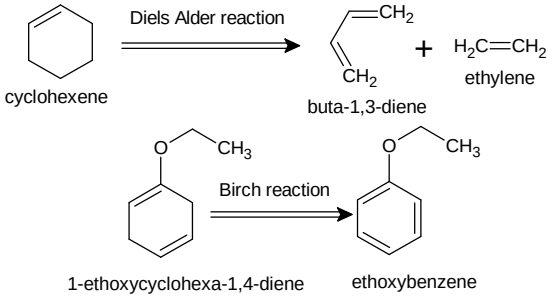


Figure-12: Ring transform.

(i) Rearrangement transform: The transform which indicates application of reaction.
Example: (i) Beckmann transform [Lactam is transformed into oxime] (ii) Favorski transform [Ester is transformed into ketone]]

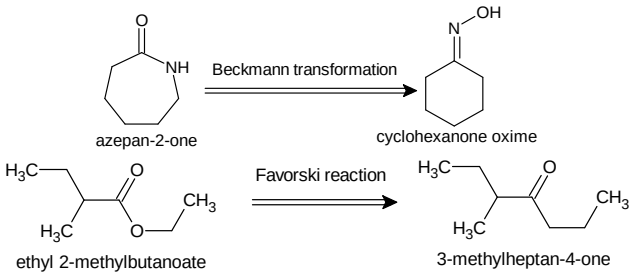


Figure-13: Rearrangement transform.

(j) Functional group removal (FGR): Sometimes the removal of a functional group becomes necessary to get more simple starting materials. It is the opposite of FGA operation.

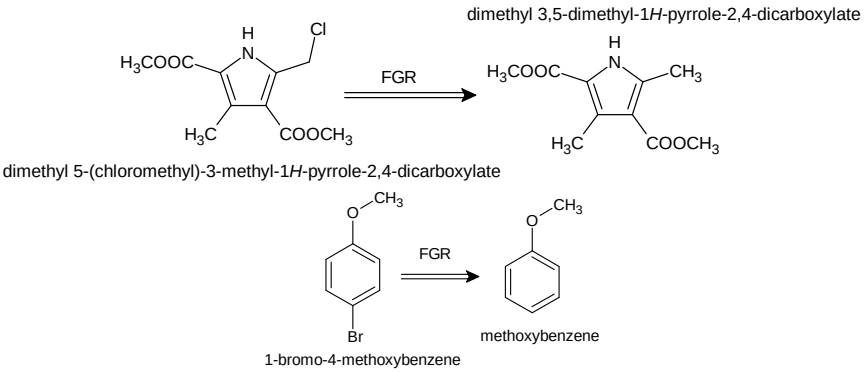


Figure-14: Functional group removal.

Problem solving techniques in synthesis: In the logic centered methodology, which is used in the planning of complex organic molecules, this implies choosing some specific strategies and using the tactical application of the different resources that modern organic chemistry offers to the chemist. In this methodology, the penetrating analysis of the structure of the target molecule can be carried out. Such an analysis leads to a limited logical set of intermediate structures which can be transformed into the original in just one reaction or synthetic step. Every structure generated is then analyzed carefully as before to give another set of structures,

which can be transformed into the preceding structures in one step. The process is repeated for every intermediate until a "tree" of such intermediate structure is obtained. By this process a set of possible alternative synthetic pathways is generated which corresponds to sequences of synthetic intermediate structure that go from possible starting material to the target molecule. It is also called "synthetic tree".[26-30]

