ORGANIC SYNTHESIS

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Summary

Organic synthesis is one of the most important driving forces towards life support and sustainable development. It provides the essential tools for building up all the molecules that help humanity to preserve health, to produce and protect crops and foods, and to improve the quality of life. Wastes cause pollution, however, and to prevent or curtail them the development of more selective and ambiently compatible processes is needed.

The present review will first examine basic organic reactions, which are the building blocks for the study of complex systems. Rate and selectivity problems are then examined and several techniques offering interesting solutions, in particular the catalytic ones, are described. A short overview of multistep syntheses follows, including oligomerization and polymerization, stepwise reactions, and sequential chain reactions, which require the solution of important chemo-, regio-, and stereoselectivity problems. In addition to the techniques based on the formation of covalent bonds, the self-assembly of molecules through weak interactions shows wide potentialities. The chemical interpretation of biological processes has also enabled chemists to develop a series of highly selective procedures, from antibody-catalyzed reactions to self-replication and autoamplification of chirality. The knowledge of the factors controlling organic synthesis has allowed the total synthesis of extremely complex molecules in one isomeric form out of the many possible. To reach such a precise goal a suitable strategy is needed. Retrosynthetic thinking and computer-aided analysis allow a careful planning of the most rational way to the desired objective. Future developments will be directed towards the design of highly selective syntheses of both known and unknown biological and chemical species.

1. Introduction

Life on earth is incessantly changing as a consequence of both natural evolution and human-operated transformation. Thus, there is a permanent need for new tools that help human life to flourish and at the same time exert a beneficial effect on the environment. Organic compounds give rise to all forms of life, and understanding the nature of their transformations is essential for the interpretation of natural phenomena and to work out life-supporting systems. As we shall see organic synthesis offers powerful and continuously evolving methods that act in this direction. Being aimed at forming derivatives of carbon, the element that is the basis of living matter, it is strongly linked to biochemistry and natural products. On the other side it has the potential for constructing a new world of purely synthetic compounds not present in nature. In any case organic synthesis is essential for providing new and advantageous ways to prepare

natural products or to modify or modulate their activity, as well as for promoting the ambiently compatible technological progress on which civilization must be based.

Looking back to the beginning of organic synthesis in the nineteenth century and comparing the state of the art at that time with the present situation leads to the conclusion that organic synthesis has been one of the most important driving forces for the development of civilization and welfare (see *History of Chemistry*). As a matter of fact, most drugs, cleaning products, detergents, disinfectants, agrochemicals, food additives, and a variety of materials (fibers, plastics, elastomers, and so on), which are capable of improving the quality of our lives, derive from organic synthesis. The dramatic change in our health conditions, which is reflected in the change of life expectancy from 40–45 years at the beginning of the nineteenth century to the present 77–80, can be largely ascribed to synthetic activity, in spite of the uncontrolled waste of polluting materials. The sustainability of these developments is now linked to the elaboration of more selective and ambiently compatible procedures and to recycling or reconverting any previously wasted by-product. To meet these requirements chemistry is evolving from the study of simple molecular systems to that of complex systems, which involve a variety of interactions with other molecular and supramolecular species such as catalysts. A revolution of organic processes has already changed a large part of the basic chemical industry through the adoption of highly selective catalytic methods and of efficient recycling and waste treatment. A similar revolution is expected to take place in fine chemical processes (e.g., pharmaceutical and specialty products).

In the following sections the fundamental organic reactions will first be examined, then the ways to make them faster and more selective. Basic synthetic methods deriving from reactivity studies on organic compounds will also be distinguished from strategies aimed at finding the most rational way to reach a target. The former teach us how to form or break bonds to carbon and to control the rate and selectivity of the process involved, while the latter go back from the desired target structures to the building blocks offered by the synthetic methods.

2. Organic Reactions

Reactivity studies are a continuous source of general methods to form or break bonds between atoms and molecules appropriately placed in the space. While specific reactions will be treated elsewhere, we shall consider here the general criteria underpinning organic synthesis.

Since chemical bonds are formed by electrons of the outer sphere of atoms, forming or breaking bonds amounts to inducing these electrons to move to or from a reaction center. Whether a bond can be formed or not is subject to thermodynamics, while whether electrons will actually undergo the expected movements is a matter of kinetics. There may be strong restrictions to overcoming the barrier offered by the transition state of a reaction, and the way to decrease or circumvent this barrier is a crucial problem of organic synthesis.

