INDORE INDIRA SCHOOL OF CAREER STUDIES

B.Sc. VI SEM

SUBJECT - CHEMISTRY

SYLLABUS

B.Sc. VI SEM

Subject – Chemistry

UNIT – 1	**A. Amino acids:** Classification, structure, stereochemistry of amino acids, acid base behaviour, isoelectric point, general methods of preparation and properties of α-amino acids. Proteins and peptides. Introduction to peptides linkage, end group analysis, classification, properties and structure of proteins (primary, secondary and tertiary). **B. Nucleic acids**: Introduction of nucleic acids and constituents of nucleic acid, Ribonucleosides, Ribonucleotides, double helical structure of DNA. **C. Elementary idea of Fats, Oils & Detergents**: Natural fats, edible and industrial oils of vegetable origin, common fatty acids, glycerides, hydrogenation of unsat
UNIT – 2	**A. Organometallic Chemistry**: Synthesis; structure and bonding in metal carbonyl complexes, metal olefin complexes and metal alkyne complexes. Oxidative addition reactions. **B. Organometallic Compounds:** Organomagnesium Compound - Grignard Reagent and Organolithium Compounds, methods of preparation, structure and synthetic applications.
UNIT -3	**A. Magnetic properties of transition metal complexes**: magnetic moment (spin only and with L-S coupling), orbital contribution magnetic moment. **B. Electronic spectra of transition metal complexes**: Spectroscopic ground and excited states, types of electronic transitions, selection rules for d-d transitions, Orgel-energy level diagram for d1 to d9 states. **C. Water Analysis:** Hardness, types of hardness, acidity and alkalinity, BOD, COD and DO.
UNIT – 4	**A. Infrared spectroscopy :** Statement of the Born-Oppenheimer approximation, rotational spectrum of diatomic molecules. Energy levels of a rigid rotator, selection rule, intensity of absorption bands, Maxwell-Boltzmann distribution and population of energy levels. **B. Energy levels of simple harmonic** oscillator, selection rules, pure vibrational spectrum, intensity and qualitative relation of force constant and bond energies, degree of freedom and modes of vibration, vibrational frequencies of different functional groups. **C. Raman Spectroscopy:** concept of polarizability, pure rotational and pure vibrational Raman spectra of diatomic molecules. Selection rules, application of Ramanspectrum

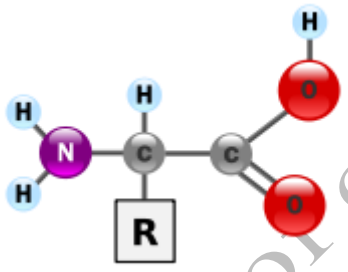
UNIT- 5	**A. NMR Spectroscopy** Principle and Instrumentation, NMR active nucleus, chemical shift, spin-spin coupling, spectrum of ethanol and ethanal. **B. Surface Phenomena and Catalysis**: adsorption of gases and liquids on solid adsorbent, Freundlich and Langmuir adsorption isotherms, determination of surface area, characteristics and mechanism of heterogeneous catalysis.

Unit – 1

Amino acid ,Nucleic acid and Fats, oils ,detergent

Amino acid →

Amino acids are biologically important organic compounds containing amine (-NH2) and carboxyl (-COOH) functional groups, along with a side-chain (R group) specific to each amino acid. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen, though other elements are found in the side-chains of certain amino acids.



About 500 amino acids are known (though only 20 appear in the genetic code) and can be classified in many ways.

They can be classified according to the core structural functional groups' locations as alpha- (α-), beta- (β-), gamma- (γ-) or delta- (δ-) amino acids; other categories relate to polarity, pH level, and side-chain group type (aliphatic, acyclic, aromatic, containing hydroxyl or sulfur, etc.). In the form of proteins, amino acids comprise the second-largest component (water is the largest) of human muscles, cells and other tissues. Outside proteins, amino acids perform critical roles in processes such as neurotransmitter transport and biosynthesis.

Amino acid

Twenty percent of the human body is made up of protein. Protein plays a crucial role in almost all biological processes and amino acids are the building blocks of it.

A large proportion of our cells, muscles and tissue is made up of amino acids, meaning they carry out many important bodily functions, such as giving cells their structure. They also play a key role in the transport and the storage of nutrients. Amino acids have an influence on the function of organs, glands, tendons and arteries. They are furthermore essential for healing wounds and repairing tissue, especially in the muscles, bones, skin and hair as well as for the removal of all kinds of waste deposits produced in connection with the metabolism.

Classifications

Experts classify amino acids based on lots of different features. One of them is whether or not people can acquire them through the diet. According to this factor, scientists recognize 3 types: the nonessential, essential, and conditionally essential amino acids. However, the classification as essential or nonessential doesn't actually reflect their importance, as all twenty of them are necessary for human health. Those 8 called essential (or indispensable) can't be produced by the body and therefore should be supplied by food: Leucine, Isoleucine, Lysine, Threonine, Methionine, Phenylalanine, Valine, and Tryptophan. One more amino acid, Histidine, can be considered semi-essential, as the human body doesn't

always need dietary sources of it. Meanwhile, conditionally essential amino acids aren't usually required in the human diet, but are able to become essential under some circumstances. Finally, nonessential ones are produced by the human body either out of the essential ones or from normal proteins breakdown. These include Asparagine, Alanine, Arginine, Aspartic acid, Cysteine, Glutamic acid, Glutamine, Proline, Glycine, Tyrosine, and Serine.

One more classification depends on the side chain structure, and experts recognize 5 types in this classification:
1. containing sulfur (Cysteine and Methionine)
2. neutral (Asparagine, Serine, Threonine, and Glutamine)
3. acidic (Glutamic acid and Aspartic acid) and basic (Arginine and Lysine)
4. alphatic (these include Leucine, Isoleucine, Glycine, Valine, and Alanine)
5. aromatic (these include Phenylalanine, Tryptophan, and Tyrosine)

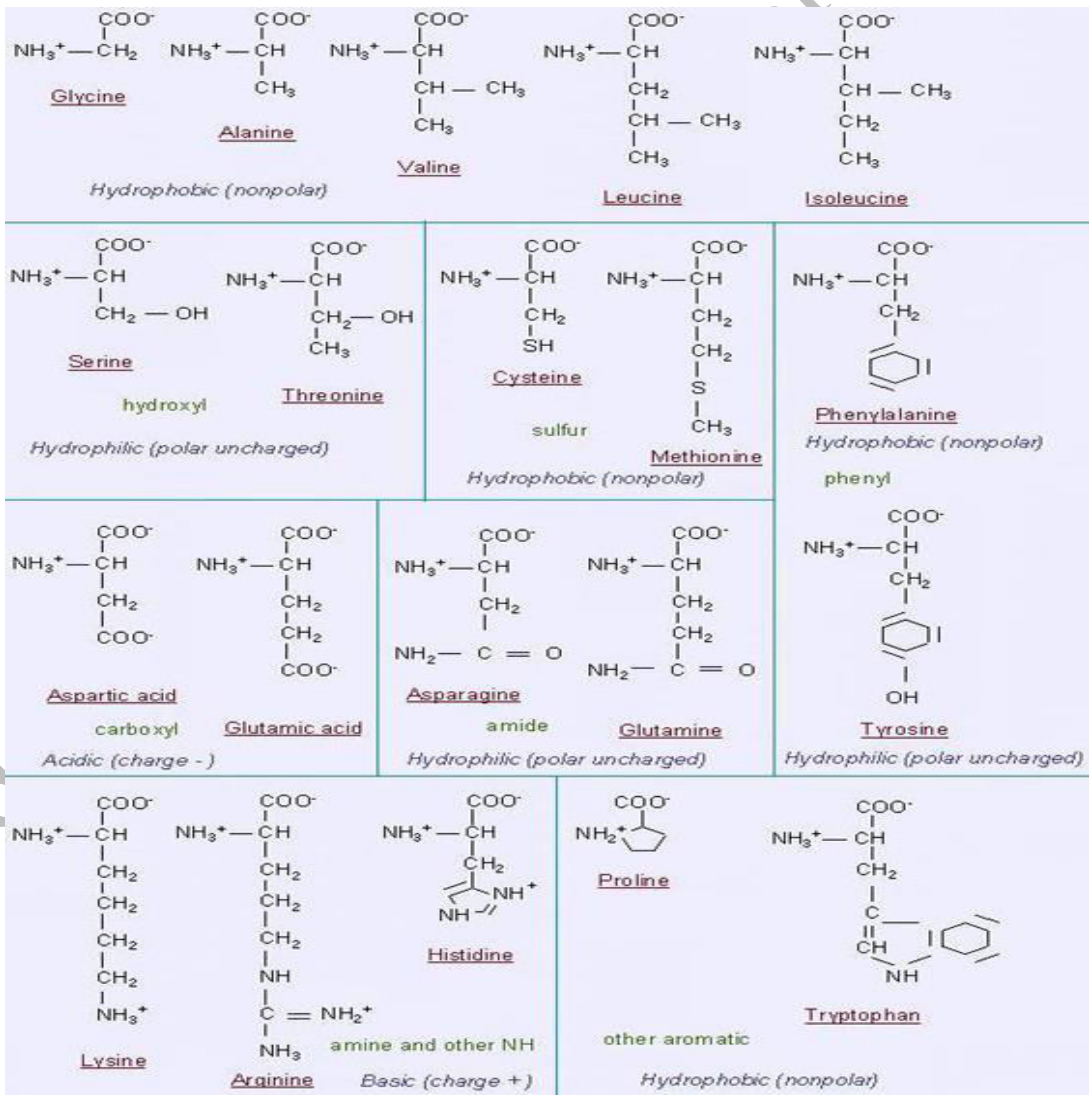
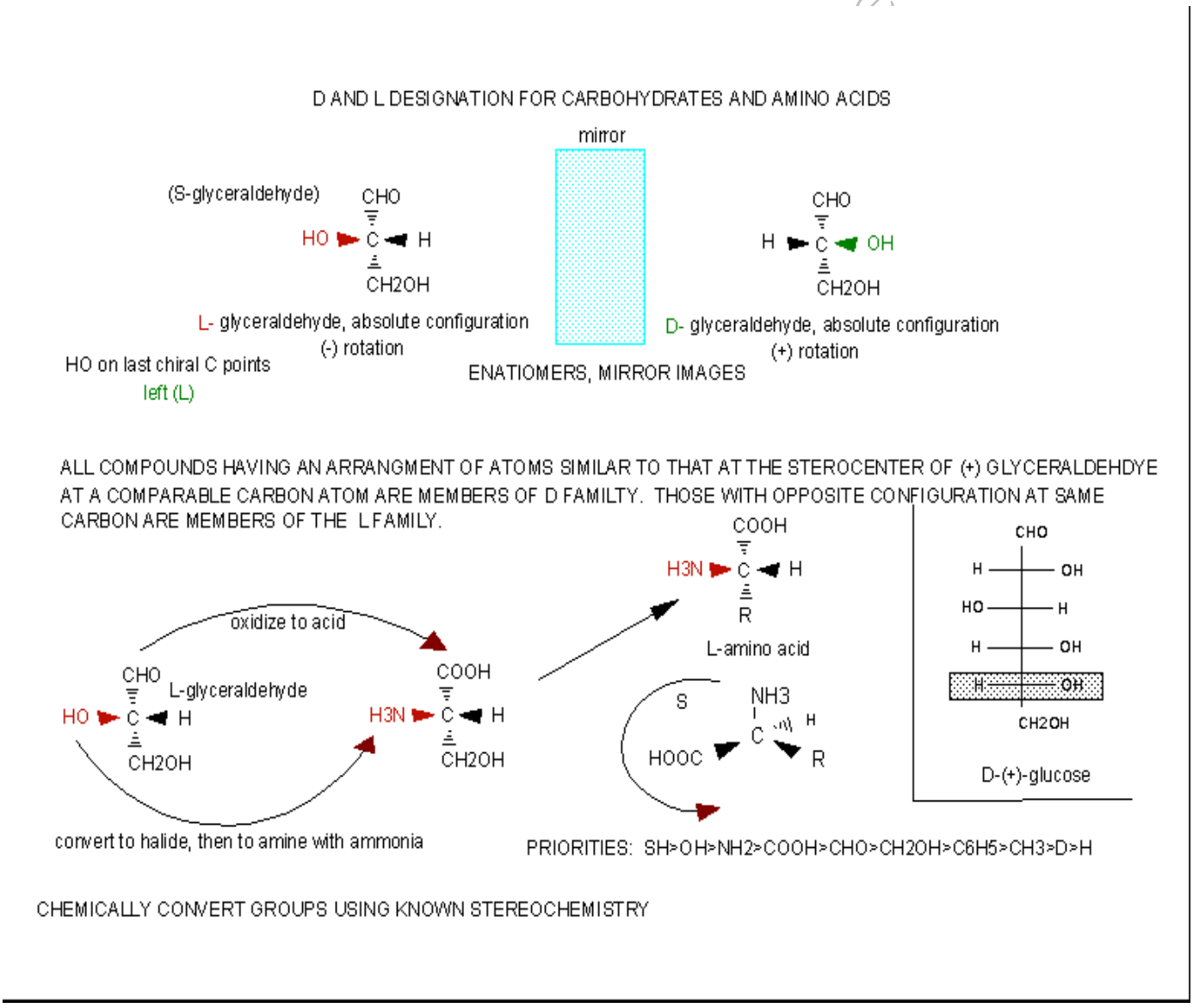


Fig. All Amino acid

Stereochemistry

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L and D nomenclature. All naturally occuring proteins from all living organisms consist of L amino acids. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids. Most naturally occurring chiral amino acids are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

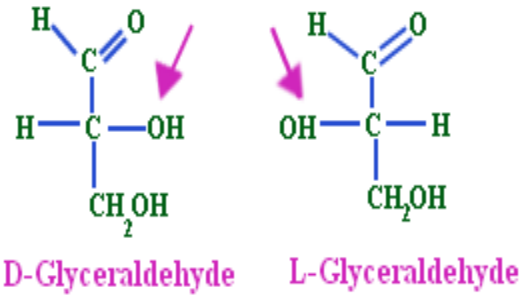
Figure: Stereochemistry of Amino Acids.



"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules.

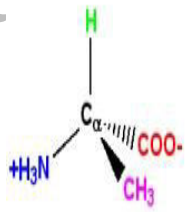
For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), but this just reflects the human decision to give a sulphur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like aminoacids and simple sugars. "

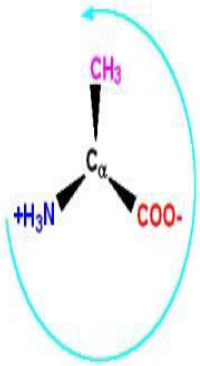


D-Glyceraldehyde

L-Glyceraldehyde



L-Alanine



(S)-Alanine

Physical property of amino acid →

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 ℃	5.0

lactic acid	$CH_3CH(OH)CO_2H$		complete	complete	53 ºC	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 ºC	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 ºC	9.8

The Isoelectric Point

As defined above, the isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value.

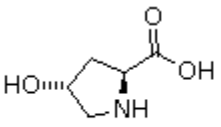
If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$).

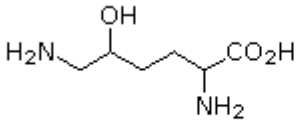
In the case of aspartic acid, the similar acids are the alpha-carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 + 3.9)/2 = 3.0. For arginine, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75.

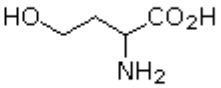
Other Natural Amino Acids

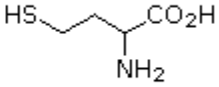
The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound.