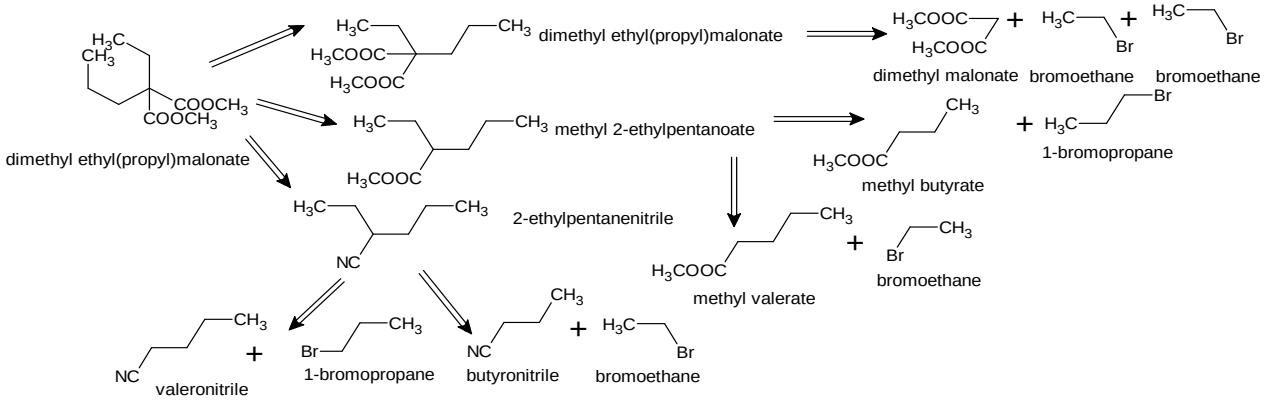


Figure-15: Synthesis tree.

Synthesis tree: The process in which a set of alternative pathways is generated which corresponds to sequences of synthetic intermediates that go from possible starting materials (I°) to the target molecule (T) It is called synthesis tree. Therefore, the synthesis tree can be pictorially represented as follows:

Synthesis tree illustrates diagrammatically the above mentioned 'golden rule'. That is so say; the derivation of the different synthetic pathways is carried out in the opposite direction to which the synthesis will be performed in the laboratory. The evaluation of different alternative pathways is sometimes immediate but in general is not so easy and several factors must be taken into account; number of steps, availability of starting materials, well known reaction that give high yield.

Examples of synthesis tree:

Strategies of synthesis: The retrosynthetic analysis strategical approach to the synthetic problem is more fascinating and more useful. The technique of systematic modification of structure in the retrosynthetic direction is guided by those strategies to uncover the latent synthetic paths. These strategies may be utilized for a complex molecule or otherwise lead to some simplification of the problem during analysis. Our main aim is to reduce the molecular complexity by using the different strategies. These are the points of molecular complexity which are given below: (i) Molecular size (ii) Cyclic connectivity (iii) Functional group content. (iv) Stereocentre content (v) Centers of high chemical reactivity.[31-35]

To overcome the above complexity following strategies may be used: (i) Transform based strategies (ii) Functional group based strategies. (iii) Structural goal based strategies (iv) Topological strategies (v) Stereochemical strategies.

(i) Transform based strategies: A strategy is the guide for retrosynthetic analysis in which the application of a particular powerful simplifying transform becomes a goal. Example: Robinson annulations to an oxydicyclohexane derivative after necessary modification.

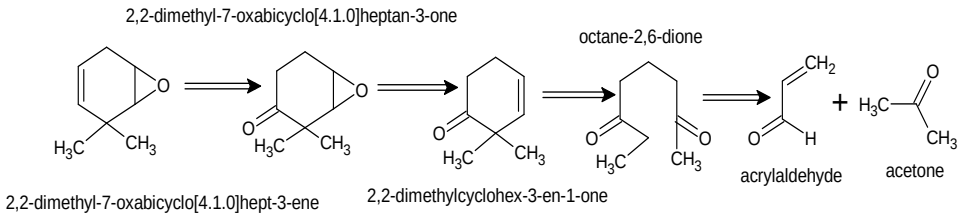


Figure-16: Transform based strategies.

(ii) Functional group based strategies: The retrosynthetic analysis of complex target molecule into sub–units depends upon the functional group or groups which helps solving the problem. The functional groups can signal the application of transform which replace functional groups or change the reactivity of functional group. Functional group interconversion is a commonly used tactics for generating retrons from a target molecule.

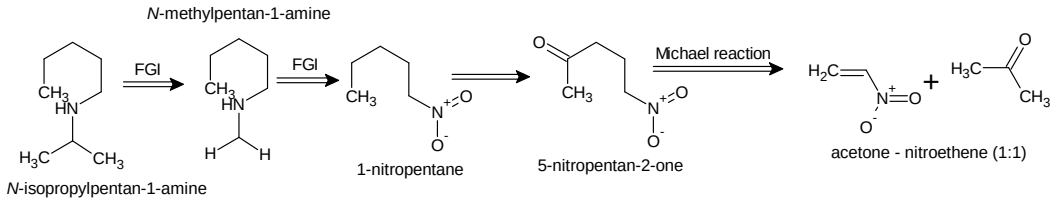


Figure-17: Functional group based strategies.