A further problem consists of learning to direct reaction selectivity. It has to be recalled that a reaction is chemoselective if it occurs selectively between a reagent and a substrate among many others possible; regioselective if it occurs within the site of a

substrate (e.g., one of the two ends of a double bond) and not with other sites; and stereoselective if it takes place at a certain position around a reaction center (e.g., at one face of a double bond) and not at other positions. The concept of stereoselection also encompasses several situations involving symmetry considerations, in particular in relation to species having identical chemical features but differing from each other by their being not superimposable (enantiomers). To envisage synthetic pathways leading selectively to one of the possible species and not to the others is thus a fundamental goal of organic synthesis (see *Chemical Thermodynamics* and *Chemical Kinetics and Dynamics*).

The methods of organic synthesis are the basic tools for building up any type of molecules. Their number is increasing at a very high rate and their detailed description is outside the scope of the present work. The reader is referred to the general books listed in the bibliography.

From a general point of view the criteria that have been followed in the elaboration of synthetic methods are based on the use of nucleophilic reagents—species having a tendency to transfer electronic density to nuclei with lower electronic density—for electrophilic substrates—namely, having affinity for electrons—and of electrophilic reagents for nucleophilic substrates. The concept of reagent is rather arbitrary since it results from the presence of an enhanced electron density or of an electron deficiency, which may also be associated with a negative or positive charge, respectively, or simply with the corresponding polarization—in some cases it is not distinguishable from the substrate. In general, however, a species that operates similar transformations on many substrates is regarded as a reagent.

Since the aim of an organic synthetic method is the formation or cleavage of at least one bond to carbon, nucleophilic or electrophilic species have to attack suitable carbon nuclei. Common nucleophiles can be metal-stabilized polar species in their monomeric or aggregate forms, such as alkoxides (e.g., $Na^+ OEt^-$), amides (e.g., $Li^+ NEt_2^-$) or carbanions (e.g., $MgBr^+ Et^-$), while their counterpart must be appropriately polarized, as in the case of the carbonyl group C = O, where oxygen withdraws electron density from the carbon nucleus, or in the case of activated olefins RCH = CH – Y, where the same function is carried out by the electron-withdrawing group Y.

According to Ingold's systematization organic reactions are classified as addition, substitution, elimination, and rearrangement reactions, and this classification will be followed within the framework of nucleophilic and electrophilic categories of reaction. The methods of organic synthesis are thus classified on the basis of the electronic nature of the reacting species (mechanistic criterium). The matter can also be regarded from the point of view of the transformation operated on carbon atoms. Thus, one can talk of oxidation or reduction processes as well as of functional group transformation (process-based criterium). Both criteria can be found variably mixed in the organic synthesis literature. Table 1 summarizes the main industrial processes.

Cracking of hydrocarbons	Ethylene, propylene, etc.
Oxidation of ethylene	Acetaldehyde
	Ethylene oxide

	Vinyl acetate
Oxidation of propylene	Propylene oxide
	Acrolein, acrylic acid
Ammoxidation of propylene	Acrylonitrile
Oxidation of cyclohexane	Cyclohexanol, cyclohexanone
Oxidation of butenes	Maleic anhydride
Oxidation of benzene	Maleic anhydride
Oxidation of benzene	Phenol
Oxidation of o-xylene	Phthalic anhydride
Ammoxidation of m-xylene	Isophthalic dinitrile
Oxidation of naphthalene	Phthalic anhydride
Chlorination of ethylene	Dichloroethane
Hydrogenation of olefins	Paraffins
Dehydrogenation of butane	Butadiene
Hydrogenation of CO	Hydrocarbons
	Methanol
	Alcohols
Hydroformylation of olefins	Aldehydes
Carbonylation of methanol	Acetic acid
Dimerization of propylene	Hexene
Codimerization ethylene-butadiene	1,4-hexadiene
Cyanation of butadiene	Adiponitrile
Metathesis of propylene	Ethylene
Metathesis of linear olefins	Internal olefins
Polymerization of olefins	Polyethylene, polypropylene,etc
Polymerization of dienes	Polybutadiene, polyisoprene, etc