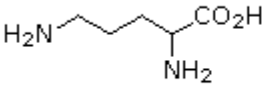
These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.


4-hydroxyproline


5-hydroxylysine

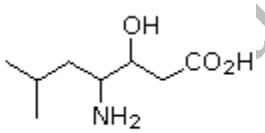

homoserine


homocysteine


ornithine


β-alanine

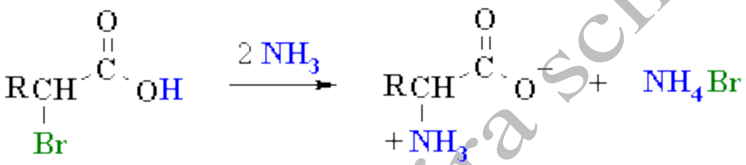

γ-aminobutyric acid (GABA)


statine

Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

Method of preperation of amino acid

Nucleophilic substitution of α-halocarboxylic acids

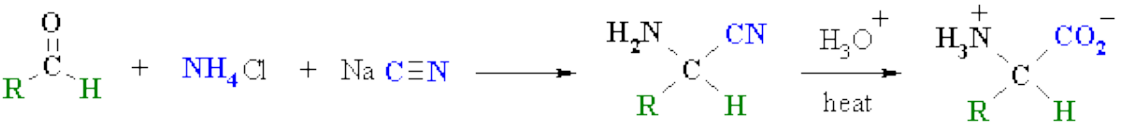


Reaction type: Nucleophilic Substitution

Summary

- Reagents : excess ammonia.
- This reaction is an example of a nucleophilic substitution with a halide as the leaving group.
- The α-halocarboxylic acid can be obtained via an α-substitution reaction of a carboxylic acid (Hell-Volhard-Zelinsky reaction).

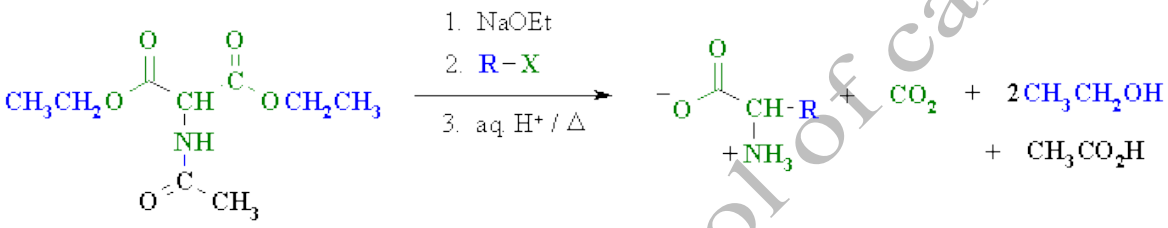
Strecker Synthesis



Reaction type: Nucleophilic Addition then Nucleophilic Acyl Substitution

- Reagents : NH_4Cl / NaCN then aq. acid / heat with a basic work-up.
- Nucleophilic cyanide ion normally adds to an aldehyde to give a cyanohydrin, an α-hydroxy nitrile.
- However, in the presence of ammonium chloride, the analogous α-amino nitrile is obtained.
- Remember that aldehydes are electrophilic at the carbonyl **C** atom.
- Hydrolysis converts the nitrile to the carboxylic acid converts so providing the α-amino acid .

Alkylation of an Acetamidomalonate



Reaction type: Nucleophilic Substitution then amide and ester hydrolysis and finally decarboxylation (!)

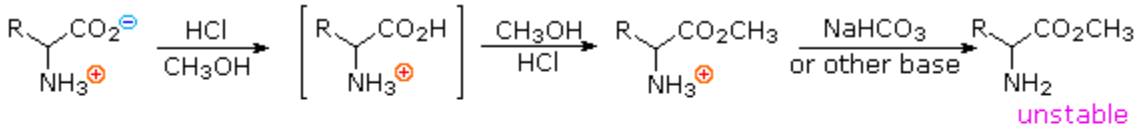
Summary

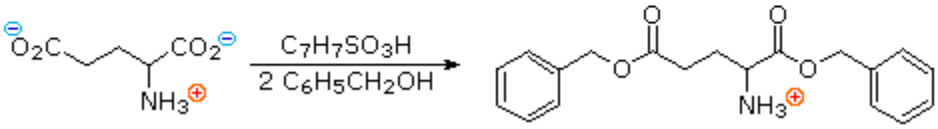
- Reagents : (1) NaOEt, (2) alkyl halide, then (3) aq. acid / heat
- Although this looks complex, it is an application of reactions seen previously:
  - alkylation of an enolate
  - hydrolysis of an amide
  - hydrolysis of an ester
  - decarboxylation of a β-dicarboxylic acid
- The malonate derivative is treated with a base to form the nucleophilic enolate that then reacts with the alkyl halide.
- Note that the *same* acetamido malonate can be used to form *any* primary α-amino acid.

Hydrolysis of the malonate ester and the amide forms an intermediate amino dicarboxylic acid Reactions of α-Amino Acids

1. Carboxylic Acid Esterification

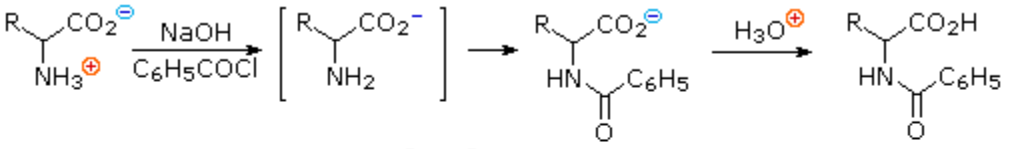
Amino acids undergo most of the chemical reactions characteristic of each function, assuming the pH is adjusted to an appropriate value. Esterification of the carboxylic acid is usually conducted under acidic conditions, as shown in the two equations written below. Under such conditions, amine functions are converted to their ammonium salts and carboxyicacids are not dissociated. The first equation is a typical Fischer esterification involving methanol. The initial product is a stable ammonium salt. The amino ester formed by neutralization of this salt is unstable, due to acylation of the amine by the ester function. The second reaction illustrates benzylation of the two carboxylic acid functions of aspartic acid, using p-toluenesulfonic acid as an acid catalyst. Once the carboxyl function is esterified, zwitterionic species are no longer possible and the product behaves like any 1°-amine.

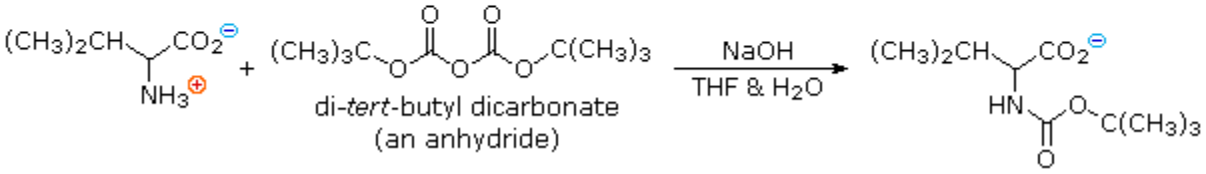




2. Amine Acylation

In order to convert the amine function of an amino acid into an amide, the pH of the solution must be raised to 10 or higher so that free amine nucleophiles are present in the reaction system. Carboxylic acids are all converted to carboxylate anions at such a high pH, and do not interfere with amine acylation reactions. The following two reactions are illustrative. In the first, an acid chloride serves as the acylating reagent. This is a good example of the superior nucleophilicity of nitrogen in acylation reactions, since water and hydroxide anion are also present as competing nucleophiles. A similar selectivity favoring amines was observed in the Hinsberg test. The second reaction employs an anhydride-like reagent for the acylation. This is a particularly useful procedure in peptide synthesis, thanks to the ease with which the t-butylcarbonyl (**t-BOC**) group can be removed at a later stage. Since amides are only weakly basic (pK_a~ -1), the resulting amino acid derivatives do not display zwitterionic character, and may be converted to a variety of carboxylic acid derivatives.



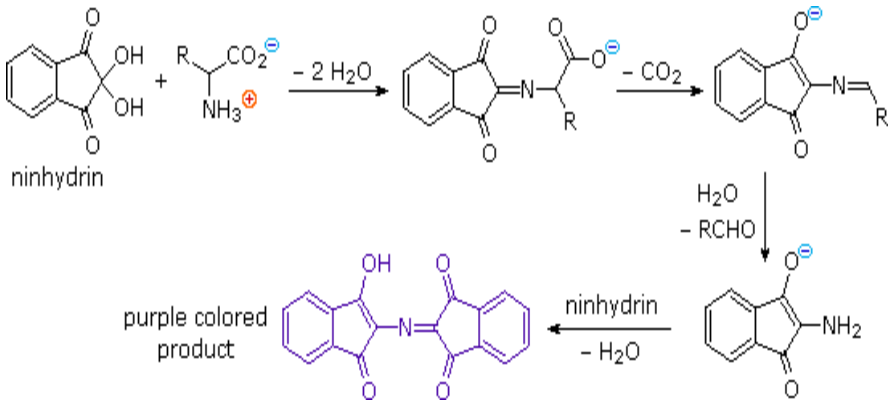


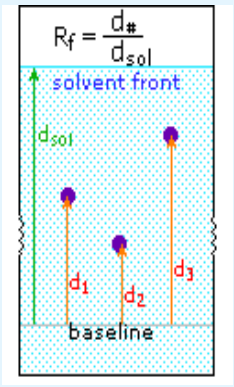
3. The Ninhydrin Reaction

In addition to these common reactions of amines and carboxylic acids, common alpha-amino acids, except proline, undergo a unique reaction with the triketohydrindene hydrate known as ninhydrin. Among the products of this unusual reaction (shown on the left below) is a purple colored imino derivative, which provides as a useful color test for these amino acids, most of which are colorless.

A common application of the ninhydrin test is the visualization of amino acids in **paper chromatography**. As shown in the graphic on the right, samples of amino acids or mixtures thereof are applied along a line near the bottom of a rectangular sheet of paper (the baseline). The bottom edge of the paper is immersed in an aqueous buffer, and this liquid climbs slowly toward the top edge. As the solvent front passes the sample spots, the compounds in each sample are carried along at a rate which is characteristic of their functionality, size and interaction with the cellulose matrix of the paper. Some compounds move rapidly up the paper, while others may scarcely move at all. The ratio of the distance a compound moves from the baseline to the distance of the solvent front from the baseline is defined as the retardation (or

retention) factor $\mathbf{R_f}$. Different amino acids usually have different R_f's under suitable conditions. In the example on the right, the three sample compounds (1, 2 & 3) have respective R_f values of 0.54, 0.36 & 0.78. To animate this diagram Click on It.





Paper Chromatography

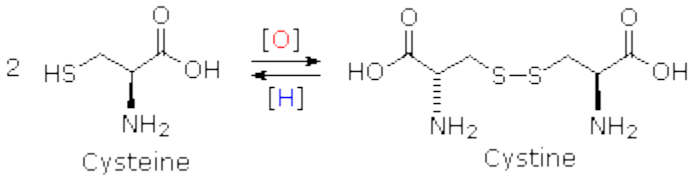
4. Oxidative Coupling

The mild oxidant iodine reacts selectively with certain amino acid side groups. These include the phenolic ring in tyrosine, and the heterocyclic rings in tryptophan and histidine, which all yield products of electrophilic iodination. In addition, the sulfur groups in cysteine and methionine are also oxidized by iodine. Quantitative measurement of iodine consumption has been used to determine the number of such residues in peptides.

The basic functions in lysine and arginine are onium cations at pH less than 8, and are unreactive in that state. Cysteine is a thiol, and like most thiols it is oxidatively dimerized to a disulfide, which is sometimes listed as a distinct amino acid

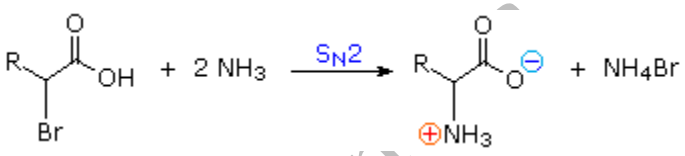
under the name **cystine**. Disulfide bonds of this kind are found in many peptides and proteins. For example, the two peptide chains that constitute insulin are held together by two disulfide links. Our hair consists of a fibrous protein called keratin, which contains an unusually large proportion of cysteine. In the manipulation called "permanent waving", disulfide bonds are first broken and then created after the hair has been reshaped. Treatment with dilute aqueous iodine oxidizes the methionine sulfur atom to a sulfoxide.

Cysteine-Cystine Interconversion

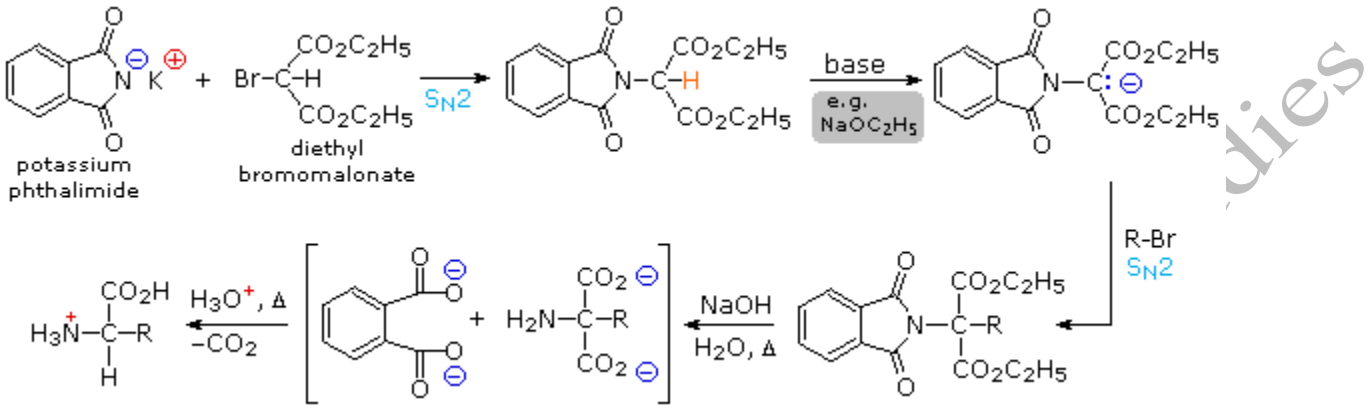


Synthesis of alpha amino acid

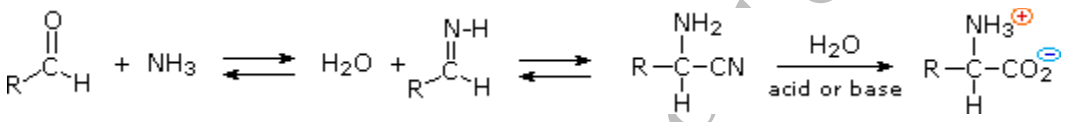
1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with $Br_2 + PCl_3$. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1º- and many 2º-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).