(iii) Structural goal based strategies: It is directed at the structure of a potential intermediate or starting material. Such a goal greatly narrows a retrosynthetic search and allows the application of bidirectional search technique.

Analysis of albuteral

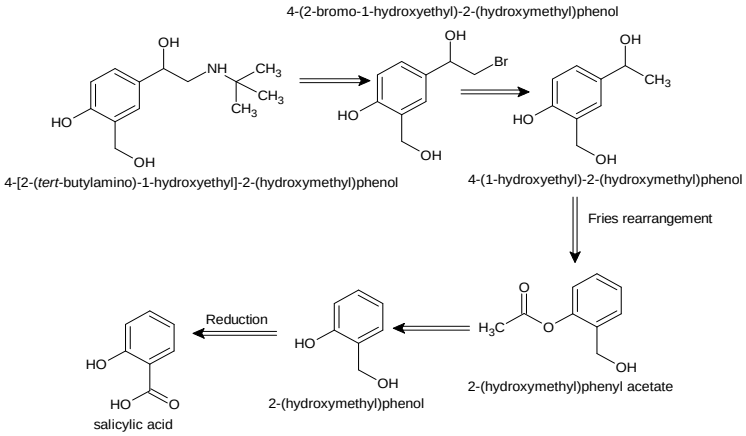


Figure-18: Structural goal based strategies.

(iv) Topological strategies: The identification of one or more individual bond disconnections is called Topological strategies. Topological strategies may also lead to the recognition of a key structure.

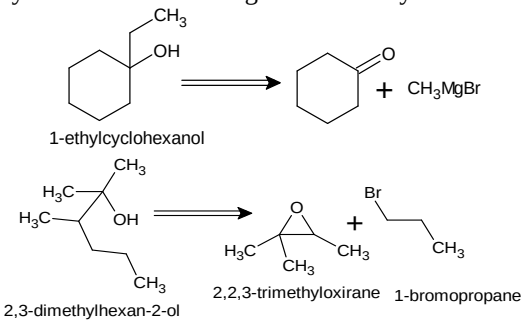


Figure-19: Topological strategies.

(v) Stereo chemical strategies: These include general strategies which remove stereocentres and stereo – relationships under stereo control. These strategies may also dictate the retention of certain stereocentre during the retrosynthetic processing or the joining of atoms in three–dimensional proximity. Example: Halo Lactonisation Transform

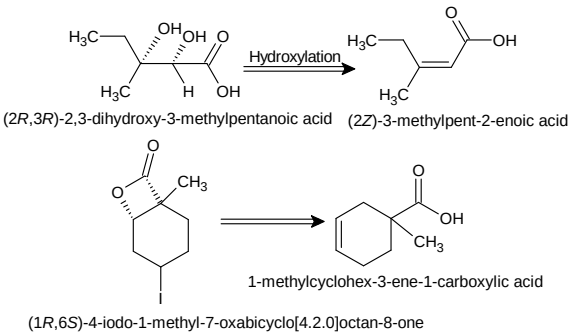
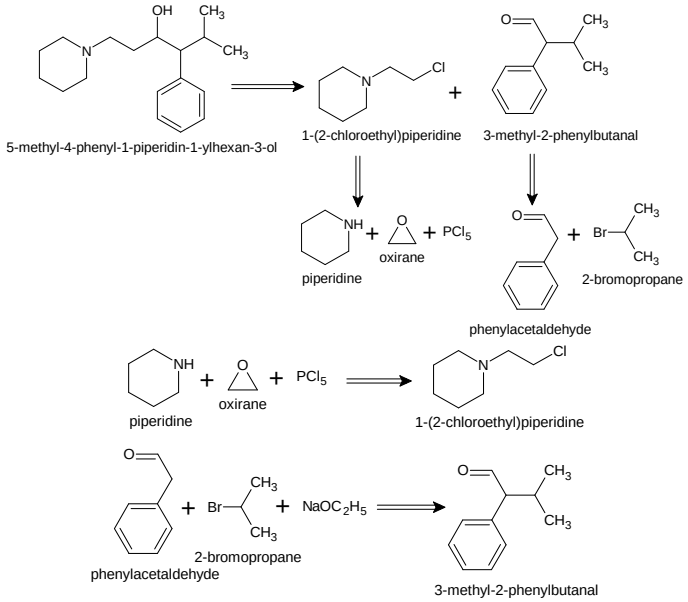


Figure-20: Stereo chemical strategies.