Table 1. A table summarizing the main industrial processes

2.1. Reactions of Nucleophilic Reagents with Electrophilic Substrates

Several reactions can be included in the general concept of nucleophilic addition to a suitably activated substrate, in particular the well-known Grignard reaction, an example of which is shown in Eq. (1):

$$\mathrm{R\,MgX} + \mathrm{R'R''C{=}O} \longrightarrow \mathrm{R\,R'R''C-OMgX} \xrightarrow{\mathrm{H^+}} \mathrm{R\,R'R''C-OH} + \mathrm{MgX^+} \qquad (1)$$

where R, $\mathrm{R''}$, $\mathrm{R''}$ are alkyl or aryl groups, and the Michael reaction (see Eq. 2).

$$\mathrm{R^- + CH_2{=}CHY} \longrightarrow \mathrm{RCH_2\dot{C}HY} \xrightarrow{\mathrm{H^+}} \mathrm{RCH_2CH_2Y} \qquad (2)$$

where $\mathrm{R^-}$ may come from metal alkoxides, or amides, or from carbanions obtained by proton abstraction from suitable substrates, such as malonates (e.g., $^-\mathrm{CH(CO_2Et)_2}$).

Several metals can act as counterions and the metal–carbon bond can show different degrees of covalency.

Zwitterions, such as those involved in the Wittig reaction $\left(PR_3 = CR'_2 = PR_3^+ - CR_2'^-\right)$ also attack carbonyl groups with concomitant deoxygenation (see Eq. 3):

$$PPh_3 = CHCO_2Me + MeCOMe \longrightarrow Me_2C = CHCO_2Me + Ph_3P = O \qquad (3)$$

Nucleophiles can also be found in the class of radical species R ,˙ which, in spite of being neutral, possess nucleophilic or electrophilic character depending on their polar character (e.g., Eq. (4), Y = electron-withdrawing group if R is nucleophilic):

$$R^{\cdot} + CH_2 = CHY \rightarrow RCH_2 - \dot{C}HY \rightarrow RCH_2CHY - CHYCH_2R \qquad (4)$$

Electron transfer from carbanions can also generate radicals from electron-acceptor substrates.

Organometallics can provide covalent metal to carbon bonds $(M - R)$, which in many cases are polarized as $M^+ - R^-$ and readily undergo an "insertion" reaction; in this case it corresponds to a type of nucleophilic attack on metal-coordinated molecules or groups, which occurs within the metal coordination sphere and can lead to olefins if reductive elimination of the metal finally occurs (see Eq. 5):

$$\begin{aligned} &M - R + CH_2 = CHY \rightarrow \left(CH_2 = CHY\right)M - R \rightarrow \\ &\rightarrow RCH_2 - CHY - M \rightarrow RCH = CHY + MH \end{aligned} \qquad (5)$$

Alternatively the nucleophile attacks a metal-coordinated olefin from "outside" the complex, as for example in the Wacker process for the synthesis of acetaldehyde from ethylene, where addition of water is coupled to dehydrogenation (see Eq. 6):

$$H_2O + \left(CH_2 = CH_2\right)PdCl_2 \rightarrow \left[HOCH_2CH_2 - Pd - Cl\right] \rightarrow CH_3CHO + 2HCl \qquad (6)$$

Besides the addition reactions mentioned above, elimination reactions leading to double bonds can be started by bases (i.e., nucleophiles having affinity for the proton). An example of an E2 reaction is shown in Eq. (7):

$$B + H - CH_2 - CH_2 - Y \rightarrow BH^+ + CH_2 = CH_2 + Y^- \rightarrow B + HY \qquad (7)$$

Alternatively, they can be initiated—in cases where a carbocation is sufficiently stable—by dissociation of Y^- and H^+ elimination from the carbocation with neutralization of HY by the base (E1 reaction). Radicals as well as organometallic species can also effect elimination reaction.