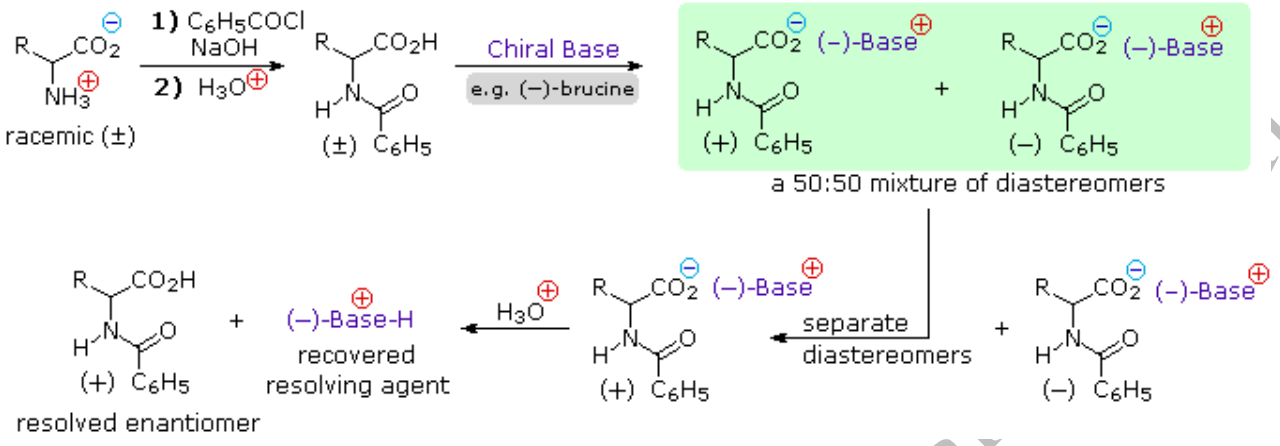
3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.



4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine).

The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.

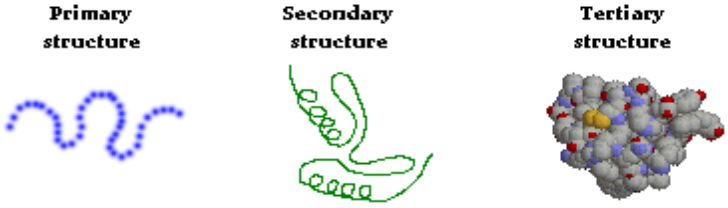


Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. By clicking on the above diagram, this alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer.

If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitter ionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

Structural features of proteins :

- **Primary structure:** the linear arrangment of amino acids in a protein and the location of covalent linkages such as disulfide bonds between amino acids
- **Secondary structure:** areas of folding or coiling within a protein; examples include alpha helices and pleated sheets, which are stabilized by hydrogen bonding.
- **Tertiary structure:** the final three-dimensional structure of a protein, which results from a large number of non-covalent interactions between amino acids.
- **Quaternary structure:** non-covalent interactions that bind multiple polypeptides into a single, larger protein. Hemoglobin has quaternary structure due to association of two alpha globin and two beta globin polyproteins.



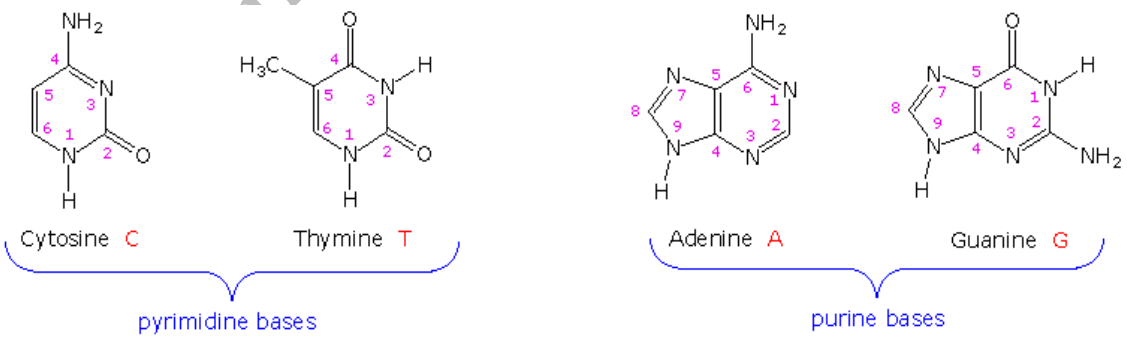
The primary structure of a protein can readily be deduced from the nucleotide sequence of the corresponding messenger RNA. Based on primary structure, many features of secondary structure can be predicted with the aid of computer programs. However, predicting protein tertiary structure remains a very tough problem, although some progress has been made in this important area.

Nucleic acid

Nucleic acids are biopolymers, or large biomolecules, essential to all known forms of life. They are composed of monomers, which are nucleotides made of three components: a 5-carbon sugar, a phosphate group, and a nitrogenous base. If the sugar is a simple ribose, the polymer is RNA (ribonucleic acid); if the sugar is derived from ribose as deoxyribose, the polymer is DNA (deoxyribonucleic acid).

Nucleic acids are among the most important biological macromolecules (others being amino acids-proteins, sugars-carbohydrates, and lipids-fats). They are found in abundance in all living things, where they function in encoding, transmitting and expressing genetic information. In other words, information is conveyed through the order of nucleotides within a DNA or RNA molecule. Strings of nucleotides strung together in a specific sequence are the mechanism for storing and transmitting hereditary, or genetic information via protein synthesis

The first isolation of what we now refer to as **DNA** was accomplished by Johann Friedrich Miescher *circa* 1870. He reported finding a weakly acidic substance of unknown function in the nuclei of human white blood cells, and named this material "nuclein". A few years later, Miescher separated nuclein into protein and nucleic acid components. In the 1920's nucleic acids were found to be major components of chromosomes, small gene-carrying bodies in the nuclei of complex cells. Elemental analysis of nucleic acids showed the presence of phosphorus, in addition to the usual C, H, N & O. Unlike proteins, nucleic acids contained no sulfur. Complete hydrolysis of chromosomal nucleic acids gave inorganic phosphate, 2-deoxyribose (a previously unknown sugar) and four different heterocyclic bases (shown in the following diagram). To reflect the unusual sugar component, chromosomal nucleic acids are called deoxyribonucleic acids, abbreviated DNA. Analogous nucleic acids in which the sugar component is ribose are termed ribonucleic acids, abbreviated RNA. The acidic character of the nucleic acids was attributed to the phosphoric acid moiety



The two monocyclic bases shown here are classified as **pyrimidines**, and the two bicyclic bases are **purines**. Each has at least one N-H site at which an organic substituent may be attached. They are all polyfunctional bases, and may exist in tautomeric forms.

Base-catalyzed hydrolysis of DNA gave four **nucleoside** products, which proved to be N-glycosides of 2'-deoxyribose combined with the heterocyclic amines. Structures and names for these nucleosides will be displayed above by clicking on

the heterocyclic base diagram. The base components are colored green, and the sugar is black. As noted in the 2'-deoxycytidine structure on the left, the numbering of the sugar carbons makes use of primed numbers to distinguish them from the heterocyclic base sites. The corresponding N-glycosides of the common sugar ribose are the building blocks of RNA, and are named adenosine, cytidine, guanosine and uridine (a thymidine analog missing the methyl group).
From this evidence, nucleic acids may be formulated as alternating copolymers of phosphoric acid (**P**) and nucleosides (**N**), as shown:

~ P – N – P – N′– P – N″– P – N‴– P – N ~

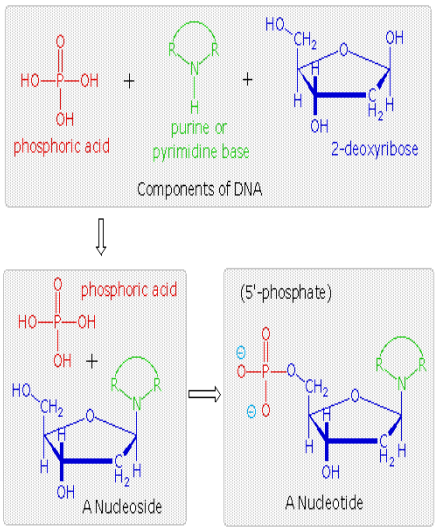
At first the four nucleosides, distinguished by prime marks in this crude formula, were assumed to be present in equal amounts, resulting in a uniform structure, such as that of starch. However, a compound of this kind, presumably common to all organisms, was considered too simple to hold the hereditary information known to reside in the chromosomes.

This view was challenged in 1944, when Oswald Avery and colleagues demonstrated that bacterial DNA was likely the genetic agent that carried information from one organism to another in a process called "transformation". He concluded that *"nucleic acids must be regarded as possessing biological specificity, the chemical basis of which is as yet undetermined."* Despite this finding, many scientists continued to believe that chromosomal proteins, which differ across species, between individuals, and even within a given organism, were the locus of an organism's genetic information.
It should be noted that single celled organisms like bacteria do not have a well-defined nucleus. Instead, their single chromosome is associated with specific proteins in a region called a "nucleoid". Nevertheless, the DNA from bacteria has the same composition and general structure as that from multicellular organisms, including human beings.

Views about the role of DNA in inheritance changed in the late 1940's and early 1950's. By conducting a careful analysis of DNA from many sources, Erwin Chargaff found its composition to be species specific. In addition, he found that the amount of adenine (A) always equaled the amount of thymine (T), and the amount of guanine (G) always equaled the amount of cytosine (C), regardless of the DNA source. As set forth in the following table, the ratio of (A+T) to (C+G) varied from 2.70 to 0.35. The last two organisms are bacteria.

The Chemical Nature of DNA

The polymeric structure of DNA may be described in terms of monomeric units of increasing complexity. In the top shaded box of the following illustration, the three relatively simple components mentioned earlier are shown. Below that on the left , formulas for phosphoric acid and a nucleoside are drawn. Condensation polymerization of these leads to the DNA formulation outlined above. Finally, a 5'- monophosphate ester, called a **nucleotide** may be drawn as a single monomer unit, shown in the shaded box to the right. Since a monophosphate ester of this kind is a strong acid (pK_a of 1.0), it will be fully ionized at the usual physiological pH (ca.7.4). Names for these DNA components are given in the table to the right of the diagram. Isomeric 3'-monophospate nucleotides are also known, and both isomers are found in cells. They may be obtained by selective hydrolysis of DNA through the action of nuclease enzymes. Anhydride-like di- and tri-phosphate nucleotides have been identified as important energy carriers in biochemical reactions, the most common being ATP (adenosine 5'-triphosphate).



Names of DNA Base Derivatives

Base	Nucleoside	5'-Nucleotide
Adenine	2'-Deoxyadenosine	2'-Deoxyadenosine-5'-monophosphate
Cytosine	2'-Deoxycytidine	2'-Deoxycytidine-5'-monophosphate
Guanine	2'-Deoxyguanosine	2'-Deoxyguanosine-5'-monophosphate
Thymine	2'-Deoxythymidine	2'-Deoxythymidine-5'-monophosphate

A complete structural representation of a segment of the DNA polymer formed from 5'-nucleotides may be viewed by clicking on the above diagram. Several important characteristics of this formula should be noted.

• First, the remaining P-OH function is quite acidic and is completely ionized in biological systems.
• Second, the polymer chain is structurally directed. One end (5') is different from the other (3').
• Third, although this appears to be a relatively simple polymer, the possible permutations of the four nucleosides in the chain become very large as the chain lengthens.
• Fourth, the DNA polymer is much larger than originally believed. Molecular weights for the DNA from multicellular organisms are commonly 10^9 or greater.

Information is stored or encoded in the DNA polymer by the pattern in which the four nucleotides are arranged. To access this information the pattern must be "read" in a linear fashion, just as a bar code is read at a supermarket checkout. Because living organisms are extremely complex, a correspondingly large amount of information related to this complexity must be stored in the DNA. Consequently, the DNA itself must be very large, as noted above. Even the single DNA molecule from an *E. coli* bacterium is found to have roughly a million nucleotide units in a polymer strand, and would reach a millimeter in length if stretched out. The nuclei of multicellular organisms incorporate chromosomes, which are composed of DNA combined with nuclear proteins called histones.

The fruit fly has 8 chromosomes, humans have 46 and dogs 78 (note that the amount of DNA in a cell's nucleus does not correlate with the number of chromosomes). The DNA from the smallest human chromosome is over ten times larger than *E. coli* DNA, and it has been estimated that the total DNA in a human cell would extend to 2 meters in length if unraveled. Since the nucleus is only about 5μm in diameter, the chromosomal DNA must be packed tightly to fit in that small volume.
In addition to its role as a stable informational library, chromosomal DNA must be structured or organized in such a way that the chemical machinery of the cell will have easy access to that information, in order to make important molecules such as polypeptides. Furthermore, accurate copies of the DNA code must be created as cells divide, with the replicated

DNA molecules passed on to subsequent cell generations, as well as to progeny of the organism. The nature of this DNA organization, or secondary structure, will be discussed in a later section

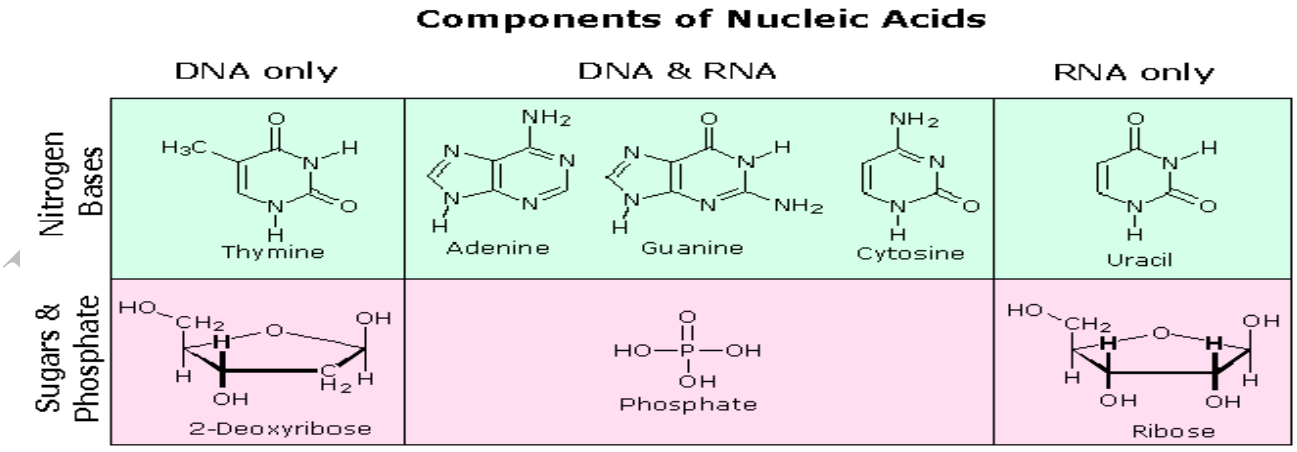
3. RNA, a Different Nucleic Acid

The high molecular weight nucleic acid, DNA, is found chiefly in the nuclei of complex cells, known as **eucaryotic cells**, or in the nucleoid regions of **procaryotic cells**, such as bacteria. It is often associated with proteins that help to pack it in a usable fashion.

In contrast, a lower molecular weight, but much more abundant nucleic acid, **RNA**, is distributed throughout the cell, most commonly in small numerous organelles called **ribosomes**. Three kinds of RNA are identified, the largest subgroup (85 to 90%) being ribosomal RNA, **rRNA**, the major component of ribosomes, together with proteins. The size of rRNA molecules varies, but is generally less than a thousandth the size of DNA.

The other forms of RNA are messenger RNA , **mRNA**, and transfer RNA , **tRNA**. Both have a more transient existence and are smaller than rRNA.

All these RNA's have similar constitutions, and differ from DNA in two important respects. As shown in the following diagram, the sugar component of RNA is ribose, and the pyrimidine base uracil replaces the thymine base of DNA. The RNA's play a vital role in the transfer of information (transcription) from the DNA library to the protein factories called ribosomes, and in the interpretation of that information (translation) for the synthesis of specific polypeptides. These functions will be described later.