Additional strategies: If a target molecule resists retrosynthetic simplification, it may require the invention of a new chemical methodology. Now it is necessary to discuss certain strategies which are used for the healthy growth of a synthesis. Two of these strategies are discussed here under the heading: (1) Convergency (2) Protective groups.

Convergency: The main variable affecting economy in synthesis plan is convergency, a concept first expressed by Vel Hultz et al. In a convergent plan the steps are assembled separately and independently then linked together afterwards near the end of the synthesis. The convergent plan may be represented graphically as shown in figure:



Synthesis–1; Magnesium+Ether=TM

The TM can be made by using transform–based strategy which is a linear one.

Figure-21: Synthon Convergency.

Protective groups: In a synthetic sequence, it is frequently necessary to carry out a transformation at one centre while another reactive site remains unchanged. The group modifying the functional group is known as the protective group. The following factors must be considered in devising a plan for functional group protection. (i) The protective group should be easy to put on selectivity at the desired site in high yield. (ii) It must withstand the reaction condition for all the steps in which the functional group is not affected and it must withstand the protection and deprotection performed on the other functional groups. (iii) It must not interfere itself as a reactant with other functional groups. (iv) Finally, it must be easy to remove selectively in high yield. The selection of protective groups in synthesis planning is as important as other factors are.

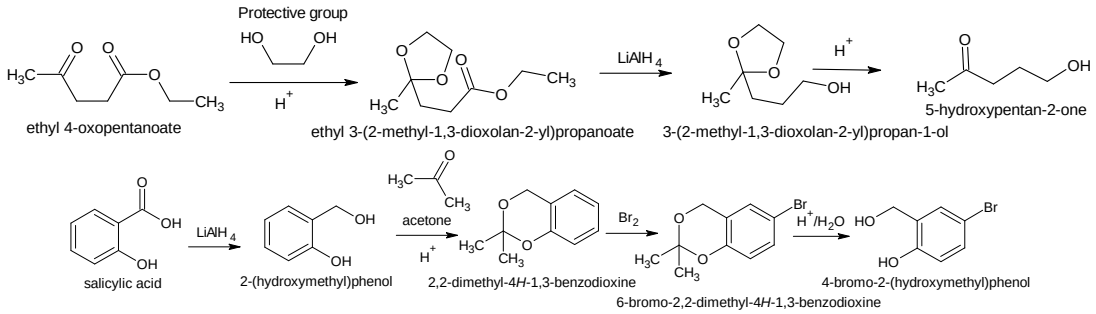


Figure-22: Protective groups.

Rules in disconnection: When one thinks of retrosynthetic analysis of a target molecule, it is a question ''where the disconnection is to be done?". This is generally governed by certain rules:

Rule–1: Disconnection of a bond should be done in such a way that it produces stable fragments. While carrying out a disconnection the molecule is broken down by one bond at a time. e.g.

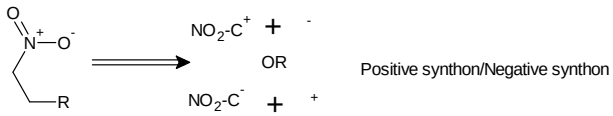


Figure-23: Rule–1 for Disconnection (generates stabilized ion fragments).

Here step–A is a correct pathway as it generates stabilized ion fragments.

Rule–2: The number of fragments generated by disconnection should be as small as possible. So, the synthesis of target molecule can be carried out in possible steps. e.g.