Analogously, substitution reactions can be induced by nucleophiles that replace a

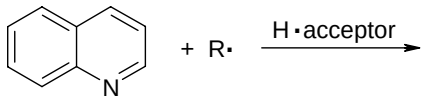
leaving group Y (SN2 reaction). An example is the amination reaction of an alkyl halide (see Eq. 8):

$$Et_2NH + RCH_2 - Y \rightarrow RCH_2NEt_2 + HY \quad (8)$$

Also, in this case it is possible that a preliminary dissociation occurs when the Y-bonded carbon can stabilize a positive charge (SN1 reaction). The area of nucleophilic substitution also includes nucleophilic aromatic substitution reactions in which the presence of electron-withdrawing groups in the aromatic nucleus favors the replacement of appropriate leaving groups by nucleophiles (e.g., Eq. (9), R = alkyl):

$$p\text{-}O_2N - C_6H_4 - F + HNR_2 \rightarrow p\text{-}O_2N - C_6H_4 - NR_2 + HF \quad (9)$$

In an analogous way nucleophilic radicals attack electron-deficient molecules (see Eq. 10):



(10)

2.2. Reactions of Electrophilic Reagents with Nucleophilic Substrates

Similar to what was described for nucleophiles, electrophilic reagents can attack suitably activated substrates. Thus, acid HX addition to alkynes and alkenes can be readily effected (e.g., Eq. 11):

$$HX + CH \equiv CH \rightarrow H - CH = CH - X \quad (11)$$

Friedel–Crafts compounds, the most popular of which is $R^+AlCl_4^-$, can alkylate or acylate $\left(RCO^+AlCl_4^-\right)$ aromatic compounds (e.g., Eq. 12):

$$C_6H_6 + R^+AlCl_4 \rightarrow C_6H_5R + HCl + AlCl_3 \quad (12)$$

Electrophilic radicals, such as those with the unpaired electron on the oxygen atom, are known to attack $C - C$ double bonds (e.g., Eq. (13), Z = electron-releasing group):

$$ROO^{\cdot} + CH_2 = CH - Z \rightarrow ROOCH_2\dot{C}HZ \quad (13)$$

Organometallic species are able to distribute electron density of the metal–carbon bond to a different extent, depending on the metal oxidation state and on the other ligands. It is thus possible that a metal-bonded hydrogen or an alkyl group R behave as an electrophile, migrating on a nucleophilic substrate (see Eq. (14), Z = electron-releasing group):

$$R-M+CH_2=CH-Z \quad \rightarrow \quad RCH(Z)CH_2-M \tag{14}$$

Nucleophilic and electrophilic reactivity appears to be the key for the rationalization of the extremely various panorama of organic synthesis. In a similar way it is possible to explain molecular rearrangements: another important class of reactions, based on the formation of an electron-deficient center, in which an electron-rich center migrates after breaking a bond and, vice versa, an electron-poor center can migrate on an electron-rich center. A well-known example is offered by the acid-catalyzed rearrangement of cumyl hydroperoxide to phenol (see Eq. 15):

$$\begin{aligned} &Ph-C(Me_2)OOH \xrightarrow{H^+} Ph-C(Me_2)O^+ + H_2O \rightarrow \\ &\rightarrow \ {}^+C(Me_2)O-Ph \xrightarrow{H_2O} HOPh + MeCOMe \end{aligned} \tag{15}$$

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Biographical Sketch

Gian Paolo Chiusoli graduated in Chemistry at the University of Padova (Padua), Italy. He later enrolled as a researcher at the Donegani Research Institute, the main industrial research center for chemistry in Italy. His activities concerned methods of organic synthesis and their application to the basic problems of the petrochemical industry, as well as to fine chemicals production (dyestuffs, pharmaceuticals, agrochemicals, and so on). He was particularly concerned with new catalytic systems based on transition metal complexes to obtain selective processes under mild conditions. In 1960 he became a university lecturer and in this way he maintained good connections between his research activities in organic synthesis at Donegani and the university's laboratories. In 1966 he became Director of the Donegani Research Institute, where he organized an efficient interchange between basic and applied research.

In 1974 he obtained the chair of Industrial Organic Chemistry at the University of Parma, Italy, where he concentrated his research on the study of complex systems, and in particular on the design of catalytic organic syntheses occurring through chain-growth processes. This research activity is at the borderline with inorganic chemistry, as far as organometallic compounds are involved, and with biochemistry, as far as the study of biological processes is a continuous source of solutions to the problems of organic synthesis. Professor Chiusoli is the author of more than 250 papers and 125 patents referring to new synthetic procedures. He is now Emeritus Professor at the University of Parma. He is or was a member of the editorial boards of several chemical journals and a member or chairman of a number of scientific councils. He also is member of the Italian Accademia Nazionale dei Lincei and of Academia Europea.