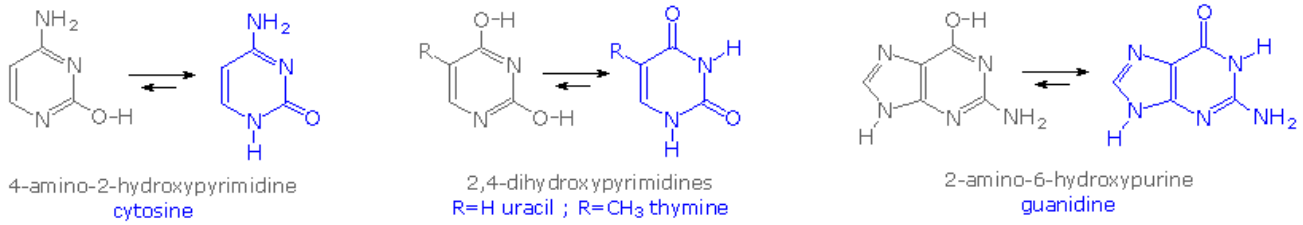
A complete structural representation of a segment of the RNA polymer formed from 5'-nucleotides may be viewed by clicking on the above diagram

4. The Secondary Structure of DNA

In the early 1950's the primary structure of DNA was well established, but a firm understanding of its secondary structure was lacking. Indeed, the situation was similar to that occupied by the proteins a decade earlier, before the alpha helix and pleated sheet structures were proposed by Linus Pauling. Many researchers grappled with this problem, and it was generally conceded that the molar equivalences of base pairs (A & T and C & G) discovered by Chargaff would be an important factor. Rosalind Franklin, working at King's College, London, obtained X-ray diffraction evidence that suggested a long helical structure of uniform thickness. Francis Crick and James Watson, at Cambridge University, considered hydrogen bonded base pairing interactions, and arrived at a double stranded helical model that satisfied most of the known facts, and has been confirmed by subsequent findings.

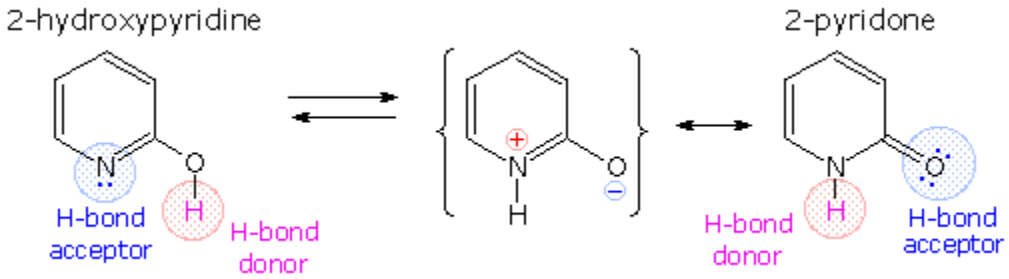
Base Pairing

Careful examination of the purine and pyrimidine base components of the nucleotides reveals that three of them could exist as hydroxy pyrimidine or purine tautomers, having an aromatic heterocyclic ring. Despite the added stabilization of an aromatic ring, these compounds prefer to adopt amide-like structures. These options are shown in the following diagram, with the more stable tautomer drawn in blue.



A simple model for this tautomerism is provided by 2-hydroxypyridine. As shown on the left below, a compound having this structure might be expected to have phenol-like characteristics, such as an acidic hydroxyl group. However, the boiling point of the actual substance is 100º C greater than phenol and its acidity is 100 times less than expected (pKa = 11.7). These differences agree with the 2-pyridone tautomer, the stable form of the zwitterionic internal salt. Further evidence supporting this assignment will be displayed by clicking on the diagram.

Note that this tautomerism reverses the hydrogen bonding behavior of the nitrogen and oxygen functions (the N-H group of the pyridone becomes a hydrogen bond donor and the carbonyl oxygen an acceptor).

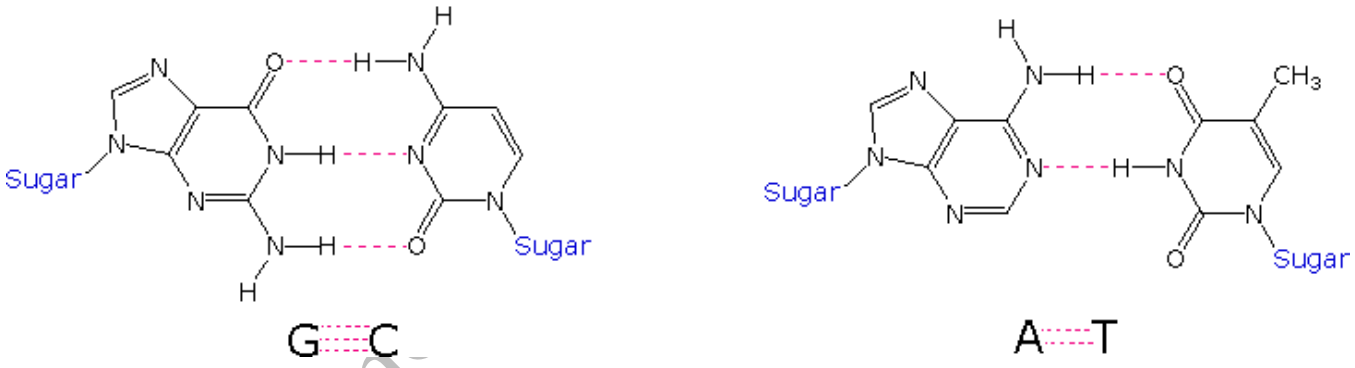


The additional evidence for the pyridone tautomer, that appears above by clicking on the diagram, consists of infrared and carbon nmr absorptions associated with and characteristic of the amide group. The data for 2-pyridone is given on the left. Similar data for the N-methyl derivative, which cannot tautomerize to a pyridine derivative, is presented on the right.

Once they had identified the favored base tautomers in the nucleosides, Watson and Crick were able to propose a complementary pairing, via hydrogen bonding, of guanosine (G) with cytidine (C) and adenosine (A) with thymidine (T). This pairing, which is shown in the following diagram, explained Chargaff's findings beautifully, and led them to suggest a double helix structure for DNA.

Before viewing this double helix structure itself, it is instructive to examine the base pairing interactions in greater detail. The G#C association involves three hydrogen bonds (colored pink), and is therefore stronger than the two-hydrogen bond association of A#T. These base pairings might appear to be arbitrary, but other possibilities suffer destabilizing steric or electronic interactions. By clicking on the diagram two such alternative couplings will be shown. The C#T pairing on the left suffers from carbonyl dipole repulsion, as well as steric crowding of the oxygens. The G#A pairing on the right is also destabilized by steric crowding (circled hydrogens).

Hydrogen Bonded Base Pairs



A simple mnemonic device for remembering which bases are paired comes from the line construction of the capital letters used to identify the bases. A and T are made up of intersecting straight lines. In contrast, C and G are largely composed of curved lines. The RNA base uracil corresponds to thymine, since U follows T in the alphabet.

The Double Helix

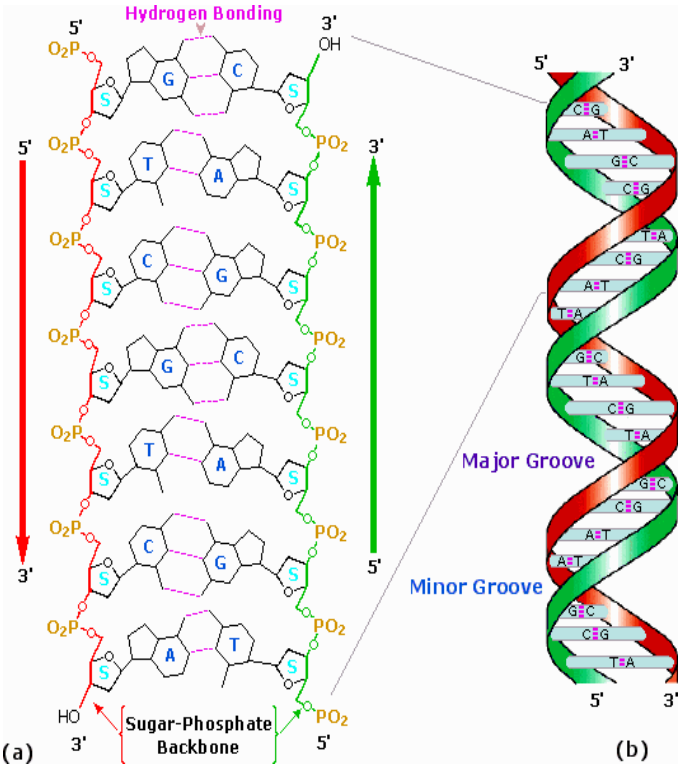
After many trials and modifications, Watson and Crick conceived an ingenious double helix model for the secondary structure of DNA. Two strands of DNA were aligned anti-parallel to each other, i.e. with opposite 3' and 5' ends , as shown in part **a** of the following diagram. Complementary primary nucleotide structures for each strand allowed intra-strand hydrogen bonding between each pair of bases.

These complementary strands are colored red and green in the diagram. Coiling these coupled strands then leads to a double helix structure, shown as cross-linked ribbons in part **b** of the diagram. The double helix is further stabilized by hydrophobic attractions and pi-stacking of the bases. A space-filling molecular model of a short segment is displayed in part **c** on the right.

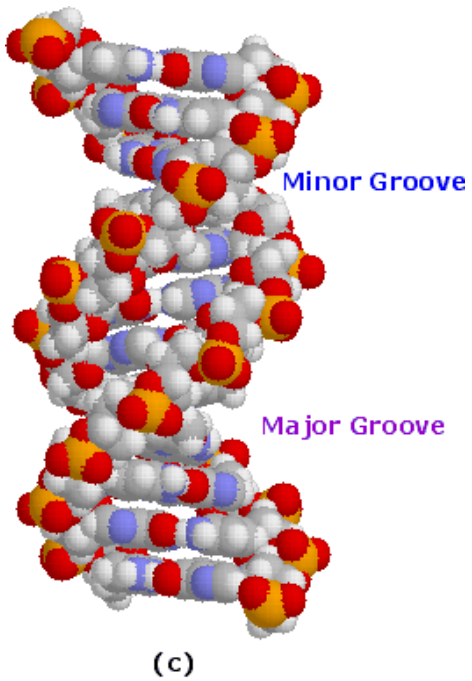
The helix shown here has ten base pairs per turn, and rises 3.4 Å in each turn. This right-handed helix is the favored

conformation in aqueous systems, and has been termed the **B-helix**. As the DNA strands wind around each other, they leave gaps between each set of phosphate backbones. Two alternating grooves result, a wide and deep **major groove** (*ca.* 22Å wide), and a shallow and narrow **minor groove** (*ca.* 12Å wide). Other molecules, including polypeptides, may insert into these grooves, and in so doing perturb the chemistry of DNA. Other helical structures of DNA have also been observed, and are designated by letters (e.g. **A** and **Z**).

The Double Helix Structure for DNA



Space-Filling Molecular Model



FATS

Fat is one of the three main macronutrients, along with carbohydrate and protein.[1] Fats, also known as triglycerides, are esters of three fatty acid chains and the alcohol glycerol.

The terms "oil", "fat", and "lipid" are often confused. "Oil" normally refers to a fat with short or unsaturated fatty acid chains that is liquid at room temperature, while "fat" may specifically refer to fats that are solids at room temperature. "Lipid" is the general term, as a lipid is not necessarily a triglyceride. Fats, like other lipids, are generally hydrophobic, and are soluble in organic solvents and insoluble in water.

Fat is an important foodstuff for many forms of life, and fats serve both structural and metabolic functions. They are a necessary part of the diet of most heterotrophs (including humans). Some fatty acids that are set free by the digestion of fats are called essential because they cannot be synthesized in the body from simpler constituents. There are two essential fatty acids (EFAs) in human nutrition: alpha-linolenic acid (an omega-3 fatty acid) and linoleic acid . Other lipids needed

by the body can be synthesized from these and other fats. Fats and other lipids are broken down in the body by enzymes called lipases produced in the pancreas.

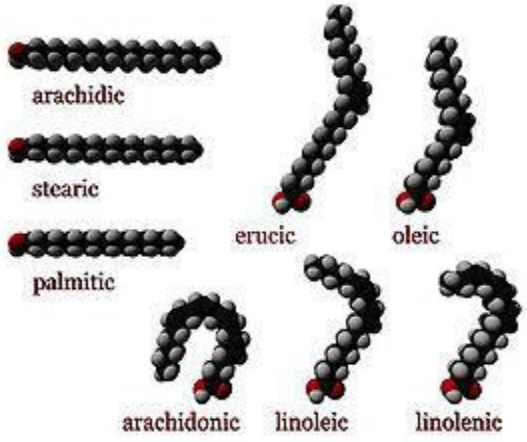
Fats and oils are categorized according to the number and bonding of the carbon atoms in the aliphatic chain. Fats that are saturated fats have no double bonds between the carbons in the chain. Unsaturated fats have one or more double bonded carbons in the chain. The nomenclature is based on the non-acid (non-carbonyl) end of the chain. This end is called the omega end or the n-end. Thus alpha-linolenic acid is called an omega-3 fatty acid because the 3rd carbon from that end is the first double bonded carbon in the chain counting from that end. Some oils and fats have multiple double bonds and are therefore called polyunsaturated fats. Unsaturated fats can be further divided into cis fats, which are the most common in nature, and trans fats, which are rare in nature.

Unsaturated fats can be altered by reaction with hydrogen effected by a catalyst. This action, called hydrogenation, tends to break all the double bonds and makes a fully saturated fat. To make vegetable shortening, then, liquid *cis*-unsaturated fats such as vegetable oils are hydrogenated to produce saturated fats, which have more desirable physical properties e.g., they melt at a desirable temperature (30–40 °C), and store well, whereas polyunsaturated oils go rancid when they react with oxygen in the air. However, trans fats are generated during hydrogenation as contaminants created by an unwanted side reaction on the catalyst during partial hydrogenation.

Saturated fats can stack themselves in a closely packed arrangement, so they can solidify easily and are typically solid at room temperature. For example, animal fats tallow and lard are high in saturated fatty acid content and are solids. Olive and linseed oils on the other hand are unsaturated and liquid.

Fats serve both as energy sources for the body, and as stores for energy in excess of what the body needs immediately. Each gram of fat when burned or metabolized releases about 9 food calories (37 kJ = 8.8 kcal).[3] Fats are broken down in the healthy body to release their constituents, glycerol and fatty acids. Glycerol itself can be converted to glucose by the liver and so become a source of energy.In chemistry, particularly in biochemistry, a **fatty acid** is a carboxylic acid with a long aliphatic chain, which is either saturated or unsaturated. Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from 4 to 28.[1]Fatty acids are usually derived from triglycerides or phospholipids. Fatty acids are important sources of fuel because, when metabolized, they yield large quantities of ATP. Many cell types can use either glucose or fatty acids for this purpose. Long-chain fatty acids cannot cross the blood–brain barrier (BBB) and so cannot be used as fuel by the cells of the central nervous system; however, free short-chain fatty acids and medium-chain fatty acids can cross the BBB in addition to glucose and ketone bodies.

Types of fatty acid



Three-dimensional representations of several fatty acids.Fatty acids that have carbon–carbon double bonds are known as unsaturated. Fatty acids without double bonds are known as saturated. They differ in length as well.

Length of free fatty acid chains

Fatty acid chains differ by length, often categorized as short to very long.