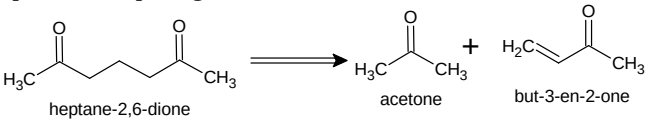


Figure-24: Rule–2 for Disconnection (Disconnected fragments should be small).

Rule – 3: A bond joining a carbon to a hetero atom always broken with the electron pair on hetero atom, e.g

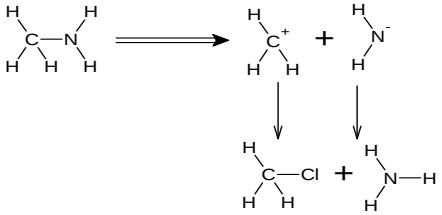


Figure-25: Rule–3 for Disconnection (Disconnection takes place always from hetero atom).

Rule– 4: Sometimes a disconnection carried out does not generate sufficient stabilized fragments, but such fragments can be obtained by using FGI or by introducing an additional electron withdrawing group and then removing it after synthesis.

Guidelines for good disconnection: Following guidelines for good disconnection: (i) Make the analysis in such a way that the synthesis becomes as short as possible. (ii) Use the only disconnections corresponding to known reliable reaction. (iii) Disconnect C–X bonds especially two group disconnections. (iv) Choose the disconnection corresponding to the highest yielding reaction, if known. (v) Disconnect back to recognizable starting materials or to compounds which can be easily be made. (vi) Disconnect C–C bonds according to the functional groups in the molecule, if possible – disconnect at the middle of the molecule. –disconnect at the branch point. – disconnect rings from chains. – use the symmetry if any. Taking the above rules into consideration any molecule with high degree of complexity in structure can be analyzed retrosynthetically.

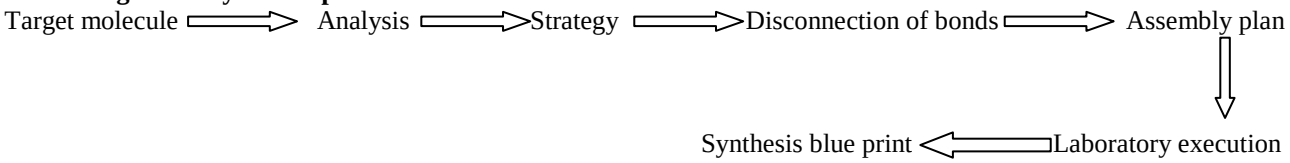
Guidelines for good synthesis: In retrosynthetic approach, there is usually more than one way to synthesize a compound. But the selection of a best desirable route is important. Thereafter the following factors are considered in order to decide which one of the routes is safe and simple to employ. (i) Availability of starting material. (ii) Which route involves the least number of separation operations? (iii) Which route gives the highest overall yield? (iv) How expensive are the starting materials and reagents? (v) Which route includes least time and effort? (vi) Miscellaneous considerations such as the case of purifying the product, stability of the intermediate, danger of the operation, toxicity of chemicals used etc.[36-40]

CONCLUSION: In this chapter, the overview is presented that a sketchy perusal of the major tools employed in organic synthesis. Our main goal is to present in a concise form, a set of underlying ideas for the elaboration of the principal methods applicable to solving the most diverse tasks in the course of construction of various organic structures. It also shows the thorough and multi–faceted analysis of the present state of the art of organic synthesis. Organic synthesis continues to react forcefully and with vitality to new challenges still ready to pursue old dreams and thus organic chemistry or organic synthesis is neither stagnating nor is 1–Base NaOEt on the decline.

Following conclusions are drawn as follows (i) Selecting the target molecules that could be collected from known structure. (ii) For a given target molecule, there is an elementary analysis carried out? (iii) From the element of analysis particular strategy is discovered. (iv) Choose the a particular strategy, which result the careful analysis of several factors. (v) After selection of a strategy, the disconnection of bonds takes place producing synthons which are converted into synthetic equivalent. The process is repeated to reach the starting material. (vi) The assembly plan may be a traditional or may have some innovation depending on the problem. (vii) Finally the synthesis blue print is prepared by writing down the reaction schemes with reagents and conditions. (viii) The

success of a synthesis plan is, however, evaluated after laboratory execution.

Floral diagram of synthesis plan



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