- Short-chain fatty acids (SCFA) are fatty acids with aliphatic tails of fewer than six carbons (e.g. butyric acid).
- Medium-chain fatty acids (MCFA) are fatty acids with aliphatic tails of 6–12 carbons, which can form medium-chain triglycerides.
- Long-chain fatty acids (LCFA) are fatty acids with aliphatic tails 13 to 21 carbons
- Very long chain fatty acids (VLCFA) are fatty acids with aliphatic tails longer than 22 carbons.

Unsaturated fatty acids

Unsaturated fatty acids have one or more double bonds between carbon atoms. (Pairs of carbon atoms connected by double bonds can be saturated by adding hydrogen atoms to them, converting the double bonds to single bonds. Therefore, the double bonds are called unsaturated.)

The two carbon atoms in the chain that are bound next to either side of the double bond can occur in a *cis* or *trans* configuration.

cis

A *cis* configuration means that the two hydrogen atoms adjacent to the double bond stick out on the same side of the chain. The rigidity of the double bond freezes its conformation and, in the case of the *cis* isomer, causes the chain to bend and restricts the conformational freedom of the fatty acid. The more double bonds the chain has in the *cis* configuration, the less flexibility it has. When a chain has many *cis* bonds, it becomes quite curved in its most accessible conformations. For example, oleic acid, with one double bond, has a "kink" in it, whereas linoleic acid, with two double bonds, has a more pronounced bend. α-Linolenic acid, with three double bonds, favors a hooked shape. The effect of this is that, in restricted environments, such as when fatty acids are part of a phospholipid in a lipid bilayer, or triglycerides in lipid droplets, cis bonds limit the ability of fatty acids to be closely packed, and therefore can affect the melting temperature of the membrane or of the fat.

trans

A *trans* configuration, by contrast, means that the adjacent two hydrogen atoms lie on *opposite* sides of the chain. As a result, they do not cause the chain to bend much, and their shape is similar to straight saturated fatty acids.

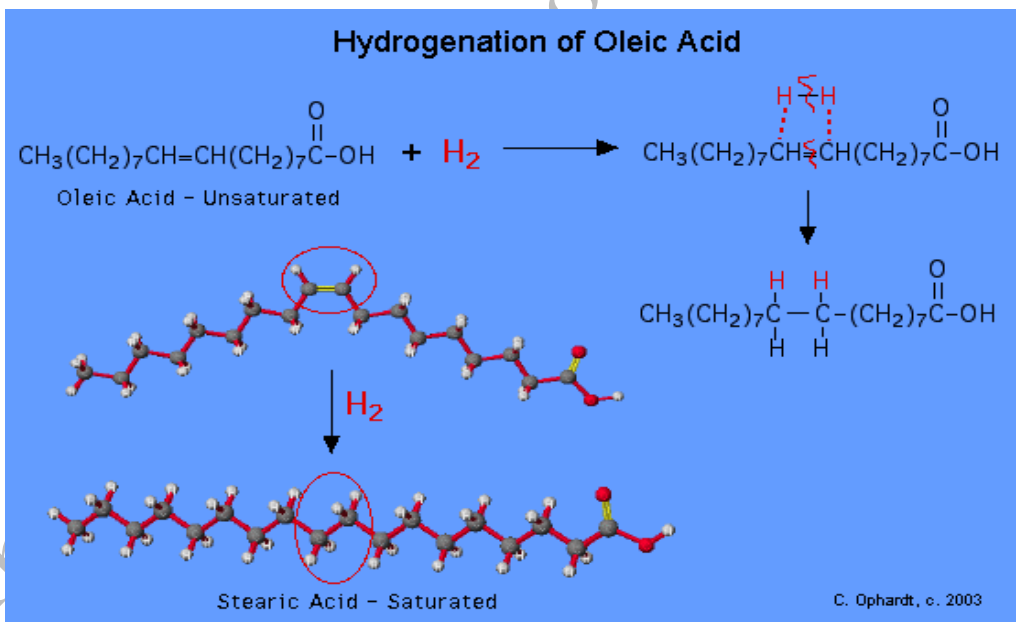
In most naturally occurring unsaturated fatty acids, each double bond has three *n* carbon atoms after it, for some **n**, and all are cis bonds. Most fatty acids in the *trans* configuration (trans fats) are not found in nature and are the result of human processing (e.g., hydrogenation).The differences in geometry between the various types of unsaturated fatty acids, as well as between saturated and unsaturated fatty acids, play an important role in biological processes, and in the construction of biological structures (such as cell membranes).

Hydrogenation of fatty acid

Unsaturated fatty acids may be converted to saturated fatty acids by the relatively simple hydrogenation reaction. Recall that the addition of hydrogen to an alkene (unsaturated) results in an alkane (saturated).

A simple hydrogenation reaction is:

$H_2C{=}CH_2 + H_2$ ---> CH_3CH_3
alkene plus hydrogen yields an alkane



Saponification value

Saponification value (or "saponification number"/"Koettstorfer number",[1] also referred to as "sap" for short) represents the number of milligrams of potassium hydroxide required to saponify 1g of fat under the conditions specified.[2] It is a measure of the average molecular weight (or chain length) of all the fatty acids present. As most of the mass of a fat/tri-ester is in the 3 fatty acids, it allows for comparison of the average fatty acid chain length. The long chain fatty acids found in fats have a low saponification value because they have a relatively fewer number of carboxylic functional groups

per unit mass of the fat as compared to short chain fatty acids. If more moles of base are required to saponify N grams of fat then there are more moles of the fat and the chain lengths are relatively small, given the following relation:

Number of moles = mass of oil/relative atomic mass

The calculated molar mass is not applicable to fats and oils containing high amounts of unsaponifiable material, free fatty acids (>0.1%), or mono- and diacylglycerols (>0.1%).Handmade soap makers who aim for bar soap use NaOH (sodium hydroxide, lye). Because saponification values are listed in KOH (potassium hydroxide) the value must be converted from potassium to sodium to make bar soap; potassium soaps make a paste, gel or liquid soap. To convert KOH values to NaOH values, divide the KOH values by the ratio of the molecular weights of KOH and NaOH (1.403).

Iodine value

The **iodine value** (or "iodine adsorption value" or "iodine number" or "iodine index") in chemistry is the mass of iodine in grams that is consumed by 100 grams of a chemical substance. Iodine numbers are often used to determine the amount of unsaturation in fatty acids. This unsaturation is in the form of double bonds, which react with iodine compounds. The higher the iodine number, the more C=C bonds are present in the fat.[1] It can be seen from the table that coconut oil is very saturated, which means it is good for making soap. On the other hand, linseed oil is highly unsaturated, which makes it a drying oil, well suited for making oil paints.

The fat is mixed with an excess of bromine. This bromine is added to the double bonds in the unsaturated fats. This reaction must be carried out in the dark, since the formation of bromine radicals is suppressed by light. This would lead to undesirable side reactions, and thus falsifying a result consumption of bromine.

Method

Then the unused bromine is reduced to bromide with iodide.

Now, the amount of iodine formed is determined by titration with sodium thiosulfate solution.

Acid value

In chemistry, **acid value** (or "neutralization number" or "acid number" or "acidity") is the mass of potassium hydroxide (KOH) in milligrams that is required to neutralize one gram of chemical substance.[1] The acid number is a measure of the amount of carboxylic acid groups in a chemical compound, such as a fatty acid, or in a mixture of compounds.

In a typical procedure, a known amount of sample dissolved in organic solvent (often isopropanol), is titrated with a solution of potassium hydroxide (KOH) with known concentration and with phenolphthalein as a color indicator.

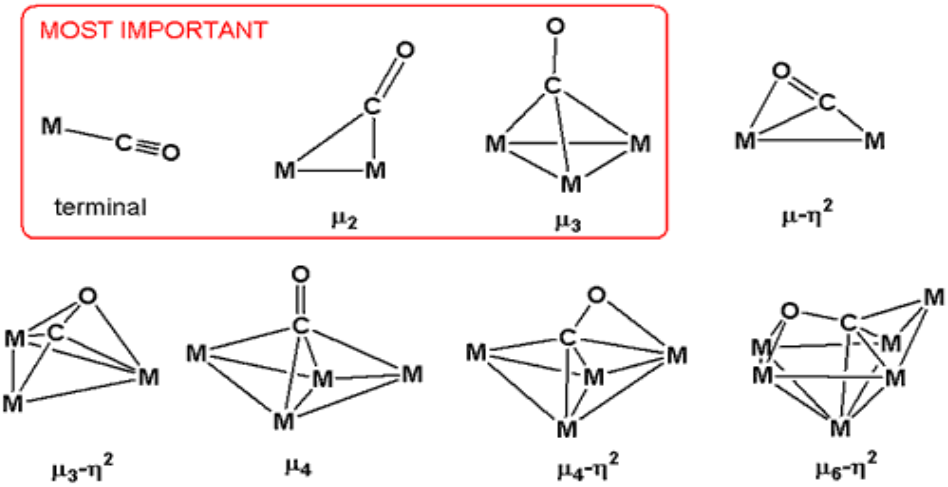
The acid number is used to quantify the amount of acid present, for example in a sample of biodiesel. It is the quantity of base, expressed in milligrams of potassium hydroxide, that is required to neutralize the acidic constituents in 1 g of sample.V_{eq} is the volume of titrant (ml) consumed by the crude oil sample and 1 ml of spiking solution at the equivalent point, b_{eq} is the volume of titrant (ml) consumed by 1 ml of spiking solution at the equivalent point, and 56.1 is the molecular weight of KOH. W_{Oil} is the mass of the sample in grams.

UNIT -2

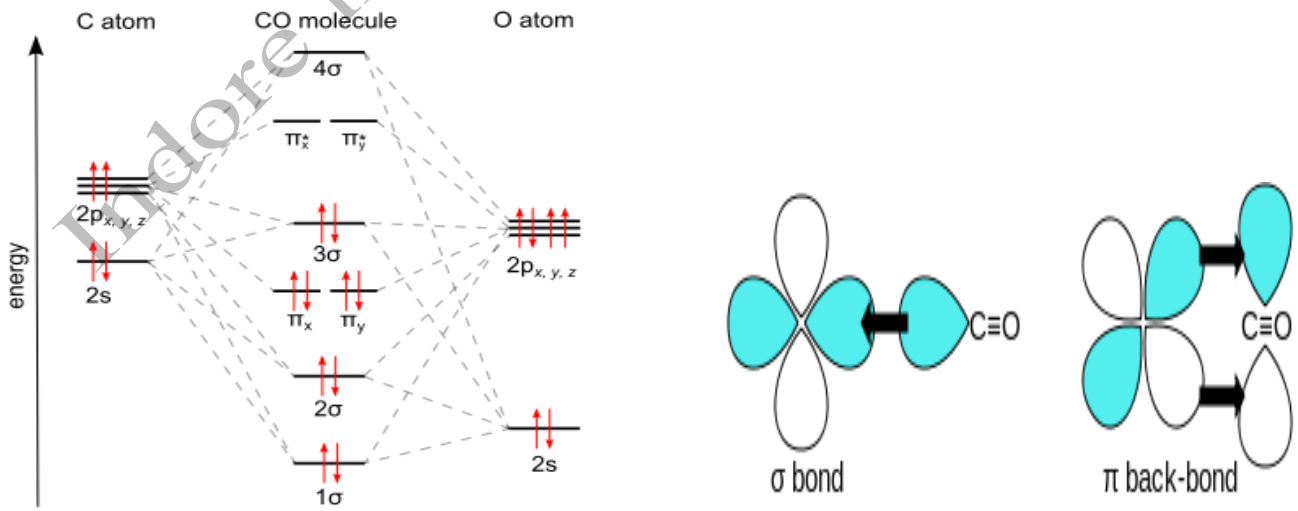
Organometallic chemistry

Metal carbonyls are coordination complexes of transition metals with carbon monoxideligands. Metal carbonyls are useful in organic synthesis and as catalysts or catalyst precursors in homogeneous catalysis, such as hydroformylation and Reppe chemistry. In the Mond process, nickel carbonyl is used to produce pure nickel. In organometallic chemistry, metal carbonyls serve as precursors for the preparation of other organometalic complexes.

Metal carbonyls are toxic by skin contact, inhalation or ingestion, in part because of their ability to carbonylate hemoglobin to give carboxyhemoglobin, which prevents the binding of O_2.



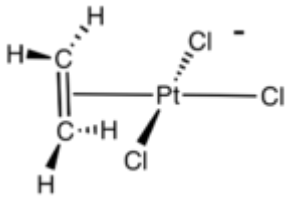
Structure and bonding



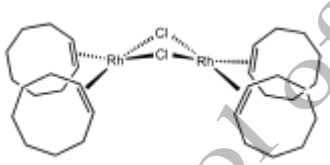
Carbon monoxide bonds to transition metals using "synergistic π^* back-bonding." The bonding has three components, giving rise to a partial triple bond. A sigma bond arises from overlap of the nonbonding (or weakly anti-bonding) sp-hybridized electron pair on carbon with a blend of d-, s-, and p-orbitals on the metal. A pair of π bonds arises from overlap of filled d-orbitals on the metal with a pair of π-antibonding orbitals projecting from the carbon atom of the CO. The latter kind of binding requires that the metal have d-electrons, and that the metal is in a relatively low oxidation state (<+2) which makes the back donation process favorable.

Metal olefin complex

In organometallic chemistry, a **transition metal alkene complex** is a coordination compound containing one or more alkene ligands. Such compounds are intermediates in many catalytic reactions that convert alkenes to other organic products.[1]



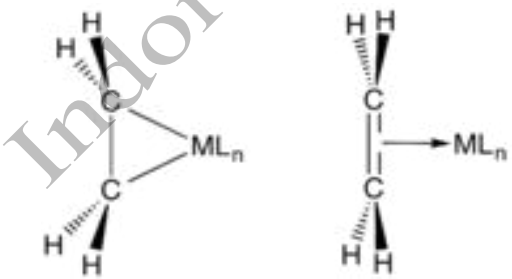
Ziess salt



Chlorobis(cyclooctene)rhodium dimer

The bonding between alkenes and transition metals is described by the Dewar-Chatt-Duncanson model, which involves donation of electrons in the pi-orbital on the alkene to empty orbitals on the metal. This interaction is reinforced by back bonding that entails sharing of electrons in other metal orbitals into the otherwise empty pi-antibonding level on the alkene. Early metals of low oxidation state (Ti(II), Zr(II), Nb(III) etc.) are strong pi donors, and their alkene complexes are often described as metallacyclopropanes. Treatment of such species with acids gives the alkanes. Late metals (Ir(I), Pt(II)), which are poorer pi-donors, tend to engage the alkene as a Lewis acid-Lewis base interaction.

Orbital interactions in a metal-ethylene complex, as described by the Dewar-Chatt-Duncanson model



Two extremes depictions of M---C_2H_4 interactions.

The greatest use of organomagnesium compounds is as a Grignard Reagent. The Grignard Reagent is basically an organomagnesium halide (RMgX) having a positively polarised metal, thereby making the alkyl group behave like a

carbanion. The preparation of a Grignard Reagent requires an ether solvent, and the entire chemistry is carried out bone dry. In the reaction, alkyl halide (preferably a bromide or iodide or a very reactive chloride such as tertiary-butyl chloride or benzyl chloride), magnesium metal, and ether (dried with sodium metal) are combined, and with a little persuasion, a vigorous reaction results in a Grignard reagent.

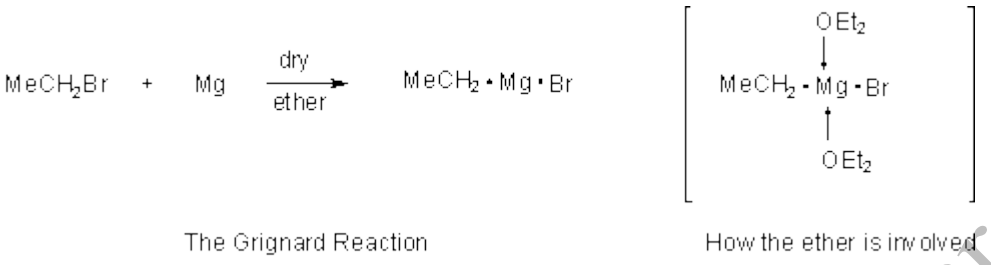


Fig. 1 - The general Grignard reaction

Preparation of organometallic compound →

Grignard Reagents can be prepared in a variety of ways. These techniques include:

a. **By reactions of metallic magnesium**

A variety of methods for preparing organomagnesium compounds utilize elemental magnesium, either in the form of chips, powder, or slurries. These options are described below:

Magnesium turnings are convenient to use and sufficiently reactive in many cases. Their reactivity is enhanced by the presence of surface dislocations resulting from their preparation.

Chips provide a form of sublimed magnesium with a large surface area.

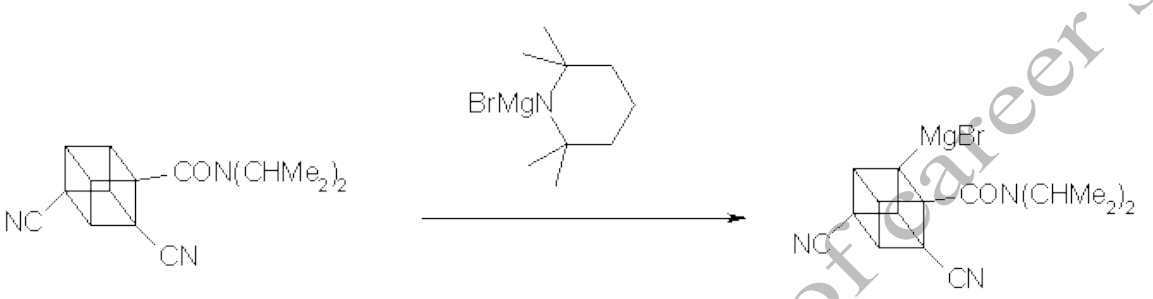
Magnesium powder has the advantage of having a large surface area, but in many cases, this advantage is outweighed by the disadvantage of increased susceptibility to surface contamination. However, this form of magnesium has been found particularly useful for reactions in hydrocarbon media.

Slurries - Several techniques have been used to prepare slurries of highly reactive magnesium, but some are difficult to carry out without special equipment. For example, magnesium vapour has been co-condensed with a solvent at 77K.Similar reactive slurries were made much more readily available by Rieke who reduced magnesium halides to the metal by alkali metals, for example, from magnesium chloride and potassium in the presence of potassium iodide, with THF as the medium.However, this procedure is still somewhat hazardous, and a more recent procedure, where the magnesium halide is reduced by lithium, with naphthalene as an electron carrier is safer, as well as giving a slurry of comparable activity to the original Rieke magnesium.

a. **preparation of organomagnesium compounds from other organomagnesium compounds via:**

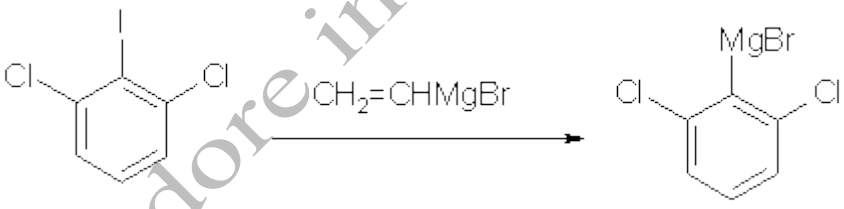
1. Metallation RMgX + R'H→R'MgX + RH

Previously, the preparation of organomagnesium compounds by metallation was only of value in the case of quite stron carbon acids (pKa < 25). However, it has now been reported that sterically hindered magnesium amides, analogous to LDA and LTMP are effective metallating agents. They are probably less powerful than the lithium agents, but have the advantage of being stable even in boiling THF. □ -metallation of carbonyl compounds (enolization) by hindered magnesium amides such as BrMgTMP promises to be useful.[13] Further, metallation by magnesium diisopropylamides or tetramethylpiperidides is relatively undeveloped but appears a promising alternative to metallation by the corresponding lithium amides.[14]



2. Metal - Halogen exchange RX + R'MgX' □ RMgX' + R'X

The preparation of organomagnesium compounds by metal-halogen exchange between Grignard reagents and organic halides is much less widely used than the corresponding reaction of organolithium compounds. Nevertheless, it does work well for certain classes of compounds, notably aryl bromides and iodides, and 1,1-dihaloalkyl halides. For the Grignard reagent, vinylmagnesium bromide has been used so as to avoid Wurtz-type coupling (the vinyl halide formed from the process is unreactive towards the arylmagnesium halide formed.)[15]

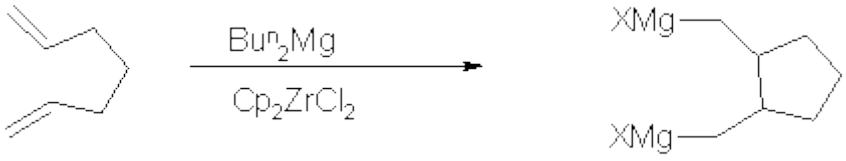


3. Hydromagnesiation

Thirty years ago it was reported that reactions of Grignard reagents with 1-alkenes, catalysed by titanium tetrachloride lead to organomagnesium compounds derived by the addition of HMgX to the carbon-carbon double bond. More recently, a related reaction has been reported in which active forms of magnesium hydride, prepared *in situ* or pre-prepared, undergo addition to alkenes, catalysed by titanium or zirconium (IV) halides, to give dialkylmagnesium compounds.[16]

$2RCH{=}CH_2 + MgH_2 \rightarrow (RCH_2CH_2)_2Mg$, catalyzed by titanium or zirconium (IV) halides

These reactions give high yields with 1-alkenes, as shown, but are less satisfactory with alkynes or non-terminal alkenes. In an extension, hydromagnesiation of 1,6-heptadiene and 1,7-octadiene is reported to result in cyclization.



b. preparation by ligand exchange on RMgX

In this section, processes which result in the substitution of the ligand X in an organomagnesium compound, RMgX:

For applications in synthesis, the most important of these are those where X is a halogen and Y is an alkyl group. Other transformations of this type are useful for preparing alkylmagnesium hydrides (Y=H), alkoxides (Y=OR'), carboxylates (Y=OCOR'), amides (Y=NR'$_2$), thiolates (Y=SR'). However, since most of these products are not extensively employed in synthesis, these transformations will not be discussed.

1. Preparation of dialkylmagnesium compounds

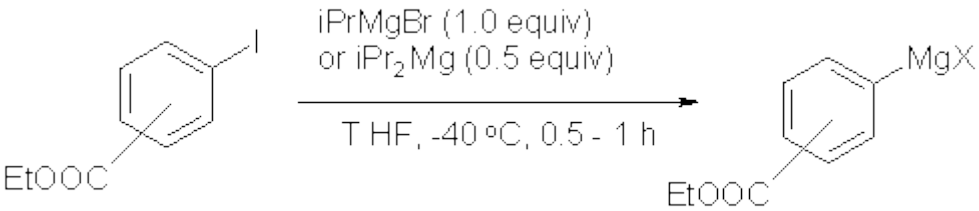
Grignard reagents in solution may be described in terms of the Schlenk equilibrium, represented in its simplest form by:

$2RMgX \rightarrow R_2MgX + MgX_2$

If this type of equilibrium is displaced to the right by selective precipitation of magnesium halide, a solution of the dialkylmagnesium compound should result. Such selective precipitation does sometimes occur, notably from hydrocarbon solutions, but it is rarely selective and/or complete to provide a useful method for obtaining dialkylmagnesium compounds. However, certain additives, such as 1,4-dioxane have been found to achieve the desired result.

Two aspects of the dioxane precipitation method should be noted: some organomagnesium species may be initially coprecipitated, and prolonged stirring may be required to achieve the desired result; and the precipitated magnesium halide complex may be very finely divided, necessitating centrifugation before filtration or decantation. It should also be noted that traces of halide may remain in solution.

Although a vast variety of methods exist with which to prepare Grignard reagents, very few functionalized organomagnesium reagents have been prepared due to the low functional-group tolerance of these reagents. However, a general route to highly functionalized arylmagnesium halides which contain functional groups such as esters, amides or cyano groups, or a halogenide substituent has been discovered.

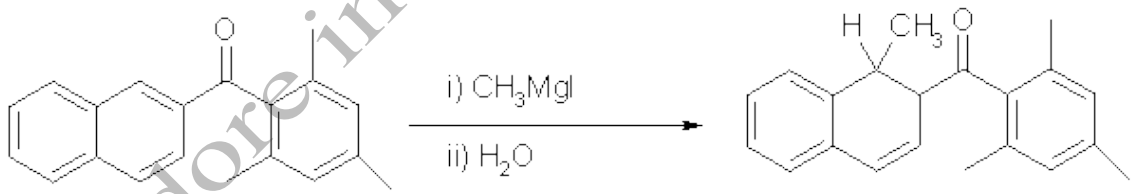


Uses of Grignard Reagent

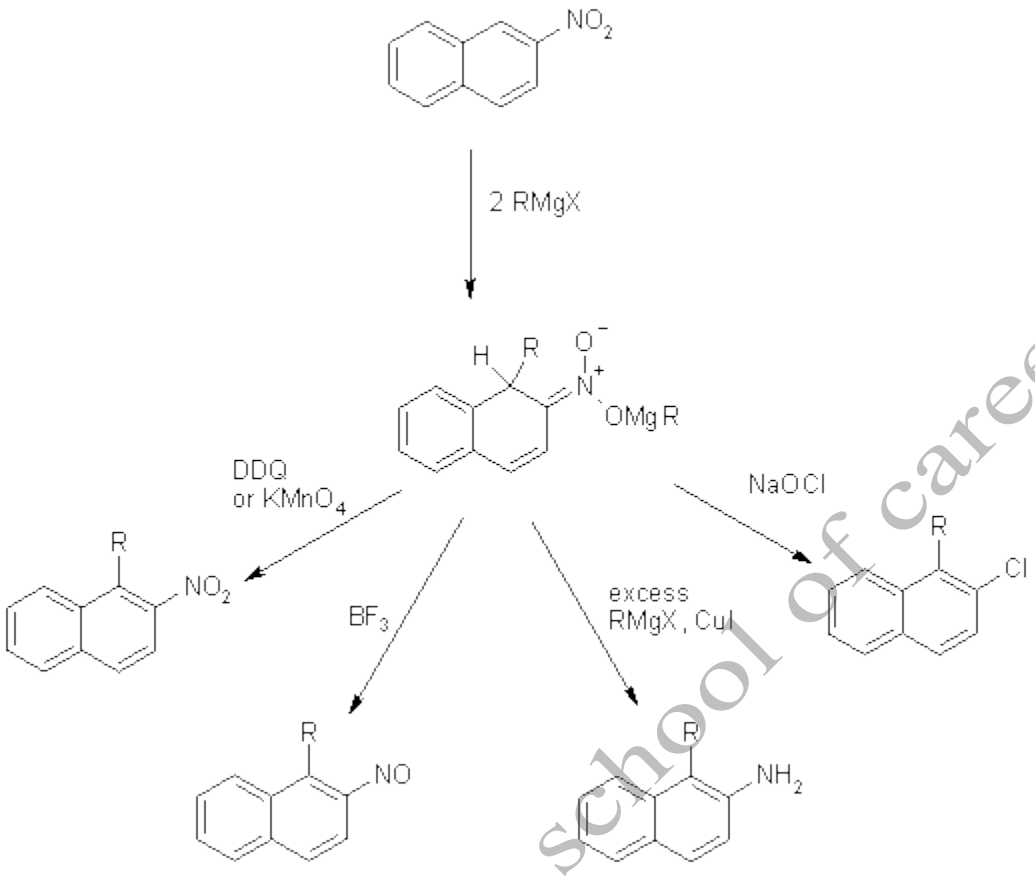
Organomagnesium reagents are extremely important in synthetic organic chemistry. Since their discovery, there has been great interest in these versatile reagents, and numerous industrial applications have been reported. Grignard reagents have been used to add substituents to carbon-carbon multiple bonds, carbon-nitrogen multiple bonds, carbonyl groups, and thiocarbonyl groups. They have also been used to induce a substitution at carbon, to promote carbenoid and arynoid reactions. They react with proton donors and can be utilised for the formation of carbon-nitrogen bonds, carbon-oxygen bonds, carbon-sulfur, carbon-selenium and carbon-tellurium bonds, carbon-halogen bonds, organoboron, organosilicon, and organophosphorus compounds, and other organometallic compounds. Due to the great variety of compounds Grignard reagents can synthesize it is unfeasable to discuss all these different cases in this paper. Therefore, this paper will focus only on addition to hydrocarbons, nitrogen bearing groups, aldehydes, and ketones.

1. Addition to Aromatic Rings

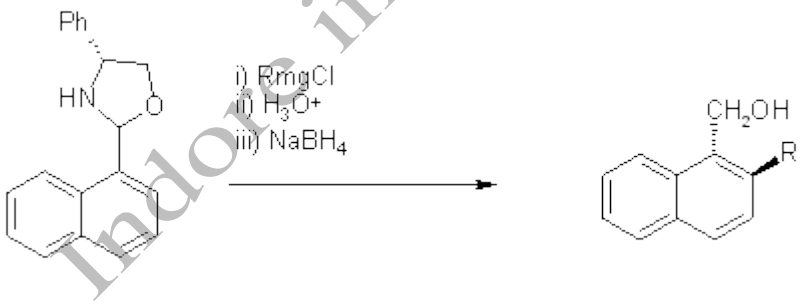
Organomagnesium compounds add to unsubstituted arenes only under forcing or "Barbier" conditions. On the other hand, aromatic rings substituted by electron-withdrawing groups are surprisingly susceptible to attack by organomagnesium compounds. The early work on reactions of hindered aryl ketones has been little further developed.



Early investigations of reactions of organomagnesium compounds with nitro compounds led to mixtures of products, and gave little indication that they might be useful. However, it has now been established that with two equivalents of an alkylmagnesium halide in THF, nucleophilic addition to the ring of a variety of nitroaromatic compounds occurs. The product of the addition is a nitronate anion, which may be converted into various products, as illustrated by the example of 2-nirtronaphthalene.

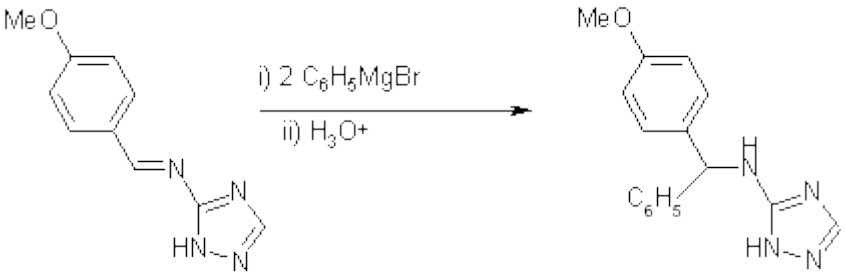


A most remarkable reaction of Grignard reagents with a 1-(oxazolidin-2-yl)naphthalene has been described, in which addition to the aromatic ring occurs, whereas organolithium, organocerium or organocopper reagents all attack the oxazolidine-2-position.[25]

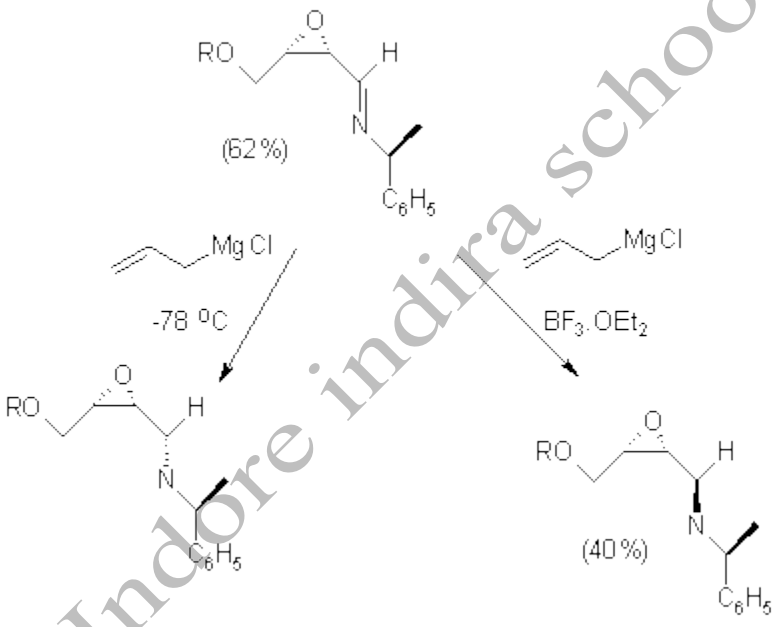


2. Addition to imines, iminium salts and related compounds

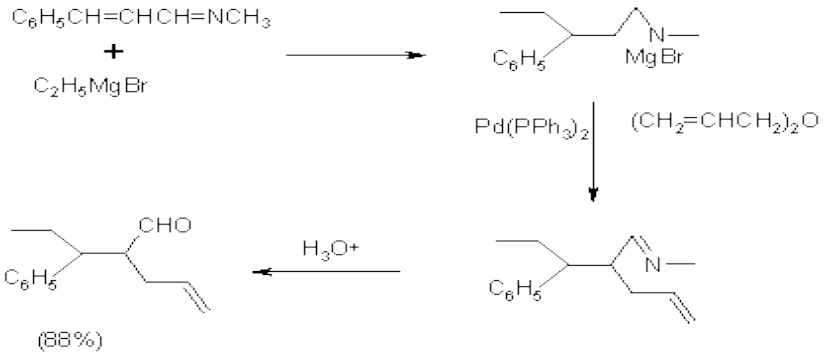
Unconjugated carbon-nitrogen double bonds are less reactive than might have been predicted towards addition of organomagnesium compounds, and when imines possess hydrogen atoms □ to carbon or nitrogen, deprotonation may compete with addition. However, addition to aromatic aldimines can give good yields, with or without hydrogen atoms to nitrogen.



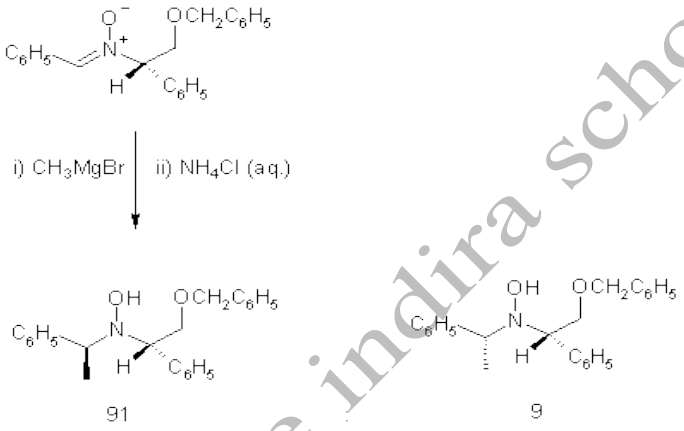
Imines may be activated by complexation with Lewis acids, but this also increases the acidity of □ -hydrogen atoms. A combination of copper(I) halide and boron trifluoride etherate is a possible solution to the problem. Activation by TMS triflate is also effective with aldimines (though not with ketimines). It should be noted that in cases where the stereochemistry of the addition is dependent on chelation control, the presence of Lewis acids may profoundly increase the selectivity.[27]



Both 1,2- and 1,4-addition of organomagnesium compounds to ethylenic imines has been reported. The latter has been used in tandem addition-alkylation sequences.



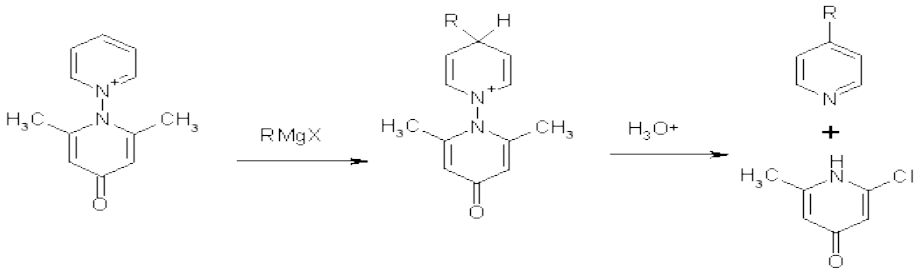
While the addition of organomagnesium compounds to nitrones was reported over 80 years ago, only occasional examples were described recently. However, two factors are likely to lead to the further exploitation of this reaction in synthesis: (a) the addition may proceed with a useful degree of stereoselectivity, and (b) the initial adducts may be readily converted into amines (for example by acylation followed by a reduction or by reduction with carbon disulfide). An example of a diastereoselective addition is shown below.



3. Addition to nitrogen heterocyclic aromatic compounds

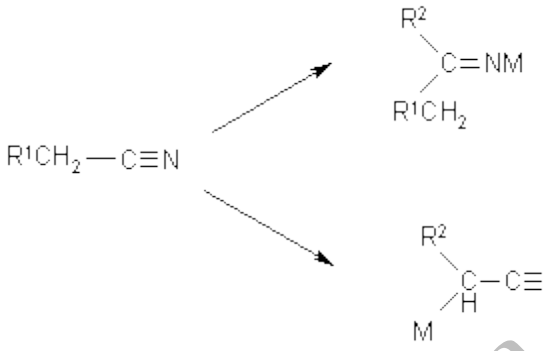
Organomagnesium compounds usually resemble organolithium compounds in their reactions with nitrogen heterocyclic aromatic compounds but they generally give inferior results for preparative purposes. Thus, as in the case of organolithium compounds, addition normally occurs at the 2-postion of pyridine, and subsequent elimination or oxidation gives the 2-substituted pyridine.

In contrast, reactions of organomagnesium compounds with pyridinium salts are more useful than those of organolithium compounds. Unsubstituted pyridinium salts have a somewhat greater tendency towards 4-alkylation than pyridine itself, and with a bulky N-substituent, 4-alkylation predominates. If the N-substituent is also a good leaving group, a viable general synthesis of 4-substituted pyridine results.



4. Addition to nitriles

Reactions of organomagnesium compounds iwht nitriles normally proceeds via initial addition to the carbon-nitrogen triple bond or via initial deprotonation:



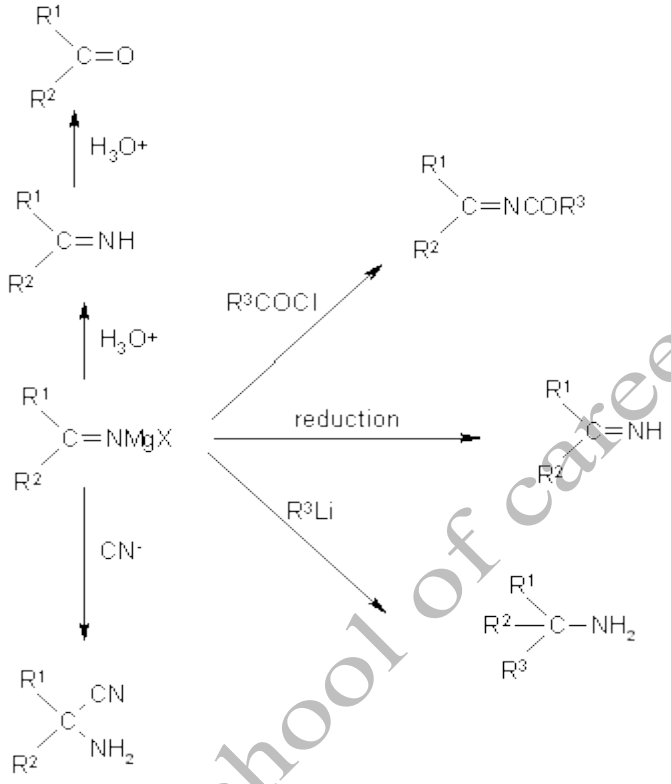
When reactions involving deprotonation are desired, it is better to use reagents such as LDA, though in favourable cases organomagnesium compounds have been employed. For reactions requiring addition to the cyano group, both organomagnesium and organolithium compounds have been used successfully, and it is difficult to predict which will be better in a particular case.

The addition reaction is most commonly used for the synthesis of ketones via hydrolysis of the intermediate imine. However, other useful reactions of the adduct include protonation to give the free imine, reaction with other electrophilic reagents to give various N-substituted imines, and reduction to give a primary amine. These reactions are summarized in the scheme below. For all of them, the key step is the initial addition, and some guidelines for optimizing this step and minimizing side reactions are as follows:

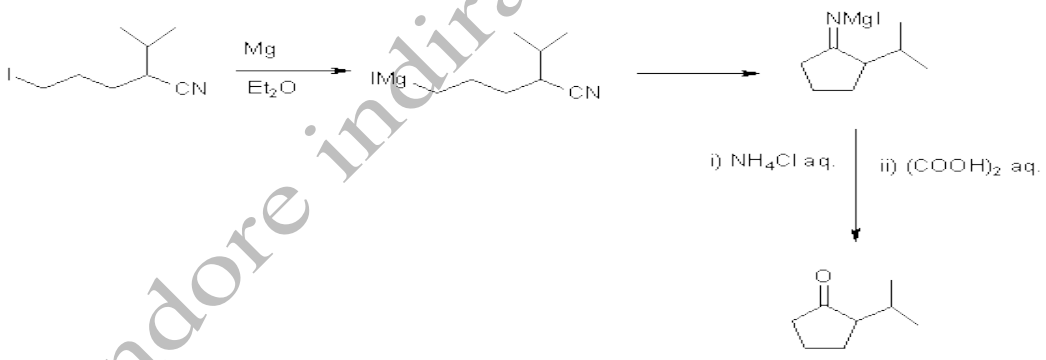
a. the rate of addition is increased, side-reactions reduced, and overall yield improved, by the use of relatively non-donor solvents, such as benzene containing only one equivalent of ether.

b. The addition reaction is catalysed by copper(I) salts

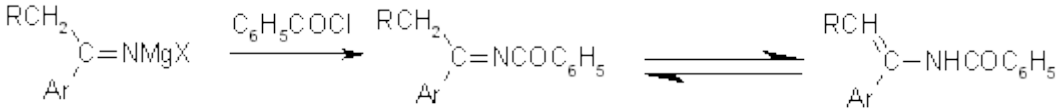
c. The difference in the reactivity between cyano groups and other functional groups is often sufficient to allow selective reactions. In general, the cyano group is less reactive towards organomagnesium compounds than carbonyl groups, but more reactive than epoxides.



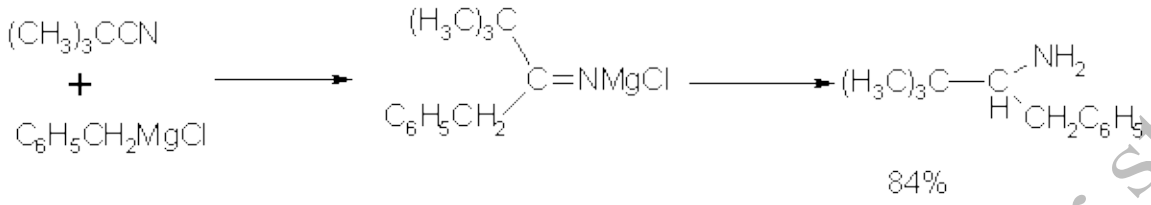
By far the most common application of the addition reaction is the synthesis of ketones, by hydrolysis of the intermediate imine *in situ*.[30]



Of the other reactions shown in the previous scheme, only acylation and reduction have found sufficient use to merit further comment. Acylation proceeds smoothly. It should be noted that when the adduct of a primary alkylmagnesium halide to an aromatic nitrile is benzoylated, the product tautomerizes to the enamide.

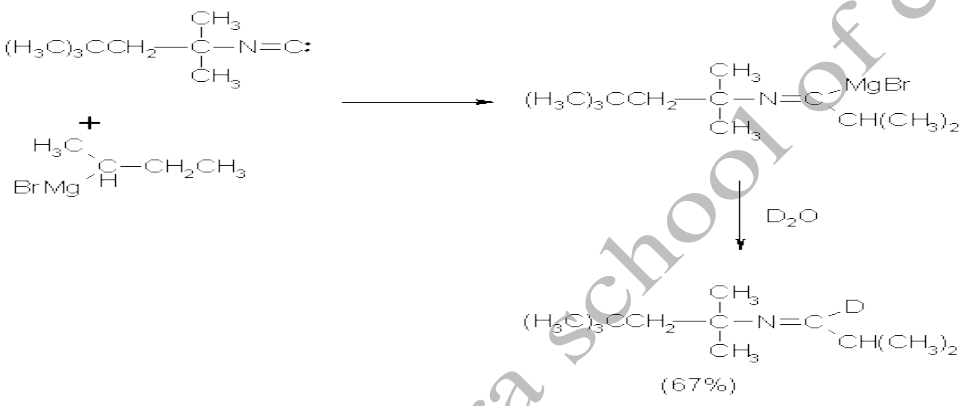


In situ reduction of the adducts was first accomplished by lithium in liquid ammonia. This method gave good yields, but reduction by sodium or zinc borohydride is also satisfactory, and experimentally more convenient.[31]



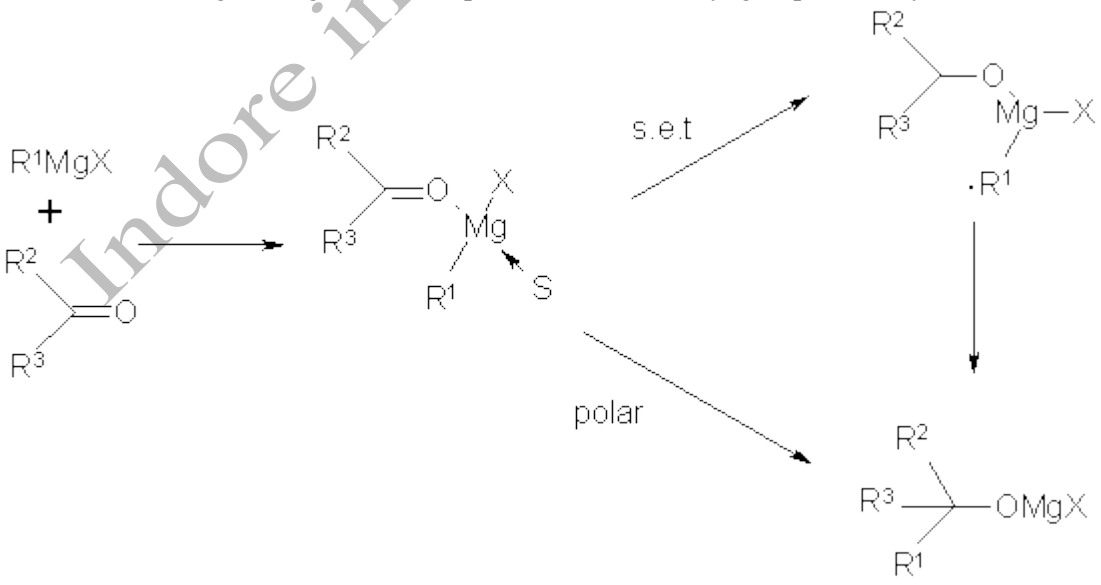
Addition to isonitriles

Organomagnesium compounds add to isonitriles, lacking alpha hydrogen atoms, to give metalloimines, which are masked acyl anion equivalents.

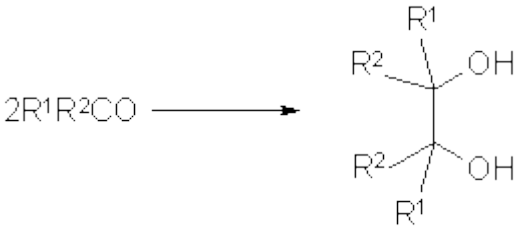


Addition to aldehydes and ketones

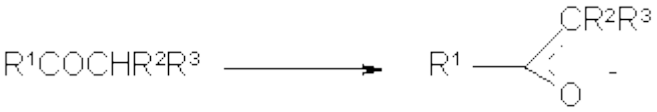
The addition of organomagnesium compounds to the carbonyl group of aldehydes and ketsones has a long history, and remains one of the most important reactions for carbon-carbon bond formation. Key features of the mechanism involved are describe below.



Besides the addition to the carbonyl group, three important side reactions may occur: reduction of the carbonyl compound to the corresponding alcohol, Bimolecular reduction to a 1,2-diol ("pinacol reduction")



And -deprotonation ("enolization")



These side reactions are rarely of preparative value, so the following discussion is centred on means of minimizing them.

i. Reduction to the alcohol may take place by at least four routes. The most important is the well-established pathway of □ -hydrogen transfer, giving the alcohol together with an alkene derived from the organomagnesium compound. When the organomagnesium comound possesses tertiary hydrogen atoms, and the carbonyl compound is sterically hindered, reduction may be the predominant reaction. This mode of reduction may be suppressed to some extent in the presence of metal salts. Alternative routes to unimolecular reduction include hydrogen abstraction by ketyls, Meerwein-Ponndorf reduction by alkoxides and reduction by a reactive form of magnesium hydride.

ii. Many addition reactions of organomagnesium compounds to carbonyl groups involve electron transfer pathways. The key intermediate in such pathways is a ketyl or related species; if this intermediate is sufficiently long lived it may react by dimerizing, and hydrolysis on work-up gives a 1,2-diol. This pathway is strongly promoted by the presence of transition metal compounds, even in trace amounts or of free magnesium. However, it can still occur to some extent even with filtered solutions of organomagnesium compounds prepared from highly purified magnesium, particularly with aromatic ketones and in more polar solvents.

iii. Organomagnesium compounds can act as bases as well as nucleophiles, and □ -deprotonation is a common side reaction of their reactions with carbonyl compounds, leading either to recovery of carbonyl compound on work-up or to aldol products. When enolate formation is troublesome, it can be reduced to some extent by the use of less polar media or low reaction temperatures. An important strategy is the conversion of the organomagnesium compound *in situ* into an organometallic reagent which is less basic, but retains nucleophilicity. Titanium(IV) and cerium (III) salts have been found particularly useful.

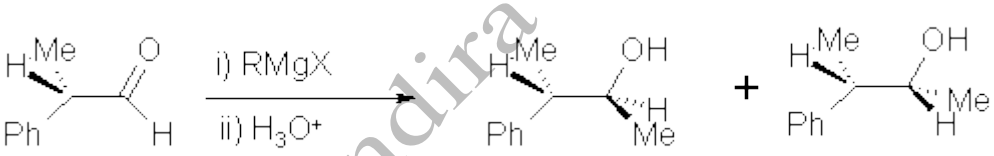
The forerunner of the reaction of preformed Grignard reagents with carbonyl compounds was the Barbier synthesis, in which an organic halide, a carbonyl compound, and magnesium react together. After many years of neglect, the Barbier synthesis has been revived. It has been improved, notably by the use of ultrasonic irradiation, and in favourable cases and/or under optimized conditions it can give excellent yields.

1. **Addition to aldehydes**

The addition of an organomagnesium compound to an aldehyde is an excellent general method for preparing secondary alcohols. Unsaturated aldehydes mainly undergo 1,2-addition. Although the reactivity of aldehydes towards organomagnesium compounds is greater than that of ketones, selective reactions of conventional Grignard reagents with formyl groups in the presence of oxo groups are not usually viable. On the other hand, it has been reported that ligand

exchange between organolithium compounds and magnesium carboxylates and sulfonates gives reagents with much greater selectivity.

Addition of an organomagnesium compound to an aldehyde gives rise to a new asymmetric carbon atom, and much effort has been devoted to maximizing the stereoselectivity of such additions. Three types of reactions have been studied: diastereoselective addition of organomagnesium compounds to chiral aldehydes, diastereoselective addition of chiral organomagnesium comopunds to aachiral aldehydes and enantioselective additions of achiral organomagnesium compouds to achiral aldehydes in the presence of chiral ligands. Of these, the first is the most important. Cram attributed the observed diastereoselectivity in the addition of organomagnesium compoudns to chiral aldehydes to steric approach control. A typical was the reaction of Grignard reagesnt with 2-phenylpropanal.



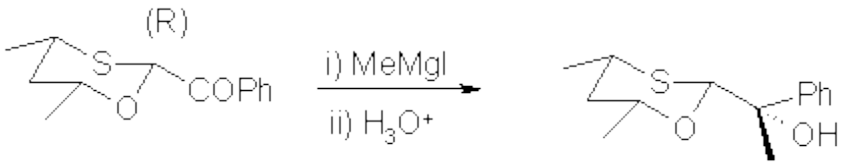
For enhancing Cram selectivity, two approaches have proved succesful: increasing the bulk of the organomagnesium reagent by using compounds such as $RMgNR'_2$, RMgOCOR' or RmgOR', where the groups R' are large; and conversion of the organomagnesium compound *in situ* into another organometallic compound. Two factors may lead to reversal of Cram selectivity: a chelation control by neighbouring groups and conversion of the organomagnesium compound into another organometallic compound.

2. **Addition to ketones**

The addition of organomagnesium compounds to the carbonyl group of ketones is somewhat more susceptible to side reactions than the corresponding reaction of aldehydes; the carbonyl group is more sterically hindered in the ketones, and generally has lower inherent reactivity. Nevertheless, satisfactory results are usually attainable.

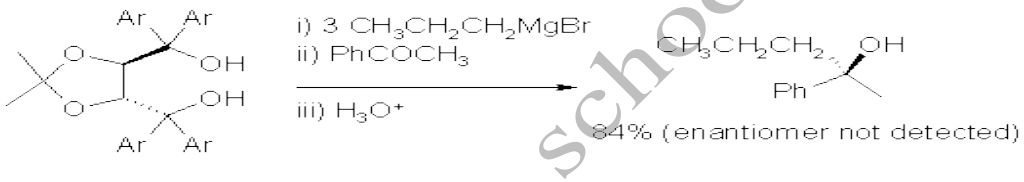
In cases of difficulty, the addition reaction is favoured by less polar media (eg. hydrocarbons containing only small proportions of ehters), by lower reaction temperatures, and by the addition of salts. Conversion of the organomagnesium compound into another organometallic compound *in situ* may also circumvent side reactions involving □ -deprotonation.

The stereochemistry of organomagnesium compounds to ketones is governed by similar factors to those influencing their addition to aldehydes. For addition of achiral organomagnesium comounds to chiral ketones, steric approach control is commonly observed, but chelation control may also operate. It is noteworthy that a pioneering asymmetric synthesis - one of the first which could be regarded as virtually stereospecific was of this type



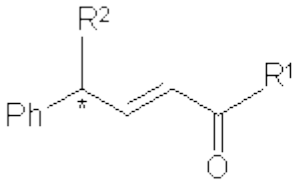
In this case, steric approach control and chelation control work in concert.

Until recently, attempts to achieve asymmetric synthesis by reactions of achiral carbonyl compounds with achiral organomagnesium compounds in the presence of chiral ligands had met with only limited success. Recently however, very promising results have been reported involving additions to ketones "TADDOLs", where the aryl groups are phenyl or 2-naphthyl are particularly effective, as in the following example.

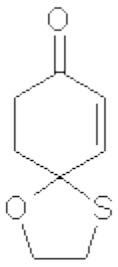


Organomagnesium compounds show a greater tendency than organolithium compounds towards conjugate addition to unsaturated ketones, and frequently give mixtures of products. Thus, when 1,2-addition is required, organolithium compounds are preferred. Probably the most generally applicable method for achieving 1,4-addition is conversion of the organometallic reagent into an organocopper species *in situ*; in many cases stoichiometric conversion is not necessary, and the addition of a catalytic amount of a copper (I) salt is sufficient. Conjugate addition is also favoured by bulky substituents on the carbonyl carbon and conditions favouring electron transfer pathways.

The stereochemistry of conjugate addition of organomagnesium compounds to unsaturated ketones is governed by similar consideration to those governing addition to saturated ketones; recent examples include diastereoselective additions to both acyclic **(3)** and cyclic **(4)** enones.

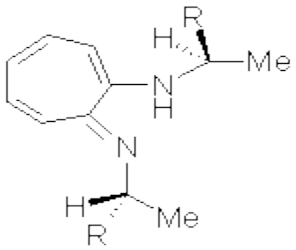


(3)

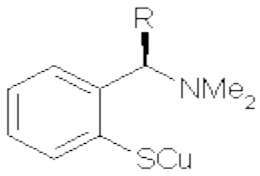


(4)

Although in some cases, copper catalysis has little effect on the stereochemistry, some asymmetric induction by chiral copper catalysts such as copper(I) complexes of aminotroponic iminates **(5)** or the chiral arylthiocopper compound[37] **(6)** has been achieved. Chiral zinc(II) complexes **(5)** also promote enantioselective conjugate addition.



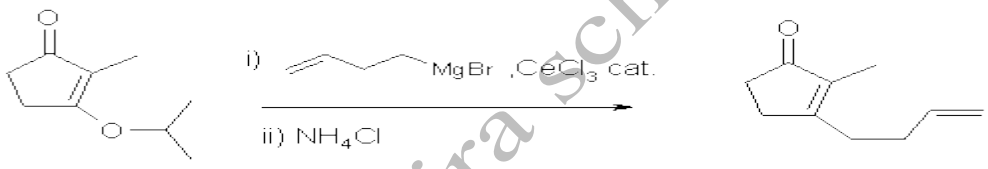
(5)



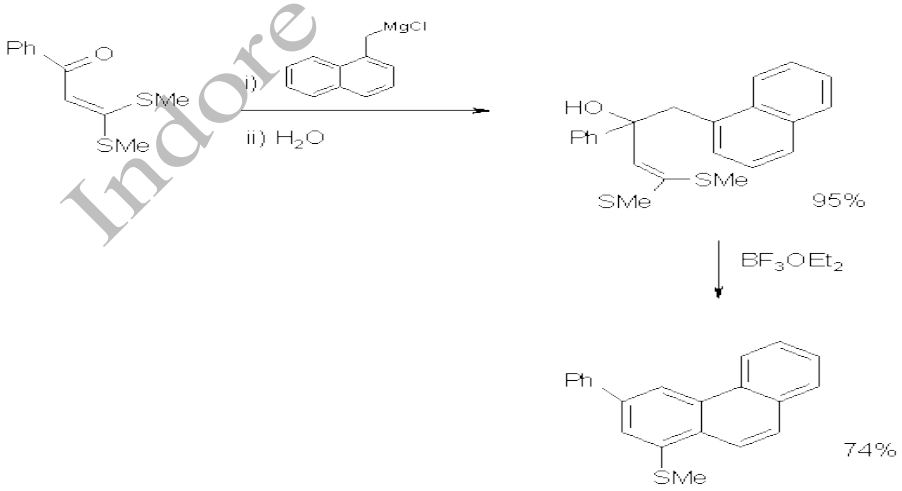
(6)

A speacial case of conjugate addition involves diaryl ketones. Conjugate addition of organomagnesium compounds may lead to products formally derived from addition to a ring. Such reactions are favoured by conditions promoting electron transfer, particularly when polar addition to the carbonyl group is sterically hindered.

One type of reaction of unsaturated ketones with organomagnesium compounds deserves special comment.-Alkoxy or alkylthio ,-unsaturated ketones tend to undergo 1,2-addition. This may be followed by elimination as in the following example.



In other examples, the initial adduct is stable, and its hydrolysis product is isolable, and is a useful intermediate for further transformations. For example, the products from reactions of organomagnesium compounds with □ -oxoketene dithioacetals may be transformed into a variety of aromatinc and heeroaromatic systems.



Organolithium reagents

Organolithium reagents are organometallic compounds that contain carbon – lithium bonds. They are important reagents in organic synthesis, and are frequently used to transfer the organic group or the lithium atom to the substrates in synthetic steps, through nucleophilic addition or simple deprotonation. Organolithium reagents are used in industry as an initiator for anionic polymerization, which leads to the production of various elastomers. They have also been applied in asymmetric synthesis in the pharmaceutical industry.

Due to the large difference in electronegativity between the carbon atom and the lithium atom, the C-Li bond is highly ionic. This extremely polar nature of the C-Li bond makes organolithium reagents good nucleophiles and strong bases. For laboratory organic synthesis, many organolithium reagents are commercially available in solution form. These reagents are highly reactive, and are sometimes pyrophoric.

Organolithium Compounds

One of the major uses of lithium is in the synthesis of organolithium compounds, RLi. They have great importance and utility in industry and chemical research. Their reactivity resembles that of Grignard reagents, but they are generally more reactive.

Synthesis

The best general method for RLi synthesis involves the reaction of an alkyl or aryl chloride with lithium metal in benzene or an aliphatic hydrocarbon (e.g., hexane),.

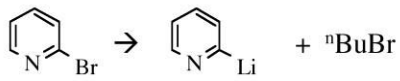
$$RCl + 2\,Li \rightarrow RLi + LiCl$$

While it is possible to use diethyl ether (Et_2O), the solvent slowly attack the resultant alkyl lithium compound, .

$$Et_2O + {}^{n}BuLi \rightarrow EtOLi + H_2C{=}CH_2 + {}^{n}BuH$$

Metal-hydrogen exchange, , metal-halogen exchange and metal-metal exchange can also be used, .

$$RH + R'Li \rightarrow R'H + RLi$$



$$2\,Li + R_2Hg \rightarrow 2\,RLi + Hg$$

All organolithium compounds are produced as solutions and are hence used in synthetic protocols by volume of solution. It is therefore important to know the exact concentration of RLi in solution. The simplest approach to quantify the amount of organolithium is to react a known volume with wate and then titrate (with acid) the resultant base that is formed.

$$RLi + H_2O \rightarrow LiOH + RH$$

However, while the concentration of freshly prepared samples of organolithium reagents can the theoretically measured in this way, real samples always contain some amount of LiOH or other bases. A simple titration inevitably results in an over estimation of the organolithium reagent. To overcome this a *double titration* method is used.